Synthetic strategies for the application of anodic coupling to the pursuit of analgetic compounds

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SYNTHETIC STRATEGIES FOR THE APPLICATION OF ANODIC COUPLING TO THE PURSUIT OF ANALGETIC COMPOUNDS.

Submitted by Christopher Devenport
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Ibergekumene tsores iz
gut tsu dertseylin.
("Troubles overcome
are good to tell.")

Yiddish proverb.

...for Dad.

ACKNOWLEDGEMENTS.

I would like to thank my supervisor Dr. Malcolm Sainsbury for his advice and encouragement, both during the course of this research and afterwards. I must also thank Professor Malcolm Campbell and the staff at the University of Bath, for their enthusiasm and invaluable suggestions. Many thanks to Dr. Tim Gallagher for his interest and other assistance, and to Dr. Dick Kinsman for his sense of humour and frequent help. I am very grateful to Dr. Dennis Edwards for his patient explanations of inorganic bismuth.

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CONTENTS.

SUMMARY.

The work discussed in this thesis derives from an interest in applying electro-oxidative reactions to the synthesis of potentially analgetic materials.

The investigation was directed towards unnatural analogues in the morphinoid and serotoninoid series, *via* syntheses of two compounds as precursors to electrochemistry. These were 7-hydroxy-4-(2-methoxyphenyloxy)-1,2,3,4-tetrahydroisoquinoline, and 3-(*N*-3,4-dimethoxybenzyl)amino-1,2,3,4-tetrahydro-carbazole.

The synthetic route directed towards syntheseis of the former target compound involved two key steps:

One of these was formation of the diaryl ether bond, which was tackled using triarylbismuth diacetate reagents. This reaction was found to be applicable for 3-methoxyphenylation of phenols, and an investigation of this chemistry is described in Chapter 3.

The first approach to the other key step was ring-closure of an acetal onto the aromatic ring in order to form the 4-4a bond of the precursor. An apparently well-favoured reaction, it was shown to be unsuccessful in this specific case.

The second approach involved formation of the tetrahydropyridyl ring *via* a Bischler-Napieralski reaction. This synthesis could not be completed, but its success seemed probable.

Synthesis of the second target compound was found to be straightforward. The compound's behaviour under conditions of electro-oxidation was investigated. The compound proved to be highly reactive, and there was no sign of the desired cyclisation. It was concluded that such a technique was unlikely to be useful in this synthetic series.

CHAPTER 1.

1. GENERAL INTRODUCTION.

1·1. The demand for analgetics.

Pain is probably the only affliction which is practically universal. Thus the desire to remedy it has persisted from time immemorial. Such "cures" traditionally arose from botanical sources. Folk-lore developed from the use of fresh leaves, to ground and dried leaves or roots, and to infusions made therefrom.

1·1·1. Historical perspective.

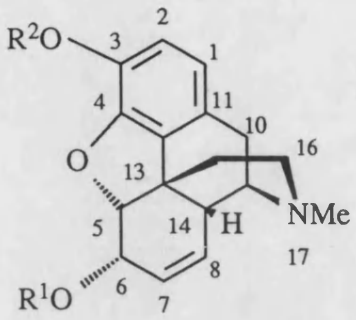
The best known crude natural substance, used to dull pain, is almost certainly opium. This is a latex from the seed-heads of the poppy *Papaver somniferum.*[1a] There are references[2,3a] to opium as early as 300 B.C. Its very long history includes use as a hallucinogenic drug of abuse, and as a medical anaesthetic. Both uses were frequently hazardous; one side-effect of opium is respiratory inhibition. Even legitimate medical use could kill, due to unpredictable biological response.[3a]

1·1·2. Focus on morphine.

This situation was altered with the announcement,[4] by Sertürner in 1806, of the separation of an active component of opium; the alkaloid morphine (**1**). Its use lead to more predictable results, and morphine may be considered the first true drug.

Other alkaloids are present in opium, but of these only codeine (**2**) and papaverine (**3**) are usually considered clinically important.[3b] The opiate heroin (**4**) is an infamous drug of abuse, but it is used, particularly in Europe, to treat terminally ill patients in extreme pain. Opiates form a sub-class of the alkaloid natural products.

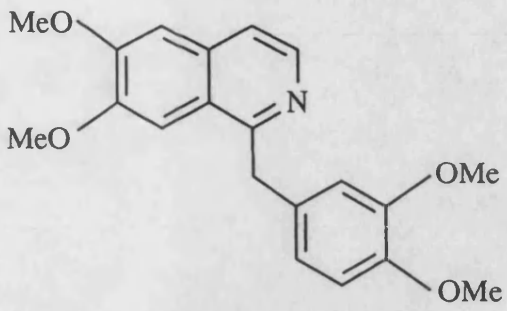
More than 2500 alkaloids have been extracted from a wide variety of



(1) $R^1 = R^2 = H$

(2) $R^1 = H, R^2 = Me$

(4) $R^1 = R^2 = COMe$



(3)

plants. Precise definition of this group is difficult, due to the great diversity of chemical structures involved. The principal common feature is a historical one; being "alkali-like" - but all contain a nitrogen-functional group, usually a cyclic amine unit.[1b] Furthermore, all these compounds appear to be secondary metabolites of natural amino acids. Many alkaloids have considerable biological importance. In the context of this thesis, however, it is feasible to consider only the opiate morphine in depth.

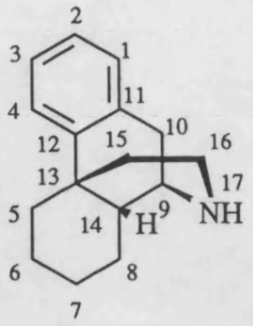
Morphine is still in widespread clinical use, despite methodology for analogue synthesis (see for example, Rapoport and co-workers).[5] Clearly, no synthetic drug is yet wholly superior. Thus, morphine remains an attractive candidate for synthetic drug design; the principal objective of this research.

1·2. Nomenclature.

The major classes of compounds encountered in this thesis are: morphinoids and isoquinoline alkaloids, the related 1,2,3,4-tetrahydroisoquinolines, and also 1,2,3,4-tetrahydrocarbazoles. The naming and numbering conventions for these are now described.

1·2·1. Morphinoids.

The *Chemical Abstracts* system for naming morphine is based on the parent compound, morphinan (**5**). Thus, this system of nomenclature names



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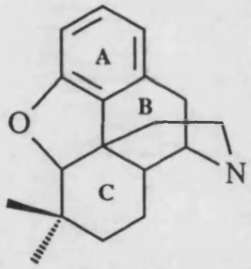


β = above plane of ring

α = below plane of ring

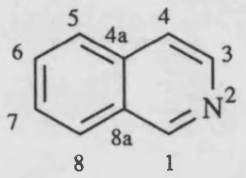
(6)

morphine as 7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol. When labelling the rings of morphine, there are several systems in use. The most obvious is to designate the rings as A-E. Unfortunately, there does not appear to be any agreement as to which ring bears which letter. Thus, an alternative system was introduced by Rapoport and co-workers.[5] The three rings belonging to the octahydrophenanthrene unit in the morphine skeleton (**6**) were labelled A-C. The furan ring was assigned O (for Oxygen ring), and the piperidine ring described as

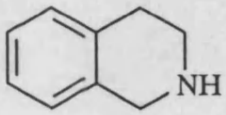
N (Nitrogen). The α-substituents are below the plane of the ring, and β- denotes groups above it.

1·2·2. Isoquinolines.

Papaverine (**3**) is an isoquinoline alkaloid; to emphasise that aspect of its structure, morphine may be regarded as a 1,2,3,4-tetrahydroisoquinoline. For this series of compounds, straightforward IUPAC nomenclature has been adopted.[6] The parent heterocycle, isoquinoline (**7**), is an isomer of quinoline (which has its nitrogen atom at position-1). Saturation is listed by numbers of the relevant carbon atoms, as usual. Derivatives of 1,2,3,4-tetrahydroisoquinoline (**8**) were synthesised during the course of this research.



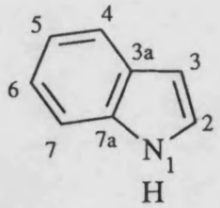
(**7**)



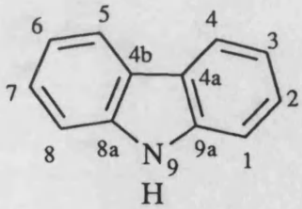
(**8**)

1·2·3. Indoles and carbazoles.

Once again, the IUPAC system is used. The conventions for numbering indole (**9**) and carbazole (**10**) are shown.



(**9**)



(**10**)

1·3. Significant aspects of pain perception.

To design an effective pain-killer, it is helpful to know something of the nature of pain transmission. Unfortunately, this very complex mechanism is still poorly understood. One problem is the definition of pain. Winter[7a] indicates some of the difficulties.

In the body, numerous peripheral receptors, or nerve endings, respond to painful stimuli. When activated, these trigger impulses to the brain and provoke a response. This view is termed the "stimulus-response" concept. It is generally agreed to essential in any definition of pain, the purpose of which appears to be protective - to prevent body tissue damage. However, that idea is controversial;[3c] one effect of severe pain can be stomach and large bowel dysfunction. It is difficult to see the protective role of this.

One component of pain perception is *learned* at an early age. Puppies reared in isolation from normal sensations, who cannot hurt themselves, show no response to painful stimuli. Unlike their normal litter-mates, they do not learn to avoid causes of pain. As an example, they repeatedly sniff at a flame, and make no attempt to withdraw if burnt.[7a]

Another aspect of pain has a psychological nature. Winter[7a] indicates responsive differences between an athlete, or soldier in battle, and a post-operative patient. The former may not perceive severe injuries as painful. However a patient awakening from anaesthesia, with similar tissue damage, often feels pain keenly.

A further problem, for pain classification, is the transition point between a pleasant sensation and a painful one. Peripheral pain receptors may differ from the others. Sensory nerve endings tend to be attenuated to one stimulus; *e.g.*, light on the retina, or pressure at the skin of the finger-tips. An appropriate activation is known as the "adequate stimulus". Sense receptors tend to be highly sensitive; low pressure on finger-tips classes as touch, but does not register pain.

Conversely, pain receptors appear to respond to *all* normal sensory inputs, but only at very high levels. This point of transition, or "pain threshold", has been shown[3c] to occur when tissue is damaged. That may be regarded as the adequate stimulus for a pain receptor. Therefore, peripheral pain sensors were named "nociceptors"[3c] by Sherrington in 1906. (The Middle English word "nocent", means "that which is injurious or hurtful"). The term "nociception" is widely used in modern studies of analgesia, to indicate severe pain.

In tests with human volunteers, pain thresholds and psychological states may be asked directly. Most such research concerns the analgetic effects of drugs. However, clinical studies are only carried out with established analgetics, or experimental compounds with proven low toxicity and mild side-effects. Neither is known for novel potential analgetics. Therefore, animal pharmacology must first be performed to assess activity and toxicity, as well as biological profiles.

All these factors complicate the assessment of analgesia using animals. Two major test parameters are biological activity and toxicity. The former is more problematical; it is no longer possible to determine the "volunteer's" pain by questioning. One cannot even be certain the animal feels pain; vocal discomfort may equally indicate fear of the experimental environment.

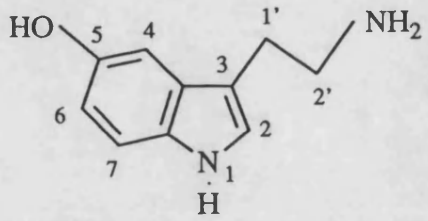
Thermal stimulation is employed in perhaps the most widely used animal test.[7b] The "tail-twitch" method is one example. The tail of an animal (often a rat) is placed on a hot-plate, and the time before it is removed measured. A temperature just above the pain threshold is chosen; a response cut-off is generally imposed, to avoid tissue-damage. This is an important feature of good tests, so repetition of a stimulus leads to similar response. A dose of the test-substance is given, and the stimulus repeated. Differences in response time, and stimulus intensity needed to provoke it, are noted. Even so, this test is not ideal, largely because precise details vary between laboratories.

Toxicity is determined by LD_{50}, the median dose required to kill a batch of test animals. This toxicity standard is chosen to reflect the wide variety of reactions to a single dose. Such an effect is seen between individuals; both human and animal. A good drug must have a high LD_{50}, ideally many times the required therapeutic dose. These aspects of drugs testing will not be considered further.

1·4. Consideration of the pain mechanism.

1·4·1. Pain transmission.

Pain is invoked by stimulation of a fine network of nerve-endings at the affected site. A variety of substances appear to trigger these chemically. Many chemicals have been shown to induce this response, whether naturally present or artificially introduced. Build-up of hydrogen ions, leakage of potassium from cells, or injection of concentrated salt solutions, all cause pain.[7c,8a] So do substances released following cell damage; such as peptides (*e.g.*, bradykinin) and amines like histamine and serotonin (**11**).[7c] The last, properly 5-hydroxytryptamine or 5-HT, is of interest in this research. It is considered in section **1·4·4**.



(11)

Pain impulses are transmitted electrically along various types of nerve fibres, and processed at the brain. This is thought to involve endogenous chemical mediators at a receptor in the brain; which analgetics seem to disrupt.[8a] It has also been shown that painful stimuli are transmitted along the same nerve

fibres used for sensory signals. This is taken to show that discrimination between pain and, say, touch, may rely on central decoding of *patterns* of signals.[8a]

As with most facets of pain, this process is very complex and not well understood. Its treatment here is brief, since biochemistry of most relevance to narcotic analgetics is that of the central nervous system (CNS) within the brain. Grollman and Grollman[8a] comment;

> "The narcotic analgesics, *e.g.*, morphine, relieve pain primarily by acting centrally, while the non-narcotic analgesics, *e.g.*, aspirin, block pain receptors at the periphery. This difference in site of action is not, however, an absolute one, since relaxation of smooth muscle may contribute to the pain-relieving action of morphine; while the central action of aspirin, reflected in its anti-pyretic effect, may contribute to the analgesic action of this drug."

Many biological functions have a distinct area of the brain associated with them. For example the optic centre controls vision; if it is destroyed blindness results, but no other functions are impaired. However, there does not seem to be any specific pain centre,[7d] and details of brain structure and function are beyond the scope of this introduction. Thus, only receptors involved in opiate analgesia will be considered.

1·4·2. Pharmacological effects of morphine.

Morphine causes many responses. It is taken up in most areas of the brain, and affects aspects of mood, psychology, and metabolism, as well as pain. Various texts[3d,8b] detail narcotic pharmacology, but salient points are noted. Analgesia may be regarded as the major pharmacological effect of morphine.

Ideas on its analgetic mode of action will be considered in **1·4·3.**

Morphine is not an ideal analgetic,[8a] exhibiting many undesirable side-effects. Regarded as most serious are tolerance and physical dependence. They are usually considered together, but are different phenomena which need not be related.[7e] All narcotic analgetics, natural and synthetic, exhibit both effects to some degree.

Tolerance, which is a gradual reduction of the analgetic effect (amongst others) obtained from a given dose, may result from medium or long-term use. Increased doses are then required. It is a spiralling process, and the tolerant individual can assimilate an otherwise fatal dose. Dependence is the adverse physical response to rapid withdrawal of a drug. It may result in elevation of body temperature and blood pressure, may cause cramps, etc., and can be life-threatening.

These need not be problems in legitimate medical use; they are not serious for gradually decreased doses. However, physical dependence affects narcotic drug abusers, leading to the possibility of addiction. This is also not easy to define. It tends to involve habitual use of a drug, and craving for its euphoric effects. It can be shown in humans and animals alike. One aim, in designing a synthetic analgetic, is to reduce these effects together with enhancing desirable activity.

As has been mentioned, morphine has an excitatory euphoric effect. Paradoxically, the dominant effect is depressive.[3d] Some excitatory effect may be ascribed to depression of the brain's inhibitory centres. More seriously, respiration is also affected. Morphine can cause sedative, hypnotic, and anesthetic effects, and constipation; it can also affect the heart, blood pressure, ocular reflexes, and digestive system.

1·4·3. Action of morphine at a receptor site.

Although formation of a drug-receptor complex may not be sufficient for analgesia to occur, it is a prerequisite. The first accepted drug-receptor model involving morphine, was proposed by Beckett and Casy[9] in 1954. Galt has summarised its development.[10]

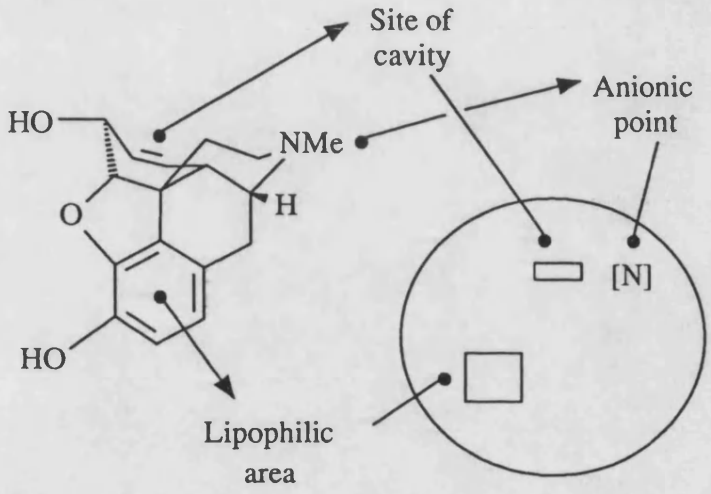
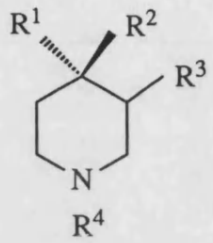


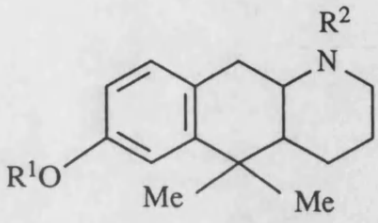
Figure 1.

Beckett and Casy contemplated the rigid structure of the compound. Its known stereochemistry allows speculation about the three-dimensional structure of the receptor. The nature of the latter may not be known, but to interact effectively with morphine, whose structure well established, it must possess certain features. This allowed a partial topography and chemical nature of the receptor site to be developed. It was suggested[9] that three essential features were an anionic site (for interaction with the protonated amine), a flat lipophilic area (to accommodate the phenyl group), and a cavity (which would accept the "T-shaped" stem). This is represented in Figure 1.

Widespread interest in opiate analgesia lead to great expansion in synthesis of unnatural analogues of the compounds. They were tested, using the tail-twitch method amongst others. Results of these tests not only indicated the



(**12**) R^1 = Ph, R^2 = O_2CEt
R^3 = Me or Hal, R^4 = Me



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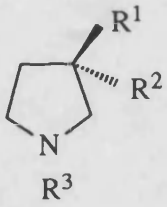
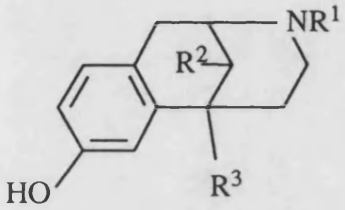
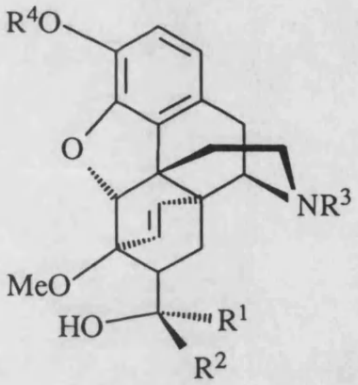


(**14**) R^1 = *m*-HOPh, R^2 = ^nPr
R^3 = Me



(**15**)



(**16**) R^1 = R^3= R^4 = Me,
R^2 = $(CH_2)_nMe$

(**17**) R^2 = $(CH_2)_nPh$

compound's suitability as a drug, but, in some cases, threw further light on a receptor's nature. A literature review, from 1966, was performed in 1971 by

Lewis, Bentley and Cowan.[11] They considered various synthetic narcotics; simpler morphine derivatives, including piperidines (**12**), (**13**), pyrrolidines (**14**), benzomorphans (**15**), also oripavines (**16**) and (**17**).

This last category was of particular interest. Compound (**16**) showed activity increasing with n, up to a maximum at C_3-C_4. Increase of analgetic potency for analogue (**17**) was more spectacular; from about 4% of morphine's to around 81,000 times that of morphine, a total rise of activity in excess of five million-fold.

Bentley and co-workers disregarded the idea that this could feasibly be due to concentration differences in the brain. An initial suggestion was that the high activity was due to tertiary hydroxyl binding. However, compounds lacking that hydroxyl group were still found to be highly potent. Lewis, Bentley and Cowan[11] then suggested a modification to the Beckett-Casy model, as shown in Figure 2. They proposed a second lipophilic site which allowed extra drug-receptor interactions for drugs with a correctly placed second phenyl group.

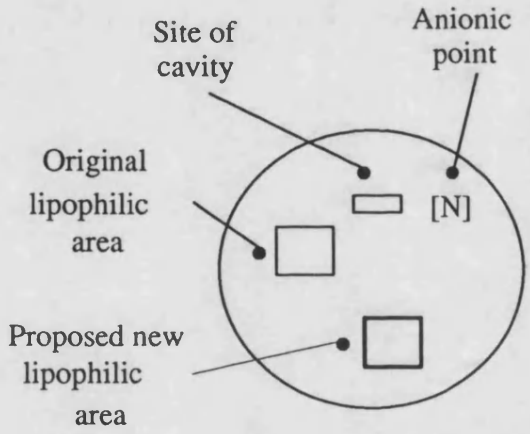
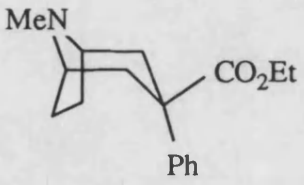


Figure 2.

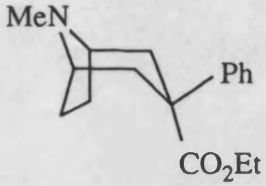
However, Bentley and co-workers noted unexpected differences in a comparison of *cis*- and *trans*-isomers of morphine and morphinan.[11] Further anomalous effects appeared with the investigation of compounds (**18**) and

(**19**).[12,13] These isomers, with the phenyl group axial *and* with it equatorial, proved to be active analgetics. The conformation of the phenyl group was apparently fixed. The significance is an unusual morphine feature; a phenyl group fixed axial to a piperidine ring. Bentley and co-workers' model included this aspect and could not account for the implied relative unimportance of the phenyl group stereochemistry.[10]

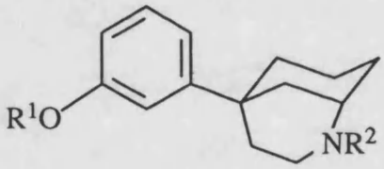
The implication was confirmed when May and co-workers[14] made fused piperidine (**20**), which was to be an active analgetic. Cochran[15] confirmed that the phenyl group was locked in an equatorial position by X-ray diffraction studies. It seemed that a further modification of the receptor site theory was required.



(**18**)



(**19**)



(**20**)

In 1977, Feinberg and co-workers[16] proposed a new receptor theory which explained this anomalous effect and a more serious one. When the morphinoid *N*-methyl group is altered to *N*-allyl, the material may display antagonist activity. An agonist may be defined[17a] as;

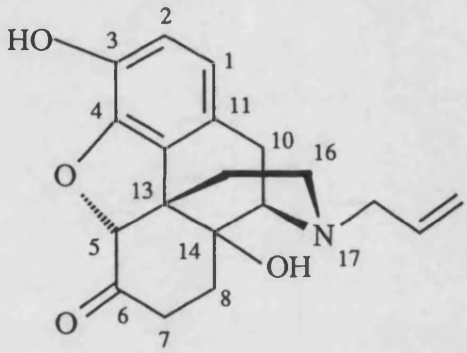
"...[a drug which can] mimic at least some of the effects of

(such) endogenous compounds by interaction with the appropriate physiological receptor;..."

Conversely, antagonists may be defined[17a] as;

"Compounds that are themselves devoid of intrinsic pharmacological activity but cause effects by inhibition of the action of a specific agonist (*e.g.*, by competition for agonist binding sites)...".

Since opiates and their analogues have several biological effects, a given compound may not be an agonist or antagonist for them all. "Pure" morphine antagonists lack analgetic and euphoric actions, but "mixed" antagonists may show both these.[16] An example of a "pure" antagonist is naloxone (**21**). The measure of "purity" for an antagonist seems to be lack of rotation of the *N*-allyl group; hindered by the 14-substituent.



