Studies directed towards the synthesis of some anti cancer alkaloids.

Najafi, Ahmad

Award date:
1978

Awarding institution:
University of Bath

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SOME ANTI CANCER ALKALOIDS

Submitted by

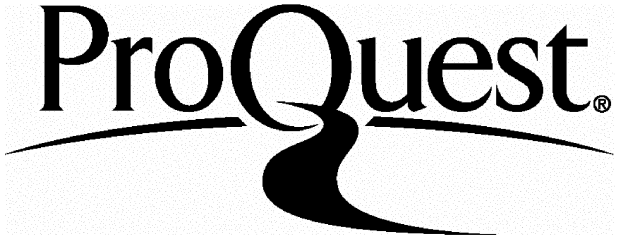
AHMAD NAJAFI, MSc

For the Degree of

DOCTOR OF PHILOSOPHY

Of The University of Bath

1978



CONTENTS

ACKNOWLEDGEMENTS

The author would like to offer his sincere thanks to all those who, in their own way, have made this work possible.

Firstly, I would like to acknowledge the advice and guidance given by my supervisor, Dr. Malcolm Sainsbury. I would also like to thank Malcolm for his friendship, which I will always value, and for the patience and understanding which he has shown to me over the last few years.

To Mrs. S. Briody, Mr. R. Brown and Mr. D. Wood, I owe a very special debt of gratitude, for without their assistance the work could never have taken place.

Thanks are also due to Miss J. Pitman for typing the thesis.

Finally, thanks to my parents — to whom I owe everything.

SUMMARY

Currently cancer chemotherapy, which is still in its infancy, is stimulating much interest, with over 250 new products as candidates for human clinical trials. Some of the more important alkaloids in this area are androcymbine, tylophorine and ellipticine and consequently the initial aim of this work was to find improved synthetic routes to these compounds.

The use of aryl-aryl coupling to prepare natural products has opened a new field in organic chemistry and introduced many new techniques, one of which is electro-anodic oxidation.

In the first part of this work some derivatives of tetrahydro-isoquinoline were subjected to electro-oxidation in an attempt to prepare androcymbine.

The preparation of tylophorine from the alkaloid septicine through the use of photochemistry and aryl-aryl coupling is discussed in Part Two of this thesis.

Finally, in the last part of this work new synthetic routes to the alkaloid ellipticine are described and the preparation of its 8-methoxy derivative is reported.

INSTRUMENTAL METHODS

All IR spectra were determined on a Perkin-Elmer 237 spectrophotometer as nujol mulls or liquid films.

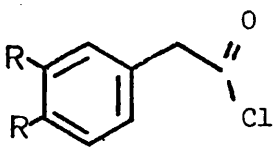
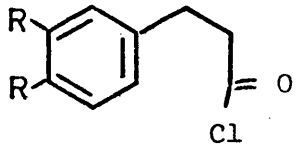
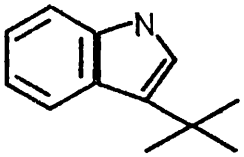
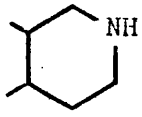
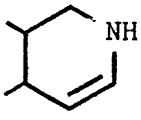
UV spectra were determined on a Perkin-Elmer 402 spectrophotometer in 95% ethanol.

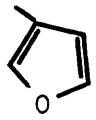
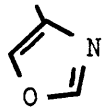
H-n.m.r. spectra were obtained using a Varian A-60 spectrometer and a J.O.E.L.P.S. 100 spectrometer; chemical shifts are expressed in ppm downfield from tetromethylsilane as internal standard.

Mass spectra were measured on an A.E.I.M.S. 12 spectrometer.
Melting points are uncorrected.

The elemental analysis were carried out by Dr. F.B. Strauss, 10 Carlton Road, Oxford, England.

ERRATUM

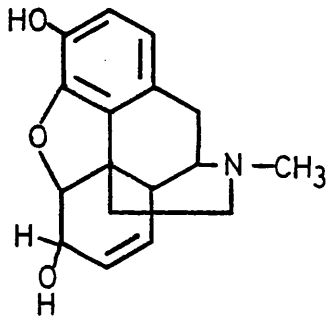
Page	*Line*	*Error*	*Correction*
2	14	Michaelies	Michaelis
30			
46	19	methyl cyanide	dry methyl cyanide
65	Third Structure		
66	2	chloride	chloride or its carbonyl analogue
88	1	-2-onyl	-1-on yl
91			
92			
93			
96	1	C.A., 80,	C.A., 1975, 80,
96	10	C.A., 55,	C.A., 1961, 55,
99	Structure (3)		
100	Structure (8)		
102	Structure (12)		

Page	*Line*	*Error*	*Correction*
104	5	(19)	(18)
106	Third Reaction	H_2O	H_2O_2
109	Structure (33)		
116	5	amide (46) prepared	amide (46)
122	26	iones	enones
127	3	was refluxed for	was refluxed in benzene ($50cm^3$) for
136	17	O-mesitylene	O-mesityl
150	4	*This Journal*	*J. Am. Chem. Soc.*

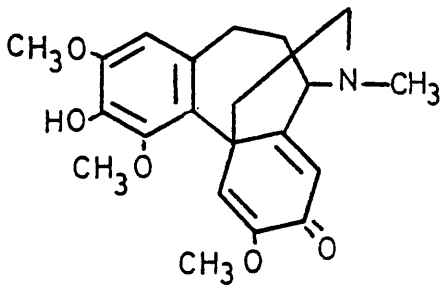
PART ONE

INTRODUCTION TO PART ONE

Many molecules occur naturally which contain the biaryl sub-structure. Some examples are shown below; perhaps the most important is morphine which is still the best analgetic, although, of course, its narcotic properties reduce its general application and limit its use to extreme cases.

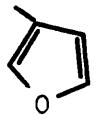
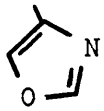


Morphine



Androcymbine

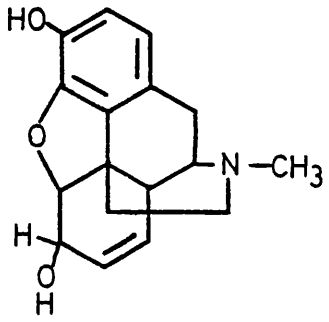
The properties of morphine, however, have stimulated much research aimed at the preparation of synthetic analogues lacking narcotic problems and in turn this has probably been the major aspiration behind the vast literature which describes routes to biaryls. Additionally since there is widespread interest in the biosynthesis of natural products and because many biaryl systems are considered to arise in nature through the oxidative coupling of phenolic substrates, much has been accomplished in biomimetic studies using inorganic oxidants, and lately electro-oxidative techniques.

Page	*Line*	*Error*	*Correction*
104	5	(19)	(18)
106	Third Reaction	H_2O	H_2O_2
109	Structure (33)		
116	5	amide (46) prepared	amide (46)
122	26	iones	enones
127	3	was refluxed for	was refluxed in benzene ($50cm^3$) for
136	17	O-mesitylene	O-mesityl
150	4	*This Journal*	*J. Am. Chem. Soc.*

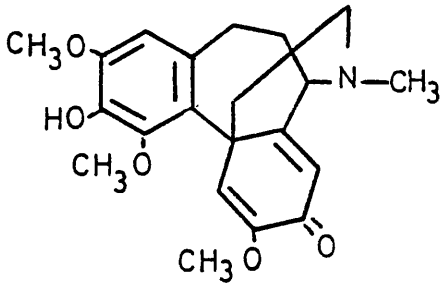
PART ONE

INTRODUCTION TO PART ONE

Many molecules occur naturally which contain the biaryl sub-structure. Some examples are shown below; perhaps the most important is morphine which is still the best analgetic, although, of course, its narcotic properties reduce its general application and limit its use to extreme cases.



Morphine

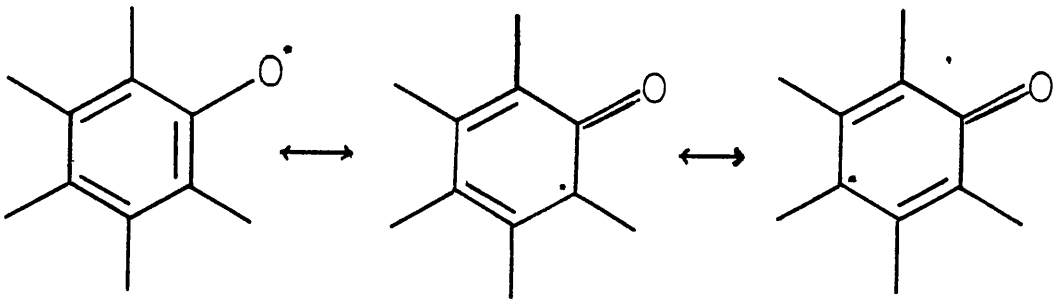


Androcymbine

The properties of morphine, however, have stimulated much research aimed at the preparation of synthetic analogues lacking narcotic problems and in turn this has probably been the major aspiration behind the vast literature which describes routes to biaryls. Additionally since there is widespread interest in the biosynthesis of natural products and because many biaryl systems are considered to arise in nature through the oxidative coupling of phenolic substrates, much has been accomplished in biomimetic studies using inorganic oxidants, and lately electro-oxidative techniques.

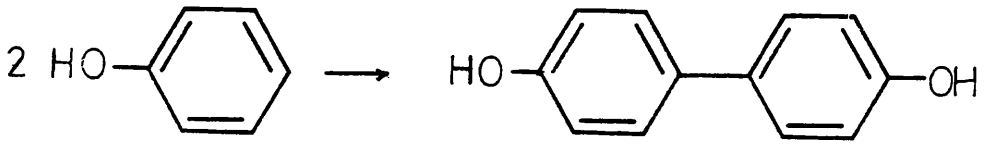
Strictly speaking most of the latter work has involved aryl ethers rather than phenols, since these are easier to handle but some investigations with phenols are recorded. The theme of phenolic coupling is relevant to this part of the thesis and some aspects of the mechanism of phenolic oxidation and coupling are now considered.

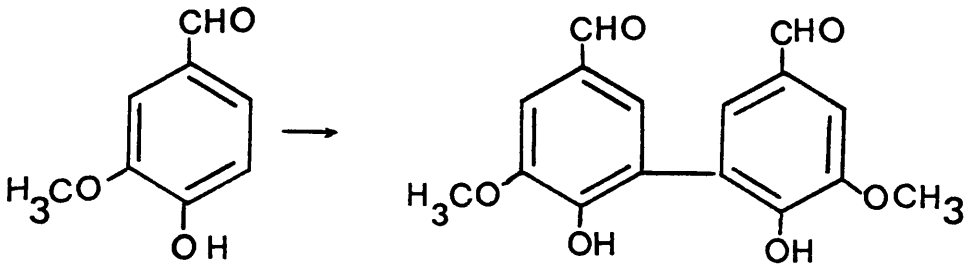
Phenols act with chemical oxidants either by loss of the hydrogen atom of the hydroxyl group or by loss of one electron from the corresponding anion to give a resonance-stabilized aryloxy radical:

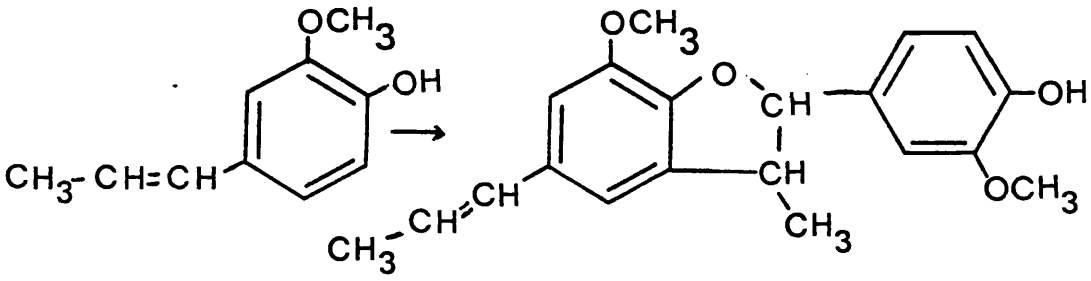


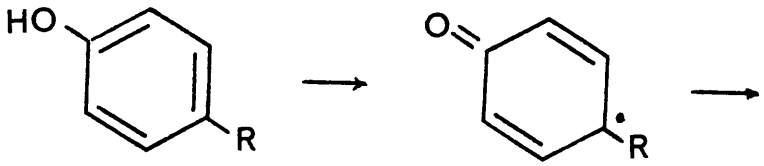
The reagents which are appropriate for this type of reaction can be organic peroxides or, more often, inorganic oxidizing agents such as potassium ferricyanide in akaline solution. It was the work of Pummerer and his collaborators[1] that first drew attention to the role of radicals as intermediates in phenolic oxidation, but other investigations, such as those of Michaelies[2] on the mechanism of the oxidation of hydroquinones are especially notable. It is now recognised that the formation of a radical is the preliminary step in the majority and perhaps in all, phenolic coupling reactions. The simplest products that can be isolated from monohydric phenols are radical dimers produced by coupling either through oxygen or through carbon atoms.

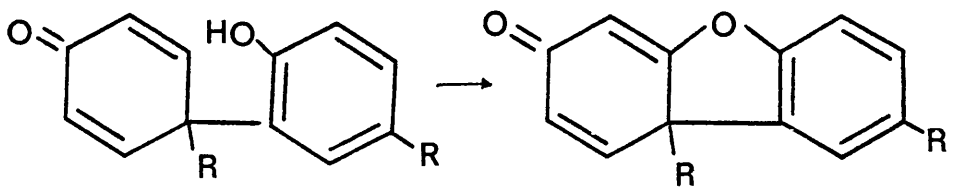
Some typical examples of coupling reactions are given below:











$R = CH_3$

Although it is known that dimeric products can be derived from the oxidation of phenols with such reagents as ferric chloride and potassium ferricyanide, these reactions are often characterised by low yields. One problem is, of course, the difficulty in manipulating phenols in alkaline media and work in the last decade has centred upon the development of new reagents which work either in buffered media or else avoid the use of phenols as such.

Outline of the Electro-Oxidative Method

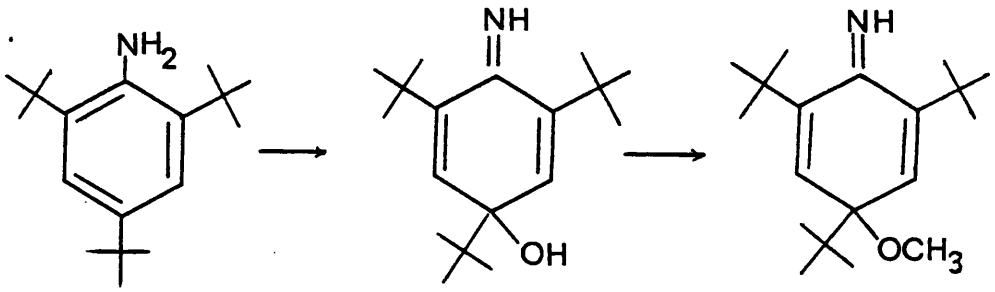
In the middle of the last century Kolbe[3] successfully coupled alkyl and aryl radicals by the electrolysis of the anions of simple carboxylic acids.

$$2RCO_2^- \xrightarrow{-2e^-} 2RCO_2^{\cdot} \longrightarrow 2R^{\cdot} + CO_2$$

$$2R^{\cdot} \longrightarrow R - R$$

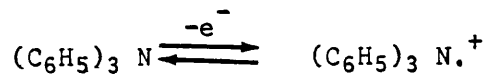
Later small processes were in use making intermediates like benzidine and anthraquinone[4,5] for the dyestuffs industry. However, largely due to the lack of instrumental control these processes were wasteful and could not compete with more conventional preparations. Although the Kolbe route to alkanes has always received much attention, organic electrochemistry excited little interest until the middle of this century when chemists turned their attention to the elucidation of the mechanisms of electrochemical reactions. Armed now with spectroscopic aids and with better means of controlling the electrode potential, the events occurring after electron loss or capture could be studied. Thus, for example, Goldschmidt[6] observed that when

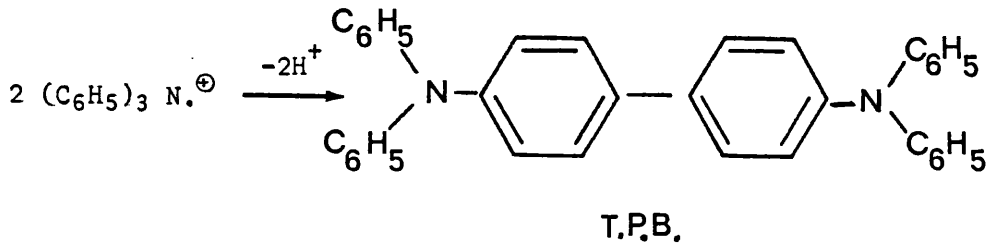
2,4,6-tri-t-butylaniline was oxidised in aqueous solution the hydroxy-imino compound (2) was formed:



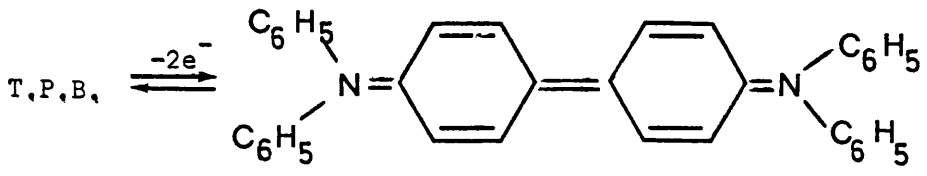
(1) (2) (3)

when methanol was substituted for water then the product of electrolysis was the methoxyimine (3) and such a result suggested to him that the solvent rapidly attacks an initially formed cationic species. Only a few years later a complete mechanistic and kinetic sequence for the dimerization of triphenylamine was proposed[7].





T.P.B.

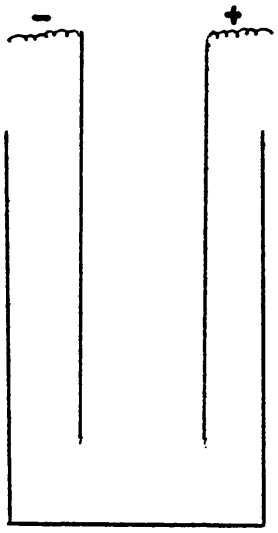


It has not been until recently that these mechanisms could be tested.

In order to elucidate the steps in an electrochemical reaction, it is necessary in the first instance to establish the exact potential needed to remove electron (s) from the substrate. It is also necessary to determine whether or not several parallel routes exist from a transition state to the final product(s).

In terms of apparatus a one compartment cell (Figure 1)[8] is all that is needed to carry out many electrochemical reactions. Contained within this cell are the cathode and the anode immersed in an electrolyte which usually comprises a solvent and the substrate, but occasionally when the electroconductivity of the solvent is not sufficient a supporting electrolyte is added. Common solvents are water and aliphatic alcohols but aprotic systems such as acetronitrile or trifluoroacetic acid are often utilised. Supporting electrolytes in many cases are ammonium tetrafluoro-borates or alkali metal perchlorates and these are of most use in non-aqueous solvents.

When the circuit is closed the substrate in a one compartment electrochemical cell gains or loses electrons to the cathode or anode respectively. Thus both cathodic reduction and anodic oxidation occur simultaneously. Such a circumstance is not desirable and to overcome this problem a two compartment cell (Figure 2) can be used in which the two compartments are divided by a glass frit.



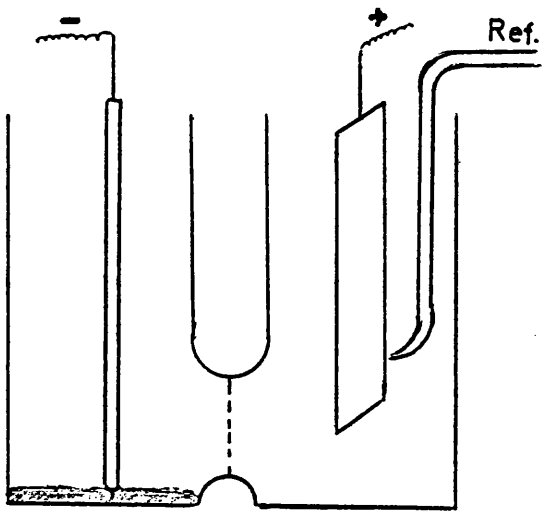


FIGURE 1

FIGURE 2

For oxidative work the cathode is commonly a mercury pool or a platinum[9] gauze but since most metals are oxidised at low potentials, platinum is the normal choice for the anode construction; carbon[10], and lead dioxide[11] may be also employed. In controlled electrolysis it is necessary to know and regulate the electrode potential and this is achieved by placing a reference electrode, standard calomel (SCE) or silver/silver oxide, as close as possible to the working electrode. Adjustment of the external voltage is then made so that the potential of the anode relative to the reference is kept constant at the desired value. What, however, is the desired value? Normally this will be the potential at which the substrate loses an electron to the anode, but frequently the first oxidation event is quickly followed by a second, or the product of the reaction is itself easily oxidised. Thus before a preparative experiment may

be undertaken these facts should be known; in the past the oxidation potentials of the substrate were deduced by plotting current/voltage curves using a polarograph connected up the 'wrong way' and employing a platinum head rather than a mercury drop.

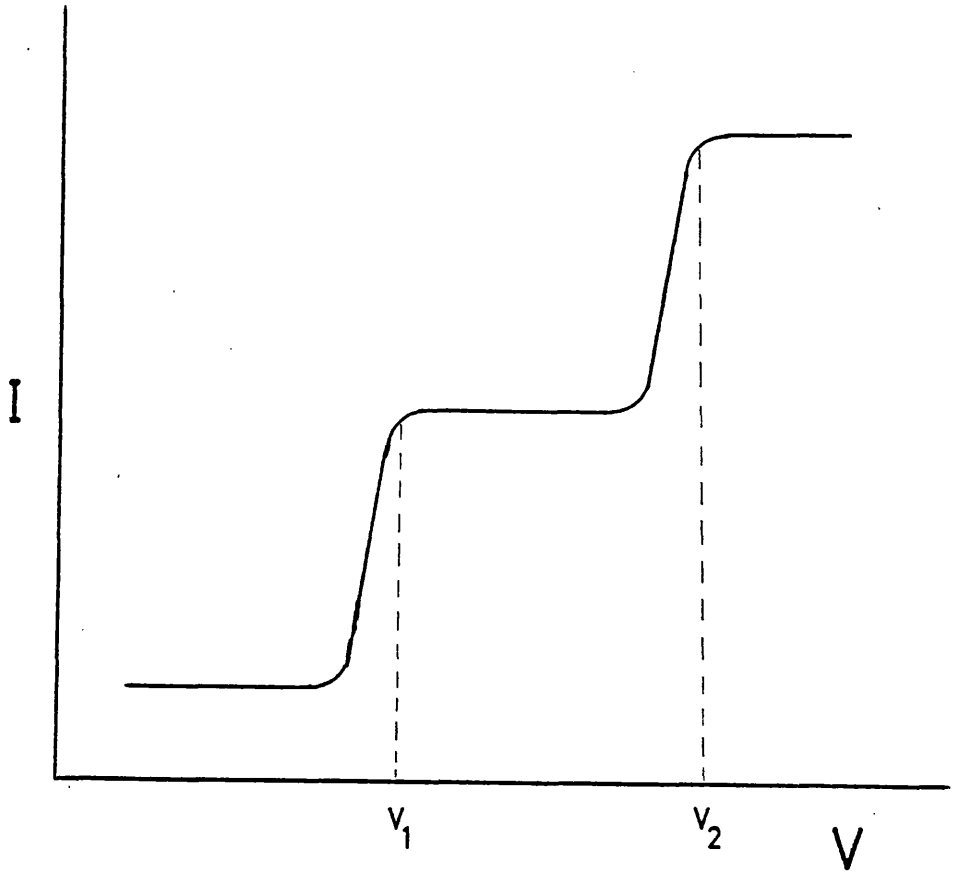
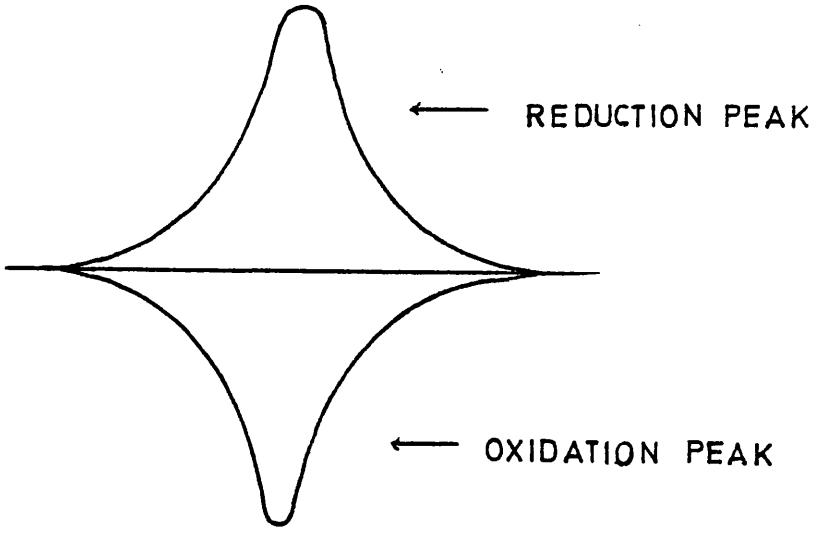


FIGURE 3 : Current/Voltage Curve for Hypothetical Substrate Showing Two Oxidation Peaks, V_1 and V_2.

Although this type of analysis is useful, it provides little information about the products of electrolysis reactions and for this the newer technique of cyclic voltammetry is widely used. The instrumentation for cyclic voltammetry consists of a simple one compartment cell using the same electrode and electrolyte systems as are to be used in the preparative experiment; power is supplied by means of a triangular wave-form generator and the voltammogram plotted on an X-Y recorder. Sweep rates are variable. In essence the potential of the working electrode is scanned first in an anodic direction (for oxidative experiments), then at a pre-set potential the voltage is reversed and recycled back, usually to zero. If an electroactive substrate is present then as the potential of the first ionization is approached current flows increasingly until a maximum is reached, thereafter the double layer surrounding the electrode is depleted of substrate and the current falls. This gives rise to an anodic peak. If the oxidation intermediate (often a radical cation) be 'stable' then it may not form product before the recycling process begins. In this way a reduction peak is produced which is almost as instense as the oxidation peak.



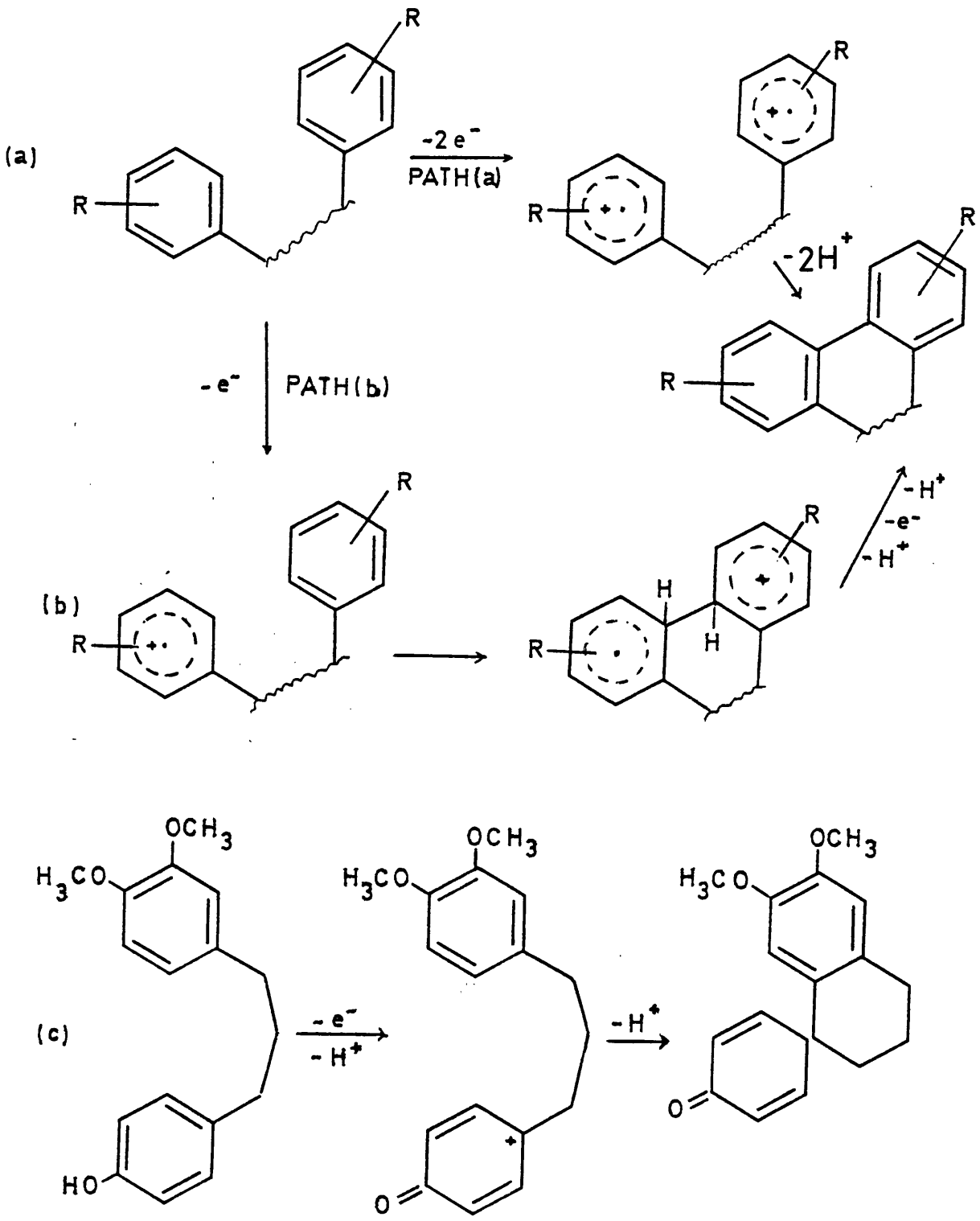
If on the other hand, the initial radical cation enters into a relatively fast product forming reaction then the intensity of the reduction peak will be less and additional peaks will appear in the voltammogram, due to the oxidation and the reduction of the product.

It is clear that many variations of cyclic voltammograms are possible depending upon the nature of the substrate and some of them will be discussed and analysed when the compounds relevant to this particular study are dealt with later in the thesis.

The Mechanism of Oxidative Coupling

The anodic oxidation of organic substrates can follow complex pathways as a result of coupling reactions followed by chemical changes and rearrangements. It is apparent from the literature that there is still no coherent understanding of the detailed mechanisms by which the various electrolysis conditions determine the efficiency and specificity of electrosynthetic reactions. Some of the changes produced by variation of solvent, electrolyte and electrode material are not even qualitative, leave alone quantitative; and further systematic studies are required for most reactions. For example, three different mechanisms of aryl-aryl coupling have been proposed[12,13,14] - these are outlined in Scheme 1. It is not known however, with certainty if these mechanisms are wide ranging or specific to the particular substrate.

SCHEME 1

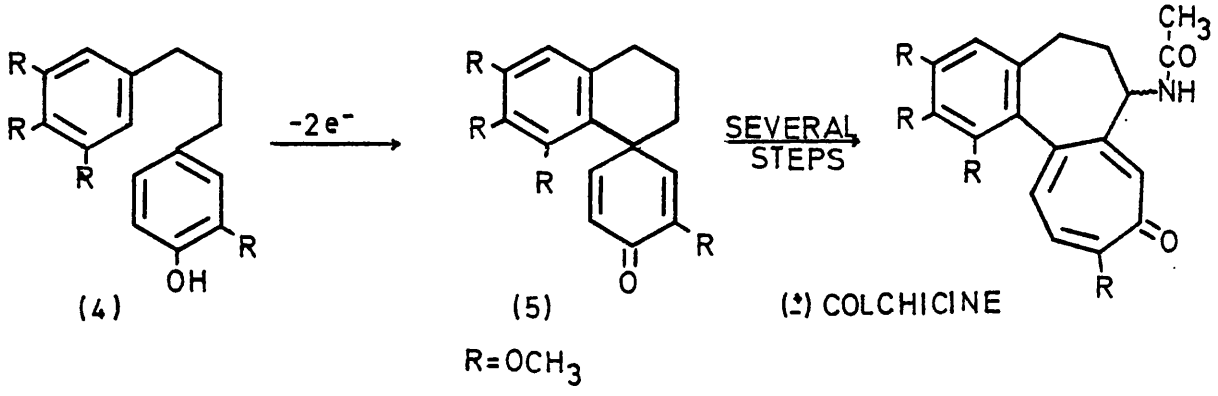


The first two routes (a) and (b) have been forwarded by Parker[12] and Nyberg[13] as general pathways, while Scheme 1(c) represents a specific reaction.

At first sight it seems that the approach of two positively charged species (Scheme 2(a)) is unlikely, but inspection of the literature shows that this type of reaction is in fact presumed to be quite common[12]. Thus there is enough evidence to indicate that if the two aryl nuclei have similar oxidation potentials then Scheme 2(a) is the major reaction pathway, although formation of products *via* Scheme 2(b) cannot be entirely precluded.

The anodic coupling of phenols has considerable practical implication to electroorganic synthesis, for it seems the drive to *para* coupling occurs even when this position is occupied by another function.

Kotani has used this principle in the synthesis of (±) colchicine[15], thus coupling to the 1- position of the 3-methoxy-4-hydroxyphenyl moiety of the diaryl propane (4) leads to the formation of the dienone (5), which may then be modified.

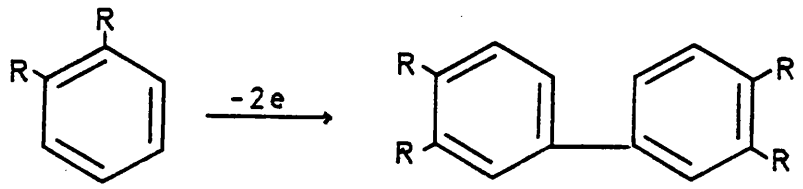


(4) (5) (±) COLCHICINE

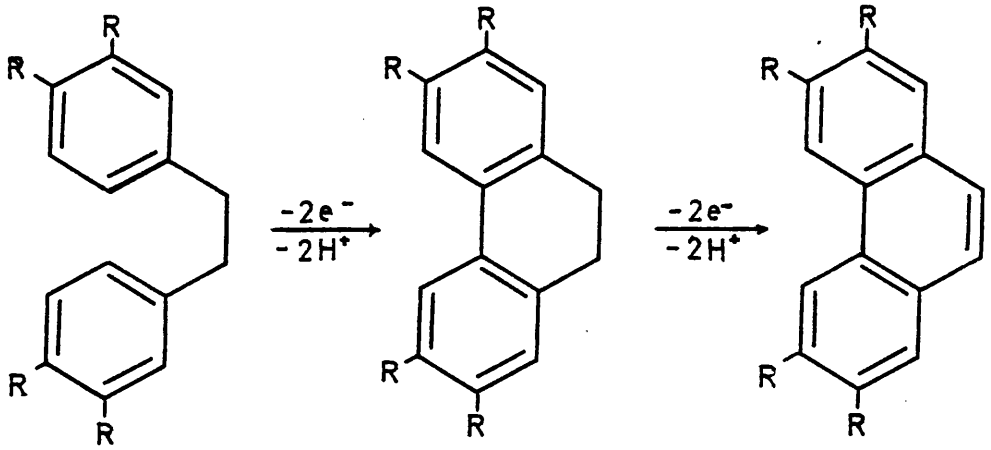
R=OCH3

One of the earliest examples of an aryl-aryl electrochemical coupling reaction is the dimerization of 1,2-dimethoxybenzene which was conducted by Fichter and his co-worker[16]. In this work platinum or lead dioxide anodes were used. Later the same author described the anodic dimerization of1-methylnaphthalene in acetone sulphuric acid-water at a lead dioxide anode[17].

$R=OCH_3$

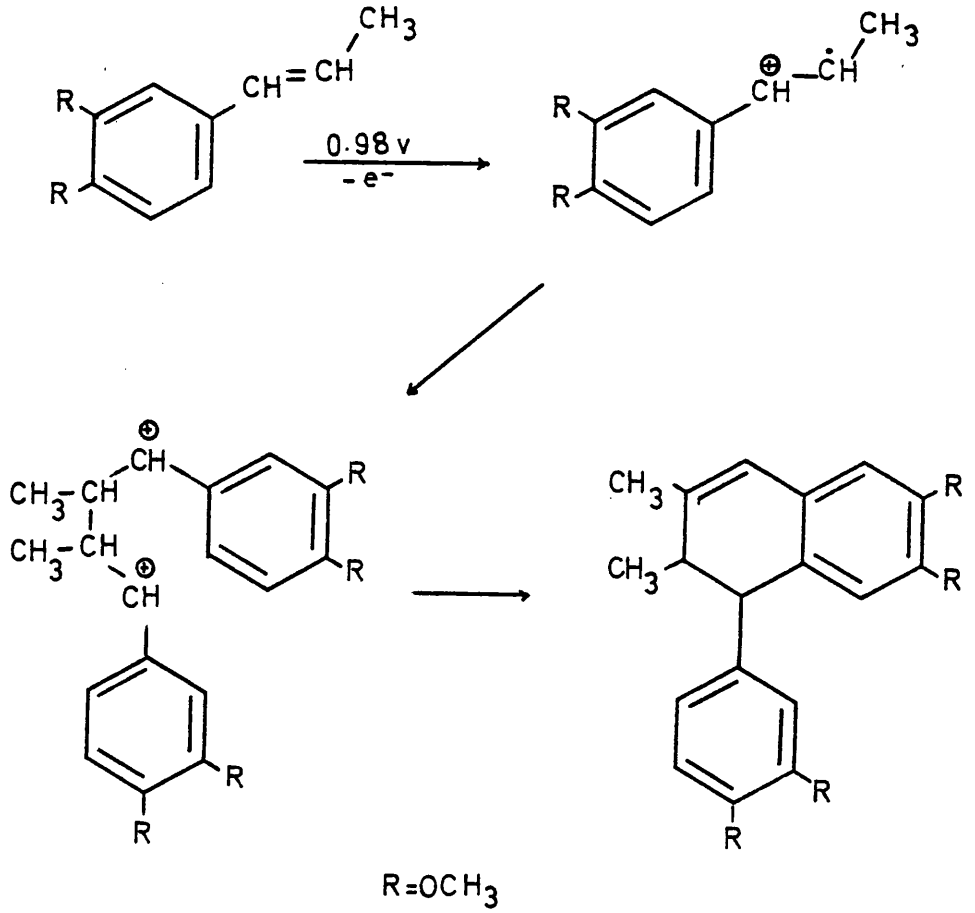


After these early studies there followed a long period of relative inactivity. Until Mallory in 1964 reported[18] that substituted phenanthrenes can be produced very efficiently by electrochemical oxidation. Thus oxidation of 1,2-bis (3,4-dimethoxyphenyl) ethane gives the corresponding phenanthrene in almost quantitative yield.

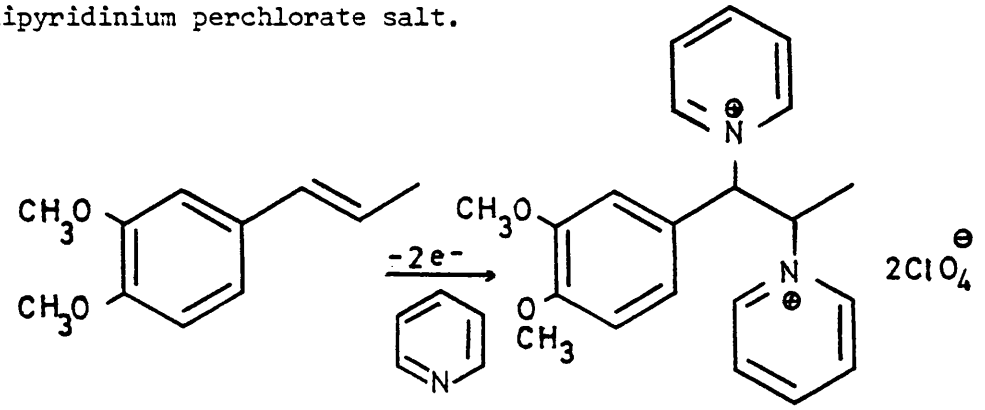


$R=OCH_3$

This reaction is said to proceed *via* the initial formation of a di-radical dication which affords the dihydrophenanthrene which then suffers further electron and proton loss to give the fully aromatised structure. In the same year O'Connor and Pearl[19] oxidised 3,4-dimethoxy-propenylbenzene in acetonitrile/sodium perchlorate but found that side chain interaction rather than aryl-aryl coupling occurs. However, Sainsbury[20] has pointed out that the product which is formed may also arise by simply adding acid to the propene. So that, this compound may not be a true electrolysis product, but rather it is the result of the action of perchloric acid, generated by other unestablished processes which also occur at the electrode.

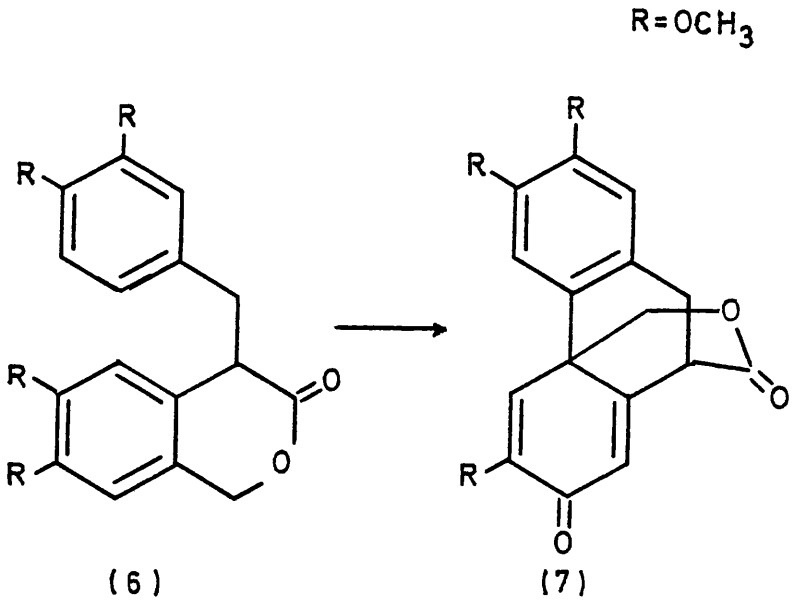


Later work by Sainsbury showed that when pyridine is present two molecules add to 3,4-dimethoxyphenylpropenylbenzene to give the dipyridinium perchlorate salt.



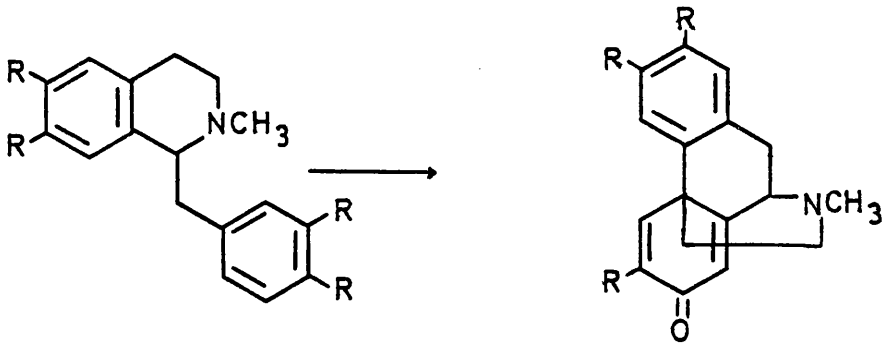
Since these early reports much more work has been done and the subject of anodic aryl-aryl coupling has been extensively reviewed[21,22].

Some interesting recent examples include the demonstration by Sainsbury and Schinazi[22] that the controlled anodic oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-isochroman-3-one gives the corresponding spirocyclohexadienone (7)



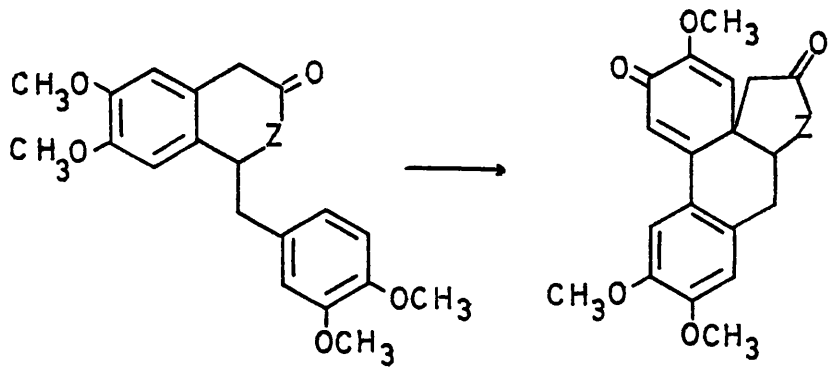
(6) (7)

and the record by Stermitz and Miller[23] that landanosine (8) affords O-methylflavanthine (9) on electrolysis.



