DECLARATION

I declare that the research presented herein, is original work carried out by the author and has not been submitted for any other degree.

Signed ..... (Author)

..... (Supervisor)

SYNTHETIC STUDIES TOWARDS

ERGOT ALKALOIDS

by

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A thesis submitted to the Council for National Academic Awards in partial fulfilment of the requirement for the degree of Doctor of philosophy.

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CONTENTS

ABSTRACT

Some of the background to the biosynthesis, synthesis and uses of ergot alkaloids has been reviewed.

A novel synthesis of the indole system has been used in an attempt to synthesise a derivative of the tricyclic Uhles ketone. A variation on this method has been carried out using 3-indole propionic acid as the starting material. The novel synthesis of the indole ring system has been developed into a synthesis of a 4-substituted indole.

A number of literature methods for the synthesis of 4-substituted indoles have been investigated, and their usefulness in the laboratory assessed. A modified Reissert synthesis has been carried out, along with a Batcho-Leimgruber synthesis. Also the use of a thallium based method and palladium catalysed carbon-carbon bond formation have been investigated.

A novel synthesis of p-benzoquinones has been discovered, by oxidation of aromatic sulphonamides. This method has not been optimised but low to moderate yields of quinones have been achieved. This method was used in an attempt to synthesise o-benzoquinones, but was found to be unsuitable.

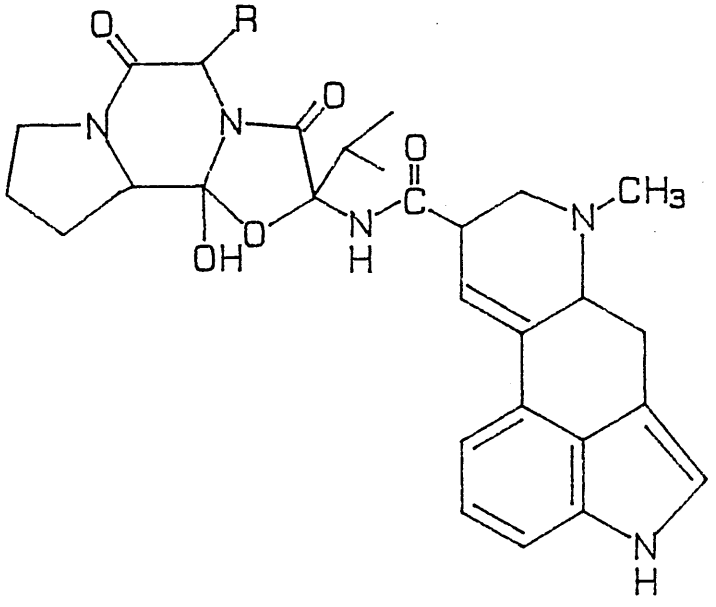
A novel synthesis of aromatic thiol esters has been developed starting from simple substituted benzaldehydes esters and methylmethylthiomethylsulphoxide. The resulting ketene thioacetal monosulphoxide was treated under the same conditions as those used in the novel indole synthesis. High yields of thiolesters were obtained.

CHAPTER 1: BACKGROUND AND AIMS.

1.1. GENERAL.

Ergot is the resting stage or dry schlerotium of the fungus Claviceps purpurea, which attacks cereals, particularly rye. Ergot alkaloids have also been isolated from other groups of fungi (Phycomycetes, Ascomycetes and Basidiomycetes) and some higher plants. Ergot was known as early as 600 B.C., as a scourge that afflicted many people.

Ergot poisoning was quite common and went under a number of names, Holy Fire and St Anthony's Fire (to name but two), the names being derived from the burning sensation and resulting gangrene in the extremities, caused by vasoconstriction of the blood vessels[1]. The earliest alkaloids to be isolated from ergot were obtained in 1905 by Barger Carr and Dale[2]. They isolated ergotoxine which was a crystalline product, and was thus thought to be a single substance. It was later found to be a mixture of three alkaloids; ergocristine (1), ergocornine (2) and ergokryptine (3). To date approximately twenty alkaloids have been isolated from ergot.



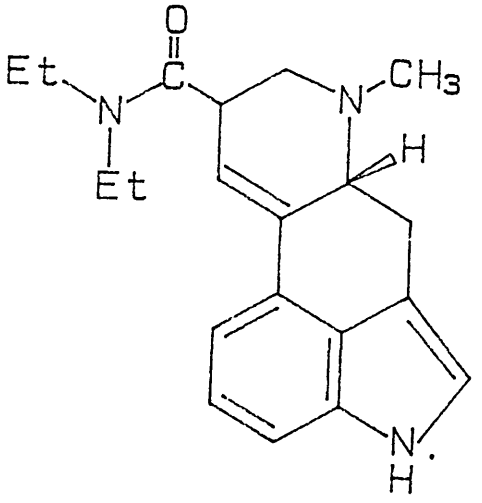
(1) R = $-CH_2Ph$

(2) R = $-CH_2CH(CH_3)_2$

(3) R (α) = $-CH_2CH(CH_3)_2$

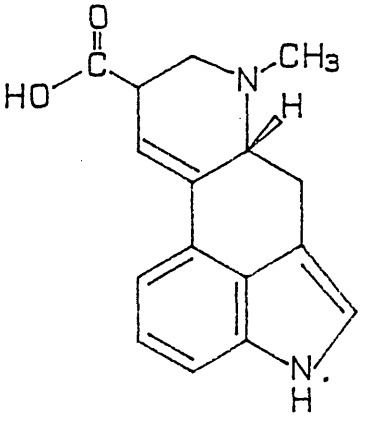
(3) R (β) = $-CH(CH_3)CH_2CH_3$

One of the first synthetic alkaloids was lysergic acid diethylamide (LSD) (4), the well known hallucinogenic drug. This was synthesised in 1939 by Albert Hoffman, who discovered its effects by ingestion of a small sample in the laboratory.

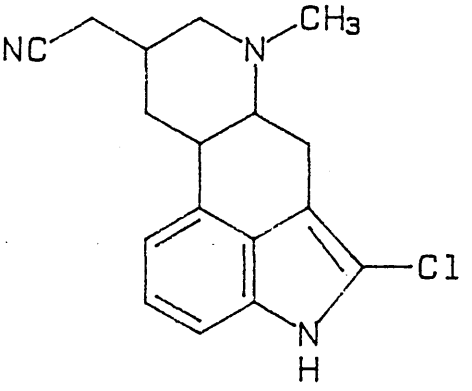


(4)

All the alkaloids are derivatives of lysergic acid (5), where the carboxylic acid hydrogen has been replaced by various side chains (either simple or complex), or the whole acid group has been replaced as in lergotrile (6).

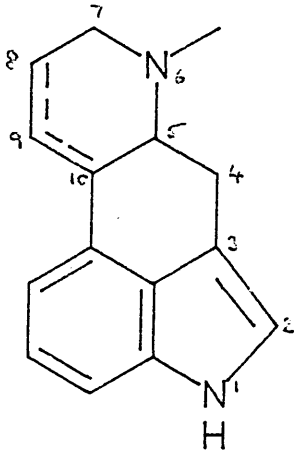


(5)

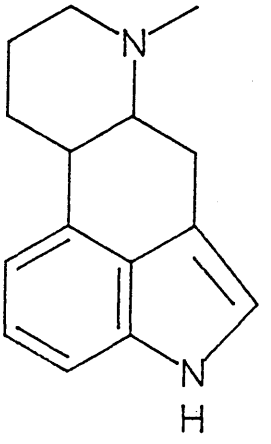


(6)

The naturally occurring, pharmacologically active alkaloids are the levo(-)isomers; the dextro(+)isomers are inactive. The ergot alkaloids all contain the tetracyclic ergolene or ergoline ring system[3].



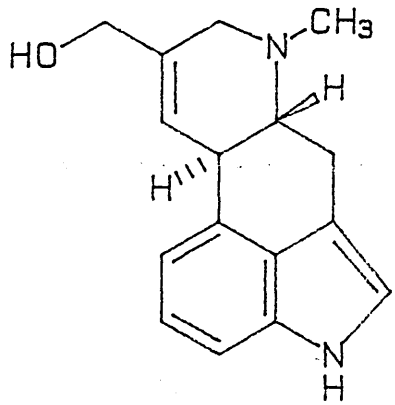
ERGOLENE



ERGOLINE

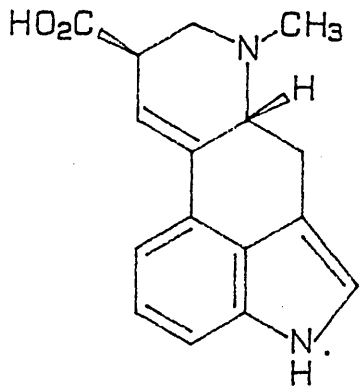
The ergot alkaloids can be divided into four main structural groups:-

1) clavine alkaloids



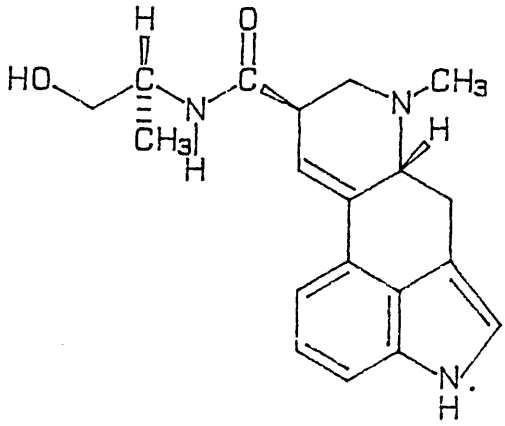
ELYMOCLAVINE (7)

2) lysergic acid group



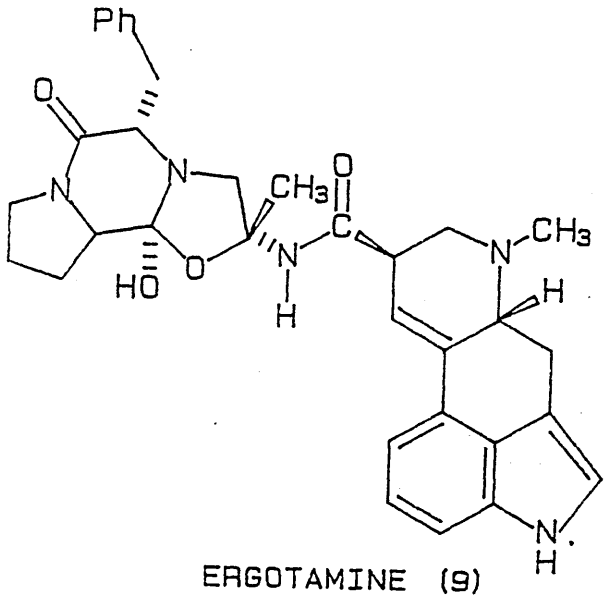
D-LYSERGIC ACID (5)

3) lysergic acid amides



ERGOMETRINE (8)

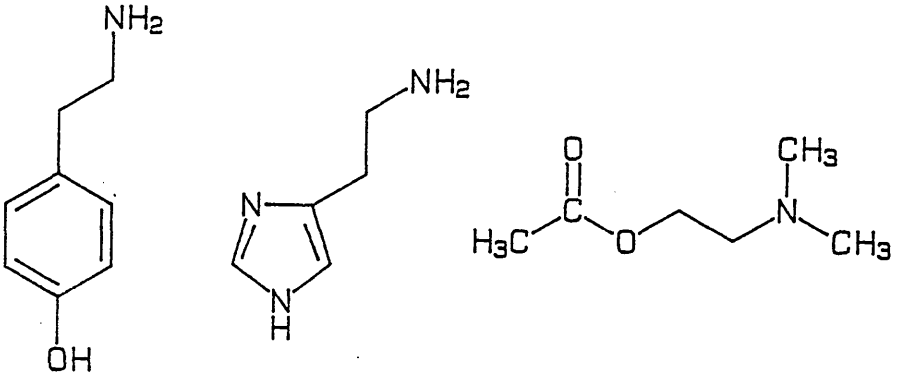
4) peptide alkaloids



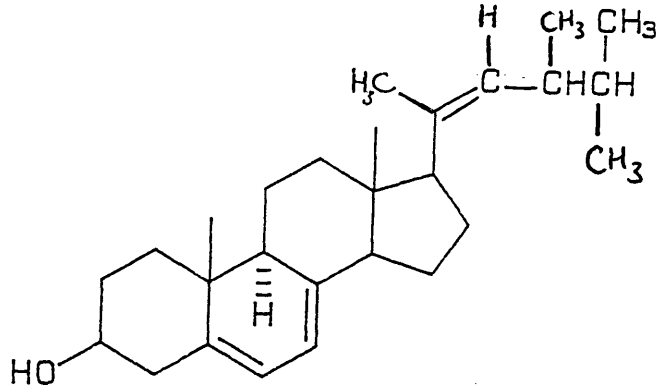
ERGOTAMINE (9)

The naturally occurring lysergic acids are divided into compounds with a double bond in the 8-9 position (8-ergolenes) and in the 9-10 position (9-ergolenes), and all members of the group are methylated at the N-6 position. Also the two asymmetric carbon atoms in positions 5 and 10 (in 8-ergolenes) or 5 and 8 (in 9-ergolenes), allow a further classification according to the steric position of the substituents in positions 8 or 10. The 5H atom always has the β-configuration[3].

There are various other classes of compound which are also isolated from ergot. They include pharmacologically active amines such as tyramine, histamine and acetylcholine, and oils such as ergosterol, which on irradiation with ultra violet light forms vitamin D_2.



Tyramine Histamine Acetylcholine



Ergosterol

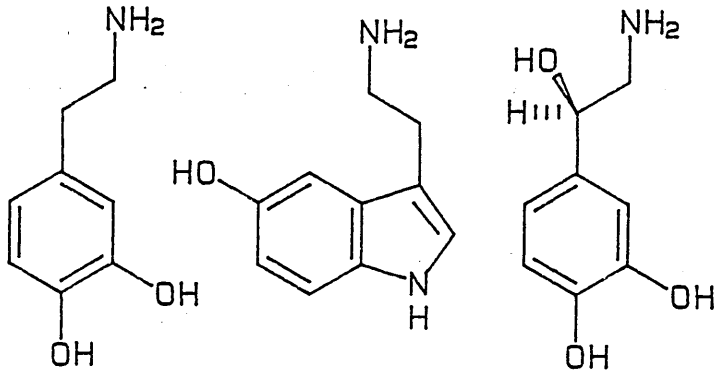
1.2. PHARMACOLOGY.

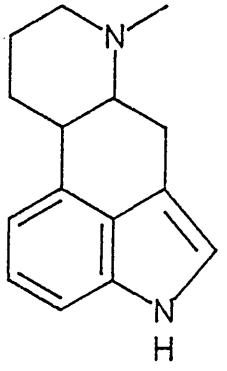
Ergots are some of the oldest drugs known, having been studied as early as 1906 by Sir Henry Dale. They have been used throughout history by midwives in obstetrics. Ergots are of interest to modern pharmacologists, owing to the multiple actions associated with them. These actions include effects on uterine and vascular smooth muscle, so ergots can be used as a tool for studying the mechanism of the sympathetic nervous system. The newer ergot derivatives show actions in the inhibition of prolactin secretion and stimulation of dopaminergic receptors (e.g. utilisation in the treatment of Parkinsons disease). Ergots have been implicated as potential therapeutic agents in the treatment of many disease states e.g. acromegaly, amenorrhea-galactorrhea, suppression of post-partum lactation, post-partum haemorrhage, breast cancer and possible cancer of the prostate gland.

Ergots when misused can also be detrimental to health, the hallucinogenic drug LSD, being one such compound. However it has been useful in the development of the field of pyschopharmacology.

Resemblance of the ergot alkaloids to useful biological molecules such as dopamine (10), serotonin (5-hydroxytryptamine (5HT)) (11) and

noradrenaline (12) can quite clearly be seen when the above compounds are superimposed onto the ergot skeleton[3].





Ergot skeleton

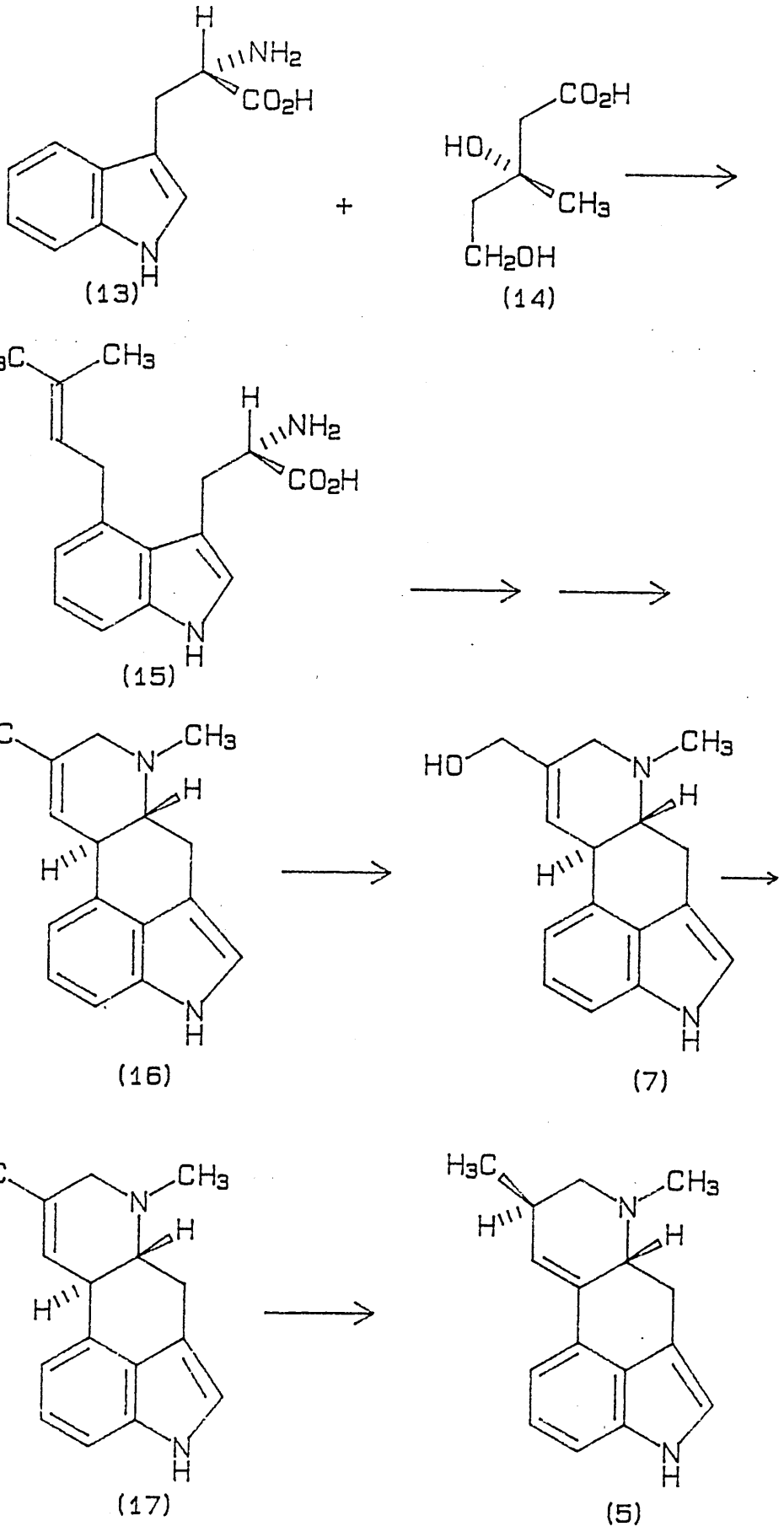
1.3. SYNTHESIS OF ERGOT ALKALOIDS.

1.3.1. BIOSYNTHESIS.

The problem of the biogenesis of ergot alkaloids has been solved, in that the building blocks used by Claviceps species are known. However there are still three main areas in the synthesis which are unclear:- (i) how rings C and D are formed, (ii) the formation of the

amides, and especially (iii), the formation of the tricyclic moiety in the peptide alkaloids. The ergolene skeleton is synthesised from a molecule of L-tryptophan (13) and L-mevalonic acid (14). The intermediate 4-dimethylallyl-L-tryptophan (15) is then converted in a number of steps by oxidation, decarboxylation and cyclisation to agroclavine (16), which is further oxidized in the 8-methyl group to elymoclavine (7) and 6-methyl-8-ergolene-8-carboxylic acid (17). This ultimately isomerises to d-lysergic acid or its derivatives. The N-methyl group in (7) was introduced in one of the steps between (15) and (16) by L-methionine[3], (scheme 1).

Scheme 1.

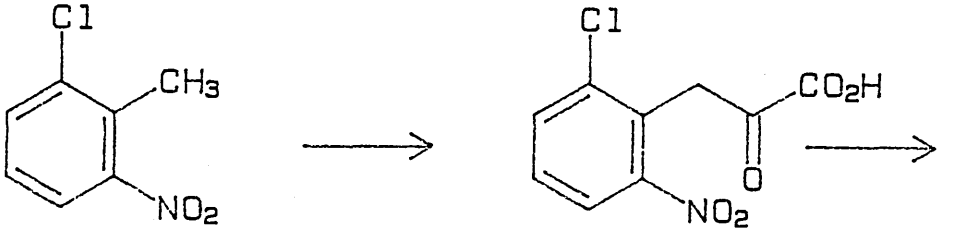


1.3.2. SYNTHETIC STRATEGIES.

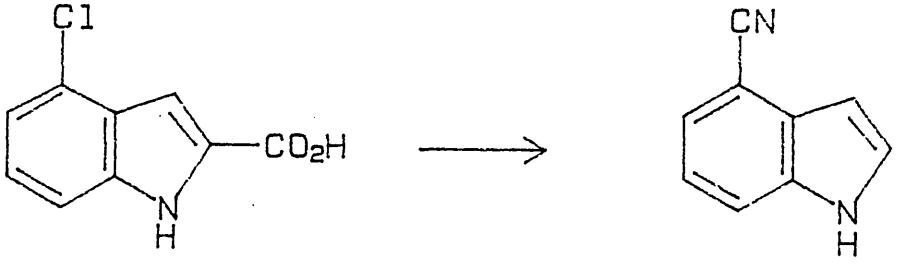
Retrosynthetic analysis of the structure of the ergot alkaloids reveals a 4-substituted indole derivative. Previous syntheses of ergots have usually begun with such indoles. A number of these syntheses have been reviewed in the literature[4], and outlined below are just three of these methods. They have been chosen because they are relevant to the work carried out in this project, and will be discussed in later chapters, in their context to our own work.

Scheme 2 shows the approach of Uhle[5], which began with the readily available substance 2-chloro-6-nitrotoluene (19), which was converted to a 4-substituted indole, and subsequently to the compound now generally known as Uhle's ketone (22), a very important precursor to the ergot alkaloids.

Scheme 2.



(19)



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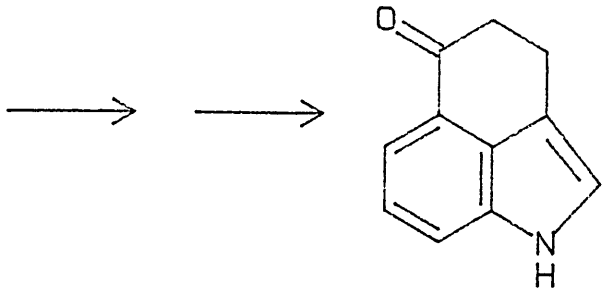
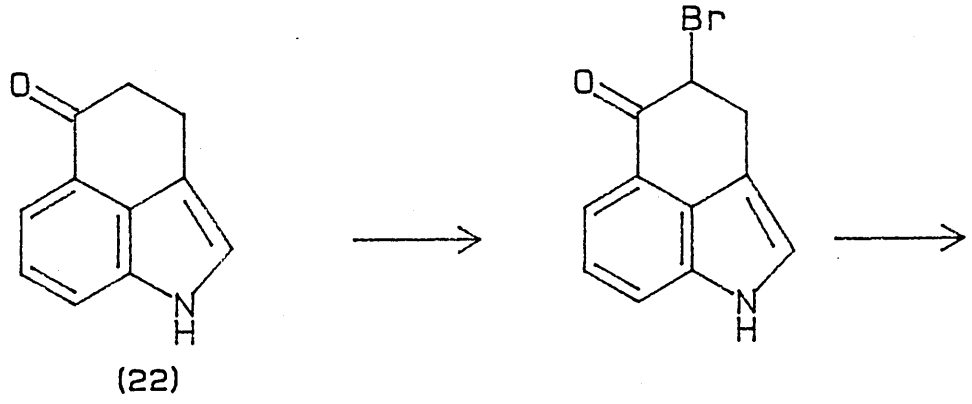


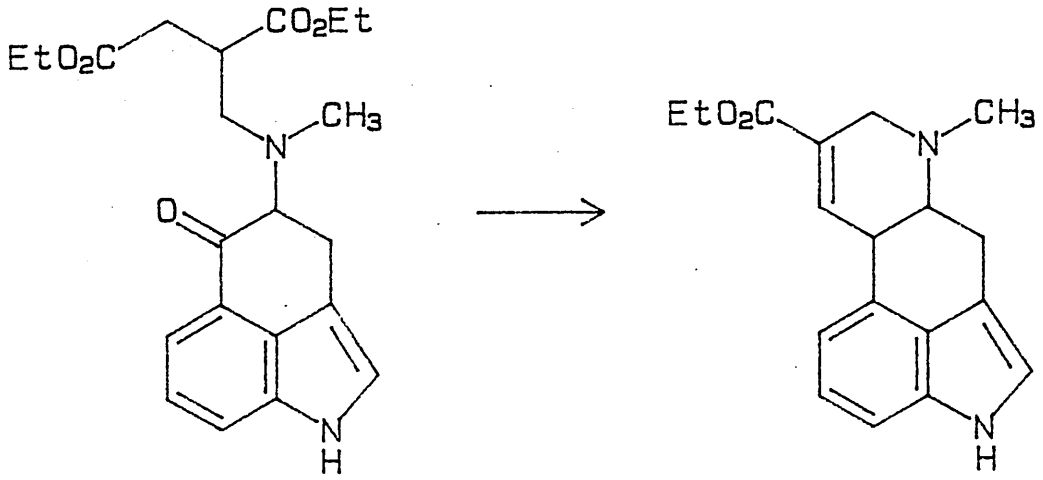
(22)

Elaboration of Uhle's ketone (22), by bromination, followed by reaction with a nitrogen nucleophile allows the required nitrogen atom to be inserted (scheme 3)[6], and hence the ergot skeleton can be completed by cyclisation to give the D ring.

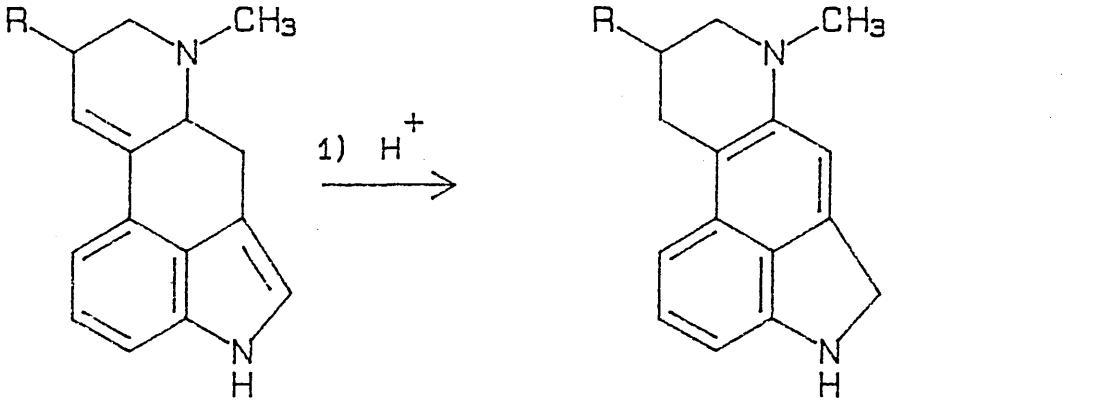
Scheme 3.



(22)



A drawback with Uhle's approach to lysergic acid, is that condensation of the ketone with an active methylene group would require the use of a strong acid or base. These conditions would cause the known isomerisation of the 9-10 ergolene to the benz[c,d]indoline, outlined below, which is irreversible under these conditions.



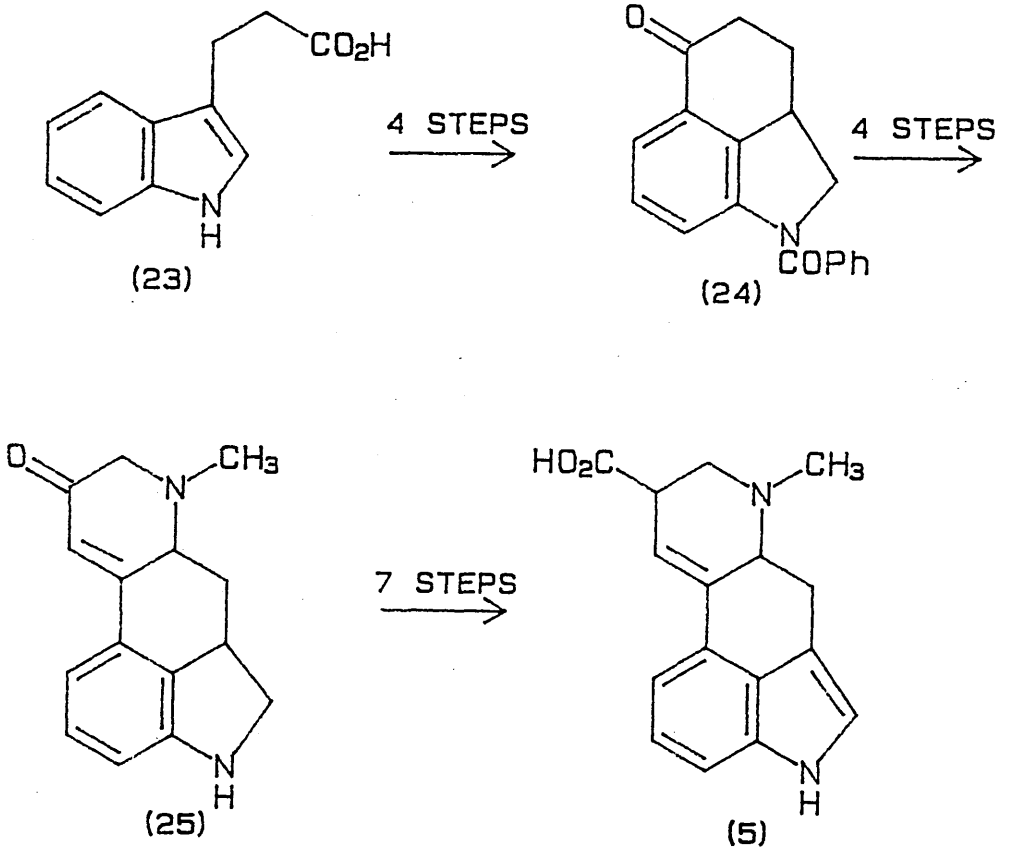
Benz[c,d]indoline

This isomerisation has been a major problem in the synthesis of the ergolene skeleton, and has thwarted many attempts at its synthesis.

The first successful total synthesis of dl-lysergic acid was achieved in 1955 by Kornfeld et al[7], in fifteen steps from 3-

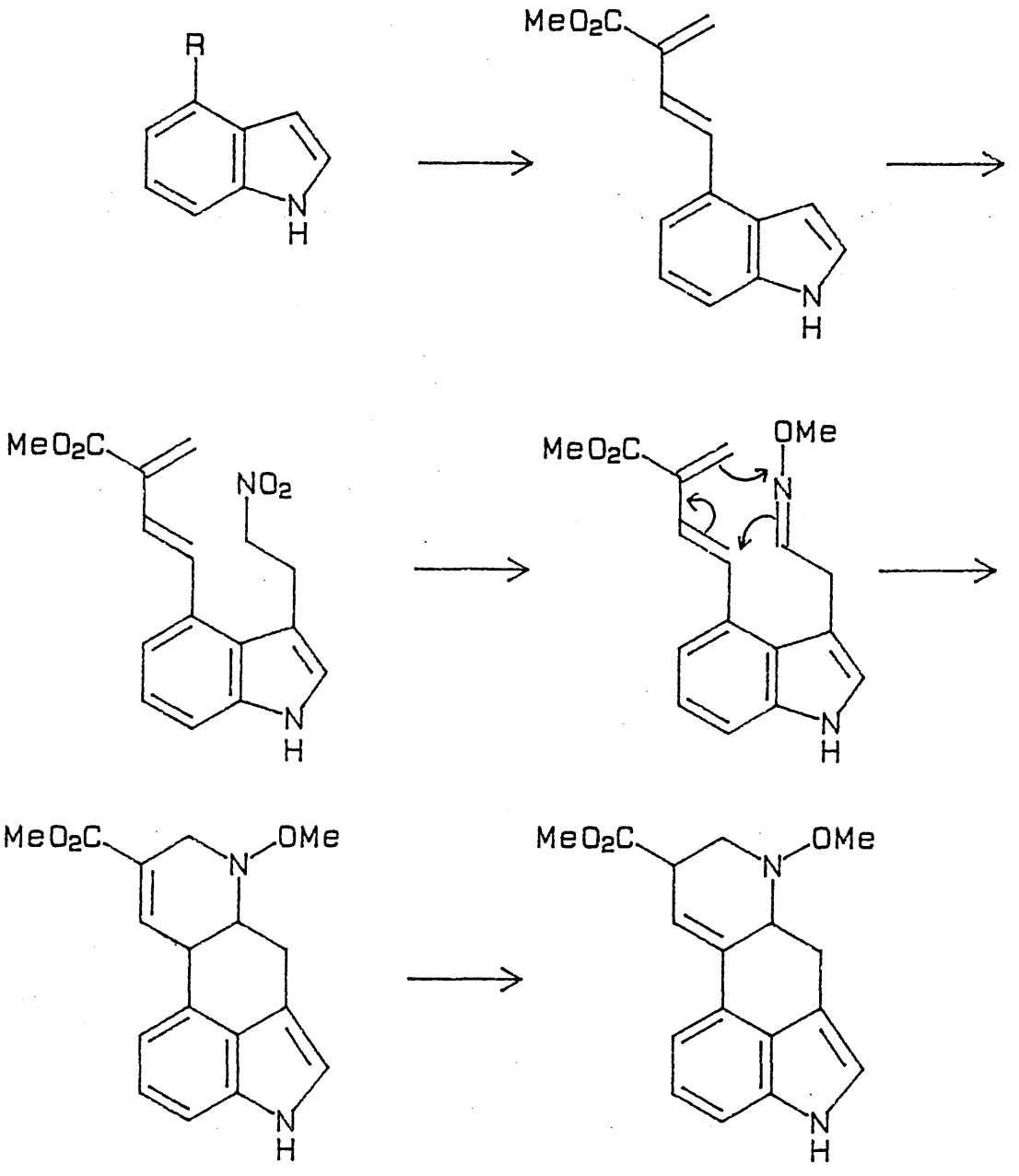
indolepropionic acid (23). This was converted to 1-benzoyl-5-keto-1,2,2a,3,4,5-hexa-hydrobenz[c,d]indole (24), which contains three of the four rings required for the ergolene skeleton. The ketone was converted to the octahydroindolo[4.3-f,e] quinoline derivative (25) and hence to lysergic acid (5), (scheme 4).

Scheme 4.



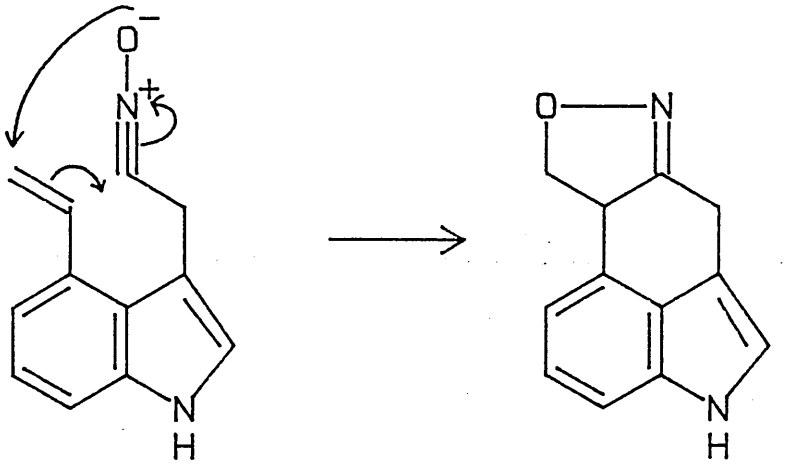
Scheme 5 outlines the approach adopted by Oppolzer, Francotte and Battig[8], which uses an intramolecular imino Diels-Alder reaction to establish the C ring.

Scheme 5.



The above cyclisation is related to the 1,3-dipolar cycloaddition, using a nitrile oxide and an olefin, as the reacting

species.



Isoxazoline

This reaction will be discussed in much more detail in chapter 3, as it has been used in a synthesis of the tetracyclic isoxazoline.

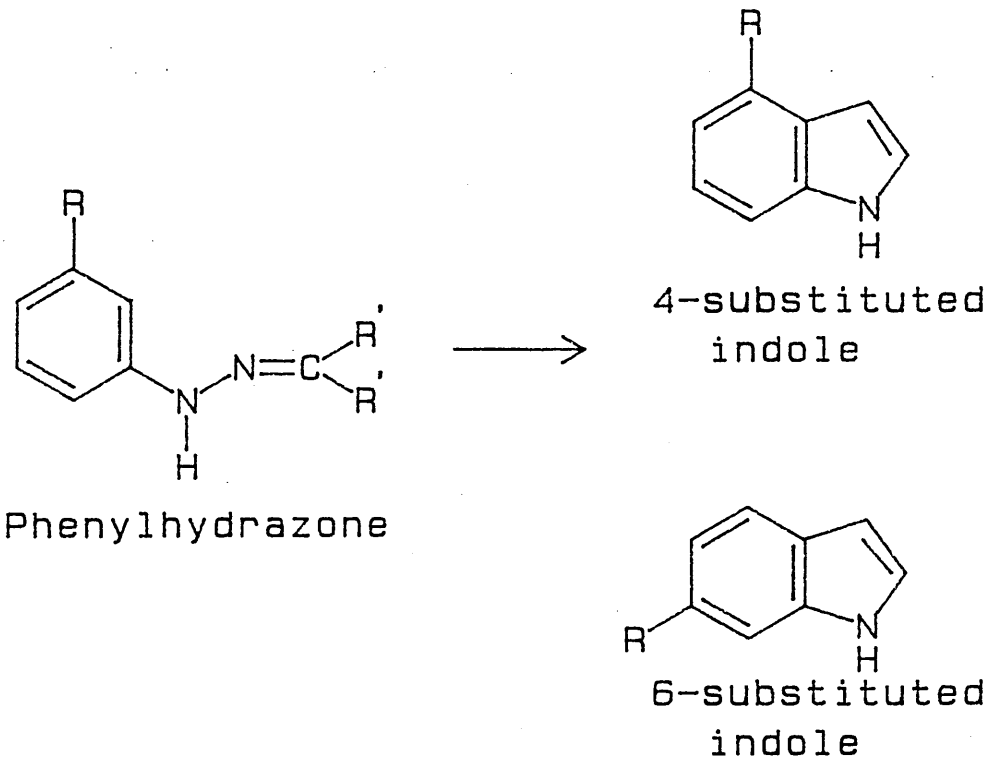
Since 1955 many other successful total syntheses of ergot alkaloids have been achieved, but are not commercially viable. The best method of manufacturing them is still by fermentation.

1.4. 4-SUBSTITUTED INDOLES.

As can be seen from the above reaction schemes, a 4-substituted indole is a very useful starting point for synthetic entry into the ergot skeleton. However such derivatives are not easily synthesised by direct substitution onto the carbocyclic ring of the indole. The most reactive position for electrophilic substitution is the 3-position; however if the 3-position is already substituted then the electrophile will react at the 2-position. The most preferable position on the carbocyclic ring is position 5.

Traditional methods of synthesising the indole skeleton (such as the Fischer indole synthesis) are not very useful in that a mixture of products (4 and 6-substituted indoles) is produced. (Scheme 6).

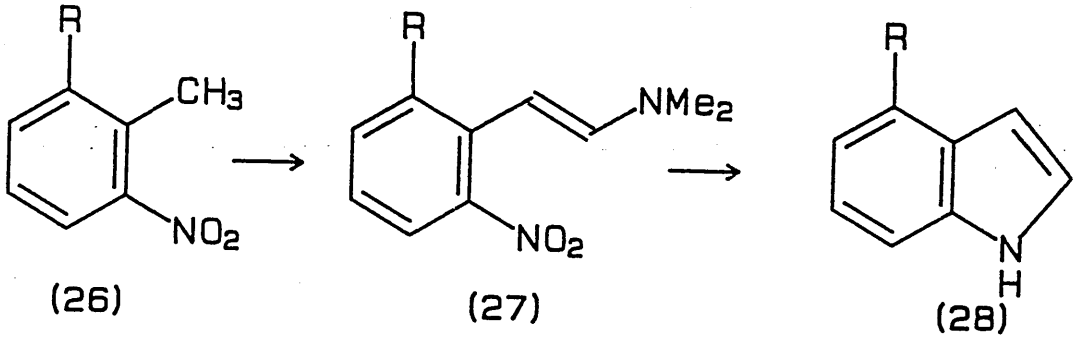
Scheme 6.



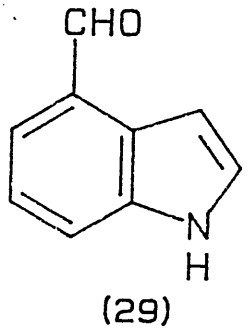
A number of successful syntheses of 4-substituted indoles have been achieved and their elaboration to the ergot alkaloids has been reviewed[9]. One of the more modern and highly specific methods for synthesising 4-substituted indoles is the so called Batcho-Leimgruber[10] indole synthesis. The method utilises a suitably substituted ortho nitrotoluene (26) as the starting material. Condensation with a dimethylformamide acetal, and subsequent reduction of the resulting enamine (27), gives the indole (28) in high

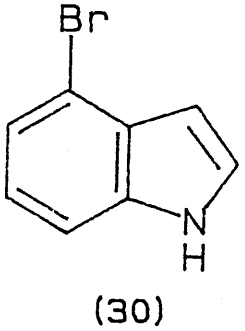
yields, (scheme 7).

Scheme 7.



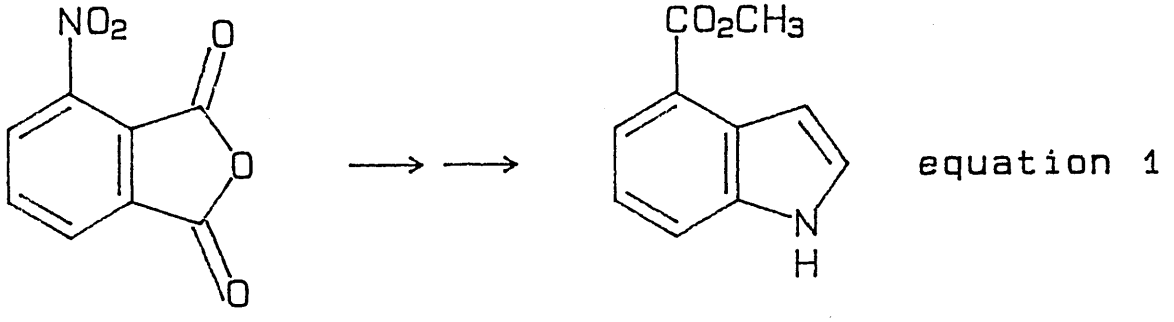
The method has been developed by a number of workers, (Kozikowski et al[11], Maehr and Smallheer[12], Ponticello and Baldwin[13] and Harrington and Hegedus[14]), into a simple but useful synthesis of 4-substituted indoles, e.g. 4-formylindole (29)[11,12,13] and 4-bromoindole (30)[14] .



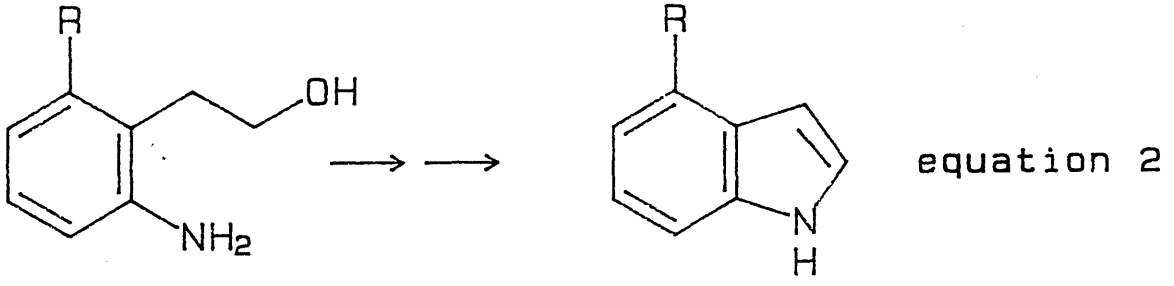


Further reactions enable side chains to be built into the 4-position using Wittig reactions, for (29) and palladium catalysed olefin coupling[14] for(30). This method has been extensively reviewed[15], and will be discussed in more detail in chapter 3.

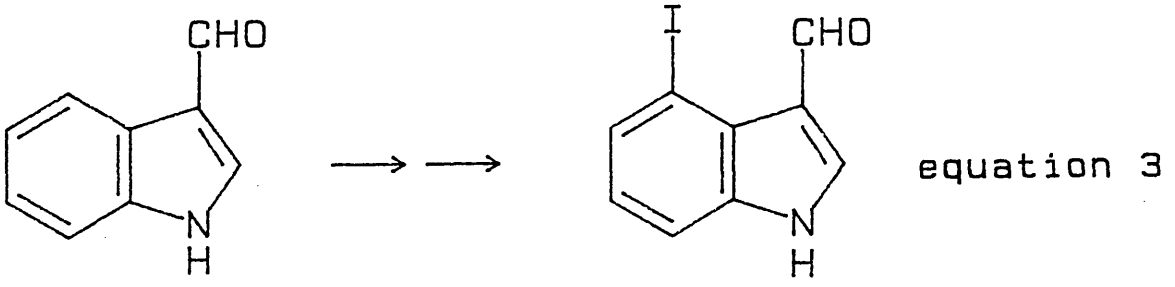
Various other novel syntheses of 4-substituted indoles have been developed, using a variety of starting materials, e.g. 3-nitrophthalic anhydride[16], (equation 1), appropriately substituted 2-aminophenyl ethanols[17], (equation 2) and 3-formylindole[18,19], (equation 3).



equation 1



equation 2



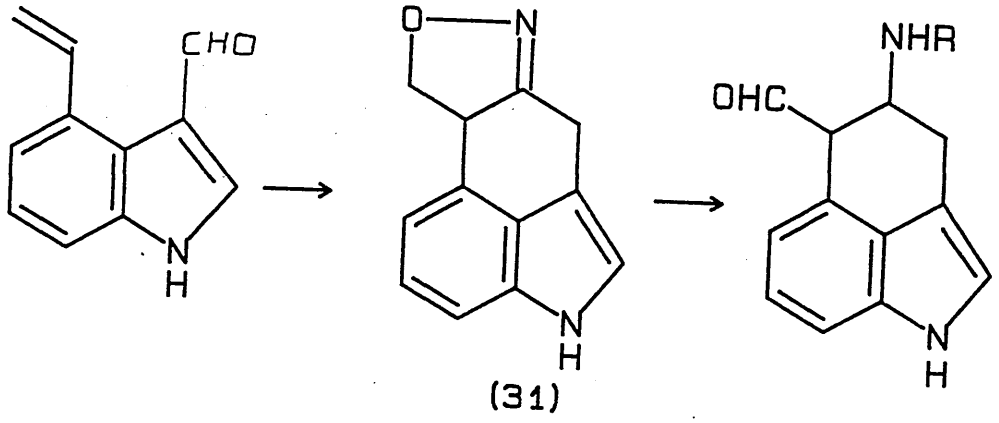
equation 3

These methods (mentioned above) will be discussed further in chapter 3 as they are all relevant to work carried out in this project.

1.5. AIMS.

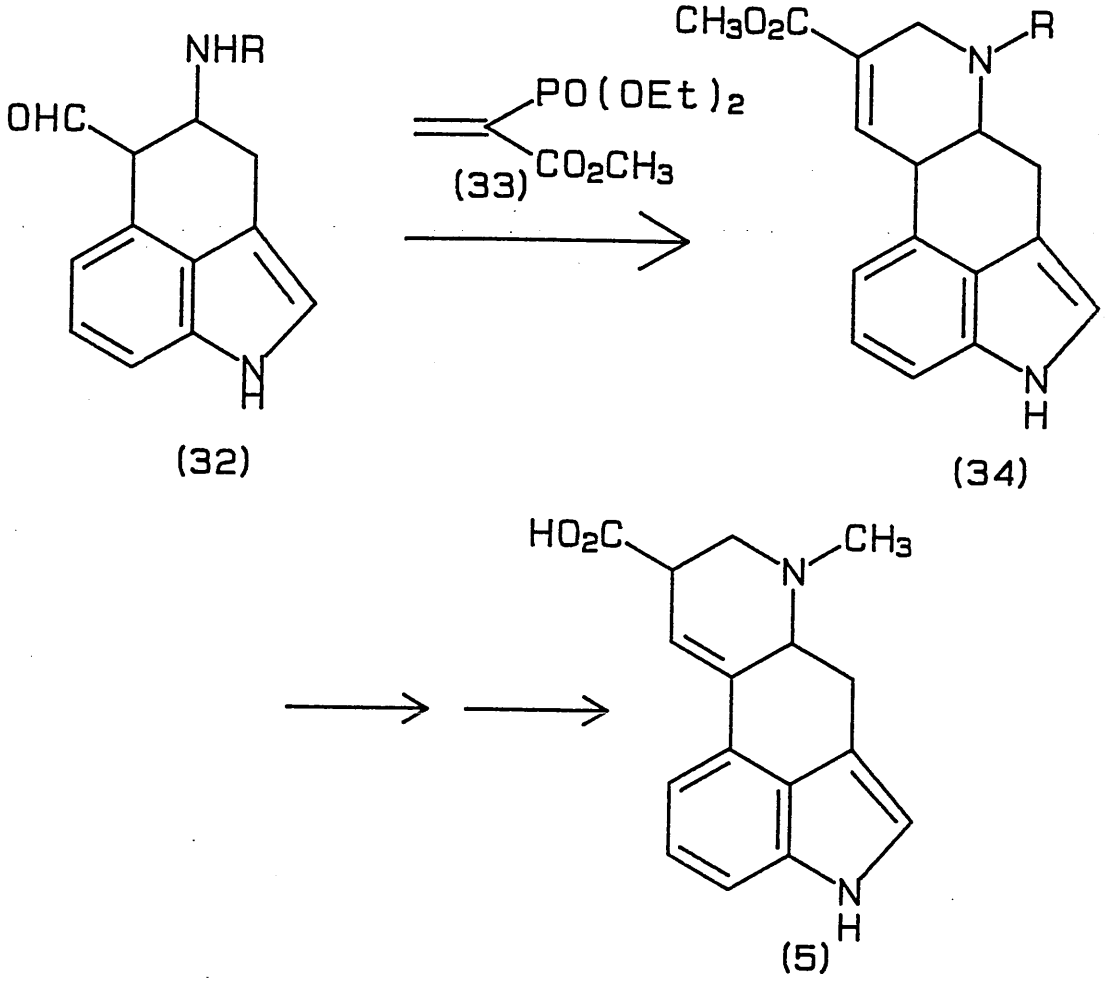
The ultimate aim of the project was to synthesise lysergic acid (5), by two complementary routes. The first was to initially synthesise a 4-substituted indole and convert this to a tetracyclic compound (31), by a 1,3-dipolar cycloaddition reaction[20,21]. Reductive cleavage of the N-O bond in the tetracyclic compound (31) followed by oxidation of the resulting intermediate alcohol would give the tricyclic aldehyde (32), (scheme 8).

Scheme 8.



It was proposed to synthesise the D ring by a cycloaddition reaction using a vinyl phosphonate ester (33), followed by modification of the resulting ergolene, lysergic acid (5), (scheme 9).

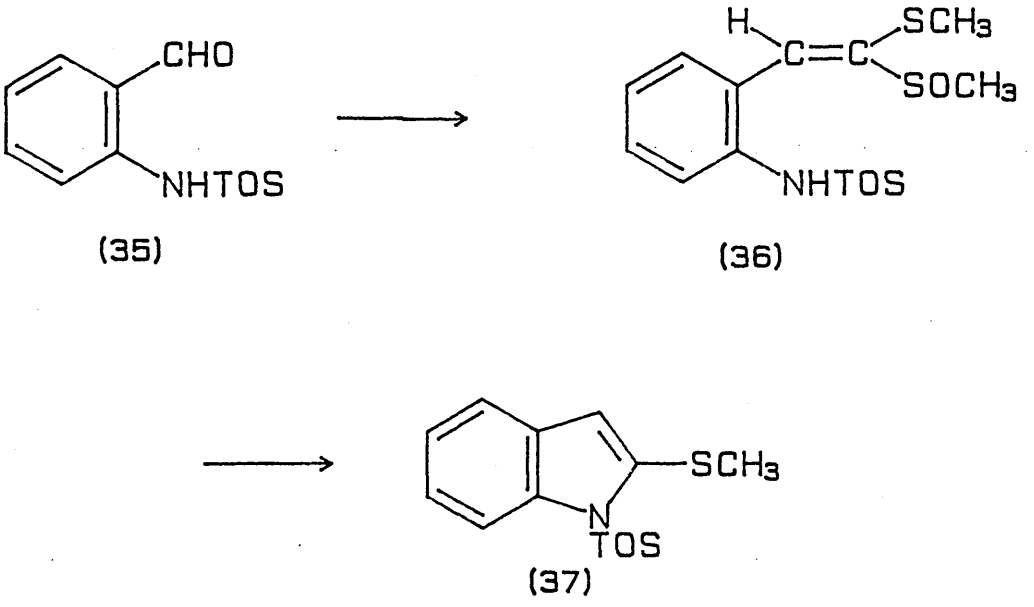
Scheme 9.



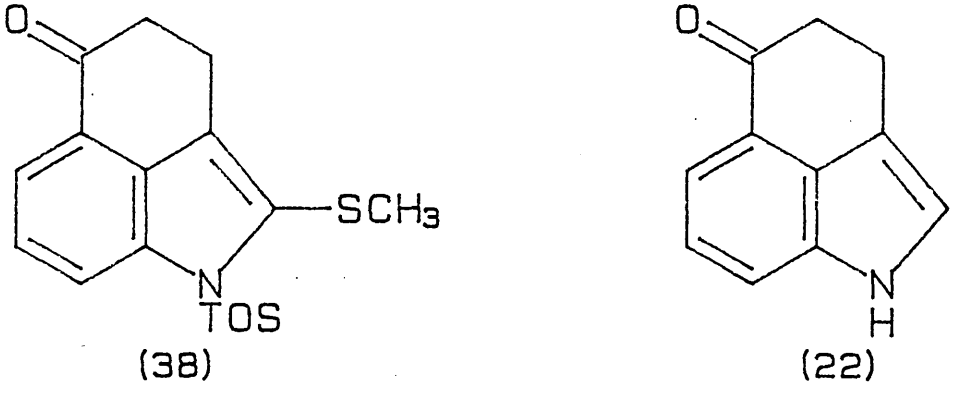
The second proposed route to lysergic acid was to start with an ortho aminobenzaldehyde (35), or equivalent compound, and form the indole skeleton by a novel route recently discovered in this department[22]. The method involves the formation of a ketenethioacetal monosulphoxide, from the aldehyde, by known methods[23]. Treatment of the ketenethioacetal monosulphoxide (36) with a strong acid, under certain conditions produces the indole (37), rather than the expected

ethyl arylacetate[23] (see later), (scheme 10).

Scheme 10.

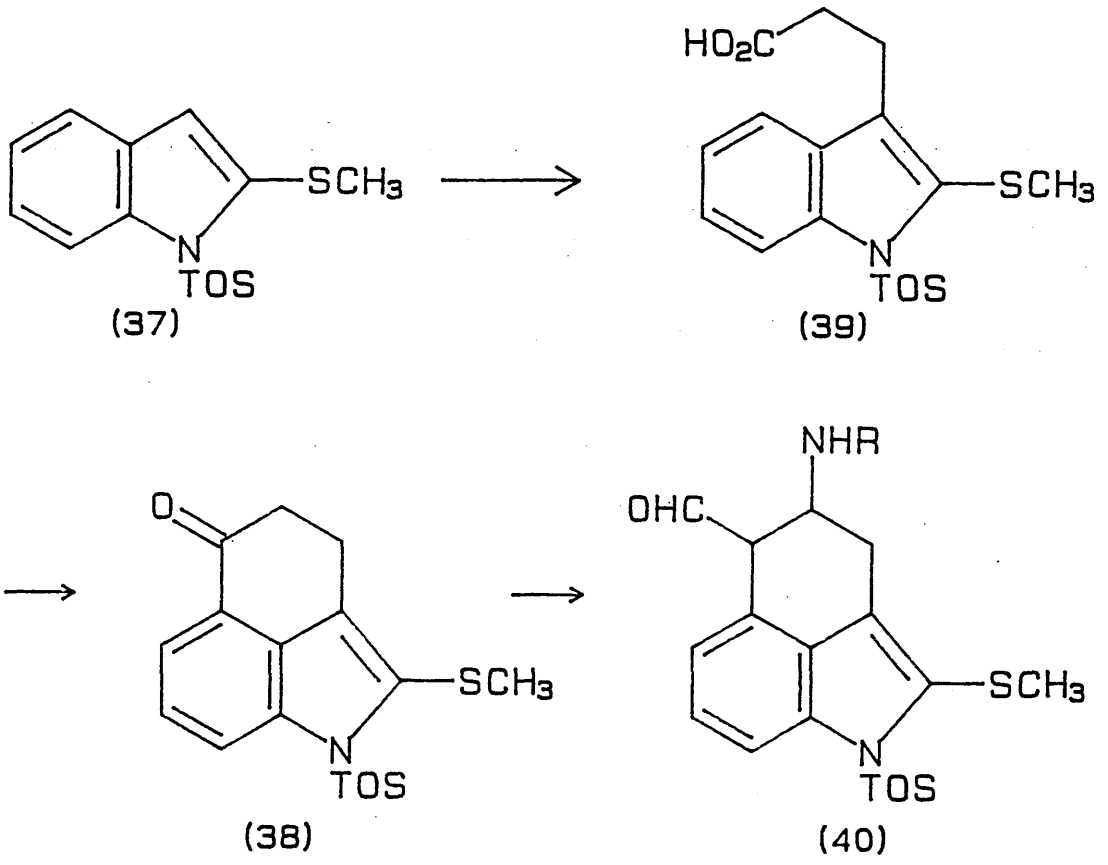


Electrophilic substitution at position 3 on compound (37), would give a useful intermediate to derivative (38) of Uhle's ketone (22).