(**21**)

Because antagonists can display analgetic activity, the key distinguishing feature from agonists seems to be mode of binding.[16] Feinberg and co-workers developed their observations into a receptor model, depicted in Figure 3. They

retained Bentley and co-workers' second lipophilic site; for agonistic action. It was labelled the "F" site, due to its interaction with the sixth ring possessed by "super-narcotics" like oripavine (**17**). Additional activity of such compounds, compared to morphine, derives from this extra stabilising feature.

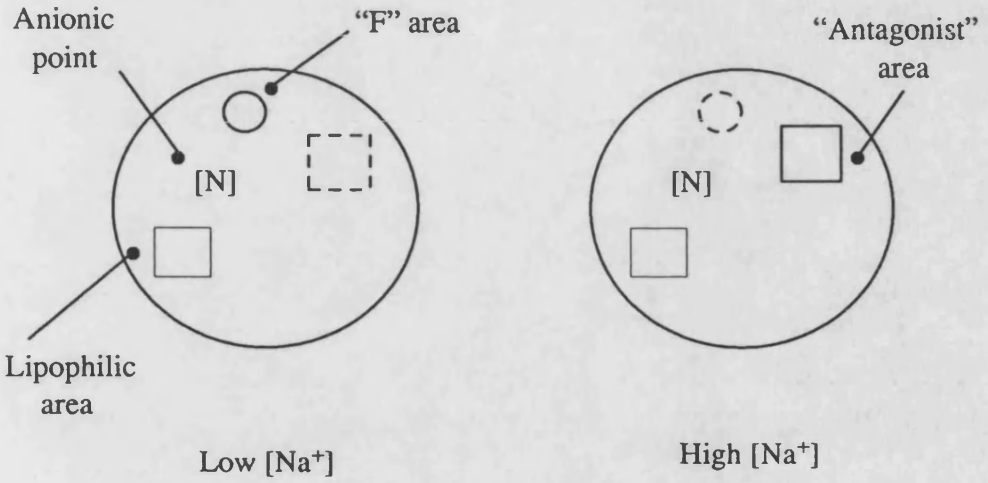


Figure 3.

Certain pharmacological or physiological features, high sodium ion concentration for instance, may trigger a change in receptor conformation.[16] In this form, the "F" site would no longer be available for binding, a new lipophilic "antagonist" site would be, but only for compounds containing a Π-electron-rich *N*-substituent (*e.g.*, allyl or phenyl). Further proposals have been made[10,18] in an attempt to account for anomalies due to enantiomers, however these will not be considered.

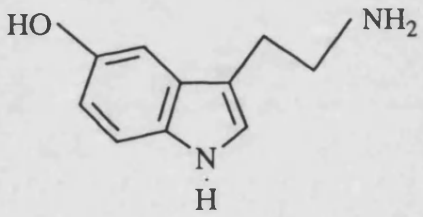
Despite these efforts to explain many features of opiate activity with a single receptor, it has become apparent that there is more than one such receptor. Four major categories of "opiate" receptor have been identified, labelled mu (μ), kappa (κ), delta (δ), and sigma (σ).[17b,c] It would also appear that there may be sub-categories of each. Analgesia has been associated with the μ and κ receptors. (Psychomimetic effects have been ascribed to the σ receptors, whilst δ receptors seem to be involved in behavioural changes. These will also not be considered

further). It also appears that a new receptor site may exist,[19] labelled lambda (λ).

The endogenous ligands for the "opiate" receptors, it has been shown, are the series of endorphin peptides found in the brain.[17b,c,20] Their role is yet to be fully determined. Detailed information about receptor sites requires different animal tests, investigating the degree of binding to the site directly.[19-21]

1·4·4. Possible role of serotonin.

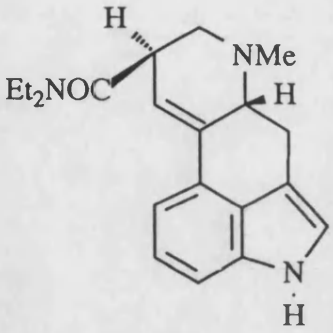
Serotonin (**11**), a potent biogenic amine with a wide range of biological activity,[8c,17d,e] often occurs in nature. A powerful vasoconstrictor, it causes strong contraction of smooth muscle. Its presence has long been inferred, but it was isolated only in 1948 by Rapport and co-workers.[22] The following year, they showed[23] it to be 5-hydroxytryptamine (**11**).



(**11**)

This was synthesised[24] in 1951, triggering an enormous amount of research interest. Twarog, Bailey and Page[25] showed that serotonin was present in the brain a year later. Lysergic acid diethylamide (LSD) (**22**) was shown to block smooth muscle responses to the structurally similar serotonin. [26,27] Also, concentrations of serotonin in the brain were found to be suppressed[28] by the tranquiliser reserpine (**23**). This added to (now confirmed) evidence that serotonin in the brain behaves as a neurotransmitter. As it may be implicated in mental illness,[29] interest in serotonin has heightened.

Much less is known about the mode of action of serotonin, and its



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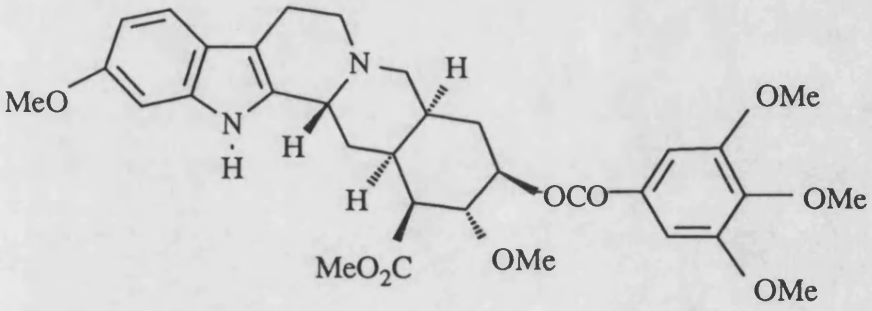
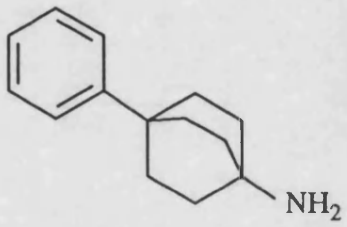


(23)



(24)

receptor site, than for the opiates. It does seem fairly certain that in at least one of its modes of action, serotonin acts at the endorphin receptors.[17d,e] Although serotonin is widely recognised for its role in, for instance, depression,[30] this must provide a case for investigating its analgetic effects.

Compounds of relatively rigid molecular structure are known to block

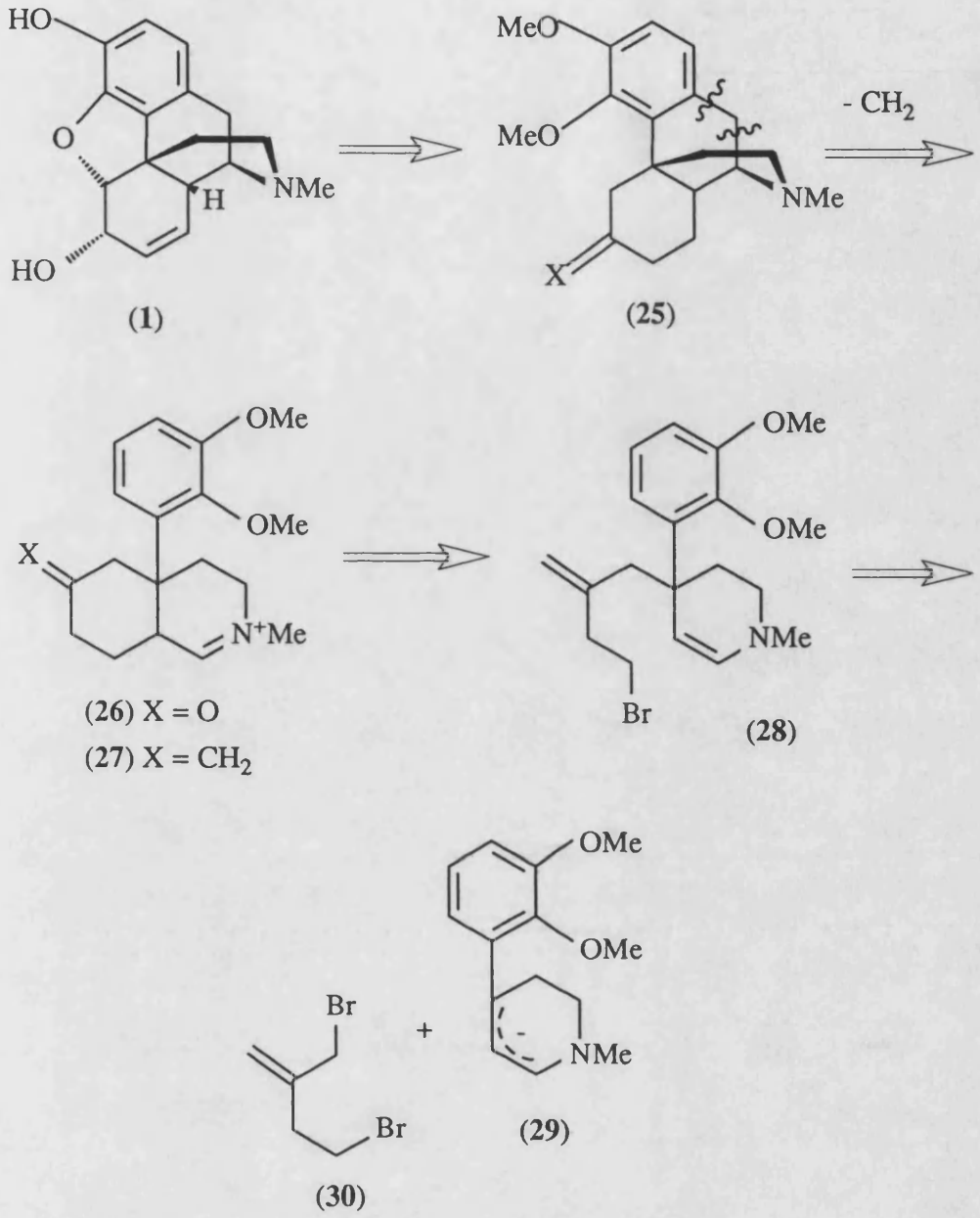
uptake of monoamines, including serotonin. One approach to investigating these effects, using rigid "tubular" analogues like cyclohexylamine (**24**), is established.[30] The key step of our approach to morphinoid analogues (see **1·6·1**) also appeared applicable to the synthesis of such compounds. This idea is outlined in **1·6·2**, and discussed in Chapter 4.

1·5. Syntheses of unnatural morphinoids.

Despite its early discovery,[4] the structure of morphine (**1**) was not unambiguously determined[31] until 1925. However, even this analysis was not confirmed by total synthesis until the work of Gates and Tschudi,[32] in 1952. Since then, morphinoids have generated great synthetic interest. The field's literature is vast, so concentration on directly relevant areas is required. More recent studies towards morphine total synthesis have been performed by Evans and co-workers.[33] These are based on the retrosynthetic analysis shown in Scheme 1.

Rapoport, and various co-workers, investigated several opiate analogues; including benzomorphans,[34] papaverine related 1,2,3,4-tetrahydroisoquinolines,[35] and orvinols.[36-38] Their research, exploring structure-activity relationships with morphinoid analogues lacking one or more rings,[5,39-42] is of most interest here. During their research, Rapoport and co-workers[5] developed a nomenclature system, described in section **1·2**, to distinguish the morphinoid rings. Principle skeletons of interest are ACN (**31**), ABN (**32**), ANO (**33**), ACNO (**34**), and ABNO (**35**), shown in Figure 4.

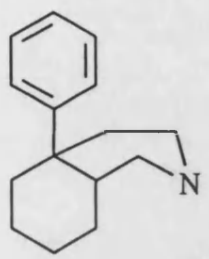
The first synthesis of an ANO (**33**) system, spiro-coumaran (**36**), was that of Bergel *et al.*[43] Sargent and Ager[44] produced an example of an ABNO system (**35**), the compound (**37**), by a degradation of codeine (**2**). Our target compound is a member of the ACNO system (**34**). Two compelling reasons for interest in this ring structure are; firstly they have been shown to be potent analgetics,[45]



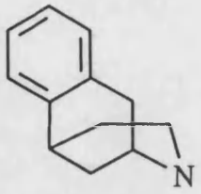
Scheme 1.

secondly they have both agonistic and antagonistic capabilities. The latter class shows more promise. It has been suggested[5] that removal, effectively, of the morphine C-10 methylene may result in separation of analgetic activity from side-effects.

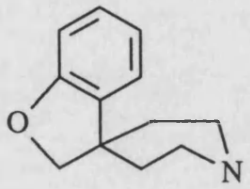
The first example of an ACNO compound, epimeric isomers (**38**) and



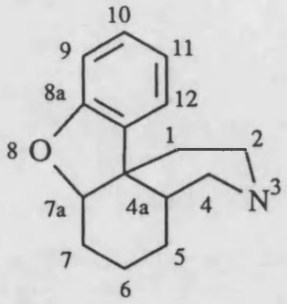
(31) ACN



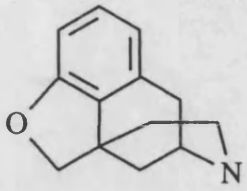
(32) ABN



(33) ANO

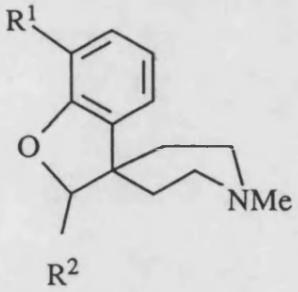


(34) ACNO

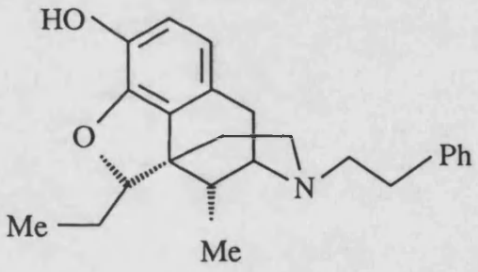


(35) ABNO

Figure 4.

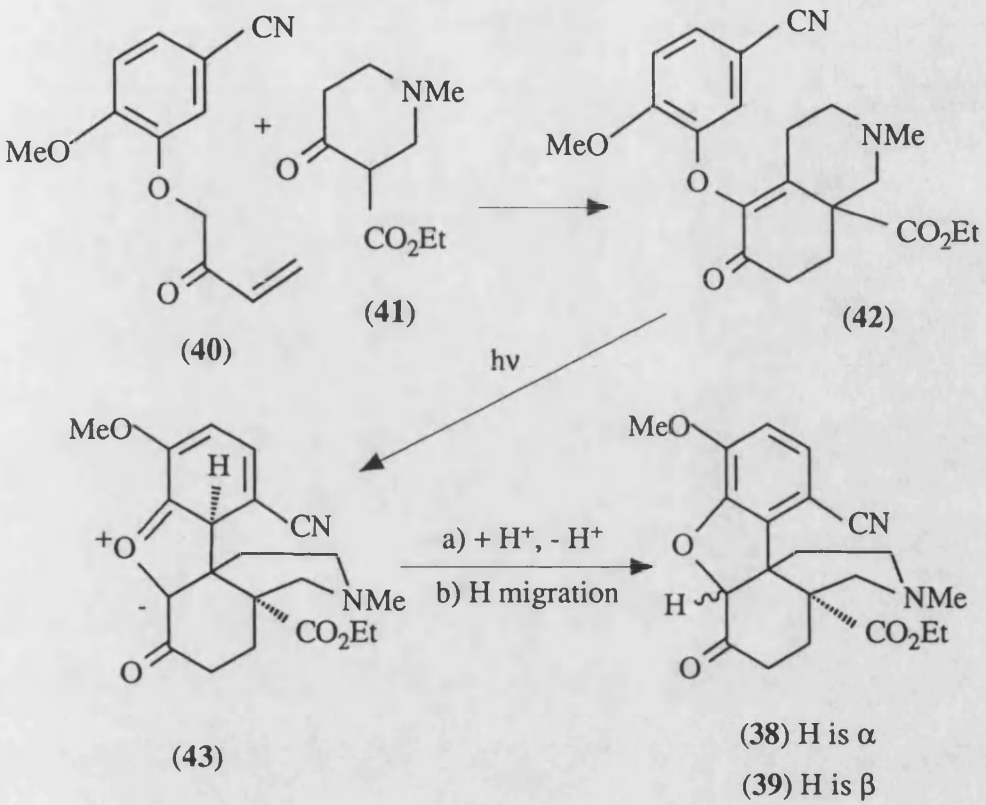


(36)



(37)

(**39**), was made in 1976. The synthesis, by Schultz and co-workers,[46,47] was *via* the heteroatom-directed photoarylation shown in Scheme 2. It proved possible to control conditions such that only epimer (**39**) was recovered. A related synthesis,[45] of analogue (**44**), having a fully saturated isoquinoline unit, was based on an intramolecular Diels-Alder reaction. It was carried out by Ciganek, as shown in Scheme 3.

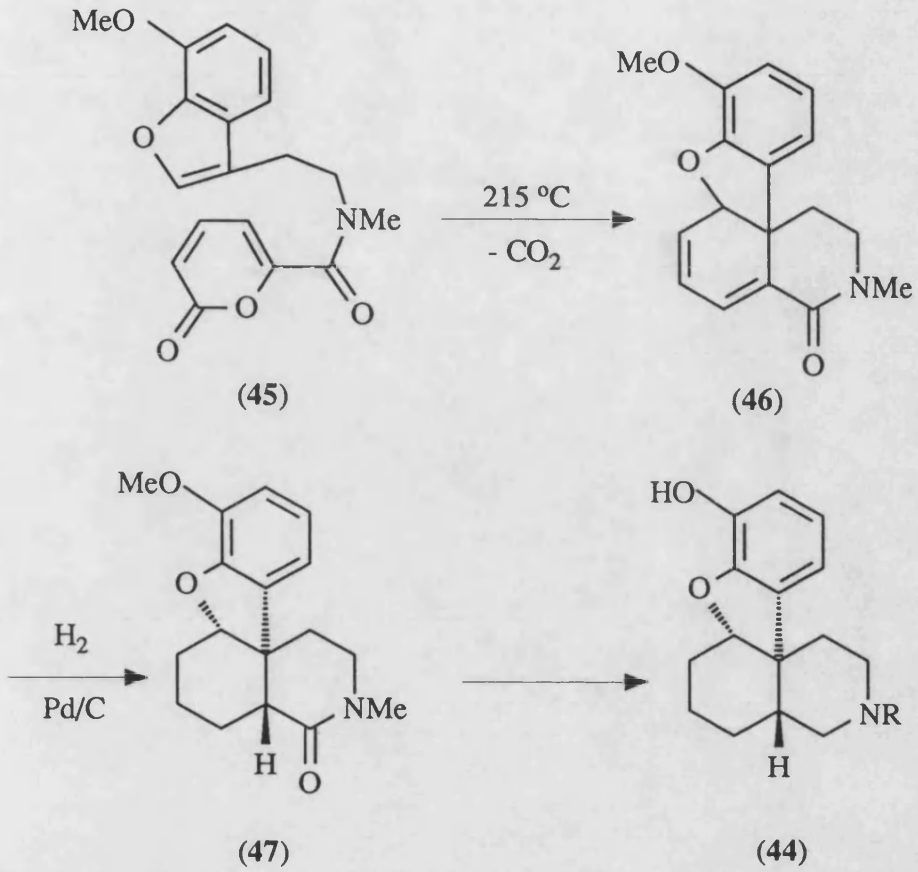


Scheme 2.

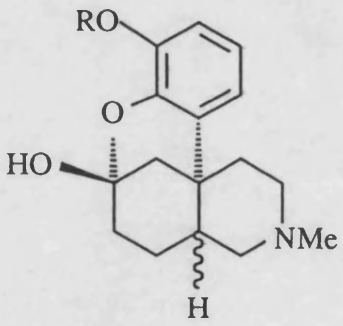
Rapoport and his various co-workers employed methodology which could be used flexibly in order to allow entry to ANO, ANCO, ABNO, and codeine-like ABCNO systems.[5,39-42] They also made analogues, such as (**48**),[40] with unnatural ring structures. This methodology, based on an α-chloro ortho ester Claisen rearrangement,[5] is illustrated for the ANCO compound (**49**) in Scheme 4. This overcame the problems of an unwanted nitrile group in epimers (**38**) and (**39**), and the difficulty of C-ring functionalisation for octahydroisoquinoline (**44**).

1·6. Synthetic applications of anodic oxidation.

Anodic oxidation of organic materials, which has a fairly long history,[48,49] has been investigated in this laboratory by Sainsbury and several co-workers.[50-54] They applied the method to tetrahydroisoquinoline (**62**),

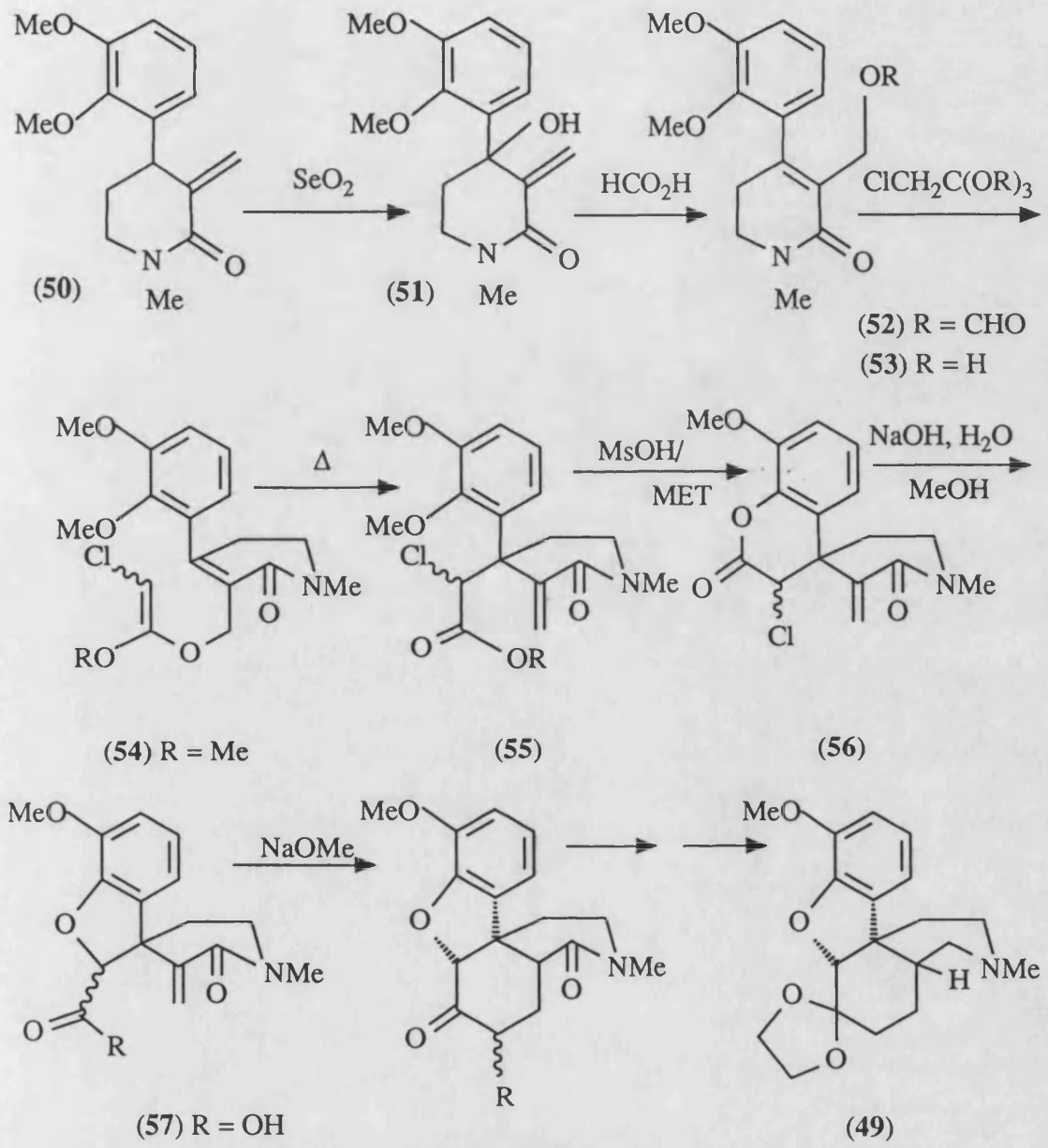


Scheme 3.