(8) R=OCH_3 (9)

In addition to electrochemical techniques, new chemical reagents, such as vanadium oxyfluoride and thallium (III) trifluoroacetate have also been recommended as suitable reagents for aryl-aryl coupling and it has been suggested that the mechanism by which they operate parallels that of anodic oxidation, i.e. initial electron abstraction followed by radical-radical coupling and then proton loss. Thus it has been shown[24] that anodic oxidation of the lactone (10) in dichloromethane-tetrafluoroborate as supporting electrolyte gives 6,12-dioxo-2,3,7-trimethoxy-6,8a,9,10-tetrahydro-9,8a-epoxyethanophenanthrene (12) in 33% yield.

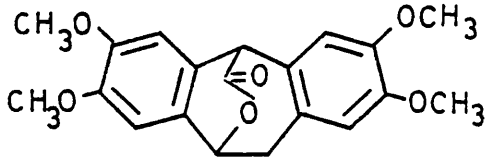


(10) Z= O
(11) Z= NCH_3

(12) Z=O
(13) Z=NCH_3

The same spirodienone (12) was isolated in 59% yield from the oxidation of the lactone (10) by vanadium oxyfluoride. An analogous dienone (13) was produced from the lactone (11) by either anodic oxidation or by treatment with vanadium oxyfluoride.

In contrast, however, it is reported that electro-oxidation of the same lactone (10) in acetonitrile with quarternary ammonium salts produces a different structure which is assigned as 2,3,7,8-tetra methoxy-13-oxo-10,5(epoxymethano) dibenzo [a,d] cycloheptadiene (14).

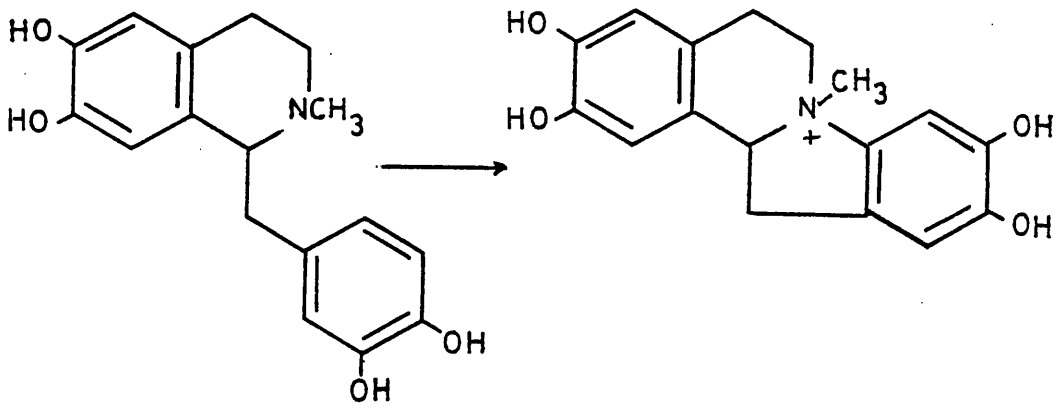


(14)

The method of aryl-aryl coupling using thallium (III) trifluoro-acetate (T.T.F.A.) and vanadium oxyfluoride (V.O.F.) is comparatively new, and it remains to be seen whether the two techniques duplicate one another, or whether they offer a complementary service to the synthetic organic chemist.

Coupling Reactions Applied to Isoquinoline Derivatives

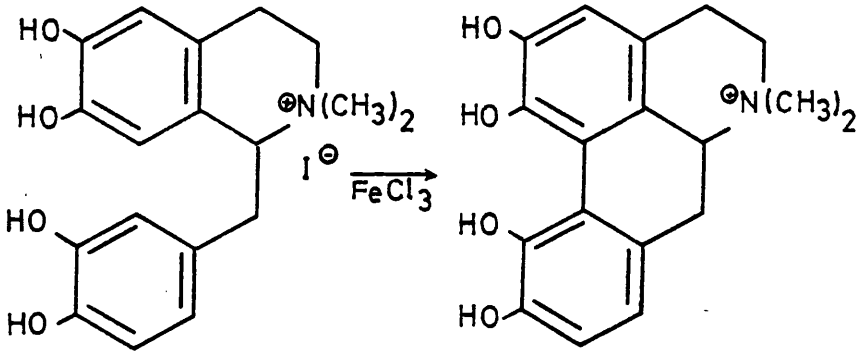
Some examples of the coupling reactions of isoquinolines have been mentioned in earlier pages and indeed, the literature in this field is daunting. One of the pioneers here, as in so many areas of organic chemistry, was Sir Robert Robinson[25] who in 1932 produced the quarternary salt (16) from the tetrahydroisoquinoline (15), instead of the morphine or aporphine structural types he was expecting. The reagent in this case was chloranil in alcoholic solution.



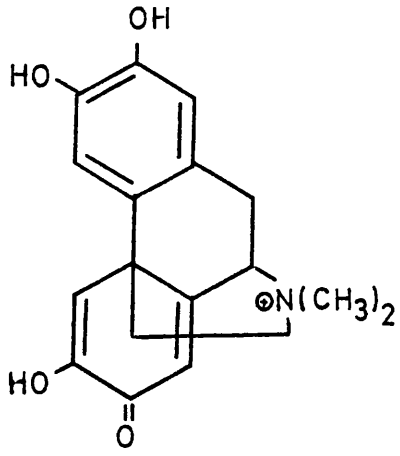
(15) (16)

In retrospect, this is not surprising and Frank[26] as shown that the presence of a nitrogen lone pair prevents C-C coupling in

such compounds but when this is masked as in the methiodide (17) C-C coupling to the aporphine (18) proceeds normally. The only unusual feature of this last result is that no *para-para* product (19) was isolated.

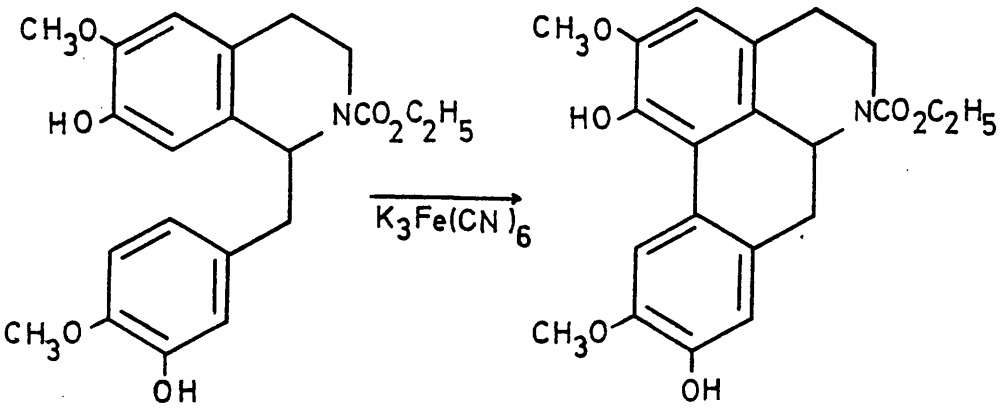


(17) (18)

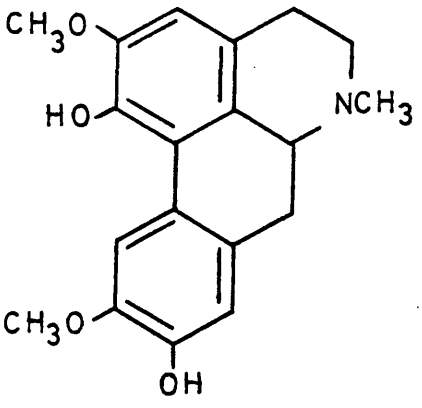


(19)

Similarly Kametani[27] has converted N-ethoxycarbonylnorreticuline (20) to the aporphine (21) using potassium ferricyanide in dilute ammonia solution. Reduction then afforded isoboldine (22).



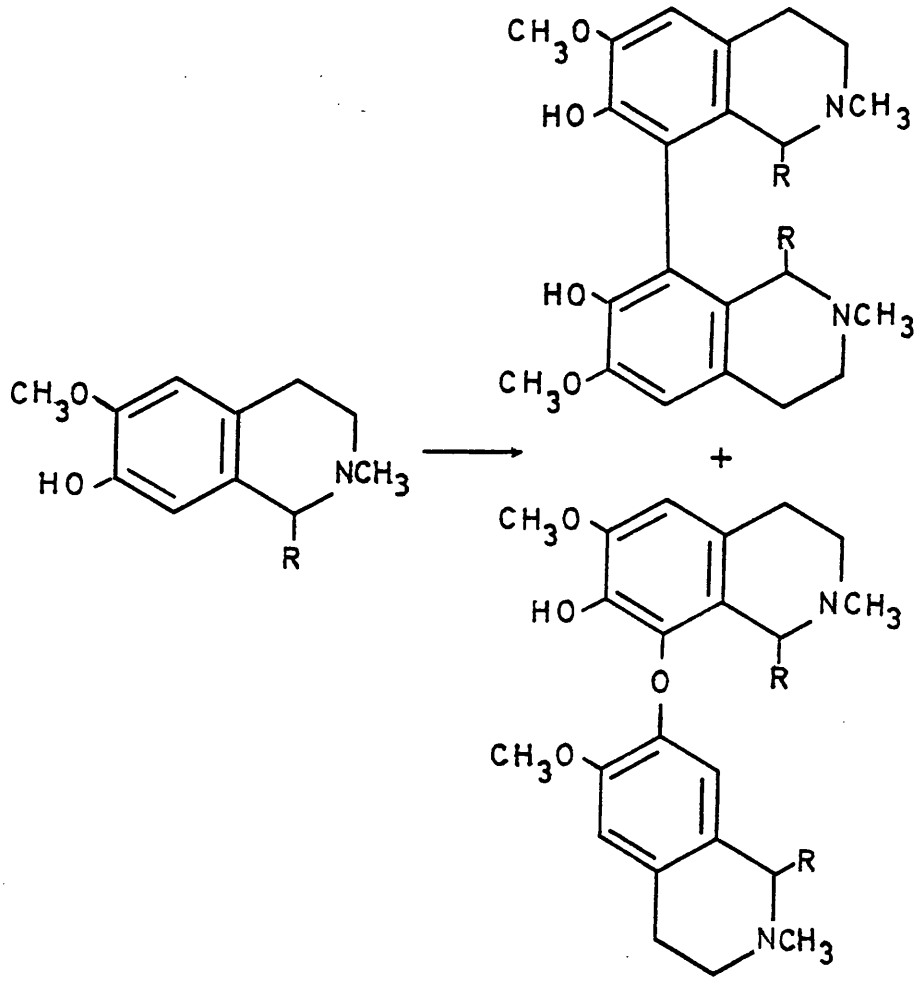
(20) (21)



(22)

The low yields in these reactions (usually less than 10%) is very disappointing and has stimulated research into more productive routes.

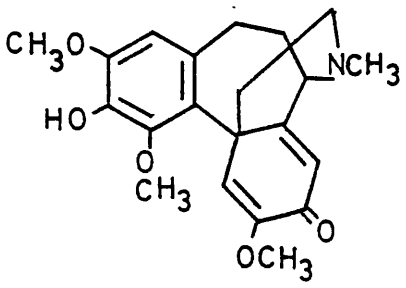
One such is, of course, electro-oxidation. Some years ago Bobbitt in the United States was able to show that certain phenolic tetrahydroisoquinolines couple intermolecularly to form biaryls and aryl-aryl ethers:



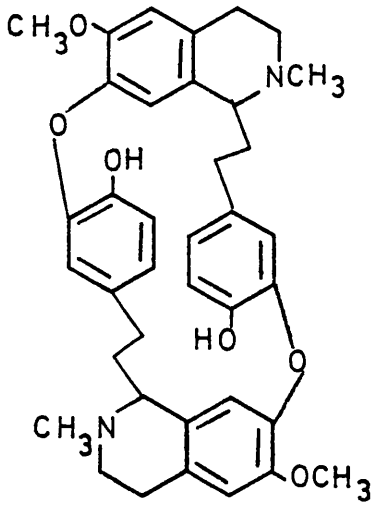
Following on from this Miller and Stermitz[23] carried out the reaction previously described on page 16 affording O-methylflavanthine (9) in high yield.

Synthetic Work in the Androcymbine Field

The androcymbine alkaloids were first isolated from *Androcymbium melanthioidine*, a tree, the extracts of which are used as folk medicine in Africa. Santavy and Herbek[28] who examined the extracts confirmed that they are pharmacologically active. Several alkaloids are present, the principal metabolite being androcymbine, shown later by Battersby[29] to have structure (23). It is accompanied by melanthioiodine (24).

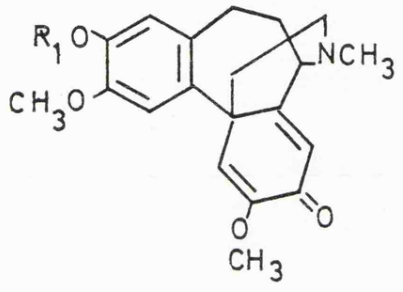


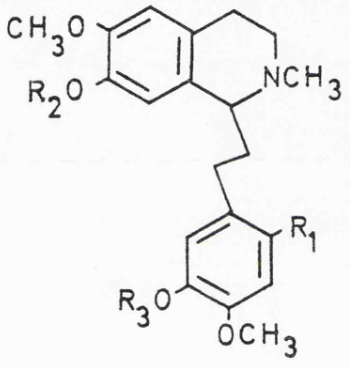
(23)



(24)

When one examines the structure of androcymbine, it may be seen that it bears the same relationship to a 1-phenethylisoquinoline as O-methylflavinathine (9) does to a 1-benzylisoquinoline and since the last pair are also related synthetically it follows that a similar route to androcymbine from a suitable 1-phenethylisoquinoline is possible. This potential was soon realised by Kametani and his group[30] who oxidised the derivative (28) and obtained the desmethoxy androcymbine (25).



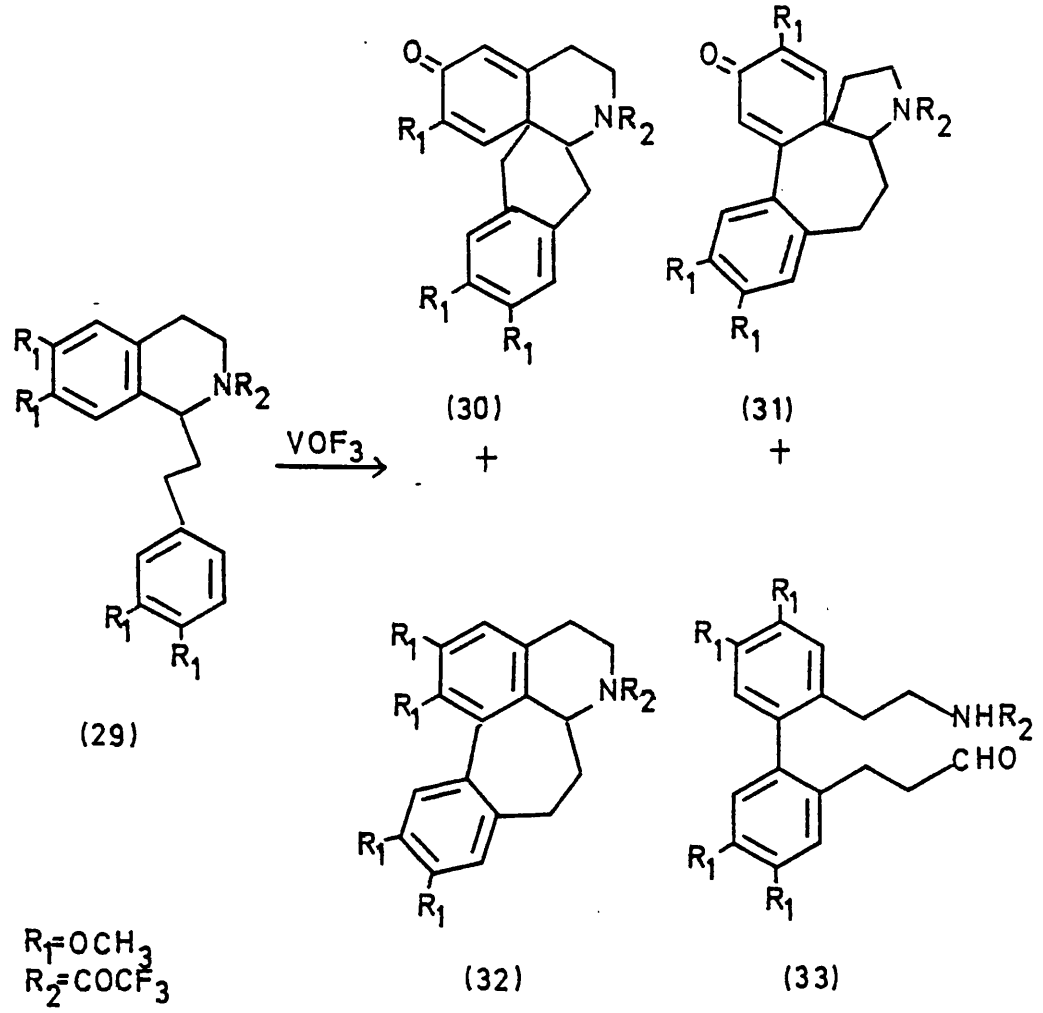


(25) $R_1 = H$
(26) $R_1 = CH_3$

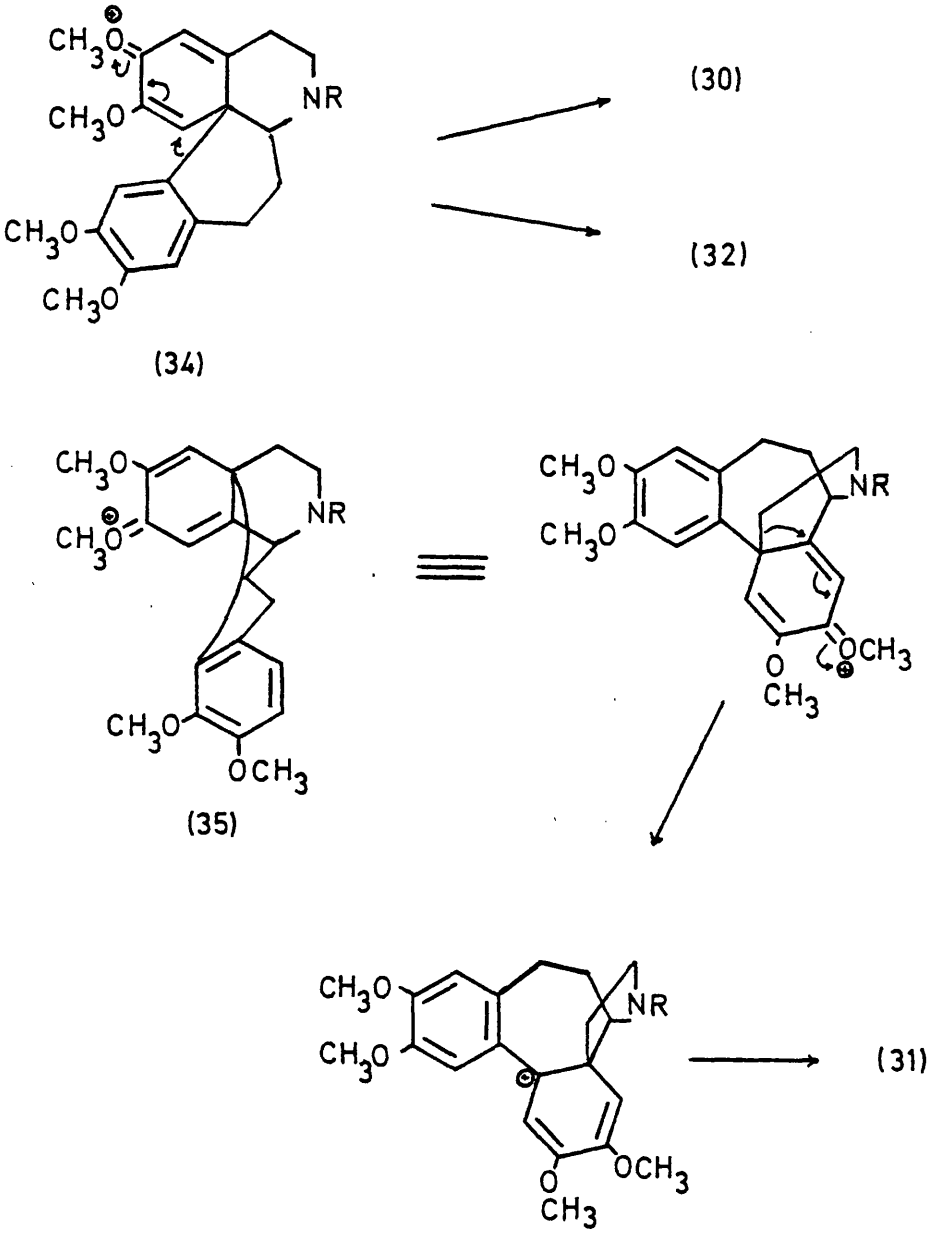
(27) $R_1 = NH_2$ $R_2 = R_3 = CH_3$
(28) $R_1 = R_2 = R_3 = H$

However, despite much attention to reagents and conditions, the best yield obtained was only 0.4%. Once again however, the oxidant was alkaline ferricyanide and the low productivity is not altogether surprising. Although Kametani's group next tried[31] a more conventional approach, utilizing as the critical step a modified Pschorr reaction upon the aminoisoquinoline (27), the yield of androcymbine was less than 2%. An attempt to form the alkaloids' skeleton by the vanadium oxyfluoride cyclisation of 2-trifluoroacetyl-1-(3,4-dimethoxyphenyl-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (29) also failed[32]

but instead four compounds - the homoproerythrinadienone (30) (5%); the homoneospirinedienone (31) (64%); the homoaporphine (32) (2%); and the ring open structure (33) (22%) were isolated:

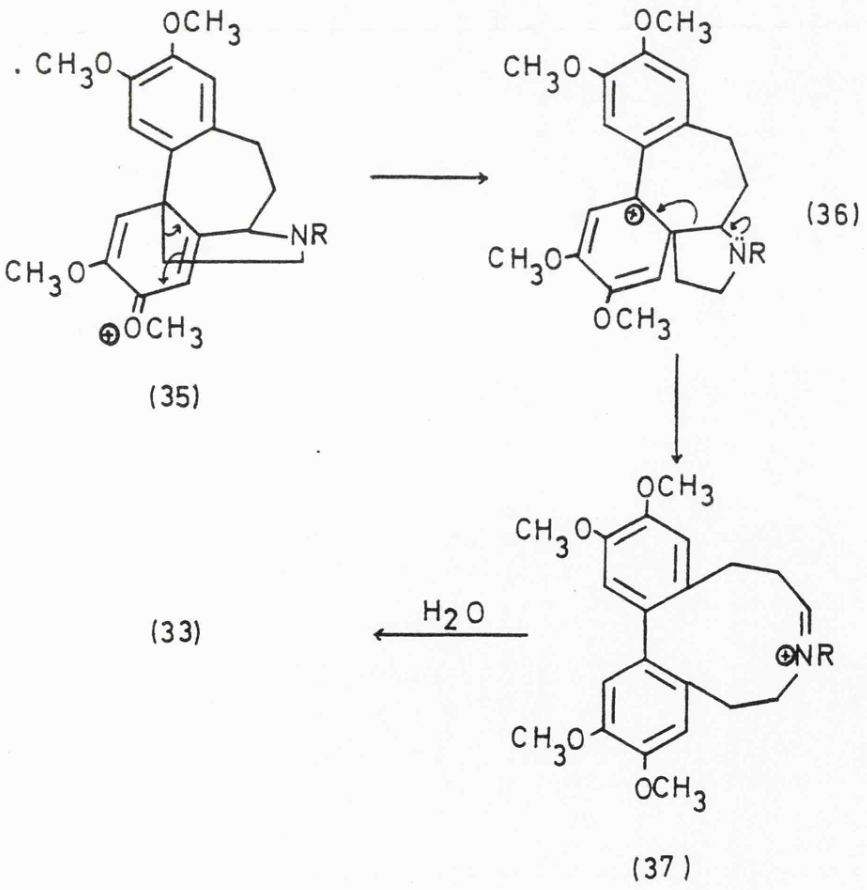


Clearly these structures are derived from alternative couplings of the starting materials initially affording the two ionic species (34) and (35) or their equivalents.



The intermediate (34) may simply demethylate to form the dienone (30) or undergo a dienone-phenol type rearrangement to give the homoaporphine (32).

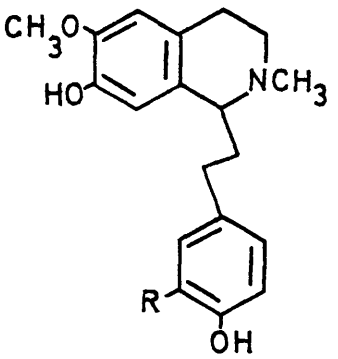
On the other hand, the suggested intermediate (35) is of course, the desired one which by demethylation should afford an O-methyl/desmethoxy derivative of androcymbine. However, under the conditions of the reaction this does not occur and instead a more fundamental rearrangement takes place leading eventually to homoneospirinedienone (31). The major product of the reaction, the ring-opened product (33) may also arise from (35) by the following route, hydrolysis of the imminium intermediate (37), occuring during work-up:

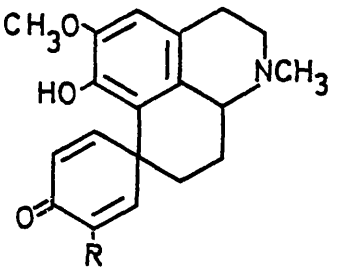


Such a result must have been rather disappointing, especially since one might suppose from the examination of molecular models that the androcymbine structure, containing seven and six membered units, would be more stable than the arrangement (31) which comprises seven and five membered rings fused in the form of a spirodienone system.

As we have already mentioned, it is believed that inorganic oxidants, exemplified by vanadium oxyfluoride, operate by a similar mechanism to that occurring at the anode. There is a fundamental difference, however, the substrate must approach the surface of the electrode prior to ionisation and since this is a rigid assembly, some stereochemical effect may be envisaged.

There are some examples known, which can be argued to illustrate this constraint[22]. Thus we decided to attempt the electro-oxidation of the 1-phenethylisoquinolines,although at the time Kupchan's work was unpublished and his results might well have discouraged us if we had been aware of them. Some electrochemical oxidation studies had, however, been conducted in this area by Bobbitt[33] at Conneticut prior to the commencement of our study. Thus, the author had oxidized the isoquinolinium chlorides (38) and (39) in aqueous tetraethylammonium perchlorate solution using a graphite felt anode, the products obtained were the <u>ortho</u> <u>para</u> coupled dienones (40) and (41) respectively.





(38) R= H

(39) R=OCH_3

(40) R= H

(41) R=OCH_3

DISCUSSION TO PART ONE

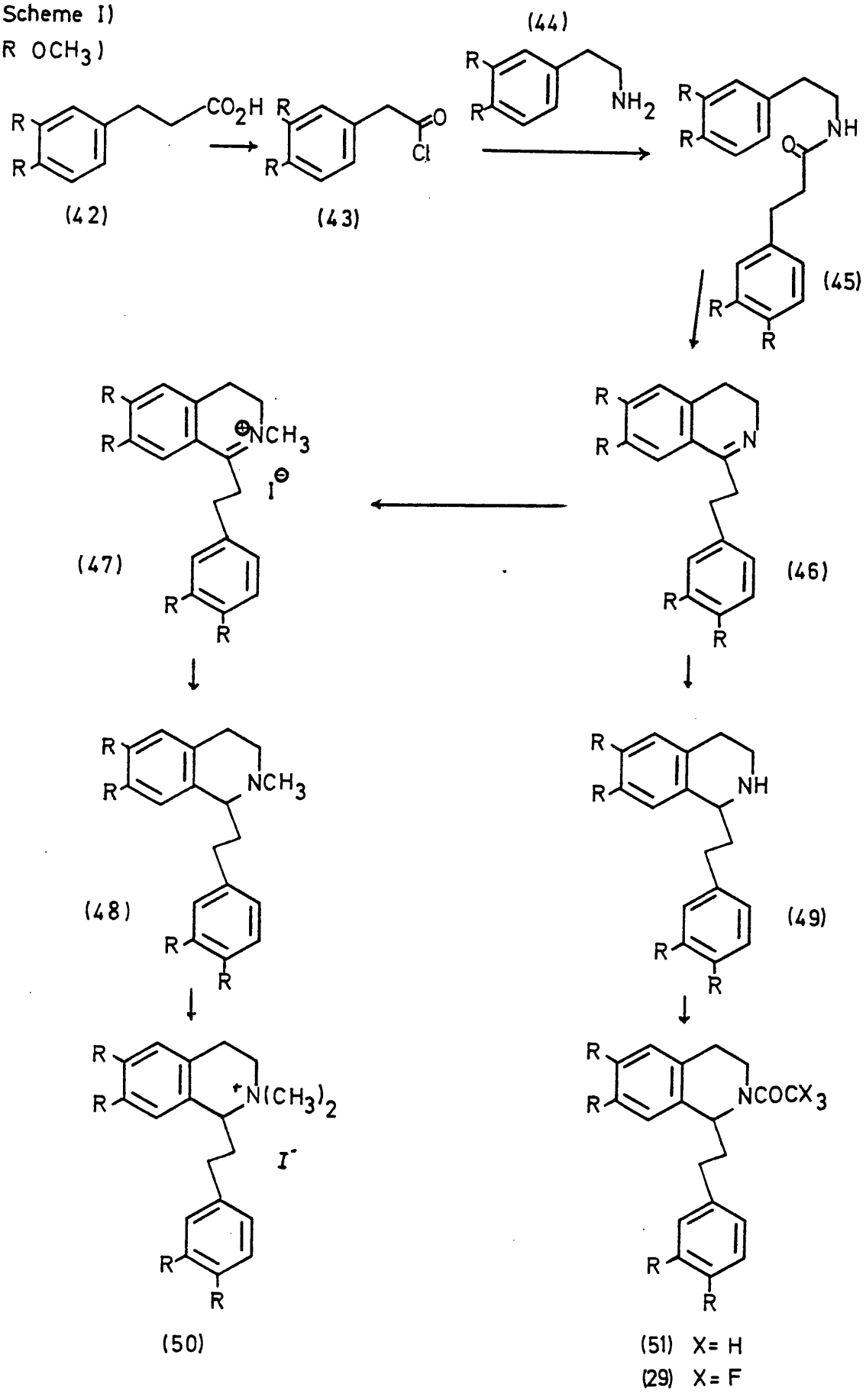
Anodic Oxidation of 1-Phenethylisoquinolines

From the previous discussion it will be noted that at the time we began our study, homologues of the laudanosine system bearing a phenethyl group at C-1, rather than a benzyl function, had not been subjected to electro-chemical oxidation.

Accordingly we began our work by preparing 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (48) *via* a conventional Bischler-Napieralski synthesis, using the β-phenethylamine (44) and 3,4-dimethoxyphenylpropionyl chloride as shown in Scheme I.
In this laboratory this last compound has a long and infamous history, tending to decompose extremely easily when impure. Normally the crude product from the parent acid and thionyl chloride is distilled under reduced pressure prior to use, affording a red oil but unless the operator is careful, this can be very unproductive. Wyatt has recently shown[36] that if the reaction and distillation procedures are carried out so that light is excluded, then a colourless oil is formed which solidifies slowly, the yield is moderate. We note, however, that the distillation step is not required if the reaction mixture, after removal of excess reagent, is extracted into hot petroleum ether (b.p. 60-80°C). When the extracts are cooled the acid chloride separates as colourless crystals, but exposure of this product to light and air, brings about gradual resinification. As just described, this modification gives a yield of 60-75%.

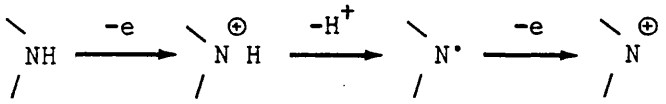
(Scheme I)

(R OCH_3)



Ring-closure of the amide (45) was achieved with phosphorus oxychloride giving 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (46). Reduction of this by sodium borohydride afforded the corresponding tetrahydroisoquinoline (49), whereas reaction with methyliodide followed by reduction of the methiodide salt (47) with sodium borohydride gave the 2-methyl derivative (48).

Secondary amines are not normally selected as candidates for electro-oxidation, since the radical cation formed by ionization of the lone pair may easily deprotonate to give a radical which may again ionize and of course, the initial oxidation step is very facile and occurs at potentials well below that at which dimethoxylated aryl rings lose an electron to a platinum anode (ca + 1.1v).



Because of this type of argument we selected the N-methyltetrahydro-isoquinoline (48) as the first target for study and as a preliminary step examined its cyclic voltammogram in acetonitrile solution containing sodium perchlorate as supporting electrolyte; this is shown in Figure 4.

The cyclic voltammogram shows on the first sweep three oxidation peaks at + 0.62 v (O_1), + 1.08 (O_2) and + 1.21 (O_3) volts. Three reduction peaks are also observed at - 1.0, - 1.18 and - 1.27v.

The origin of the last reduction peak is uncertain, but the remaining two are most likely associated with the oxidation peaks which occur at similar, but positive potentials.

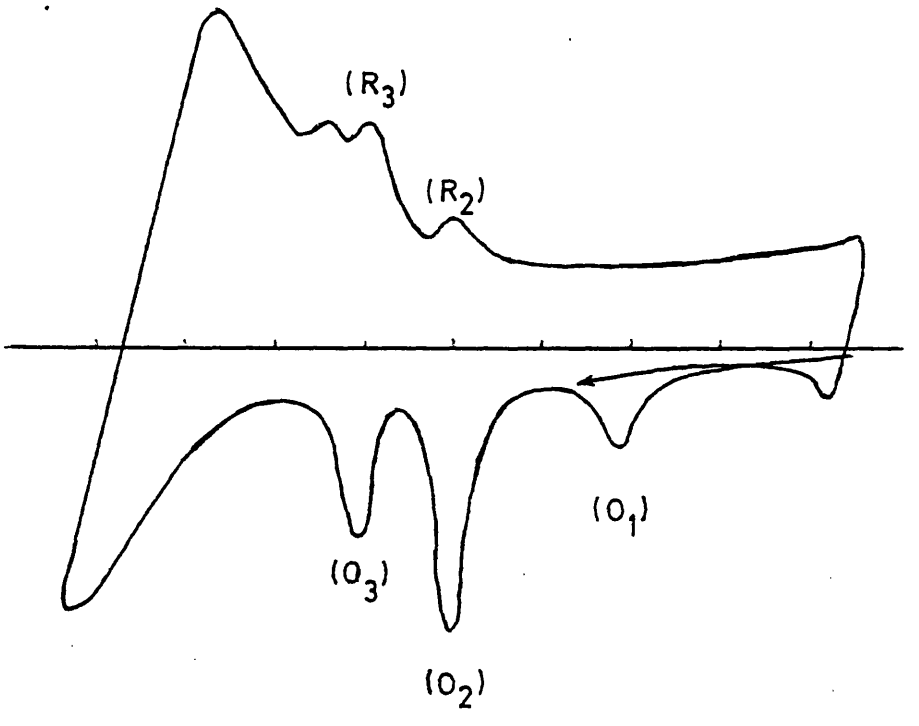


FIGURE 4 : Cyclic Voltammogram of the N-methyltetrahydroisoquinoline (48) at (200 mv/sec).

The peak heights are not the same, however, and thus it is clear that chemical reactions are occurring at appreciable rates compared with the speed of the analytical sweep.

Additionally, if the first sweep is allowed to over-run into a second cycle (O_1) disappears. This is rather interesting and we decided to try and determine the origin of the last peak and also those of (O_2) and (O_3).

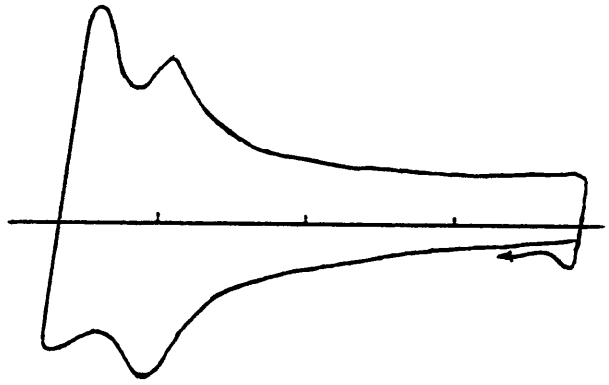


FIGURE 5

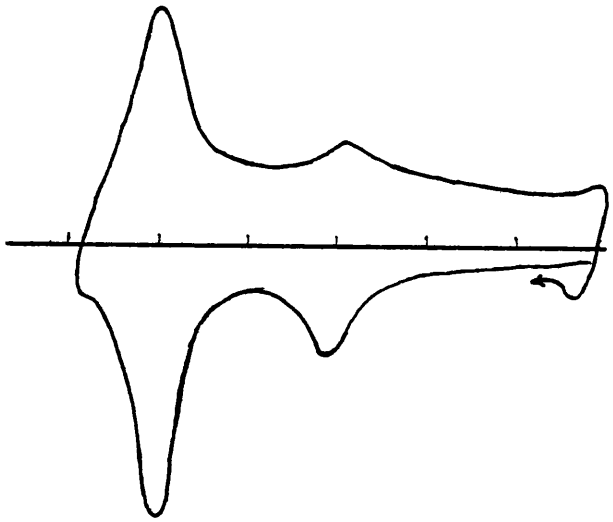
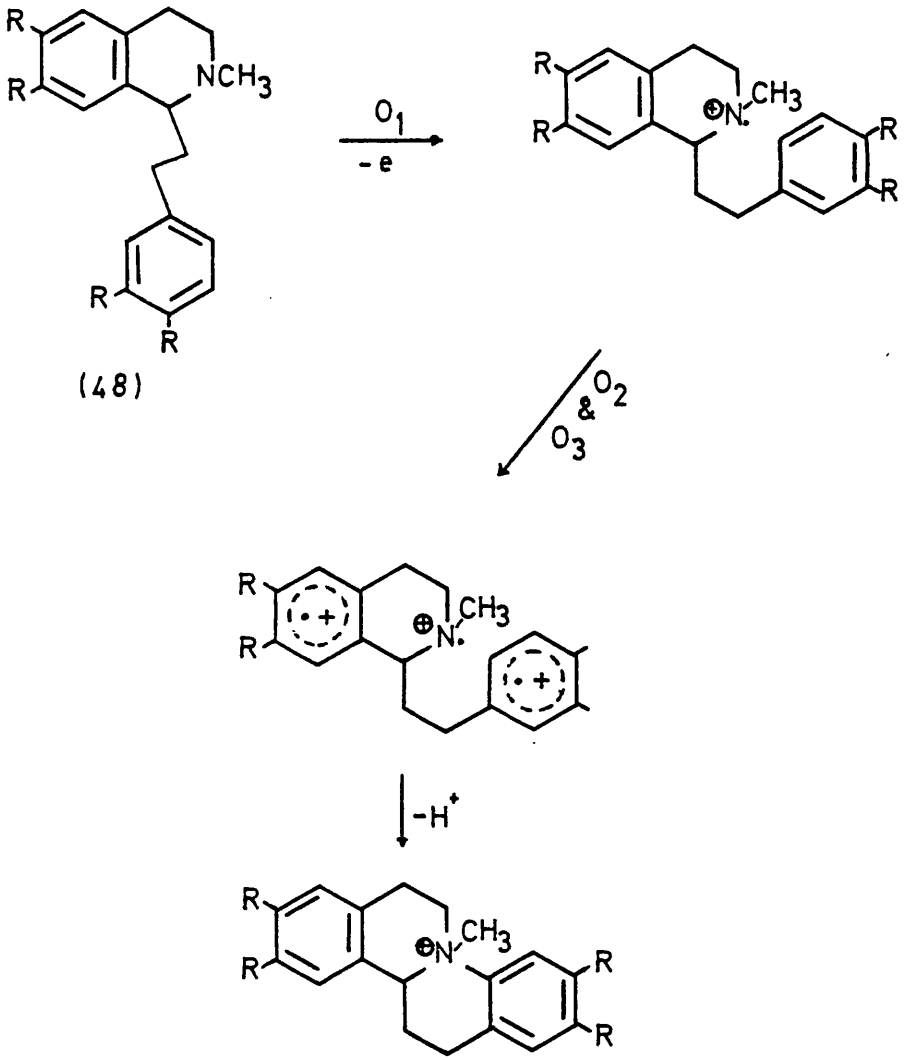


FIGURE 6

Figures 5 and 6 show the result of limited potential scans using this substrate and the first illustrates the result of a cyclic voltammogram stopped just after (O_1). Here this oxidation is associated with an equally intense reduction peak and obviously together these form a stable redox system. It is clear therefore, that the species formed at (O_1) may only react with another intermediate produced at higher potentials.

Such an intermediate is not formed at (O_2) because as exhibited in Figure 6 the voltammogram swept up to just above this potential but below (O_3) still shows the low potential redox couple. It is noticeable, however, that the intensity of the reduction peak associated with (O_1) is now somewhat reduced, indicating that the species is undergoing decomposition at a rate comparable with the sweep time of this restricted cycle. From these results it is clear that (O_3) is the critical potential and whatever is formed at this voltage reacts with the species produced at (O_1). The rate of this reaction is fast and the diffusion layer around the electrode is then depleted of oxidisable substrate.

As stated earlier there is a wealth of information to establish that dimethoxylated aryl rings lose an electron to a platinum anode at $\sim$ + 1.1v. Thus (O_1) must be due to an alternative ionization and this is probably the ionization of the lone-pair electrons upon the nitrogen atom. If this is so, then it is difficult to see how an intramolecular reaction between the nitrogen atom and the fused benzene ring of the isoquinoline unit can occur, but a reaction with the 1-phenethyl substituent is possible e.g.



R= OCH_3

Intermolecular processes are not ruled out but this sequence does give rise to a cation which is unlikely to be oxidised at potentials below +1.1v. The peak (O_2) is due to the oxidation of the fused benzenoid ring of the heterocycle and since it does not react, this simply gives rise to a redox couple, see Figure 4.

This hypothesis was confirmed when a preparative electrolysis conducted at an anode potential of +1.3v, using the customary electrolyte system was performed. After work-up, a crystalline perchlorate salt was isolated which in the ^{1}Hn.m.r. spectrum shows four low field singlets each due to one proton, these may be assigned to the resonances of the four aromatic protons of the tetracycle (53) and together with elemental analysis and other spectroscopic data, clearly prove the product to be 6b-methyl-4,5,10,11-tetramethoxy-dibenzo [c,h] quinolizinium perchlorate (53).

As the intention of this experiment was the synthesis of an androcymbine type structure, another substrate is required in order to overcome the problem of N-C cyclisation in the manner of the last experiment. On the other hand it would be nice to use an isoquinoline which might produce this structure but as a free base, rather than as the salt.

2,2-Dimethylisoquinolinium iodide (50) was chosen as a model since in the substrate there are no lone pair electrons to participate in the oxidation sequence. This isoquinoline was prepared by the simple expedient of reacting the isoquinoline (48) with methyl iodide and its cyclic voltammogram is shown in Figure 7.

Three oxidation peaks at + 1.1v (O_1); + 1.2v (O_2) and + 1.38v (O_3) are observed but there is only one reduction (R_1) peak, at - 1.02v. The origin of the two oxidation peaks (O_1) and (O_2) are most likely associated with the oxidation at the two benzene rings; but the source of the oxidation peak (O_3) is uncertain, although, the fact that this peak increased in intensity after several scans suggests that it is due to the oxidation of a chemical product.