Modification of (38) would then lead to product (40) related to (32), (scheme 11).

Scheme 11.



From scheme 11, a useful compound is a 3-substituted-2-methylthioindole (39). This was therefore a good target molecule to aim for. Three routes to this were proposed, and will be discussed in detail in chapter 2.

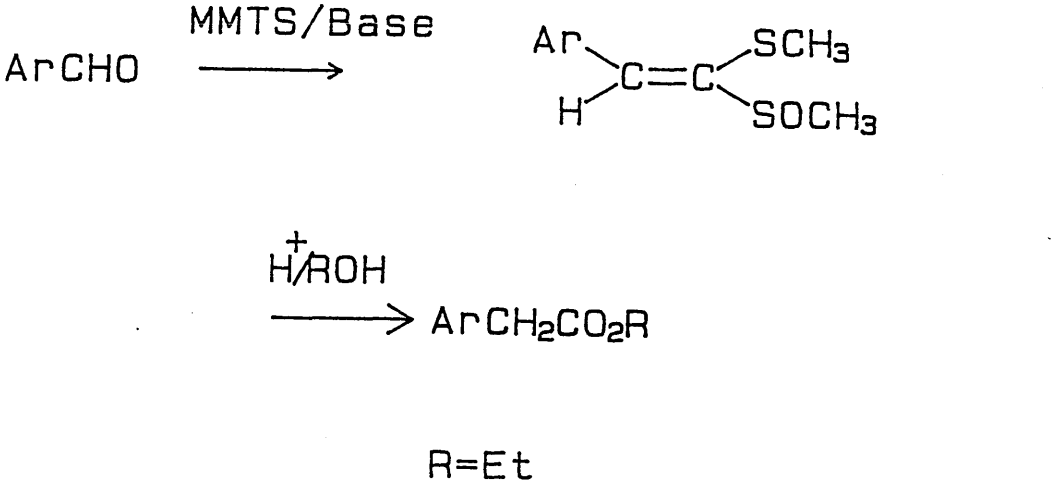
CHAPTER 2.

A NOVEL INDOLE SYNTHESIS AND ELABORATION TO "UHLE'S" KETONE.

2.1. BACKGROUND.

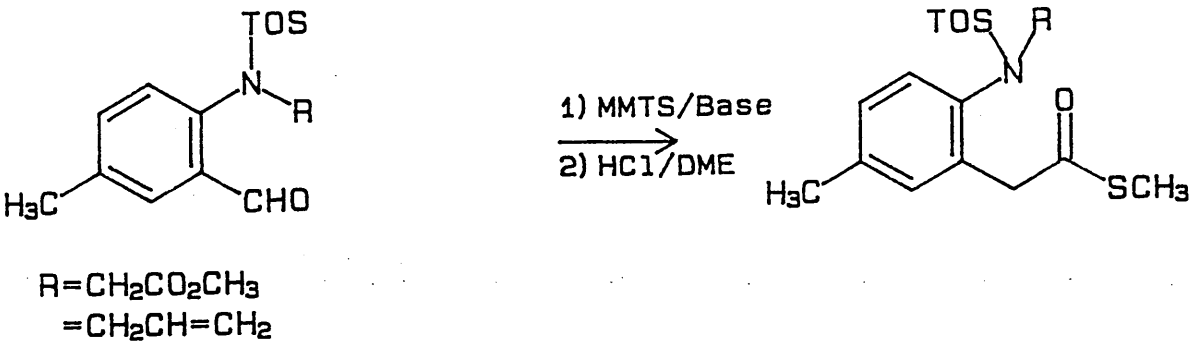
As outlined in chapter 1, a novel synthesis of the indole skeleton has recently been discovered in this department. Formation of the ketenethioacetal monosulphoxide (36) was achieved by following the method of Ogura[23]. Condensation of a benzaldehyde with methyl methylthiomethylsulphoxide (MMTS) under basic conditions, results in the ketenethioacetal monosulphoxide. When Ogura treated this with acid in ethanol, the product obtained was an ethyl arylacetate, (scheme 12).

Scheme 12.



However when a previous research student in this department treated the ketenethioacetal monosulphoxide with acid in dimethoxyethane, low yields of thiol esters were isolated, (see chapter 4), (scheme 13).

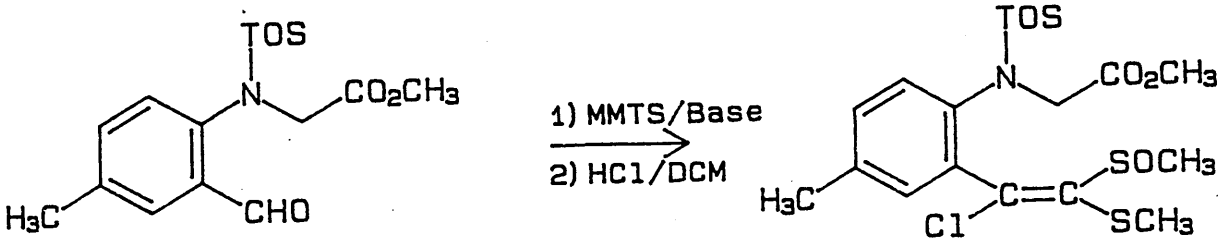
Scheme 13.



R=$CH_2CO_2CH_3$
=$CH_2CH=CH_2$

It was hoped that by altering the solvent, the yields of the thiol esters could be improved. However it was found when dichloromethane was used an improvement of the yields of the thiol esters did not result. A different compound was isolated, and was shown to be the chloroketenedithioacetal shown in (scheme 14).

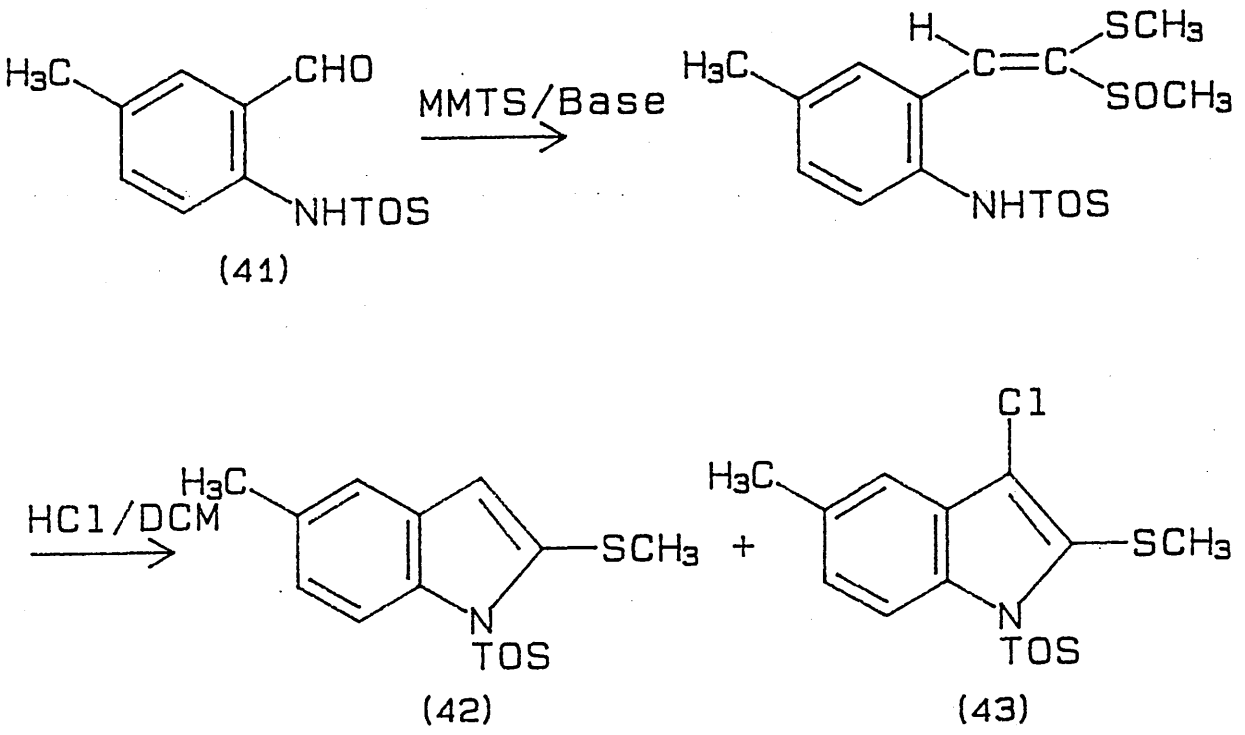
Scheme 14.



When the above reactions were repeated on the secondary sulphonamide (41), it was found that a mixture of two products (42)

and (43) were isolated, (scheme 15)

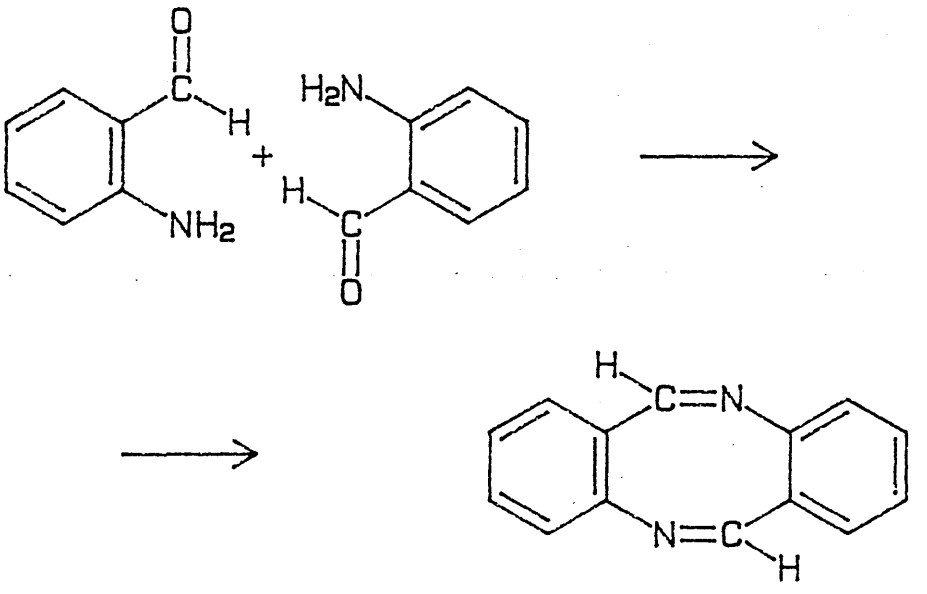
Scheme 15.



This method has now been developed into a high yielding general synthesis of the indole skeleton, although 4-substituted indoles are quite difficult to achieve simply (see later).

2.2. SYNTHESIS OF N-TOSYL-2-METHYLTHIOINDOLE.

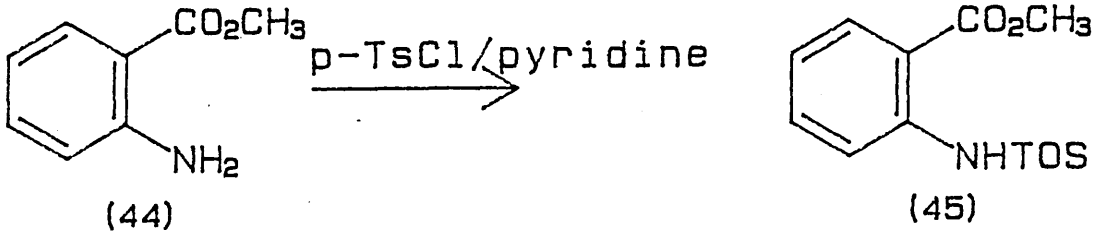
The title compound was synthesised from the cheap starting material, methyl anthranilate (44), in five steps. The ideal starting material would have been 2-aminobenzaldehyde, but it was unsuitable due to its ability to condense with itself.



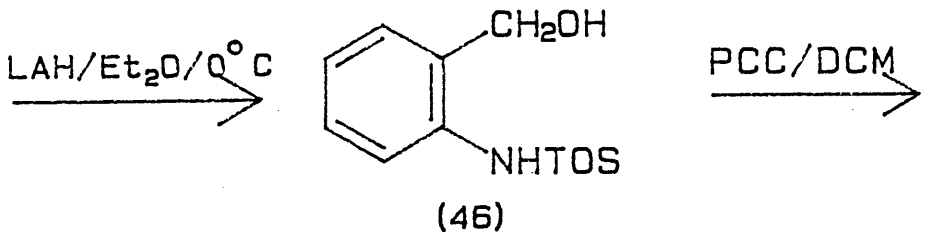
A DIIMINE

Methyl anthranilate was treated with p-toluenesulphonyl chloride in pyridine to form the protected amine (45). Manipulation of the carbonyl group by reduction with lithium aluminium hydride (LAH), followed by oxidation with pyridinium chlorochromate (PCC), gave the require benzaldehyde (35), (scheme 16).

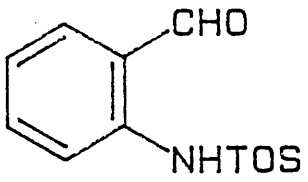
Scheme 16.



(44) (45)



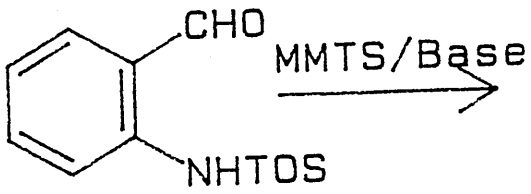
(46)



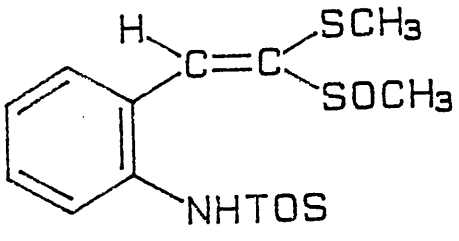
(35)

Condensation of the aldehyde (35) with the anion of methyl methylthiomethylsulphoxide (MMTS)[23] gave the ketenethioacetal monosulphoxide (36) in 60% yield. Treatment of this with concentrated hydrochloric acid in dichloromethane gave a mixture of indoles (37) 37.5% and (47) 36.6%, (scheme 17).

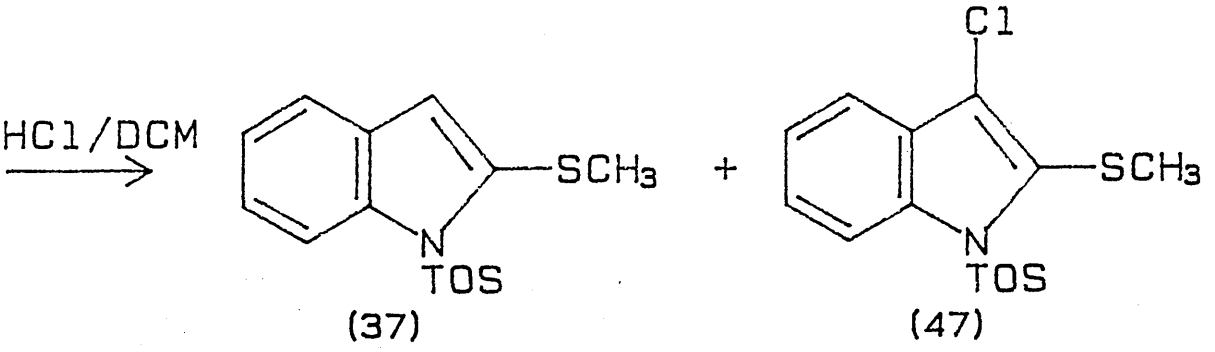
Scheme 17.



(35)



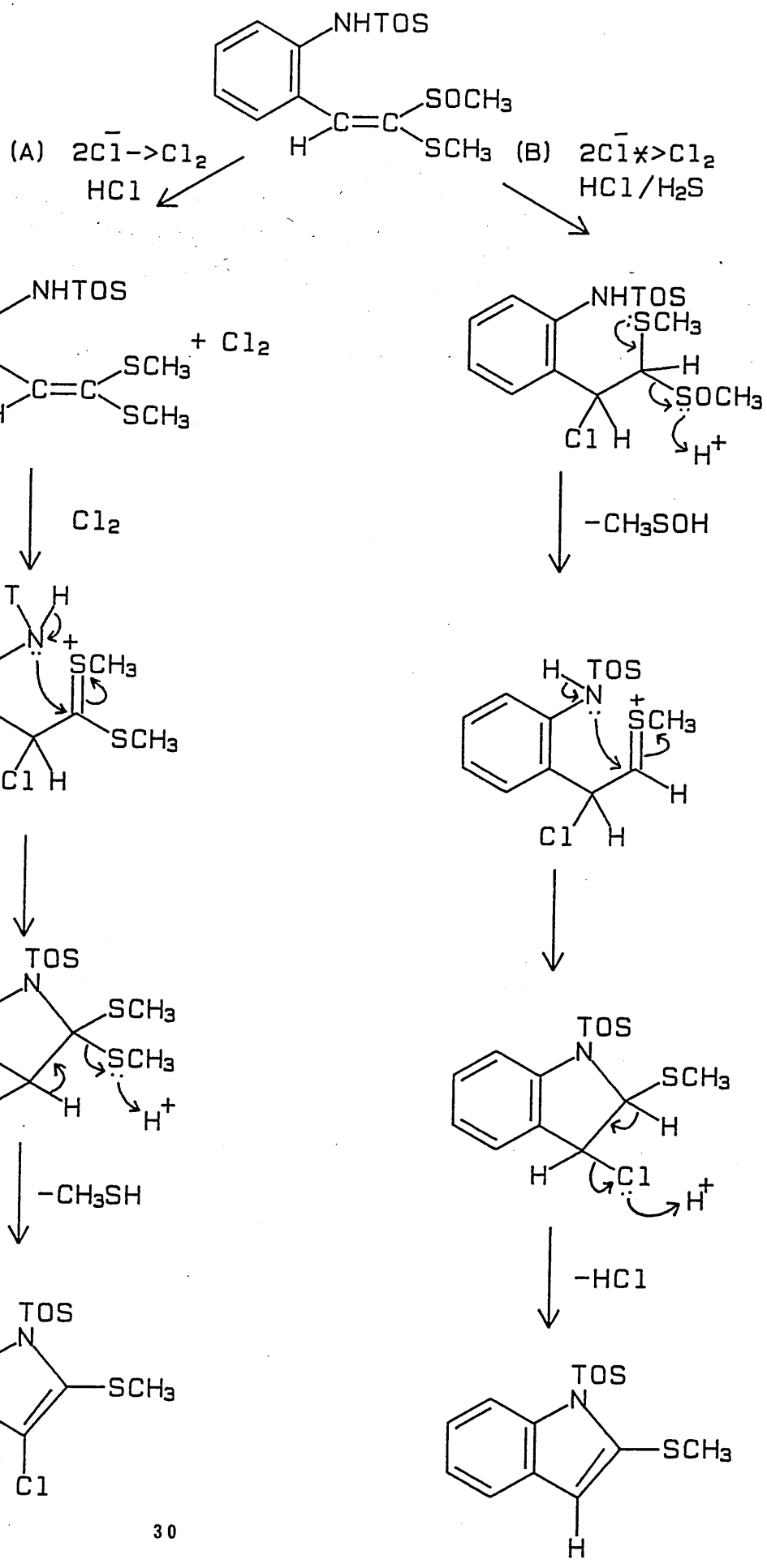
(36)



The identity of (47) was confirmed by treatment of the mixture of indoles with sulphuryl chloride. The product obtained had identical TLC properties to the product obtained when pure (37) was treated with sulphuryl chloride. It is known that indoles are halogenated in the 3-position by electrophilic substitution[24] i.e. "Cl^+" is needed to do this. This was readily available in the form of sulphuryl chloride.

The structure of (47) was confirmed by NMR and Mass Spectral data. It was later found that during the cyclisation step, if dichloromethane was presaturated with hydrogen sulphide gas, only a single product (37) was formed in over 70% yield.

It has been proposed that in the absence of hydrogen sulphide, two competing routes are possible, which results in a mixture of products. However, when hydrogen sulphide was present, the oxidation of chloride ion to molecular chlorine in route A (below) was blocked, and as a result only route B was available. The proposed mechanism is outlined below:-


NHTOS
SOCH3
C=C
H
SCH3
(A) 2Cl⁻->Cl2
HCl
(B) 2Cl⁻*>Cl2
HCl/H2S
+ Cl2
Cl2
SOT
H
SCH3
Cl
H
TOS
-CH3SH
-CH3SOH
-HCl
H+

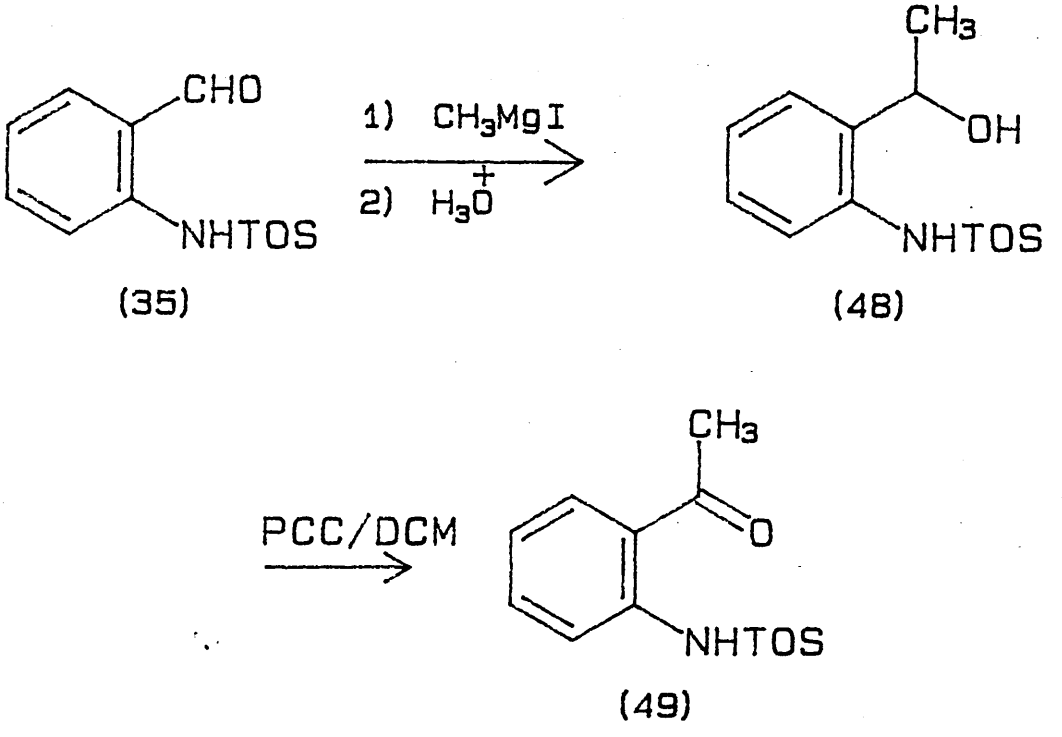
2.3. ATTEMPTED SYNTHESIS OF 3-SUBSTITUTED-2-METHYL-THIOINDOLES.

From chapter 1 it was seen that the target molecule (38), a derivative of Uhle's ketone, should be available via the acid (39). We considered three possible routes to this compound:- (i) modification of the chemistry in 2.2., to give a 3-substituted-2-methylthioindole, (ii) 3-substitution of 2-methyl-thioindoles and (iii) 2-sulphenylation of indole-3-propionic acid derivatives. Attempted development of these three routes are discussed below.

2.3.1. MODIFICATION OF THE CHEMISTRY IN 2.2.

The required starting material for the sequence was the ketone (49), which was prepared from the aldehyde (35), by use of a Grignard reagent. This gave the secondary alcohol (48), which was then oxidized to the ketone with pyridinium chlorochromate, in high yield, (scheme 18).

Scheme 18.



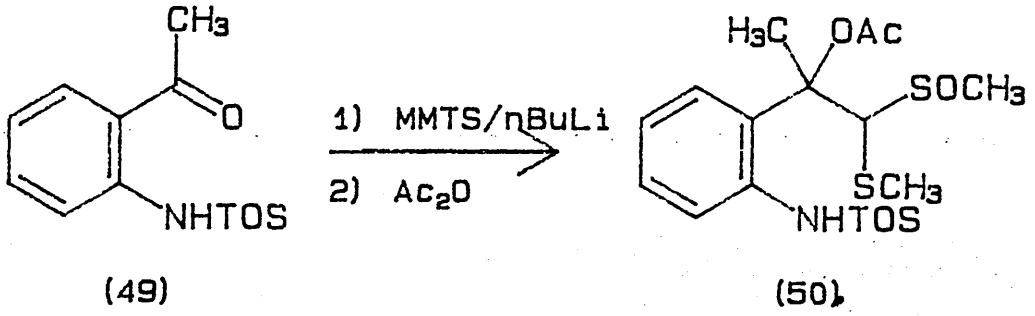
(35) (48) (49)

The proposed reaction of the ketone with MMTS, and triton B resulted in no reaction, and starting material was isolated, in high yield.

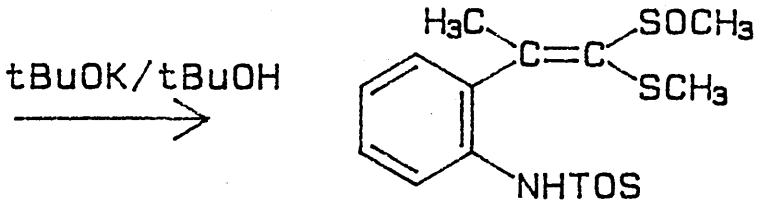
An alternative to this direct method of synthesising the ketenethioacetal monosulphoxide, was to synthesise the β-acetoxyaldehyde dimethyldithioacetal monosulphoxide (50)[25]. Reaction

of (50) with potassium t-butoxide in t-butanol, would give the ketenethioacetal monosulphoxide (51), (scheme 19).

Scheme 19.



(49) (50)

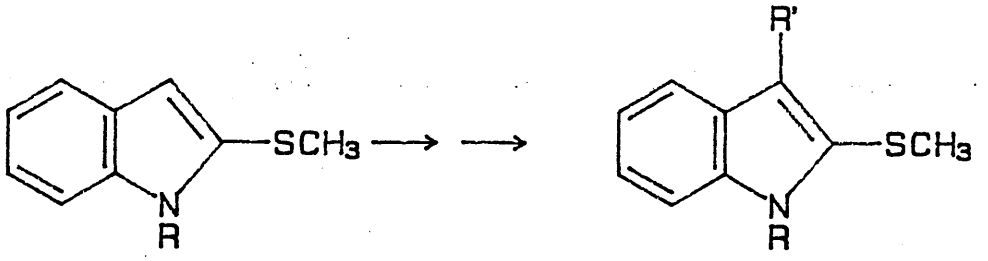


(51)

This route was abandoned after the first step, since a large number of inseparable products were apparent on a TLC plate, and the intermediate (50) could not be isolated. The NMR of the crude product was extremely complex. It is a well known fact that acetophenones are very resistant towards nucleophilic attack; this is due to the aromatic nucleus reducing the electron deficiency at the carbonyl carbon. The presence of the aromatic ring also increases steric hinderance, and thus also reduces its reactivity, and all this leads to the ketone being readily enolised[26].

2.3.2. 3-SUBSTITUTION OF 2-METHYLTHIOINDOLES.

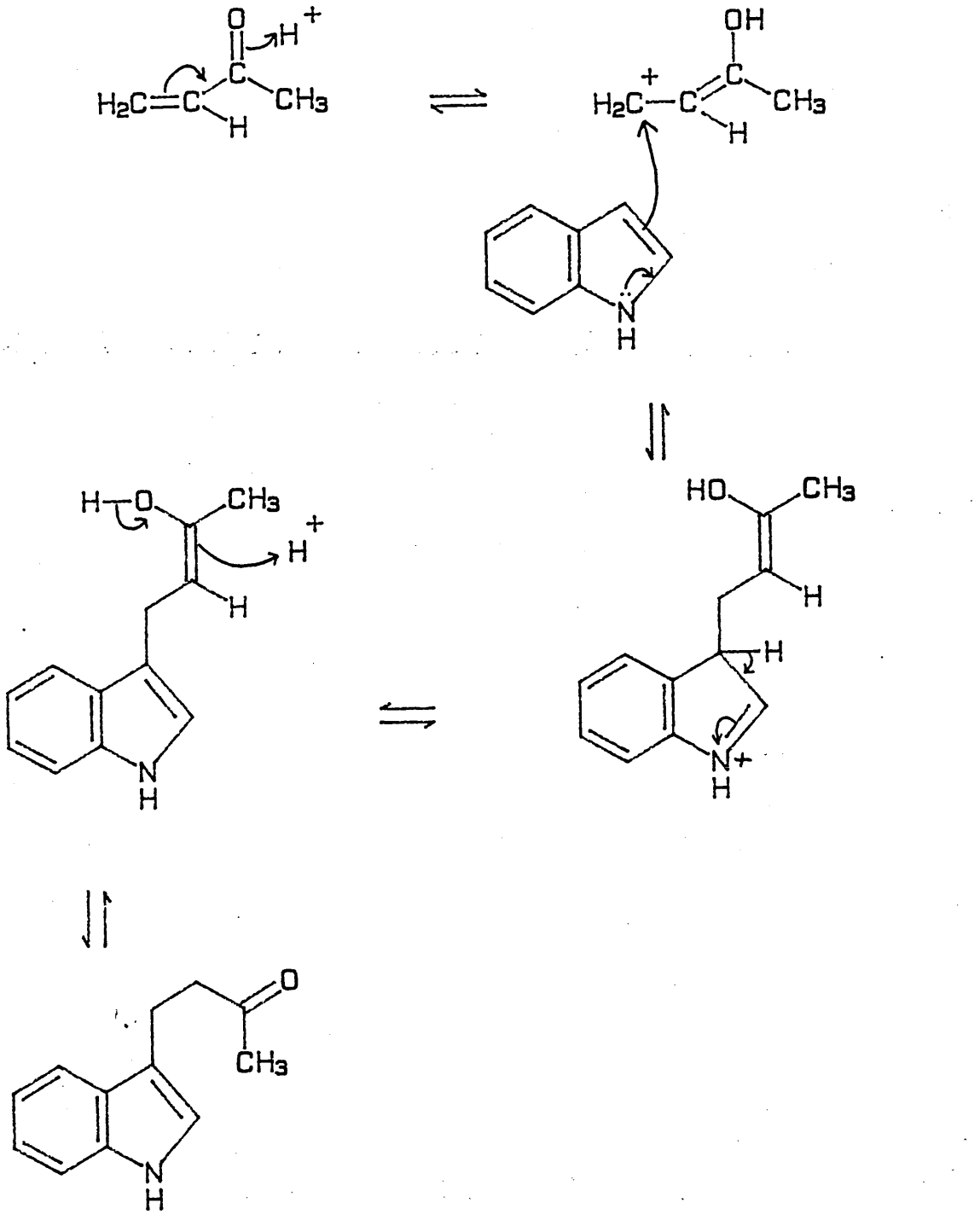
An alternative route towards 3-substituted-2-methylthioindoles would be:-



Since the required starting material was available from our indole synthesis we thought it worthwhile investigating this process.

3-functionalisation of indoles has been carried out by alkylation reactions, in particular "Michael" (conjugate) addition to unsaturated carbonyl compounds or similar.

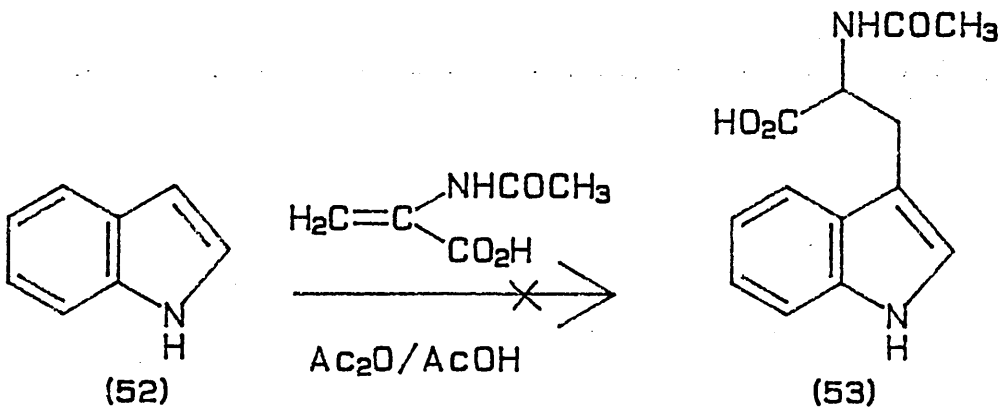
Before attempting to elaborate the 3-position of the indole (37), a number of model reactions were tried on the more readily available indole (52) itself. This was to establish the best route to an indole with the appropriate three carbon side chain. A number of methods were found in the literature, which involved the addition to the indole-3-position of an electron deficient olefin (or equivalent), such as acrylic acid[27], dl-serine[27], α-acetamidoacrylic acid[28], acrylonitrile[29,30] and nitroethylene[31]. These reactions proceed by acid catalysed electrophilic attack of the carbonyl compound at the 3-position of the indole[32]. Thus for methyl vinyl ketone.



The synthesis of N-acetyl tryptophan (53) from indole and α-acetamidoacrylic acid in acetic anhydride/acetic acid[28] was first tried. After working up the reaction, a brown solid was obtained,

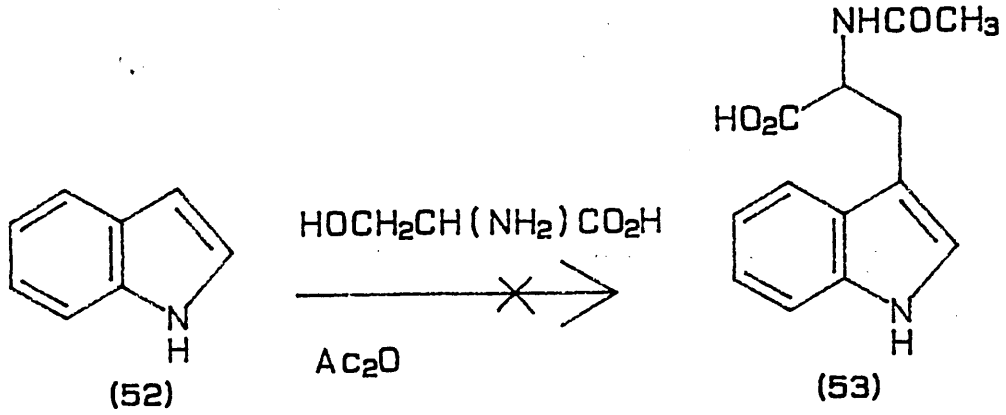
which was quite insoluble in most solvents used for NMR analysis. An infra red spectrum was obtained of the brown solid, but this did not agree with a published spectrum of N-acetyl tryptophan. The paper suggested a 57% yield for this reaction, (scheme 20).

Scheme 20.



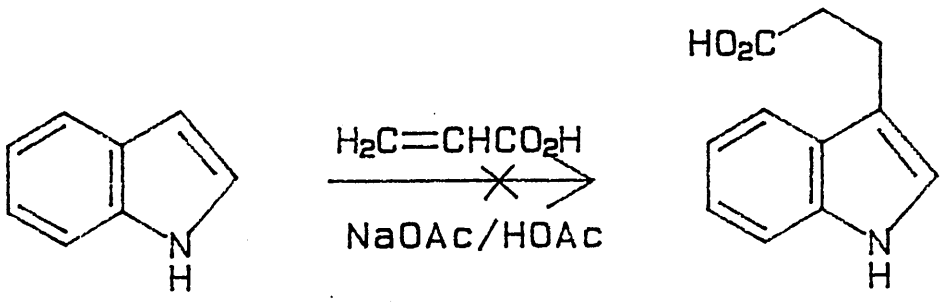
The synthesis was repeated, but dl-serine[27] was used instead of α-acetamidoacrylic acid, (scheme 21).

Scheme 21.



This reaction again resulted in a brown solid, whose infra red spectrum did not agree with that published. A similar reaction was carried out using acrylic acid and sodium acetate in acetic acid, hoping to obtain indole-3-propionic acid (23)[27], (scheme 22).

Scheme 22.

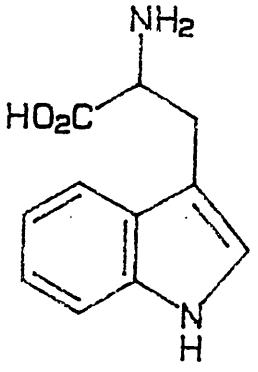


(52) (23)

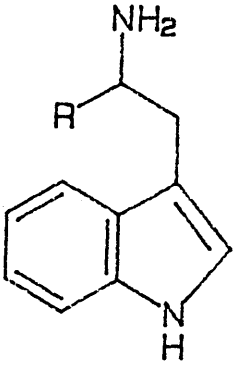
This reaction also gave a brown solid, which would not recrystallise from ethanol. Infra red and NMR spectra did not agree with those obtained from an authentic sample (purchased from ALDRICH). From these failed reactions, the published methods for adding an electron deficient olefin to an indole under acidic conditions seem to be unsuitable in practice, at least in our hands.

We then decided to look at the method of H.R Snyder et al[33], and use a gramine intermediate, to produce indole-3-propionic acid (23). This method of using a gramine intermediate has been used by a number of workers with successful results (Heinzelmann et al[34], Snyder and Smith[35], and Albertson[36]), to synthesise trytophan (13). Also α-alkyltryptamines (54), have been synthesised by direct combination of

gramine with aliphatic nitro compounds[37,38], followed by reduction of the nitro group to the amine.



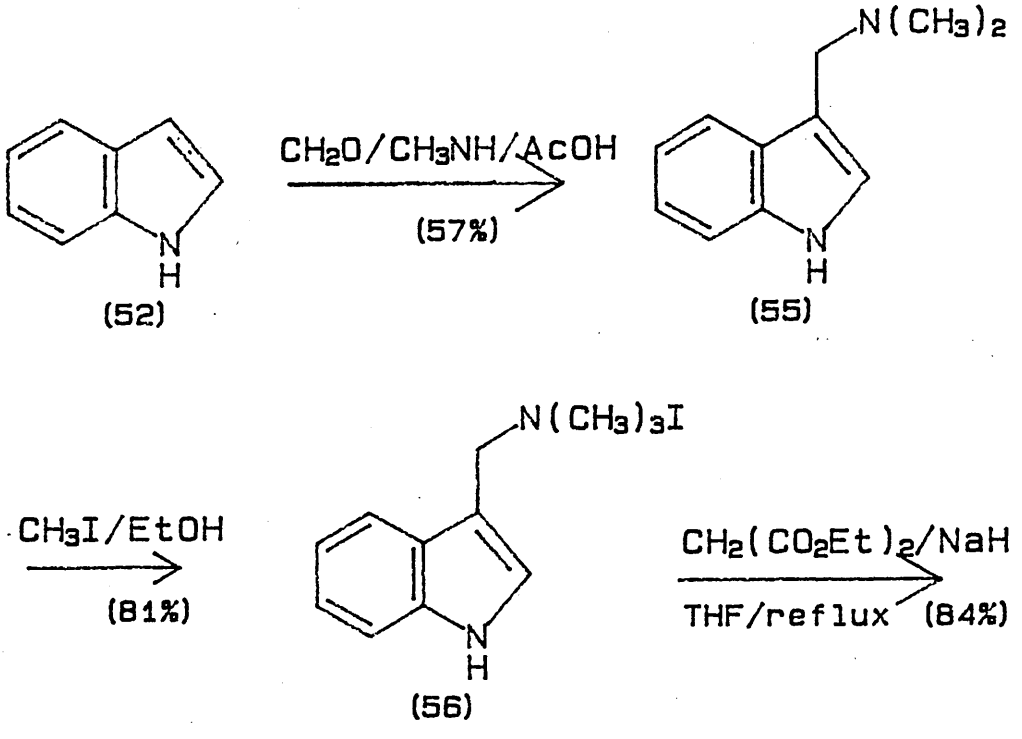
(13)

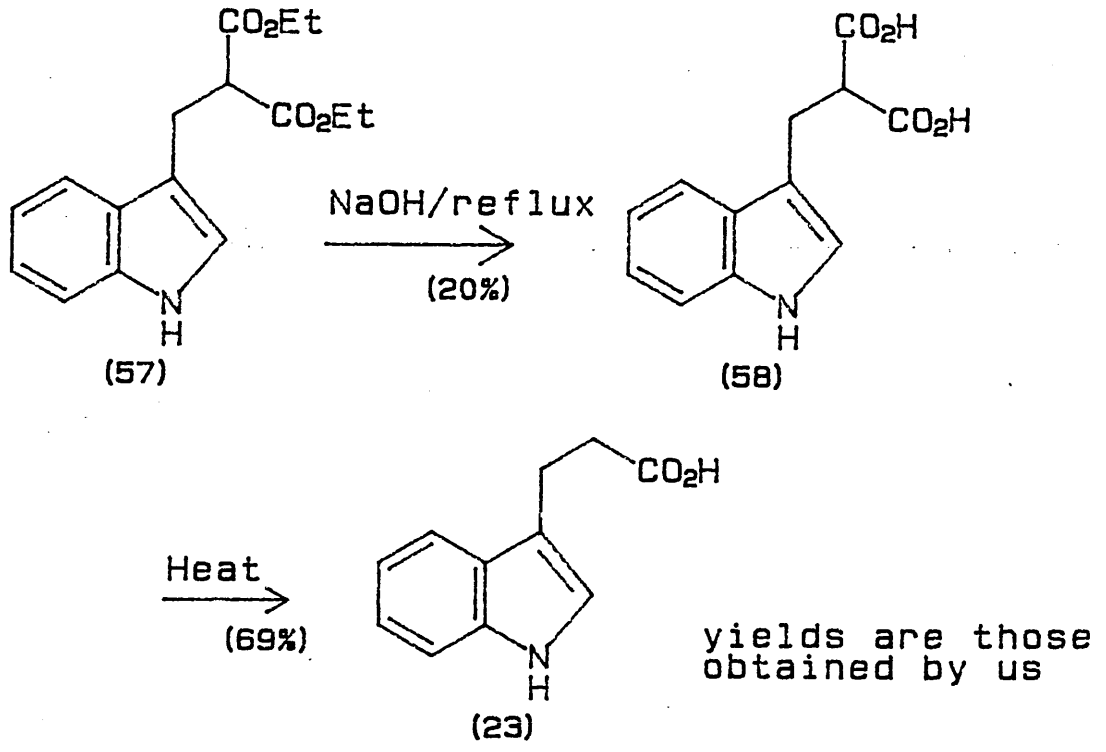


(54)

The method involved quaternisation of gramine (55) to its quaternary ammonium salt (56), which was then used as an alkylating agent, (scheme 23).

Scheme 23.





The alkylation step of this reaction was modified, in that sodium hydride was used as the base, to make the sodium salt of diethylmalonate, rather than the recommended method of using powdered sodium, which was considered more dangerous; also the solvent was change from butylether to tetrahydrofuran. This method appears to be the most useful of those tried for the synthesis of an indole-3-propionic acid derivative. This should therefore be a method which we can use to convert our indole (37) or its detosylated derivative to the corresponding indole propionic acid derivative (59), and then cyclise to the Uhles ketone derivative (38). However in the event the method was not applied to (37), because we had developed the method

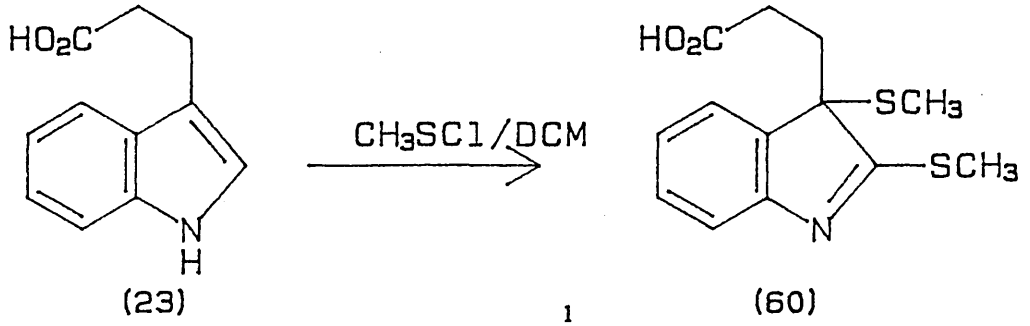
discussed below in section 2.3.3.

2.3.3. SULPHENYLATION OF INDOLE-3-PROPIONIC ACID.

A third approach, which actually appears very direct, was to sulphenylate indole-3-propionic acid derivatives. This method was eventually chosen in preference to the one described in 2.3.2.

A methylthio group may be added to the indole-2-position, by the method of Fontana et al[39], which adds a sulphenyl side chain into the 2-position of tryptophan residues, in peptides. The method, which uses sulphenyl halides, has been shown to be a general procedure for the sulphenylation of indole derivatives.

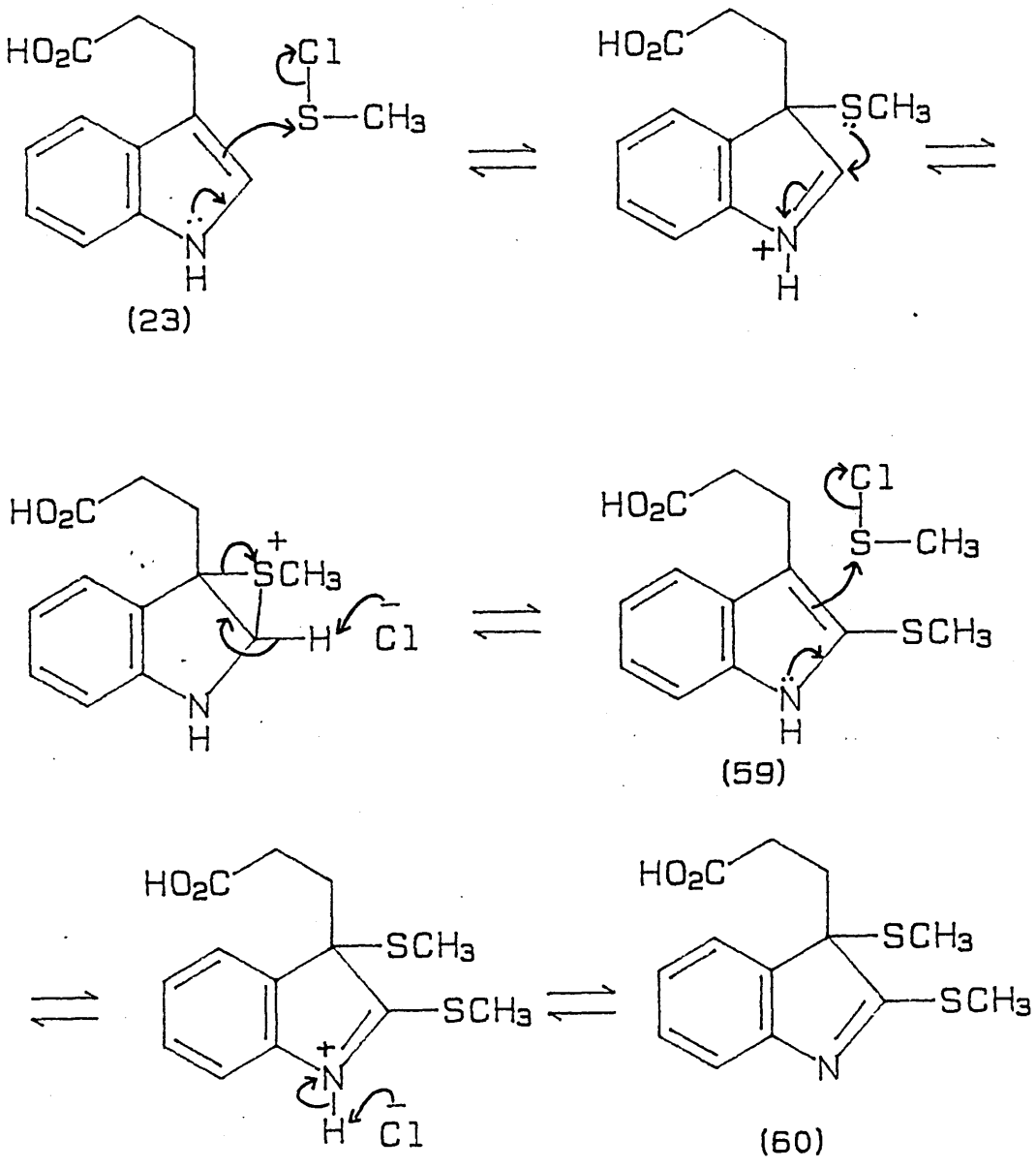
Methanesulphenyl chloride was prepared by modification of the method of Brintzinger[40], by dropwise addition of sulphuryl chloride to dimethyl disulphide in dichloromethane at 0°C. This solution was then added dropwise to a **suspension** of indole-3-propionic acid in dichloromethane. The suspension dissolved during the reaction, and after working up a white crystalline product was obtained. However when the product was analysed by NMR, an extra singlet peak was observed at around 1.5ppm, and integration suggested that this was a methyl peak. This was later confirmed by mass spectrometry and microanalysis.



(23) (60)

What appears to have happened is that one equivalent of methanesulphenyl chloride has reacted with indole-3-propionic acid, giving an initial product (59), which was more soluble in dichloromethane than indole-3-propionic acid. This then reacted faster with the remaining methanesulphenyl chloride, than the initial indole-3-propionic acid, still in suspension. The mechanism for this is outlined below, in (scheme 24).

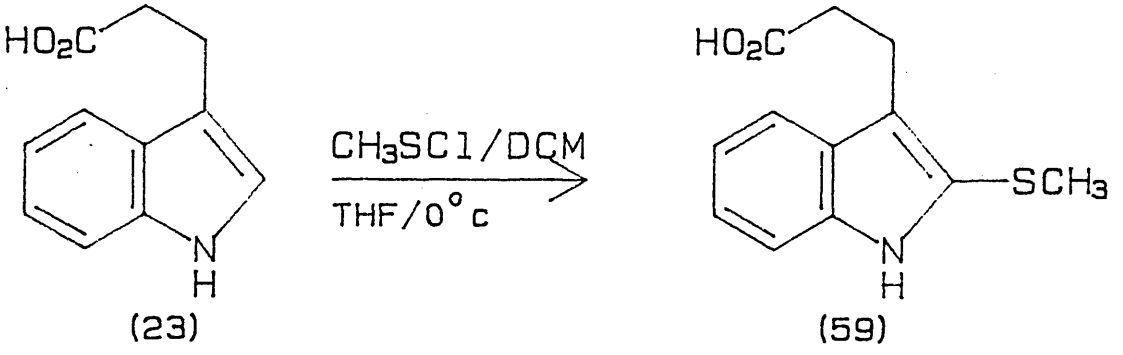
Scheme 24.



A double electrophilic attack at position 3 has occurred, however the second methylthio group is unable to migrate to position 2, thus the resulting compound was an indolenine, 2,3-dimethyldithioindoleline-3-propionic acid (60), isolated in 64% yield.

The desired 2-methylthio derivative (59) was obtained when one molar equivalent of methanesulphenyl chloride in dichloromethane, was added dropwise, to a **solution** of indole-3-propionic acid in tetrahydrofuran, (scheme 25).

Scheme 25.



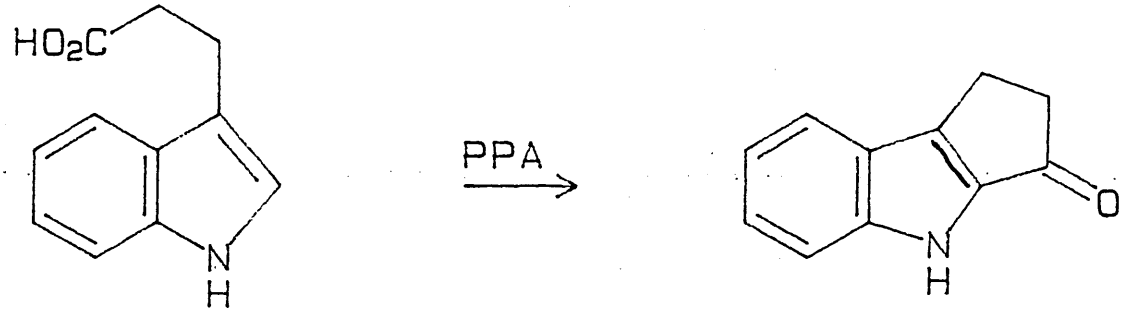
(23) (59)

This product was obtained in 70% yield. Having developed a method for the preparation of (59), we turned to an investigation of the cyclisation to form the ergot C ring.

The precedent for our synthesis of the indole propionic acid derivative (59) was that of Uhles ketone derivative (62) with a carboethoxy group in the 2-position, synthesised by Meyer and Kruse[41], from the corresponding indole propionic acid derivative (61), by a Friedel-Crafts cyclisation in polyphosphoric acid, (equation 4). Attempts at the Friedel-Crafts cyclisation without a blocking group in the 2-position, have resulted in the cyclisation taking place at

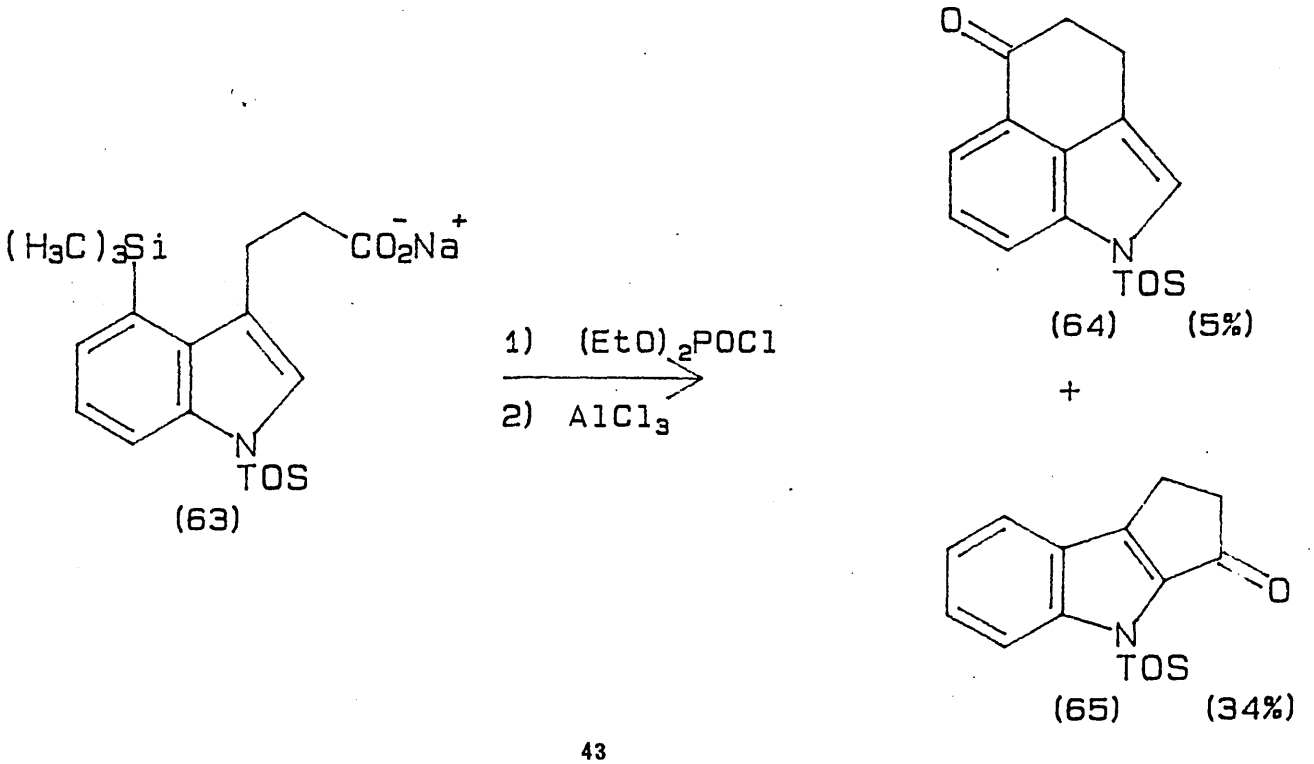
the 2-position[42], (equation5).

equation 5

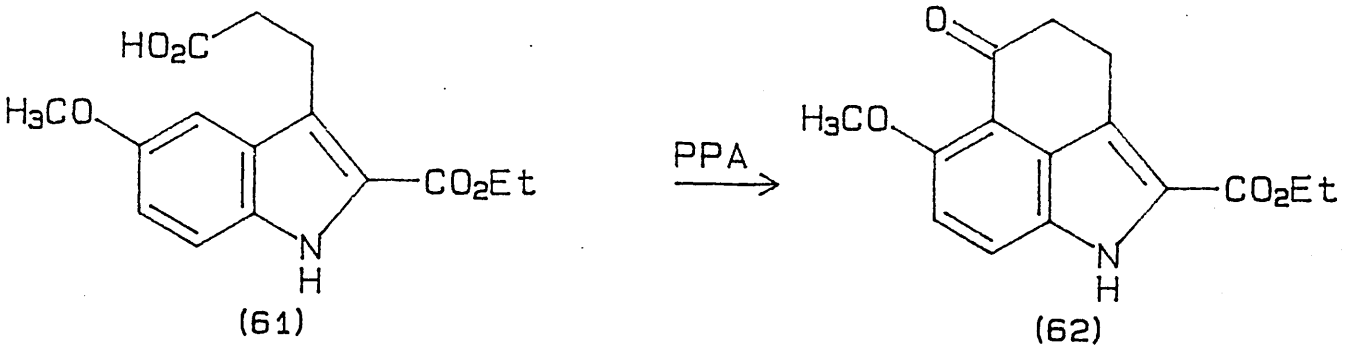


Barrett et al[43] attempted the Friedel-Crafts cyclisation on the N-protected-4-substituted indole propionic acid derivative (63), using diethylchlorophosphate and aluminium chloride to give the Uhles ketone (64). However they isolated a higher yield of the 2-cyclisation product (65), (scheme 26).

Scheme 26.



equation 4



(61) (62)

Although Barrett's compound (63) had an easily displaced silyl group, the preferred cyclisation was to the 2-position. The angle strain required for the cyclisation to the 4-position was obviously great enough to overcome the influence of the trimethylsilyl group.

From the above two examples it would seem that there is a good precedent for our synthesis of Uhle's ketone with a methylthio group blocking the 2-position. When the cyclisation was tried on compound (59), with polyphosphoric acid, no cyclisation product was observed on TLC plate (no reaction with DNP spray), and a black tar resulted, which remained on the base line of the TLC plate. We thought that because of this a milder method might be required for the cyclisation. The acid (59) was reacted with oxalyl chloride followed by anhydrous aluminium chloride. No reaction was observed, and a high yield of starting material was recovered.