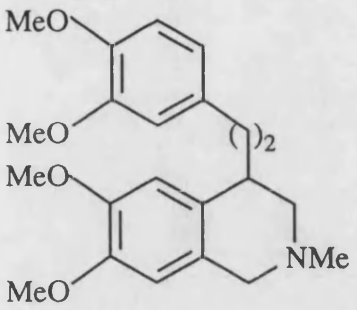
(48)

isolating compound (**63**),[50] which seems to derive from intermediate (**64**) rearranging to restore aromaticity. This technique is explored more fully in



Scheme 4.

Chapter 4.



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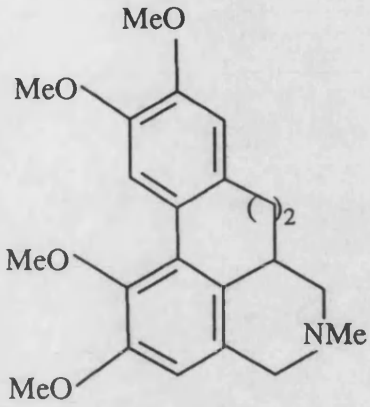
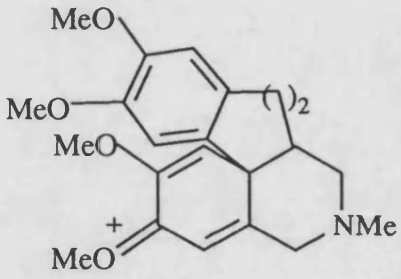


(63)



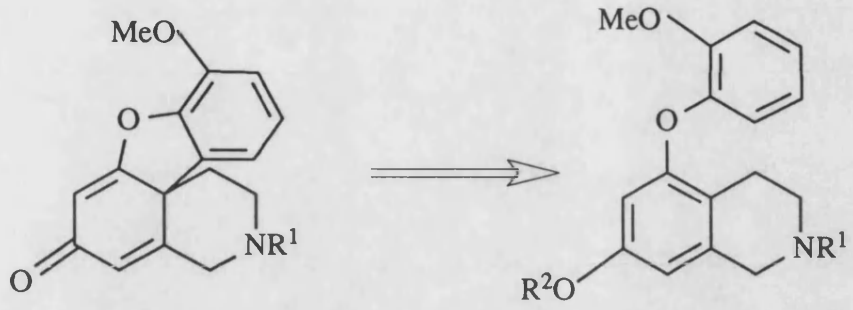
(64)

1·6·1. Morphinoid target compound.

Planning a new entry into the ACNO ring system, we noted the apparent applicability of bond formation by anodic oxidation. Key intermediate furan (**65**) could be formed by anodic oxidation of tetrahydroisoquinoline (**66**), as shown in Scheme 5. The aryl ether should stop rearrangement. Approaches to compound (**66**) form the basis of the next Chapter.

We expected electrochemistry of (**66**) to be promising. Each aromatic ring possesses an activating oxygen function *ortho*- or *para*- to the bond to be formed. An alternative mode of cyclisation would be possible, however. This would lead to dibenzofuran (**67**), which would not appear to be much use as an active analgetic. We did not anticipate that compound (**67**) would be a major product, since it would seem to be more sterically constrained than furan (**65**).

We also wished to make tetrahydroisoquinoline (**68**), isomeric with



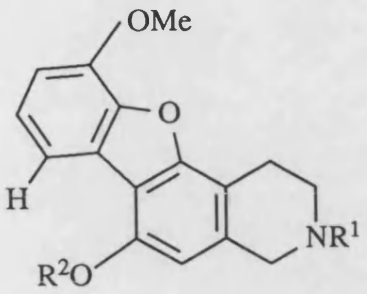
(65) (66)

Scheme 5.

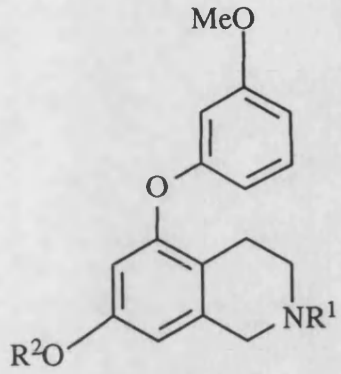
electrochemical precursor (**66**). The former may be regarded as a good model compound for anodic oxidation. *Both* aromatic rings are symmetrically activated to coupling, and therefore of more closely matched oxidative potentials (see Chapter 4). In addition, unwanted positional isomers (**69**) and (**70**), appear more sterically hindered than the isomeric dibenzofuran (**67**). Finally, according to the model of Feinberg *et al.*,[16] the regiochemistry of the phenol may not be crucial for morphinoid-receptor interaction. Therefore, the analgetic activity of the unnaturally substituted analogue (**71**) is of interest.

1·6·2. Serotoninoid target compound.

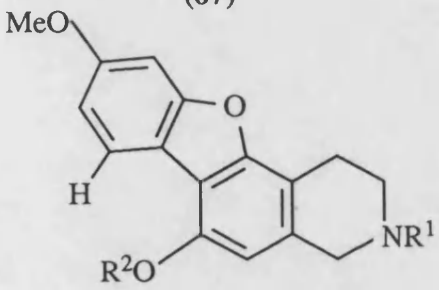
We wished to extend anodic oxidation to synthesis of potential serotoninoid analogues. To this end, the 1,2,3,4-tetrahydrocarbazole (**72**) was a candidate precursor. Intramolecular coupling of indoles has been seen by Sainsbury and Powell.[50] We speculated on the behaviour of compound (**72**) under the proposed conditions; the pentacycle (**73**) and the novel spiro compound (**74**) seemed possible products. These may be serotoninoid analogues of well defined rigidity. The synthesis of precursor (**72**) and its electrochemistry are discussed in Chapter 4.


OMe
O
H
NR1
R2O

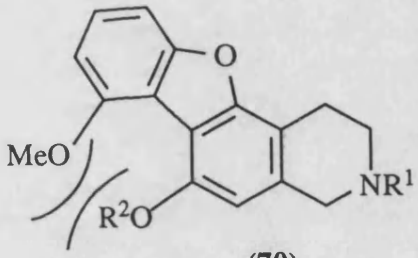
(67)


MeO
O
NR1
R2O

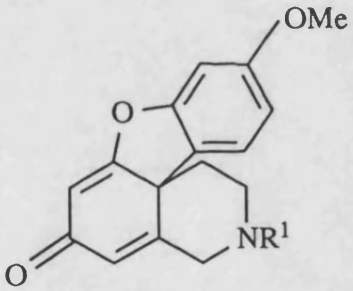
(68)


MeO
O
H
NR1
R2O

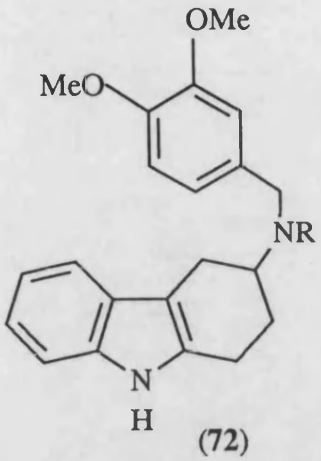
(69)


O
MeO
NR1
R2O

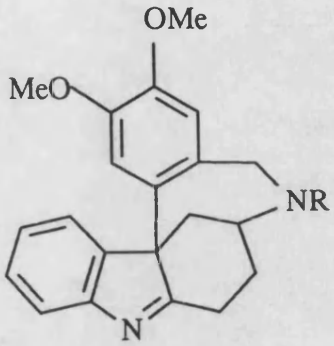
(70)


OMe
O
NR1
O

(71)



(72)



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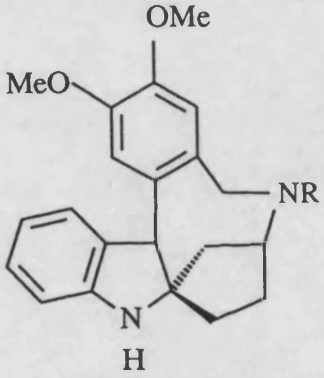


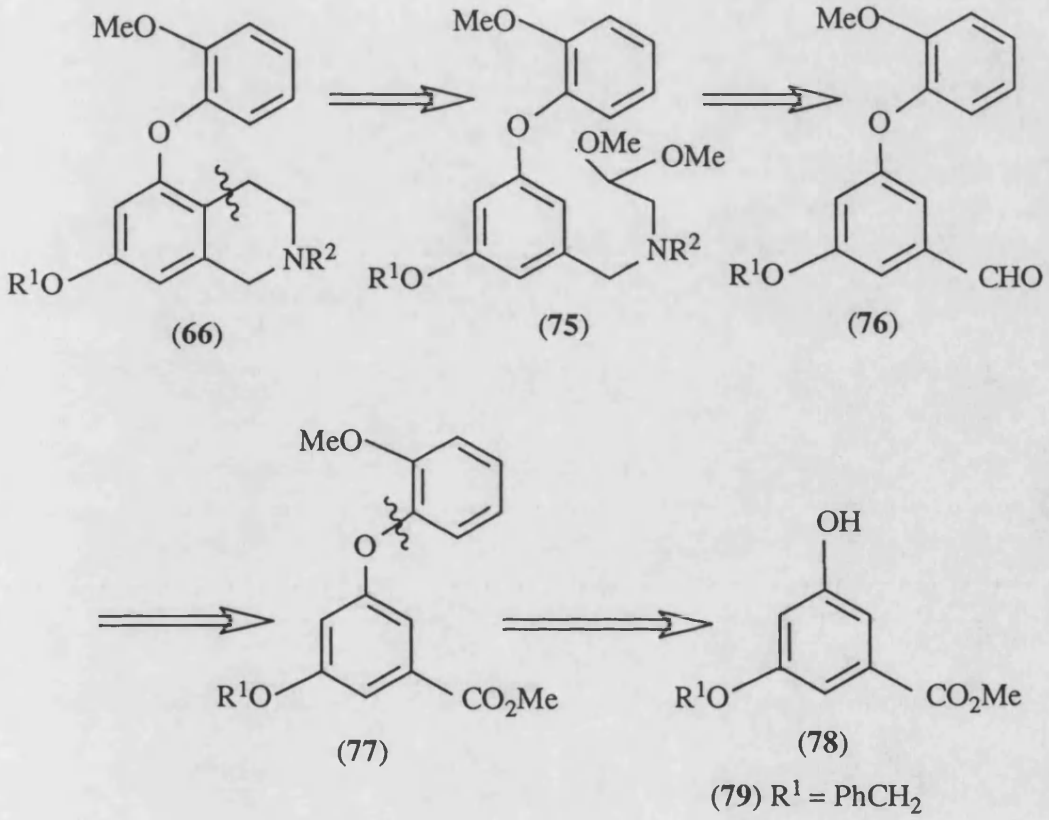
(74)

CHAPTER 2.

2. IN SEARCH OF MORPHINOID ANALOGUES.

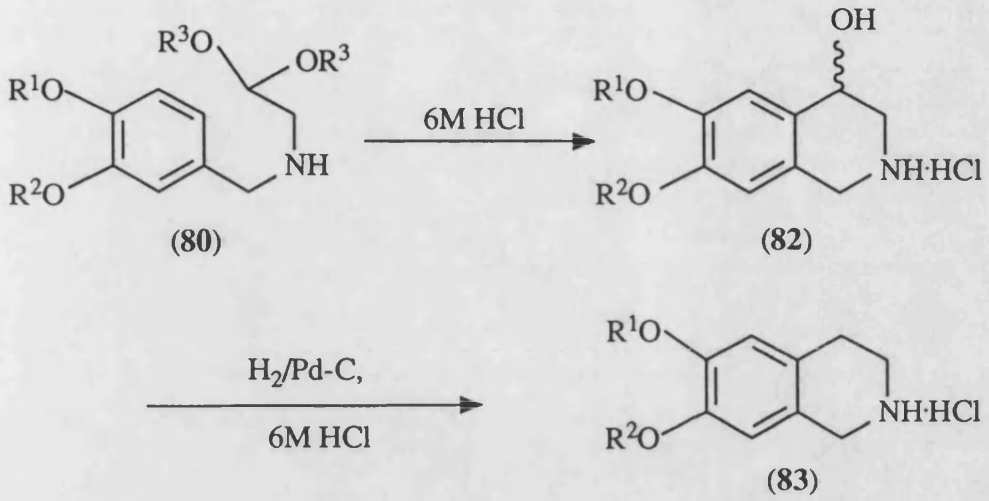
2·1. Introduction.

In the previous chapter, we indicated that the initial target compound was to be novel diaryl ether (**66**). Scheme 6 shows our retrosynthetic strategy for this key intermediate.



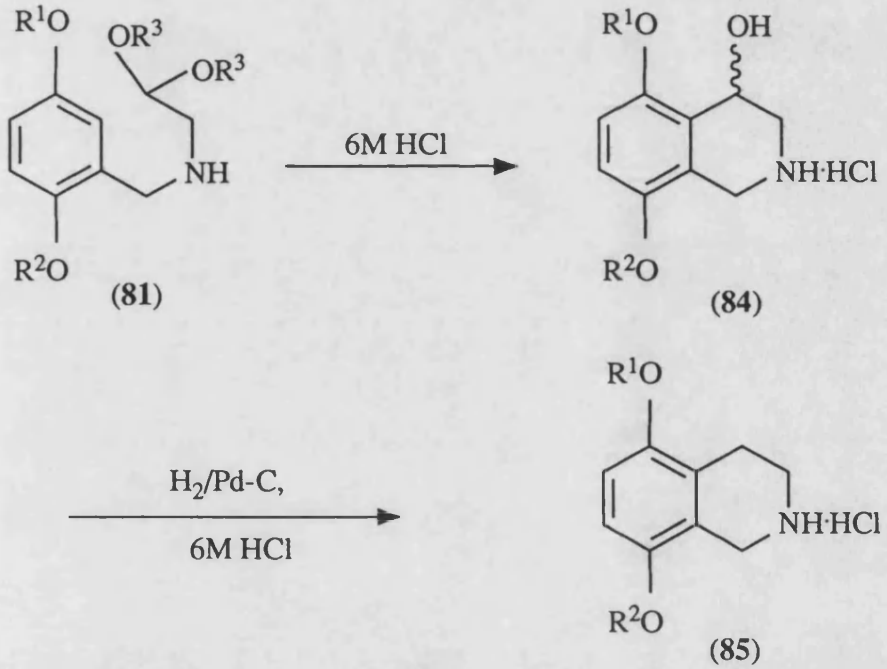
Scheme 6.

Bobbitt and co-workers[55,56] have investigated the ring-closure outlined in Scheme 7, upon which our first disconnection was based. They optimised acidic reaction conditions using various starting acetals (**80**) and (**81**). At first it seemed that this reaction involved a 1,2-dihydroisoquinoline.[55] However, Bobbitt and Sih[56] later proved the true intermediates to be 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**82**) and (**84**); many of which can be isolated.



(80) (82) (83)

A



(81) (84) (85)

B

R^1 = H or Me R^3 = Et

R^2 = Me or H

Scheme 7.

Such a reaction pathway implies the acetal group undergoes deprotection to the corresponding aldehyde; which is the true starting material. Conversely,

reaction of acetals such as (**80**) with boron trifluoride leads to formation of 4-ethoxy-1,2,3,4-tetrahydroisoquinolines.[57] Seemingly, direct reaction between the acetal function and the aromatic ring is involved. Benzyl alcohols (**82**) and (**84**) are clearly stable under the acidic conditions.

Bobbitt ring-closure does not appear to have been applied to 5,7-disubstituted compounds such as acetal (**75**). However, our acetal apparently possesses superior activation for this well investigated[56,57] reaction. Thus we believed such chemistry would be suitable for our crucial ring-closure at a late synthetic stage.

We were less certain of how easily the other key disconnection, aryl ether formation, may be achieved. For that reason, we planned its inclusion as early as possible in our synthesis of diaryl ether (**66**).

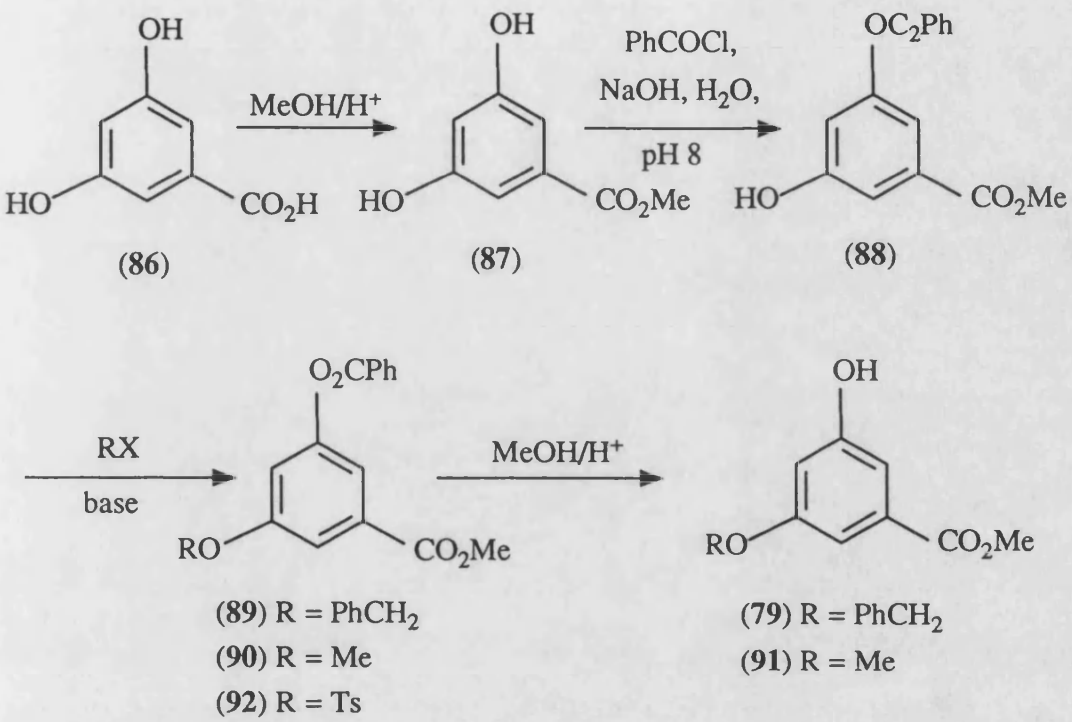
2·2. Discussion.

2·2·1. Approach to diaryl ether (66) *via* early arylation.

Phenol (**79**) is readily obtained by the route of Schwender, Pike, and Shavel,[58] outlined in Scheme 8. This synthesis starts from commercially available 3,5-dihydroxybenzoic acid (**86**). Dihydroxybenzoic acid methyl ester (**87**) can be monoprotected with benzoyl chloride and sodium hydroxide, provided pH is controlled.

We were unable to reproduce the melting point (110-112 °C) obtained for benzoate (**88**) by Schwender and co-workers. Despite recrystallisation twice, our sample consistently melted 6 °C higher than this. Treating the phenol (**88**) with benzyl bromide and potassium carbonate, in refluxing acetone, yielded diester (**89**). The benzoyl group was removed by acid methanolysis, affording phenol (**79**) - the desired starting material for formation of diaryl ether (**66**).

Our approach to synthesis of diaryl ether (**77**) involved methodology derived by Barton and various co-workers.[59] The resulting chemistry is discussed



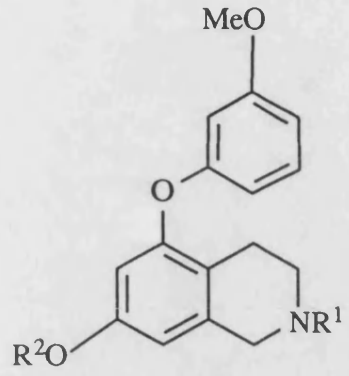
Scheme 8.

fully in Chapter 3, so only two relevant points are made here. We found the method fails when applied to synthesis of ether (**77**). It was very successful, however, in production of isomeric diaryl ether (**93**). (Experimental details are to be found in Chapter 3).

This methodology should allow an entry to our subsidiary target compound, ether (**68**). Therefore, we elected to postpone further investigation of phenol 2-methoxyphenylation. Instead we pursued synthesis of ether (**68**).

2·2·2. Approach to diaryl ether (68) *via* late arylation of phenol (94).

The ease with which diaryl ether (**93**) could be prepared allowed further refinement of our original synthetic strategy. Barton[59] arylation is efficient, but a low overall yield for the required reagent (see Chapter 3), now favoured arylation *late* in our synthetic programme. Such a tactic had the additional advantage of



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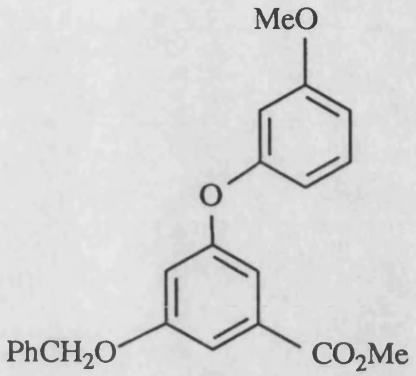
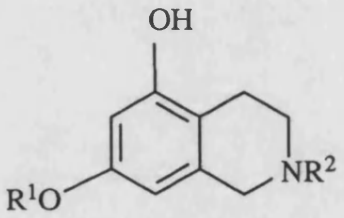


(93)

allowing us to test our second key disconnection earlier than anticipated. Therefore, tetrahydroisoquinoline (**94**) became our next synthetic objective.

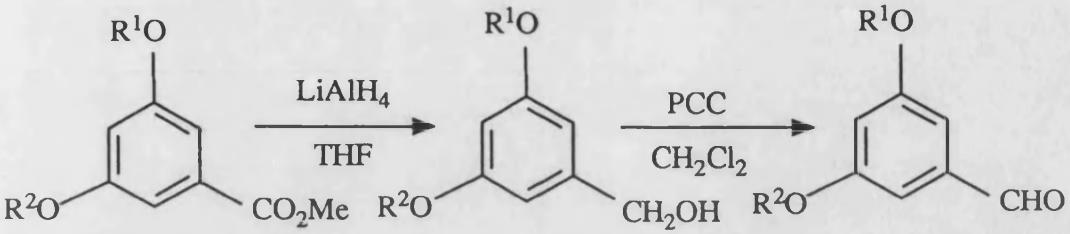


(94)

2·2·2·1. First approach to phenol (94) using a Bobbitt ring-closure technique.

Where acetals such as (**80**) may cyclise either *ortho*- or *para*- to a phenol, the latter ring-closure is preferred.[55] Thus, our first approach to the desired tetrahydroisoquinoline (**94**), shown in Scheme 9, centred on phenol (**95**). Protection of the phenol group followed by demethylation would afford phenol (**94**). A methyl group was chosen as R^1 because, unlike benzyl, it displays low lability under strongly acidic conditions.

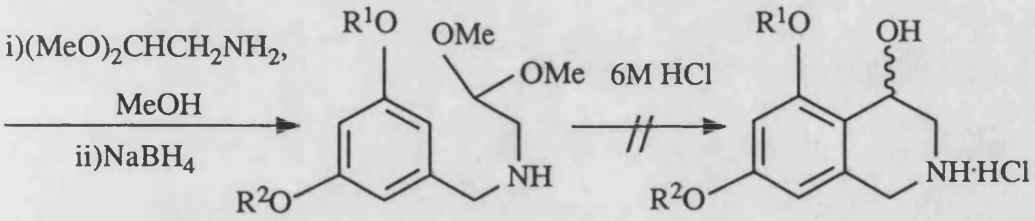
Reaction of phenol (**88**) with methyl iodide (see Scheme 8) afforded crude



(**91**) R^1 = Me, R^2 = H
(**92**) R^1 = Ts, R^2 = COPh

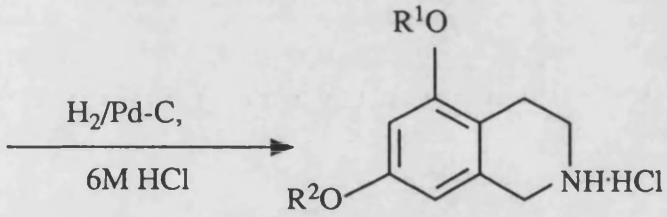
(**96**) R^1 = Me, R^2 = H
(**100**) R^1 = Ts, R^2 = H

(**97**) R^1 = Me, R^2 = H
(**101**) R^1 = Ts, R^2 = H
(**102**) R^1 = Ts, R^2 = Me



(**98**) R^1 = Me, R^2 = H
(**103**) R^1 = Ts, R^2 = Me

(**99**) R^1 = Me, R^2 = H
(**104**) R^1 = Ts, R^2 = Me



(**95**) R^1 = Me, R^2 = H
(**105**) R^1 = Ts, R^2 = Me

PCC = pyridinium chlorochromate

Scheme 9.

methyl ether (**90**). In contrast with the behaviour of benzyl ether (**89**), precipitation of purified product did not result from trituration of the oily crude mixture. Methanolysis of the benzoyl group produced methoxyphenol (**91**) in

48% yield. Treatment with lithium aluminium hydride afforded crystalline benzyl alcohol (**96**) in 55% yield. Oxidation with pyridinium chlorochromate[60] afforded the aldehyde (**97**). After crystallisation the overall yield, from phenol (**88**), was only 2%.