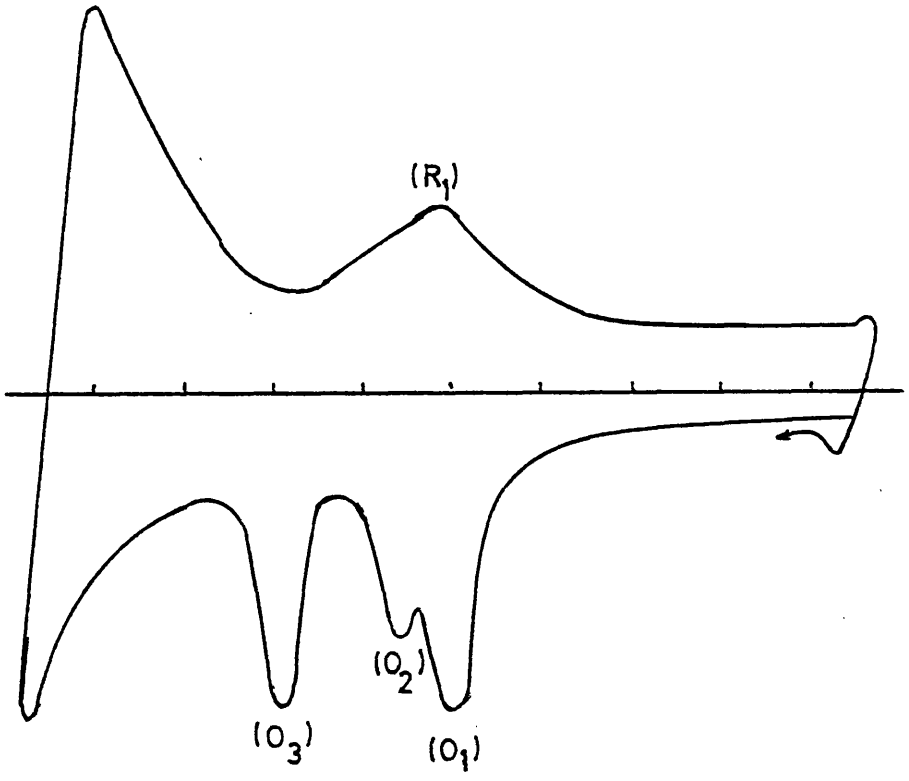
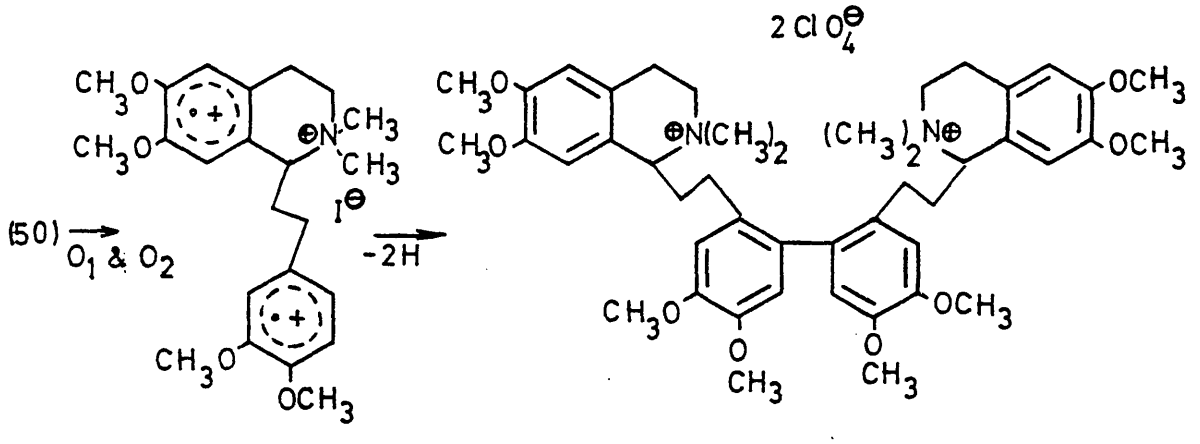


FIGURE 7 : Cyclic Voltammogram of the 2,2-dimethyisoquinolinium methiodide (50).

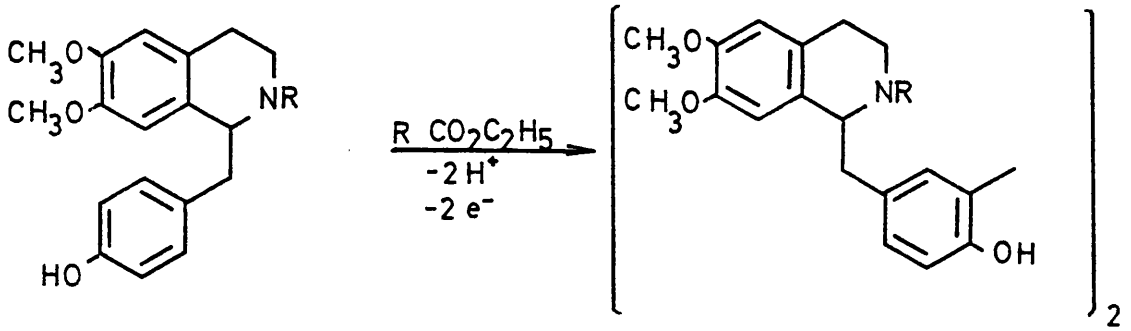
Initially we found the nature of the reduction peak (R_1) also difficult to explain, but now we believe that it represents half of the redox couple arising from the chemical product formed through the coupling reaction of two radical cations generated from the two benzenoid rings at potentials (O_1) and (O_2).

A preparative experiment conducted at + 1.2v gave the intermolecularly coupled 'dimer' (54) and no sign of an intramolecular product.



(54)

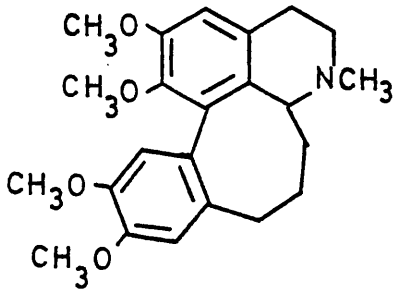
The structure of this compound follows from analytical data and spectroscopy; the 'Hnmr spectrum, for example, shows four proton resonances which at 60 MHz resonate as singlets in the aromatic region. These may be assigned to the benzenoid protons of the 'dimer'. The twenty four methoxy protons resonate as singlets at δ 3.8, 3.6 and 3.5 ppm but the remaining signals form two relatively complex systems centred at δ 3.1 and 2.85 ppm. The integral trace does, however, provide the correct proton count. This type of intermolecular coupling closely resembles that found by Bobbitt[34] who showed that the electro-oxidation of the 1-benzylisoquinoline (55) led to the 'dimeric' structure (56).



(55) (56)

In this case, however, the phenolic unit is much more easily oxidised and would give rise to a radical cation at a potential well below that at which the fused benzene ring can be effected. The radical cation may then either couple with a similar species directly or deprotonate to a radical which then undergoes intermolecular coupling. The oxidation potentials of the 'halves' of our substrate are similar and one might have expected some intramolecular interaction but in our hands the 'dimeric' compound was the only isolated product. However, almost a year after our investigation was completed Kupchan[35] reported that the electro-oxidation of isoquinoline (48) in a mixture of trifluoroacetic acid and trifluoroacetic anhydride containing tetraethylammonium tetrafluoroborate

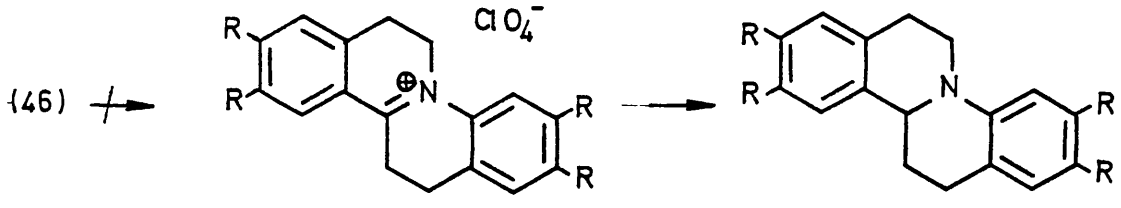
as the supporting electrolyte at + 1.3v gave the homoaporphine (57) in 34% yield. He did not obtain any evidence for the dimer and clearly the factors which control this reaction are subtle (see page 17).



(57)

Our isolation of the tetracyclic salt (53) caused us to examine the oxidation of the 3,4-dihydroisoquinoline (46) which might give rise, first to the perchlorate (58) and then through reduction, to the base (59). The latter would be of more interest pharmacologically than the salt (53).

R= OCH_3



(58) (59)

In the cyclic voltammogram (Figure 8) the 3,4-dihydroisoquinoline (46) showed on the first sweep three oxidation peaks at + 0.9v (O_1), + 1.1v (O_2) and + 1.45v (O_3) and two reduction peaks at - 1.0v (R_2) and - 0.3v (R_1), the oxidation peak (O_1) is most likely associated with the oxidation of the nitrogen lone pair and the oxidation peak at 1.1v (O_2) the combined oxidation potentials of the two benzene rings.

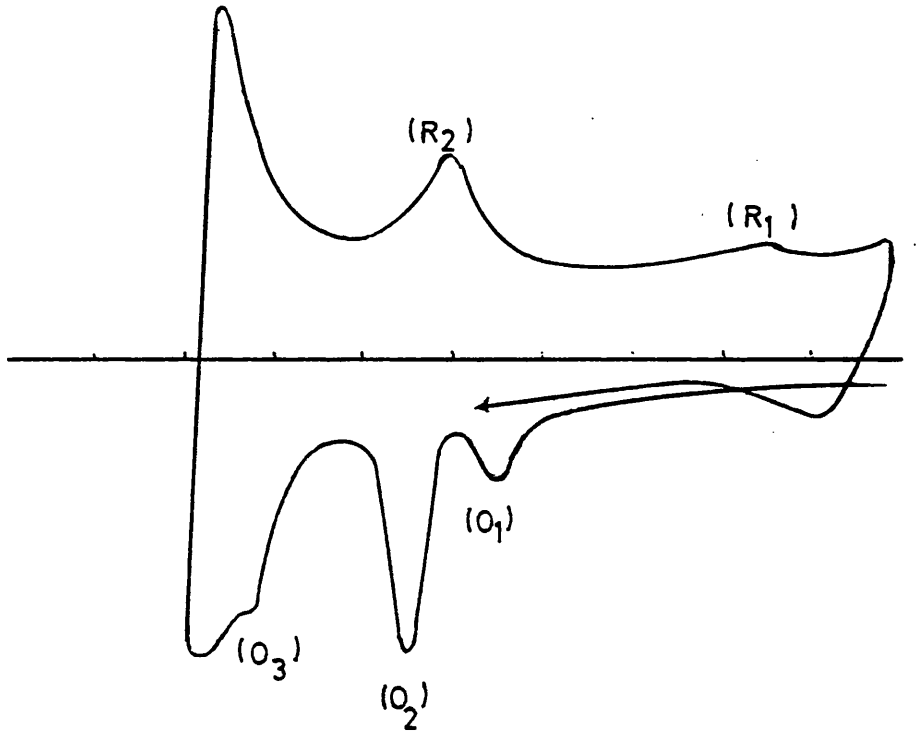
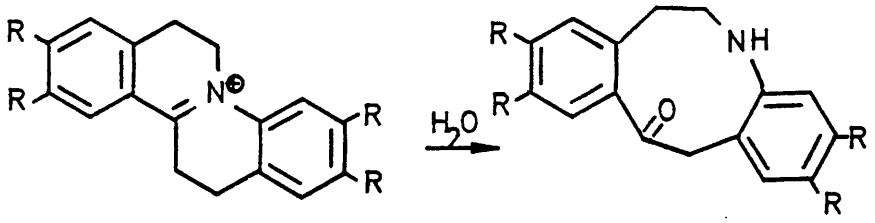


FIGURE 8 : Cyclic voltammogram of the 3,4-dihydroisoquinoline (46).

The origin of the peak (O_3) is uncertain but reduction peak (R_2) can be either associated with the oxidation peak (O_2) or the reduction of a chemical product. These uncertainties are not totally resolved by limited potential sweeps; possibly (R_2) is a combination of both effects; however, the reduction peak (R_1) at - 0.3v is typically due to the reduction of hydrogen ions.

A preparative electro-oxidation conducted at + 1.2v gave on work-up only the perchlorate salt of the starting materials (46), together with much dark resin. From the cyclic voltammogram it is clear that electrolysis gives rise to protons,so a chemical reaction is occurring and this conclusion is confirmed by the isolation of the salt from the electrolysis which is carried out under neutral conditions. Should the product (58) form, it is probable that it would ring-open to the keto-amine* (60) and this may then undergo further oxidation, perhaps in an uncontrollable way at this high potential, it is after all an aromatic amine. We cannot confirm this speculation since chromatography of the resinous product was unsuccessful; TLC analysis merely shows a broad streak in various solvent systems.



(58) (60)

R= OCH_3

* *Water is always present in the* CH_3CN *even after drying.*

From these results it is apparent that cyclisation involving basic 1-phenethylisoquinoline derivatives proceed either to quinolizines or are not productive and so in a final attempt at androcymbine sythesis we examined the amides (51) and (29). The first gives rise to the voltammogram shown in Figure 9, two oxidation peaks are observed at + 1.0v and + 1.2v. The first peak forms a stable redox couple which is not promising, but a small peak at - 0.2v due to the reduction of protons, indicates that some chemical reaction is proceeding. A similar voltammogram is produced from the trifluoroacetyl analogue (29) but preparative electrolysis with either leads only to dark resins.

We tried hard to purify and isolate the components of these resins, especially as Kupchan[32] and his co-workers used the last substrate (29) in their oxidations with vanadium oxyfluoride (Reference 32, page 24) but to no avail and it is interesting that in their later paper[35] the Americans do not mention the anodic oxidation of this compound, although they compare results of the two techniques with the other key substrates. With vanadium oxyfluoride the amide (29) affords the homoaporphine (32).

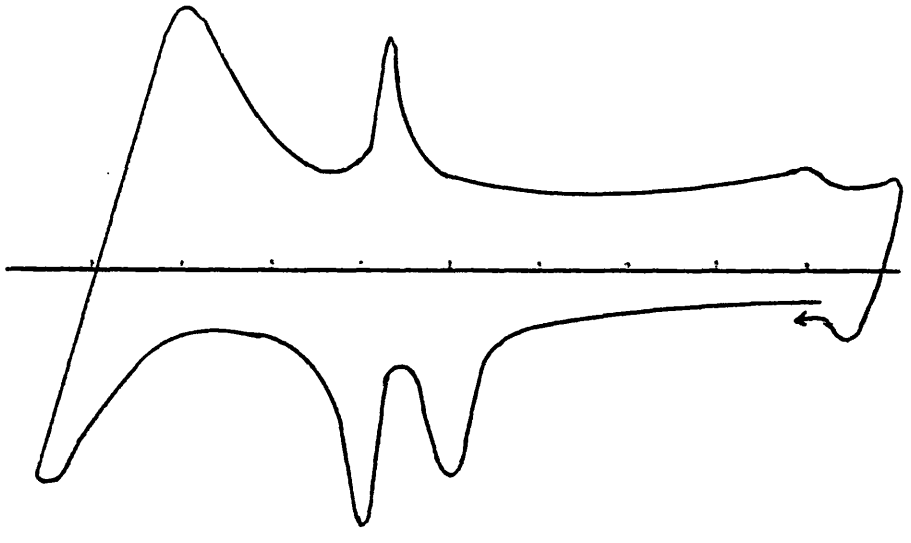


FIGURE 9 : Cyclic Voltammogram of isoquinoline (51)

EXPERIMENTAL TO PART ONE

3,4-Dimethoxyphenylcinnamic Acid

3,4-Dimethoxybenzaldehyde (30 g) was dissolved in pyridine (100 cm^3) in a 500 cm^3 two-necked flask and malonic acid (38 g) then added. The mixture was warmed to give a clear solution and piperidine (3 cm^3) introduced. After warming to 80°C during 30 minutes. The reaction mixture was maintained at this temperature for a further one hour, before it was heated at reflux for two hours more. Finally the product was added to cold water (500 cm^3) and acidified with concentrated hydrochloric acid (170 cm^3) and the solid so formed then filtered off and recrystallised from methanol (27 g, 72%) m.p. 168° (lit.,[36] 169°C); ν_{max} 3100-2500, 1675, 1624, 1596 cm^{-1}, $m/_e$ 208 (M^+).

β-(3,4-Dimethoxyphenyl) Propionic Acid (42)

3,4-Dimethoxyphenylcinnamic acid (10 g) was dissolved in dimethylformamide (100 cm^3) and to the solution was added 10% platinum on charcoal (10 mg), this suspension was then hydrogenated at 100 lb/in^2 and 50°C for three hours. After this time, the catalyst was removed and the filtrate evaporated to give a colourless product which was recrystallised from petroleum ether (b.p. 60-80°C). (9.5 g, 95%), m.p. 95-96 (lit.,[36] 96-97°C); ν_{max} 3200-2250, 1695, 1610 cm^{-1}; δ ($CDCl_3$) 2.70 (2H, t, $\underline{J}$ = 7Hz), 2.92 (2H, t, $\underline{J}$ = 7Hz), 3.87 (6H, S), 6.70-6.84 (3H, m), 11.0 (1H, S); $m/_e$ 210 (M^+).

β-(3,4-Dimethoxyphenyl) Propionyl Chloride (43)

β-(3,4-Dimethoxyphenyl) propionic acid (9 g) in dry benzene (100 cm^3) was heated at reflux with redistilled thionylchloride (30 cm^3) for two hours, the solvent was then evaporated to yield an oily product which recrystallised from petroleum ether (b.p. 60-80°C) to form white crystals. This compound was used immediately for the next reaction. ν_{max} 1800 cm^{-1}.

N-[2(3,4-Dimethoxyphenyl)ethyl)ethyl] 3,4-Dimethoxyphenylethylamine (45)

The previous acid chloride (10 g) was dissolved in dry benzene (50 cm^3) and added dropwise to a stirred solution of homoveratrylamine (7.38 g) and pyridine (3.22 g) in dry benzene over 30 minutes. The mixture was then heated at reflux for another 30 minutes, cooled, and the pyridine hydrochloride which had formed filtered off. Finally, the benzene was removed to give an oily product (15 g, 99%), ν_{max} 1700, 1010, 820, 750 cm^{-1}.

3,4-Dihydro-6,7-Dimethoxy-1(3,4-Dimethoxyphenethyl) Isoquinoline (46)

A mixture of the amide (45) (15 g) phosphorusoxychloride (30 cm^3) and dry benzene (300 cm^3) was heated under reflux for 2.5h and then the solvent was removed in *vacuo* to give an oil (14 g, 98%); ν_{max} 1625, 1600, 1590, 1570 cm^{-1}, δ ($CDCl_3$) 2.5-2.7 (2H, m), 2.96 (4H, S), 3.58-3.75 (2H, m), 3.8 (3H, S), 3.86 (6H, S), 3.95 (3H, S), 6.7 (1H, S), 6.8 (3H, S), 6.98 (1H, S); $m/_e$ 355 (M^+).

6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-2-Methyl-1,2,3,4-Tetrahydroisoquinoline (48)

The above dihydroisoquinoline (14 g) in methanol (40 cm^3) was treated with methyl iodide (15 cm^3) and stirred at room temperature for 2 h. The solvent and excess reagent were then removed to give a yellow solid residue which was dissolved in methanol (500 cm^3) and treated with sodium-borohydride (1.5 g) in portions. The solution was stirred for 2 h., and finally the solvent was removed to afford a colourless residue which was extracted to chloroform. The combined extracts were dried over sodium carbonate, the solvent removed and the product re-crystallised from petroleum ether (b.p. 60-80°C) to give white crystals (8 g, 50%); m.p. 58-59 (lit.,[31] reports a viscous syrup); ν_{max} 1610, 1600, 860, 790 cm^{-1}; δ ($CDCl_3$) 1.95-2.15 (2H, m), 2.5 (3H, S), 2.6-2.85 (5H, m), 3.1-3.25 (1H, m), 3.5 (1H, t, $\underline{J}$ = 7Hz), 3.9 (12H, S), 6.58 (1H, S), 6.6 (1H, S), 6.73-6.8 (3H, m); $m/_e$ 371 (M^+). (Found: C,71.8; H,7.7; N,3.8; $C_{22}H_{29}NO_4$ requires C,71.1; H,7.8; N,3.8%).

6b-Methyl-4,5,10,11-Tetramethoxydibenzo[c,h]quinolizinium Perchlorate (53)

The previously made tetrahydroisoquinoline (1.0 g) was dissolved in 10% sodium perchlorate in methyl cyanide (50 cm^3) (the salt was dried overnight in a vacuum oven at 80°C before use) and a few drops of tetrafluoroacetic acid was added to the anolyte compartment for an H-type cell and a potential of + 1.3v (versus SCE) applied to the platinum anode. Electrolysis commenced with a current through the cell of ∿ 50.mA and this was maintained until 1.8F mol^{-1} of current

had been consumed. The solvent was then removed and the product was extracted with chloroform and the combined extracts dried over sodium sulphate Finally the chloroform was evaporated, the product was dissolved in hot ethanol (10 cm^3) and the solution was left to cool overnight. Next day yellow crystals of title product were collected (0.73 g, 60%), m.p. 172-173°C; ν_{max} 3150, 1600, 1250, 860, 790 cm^{-1}, δ (DMSO) 2.6-3.8 (8H, m), 2.9 (3H, S), 3.8 (12H, S), 4.37 (1H, t, J = 7Hz), 6.7 (1H, S), 6.85 (3H, m). (Found: C,55.5; H,6.2; N,2.8, Cl 7.3. $C_{22}H_{28}Cl\ NO_8$ requires C,56.3; H,6.0; N,3.0; Cl,7.6%).

6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-2-Methyl-1,2,3,4-Tetrahydroisoquinoline Methiodide (50)

6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (1.0 g) in methanol (20 cm^3) was heated under reflux with methyl iodide (5 cm^3) for 2 h. The solvent was then removed to give yellow crystals (1.2 g, 90%), m.p. 62-63°C (ethanol); ν_{max} 1620, 1600, 1020, 860, 810, 730 cm^{-1}, δ (T.F.A.) 2.6-4.5 (9H, m), 3.2 (3H, S), 3.4 (3H, S), 3.95 (12H, S), 6.75 (1H, S), 6.9-7.02 (4H, m).

Attempted Cyclization of 6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-2-Methyl-1,2,3,4-Tetrahydroisoquinoline Methiodide

The isoquinoline methiodide from the previous experiment (1.2 g) was dissolved in 10% sodium perchlorate in methyl cyanide (50 cm^3) containing a few drops of tetrafluoroacetic acid and electrolysed to an anode potential of + 1.2v (versus SCE) until 1.8F mol^{-1} of current had been consumed. The solvent was then removed to afford a solid residue, this was extracted with chloroform and the combined extracts dried over sodium sulphate. After removal of the chloroform, the product was crystallised from ethanol to afford colourless prisms shown to be 6'-6'-Bis [6,7-dimethoxy-1-(3,4-dimethoxyphenethyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolium perchlorate] (0.45 g, 39%), m.p. 232°-234°C; ν_{max} 3600, 3550, 1600, 1080, 620 cm^{-1}; λ_{max} 250 and 290 nm; δ (DMSO) 2.00-4.2 (18H, m), 2.84 (6H, S), 3.1 (6H, S), 3.5 (6H, S), 3.6 (3H, S), 3.75 (12H, S), 6.25 (2H, S), 6.33 (2H, S), 6.67 (2H, S), 6.7 (2H, S). (Found: C,56.9; H,6.6; N,2.8 $C_{46}H_{62}N_2O_{16}Cl_2$ requires C,57.0; H,6.4; N,2.9%).

Attempted Cyclization of 3,4-Dihydro-6,7-Dimethoxy-1-(3,4-Dimethoxy-Phenethyl) Isoquinoline (46)

The dihydroisoquinoline (1.0 g) in 10% sodium perchlorate in methyl cyanide (50 cm^3) was electrolysed at + 1.25v. When 1.8F mol^{-1} of current had been consumed, the solvent was removed and the product was extracted into chloroform, the combined extracts were dried over sodium sulphate and the solvent then removed to afford a colourless solid.

On work-up this proved to be unreacted starting material present as the perchlorate salt (0.8 g, 62%), δ ($CDCl_3$) 2.9-3.15 (5H, m), 3.3-3.5 (3H, m), 3.8 (6H, S), 3.9 (3H, S), 4.0 (3H, S), 6.6 (1H, dd, $\underline{J}$ = 8Hz, $\underline{J}$ = 1.5Hz), 6.74 (1H, d, $\underline{J}$ = 8Hz), 6.79 (1H, d, $\underline{J}$ = 1.5Hz), 6.86 (1H, S), 7.14 (1H, S), 10.8 (1H, S).

6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-1,2,3,4-Tetrahydroisoquinoline (49)

3,4-Dihydro-6,7-dimethoxy-1-(3,4-dimethoxyphenethyl) isoquinoline from the previous experiment (5.0 g) was dissolved in 50% aqueous ethanol and sodium borohydride (1.0 g) was added in portions while the solution was stirred. Agitation was continued for a further hour before the solvent was removed and the residual product was extracted into chloroform. The combined extracts were dried over sodium sulphate, the chloroform removed and the product purified by the process of sublimation in high vacuum. This gave a yellow solid which subsequently turned to a dark oil within a few hours (4.0 g, 80%); ν_{max} 3400, 1630, 810, 750 cm^{-1}; δ ($CDCl_3$) 2.0-2.2 (3H, m), 2.5-3.4 (6H, m), 3.8 (12H, S), 6.55 (1H, S), 6.58 (1H, S), 6.78 (3H, S).

2-Acetyl-6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-1,2,3,4 Tetrahydroisoquinoline (51)

6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline (1.0 g) was heated at reflux in acetic anhydride for 30 minutes. The solvent was then removed in high vacuum to yield a yellow oil, (1.0 g, 89%); γ_{max} 1721, 1640, 1030, 855, 750 cm^{-1}; δ ($CDCl_3$ 1.9-3.7 (9H, m), 2.17 (3H, S), 3.8 (12H, S), 6.55 (2H, S), 6.7 (3H, S).

6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-1,2,3,4-Tetrahydro-2-Trifluoroacetylisoquinoline (29)

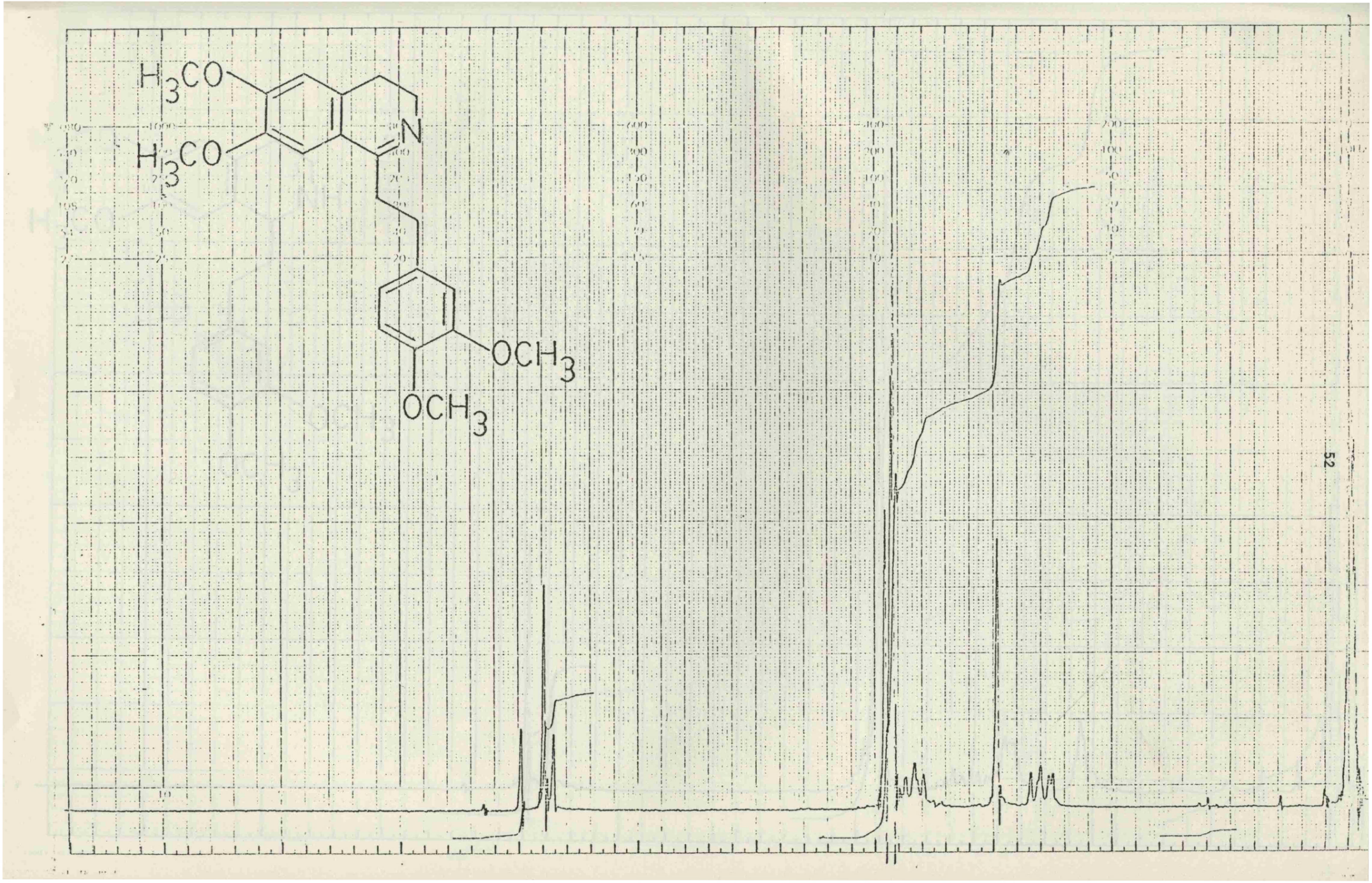
6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline (1.0 g) was heated at reflux in trifluoroacetic anhydride for 30 minutes. The solvent was then removed in high vacuum to yield an oil (1.1 g, 86%). ν_{max} 1700, 1600, 960, 820 cm^{-1}; m/e 453 (M^+).

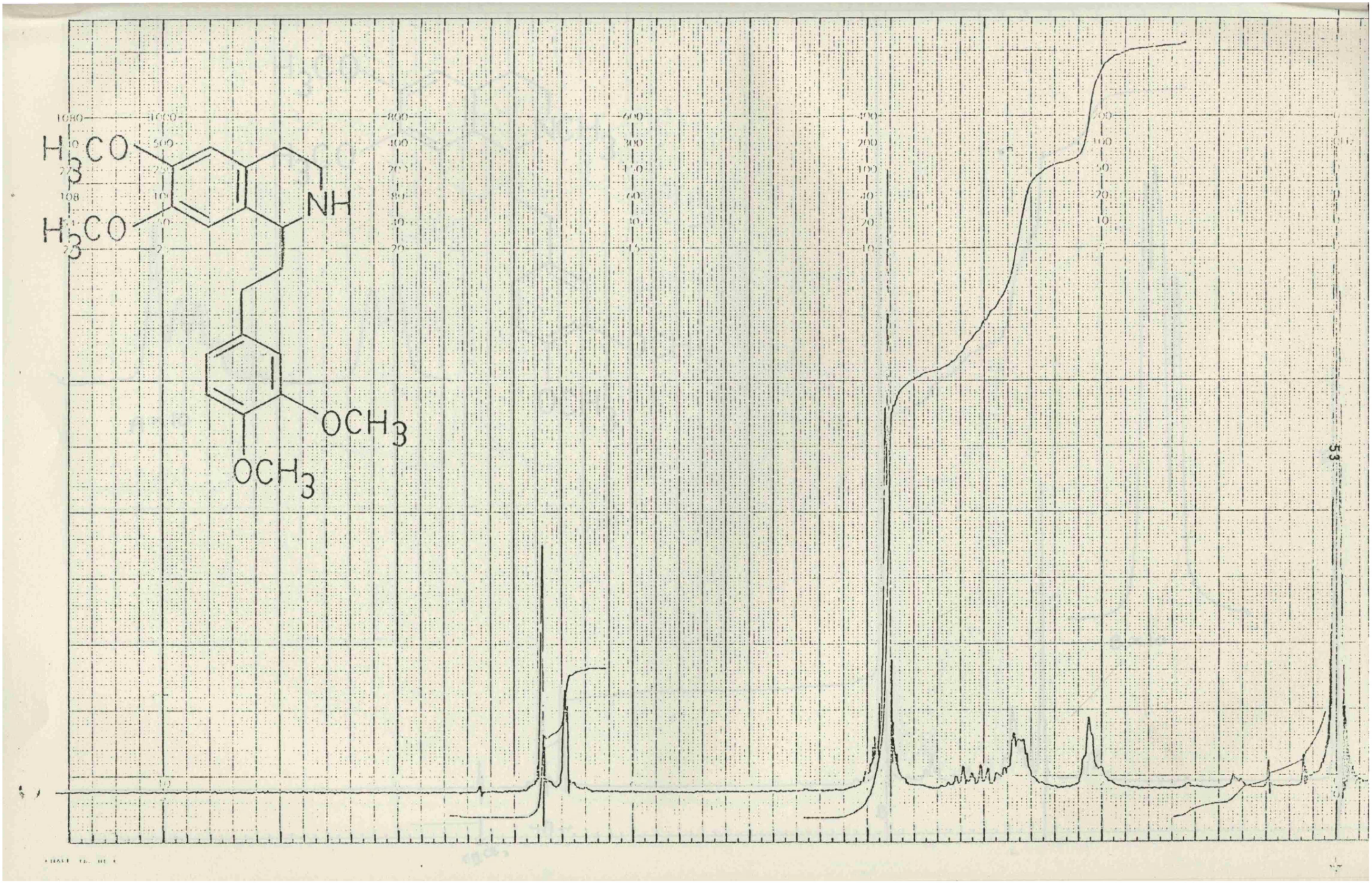
Attempted Electrolysis of 2-Acetyl-6,7-Dimethoxy-1-(3,4-Dimethoxy-phenethyl-1,2,3,4-Tetrahydroisoquinoline

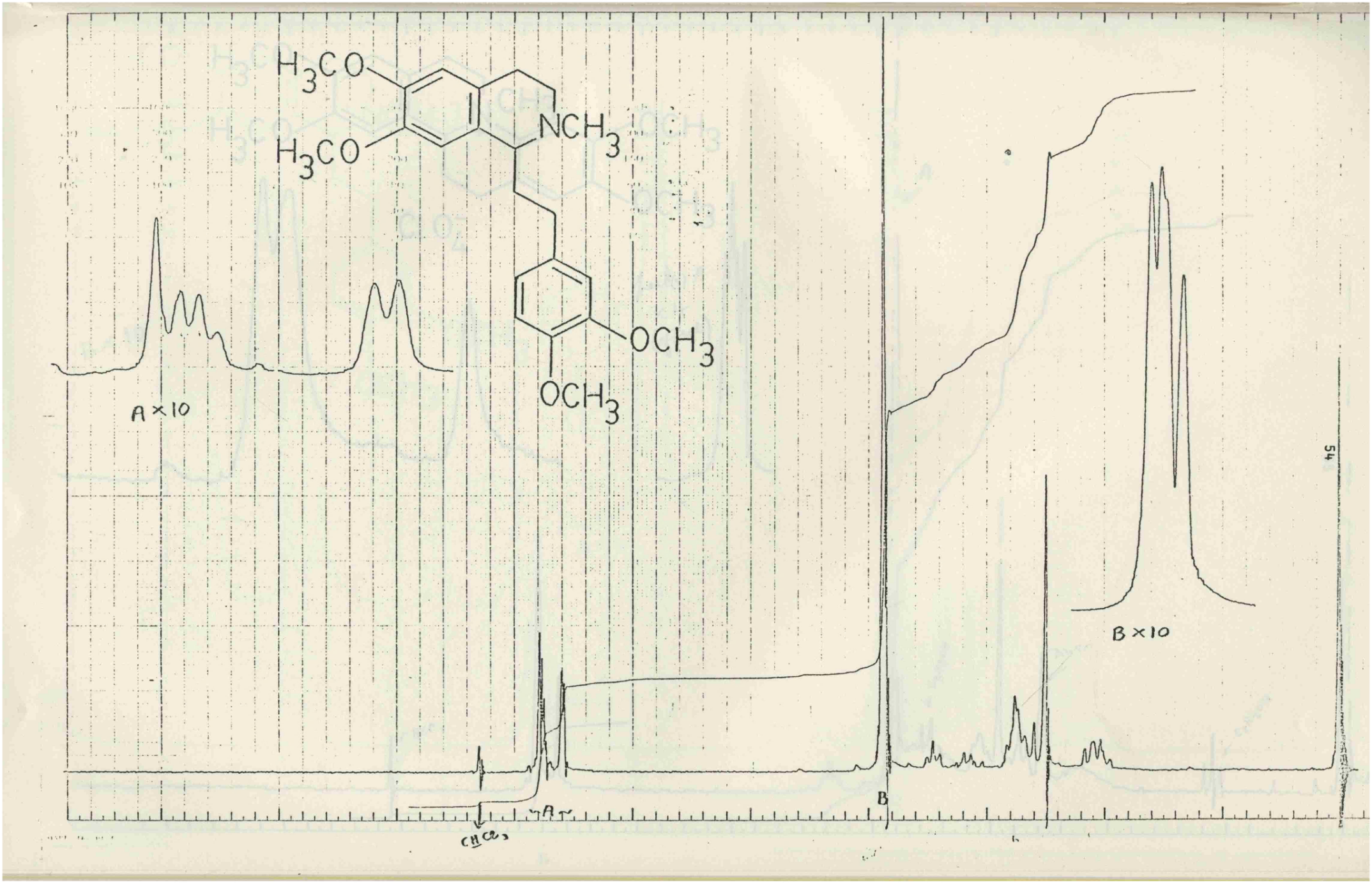
The 2-Acetyl isoquinoline from a prior experiment (1.0 g) in 10% sodium perchlorate in methyl cyanide (50 cm^3) electrolysed at + 1.15v until 1.8F mol^{-1} of current had been consumed. The solvent was evaporated and the residue extracted with chloroform. The combined extracts were dried over sodium sulphate, the solvent was then removed to give a dark resin.

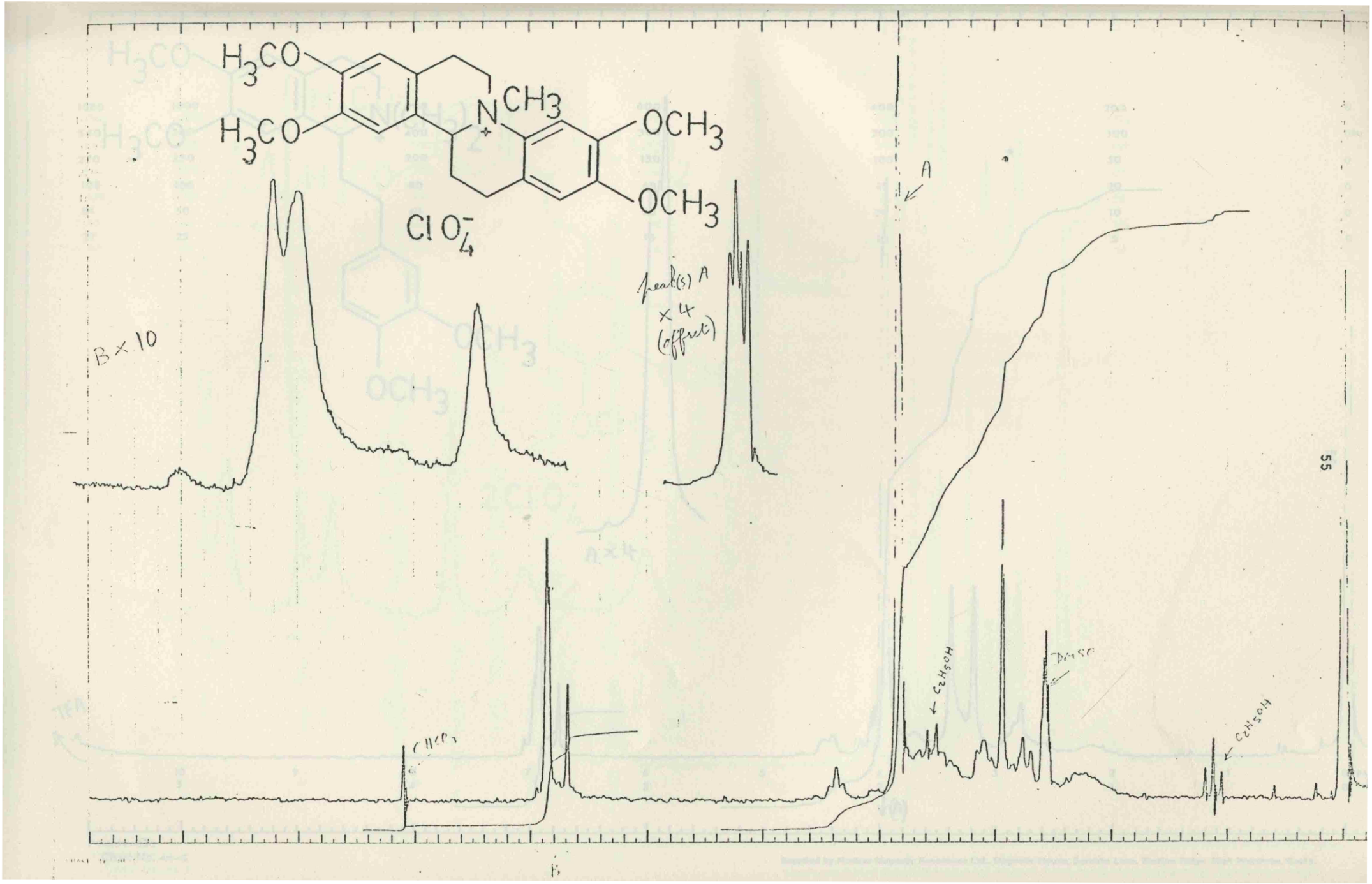
Attempted Electrolysis of 6,7-Dimethoxy-1-(3,4-Dimethoxyphenethyl)-1,2,3,4-Tetrahydro-2-Trifluoroacetylisoquinoline

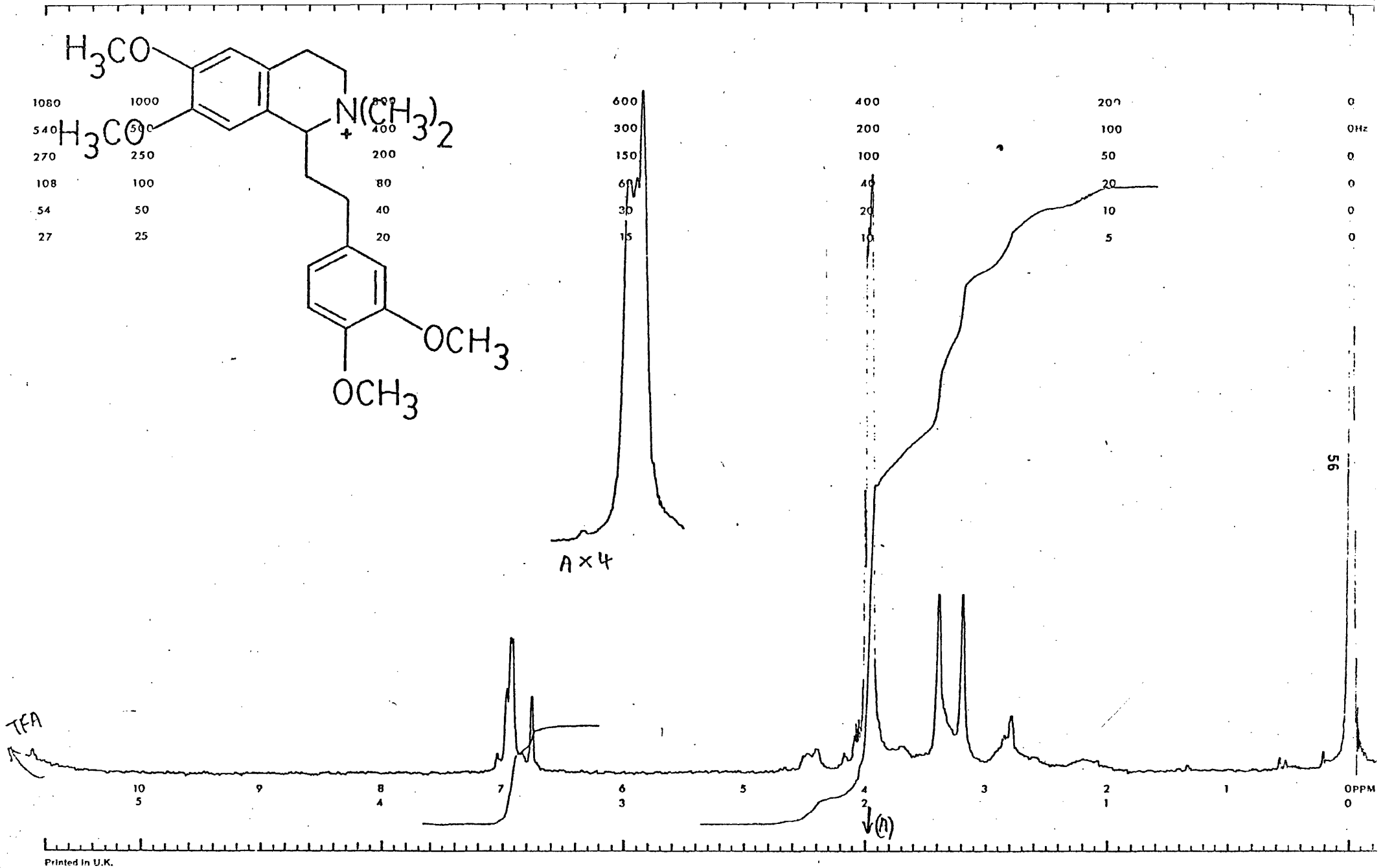
The same electrolysis conditions as in the previous experiment were attempted on the 2-trifluoroacetylisoquinoline (29). Some starting material contaminated with resinous products was isolated.