We then decided to protect the nitrogen of the indole as the tosyl derivative, hoping that cyclisation might occur without degradation of the indole system by PPA. An attempt was made to tosylate the free acid by using the method of Bowman et al[44], which uses anhydrous potassium carbonate in refluxing methyl ethyl ketone, as the base. Only starting material was recovered under these conditions. Thus before the tosylation was carried out the acid was

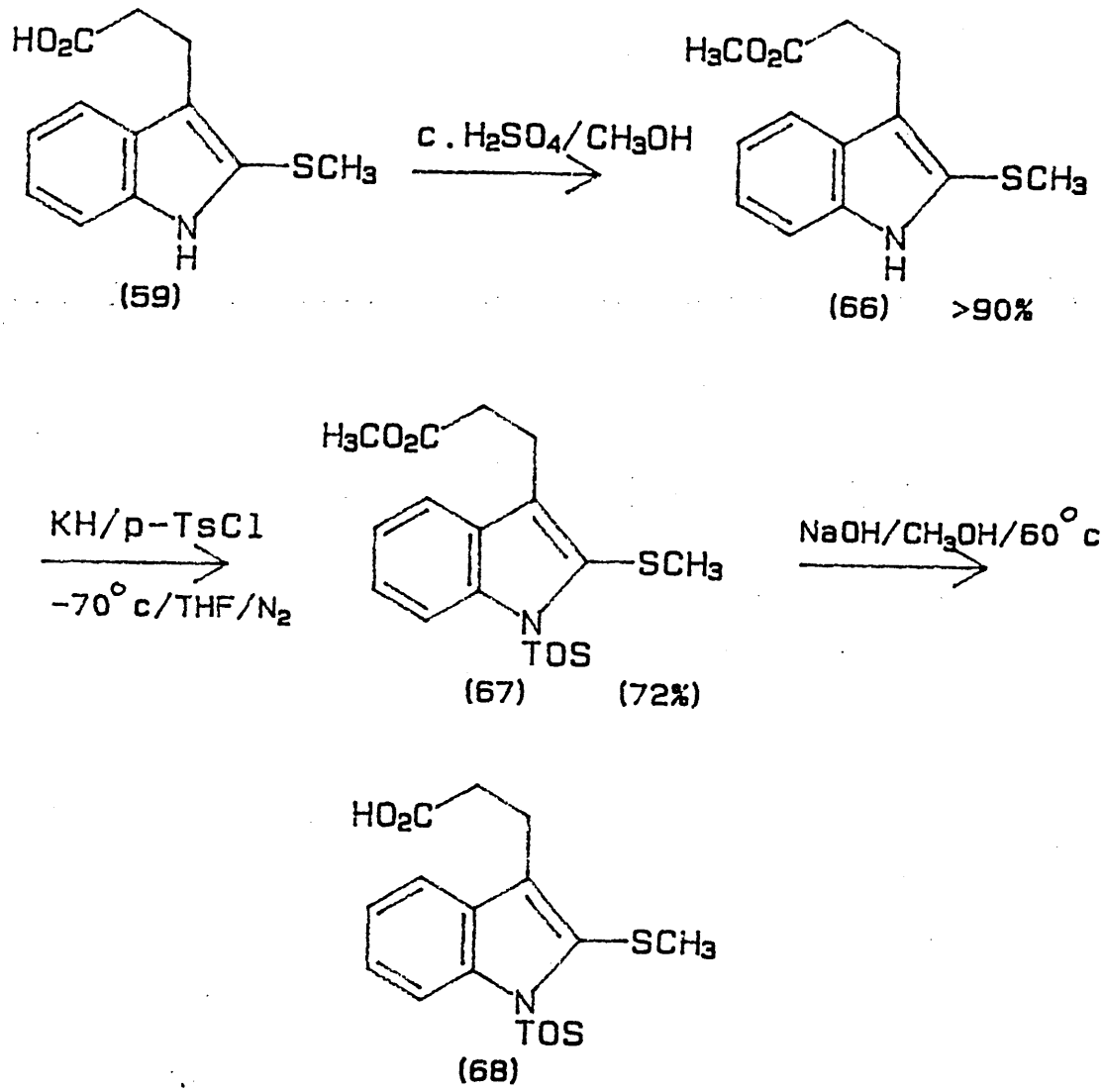
esterified. This was achieved by stirring the acid at room temperature, in methanol with conc. sulphuric acid.

The tosylation of the ester was attempted using a number of different methods, the first being a repeat of Bowmans work, using potassium carbonate in methyl ethyl ketone. The imino nitrogen is readily tosylated under these conditions when an electron withdrawing group is present in the 3, 4 or 5-position of the indole. The electron withdrawing group delocalises the electrons in the lone pair of the nitrogen, rendering the imino proton more acidic. However, this group of workers failed to tosylate the nitrogen in methyl indole-2-carboxylate. We also failed to tosylate the nitrogen with our 2-methylthio group present, and recovered only starting material.

The second method tried, was to use potassium hydroxide as the base, in dimethoxyethane. However, again only starting material was recovered.

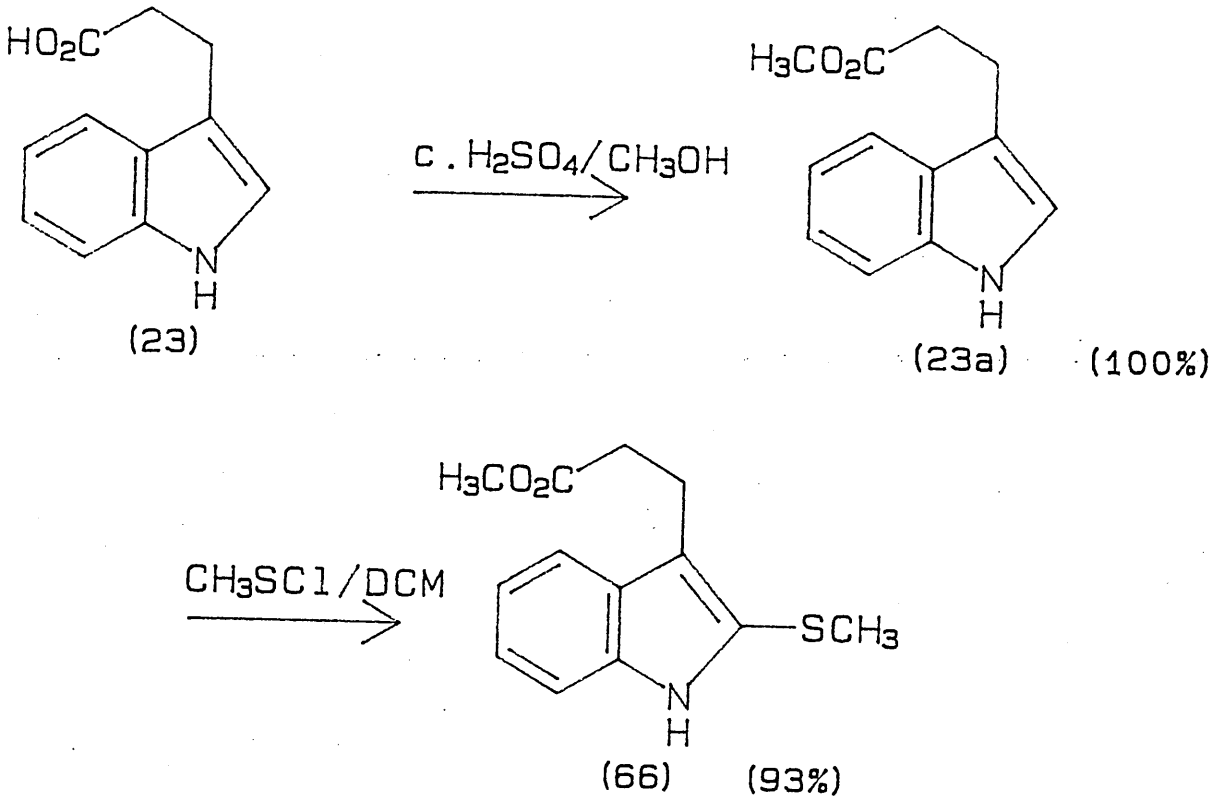
The method of tosylation which was eventually used was that of Barrett et al[43], which uses potassium hydride as the base, which is much more powerful in its ability to deprotonate the imino nitrogen than either potassium carbonate or potassium hydroxide. The tosylated indole was obtained in 70% yield by this method. The ester was hydrolysed back to the acid by warming to 60°C for three hours with excess 2N sodium hydroxide in methanol, (scheme27).

Scheme 27.



It was later found that a higher yield of compound (66) could be obtained if indole-3-propionic acid was esterified first and then sulphenylated, (scheme 28).

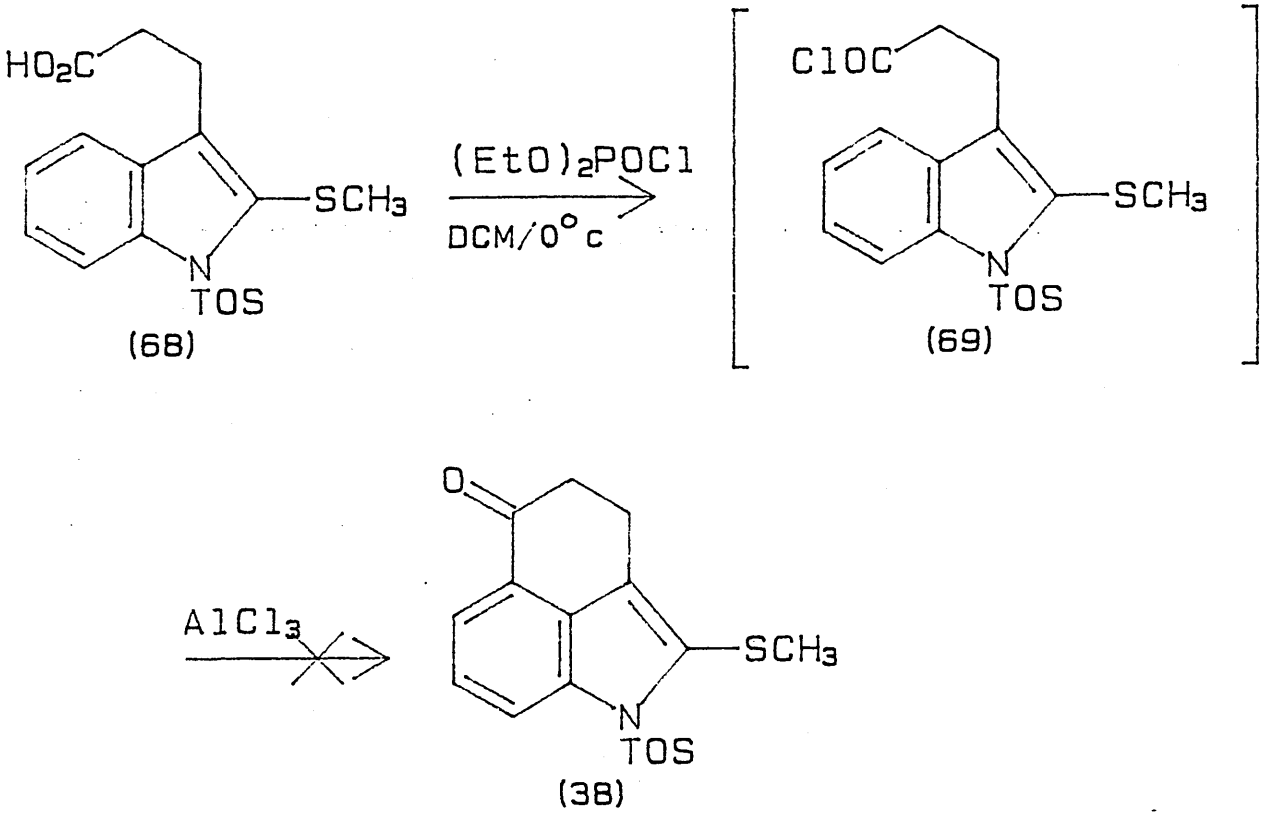
Scheme 28.



The next step was to attempt to cyclise to the Uhles ketone derivative (38), using polyphosphoric acid. This again resulted in a black tar which remained on the base line of the TLC plate. From this and previous attempts at the polyphosphoric acid cyclisation, it would seem that the sulphur has an adverse effect on the required cyclisation, and probably allows degradation of the indole system to occur.

Again we decided to try one of the milder, lower yielding methods, of using the acid chloride. The first procedure followed was that of Barrett et al[43], using diethylchlorophosphate, as the reagent for converting the acid chloride (69), and then cyclising with anhydrous aluminium chloride, (scheme 29).

Scheme 29.



From this reaction only the starting acid was recovered, which suggests that if the acid chloride (69) had been formed, then cyclisation did not occur, as on work up it would have hydrolysed back to the acid. From this we cannot say for certain that the acid chloride was not formed in the first step.

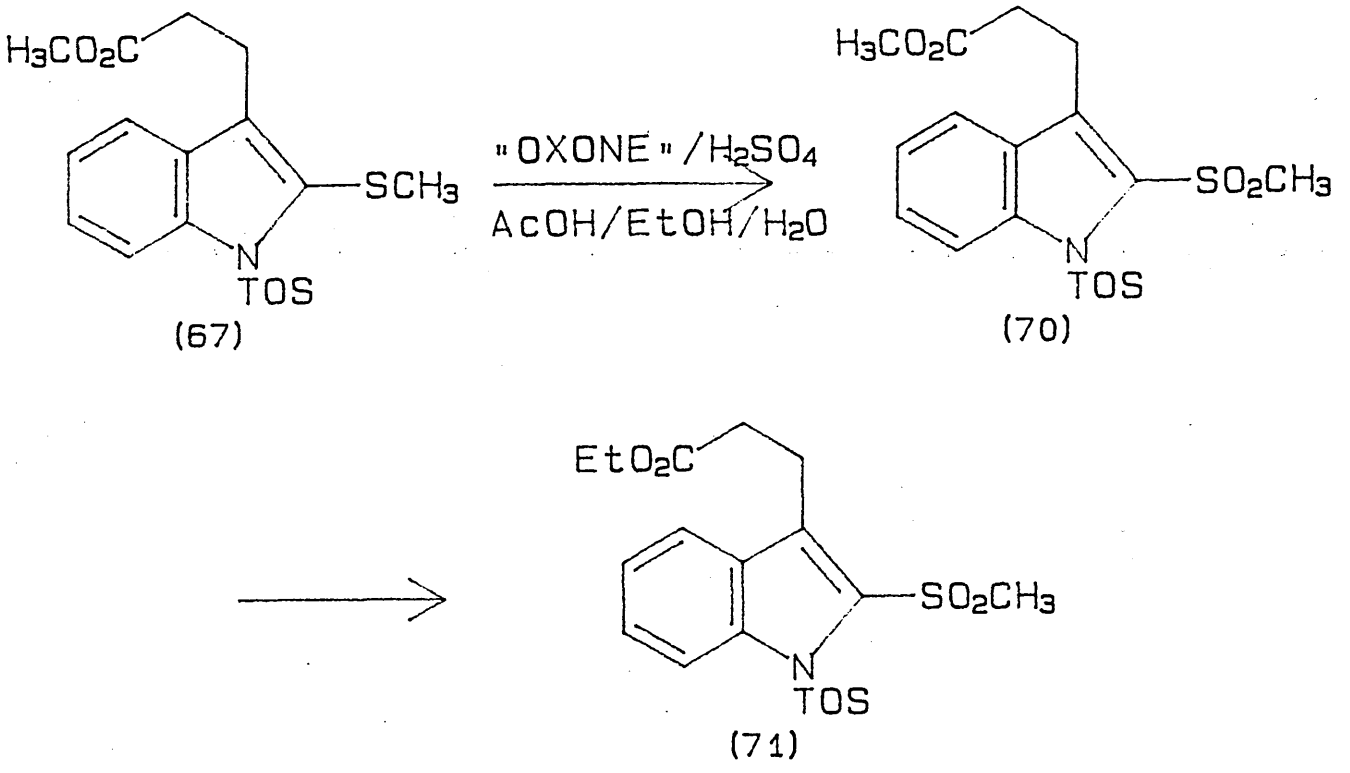
A second method of preparing the acid chloride was looked at, which uses oxalyl chloride and dimethyl formamide in dichloromethane to effect the conversion from the acid[45]. This mixture was then cooled

to 15°C and anhydrous aluminium chloride was added, which should then have resulted in a straightforward Friedel-Crafts acylation. However on work up, the NMR spectrum showed only starting material to be present. From this we concluded again that somehow the sulphur was interferring with the expected cyclisation reaction.

It was proposed that to make our compound more like that used by Meyer and Kruse[41], we should then oxidise the sulphide to the sulphone. The reagent we chose to do this was " OXONE " (potassium peroxymonosulphate), which is a good reagent for the above mentioned conversion. It was initially tried on 2-methylthioindole-3-propionic acid, but was found to be too strong an oxidising reagent. No product or starting material was isolated. A TLC plate showed a streak from the base line up the plate. It is known that unprotected indoles, are very susceptible to attack by oxidising agents, which break down the five membered ring. It was therefore thought a better idea to oxidise the tosylated ester (67).

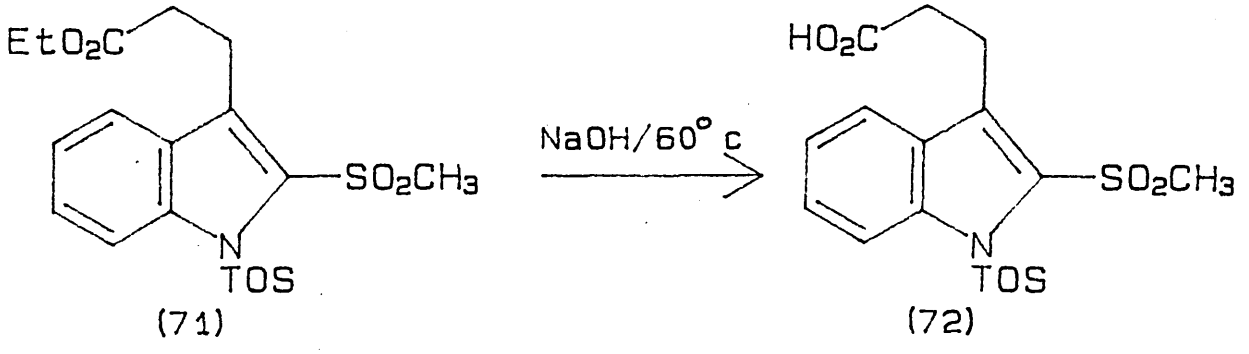
Compound (67) was added to a solution of "OXONE" in acetic acid: ethanol: water: conc. sulphuric acid (1:1:1:0.5), over 20 minutes, and left to stir at room temperature[46]. After three and a half hours, the reaction was worked up and the TLC showed a number of spots. The main spot was isolated by column chromatography and an NMR was obtained. The NMR however was not as expected; instead a quartet (3.9ppm) and triplet (1.1ppm) appeared, which suggested that the methyl ester (70) had undergone an ester exchange to produce the ethyl ester (71), (scheme 30).

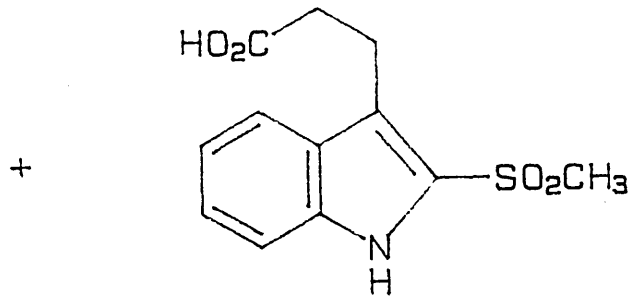
Scheme 30.



This was confirmed when the ester was hydrolysed to the acid (72), by sodium hydroxide, although the NMR of the product indicated that some detosylation had also occurred, (scheme 31).

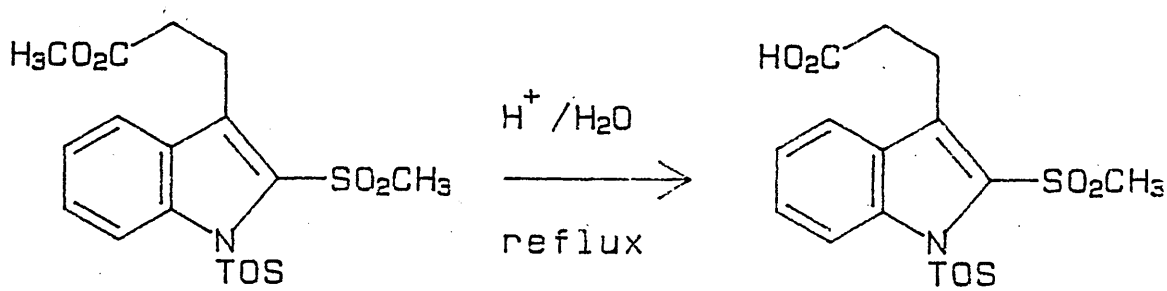
Scheme 31.





(73)

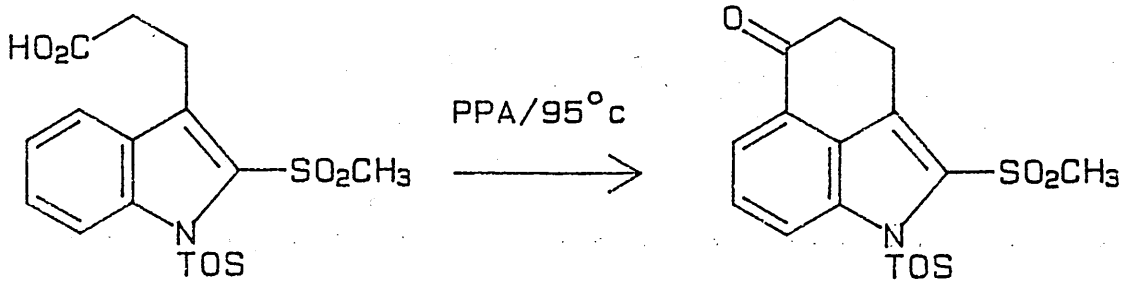
The required compound (70) was synthesised by carrying out the oxidation in acetic acid, methanol, water and sulphuric acid. This prevents the transesterification from occurring. Attempted hydrolysis of this ester with sodium hydroxide at 60°C again resulted in some detosylation of the product. The hydrolysis of the ester was achieved, without detosylation, by refluxing the ester in a mixture of water and concentrated hydrochloric acid.



(67) (72)

The acid (72) was treated with polyphosphoric acid at 95 °C, which

should have resulted in the cyclisation to the Uhles ketone derivative (74).



(72) (74)

When the reaction was worked up, a brown solid precipitated, which was filtered off, and washed with both water and ethyl acetate. The solid was insoluble in both of these solvents. A brown oil was extracted, in very low yield, however the NMR of this did not suggest that the product was compound (74). The methyl singlet at 3.5ppm was not present, also the aromatic peaks had almost disappeared. This would suggest that again the cyclisation had failed, but we were unable to proceed any further with this investigation due to lack of time. The cyclisation may have been achieved by one of the acid chloride/aluminium chloride methods.

CHAPTER 3.

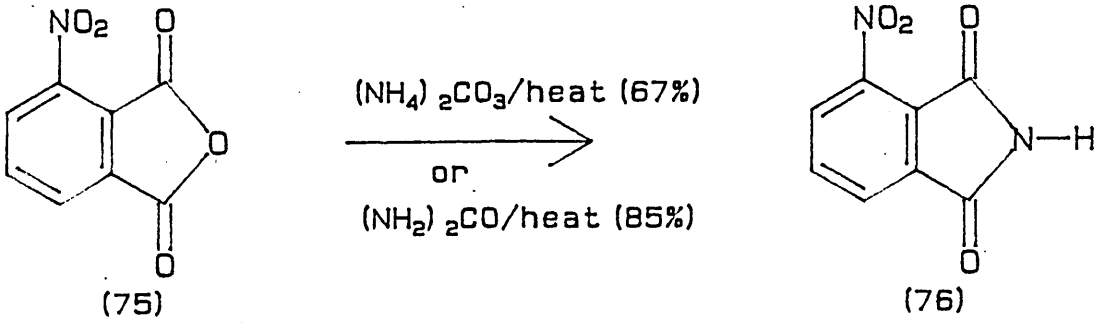
3 4-SUBSTITUTED INDOLES.

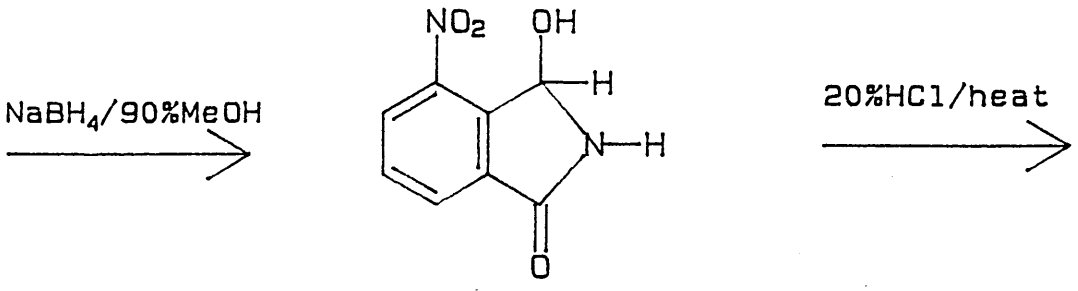
As was seen in Chapter 1, 4-substituted indoles are very useful compounds from which to begin a synthesis of the ergot alkaloids. As was also mentioned they are quite difficult to synthesise by traditional methods. We have evaluated a number of literature methods, to assess their practicality in terms of yield and ease of synthesis. Where appropriate, modifications have been attempted in order to make improvements on the published procedures. This work is described in the following sections.

3.1 SYNTHESIS OF METHYL INDOLE-4-CARBOXYLATE.

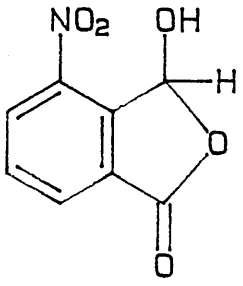
The procedure followed for this synthesis was that of Watanabe et al[16], which begins with 3-nitrophthalic anhydride (75). This was fused with ammonium carbonate, to give the product, 3-nitrophthalimide (76) in 67% yield. It was found that if the ammonium carbonate was replaced with urea, a higher yield (85%) of 3-nitrophthalimide was obtained. The 3-nitrophthalimide was then treated with sodium borohydride in 90% aqueous methanol, to give 3-hydroxy-4-nitrophthalimidine (77), which was subsequently hydrolysed with 20% hydrochloric acid at reflux, to give 3-hydroxy-4-nitrophthalide (78), (scheme 32).

Scheme 32.





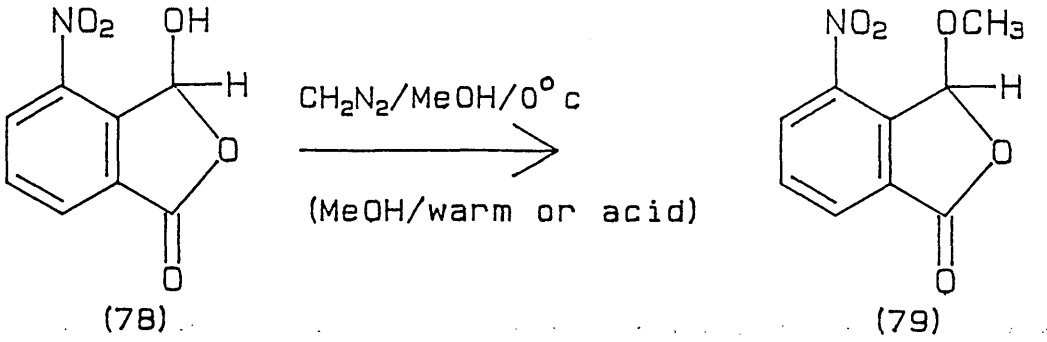
(77)



(78)

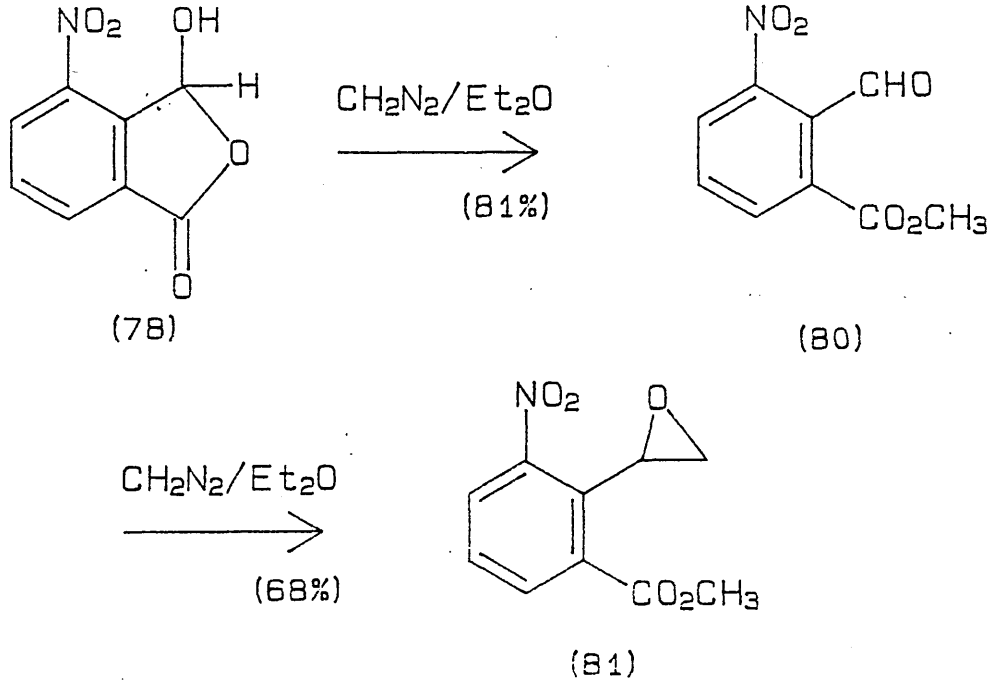
Treatment of (78) with excess diazomethane was reported to result in the formation of the nitrostyrene oxide (81). However, because (78) was insoluble in ether, it was dissolved in methanol, and cooled in ice, while diazomethane was bubbled through. On work up the product isolated was not the nitrostyrene oxide, but 3-methoxy-4-nitrophthalide (79) (confirmed by NMR spectroscopy). Watanabe claims that this product can be isolated when (78) is treated with warm methanol, or dilute acid in methanol, (scheme 33).

Scheme 33.



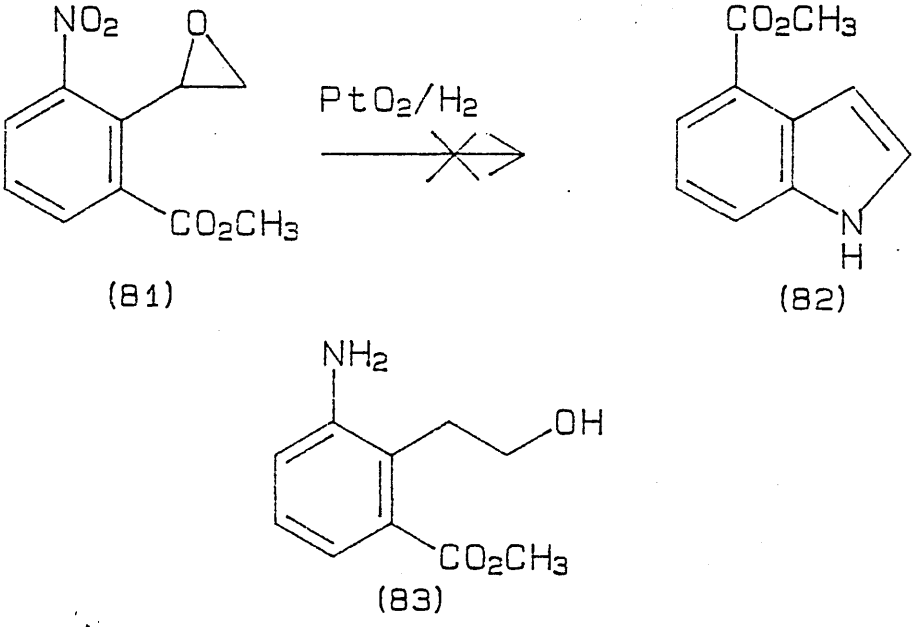
The reaction with diazomethane was repeated, but a suspension of (78) in ether was used. The compound isolated again was not the nitrostyrene oxide, but methyl-2-formyl-3-nitrobenzoate (80). This compound was treated with a further excess of diazomethane, and the desired nitrostyrene oxide (81) was isolated in 68% yield, (scheme 34).

Scheme 34.



The next step was to reductively cyclise the nitrostyrene oxide, to the indole (82), by catalytic hydrogenation, using platinum (IV) oxide as catalyst. The reaction gave a number of products (TLC), none of which was the desired indole. The major product (12.6%) was isolated, and NMR suggested this to be an aminophenyl ethanol (83), although this was not fully characterised, (scheme 35).

Scheme 35.



(81) (82)

(83)

This route was not continued, due to a number of difficulties arising during the synthesis: (i) the difficulty in obtaining the nitrostyrene oxide in a large scale reaction, being limited by the amount of diazomethane we could safely produce, and (ii) the failure of the catalytic hydrogenation to give the desired indole.

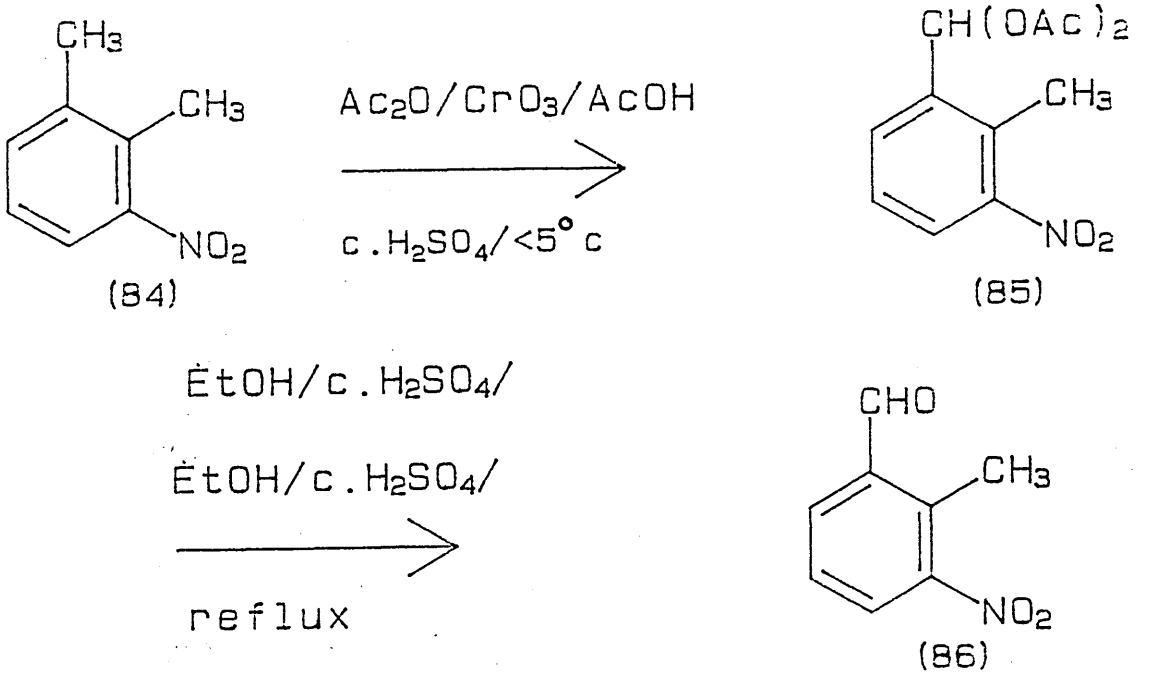
3.2 CYCLISATION OF AMINOPHENYL ETHANOLS.

A tentative investigation of the method of Tsuji et al [17] was

undertaken. This method uses an aminophenyl ethanol as the starting material, which is cyclised to the indole, using tris-triphenylphosphine ruthenium (11) chloride as a catalyst. We investigated the method, to try to synthesise 4-formylindole (29).

The starting material for this synthesis was 2-methyl-3-nitrobenzaldehyde (86), which was made from 3-nitro-o-xylene (84), by way of a Thiele oxidation[12], which uses chromyl acetate as the oxidant. The resulting diacetate (85) was refluxed with ethanol and conc. sulphuric acid, to give the aldehyde (86) (scheme 36).

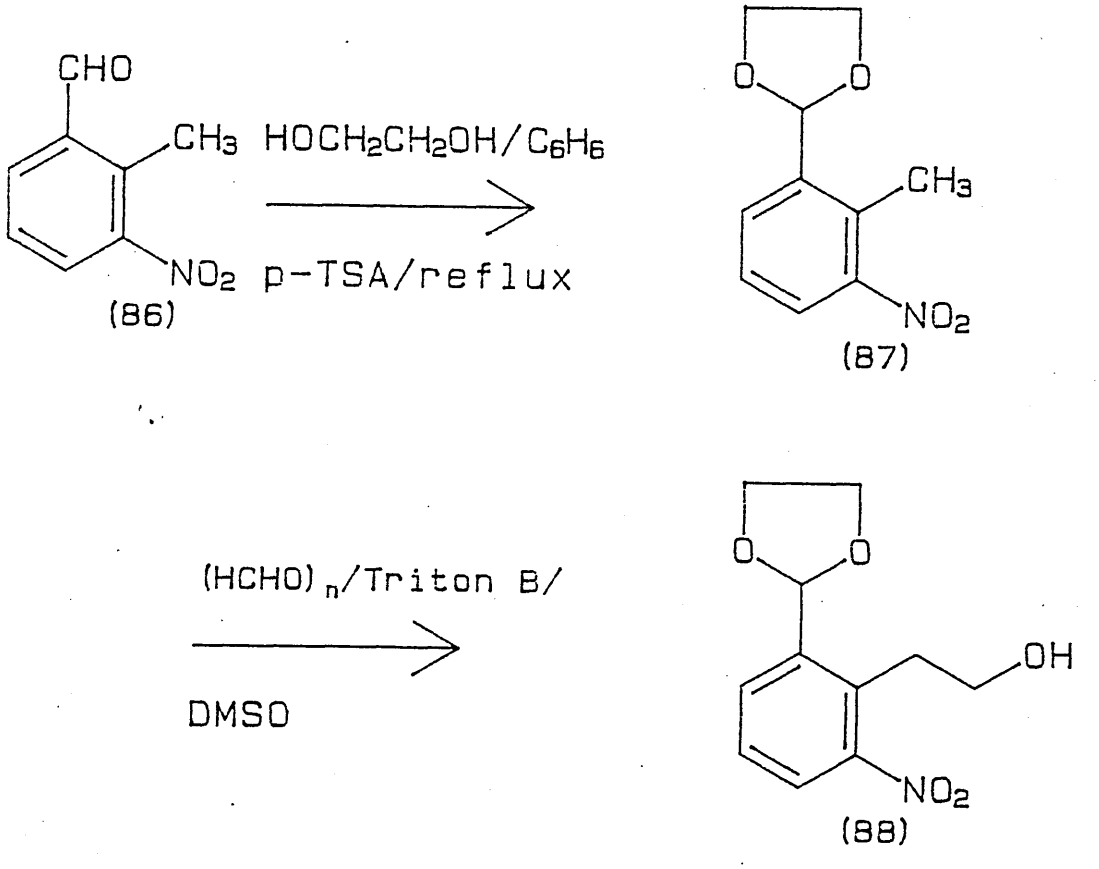
Scheme 36.

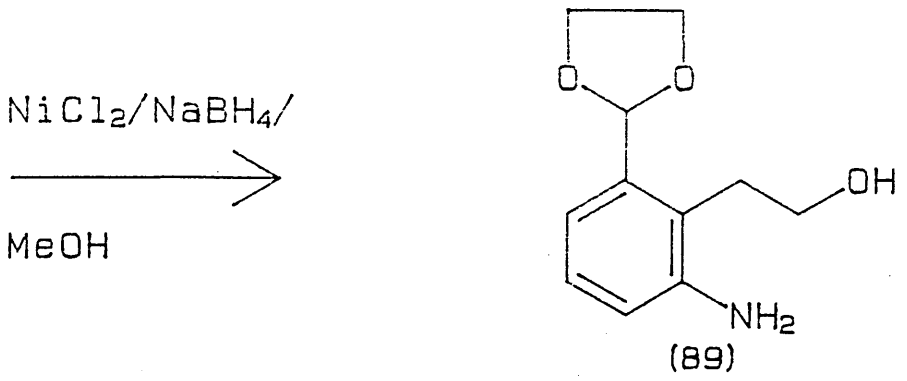


It was decided at this stage that it would be sensible to protect the aldehyde as the dioxolane (87), thus allowing manipulation of the other groups, without affecting the aldehyde. The protected

aldehyde was then treated with paraformaldehyde and triton B (40% in water) in dimethyl sulphoxide at 95°C, (a lower yield of alcohol (88) was obtained when triton B 40% in methanol was used), followed by reduction of the nitro group to the amine, using zinc and calcium chloride in water. This reduction gave poor results in our hands, (20% yield) so nickel (11) chloride and sodium borohydride in methanol[67] was used but only a low yield (46%) of the amine (89) was obtained, a number of other by products being produced as shown by TLC, (scheme 37).

Scheme 37.

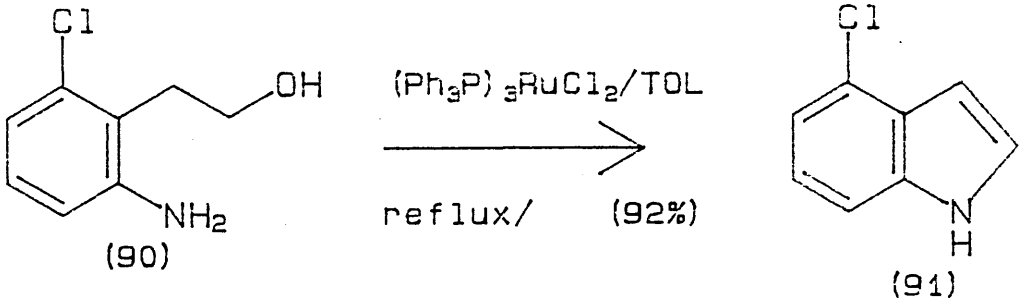




(89)

The cyclisation reaction was attempted, initially, on compound (90), which would have led to 4-chloroindole (91), (scheme 38).

Scheme 38.



(90) (91)

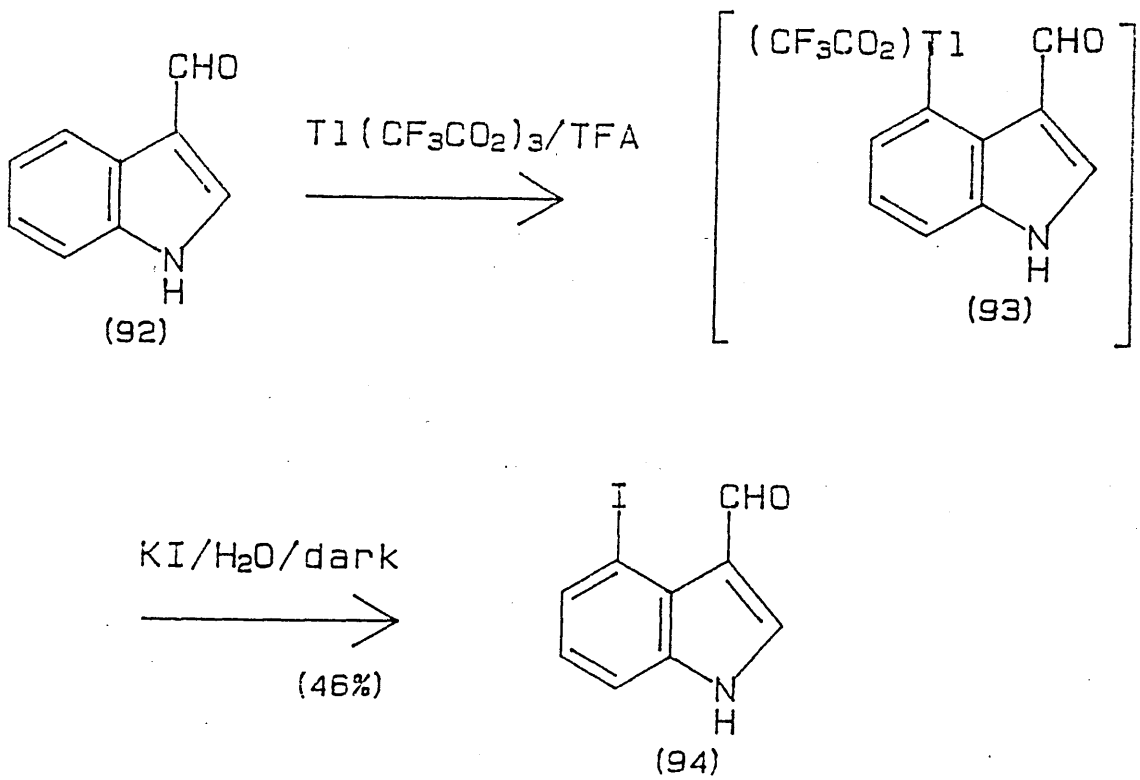
A yield of 92% was quoted by Tsuji et al[17], but in our hands this was not duplicated, and the reaction produced no indole. Two products were seen on TLC, both of which failed to give a positive test for an indole with Ehrlichs reagent (i.e. pink to mauve colour); both compounds gave a yellow colour, which suggested they were amines rather than indoles. The reaction was therefore not tried on the dioxolane, which had not been obtained in pure form and only in low yields. This route was therefore discontinued. Furthermore the cost of

the catalyst was considered too high to enable the synthesis to be carried out on a multigram scale.

3.3. INTRAMOLECULAR NITRILE OXIDE CYCLISATION (INOC) ROUTE

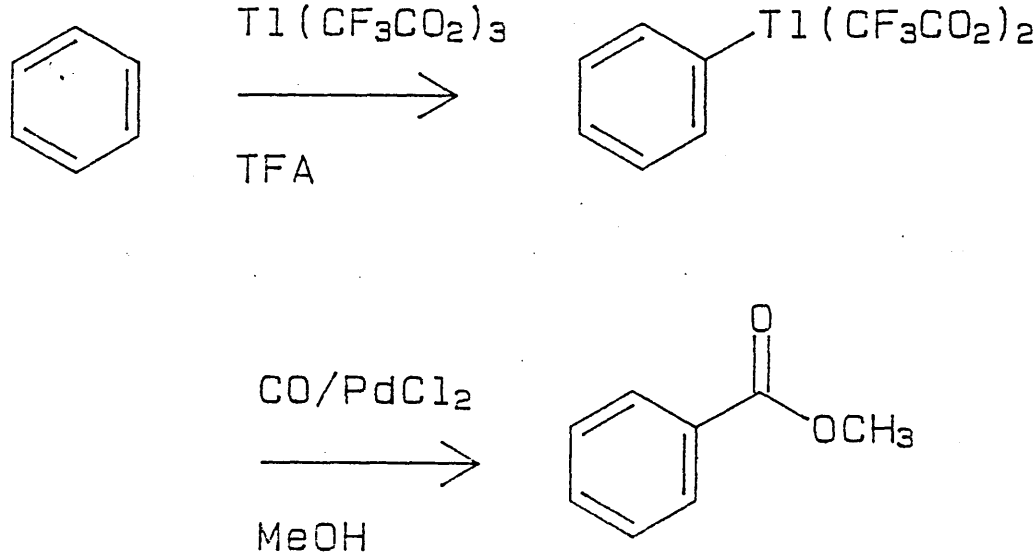
This route began with the indole skeleton already formed and followed the synthesis used by Somei et al[18,19]. Indole-3-carboxaldehyde (92) was treated with thallium trifluoroacetate in trifluoroacetic acid to give the thallium intermediate (93), which was not isolated. This was then treated with aqueous potassium iodide, in the dark, for 24 hours . The product was then filtered off and soxhlet extracted for three days to give 4-iodoindole-3-carboxaldehyde (94), in 46% yield, (scheme 39).

Scheme 39.

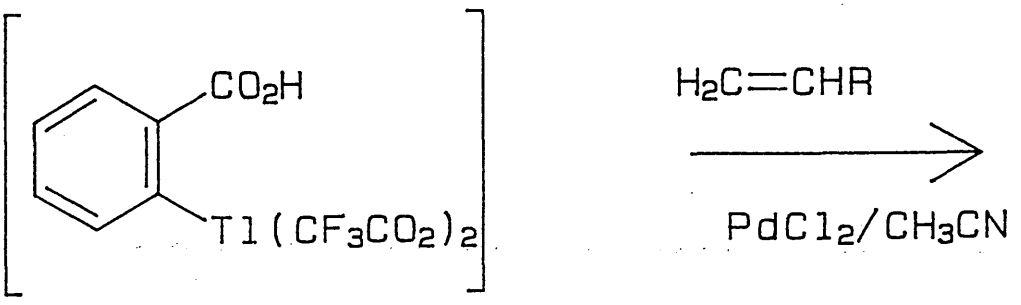


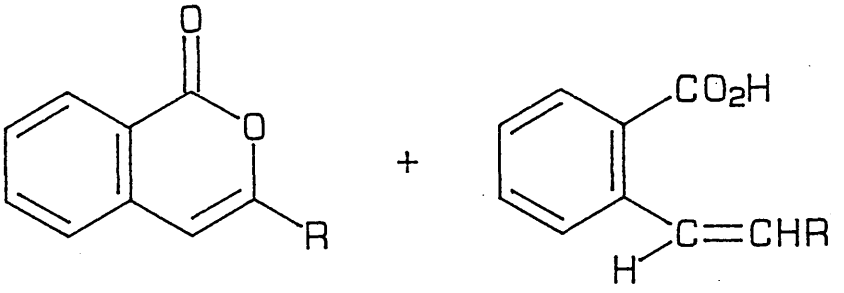
Organothallium reagents are very useful and versatile in the syntheses of aromatic[47] and heterocyclic[48] iodine compounds, which ultimately lead to a variety of products, by a variety of substitution reactions. However they are not widely used because of the high toxicity associated with them. The most widely used organothallium reagent is thallium tris-trifluoroacetate (although others are used). Organothallium reagents react at the 4-position in indoles if a carbonyl function is present in the 3-position allowing co-ordination between the thallium and the carbonyl oxygen. Secondly the 2-position is more strongly deactivated than the 4-position in the presence of a carbonyl group. Thallium reagents do not react with 3-alkylindoles, and only result in decomposition of the starting material. Aromatic organothallium intermediates can also lead to other classes of compounds, for example, carbonyl compounds[49], by carbonylation using carbon monoxide and palladium (0), and olefins, by olefination[50], as outlined below:-

1

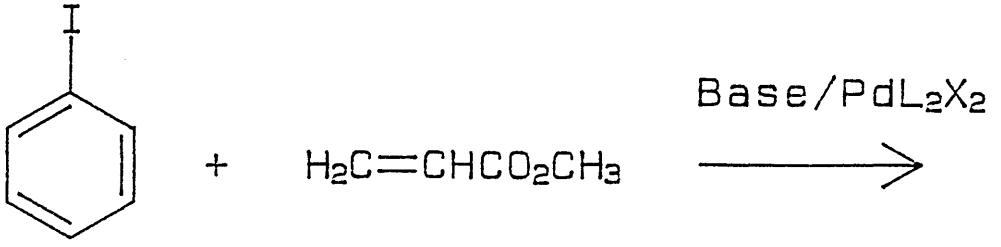


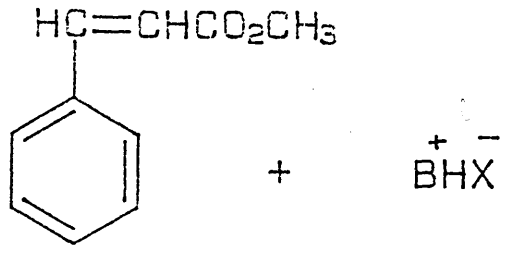
2





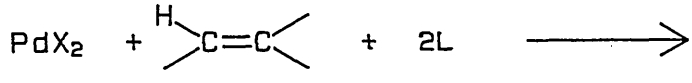
4-Iodoindole-3-carboxaldehyde was treated with trimethylsilyl acetylene and a palladium (0) catalyst, a reaction very similar to a Heck reaction[51,52]. This is a very useful method of forming a carbon-carbon bond, by vinylation of an organic halide for example.

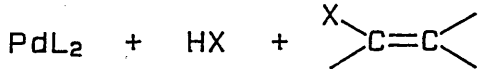




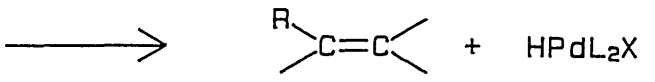
The reaction is catalytic in the amount of palladium used if a cuprous halide is present; the detailed mechanism has not been fully established, but a fairly accurate approximation is outlined below[52].

Catalyst formation





Catalytic cycle

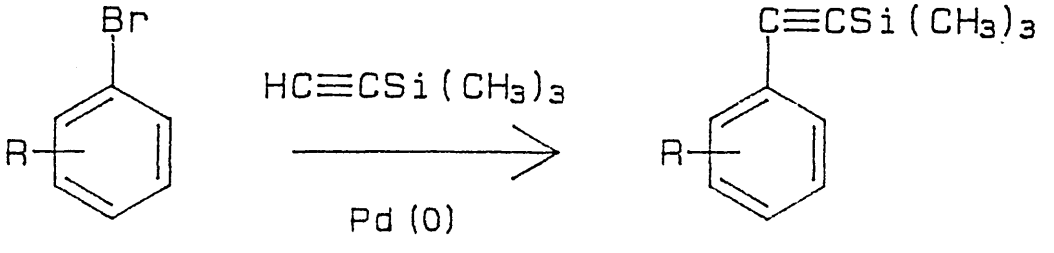


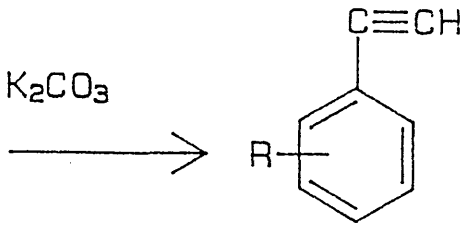
$HPdL_2X + Base \longrightarrow PdL_2 + Base.H^+ X^-$

R = aryl, heterocyclic, benzyl or vinyl.
X = halide.
L = ligand (e.g. triphenylphosphine).

When a palladium (II) complex or salt is used, it must be reduced under the reaction conditions, presumably by oxidising some of the olefin present. The palladium (0) formed then reacts with some of the organic halide to form the organopalladium halide intermediate. The organopalladium complex adds to the double bond of the olefin, the resulting intermediate is then believed to undergo elimination of a hydridopalladium halide. In the presence of base, this dissociates reversibly and the base shifts the equilibrium to palladium (0), which then begins the cycle again[52].

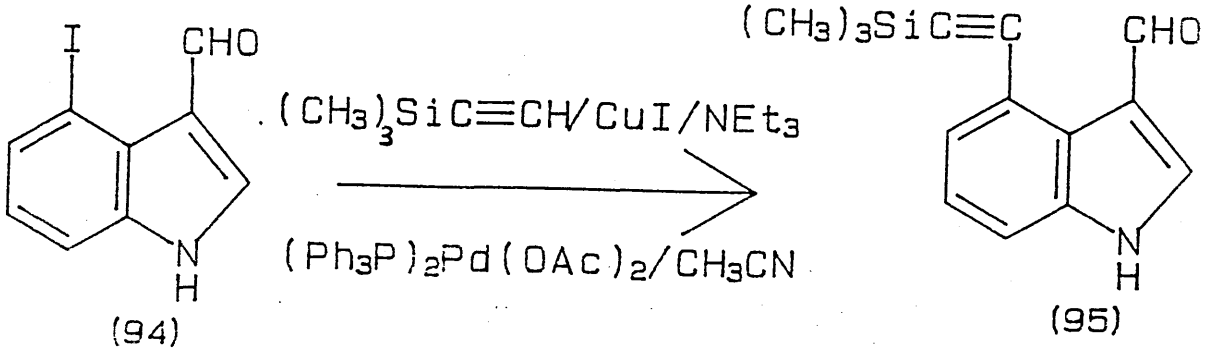
The conditions used were those described by Austin et al[53], who converted a number of aromatic halides to the corresponding acetylenes with trimethylsilyl acetylene and palladium catalysts, outlined below.

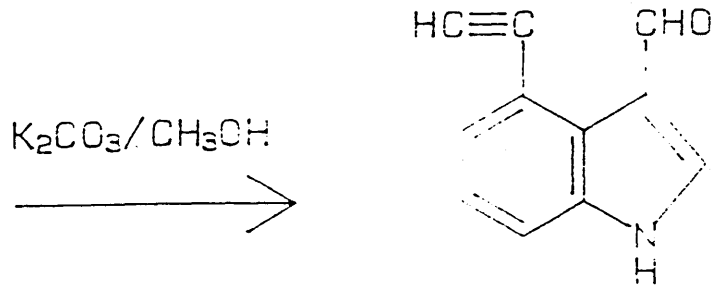




The R groups varied from simple monosubstituted groups such as o, p, m-CHO to complicated aromatic systems consisting of 4 or 5 rings. Thus a good precedent for trying the reaction on our indole system was available. 4-iodoindole-3-carboxaldehyde (94) was treated with trimethylsilyl acetylene in the presence of bis triphenylphosphine palladium acetate, cuprous iodide, and triethylamine, to give the 4-trimethylsilyl acetylene derivative (95). This was then desilylated with potassium carbonate in methanol to give the acetylene (96), (scheme 40).