Dimethyl acetal (**98**) was formed by stirring a methanol solution of 2,2-dimethoxyethylamine and aldehyde (**97**). The reaction was monitored by i.r. spectroscopy. Aliquots from the mixture were concentrated and dissolved in chloroform for this purpose. When an imine signal (1630 cm^{-1}) had largely replaced that of the carbonyl group (1675 cm^{-1}), the reaction mixture was treated with sodium borohydride, followed by acid. The pH of solution was not allowed to fall below 2, in order to prevent deprotection of the acetal function. Neutralisation and ether extraction afforded crude oily amine (**98**).

No satisfactory method of purification was found; attempted vacuum distillation caused decomposition, and chromatography resulted in loss of material. Therefore crude amine (**98**) was characterised by ^1H n.m.r., and i.r. spectroscopy, as well as high resolution accurate mass spectrometry. The n.m.r spectrum showed an acetal methine proton, a triplet at δ 4·41, and the benzylamine singlet at δ 3.98. I.r spectroscopy showed amine bands at 3640 and 3270 cm^{-1}.

Acetal (**98**) was dissolved in 6M hydrochloric acid, and the solution was allowed to stand overnight. The mixture was neutralised, and concentrated to dryness *in vacuo*, affording a pale yellow non-crystalline solid. T.l.c indicated a complex mixture, and physical data were unhelpful.

The crude product was redissolved in 6M hydrochloric acid, and palladium (10%) on charcoal was added. Hydrogenation, for five hours at atmospheric pressure, filtration, and removal of solvent, yielded a second non-crystalline yellow solid. The crude material would not crystallise, and could not be purified by chromatography on silica gel. Physical data acquired for the

crude product indicated the presence of a substantial number of components. We were unable to characterise this material.

Bobbitt and Sih[56] report failure to isolate some of their 4-hydroxy-1,2,3,4-tetrahydroisoquinolines. They inferred intermediacy of such compounds, because hydrogenolysis of the reaction mixtures allowed recovery of the corresponding 1,2,3,4-tetrahydroisoquinolines.

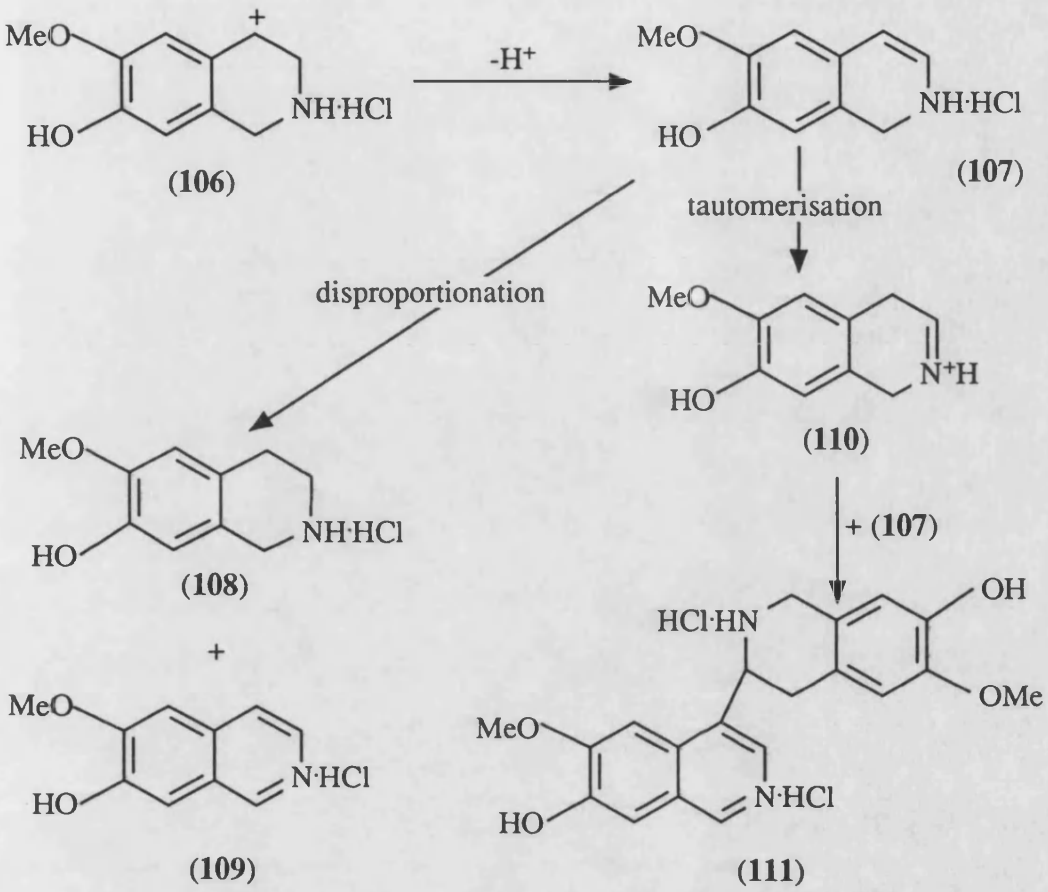
In such cases, the starting acetals either had a 7-hydroxy or a 7-methoxy substituent. Therefore, we repeated the reaction on acetal (**98**) with no attempt to isolate the 4-hydroxy-intermediate (**99**). Subsequent repetitions employed variation in reaction time, or use of hydrogenation from the outset. The results were consistent only in producing inseparable mixtures, which we could not characterise.

In general, benzyl alcohols (**82**) exhibit stability under Bobbitt's optimised ring-closure conditions. Nonetheless, harsher reaction[55] leads to undesirable by-products, presumably similar to those observed in our case. In their reaction, Bobbitt and co-workers isolated compounds which suggested benzylic carbonium ion (**106**), shown in Scheme 10, as the common reactive intermediate.

We concluded that alcohol (**99**) must dehydrate with more than usual ease, forming a corresponding benzylic carbonium ion. We had expected reinforcing electron-donation, from the 5,7-disubstitution in acetal (**98**), to assist formation of alcohol (**99**). This does appear to be the case. However, that effect may *also* stabilise a subsequent cation formed in position-4; which would account for the dramatic difference in reactivity seen between acetals (**80**) and acetal (**98**).

2·2·2·2. Repetition of a literature ring-closure.

Before embarking on a modified synthesis of phenol (**94**), we felt it prudent to repeat ring-closure of an acetal used by Bobbitt and co-workers. We



Scheme 10.

decided to make tetrahydroisoquinoline (**83**, R^1, R^2 = Me), (see Scheme 7). The reason for this choice was the availability of an authentic sample from Aldrich.[61]

Acetal (**80**, R^1, R^2, R^3 = Me) was made from 2,2-dimethoxyethylamine and 3,4-dimethoxybenzaldehyde. The intermediate imine was formed in methanol solution, and reduced by hydrogenation[55] without isolation. This crude oily acetal was subjected to Bobbitt and Sih's[56] reaction conditions. The crude mixture was concentrated *in vacuo* to less than half its volume and addition of ethanol precipitated a crystalline solid.

This material was collected and characterised as 6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**82**, R^1, R^2 = Me). ^{1}H n.m.r. spectroscopy

indicated the presence of an asymmetric centre in the ring, with the amine protons resonating at δ 10·16 and δ 9.48. The signal for the proton at C-4 was also visible, as the expected triplet at δ 4.79; in accord with values reported by Bobbitt and Sih.[56]

Atmospheric pressure hydrogenation of this alcohol produced 5,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**83**, R^1, R^2 = Me). This was characterised by m.p., mixed melting point, and ^{13}C and ^{1}H n.m.r. spectroscopy. The spectra were identical to those recorded using an authentic sample. For all three of these compounds, ^{13}C, ^{1}H n.m.r., i.r. and mass spectra were as expected and elemental analyses were satisfactory.

2·2·2·3. Second approach to phenol (94) using a Bobbitt ring-closure technique.

This result supported our belief that alcohol (**99**) undergoes uncommonly facile dehydration. For further corroboration, and to continue our programme, we sought to synthesise a less electron-rich precursor to ring-closure. Therefore, we prepared acetal (**103**), which possesses an electron-withdrawing *para*-toluenesulphonyloxy substituent. This synthesis involved only a minor modification of our previous approach, as illustrated in Scheme 9.

Preparation of aldehyde (**102**) was achieved by tosylation of phenol (**97**). Thus the sequence from phenol (**88**) was: methylation, de-esterification of benzoate (**90**), reduction of methyl ester (**91**), oxidation of alcohol (**96**), and finally tosylation of aldehyde (**97**), affording tosylate (**102**). The overall yield for these five steps was less than 1%.

We next adopted an alternative approach, avoiding involvement of benzoate (**90**). From phenol (**88**), this sequence was: tosylation, hydride reduction of diester (**92**), oxidation of alcohol (**100**), and methylation of phenol (**101**), affording tosylate (**102**) in 27% overall yield.

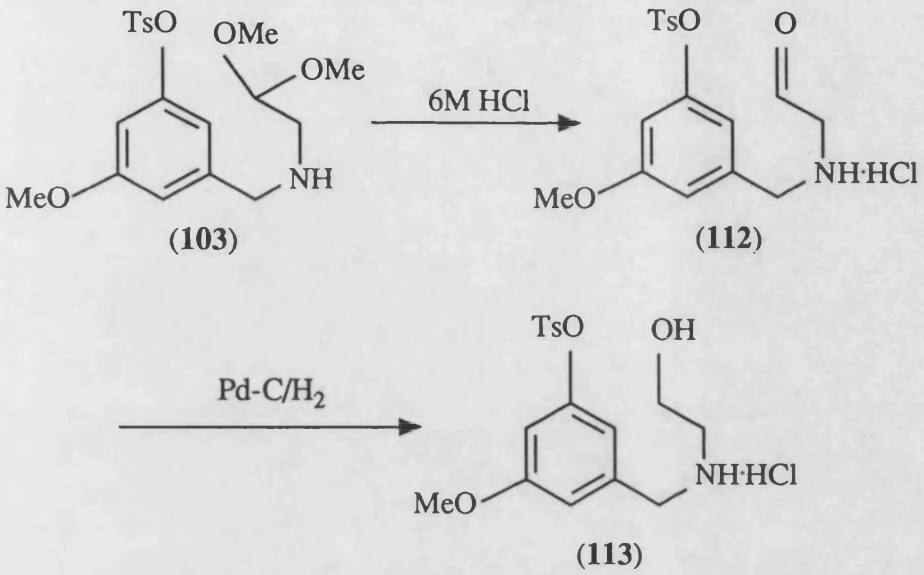
Acetal (**103**) was made by the procedure used previously, and was satisfactorily characterised. The crude material was treated with 6M hydrochloric acid, with no attempt to isolate intermediate 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**104**). After the reaction mixture had stood for 18 hours, palladium (10%) on charcoal was added, followed by hydrogenolysis at atmospheric pressure. Following work-up, many components were observed to be present in the crude reaction mixture. Similar variation of conditions to those tried with acetal (**98**) did not effect any visible alteration in the result.

However, ^{1}H n.m.r. spectroscopy allowed partial interpretation of the outcome of the reaction. Three signals were significant; two doublets of doublets at δ 7·30 and δ 7·06 (J = 2 and 1 Hz), and a triplet at δ 6·85 (J = 2 Hz). These correspond well with protons 2-H, 6-H (δ 7·29, and δ 7.06, respectively, dd, J = 2, 1 Hz), and 4-H (δ 6·85, t, J = 2 Hz) in aldehyde (**102**). Although starting material had been consumed, it was apparent ring-closure had not occurred.

2·2·2·4. Final approach to phenol (94) using a Bobbitt ring-closure technique.

We concluded that the *para*-toluenesulphonyloxy substituent of acetal (**103**) was sufficiently electron-withdrawing to prevent the desired reaction. In the case of 5,7-disubstitution, successful Bobbitt ring-closure would seem to require a starting material of reactivity intermediate between acetal (**98**) and acetal (**103**). Unfortunately, less electron-attracting substituents, such as acetyl, would be unstable under the reaction conditions.

The undoubted utility of the Bobbitt ring-closure persuaded us to attempt a different modification. We felt it may be possible to prevent over-exposure of sensitive 4-hydroxy-1,2,3,4-tetrahydroisoquinolines to acid. We realised that hydrogenolysis of such intermediates as they form is not viable. Bobbitt and



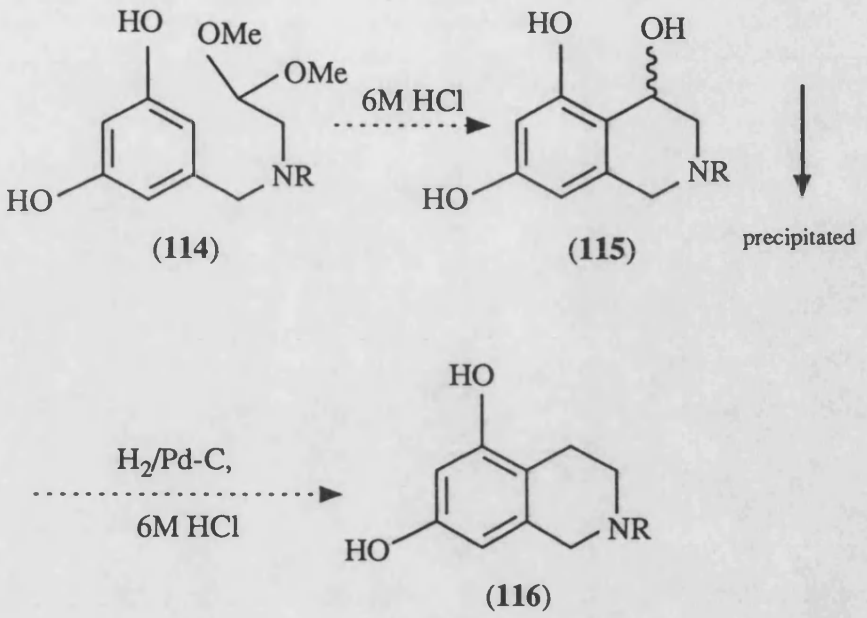
Scheme 11.

co-workers[55] discovered premature reduction results in poor yields, due to competing hydrogenation of the deprotected aldehyde. This is illustrated, for the case of acetal (**98**), in Scheme 11.

Instead, by analogy with the synthesis of benzoate (**88**),[58] precipitation of 4-hydroxy intermediates on formation looked like a promising technique. Suitably protecting the amine function ought to achieve this aim, as depicted in Scheme 12.

Trifluoromethanesulphonyl[62] appeared an ideal *N*-protecting group. It is acid-stable and, furthermore, sufficiently electron-withdrawing to prevent unwanted involvement of the amine lone-pair (see Scheme 10). On that basis, we prepared triflamide (**114**), as shown in Scheme 13, requiring only a further minor modification to the existing routes for acetal synthesis.

Benzylation of diphenol (**87**) afforded ester (**117**), which was reduced to the corresponding alcohol (**118**), and oxidised to aldehyde (**119**). Acetal (**120**), formed as on previous occasions, underwent reaction with freshly prepared

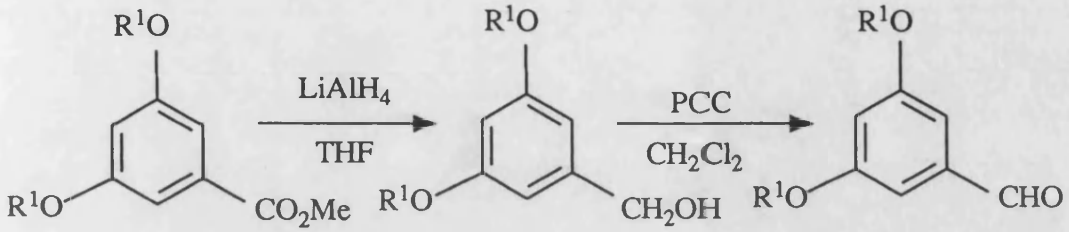


Scheme 12.

trifluoromethanesulphonic anhydride[63,64] at -78 °C, to yield crude triflate (**121**). Chromatography and crystallisation gave the purified solid in 63% yield. Atmospheric hydrogenation produced the desired precursor for Bobbitt ring-closure, acetal (**114**).

Slight adaptation of ring-closure conditions[56] was necessary. It was difficult to dissolve acetal (**114**) in a wholly aqueous system. This was overcome by diluting concentrated hydrochloric acid to 6M using methanol. A methanol solution of acetal (**114**) was added to the methanolic acid. The stirred mixture rapidly produced a pale yellow precipitate which was collected, or extracted with ether.

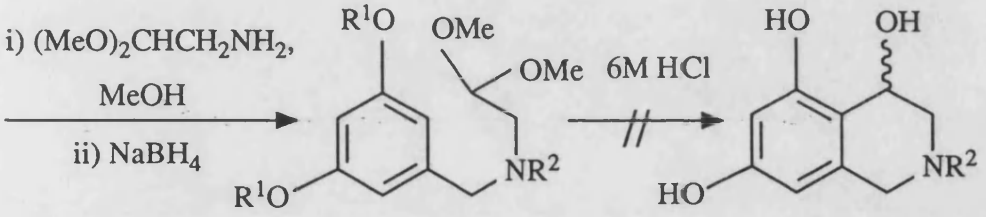
The product was found to be non-crystalline, and decomposed, without melting, at 250 °C. Physical data showed a complex mixture, which we were unable to separate. Fast atom bombardment mass spectrometry indicated that the



(**87**) $R^1 = H$
(**117**) $R^1 = PhCH_2$

(**118**) $R^1 = PhCH_2$

(**119**) $R^1 = PhCH_2$



(**120**) $R^1 = PhCH_2$, $R^2 = H$
(**121**) $R^1 = PhCH_2$, $R^2 = SO_2CF_3$
(**114**) $R^1 = H$, $R^2 = SO_2CF_3$

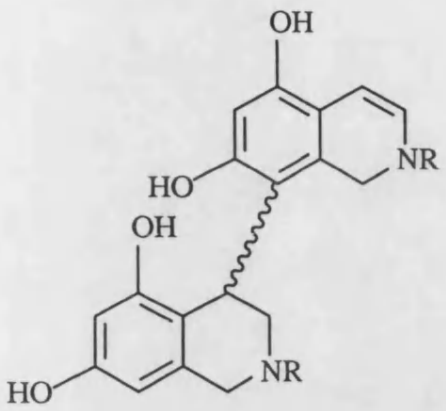
(**115**) $R^2 = SO_2CF_3$

Scheme 13.

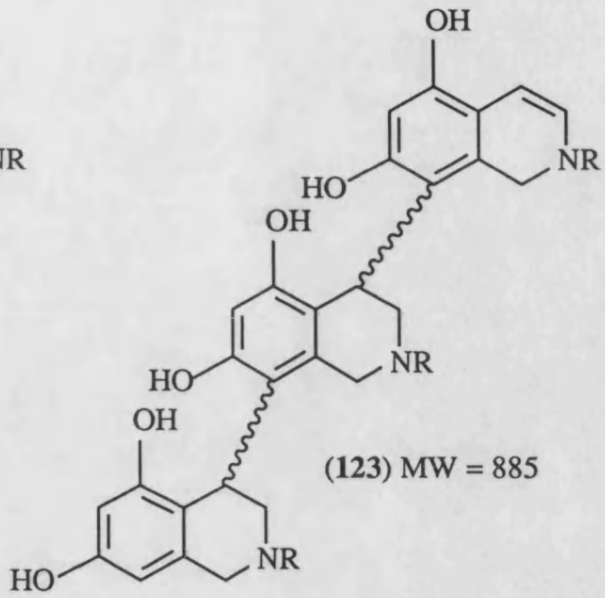
presence of two compounds could be inferred.

These are dimer (**122**) and trimer (**123**), resulting from the desired 4-hydroxy intermediate (**115**). In the mass spectrum, a cluster of peaks is visible around each of the required molecular weights, *m/z* = 591 and *m/z* = 885. Furthermore, peaks representing eliminations of trifluormethanesulphinic acid - one molecule from dimer (**122**), both one and two molecules from trimer (**123**) - were seen.

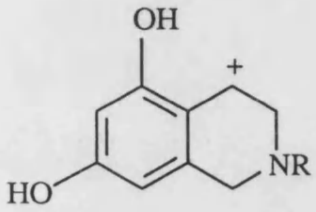
The structures indicated were assigned because dimerisation seen by Bobbitt and co-workers[55] (Scheme 10) requires involvement of nitrogen. However nucleophilic attack by phenol (**114**), at its *para*-carbon atom, on carbonium species (**124**), is feasible. Loss of water from the resulting product would form a second carbonium ion, and further polymerisation may occur.



(**122**) MW = 591



(**123**) MW = 885



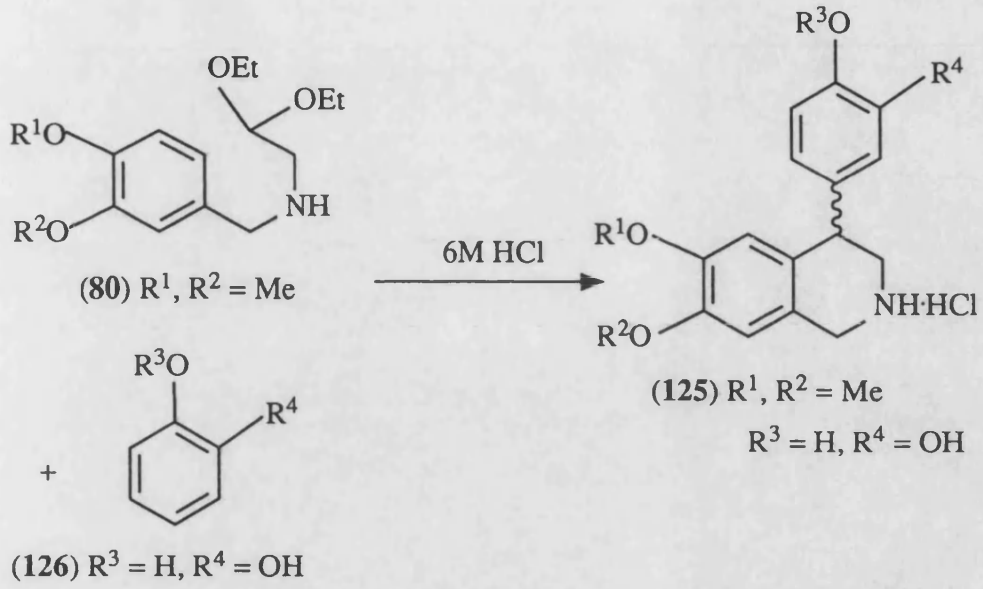
(**124**)

$R = SO_2CF_3$

Alternatively, addition of carbonium ion (**124**) may be terminated by elimination of a hydrogen ion. This would lead to the formation of many inseparable products, in accord with our observations.

There is a literature precedent for this type of nucleophilic attack of a phenol on 4-hydroxy-1,2,3,4-tetrahydroisoquinolines. Bobbitt and Shibuya[65] found addition of phenol or anisole, to the ring-closure reactions of acetal (**80**, R^1, R^2 = Me), resulted in formation of 4-aryl-1,2,3,4-tetrahydroisoquinolines (**125**). This is shown in Scheme 14. Reaction times of 12-15 hours were required for tetrahydroisoquinoline (**125**) to precipitate. In the case of dimer (**122**) and trimer (**123**), only a few minutes were necessary.

This drastic difference in reactivity suggests the operation of two different mechanisms. In the former case, SN2 attack at the protonated C-4 hydroxyl group



Scheme 14.