H3CO
H3CO
N
OCH3
OCH3


H3CO
H3CO
NH
OCH3
OCH3

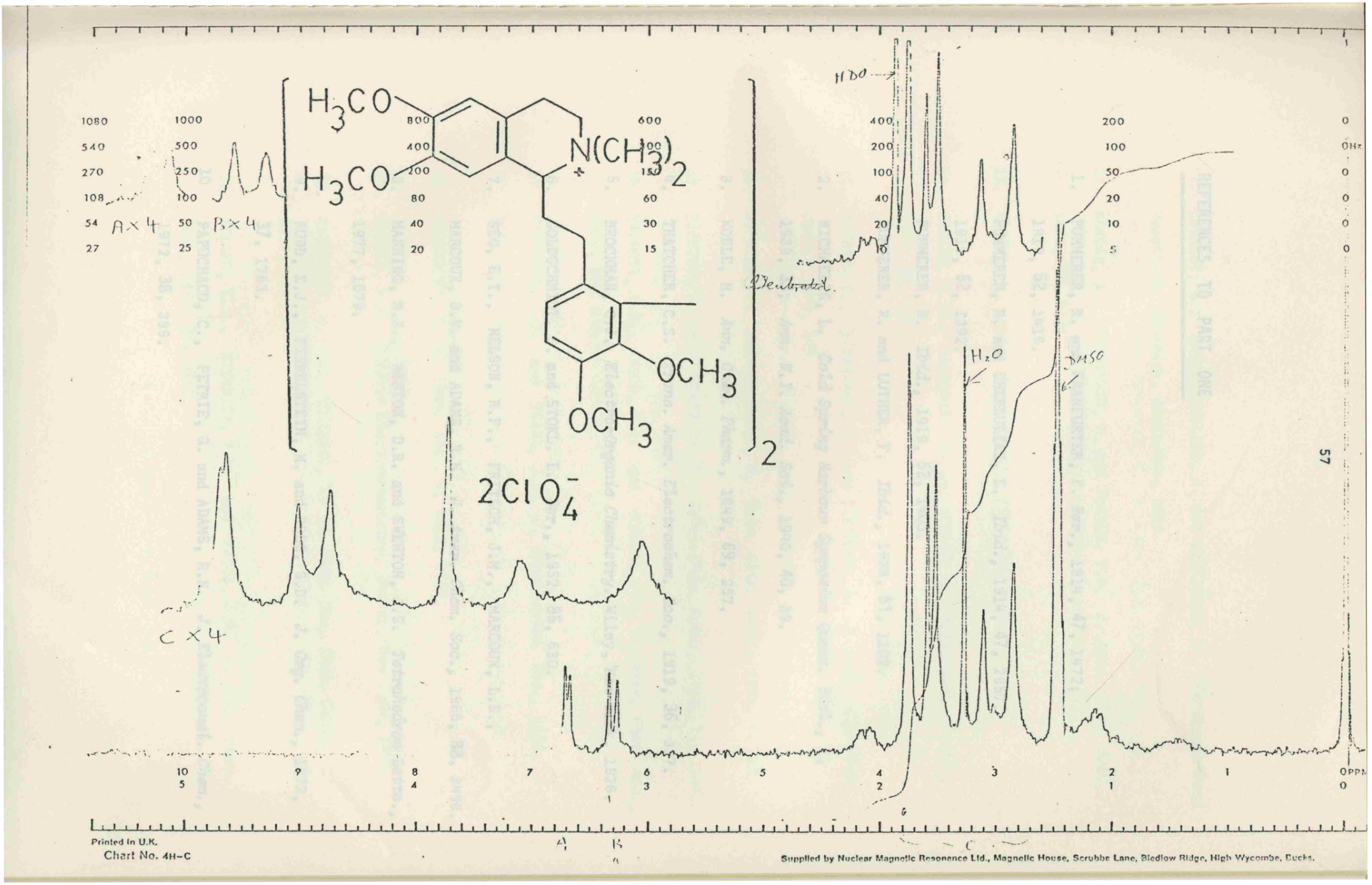

H_3CO
H_3CO
NCH_3
OCH_3
OCH_3
A×10
B×10
B
A
CH_3Cl


H3CO
H3CO
N
CH3
OCH3
OCH3
ClO4−
B × 10
peak(s) A
× 4
(offset)
A
CH2Cl2
C2H5OH
DMSO
C2H5OH
55
B



Printed in U.K.
Chart No. 4H-C

Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.



Printed in U.K.
Chart No. 4H–C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

REFERENCES TO PART ONE

1. PUMMERER, R. and FRANFURTER, F. *Ber.*, 1914, **47**, 1472;
1919, **52**, 1416.
PUMMERER, R. and CHERBULIEZ, E. *Ibid.*, 1914, **47**, 2957.
1919, **52**, 1392.
PUMMERER, R. *Ibid.*, 1919, **52**, 1403.
PUMMERER, R. and LUTHER, F. *Ibid.*, 1928, **61**, 1102.

2. MICHAELIS, L. *Cold Spring Harbour Symposium Quant. Biol.*, I, 1939, **33**; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 39.

3. KOBLE, H. *Ann. Chem. Pharm.*, 1849, **69**, 257.

4. THATCHER, C.S. *Trans. Amer. Electrochem. Soc.*, 1919, **36**, 337.

5. BROCKMAN, C.J. *Electro-Organic Chemistry*. Wiley, New York, 1926.

6. GOLDSCHMIDT, S. and STOKL. E. *Ber.*, 1952, **85**, 630.

7. SEO, E.T., NELSON, R.F., FRITSCH, J.M., MARCOUX, L.S., MARCOUX, D.W. and ADAMS, R.N. *J. Amer. Chem. Soc.*, 1966, **88**, 3498.

8. MANNING, M.J., HENTON, D.R. and SWENTON, J.S. *Tetrahedron Letts.*, 1977, 1679.

9. RUDD, E.J., FINKELSTEIN, M. and ROSS, S.D. *J. Org. Chem.*, 1972, **37**, 1763.

10 PAPUCHACO, C., PETRIE, G. and ADAMS, R.N. *J. Electroanal. Chem.*, 1972, **38**, 389.

11. CHORLOT, G., BADOZ-LAMBLING, J. and TREMILLON, B. *Electrochemical Reactions*, Elsevier, Amsterdam, 1962.

12. RONLÁN, A., HAMMERICH, O. and PARKER, V.D. *J. Amer. Chem. Soc.*, 1973, **95**, 7132.

13. NYBERG, K. *Acta. Chem. Scand.*, 1971, **25**, 2499.

14. PARKER, V.D., PALMQUIST, V. and RONLÁN, A. *Acta. Chem. Scand.*, 1974, **28**, 1241.

15. KOTANI, E., MIYANZAKI, F. and TOBINAGA, S. *J. Chem. Soc. Chem. Comm.*, 1974, 300.

16. FICHTER, F. and DIETRICH, W. *Helv. Chim. Acta.*, 1924, **7**, 131.

17. FICHTER, F. and HERSBEIN, S. *Helv. Chim. Acta.*, 1928, **11**, 1264.

18. MALLORY, F.B., WOOD, C.S. and GORDON, J.T. *J. Amer. Chem. Soc.*, 1964, **86**, 3094.

19. O'CONNOR, J.J. and PEARL, J.A. *J. Electrochem. Soc.*, 1964, **111**, 335.

20. SAINSBURY, M. *J. Chem. Soc.*, C, 1971, 2888.

21. BAIZER, M.M. *Organic Electrochemistry*, Dekker, New York, 1973.

22. SAINSBURY, M. and SCHINAZI, R. *J. Chem. Soc. Chem. Comm.*, 1972, 718.

23. MILLER, L.L., STERMITZ, F.R. and FALCK, J.R. *J. Amer. Chem. Soc.*, 1973, **95**, 2651.

24. ELLIOTT, I.W. *J. Org. Chem.*, 1977, **42**, 1090.

25. ROBINSON, R. and SUGASAWA, S. *J. Chem. Soc.*, 1932, 789.

26. FRANK, B. and SCHLINGLOFF, G. *Liebigs Ann. Chem.*, 1962, **132**, 659.

27. KAMETANI, T., SUGAHARA, T. and FUKUMOTO, K. *Tetrahedron*, 1969, **25**, 3667.

28. HERBEK, J. and SANTAVY, F. *Coll. Czech. Chem. Comm.*, 1962, **27**, 255.

29. BATTERSBY, A.R., HERBERT, R.B., PYEWSKA, L. and SANTAVY, F. *Chem. Comm.*, 1965, 228.

30. KAMETANI, T., FUKUMOTO, K., KOIZUMI, M. and KOZUKA, A. *J. Chem. Soc.*, C, 1969, 1295.

31. KAMETANI, T., FUKUMOTO, K., SATON, F. and YAGI, H. *J. Chem. Soc.*, C, 1968, 3084.

32. KUPCHAN, S.M., DHINGRA, O.P., KYUKIEM, C. and KAMESWARON, V. *J. Org. Chem.*, 1976, **41**, 4047.

33. BOBBITT, J.M., NOGUCHI, I., WARE, R.S., CHIONG, K.N. and HUONG, S.J. *J. Org. Chem.*, 1975, **40**, 2924.

34. BOBBITT, J.M. and HALLCHER, B.C. *Chem. Comm.*, 1971, 543.

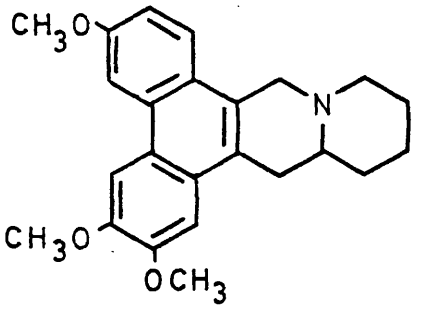
35. KUPCHAN, S.M., DHINGRA, O.P., KIM, C.K. and KAMESWARAN, V. *J. Org. Chem.*, 1978, **43**, 2521.

36. WYATT, J. *Ph.D. Thesis*, University of Bath, 1978, 191.

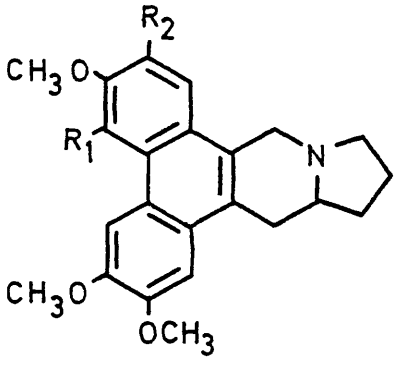
PART TWO

INTRODUCTION TO PART TWO

Cryptopleurine (1), tylophorine (2) and tylocrebrine (3) are alkaloids which occur in various perennial creepers of the Asclepiadaceae[1,4] family growing in tropical regions. The first compound was shown to have a phenanthroquinolinizidine as long ago as 1955[2], but the chemistry of this group still commands attention, since the alkaloids show vesicant and antitumour properties. Cryptopleurine (1) also stimulates the growth of nerve tissue but unfortunately it is rather toxic.



(1)

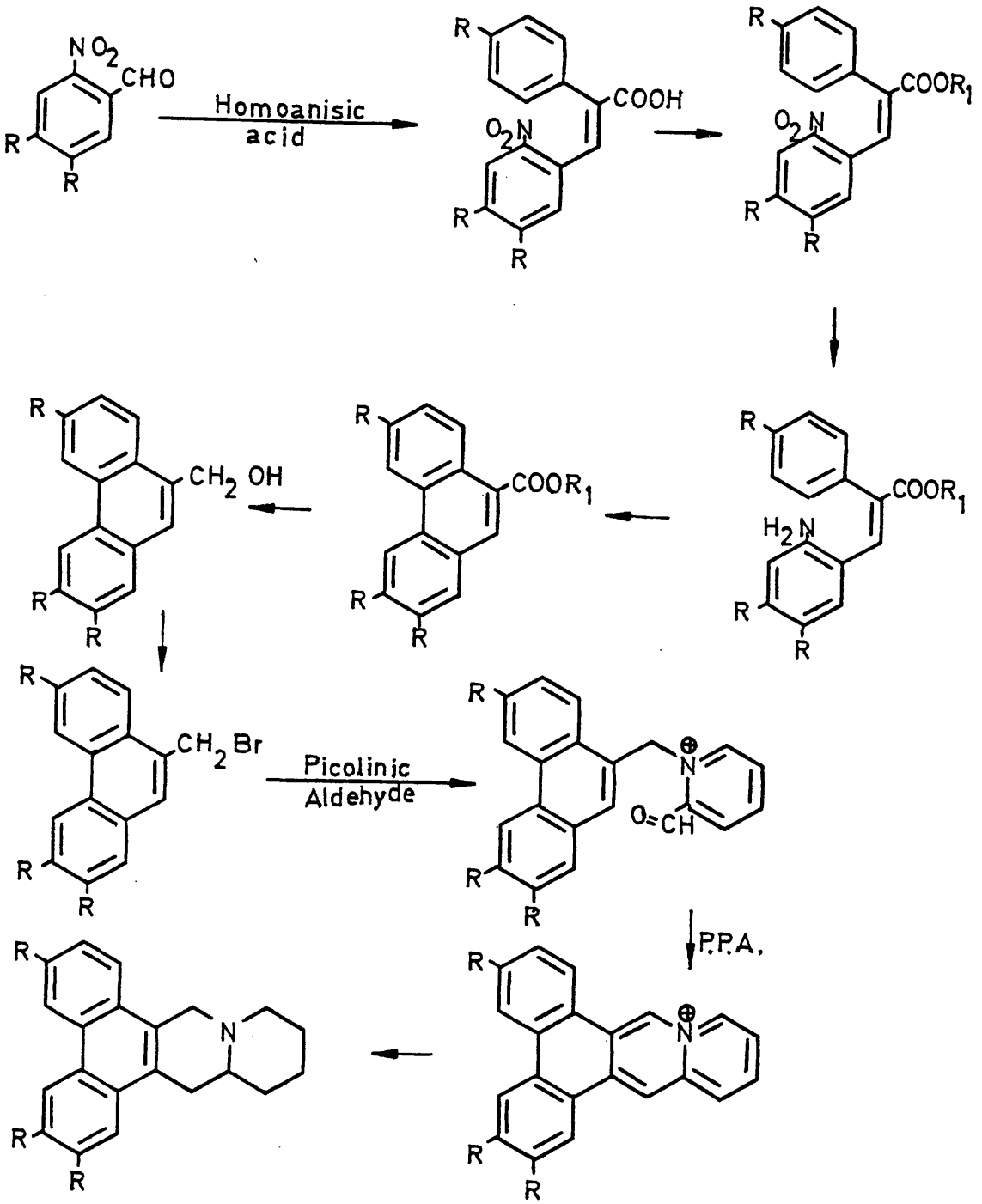


(2) $R_1 = H$, $R_2 = OCH_3$

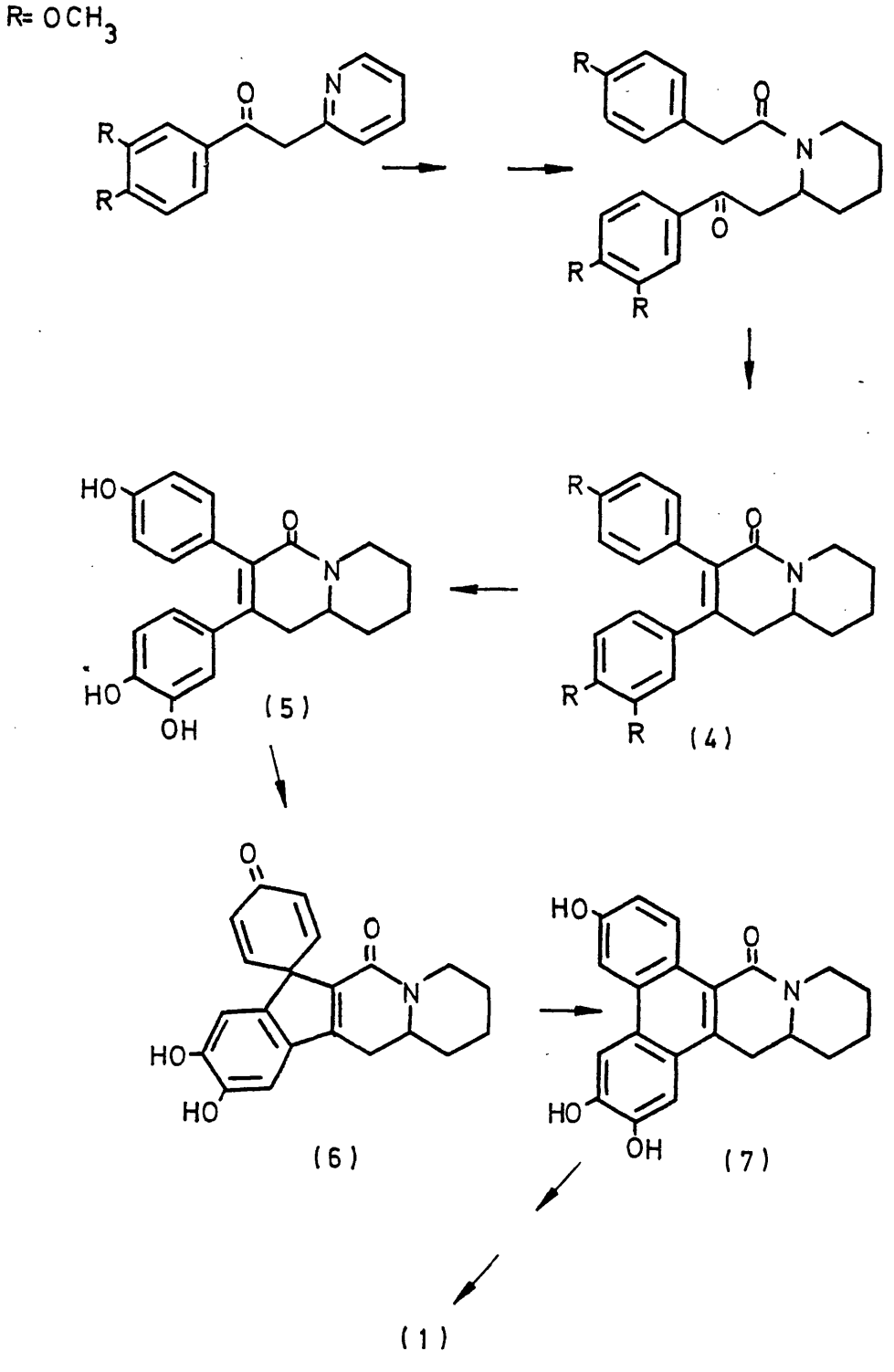
(3) $R_1 = OCH_3$, $R_2 = H$

Some early chemistry on these compounds is recorded by Hooper[3] but the main investigations at least of the Indian plant extracts have been made and summarised by Govindachari[4] and his school. After the proof of the structures[5], synthetic work flourished and, for example, Bradsher and Berger[6] announced the synthesis, albeit in low yield, of cryptopleurine in 1958. Their route is outlined on the next page.

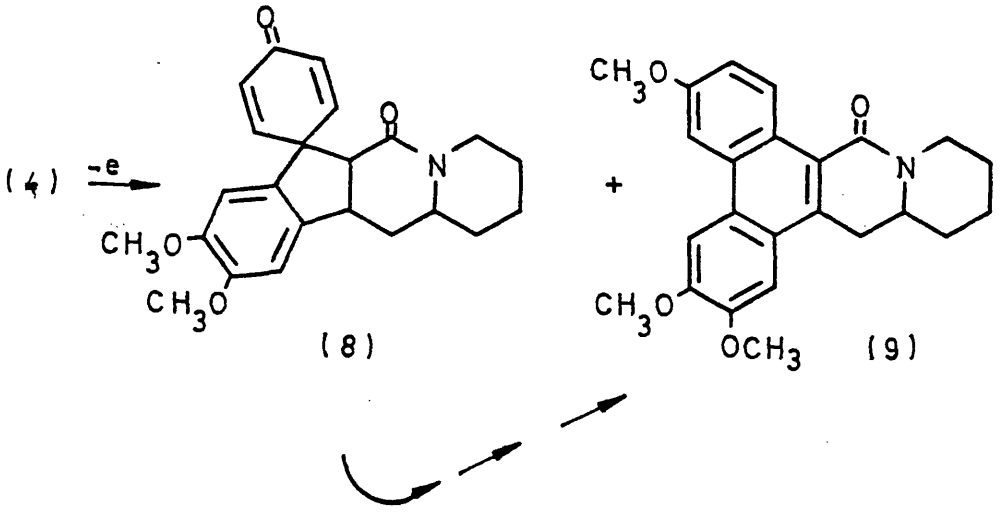
R = OCH_3


NO2
CHO
Homoanisic
acid
COOH
COOR1
O2N
H2N
CH2 OH
CH2 Br
Picolinic
Aldehyde
O=CH
P.P.A.
N
R

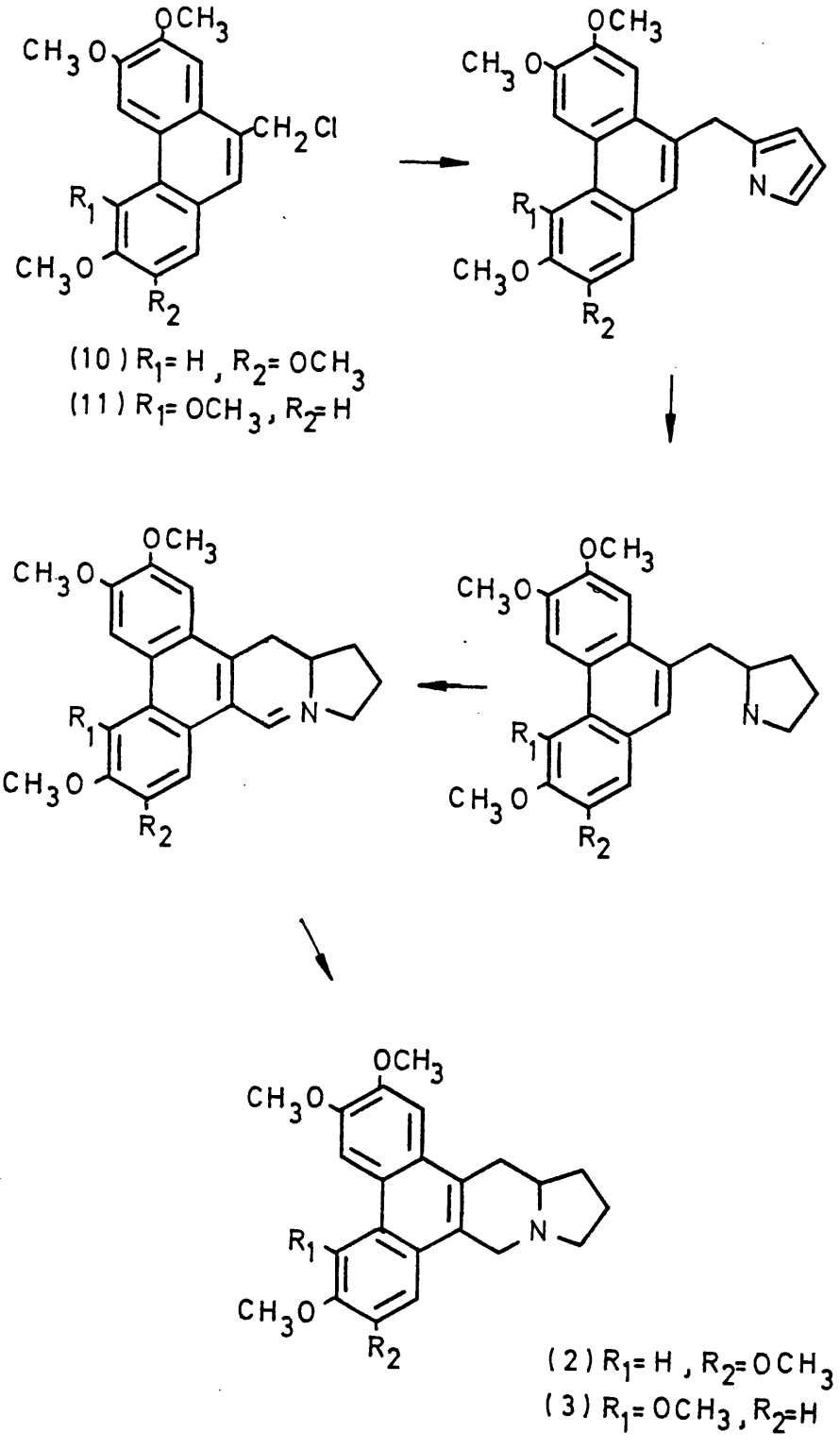
In 1968 Paton and his co-workers[7] prepared cryptopleurine (1) by a phenolic coupling reaction using the quinolizidinone (5). In this case the final oxidant was manganese dioxide but the yield was poor.



Anodic oxidation has proved to be a rather better technique. Kotani and his co-workers in 1974 reported[8] that the anodic oxidation of the quinolizidinone (4) produced two products (8) and (9) in 60% and 31% yield respectively. The spirodienone (8) can be re-arranged in acid to give the quinolizidine (9) in 80% yield and this was reduced with lithium aluminium hydride to cryptopleurine (1).



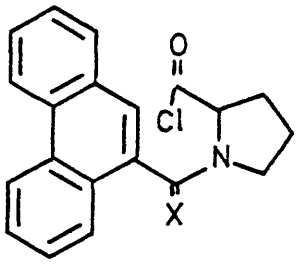
By contrast an Indian group synthesized tylophorine (2)[9] and tylocrebrine (3)[10] by modification of the Bradsher route using the phenanthrenes (10) and (11) respectively. The productivity of this approach was moderate.



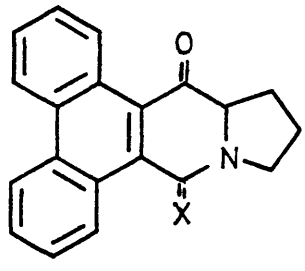
(10) R_1= H , R_2= OCH_3
(11) R_1= OCH_3 , R_2= H

(2) R_1= H , R_2= OCH_3
(3) R_1= OCH_3 , R_2= H

More interestingly Italian chemists[11] reported that Friedel Craft's cyclization of 1-(9-phenonthryl-methyl) pyrrolyl-2-carbonyl chloride (12) affords the phenanthroindolizidinone structure (13) but yields were not mentioned.



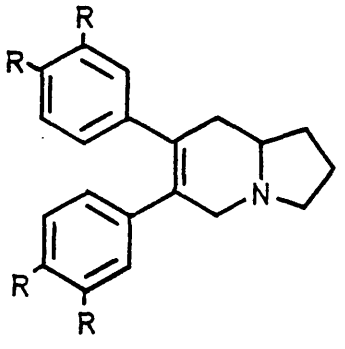
(12) X=O, H_2



(13) X=O, H_2

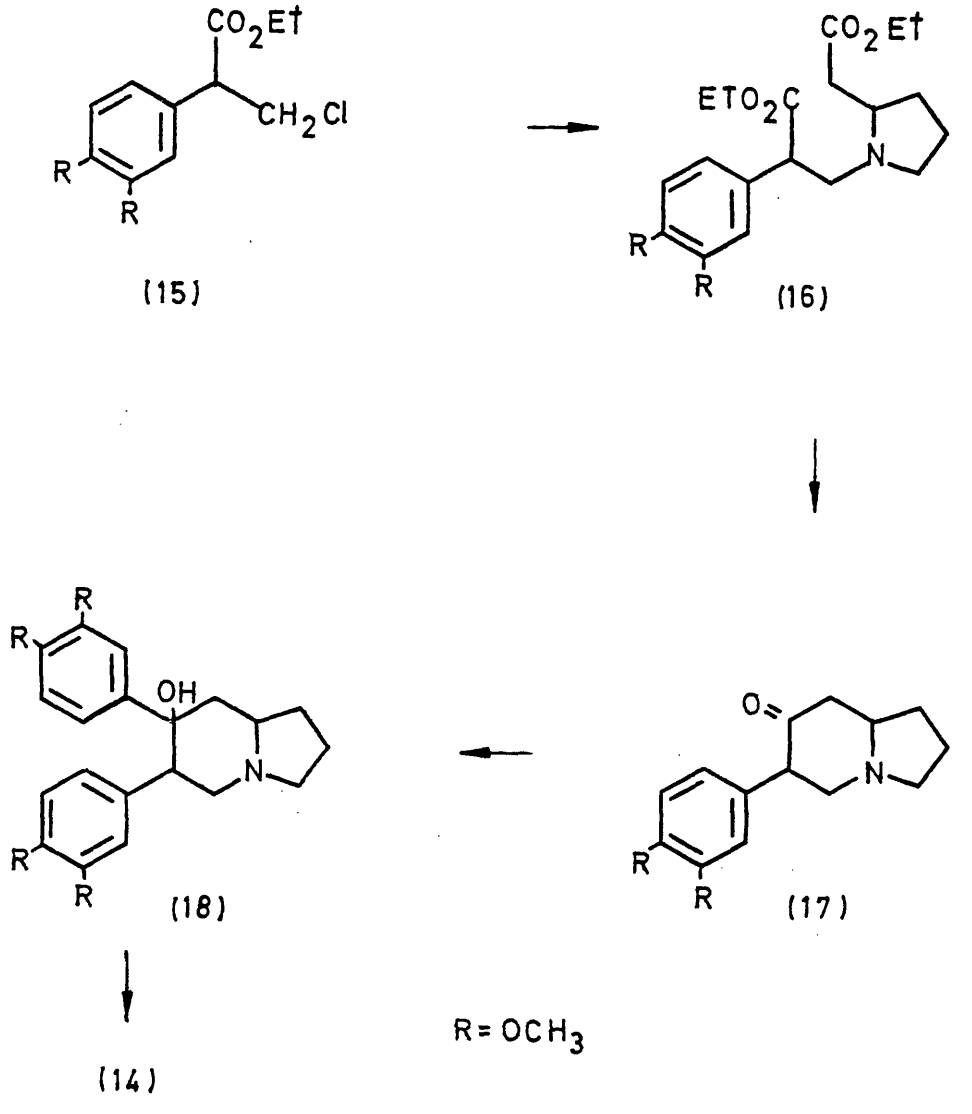
DISCUSSION TO PART TWO

It is apparent from the literature[12] that the key intermediates to the alkaloid tylophorine contain the septicine type skeleton (14) which can be coupled to give the desired compound. In turn this means that an economical and practical synthesis of septicine (14) is desirable.



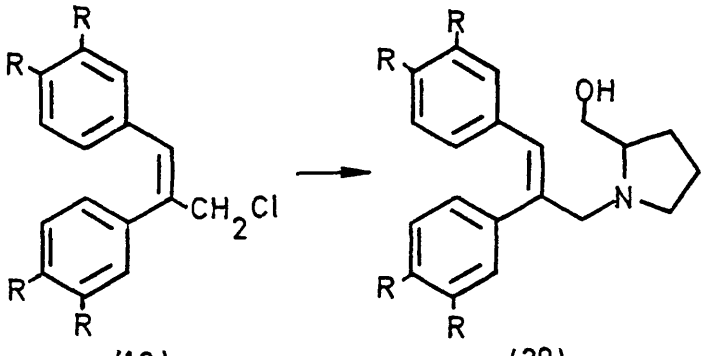
(14) R = OCH_3

Our work in this part of the thesis began with a search for a preparation of septicine (14) in sufficient yield to enable us to effect a synthesis of tylophorine by direct anodic coupling. The alkaloid septicine (14) has a history of its own, it was first isolated from *Ficus septica* by Govindachari[4] and synthesized by two methods: (a) the diester (16) obtained from the chloride (15) and ethyl-2-pyrolidinyl acetate was subjected to Dieckmann cyclisation to afford the ketone (17). This was reacted with veratryl lithium to give the carbinol (18). Dehydration of the carbinol (18) gave septicine (14).



(b) Reaction of the chloro-compound (19) with prolinol gave the amino alcohol (20), which on treatment with sodium hydride in dimethylformamide gave septicine (14). In neither of the two syntheses was the productivity high and our initial thoughts were to seek to improve them.

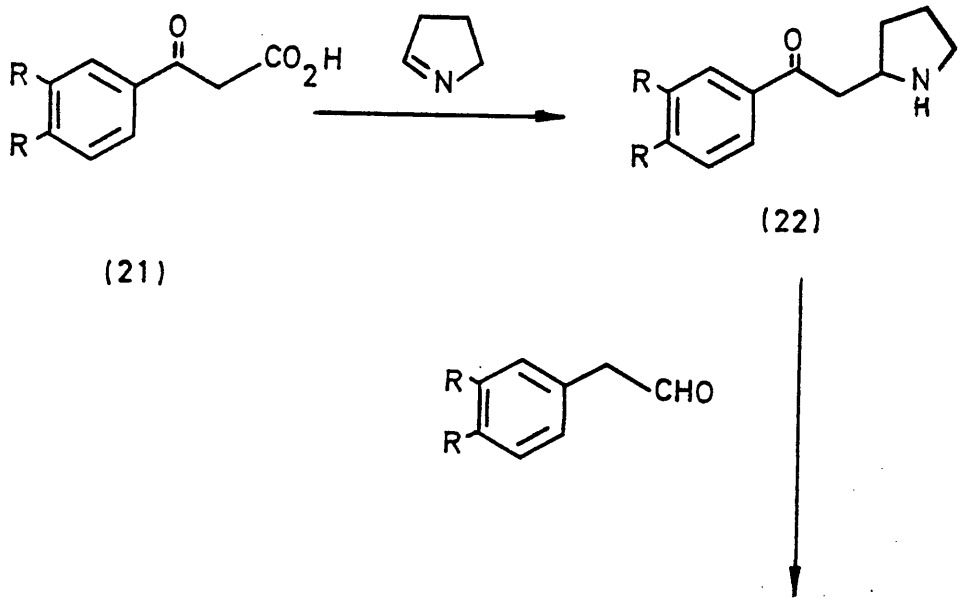
R= OCH_3



(14)

However, immediately prior to the commencement of laboratory work a report from Dr. Herbert at Leeds University announced[12] an efficient preparation of septicine (14) : 3,4-dimethoxyphenylpyruvic acid was converted into the amine (22) by reaction with pyrroline. This when reacted with 3,4-dimethoxyphenylacetaldehyde gave septicine as shown in the following sequence:

R=OCH_3



(21)

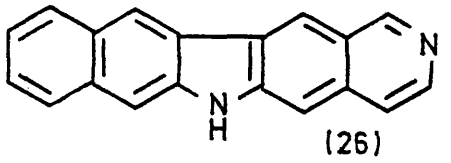
(22)

(14)

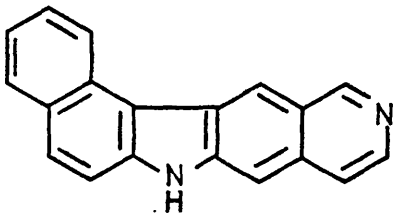
All that remains then is to carry out an anodic coupling reaction upon septicine in order to obtain tylophorine, and we set out to repeat Herbert's synthesis of the alkaloid.

Ethyl 3,4-dimethoxypyruvic acid was prepared by a literature[13] method and hydrolysed to give the necessary starting acid. Unfortunately, try as we might, the reaction between pyrroline and the acid gave very much poorer yields (less than 2%) of the amine (22) than reported in the original paper. Since this report was in communication form, with little experimental detail, the author visited Leeds in order to gain first hand knowledge of this reaction but, perhaps through inexperience, the productivity was not raised.

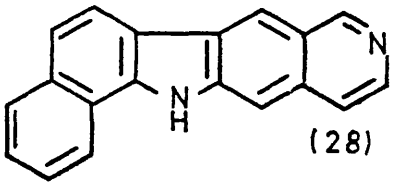
Within a few months however, Liepa[14] completed the formal synthesis of tylophorine by the vanadium oxyfluoride induced coupling of oxysepticine (25). Septicine was converted directly to tylophorine by a similar oxidation[15], and so we no longer felt justified in proceeding with this work and turned instead to the synthesis of a benzoanalogue of tylophorine, since the group at Bath were deeply interested in the synthesis of benzoellipticines (26), (27) and (28) for anti-cancer testing at this time and we wondered if the benzo-analogue (33) would show enhanced activity.



(26)

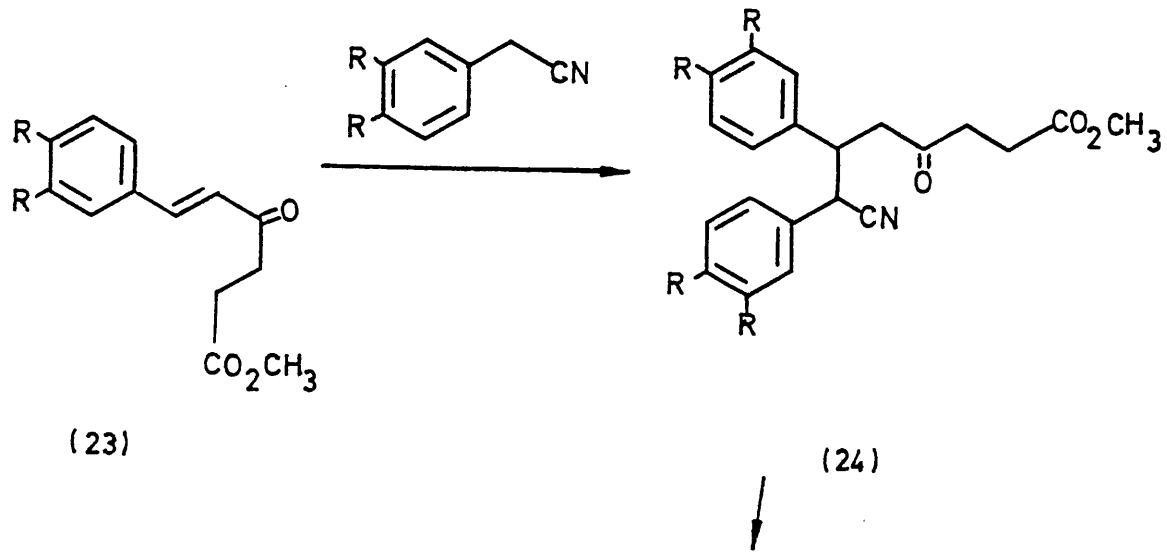


(27)



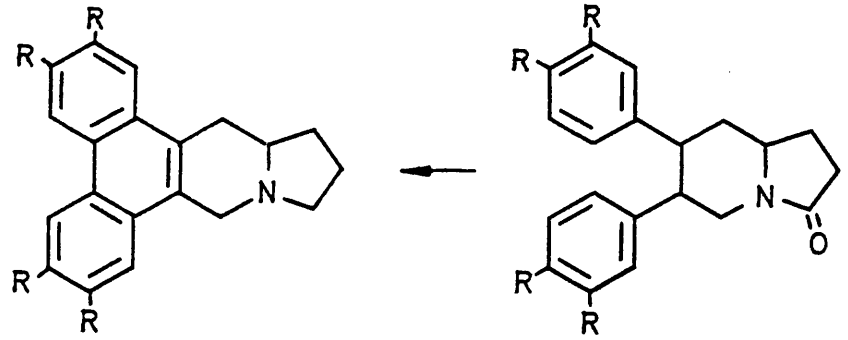
(28)

R= OCH_3



(23)

(24)

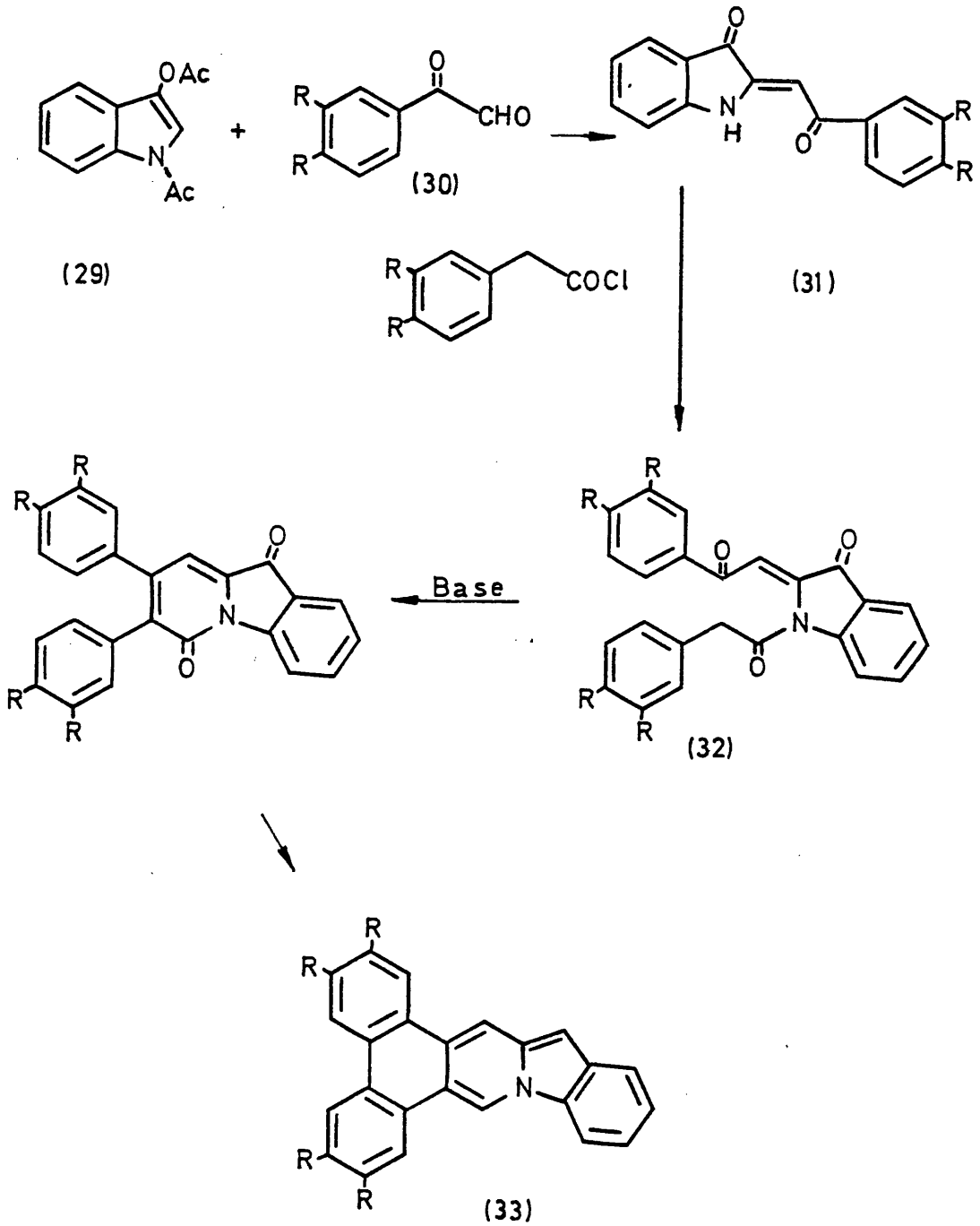


(3)

(25)

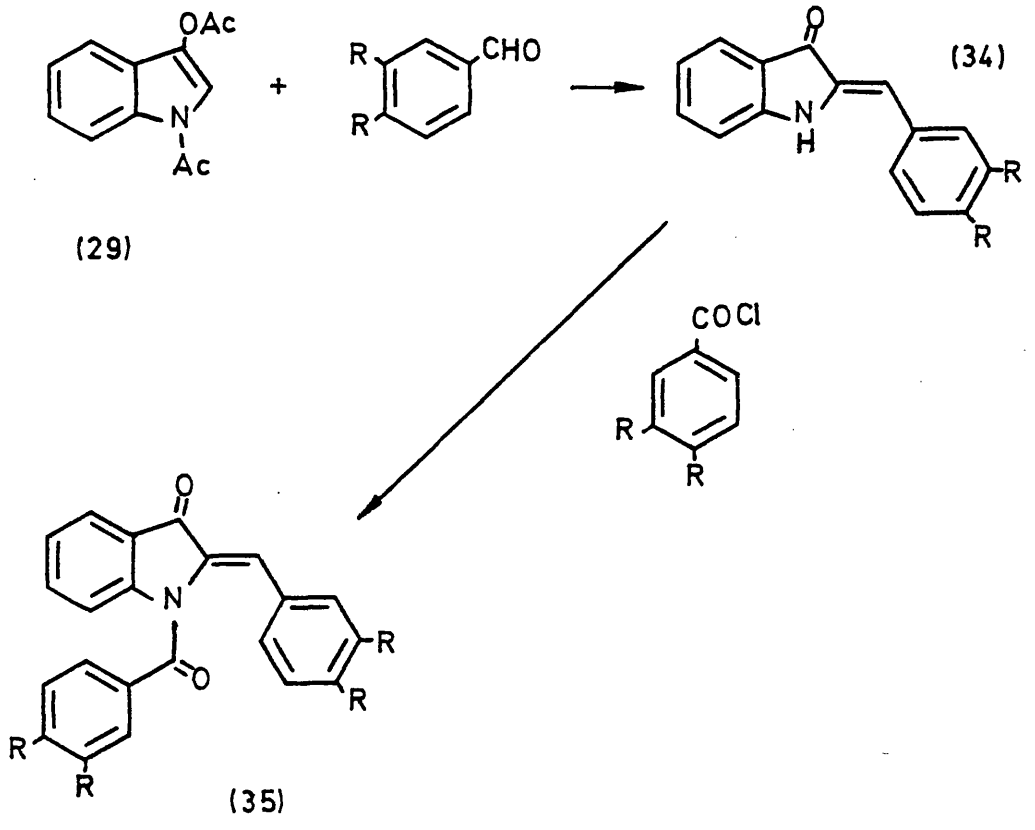
Our first projected route was as follows:

R=OCH_3



Clearly this is somewhat ambitious but the intermediate (32), if easily prepared, is very versatile and other sequences to the desired end product are easily envisaged. Before beginning upon this, however, we decided to examine the preparation of the model (35). This was made by reacting veratraldehyde with 1,3-diacetylindoxyl, followed by acylation with 3,4-dimethoxybenzoyl chloride:

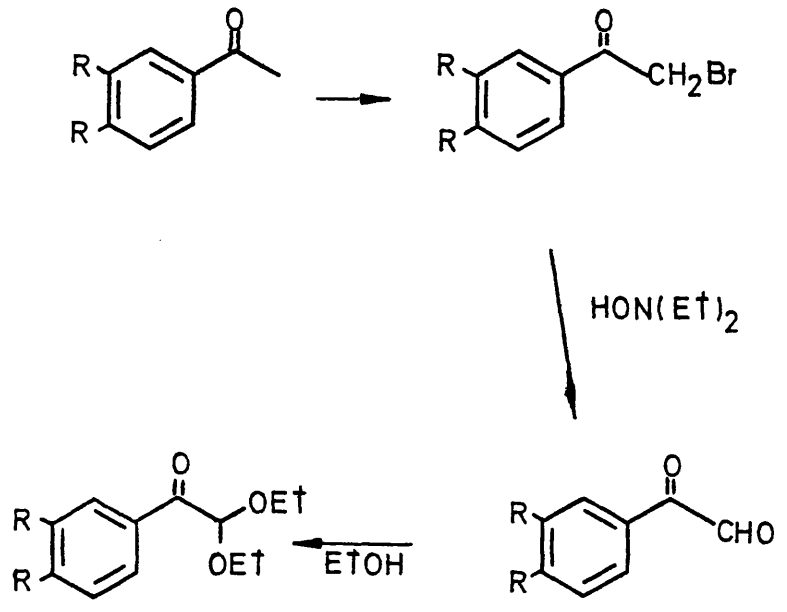
$R = OCH_3$



The condensation of many ketones with 1,3-diacetylindoxyl has been achieved in this laboratory; a fact which we will discuss later in Part Three of this thesis.