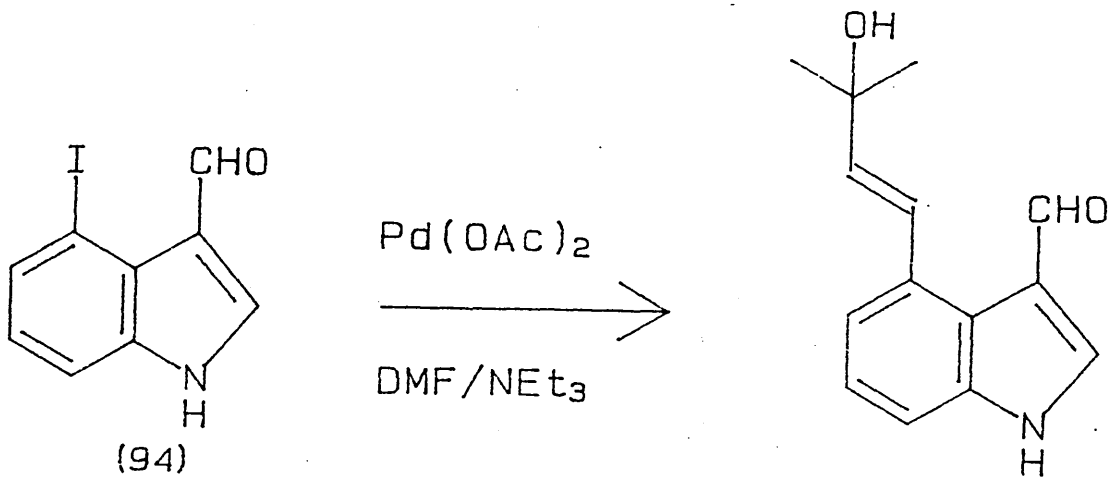
Scheme 40.





(96)

Somei et al[54] prepared 1-(3-formylindol-4-yl)-3-methyl-1-buten-3-ol (97) by a similar 'Heck' reaction using palladium acetate as a catalyst.

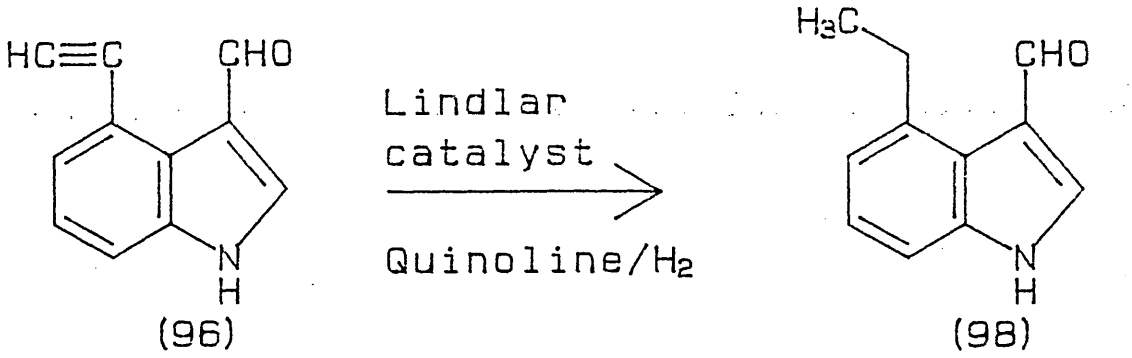


(94) (97)

In our compound we required a vinyl group in the 4-position of the indole, so reduction of the acetylene was necessary. This was first attempted by catalytic hydrogenation using Lindlar catalyst (10% palladium on calcium carbonate, poisoned with lead). However it was found that the hydrogenation did not stay at the olefin, but carried

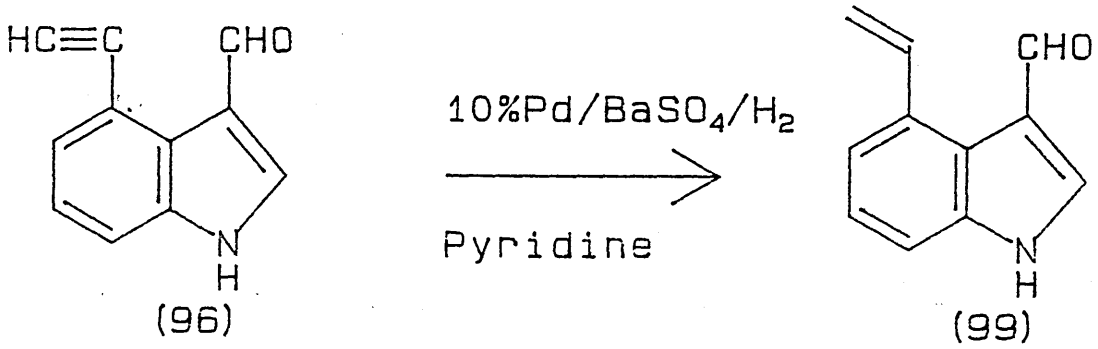
on reducing through to the ethyl derivative (98), whose structure was confirmed by NMR spectroscopy, (scheme 41).

Scheme 41.



The reduction was successfully stopped at the vinyl stage when 10% palladium on barium sulphate was used as a catalyst and pyridine as the solvent[55] (scheme 42).

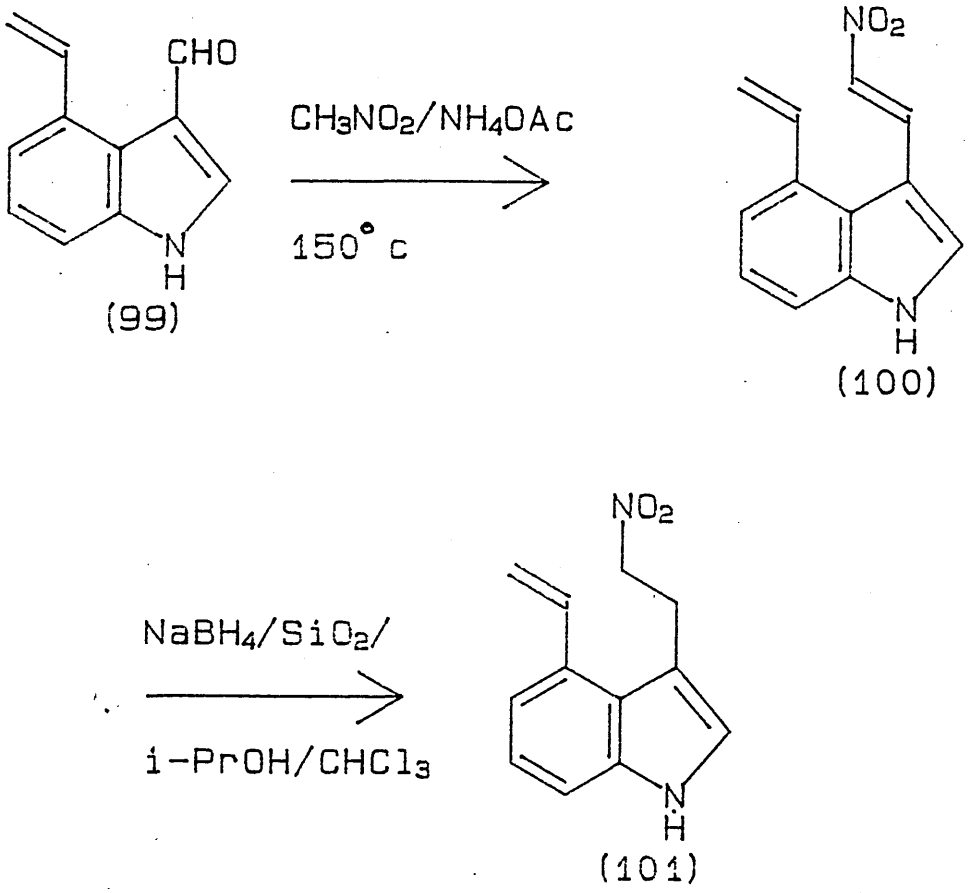
Scheme 42.



The compound that is needed to enable the intramolecular nitrile oxide cyclisation to take place has a 2-nitroethyl group at the indole-3-position. This was formed from (99) by firstly heating with

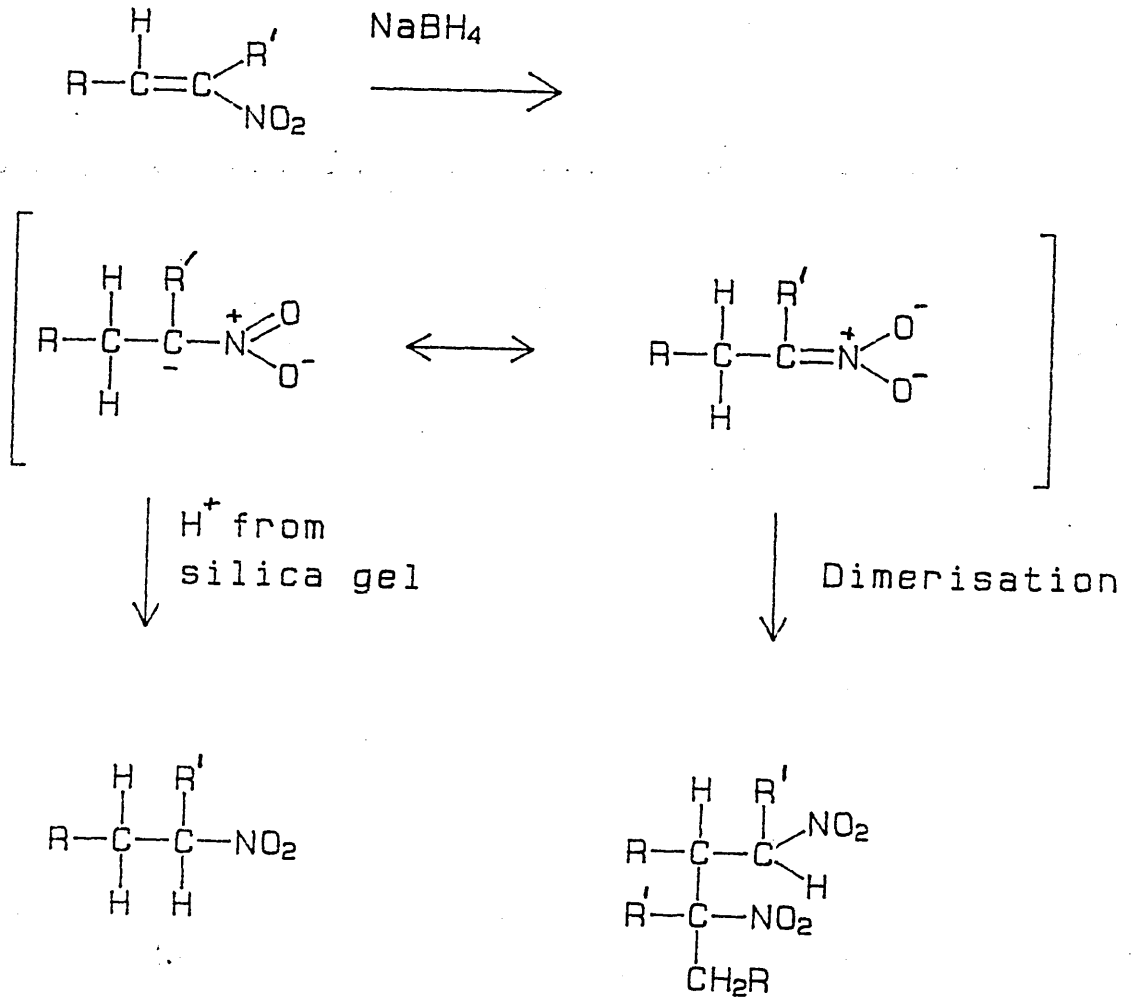
nitromethane and ammonium acetate[56], followed by selective reduction of the internal double bond of the nitroethylene (100) with sodium borohydride in chloroform and isopropanol, in the presence of silica gel[57,58], (scheme 43).

Scheme 43.



The presence of the nitro group makes the double bond of the nitroethylene much more reactive towards reduction, than is the terminal alkene, thus leading to selectivity in the reduction. The silica gel prevents dimerisation occurring, by protonating the α-

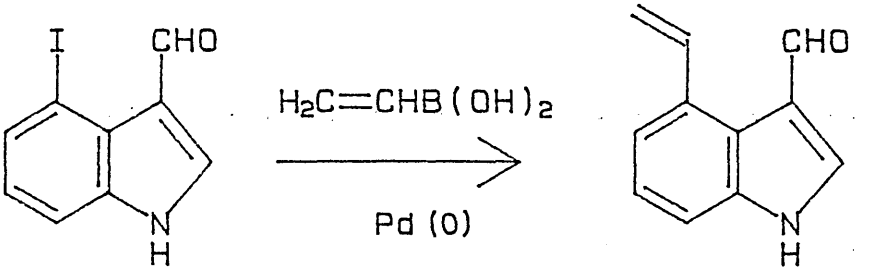
carbanion, which is resonance stabilised, before it can undergo a Michael addition[57], e.g.



The nitroethyl derivative (101) now had the correct groups, and correct orientation to allow nitrile oxide formation, and resulting cyclisation of the reactive dipole, with the olefin, to give the tetracyclic compound (31)[59].

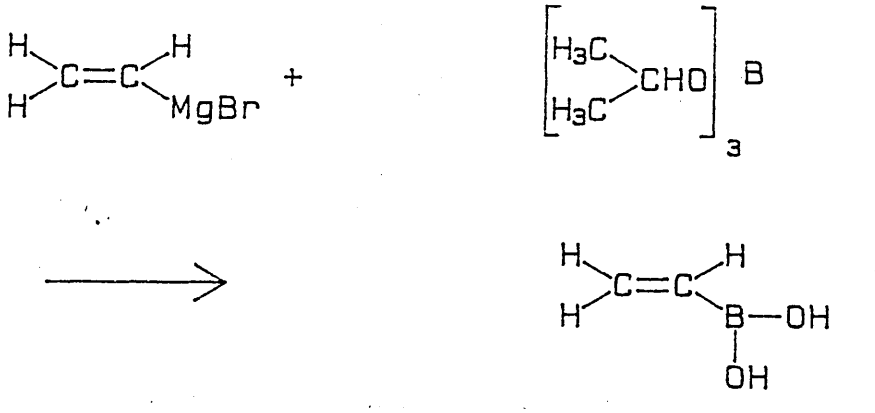
3.3.1 AN ALTERNATIVE HECK REACTION.

An alternative method of synthesising compound (99) was briefly investigated. This would allow a vinyl group to directly replace the iodine in compound (94) hence allowing a more economical synthesis.



(94) (99)

The method chosen to do this was to use vinyl boronic acid, which had to be first synthesised. This was attempted by reaction of vinyl magnesium bromide with triisopropyl borate[80].



vinyl boronic acid

However when the reaction was worked up, a gel was produced, which was quite insoluble (even in DMSO-D_6). An attempt was made to dissolve

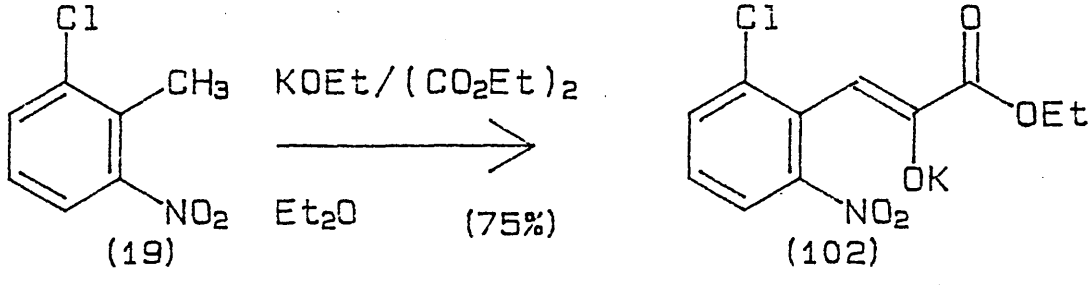
this in sodium hydroxide and to isolate the sodium salt, but the gel would not dissolve. It was later discovered that vinyl boronic acid immediately polymerises on contact with oxygen[81].

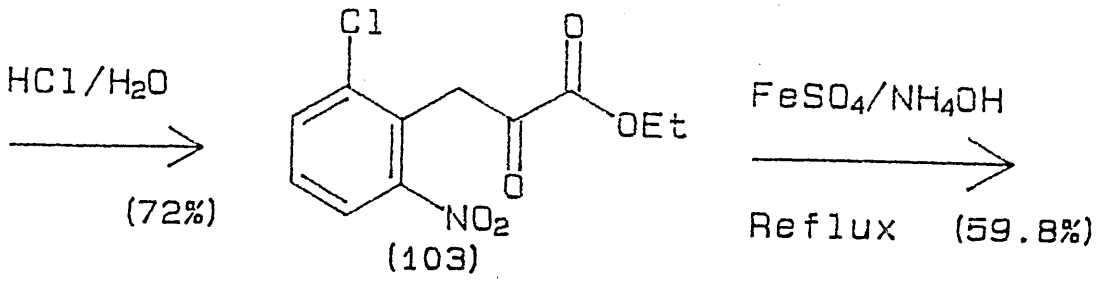
3.4 UHLE'S METHOD.

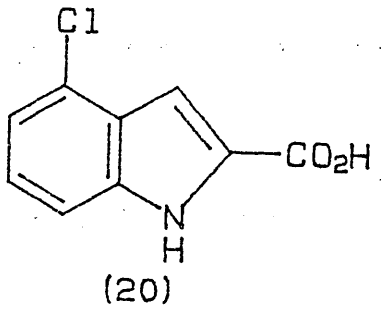
A cheap and simple method of preparing 4-substituted indoles was to follow the method of Uhle[5], with slight modification to improve yields of products. The procedure begins with a cheap starting material 2-chloro-6-nitrotoluene (19), but Uhle's first step gives a product in only 42% yield. We felt that this could be improved by modification of this step, firstly by using potassium ethoxide instead of sodium ethoxide as the base, and secondly by isolating the intermediate salt instead of hydrolysis and steam distillation.

A solution of potassium ethoxide in ether was carefully made[60], and then to this was added diethyloxalate, followed by 2-chloro-6-nitrotoluene. The red salt (102) was filtered off and then acidified with hydrochloric acid to give the pyruvate ester (103). This ester was then subjected to reduction and hydrolysis with ferrous sulphate and conc. ammonia solution, to give 4-chloroindole-2-carboxylic acid (20), (scheme 44).

Scheme 44.



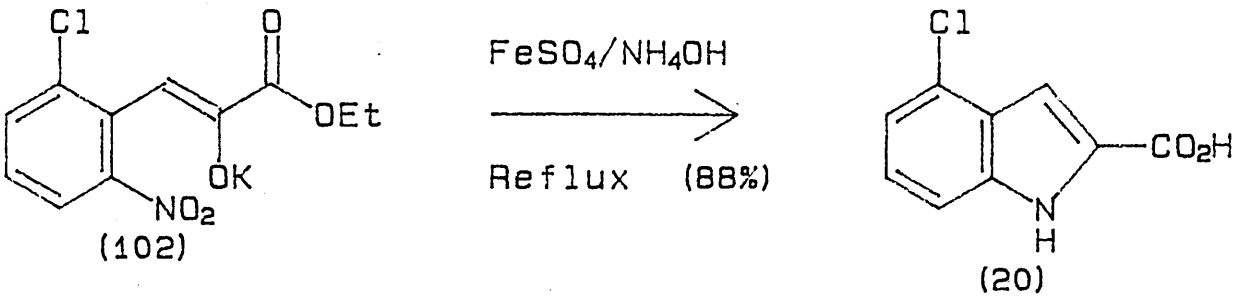




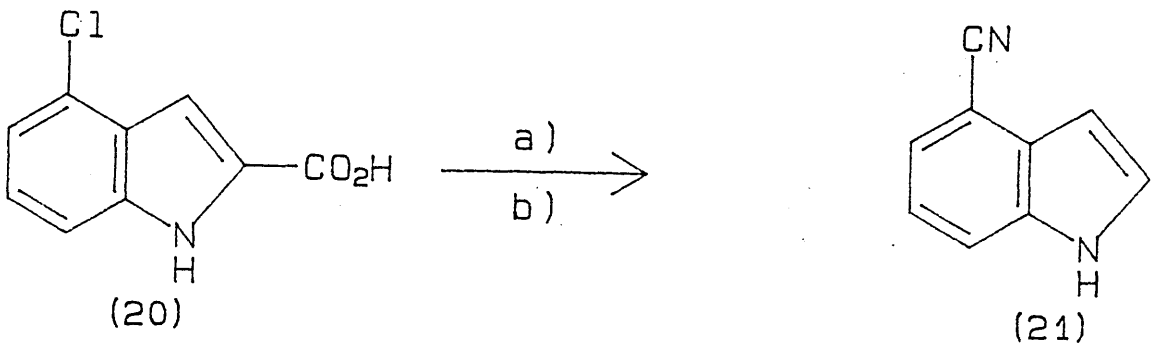
A further improvement to this method was to directly reduce the intermediate potassium salt (102) to the indole (20) using the ferrous sulphate/ammonia method:-

The overall yield of 4-chloroindole-2-carboxylic acid (20), obtained by Uhle, from 2-chloro-6-nitrotoluene was 38.6%, compared with our overall yield of 66%. However the one drawback with our method was that it took much longer for the reduction step, (72 hours against 5 minutes) but this was not a major problem.

The next step in Uhle's synthesis was to simultaneously replace the chlorine atom with a cyano group, and remove the carboxylic acid group. Following Uhle's method of refluxing 4-chloroindole-2-carboxylic acid (20) with cuprous cyanide in quinoline, produced the desired 4-cyanoindole. However the reaction was temperamental and the yield varied between 19% and 45%, (Uhle reported ayield of 57%[5]). To try to improve the yield, the solvent was changed to


Cl
O
OEt
OK
NO2
(102)
FeSO4/NH4OH
Reflux (88%)
Cl
CO2H
N
H
(20)

N-methylpyrolidone, in which cuprous cyanide is soluble above 90°C. Again the yield of reaction varied this time between 29% and 37%. Both these reactions were repeated a number of times, with slight variations (e.g. by refluxing longer than 20 hours, of by adding a small quantity of potassium iodide) but no improvement was found. The reaction was even tried at room temperature in an ultrasonic bath, but only the starting material was isolated in this case.



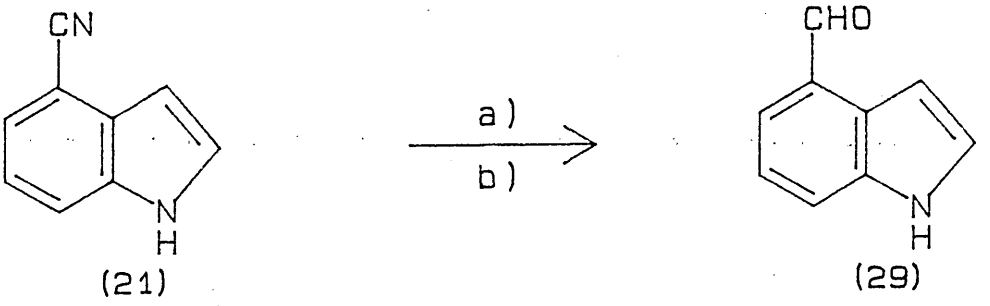
(20) (21)

a) CuCN/Quinoline/237°c
b) CuCN/N-methylpyrrolidine/202°c

It was disappointing to find we had been able to improve the yields in the early stages, but not in the cyanide displacement. However the 4-cyanoindole (21) produced was converted to indole-4-carboxaldehyde (104) by by reduction with diisobutyl aluminium hydride (DIBAL)[61], in 67% yield. Unfortunately this reaction was not reproducible, so another method was needed. The method was that of Backeberg and Staskun[62], which uses sodium hypophosphite and Raney nickel as the reducing agents. This method was quite reproducible and

the yield of product isolated was higher (87%) than that from the DIBAL reduction, (scheme 45).

Scheme 45.



a) DIBAL/Toluene/N_2
b) NaH_2PO_4/RaNi/H_2O/HOAc/Pyridine

Overall this development of Uhle's original method suffers badly from the low yield in the cyanide displacement step. This makes it difficult to produce large quantities of 4-formylindole by this route.

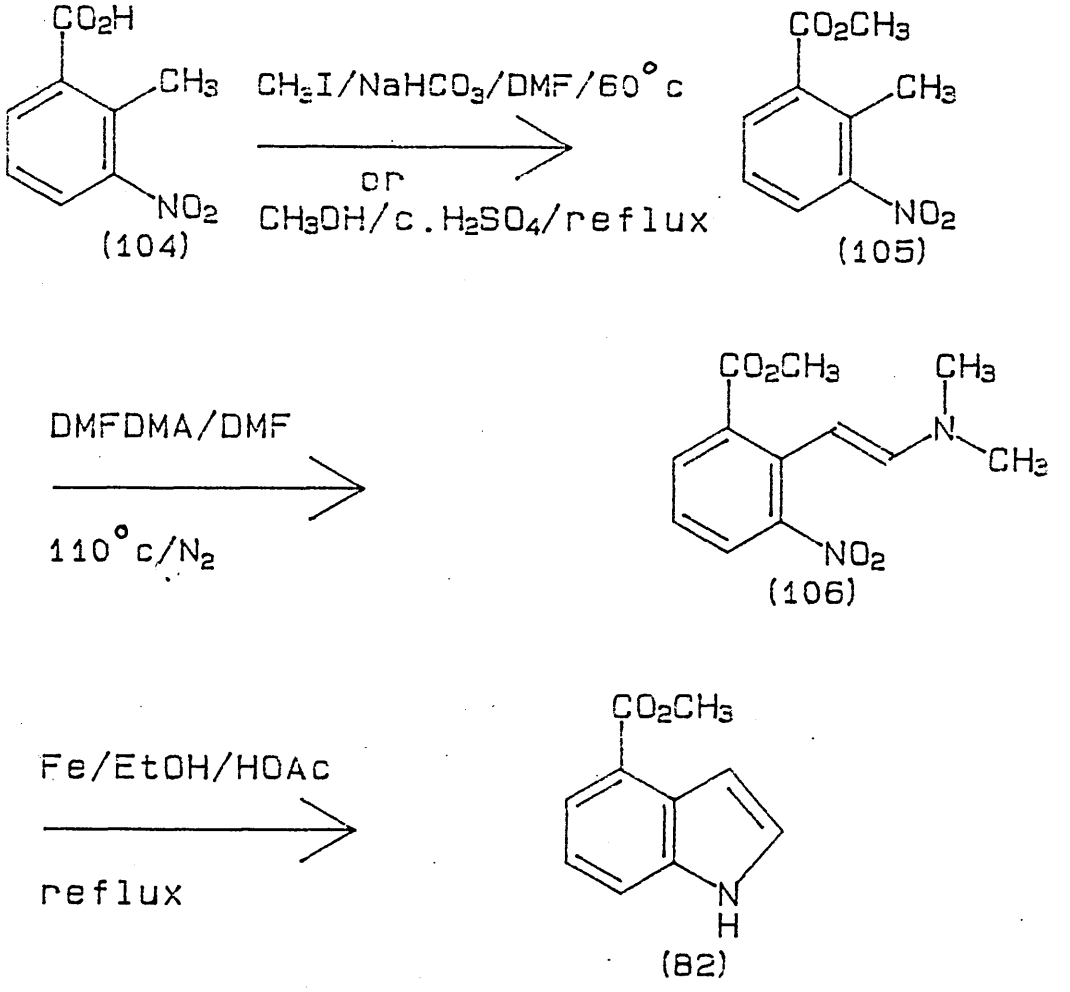
3.5 THE BATCHO-LEIMGRUBER SYNTHESIS.

As stated in chapter 1 this is one of the best methods of preparing a 4-substituted indole. We anticipated that this would give us a good supply of a 4-substituted indole quite quickly, but it was not the case.

The first method followed was that of both Kozikowski[11] and Ponticello and Baldwin[13]. 2-methyl-3-nitrobenzoic acid (104) was first esterified using methyl iodide and sodium bicarbonate in DMF to give the methyl ester (105) in 85% yield, (methanol and conc. sulphuric acid gave 93%)[11]. The ester was then treated with dimethylformamide dimethylacetal (DMFDMA) in DMF at 110°C for 2 days. After removal of the DMF, the resulting enamine (106) was relatively pure and did not

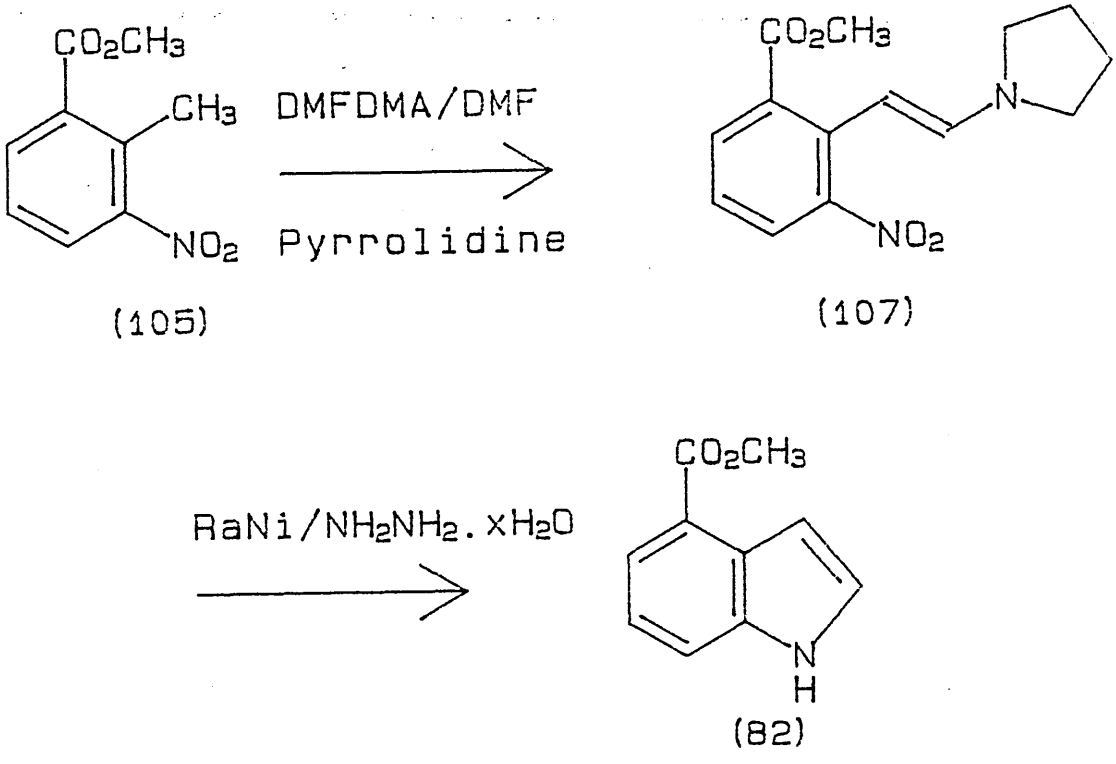
need purification. The next step was to reductively cyclise to methylindole-4-carboxylate (82). However access to medium pressure hydrogenation equipment was not available at that time, so the method of Ponticello and Baldwin[13] was used. The reduction was carried out with iron powder in refluxing ethanol and acetic acid, but this gave only a low yield (32%) of the impure indole, (scheme 46).

Scheme 46.



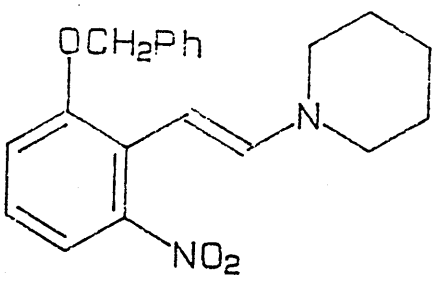
The reaction was repeated by using a mixture of DMFDMA and pyrrolidine[12], followed by reduction with Raney nickel and hydrazine hydrate, (scheme 47).

Scheme 47.



This reaction on work up gave 0.66g of a yellow solid (from 7.4g of (107)), and the NMR showed it was not the required indole.

A further attempt was made to synthesise methylindole-4-carboxylate (82). The method of reductive cyclisation was that of Lloyd and Nichols[67], using a combination of nickel boride and hydrazine hydrate. They prepared 4-benzyloxyindole (119) in 90% yield, from tripiperidino methane enamine (108).

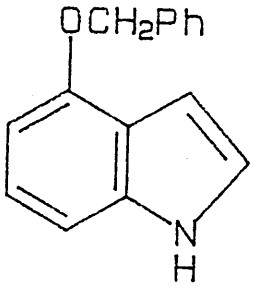


(108)

$Ni_2B/NH_2NH_2.xH_2O$

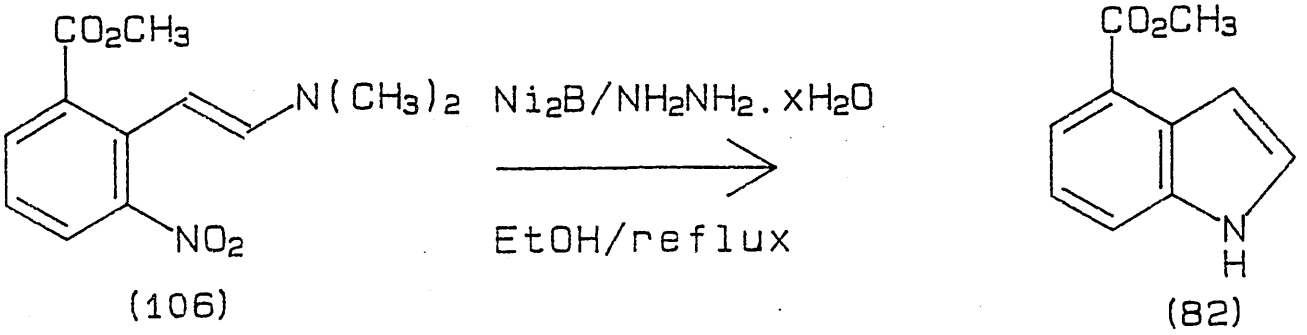
EtOH/reflux

(90%)



(119)

The nickel boride was freshly prepared, by addition of nickel acetate tetrahydrate to a solution of sodium borohydride in sodium hydroxide solution. The nickel boride separated as a black solid, which was filtered off, washed several times and then suspended in ethanol. This suspension was added to the enamine (106), and the resulting mixture heated to reflux before hydrazine hydrate was added.

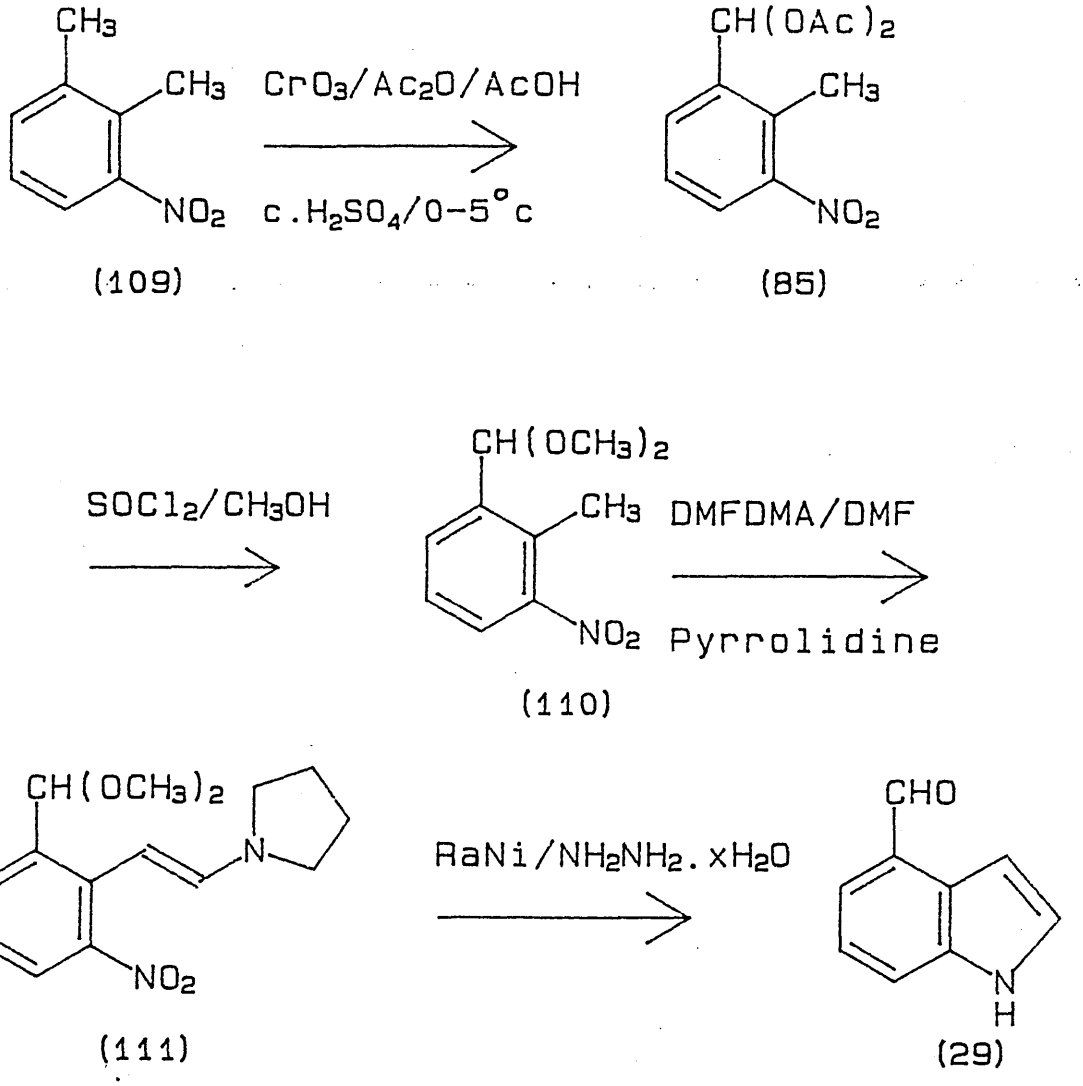


(106) (82)

A TLC plate showed that some indole was present (pink with Ehrlichs reagent), but the reaction was far from clean, and several other products were present, none of which looked like a major product.

A slightly different approach was next tried, which followed the method of Maehr and Smallheer[12]. This starts with 3-nitro-o-xylene (109), which was oxidized by a Thiele oxidation (already mentioned in section 3.2) using chromylacetate,to give 2-methyl-3-nitrobenzene methanediol diacetate (85) in 43% yield (lit. 52%)[12]. This was then treated with thionyl chloride in methanol to give the acetal (110). This was treated with DMFDMA, pyrrolidine and DMF to form the intermediate enamine (111), followed by reduction with Raney nickel and hydrazine hydrate. This should have resulted in the formation of 4-formylindole (29), (scheme 48).

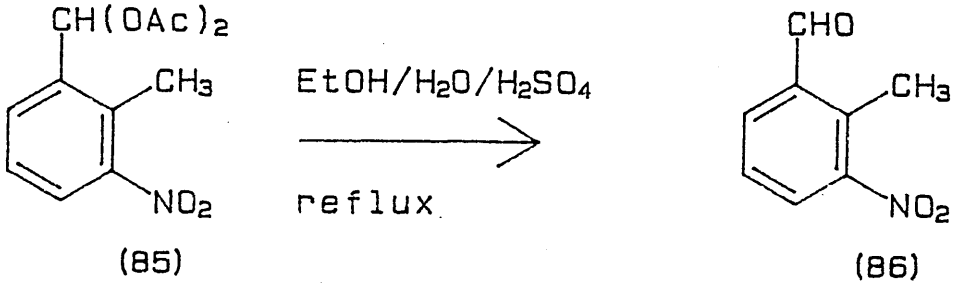
Scheme 48.



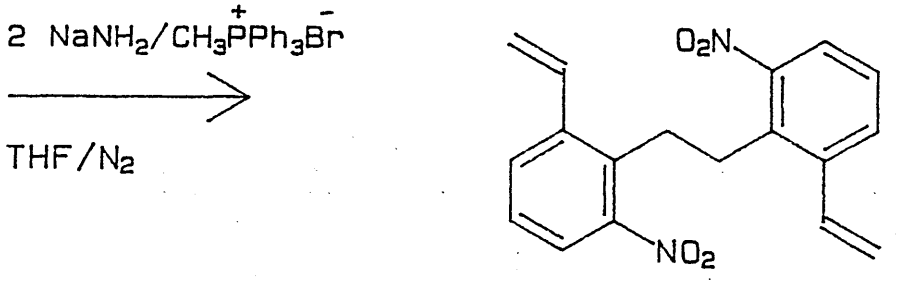
(109) (85) (110) (111) (29)

When the product was isolated (in the form of pink crystals), an NMR spectrum indicated that there was no 4-formylindole present, but something that was very similar to the enamine. The failure of these reductions using Raney nickel, was surprising in view of the results obtained by Maehr and Smallheer. It is possible that the problem lay in the activity of the Raney nickel, but this point was not investigated further since a superior method was being developed (see later).

A variation on the work described above involved the development of the vinyl group before synthesis of the indole ring. The diacetate (85) was converted to the benzaldehyde (86) by refluxing with 50% aqueous ethanol and conc. sulphuric acid. The aldehyde was then subjected to a Wittig reaction, to form the styrene derivative (112), using two equivalents of "instant ylid" (sodium amide and methyltriphenylphosphonium bromide) in THF. The pale brown solid product obtained (62.5%) was clearly not the desired styrene (112) as shown by its proton NMR spectrum. This showed a multiplet (8H) around 7.4 , a multiplet (4H) at 5.5 and a singlet (4H) at 3.16 . A possible explanation for this spectrum would lie in the formation of the dimer (113) and this was confirmed by spectroscopy and microanalysis.



(85) (86)

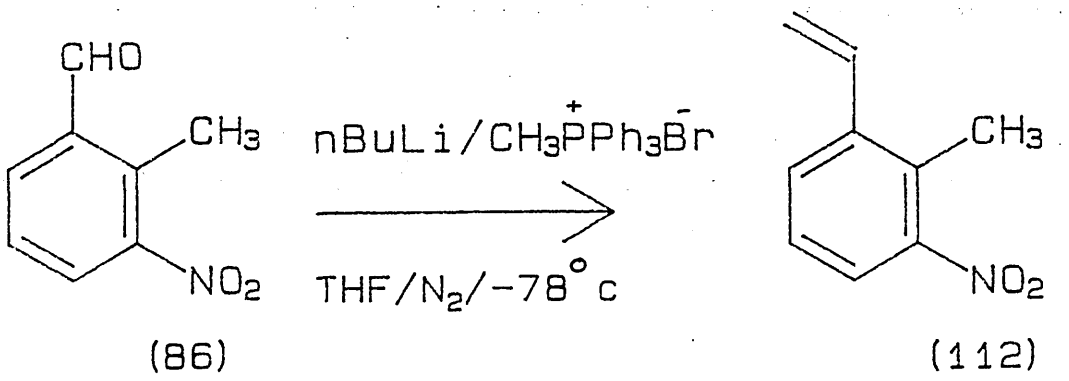


(113)

Presumably this reaction proceeds by removal of a proton from the relatively acidic methyl group in the initially formed styrene

(112), by the extra equivalent of base present. The resulting anion must then be oxidatively coupled (probably via a radical process).

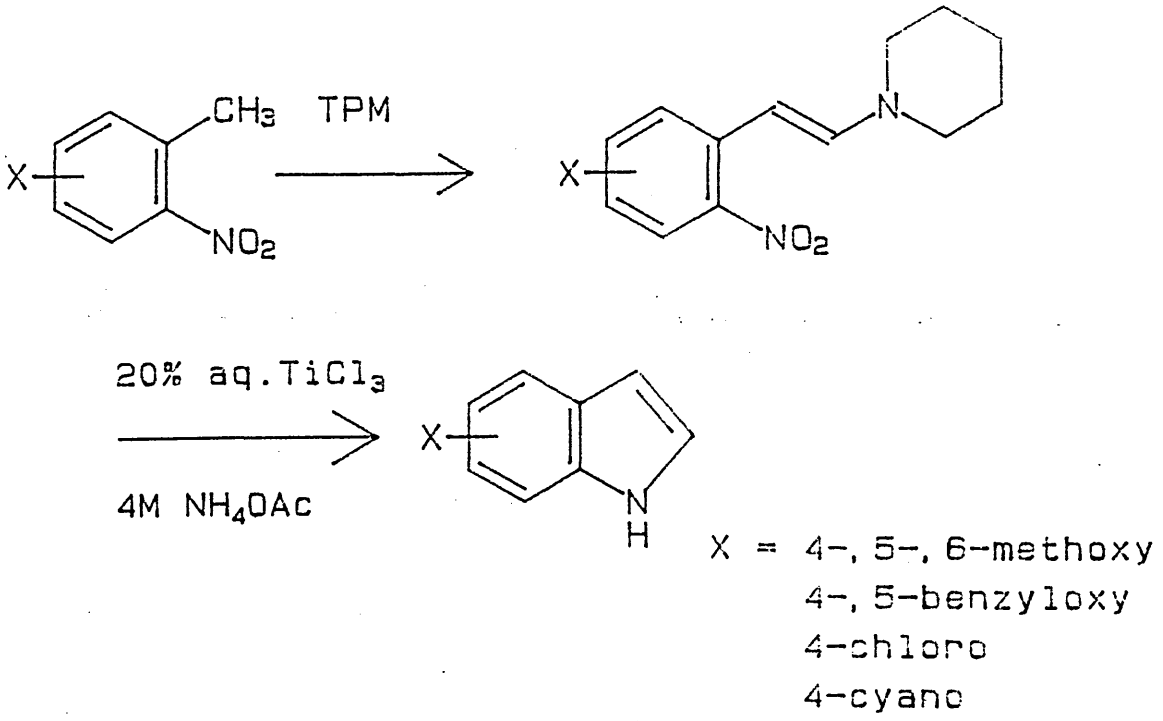
The required product (112) was obtained (in 70% yield) when only one equivalent of base and one equivalent of methyl triphenylphosphonium iodide were used, i.e.:-



(86) (112)

The styrene was then treated with DMFDMA in DMF, to give the enamine (116), which was not purified for the next step. The reductive cyclisation step was then carried out by using titanium trichloride in methanol. This method has been used by Somei and co workers[63,64,65] to synthesise a variety of indoles containing different funtional groups (e.g. 4-hydroxy, 4-halo, 4-amino, 4-nitro) and their 1-hydroxy derivatives. The method has also been used successfully by Lloyd and Nichols[66]. They firstly prepared the intermediate enamine using tripiperodinomethane (TPM) then reductively cyclised with titanium trichloride, (scheme 49).

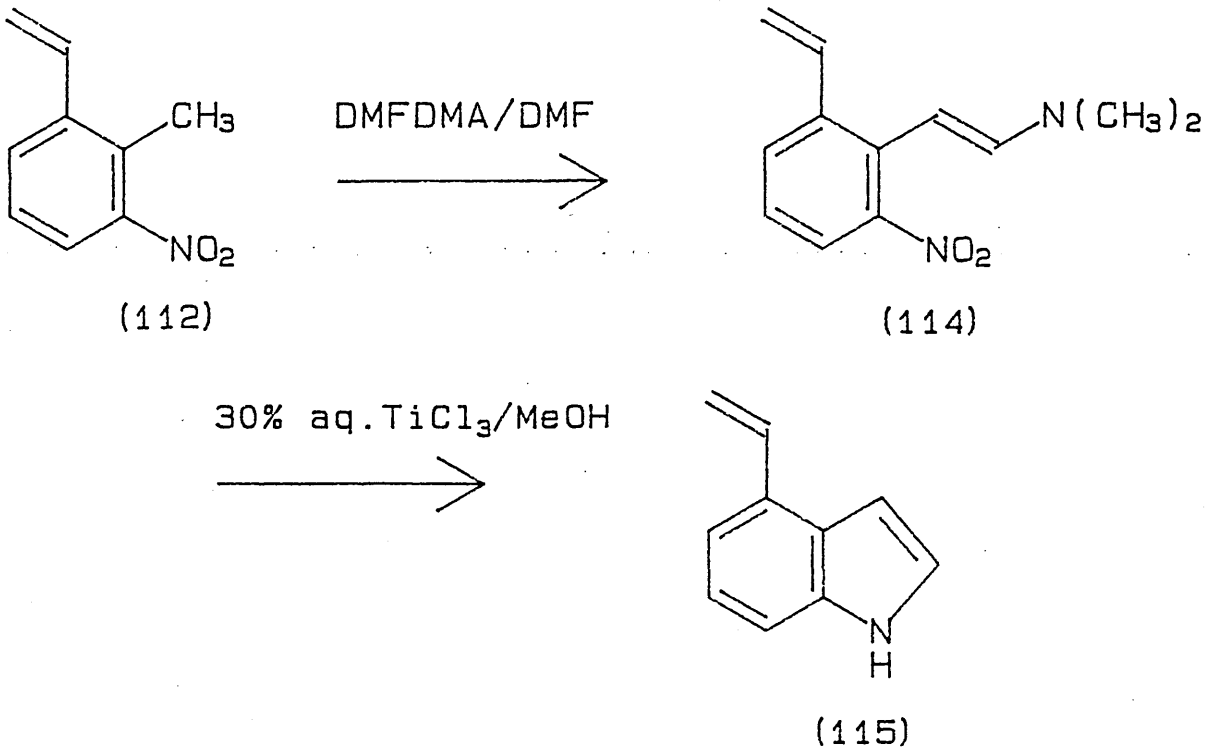
Scheme 49.



The usual Batcho-Leimgruber conditions using DMFDMA are known to be unsuitable for the preparation of 4-methoxy and 4-benzyloxy indoles, due to their slow reaction times. The above method improved on this.

The enamine (114) was treated with 6.5 equivalents of 30% aqueous titanium trichloride in methanol. However a TLC of the reaction mixture showed a number of spots, none of which gave the characteristic violet colour with Ehrlichs reagent. A yellow spot was visible, which suggested that a primary amine was present. A further 6 equivalents of titanium trichloride were added. and a TLC showed a complex mixture of spots, one of which did colour up violet with Ehrlichs reagent. This product was not isolated due to it being only a minor component, (scheme 50).

Scheme 50.

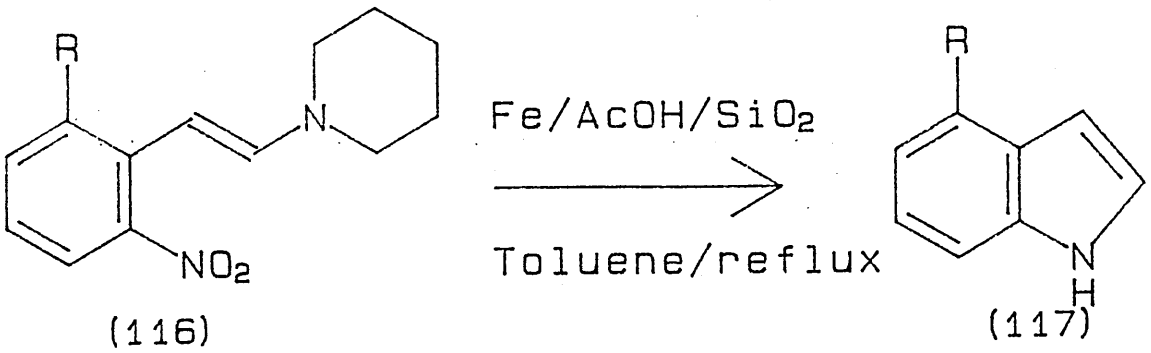


(112) (114) (115)

The reduction was repeated, but this time 10% acetic acid was added to the reaction medium. The result was practically the same as previously, with a large number of by products present. An attempt at isolating the correct product was made by column chromatography, but this failed. An impure product (of only 5.6% yield) was obtained, whose NMR spectrum was very complex. From these results it was deduced that the titanium trichloride reduction was not suitable for the reductive cyclisation, in this case.

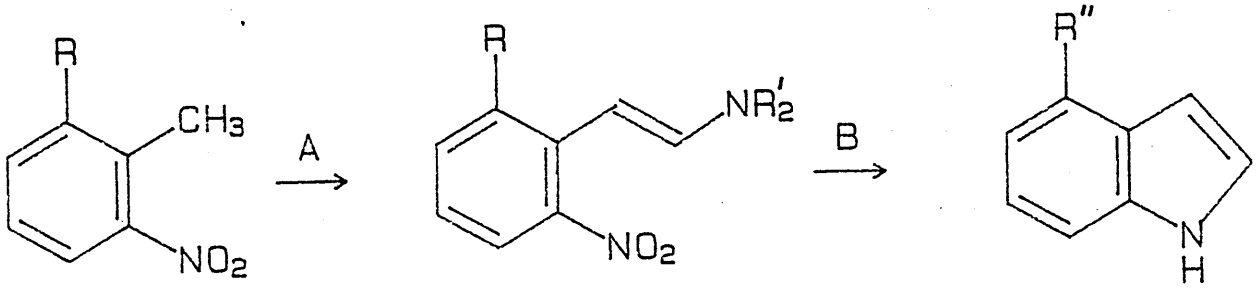
At this stage our work on the Batcho-Leimgruber synthesis was about to be abandoned, due to the difficulty in getting the reductive cyclisation to work. However at the end of 1987 a paper was published by Kowase et al[68], who used a modification of the iron/acetic acid

reduction. They found that a number of indoles (4-halo,4-methoxy, and 4-benzyloxy) could be prepared in high yields (>80%), when silica gel (chromatography grade) was added to the reaction medium:



(116) (117)

We thought that this method would be worth trying on our enamine (106) in a final attempt to prepare methylindole-4-carboxylate (82). A TLC of the reaction mixture showed a major spot (pink with Ehrlichs reagent), which was purified by column chromatography to give the indole (82) in 86% yield.



(118) (118a) (118b)

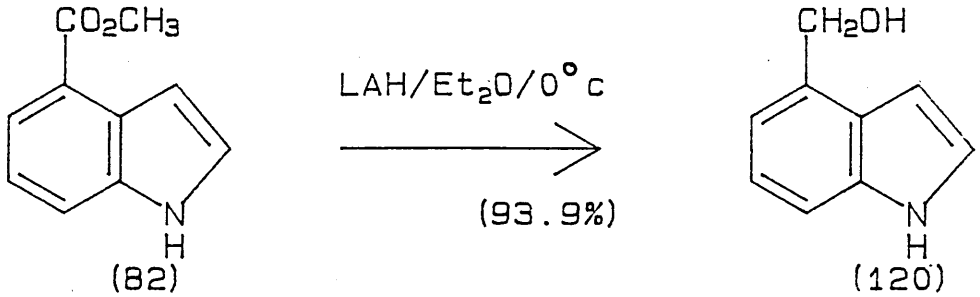
TABULATED SUMMARY OF BATCHO-LEIMGRUBER SYNTHESIS.

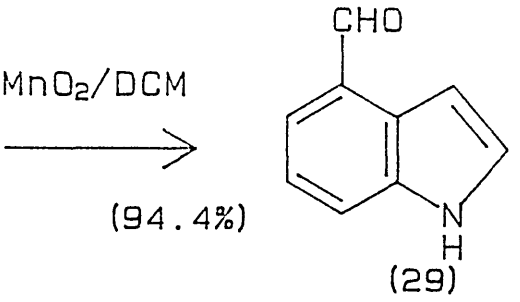
R	A	R'	B	R''	Yield (%)
CO_2CH_3	DMFDMA	CH_3	Fe/AcOH	CO_2CH_3	32
CO_2CH_3	DMFDMA/pyr	⬠	RaNi/NH_2NH_2	CO_2CH_3	-
CO_2CH_3	DMFDMA	CH_3	Ni_2B/NH_2NH_2	CO_2CH_3	-
$CH(OCH_3)_2$	DMFDMA/pyr	⬠	RaNi/NH_2NH_2	CHO	-
$H_2C{=}CH$	DMFDMA	CH_3	$TiCl_3$	$H_2C{=}CH$	-
CO_2CH_3	DMFDMA	CH_3	Fe/AcOH/SiO_2	CO_2CH_3	86

3.5.1 ELABORATION OF METHYLINDOLE-4-CARBOXYLATE.

Methylindole-4-carboxylate(82) was reduced using lithium aluminium hydride (LAH) in ether at 0 °C, to give indole-4-methanol (120) in 94% yield. Kozikowski et al[11] carried out the conversion using DIBAL, but we found that it was much easier and cheaper to use LAH. Indole-4-methanol (120) was then oxidised with active (brown) manganese (IV) oxide in dichloromethane to give 4-formylindole (29) in high yield, (scheme 51).

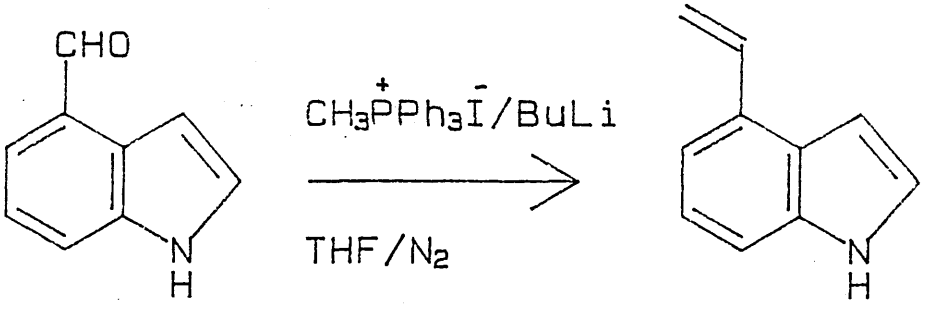
Scheme 51.





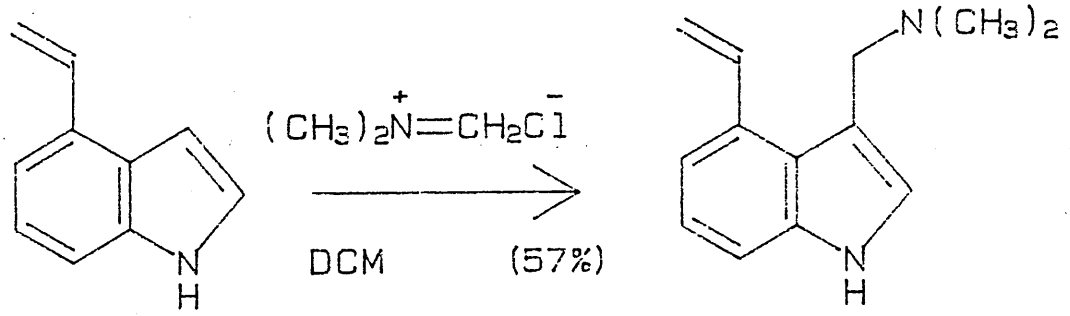
(29)

The aldehyde (29) was then subjected to a Wittig reaction using methyl triphenylphosphonium iodide and butyllithium, to give 4-vinyl indole (115). However when the product had been purified by column chromatography, the solvent was removed under reduced pressure. To this was then added carbontetrachloride (used to azeotrope out any ethyl acetate, to allow a solvent free NMR spectrum to be obtained) the brown oil began to froth and turn purple. 4-vinyl indole is known to readily polymerise[89], and this was probably what was happening. After recolumning this residue the yield of product was only 19%. The reaction was repeated, and after columning on silica gel a yield of 93% was obtained. The product was stored under nitrogen in a freezer to prevent any polymerisation taking place, until needed for next step.