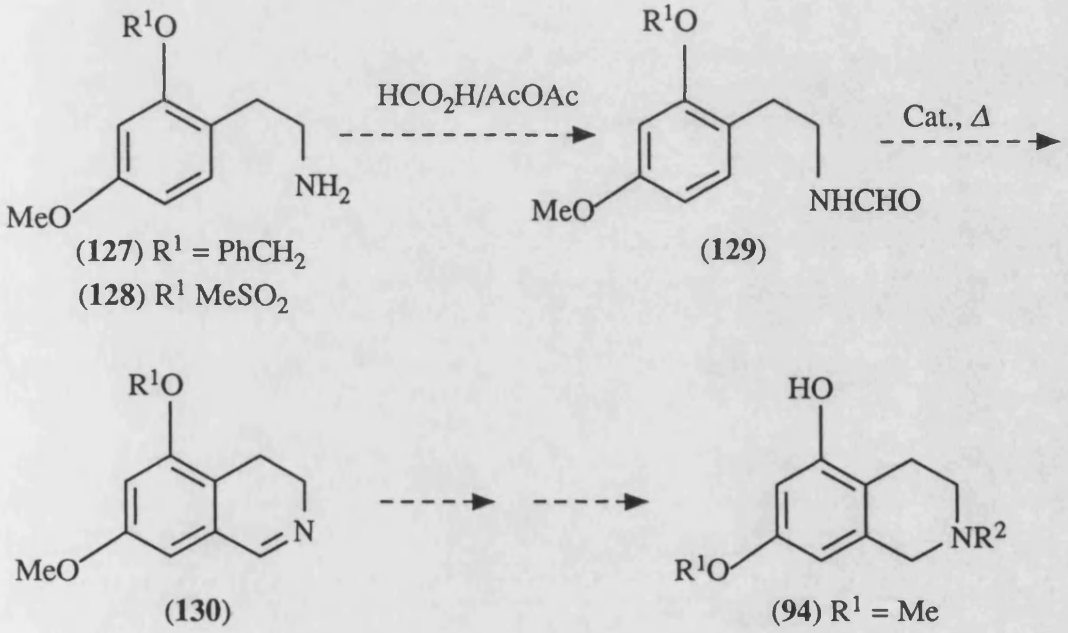
may be postulated. The rapid reaction of acetal (**114**), in the latter case, suggests SN1 attack at carbonium species (**124**). That products from this reaction were detected appears to reflect the absence of participation by amine.

For benzylic cation (**124**) to have formed so rapidly, its stabilisation by reinforcing substituents *ortho-* and *para-* to C-4 must be *much* greater than we had appreciated. Far from being a minor effect, such stabilisation clearly appears to be a serious driving force for loss of water. This is not seen where one substituent is *meta-* to C-4. Our experience indicates that the chemistry of 4,5,7-trihydroxy-1,2,3,4-tetrahydroisoquinolines differs markedly from that of other disubstituted isomers.

We now feel that it may not be possible to prepare such 4-hydroxy-1,2,3,4-tetrahydroisoquinolines *via* Bobbitt ring-closure, and that this is not a practical synthesis for phenol (**94**).

2·2·3. Approach to phenol (94) *via* the Bischler-Napieralski reaction.

The Bischler-Napieralski isoquinoline reaction[66] was the object of our next attempted synthesis of phenol (**94**), as indicated in Scheme 15. Both substituents are *meta*- to the point of ring-closure, which avoids the problems previously encountered. Examples of compounds which are not directly activated undergoing ring-closure, with a variety of catalysts, are documented.[67-70]

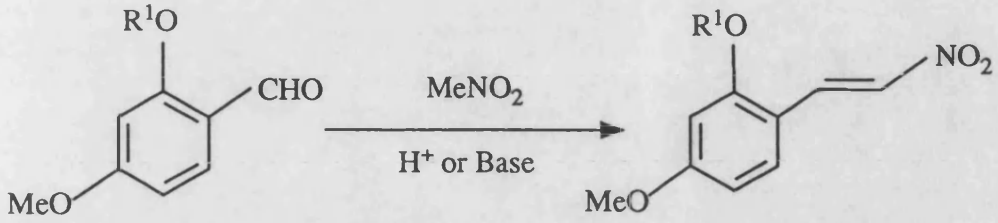


Scheme 15.

2·2·3·1. Use of 2-benzyloxy-4-methoxybenzaldehyde.

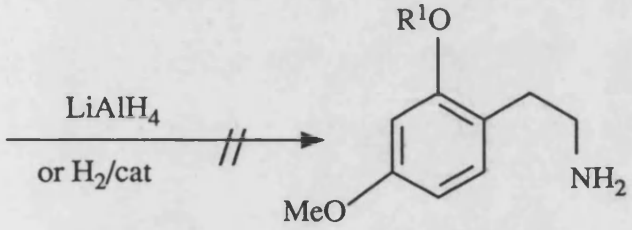
We chose benzyl as protecting group R^1 in the first instance, and our attempted preparation of amine (**127**) is detailed in Scheme 16. The compound 2-hydroxy-4-methoxybenzaldehyde (**131**) is available from Aldrich. This was benzylated, affording aldehyde (**132**). Some difficulty was encountered in condensing the aldehyde with nitromethane. After five days reflux in acetic acid,[71] followed by chromatography and crystallisation, the reaction gave a 27%

yield. It failed altogether under basic conditions. This is not surprising because the electron-rich carbonyl function of aldehyde (**132**) is a poor electrophile, unless protonated.



(**131**) $R^1 = H$
(**132**) $R^1 = PhCH_2$
(**134**) $R^1 = MeSO_2$

(**133**) $R^1 = PhCH_2$
(**135**) $R^1 = MeSO_2$



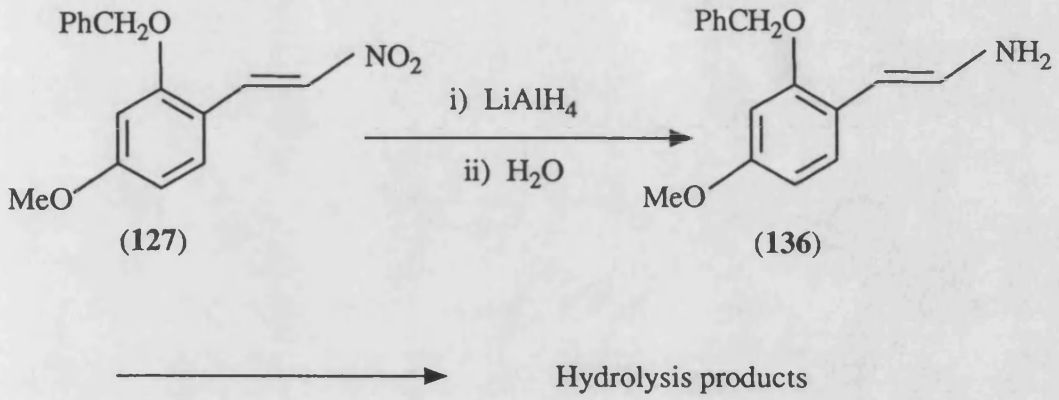
(**127**) $R^1 = PhCh_2$
(**128**) $R^1 = MeSO_2$

Scheme 16.

Lithium aluminium hydride reduction of nitrostyrene (**133**) was attempted, in order to avoid deprotection of the benzylated phenol group. The oily crude product was found to be a mixture of many compounds. It did not prove possible to separate any of these by chromatography, which lead to loss of material. Discolouration of the oil on standing overnight discouraged attempting vacuum distillation. The crude mixture could not be characterised by the usual physical methods, but contained no nitro group signals in i.r. or ^1H n.m.r. spectra.

An explanation for failure of this reaction is nitrostyrene (**133**) being too electron-rich to undergo the usual Michael attack by hydride. Were attack to occur directly at the nitro group, work-up may result in the formation of imine

(**136**), and its subsequent hydrolysis, shown in Scheme 17. However there was no indication of the presence of carbonyl or imine in the crude product, so we were unable to substantiate this speculation. It does seem probable that the concerted effect of the two ether groups was involved.



(**127**) (**136**)

Scheme 17.

2·3·2. Use of 2-methanesulphonyloxy-4-methoxybenzaldehyde.

We next used methanesulphonyl as a protecting group. Sulphonylation of phenol (**131**) afforded aldehyde (**134**) in 43% yield. Reflux with acetic acid and nitromethane resulted in a 46% yield of nitrostyrene (**135**), following chromatography and crystallisation.

Reduction of nitrostyrene (**135**) by hydrogenation was used in an attempt to prepare amine (**128**). This resulted in formation of a further complex and inseparable mixture. We could not characterise the mixture, although i.r. spectrophotometry indicated the presence of the sulphonyloxy group. Thorough degassing of the solution, and of the palladium catalyst, was to no avail. We offer no explanation for the failure of this reaction.

2·2·4. Future research.

We were unable to proceed with this synthesis due to lack of time. Reduction of nitrostyrene (**135**) by treatment with lithium aluminum hydride may be possible, due to the electron-attracting effect of the methanesulphonyloxy group. Formation of amine (**128**) is the only step likely to be affected adversely by the methoxy substituent. Bischler-Napieralski reaction of amine (**128**) ought to succeed, although prior removal of the methanesulphonyl group may be necessary. From the work of Barton and co-workers,[59] and the research detailed in Chapter 3, synthesis of 7-hydroxy-4-(3-methoxyphenyloxy)-1,2,3,4-tetra-hydroisoquinoline (**94**) should then prove straightforward. This would allow investigation of the anodic electrochemistry of that compound.

2·3. Experimental.

Melting points were recorded on an Electrothermal Mk. II, or a Gallencamp melting point apparatus, and are uncorrected.

Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyser.

Ultraviolet spectra were acquired with a Perkin-Elmer Lambda 3 UV/VIS Spectrometer and R 100 recorder, as solutions in 95% ethanol, over the range 390-190 nm.

Infrared spectra were determined as either a thin liquid film, a Nujol mull, a pressed disc in potassium bromide, or a chloroform solution, as stated. A Perkin-Elmer 1310 Infrared Spectrophotometer or a Nicolet 20 SXB spectrophotometer were used.

All n.m.r. spectra were recorded in solution using tetramethylsilane (δ 0·00, s) as the internal standard. Assignment of signals was made by comparison with the most appropriate correlation table.[72]

^{1}H n.m.r spectra were recorded on one of the following n.m.r. spectrometers; Hitachi Perkin-Elmer R-24 B or Varian EM 360 (60 MHz), Jeol P.S. 100 (100 MHz), Varian XL-200 (200 MHz), or a Jeol GMNGXFT-270 spectrometer (270 MHz). Multiplicities of the signals quoted with the spectroscopic data are; multiplet (m), quartet (q), triplet (t), doublet (d), and singlet (s). All values of chemical shifts and coupling constants for 60 and 200 MHz spectra are approximate.

^{13}C n.m.r. were recorded either on a Jeol FX 92 spectrometer (22·5 MHz), the Varian XL-200 spectrometer (50 MHz), or on the Jeol GMNGXFT-270 spectrometer (67·8 MHz). All signals were proton decoupled during acquisition. The degree of substitution for each atom was determined by DEPT experiments and, although not quoted, was at all times consistent with the assignments given. Assignment of signals was made by comparison with an appropriate correlation

table.[72]

Mass spectrometry was carried out on a VG 7070 E instrument, using a VG 200 data system. The spectra were determined under electron impact (70 or low eV), chemical ionisation (using isobutane or ammonia), or Fast Atom Bombardment, as stated. Where appropriate, High Resolution (HR) accurate mass data are quoted.

Thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} silica on aluminium foil plates, or Camlab silica on plastic plates, unless stated otherwise. Plates were developed in unlined tanks, with the eluant stated.

Column chromatography was performed using the medium pressure[73] or dry[74] "flash" techniques, with Merck Kieselgel 60_H No. 7736 silica gel, unless stated otherwise.

Measurement of pH was carried out using the appropriate range Whatman indicator paper.

Preparation of 3,5-Dihydroxybenzoic acid methyl ester (**87**).——A solution of 3,5-dihydroxybenzoic acid (262·5 g, 1·7 mol) in methanol (2·5 L) was heated reflux for 2 days. The pH of the cooled solution was adjusted to 7 with sodium hydroxide solution (30% w/v), and solvent was removed *in vacuo*. The wet, crude, product was recrystallised from water (2 L), following hot-filtration through celite. The residue was dried (vacuum-desiccator) to yield 3,5-dihydroxybenzoic acid methyl ester (231·6 g, 81%), m.p. 164-166 °C (lit.,[75,76] 165-165·5 °C from ethyl acetate-hexane, 165 °C) (Found: C, 57·3; H, 4·8. Calc. for $C_8H_8O_4$: C, 57·15; H, 4·8%); R_f 0·4 (methanol-chloroform 1:9); $\upsilon_{max.}$ (Nujol) 3360, 3210s, br (OH), 1675s cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 9·8 (2H, br s, OH), 7·0 (2H, d, *J* 3 Hz, 2-H and 6-H), 6·6 (1H, t, *J* 2 Hz, 4-H), 3·9 (3H, s, CH_3).

3-Benzoyloxy-5-hydroxybenzoic acid methyl ester[58] (**88**).——To a three-necked round-bottomed flask, equipped with a mechanical stirrer and two dropping-funnels, was added ester (**87**) (68·5 g, 0·41 mol). This was dissolved in water (820 ml), the pH was adjusted to 8 with sodium hydroxide solution (10% w/v), and the stirred solution was warmed at 40° (water-bath). Benzoyl chloride (52 ml, 0·50 mol) was added simultaneously with sodium hydroxide solution (163 ml) over a 30-40 minute period. The solution was maintained as close as possible to pH 8 throughout. The reaction mixture was stirred for a further 1 hour at 30-35°C, cooled, and the product extracted, with some difficulty, into chloroform (3 x 500 ml). The combined organic extracts were washed with saturated brine (2 x 250 ml) and water (250 ml) and dried (sodium sulphate). Evaporation of chloroform *in vacuo* gave the crude material, which was recrystallised twice from benzene to give benzoate (**88**) (58·3 g, 48%), m.p. 118·5-119·5 °C (lit.,[58] 110-112 °C) (Found: C, 66·3; H, 4·35. Calc. for

$C_{15}H_{12}O_5$: C, 66·15; H, 4·45%); R_f 0·2, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 3600-2900m (OH), 1800-1650s cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 10·3 (1H, s, OH), 8·15 (2H, m, 2'-H, 6'-H), 7·7 (3H, m, 3'-H, 4'-H, 5'-H), 7·3 (2H, d, *J* 4 Hz, 2-H and 6-H), 7·0 (1H, t, *J* 3 Hz, 2-H), 3·85 (3H, s, CH_3); *m/z* (70 eV EI) 272 (M^+, 4%), 241 (M^+-OMe, 2), 122 (40), 105 (PhCO, 100), 77 (Ph, 50).

3-Benzoyloxy-5-benzyloxybenzoic acid methyl ester[58] (89).——To a solution of benzoate (88) (1·7 g, 6·5 mmol) in acetone (20 ml) was added potassium carbonate (1·3 g, 9·5 mmol) and benzyl bromide (1·15 ml, 9·5 mmol). The magnetically stirred mixture was heated at reflux for 3 hours, before being poured into ice (15 ml) and extracted with chloroform (2 x 10 ml). The combined organic extracts were washed with sodium hydroxide solution (10%; 13 ml) and water (2 x 10 ml), before being dried (magnesium sulphate). Removal of solvent *in vacuo* produced an oily crude product (2·95 g), which clearly contained benzyl bromide. Light petroleum (b.p. 60——80 °C)(10 ml) was added to the crude material, which was stirred magnetically at 10 °C for 1 hour. The resultant white precipitate was collected by vacuum filtration, and the trituration was repeated to yield the purified product (1·65 g, 72%), m.p. 68·5-69·5 °C (lit.,[58] 69-70 °C) (Found: C, 72·8; H, 4·85. Calc. for $C_{22}H_{18}O_5$: C, 72·9; H, 5·0%); R_f 0·55, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 1790-1650s cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 8·20 (2H, dt,* *J* 7, 2 Hz, 2'-H, 6'-H), 7·66 (1H, tt, *J* 8, 1 Hz, 2-H), 7·59 (1H, dd, *J* 3, 1 Hz, 6-H), 7·52 (3H, m,* 3'-H, ,4'-H, 5'-H), 7·46-7·29 (5H, m, $CH_2C_6H_5$), 7·08 (1H, t, *J* 2 Hz, 4-H), 5·12 (2H, s, CH_2), 3·91 (3H, s, CH_3); *m/z* (70 eV EI) 362 (M^+, 5%), 331 (M^+-OMe, 2), 105 (COPh, 100), 91 ($PhCH_2$, 75), 77 (Ph, 25).

*One triplet was poorly resolved as a broad singlet.

*Appeared as a triplet with fine-structure. This could have been due to tt (3'-H, 5'-H), and dd (4'-H) superimposed, however such a definite assignment cannot be made.

5-Benzyloxy-3-Hydroxybenzoic acid methyl ester[58] (**79**).——To a solution of benzoate (**89**) (1·55 g, 4·2 mmol) in methanol (10 ml) was added *p*-toluenesulphonic acid (0·40 g, 2·1 mmol), and the reaction mixture was heated at reflux for 18 hours. Solvent was removed *in vacuo* and the resultant crude material was dissolved in chloroform (10 ml), washed with saturated sodium hydrogen carbonate solution (10 ml) and water (10 ml), and dried (magnesium sulphate). Solvent was evaporated *in vacuo* to give the product as an oil. Trituration, twice, of this residue with light petroleum (b.p. 60——80 °C) yielded phenol (**79**) as a white crystalline solid (0·85 g, 77%), m.p. 96·5-97·5 °C (lit.,[58] 97-98 °C) (Found: C, 69·4; H, 5·4. Calc. for $C_{15}H_{14}O_4$: C, 69·75; H, 5·45%); R_f 0·2, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 3620-2800m (OH), 1750-1660s cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 7·46-7·29 (6H, m, C_6H_5, 2-H), 7·18 (1H, dd,* 6-H), 6·69 (1H, t, *J* 2 Hz, 4-H), 5·06 (2H, s, CH_2), 3·90 (3H, s, CH_3); *m/z* (low eV EI) 258 (M^+, 100%), 226 (M^+-MeOH, 40), 91 ($PhCH_2$, 65).

*Too poorly resolved for determination of coupling constants.

3-Benzoyloxy-5-methoxybenzoic acid methyl ester (**90**).——Procedure as for benzoate (**89**), using dihydric phenol (**88**) (50·75 g, 0·19 mol), potassium carbonate (129 g, 0·9 mol), and methyl iodide (39·7 g, 0·3 mol). Work-up gave an oil, which, on standing, crystallised the product. Crystallisation from ethanol-water yielded *3-benzyloxy-5-methoxybenzoic acid methyl ester* (25·6 g,

48%), m.p. 48-50 °C (Found: C, 67·5; H, 4·9. $C_{16}H_{14}O_5$ requires C, 67·15; H, 4·95%); R_f 0·25, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 1715br cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 8·23-8·18 (2H, m, 2'-H, 6'-H), 7·69-7·62 (4H, m, 6-H, 3'-H, 4'-H, 5'-H), 7·66 (1H, tt, *J* 7, 2 Hz, 2-H), 6·99 (1H, t, *J* 2 Hz, 4-H), 3·92 (3H, s, CH_3), 3·87 (3H, s, CO_2CH_3); *m/z* (low eV EI) 286 (M^+, 90%), 105 (PhCO, 100) additionally, (70 eV EI) 77 (Ph, 25).

3-Hydroxy-5-methoxybenzoic acid methyl ester (**91**).——Procedure as for phenol (**79**), using phenol (**90**)(0·48 g, 1·7 mmol). Work up produced a pale yellow oil, from which the product crystallised overnight. Trituration with light petroleum (b.p. 60——80 °C) yielded a fine white solid, 3-hydroxy-5-methoxybenzoic acid methyl ester (0·15 g, 48%), m.p. 94-95°C (Lit.,[77,78] 104-106 °C from ether- light petroleum, 94-95 °C from ether-hexane) (Found: C, 58·6; H, 5·45. Calc. for $C_9H_{10}O_4$: C, 59·35; H, 5·55%); R_f 0·15, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 3280br (OH), 1710 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6) 9·89 (1H, s, OH), 6·98 (1H, dd,* 2-H), 6·92 (1H, dd,* 6-H), 6·59 (1H, t, *J* 2 Hz, 4-H), 3·82 (3H, s, CH_3), 3·75 (3H, s, CO_2CH_3); *m/z* (70 eV EI) 182 (M^+, 95%), 151 (M^+-MeO, 100), 123 (M^+-CO_2Me, 40).

*Both coupling constants for the signal were *ca.* 2 Hz. so the two central peaks were poorly resolved.

3-Hydroxy-5-methoxybenzyl alcohol (**96**).——A round-bottomed flask (500 ml) was flame-dried under a stream of dry nitrogen. Lithium aluminium hydride (6·0 g, 0·15 mol) was added, and dry THF (200 ml), and the slurry stirred at 0 °C. Benzoate (**91**) (22·8 g, 0·13 mol) dissolved in THF (50 ml) was added

dropwise and stirred for 1 hour, during which time the solution warmed to room temperature. The stirred mixture was again chilled to 0 °C and the following were added dropwise; water (6 ml), 15% (w/v) sodium hydroxide solution (6 ml) and water (18 ml). The solution was filtered through celite to remove the resultant precipitate, and freed of solvent *in vacuo* to produce a colourless oil, from which a white solid (8·8 g) rapidly crystallised. Recrystallisation from ethanol yielded 3-hydroxy-5-methoxybenzyl alcohol (6·8 g, 35%), m.p. 83·5-84·5 °C (Found: C, 62·3; H, 6·5. Calc. for $C_8H_{10}O_3$: C, 62·35; H, 6·55%); R_f 0·0, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ (Nujol) 3480 cm^{-1} (OH); δ_H (270 MHz; DMSO-D_6) 9·31* (1H, s, OH), 6·35-6·29 (2H, m, 2-H, 6-H), 6·17 (1H, t, *J* 2 Hz, 4-H), 5·09* (1H, t, *J* 6 Hz, CH_2OH), 4·36 (2H, d,* *J* 6 Hz, CH_2), 3·67 (3H, s, CH_3); *m/z* (70 eV EI) 154 (M^+, 100%), 125 (M^+-CHO, 35).

*On addition of D_2O, the shifts at δ 9·31 and δ 5·09 disappeared, and the signal at δ 4·36 collapsed to a singlet.

Pyridinium chlorochromate.[60]——Chromium trioxide (100 g, 1 mol) was added quickly to stirred 6M hydrochloric acid (184 ml) in a conical flask (500 ml). After 5 minutes, the dark red-orange solution was cooled to 0 °C, using an ice-bath which was then removed. Pyridine (79·5 ml) was added dropwise to the stirred solution, during the course of 10-12 minutes. This caused the solution to warm to 35-40 °C , and some precipitation of product. Chilling the mixture in an ice-bath precipitated the product, which was collected and dried in a vacuum-desiccator overnight to yield pyridinium chlorochromate (196 g, 91%) (Found: C, 27·85; H, 2·8; N, 6·45. Calc. for $C_5H_6ClCrNO_3$: C, 27·85; H, 2·8; N, 6·5%).

3-Hydroxy-5-methoxybenzaldehyde (**97**).——The benzyl alcohol (**96**)(6·5 g, 42 mmol) dissolved in dichloromethane (25 ml) was added to a suspension of pyridinium chlorochromate[60] (13·7 g, 64 mmol) in dichloromethane (50 ml), stirred at 0° in a round-bottomed flask equipped with a reflux condenser. The mixture, which rapidly became dark brown-black, was allowed to warm to room temperature. After 2 hours t.l.c. showed only a trace of starting alcohol. Ether (75 ml) was added, and the resultant mixture was filtered through a plug of magnesium trisilicate (or Florisil). The residue and plug were washed with ether (3 x 20 ml), and the filtrate was freed of solvent *in vacuo* to produce a pale yellow-green oil (3·1 g) which solidified overnight. The crude product was crystallised from ethanol-water to yield 3-hydroxy-5-methoxybenzaldehyde (1·1 g, 17%), m.p. 116-118 °C (Lit.,[79] 129-130 °C from water) (Found: C, 63·4; H, 5·55. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3%); R_f 0·3, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 3260br (OH), 1675 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6) 9·99* (1H, s, OH), 9·86 (1H, s, CHO), 6·91 (1H, dd, *J* 2, 1 Hz, 2-H), 6·88 (1H, dd, *J* 2, 1 Hz, 6-H), 6·64 (1H, t, *J* 2 Hz, 4-H), 3·77 (3H, s, CH_3); *m/z* (70 eV EI) 152 (M^+, 100%), 151 (55), 123 (M^+-CHO, 25), 108 (123-Me, 10). * Removed by addition of D_2O.