Normally this reaction is slow at room temperature in aqueous alkali but as expected, the aldehyde was much more reactive and 2-(3,4-dimethoxybenzylidine) indoline-3-one (34) was formed within a few minutes. The reaction of this product with the acid chloride was then attempted with a variety of bases, but the best yields were obtained when sodium hydride was used. Reactions involving sodium alone were unsuccessful. The product 1-(3,4-dimethoxybenzoyl)-2-(3,4-dimethoxybenzylidine) indoline-3-one is a coloured solid which appears to be a single isomer and has physical data compatible with structure (35). Having completed the preliminaries, we now felt that the synthesis of the required intermediate (32) was feasible and to effect this it was necessary to prepare 3,4-dimethoxyphenylethane-2-onal (30) as a substitute for 3,4-dimethoxybenzaldehyde. This compound is known and have been previously made in this laboratory[16] by the oxidation of acetoveratrone with selenium dioxide. However, since the product is always contamined with selenium, we chose to use an improvement developed by Myra McCartney of this department, which employs the reaction of N,N-diethylhydroxylamine upon bromoacetoveratrone. The product was isolated as hemiacetal.

R= OCH_3



(36)

Addition of acid to the diethylacetal (36) is sufficient to cause conversion to the parent aldehyde but this was only carried out immediately prior to reaction with the indoxyl (29). As before the indolidene was produced in good yield and crystallised in the form of red prisms. Spectral evidence, and analytical data are in accord with the required structure which exists exclusively in the E-form. We then made several attempts to combine this compound with homoveratroyl chloride, all without success, although it was clear from the various colour changes noted on the addition of sodium hydride to (31) that the corresponding anion was being formed. Work-up however, afforded unchanged indolinene, very little homoveratric acid was isolated and we suspected that ketene formation was a competing reaction.

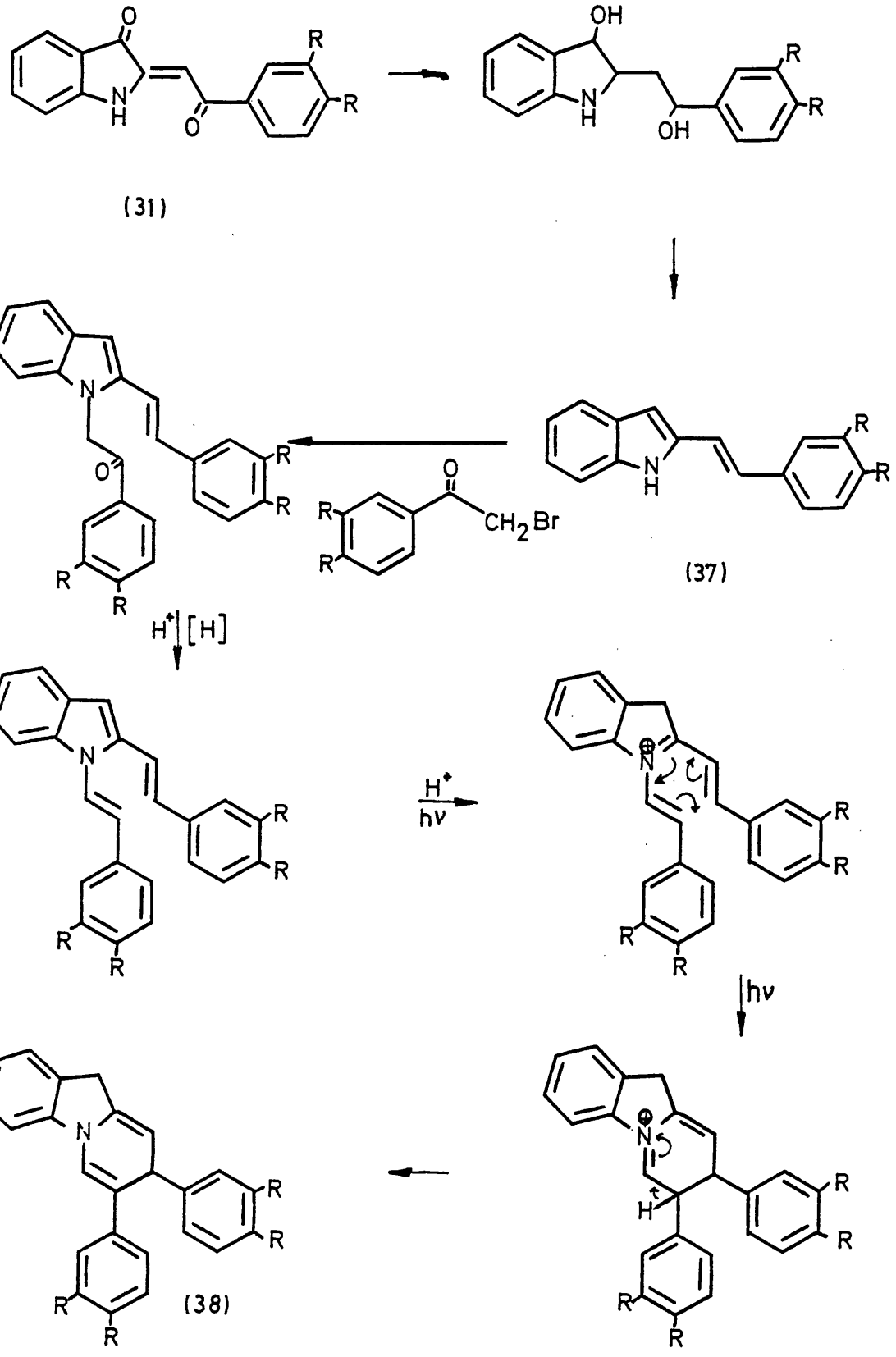
Indeed circumstantial evidence in support of this comes from the fact that when only half the molar quantity of the acid chloride was used some of the required product (32) was obtained but now contaminated with starting indolinene.

We experimented with numerous molecular ratios of base to starting materials but at no time did we effect a satisfactory conversion and the required product was extremely difficult to purify. In the end this approach was abandoned.

One may soon appreciate that homoveratroyl chloride is not the only choice of reagent and that other N-substitutents might serve to complete the project. Thus bromoveratrone and 3,4-dimethoxyphenethyl bromide were tried but the results were also very disappointing. In the latter base catalysed elimination of hydrogen bromide is possible under the conditions used and the formation of a carbene from bromoveratrone is conceivable.

In a final attempt we decided to modify the indolinene to a substrate which requires more mild conditions of base treatment prior to N-alkylation or acylation. The corresponding indole is an obvious choice and we considered the implementation of the following rather speculative sequence:

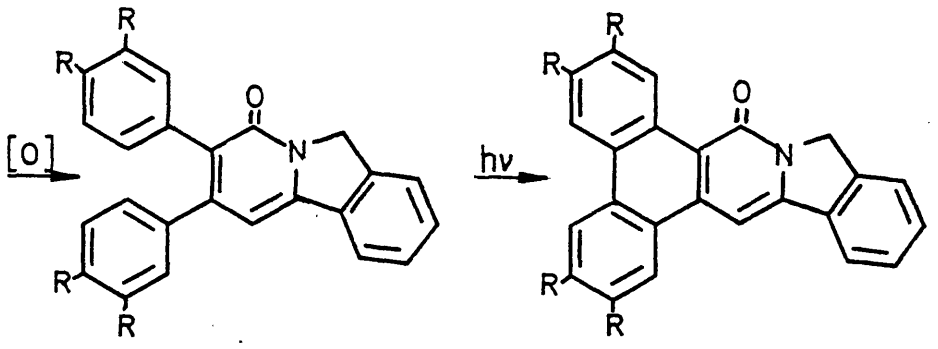
R= OCH_3



Such a product would be easily oxidised and might even afford a benzo-oxytylophorine derivative directly under the reaction conditions by further photochemical cyclisation.

$R = OCH_3$

(38)



It is well understood that indole magnesium derivatives favour β-attack with electrophiles, whereas sodium or potassium indolyl salts can be N-substituted; but some isomer formation is expected, since these reactions are not mutually exclusive. In the event we were not able to examine N-alkylation, since although the required indole (37) was formed easily from the indolinene (sodium borohydride reduction followed by treatment with hydrogen chloride) it was rather unstable and on treatment with sodium decomposed into a resin.
At this point in time, we had spent almost a year upon this particular project and although there is still scope for further work, more pressing studies were in progress elsewhere in the laboratory and the author felt that a change of emphasis would be to his advantage.

EXPERIMENTAL TO PART TWO

Veratric Acid Chloride

Veratric acid (20 g) was dissolved in dry benzene (250 cm^3) and refluxed with thionyl chloride (40 g) for 2 h. The solvent was then removed in vacuum to yield a red oil which crystallised from petroleum ether (b.p. 60-80^oC) to give white product (19.0 g, 80%). γ_{max} 1800, 1600, 1000, 920, 800, 700 cm^{-1}.

3,4-Dimethoxybenzoylethylacetoacetate

To a solution of ethylacetoacetate (106 g) in dry ether (750 cm^3) was added sodium (16.5 g) in small portions under dry nitrogen. The mixture was stirred for 20 h. until the sodium was completely dissolved. A solution of veratric acid chloride (75.2 g) in dry ether (400 cm^3) was added slowly to the mixture before it was heated for 5 h. on a water-bath. The precipitate was filtered off after letting the mixture stand overnight. The precipitate was then dissolved in cold water (1.5 L) and made just acidic with hydrochloric acid (10%) to give an oily residue (70 g, 76%), which was used for the next stage without further purification.

3,4-Dimethoxybenzoylethylacetate

The product from the previous reaction (70 g) was taken up in water (500 cm^3) containing ammonium chloride (25 g) and ammonium hydroxide (100 cm^3). The solution was then heated at 40-50°C for 30 minutes and cooled. The mixture was extracted with ether. The combined extracts were dried over sodium sulphate. The solvent was evaporated and the product was distilled in reduced pressure (32 g, 53%). b.p.$_{1.0}$ 230-250°C; (lit.[17], b.p.$_{1.0}$ 240-260°C). δ($CDCl_3$) 1.25 (3H, t, $\underline{J}$ = 7Hz), 3.95 (8H, S), 4.22 (2H, q, $\underline{J}$ =7Hz), 6.9 (1H, d, J = 8Hz), 7.54 (1H, d, $\underline{J}$ = 2Hz), 7.6 (1H, dd, $\underline{J}$ =8Hz, $\underline{J}$ = 2Hz).

Δ'-Pyrroline

This was prepared by a modification of Jackaby's method[18]; DL-ornithine monohydrochloride (13.3 g) was dissolved in water (160 cm^3) in a three necked flask to which was fitted a nitrogen inlet, a mechanical stirrer and a condenser. The top of the condenser was attached to a tube which had a funnel, whose edge was just touching a 40% solution of potassium iodide. The ornithine solution was cooled in an ice bath and N-bromosuccinimide (14 g) added slowly over a period of 30 minutes to the vigorously stirred solution. When the addition completed the reaction mixture was stirred for a further hour. After this time the yellow solution was warmed on a steam bath for 5 minutes. This fresh aqueous solution was used as such for the next step.

3,4-Dimethoxyphenacyl-2-pyrrolidine

3,4-Dimethoxybenzoylethylacetate (8.8 g) was hydrolysed in 2% potassium hydroxide for 36 h. at room temperature. After this time, the solution was extracted with ether, the aqueous layer separated, cooled to $0^{\circ}C$ and acidified slowly with ice cold 1N sulphuric acid. The acidic aqueous layer and its white precipitate was extracted with ether and the ether extracts dried over sodium sulphate. Removal of the ether, in the cold and vacuum gave the acid which was used as such for the next step.

The acid (7.0 g) was dissolved in methanol (150 cm^3) and 1M sodium phosphate buffer (pH = 7.25, 10 cm^3) was added along with the Δ'-pyrroline solution (160 cm^3). The pH was adjusted to 7 by adding 1M sodium hydroxide solution and the reaction mixture was then stirred in a stoppered flask for 48 h. at room temperature. After this time, the brown solution was acidified to Congo red with 2N sulphuric acid, cooled and extracted with ether. The acidic aqueous layer was cooled and basified with a saturated potassium carbonate solution and then extracted with chloroform several times by hand and then continuously for 6h. The combined extracts were dried over sodium sulphate and evaporated to give brown oil. This crude oil was purified by preparative plate chromatography eluting with 1% NH_3 in 50% MeoH, $CHCl_3$ to give a colourless oil (0.15 g, 1.7%) which rapidly darkened at room temperature in presence of air. γ_{max} 3350, 1680, 1600, 820, 780 cm^{-1}; $\delta(CDCl_3)$ 1.2-2.2 (4H, m), 2.8-3.3 (3H, m), 3.5-3.9 (2H, m), 3.9 (6H, S), 4.5 (1H, S), 6.87 (1H, d, $\underline{J}$ = 8Hz), 7.52 (1H, d, $\underline{J}$ = 1.5Hz), 7.6 (1H, dd, $\underline{J}$ = 8Hz, $\underline{J}$ = 1.5 Hz).

N-(2-Carboxyphenyl) Glycine

A solution of anthranilic acid (50 g) and sodium hydroxide (15.4 g) in water (60 cm^3) was warmed to 40°C and added to a warm solution of chloroacetic acid (34.7 g) and sodium carbonate (20 g) in water (50 cm^3). The mixture was kept at 40°C for one day, the solid was filtered off and dissolved in a solution of sodium hydroxide (15 g) in water (400 cm^3), which then acidified with concentrated hydrogen chloride to give white solid (54 g, 76%). This product was used directly in the next reaction.

1,3-Diacetylindoxyl (29)

The acid formed in the previous reaction (54 g) was dissolved in a solution of sodium carbonate (47 g) in water (470 cm^3) and stirred as acetic anhydride (41.5 g) was added. The mixture was stirred for a further 20 minutes and then acidified with concentrated hydrochloric acid to give white crystals. This product was dissolved in acetic anhydride (250 cm^3) and to this solution triethylamine (50 cm^3) was added. The mixture was refluxed for 20 minutes, then the solvent was removed under reduced pressure and the residue extracted with hot petroleum ether (b.p. 60-80°C). The extracts were boiled with charcoal, filtered, and left at room temperature overnight, thereby affording needles (29 g, 48%), m.p. 86-87°C; $\delta(CDCl_3)$ 2.36 (3H, S), 2.6 (3H, S), 7.2-7.8 (4H, m), 8.4-8.7 (1H, m).

2-(3,4-Dimethoxybenzylidene) Indoline-3-one (34)

In a two necked 250 cm^3 flask fitted with a condenser, nitrogen inlet and magnetic stirrer, was added 3,4-dimethoxybenzaldehyde (3.0 g), 1,3-diacetylindoxyl (4.0 g) and 50% aqueous methanol (50 cm^3). This mixture was stirred under nitrogen for four hours, before potassium hydoxide (10 g) was added slowly. This turned the colour of the mixture red. The reaction vessel was left protected from oxygen overnight before the red crystals which had formed were collected (4.5 g, 88%), m.p. 138-139°C. $\gamma_{max.}$ 3330, 1690, 1640, 1620, 1600, 1040, 770 cm^{-1}; $\lambda_{max.}$ 240, 284 and 360 nm; $\delta(CDCl_3)$ 3.7 (6H, S), 6.5-7.5 (9H, m); $m/_e$ 281 (M^+).

2-(3,4-Dimethoxybenzyl)-3-Hydroxyindoline

2-(3,4-Dimethoxybenylidene) indolin-3-one (4.5 g) was dissolved in 50% ethanol (50 cm^3) and stirred while sodium borohydride (1.0 g) was added in portions. The solution was then agitated for a further 2h. The solvent was then removed under reduced pressure and the product extracted with chloroform, the combined extracts were dried over sodium sulphate before evaporation, which yielded an oily product that crystallised from petroleum ether (b.p. 60-80°C), to give white prism (3.3 g, 68%), m.p. 43-44°C; $\gamma_{max.}$ 3400, 1600, 1030, 800, 750 cm^{-1}; $\delta(CDCl_3)$ 2.4-3.2 (4H, m), 3.8 (6H, S), 4.9 (1H, m), 6.6-7.4 (8H, m). (Found: C, 71.8; H,6.1 $C_{17}H_{19}NO_3$ requires: C, 71.6; H, 6.7%).

2-(3,4-Dimethoxybenzyl) Indole

2-(3,4-Dimethoxybenzyl)-3-hydroxyindoline (2.0 g) was dissolved in chloroform (50 cm^3) and dry hydrochloric acid gas was bubbled through it. The mixture was then basified with 2N sodium hydroxide (50 cm^3). The chloroform layer was washed with water and dried over sodium sulphate before it was removed in vacuum to yield a yellow oil which crystallised from petroleum ether (b.p. 60-80°C) to give white prism (1.3 g, 70%): m.p. 129-130°C; $\gamma_{max.}$ 3400, 1600, 1040, 800, 760 cm^{-1}; $\lambda_{max.}$ 243 and 285 n.m; $\delta(CDCl_3)$ 3.77 (3H, S), 3.83 (3H, S), 4.02 (2H, S), 6.3 (1H, m), 6.7-7.55 (7H, m), 7.9 (1H, bS); $m/_e$ 267 (M^+).

1-(3,4-Dimethoxybenzoyl)-2-(3,4-Dimethoxybenzylidene) Indoline-3-one (35)

To the solution of 2-(3,4-dimethoxybenzylidine) indoline-3-one (1.0 g) in dimethylformamide (20 cm^3) was added a mixture of sodium hydride (85 mg) in dimethylformamide (20 cm^3) under dry nitrogen. The mixture which turned green was stirred for 2h. before veratric acid chloride (0.71 g) in dimethylformamide (20 cm^3) was introduced dropwise over 20 minutes. The mixture then slowly turned red again and was stirred for a further 1h., then a few drops of water were added to the mixture very carefully (under nitrogen) before the solvent was evaporated in vacuum. The product was extracted with petroleum ether (b.p. 60-80°C) to yield orange crystals (1.2 g, 75%), m.p. 162-163°C; $\gamma_{max.}$ 3300, 1680, 1670 sh, 1660 sh, 1600, 1020, 750 cm^{-1}; $\lambda_{max.}$ 225, 260 and 290 n.m; $\delta(CDCl_3)$ 3.95 (12H, S), 6.75-7.9 (11H, m) (Found: C, 69.9; H, 5.2 $C_{26}H_{23}NO_6$ requires: C, 70.1; H, 5.2%).

Acetoveratrone

To the solution of veratrole (50 g) in dichloromethane (200 cm^3) was slowly added finely powdered aluminium chloride (50 g). The suspension was warmed and stirred until solution was complete. Acetyl chloride (28 g) was then added slowly to the mixture before it was heated under reflux for 1h. The reaction mixture was then cooled and poured onto ice (250 g), the aqueous layer was extracted with dichloromethane, the combined extracts were washed with water and dried over sodium sulphate. The solvent then evaporated in vacuum and the product distilled to yield a colourless liquid which later solidified (56 g, 83%); b.p.$_{3.0}$ 95-100°C (lit.[19], b.p.$_{2.0}$ 126-132°C); $\delta(CDCl_3)$ 2.55 (3H, S), 3.9 (6H, S), 7.0 (1H, d, $\underline{J}$ = 2Hz), 7.6-7.8 (2H, m, $\underline{J}$ = 2Hz, $\underline{J}$ = 6Hz).

Bromoacetoveratrone

A solution of bromine (13.5 g) in dichloromethane (80 cm^3) was added dropwise to a stirred solution of acetoveratrone (45 g) in dichloromethane (600 cm^3) over 1h. After further stirring for 30 minutes, the solution was washed with solution of 2N sodium carbonate which turned the solution yellow. This was then washed with water (250 cm^3) and dried over sodium sulphate. The solvent was then removed to yield a red oil which slowly solidified and crystallised from 95% ethanol (50 g, 77%); $\delta(CDCl_3)$ 3.9 (6H, S), 4.4 (2H, S), 6.9 (1H, d, $\underline{J}$ = 8Hz), 7.5-7.7 (2H, m, $\underline{J}$ = 8Hz, $\underline{J}$ = 2Hz).

3,4-Dimethoxyphenylethan-2-onal

A solution of bromoacetoveratrone (28 g) in methanol (300 cm^3) and N,N-diethylhydroxylamine (9.6 g) was refluxed and stirred for 2½h. The solvent was then removed in vacuum to yield a dark red oil to which was added ether (400 cm^3). Diethylamine hydrobromide was then filtered off and the ether removed in vacuum to yield another reddish oil, to which was added 95% ethanol (10 cm^3). The solution was then cooled in a refridgerator for 2h; after which time, crystals of the product were filtered off (20 g, 77%); m.p. 77-79°C (lit.[19], m.p. 77-79°C); δ($CDCl_3$) 1.3 (3H, t, $\underline{J}$ = 6Hz), 3.8 (2H, q, $\underline{J}$ = 6Hz), 4.0 (6H, S), 6.94 (1H, d, $\underline{J}$ = 8Hz), 7.6-7.9 (2H, m).

2-(3,4-Dimethoxyphenacylidene) Indoline-3-One (31)

A mixture of 1,3-diacetylinoxyl (4.3 g) and 3,4-dimethoxyphenylethane-2-onal (4.8 g) in 50% aqueous methanol (60 cm^3) was stirred for 4h. in a three necked flask fitted with a nitrogen inlet, a reflux condenser and a dropping funnel. Acetic acid (1.2 g) was then added and the mixture then stirred for a further 1h. Sufficient pelletised potassium hydroxide to turn the mixture red in colour was slowly added; the reaction vessel was then protected from oxygen and allowed to stand overnight. The next day a red crystalline product was collected (5.6 g, 91%); m.p. 165°C (ethanol); $\gamma_{max.}$ 3400, 1720, 1660, 1620, 1605, 1040, 770 cm^{-1}; $\lambda_{max.}$ 253 and 305 n.m; δ($CDCl_3$) 4.0 (6H, S), 6.9-8.0 (8H, m), 10.2 (1H, bs); $m/_e$ 309 (M^+) (Found: C, 70.1; H, 4.8 $C_{18}H_{15}NO_4$ requires: C, 69.9; H, 4.85%).

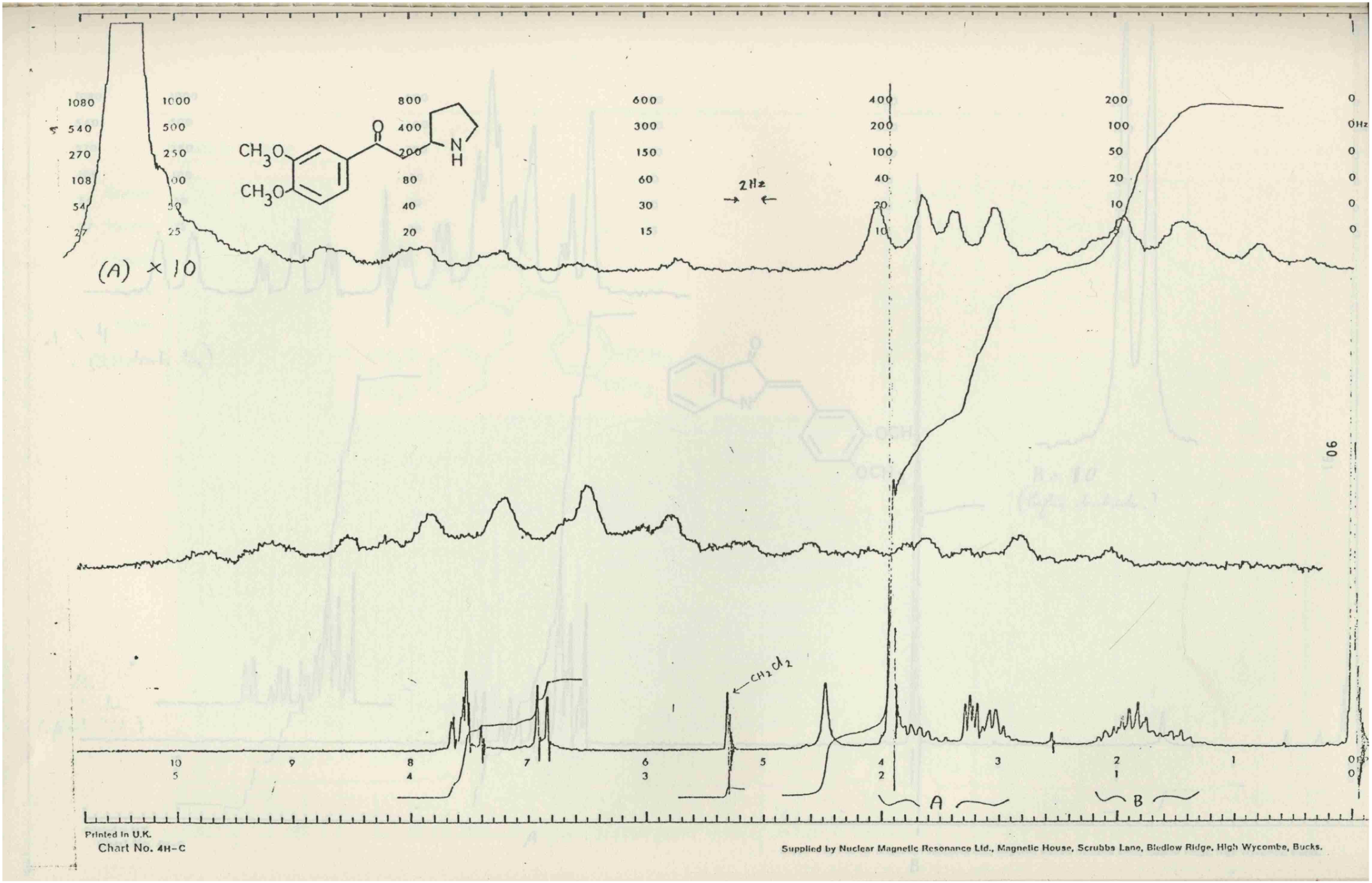
1-[2-(3,4-Dimethoxyphenyl) eth-2-onyl]-2-(3,4-dimethoxyphenacylidene) Indoline-3-one (32)

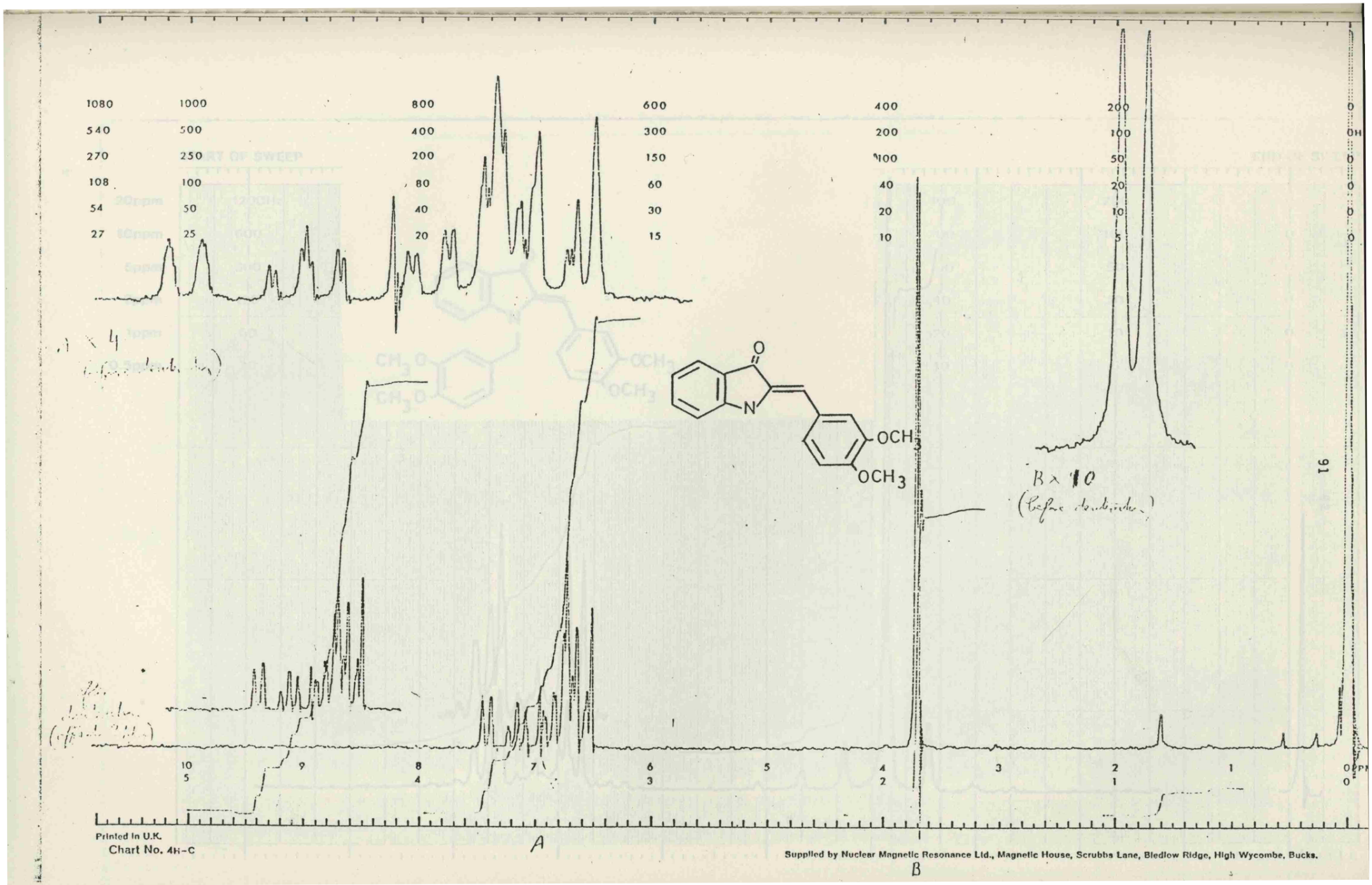
To a stirred solution of 2-(3,4-dimethoxyphenacylidene) indolin-3-one (1.85 g) in dimethylformamide (30 cm^3), was added a solution of sodium hydride (144 mg) in dimethylformamide (20 cm^3). The mixture was stirred for 1h., during which time the solution turned green. A solution of chloroveratrone (0.65 g) was then introduced followed by a further stirring for 1h., when the mixture turned red again, the solvents were removed in vacuum to yield a red solid which was extracted with hot ethanol to leave red powder (0.1 g, 3.5%), m.p. 188°C; $\gamma_{max.}$ 1720, 1700, 1660, 1600, 830, 780 cm^{-1}; $\lambda_{max.}$ 257 and 303 n.m; $\delta(CDCl_3)$ 3.87 (6H, S), 3.91 (3H, S), 3.95 (3H, S), 5.9 (2H, S), 6.78-7.15 (5H, m), 7.4-7.8 (6H, m); $m/_e$ 487 (M^+) (Found: C, 69.2; H, 5.1 $C_{28}H_{25}NO_7$ requires C, 69.0; H, 5.1%).

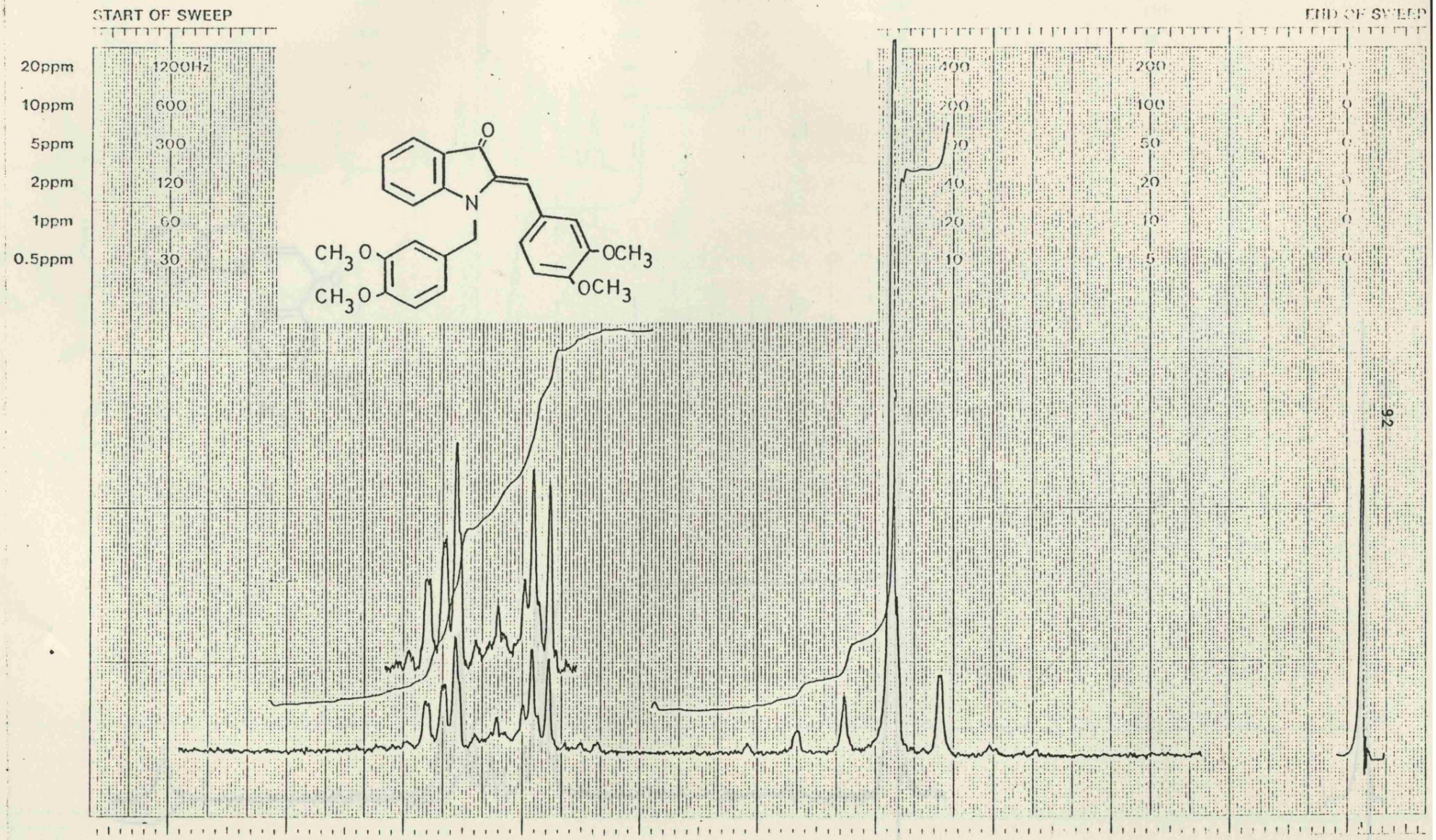
2-(3,4-Dimethoxyphenethylene) indole (37)

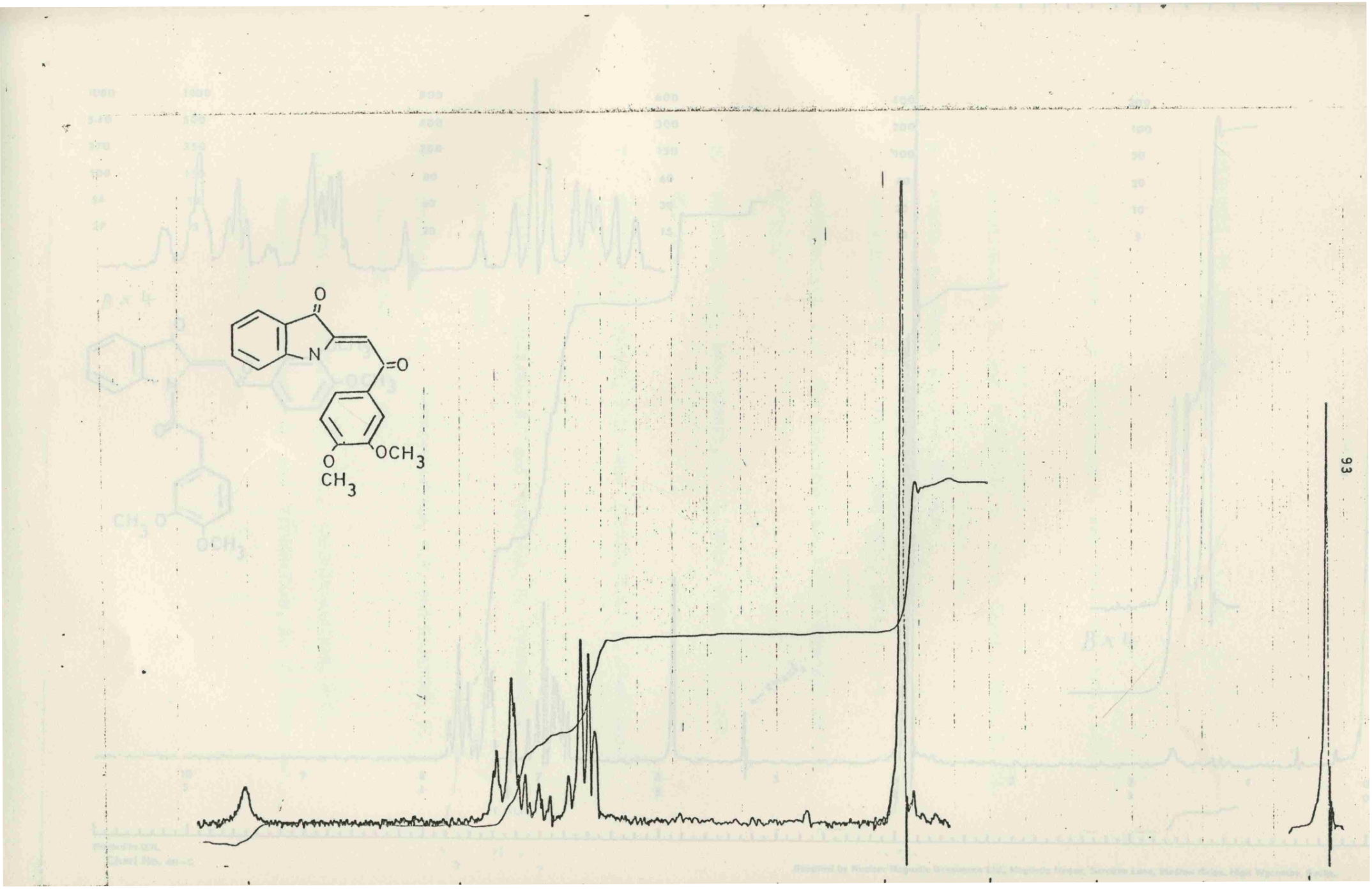
To a solution of 2-(3,4-dimethoxyphenacylidene) indolin-3-one (3.0 g) in 50% aqueous ethanol (50 cm^3) was added sodium borohydride in portions until the solution turned yellow, the solvent was then evaporated in vacuum and the product was extracted with chloroform. The combined extracts were dried over sodium sulphate before hydrogen chloride gas was bubbled into the solution. The mixture was then basified with 2N sodium hydroxide. The chloroform layer was then separated and washed with water before being dried over sodium sulphate. The solvent was then removed and the product was extracted with petroleum ether (b.p. 60-80°C) and left to cool to give a white powder (2.4 g, 86%)

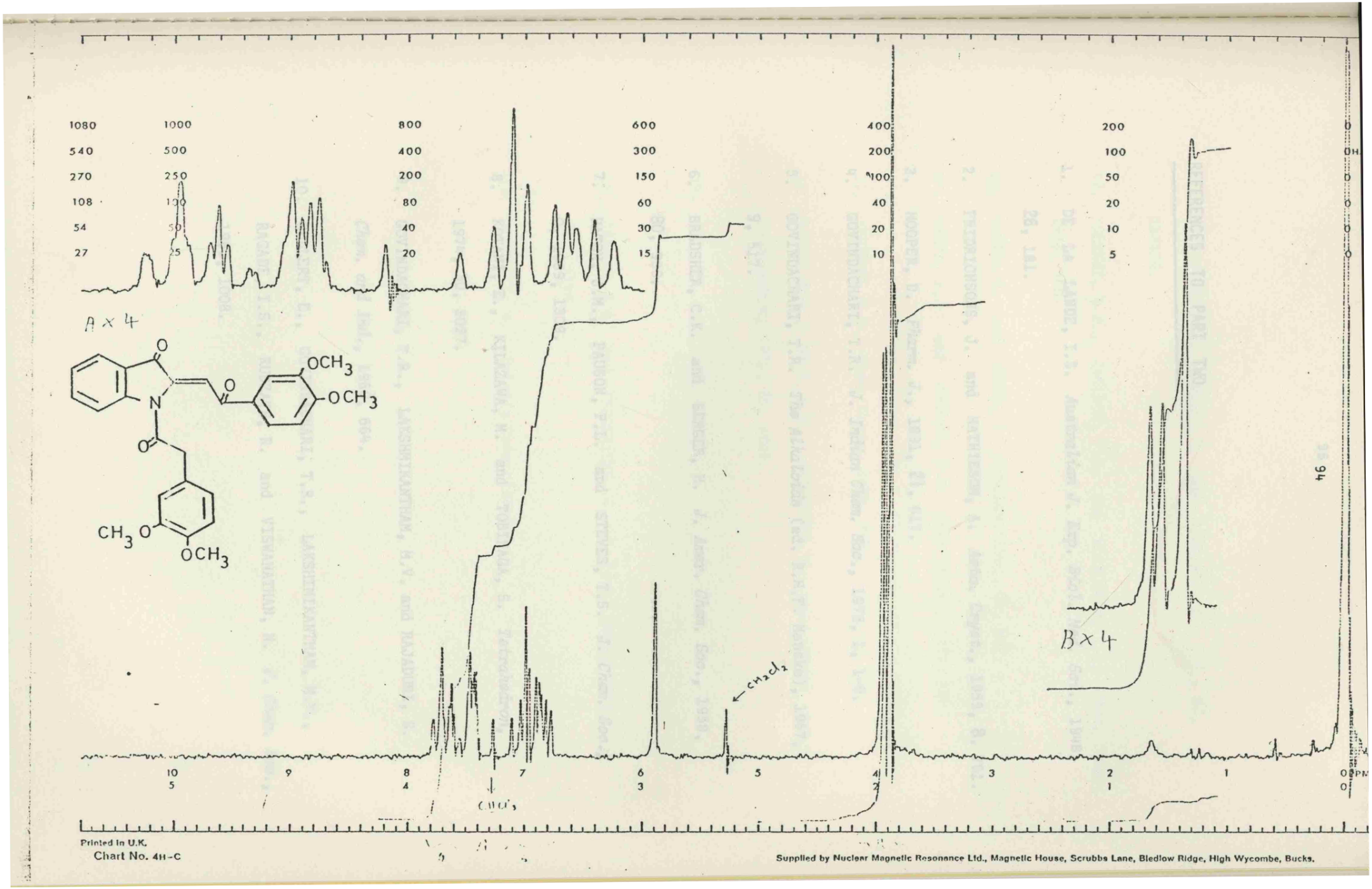
m.p. 172-173°C; $\gamma_{max.}$ 3440, 1620, 1600, 820, 760 cm^{-1};
$\lambda_{max.}$ 255 and 353 n.m; $\delta(CDCl_3)$ 3.9 (6H, S), 4.5 (1H, bS),
6.9-8.0 (10H, m): $m/_e$ 279 (M^+).