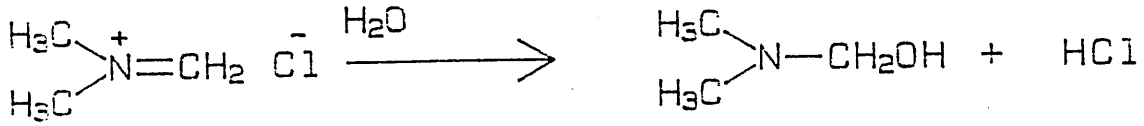
(29) (115)

At this stage two options were available, for adding a nitroethyl group to the 3-position of 4-vinylindole. The first was to follow the route of Kozikowski et al[59], in which the gramine derivative (121), was first synthesised by exposure to the unstable imminium salt, N,N-dimethyl imminium chloride[69].



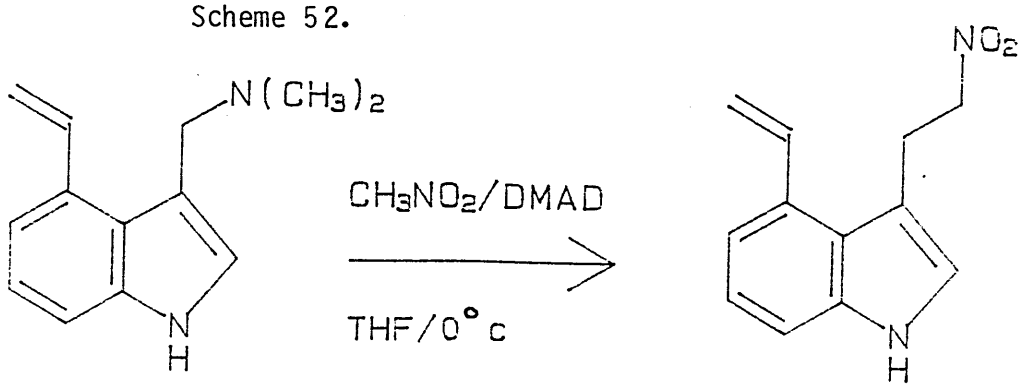
(117) (121)

This salt had to be prepared immediately before use and under an inert atmosphere, due to its instability in air. This salt is very hygroscopic and reacts quickly with moisture in the air to form an amino alcohol:

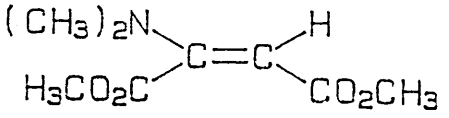


Kozikowski et al[59] converted (121) to the nitroethyl derivative (101) by reaction with nitromethane and dimethyl acetylene dicarboxylate (DMAD)[70]. The reaction was repeated by us, but on work up, the only product isolated was the alkene (122) derived from the DMAD, (scheme 52).

Scheme 52.



(121) (101)

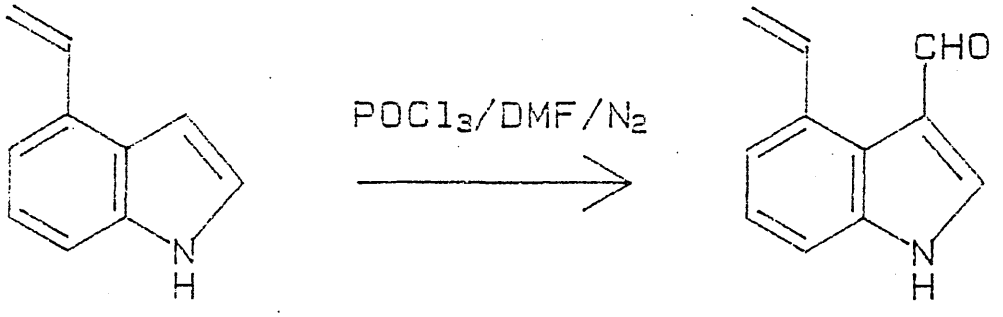


(122)

The NMR of the crude product showed that a loss of the vinyl group had taken place, which immediately suggested that the reaction had not gone according to the literature.

The second route to be investigated was to prepare compound (99) by performing a Vilsmeier-Haak reaction on 4-vinylindole (115). This is the standard method of synthesising 3-formylindoles. 4-vinylindole (115) was added to a solution of phosphorous oxychloride in dry DMF. The product (99) was isolated in 44% yield, but this was the result from a single attempt, and could probably be improved with further experimentation, (scheme 53).

Scheme 53.

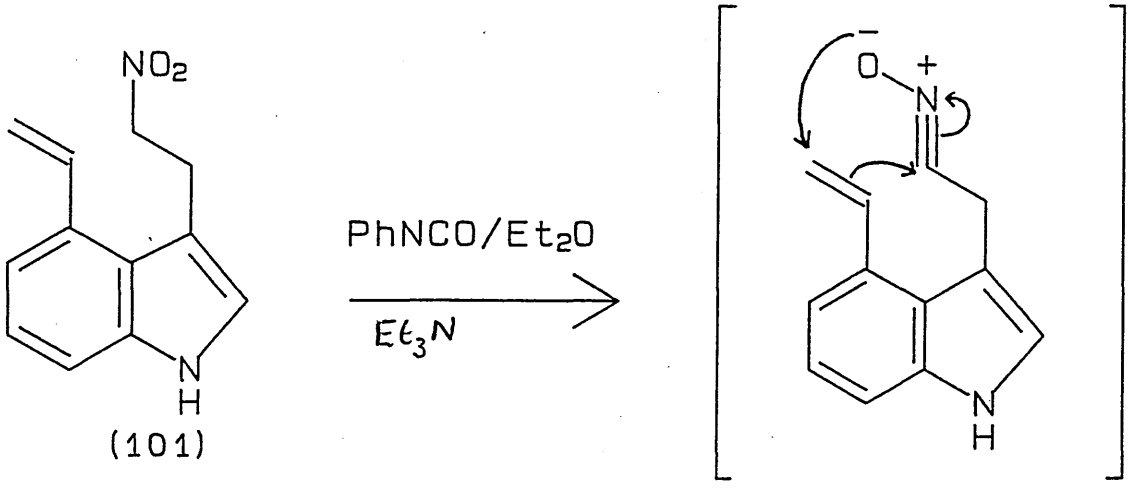


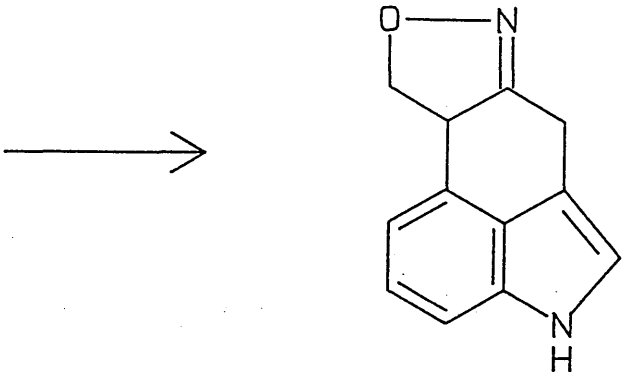
(115) (99)

From the results of the above section and section 3.3, we have two routes to compound (99), both of which are fairly simple to carry out. The second route has a slight advantage over the first route, in that toxic thallium reagents are not used. Thallium waste poses a problem when large quantities are used. Thus the second route is more acceptable on a multigram scale.

Compound (99) was then treated as previously decribed in section 3.3, with nitromethane and ammoniumacetate, to give the nitroethylene (100), which was reduced to the nitroethyl derivative (101), using sodiumborohydride and silica gel. The nitroethyl compound (101) was then treated with phenylisocyanate, which should then have given the nitrile oxide (which is not isolated), which cyclises to the tetracyclic isoxazoline (31), (scheme 54).

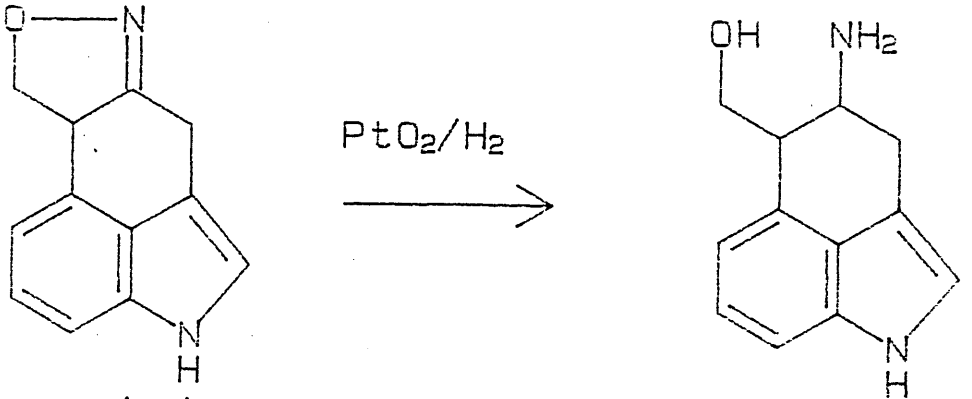
Scheme 54.





(31)

On working up the reaction, three spots were visible on a TLC plate. Chromatography led to a mixture of two close running compounds, and a mass spectrum of this mixture showed that the isoxazoline was present (molecular ion 198) and also N,N-diphenyl urea (molecular 212). The reduction of the isoxazoline should have led to the β-amino alcohol (123)[71].



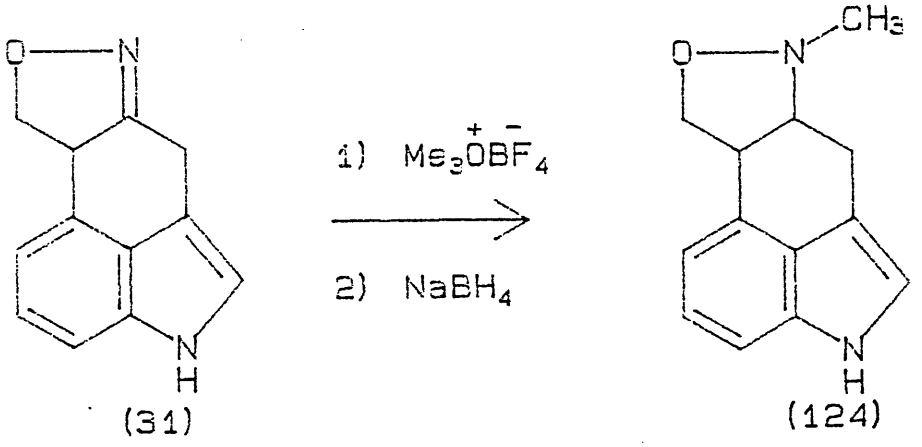
(31) (123)

Hydrogenation of this mixture over platinum oxide, gave a single product on a TLC plate, running in the same place as one of the original spots. The second spot had disappeared without the appearence

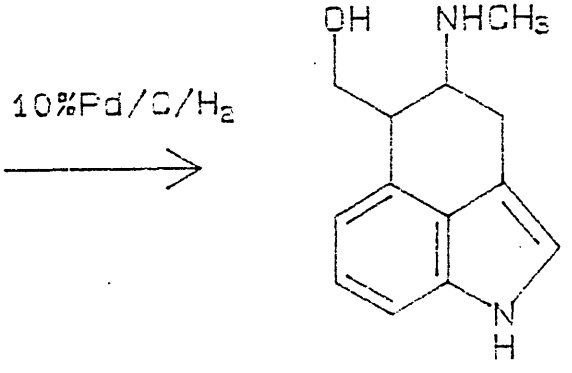
of a new product spot, which was expected nearer to the base line than either of the two original spots. The remaining spot was isolated, and found to be the N,N-diphenyl urea (a carbonyl peak was seen in the infra red spectrum, which corresponded to an aromatic amide, 1650cm^{-1}).

From the literature, the isoxazoline (31), synthesised by Kozkowski was not reduced to the β-amino alcohol (123), but was first alkylated at the nitrogen with Meerweins salt [59,88], followed by reduction of the resulting salt with sodium borohydride. The N-O bond was thencleaved by hydrogenation over 10% palladium on carbon, to give the amino alcohol (125), (scheme 55).

Scheme 55.

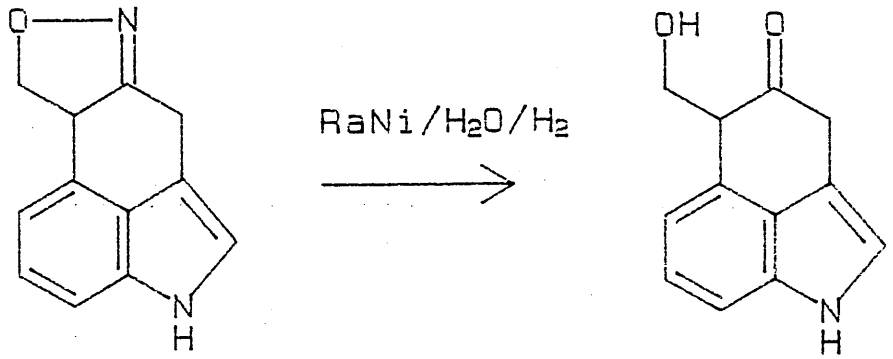


(31) (124)



(125)

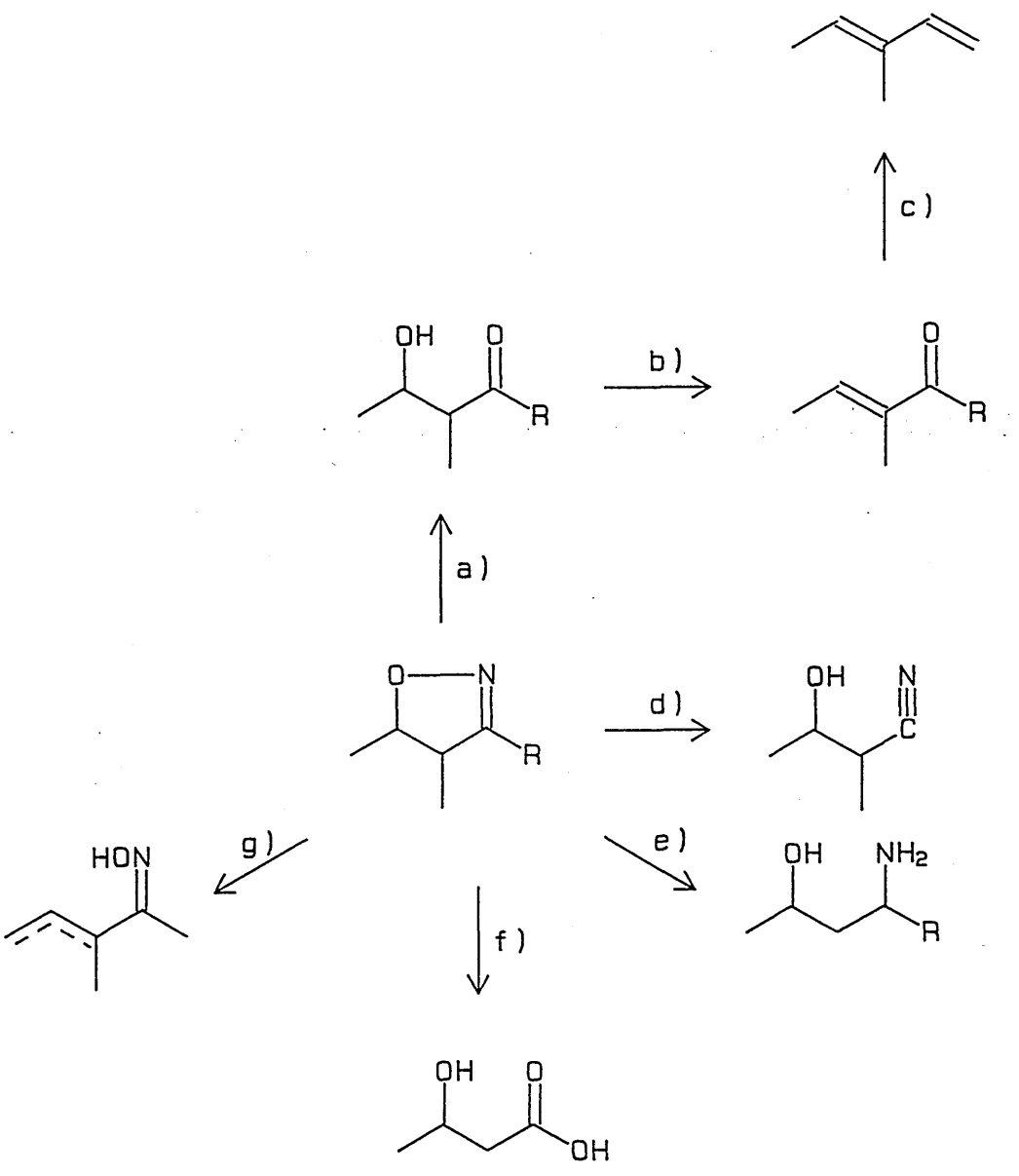
If the catalyst in the hydrogenation of the isoxazoline is changed to Raney nickel, the product obtained is the hydroxy ketone.



(31) (126)

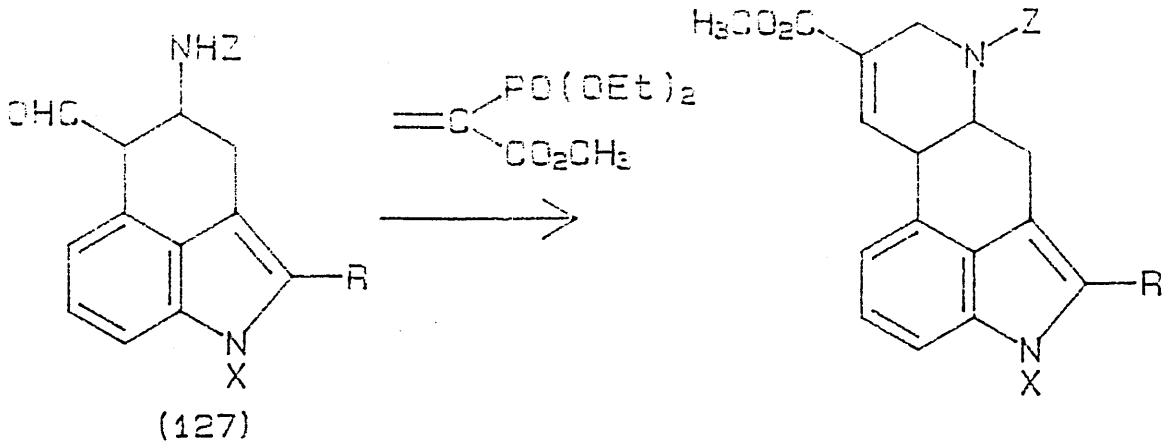
If palladium or carbon is used to directly reduce the isoxazoline, then variable mixtures of the hydroxy ketone and the β-amino alcohol are obtained. The platinum oxide method used by us was based on the work of Curran[71] who reduced a number of isoxazolines which resulted in a variety of compounds, depending on the catalyst used in the reduction step. Isoxazolines are versatile compounds in that they can lead directly (or indirectly) to a wide variety of compounds[90,92,94,95]. as shown below.

a) $RaNi/H_2$
b) p-TSA/benzene
c) (i) $H_2NNHTOS/MeOH$
   (ii) MeLi
d) OH^- : H^+/reflux
e) PtO_2/H_2
f) (i) $RaNi/H_2/AlCl_3$
   (ii) H_5IO_6
g) LDA/THF/-78° c



3.5.2 INVESTIGATION OF THE SYNTHESIS OF THE D RING OF THE ERGOT ALKALOIDS.

The original proposal for this project involved the synthesis of the ergot D ring by a novel vinyl phosphonate ester cyclisation:-



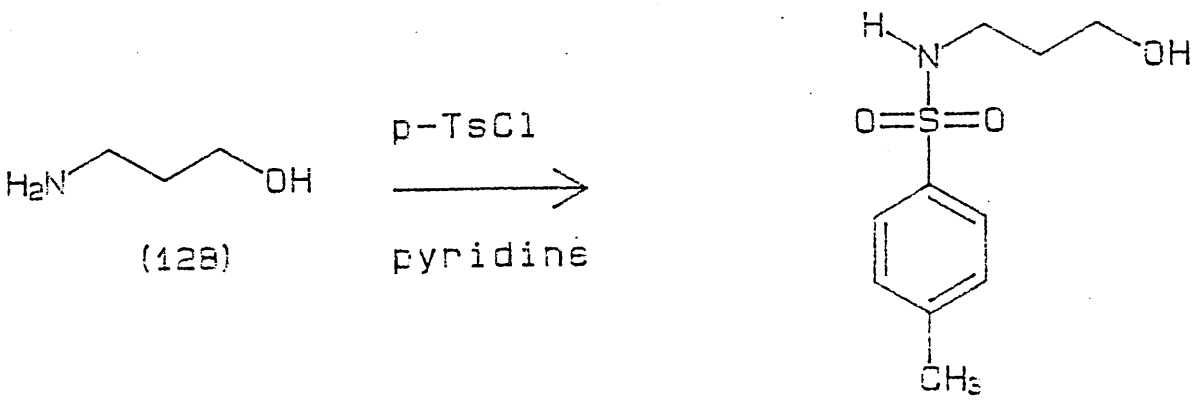
(127)

R = H or SCH_3 or SO_2CH_3
X = TOS or H
Z = CO_2CH_3 or CHO or CH_3

The aminoaldehyde derivative (127) would be obtained either from our own novel synthesis (chapter 2) of the indole ring system, or from the Batcho-Leimgruber synthesis followed by the INOC route.

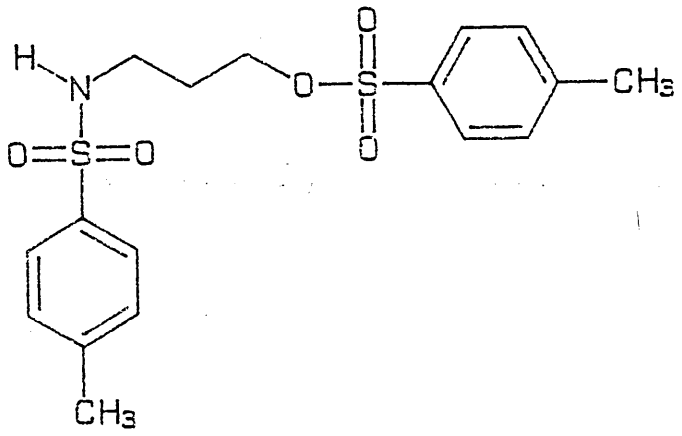
In order to develop suitable conditions for this cyclisation (of the D ring), a number of model reactions were tried. The compound used for this was the readily available aldehyde derivative from 3-amino propanol (128). Before oxidation to the aldehyde, the amino group was protected. The tosyl derivative (129) was the first product to be made, isolated in 57% yield. A second compound, isolated in 14% yield, was shown to be the ditosylated compound (130), (scheme 56).

Scheme 56.



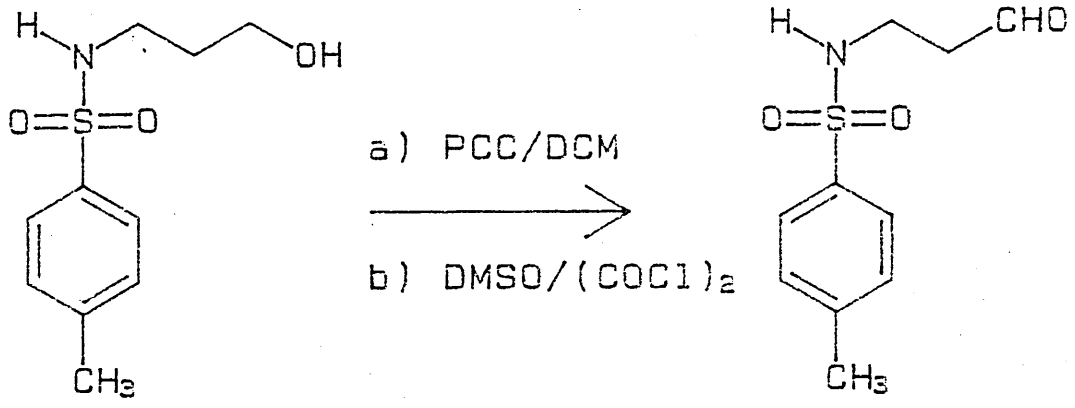
(128) (129)

+



(130)

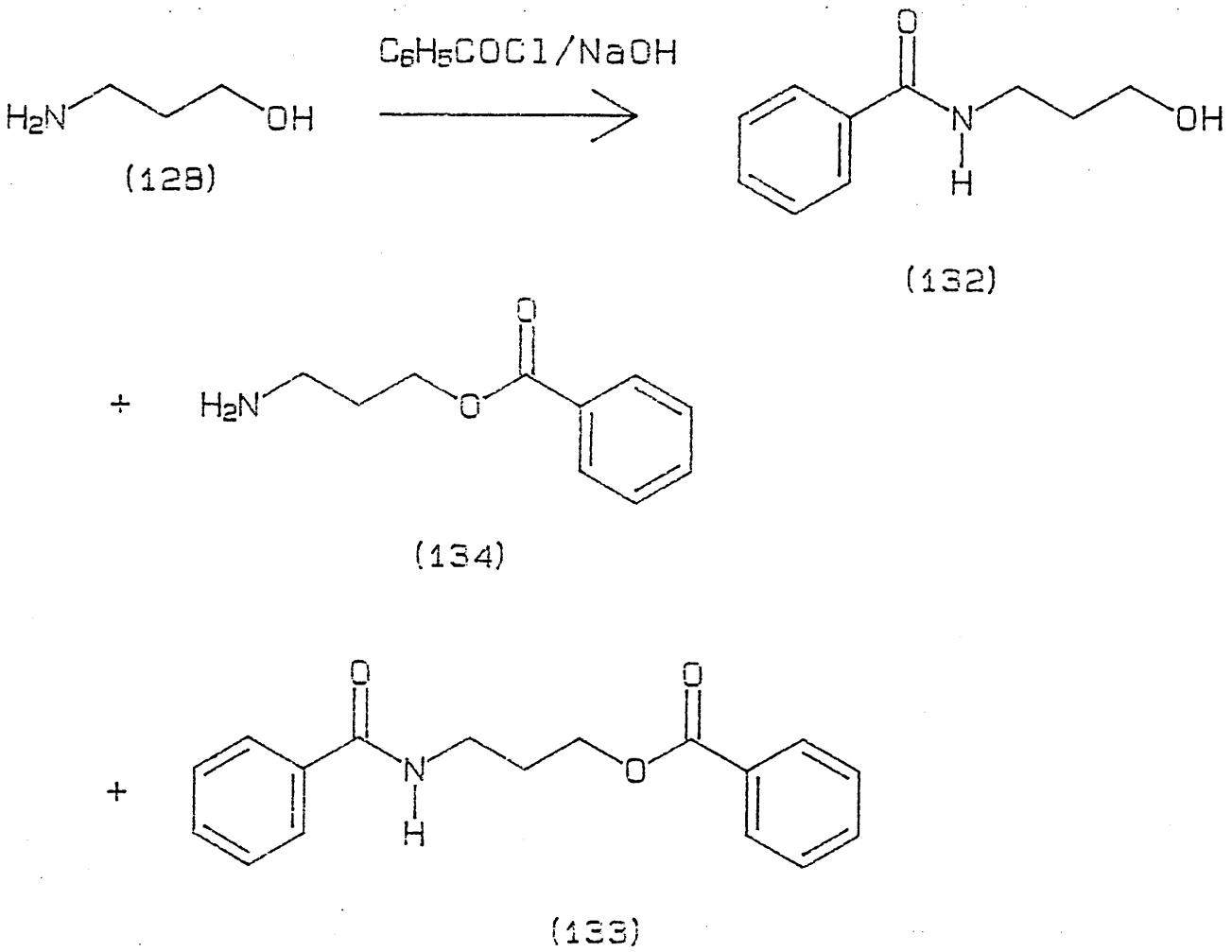
Compound (129) was oxidised to the aldehyde (131), using pyridinium chlorochromate, in approximately 25% yield. An improvement in the yield of the aldehyde (131) was obtained by a Swern oxidation[85], using DMSO/oxalyl chloride as the oxidant:



(129) (131)

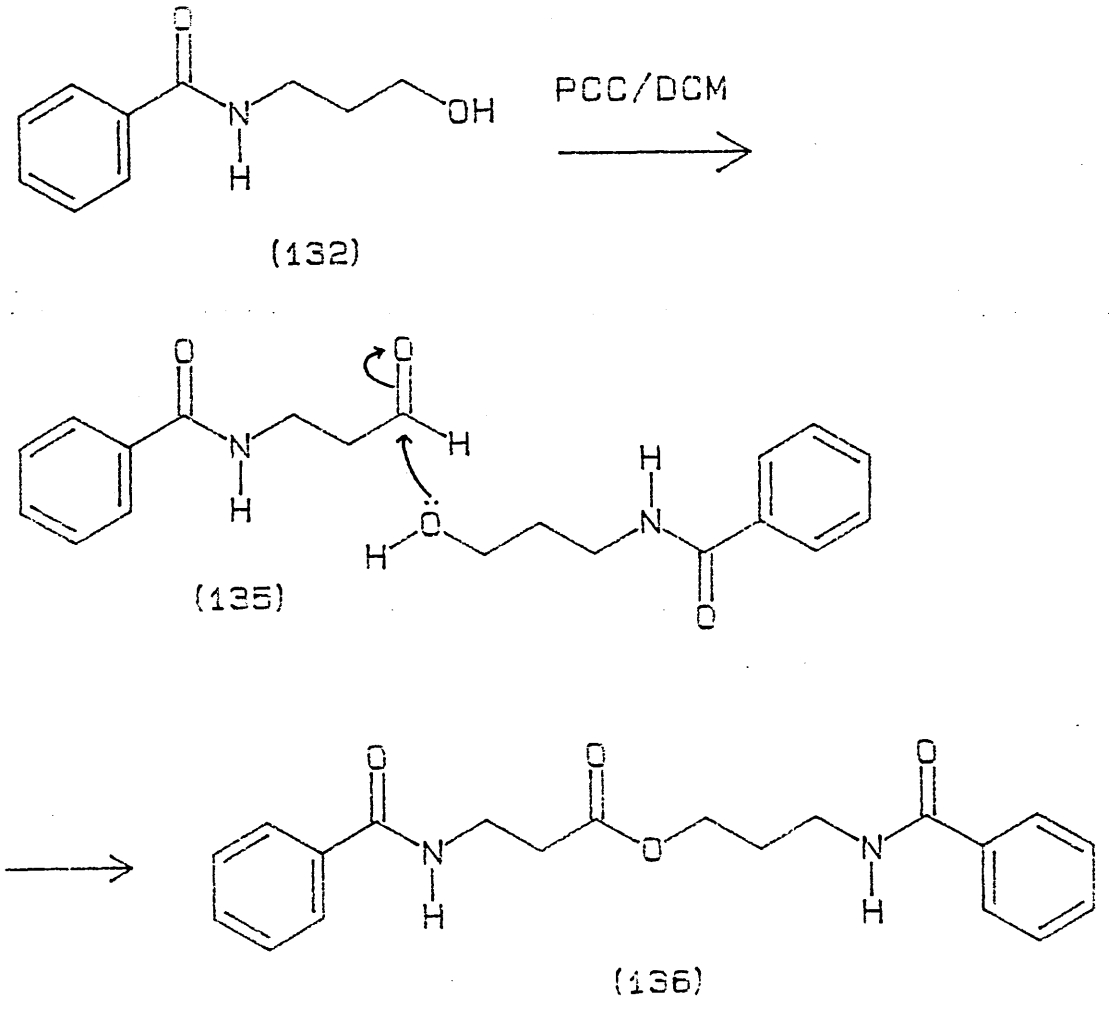
The amine (128) was also protected as the benzoyl derivative (132), but again some dibenzoylated product (133) was also isolated in low yield (3.2%), together with some of the product, monobenzoylated at oxygen (134) (2.7%), (scheme 57).

Scheme 57.



Oxidation of the alcohol (132) with PCC resulted in a very low yield (7.25%) of a single white crystalline solid. NMR showed this not to be the expected aldehyde (135), but the ester (136), formed as shown in scheme 58.

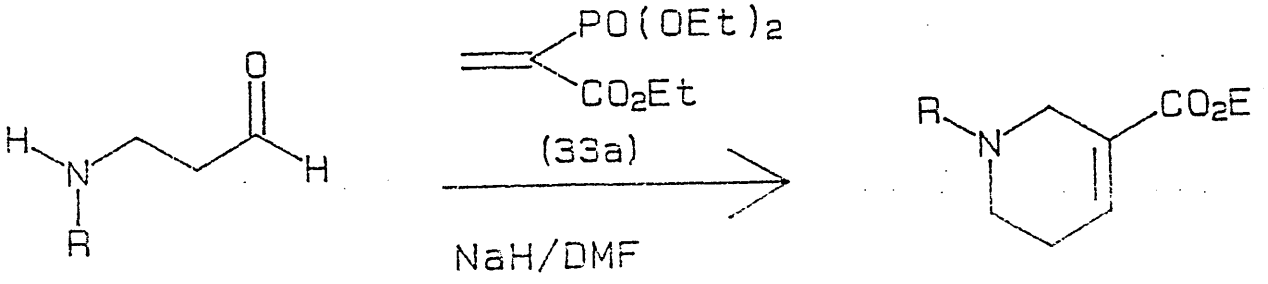
Scheme 58.



The aldehyde (135) was successfully synthesised, by using the Swern method, in 35% yield. The next step was to produce a cyclic tetrahydropyridine derivative (137) or (138) by reaction of the appropriate aldehyde with a vinylphosphonate ester (33a)[86]. The vinylphosphonate ester was made by a fellow research student using the method of Semmelhack et al[91]. The aldehyde was added to a suspension of sodium hydride in DMF, followed after a short time by the vinylphosphonate ester[86]. Cyclisation should have taken place, according to scheme 59, but on work up, base line material was found

in both cases, (tosyl or benzoyl).

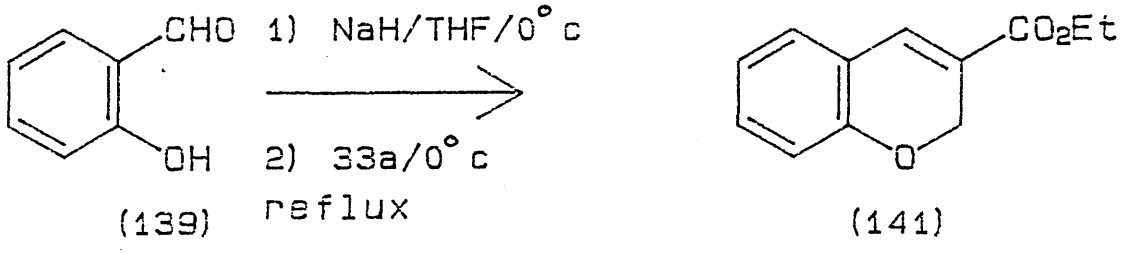
Scheme 59.



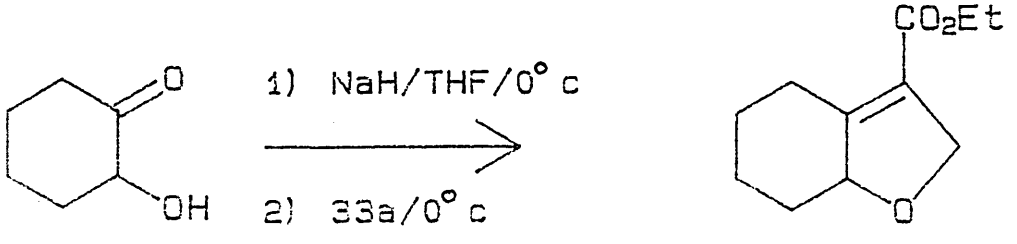
(129) R = Tosyl
(132) R = Benzoyl

(137) R = Tosyl
(138) R = Benzoyl

The phosphonate ester (33a) has been used in related cyclisations by Kleschick and Heathcock[86]. Both o-hydroxybenzaldehyde (139) and 2-hydroxycyclohexanone (140) gave good yields of cyclic products with 33a:

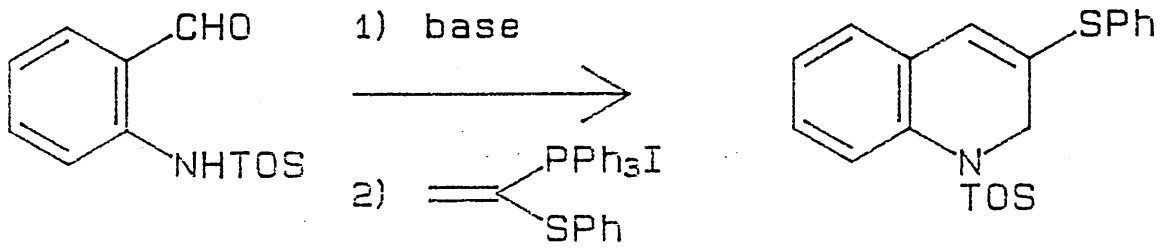


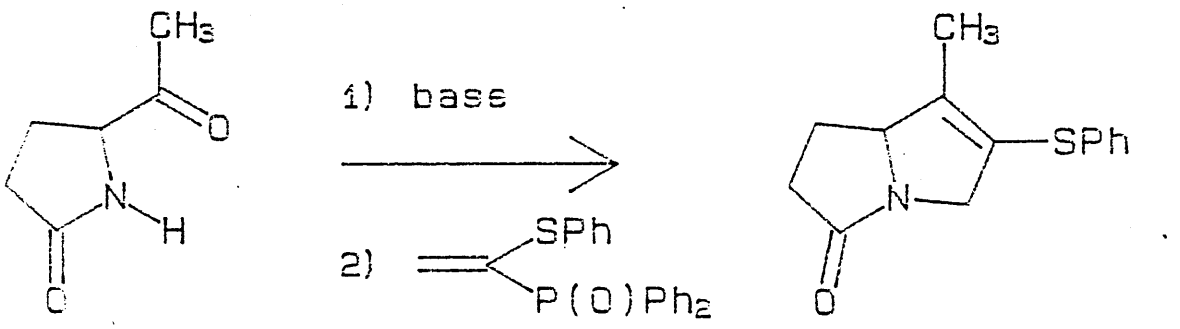
(139) (141)



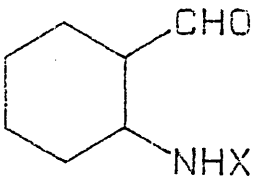
(140) (142)

In our case it is obvious that the nucleophilic atom is nitrogen rather than oxygen, but other work in this department has shown related reactions using nitrogen nucleophiles to be successful[87,93].





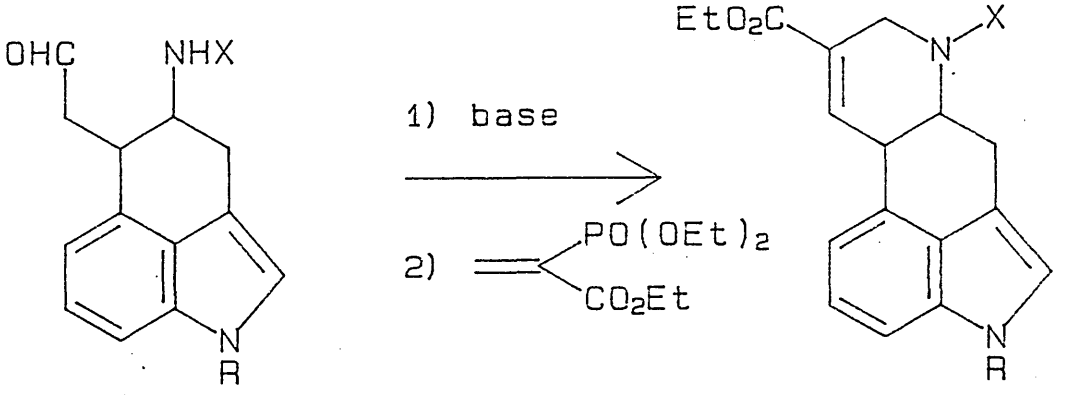
The other difference between the cyclisations using (129) and (132), and those shown in the above equations, lies in the flexibility of any intermediate anion in the process. The relatively flexible open chain structure, compared with the relatively rigid ring systems could be making cyclisation to the tetrahydropyridines too unfavourable. With hindsight, a better model system might have been the cyclohexyl amino aldehyde derivative (143).



X = Tosyl or Benzoyl

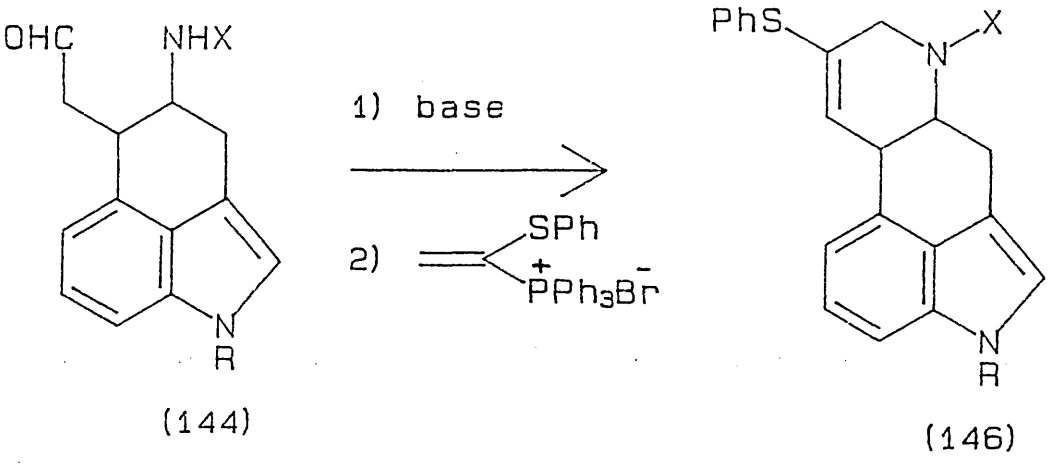
(143)

From the model reactions carried out on the 3-aminopropanol derivatives, the cyclisation failed. This does not however conclusively suggest that the phosphonate route would fail with the tricyclic compound, this next step is shown below.

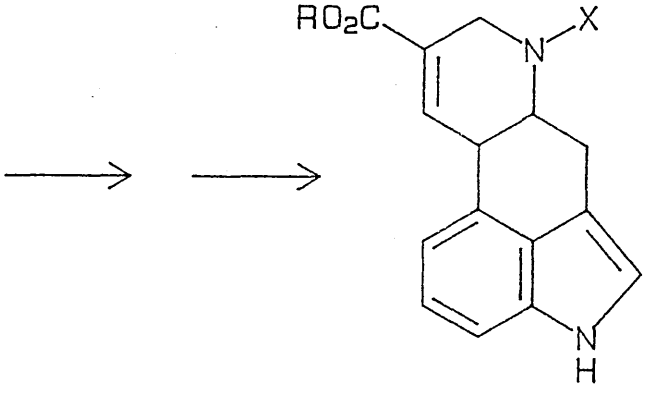


(144) X = Tosyl or Benzoyl (145)

However if this did fail, then the cyclisation could be tried with a vinyl phosphonium salt, which would lead to the tetracyclic with a -SPh group (or similar), where the ester group is normally found. This could then be converted to the ergot in a few steps.



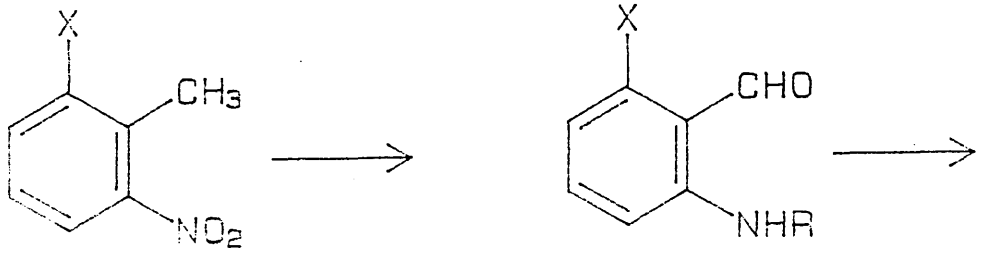
(144) (146)

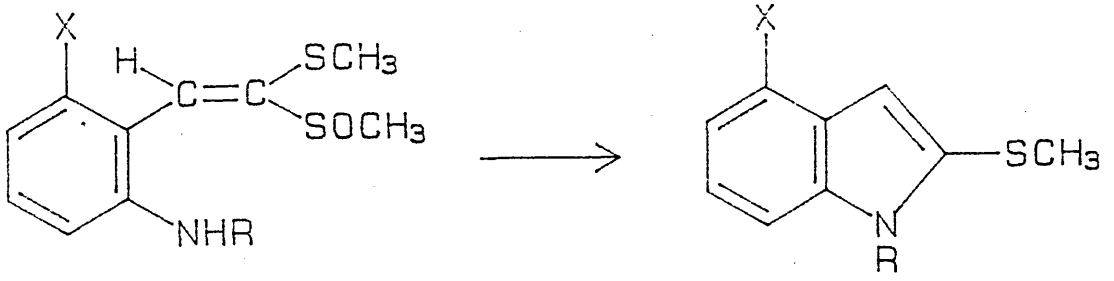


(147)

3.6 NOVEL SYNTHESIS OF A 4-SUBSTITUTED INDOLE.

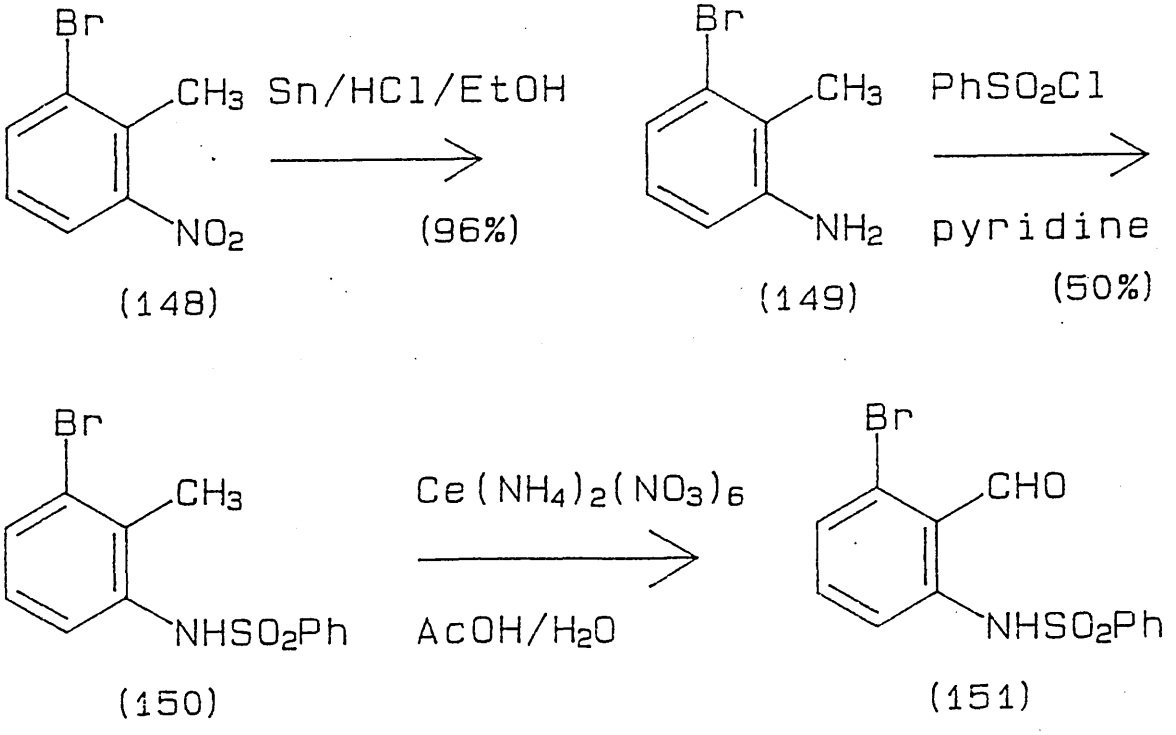
The novel indole synthesis discussed in chapter 2, was developed so that it could be used for the synthesis of a 4-substituted indole. When put down on paper the suggested route to a 4-substituted indole looked quite straight forward. The proposed route is shown below:



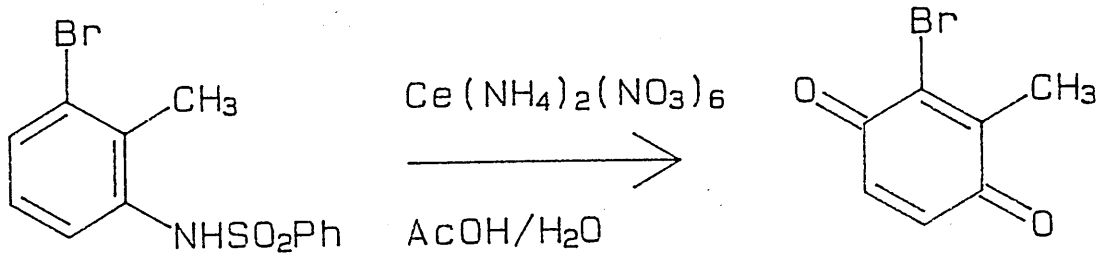


However when put into practice a number of difficulties were encountered at various stages in the synthesis. The chosen starting material was 2-bromo-6-nitrotoluene (148), and the key target molecule was the sulphonamide (151). The simplest proposed route comprised of three steps, (scheme 60).

Scheme 60.



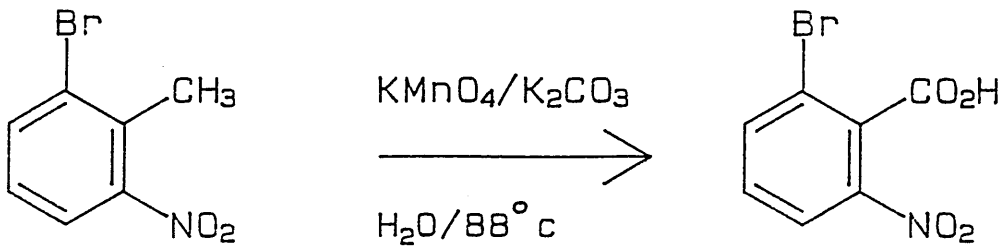
The final step (oxidation of methyl to formyl) did not occur as anticipated, although a good precedent for such a reaction taking place was available in the literature[72]. A number of toluenes had been oxidised to the corresponding aldehydes in good yields, the closest analogy to our case being o-acetamidotoluene, whose oxidation was reported to occur in over 90% yield. The product which was isolated in our case was found to be a p-benzoquinone (152), (see later for discussion of this).



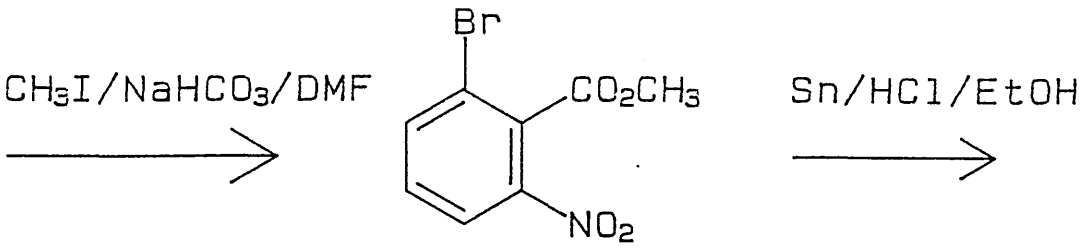
(150) (152)

We therefore decided to oxidise the methyl group to an aldehyde or equivalent group, prior to reduction of the nitro group. Two options were now open, the first was to synthesise the benzoic acid (153) and ester (154), and then reduce the nitro compound to the amine (155), (scheme 61).

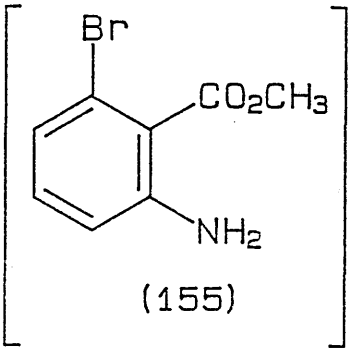
Scheme 61.



(148) (40% small scale) (28% large scale) (153)



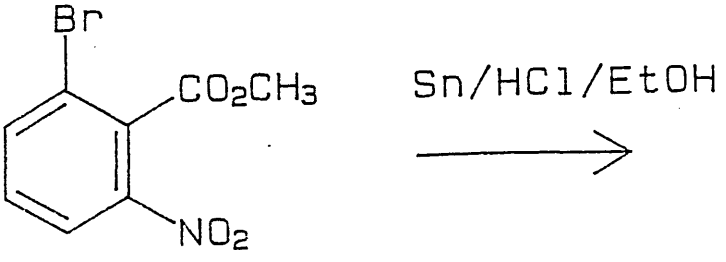
(154)



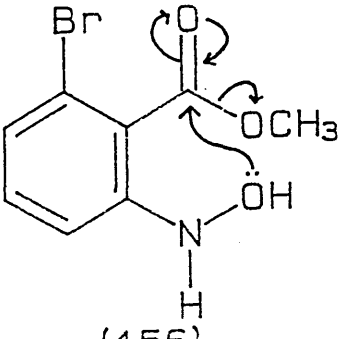
(155)

Difficulties arose in the final step, in this scheme. Instead of complete reduction to the amine (155) taking place, the reduction stopped at the hydroxamic acid (156), which then cyclised to give 4-bromo-2,1-benzisoxazol-3(1H)-one (157), (scheme 62).

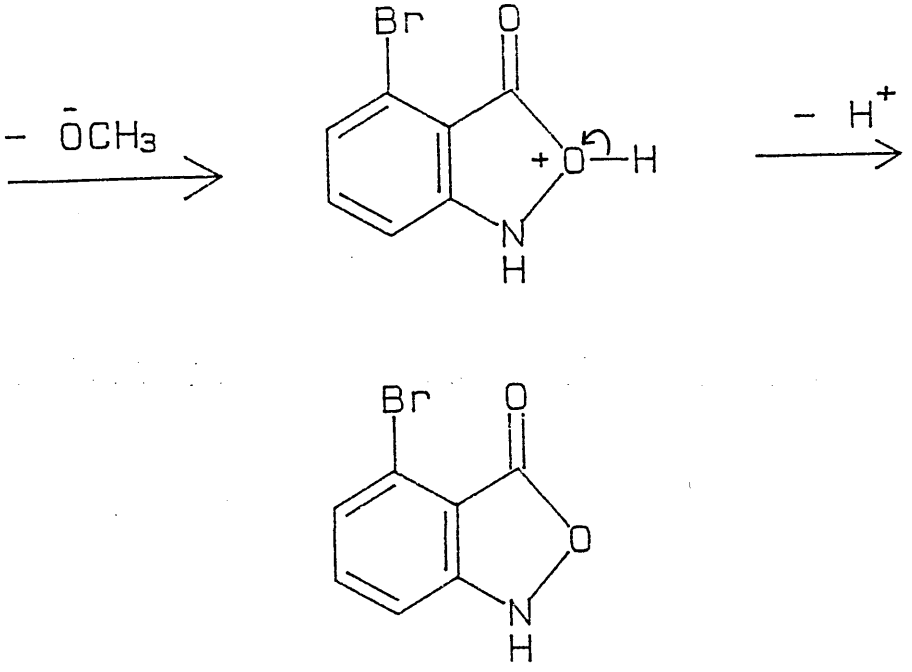
Scheme 62.



(154)

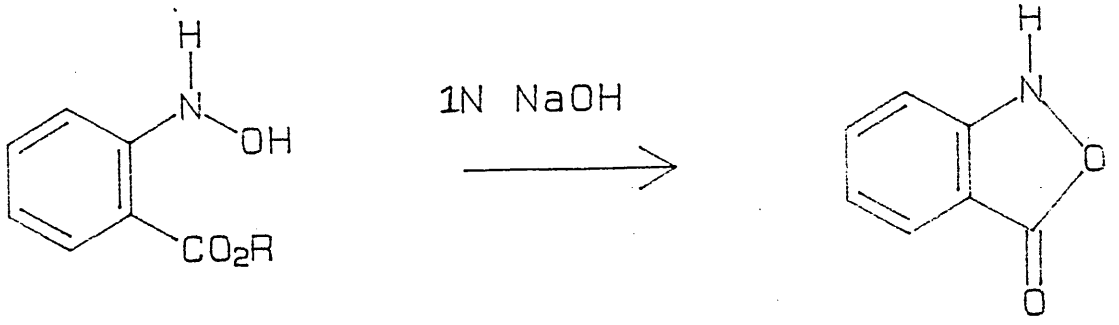


(156)

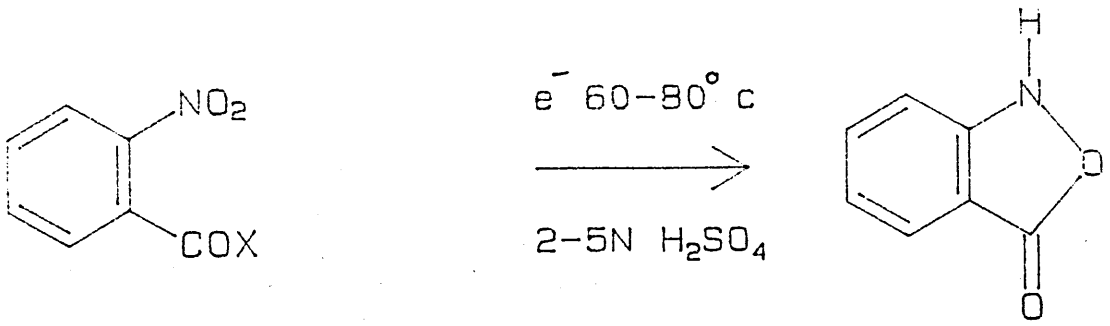


(157)

This type of reaction is known, and has been effected by treatment of a hydroxamic acid with sodium hydroxide at room temperature[73]. A similar reaction was proposed by Le Guyader et al[74], in acidic solution, but no structural evidence was available.