3-Hydroxy-5-methoxy-N-*(2,2-dimethoxyethyl)benzylamine* (**98**).——2,2-Dimethoxyethylamine (0·8 ml, 7·5 mmol) was added to aldehyde (**97**)(1·05 g, 7 mmol) dissolved in methanol (15 ml), and the solution was stirred overnight. Thereafter, no carbonyl stretch remained in the i.r. spectrum of an aliquot, concentrated and dissolved in chloroform. Sodium borohydride (1·3 g, 35 mmol) was added, with stirring continued for a further hour. The solution was acidified to pH 2, with concentrated hydrochloric acid, and allowed to stir for about an hour. The reaction mixture was next filtered and washed with ether,

before being carefully neutralised, and concentrated *in vacuo*, to remove methanol. The resultant solution was extracted with ether (3 x 50 ml) and the separated organic layer was dried (sodium sulphate). T.l.c., with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1) as eluant, showed that the major component was at the baseline; however there were also significant impurities at higher R_f values. Removal of solvent yielded crude *3-hydroxy-5-methoxy*-N-*(2,2-dimethoxyethyl)benzylamine*, as a viscous pale yellow oil (0·35 g, 21%). Data were collected on this crude material, $M^+ = 241{\cdot}1316$ ($C_{12}H_{19}NO_4$ requires: *M*, 241·1310); $\upsilon_{max.}$ ($CHCl_3$) 3640 (OH), 3270 cm^{-1} (NH); δ_H (270 MHz; DMSO-D_6) 9·35* (1H, s, OH), 7·75* (br m), 6·33 (2H, br s, 2-H, 6-H) 6·19 (1H, t, *J* 2 Hz, 4-H), 4·41 (1H, t, *J* 5 Hz, CH), 3·68 (3H, s, $ArOCH_3$), 3·59* (2H, s, $ArCH_2$), 3·25 (6H, s, CH_3), 2·56 (2H, d, *J* 5 Hz, CH_2); *m/z* (70 eV EI) 241 (M^+, 5%), 209 (M^+-MeOH, 2), 178 (209-MeO, 10), 166 (M^+-$(MeO)_2CH$, 35), 137 (166-CHO, 80), 75 ($(MeO)_2CH$, 100).

*Signals removed by addition of D_2O. Shift at δ 7·75 was assigned as NH solely on this basis, although the integral is not quite one.

*Signal *apparently* removed by addition of D_2O. It is more likely that it became coincident with the DMSO signal from which it was initially just resolved.

Attempted Synthesis of 7-Hydroxy-5-methoxy-1,2,3,4-tetrahydroiso-quinoline (95).——The following is a typical procedure:

Attempted isolation of the 4-hydroxy-intermediate (99). The crude diacetal amine (98)(0·35 g, 1·5 mmol) was dissolved in 6M hydrochloric acid (5 ml), and stirred for 18-24 hours. T.l.c. with various eluants indicated a large number of components. The aqueous solvent was removed, *in vacuo* at room temperature, to yield a pale yellow gum (0·17 g), *m/z* (70 eV EI) many peaks, but M^+ was not seen.

Hydrogenation of Product from Treatment of acetal (98) *with Hydrochloric Acid.*——The crude gum from the previous reaction (0·13 g) was dissolved in 6M hydrochloric acid (3-5 ml), and palladium (10%) on charcoal (0·35 g) was added. The round-bottomed flask (50 ml) was attached to an atmospheric hydrogenater. The apparatus was thrice evacuated and flushed with hydrogen, before being charged with the same gas, and equalised with atmospheric pressure. Reaction was initiated by magnetic stirring. After 5 hours, the apparatus was thrice evacuated and flushed with air, the mixture was then filtered through a plug of celite. Cautious removal of the aqueous solvent, *in vacuo* at room temperature, yielded a yellow gum which solidified overnight (0·11 g), m.p. 275-280 °C (dec.) (Found: C, 43·9; H, 5·6; N, 4·5. $C_{10}H_{14}ClNO_2$ requires C, 55·7; H, 6·55; N, 6·5%); $\upsilon_{max.}$ (KBr) 3420 (OH), 3170 cm^{-1} ($R_2NH_2^+$); δ_H (200 MHz; DMSO-D_6) broad and ill-resolved peaks at 9·45, 6·37, 4·30, 3·67; *m/z* (^{i}Bu CI) many peaks - all fragments from acetal (98) appear, also 175 (55%).

3,4-Dimethoxy-N-*(2,2-dimethoxyethyl)benzylamine*[55] (80, R^1, R^2, R^3 = Me).——3,4-Dimethoxybenzaldehyde (3·5 g, 21 mmol), was dissolved in methanol (35 ml), and 2,2-dimethoxyethylamine (2·2 g, 21 mmol) was added. The solution was left to stir overnight. The solution was transferred to a Paar hydrogenation bomb and degassed thoroughly with dry nitrogen gas. Palladium (10%) on charcoal (0·54 g), suspended in methanol (10 ml), which was also degassed. The catalyst was added to the bomb, and following three evacuation and hydrogen flush cycles, the mixture was hydrogenated, at room temperature and 60 p.s.i., for three hours. The evacuation and flush cycles were repeated, using nitrogen gas, and the bomb was pressurised with nitrogen and agitated for 15 minutes. The solution was filtered through celite, and removal of methanol *in*

vacuo yielded a straw-coloured, viscous, oil, 3,4-dimethoxy-*N*-(2,2-dimethoxyethyl)benzylamine (5·1 g, 94%) (Found: C, 60·0; H, 8·25; N, 5·3. Calc. for $C_{13}H_{21}NO_4$: C, 61·15; H, 8·3; N, 5·45%); M^+ = 255·1401 (Calc. for $C_{13}H_{21}NO_4$: *M*, 255·1469); R_f 0·0, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1); $\upsilon_{max.}$ (film) 3460br cm^{-1} (NH); δ_H (270 MHz; $CDCl_3$) 6·88 (1H, d, *J* 2 Hz, 6-H), 6·83 (2H, t, *J* 2 Hz, 2-H, 5-H), 4·49 (1H, t, *J* 5 Hz, CH), 3·88, (3H, s, $ArOCH_3$), 3·85 (3H, s, $ArOCH_3$), 3·74 (2H, s, $ArCH_2$), 3·36 (6H, s, CH_3), 2·74 (2H, d, *J* 5 Hz, CH_2) 1·87* (br s); δ_C (68 MHz; $CDCl_3$) 148·71 (C-3), 147·81 (C-4), 132·53 (C-1), 119·97 (C-6), 111·15 (C-5), 110·83 (C-2), 103·56 (C-2'), 55·59, 55·53 ($ArOCH_3$), 53·58 (CH_3), 53·36 (C-1'), 50·11 ($ArCH_2$); *m/z* (^{i}Bu CI) 447 (2(M^+-MeOH)+1, 5%), 256 (M^++1, 50), 192 (256-2MeOH, 40), 151 ($(MeO)_2PhCH_2$, 100).

*Water signal may include amine proton resonance.

6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[56] (**82**, R^1, R^2 = Me).——Process similar to that for attempted synthesis of benzyl alcohol (**99**). The crude, oily, amine (**80**, R^1, R^2, R^3 = Me) (1·0 g, 4 mmol) was dissolved in 6M hydrochloric acid (5 ml). This produced a clear orange solution which was allowed to stand overnight. There was no precipitate, even after concentration *in vacuo* to half the original volume. Addition of ethanol (10 ml) lead to gradual separation of pale yellow crystals. The mixture was chilled to 0 °C, and the crystals were collected and washed with a small volume of ice-cold ethanol. After drying in a vacuum-desiccator overnight, 6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride was recovered as a white solid (0·29 g, 29%), m.p. 181-183 °C (dec.) (lit.,[80] 192 °C from propan-2-ol) (Found: C, 54·0; H, 6·7; N, 5·65. Calc. for $C_{11}H_{16}ClNO_3$: C, 53·75; H, 6·55; N, 5·7%); $\upsilon_{max.}$ (Nujol) 3310 cm^{-1} (OH and NH); δ_H (270 MHz; DMSO-D_6) 10·16*

(1H, br s, $R_2NH_2^+$), 9·48* (1H, br s, $R_2NH_2^+$), 7·02 (1H, s, 5-H or 8-H), 6·84 (1H, s, 8-H, or 5-H), 6·4-5·2* (1H, br s, OH), 4·79 (1H, t, *J* 4 Hz, CH), 4·12 (2H, br s, ArCH_2), 3·75 (3H, s, CH_3), 3·74 (3H, s, CH_3), 3·21, 3·35* (2H, m, CH_2); δ_C (68 MHz; DMSO-D_6) 148·75 (C-7), 148·36 (C-6), 127·82 (C-8a), 120·59 (C-4a), 111·67 (C-8 or C-5), 109·30 (C-5 or C-8), 61·69 (C-4), 55·72, 55·65 (CH_3), 47·35 (C-3), 43·36 (C-1); *m/z* (70 eV EI) 209 (M^+, 20%), 180 (M^+-1-CO, 100), 179 (40), 36 (HCl, 25), additionally (^{i}Bu CI) 192 (M^+-OH, 100), 190 (30).

*Removed by the addition of D_2O.

*Expansion indicates this was what was assumed to be two very poorly resolved multiplets. The signals apparently collapse to a triplet on addition of D_2O.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**83**, R^1, R^2 = Me).——The white solid benzyl alcohol (**82**, R^1, R^2 = Me)(0·12 g, 0·5 mmol) was dissolved in 6M hydrochloric acid (5 ml), to which was added palladium (10%) on charcoal (0·12 g). The mixture was hydrogenated as for attempted synthesis of compound (**95**). Work-up gave pale yellow crude product (23 mg), which was recrystallised from ethanol to yield 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**83**, R^1, R^2 = Me)(17 mg, 15%), m.p. 253-255°C (mixed m.p. 254-256 °C; lit.,[55,61,81] 251-252 °C, 263-265 °C, 253°C) (Found: C, 57·3; H, 7·0; N, 6·0. Calc. for $C_{11}H_{16}ClNO_2$: C, 57·5; H, 7·0; N, 6·1%); $\upsilon_{max.}$ (Nujol) no peaks of interest - $R_2NH_2^+$ obscured by Nujol; δ_H (270 MHz; DMSO-D_6) 9·80* (2H, s, $R_2NH_2^+$), 6·82 (1H, s, 5-H or 8-H), 6·78 (1H, s, 8-H or 5-H), 4·10 (2H, s, Ar$CH_2NH_2^+$), 3·73 (3H, s, CH_3), 3·72 (3H, s, CH_3), 3·27 (2H, t, *J* 6 Hz, ArCH_2), 2·92 (2H, t, *J* 6 Hz, CH_2); δ_C (DMSO-D_6) 148·07 (C-6), 147·51 (C-7), 123·68 (C-8a), 120·27 (C-4a), 111·70 (C-8 or C-5), 109·83 (C-5 or C-8), 55·50, 55·43 (CH_3), 43·17 (C-3), 40·58 (C-1), 24·10 (C-4); *m/z* (70 eV EI) 193 (M^+, 65%), 192 (65), 164 (192-2Me, 100).

All physical data were in good accord with those obtained from an authentic sample.

*Removed by the addition of D_2O.

*3-Benzoyloxy-5-*p*-toluenesulphonyloxybenzoic acid methyl ester* (**92**).——Procedure as for ether (**89**), using benzoate (**88**) (2·0 g, 7·5 mmol), potassium carbonate (2·1 g, 15·1 mmol), and *p*-toluenesulphonyl chloride (1·6 g, 8·3 mmol). Work-up gave an oil, which was triturated with methanol. Crystallisation from methanol-water gave the crude product (3·1 g). Trituration of this material with light petroleum (b.p. 60——80 °C) yielded *3-benzoyloxy-5-*p*-toluenesulphonyloxybenzoic acid methyl ester* (2·4 g, 75%), 86·5-87·5 °C (Found: C, 62·1; H, 4·2. $C_{22}H_{18}O_7S$ requires C, 61·95; H, 4·25%); R_f 0·4, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 1770-1680s (C=O), 1370, 1170m cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$) 8·17 (2H, m, Ph 2-H, Ph 6-H), 7·82 (1H, dd, *J* 2, <2 Hz, 6-H), 7·76 (2H, d, *J* 8 Hz, 2'-H, 6'-H), 7·67 (1H, tt, *J* 7, 1 Hz, Ph 4-H), 7·56 (2H, m, Ph 3-H, Ph 5-H), 7·52 (1H, d, *J* 8 Hz, 2-H), 7·34 (2H, d, *J* 8 Hz, 3'-H, 5'-H), 7·40 (1H, t, *J* 2 Hz, 4-H), 3·90 (3H, s, CO_2CH_3), 2·45 (3H, s, CH_3); *m/z* (70 eV EI) 426 (M^+, 70%), 395 (M^+-OMe, 35), 155 (Ts, 37), 105 (PhCO, 100).

*3-Hydroxy-5-*p*-toluenesulphonyloxybenzyl alcohol* (**100**).——Procedure as for alcohol (**96**) using benzoate (**92**)(5·1 g, 12 mmol) in THF (10 ml), and lithium aluminium hydride (1·2 g, 32 mmol) in THF (35 ml). Work-up gave the crude product (3·2 g) which was crystallised from ethanol to yield *3-hydroxy-5-*p*-toluenesulphonyloxybenzyl alcohol* (1·8 g, 50%), m.p. 99-100 °C (Found: C, 56·9; H, 4·75. $C_{14}H_{14}O_5S$ requires C, 57·15; H, 4·8%); R_f 0·2, ethyl

acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 3260br (OH), 1360, 1170m cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$-DMSO-D_6) 9·23 (3H, s, ArOH), 7·72 (2H, d, *J* 8 Hz, 2'-H, 6'-H), 7·33 (2H, d *J*, 8 Hz, 3'-H, 5'-H), 6·76 (1H, br s,* 6-H), 6·48 (1H br s,* 2-H), 6·40 (1H, t, *J* 2 Hz, 4-H), 4·47 (2H, s,* CH_2), 2·46 (3H, s, CH_3); *m/z* (low eV EI) 294 (M^+, 100%), 258 (M^+-$2H_2O$, 50), 230 (M^+-SO_2, 45), 226 (25), 212 (230-H_2O, 25), 91 (MeC_6H_4, 100).

*Poorly resolved, probably triplets or doublets of doublets.

*Broad H_2O peak at δ 2·82 may have incorporated CH_2OH shift, which would explain the absence of the anticipated coupling in the benzylic signal.

3-Hydroxy-5-p-*toluenesulphonyloxybenzaldehyde* (**101**).——Procedure as for aldehyde (**97**), using alcohol (**100**)(1·5 g, 5 mmol), in dichloromethane (10 ml), and pyridinium chlorochromate (1·6 g, 7 mmol). Work-up provided the crude aldehyde, which was crystallised from ethanol-water to yield *3-hydroxy-5*-p-*toluenesulphonyloxybenzaldehyde* (1·4 g, 90%), m.p. 110-112 °C (Found: C, 57·0; H, 4·25. $C_{14}H_{12}O_5S$ requires C, 57·55; H, 4·15%); R_f 0·5, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 3240br (OH), 1690 (C=O), 1365, 1160m cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$) 9·82 (1H, s, CHO), 7·74 (2H, d, *J* 8 Hz, 2'-H, 6'-H), 7·34 (2H, d, *J* 8 Hz, 3'-H, 5'-H), 7·27 (1H, dd, *J* 2, 1 Hz, 2-H), 7·04 (1H, dd, *J* 2, 1 Hz, 6-H), 6·88 (1H, t, *J* 2 Hz, 4-H), 5·90 (1H, s, OH), 2·46 (3H, s, CH_3); *m/z* (low eV EI) 292 (M^+, 95%), 228 (M^+-SO_2, 100), 155 (Ts, 60).

5-Methoxy-3-p-*toluenesulphonyloxybenzaldehyde* (**102**).——*Method A*. Procedure as for ether (**89**), using phenol (**101**)(1·35 g, 4·6 mmol), potassium carbonate (1·9 g, 13·9 mmol), and methyl iodide (0·45 ml, 6·9 mmol). Work-up gave a pale yellow solid (1·4 g), which was crystallised from ethanol to

yield *5-methoxy-3*-p-*toluenesulphonyloxybenzaldehyde* (1·1 g, 79%), m.p. 66-70 °C 66-70°C (Found: C, 58·7; H, 4·55. $C_{15}H_{14}O_5S$ requires C, 58·8; H, 4·6%); R_f 0·7, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1); $\upsilon_{max.}$ ($CHCl_3$) 1695 (C=O), 1370, 1175m cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$) 9·85 (1H, s, CHO), 7·74 (2H, dt, *J* 8, <1 Hz, 2'-H, 6'-H), 7·34 (2H, dd, *J** 8, <1 Hz, 3'-H, 5'-H), 7·29 (1H, dd, *J* 2, 1 Hz, 2-H), 7·06 (1H, dd, *J* 2, 1 Hz, 6-H), 6·85 (1H, t, *J* 2 Hz, 4-H), 3·82 (3H, s, OCH_3), 2·46 (3H, s, CH_3); *m/z* (low eV EI) 306 (M^+, 100%), 242 (M^+-SO_2, 55), 214 (M^+-MePh, 55), 155 (Ts, 40).

*Fine structure visible, however the additional coupling constant(s) could not be resolved.

Method B. Procedure as above, using phenol (**97**) (68 mg, 0·5 mmol), potassium carbonate (0·68 g, 5 mmol), and *p*-toluenesulphonyl chloride (0·10 g, 0·6 mmol). Work-up gave the crude product (0·13 g) and crystallisation yielded tosylate (**102**), (59 mg, 43%), m.p. 65-67 °C (Found: C, 59·0; H, 4·6%); all other physical data in good accord with that from the previous sample.

5-Methoxy-3-p-*toluenesulphonyloxy*-N-*(2,2-dimethoxyethyl)benzylamine* (**103**).——Procedure as for benzylamine (**98**), using benzaldehyde (**102**)(98 mg, 0·3 mmol), dissolved in methanol (10 ml), and 2,2-dimethoxyethylamine (37 mg, 0·4 mmol). The mixture was reduced as before, to yield a yellow oil; crude *5-methoxy-3*-p-*toluenesulphonyloxy*-N-*(2,2-dimethoxyethyl)benzylamine* (0·12 g, 91%) (Found: C, 57·1; H, 3·0; N, 6·4. $C_{19}H_{25}NO_6S$ requires C, 57·7; H, 3·55; N, 6·35%); M^+ = 395·1430 ($C_{19}H_{25}NO_6S$ requires: *M*, 395·1400); R_f 0·0, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1); $\upsilon_{max.}$ (film) 3305w (NH), 1355, 1170 cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$) 7·74 (2H, d, *J* 8 Hz, 2'-H, 6'-H), 7·46 (2H, d, *J* 8 Hz, 3'-H, 5'-H), 6·85 (1H, dd,* 2-H), 6·59 (1H, dd,* 6-H), 6·40 (1H, t,

J 2 Hz, 4-H), 4·35 (1H, t, *J* 6 Hz, CH), 3·66 (3H, s, $ArOCH_3$), 3·60 (2H, s, $ArCH_2$), 3·24 (6H, s, CH_3), 2·43 (2H, d,* *J* 5 Hz, CH_2), 2·42 (3H, s,* CH_3), NH not seen; *m/z* (^{i}Bu CI) 396 (M^++1, 65%), 364 (M^+-OMe, 100), 332 (364-MeOH, 40), 320 (M^+-$CH_2(OMe)_2$, 30), 291 ((TsO)(MeO)$PhCH_2$, 25), 75 ($CH_2(OMe)_2$, 60).

*Fine structure visible, however coupling constants could not be resolved.

*Shifts overlapped appearing as a lopsided doublet; assigned as quoted above.

*Attempted Synthesis of 7-Methoxy-5-*p*-toluenesulphonyloxy-1,2,3,4-tetrahydroisquinoline hydrochloride* (**105**).——The same procedure as for treatment of acetal (**98**) was applied:

With no attempt to isolate the 4-hydroxy-intermediate (**104**). Acetal (**103**)(1·1 g, 2·8 mmol) was dissolved in 6M hydrochloric acid (5 ml), with palladium (10%) on charcoal (0·56 g). Hydrogenation for 24 hours and work-up once more yielded a pale yellow gum (0·18 g). As with the attempted isolation of benzyl alcohol (**99**), t.l.c. (various eluants) indicated a complex mixture. Chromatography over silica gel resulted solely in loss of material, and physical data were acquired for the crude material (Found: C, 43·8; H, 4·8; N, 3·0. $C_{17}H_{20}ClNO_4S$ requires C, 55·2; H, 5·45, N, 3·8%); M^+ = 333·0812 (Calc. for $C_{17}H_{19}NO_4S$: *M*, 333·1034); $\upsilon_{max.}$ ($CHCl_3$) 3320br (OH), 2920, 2770w (RNH_2^+), 1590br, 1370, 1170w cm^{-1} (SO_3); δ_H (270 MHz; DMSO-D_6) included 9·85 (<1H, s), 7·75 (2H, dt, *J* 8, <1 Hz), 7·35 (2H, d, *J* 8 Hz), 7·30 (1H, dd, *J* 2, 1 Hz), 7·06 (1H, dd, *J* 2, 1 Hz), 6·85 (1H, t, *J* 2 Hz), 3·82 (<3H, s); m/z (^{i}Bu CI) included peaks of interest, 350 (20%), 334 (M^++1, 40), 307 (40).

Attempted isolation of the 4-hydroxy-intermediate (**104**). Diacetal amine (**103**)(27 mg, 0·05 mmol), was dissolved in 6M hydrochloric acid (2-3 ml), and stirred for

18-24 hours. Work-up as above yielded a pale yellow gum (22 mg), $\upsilon_{max.}$ ($CHCl_3$) 3320br (OH), 2920, 2770w ($R_2NH_2^+$), 1590br, 1370, 1170w cm^{-1} (SO_3); δ_H (270 MHz; DMSO-D_6) spectrum of complex mixture; *m/z* (70 eV EI) 349 (M^+, 60%), 348 (50), 320 (M^+-CO, 40), 165 (320-Ts, 75), 155 (Ts, 45), 91 (MeC_6H_4, 100), 36 (HCl, 95), (^{i}Bu CI) additionally, 332 (M^+-OH), 307 ((MeO)(TsO)PhCHO+1, 30), 291 ((MeO)(TsO)PhCH_2+1, 100), 176 (332-TsH, 45).

Hydrogenation of Product from Treatment of acetal (**103**) *with Hydrochloric Acid.* The crude gum from the previous reaction (12 mg) was dissolved in 6M hydrochloric acid (2-3 ml), and palladium (10%) on charcoal (0·05 g) was added. Hydrogenation followed by work-up produced a yellow gum which solidified overnight (9 mg), δ_H* (270 MHz; DMSO-D_6) 7·84 (m), 7·51 (m), 6,88 (d, *J* 2 Hz), 6·67 (d, *J* 2 Hz), 6·52 (dd, *J* 6, 2 Hz); *m/z* (^{i}Bu CI) 350 (349+1, 50%), 333 (M^+ for tetrahydroisoquinoline (**105**), 25), 332 (110), 330 (35), 320 (40), 176 (25), 91 (30). Other physical data were comparable to that for the previous reaction.

*All chemical shifts and coupling constants are approximate.

3,5-Dibenzyloxybenzoic acid methyl ester (**117**).——Procedure as for benzyl ether (**89**), using diphenol (**87**)(52·6 g, 0·31 mol) dissolved in acetone (500 ml), potassium carbonate (216·0 g, 1·6 mol), and benzyl bromide (117·6 g, 0·69 mol). Work-up afforded a pale yellow oil which from which the crude product (101 g) crystallised. Recrystallisation from propan-2-ol provided purified 3,5-dibenzyloxybenzoic acid methyl ester (85·3 g, 78%), m.p. 67-68 °C (lit.,[75,82] 68-69.5 °C from ethanol, 63-66 °C from benzene-hexane) (Found: C, 75·9; H,

5·8. Calc. for $C_{22}H_{20}O_4$: C, 75·8; H, 5·8%); R_f 0·45, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2); $\upsilon_{max.}$ (KBr) 1720 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 7·44-7·30 (10H, m, C_6H_5), 7·28 (2H, d, *J* 2 Hz, 2-H, 6-H), 6·78 (1H, t, *J* 2 Hz, 4-H), 5·03 (4H, s, CH_2), 3·87 (3H, s, CH_3); *m/z* (EI) included 348 (M^+, 30%), 333 (M^+-Me, 1), 317 (M^+-MeO, 5), 289 (M^+-CO_2Me, 1), 271 (M^+-Ph, 1), 257 (M^+-CH_2Ph, 1), 91 ($PhCH_2$, 100).