(A) × 10
2Hz
CH2Cl2
A
B
90
Printed in U.K.
Chart No. 4H-C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.


1080 1000 800 600 400 200 0
540 500 400 300 200 100 0
270 250 200 150 100 50 0
108 100 80 60 40 20 0
54 50 40 30 20 10 0
27 25 20 15 10 5 0
OCH3
OCH3
A × 4
B × 10
10 9 8 7 6 5 4 3 2 1 0 PPM
5 4 3 2 1 0
A
B
Printed in U.K.
Chart No. 4H-C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.


START OF SWEEP
END OF SWEEP
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
1200Hz
600
300
120
60
30
400
200
100
50
20
10
5
0
92
O
N
CH3O
CH3O
OCH3
OCH3


O
N
O
OCH3
O
CH3



Printed in U.K.

Chart No. 4H-C

Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

REFERENCES TO PART TWO

1. DE LA LANDE, I.S. *Australian J. Exp. Biol. Med. Sci.*, 1948, **26**, 181.

2. FRIDRICHSONS, J. and MATHIESON, A. *Acta. Cryst.*, 1955, **8**, 761.

3. HOOPER, D. *Pharm. J.*, 1891, **21**, 617.

4. GOVINDACHARI, T.R. *J. Indian Chem. Soc.*, 1973, L, 1-9.

5. GOVINDACHARI, T.R. *The Alkaloids* (ed. R.H.F. Manske), 1967, **9**, 517.

6. BRADSHER, C.K. and BERGER, H. *J. Amer. Chem. Soc.*, 1958, **80**, 930.

7. PATON, J.M., PAUSON, P.L. and STEVES, T.S. *J. Chem. Soc.*, C, 1969, 1309.

8. KOTANI, E., KILAZAWA, M. and TOBINAGA, S. *Tetrahedron*, 1974, **30**, 3027.

9. GOVINDACHARI, T.R., LAKSHMIKANTHAM, M.V. and RAJADURI, S. *Chem. and Ind.*, 1960, 664.

10. GELLERT, E., GOVINDACHARI, T.R., LAKSHIMIKANTHAM, M.V., RAGADE, I.S., RUDZATS, R. and VISWANATHAN, N. *J. Chem. Soc.*, 1962, 1008.

11. DE MARTINO, G., SCALZO, M. and GIULIANO, S. *C.A.*, **80**, 83350q.

12. HERBERT, R.B., JACKSON, F.B. and NICHOLSON, I.T. *Chem. Comm.*, 1976, 450.

13. MEYER, R. and TOGEL, K. *Annalen*, 1906, **55**, 347.

14. LIEPA, A.J. and SUMMONS, R.E. *Chem. Comm.*, 1977, 826.

15. HERBERT, R.B. *Chem. Comm.*, 1978, 794.

16. BROWN, D.W., DYKE, S.F., SAINSBURY, M. and LUGTON, W.G.D. *Tetrahedron*, 1970, **26**, 4985.

17. OKI, M. *C.A.*, **55**, 4469e.

18. JAKABY, W.B. and FREDERICKS, J. *J. Biol. Chem.*, 1959, **234**, 2145.

19. McCARTNY, M. Private Communication.

PART THREE

INTRODUCTION TO PART THREE

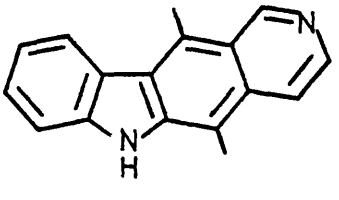
Cancer is a combination of diseases that is killing increasing numbers of people every year in virtually all countries of the world[1]. Surgery and/or radiation therapy are often effective against localised tumours but unfortunately by the time many tumours are detected they have spread to other organs. Currently the principal treatment for disseminated cancer is chemotherapy, although immunotherapy holds encouraging promise for the future.

Unfortunately, drugs now available are not highly effective against solid tumours, such as those of the colon or the lung, which have a low rate of DNA synthesis. Thus, for example, the median survival rate of all lung cancer patients from diagnosis to death remains less than six months[2]. To achieve a major advance here, we need a better understanding of the mechanism of action of anti-tumour agents, greater drug mobility and a reduction in general toxicity. The identification of the target for anti-tumour agents is of major importance, and it is generally believed that a rational design of cancer drugs should be based on an exploitable biochemical difference between normal host cell and the invading cells. Some drugs showing anti-cancer activity are thought to function through intercalation with DNA. Such intercalation is rather well understood and it is almost the only case where the structure of what is thought to be the pharmacological receptor is known at molecular resolution[3]. If indeed, DNA is the real receptor of these drugs and if we are able to design DNA intercalating compounds with the highest possible

affinity for DNA, we would have a much better chance of finding active anti-cancer drugs among these compounds. However, although high DNA reactivity is necessary for conferring potential cytotoxicity, it is insufficient for conferring a specificity directed towards the cancerous cells. Therefore, the correlation between DNA reactivity and the pharmacological activity should also be considered.

The ability of drugs to intercalate in DNA is conditioned by such stereochemical parameters as, size, shape, and planarity, as well as by their specific electronic configuration which controls the size of the interaction energy with DNA[4] and, of course, the ability of the drug to cross cell membranes.

Derivatives of 6-H-pyrido[4,3-b]carbazoles (ellipticines) (1) have most of the required characteristics. In particular, the size and the arc shaped form of these molecules is remarkably suited for DNA intercalation. That is to say they insert between the base pairs of the super coiled helix and once present interfere with the normal replication process. The final part of this thesis is concerned with the synthesis of various ellipticines in order to test some ideas upon the binding processes which may occur within the helix.

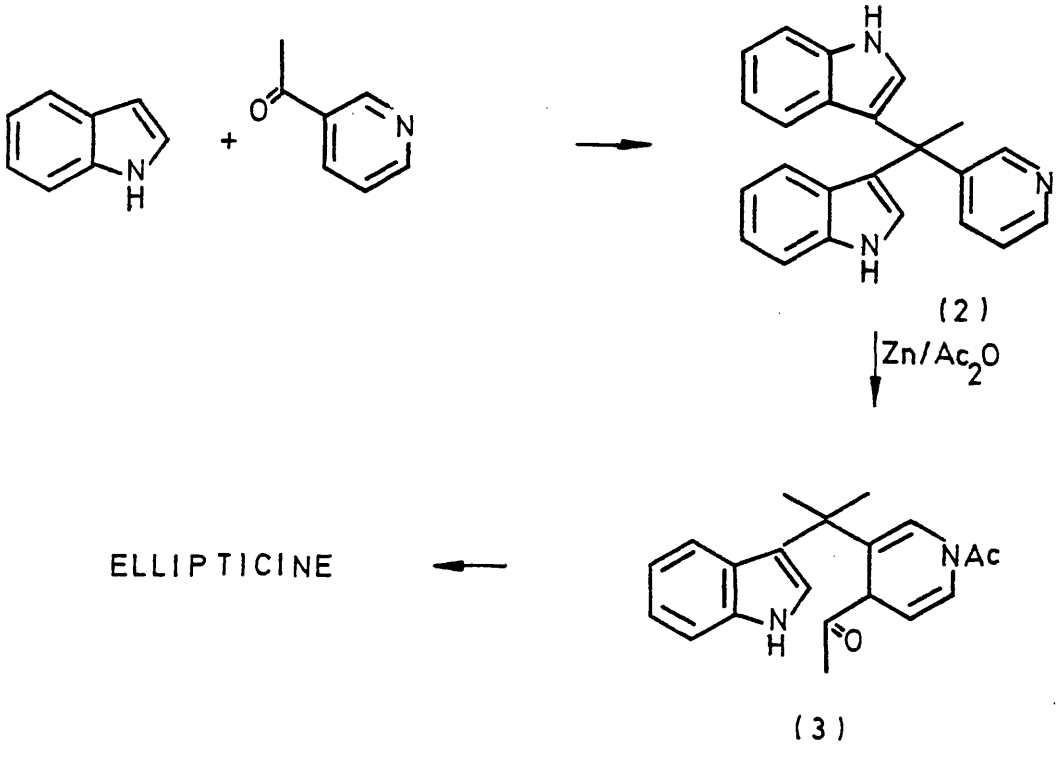


(1)

The alkaloid ellipticine (1) was first isolated from the tropical shrubs *Ochrosia elliptica* and *O. sandwicensis* and then subsequently from *Aspidosperma subincanum* as well as from many other plants[5] of the Apocynaceae. This compound and its 9-methoxy derivative, an alkaloid in its own right, has stimulated much interest because they exhibit anti-tumour activity[6]. The first reported synthesis of ellipticine was by Woodward[7] and this work also served to confirm the structure of the alkaloid.

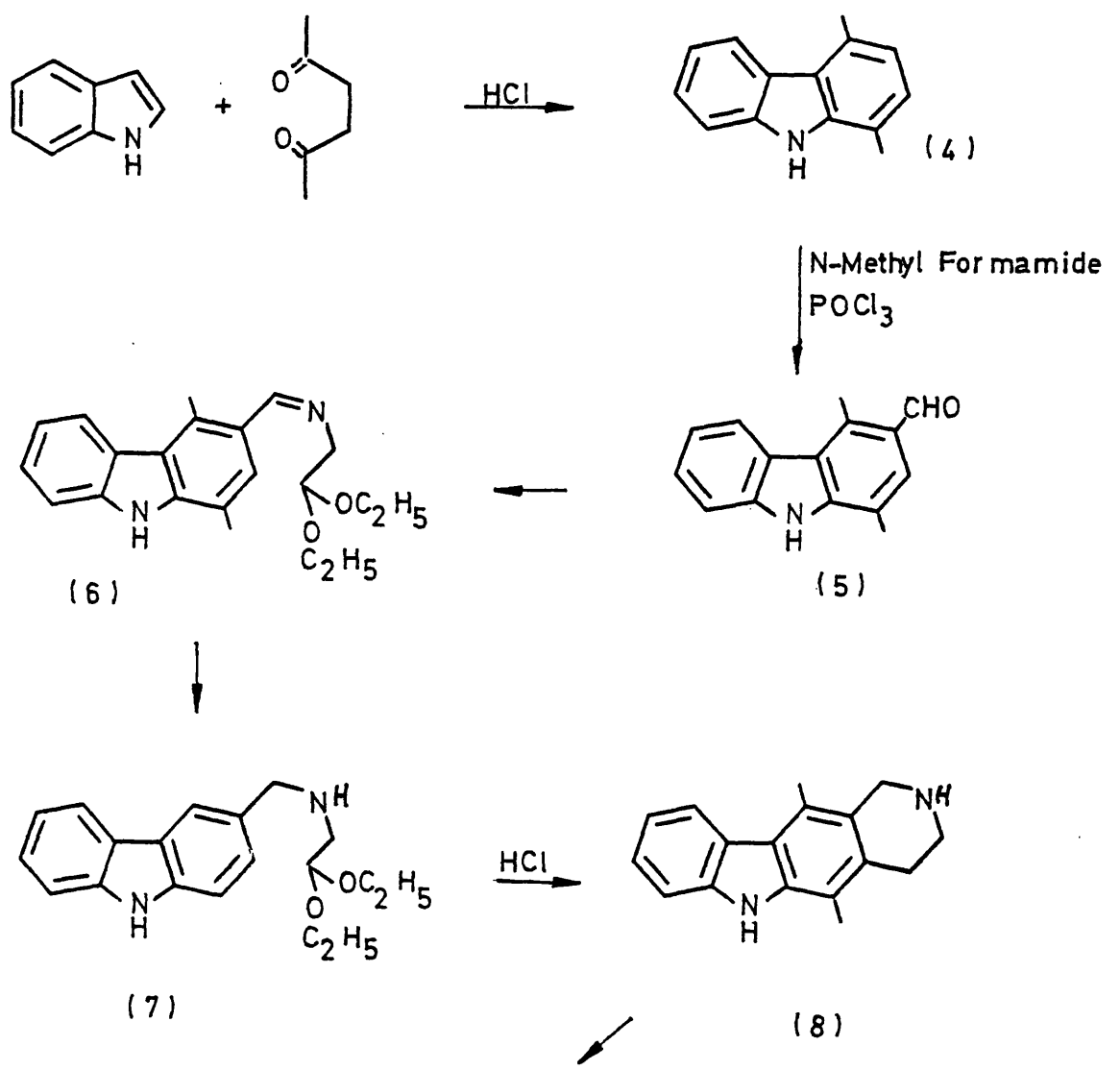
In this work (Route 1) the methane derivative (2) formed by the reaction 3-acetylpyridine and indole after reductive acylation with zinc and acetic anhydride gave the intermediate (3). Pyrolysis of this last compound *in vacuo* gave ellipticine in an overall yield of 2%.

ROUTE 1



Clearly, this approach has no practical application, but a few years later Cranwell and Saxton[8,9] published a second synthesis of ellipticine (Route 2) which involved the initial preparation of 1,4-dimethylcarbazole (4) through the reaction of indole and hexane-2,5-dione. This was formylated to give the aldehyde (5) contaminated with some of the 3,6-diformyl product.

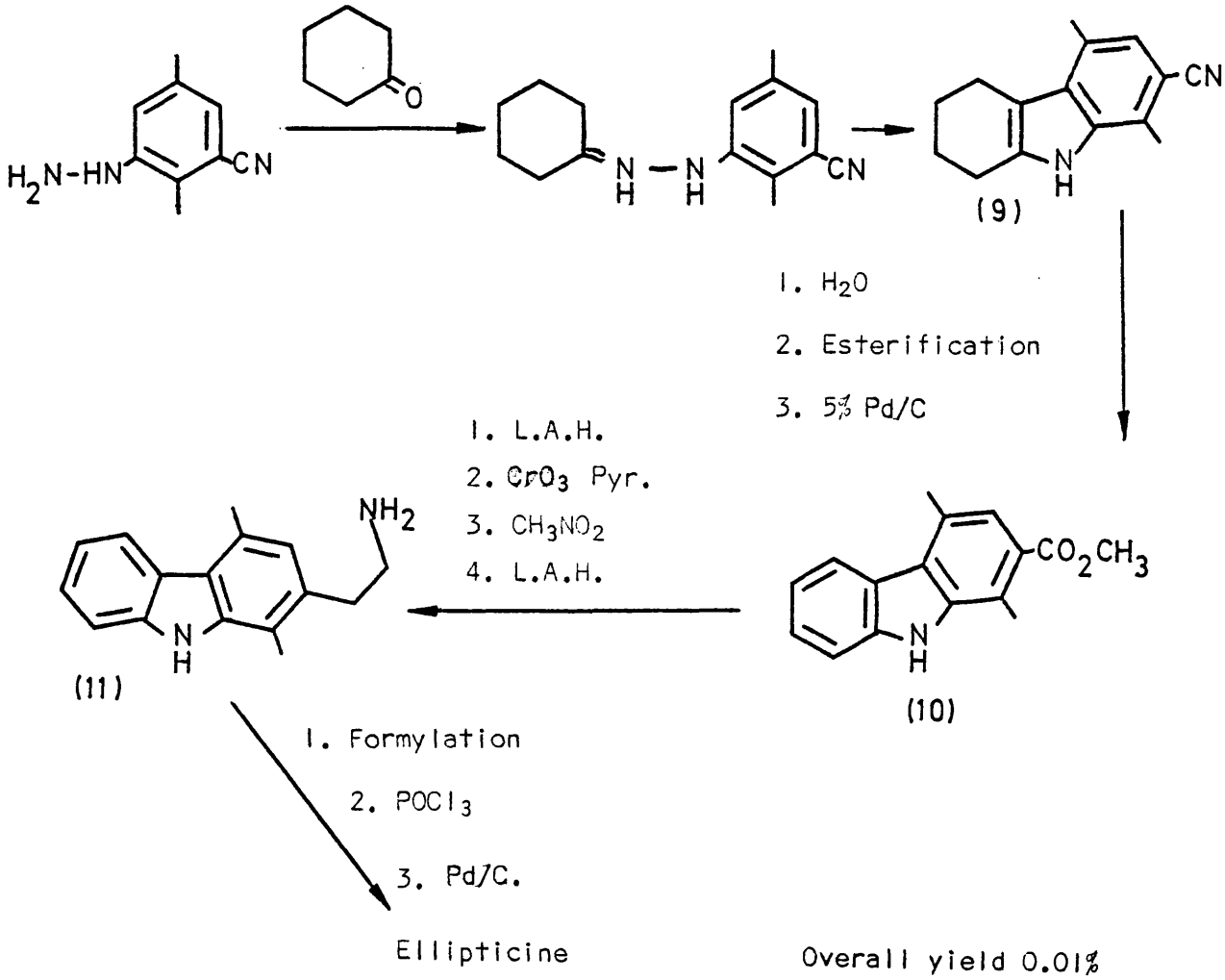
ROUTE 2



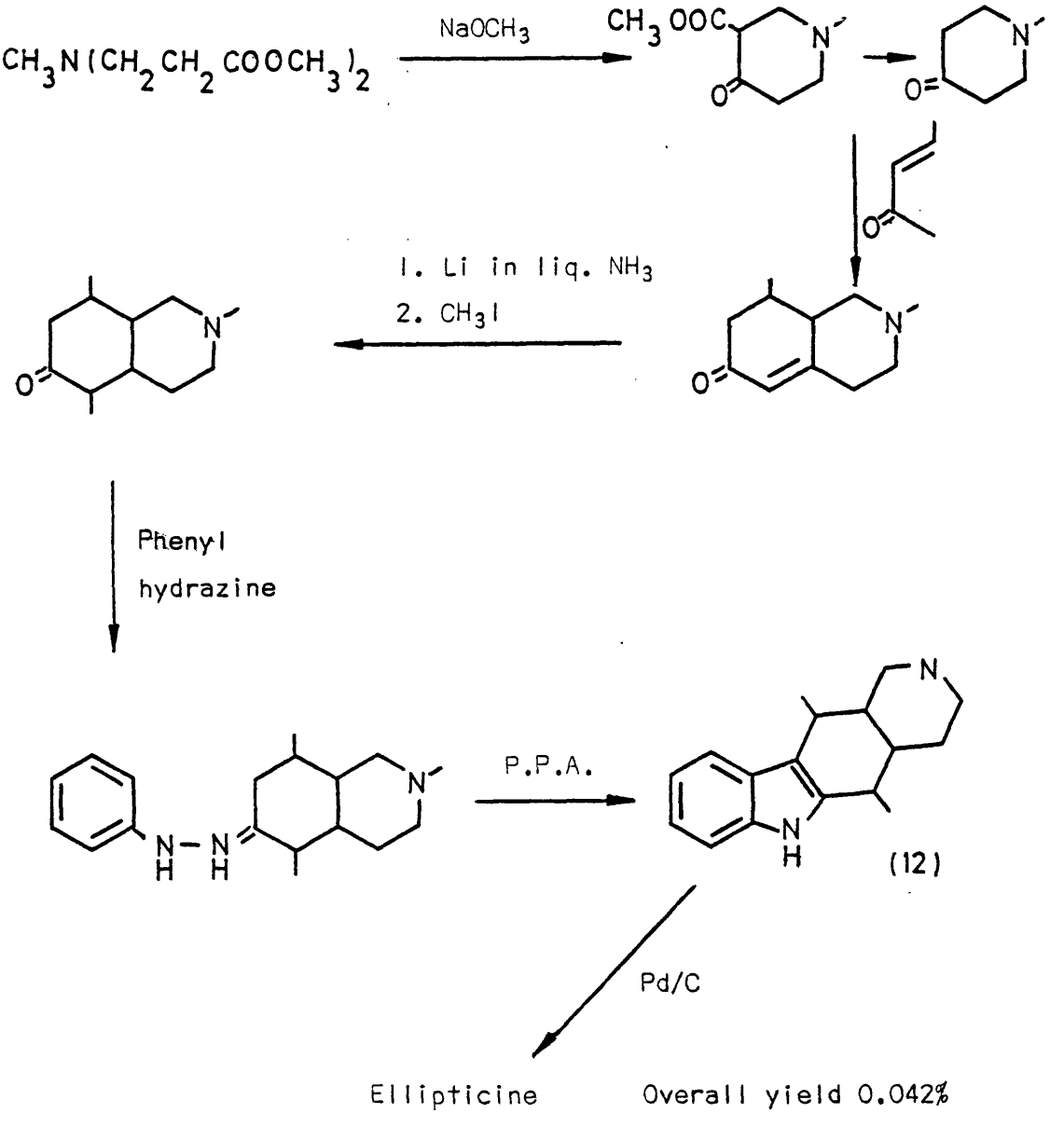
Although 3-formyl carbazole (5) condenses with 2,2-diethoxyethylamine to give the Schiff's base (6) in a good yield, this compound could not be cyclised directly in an efficient manner, however, its dihydro derivate (7) was successfully cyclised and dehydrogenated to ellipticine. The overall yield in this sequence was 1.3%. Although this yield is low, this route has subsequently been successfully modified and will be described later.

After these two reports other routes were described, one by Govindachari[10] and the other by Stilwell[11], but with yields even lower than in the previous syntheses. These studies are summarised in (Routes 3 and 4).

ROUTE 3



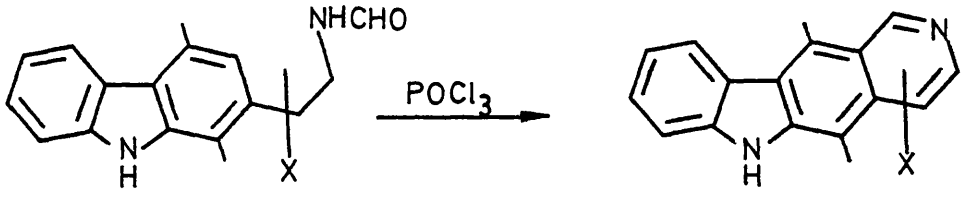
ROUTE 4



At this point in time Dalton[12] improved Cranwell and Saxton's method and cyclised the Schiff's base (6) directly to ellipticine by the action of 91% orthophosphoric acid which improved the overall yield.

In attempts to prepare numerous derivatives it was found that electron donating groups in the C-6 position of the Schiffs base (6) assisted ring-closure, whereas electron withdrawing functions had the opposite effect and gave[13] negligible yields of cyclised product. However, the presence of electron donating groups in the non-methylated benzene ring of the carbozole nucleus presents another problem, since on formylation the incoming substituent may now enter other positions than at C-3 as required. Thus, it is reported[13] that electron donating at C-7 of the carbazole results in no 3-formyl derivative, but gives mainly the 6-formyl derivative contaminated with the 8-formyl isomer. Nevertheless, accepting these limitations, a number of 9-substituted ellipticine have been prepared.

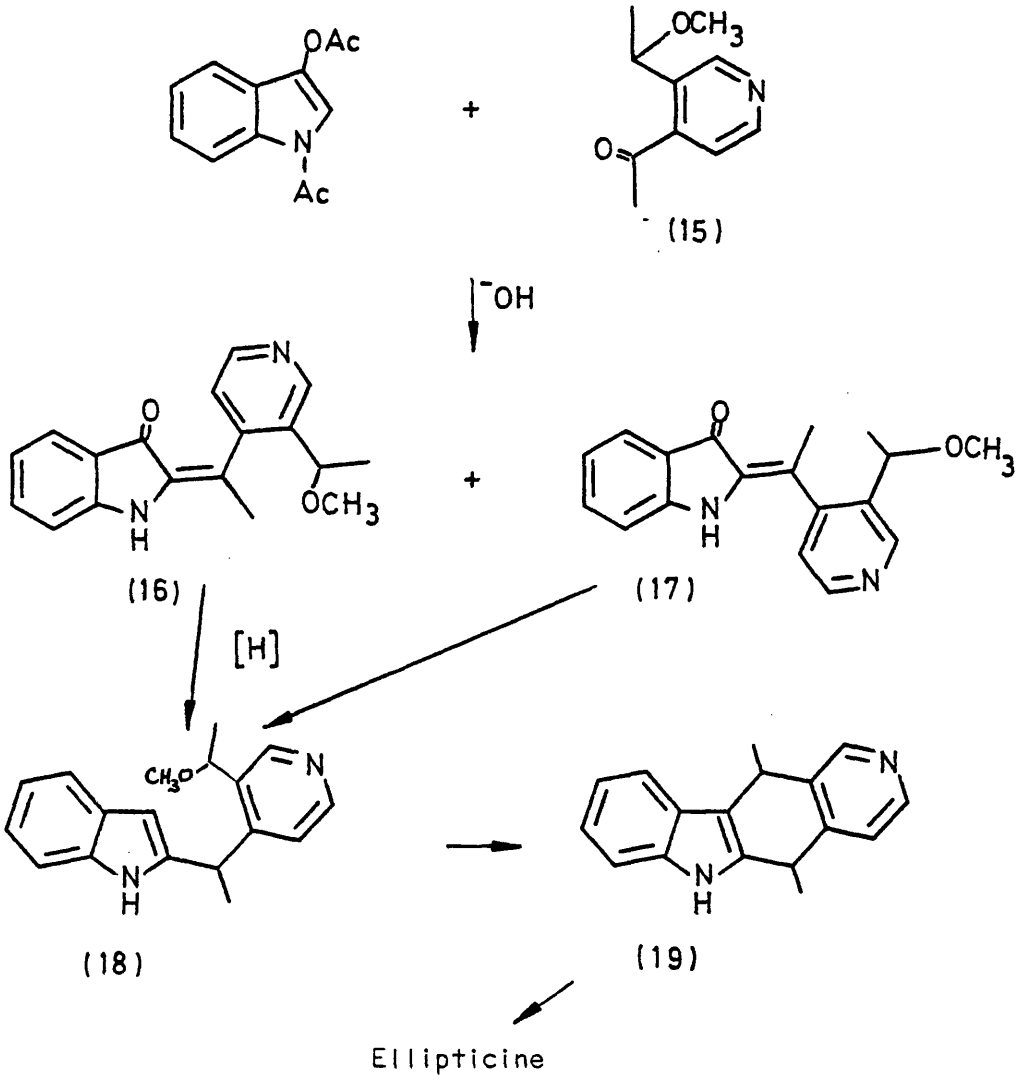
A variation of this approach has been made by a Swiss group[14] who cyclised 2-substituted carbazoles by a Bischler Napieralski procedure to obtain products substituted in ring D.



(13) (14)

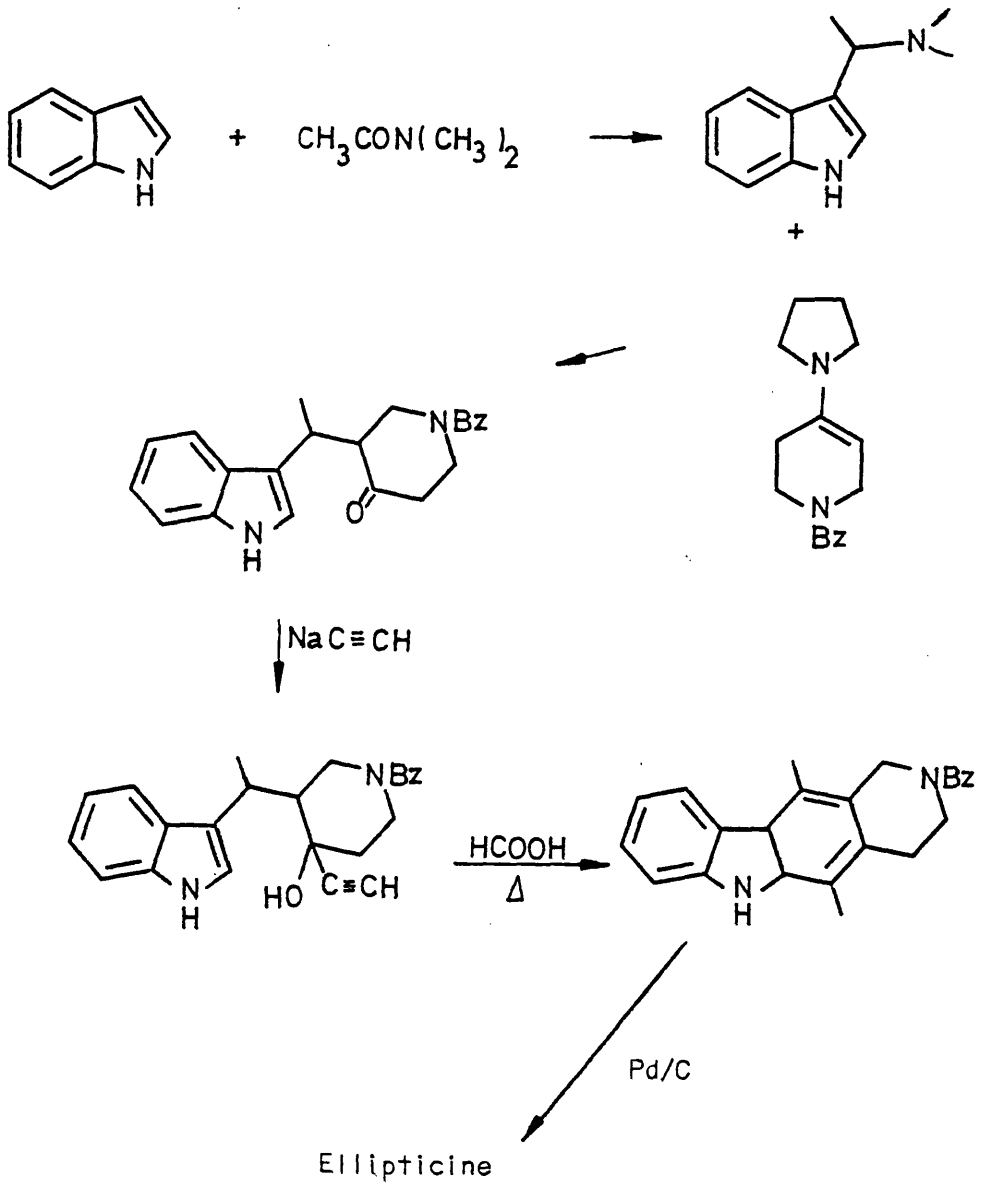
An interesting synthesis of ellipticine was achieved in this laboratory[15] (Route 5), where 4-acetylpyridine was condensed with 1,3-acetylindoxyl to give a mixture of the geometric (E)- and (Z)-isomers, (16) and (17). Reduction and dehydration then gives the indole (19) which may be cyclised in aqueous hydrobromic acid. The product 5,11-dihydroellipticine (19) undergoes spontaneous oxidation in air to give ellipticine in 31% yield.

ROUTE 5



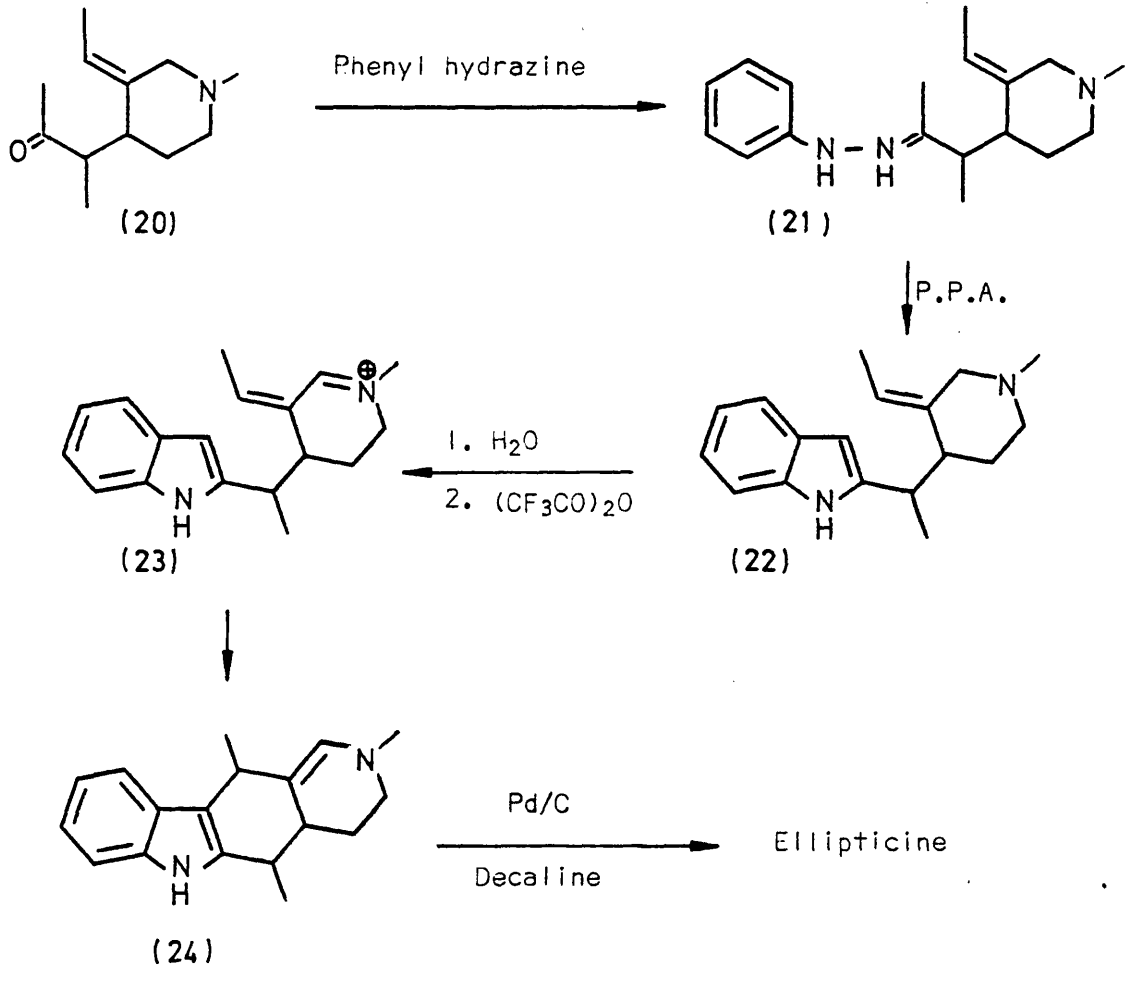
In 1973 Le Goffic[16] reported yet another ellipticine preparation, the tetracycle was constructed in a six stage process from indole *via* an initial Vielsmeier type reaction in an overall 24% yield (Route 6).

ROUTE 6



More recently still Potier[17] has described a synthesis in which the ketone (20) was transformed (Route 7) to the phenylhydrazone (21), which when treated with polyphosphoric acid, in a Fischer cyclisation reaction produced the indole (22). This was converted to the N(b)-oxide and then treated with trifluoroacetic anhydride to give the enamine (24) *via* the conjugated immonium ion (23). Finally this was oxidised to give ellipticine in an overall 18% yield.

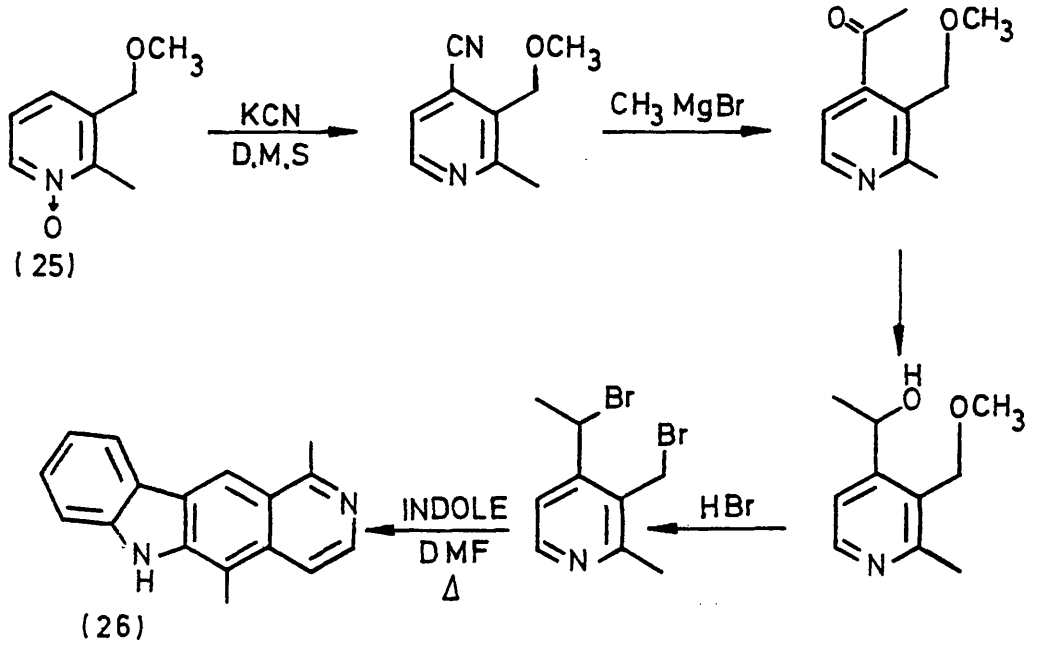
ROUTE 7



Although on paper this route looks attractive, because many substituted ellipticines are likely to be thermally unstable, the ultimate pyrolytic dehydrogenation step is undesirable.

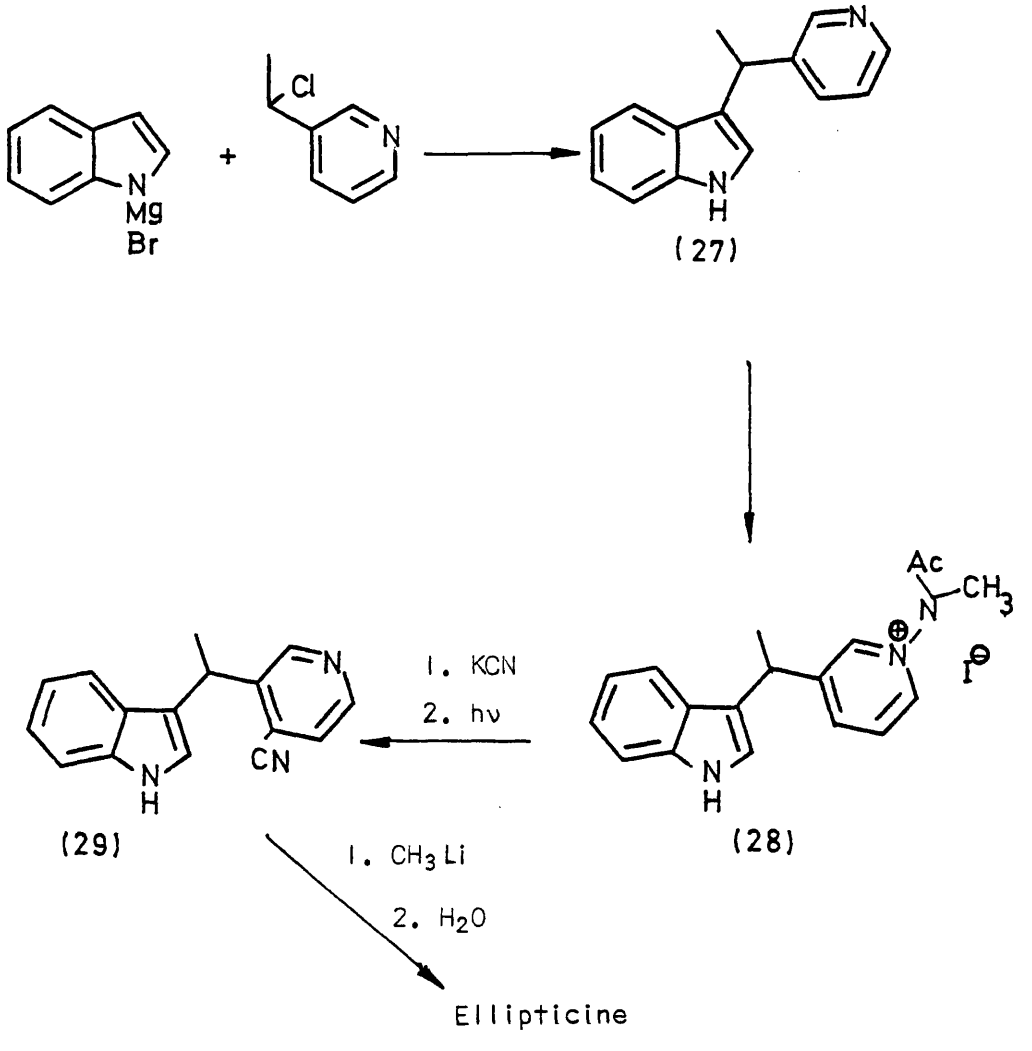
After these preliminary studies there have been many other reported syntheses[18,19,20] of pyrido [4,3-b]carbazoles which are either modifications of Dalton's method or are based upon the work of Govindachari. They all suffer from low productivity. Meanwhile, Kametani[21,22] has reported two different methods which again are not very practical, but in his latest publication[23] in this area, he has reported a novel route (8) to olivacine (26) which is a related alkaloid found in members of the family *Apocyanaceae*[24]; the yield was 3.6%, based upon the relatively inacessible pyridine (25).