R = $-CH_3$ or $-C_2H_5$

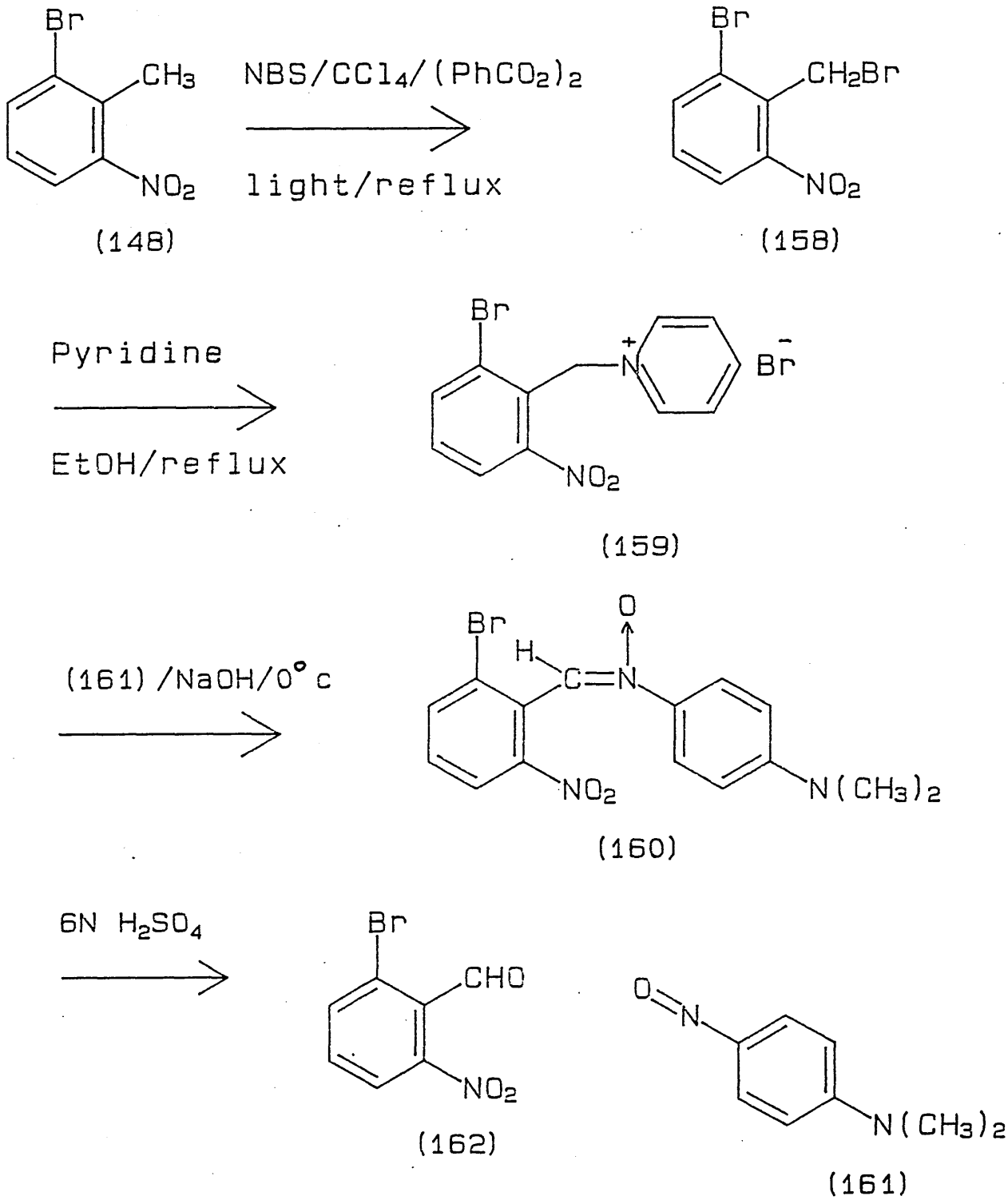


X = OH, OEt, NH_2

Note in this second example that the reaction is an electrochemical reduction of the nitro group. NMR data for this type of reaction was obtained by Cohen and Gray[75], which agreed with the NMR data we obtained for compound (157).

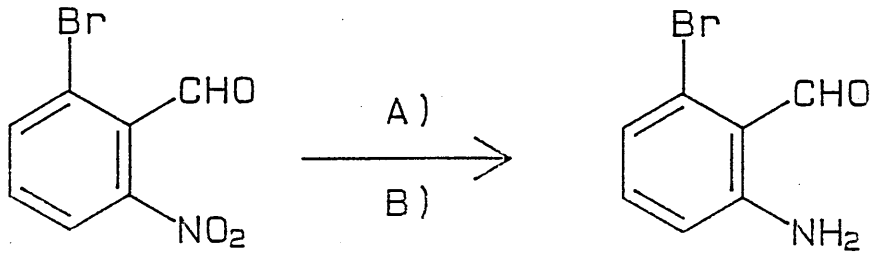
The alternative route involved methyl group oxidation by the Khronke method[76], which gave the nitrobenzaldehyde (162) in good, overall, reproducible yields. The method involved bromination of the bromonitrotoluene (148), with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride, in the presence of benzoyl peroxide and a bright light. The benzyl bromide (158) was converted to its pyridinium salt (159), and then the nitrone (160), using p-nitroso-N,N-dimethylaniline (161) in basic solution. Treatment of the nitrone with 6N sulphuric acid gave the required nitrobenzaldehyde (162) in high yield and purity, (scheme 63).

Scheme 63.


Br
CH3
NO2
NBS/CCl4/(PhCO2)2
light/reflux
Br
CH2Br
NO2
(148)
(158)
Pyridine
EtOH/reflux
Br
N+
Br-
NO2
(159)
(161) /NaOH/0° c
Br
H
C=N
O
NO2
N(CH3)2
(160)
6N H2SO4
Br
CHO
NO2
(162)
O=N
N(CH3)2
(161)

An attempt at preparing the aminobenzaldehyde (163), was made using ferrous sulphate and ammonia[77], to reduce the nitro group to the amine, followed by steam distillation, but only a 30% yield of product was isolated. Similarly reduction was attempted by using sodium dithionite and potassium carbonate as the reducing agent, but only a 15% yield was isolated in this case, (scheme 64).

Scheme 64.



(162) (163)

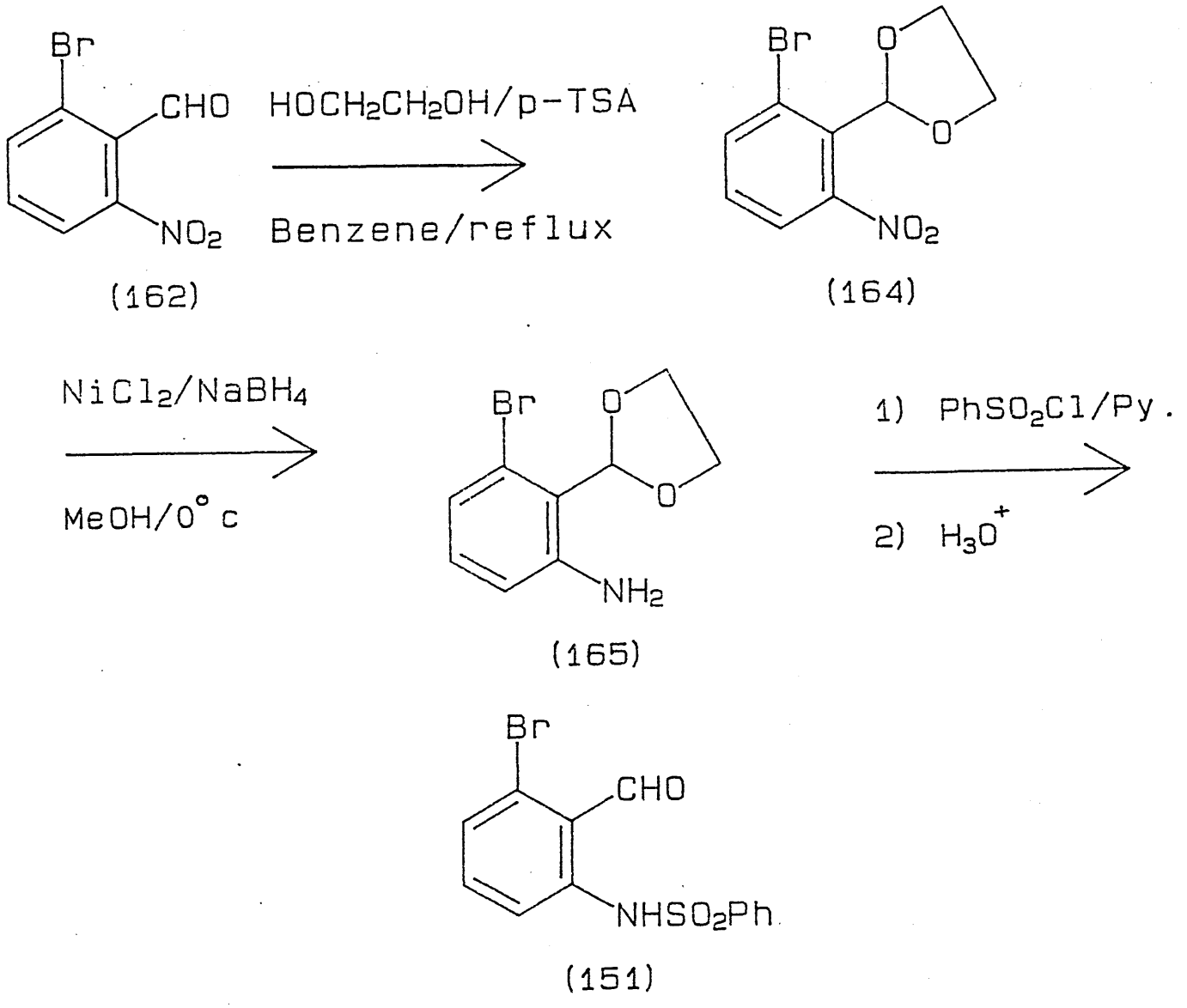
A) $FeSO_4/NH_4OH/H_2O/90^\circ c$

B) $Na_2S_2O_3/K_2CO_3/H_2O/25^\circ c$

When this aminobenzaldehyde was treated with benzenesulphonyl chloride on pyridine, it gave a product, which when investigated by NMR and IR lacked a free aldehyde. The NMR showed the aromatic peaks, which when the actual compound was made, were different from it. An acceptable conversion of the nitro compound (162), to the sulphonamide (151), was finally achieved by protection of the aldehyde group, as the dioxolane (164). Reduction of this with nickel chloride and sodium borohydride[78] gave the amine (165) in 50 - 60% yield. Although the reaction produced a number of spots on a TLC plate, a satisfactory

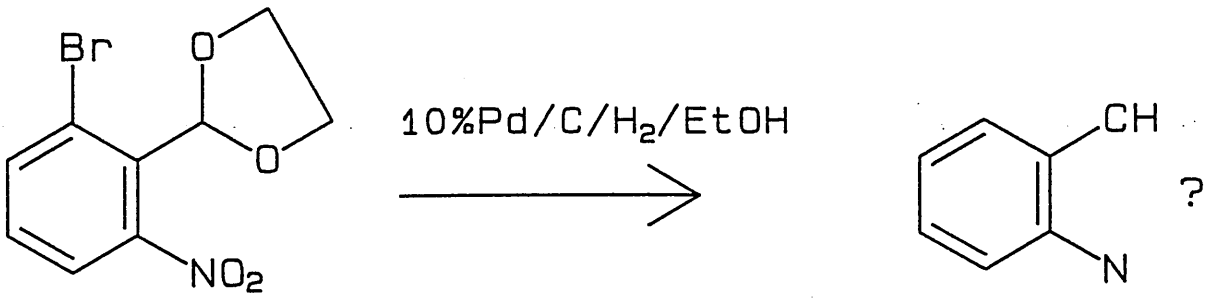
separation was achieved. The amine (165) was then treated with benzenesulphonyl chloride in pyridine to give, after acidic work up, the desired sulphonamide, (151), (scheme 65).

Scheme 65.



Other methods of affecting the reduction of (164) to (165) were briefly looked at to try to improve the yield. The first was an

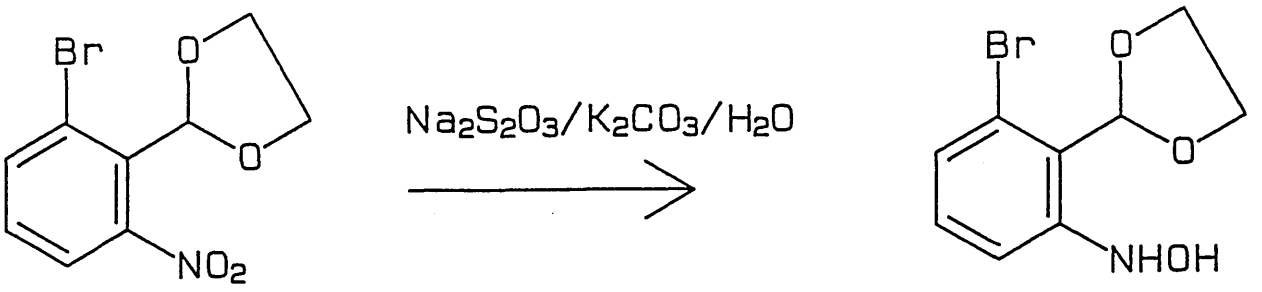
attempt at catalytic hydrogenation using 10% palladium on carbon. The product obtained however, showed removal of the bromine from the benzene ring and removal of the acetal protection. The product was not characterised because of this and was not investigated further.



(164)

The second method of reduction looked at was to use anhydrous stannous chloride in ethanol[79]. This method was supposed to be non acidic, but the solution produced by the stannous chloride and ethanol turned universal indicator paper red, indicating that the medium was in fact acidic. The product obtained from the reaction was the nitroaldehyde (162), shown by comparison with an authentic sample, by TLC.

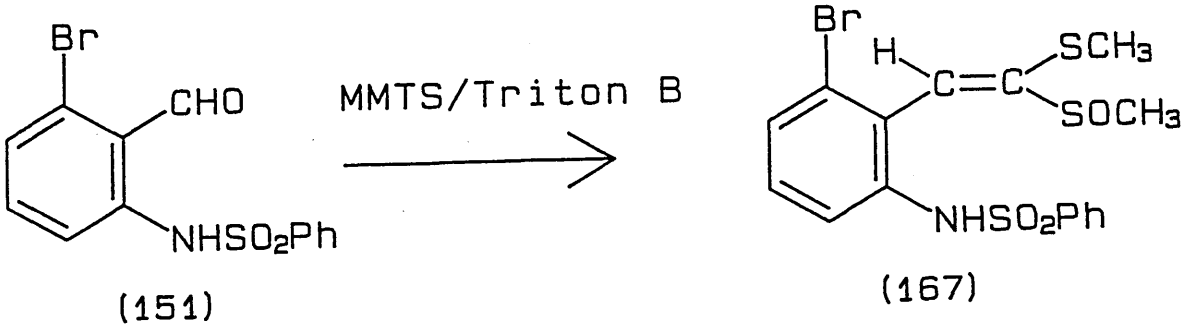
The third method tried, was to use sodium dithionite, in potassium carbonate, to keep the reaction basic. The product obtained was not the required amino acetal (165), but the NMR and IR suggested the hydroxylamine (166).



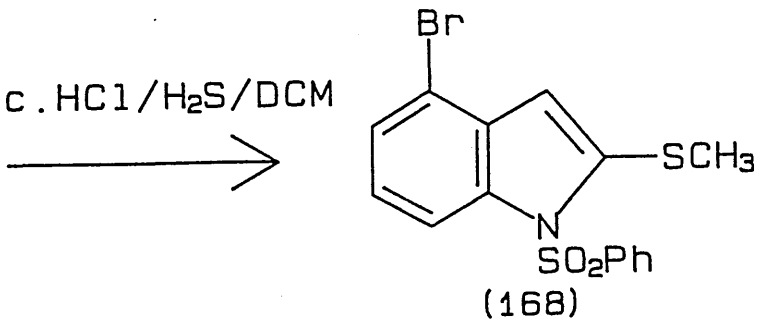
(164) (166)

From the nickel boride reduction, enough of the protected aminoaldehyde (165) was available to carry out further reactions. Treatment of compound (165) with MMTS and Triton B resulted in the preparation of the ketenethioacetal monosulphoxide (151), in 60% yield. This was then added to dichloromethane, saturated with hydrogen sulphide gas, and a suspension formed. To this was added conc. hydrochloric acid, and within one hour, the suspension had dissolved, and no starting material was left. The product isolated was the 4-bromoindole (168) in 75% yield, (scheme 66).

Scheme 66.

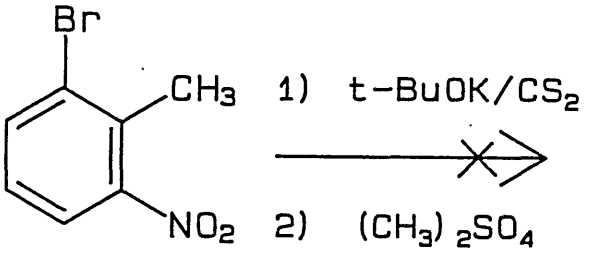


(151) (167)

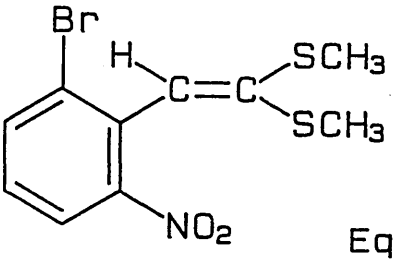


(168)

Two minor attempts at improving the above synthetic route were made, in the hope that the method could be made shorter. The first was to try to make the ketenedithioacetal (169) before manipulating the nitro group, which would be easier to convert to the sulphonamide, resulting in a shorter synthesis, (equation 6).



(148)

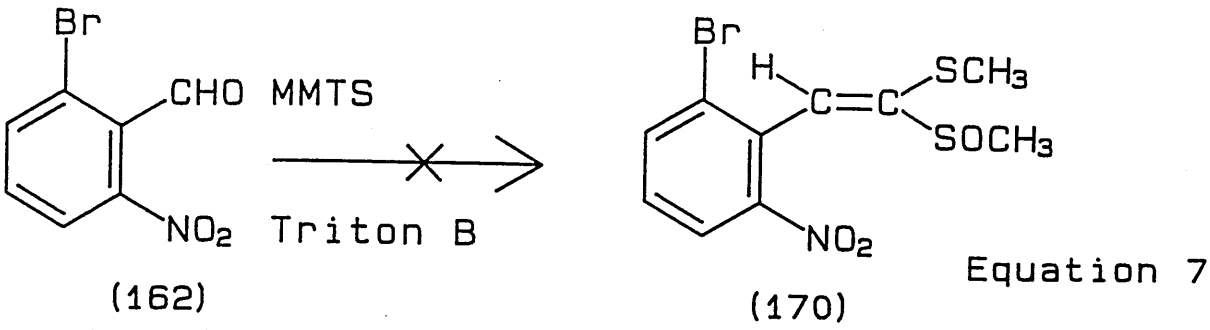


(169)

Equation 6

The first step of this reaction produced a black solution, which when investigated by TLC showed that the starting material had disappeared, and a large number of spots had appeared. Therefore the second step was not attempted.

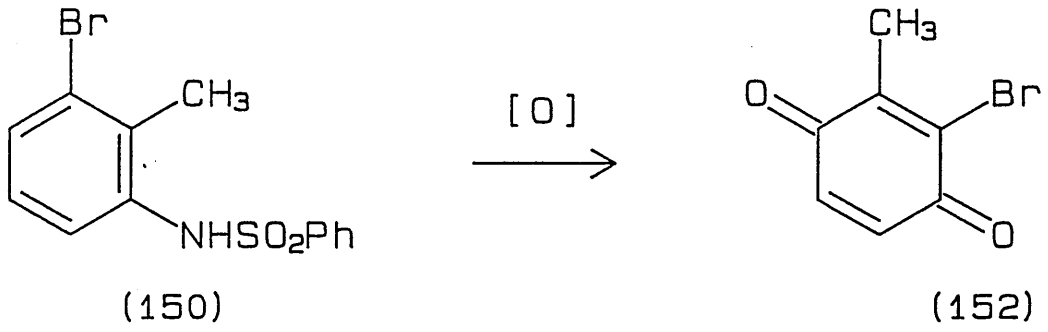
A second method of trying to improve the route, was to make the ketenethioacetal monosulphoxide (170) with the nitro group still present, (equation 7).



Equation 7

However after 3 days at reflux, the only product present was unchanged starting material. Thus, unfortunately, because of the various difficulties in obtaining an appropriately substituted o-aminobenzaldehyde derivative, our indole synthesis has not so far been developed for an efficient route to 4-substituted indoles.

3.7 SYNTHESIS OF P-QUINONES.

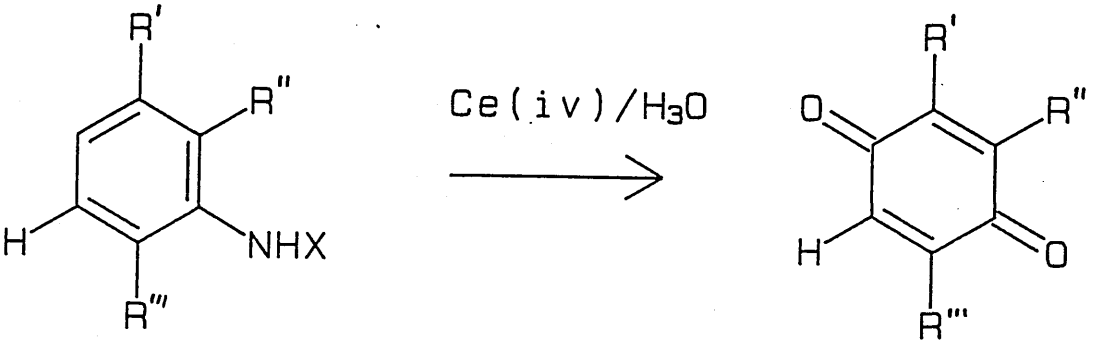


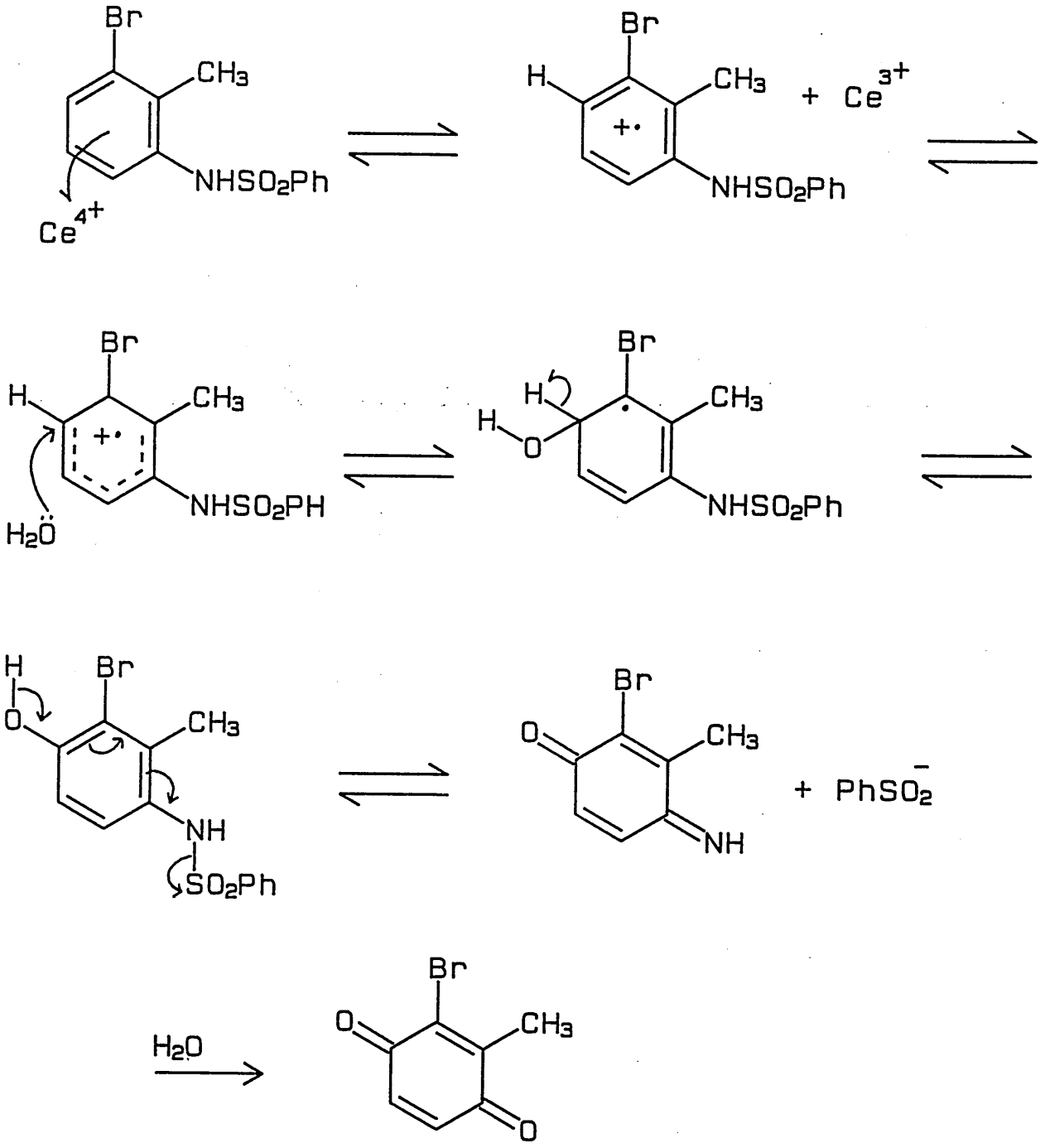
This reaction, as mentioned above, was discovered when the conditions of Syper[72], were used in an attempt to oxidise (150) to the aldehyde (151). Under the conditions of Syper, cerium (IV) in acid, oxidation of the benzene ring instead of the alkyl side chain took place. Cerium (IV) is a powerful oxidising agent, and is capable of

oxidising benzyl alcohols to the corresponding aldehydes[82]. Cerium (IV) is also of interest, in that it is capable of effecting only one electron transfer, (unlike others which transfer two electrons). Syper claims to have accomplished the oxidation of a number of toluenes in various acidic conditions. The reagent was said not to affect other groups in the benzene ring. From the results obtained by Syper, we concluded that our compound (151) was a good candidate for the reaction. The compounds that Syper oxidised, which were comparable to ours, were ortho-chlorotoluene (74%) and ortho-acetamidotoluene (93%). (We have recently attempted, several times, to prepare the benzaldehyde derived from ortho-acetamidotoluene, but have failed to isolate any of the desired product.)

When we carried out the oxidation of our compound (151) using 90% acetic acid (even at elevated temperatures), no oxidation of the methyl group took place. The compound isolated was assigned structure (152), after careful study of its spectral data. The possibility that the compound was an ortho quinone, was rejected on the basis of its infra red spectrum. This showed a single carbonyl stretching frequency, if it had been an ortho quinone, two peaks would have been observed. The compound was found to be identical to that synthesised by Inoue, in five steps from 2-amino-3-nitro-toluene[83].

The proposed mechanism for the oxidation is outlined below :-



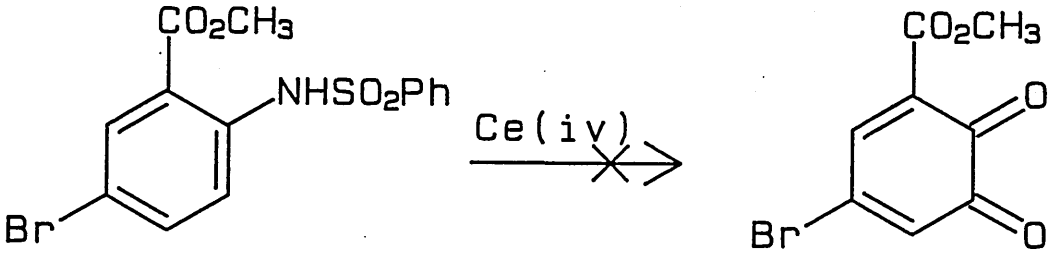


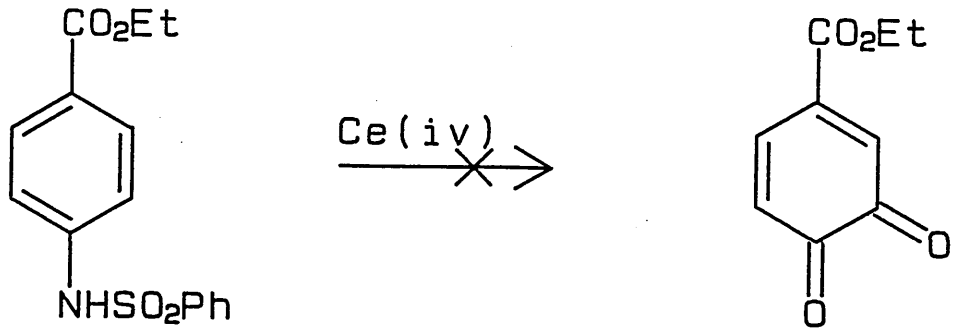
An investigation into this method was carried out to see if it was general for the synthesis of p-benzoquinones. The reaction was carried out by oxidising a range of sulphonamides in acetic acid, although one attempt was made using 2N sulphuric acid as solvent. The reaction produced only low to moderate yields of quinones but this was

not optimised. Tabulated below are the results for the synthesis of the p-quinones which were investigated.

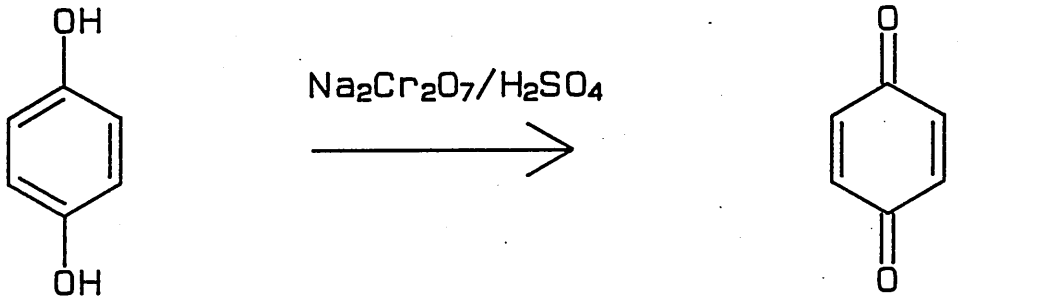
R'	R''	R'''	X	Acid	Quinone	yield(%)
Br	CH_3	H	SO_2Ph	HOAc	(128)	30
CO_2CH_3	CH_3	H	TOS	HOAc	(147)	29
H	H	H	TOS	HOAc	(148)	49
H	Cl	H	TOS	HOAc	(149)	18
CH_3	CH_3	H	SO_2Ph	HOAc	(150)	41
H	Cl	Cl	SO_2Ph	HOAC	(151)	34
H	H	H	TOS	H_2SO_4	(148)	-
OCH_3	H	H	SO_2Ph	HOAc	(152)	-
H	OCH_3	H	SO_2Ph	HOAc	(152)	-

The failure of the bottom two entries in the table was probably due to the methoxy group being electron donating. This therefore makes the benzene ring electron rich, thus allowing for easy reaction with the oxidant, which effectively is electron deficient. The result of this is probably to over oxidise and thus break down the benzene ring, resulting in no product. The reaction was carried out on two sulphonamides which when oxidised by cerium (IV), might have given ortho quinones, e.g.

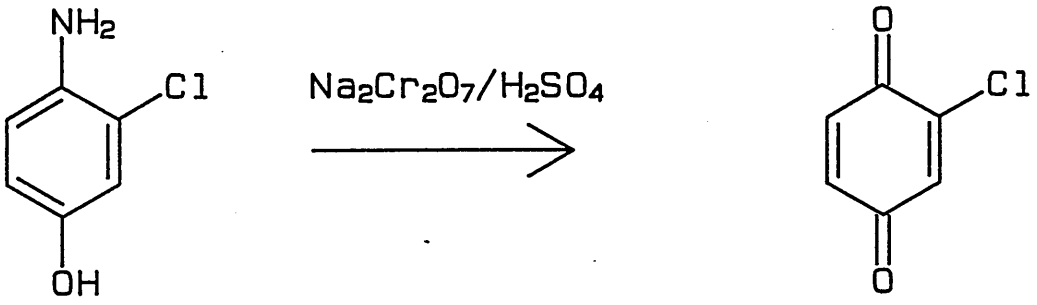


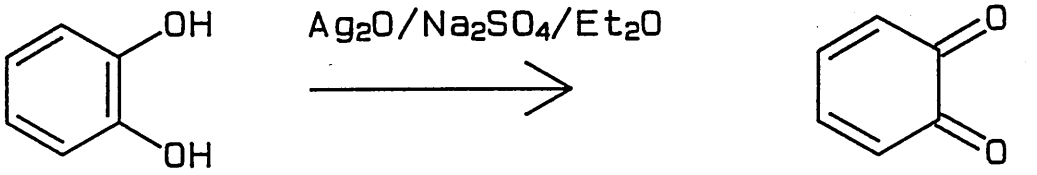


TLC analysis showed that no quinones were produced, and NMR (of the crude sample) indicated that no olefinic peaks were present in the expected regions of the spectrum. Therefore the reaction does not seem to produce ortho quinones. Most quinones are synthesised by oxidation of the corresponding anilines or phenols. However using a sulphonamide eliminates the problem of using neat anilines, which are potentially quite hazardous. Quinones are synthesised by use of a number of different reagents, as shown below :

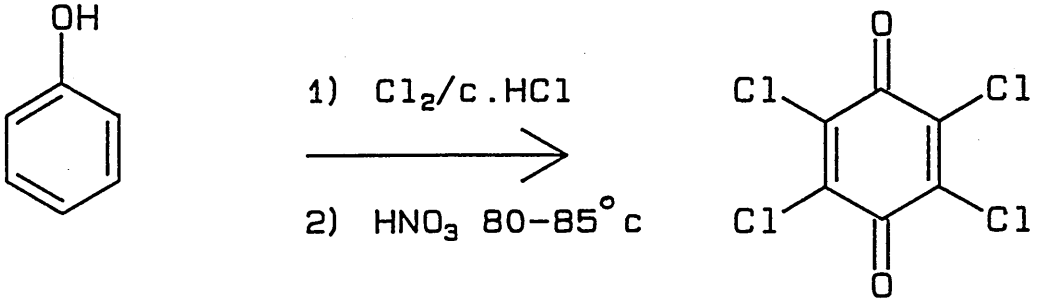


hydroquinone





catechol



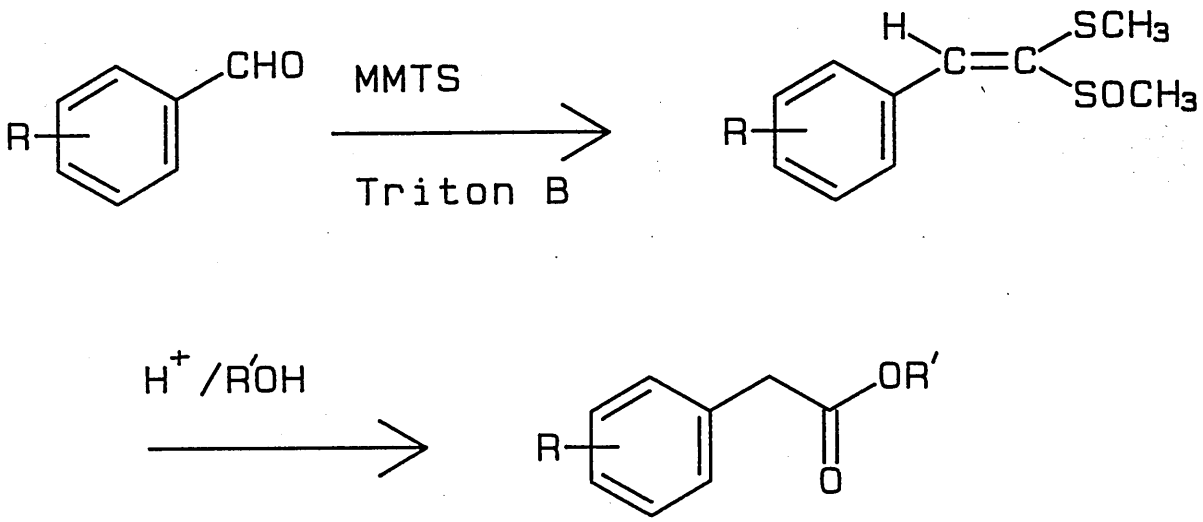
chloranil

CHAPTER 4

4.1 SYNTHESIS OF AROMATIC THIOLESTERS.

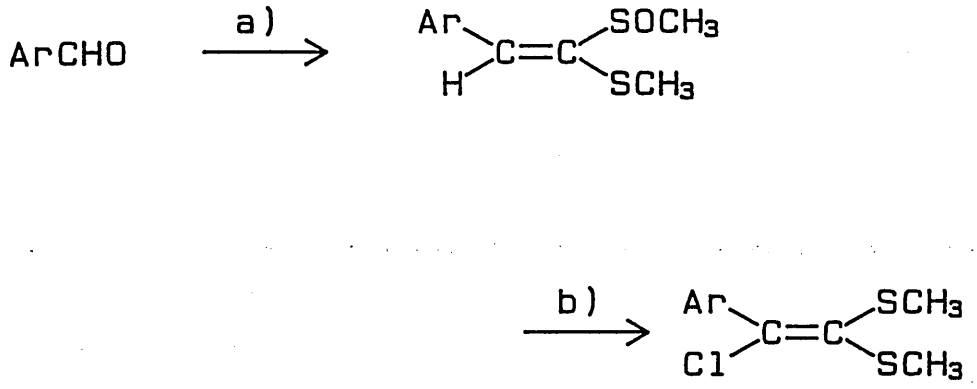
The basis of our own indole synthesis, involving the ketenethioacetal monosulphoxide intermediate, was the work done by Ogura and co-workers[23]. They synthesised phenyl acetic acid derivatives from benzaldehydes and MMTS, (scheme 67).

Scheme 67.

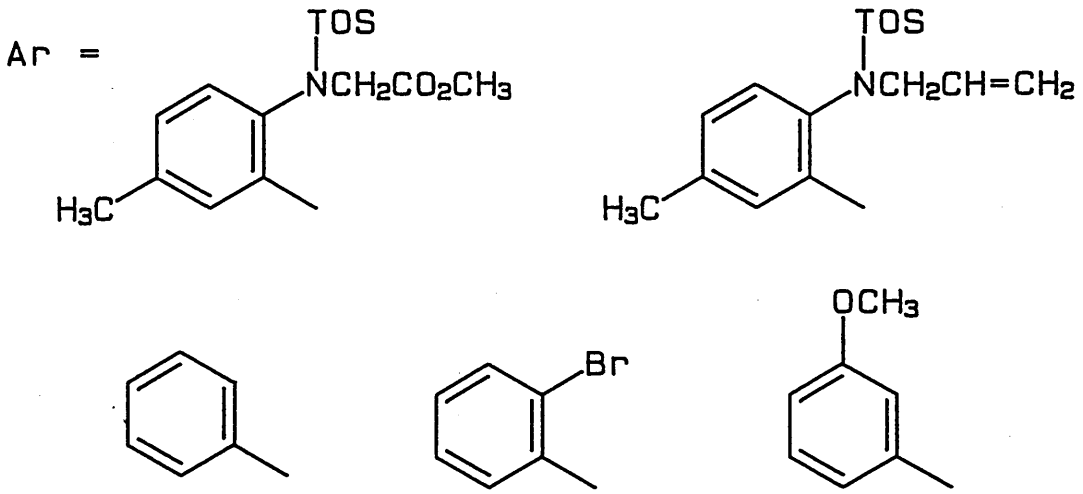


When this work was repeated by a previous research student in this department, the above results were not confirmed. A number of aldehydes (see below) were used as starting materials. However when the intermediate ketenethioacetal monosulphoxides were hydrolysed with strong acid in dichloromethane, products isolated were assigned the structures shown below, that is the chloroketene dithioacetals, (scheme 68).

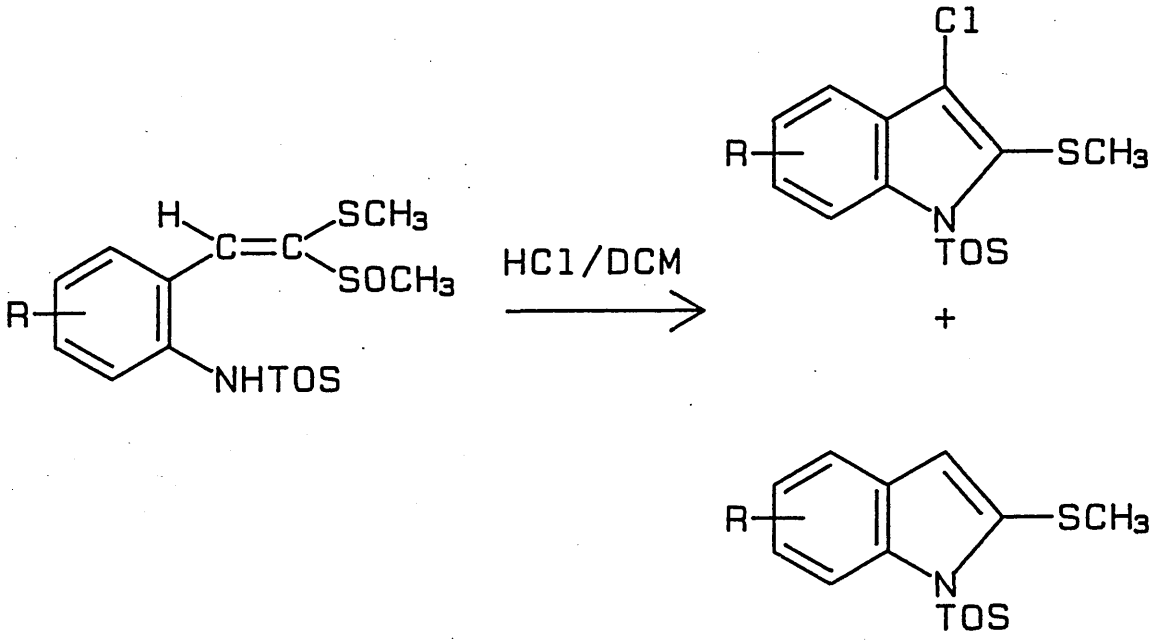
Scheme 68.



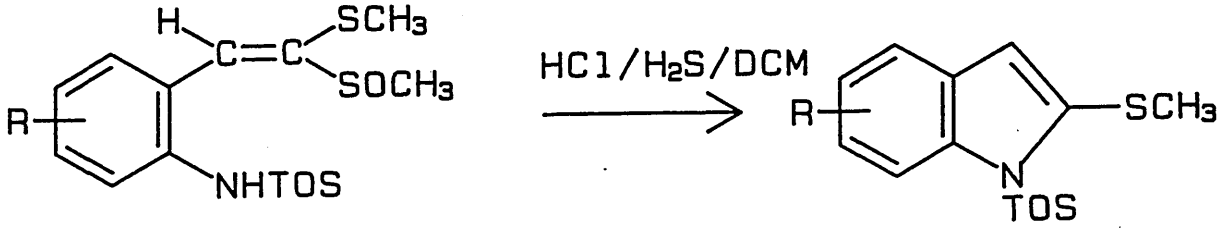
a) MMTS/Triton B/THF/reflux
b) c.HCl/DCM



When the reaction was repeated on the ketenethioacetal monosulphoxide, derived from N-tosyl-o-aminobenzaldehyde the result was a mixture of two compounds, shown to be the indoles, (discussed in chapter 2).



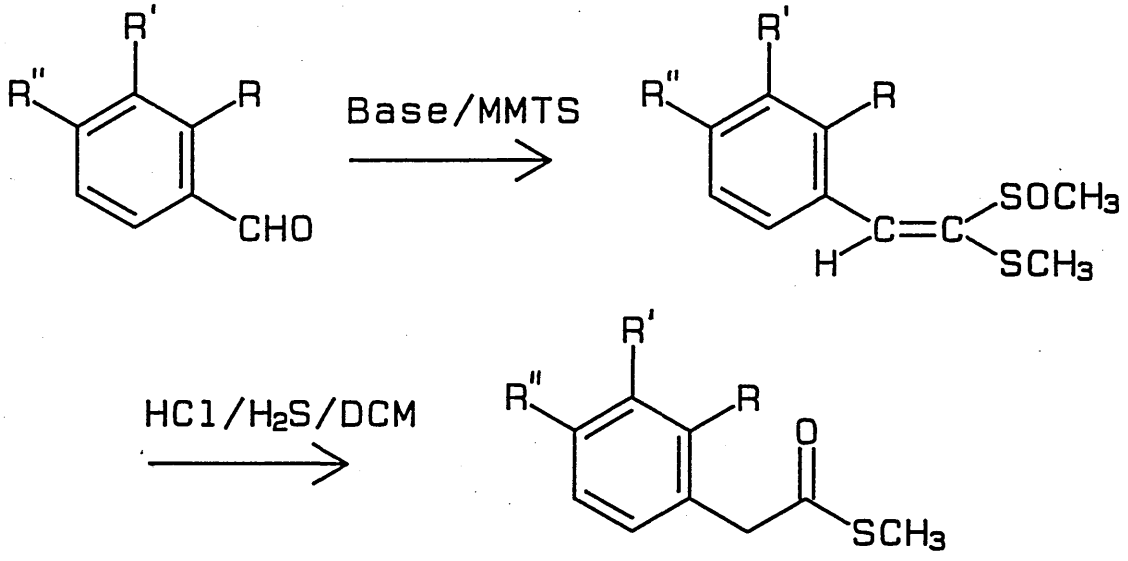
When this reaction was carried out with hydrogen sulphide present in the reaction mixture, only one indole was prepared, i.e.



From the above reactions it can be seen that to complete the picture the reaction, using hydrogen sulphide, should be tried on benzaldehyde derivatives other than those with a NH-tosyl group ortho to ketenethioacetal monosulphoxide.

We decided to apply the above conditions (with hydrogen sulphide present), to a number of simple substituted aromatic benzaldehydes. On completion of the reaction, the products isolated were found to be aromatic thiol esters.

Scheme 69.



The results for the investigation of various substituted benzaldehydes are tabulated below:

Benzaldehyde			yield of KTMS (%)	yield of thiol ester (%)
R	R'	R''		
H	H	OC_2H_5	80	(179a) 57
H	H	H	53	(180a) 61
H	H	CH_3	53	(181a) 19
H	H	Cl	66	(182a) 43
H	H	C_2H_5	56[a]	(183a) 47
H	OCH_3	H	84	(184a) 59
OCH_3	OCH_3	H	80[a]	(185a) 86
H	Cl	H	58	(186a) -

a base = NaH

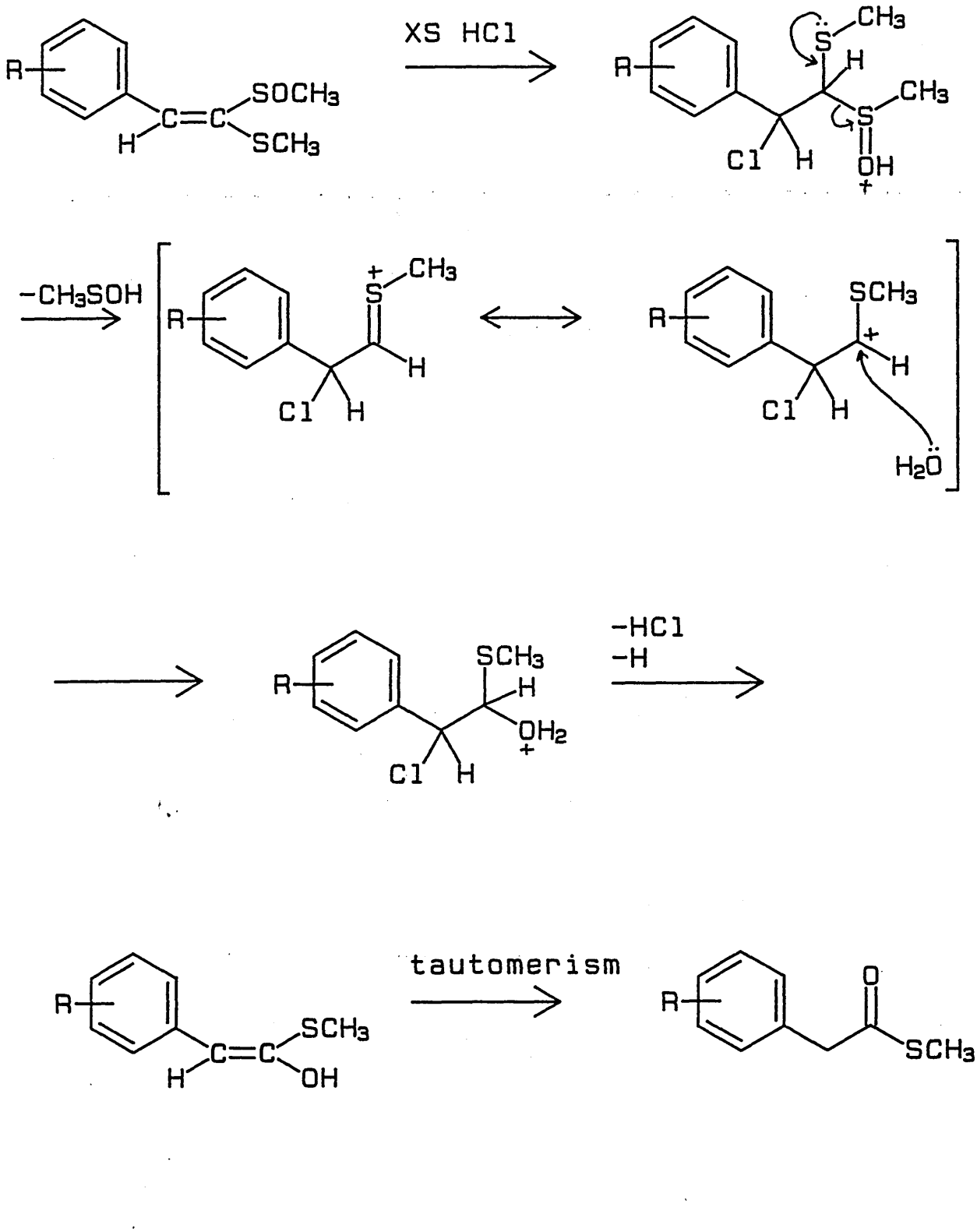
From the table above it may be noted that the m-chloro thiol ester was not isolated. NMR of the product isolated showed it to be unreacted starting material. This reaction was attempted several times, but with the same result, the isolation of starting material. This was quite surprising and no reason could be found which would account for the failure of the reaction. One compound which did not produce the intermediate ketenethioacetal monosulphoxide, was 3-nitrobenzaldehyde. A TLC of the reaction mixture showed a large number of products, which wereinseparable by column chromatography. The structure of the thiol esters have been confirmed by NMR and IR spectroscopy, and some have been shown to be correct by low resolution mass spectroscopy. Due to the products being unstable satisfactory microanalyses have not been obtained. Further confirmation has been obtained for the p-chloro,p-ethoxy and unsubstituted thiol esters

which have been prepared by an alternative synthesis, involving the condensation of the appropriate phenylacetic acid and methane thiol in the presence of dicyclohexyl carbodiimide (DCC).

4.2 THE MECHANISM OF THE THIOL ESTER FORMATION

The mechanism for the preparation of the thiol esters is very similar to that of the mechanism for the preparation of the indoles (in chapter 2). With hydrogen sulphide present, the initial step is the addition of HCl across the double bond, followed by loss of methane sulphenic acid. Addition of water to the resulting cation, followed by loss of a proton and HCl results in the enol, which rapidly tautomerises to the thiol ester, (scheme 70).

Scheme 70.



CHAPTER 5. EXPERIMENTAL.

5.1 GENERAL.

Proton magnetic resonance spectra were obtained from a Jeol 60MHz C.W. instrument or a Bruker 250MHz F.T. instrument. Data is given on the δ scale in ppm and tetra methyl silane was added as internal standard, and was given the value of Oppm. Abbreviations for the form of the signal are as follows:-

s = singlet, d = doublet, t = triplet, q = quartet,

qn = quintet, sx = sextet and m = multiplet.

Solvents used were $CDCl_3$ or $(CD_3)_2CO$ or others stated.

Infra red spectra were obtained on a Pye Unicam SP3-100 spectrophotometer or a Perkin Elmer 737 spectrophotometer. Spectra were obtained as potassium bromide (KBr) discs, liquid films, nujol mulls or solutions in bromoform. Data is given in cm^{-1}.

Ultra violet spectra were obtained on a Pye Unicam SP800-A spectrophotometer, and were run in methanol. The data are quoted in nm.

Microanalyses were performed by The City University, London, or Glaxo Group Research, Ware, Hertfordshire.

Mass spectra were obtained on a V.G. Micromass 30F mass spectrometer with an accelerating voltage of 70eV.

Short path column chromatography was performed on Merck 7729, 7734, 7736 and 9385 silica gel, petrol and ethyl acetate were distilled prior to use. Petrol refers to the fraction that boils between 40-60°C.

Thin layer chromatography (TLC) was performed on Merck 5554 Alufolien Kiesel gel $60f_{254}$ plates.

Dry THF was distilled from potassium metal. Dry diethyl ether was obtained by drying over sodium metal. Dry dichloromethane was distilled from phosphorous pentoxide and stored over 4A molecular sieves. Dry dimethyl formamide was distilled, under reduced pressure, from calcium hydride and stored over 4A molecular sieves. Dry pyridine was obtained by storage over potassium hydroxide pellets. All reactions requiring an inert atmosphere were done under nitrogen. Melting points were obtained on electrothermal apparatus and are uncorrected.

5.2 EXPERIMENTAL METHODS.

METHYL N-(4-TOLUENESULPHONYL)-2-AMINOBENZOATE (45).

To a solution of p-toluenesulphonyl chloride (13.88g,73mmol) in dry pyridine (50ml), and cooled to 0°C, was added a solution of methyl anthranilate (11.00g,73mmol), over 20 minutes. The mixture was allowed to stir for a further hour at 0°C, and was then acidified with dilute hydrochloric acid. A precipitate formed, which was filtered off, and washed with dilute hydrochloric acid followed by water. The product was dried in an oven, to give pure product as an off white solid, 16.7g, 55mmol, 75%, mpt. 113-116°C.

IR (KBr disc) cm^{-1} 3120, 1680, 1580, 1490, 1250, 1150, 1085, 920, 755.

NMR ($CDCl_3$) δ ppm 10.5(brs,1H); 7.5(m,8H); 3.85(s,3H); 2.33(s,3H).

N-(4-TOLUENESULPHONYL)-2-AMINOBENZYLALCOHOL (46).

A flame dried two necked flask was fitted with a reflux condenser, dropping funnel, and a nitrogen atmosphere. To the flask was added dry THF (20ml), and LAH (2.45g,64.6mmol), this was allowed to stir for 10 minutes at room temperature. A solution of (45) (9.40g,32.3mmol), in dry THF (20ml) was added dropwise to the LAH, after which the mixture was refluxed for 1 hour. 2N hydrochloric acid

was added until effervescence ceased, then ether (50ml) was added. The inorganic salts were separated from the organic solvent, and were washed with further quantities of ether (2x50ml). The combined organic extracts were washed with saturated sodium bicarbonate solution and brine. The solvent was then dried over magnesium sulphate, and evaporated to dryness, to leave a white solid, 8.02g, 28.9mmol, 89.5%, mpt.147.5-150°C. (used without further purification).

IR (KBr disc) cm^{-1} 3420, 3060, 2920, 2800, 1590, 1450, 1310, 1030, 715.

NMR ($CDCl_3$) δ ppm 7.56(m,4H); 7.13(m,6H); 4.22(s,2H); 2.33(s,3H).

N-(4-TOLUENESULPHONYL)-2-AMINOBENZALDEHYDE (35).

In a flask fitted with a mechanical stirrer was placed dry distilled DCM (50ml), and PCC (3.25g,15mmol). The resulting suspension was stirred for 10 minutes. Added to the suspension was a solution of (35) (2.75g,9.9mmol), in dry DCM (100ml). The solution was allowed to stir at room temperature for 2 hours. Ether (50ml) was added, and the solvent was decanted off the insoluble salts, which were then washed with further quantities of ether (3x50ml). The solvent was removed under reduced pressure, and the product purified by filtration down a column of silica gel. Pure product was obtained as a white solid,2.49g, 91.4%, mpt. 124-127°C.

IR (KBr disc) cm^{-1} 3100, 2905, 1650, 1590, 1570, 1480, 1400, 1150, 830, 750.

NMR ($CDCl_3$) δ ppm 10.43(brs,1H); 9.56(s,1H); 7.56(m,4H); 7.03(m,4H); 2.33(s,3H).

N-(4-TOLUENESULPHONYL)-2-AMINO(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYL BENZENE (36).

The aldehyde (35) (10.00g,26mmol) was dissolved in dry THF (200ml), under a nitrogen atmosphere. To this was added MMTS (4.1ml,39mmol) and 40% Triton B in methanol (30ml,66mmol). The mixture was then refluxed for 4 days, then poured into a 50/50 mixture of ethyl acetate and saturated ammonium chloride. The two layers were separated, and the aqueous phase extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with brine and dried over magnesium sulphate. The solvent was evaporated to dryness, to leave a pale brown residue. This was purified by recrystallisation from ethyl acetate, to give pure product as white crystals, 8.93g, 23mmol, 88%, mpt.165-168^{o}C.

IR (KBr disc) cm^{-1} 3100, 2900, 2820, 1600, 1490, 1340, 1040, 820, 780, 675.

NMR ($CDCl_3$) δ ppm 7.63(m,5H); 7.26(m,4H); 2.82(s,3H); 2.33(s,3H); 2.19(s,3H).

$C_{17}H_{19}NO_3S_3$ requires C,53.52; H,5.02; N,3.67; found C,53.50; H,4.98; N,3.34%

N-(4-TOLUENESULPHONYL)-2-METHYLTHIOINDOLE (37).

Dry DCM (30ml) was presaturated with hydrogen sulphide gas for 30 minutes. To this was added compound (36) (5.00g,13mmol), which formed a suspension. To this was added conc. hydrochloric acid (1.5ml), after which the suspension turned yellow and gradually dissolved. The reaction had gone to completion after 1 hour. The solution was basified with saturated sodium bicarbonate solution, and the two layers separated. The aqueous phase was extracted with DCM (20ml), and the combined organic extracts were washed with saturated sodium

bicarbonate and brine. They were then dried over sodium sulphate, and evaporated to dryness to leave a yellow oil, which slowly solidified. Pure product was obtained by recrystallisation from ethanol, as white crystals, 3.24g, 10mmol, 77%, mpt. 117.5-119.5°C.

IR (KBr disc) cm^{-1} 3080, 2920, 1600, 1490, 1375, 1180, 1090, 810, 740.

NMR ($CDCl_3$) δ ppm 8.16(m,4H); 7.49(m,4H); 6.53(s,1H); 2.57(s,3H); 2.43(s,3H).

$C_{16}H_{12}NO_2S_2$ requires C,60.54; H,4.76; N,4.41; S,20.20 found C,60.60; H,4.82; N,4.28; S,20.21%.

N-(4-TOLUENESULPHONYL)-3-CHLORO-2-METHYLTHIOINDOLE (47).

The indole (37) (121mg,0.38mmol) was dissolved in dry DCM (1ml). To this was added sulphuryl chloride (3 drops), and the solution allowed to stir for 30 minutes at room temperature, under nitrogen. The solution was then poured into a 50/50 mixture of water and ethyl acetate (20ml). The two layers were separated, and the organic phase was washed with brine, and then dried over sodium sulphate. The solvent was removed under reduced pressure, to leave an off white solid, 99mg, 0.28mmol, 74%.