3,5-Dibenzyloxybenzyl alcohol (**118**).—— Procedure as in the case of benzyl alcohol (**96**) using ester (**117**)(12·9 g, 37·1 mmol) in THF (25 ml), and lithium aluminium hydride (2·1 g, 58·6 mmol) in THF (100 ml). Work up gave the crude product as a off-white solid (11·1 g) This was crystallised, with difficulty, from ethanol-water to yield 3,5-dibenzyloxybenzyl alcohol (9·8 g, 83%), m.p. 79-80 (Lit.,[75,82] 80-80.5 °C from ether, 81.5-82 °C from benzene-hexane)(Found: C, 78·5; H, 6·35. Calc. for $C_{21}H_{20}O_3$: C, 78·75; H, 6·3%); R_f 0·2, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2); $\upsilon_{max.}$ (KBr) 3330 cm^{-1} (OH); δ_H (200 MHz; DMSO-D_6) 7·51-7·27 (10H, m, C_6H_5), 6·62 (2H, d, *J* 2 Hz, 2-H, 6-H), 6·55 (1H, t, *J* 2 Hz, 4-H), 5·13* (1H, t, *J* 6 Hz, OH), 5·10* (4H, s, $PhCH_2$), 4·27 (2H, d, *J* 6 Hz, CH_2); *m/z* (EI) Included 320 (M^+, 20%), 304 (M^+-O, 1), 289 (M^+-MeO, 5), 229 (M^+-CH_2Ph, 5), 211 (229-H_2O, 5), 199 (229-CH_2O, 1), 91 (CH_2Ph, 100).

*Signal at 5·10 overlapped one outer peak of the triplet at 5·13.

3,5-Dibenzyloxybenzaldehyde (**119**).——Procedure as for aldehyde (**97**), using benzyl alcohol (**118**)(4·5 g, 14 mmol), in dichloromethane (20 ml), and pyridinium chlorochromate (4·6 g, 21 mmol). Work-up provided the crude solid aldehyde (5·4 g), which was crystallised from propan-2-ol to yield

3,5-dibenzyloxybenzaldehyde (3·2 g, 71%), m.p. 78·5-79·5 °C (Lit.,[82] 76.5-77 °C from benzene-hexane) (Found: C, 79·0; H, 5·7. Calc. for $C_{21}H_{18}O_3$: C, 79·25; H, 5·7%); R_f 0·45, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2); $\upsilon_{max.}$ (KBr) 1690 cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 9·83 (1H, s, CHO), 7·44-7·24 (10H, m, C_6H_5), 7·07 (2H, d, *J* 2 Hz, 2-H, 6-H), 6·83 (1H, t, *J* 2 Hz, 4-H), 5·06 (4H, s, CH_2); *m/z* (EI) included 318 (M^+, 95%), 300 (M^+-H_2O, 1), 290 (M^+-CO, 1), 227 (M^+-CH_2Ph, 5), 199 (227-CO, 5), 91 (CH_2Ph, 100).

3,5-Dibenzyloxy-N-*(2,2-dimethoxyethyl)benzylamine* (**120**).——Procedure as for amine (**98**), using aldehyde (**119**)(2·9 g, 9·2 mmol), dissolved in methanol (50 ml), and 2,2-dimethoxyethylamine (1·1 g, 10·2 mmol). Reduction and work-up yielded a pale yellow oil; crude *3,5-dibenzyloxy*-N-*(2,2-dimethoxyethyl)benzylamine* (3·2 g, 85%) (Found: C, 72·0; H, 3·3; N, 7·15. $C_{25}H_{29}NO_4$ requires C, 73·7; H, 3·45; N, 7·15%); M^+ = 407·2117 ($C_{25}H_{29}NO_4$ requires: *M*, 407·2093); R_f 0·05, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2); $\upsilon_{max.}$ (film) 3300 cm^{-1} (NH); δ_H (200 MHz; DMSO-D_6) 7·48-7·26 (10H, m, C_6H_5), 6·61 (2H, d, *J* 2 Hz, 2-H, 6-H), 6·54 (1H, t, *J* 2 Hz, 4-H), 5·06 (4H, s, PhCH_2), 4·39 (1H, t, *J* 6 Hz, CH), 3·64 (2H, s, ArCH_2), 3·24 (6H, s, CH_3), 2·55 (2H, d, *J* 6 Hz, CH_2), 1·95 (1H, br s, NH); *m/z* (EI) included 407 (M^+, 5%), 375 (M^+-MeOH, 5), 364 (1), 344 (375-MeO, 10), 333 (10), 332 (M^+-$CH(OMe)_2$, 40), 319 ($(BnO)_2PhCH_2NH_2$, 5), 303 (319-NH_2, 45), 242 (333-CH_2Ph, 1), 211 (303-PhMe, 5), 105 ($(MeO)_2CHCH_2NH_2$, 5), 91 (CH_2Ph, 100).

Trifluoromethanesulphonic anhydride.[63]—— Trifluoromethane sulphonic acid (10 ml, 11·3 mmol) was pipetted rapidly into the pear-shaped flask of a one-piece, "short-path" distillation apparatus, which had been oven-dried.

Phosphorous pentoxide (10 g) was added, and the sealed apparatus was left to stand for five hours. The still-head was then well lagged, and the reaction flask was heated (oil-bath) to between 100-120 °C. The colourless fraction boiling at 80-82 °C (lit.,[64] 84 °C) was collected, and stored over 4Å molecular sieves, yielding trifluoromethanesulphonic anhydride (3·4 g, 22%). This was stored in an air-tight Wheaton serum bottle over 4 Å molecular sieves.

3,5-Dibenzyloxy-N-*(2,2-dimethoxyethyl)*-N-*trifluoro-methanesulphonylbenzylamine* (**121**).——All glassware was flame-dried. Crude amine (**120**)(2·8 g, 6·8 mmol) was dissolved in dry dichloromethane (15 ml) and stirred at -78 °C (cardice-acetone bath), under a flow of dry nitrogen gas. Triethylamine (1·3 ml, 8·1 mmol) was added, and the solution was stirred for 10 minutes. Trifluoromethanesulphonic anhydride (1·1 ml, 6·8 mmol) was added dropwise, over the course of 5-8 minutes, leading to slight yellowing of the solution. After 15 minutes, the bath was removed and the stirred solution was allowed to warm to about 0°C. Saturated brine (25 ml) was added, with no fuming, and the mixture was transferred to a separating funnel. The organic phase was washed with 2M hydrochloric acid (25 ml) and saturated brine (25 ml), before being dried (sodium sulphate). Removal of solvent *in vacuo* produced a bright yellow oil (3·8 g). T.l.c., with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3) as eluant, showed this to contain one major component at R_f 0·65 and minor ones at R_f 0·5 and R_f 0·25. Chromatography on silica gel with the same eluant yielded a viscous, colourless, oil. Addition of methanol caused precipitation of a white solid, *3,5-dibenzyloxy*-N-*(2,2-dimethoxyethyl)*-N-*trifluoromethanesulphonylbenzylamine* (2·3 g, 63%), m.p. 55 °C (Found: C, 58·0; H, 5·25; N, 2·55. $C_{26}H_{28}F_3NO_6S$ requires C, 57·9; H, 5·25; N, 2·6%); R_f 0·65, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 1365, 1135

cm^{-1} (NSO_2); δ_H (270 MHz; $CDCl_3$) 7·46-7·34 (10H, m, C_6H_5), 6·57 (3H, s, 2-H, 4-H, 6-H), 5·03 (4H, s, PhCH_2), 4·55 (2H, br s, ArCH_2), 4·43 (1H, t, *J* 5 Hz, CH), 3·34 (6H, s, Me), 3·29 (2H, br d,* CH_2); *m/z* (70 eV EI) 539 (M^+, 5%), 346 ($(BnO)_2PhCH_2NCHCH_3$, 3), 303 ($(BnO)_2PhCH_2$, 2), 217 (1), 181 ($(HO)_2PhCH_2NHCH_2CHO$, 5), 149 ($CF_3SO_2NH_2$, 2), 111 (1), 91 (CH_2Ph, 100), 75 ($(MeO)_2CH$, 95), additionally (^{i}Bu CI) 508 (M^+-MeO,30).

*Poorly resolved; coupling constant could not be determined.

3,5-Dihydroxy-N-*(2,2-dimethoxyethyl)*-N-*trifluoro-methanesulphonylbenzylamine* (**114**).——Dibenzyloxy triflate (**121**)(1·6 g, 3·0 mmol), was dissolved in methanol (25 ml) by gentle warming. Palladium (10%) on charcoal (0·16 g) was added in methanol (5-6 ml). Hydrogenation was carried out, on the cooled mixture, as for the attempted synthesis of tetrahydroisoquinoline (**95**). After 3 hours, the mixture was worked-up. Removal of solvent *in vacuo* produced an orange-red oil. Chromatography on silica gel with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2) as eluant yielded a colourless oil, *3,5-dihydroxy*-N-*(2,2-dimethoxyethyl)*-N-*trifluoro-methanesulphonlybenzylamine* (1·0 g, 90%) (Found: C, 41·8; H, 5·15; N, 3·4. $C_{12}H_{16}F_3NO_6S$ requires C, 40·1; H, 4·5; N, 3·9%); M^+ = 359·0642 (Calc. for $C_{12}H_{16}F_3NO_6S$: *M*, 359·0648); R_f 0·3, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:2); $\upsilon_{max.}$ (film) 3450 (OH), 1370, 1140 cm^{-1} (NSO_2); δ_H (270 MHz; DMSO-D_6) 9·41 (2H, s, OH), 6·23 (2H, d, *J* 2 Hz, 2-H, 6-H), 6·18 (1H, t, *J* 2 Hz, 4-H), 4·44 (2H, br s, ArCH_2), 4·37 (1H, t, *J* 5 Hz, CH), 3·31* (2H, br s, CH_2), 3·25 (6H, s, CH_3); *m/z* (^{i}Bu CI) 359 (M^+, 1%), 328 (M^+-MeO, 60), 296 (328-MeOH, 60), 226 (M^+-SO_2CF_3, 15), 162 (226-2MeOH, 10), 123 ($(HO)_2PhMe$, 10), 75 ($(MeO)_2CH$, 100).

*Unresolved; perhaps a doublet.

Attempted Synthesis of 4,5,7-Trihydroxy-2-trifluoromethanesulphonyl-1,2,3,4-tetrahydroisoquinoline (**115**).——The procedure was similar to that used in the attempted preparation of benzyl alcohol (**99**). Acetal (**114**)(1·15 g, 3·2 mmol) was dissolved in methanol (1 ml). 6M Hydrochloric acid (50 ml), made up from conc. hydrochloric acid dissolved in methanol, was added. The resultant cloudy white solution was stirred magnetically and after a few minutes a yellow-white solid rapidly separated. The clear aqueous layer was extracted* with ether (2 x 50 ml), and the combined organic extracts were washed with brine (2 x 75 ml) and dried (sodium sulphate). Removal of solvent *in vacuo* yielded a pale yellow foam, which rapidly hardened to give a non-crystalline yellow solid (0·99 g). T.l.c with various eluants indicated the material consisted of several components, but column chromatography resulted merely in the loss of material. Data were collected for the crude solid, m.p. above 250 °C (dec.) (Found: C, 42·2; H, 3·8; N, 4·2. $C_{10}H_{10}F_3NO_5S$ requires C, 38·35; H, 3·2; N, 4·45%); $\upsilon_{max.}$ (Nujol) 3460br (OH), 1375, 1145 cm^{-1} (NSO_2); δ_H (270 MHz; DMSO-D_6) spectrum of complex mixture; *m/z* (+F.A.B.)* 888, (1%), 887 (1), 886 (3), 885 (M_3^++1 = trimer,* 1), 752 (M_3^+-CF_3SO_2H, 5), 618 (752-CF_3SO_2H, 2), 591 (M_2^+= dimer,* 10), 457 (M_2^+-CF_3SO_2H, 10); (-F.A.B.) 885 (1%), 750 (1), 589 (3), 457 (1), 455 (5), 319 (4); (70 eV EI) 300 (2), 217 (3), 172 (2), 149 ($CF_3SO_2NH_2$, 4), 135 (1), 119 (C_2F_5, 1), 74 ($C_3H_6O_2$, 65), 59 (C_3H_7O, 100).

*On other occasions, the mixture was filtered instead.

*See Discussion.

2-Benzyloxy-4-methoxybenzaldehyde (**132**).—— Procedure as for ether (**89**), using 2-hydroxy-4-methoxybenzaldehyde (5·0 g, 33 mmol), potassium

carbonate (45·5 g, 0·3 mol), and benzyl bromide (5·6 g, 33 mmol). Work-up gave a pale yellow oil which, on trituration with light petroleum (b.p. 60——80 °C), crystallised the crude product (7·3 g, 91%), m.p. 59-63 °C (Lit.,[83] 69-70 °C from methanol) (Found: C, 73·9; H, 5·8. Calc. for $C_{15}H_{14}O_3$: C, 74·35; H, 5·8%); R_f 0·3, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 1665 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 10·37 (1H, d, *J* <1 Hz, CHO), 7·82 (1H, d, *J* 8 Hz, 6-H), 7·46-7·32 (5H, m, C_6H_5), 6·53* (1H, dd, *J* 8, 2 Hz, 5-H), 6·50 (1H, d, *J* 2 Hz, 3-H), 5·12 (2H, s, CH_2), 3·81 (3H, s, CH_3); δ_C (68 MHz; $CDCl_3$) 188·06 (CHO), 165·97 (C-4), 162·66 (C-2), 135·87 (C-1'), 130·32 (C-6), 128·60 (C-4'), 128·15 (C-3', C-5'), 127·18 (C-2', C-6'), 119·23 (C-1), 106·19 (C-5), 99·12 (C-3), 70·32 (CH_2), 55·50 (CH_3); *m/z* (low eV EI) 242 (M^+, 100%), 213 (M^+-CHO, 40), 151 (M^+-CH_2Ph, 25), 91 (CH_2Ph, 95).

*Each of the four peaks further split by an unresolved amount. Presumably this resulted from coupling to CHO.

2-Benzyloxy-4-methoxy-2'-nitrostyrene[71] **(133).**——

Synthesis under acidic conditions. Aldehyde **(132)** (1·6 g, 6·7 mmol) was dissolved in glacial acetic acid (15 ml), together with ammonium acetate (0·26 g, 3·4 mmol) and nitromethane (0·45 g, 7·4 mmol). The stirred solution was heated at reflux for five days. The cooled reaction mixture was poured into water (150 ml), and basified with saturated potassium carbonate solution, leading to the formation of a dark yellow-black solution and a black gum. The solution was extracted with chloroform (3 x 150 ml), and the combined extracts were washed with saturated brine (100 ml). The organic layer was dried (sodium sulphate), and removal of solvent gave a black, gummy, solid (1·7 g). Chromatography on silica with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:7) as eluant, followed by recrystallisation from ethanol yielded *2-benzyloxy-4-methoxy-2'-nitrostyrene*

(0·51 g, 27%), m.p. 109-110 °C (Found: C, 66·7; H, 5·25; N, 4·75. $C_{16}H_{15}NO_4$ requires C, 67·35; H, 5·3; N, 4·9%); R_f 0·35, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ 1550, 1320 cm^{-1} (NO_2); δ_H (270 MHz; $CDCl_3$) 8·12 (1H, d, *J* 13 Hz, ArC*H*), 7·79 (1H, d, *J* 14 Hz, $CHNO_2$), 7·45-7·34 (6H, m, C_6H_5, 6-H), 6·57 (1H, d, *J* 2 Hz, 5-H), 6·54 (1H, d, *J* 2 Hz, 3-H), 5·17 (2H, s, CH_2), 3·83 (3H, s, CH_3); δ_C (68 MHz; $CDCl_3$) 164·22 (C-2), 160·16 (C-4), 136·10 (C-6, C-1'), 135·55 (ArC*H*), 134·18 ($CHNO_2$), 128·86 (C-4'), 128·51 (C-3', C-5), 127.44 (C-2', C-6'), 112·61 (C-1), 106·29 (C-5), 99·96 (C-3), 70·77 (CH_2), 55·59 (CH_3); *m/z* (70 eV EI) 285 (M^+, 2%), 239 (M^+-NO_2, 2), 126 (20), 91 (CH_2Ph, 100).

Attempted synthesis under basic conditions.[71] Into a three-necked round-bottomed flask (100 ml), equipped with a mechanical stirrer, a dropping funnel and a thermometer, was added aldehyde (**132**)(3·2 g, 13·2 mmol). The starting material was dissolved in *p*-dioxane (20 ml), and nitromethane (0·89 g, 14·6 mmol) was added. The stirred solution was cooled to 0 °C (ice-bath). Sodium hydroxide (0·56 g, 13·9 mmol) was dissolved in water (5 ml) and the solution was made up to 10 ml with ice-water. The cold solution was added, dropwise, with vigorous stirring. When it became apparent that there was no violent reaction, the mixture was allowed to warm to room temperature. There was no "bulky white precipitate",[71] although each drop of alkali had caused a temporary milky whiteness. The mixture was stirred for a further 30 minutes, then left to stand for 15 minutes. The mixture was added to a separating funnel, and washed in with ice-water (50 ml), before being added slowly to 4M hydrochloric acid (25 ml) in a conical flask (250 ml). This produced a fluorescent green-yellow solution which was extracted with chloroform (2 x 50 ml), and the combined, coloured, organic layer was washed with saturated brine (50 ml) and

dried (sodium sulphate). Removal of solvent *in vacuo* produced a yellow-orange solid (0·73 g), which was recrystallised from ethanol twice to give a solid of the same colour which became darker orange on storing (0·22 g). This material was shown, by t.l.c. with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3) as eluant, by i.r., and ^{1}H n.m.r., to be a mixture of starting aldehyde (**132**) and the desired product, nitrostyrene (**133**).

Attempted Synthesis of 2-Benzyloxy-4-methoxy-2'-aminoethylbenzene (**127**).——The procedure was the same as for preparation of benzyl alcohol (**96**), using lithium aluminium hydride (77 mg, 2·0 mmol) stirred in dry THF (15 ml). A solution of nitrostyrene (**133**)(0·45 g, 1·6 mmol) in dry THF (5 ml) was added with rapid discharge of the yellow colour. The reaction mixture was worked-up as before, and t.l.c. with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3) as eluant revealed several spots at and near the baseline. Removal of solvent *in vacuo* yielded a yellow oil (0·27 g) (Found: C, 73·0; H, 4·35; N, 6·3. $C_{16}H_{19}NO_2$ requires C, 74·5; H, 5·5; N, 7·5%); $\upsilon_{max.}$ ($CHCl_3$) 3500-3200 cm^{-1}, no peaks at 1550 and 1320 cm^{-1} (NO_2); δ_H (270 MHz; DMSO-D_6) spectrum of complex mixture; *m/z* (70 eV EI) included 316 (1%), 271 (4), 257 (M^+, <1), 254 (3), 242* (3), 239 (3), 162 (6), 151* (1), 149 (6), 136 (3), 121 (2), 91 (100).

*See mass spectrum for aldehyde (**132**).

2-Methanesulphonyloxy-4-methoxybenzaldehyde (**134**).——2-Hydroxy-4-methoxybenzaldehyde (3·3 g, 22 mmol), was dissolved in dry ether (35 ml). Triethylamine (15·1 ml, 0·11 mol) was added to the magnetically stirred solution together with methanesulphonyl chloride (1·9 ml, 24 mmol). Work-up, as for aldehyde (**132**), gave a pale yellow oil (4·6 g), which was twice triturated with

light petroleum (b.p. 60——80 °C), to afford *2-methanesulphonyloxy-4-methoxybenzaldehyde* (2·1 g, 43%), m.p. 58-60 °C (Found: C, 47·0; H, 4·4. $C_9H_{10}O_5S$ requires C, 46·95; H, 4·4%); R_f 0·2, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ ($CHCl_3$) 1675 (C=O), 1370sh, 1175 cm^{-1} (SO_3); δ_H (270 MHz; $CDCl_3$) 10·13 (1H, d, *J* <1 Hz, CHO), 7·91* (1H, dd, *J* 8, <1 Hz, 6-H), 6·96* (1H, qd, *J* 9, 2, 1 Hz, 5-H), 6·93 (1H, d, *J* 2 Hz, 3-H), 3·90 (3H, s, OCH_3), 3·31 (3H, s, CH_3); δ_C (68 MHz; $CDCl_3$) 186·70 (CHO), 165·16 (C-4), 151·15 (C-2), 131·78 (C-6), 122·65 (C-1), 113·49 (C-5), 108·88 (C-3), 55·98 (OCH_3), 38·14 (CH_3); *m/z* (70 eV EI) 230 (M^+, 60%), 151 (M^+-$MeSO_2$, 100), 150 (55), 134 (151-OH, 55) 95 ($MeSO_3$, 25).

*Smaller or smallest coupling constant is probably from coupling to CHO.

2-Methanesulphonyloxy-4-methoxy-2'-nitrostyrene (**135**).——Procedure as for nitrostyrene (**133**) (acid-catalysed synthesis), using aldehyde (**134**)(1·2 g, 5·2 mmol), glacial acetic acid (15 ml), ammonium acetate (0·20 g, 2·6 mmol), and nitromethane (0·3 ml, 5·7 mmol). The mixture was also refluxed for five days, and worked-up as above. Chromatography, under the same conditions as for nitrostyrene (**133**), followed by crystallisation from ethanol, yielded *2-methanesulphonyloxy-4-methoxy-2'-nitrostyrene* (0·65 g, 46%) m.p. 141-143 °C (Found: C, 43·6; H, 4·05; N, 4·95. $C_{10}H_{11}NO_6S$ requires C, 43·95; H, 4·05; N, 5·15%); R_f 0·2, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3); $\upsilon_{max.}$ (Nujol) 1560w, 1345, 1330 (NO_2), 1375, 1175 cm^{-1} (SO_3); δ_H (270 MHz; DMSO-D_6) 8·22 (1H, d, *J* 14 Hz, ArC*H*), 8·10 (1H, d, *J* 12 Hz, $CHNO_2$), 8·06 (1H, d, *J* 7 Hz, 6-H), 7·13 (1H, dd, *J* 8, 2 Hz, 5-H), 7·08 (1H, d, *J* 2 Hz, 3-H), 3·89 (3H, s, OCH_3), 3·61 (3H, s, CH_3); δ_C (68 MHz; $CDCl_3$-DMSO-D_6) 162·47 (C-4), 148·39 (C-2), 136·13 (C-6), 131·46 (ArC*H*), 129·55 ($CHNO_2$), 115·11 (C-1), 112·87 (C-5), 108·01 (C-3), 54·98 (OCH_3), 37·36 (CH_3); *m/z* (70 eV EI)

273 (M^+, 40%), 226 (M^+-HNO_2, 35), 178 (M^+-$MeSO_3$, 35), 148 (226+1-$MeSO_2$, 100), 133 (148-Me, 70), 77 (20).

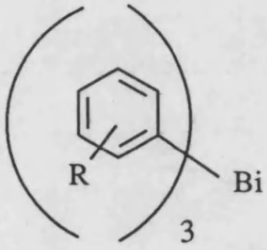
Attempted Synthesis of 2-Methanesulphonyloxy-4-methoxy-2'-aminoethylbenzene (**128**).——Palladium (10%) on charcoal (0·2 g) suspended in methanol (5 ml) was added to a degassed solution of nitrostyrene (**135**)(0·19 g, 0·65 mmol) in methanol (50 ml). Hydrogenation and work-up, as for synthesis of (**80**, R^1, R^2, R^3 = Me), produced a pale yellow oil (79 mg). T.l.c. with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1) as eluant indicated that this crude material contained many components, and data were collected without purification. (Found: C, 45·6; H, 6·0; N, 3·7. $C_{10}H_{15}NO_4S$ requires C, 48·95; H, 6·15; N, 5·7%); $\upsilon_{max.}$ ($CHCl_3$) 1350, 1175w cm^{-1} (SO_3); δ_H (270 MHz; DMSO-D_6) spectrum of complex mixture; *m/z* (^{i}Bu CI) 288 (274+CH_2, 45%), 274 (215+C_4H_{11}, 100), 260 (274-CH_2, 60), 246 (M^++1, 25), 216 (25), 215 (M^+-MeO, 25), 137 (216-$MeSO_2$, 25), 72 (70).

CHAPTER 3.

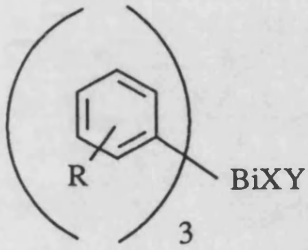
3. THE CHEMISTRY OF TWO BISMUTHINE ARYLATING REAGENTS.

3-1. Introduction.

Compounds such as (**137**) and (**138**) have been known for around a hundred years.[84-86] Early in this century some of these compounds were investigated,[87] and tested in the treatment of trypanosomes and spirochetes.[88] Recently, Barton and co-workers[89] probed the potential of organic derivatives of bismuth (V) as selective, non-electrophilic, oxidising reagents which would operate under neutral conditions.