ROUTE 8



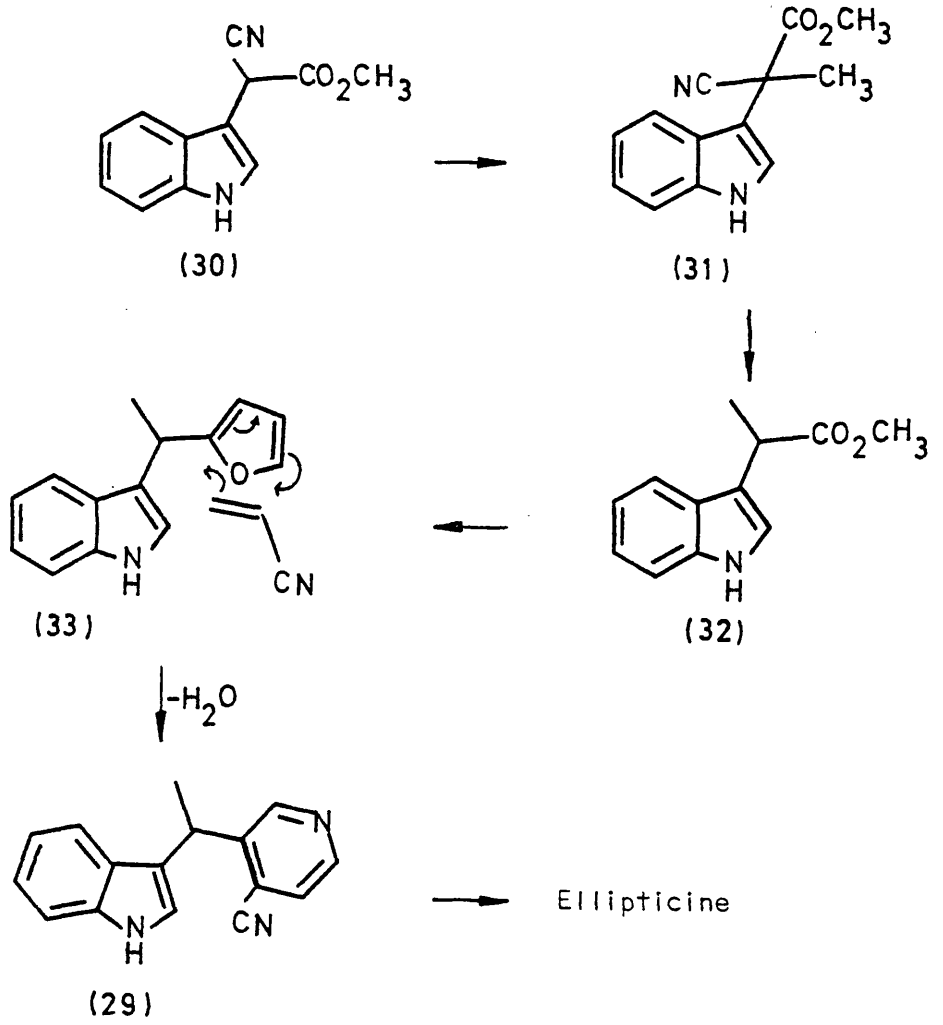
A more rewarding experiment has been carried out in this laboratory[25] by Sainsbury and Schinazi (Route 9) who prepared the indole (27) and cyclised it in three steps to ellipticine. Not only is the overall yield 25-30% but this route also does not suffer from any limitations imposed by pyrolytic conditions since all stage proceed at room temperature or below.

ROUTE 9



Another very interesting reported synthesis of the intermediate (29) is just recently published[26]. In this a Diels Alder reaction of a substituted oxazole (33) with acrylonitrile is required (Route 10). The intermediate oxazole (33) was made by treatment of the indole (30) with sodium methoxide and methyl iodide to give the indole (31) which after hydrolysis, decarboxylation and esterification produced 2-(3-indolyl) propionate (32). This when reacted with α-lithiated methyl isocyanide gave the oxazole (33).

ROUTE 10

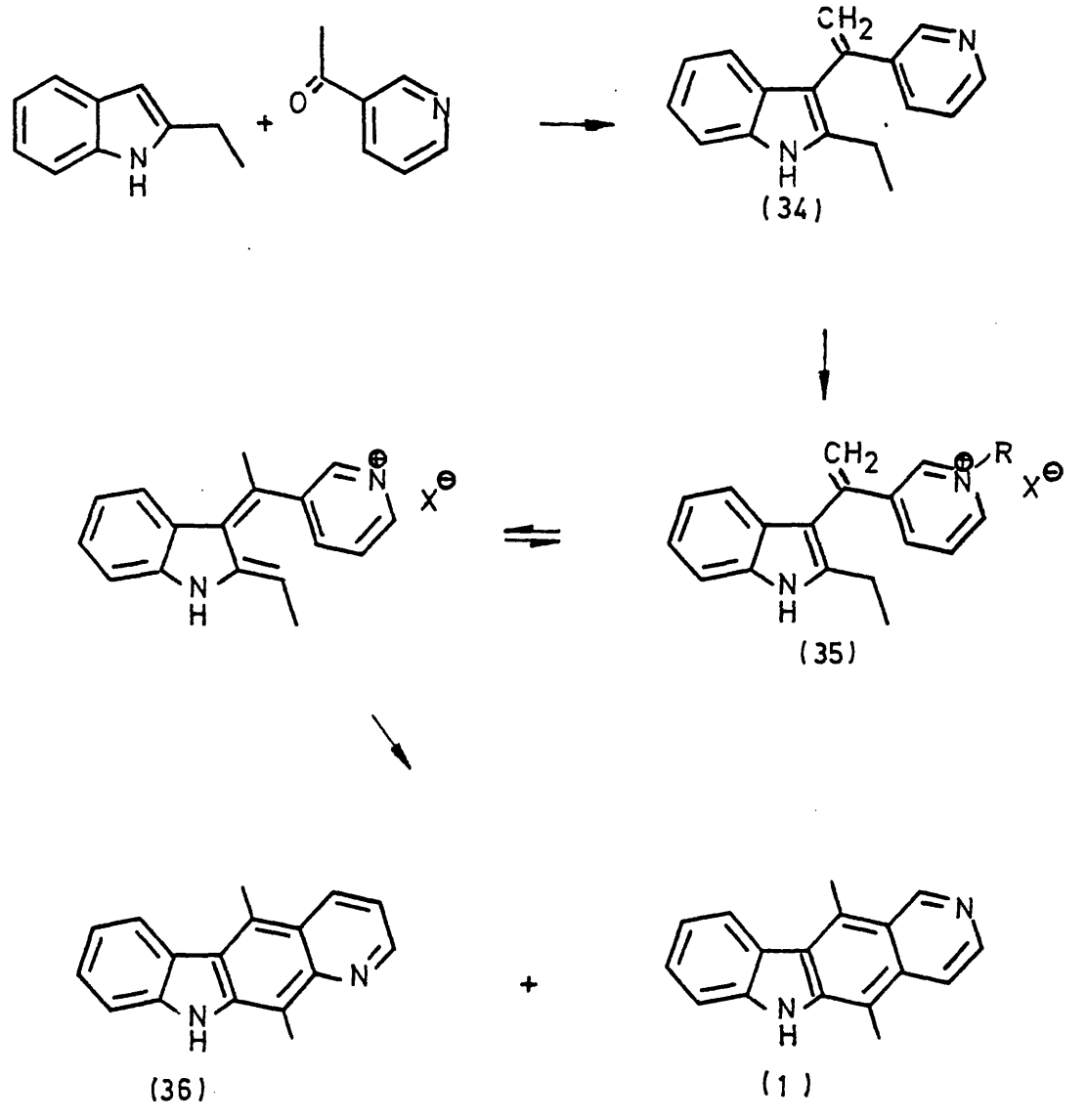


In an economical approach Bergman and Carlsson showed that the indole (35) can be thermally cyclised to ellipticine[27] (1). The indole (34) was made by this group some years before[28] but under mild conditions cyclisation failed. Recently though they found that the $N_{(b)}$ butyl salt (35, R = nC_4H_9, X = Br) when heated at + 350°C for five minutes gave ellipticine (1) in 72% yield (Route 11), other N-alkyl salts also afforded ellipticine but in lower yield. The desired product (1) is always contaminated with isoellipticine (36). The ratios of the products versus the alkyl substituent are summarised in Table 1.

TABLE 1

R	X	Ratio (1):(36)
$CH_3CH_2CH_2CH_2$-	Br	13.3
$(CH_3)_2CHCH_2$-	Br	2.0
$CH_3(CH_2)_5CH_2$-	Br	1.7
CH_3	I	1.3
$(CH_3)_2CHCH_2CH_2$-	Br	1.0
$C_6H_5CH_2$	Cl	1.0
$(CH_3)_2CH$ -	I	0.7
Cyclohexyl	Br	0.1

ROUTE 11

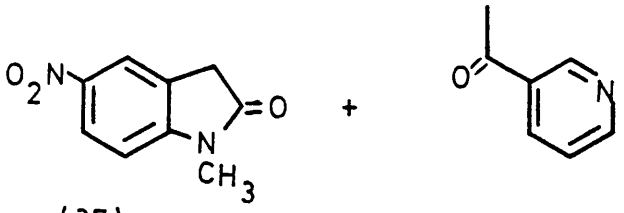


However, although this method like so many of its predecessors, is plagued with a high temperature pyrolysis step. This, and the problem of isomer formation, detracts from its general applicability.

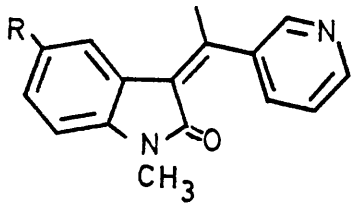
DISCUSSION TO PART THREE

All methods of ellipticine synthesis are relatively tedious and the obvious thing to do would be to prepare a single derivative which then may be easily converted by simple reactions to others. Thus a nitro group may be easily converted into a host of other functions and the preparation of various nitro substituted ellipticines is very desirable, so that the biological properties of the pyrido [4,3-b]carbazole system can be properly assessed. Nitration of ellipticine is not very successful, thus we decided to attempt the synthesis of 6-methyl-9-nitroellipticine (41) following the route pioneered by Kilminster and Sainsbury[29]. We planned to condense 3-acetylpyridine with 1-methyloxindole and reduce the mixture of isomers (38, R = NO_2) so obtained with lithium aluminium hydride to afford the indole (40) or the corresponding indoline. We and others[30] have observed that oxindoles unsubstituted at position -1 might not easily be reduced, however, N-alkyloxindoles are claimed to undergo facile reaction with lithium aluminium hydride[30,31] and this determined our choice of a N(a) substituted ellipticine as a primary target.

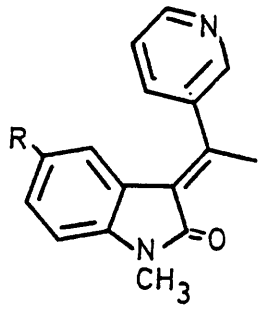
N-Methyloxindole was made by a standard procedure[33] and nitrated with concentrated nitric acid to give 1-methyl-5-nitro-oxindole (37). Surprisingly this product did not react with 3-acetyl pyridine. Such a result is not easy to understand since on the face of it the anion derived from the loss of a proton at position -3 of the nitro-oxindole should form more easily than that of oxindole itself.



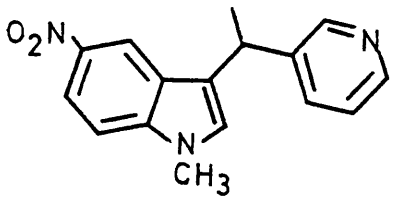
(37)



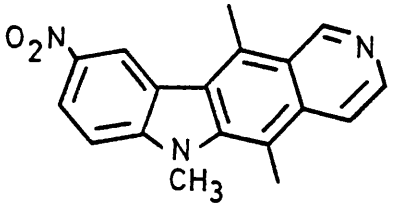
(38)



(39)

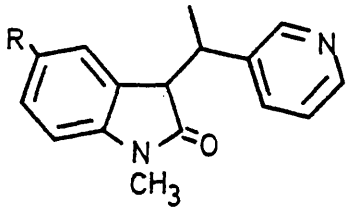


(40)



(41)

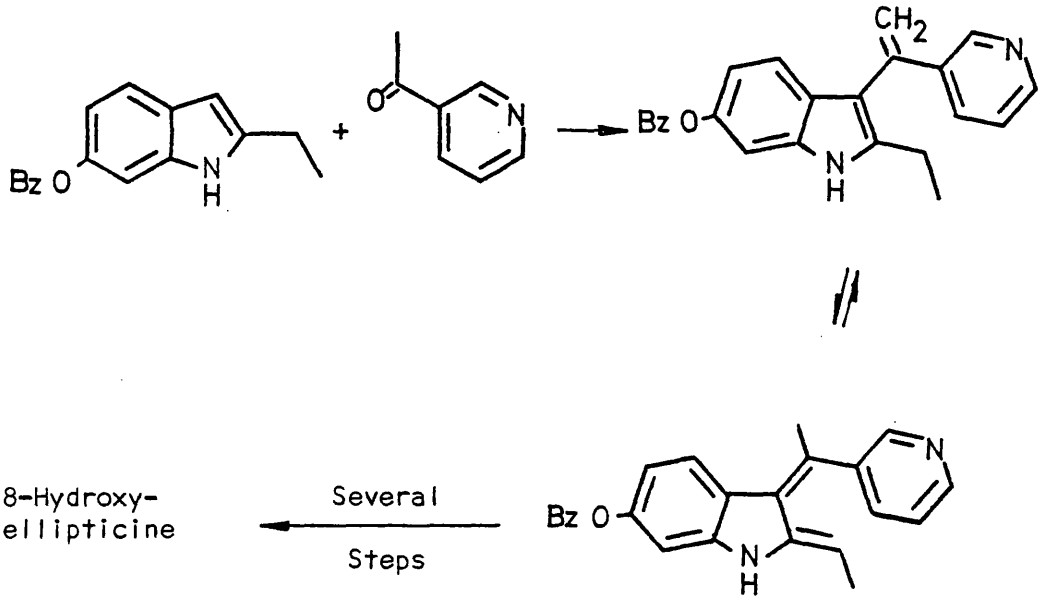
We encountered another disappointment when, after reacting the parent 1-methyloxindole with 3-acetylpyridine and obtaining the E-isomer (39, R = H) as the sole product, this decomposed under nitration conditions. 5-Bromo-1-methyloxindole reacts similarly with 3-acetylpyridine to give the corresponding indolinone but when this is reduced with sodium borohydride the product (42, R = Br) is fragmented with lithium aluminium hydride. There are many other reagent combinations described in the literature for the reduction of amides. For example, diborane or reduction with sodium in propanol[34]. In this laboratory, however, oxindoles of the type under discussion do not yield clean one component products and so this particular approach was abandoned.



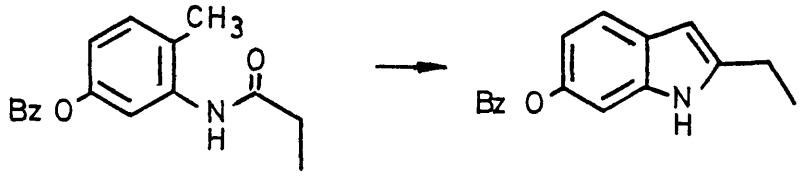
(42)

At this point news came from the testing centre at Vilsjuif in France that, although 9-hydroxyellipticine is highly active, its 7-hydroxy counterpart shows no anti-cancer properties. This stimulated us to attempt the synthesis of 8- and 10-hydroxy-ellipticines to see if 9-hydroxylation is mandatory for bioactivity.

The author's target was 8-hydroxyellipticine and the route envisaged was as follows:

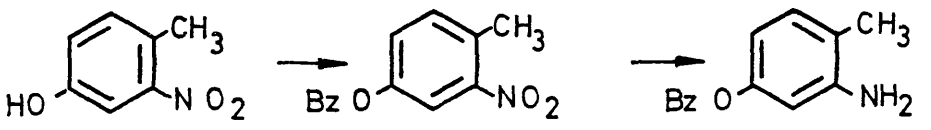


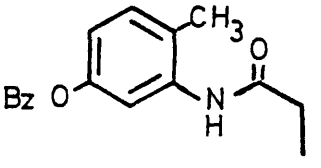
The initial problem was the synthesis of 6-benzyloxy-2-ethyl indole, but we thought that this would be easily achieved by a Madelung reaction on the amide (44).



(44) (45)

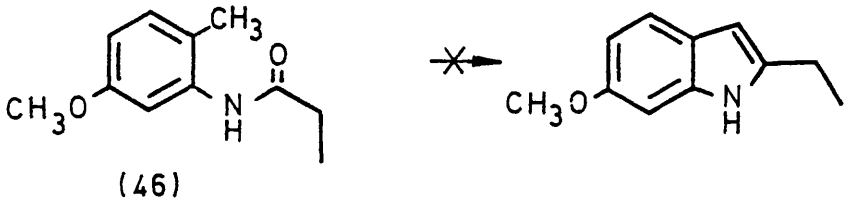
The starting material was prepared without difficulty from 2-nitro-4-cresol by the route shown below:





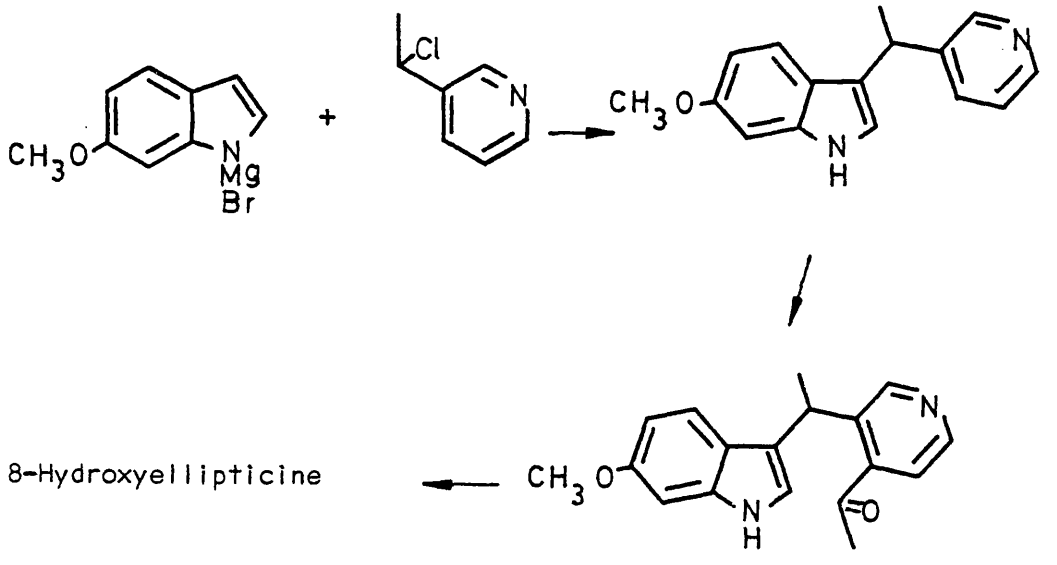
but the severe condition of the Madelung reaction (sodium hydride at 250°C) caused it to decompose violently.

A similar experiment was carried out on the amide (46) prepared but decomposition also occurred.

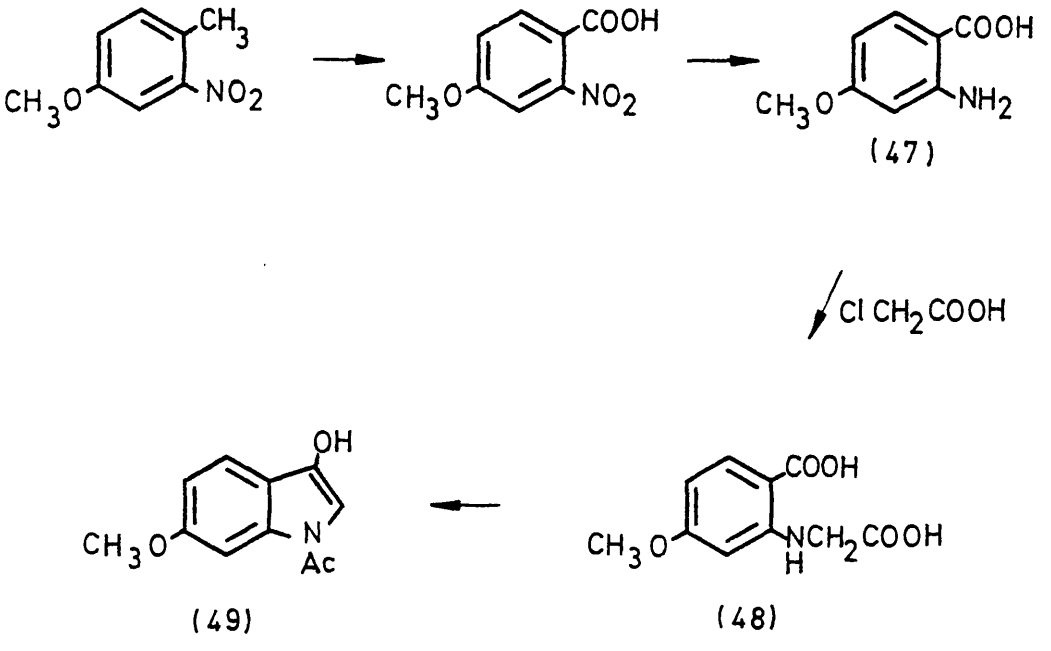


(46)

An alternative route to 8-hydroxyellipticine would be to utilize 6-methoxyindole and follow the scheme shown below:



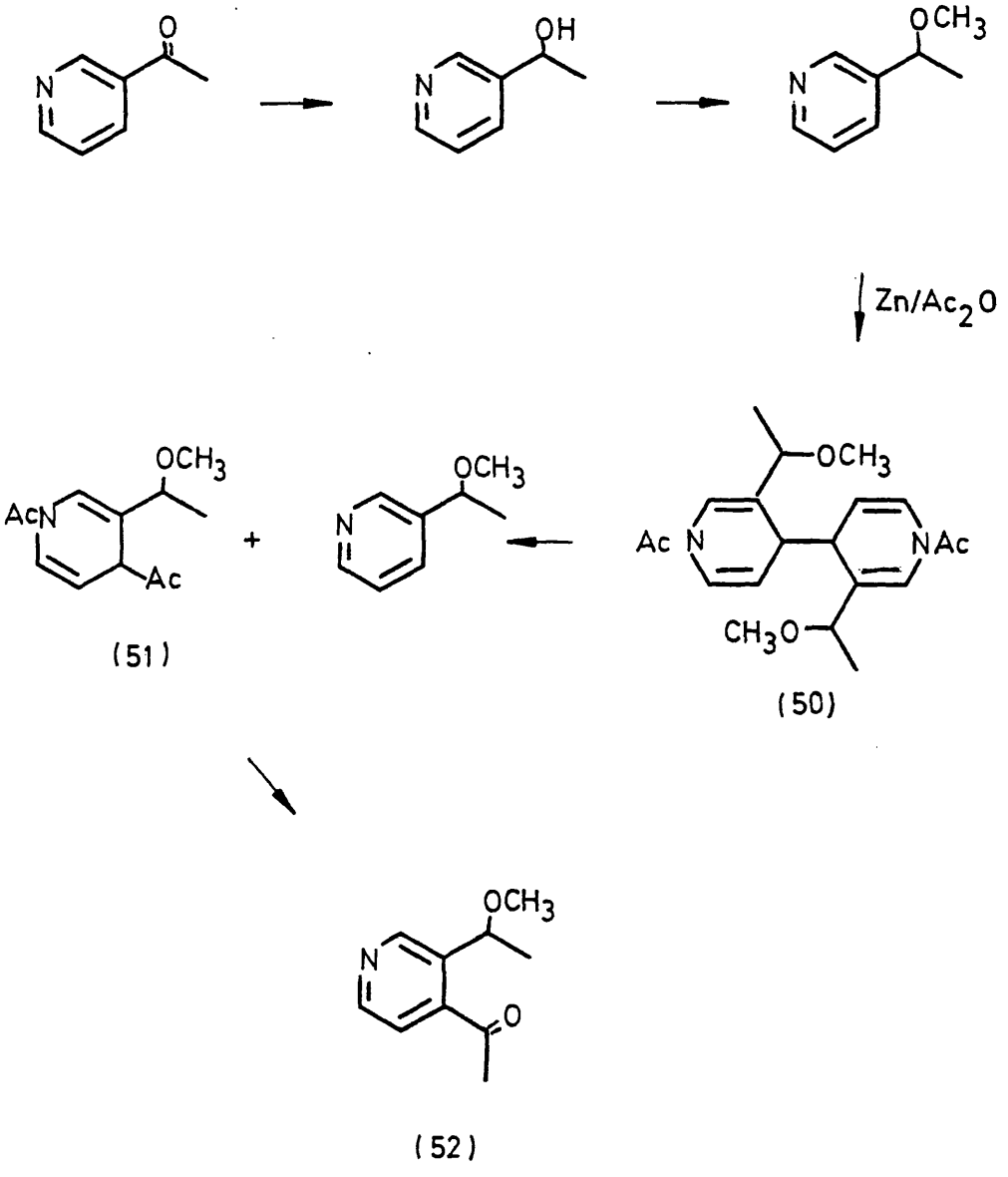
This is, of course, a modification of Sainsbury and Schinazi's route. 6-Methoxyindole is a known compound but published routes to it are very unrewarding and new methods are being sought by the author's colleague Mr. David Dolman. In the meantime, this promising avenue of research was put aside in favour of an approach based upon the 1,3-diacetylindoxyl (Route 5, page 104); in order to begin this sythesis 4-methoxy-2-nitro toluene was oxidised to the corresponding benzoic acid and this reduced with hydrogen over Adam's catalyst to the anthranilic acid (47). This was cyclised to the indoxyl (49) by reaction first with chloroacetic acid and then treatment of the glycine with acetic anhydride. We were surprised to isolate this product, since normally the 1,3-diacetyl compound is formed in similar reactions, however, this was next condensed in alkaline solution with the pyridine (52).



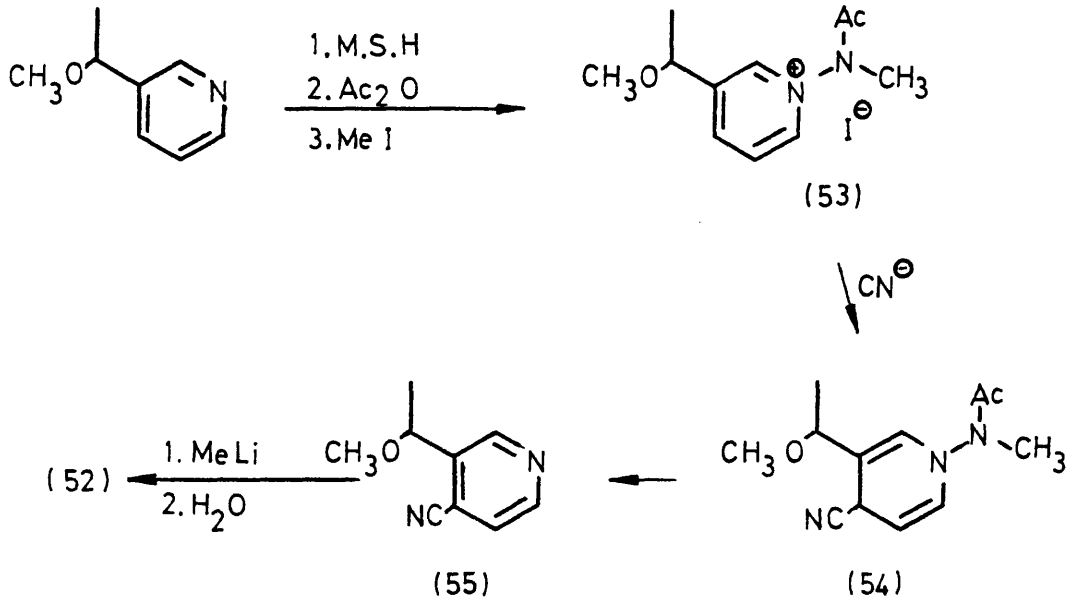
This last compound has been prepared by Wibaut and Arens through reductive acetylation of 3-(1-methoxy) ethylpyridine with zinc and acetic anhydride but this is an untrustworthy process with yields varying from only 10-30%[37].

The reaction is said to proceed *via* a dimeric species which then disproportionates into (51) and starting compound; therefore the maximum yield cannot exceed 50%, and in addition the purification of the product 1,4-dihydropyridine is always a problem.

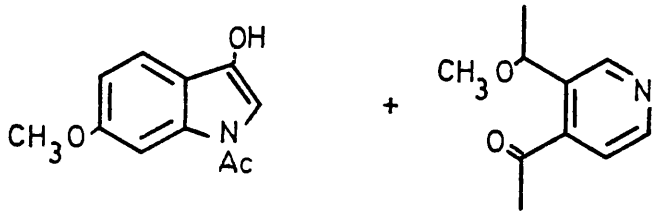
Oxidation to 4-acetyl-3(1-methoxy) ethylpyridine is normally carried out by heating the 1,4-dihydropyridine (51) in methanol for several hours, however, Webb[38] and Schinazi[13] have tried many different oxidising agents: chromium trioxide, choranil and D.D.Q. without achieving any better results.



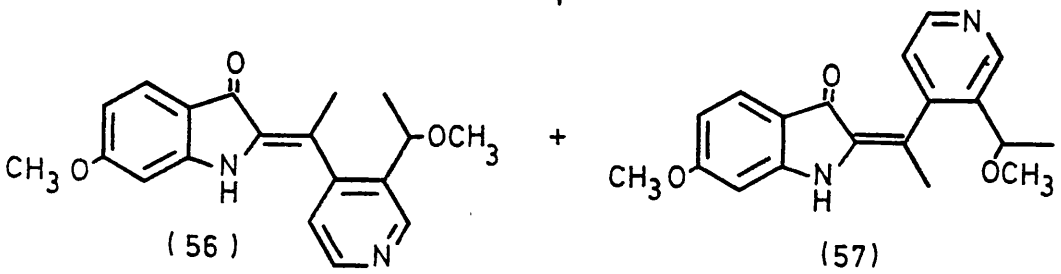
A more practical way to synthesise the compound (52) is *via* the amination of 3-(1-methoxy) ethylpyridine using O-mesitylene sulphonyl hydroxylamine. Acetylation and methylation afford the methiodide salt (53) which when treated with cyanide ion gives the dihydro compound (54) which may be aromatised to (55) by photolysis. The cyanide (55) when treated with methyl lithium gives the desired pyridine (52).



In the initial condensation between the indoxyl (49) and the pyridine (52) the products are a mixture of E and Z-isomers existing individually as diastereomers. The latter effect is caused by restricted rotation and the presence of a chiral centre. This phenomenon was extensively investigated by Kilminster and by Webb but both authors noted that when the geometrical isomers failed to crystallise attempts to separate them proved very tedious and in general it was best to proceed with the

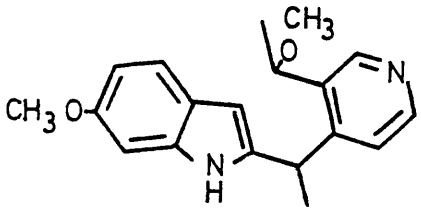


NaOH
H_2O



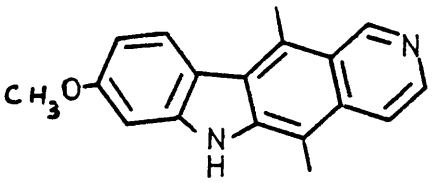
(56) (57)

$[H]$
$-H_2O$



(58)

HBr

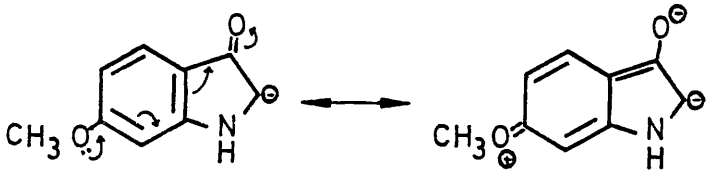


+ 8-hydroxyelliptieine ?

reaction sequence. In the next stage, however, reduction of the mixed isomers leads to a product with three chiral centres and the effect of diastereoisomerism is even more complex. The situation is relieved somewhat in the ensuing step when the indoline alcohol is dehydrated to the indole. Only two chiral centres are present and most often in the past these indoles now crystallise and may be purified.

In our case this did not happen and a resin was obtained, although mass spectrometry indicated this material to be the required product we spent many frustrating hours attempting to get a specimen in a crystalline form. TLC, plate and column chromatography were all tried without success and most of our crude product was used up in this way. Indeed, the compound(s) is not particularly stable and in some cases further resinification occurred.

Finally in desperation a few milligrams were heated with 60% aqueous hydrogen bromide and a yellow solid obtained which shows the characteristic ultraviolet spectrum of a pyrido [4,3b] carbazole (λ_{max} 282, 295, 301 nm - ellipticine has λ_{max} 276, 287, 296 nm). However, the amount available was less than two milligrams and an attempt to purify this compound by sublimation was not successful. We wish now that we had committed all of our crude indole in this way but it is clear that this route will provide enough of the required product when the problems described can be resolved. In particular the indoxyl (49) is the least reactive of any used in this laboratory before, perhaps through the destabilisation of the anion (59) as shown, and the presence of unused starting materials in subsequent reactions must be avoided. It is clear therefore that every attempt must be made to purify the inones (56) and (57), which are comparatively stable, before the more reactive indoline alcohol and indole are encountered.



(59)

EXPERIMENTAL TO PART THREE

N-Methylchloroacet-2-Toluidide

Chloracetyl chloride (56.5 g) was slowly added to a solution of N-methyl-2-toluidine (53.5 g) in benzene (400 cm^3) and pyridine (39.5 g). The mixture was refluxed for 2 h after the addition was completed and then the solvent layer was washed with acid and then with water before it was dried over sodium sulphate. The solvent was evaporated to give an oil which crystallised from petroleum ether (b.p. 60-80°C), m.p. 58°C; γ_{max} 1700, 1600, 1050, 800 cm^{-1}; $\delta(CDCl_3)$, 3.35 (3H, S), 3.9 (2H, S), 7.2-7.6 (5H, m).

1-Methylindolin-2 (3H) one (1-Methyloxindole)

A mixture of N-methylchloroacet-2-toluidide (50 g), aluminium chloride (80 g) and sodium chloride (15 g) was heated at 180-185°C for 8 h and then cooled. The powdered product was added to ice in portions and extracted with benzene. The solvent was dried over sodium sulphate and evaporated in vacuum to give a brown solid which recrystallised from petroleum ether, (b.p. 60-80°C) as colourless crystals (24 g, 60%); m.p. 78-79°C; $\delta(CDCl_3)$ 3.2 (3H, S), 3.5 (2H, S), 6.7-7.5 (4H, m).

5-Bromo-1-Methyloxindole

A solution of bromine (5 g) and potassium bromide (7.5 g) in water (15 cm^3) was added over a 20 minute period at 85-90°C to a solution of 1-methyloxindole (4.6 g) and sodium acetate (10 g) in water (250 cm^3). The mixture was held at 85-90°C for ten minutes and then filtered hot. The insoluble portion was extracted three times with filtrate, each time cooling to obtain the precipitated product as white crystals (3.2 g, 45%), m.p. 128-129°C (lit.[39], m.p. 130-132°C); $\delta(CDCl_3)$ 3.17 (3H, S), 3.5 (2H, S), 6.7 (1H, d, $\underline{J}$ = 8Hz), 7.3-7.6 (2H, m).

1-Methyl-5-Nitrooxindole (37)

1-Methyloxindole (4.6 g) was added in small portions to a stirred solution of concentrated nitric acid (10 cm^3) at 0°C. When the reaction was complete the solution was added to ice (100 g) and the yellow crystals of the product which appeared were collected by filtration (2.6 g, 41%), m.p. 199-200°C (lit.[39], m.p. 198°C); δ(DMSO) 3.3 (2H, S), 3.4 (3H, S), 7.05 (1H, d, $\underline{J}$ = 8Hz), 7.95 (1H, dd, $\underline{J}$ = 8Hz, $\underline{J}$ = 2Hz), 8.6 (1H, d, J = 2Hz); γ_{max} 1670, 1616, 980, 740 cm^{-1}.

E-1-Methyl-3-[1-(3-pyridyl) ethylidine]indolin-2-one (39, R = H)

A mixture of 1-methyloxindole (4.6 g) and 3-acetylpyridine (3.8 g) and pyrrolidine (0.5 cm^3) in benzene (150 cm^3) was refluxed for 8 h. After this time the solvent was evaporated in vacuum to give a dark red oil which was extracted with petroleum ether (b.p. 60-80°C) to give yellow crystals (3.5 g, 45%), m.p. 126-127°C; δ($CDCl_3$) 2.6 (3H, S), 3.25 (3H, S), 6.2 (1H, d, J = 8Hz), 6.5-7.8 (5H, m), 8.6 (1H, d, J = 1.5 Hz), 8.75 (1H, dd, J = 6 Hz, J = 1.5 Hz); $m/_e$ 250(M^+) (Found: C, 77.0; H, 5.6 $C_{16}H_{14}N_2O$ requires C, 76.8; H, 5.6%).

E-5-Bromo-1-methyl-3-[1(3-pyridyl) ethylidine]indolin-2-one (39, R = Br)

A mixture of 5-bromo-1-methyloxindole (7.0 g) and 3-acetylpyridine (3.8 g) and pyrrolidine (0.5 cm^3) in benzene (150 cm^3) was refluxed for 4 h. After this time the solvent was evaporated in vacuum to give a dark red oil which was extracted with petroleum ether (b.p. 60-80°C) to give yellow crystals (4.0 g, 39%), m.p. 140-141°C; δ($CDCl_3$) 2.8 (3H, S), 3.25 (3H, S), 6.2 (1H, d, J = 1.5 Hz), 6.6 (1H, d, J = 8 Hz), 7.15-7.75 (3H, m), 8.5-8.6 (1H, m), 8.75 (1H, dd, J = 2 Hz, J = 5 Hz), $m/_e$ 328 (M^+), 330(M^+ + 2).

Attempted Reaction of 1-Methyl-5-Nitrooxindole with 3-Acetylpyridine

A mixture of 1-methyl-5-nitrooxindole (6.0 g) and 3-acetylpyridine (3.8 g) and pyrrolidine (0.5 cm^3) was refluxed for 14 h. After this time the solvent was evaporated in vacuum to give a red gum. TLC analysis of this indicated that it was comprised mainly of starting materials. Other attempts using more vigourous reaction conditions also failed.

1-Methyl-3-[1-(3-Pyridyl) ethyl]indoline-2-one (42, R = H)

Sodium borohydride (1.0 g) was added to the stirred solution of 1-methyl-3[1(3-pyridyl) ethylidine] indoline-2-one (2.5 g) in 50% acqueous ethanol (50 cm^3) and the mixture was left to stir until solution was complete. The solvent was then evaporated and the product extracted into chloroform. The extracts were then dried over sodium sulphate and evaporated to give a yellow oil which was dissolved in boiling petroleum ether (b.p. 40-60°C). When the solution was cooled to -50°C white crystals were obtained (2.3 g, 91%) m.p. 55°C; $m/_e$ 252 (M^+).

5-Bromo-1-Methyl-3-[1(3-pyridyl) ethyl] indoline-2-one (42, R = Br)

Sodium borohyride (1.0 g) was added in portions to a stirred solution of 5-bromo-1-methyl-3-[1(3-pyridyl) ethylidine] indoline-2-one (3.3 g) in 50% aqueous ethanol (50 cm^3) and the mixture was left stirring for 2 h. The solvent was then evaporated and the product extracted with chloroform. The extracts were dried over sodium sulphate and then evaporated to give a yellow oil which was dissolved in boiling petroleum ether (b.p. 60-80°C) when this solution was cooled to -50°C white crystals formed (3.0 g, 90%); m.p. 66-67°C; $m/_e$ 330 (M^+), 332 ($M^+ + 2$).

Attempted Reduction of 1-Methyl-3-[1(3-pyridyl) ethyl] indoline-2-one

(a) To a solution of 1-methyl-3-[1(3-pyridyl) ethyl] indoline-2-one (1.0 g) in tetrahydrofuran (50 cm^3) was added lithium aluminium hydride (0.15 g) in portions. The mixture was then stirred for 20 minutes before a few drops of 95% ethanol were added to the mixture. The solvent was then evaporated the product (0.3 g) crystallised from petroleum ether (b.p. 60-80°C). It has m.p. 78-79°C and was shown by mixed m.p. comparison of specta etc. to be identical with 1-methyloxindole.

(b) To a solution of 1-methyl-3-[1(3-pyridyl) ethyl] indoline-2-one (1.0 g) in propyl alcohol (20 cm^3) was added sodium(0.5 g). The mixture was then stirred under reflux until the solution was complete. The excess solvent was then removed and the product was extracted in

petroleum ether (b.p. 60-80°C), when these extracts were cooled yellow crystals formed and was shown by mixed m.p. and comparison of the spectra to be identical with starting compound.

(c) Diborane was generated by adding a solution of sodium borohydride (1.0 g) in diglyme (30 cm^3) to a solution of an excess of boron trifluoride etherate (9.0 g) in diglyme (30 cm^3)[40]. The generator consisted of a 250 cm^3 3-necked flask equipped with a pressure-equalised dropping funnel, an inlet for nitrogen, an outlet for the diborane and a magnetic stirrer. The diborane outlet was connected by a short length of tygon tubing to a 2-necked flask equipped with a magnetic stirrer and a condenser which was connected to another tube leading the excess diborane into an acetone solution. In the 2-necked flask was placed a solution of 1-methyl-3-[1(3-pyridyl) ethyl] indoline-2-one (1.0 g) in digylym (20 cm^3). The apparatus was flushed with nitrogen; the nitrogen flow was reduced almost to zero, and the sodium borohydride solution was added slowly to the generator over a period of 2 h. When the addition was complete, the generator was warmed to 60-70°C and after a few minutes the nitrogen flow increased for several minutes to drive residual diborane into the reaction flask, then the reaction mixture was evaporated in vacuum to give a dark resin. The same experiments were carried out on 5-bromo derivative (42, R = Br) but similar results were obtained.

p-Tolylcarbonate

To a solution of sodium hydroxide (28 g) in water (200 cm^3) was added 4-hydroxytoluene (54 g), this was stirred at 40°C and 12.5% w/v phogene in toluene (198 cm^3) was slowly added over 2 h, keeping the temperature at 40-50°C throughout. After a further 4 h, nitrogen was bubbled through the mixture overnight to remove excess phosgene and then the toluene layer was separated and the aqueous layer extracted with chloroform. The combined extracts plus the toluene layer were dried over sodium sulphate and the solvent was then evaporated to give the product as white crystals (55 g, 90%); $\delta(CDCl_3)$ 2.3 (6H, S), 7.15 (8H, S).

4-Hydroxy-2-Nitrotoluene

A mixture of sulphuric acid (40 g, 99-100%) and nitric acid (30 g, 86-92%) at 10-12°C was gradually added to a stirred solution of p-tolyl carbonate (40 g) in 99-100% sulphuric acid (200 g) at 12-15°C. The mixture, after being stirred for 2 h at 18-20°C was poured on ice (300 g) when a yellow solid was deposited, the crude product was collected and pressed between filter papers, this material was then boiled with aqueous sodium carbonate (35 g in water, 350 cm^3) for 2 h, the solution was at once acidified at 35°C and 3-nitro-4-hydroxytoluene removed by distillation in steam. The residual 2-nitroisomeride was decolourised by boiling in benzene with animal charcoal and was then isolated as yellow crystals (21 g, 42%), m.p. 75°C (lit.[41], m.p. 76-77°C).

4-Benzyloxy-2-Nitrotoluene

4-Hydroxy-2-nitrotoluene (10 g) was dissolved in 3.5% alcoholic sodium hydroxide (100 cm^3) and treated with benzyl chloride (12.3 g), finally the solution was heated under reflux for 3 h. The solvent was then evaporated and the product extracted with chloroform, the combined extracts were washed first with 10% sodium carbonate, then with N-sodium hydroxide and then finally with water. The solvent was evaporated and the product crystallised from petroleum ether (b.p. 60-80°C) to give yellow crystals (11 g, 70%), m.p. 34-35°C; $\delta(CDCl_3)$ 2.6 (3H, S), 5.1 (2H, S), 6.95-7.5 (8H, m).

4-Methoxy-2-Nitrotoluene[41]

A mixture of 4-hydroxy-2-nitrotoluene (15.3 g), toluene (100 cm^3), methyl sulphate (14 g), and anhydrous sodium carbonate (12.7 g) was heated and stirred at 110-112°C for 5 h. After removal of solids by filtration the solvent was evaporated to give a pale yellow oil (13.0 g, 77%); $\delta(CDCl_3)$ 2.55 (3H,bS), 3.9 (3H, S), 7.1-7.3 (2H, S), 7.55 (1H, d, $\underline{J}$ = 2Hz) (Found: C,57.1; H, 5.3; $C_8H_9NO_3$ requires C, 57.5; H, 5.4%).