NMR ($CDCl_3$) δ ppm 8.50(m,2H); 7.90(d,2H); 7.46(m,4H); 2.36(s,3H); 2.26(s,3H).

$C_{16}H_{11}ClNO_2S_2$ requires C,54.61; H,4.01; N,3.98; Cl,10.08; S,18.22; found C,55.15; H,3.95; N,3.86; Cl,10.40; s,16.98%.

N-(4-TOLUENESULPHONYL)-2-AMINOPHENYL-1-ETHANOL (48)

Magnesium turnings (350mg, 15mmol) and dry ether (30ml) were placed in a flask. To this was added dropwise a solution of methyl iodide (2.06g,15mmol) in dry ether (10ml). After all the methyl iodide had been added, the solution was refluxed for 15 minutes, then cooled

to 0°C. The aldehyde (35) (2.00g,6.62mmol) in dry THF (10ml) was added dropwise with cooling and stirring. The mixture was refluxed for 2 hours, and then cooled to room temperature. 2N hydrochloric acid was added until effervescence ceased, and the two layers were then separated. The aqueous layer was washed with ether (2x25ml). The combined ether extracts were dried over magnesium sulphate, and then evaporated off to leave a yellow oil. The product was purified on a column of silica gel (Merck7734), using chloroform as the eluent. Pure product was obtained as a yellow oil, 1.13g, 3.88mmol, 53%.

IR (liquid film) cm^{-1} 3480, 3220, 3000, 2980, 1590, 1490, 1150, 750.

NMR ($CDCl_3$) δ ppm 8.03(brs,1H); 7.46(m,4H); 7.06(m,5H); 4.73(q,1H); 2.33(s,3H); 1.33(d,3H).

N-(4-TOLUENESULPHONYL)-2-AMINOPHENYLMETHYLKETONE (49).

Dry DCM (30ml) and PCC (730mg,34mmol) were placed in a flask, to this was added the alcohol (48) (990mg,34mmol) in dry DCM (30ml). The mixture was allowed to stir at room temperature for 2 hours. Ether (50ml) was then added, and the organic solvent was decanted off the insoluble salts, which were then washed with a further quantity of ether (2x20ml). The organic layer was filtered, and evaporated to leave a brown oily solid. The product was purified by short path column chromatography on silica gel (Merck7736), using chloroform as the eluent. The pure product was obtained as a white solid, 650mg, 22.5mmol, 66%, mpt.143-146°C.

IR (KBr disc) cm^{-1} 3060, 2920, 1640, 1590, 1575, 1490, 1380, 1250, 1160, 920, 820, 755, 650.

NMR ($CDCl_3$) δ ppm 7.70(m,5H); 7.20(m,4H); 2.50(s,3H); 2.33(s,3H).

THE α-ACETOXYALDEHYDE DIMETHYLDITHIOACETALMONOSULPHOXIDE (50).

In a flame dried 3-necked flask fitted with a nitrogen atmosphere, was placed dry THF (10ml). To this was added MMTS (0.5ml,3.5mmol). The solution was cooled to around -20°C, (ice/salt bath) and n-butyllithium (5ml,7.5mmol) was added. The resulting yellow solution was cooled further, to -70°C (CO_2/acetone), and the ketone (49) (1.00g,3.5mmol) in dry THF (10ml) was added.This was left to stir for 20 minutes, then distilled acetic anhydride (0.4ml,3.5mmol) was added. A yellow precipitate formed. The mixture was allowed to warm to room temperature, and was stirred overnight. Saturated sodium bicarbonate solution was added, and the organics were extracted with dichloromethane (2x50ml). The combined organic fractions were washed with water followed by saturated brine, and then dried over magnesium sulphate. The product, after evaporation of the solvent, was a brown oil (1.81g), which was made up of a large number of inseparable products, shown by TLC (20% ethyl acetate in petrol).

N-ACETYLTRYPTOPHAN (53).

A) Indole (52) (2.00g,17mmol), acetamido acrylic acid (4.41g,34mmol) acetic acid (25ml) and acetic anhydride (10ml), were heated at 95°C (oil bath temp.) for 45 minutes. The white suspension turned salmon pink, then dissolved to produce a dark red solution. This was then cooled in ice and diluted with ether, then it was made basic with 30% sodium hydroxide solution. The ether phase was extracted several times with 30% sodium hydroxide, then sodium dithionite was added to this solution. It was then cooled in ice and acidified to congo red. This solution was left to stand in a refrigerator for 36 hours, and the resulting precipitate was collected by filtration under vacuum, and washed with water. The brown solid was not the required product,

(determined by NMR).

B) A solution of indole (52) (1.8g,15mmol) and dl-serine (1.50g,15mmol) in acetic anhydride (15ml) was heated at reflux for 1 hour, and then left to stand at room temperature, overnight. Acetic anhydride was removed under reduced pressure, and water was added. The aqueous layer was then made basic, and again extracted with ether. The aqueous phase was then acidified with dilute hydrochloric acod, and the resulting precipitate was collected by filtration. This was not N-acetyl tryptophan, determined by comparison of its infra red spectrum with that of a published spectrum.

INDOLE-3-PROPIONIC ACID (23).

Indole (52) (4.2g,36mmol), sodium acetate (4.0g,49mmol) and acrylic acid (6.49g,90mmol) were dissolved in acetic acid (8ml). The solution was allowed to stir at room temperature for 4 days. The acetic acid was removed under reduced pressure, and the residue basified with 20% sodium hydroxide, and impurities were filtered off. The filtrate was then acidified with conc. hydrochloric acid, and the resulting precipitate filtered off. The NMR spectrum did not agree with a spectrum of a sample of authentic indole-3-propionic acid, (obtained from ALDRICH).

3-DIMETHYLAMINO METHYL INDOLE (GRAMINE) (55).

To 40% aqueous dimethylamine (11.85g,100mmol) was added glacial acetic acid (14.00g,230mmol). This mixture was cooled to 5°C and then 37-40% aqueous formalin (7.69,100mmol) was added. The mixture was agitated and then poured into a conical flask containing indole (11.72g,100mmol). The whole mixture was shaken until the indole had dissolved, during which time the temperature rose to 44.5°C. A viscous

orange solution was produced, which was left to stand overnight. The solution was then poured into a solution of sodium hydroxide (14.00g) in water (100ml). The resulting suspension was cooled in ice for 2 hours, and then the gramine was collected by vacuum filtration, and washed with water. The solid was pressed dry, then further dried in a vacuum dessicator. The white solid was recrystallised from acetone/hexane to yield white platey crystals, 10.19g, 59mmol, 59%, mpt. 126-129°C, (lit.127-128°C)[33].

IR (KBr disc) cm^{-1} 3100, 2960, 2850, 2770, 1550, 1450, 1350, 1235, 1110, 990.

NMR ($CDCl_3$) δ ppm 9.00(brs,1H); 7.80(m,1H); 7.10(m,4H); 3.83(s,2H); 2.46(s,6H).

GRAMINE METHIODIDE (56).

To a solution of gramine (55) (10.0g,53mmol) in ethanol (60ml) was added methyl iodide (8.00g,56mmol) over a period of 20 minutes. The mixture was left to stir for 24 hours, at room temperature. It was then cooled to 0°C, and stirred for 6 hours, the white precipitate was then filtered off. The precipitate was washed with ethanol (3x10cm^3) and dry ether (3x10cm^3). Pure product was obtained as a white solid, 11.44g, 43mmol, 81.1%, mpt.163-166°C.

ETHYL-2-CARBOETHOXY-3-(3-INDOLE)-PROPIONATE (57).

To a suspension of sodium hydride (150mg,3.75mmol) in dry THF (2ml), under nitrogen, was added diethyl malonate (600mg,3.72mmol). The mixture was stirred for 10 minutes, then gramine methiodide (1.00g,3.72mmol) was added, then the resulting suspension was refluxed for 2 hours. Water was added, and then extracted with ethyl acetate. The organic phase was washed with brine, and the dried over magnesium sulphate. The solvent was evaporated off to leave the product as a

white solid, 900mg, 84%, mpt. 61-64°C, (lit.60°C)[33].

IR (KBr disc) cm^{-1} 3350, 3060, 2990, 1740, 1710, 1455, 1340, 1295, 1150, 1050, 1005, 740.

NMR ($CDCl_3$) δ ppm 8.40(brs,1H); 7.22(m,1H); 4.24(q,4H); 3.80(t,1H); 3.45(d,2H); 1.16(t,6H).

2-CARBOXY-3-(3-INDOLE)PROPIONIC ACID (58).

The diester (57) (8.00g,28mmol) was heated at reflux with 30% sodium hydroxide solution (30ml) for 4 hours. The solution was cooled, and then acidified with 2N hydrochloric acid. The aqueous solution was extracted with ethyl acetate (50ml), which was washed with brine and then dried over magnesium sulphate. The solvent was evaporated, to leave a red oil. This was triturated and recrystallised from chloroform, to give pale orange crystals, 1.28g, 5.5mmol, 20%, mpt. 169-171°C, (lit.178°C decomp.)[33].

IR (KBr disc) cm^{-1} 3420, 3380, 3200-2700, 1700, 1440, 1400, 1260, 900, 750.

NMR ($(CD_3)_2CO$) δ ppm 9.82(brs,1H); 8.92(brs,2H); 7.76-6.90(m,1H); 3.90(m,1H); 3.40(d,2H).

INDOLE-3-PROPIONIC ACID (23).

The diacid (58) (540mg,2.32mmol) was heated in an oil bath at 180°C. The orange/pink solid begins to melt at 120°C, and turn red. By the time the oil bath reached 180°C the solid had all melted, and frothing had stopped. After cooling, the residue was dissolved in 50% sodium dithionite. The acid was reprecipitated by acidification with hydrochloric acid, and left to stand overnight. Pale brown needle like crystals formed, which were filtered off, and washed with water. Product was pale brown crystals, which turned purple on exposure to

air, 300mg, 1.59mmol, 69%, mpt. 127.5-129°C, (lit.132-133°C)[33].

IR (KBr disc) cm^{-1} 3440, 3200-2500, 1690, 1420, 1285, 1205, 740.

NMR ($CDCl_3$) δ ppm 9.7(brs,1H); 7.1(m,6H); 2.9(m,4H).

2,3-DIMETHYLDITHIOINDOLENINE-3-PROPIONIC ACID (60).

A solution of methane sulphenyl chloride was prepared in DCM by adding sulphuryl chloride (0.81g,6mmol) dropwise to dimethyl disulphide (0.6g,6mmol) at 0°C. This solution was then added dropwise to a suspension of indole-3-propionic acid (2.0g,10mmol) in DCM. This was then stirred at 0°C for 10 minutes and warmed to room temperature for 2 hours. Water was added to the reaction, and the two layers separated. The aqueous phase was extracted with dichloromethane (20ml) and the organic phases combined. These were then washed with saturated brine, and dried over sodium sulphate. After evaporation of the solvent a yellow solid was obtained, which was recrystallised from ethanol. The pure product was obtained as off white crystals, 1.79g, 64%, mpt. 151.5-152.5°C.

IR (KBr disc) cm^{-1} 3500, 2900, 2910, 1710, 1500, 1200, 910, 730.

NMR ($CDCl_3$) δ ppm 10.16(brs,1H); 7.16(m,4H); 2.63(s,3H); 2.00(m,4H); 1.40(s,3H).

$C_{13}H_{15}NO_2S_2$ requires C,55.49; H,5.37; N,4.97; found C,55.77; H,5.42; N,4.85%.

MS ($M\cdot^+$281) 266, 222, 210, 174, 130.

2-METHYLTHIOINDOLE-3-PROPIONIC ACID (59).

A solution of methane sulphenyl chloride was prepared (as above) from sulphuryl chloride (2.2ml) and dimethyl disulphide (2.65ml). This was added to a solution of indole-3-propionic acid (10.0g,53mmol) in dry THF (100ml), dropwise. The resulting solution was stirred at 0°C for a further hour, and then warmed to room temperature and stirred

for a further 24 hours. The solution was poured into water, and extracted with ethyl acetate (3x50ml), the combined organic extracts were then washed with saturated brine, and dried over sodium sulphate. After evaporation of the solvent the crude product (19.40g) was subjected to short path column chromatography on silica gel (Merck7736) using 35% ethyl acetate in petrol, followed by recrystallisation from ethanol and chloroform. Pure product was obtained as a white solid, 8.01g, 64%, mpt. 157-159°C.

IR (KBr disc) cm^{-1} 3495, 2930, 2860, 1715, 1430, 1310, 1220, 760.

NMR ($CDCl_3$) δ ppm 10.00(brs,1H); 8.70(brs,1H); 7.13(m,4H); 2.86(m,4H);2.39(s,3H).

$C_{12}H_{13}NO_2S$ requires C,61.25; H,5.56; N,5.95; found C,61.50; H,5.72; N,5.91%.

MS ($M^{\cdot+}$235) 190, 176, 161, 130, 117.

ATTEMPTED CYCLISATION OF 2-METHYLTHIOINDOLE-3-PROPIONICACID (I).

Polyphosphoric acid was warmed to 80°C, and stirred with a mechanical stirrer. To it was added 2-methylthioindole-3-propionic acid (2.56g,10.9mmol), this yellow suspension was warmed to 90°C and stirred for 24 hours, by which time it had turned dark brown. This was then poured onto ice, and extracted with ethyl acetate (50ml), the organic extract was washed with 10% sodium sulphate, 8% sodium bicarbonate, and saturated brine. The ethyl acetate was dried over sodium sulphate, and evaporated down to leave a black tar. A TLC of this showed mainly base line material.

ATTEMPTED CYCLISATION OF 2-METHYLTHIOINDOLE-3-PROPIONIC ACID (II).

The acid (1.00g, 4.25mmol) was dissolved in dry dichloromethane (20ml), and added to this was one drop of dry DMF. The mixture was

cooled to 0°C, and oxalyl chloride (0.5ml, 5.6mmol) was added. The mixture was stirred under nitrogen at room temperature for 1.5 hours, then anhydrous aluminium chloride (1.1g, 8.25mmol) was added. The mixture was stirred overnight, after which the green solution was poured into water, and the organic phase separated. The aqueous layer was extracted with ethyl acetate (20ml) and the combined organic phases were washed with saturated brine, and dried over sodium sulphate. After evaporation of the solvent, a green oily solid remained, whose NMR showed it to be starting material.

METHYL 2-METHYLTHIOINDOLE-3-PROPIONATE (66).

A) 2-methylthioindole-3-propionic acid (2.04g, 8.67mmol) was stirred at room temperature in a solution of methanol and conc. sulphuric acid for 3.5 hours. The methanol was evaporated off, and the residue was then dissolved in ethyl acetate, and the organic phase was then washed with saturated sodium bicarbonate solution, followed by saturated brine. The organic phase was dried over sodium sulphate, and the solvent evaporated off to leave an oil, 2.32g, >90%, without purification.

B) Indole-3-propionic acid (5.02g, 26.5mmol) was dissolved in methanol (60ml) and stirred at room temperature with conc. sulphuric acid (2ml) for 2 hours. The solution was then poured into saturated sodium bicarbonate solution, when basic this was then extracted with ethyl acetate (2 x 50ml). The combined organic extracts were then washed with saturated brine, and dried over sodium sulphate. The solvent was evaporated off to leave a brown oil, 5.40g, 26.5mmol, 100%. This was used without purification.

A solution of methane sulphenyl chloride was prepared (as above) from sulphuryl chloride (1.05ml, 11.7mmol) and dimethyl disulphide

(1.27ml, 11.7mmol), in dichloromethane (20ml). This was added dropwise to a solution of the oil (5.17g, 25.4mmol) (from above) in dry DCM (50ml) cooled to 0°C. This was left to stir at room temperature for 3 days, after which time water was added. The two layers were separated, and the organic phase washed with saturated sodium bicarbonate solution followed by saturated brine. The organic phase was dried over sodium sulphate, and the solvent evaporated off to give a brown oil (6.62g). This was purified by short path column chromatography on silica gel (Merck7736) using 20% ethyl acetate in petrol as eluent. This gave pure product as a brown oil, 5.90g, 23.7mmol, 93%.

IR (liquid film) cm^{-1} 3380, 3060, 2900, 2850, 1720, 1440, 1340, 1200, 1040, 910, 750.

NMR ($CDCl_3$) δ ppm 8.66(brs,1H); 7.33(m,1H); 7.00(m,3H); 3.50(s,3H); 3.10(m,2H); 2.60(m,2H); 2.16(s,3H).

METHYL N-(4-TOLUENESULPHONYL)-2-METHYLTHIOINDOLE-3-PROPIONATE(67).

The indole (66) (5.9g, 23.7mmol) was dissolved in dry THF (20ml). This was added to a suspension of potassium hydride (35% dispersion in mineral oil) washed free of oil with petrol (5.45g, 47.4mmol) in dry THF (20ml), cooled to -78°C, under nitrogen. This was stirred for 45 minutes, then p-toluenesulphonyl chloride (5.72g, 30mmol) in THF (20ml) was added slowly. The mixture was allowed to warm to room temperature, then stirred overnight. Dilute hydrochloric acid was added until effervescence ceased, and the two layers were separated. The aqueous layer was extracted with ethyl acetate (50ml), and the combined organic phases were washed with sodium bicarbonate solution and saturated brine, and dried over sodium sulphate. The solvent was evaporated off to leave a brown oil, (9.72g). This was subjected to

column chromatography on alumina (basic grade III) with 10% ethyl acetate in petrol as eluent. The product was then crystallised from methanol to give the pure compound as a white solid, 6.87g, 17mmol, 72%, mpt. 71-73 ^{o}C.

IR (KBr disc) cm^{-1} 1810, 1500, 1420, 1210, 1170, 980, 920, 810.

NMR ($CDCl_3$) δ ppm 8.23(dd,1H); 7.66(d,2H); 7.16(m,5H); 3.50(s,3H); 3.20(m,2H); 2.56(m,2H); 2.40(s,3H); 2.23(s,3H).

$C_{20}H_{21}NO_4S_2$ requires C,59.53; H,5.24; N,3.47; found C,59.45; H,5.18; N,3.47%.

MS ($M^{\cdot+}$403) 283, 248, 216, 206, 176, 153, 91, 84.

N-(4-TOLUENESULPHONYL)-2-METHYLTHIOINDOLE-3-PROPIONIC ACID (68).

The ester (67) (1.14g, 2.8mmol) was dissolved in methanol (15ml), added to this was 2N sodium hydroxide (14ml, 28mmol). The solution was heated at 60 ^{o}C for 3 hours. The solution was cooled and poured into dilute hydrochloric acid, this was then extracted with ethyl acetate (50ml). The organic phase was separated and then washed with saturated sodium bicarbonate. The aqueous phase was then acidified, and re-extracted with ethyl acetate, then dried over sodium sulphate. After evaporation an off white solid remained, 0.82g, 2.1mmol, 75%, mpt. 176-178 ^{o}C.

IR (KBr disc) cm^{-1} 3400-2700, 2920, 1710, 1590, 1435, 1370, 1180, 1140, 750, 670.

NMR [$(CD_3)_2CO$] δ ppm 8.10(dd,1H); 7.56(d,2H); 7.13(m,5H); 5.6(brs,1H); 3.0(m,2H); 2.50(m,2H); 2.36(s,3H); 2.26(s,3H).

$C_{19}H_{19}NO_4S_2$ requires C,58.59; H,4.92; N,3.60; found C,58.51; H,4.85; N,3.65%.

MS ($M^{\cdot+}$389) 234, 216, 194, 192, 174, 130, 91.

ATTEMPTED CYCLISATION OF N-(4-TOLUENESULPHONYL)-2-METHYLTHIOINDOLE-3-PROPIONIC ACID (I).

Polyphosphoric acid (20ml) was heated to between 80-90°C, then the acid (68) (0.8g, 2mmol) was added in small quantities. A black solution formed. This was stirred overnight, and then poured onto ice. The organics were extracted with ethyl acetate (50ml) . The organic phase was then washed with saturated brine and dried over sodium sulphate. The solvent was evaporated off to leave a brown oil, which remained on the base line on a TLC plate (50% ethyl acetate/petrol), and an NMR of the crude product suggested that the product may still be unreacted starting material.

ATTEMPTED CYCLISATION OF N-(4-TOLUENESULPHONYL)-2- METHYLTHIOINDOLE-3-PROPIONIC ACID (II).

The acid (1.03g, 2.6mmol) was dissolved in dry dichloromethane (20ml), and one drop of dry DMF was added, the solution was then cooled to 0°C. Oxalyl chloride (0.25ml, 2.8mmol) was added, and the solution stirred under nitrogen at room temperature for 1.5 hours. Anhydrous aluminium chloride (0.7g, 5.25mmol) was added, with cooling, and left to stir overnight. The solution was then poured into water, and extracted with ethyl acetate (50ml), washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure to leave a green oily solid, whose TLC suggested the starting acid.

ATTEMPTED CYCLISATION OF N-(4-TOLUENESULPHONYL)-2-METHYLTHIOINDOLE-3-PROPIONIC ACID (III).

The acid (540mg, 1.4mmol) was dissolved in dry dichloromethane (20ml) and cooled to 0°C. To this was added diethyl chlorophosphate (290mg, 1.68mmol), and the mixture stirred at 0°C for 30 minutes. Anhydrous aluminium chloride (400mg, 3mmol) was added, and the mixture

stirred overnight at room temperature. Water was added, and the two layers separated. The aqueous phase was extracted with dichloromethane, and the combined organics washed with saturated brine, dried over sodium sulphate, and evaporated down. The dark green residue was subjected to short path column chromatography on silica gel (Merck7736), using 25% ethyl acetate in petrol as eluent. The product (450mg) was shown to be the starting acid by NMR.

ETHYL N-(4-TOLUENESULPHONYL)-2-METHYLSULPHONYL INDOLE-3-PROPIONATE (71).

The sulphide (67) (1.00g) was added to a solution of "OXONE" (2.46g) in acetic acid (7ml), ethanol (7ml), distilled water (7ml) and conc. sulphuric acid (3.5ml), over 20 minutes. The mixture was stirred at room temperature for 3.5 hours. It was then diluted with water, and extracted into ethyl acetate (30ml). The organic phase was washed with saturated sodium bicarbonate followed by saturated brine. The ethyl acetate was dried over sodium sulphate and evaporated down to leave a brown oil (1.04g). This was purified by short path column chromatography on silica gel (Merck7736), with 10% ethyl acetate in petrol. The pure product was obtained as a white crystalline solid, 0.24g, 21.5%.

IR (KBr disc) cm^{-1} 2995, 1750, 1480, 1320, 1190, 1140, 955, 755.

NMR ($CDCl_3$) ppm 7.96(d,1H); 7.70(d,2H); 7.33(m,3H); 6.93(d,2H); 3.90(q,2H); 3.46(s,3H); 3.36(t,2H); 2.60(t,2H); 2.30(s,3H); 1.16(t,3H).

$C_{21}H_{23}NO_6S_2$ requires C,56.11; H,5.16; N3.12;

found C,55.87; H,4.93; N,3.30%.

MS ($M^{\cdot+}$449) 370, 294, 248, 221, 215, 115, 91, 65, 39.

METHYL N-(4-TOLUENESULPHONYL)-2-METHYLSULPHONYL INDOLE-3-PROPIONATE (70).

The sulphide (67) (1.53g,3.79mmol) was added to a solution of "OXONE" (4.9g,8mmol) in methanol (10ml), acetic acid (10ml), distilled water (10ml) and conc. sulphuric acid (5ml). The mixture was stirred for 24 hours. The solution was diluted with water, and the two layers separated. The aqueous phase was extracted with ethyl acetate (30ml), the combined organic extracts were washed with saturated sodium bicarbonate solution and saturated brine. The ethyl acetate was dried over sodium sulphate, the solvent was evaporated off to leave an orange oil. This was crystallised from methanol to leave a white solid, 1.32g, 3.03mmol, 79.9%, mpt. 127-129°C.

IR (KBr disc) cm^{-1} 3020, 2995, 1740, 1600, 1400, 1320, 1300, 1180, 960, 760.

NMR ($CDCl_3$) δppm 8.13(s,6H); 7.80(d,2H); 7.50(m,3H); 7.13(d,2H); 3.50(s,6H); 3.36(t,2H); 2.66(t,2H); 2.30(s,3H).

$C_{20}H_{21}NO_6S_2$ requires C,55.15; H,4.86; N,3.21;

found C,54.92; H,4.79; N3.15%.

MS ($M^{\cdot+}$435) 356, 280, 248, 221, 201, 169, 155, 115, 91, 65.

N-(4-TOLUENESULPHONYL)-2-METHYLSULPHONYL INDOLE-3-PROPIONIC ACID (72).

A) The ethyl ester (71) (0.2g,0.44mmol) was dissolved in methanol (15ml), added to this was 2N sodium hydroxide (1ml,2mmol). The mixture was stirred and warmed to 60°C, for 3 hours. Dilute hydrochloric acid was added, and the product was extracted with ethyl acetate. This was washed with saturated sodium bicarbonate, and was then acidified and re-extracted with ethyl acetate. The organic phase was then dried over sodium sulphate, and evaporated down, to leave the product as an oil, 0.19g. An NMR of this crude product showed that a mixture of the

required product and some detosylated product was present. This was determined by the disappearence of the tosyl methyl peak at 2.30 δ ppm.

B) The methyl ester (70) (1.95g,4.48mmol) was refluxed with a mixture of water (75ml) and conc. hydrochloric acid (15ml) for 2 days. The mixture was then cooled to room temperature, and the suspended solid extracted into ethyl acetate (100ml). The ethyl acetate was washed with saturated sodium bicarbonate solution, several times. The combined aqueous phases were then acidified with hydrochloric acid, and re-extracted with ethyl acetate (100ml). The organic phase was washed with saturated brine, dried over sodium sulphate and evaporated to dryness. The product was obtained as an off white crystalline solid, 1.68g, 3.99mmol, 89%, mpt. 188-190 ^{o}C (decomposed).

IR (KBr disc) cm^{-1} 3350, 1705, 1600, 1310, 1030, 990, 770.

NMR ($CDCl_3$/$(CD_3)_2SO$) δ ppm 8.06(d,1H); 7.70(d,2H); 7.46(m,3H); 7.13(d,2H); 3.53(s,3H); 3.33(t,2H); 2.59(t,2H); 2.36(s,3H).

$C_{19}H_{19}NO_6S_2$ requires C,54.14; H,4.54; N,3.32;

found C,54.36; H,4.56; N,3.41%.

MS ($M^{\cdot+}$421) 267, 221, 208, 188, 169, 156, 139, 115, 91, 65, 39.

ATTEMPTED CYCLISATION TO UHLES KETONE DERIVATIVE (74).

Polyphosphoric acid (20ml) was heated to 90° C, and to this was added the acid (72) (0.5g, 1.19mmol). The mixture was stirred for about 1 hour during which time it changed from pale orange to black. The black solution was then poured onto ice, and a brown precipitate separated. An attempt was made to extract this into ethyl acetate, but was found to be insoluble.

The precipitate was then filtered off through hyflo supercel filter aid, and washed with both water and ethyl acetate. The aqueous

phase was then extracted with ethyl acetate, which was washed with saturated sodium bicarbonate and brine. The organic phase was dried over sodium sulphate and then evaporated off, to leave a brown oil 0.03g. A TLC indicated a large number of spots, none of which produced an orange colour with DNP spray. An NMR of this crude material showed a virtual disappearance of the aromatic peaks, and an absence of the methyl peak at 3.5ppm.

3-NITROPHTHALIMIDE (76)

A) 3-nitrophthalic anhydride (75) (10g, 52mmol) and ammonium carbonate (3.5 g, 36 mmol) were mixed together and then heated until both solids had melted. The mixture was kept in the molten state for 45 minutes, and then allowed to cool. Water (20ml) was added, to disintegrate the solid, which was filtered under reduced pressure, washed with water and dried in an oven. Product was a pale yellow solid 6.71g, 35mmol, 67.3%, mpt. 220-223°C (lit.[16] 217-218°C)

B) 3-nitrophthalic anhydride (20.00g, 104mmol) and urea (3.12g, 52mmol) were thoroughly mixed, and then heated until molten. The heating was continued until effervescence had ceased. The brown liquid was cooled, to a brown solid, then water was added. The pale brown precipitate was filtered off, and dried at 100°C in an oven. The pure product was obtained, 16.87g, 88mmol, 84.6%, mpt. 222-224°C (lit. 217-218°C)[16].

IR (KBr disc) cm^{-1} 3500, 3100, 3000, 2720, 1960, 1900, 1780, 1720, 1600, 1540, 1360, 1315, 1075, 800, 730, 660.

NMR ($DMSO-D_6$) δ ppm 8.03(m,4H).

3-HYDROXY-4-NITROPHTHALIMIDINE (77).

3-nitrophthalimide (6.50g, 34mmol) was dissolved in 90% aqueous methanol (75ml). To this was added sodium borohydride (2.53g, 67mmol)

over a period of 30 minutes, while vigorously stirring at room temperature. The suspension was stirred for a further 2 hours, and then the mixture was acidified with 20% hydrochloric acid. The methanol was evaporated off, and the residue was dissolved in acetone. The acetone was removed under reduced pressure, and the resulting brown solid was recrystallised from acetone. The product obtained was impure, 5.01g, approximately 60% , mpt. 145-150°C (lit 214-215°C)[16].

IR (KBr disc) cm^{-1} 3680-2900, 1770, 1710, 1630, 1530, 1470, 1350, 1200, 1055, 800, 760.

NMR (DMSO-D_6) δ ppm 9.06(brs,1H); 7.83(m,3H); 6.26(s,1H); 5.39(s,1H).

3-HYDROXY-4-NITROPHTHALIDE (78).

Compound (77) (10.23g, 53mmol) was dissolved in 20% hydrochloric acid (100ml), and stirred at 80-90°C for 20 hours. The hydrochloric acid was then distilled off under reduced pressure, and the brown residue taken up in acetone. The solution was filtered, and the filtrate evaporated to dryness. The product was purified by column chromatography on silica gel (Merck7736). The impurities were removed using chloroform as eluent, and the product was washed off the column with ethyl acetate. Pure product was obtained as a pale brown solid, 5.02g, 26mmol, 49%, mpt. 157-159°C (lit. 155-156°C)[16].

IR (KBr disc) cm^{-1} 3450, 3250, 3110, 2990, 1770, 1630, 1600, 1460, 1350, 1100, 950, 800, 740.

NMR (DMSO-D_6) δ ppm 8.52(d,1H); 8.32(d,1H); 7.85(t,1H); 7.15(s,1H).

3-METHOXY-4-NITROPHTHALIDE (79).

3-hydroxy-4-nitrophthalide (5.12mmol) was dissolved in methanol (50ml). To this was added a solution of diazomethane in ether (20ml). [The diazomethane solution was prepared by dissolving diazald (2.21g, 10.3mmol) in ether (50ml), and adding to this potassium hydroxide (0.6g, 10.3mmol) in 96% aqueous ethanol (10ml). The mixture was warmed and the diazomethane was distilled into ether]. After no more reaction was evident, the ether solution was tested for the presence of diazomethane, by adding a drop of acetic acid. When the diazomethane had been destroyed, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, and then washed with saturated sodium bicarbonate solution and brine. The solvent was dried over magnesium sulphate and evaporated off under reduced pressure, to leave a yellow waxy solid. This was purified by short path column chromatography on silica gel (Merck7736) using 25% ethyl acetate in petrol. The product was then recrystallised from ether, to leave pale yellow crystals, 0.64g, 60%, mpt. 134-136°C.

IR (KBr disc) cm^{-1} 3100, 3040, 2980, 1770, 1620, 1590, 1525, 1350, 1080, 740.

NMR ($CDCl_3$) δ ppm 8.56(d,1H); 8.32(d,1H); 7.90(t,1H); 6.76(s,1H); 3.76(s,3H).

METHYL 2-FORMYL-3-NITROBENZOATE (80).

The above method was repeated, but 3-hydroxy-4-nitrophthalide was suspended in ether, rather than dissolved in methanol. After all the diazomethane had been destroyed the ether was filtered to remove any undissolved solid. The ether was removed under reduced pressure. The product was not purified, but an NMR of the crude product suggested the aldehyde. The product was used without purification in

an attempt to make the nitrostyrene oxide.

2-METHOXYCARBONYL-6-NITROSTYRENE OXIDE (81).

The crude aldehyde (0.87g) was dissolved in ether (10ml). A stream of diazomethane was bubbled through. After excess diazomethane had been destroyed, the ether was removed under reduced pressure. The product was purified by short path column chromatography on silica gel (Merck7736) using 20% ethyl acetate in petrol as the eluent. The pure product was obtained as a yellow solid, 0.63g, 68%, mpt. 54-57°C, (lit. 62-64°C)[16].

IR (KBr disc) cm^{-1} 2990, 1720, 1600, 1530, 1360, 1220, 1020, 760.

NMR ($CDCl_3$) δ ppm 7.90(m,3H); 4.40(t,1H); 3.96(s,3H); 3.13(t,1H); 2.50(dd,1H).

METHYL 2-(2-HYDROXYETHYL)-3-AMINO BENZOATE (83).

The nitrostyrene oxide (0.6g, 2.69mmol) was dissolved in anhydrous methanol (50ml). To this was added, platinum (IV) oxide (0.06g). This was stirred under a hydrogen atmosphere until no starting material was left (by TLC), about 50 hours. The catalyst was filtered off, through hyflo and washed with methanol. The methanol was removed under reduced pressure, and the residue (0.4g) was purified by column chromatography on silica gel (Merck7736) using 50/50 ethyl acetate/petrol as elvent. The major spot 0.06g, 12.6%, of brown oil, was not the indole required, but was thought to be methyl 2-(2-hydroxyethyl)-3-amino benzoate, but this was not characterised.

3-DIACETOXYMETHYL-2-METHYLNITROBENZENE (85)

Concentrated sulphuric acid (42.5ml) was added to a cooled solution of 3-nitro-o-xylene (30.0g, 198mmol) in acetic anhydride (235ml) and glacial acetic acid (285ml). This solution was cooled to

0°C, and chromium trioxide (50.0g,500mmol) in acetic anhydride (75-150ml) was added at such a rate, that the temperature stayed between 5 and 10°C (1.5 hours). The green solution was left to stir at this temperature for a further 0.5 hours. The solution was then poured into ice/water (2.5l) and left to stand overnight. The precipitate was filtered off and washed with water to leave dirty yellow crystals. These were then suspended in 5% sodium bicarbonate and stirred for 10 minutes. The crystals were again filtered, and washed with water, and then recrystallised from 50/50 ethanol/water, to give pure product as pale yellow crystals, 22.85g, 86mmol, 43.2%, mpt. 77-79°C, (lit. 84-85°C)[12].

IR (KBr disc) cm^{-1} 3110, 2900, 1760, 1600, 1540, 1370, 1240, 1200, 1000, 815, 740.

NMR ($CDCl_3$) δ ppm 7.65(m,4H); 2.53(s,3H); 2.12(s,6H).

2-METHYL-3-NITROBENZALDEHYDE (86).

The diacetate (85) (30.0g, 110mmol) was refluxed with 50% aqueous ethanol (172ml) and concentrated sulphuric acid (7ml) for 45 minutes. The mixture was then filtered hot, and the filtrate evaporated to small bulk. When the solution was cooled, it went cloudy and a yellow liquid separated from the aqueous layer, which later solidified. The solid was filtered off and recrystallised from ethanol to leave pure product as yellow needles, 16.92g, 91%, mpt. 53-54°C (lit. 54-55°C)[12].

IR (KBr disc) cm^{-1} 3100, 2905, 2880, 1690, 1605, 1535, 1355, 1250, 820, 740.

NMR ($CDCl_3$) δ ppm 10.13(s,1H); 7.89(m,2H); 7.46(m,1H); 2.73(s,3H).

2-(2-METHYL-3-NITROPHENYL) DIOXOLANE (87).

2-methyl-3-nitrobenzaldehyde (86) (3.5g, 21.2mmol) and ethylene glycol (1.55g, 25mmol) were dissolved in benzene (50ml), and added to

this was p-toluene sulphonic acid (catalytic amount). The mixture was refluxed for 2 hours in a Dean-Stark apparatus. The solution was then cooled, and water (20ml) was added. The two layers were separated, the aqueous phase was extracted with ethyl acetate (30ml), and combined with the benzene. The combined organic phases were washed with saturated sodium bicarbonate, and saturated brine. The organic phase was then dried over magnesium sulphate, and evaporated to dryness. A pale yellow solid resulted, 4.6g, (quantitative yield) mpt. 60-62°C.

IR (KBr disc) cm^{-1} 2900, 1510, 1360, 1100, 800.

NMR ($CDCl_3$) δ ppm 7.60(m,2H); 7.16(t,1H); 5.83(s,1H); 3.96(s,4H); 2.43(s,3H).

$C_{10}H_{11}NO_4$ requires C,57.41; H,5.3; N,6.70;

found C,57.83; H,5.39; N,6.82%.

MS ($M^{\cdot+}$209) 195, 165, 149, 121, 92, 90, 73, 66, 45, 39.

2-[2-(2-HYDROXYETHYL)-3-NITROPHENYL] DIOXOLANE (88).

Compound (87) (5.5g, 26.3mmol) and paraformaldehyde (1.26g, 14mmol), were dissolved in dimethyl sulphoxide (50ml). Added to this was aqueous Triton B (40%) (1ml, 2.53mmol), and the mixture was heated to 72°C for 3 hours. The mixture was then poured into a mixture of saturated ammonium chloride solution and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the two layers separated. The organic phase was washed with brine, and then dried over sodium sulphate. After evaporation of the solvent an orange oil remained, (7.30g) which was purified by column chromatography on silica gel (Merck7736) using 50% ethyl acetate in petrol as eluent. Product was an oil, 5.6g, 23.5mmol, 89%.

IR (liquid film) cm^{-1} 3450, 2900, 1650, 1600, 1550, 1485, 1360, 1110, 1050, 815, 740.

NMR ($CDCl_3$) ppm 7.60(m,2H); 7.20(t,1H); 5.90(s,1H); 3.96(s,4H); 3.70(t,2H); 3.10(t,2H).

2-[3-AMINO-2-(2-HYDROXYETHYL)PHENYL] DIOXOLANE (89).

The nitro compound (88) (2.00g, 8.4mmol) and nickel (11) chloride hexahydrate 4.04g,17mmol) were dissolved in methanol (30ml), and cooled to 0°C. To this was added (slowly) portion wise, sodium borohydride (1.29g,34mmol), the resulting black mixture was allowed to warm to room temperature and stirred overnight. The nickel boride was filtered off through hyflo, the methanol was basified with sodium hydroxide and the remaining nickel hydroxide was also filtered off through hyflo. The methanol and sodium hydroxide were extracted with ethyl acetate. The organic phase was then washed with saturated brine and dried over sodium sulphate, the solvent was evaporated off to leave a brown oil, (0.97g). This was passed through silica gel (Merck7736) column, using 50% ethyl acetate/petrol as eluent, to give an orange oil, 0.82g, 3.9mmol, 46%, (impure).

4-IODO-3-INDOLE CARBOXALDEHYDE (94).

Indole-3-carboxaldehyde (25.05g, 170mmol) and thallium trifluoro acetate (100g, 180mmol) were stirred together with TFA (300ml) at room temperature in the dark for 5 hours, after which it was cooled to -15°C. The product was filtered off and washed with cyclohexane (250ml). This was then added to a solution of potassium iodide (60g, 360mmol) in water (600ml). This mixture was stirred overnight, and the resulting solid was filtered off and washed with potassium iodide solution and water. The grey powder was dried in a vacuum oven at 45°C for 3.5 hours. The product was then soxhlet extracted with chloroform,

overnight. The resulting red solution was then dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue was dissolved in ethyl acetate, and this solution was then washed with 10% sodium thiosulphate solution (to remove excess iodine). The solvent was again dried (over sodium sulphate) , and evaporated to leave a red/orange solid, which was recrystallised from chloroform to leave pure compound as dark red needles, 11.84g, 44mmol, 26%, 181-183^{o}C.

NMR ($CDCl_3/CD_3OD$) ppm 11.1(s,1H); 8.2(s,1H); 7.8(d,1H); 7.6(d,1H); 7.0(t,1H).

C_9H_6INO requires C,39.88; H,2.23; N5.17;

found C,38.70; H,2.41, N,4.99%.

4-(TRIMETHYLSILYLACETYLENE)-INDOLE-3-CARBOXALDEHYDE (95).

A solution of 4-iodo-3-indole carboxaldehyde (94) (1.00g,3.69mmol) palladium (11) acetate (10mg), triphenyl phosphine (20mg) and trimethylsilylacetylene (0.6ml,8.75mmol) in acetonitrile (20ml) and triethylamine (2ml), was heated at 60^{o}C, under nitrogen. To this was added cuprous iodide (10mg), and the mixture was then kept at 60^{o}C for 12 hours. The solution was cooled, and poured into water, from which it was extracted with ethyl acetate (3x20ml). The combined organic extracts were then washed with brine, and dried over magnesium sulphate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (Merck7729) using 50% ethyl acetate in hexane as the eluent. The product was obtained as a pale brown solid, 770mg, 86%, mpt. 138^{o}C,(decomp.).

IR (KBr disc) cm^{-1} 3270, 2960, 2150, 1640, 1505, 1390, 1300, 860.

NMR ($CDCl_3$) δ ppm 10.56(s,1H); 9.40(brs,1H); 7.80(d,1H); 7.15(m,3H); 0.25(s,9H).

A number of attempts at obtaining a pure sample for microanalysis have failed. Each time a blue solution was washed off the column prior to the product. The best microanalysis obtained is given below.

$C_{14}H_{15}NOS$ requires C,69.66; H,6.26; N,5.80;

found C,67.99; H,6.35; N,5.57%.

MS ($M^{\cdot+}$241) 225, 210, 167, 152, 106, 73.

4-ACETYLENEINDOLE-3-CARBOXALDEHYDE (96).

The silylated indole (95) (0.7g, 2.9mmol) was dissolved in methanol (20ml). Added to this was potassium carbonate (anhydrous) (0.1g). The mixture was stirred for 4 hours at room temperature under nitrogen. The methanol was removed under reduced pressure and the dark red residue was taken up in ethyl acetate. This was washed with saturated brine and dried over magnesium sulphate. The residue was purified by column chromatography on silica gel (Merck7729) with 20% ethyl acetate in petrol to leave pure product as a pale brown solid, 0.32g, 1.9mmol, 65.5%, mpt. 157-158^{o}C.

IR (KBr disc) cm^{-1} 3480, 3420, 1730, 1600, 1485, 1400, 840.

NMR ($(CD_3)_2CO$) δ ppm 10.63(s,1H); 8.03(d,1H); 7.33(m,3H); 3.90(s,1H).

$C_{11}H_7NO$ requires C,78.09; H,4.17; N,8.27;

found C,76.65; H,4.06; N,8.15%.

MS ($M^{\cdot+}$169) 141, 114, 88, 63.

This compound is not very stable, in that it turns black on exposure to air.

4-ETHYLINDOLE-3-CARBOXALDEHYDE (98).

The acetylene (96) (0.22g, 1.3mmol) was dissolved in methanol (20ml), added to this was Lindlar catalyst (40mg). The product was

hydrogenated at atmospheric pressure for 3 hours, after which time 58ml. of hydrogen had been taken up (theoretical amount 29.12ml). The catalyst was filtered off through hyflo, and the solvent evaporated down to dryness. The residue was purified by short path column chromatography on silica gel (Merck7729) using 25% ethyl acetate in petrol as the eluent. Pure product was obtained as a brown solid, 0.20g, 1.15mmol, 89%.

IR (KBr disc) cm^{-1} 3300, 2980, 2930, 2840, 2780, 1650, 1510, 1400, 760.

NMR ($(CD_3)_2CO$) δ ppm 9.73(s,1H); 7.93(d,1H); 7.03(m,3H); 3.30(q,2H); 3.0(brs,1H); 1.23(t,3H).

MS ($M^{\cdot+}$173) 172, 158, 156, 154, 144, 130, 115, 77.

4-VINYLINDOLE-3-CARBOXALDEHYDE (99).

A) 4-acetylene indole-3-carboxaldehyde (96) (1.88g,11.1mmol) was dissolved in pyridine (30ml), and added to this was the catalyst, 10% palladium on barium sulphate. The mixture was hydrogenated at atmospheric pressure until 248ml (theory) of hydrogen had been taken up. The catalyst was filtered off through hyflo, and then washed with ethyl acetate. The organic phase was then washed with dilute hydrochloric acid to remove the pyridine, followed by saturated brine. The ethyl acetate was then dried over sodium sulphate and evaporated to leave a brown solid (2.26g). This was then purified by column chromatography on silica gel (Merck7729) using 50% ethyl acetate/petrol as eluent, to give pure product as a pale brown solid, 1.19g, 6.95mmol, 63%, mpt. 145-147°C.

IR (KBr disc) cm^{-1} 3110, 2750, 1650, 1510, 1450, 1405, 1295, 1000, 990, 770, 755.

NMR ($(CD_3)_2CO$) δ ppm 9.70(s,1H); 8.23(J=11Hzdd,1H); 8.06(d,1H); 7.26(m,3H); 5.63(J=17Hzdd,1H); 5.16(J=11Hzdd,1H).

$C_{11}H_9NO$ requires C,77.17; H,5.29; N,8.18; found C,76.27; H,5.25; N,8.10%.

MS ($M\cdot^+$171) 169, 143, 141, 140, 115, 114, 113, 89, 70, 63.

4-VINYL-3-(2-NITROVINYL)INDOLE (100)

A mixture of (99) (500mg, 2.9mmol), ammonium acetate (280mg,3.6mmol) and nitromethane (1.7ml, 3.1mmol) was heated at 150°C for 5 minutes. A dark red solution formed, which was allowed to cool to room temperature, during which time a red precipitate settled out. This was filtered off under vacuum, then washed with water and allowed to dry in air. Product was obtained as a red solid, 520mg, 2.43mmol, 84%, mpt. >160°C (decomposed).

IR (KBr disc) cm^{-1} 3110, 1610, 1565, 1500, 1480, 1250, 1130, 980, 960, 815, 755.

NMR ($(CD_3)_2CO$) δ ppm 8.46(J=6Hzd,1H); 8.13(J=6Hzd,1H); 7.70(J=12Hzd,1H); 7.16(m,4H); 5.70(J=19Hzdd,1H); 5.16(J=20Hzdd,1H).

MS ($M\cdot^+$214)184, 168, 167, 166, 154, 139, 127, 115, 84, 63.

Results comparable with those obtained later.

4-VINYL-3-(1-NITROETHYL)INDOLE (101).

The nitroethylene (100) (720mg, 3.36mmol) was suspended in chloroform (30ml) and isopropanol (30ml). Added to this was silica gel (Merck7734) (6g). This suspension was stirred, cooled in an ice bath, then sodium borohydride (1.03g, 27.3mmol) was added, portion wise. The reaction was left to stir at room temperature for 30 minutes, then dilute hydrochloric acid was added. The silica gel was filtered off and washed with chloroform. The two layers separated, and the aqueous phase was washed with chloroform. The combined organic extracts were

washed with saturated brine, and dried over sodium sulphate. The solvent was evaporated off to leave an orange oil (1.15g), which was purified by column chromatography on silica gel (Merck7729) using dichloromethane as eluent. Product was obtained as a pale brown oil, 360mg, 1.66mmol, 49%, (79% based on recovered starting material).

IR (liquid film) cm^{-1} 3410, 2930, 2870, 1610, 1545, 1385, 990, 920, 750.

NMR ($(CD_3)_2CO$) δ ppm 9.73(brs,1H); 7.43(J=11Hzd,1H); 7.03(m,4H); 5.60(J=17Hzdd,1H); 5.26(J=11Hzdd,1H); 4.60(t,2H); 3.46(t,2H).

MS ($M^{\cdot+}$216) 102, 89, 77, 75, 63, 51, 39.

INTRAMOLECULAR NITRILE OXIDE CYCLISATION.

A mixture of compound (101) (320mg, 1.48mmol), phenylisocyanate (0.16ml, 1.48mmol) and triethylamine (catalytic amount) in ether was stirred for 24 hours, under nitrogen, at room temperature. The mixture was then dissolved in ethyl acetate, and washed with saturated ammonium chloride, and saturated brine. The organic phase was then dried over sodium sulphate and evaporated to dryness, to leave an orange solid 840mg. This was purified by column chromatography on silica gel (Merck7729) with 20% ethyl acetate in petrol. Pale brown solid was obtained 200mg, which was not 100% pure, a small quantity of diphenyl urea was inseparable from the product.

NMR ($(CD_3)_2CO$) δ ppm 9.86(brs,1H); 7.16(m,3H); 6.66(d,1H); 4.86(d,2H); 3.83(t,2H); 2.80(s,1H).

MS ($M^{\cdot+}$212 diphenyl urea) ($M^{\cdot+}$198 isoxazoline) 168, 119, 93, 77, 65, 39.

ATTEMPTED REDUCTION OF THE ISOXAZOLINE MIXTURE.

The isoxazoline mixture (40mg, 0.2mmol) was dissolved in a mixture of water/acetic acid/methanol 1:1:1 (6ml) and added to this was platinum oxide (catalytic amount). The mixture was hydrogenated at atmospheric pressure until 13ml. of hydrogen had been taken up (theoretical value 8.96ml). The catalyst was filtered off, and the filter cake was washed with ethanol. The filtrate was made basic with sodium hydroxide. The product was extracted with ethyl acetate, and then washed with water followed by saturated brine. The solvent was dried over sodium sulphate and evaporated down to leave a black solid, 30mg, which was one spot on a TLC plate. The infra red indicated it to be N,N-diphenyl urea.

IR (KBr disc) cm^{-1} 2350, 1650, 1550, 1500, 1450, 1320, 1240, 900, 755, 700.

VINYL BORONIC ACID.

In a dry flask was placed dry magnesium turnings (1.17g, 48mmol) and enough dry THF to just cover the magnesium. To this was added vinyl bromide (1ml). After the reaction had started, more THF (50ml) was added, followed by the rest of the vinyl bromide (2.36ml) in THF (20ml), added at such a rate as to keep a moderate reflux. The solution was then refluxed for a further 30 minutes. The resulting green coloured solution was cooled to -70°C in a dry ice/acetone bath, and flushed with nitrogen. To this was added triisopropyl borate (12.3ml,53mmol), and left to stir for 1-2 hours, gradually attaining room temperature. Sodium hydroxide solution was added, and the solution was then washed with ether. The aqueous phase was acidified with dilute hydrochloric acid, and then extracted with ether (100ml). The organic phase was washed with brine, and dried over sodium

sulphate. Evaporation of the solvent left a jelly, 3.55g, which was insoluble in deuterated chloroform and DMSO. An attempt was made to isolate the sodium salt, by dissolving in sodium hydroxide, but the gel was not soluble. (Vinyl boronic acid polymerises on contact with oxygen).

ETHYL 2-CHLORO-6-NITROPHENYL PYRUVATE (102).

In a 2l 3-necked flask was placed dry ether (90ml), the flask was fitted with a reflux condenser and dropping funnel, calcium chloride drying tube and a nitrogen inlet. Potassium metal (11.3g, 290mmol) was added, and a stream of nitrogen passed over the surface. A mixture of absolute ethanol (72.5ml) and dry ether (58ml) was added slowly so as to keep the ether at a gentle reflux. When all the potassium had dissolved the solution was diluted with dry ether (720ml), and diethyl oxalate (42g, 290mmol) was added. A yellow precipitate formed which was stirred for a further 10 minutes, after which, 2-chloro-6-nitrotoluene (50g,290mmol) was added. The yellow precipitate turned to a red solution, after 10 minutes this had solidified. The solid was left to stand for 24 hours, and then filtered under vacuum, the solid was washed with dry ether, and then acidified with dilute hydrochloric acid. The product was extracted into ethyl acetate, and washed with saturated brine. The solvent was dried over magnesium sulphate and evaporated to leave a red oil, 55.90g, 210mmol, 72%.

IR (liquid film) cm^{-1} 3100, 3000, 2950, 2880, 1750, 1600, 1525, 1450, 1350, 1280, 1115, 1060, 810, 730.

NMR ($CDCl_3$)δ ppm 7.50(m,3H); 4.63(s,2H); 4.30(q,2H); 1.40(t,3H).

MS ($M^{\cdot+}$272) 198, 170, 154, 140, 138, 136, 112, 89, 63, 44.

4-CHLOROINDOLE-2-CARBOXYLIC ACID (20)

A) A solution of the pyruvate ester (103) (1g, 3.68mmol) in dilute ammonium hydroxide (20ml) was added to a suspension of ferrous hydroxide, prepared from ferrous sulphate heptahydrate (6.12g, 22mmol), conc. ammonia solution (2.55ml) and water (22ml). The mixture was maintained at reflux for 2.5 hours, then allowed to cool. The ferric hydroxide was filtered off through hyflo and washed with dilute ammonium hydroxide and water. The filtrate was then acidified with 2N hydrochloric acid, and a pale yellow precipitate formed. This was filtered under vacuum and washed with water, and thendried in an oven to leave the product as a pale buff solid, 430mg, 2.2mmol 59.8%, mpt. 262-264°C (lit. 259-260°C)[5].

B) The potassium salt of ethyl 2-chloro-6-nitrophenylpyruvate (102) was prepared as above. The reaction was carried out using potassium metal (12.45g, 320mmol) 2-chloro-6-nitrotoluene (54g, 320mmol) and diethyl oxalate (47g, 320mmol). The yield of isolated product was 67.32g, 217mmol, 75%.

The salt (50g, 161mmol) was then subjected to reduction using ferrous hydroxide made from ferrous sulphate (283.7g,1.02mol) water (1.5 l) conc. ammonium hydroxide (115ml) and dilute ammonium hydroxide (1 l). The mixture was refluxed for 72 hours. The reaction was then cooled and ferric hydroxide filtered off, the filtrate was then acidified and the resulting precipitate filtered off under vacuum. The product was washed with water and dried to leave a pale brown solid. This was recrystallised from ethanol to give the product as brown needle-like crystals, 27.73g, 142mmol, 88%, mpt. 253-255°C).

IR (KBr disc) cm^{-1} 3360, 3050(br), 1710, 1620, 1500, 1430, 1350, 1200, 950, 770.

NMR $(CD_3)_2CO$ δppm 10.80 (brs,1H); 9.60(brs,1M); 7.36(dd,1H); 7.03(m,3H).

M/S ($M.^+$195) 194, 177, 149, 123, 114, 88.

4-CYANOINDOLE (21).

A) A mixture of 4-chloroindole-2-carboxylic acid (20) (7.8g 39.9mmol) cuprous cyanide (5.25g, 58.6mmol) and quinoline (35g) was maintained at reflux (237°C) for 21.5 hours. The hot brown solution was poured onto ice and extracted with ether (several times), the combined organic extracts were washed with dilute hydrochloric acid, followed by saturated sodium bicarbonate solution. The ether was then dried over sodium sulphate and evaporated under reduced pressure, to leave a brown oil (7.71g). This was purified by column chromatography on silica gel (Merck7729) using 15% ethyl acetate in petrol, then recrystallised from water. The pure product was obtained as a pale brown solid, 2.00g, 14.1mmol, 35%, mpt. 116-117°C (lit. 120-121°C)[5].

IR (KBr disc) cm^{-1} 3320, 2215, 1500, 1430, 1350, 1110, 750.

NMR ($CDCl_3$) ppm 8.70(brs,1H); 7.50(J=9Hzd,1H); 7.0(m,3H); 6.4(t,1H).

MS ($M\cdot^+$142) 115, 114, 88, 71.

B) A mixture of 4-chloroindole-2-carboxylic acid (2.00g, 10.2mmol), cuprous cyanide (1.35g, 15mmol) and N-methylpyrrolidone (30ml), were refluxed (202°C) for 24 hours. The hot brown solution was poured onto ice, and extracted with ethyl acetate, which was then washed with water, dilute hydrochloric acid, water and sodium bicarbonate solution. The organic phase was dried over sodium sulphate and evaporated under reduced pressure to leave a brown oil, 1.92g, which was purified by column chromatography on silica gel (Merck7729) with 20% ethyl acetate in petrol as eluent, to give a pale yellow solid as

product, 0.54g, 3.8mmol, 37%.

Data as above.

4-FORMYLINDOLE (29).

A) 4-cyanoindole (2.00g, 14.1mmol) was dissolved in dry benzene (30ml), added to this, under nitrogen, was a 1.0 molar solution of diisobutyl aluminium hydride (DIBAL) in toluene (30ml, 30mmol). The resulting orange solution was stirred at room temperature for 24 hours, after which time a layer of red gel was visible. The DIBAL was destroyed by the slow addition of dilute hydrochloric acid, the insoluble salts were filtered off and the filtrate extracted with ethyl acetate. This was washed with water followed by saturated brine, and then dried over sodium sulphate, the solvent was then removed under reduced pressure to leave a red solid, 3.15g. This was purified by column chromatography on silica gel (Merck7736) using 20% ethyl acetate in petrol, to leave pure product as a pale brown solid, 1.38g, 9.51mmol, 67%, mpt. 135-137°C (lit. 138°C)[11].

B) 4-cyanoindole (1.38g, 9.7mmol) and sodium hypophosphite (2.64g, 30mmol) were dissolved in a 1:1:2 mixture of water, acetic acid and pyridine (50ml). To this was then added a 50% suspension of Raney nickel in water (2ml). The mixture was warmed to 45°C and stirred for 1 hour. The Raney nickel was filtered off and washed with ethanol, the product was extracted with ether (50ml), and washed sequentially with dilute hydrochloric acid, saturated sodium bicarbonate, and saturated brine. The ether was then dried over sodium sulphate and evaporated to dryness. Product was obtained pure, (one spot only on TLC) as a yellow solid, 1.22g, 8.4mmol, 87%, mpt. 138-140°C.

IR (KBr disc) cm^{-1} 3300, 1670, 1575, 1500, 1350, 1110, 950, 750.

NMR ($(CD_3)_2CO$) δ ppm 9.96(s,1H); 7.30(m,5H).

MS ($M^{\cdot+}$ 245) 144, 116, 89, 64, 59.

METHYL 2-METHYL-3-NITROBENZOATE (105).

A large flask fitted with reflux condenser and nitrogen atmosphere was charged with dry distilled DMF (200ml). To this was added 2-methyl-3-nitrobenzoic acid (13.5g, 69mmol), methyl iodide (42.75g, 300mmol) and sodium bicarbonate (25g, 300mmol). The mixture was stirred and heated at 60°C for 24 hours. After which time a TLC showed no acid was present. The mixture was cooled to room temperature, and filtered. The filtrate was concentrated in vacuo to leave a yellow residue, which was taken up in ethyl acetate (100ml), a white precipitate formed (sodium iodide) which was removed by filtration, and washed with ethyl acetate. The organic phase washed sequentially with saturated sodium bicarbonate, dilute hydrochloric acid and saturated sodium chloride solutions. The ethyl acetate was dried over magnesium sulphate and then evaporated to dryness to leave a yellow/brown solid. This was recrystallised from ethanol to leave pure product, 11.04g, 58mmol, 84% as a white crystalline solid, mpt. 65.5-67.5°C lit 66°C)[11].