2-Amino-4-Benzyloxytoluene

A mixture of 4-benzyloxy-2-nitrotoluene (10 g) and 20% sodium hydroxide (10 cm^3) and 95% ethanol (50 cm^3) was brought to the boil and zinc dust (10 g) was added to the mixture in such a manner as to just keep the solution boiling. The solution was then heated under reflux for a further 1 h. The solution was then filtered and solvents removed to give an oil which was crystalised from petroleum ether (b.p. 60-80°C), m.p. 108-109°C (7.0 g, 80%); γ_{max} 3450, 1620, 820 cm^{-1}; $\delta(CDCl_3)$ 2.0 (3H, S), 3.4 (2H, bS), 4.85 (2H, S), 6.2 (1H, d, $\underline{J}$ = 2Hz), 6.3 (1H, dd, $\underline{J}$ = 8Hz, $\underline{J}$ = 2Hz), 6.9 (1H, d, $\underline{J}$ = 8Hz), 7.2-7.4 (5H, m).

2-Amino-4-Methoxytoluene

A mixture of 4-methoxy-2-nitrotoluene (10 g) and 20% sodium hydroxide (10 cm^3) and 95% ethanol (50 cm^3) was treated as in the previous experiment to give the title product, m.p. 46-47°C (lit.[42], m.p.47°C); (6.6 g, 82%); γ_{max} 3300, 1600 cm^{-1}.
The next step was carried out on this compound straightaway.

4-Benzyloxy-2-Propionamidotoluene

2-Amino-4-benzyloxytoluene (6.0 g) was dissolved in proprionic anhydride (30 cm^3) and refluxed for 2 h. The excess solvent was then removed to give crystals which were washed with ethanol (4.0 g, 53%); m.p.118°C; $\delta(CDCl_3)$ 1.25 (3H, t, $\underline{J}$ = 7Hz), 2.2 (3H, S), 2.4 (2H, q , $\underline{J}$ = 7Hz), 5.0 (2H, S), 6.5-7.8 (9H, m); $m/_e$ 269 (M^+).

4-Methoxy-2-Propionamidotoluene

A similar experiment to that described above, using this time 2-amino-4-methoxytoluene (5.0 g) gave the corresponding amide (4.0 g, 47%); m.p. 58°C; δ($CDCl_3$) 1.25 (3H, t, J = 7Hz), 2.2 (3H, S), 2.4 (2H, q, J = 7Hz), 3.75 (3H, S), 6.65 (1H, dd, J = 8Hz, J = 2Hz), 7.0-7.4 (2H, m), 7.6 (1H, bS).

Attempted Preparation of 6-Benzyloxy-2-Ethylindole

(a) 4-Benzyloxy-2-propionamidotoluene (1.0 g) was mixed with finely divided sodamide (0.2 g) and heated under nitrogen. As soon as the temperature reached 105°C a black smoke was emitted and the reaction was stopped. Work-up only gave a small amount of the starting compound and much charred material.

(b) When the reaction was repeated now with a slower rate of heating and the mixture left at 100°C for a longer period a black gam was produced. This was not soluble in organic solvents.

(c) Sodium (0.5 g) was dissolved in tert-butyl-alcohol (10 cm^3) under nitrogen and it was stirred on a water bath when 4-benzyloxy-2-propioamido-toluene (1.0 g) was added to the solution. The mixture was stirred for 4 h. Work-up only gave the starting compound and this approach was abandoned.

Attempted Preparation of 2-Ethyl-6-Methoxyindole

Exactly the same reactions described in the previous experiment were performed on 4-methoxy-2-propionamidotoluene and the same result was obtained.

4-Methoxy-2-Nitrobenzoic Acid

In a 1 litre flask with stirrer and reflux condenser were placed potassium permanganate (50 g), 4-methoxy-2-nitrotoluene (26 g), and water (600 cm^3). The mixture was slowly heated to boiling with continual stirring until the permanganate colour had disappeared (this requires one to two hours). The mixture was then filtered and the hydrated manganese dioxide which had been thus removed, washed with hoter water (2 x 50 cm^3). The combined filtrate and washings were concentrated to about 200 cm^3, then the mixture was washed with ether (200 cm^3) and the aqueous solution acidified with concentrated hydrochloric acid. The product separated as white crystals (14.0 g, 44%); m.p. 191-192°C; $\delta(CDCl_3$, DMSO) 3.95 (3H, S), 7.05-7.35 (2H, m), 7.75-8.0 (1H, dd, $\underline{J}$ = 8Hz, $\underline{J}$ = 2Hz); $m/_e$ 197 (M^+).

4-Methoxyanthranilic Acid (47)

A suspension of 4-methoxy-2-nitrobenzoic acid (5.0 g) in ethanol (100 cm^3) and 10% platinum dioxide in charcoal was hydrogenated at 100 lb/in^2 pressure and 50°C for 2 h. The catalyst was then filtered off and the solvent evaporated to give a white crystalline product (3.9 g, 93%); m.p. 170-171°C; ν_{max} 3500, 3360, 1680 cm^{-1}; δ(DMSO) 3.75 (3H, S), 6.15 (1H, dd, $\underline{J}$ = 9Hz, $\underline{J}$ = 2Hz), 6.3 (1H, d, $\underline{J}$ = 2Hz), 7.7 (1H, d, $\underline{J}$ = 9Hz), 8.0 (3H, bS); $m/_e$ 167 (M^+).

N-(2-Carboxy-4-Methoxyphenyl) glycine (48)

A solution of 4-methoxyanthranilic acid (9.0 g) in water (10 cm^3) containing sodium hydroxide (2.12 g) was added to a solution of chloroacetic acid (5.0 g) and sodium carbonate (2.8 g) in water (10 cm^3) at 40°C. This mixture was kept at this temperature for two days until a crystal product was obtained (2.64 g, 22%); m.p. 182-183°C; δ($CDCl_3$) 3.85 (3H, S), 4.0 (2H, S), 6.05 (1H, d, $\underline{J}$ = 2Hz), 6.25 (1H, dd, $\underline{J}$ = 9Hz, $\underline{J}$ = 2Hz), 7.85 (1H, d, J = 9Hz).

1-Acetyl-3-Hydroxy-6-Methoxyindole (49)

The glycine from the previous reaction (2.5 g) was dissolved in water (19 cm^3) containing sodium carbonate (1.9 g) and stirred while the acetic anhydride (1.66 g) was added. The mixture was stirred for a further $\frac{1}{2}$ h. and then acidified with concentrated hydrochloric acid to give the acetylated derivative which was filtered off and dried in a vacuum desiccator. This was then dissolved in acetic anhydride (10 cm^3) and triethylamine (2.5 cm^3) and refluxed for 20 minutes. The solvent was then evaporated to give a red oil which was crystallised from petroleum ether (b.p. 60-80°C) to give yellow prisms (0.496 g, 22%); m.p. 166°C; δ($CDCl_3$, DMSO) 2.45 (3H, S), 3.95 (3H, S), 5.2-5.7 (1H, bS), 6.95 (1H, d, $\underline{J}$ = 2Hz), 7.1 (1H, dd, $\underline{J}$ = 9Hz, $\underline{J}$ = 2Hz), 8.05 (1H, d, $\underline{J}$ = 9Hz), 8.1 (1H, S). Found: C, 64.7; H, 5.4 $C_{11}H_{11}NO_3$ requires: C, 64.4; 5.4%).

1-(N-Methylacetamido)-3-(1-Methoxyethyl) pyridinium iodide (53)

3-(1-Methoxyethyl) pyridine (20 g) was cooled in an ice bath and then dissolved in dichloromethane (45 cm^3) at 0°C. O-Mesitylene sulphonyl hydroxlamine (29 g) was dissolved in dichloromethane (90 cm^3) and cooled to 0°C. The two solutions were quickly mixed and stirred for 30 minutes in an ice bath. This mixture was then poured onto ice and ether (500 cm^3) and then stirred for a further 90 minutes, during which time an oil separated. The ether was decanted and evaporated to give more oil which was added to the first product, this was then dissolved in cooled water (60 cm^3) and acetic anhydride (150 cm^3) chilled to

below 5°C was added. The solution was left stirring for 15 minutes. Then a solution of 50% sodium carbonate was added dropwise until the solution was just basic (cooling required). The solution was extracted with chloroform and the extracts dried before evaporation to give a brown oil to which was quickly added methyl iodide (160 cm^3) and the mixture was refluxed for 45 minutes. The mixture was then concentrated to about 20 cm^3, and left in a refridgerator to yield yellow crystals of the title compound (3.0 g, 6%);
δ(DMSO) 1.55 (3H, d, J = 6Hz, $\underline{CH_3}$-CH-), 2.3 (3H, bS, CH_3CO), 3.3 (3H, S, N-CH_3), 3.8 (3H, S, OCH_3), 4.74 (1H, q , J = 6Hz, $\underline{CH}$-CH_3), 8.3-8.5 (1H, m, Ar), 8.7-8.9 (1H, m, Ar), 9.2-9.4 (2H, m, Ar).

4-Acetyl-3[1(Methoxy) ethyl] pyridine (52)[43]

The pyridinum iodide from the previous raction (3.0 g) and ammonium chloride (0.87 g) were dissolved in warm water and potassium cyanide (0.715 g) was then added portionwise over 8 minutes. Then the solution was stirred for a further hour. The mixture was then extracted with chloroform and the combined extracts dried over sodium sulphate before evaporation to give a brown oil, which was dissolved in ethanol and stirred for one hour under soft U.V. light. After this time the ethanol was removed and the residue partitioned between ether and water; the ether layer was separated and washed three times with water before it was dried over sodium sulphate and evaporated to give a dark brown oil which was dissolved in dry ether (10 cm^3) and added over 30 minutes to a cold (-5°C) solution of methyl lithium.

After this addition the mixture was stirred for one hour before aqueous ammonium chloride was added. The mixture was then extracted with chloroform and the combined extracts dried and evaporated to give an oil which was dispensed in 60% acetic acid (10 cm^3) and stirred for 30 minutes at 5°C. After this the solution was slowly basified (temperature maintained below 5°C) with sodium carbonate and then the solution was extracted with chloroform. The combined dry extracts were evaporated to yield a dark brown viscous oil (0.5 g, 31%); γ_{max} 1700, 1600, 840, 760 cm^{-1}. The spectral characteristics of this material were identified with those of an authentic sample of the title compound previously made and fully characterised in this laboratory.

Attempted Preparation of 8-Methoxy-Ellipticine

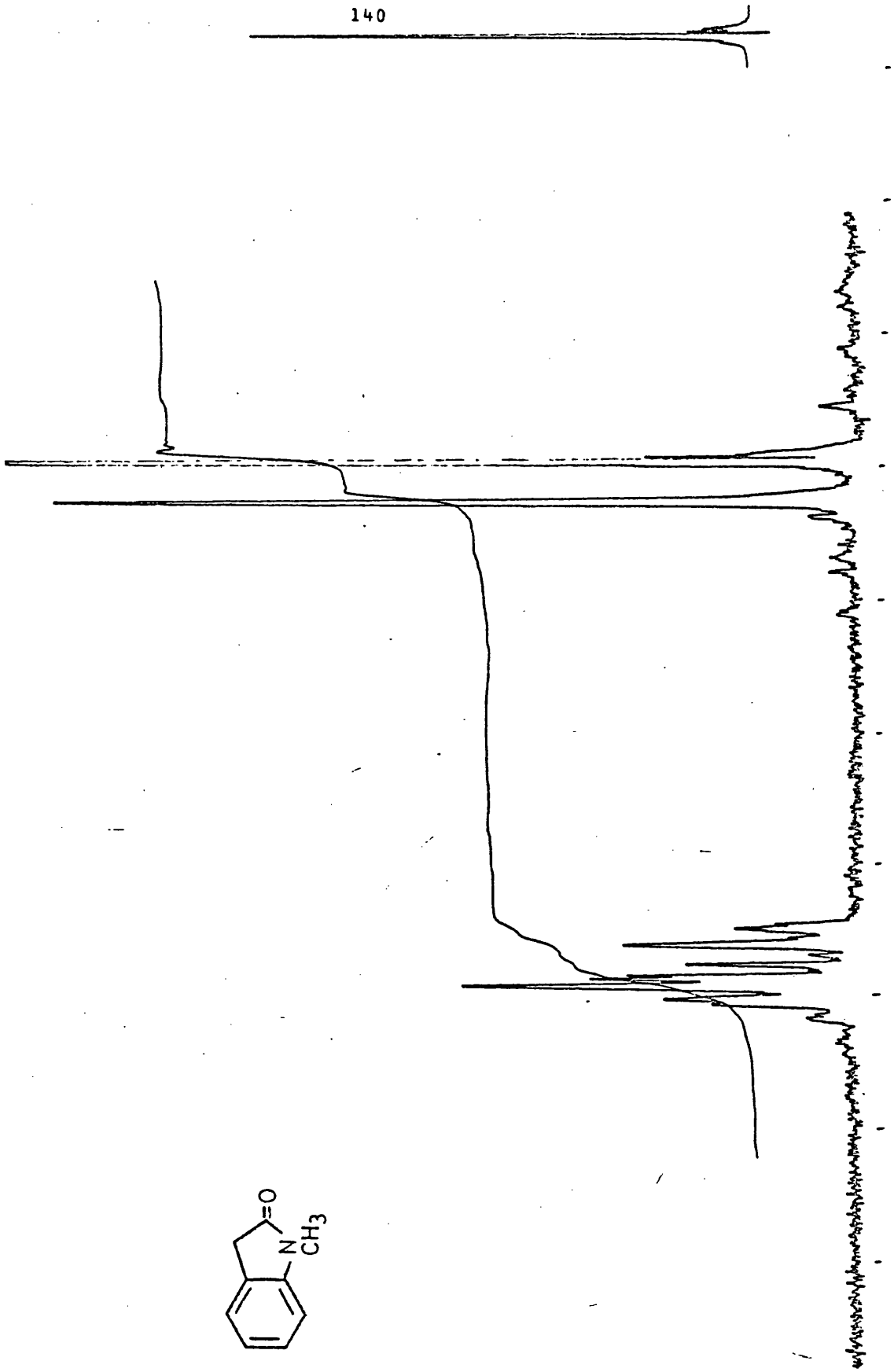
1-Acetyl-3-hydroxy-6-methoxyindole (0.496 g) and 4-acetyl-3[(1-methoxy) ethyl] pyridine (0.5 g) were dissolved in 50% aqueous methanol (10 cm^3) and the mixture was degassed by bubbling in nitrogen for 4 h, before potassium hydroxide (1.6 g) was added slowly over 15 minutes, during which time the temperature was kept below 5°C. After the addition the reaction vessel was left for two weeks but, during this time no crystals had formed (normally in similar condensations the product separates out). The mixture was then extracted with chloroform and the dried extracts evaporated to yield a red oil which was dissolved in aqueous ethanol (10 cm^3) and treated with sodium borohydride (0.5 g). The mixture was left for 4 h, during this time the colour of the solution slowly disappeared.

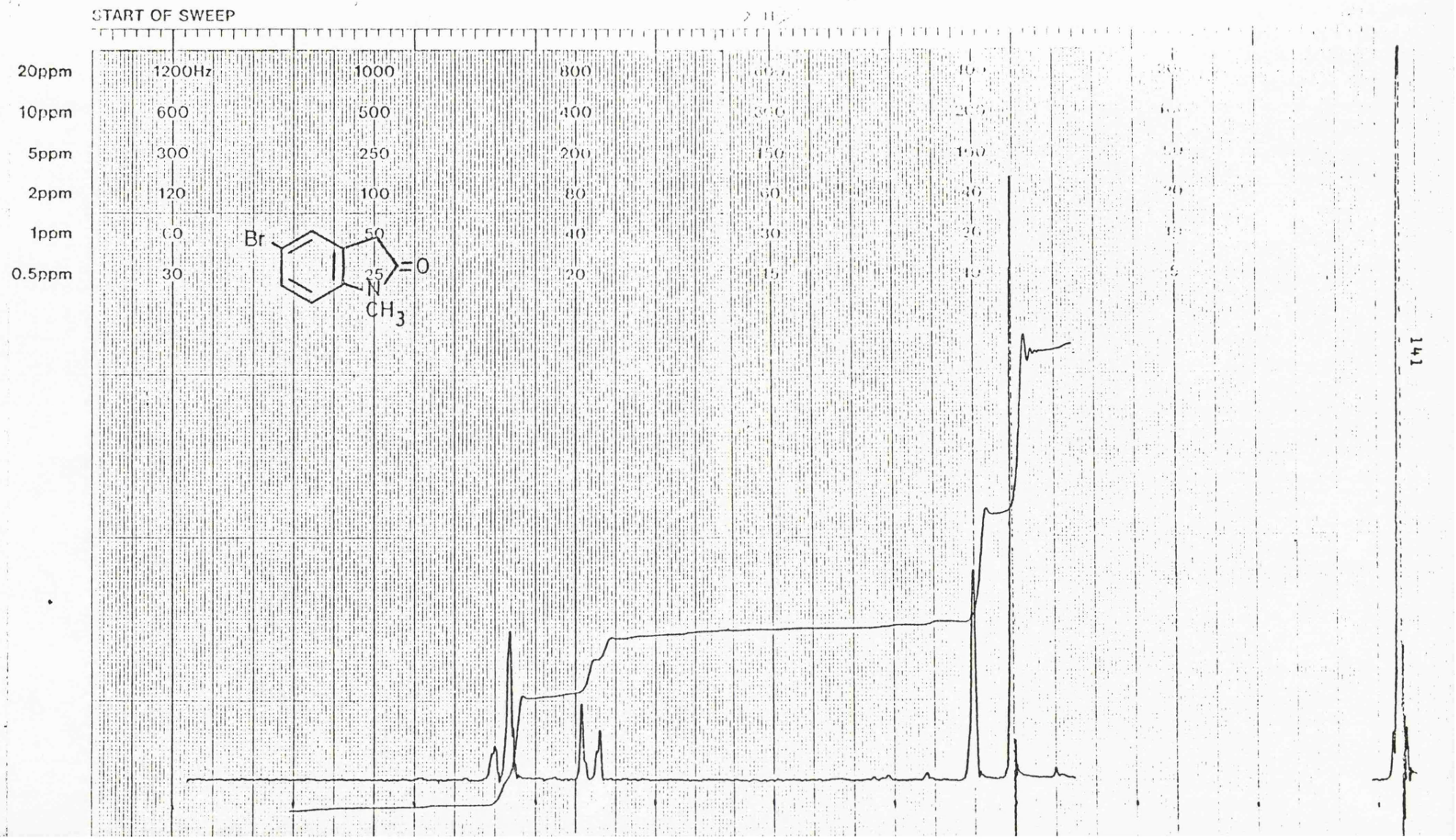
The solvent was then evaporated in vacuum and the product was extracted with chloroform. Dry hydrogen chloride gas was then bubbled through the dried extracts to give a yellow oil. This oil was then basified with 2N sodium hydroxide and extracted with chloroform. The combined extracts were dried over sodium sulphate before the solvent was evaporated to yield another yellow oil, $m/_e$ 310. This oil was divided into three parts and these were treated as follows:

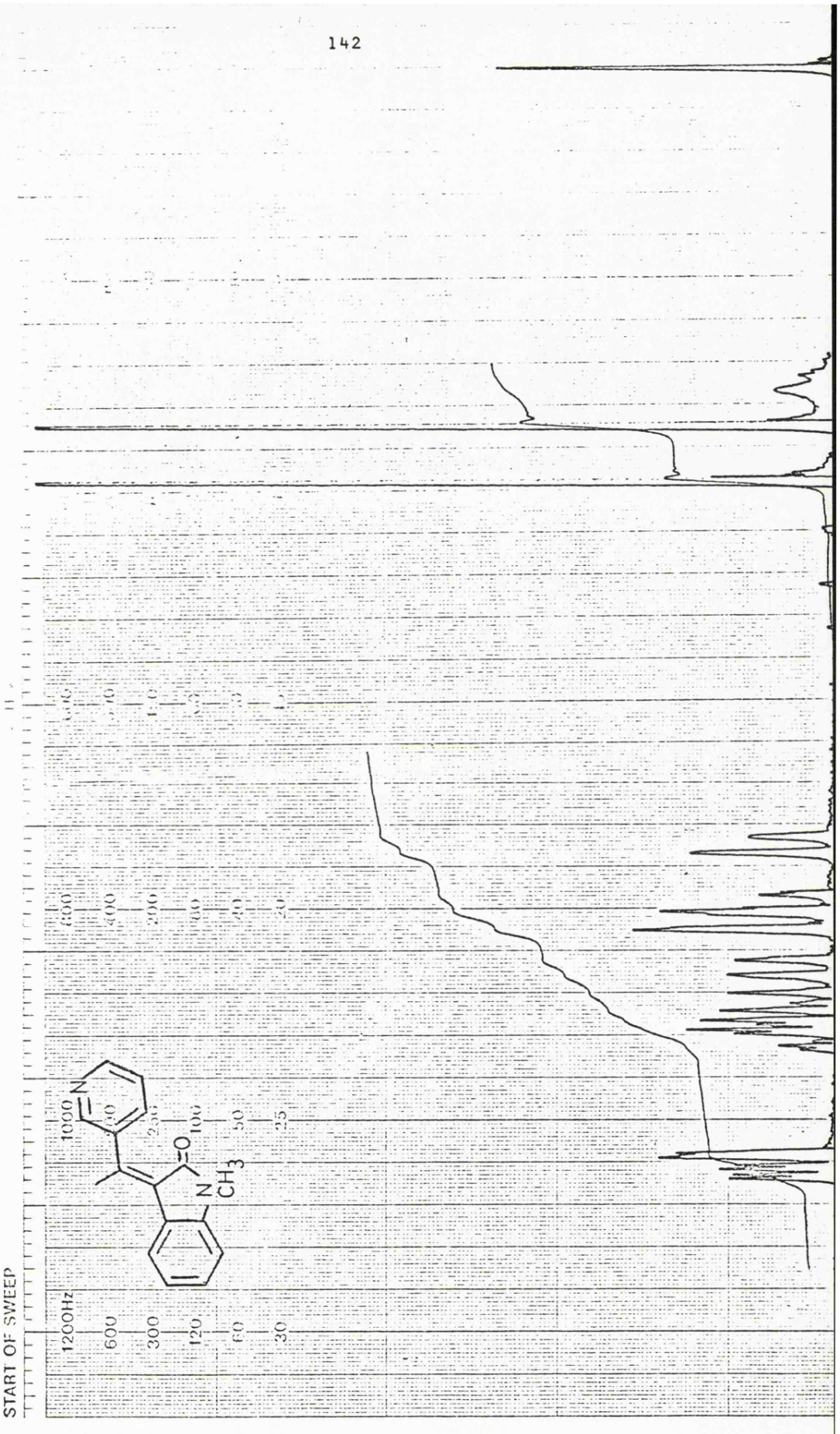
In the first case the oil was dissolved in many different solvents and left for some time in a refrigerator but no crystals were obtained.

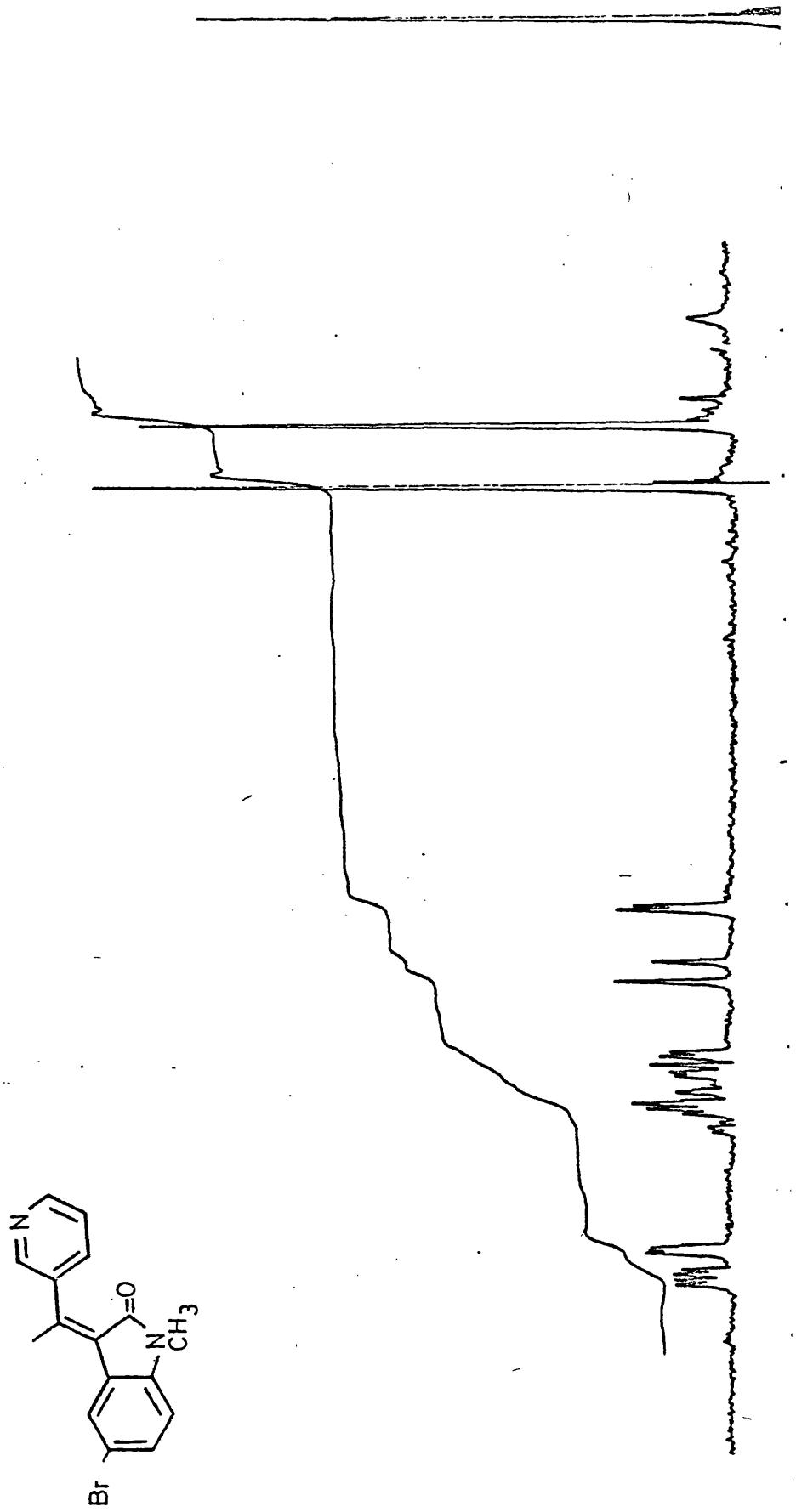
In the second attempt at purification the material was chromatographed on silica. However, no single fraction thus obtained yielded crystalline products, all were mixtures.

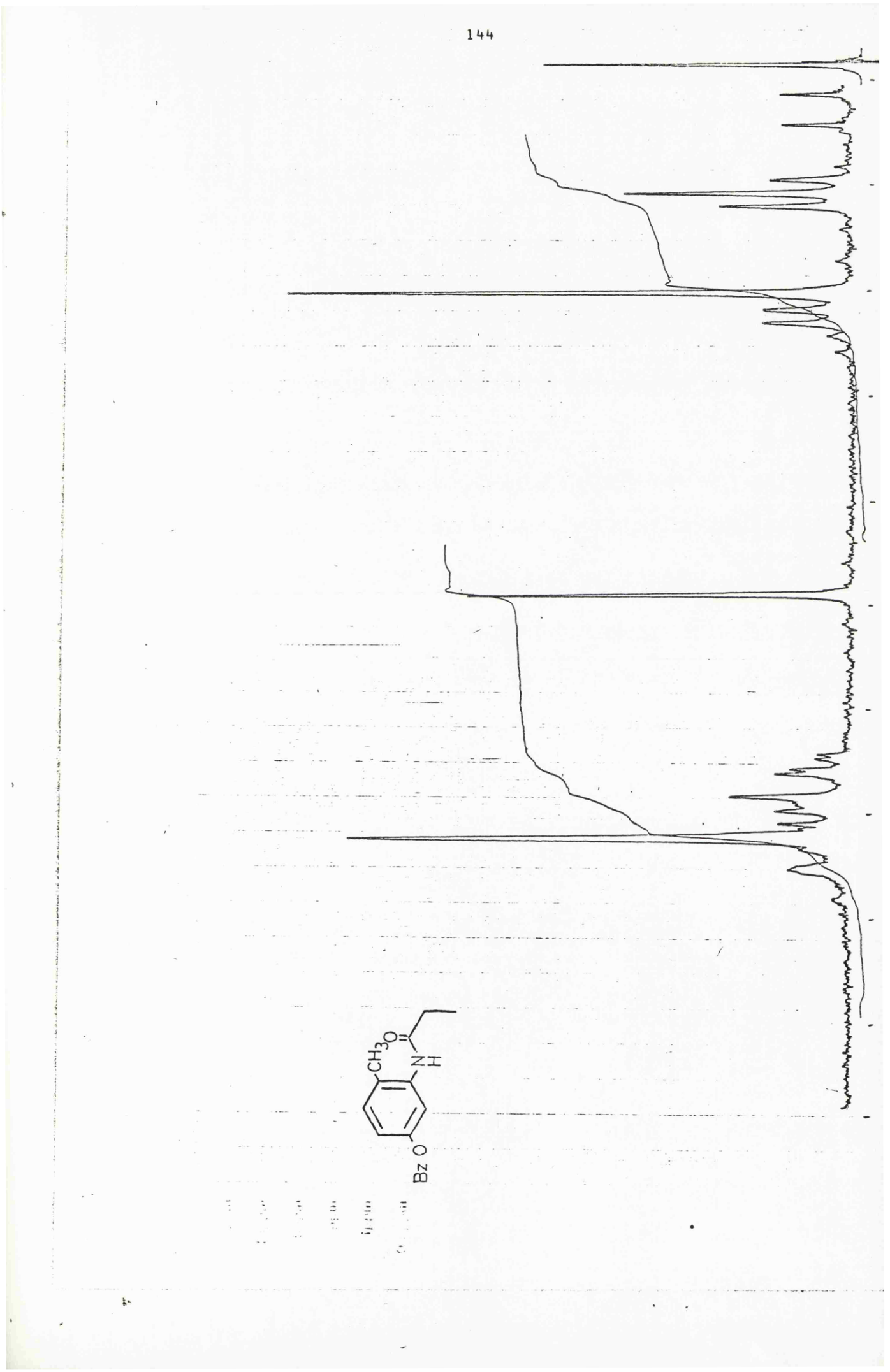
Finally, the third part was heated at 50°C and stirred with aqueous 60% hydrogen bromide for one hour, after which time the mixture was basified and extracted with chloroform. The combined extracts were dried over sodium sulphate before the solvent was evaporated to give a yellow product ($\sim$ 1.0 mg): m.p. $\sim$ 295°C (dec), λ_{max} 282, 295 and 301 n.m; $m/_e$ 262 (M^+), 247 ($M^+ - 15$), 231 ($M^+ - 31$), 201 $[M^+ - (15 + 31)]$.

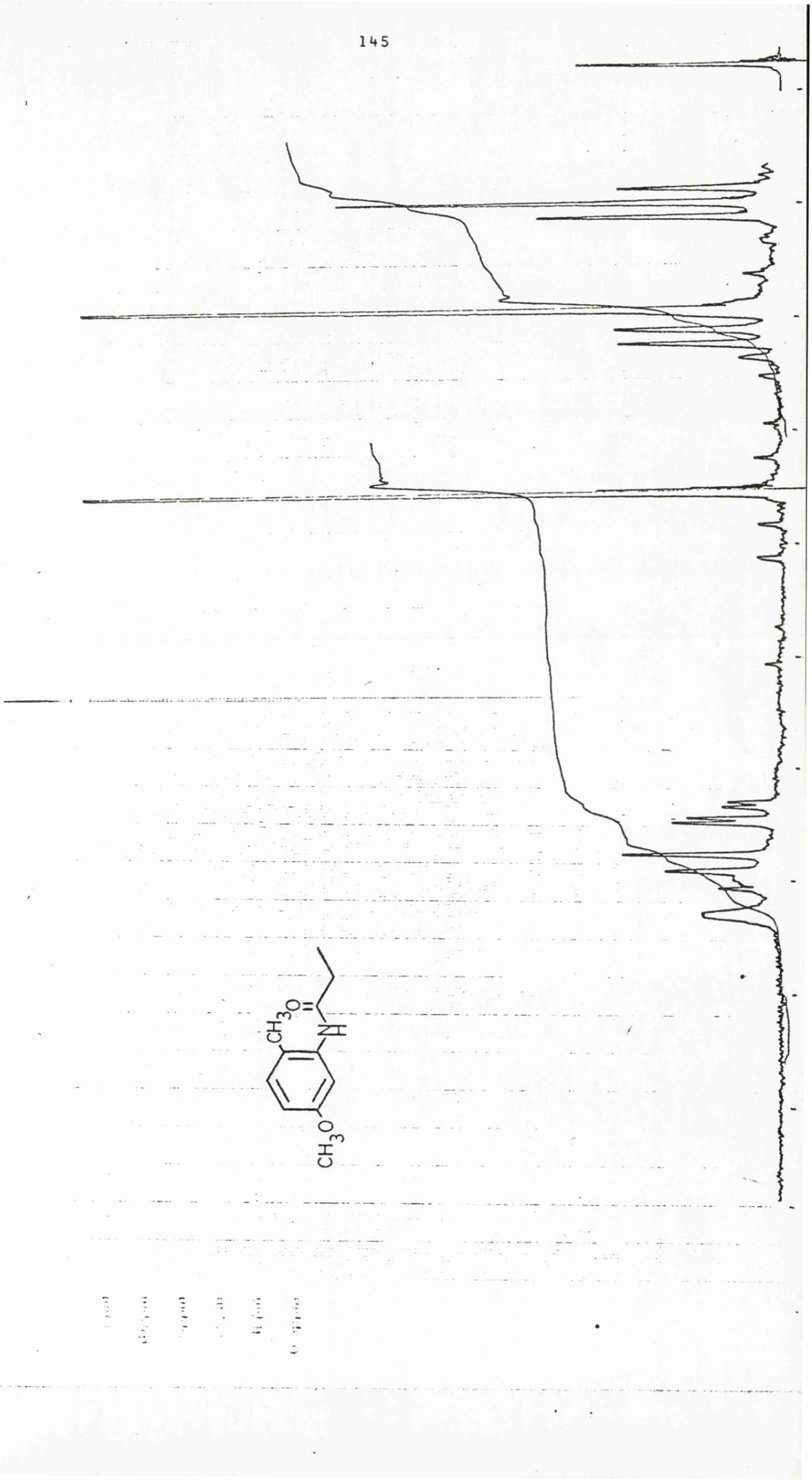

O
N
CH3

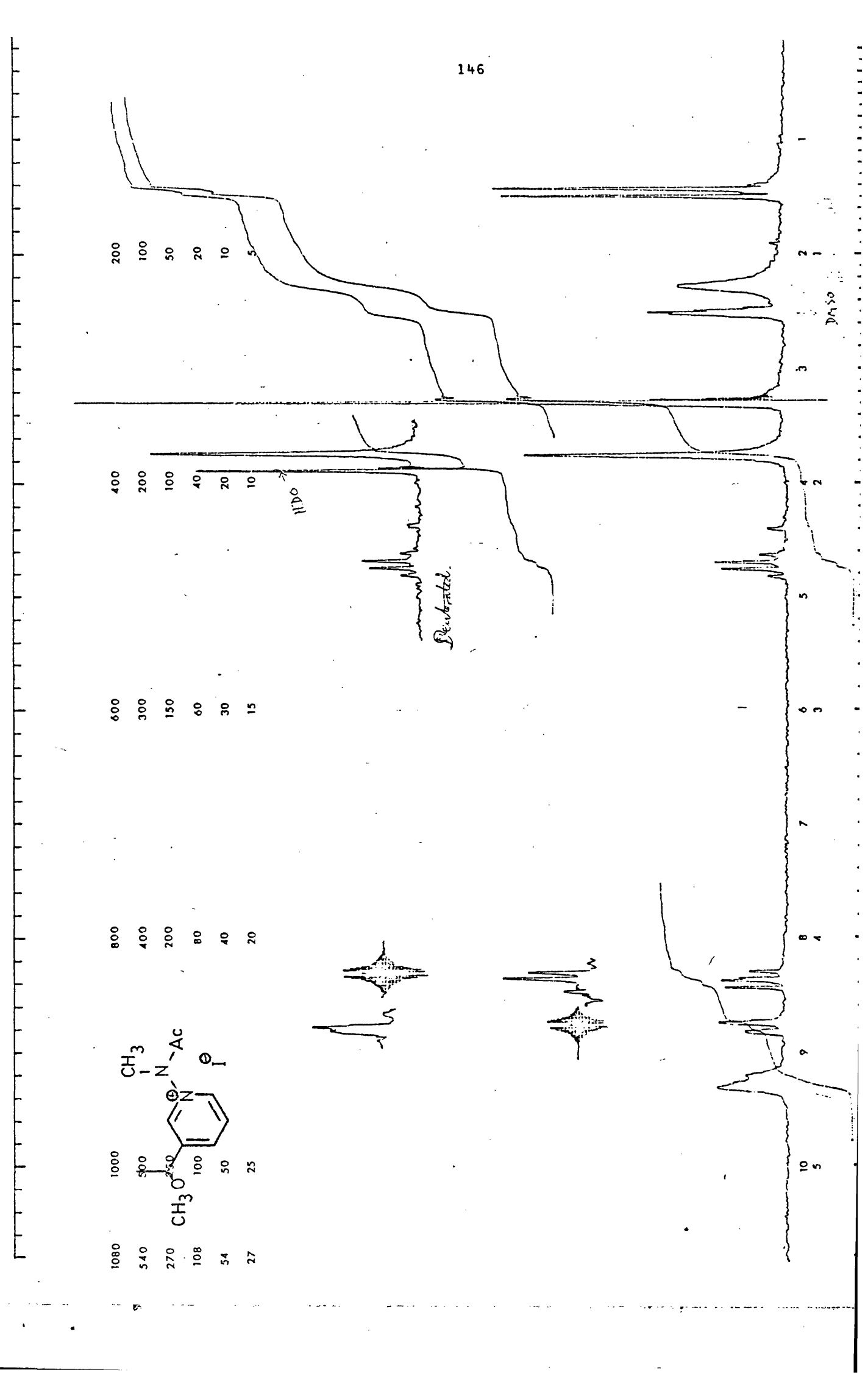

START OF SWEEP
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
1200Hz
600
300
120
60
30
1000
500
250
100
50
25
800
400
200
80
40
20
Br
O
N
CH3
141


START OF SWEEP
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
1200Hz
600
300
120
60
30
800
400
200
100
50
25
N
O
N
CH3


N
O
N
CH3
Br


CH3
O
N
H
Bz O


CH3O
O
N
H
CH3O


CH3
N-Ac
CH3O
I
Reduced.
DMSO

REFERENCES TO PART THREE

1. NCI 1973 Fact Book, US Dept. of Health, Education and Welfare, Washington, DC; '75 Cancer Facts and Figures; American Cancer Society, NY, 1975.

2. SELAWRY, O.S. *Cancer Chemotherapy Reports*, Part 3, 1973, 4 (2), 5.

3. ROSENBERG, J.M, SEEMAN, N.C., KIM, J.P., SUDDATH, F.L., NICHOLAS, H.B. and RICH, A. *Nature*, 1973, 243, 150.

4. GILBERT, M. and GLAVERIE, P. (1968). *Molecular Associations in Biology*, (ed. Pullman, B.),(Academic Press, NY), 245.

5. GILBERT, B. *The Alkaloids* (ed. R.H.F. Manske), 1965, 8, 477.

6. SVOBODA, G.H., POORE, G.A. and MONTFORT, M.L. *J. Pharm. Sci.*, 1968, 57, 1720.

   LE MEN, J., HAYAT, M., MATHE, G., GUILLON, J.C., CHENU, E., HUMBOLT, M. and MASSON, Y. *European Clinical and Biol. Res.*, 1970, 15, 534.

7. WOODWARD, R.B., JACOBUCCI, G.A. and HOCHSTEIN, F.A. *J. Amer. Chem. Soc.*, 1959, 81, 4434.

8. CRANWELL, P.A. and SAXTON, J.E. *Chem. and Ind.*, 1962, 45.

9. CRANWELL, P.A. and SAXTON, J.E. *J. Chem. Soc.*, 1962, 3482.

10. GOVINDACHARI, T.R., RAJAPPA, S. and SUDARSANAM, V. *Indian J. Chem.*, 1963, 1, 247.

11. STILLWELL, R.N. *Dissertation Abstracts*, 1964, 64-11, 563.

12. DALTON, L.K., DEMERAC, S., ELMES, B.C., LODER, J.W., SWAN, J.M. and TEITEI, T. *Aust. J. Chem.*, 1967, 20, 2715.

13. SCHINAZI, R.F. *Ph.D. Thesis, University of Bath*, 1975.

14. WANDER, A. *Swiss Patent* 386,023 (C.I.C07d), (1966).

15. KILMINSTER, K.N. and SAINSBURY, M. *J. Chem. Soc., Perkin I.*, 1972, 2264.

16. LE GOFFIC, F., GOUYETTE, A. and AHOND, A. *Tetrahedron*, 1973, 29, 3357; *C.R. Acad. Sc.* (Paris), 1972, 274C, 2008.

17. LANGLOIS, Y., LANGLOIS, N. and POTIER, P. *Tetrahedron Letters*, 1975, 11, 955.

18. FJUIWARA, A.N., ACTON, E.M. and GOODMAN, L. *J. Med. Chem.*, 1967, 10 (1), 126.

19. KATNEY, J.P. and GRIESON, D. *Heterocycles*, 1975, 3 (2), 171.

20. WINCHESTER, M. and POPP, F.D. *J. Heterocyclic Chem.*, 1975, 12 (3), 547.

21. KAMETANI, T., SUZUKI, T., TAKAHASHI, T. and FUKUMOTO, K. *Heterocycles*, 1974, 2, 9.

22. KAMETANI, T., SUZUKI, T., KAKAHASHI, T., ICHIKAWA, Y. and FUKUMOTO, K. *J. Chem. Soc. Perkin I.*, 1975, 5, 413.

23. KAMETANI, T., ICHIKAWA, Y., SUZUKI, T. and FUKUMOTO, K. *Heterocycles*, 1975, 5 (3), 401.

24. SAINSBURY, M. *Synthesis*, 1977, 7, 437 and refs. cited therein.

25. SAINSBURY, M. and SCHINAZI, R.F. *Chem. Comm.*, 1975, 540.

26. KOZIKOWSKI, A.P. and HASA, N.M. *J. Org. Chem.*, 1977, 42, 2039.

27. BERGMAN, J. and CARLSSON, R. *Tetrahedron Letters*, 1977, 52, 4663.

28. BERGMAN, J. and CARLSSON, R. *J. Het. Chem.*, 1972, 9, 833.

29. KILMINSTER, K.N. and SAINSBURY, M. *J. Chem. Soc. Perkin I.*, 1972, 2264.

30. JULIAN, P.L. and PRINTY, H.C. *J. Amer. Chem. Soc.*, 1949, 71, 3206.

31. JULIAN, P.L. and MAGNANI, A. *J. Amer. Chem. Soc.*, 1949, 71, 3207.

33. COOK, J.W., GAILEY, R.M. and LOUDON, J.D. *J. Chem. Soc.*, 1954, 568.

34. PIETRA, S. and TACCONI, G. *Gazz. Chim. Ital.*, 1959, 89, 2304.

35. BLAIKIE, K.G. and PERKIN, W.H. *J. Chem. Soc.*, 1924, 125, 296.

36. KERMAK, W.O., PERKIN, W.H. and ROBINSON, R. *J. Chem. Soc.*, 1921, 119, 1602.

37. WIBAUT, J.P. and ARENS, J.F. *Rec. Trav. Chim.*, 1941, 60, 119.

38. WEBB, B. *Ph.D. Thesis, University of Bath,* 1972.

39. BECKETT, A.H., DAISLEY, R.W. and WALKER, J. *Tetrahedron,* 1968, **24**, 6093.

40. BROWN, H.C. and SUBBA RAO, B.C. *This Journal,* 1959, **81**, 6428.

41. COPISAROW, M. *J. Chem. Soc.,* 1929, 251.

42. Handbook of Chemistry and Physics, 56th Edition, 1975-1976, CRC Press.

43. DOLMAN, D. *M.Sc. Thesis, University of Bath,* 1978.