IR (KBr disc) cm^{-1} 3020, 2950, 1730, 1540, 1380, 1280, 1130, 880, 730.

NMR $CDCl_3$) δ ppm 8.00(t,2H); 7.50(t,1H); 4.00(s,3H); 2.66(s,3H).

ETHYL TRANS-2-[-(DIMETHYLAMINO)VINYL]-3-NITROBENZOATE (106).

A dry flask was fitted with a reflux condenser and charged with dry distilled DMF (50ml). To this was added methyl 2-methyl-3-nitrobenzoate (9.75g, 50mmol) and DMFDMA (17.85g, 150mmol). The red solution was heated (oil bath 150°C) under nitrogen for 6 hours. The DMF and other volatiles were distilled off, and the residue bulb to

bulb distilled, under vacuum. Product was a dark red oily liquid, 8.04g, 32mmol, 64%.

IR (liquid film) cm^{-1} 2940, 1715, 1660, 1520, 1270, 905, 730.

NMR ($CDCl_3$) δ ppm 7.86(d,2H); 7.20(t,1H); 6.49(d,1H); 5.76(d,1H); 3.95(s,3H); 2.90(s,6H).

METHYL INDOLE-4-CARBOXYLATE (82).

A) The enamine (106) (3.99g) was placed in a flask with iron powder (10g, 180mmol), ethanol (50ml) and acetic acid (50ml). The mixture was heated on a steam bath, while being stirred mechanically, to 50°C. The heat was removed and the reaction allowed to warm to 85°C (exothermically), cooling in an ice bath. When the reaction had cooled down, it was then heated at reflux for 1.5 hours. The mixture was then cooled and poured into water (200-300ml), and this then filtered through hyflo, and washed with ether (200ml). The two layers of the filtrate were separated, and the aqueous layer was washed with ether (3 x 50ml). The combined organic extracts were washed with 15% sodium carbonate solution until basic, followed by saturated brine. The ether was dried over magnesium sulphate, and evaporated under reduced pressure, to leave an orange oil. This was purified by column chromatography on silica gel (Merck7736) to give a brown solid, 0.86g, 4.91mmol, 32%.

IR (KBr disc) cm^{-1} 3400, 2950, 1700, 1620, 1580, 1430, 1350, 1280, 1145, 900, 760.

NMR ($CDCl_3$) δ ppm 9.39(brs,1H); 8.23(d,1H); 7.80(d,1H); 7.40(m,3H); 4.06(s,3H).

B) The crude enamine (1060 (140mmol) was dissolved in toluene/acetic acid, 5:3 (420ml) and added to a stirred mixture of iron powder

(140g), silica gel (310g) in toluene/acetic acid (182ml). The mixture was refluxed under nitrogen for 1.25 hours, and then cooled to 25°C, followed by filtration through hyflo. The filter cake was washed with DCM, and then the filtrate was evaporated down under reduced pressure. The residue was taken up in ethyl acetate, which was washed with 2M sodium thiosulphate, 15% sodium carbonate and brine. The organic phase was dried over sodium sulphate and evaporated down, to leave a brown oil, 26.21g. This was purified by column chromatography on silica gel (Merck7736) using 20% ethyl acetate in petrol as eluent. Pure product was obtained as pale brown crystals, 20.74g, 85.7%, mpt 62-64°C (lit. 64°C)[13].

NMR and IR data as above.

C) The enamine (107) was prepared by using the above conditions except pyrrolidine was added to the reaction mixture. The enamine (7.4g, 27mmols) was dissolved in methanol (5mml) and dry THF (54ml). This was stirred under nitrogen at 30°C. Added to this was Raney nickel (0.6ml), followed by hydrazine hydrate (2.4ml, 41mmol). The reaction was warmed to between 45-50°C and maintained at this temperature throughout the reaction. Hydrazine hydrate (2.4ml) was added after 30 mins and 90 mins after the initial addition. The reaction was kept between 45 and 50°C for a further 2 hours, and then cooled to room temperature. A TLC of the reaction mixture showed that no indole was present (no violet colour with Ehrlich's reagent), but a number of other spots were visible. The reaction was not continued any further.

D) The enamine (106) (1.00g, 3.99mmol) was dissolved in ethanol (20ml), and then added to this was freshly prepared nickel boride (1g). The suspension was then heated to reflux. To this was then added hydrazine hydrate (2mls) over 15 minutes. A TLC of the reaction mixture showed some

indole (pink with Ehrlich's reagent), but also there was a number of other spots, which were inseparable by chromatography.

1-(DIMETHOXYMETHYL)-2-METHYL-3-NITROBENZENE (110)

A solution of the diacetate (55) (20.00g) 75mmol) in anhydrous methanol (1000cm^3) was cooled to 72°C in an ethanol/dry ice bath, with vigorous stirring. To this was added (dropwise) thionyl chloride (100ml). After this had all been added, the mixture was allowed to stand at room temperature for 1 hour, after which the pale yellow solution was poured into water and crushed ice (2l), containing sodium hydroxide (120 g). This was stirred and then left to stand at room temperature for 2 hours. The product was extracted with DCM, washed with water, and dried over magnesium sulphate. The solvent was evaporated off under reduced pressure to leave a yellow oil, 9.66g, 46mmol, 61%.

IR (liquid film) cm^{-1} 2995, 1600, 1540, 1360, 1220, 1010, 760.

NMR ($CDCl_3$) δ ppm 7.55(m,3H); 5.50(s,1H); 3.33(s,6H); 2.45(s,3H).

4-FORMYL INDOLE (29).

A solution of the acetal (110) (5g, 23.7mmol) in dry DMF (25ml) was kept under nitrogen while DMFDMA (3.65ml) and pyrrolidine (2.3ml) were added. The mixture was heated at reflux with stirring for 4 hours. The DMF was evaporated off at 2.5 torr and 80°C. The residue, which was used without further purification, was taken up in THF/methanol (1:1, 50ml). To this was added (under nitrogen), Raney nickel, suspended in ethanol, (2ml). The mixture was stirred at 30°C while hydrazine hydrate (2.5ml) was added dropwise. The mixture was warmed to between 45-50°C, while further quantities of hydrazine hydrate (2.5ml) were added at 30 and 90 minutes after the initial addition. The reaction was kept between 45-50°C for a further 2 hours, after which time the mixture was filtered through hyflo, and the filter cake washed with DCM. The solvent was evaporated off and the residue chromatographed on silica gel (Merck7736) with DCM as eluent. The isolated product was not the desired indole.

BIS 2-METHYL-3-NITROSTYRENE (113).

Instant ylid (methyltriphenyl phosphonium bromide + sodium amide) (10.0g, 24mmol) was dissolved in dry THF (50ml). This was then cooled to 0°C, under a nitrogen atmosphere. The benzaldehyde (86) (1.98g, 12mmol) was dissolved in dry THF (5ml), and added to the solution of the ylid. The resulting suspension was stirred at 0°C for 1 hour, after which time observation by TLC showed disappearance of starting material. The reaction mixture was then diluted with water, and extracted into ether (3 x 30ml). The combined organic extracts were washed with water, and then dried over magnesium sulphate, the solvent was evaporated off to leave a brown oil. This was purified by column chromatography on silica gel (Merck7736) using 4:1 cyclohexane/DCM as

eluent. The pure product was obtained as a pale brown solid, 2.43g, 7.5mmol, 62.5%, mpt. 131-133 °C.

IR (KBr disc) cm^{-1} 2925, 1530, 1370, 990, 930, 815, 715.

NMR ($CDCl_3$) δ ppm 7.40(m,8H); 5.50(m,4H); 3.16(s,4H).

$C_{18}H_{16}N_2O_4$ requires C,66.65; H,4.97; N,8.63;

found C,66.56; H,5.19; N,8.04%.

2-METHYL-3-NITROSTYRENE (112).

Methyltriphenyl phosphoniumiodide (3.00g, 7.27mmol) was suspended in dry THF (50ml), and cooled to -78°C. To this was added n-butyllithium (4.6ml, 7.27mmol). This was allowed to stir for about 1.5 hours. The aldehyde (86) (1.00g, 6.06mmol) was added, under nitrogen. The mixture was allowed to warm up to room temperature, and then left to stir overnight. The pinky/brown suspension was diluted with water, and extracted into ether (3 x 30ml). The combined organic extracts were washed with brine, and dried over sodium sulphate. The solvent was evaporated off to leave a red oil. This was purified by column chromatography on silica gel (Merck7736) using 4:1 cyclohexane/ DCM, to leave a brown solid, 690mg, 4.23mmol, 70%.

IR (KBr disc) cm^{-1} 3080, 2980, 2960, 2860, 1600, 1525, 1350, 990, 930, 810, 745, 725.

NMR ($CDCl_3$) δ ppm 7.5(m,3H); 6.85(4xs,1H); 5.60(m,2H); 2.98(s,3H).

INDOLE-4-METHANOL (120).

Methyl indole-4-carboxylate (82) (20.00g, 114mmol) was dissolved in dry ether (200ml). This was added dropwise to a suspension of LAH (8.73g, 230mmol) in dry ether (150ml), cooled in ice under a nitrogen atmosphere. The resulting suspension was stirred for a further 2 hours, while warming up to room temperature, after which time dilute

hydrochloric acid was added. After effervescence had ceased, the solid was removed by filtration through hyflo. The cake was washed with ethyl acetate. The filtrate was then dried over sodium sulphate, and evaporated down to leave a brown oil, which was purified by column chromatography on silica gel (Merck7736) using 20% ethyl acetate in petrol as eluent. Pure product was obtained as a white solid, 15.68g,107mmol, 93.9%, mpt. 53-55°C (lit.56-57°C)[11].

IR (KBr disc) cm^{-1} 3600-3000, 1600, 1500, 1350, 1160, 1120, 900.

NMR ($CDCl_3$)δ ppm 8.4(brs,1H); 7.06(m,4H); 6.53(m,1H); 4.86(s,2H); 2.16(s,1H).

4-FORMYL INDOLE (29).

Indole-4-methanol (15.68g, 107mmol) was dissolved in dry DCM (600ml). To this was added active (brown) manganese dioxide (58.61g), and the suspension was then stirred at room temperature for 2 days. The manganese dioxide was then filtered off through hyflo, and the filter cake was washed with DCM. The filtrate was evaporated down to leave an off white solid, 14.64g, 101mmol, 94.4%, mpt. 141-143°C (lit.138°C[11],142°C[13]).

IR (KBr disc) cm^{-1} 3300, 1670, 1595, 1350, 1110, 900, 750.

NMR ($(CD_3)_2CO$)δ ppm 10.00(s,1H); 7.30(m,5H); 6.60(d,1H).

MS ($M^{\cdot+}$145) 144, 116, 89, 64, 59.

4-VINYL INDOLE (115).

METHOD A

A solution of 2-methyl-3-nitrostyrene (112) (3.29g, 20mmol) and DMFDMA (7.15g, 60mmol) in dry DMF (30ml) was heated at 130°C under nitrogen for 6 hours. The DMF was then removed by distillation (99°C/0.2mmHg), and the residue bulb to bulb distilled (130°C/0.5mmHg). The product (114) obtained was used in the next step.

The enamine (114) (3.95g, 18mmol) was taken up in methanol (30ml) and to this was added 30% aqueous titanium trichloride (60ml, 117mmol) and stirred at room temperature for 7 minutes. Water (75ml) was added, and the product extracted with DCM/methanol 9:1. Conc. ammonia was added to the organic extract, which was then washed with brine. The solvent was then dried over sodium sulphate, and evaporated down to leave a brown gum. A TLC of this showed the absence of any indole, (by Ehrlichs reagent), only yellow spots were visible. The product was dissolved in methanol and a further 117 mmol of titanium trichloride was added, a TLC of the mixture showed a large number of spots giving a violet colour with Ehrlichs reagent. No attempt was made to isolate this due to the complexity of the TLC.

4-VINYL INDOLE (115).

METHOD B

To a suspension of methyltriphenyl phosphonium iodide (38.15g, 96mmol) in dry THF (500ml), under nitrogen cooled to 0°C, was added n-butyllithium (60ml, 96mmol). This was stirred at room temperature for 30 minutes, then added to this was 4-formyl indole (7g, 48mmol) in dry THF (50ml). The resulting suspension was stirred at room temperature for 1 hour, water was added, and the two layers separated. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, and dried over sodium sulphate. The solvent was removed under reduced pressure to leave a brown oil, 29.75g, which was purified by column chromatography on silica gel (Merck7736). Pure product was obtained as a straw coloured oil, 6.42g, 44.8mmol, 93%.

IR (liquid film) cm^{-1} 3450, 1500, 1410, 1350, 1135, 1000, 920, 755.

NMR ($CDCl_3$) δ ppm 7.56(brs,1H); 6.83(m,5H); 6.50(m,1H); 5.7(J=18Hz+2Hzdd,1H); 5.19(J=10Hz+2Hzdd,1H).

MS ($M^{\cdot+}$143) 142, 115, 88.

4-VINYL GRAMINE (121).

N,N-dimethyl imminium chloride was prepared immediately before use. Tetramethyl diamino methane (1.25ml, 9.1mmol) was dissolved in dry ether (20ml), in a Buchner flask. The side arm was connected to a nitrogen line. Acetyl chloride (0.64ml, 9.1mmol) was added with vigorous stirring. The resulting white precipitate was filtered under reduced pressure in a nitrogen atmosphere. The product was immediately added to a solution of 4-vinyl indole (1g, 7mmol) in dry DCM (20ml), and left to stir for 10 minutes under nitrogen. Water (10ml) was added, and the mixture left to stir for a further 2-3 minutes. The aqueous phase was made basic with 2N sodium hydroxide, and then extracted with ethyl acetate. The combined organic phases were washed with brine, and then dried over sodium sulphate. The solvent was evaporated off to leave a brown oil, 1.26g, which was purified by column chromatography on alumina (basic grade 111) using ethyl acetate as eluent. Pure product was obtained as an oil, 810mg, 4mmol, 57%.
NMR ($CDCl_3$) δ ppm 8.73(brs,1H); 7.6(J=10Hzdd,1H); 7.1(m,3H); 6.6(d,1H); 5.6(J=17Hzdd,1H); 5.2(J=10Hzdd,1H); 3.46(s,2H); 2.26(s,6H).

ATTEMPTED SYNTHESIS OF 4-VINYL-3-NITROETHYL INDOLE (101).

A mixture of the gramine derivative (121) (800mg, 4mmol) and nitromethane (5ml) were cooled to 0 ^{o}C, in THF (10ml). Added to this was DMAD (680mg, 4.8mmol). The mixture was left to stir for 5 hours, after which time water was added. The product was extracted into ethyl acetate, and the organic extract was then washed with brine. The solvent was then dried over sodium sulphate and then evaporated down to leave a red oil, 2.31g. This was purified by column chromatography on silica gel (Merck7736) using 40% ethyl acetate in petrol to leave

an oil 660mg. NMR suggested the alkene derived from DMAD.

NMR ($CDCl_3$) δ ppm 6.98(s,1H); 2.49(s,6H); 2.23(s,6H).

4-VINYL INDOLE-3-CARBOXALDEHYDE (99).

B) Dry DMF (6.2ml) was cooled to between 10-20°C under nitrogen, then phosphorous oxychloride (2ml) was added dropwise, to form an orange solution, which was left to stir for 10 minutes. To this was added 4-vinyl indole (2.00g, 14mmol) in dry DMF (5ml). The solution was stirred at 35°C for 45 minutes, and then poured onto ice, which was then made basic with 2N sodium hydroxide. A yellow precipitate formed, and the mixture was boiled for 10 minutes. The aqueous phase was extracted with ethyl acetate, which was washed sequentially with saturated sodium bicarbonate, dilute hydrochloric acid, and brine. The organic phase was then dried over sodium sulphate, and evaporated down to leave a dark brown solid, 3.46g. This was purified by column chromatography on silica gel (Merck7736) using 50% ethyl acetate/petrol, to leave pure product as a brown solid, 1.05g, 6.1mmol, 43.6%, mpt. 146-148°C. NMR, IR and MS data were identical to those for the compound produced by route A.

N-TOSYL-3-AMINOPROPANOL (129).

To a solution of 3-aminopropanol (10g, 133mmol) in dry pyridine (50ml) was added p-toluene sulphonyl chloride (25.36g, 133mmol) in two portions. This was stirred at 0°C, slowly warming to room temperature over 3 hours. The solution was then poured into dilute hydrochloric acid. The product was extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with dilute hydrochloric acid, and brine. They were then dried over sodium sulphate, and evaporated, to leave an orange oil. This was purified by column chromatography on

silica gel (Merck 7736) using 3:1 ethyl acetate/petrol as eluent. The first product isolated was the ditosylated product (130), 7.06g, 18.1mmol, 14%, mpt. 114-116°C.

IR (KBr disc) cm^{-1} 3300, 1600, 1360, 1180, 940, 850.

NMR ($CDCl_3$) δ ppm 7.33(dd,A,B pattern,8H); 5.16(t,1H); 3.96(t,2H); 2.93(q,2H); 2.39(s,6H); 1.83(qn,2H).

MS ($M^{\cdot+}$384) 228, 212, 184, 155, 91, 56.

$C_{17}H_{21}NO_5S_2$ requires C,53.24; H,5.51; N,3.65;

found C,53.27; H,5.60; N,3.63%.

The second product from the column was the desired product (129) as a yellow oil.

IR (liquid film) cm^{-1} 3350, 2940, 2880, 1600, 1410, 1320, 1160, 910.

NMR ($CDCl_3$) δ ppm 7.46(dd,A,B,4H); 3.66(t,2H); 3.03(t,2H); 2.40(s,3H); 1.70(qn,2H).

$C_{10}H_{15}NO_3S$ requires C,52.38; H,6.59; N,6.11;

found C,52.50; H,6.64; N.6.05%.

N-TOSYL-3-AMINOPROPIONALDEHYDE (131).

A) To a suspension of PCC (17.5g, 81mmol) in dry DCM (120ml) was added the alcohol (129) (12.35g, 54mmol) in dry DCM (100ml), this was stirred at room temperature overnight. The insoluble salts were filtered off , and then the filtrate was evaporated down to leave a brown oil, which was purified by column chromatography on silica gel (Merck7736) using 4:1 petrol/ethyl acetate followed by 13:7 petrol/ethyl acetate, to give pure product as a yellow oil, 3.38g, 14.9mmol, 27.6%.

B) Oxalyl chloride (1.45g, 11.4mmol) was dissolved in DCM (25ml). This was cooled to -70°C, and then DMSO (1.95g, 25mmol) was added, dropwise in DCM (5ml). This was stirred for 10 minutes, then the

alcohol (129) (2.4g, 10.4mmol) in DCM (10ml) was added dropwise. This mixture was stirred at -70°C for a further 15 minutes, then triethylamine (7.25ml, 52mmol) was added dropwise. The mixture was warmed to room temperature, and then water (30ml) was added, and the mixture stirred for 10 minutes. The two layers separated, and the aqueous phase was extracted with DCM (2 x 50ml). The combined organic phases were washed sequentially with dilute hydrochloric acid, water, saturated sodium bicarbonate, and brine. The organics were then dried over sodium sulphate and evaporated to leave a yellow oil, 2.04g. This was purified by column chromatography on silica gel (Merck7736) using 45% ethylacetate/petrol to give pure product as a yellow oil, 1.48g, 6,5mmol, 62.5%.

IR (liquid film) cm^{-1} 3300, 2990, 1740, 1600, 1340, 1160, 1095, 910.

NMR ($CDCl_3$) δ ppm 9.33(s,1H); 7.30(dd,A,B,4H); 5.56(t,1H); 3.06(q,2H); 2.60(t,2H); 2.30(s,3H).

N-BENZOYL-3-AMINOPROPANOL (132).

To a solution of 3-aminopropanol (11.6g, 154mmol) in 2N sodium hydroxide (200ml), was added benzoyl chloride (17.35g, 123mmol), the mixture was stirred for 20 minutes. The product was extracted with ethyl acetate, which was then washed with brine. The organics were then dried over sodium sulphate, and then the solvent was evaporated off to leave a colourless oil. The product was purified by column chromatography on silica gel (Merck7736) with 1:1 ethyl acetate/petrol as eluent. The first product which came off the column was the dibenzoylated product (133) as a colourless oil, 1.12g, 1.95mmol, 3.2%.

IR (liquid film) cm^{-1} 3450, 3100, 2995, 1700, 1640, 1620, 1440, 1290, 1110, 920.

NMR ($CDCl_3$) δ ppm 7.73(m,4H); 7.16(m,6H); 4.23(t,2H); 3.46(q,2H);1.96(qn,2H).

The second product off the column was the product benzoylated at the oxygen (134), 0.59g, 3.29mmol, 2.7%.

IR (liquid film) cm^{-1} 3400, 3100, 1740, 1640, 1620, 1560, 1250, 1050, 920.

NMR ($CDCl_3$) δ ppm 7.66(m,2H); 7.26(m,3H); 4.06(t,2H); 3.40(q,2H); 2.00(s,2H); 1.93(qn,2H).

The desired product was the last one off the column, as a colourless oil, 16.34g, 91.2mmol, 74.1%.

IR (liquid film) cm^{-1} 3350, 3000, 2900, 1660, 1560, 1320, 1090.

NMR ($CDCl_3$) δ ppm 7.66(m,2H); 7.30(m,4H); 3.46(qn,6H); 1.76(qn,2H).

MS ($M^{\cdot+}$179) 161, 135, 134, 105, 77, 51.

$C_{10}H_{13}NO_2$ requires C,67.02; H,7.31; N,7.82;

found C,67.13; H,7.39; N,7.86%.

THE ESTER (136).

A solution of the alcohol (132) (9.00g, 50.2mmol) in dry DCM (100ml) was added to a suspension of PCC (16.5g, 76.5mmol) in dry DCM (200ml), and the resulting mixture stirred for 3.5 hours. The insoluble chromium salts were filtered off, and the filtrate was evaporated off to leave a brown oil, 13.58g. This was passed through a column of coarse silica using 50% ethyl acetate in petrol as the eluent. The product obtained was the ester (136), 1.29g, 3.64mmol, 7.25%, as a white solid, mpt. 146-148°C.

IR (KBr disc) cm^{-1} 3340, 3050, 2900, 1720, 1640, 1600, 1540, 1300, 1080, 1000, 800.

NMR ($CDCl_3$) δ ppm 8.26(brs,2H); 7.80(m,4H); 7.36(m,6H); 4.13(t,2H); 3.50(sx,4H); 2.60(t,2H); 1.96(qn,2H).

$C_{20}H_{22}N_2O_4$ requires C,67.78; H,6.25; N,7.90;

found C,67.94; H,6.31; N,7.96%.

N-BENZOYL-3-AMINOPROPION ALDEHYDE (135).

To a solution of oxalyl chloride (3.9g, 30.7mmol) in dry DCM (20ml), cooled to -70°C, was added dropwise, DMSO (4.8g, 61.4mmol). The resulting mixture was stirred for 10 minutes, thenthe alcohol (132) (14.12g, 139.5mmol) was added, and allowed to warm to room temperature. Water (100ml) was added, and the two layers were separated. The aqueous phase was extracted with DCM (3 x 50ml). The combined organic layers were washed with dilute hydrochloric acid, water, saturated sodium bicarbonate, and brine. The DCM was dried over sodium sulphate and evaporated down to leave a yellow oil, 2.13g. The product was obtained in pure form, by column chromatography on silica gel (Merck7736) using 1:1 ethyl acetate/petrol, as a colourless oil, 1.71g, 9.65mmol, 35%.

IR (liquid film) cm^{-1} 3350, 1750, 1660, 1600, 1350, 1170, 1080, 760.

NMR ($CDCl_3$) δ ppm 9.50(s,1H); 7.60(m,2H); 7.26(m,3H); 3.43(q,2H); 2.66(t,2H).

ATTEMPTED VINYL PHOSPHONATE ESTER CYCLISATION.

A) To a suspension of sodium hydride (60% dispersion in oil) (37mg, 0.92mmol), washed with petrol, in dry THF (5ml) and cooled to 0°C, was added the aldehyde (131) (200mg, 0.88mmol) in dry THF (2ml).

This was left to stir for 1 hour, and the vinyl phosphonate ester (33a) (200mg, 0.88mmol) in dry THF (2ml). This was allowed to warm to room temperature, stirred for 1 hour, then refluxed for 1.5 hours. The reaction mixture was cooled and water was added. The aqueous phase was

extracted with ethyl acetate, and washed with brine, the organic phase was dried over sodium sulphate, and evaporated to leave an orange/brown oil, 0.27g. This material was highly polar and remained on the base line of a TLC plate.

B) To a suspension of sodium hydride (60% dispersion in oil) (420mg, 10.5mmol), washed with petrol, in dry DMF (5ml), was added the aldehyde (135) (1.7g, 9.6mmol)in dry DMF (13ml). This was stirred at 0°C for 1 hour, to this was added the vinyl phosphonate ester (2.27g, 9.6mmol) in dry DMF (10ml). The mixture was stirred at room temperature for 2.5 hours. The reaction was then diluted with water (30ml), and then extracted with ethyl acetate. The combined organic extracts were washed with water and brine, and then dried over sodium sulphate. The solvent was evaporated off to leave an orange oil, 2.62g, which again remained on the base line of a TLC plate.

2-AMINO-6-BROMOTOLUENE (149).

2-bromo-6-nitrotoluene (2.00g, 9.26mmol) was suspended in ethanol (20ml), to this was added powdered tin (1.66g, 14mmol),and concentrated hydrochloric acid (2ml), slowly with stirring the temperature rose to 60°C. The mixture was left to stir for 2 hours then the tin was filtered off through hyflo, and the pad washed with water followed by ethyl acetate. The filtrate was basified with 2N sodium hydroxide. The product was extracted with ethyl acetate (3 x 50ml), and the combined organic extracts were washed with brine and dried over magnesium sulphate. The solvent was evaporated off under reduced pressure, to leave the product as a brown oil, 1.66g, 8.92mmol, 96%.

IR ($CHBr_3$ Soln.) cm^{-1} 3480, 3375, 1620, 1515, 1000, 855, 770.

NMR ($CDCl_3$) δ ppm 6.95(d,1H); 6.80(t,1H); 6.52(d,1H); 3.62(brs,2HO; 2.20(s,3H).

C_7H_8BrN requires C,45.19; H,4.33; N,7.53; Br,42.95;

found C,45.21; H,4.43; N,7.44; Br,42.99%.

N-(BENZENESULPHONYL)-2-AMINO-6-BROMOTOLUENE (150).

Benzenesulphonyl chloride (4.35ml, 18mmol) was dissolved in dry pyridine (10ml), and cooled to 0°C. 2-amino-6-bromotoluene (200g, 11mmol) was dissolved in dry pyridine (10ml), and then added dropwise to the benzenesulphonyl chloride solution. The resulting yellow/orange mixture was stirred for a further 2.5 hours, then poured into dilute hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3 x 50ml), and the combined organic extracts were washed with dilute hydrochloric acid and brine. The organic phase was dried over magnesium sulphate, then evaporated to dryness under reduced pressure. A yellow solid was left, which was dissolved in hot ether, to which hexane was added. Pure product was obtained as a white crystalline solid, 2.9g,81%,mpt.117-118°C.

IR (nujol) cm^{-1} 3200, 2880, 1450, 1330, 1160, 725.

NMR ($CDCl_3$) δ ppm [7.75(m)+7.59(m)+7.48(d)+7.40(m)] = (7H); 7.25(t,1H); 6.84(brs,1H); 2.11(s,3H).

$C_{13}H_{12}BrNO_2S$ requires C,47.86; H,3.71; N,4.29; Br,24.49; O,9.81; S,9.84;

found C,47.93 H,3.67; N,4.15; Br,24.34; O,10.12; S,9.79%.

2-BROMO-3-METHYL-P-BENZOQUINONE (152)

The sulphonamide (150) (1.00g, 3.1mmol) was dissolved in 80% aqueous acetic acid (25ml). To this was added, dropwise, a solution of

ceric ammonium sulphate (6.62g, 12.1mmol), in 80% aqueous acetic acid (75ml). The resulting red solution was allowed to stir at room temperature for 48 hours, then the mixture was poured into water. A brown precipitate formed, which was dissolved in ether, and the two layers were separated. The aqueous layer was extracted with ether (2 x 30ml). The combined organic extracts were washed with brine, and dried over sodium sulphate. The solvent was removed under reduced pressure, to leave a brown oily solid. This was purified by short path column chromatography on silica gel (Merck7729) using 9:1 hexane/ethyl acetate as eluent. Pure product was obtained as a yellow solid, 0.19g, 0.95mmol, 30.6%, mpt. 62-63 ^{o}C, (lit. 65.4-65.7 ^{o}C)[83].

IR ($CHBr_3$) cm^{-1} 1710, 1590, 1370, 1265.

UV (CH_3OH) nm 207, 253, 289, 345.

NMR ($CDCl_3$) δ ppm 6.95(d,1H); 6.82(d,1H); 2.26(s,3H).

$C_7H_5BrO_2$ requires C,41.83; H,2.51; Br,39.75; O,15.91;

found C,41.31; H,2.36; Br,37.98; O,18.35%.

2-BROMO-6-NITROBENZOIC ACID (153).

2-bromo-6-nitrotoluene (2.00g, 9.26mmol) and sodium carbonate (4.53g, 42mmol) were dissolved in hot water (140ml). To this was added potassium permanganate (5.85g, 37mmol). The solution was refluxed overnight, and after cooling it was filtered through hyflo, to remove the manganese dioxide. The filtrate was acidified with dilute hydrochloric acid, and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure, to leave a pale brown solid, which was one spot pure by TLC, 0.92g, 40%, mpt. 172-173 ^{o}C.

IR (nujol) cm^{-1} 3200-2800, 1710, 1530, 1150, 750.

NMR ($CDCl_3$) δ ppm 7.19(d,1H); 7.00(d,1H); 6.55(t,1H).

$C_7H_4BrNO_4$ requires C,34.17; H,1.64; N,5.69; Br,32.48; O,26.01;

found C,33.77; H,1.50; N,5.29; Br,31.83; O,27.81.

METHYL 2-BROMO-6-NITROBENZOATE (154).

2-bromo-6-nitrobenzoic acid (8.00g, 33mmol) was dissolved in dry DMF (50ml). To this was added sodium bicarbonate (11.09g, 132mmol) and methyl iodide (85ml, 132mmol). The mixture was heated at 60°C, under nitrogen for 24 hours. The solution was cooled and poured into dilute hydrochloric acid, the resulting precipitate was filtered off, and washed with water. The resulting white solid was dried in air, to give the product 6.46g, 25mmol, 76%, mpt. 83-85°C.

IR (nujol) cm^{-1} 1735, 1540, 1465, 1360, 1285, 750, 725.

NMR ($CDCl_3$) δ ppm 8.19(d,1H); 7.93(d,1H); 7.49(t,1H); 4.03(s,3H).

$C_8H_6BrNO_4$ requires C,36.95; H,2.33; N,5.39; Br,30.73; O,24.61;

found C,36.87; H,2.19; N,5.24; Br,30.52; O,25.18%.

4-BROMO-2,1-BENZISOXAZOL-3(1H)-ONE (157).

Methyl 2-bromo-6-nitrobenzoate (6.00g, 23mmol) was dissolved in ethanol (50ml),and added to this was powdered tin (5.46g, 46mmol), and conc. hydrochloric acid (5ml). The mixture was stirred for 24 hours. The tin was filtered off through hyflo, and the pad washed with water. The filtrate was basified with sodium bicarbonate, and the resulting precipitate removed by filtration. The filtrate was extracted with ethyl acetate (3 x 50ml), and the combined extracts washed with saturated brine, then dried over magnesium sulphate. The solvent was removed under reduced pressure, and the product purified by column chromatography on silica gel (Merck7729), using 25% ethyl acetate in hexane. Pure product was obtained as an off white solid, 1.6g, 33%,

mpt. 143.5°C (decomposes).

IR (nujol) cm^{-1} 3240-3040, 1730, 1610, 1470, 1330, 1165, 1080, 790.

NMR (DMSO-D_6) ppm 7.55(t,1H); 7.38(d,1H); 7.29(d,1H).

$C_7H_4BrNO_2$ requires C,39.28; H,1.88; N,6.54; Br,37.34; O.14.95;

found C,39.60; H,1.78; N,6.40, Br,37.18; O,15.04%.

α,2-DIBROMO-6-NITROTOLUENE (158)

2-bromo-6-nitrotoluene (25.00g, 116mmol) and N-bromosuccinimide (26.88g, 151 mmol) were dissolved in carbon tetrachloride (400ml). Added to this was benzoyl peroxide (20mg). The solution was heated at reflux under a nitrogen atmosphere, and irradiated with a 150 watt lamp for 8 days. The mixture was cooled to room temperature, and the succinimide was filtered off through hyflo. The filtrate was dried over magnesium sulphate, and the solvent removed under reduced pressure, to leave an orange solid. This was recrystallised from hexane, to give pure product as a beige crystalline solid, 34.32g, 116mmol, 100%, mpt. 61.5-63°C.

IR (nujol)cm^{-1} 1525, 1465, 1350, 810, 750.

NMR ($CDCl_3$) δ ppm 7.89(d,2H); 7.35(t,1H); 4.89(s,2H).

$C_7H_5Br_2NO_2$ requires C,28.51; H,1.71; N,4.75; Br,54.19; O,10.85.

found C,28.57; H,1.61; N,4.71; Br,53.99; O,11.12%.

1-(2-BROMO-6-NITROBENZYL)PYRIDINIUM BROMIDE (159)

α-2-dibromo-6-nitrotoluene (34.30g, 116mmol) was dissolved in ethanol (300ml), to this was added pyridine (10ml, 130mmol). The solution was heated on a steam bath for 1 hour, the solvent was then removed under reduced pressure. The solid residue was recrystallised from absolute ethanol to leave pure product as pale orange crystals,

37.21g, 86.2%, mpt. 202-205°C (lit.210°C)[76].

IR (nujol) cm^{-1} 1625, 1535, 1430, 1345, 1165, 740.

NMR (DMSO-D6) δ ppm 9.00(d,2H); 8.75(t,1H); 8.28(m,4H); 7.85(t,1H); 6.22(s,2H).

$C_{12}H_{10}Br_2N_2O_2$ requires C,38.53; H,2.69; N,7.49; Br,42.73; O,8.56.

found C,38.50; H,2.58; N,7.32; Br,42.26; O,9.34%.

2-BROMO-6-NITROPHENYL-N-(p-DIMETHYLAMINOPHENYL)NITRONE (160)

The pyridinium salt (159), (37.21g, 100ml) and p-nitroso-N,N-dimethyl aniline (18.02g, 120mmol) were added to a flask containing ethanol (300 ml). This was cooled to 0°C, then added to this was sodium hydroxide (10g) dissolved in water (90ml), dropwise, keeping the temperature below 5°C. The mixture was stirred for 1½ hours, and then poured into ice/water and stirred. A dark yellow/orange precipitate was produced, which was filtered off by suction, and washed with water. The product was not purified further.

IR (nujol) cm^{-1} 1600, 1540, 1460, 1360, 1180, 790, 740.

NMR ($CDCl_3$) δ ppm 8.18(s,1H); 7.97(d,1H); 7.88(d,1H); 7.70(d,2H); 7.41(t,1H); 6.69(d,1H); 3.04(s,6H).

2-BROMO-6-NITROBENZALDEHYDE (162)

The nitrone (36g), was stirred for 10 minutes with 6N sulphuric acid (500ml). Crushed ice was then added, and the resulting yellow precipitate was filtered off. The yellow solid was recrystallised from ethanol, to leave pure product as a yellow crystalline solid, 19.85g, 86mmol, 74.5%, mpt. 78-80°C, (lit. 82°C)[76].

IR (nujol) cm^{-1} 1710, 1530, 1340, 1180, 810, 740, 725.

NMR ($CDCl_3$) δ ppm 10.25(s,1H); 8.01(d,1H); 7.95(d,1H); 7.55(t,1H).

2-AMINO-6-BROMOBENZALDEHYDE (163)

A) Into a 3-necked flask was placed water (100ml), ferrous sulphate

heptahydrate (58g, 210mml), conc. hydrochloric acid (0.3ml) and 2-bromo-6-nitrobenzaldehyde (500g, 22mmol). The mixture was heated to 90°C and conc. ammonia solution (14ml) was added, followed by 3 x 6ml portions of conc. ammonia at 2 minute intervals. Immediately after the last portion was added, the mixture was steam distilled.

A yellow precipitate formed in the condensate, which was filtered off and dried, to give product as a yellow powder, 133g, 30% mpt. 81-83 °C.

IR (nujol) cm^{-1}, 3440, 3330, 1660, 1610, 1455, 1220, 790, 780.

NMR ($CDCl_3$) ppm 10.40(s,1H), 7.10(t,1H); 6.90(d,1H); 6.58(d,1H); 6.48(brs,2H).

C_7H_6BrNO requires C,42.08; H,3.02; N,7.00; Br,39.95; O,8.00.

found C,42.31; H,3.02; N,6.95; Br,39.66; O,8.06%.

B) 2-bromo-6-nitrobenzaldehyde (1.00g, 4.35mmol) was suspended in water (20ml), added to this was sodium dithionite (5.91g, 39mmol), and sodium carbonate (2.77g, 18mmol). The temperature rose to 42°C, while the mixture was stirred for 30 minutes. The product was then extracted with ethyl acetate, (3 x 20 ml) and the combined organic layers washed with brine. The organic phase was dried over magnesium sulphate, and evaporated to dryness. The residue was purified by column chromatography on silica gel (MERCK 7729) with 25% ethyl acetate in hexane. Pure product was obtained as yellow solid 0.13g 15% mpt. 80-82°C. Spectral data as above.

2-(2-BROMO-6-NITROPHENYL)DIOXOLONE (164)

2-bromo-6-nitrobenzaldehyde (25.00g, 100mmol) was dissolved in dry benzene (350ml). To this was added ethylene and glycol (803g, 129mmol) and p-toluene sulphonic acid (catalytic amount). The

solution was refluxed for 24 hours (Dean-Stark apparatus), after which time sodium bicarbonate solution was added, and the two layers separated. The organic layer was washed with brine and then dried over magnesium sulphate. The solvent was removed under reduced pressure, to leave a pale brown solid residue. This was recrystallised from ethanol to leave a white crystalline solid 26.77g, 107mmol 98% mpt. 71.5-72.5°C.

IR (nujol) 1535, 1460, 1370, 1230, 1200, 980, 745, 710.

NMR ($CDCl_3$) ppm 7.75 (dd,1H), 7.35(m,2H); 6.20(s,1H); 4.09(m,4H).

$C_9G_8BrNO_4$ requires C,39.44; H,2.94; N,5.11; Br,29.15.

found C,39.43; H,2.94; N,5.12; Br,29.45%.

OTHER ATTEMPTS AT REDUCTION OF COMPOUND (164) TO (165)

A) The acetal (164) (1.77g, 7.1mmol) was dissolved in ethanol (20ml) and THF (15ml). The solution was hydrogenated with 10% palladium on carbon (0.5g), and monitored for the uptake of 477 mml of hydrogen. A total of 815ml was taken up. A TLC showed only baseline materials. When a small sample was dissolved in nitric acid, and silver nitrate added, a thick precipitate was observed, which suggested that the baseline material contained inorganic bromine, possibly as a hydrobromide salt. Treatment of this with sodium hydroxide, followed by TLC, showed a product which was yellow with Erhlich's reagent, probably an amine, but the product was not characterised.

B) The acetal (164) (1.8g, 7.2mmol) was dissolved in THF (5ml), and added to a solution of sodium dithionite (1.38g, 7.92mmol) in 15% sodium carbonate solution (50ml). This was stirred for 10 minutes, then more sodium dithionite (1.38g, 7.92mml) was added. The mixture was left to stir overnight. The resulting precipitate was dissolved

in water, and then extracted with ethyl acetate (30ml). The organic phase was separated, washed with brine and dried over sodium sulphate, then evaporated off to leave an orange oil. This was purified by column chromatography on silica gel (MERCK 7729) using 50% ethyl acetate/petrol as eluent. The product was obtained as orange crystals 0.39g. The product was not the correct one by comparison with a TLC of the authentic material, and was thus not characterised.

C) Anhydrous stannous chloride (760mg, 4mmol) was dissolved in dry ethanol (10ml). To this was added the acetal (164) (500mg, 2mmol), and a few drops of THF to help dissolve the acetate. After 24 hours, a TLC showed that no amine was present, but one product which corresponded to the aldehyde (162). The acetal protection had been removed due to the acidic nature of the reaction medium.

2-(2-AMINO-6-BROMOPHENYL)DIOXOLANE (165)

The nitro acetal (164 (25.00g, 100mmol) and nickel chloride hexahydrate (47.54g, 200 mmol) were dissolved in methanol (600ml), and cooled to 0°C. To this was added slowly (keeping the temperature at 0°C), sodium borohydride (15.13g, 400mmol). The black suspension was stirred for 30 minutes at this temperature, and then allowed to warm to room temperature, at which point it was stirred for a further 5 hours. The black nickel boride was filtered off through hyflo, and the filtrate evaporated down to small bulk. The residue was taken up in ethyl acetate, which was washed with brine, and dried over sodium sulphate, and then evaporated down to leave an orange oil. This was purified by column chromatography on silica gel (MERCK 7729) using 20% ethyl acetate in hexane as eluent. Pure product was obtained as a yellow solid 12.32g, 56% mpt. 74-76°C.

IR (nujol) cm^{-1} 3440, 1610, 1595, 1470, 1070, 955, 780.

NMR ($CDCl_3$ δ ppm 6.93(m,2H); 6.58(dd,1H); 6.22(s,1H); 4.60(brs,2H); 4.15(m,4H).

$C_9H_{10}BrNO_2$ requires C,44,29; H,4.13; N,5.74.

found C,44.91; H4.09; N,5.77%.

N-(BENZENESULPHONYL)-2-AMINO-6-BROMOBENZALDEHYDE (157)

The amino acetal (165), (141mg, 0.64mmol) in dry pyridine (2ml) was added to a solution of benzene sulphonyl chloride (0.19ml, 0.77mmol) in dry pyridine (2ml). The solution was stirred at 0°C for 3 hours. 5N hydrochloric acid (4ml) was added, and the mixture stirred for a further 30 minutes. The solution was then extracted with ethyl acetate (3ml), which was then washed with dilute hydrochloric acid, and brine. The ethyl acetate was dried over magnesium sulphate, the solvent evaporated off under reduced pressure. The residue was purified by short path column chromatography on silica gel (Merck7729) using 20% ethyl acetate in hexane as eluent. Pure product was obtained as a white crystalline solid 115mg 53% mpt 103-104 °C.

IR (nujol cm^{-1}, 3100, 1660, 1440, 1380, 1165, 930.

NMR ($CDCl_3$) δ ppm 1140(brs,1H); 10.25(s,1H); 7.9(m,2H); 7.68(m,1H); 7.50(m,2H); 7.30(d,1H); 7.26(s,1H).

$C_{13}H_{10}BrNO_3S$ requires C,45.90; H,2.96; N4.12; Br,23.49; S,9.42.

found C,46.38; H,3.13; N,3.82; Br,22.21; S,9.76%.

N-(3-BROMO-2-[2-(METHYLSULPHINYL)-2-(METHYLTHIO)ETHENYL]-PHENYL)BENZENESULPHONAMIDE, (167)

The benzaldehyde (151) (500mg, 1.47mmol) was dissolved in dry THF (5ml), to this was added MMTS (0.16ml), 1.5 mmol) and Triton B (0.5ml, 294mmol). The mixture was refluxed under nitrogen for 72 hours. The

solution was cooled, and then poured into a beaker containing ethyl acetate (50ml) and saturated ammonium chloride solution (50ml). The two layers were separated, and the aqueous layer extracted with ethyl acetate (20ml). The combined organic extracts were washed with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a brown oil. The oil was purified by short path column chromatography on silica gel (Merck7729) using 50/50 ethyl acetate/petrol, to give pure product as a white solid 390mg 60% mpt. 181.5-183.5°C.

NMR ($CDCl_3$) δ ppm 7.78(m,1H); 7.50(m,7H); 7.20(m,1H); 2.86(s,3H); 2.11(s,3H).

$C_{16}H_{16}BrNO_3S_3$ requires C,43.05; H,3.61; N,3.14; Br,17.90; S,21.52.

found C,43.61; H,3.62; N,3.14; Br,18.49, S,20.62%.

N-(BENZENESULPHONYL)-4-BROMO-2-METHYLTHIOINDOLE (168)

Dry DCM (20ml) was presaturated with hydrogen sulphide gas for 20 minutes. To this was added compound (167) (860mg, 1.93mmol), and conc hydrochloric acid (30 drops). The mixture was stirred vigorously for 1 hour. 15% sodium carbonate was added until basic, then the layers were separated. The aqueous phase was extracted with DCM (2 x 20ml), and the combined organic extracts were then washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel (MERCK 7729) using 10% ethyl acetate in petrol. The product was obtained as a green solid, which was then recrystallised from ethanol, to give the pure compound as white crystals 550mg, 1.44mmol, 75% mpt. 132-133°C.

IR(KBr disc)cm^{-1} 1500, 1410, 1370, 1170, 770, 725, 680, 640.

NMR ($CDCl_3$) δ ppm 7.90(m,3H); 7.40(m,5H); 6.43(s,1H); 2.50(s,3H).

$C_{15}H_{12}BrNS_2O_2$ requires C,47.13; H,3.16; N,3.66.

found C,47.39; H,3.03; N,3.59%.

ATTEMPTED PREPARATION OF THE KETENETHIOACETALMONOSULPHOXIDE (170)

2-bromo-6-nitrobenzaldehyde (2.00g, 8.69mmol) was dissolved in THF (60ml), and a stream of nitrogen passed through this. Then MMTS (1.6ml, 10mmol) and Triton B (9mls, 19mmol) were added. The mixture turned black, and was refluxed for 3 hours. The mixture was then poured into saturated ammonium chloride solution, and extracted with ethyl acetate (50ml). This was washed with brine and dried over sodium sulphate. A TLC showed that no reaction had taken place.

GENERAL SYNTHESIS OF P-QUINONES

A number of sulphonamides were available in the laboratory, by reaction of the corresponding anilines with either benzene sulphonyl chloride of p-toluenesulphonyl chloride in pyridine.

The sulphonamides (1 mole) were dissolved in 80% aqueous acetic acid. This was added to a solution of ceric ammonium nitrate (4 mole) in 80% aqueous acetic acid. The reactions were left to stir for 48 hours, after which time they were diluted with water. The products were extracted with ether, and then washed with saturated sodium bicarbonate. The organic extract was dried over sodium sulphate and evaporated. The product was purified by column chromatography or in the case of the quinone produced from aniline, the product was purified by vacuum sublimation. The results are tabulated in chapter 3.7.

SPECTRAL DATA FOR THE QUINONES

2-METHOXYCARBONYL-3-METHYL-P-QUINONE (171)

IR (liq. film) cm^{-1} 2950, 1740, 1660, 1300, 1240, 1060, 840.

NMR ($CDCl_3$) δ ppm 6.73(s,2H); 3.90(s,3H); 2.04(s,3H).

U.V. (CH_3OH) nm 247, 305.

M/S ($M^{+\cdot}$ 180), 148, 121, 120, 91, 82, 67, 65, 54, 53, 39.

$C_9H_8O_4$ requires C,60.00; H,4.47.

found C,59.31; H,4.52.

P-BENZOQUINONE (172)

Mpt. 111.5-113°c (Lit. 113-115 °C.

IR (KBr disc) 1650, 1595, 1310, 1090, 950, 900.

NMR ($CDCl_3$) δ ppm 6.61(s,4H).

U.V. (CH_3OH) nm 244, 290.

2-CHLORO-P-BENZOQUINONE (173)

Mpt. 57-59°C (lit. 57°C)[89]

IR (KBr disc) 1640, 1590, 1510, 1480, 1220, 880.

NMR ($CDCl_3$) 7.13(s,1H); 6.63(s,2H).

U.V. (CH_3OH) nm 243, 290, 320.

2,3-DIMETHYL-P-BENZOQUINONE (174)

Mpt. 54-56°C (lit. 56.5-57.5°C)[89]

IR (KBr disc) cm^{-1} 3060, 1660, 1600, 1385, 1370, 1310, 1140, 1070, 850.

NMR ($CDCl_3$) δ ppm 6.66(s,2H); 2.00(s,6H).

U.V. (CH_3OH) nm 240, 260, 335.

2,6-DICHLORO-P-BENZOQUINONE (175)

Mpt. 115-116°C (lit. 121°C)[89]

IR (KBr disc) cm^{-1} 1700, 1650, 1580, 1330, 1090, 870, 830.

NMR ($CDCl_3$) δ ppm 6.90(s,2H).

U.V. $(CH_3)OH$ nm 243, 337.

GENERAL SYNTHESIS OF KETENE THIOACETALMONOSULPHOXIDES

A) To a solution MMTS (1 mole) and the benzaldehyde (1 mole) in dry THF was added Triton B (1.1 mole). The resulting solution was refluxed for 24 hours. The solution was cooled, and then poured into saturated ammonium chloride solution, and then extracted with ethyl acetate. The products were purified by column chromatography on silica gel.

B) To a suspension of sodium hydroxide (1.1 mole) in dry THF was added MMTS (1 mole) and the benzaldehyde (1 mole). No reaction took place until 40°C was reached, then vigorous effervescence occurred. The reaction was refluxed for 30 mins, then cooled, and then poured into saturated ammonium chloride. The product was extracted with ethyl acetate, and purified by column chromatography.

SPECTRAL DATA FOR KETENETHIOACETAL MONOSULPHOXIDES

4-ETHOXY-(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (179)

Mpt. 50-52°C.

IR (KBr disc) cm^{-1} 3000, 2450, 2145, 1600, 1520, 1485, 1250, 1175, 1050, 760, 730.

NMR ($CDCl_3$) 7.95(d,2H); 7.60(s,1H); 6.95(d,2H); 4.17(q,2H); 2.76(s,3H); 2.36(s,3H); 1.50(t,3H).

$C_{12}H_{16}O_2S_2$ requires C,56.21; H,6.29.

found C,56.44; H,6.48%.

2-METHYLSULPHINYL-2-METHYLTHIOETHENYLBENZENE (180

IR (liq. film) cm^{-1} 3010, 3000, 2850, 2250, 1600, 1500, 1420, 1070, 940, 760.

NMR ($CDCl_3$) δ ppm 8.10(m,2H); 7.80(s,1H); 7.53(m,3H); 2.83(s,3H); 2.39(s,3H).

4-METHYL-(2-METHYLSULPHINYL-2-METHYLTHIOOETHENYLBENZENE (181)

IR (liq. film) cm^{-1} 2990, 2920, 2230, 1600, 1500, 1415, 1060, 810, 730.

NMR ($CDCl_3$) δ ppm 7.90(d,2H); 7.70(s,1H); 7.25(d,2H); 2.77(s,3H); 2.38(s,3H).

4-CHLORO-(2-ETHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (182)

IR (liq. film) cm^{-1} 2970, 2910, 1580, 1475, 1400, 1240, 1050, 810.

NMR ($CDCl_3$) 8.00(s,1H); 7.80(s,1H); 7.60(s,1H); 7.50(s,1H); 7.40(s,1H); 2.80(s,3H); 2.31(s,3H).

4-ETHYL-(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (183)

IR liq. film) cm^{-1} 3010, 2970, 2930, 2880, 1660, 1505, 1415, 1240, 1060, 830.

NMR ($CDCl_3$) δ ppm 7.92(d,2H); 7.70(s,1H); 7.33(d,2H); 2.80(s,3H); 2.68(q,2H); 2.30(s,3H); 1.25(t,3H).

3-METHOXY-(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (184)

IR (liq. film) cm^{-1} 3040, 2980, 2905, 1590, 1565, 1250, 1150, 1055.

NMR ($CDCl_3$) δ ppm 6.95(m,5H); 3.70(s,3H); 2.60(s,3H); 2.23(s,3H).

2,3-DIMETHOXY-(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (185)

IR (liq. film) 3080, 3000, 2940, 2840, 1575, 1470, 1435,1270, 1070, 790, 750.

NMR ($CDCl_3$) δ ppm 8.25(s,1H); 8.10(dd,1H); 7.38(m,2H); 4.06(2s,6H); 2.90(s,3H); 2.38(s,3H).

3-CHLORO-(2-METHYLSULPHINYL-2-METHYLTHIO)ETHENYLBENZENE (186)

IR liq. film cm^{-1} 3000, 2900, 2240, 1600, 1560, 1470, 1430, 1070, 720.

NMR ($CDCl_3$) δ ppm 7.30(m,4H); 6.54(s,1H); 2.29(s,3H); 2.00(s,3H).

GENERAL SYNTHESIS OF THIOLESTERS

The ketene thioacetal monosulphoxide (1 mole) was dissolved in

dry DCM which had been presaturated with hydrogen sulphide gas for 30 minutes. To this was added conc. hydrochloric acid (approximately 1ml). The mixture was stirred vigorously at room temperature for 1 hour, and then neutralised with sodium bicarbonate solution. The two layers were separated, and the aqueous phase was extracted with a further quantity of DCM. The combined organic extracts were washed with brine, and dried over magnesium sulphate. The products were purified by column chromatography on silica gel (MERCK 7736).

SPECTRAL DATA FOR THE THIOLESTERS

METHYL 4-ETHOXYPHENYLTHIOACETATE (179a)

IR (liq. film)cm^{-1} 2980, 2920, 1680, 1605, 1510, 1300, 1250, 1050, 780.

NMR ($CDCl_3$) δ ppm 7.19(q,4H); 4.13(q,2H); 3.80(s,2H); 2.33(s,3H); 1.44(t,3H).

M/S ($M^{+\cdot}$ 210), 135, 107, 77, 40.

METHYL PHENYLTHIOACETATE (180a)

IR (liq. film) cm^{-1} 3005, 2900, 1690, 1600, 1555, 1500, 1430, 1310, 1030, 700.

NMR ($CDCl_3$) δ ppm 7.40(s,5H); 3.88(s,2H); 2.27(s,3H).

METHYL 4-METHYLPHENYLTHIOACETATE (181A)

IR (liq. film) cm^{-1} 3000, 2420, 1680, 1510, 1420, 1020, 730.

NMR ($CDCl_3$) δ ppm 7.22(s,4H) 3.82(s,2H); 2.33(s,3H); 2.30(s,3H).

METHYL 4-CHLOROPHENYLTHIOACTETATE (182a)

Mpt. 28-30 °C.

IR (liq. film) cm^{-1} 2920, 1685, 1595, 1495, 1410, 1020.

NMR ($CDCl_3$) δ ppm 7.50(s,4H); 3.93(s,2H); 2.40(s,3H).

MS ($M^{+\cdot}$200), 153, 125, 89.

METHYL 4-ETHYLPHENYLTHIOACETATE (183a)

IR (liq. film) cm^{-1} 3010, 2980, 2930, 2880, 1690, 1315, 1110, 1020, 820, 680.

NMR ($CDCl_3$) δ ppm 7.11(s,4H); 3.75(s,2H); 2.63(q,2H); 2.23(s,3H); 1.20(s,3H).

METHYL 3-METHOXYPHENYLTHIOACETATE (184a)

IR (liq. film) cm^{-1} 3015, 2940, 2845, 1686, 1350, 1000.

NMR (CCl_4) δ ppm 6.96(m,4H); 3.68(s,3H); 3.63(s,2H); 2.19(s,3H).

METHYL 2,3-DIMETHOXYPHENYLTHIOACETATE (185a)

IR (liq. film) cm^{-1} 3000, 2940, 2840, 1690, 1590, 1480, 1275, 1080, 1010, 760.

NMR ($CDCl_3$) δ ppm 6.86(m,3H); 3.83(s,8H); 2.25(s,3H).

NMR (C_6D_6) δ ppm 7.04(m,3H); 3.93(s,2H); 3.90(s,3H); 3.63(s,3H); 2.14(s,3H).

MS ($M^{+\cdot}$ 226), 151, 136, 91, 65.

ALTERNATIVE SYNTHESIS THIOLESTERS

A solution of methanethiol was prepared by adding a solution of dimethyldisulphide (1 mole) in dry ether, to a suspension of LAH (1 mole) in dry ether at 0°C. This was left to stir under nitrogen for 1 hour. This solution was filtered through hyflo, to leave an ethereal solution of methane thiol. A phenyl acetic acid (2 mole) was dissolved in dry ether, and added to this was DCC (2.2 mole). The ethereal methane thiol was added to the above solution at 0°C, and then stirred for 1 hour under nitrogen. The dicyclohexyl urea was removed by filtration through hyflo, then the filtrate was evaporated to dryness under reduced pressure. The product was purified by column chromatography. The spectral data for compounds (179a), (180a) and (182a) were identical to those prepared by our novel method.

ABBREVIATIONS

Ac	Acetyl
Bu	Butyl
BuLi	Butyllithium
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIBAL	Diisobutylaluminiumhydride
DMAD	Dimethylacetylenedicarboxylate
DMDS	Dimethyldisulphide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	Dimethylformamide dimethylacetal
DMSO	Dimethylsulphoxide
Et	Ethyl
INOC	Intramolecular nitrile oxide cyclisation
IR	Infrared
LAH	Lithium aluminium hydride
LSD	Lysergic acid diethylamide
Me	Methyl
MMTS	Methylmethyl thiomethylsulphoxide
MS	Mass spectrometry
MVK	Methyl vinyl ketone
NMP	N-methylpyrrolidone
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PPA	Polyphosphoric acid
Pr	Propyl
Py	Pyridine

RaNi	Raney nickel
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TOS	Toluene sulphonyl
TPM	Tripiperodinomethane
p-TSA	p-Toluenesulphonic acid
p-TS-Cl	p-Toluenesulphonyl chloride
U.V.	Ultra violet

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STUDY PROGRAMME

CONFERENCES ATTENDED

RSC Organic Chemistry, Trent Polytechnic, December 1985.

RSC Organic Chemistry, Nottingham University, December 1986.

Sheffield Stereochemistry Symposium, Sheffield University, December 1986.

RSC Organic Chemistry, Leicester University, December 1987.

LECTURE COURSES ATTENDED AT SHEFFIELD UNIVERSITY

(i) Chirality in organic synthesis.

(ii) Functional group interconversion (oxidation).

(iii) Enzymes in organic synthesis.

BOOKS READ

The Chemistry of Indoles, R.J. Sundberg.

Heterocyclic Chemistry, J.A. Joule.

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