(**137**)



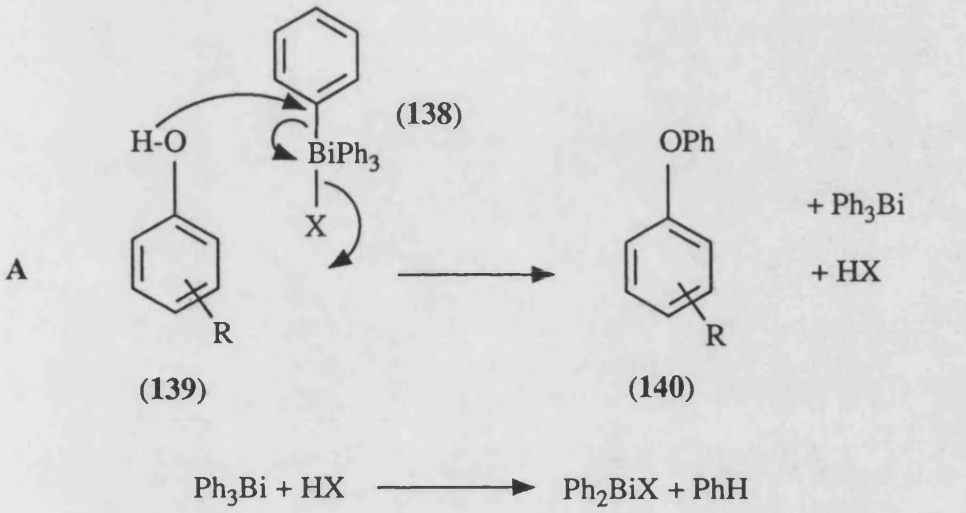
(**138**)

R = Me, NO_2, MeO, H
X, Y = Hal, NO_3, OAc, OH, Ar
XY = CO_3, O

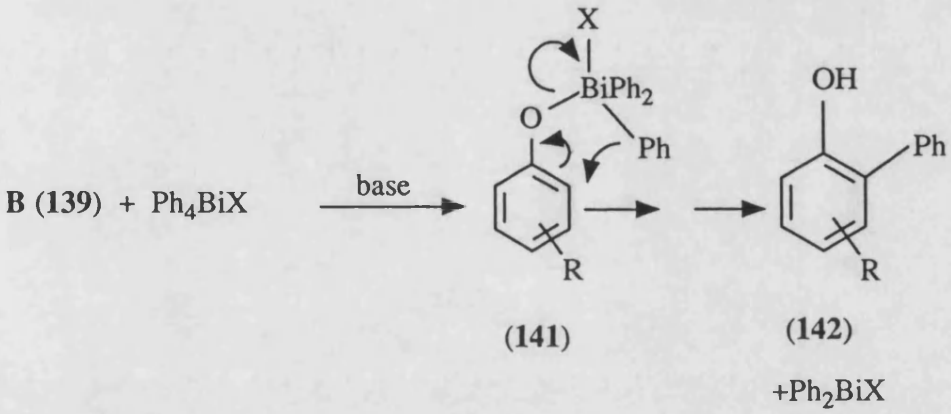
During these studies it was shown that, under some conditions, certain hydroxyl groups were phenylated[90] by bismuthines such as (**138**). The value of facile formation of *O*-aryl bonds was immediately recognised, and the reaction was investigated by David and Thieffry,[91] as well as by Barton and co-workers. In the case of phenols coupling with bismuthines (**138**), the results were variable.[92] Depending on conditions, phenylation could occur predominantly at the hydroxyl function or at the *ortho*-carbon of the phenol.

Barton *et al.* proposed two mechanisms to explain these differing regiochemistries.[92] The first argues for direct nucleophilic displacement of a bismuth fragment from bismuthine (**138**) by the phenol (**139**), as shown in

Scheme 18A. It was noted that this was a remarkable proposal, but there is supporting evidence. The reaction occurs in high yield in polar solvents, but fails, or gives low yields, in non-polar ones. Despite attempting to trap possible radical intermediates, there is no evidence for the existence of such species. Both these points suggest probable ionic mechanisms.



$$Ph_3Bi + HX \longrightarrow Ph_2BiX + PhH$$

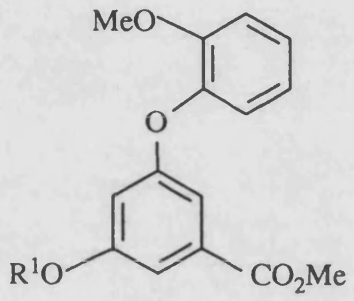


Scheme 18.

The second mechanism involves formation of the intermediate (**141**) shown in Scheme 18B, under basic conditions. It is suggested this species decomposes on warming to give solely the product of *ortho*-phenylation, perhaps

by a concerted process. It that use of the harder phenolate anion affords attack at the harder electrophilic site on the bismuth atom.

Barton and co-workers also investigated the effect on the reaction of copper catalysis.[93] This had a drastic influence, removing the need for an induction period, the requirement of light irradiation, and solvent dependency which is sometimes observed. Reaction rates were also greatly increased. Furthermore, when applied to reaction of phenols, copper catalysis lead to exclusive *O*-phenylation.[59] It was these reaction conditions which seemed to be ideally suited for application to the synthesis of our diaryl ether (**77**).



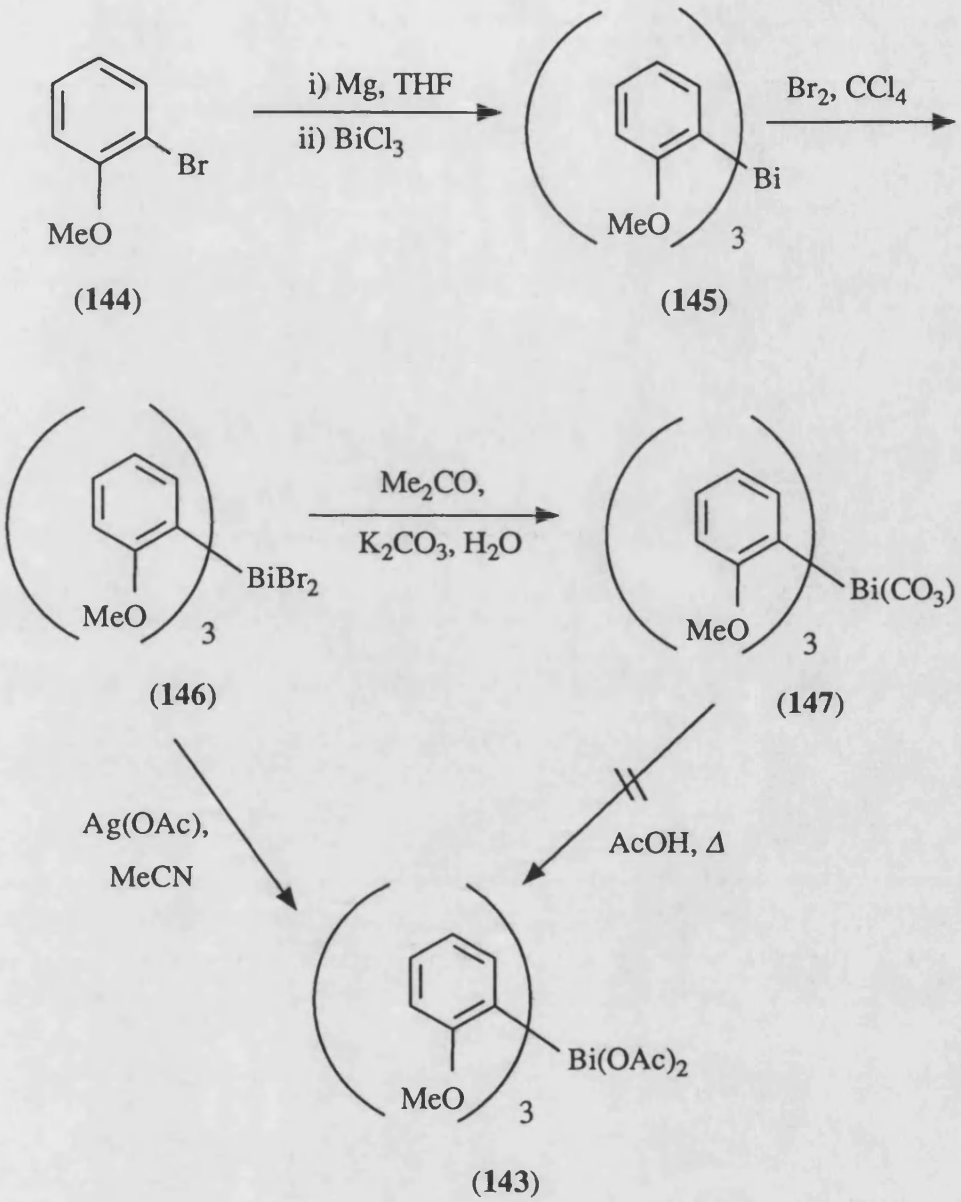
(**77**)

3-2. Discussion.

3-2-1. Synthesis and reaction of tri-(2-methoxyphenyl)bismuth diacetate.

Organobismuth reagent (**143**) was chosen for the arylation, since Barton *et al.* had already achieved good results with the triphenyl analogue.[59] Diacetate (**143**) was prepared by the method shown in Scheme 19.

Grignard reaction of 2-bromoanisole (**144**) with bismuth trichloride afforded (**145**) in 43% yield. This was in line with the literature[88] yield, although the melting point was about 10 °C lower than that quoted. Melting points of such bismuthines are known to be variable, however, and show sensitivity to rate of



Scheme 19.

heating.[88]

Supniewski and Adams[88] report that they could not isolate the dibromide (**146**) by reacting the bismuthine (**145**) with 10% bromine solution in tetrachloromethane. Barton and co-workers[89] refer to the *para*-isomer of dibromide (**146**) as "This unstable substance...". In our hands, with 0·2 M

bromine solution, the reaction proceeded smoothly and in high yield. Dibromide (**146**) precipitated from solution and was not appreciably unstable.

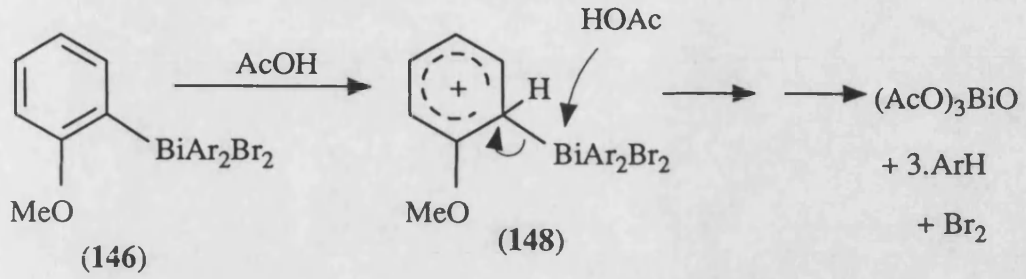
The improved preparation of triphenylbismuth carbonate reported by Barton *et al.*[89,92] was applied in the synthesis of the carbonate (**147**). Our starting material, dibromide (**147**), behaved differently to its triphenyl analogue. The former was almost insoluble in acetone and reaction was sluggish, requiring more than 12 hours for completion. Progress was monitored by t.l.c. and by the colour change of the precipitate, from bright yellow to cream.

The chemistry of the carbonate (**147**) also differed from that of the triphenyl series. For example, when it was warmed with glacial acetic acid[87] the diacetate (**143**) was not produced. Instead a product was isolated, elemental analysis of which showed little carbon or hydrogen to be present. The infrared spectrum exhibited no aryl bands, and was consistent with the formation of acetoxy bismuth oxide.[94]

The reason for failure of the anticipated reaction is clearly the presence of the *ortho*-methoxy groups. It is known that trianisylbismuthines are sensitive to concentrated strong acids,[88] but that triphenylbismuth carbonate is stable to warm glacial acetic acid.[87,88] The anomalous chemistry of the carbonate (**147**), in mild acid, probably arises from ready protonation of the C-Bi bond, facilitated by electron-donation from the *ortho*-methoxy group. In that case, substitution of aryl groups by acetoxy would follow, as observed, see Scheme 20.

Goel and Prasad[95] formed triphenylbismuth diacetate using a two phase reaction between triphenylbismuth dibromide and silver acetate. We modified this reaction, using a single acetonitrile phase, for application to the dibromide (**146**). When performed in the dark, this procedure provided the dibromide (**143**) in 61% yield.

Reaction of that compound with phenol (**79**) did not result in the expected arylation, although the conditions chosen were those of Barton and co-workers:[59]

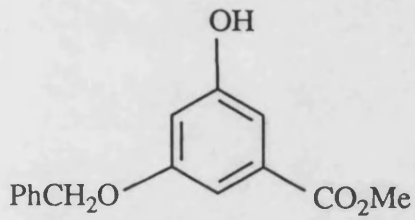


Ar = 2-methoxyphenyl

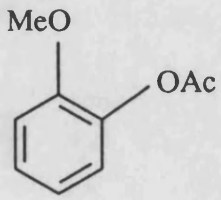
Scheme 20.

dichloromethane solvent, copper metal catalyst, under an atmosphere of argon. Starting phenol was recovered, by "flash" column chromatography, even though the bismuth reagent (**143**) had been consumed.

The only other product to be isolated from this reaction was a small quantity of 2-methoxyphenyl acetate (**149**). Unfortunately this compound could not be completely freed from minor contaminants, although its physical data are fully in accord with literature values.[72,96]



(**79**)



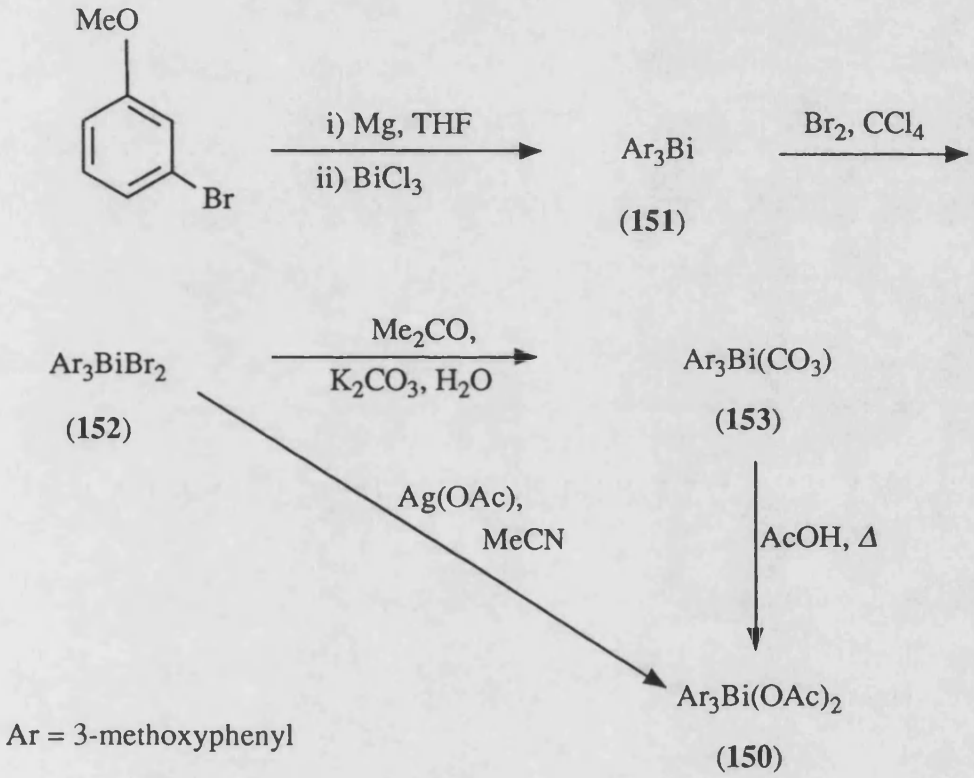
(**149**)

We concluded that failure of this reaction is also due to the electron-releasing effect of the *ortho*-methoxy function. Reaction of a pentavalent bismuthine to form compounds analogous to the acetate (**149**) is not unprecedented. It is well known[97] that, on warming, triarylbismuth dihalides

undergo reductive elimination of arylhalide. It seems likely that the comparable process we observed with diacetate (**143**) is catalysed by copper, in preference to the desired arylation reaction.

3·2·2. Synthesis and reaction of tri-(3-methoxyphenyl)bismuth diacetate.

One way to investigate the above idea is to repeat the arylation, using an isomer of the diacetate (**143**) which possesses no *ortho*-electron-releasing function. So we targeted the tri-(3-methoxyphenyl) isomer (**150**).

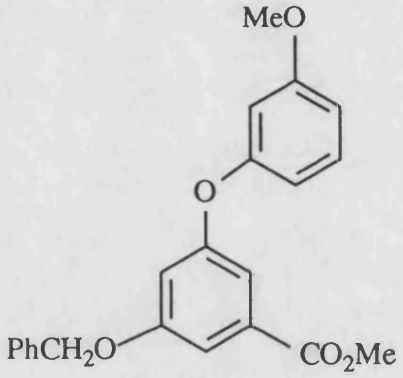


Scheme 21.

Preparation of this compound is shown in Scheme 21, and follows from the analogous work with compound (**143**). From an early stage in the synthesis of isomer (**150**), the behaviour of the intermediates was closer to that of known triphenyl analogues.[88] Bromination of the triarylbismuthine (**151**) did not precipitate the corresponding dibromide (**152**) out of solution, until work-up.

However, the carbonate (**153**), obtained from this dibromide, was insoluble in acetone. This last reaction was as sluggish as that for the starting material (**146**). It was noted that the carbonate (**153**) did form the diacetate when it was warmed in glacial acetic acid, although at a much slower rate than the similar process reported by Challenger and Goddard.[87] In fact the reaction did not go to completion, and a ^{1}H n.m.r. spectrum of the product indicated it consisted of a mixture of triarylbismuth carbonate (**153**) and diacetate (**150**). Fortunately, this diacetate was formed more conveniently by reaction of the dibromide (**152**) with silver acetate.[95]

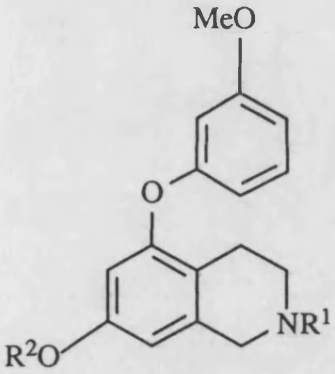
The phenol (**79**) was smoothly arylated by the diacetate (**150**), as had been hoped. Two applications of "flash" chromatography were sufficient to separate the diaryl ether (**93**) from bismuthine side products, which were not characterised. Trituration of the resulting oil with methanol, and crystallisation from the same solvent, afforded the desired product in analytical purity. The structure of the ether (**93**) was confirmed by ^{1}H, and ^{13}C n.m.r. spectroscopy. Infrared and mass spectra were also fully consistent with the desired structure.



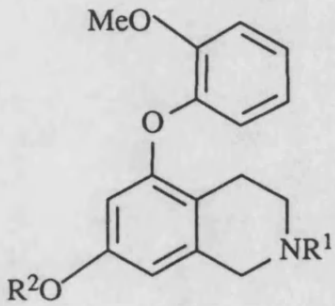
(**93**)

It now seemed that use of diacetate (**150**) should allow synthesis of tetrahydroisoquinoline (**68**). It may be anticipated that the regioisomer (**66**) would be accessible *via* a similar approach. Therefore a bismuth reagent would be

required, analogous to the diacetate (**143**), but bearing electron-withdrawing substituents capable of easy transformation into phenolic groups. The preparation of such a compound may be problematical due to general instability of such functions to Grignard conditions. We felt it advisable to delay this preparation until the reagent was needed.



(**68**)



(**66**)

3·2·3. Mechanistic speculations.

Before continuing our planned synthesis of the diaryl ether (**68**), we wished to investigate the involvement of copper in the generation of the acetate (**149**) from the diacetate (**143**). Therefore the latter compound was stirred overnight with copper granules, under the previous conditions.[59] To our surprise, the solution became deep green and only the bismuthine (**145**) could be isolated. The isomer (**150**) behaved similarly, giving impure tri-(3-methoxyphenyl)bismuth (**151**), however, in this case the solution remained cloudy white.

The origin of the trivalent bismuthines, from reductive elimination of both acetoxy groups, is clear. Less obvious is the cause of an alternative reductive elimination, of acetate (**149**), from diacetate (**143**) in the presence of a phenol. For that reason, it seemed certain the phenol must be involved in the reaction.

This lead to mechanistic speculations about the various reactions we had observed. We consider it probable that all these products may arise from a common intermediate or transition state. Its subsequent behaviour would then be dependent on the precise conditions.

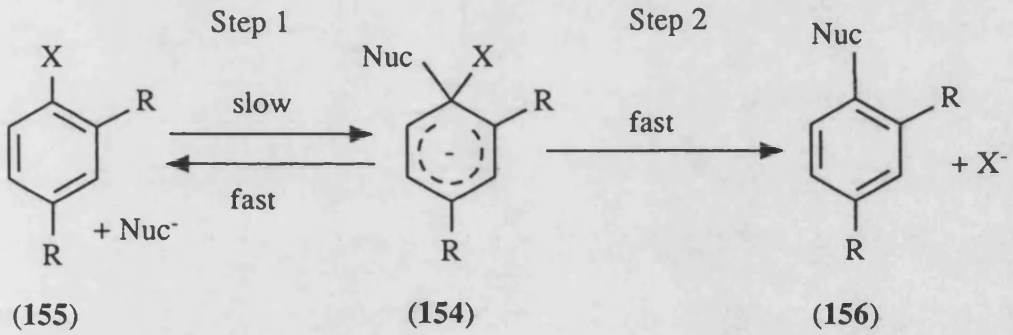
The shifts of the C-1 carbon atoms, in the ^{13}C n.m.r. spectra, of diacetate (**143**) and isomer (**150**) are of some significance. In the case of diacetate (**143**), assignments are achieved by a process of elimination. There are six aromatic carbon resonances at δ 158·3 (C-2), δ 151·1 (C-1), δ 133·5 (C-6), δ 131·5 (C-4), δ 122·8 (C-5), δ 112·85 (C-3). Since five of these are close to the four values (excluding the methoxy carbon) calculated for anisole, it may be assumed the anomalous one, at δ 151·1, is due to the resonance of a carbon atom bonded to bismuth.

A further shift downfield for C-1 of the diacetate (**150**) would be expected, since there is no longer a methoxy group at C-2. In fact, there were only five aromatic signals in the spectrum; at δ 161·6 (C-3), δ 131·35 (C-5), δ 125·6 (C-6), δ 119·15 (C-2), δ 116·85 (C-4). The C-1 signal may either be very weak, due to relaxation effects for the quaternary carbon, or be coincident with C-3 at δ 161·6. A downfield shift of +Δ 10.51 ppm for C-1 of diacetate (**150**), from the corresponding signal in the spectrum of isomer (**143**), is consistent with calculation.[72a]

Which of these possible explanations is correct is not really relevant here. The significance is the magnitude of downfield shift, ≈ +Δ 37 ppm, for C-1 of diacetate (**143**) compared to that of anisole. This value is comparable to the deshielding effect of a fluorine atom on the aromatic carbon atom to which it is bonded; namely +Δ 35.1 ppm.[72a] Such evidence supports the assertion[92] that uncatalysed *O*-arylation of phenols occurs *via* nucleophilic aromatic substitution.

A brief summary of that well known reaction[98] will illustrate the point, as shown in Scheme 22. Where the reaction occurs it is *via* an unfavoured

intermediate (**154**), and the first step is generally rate-determining. In which case, rate of reaction is dominated by the electronegativity of the leaving group X. If that is fluoride, then the first step is relatively facile. If one or both R groups are nitro, the reaction occurs at room temperature. The effect of *ortho*- and *para*-nitro groups is to stabilise the intermediate anion (**154**). Thus, they serve to increase the rate of the second step. This is significant for the very strong C-F bond. In the case of a strong C-X bond, or unusually disfavoured transition state, the second step can become rate determining.



Scheme 22.

These considerations may be applied to the analogous reaction of triphenylbismuth diacetate, in the absence of copper catalysis. It is plausible that depleted electron-density at C-1 facilitates the first step; formation of intermediate (**154**). In the absence of *ortho*- or *para*-nitro groups the second step could be rate-limiting, depending on the strength of the C-Bi bond. However, an *ortho*- or *para*-methoxy group would destabilise a potential anionic intermediate. The strength of the C-Bi bond is unlikely to compare with that of the C-F bond, but Barton and co-workers found the reaction unpredictable.[92,93] The need for heat or irradiation[93] is consistent with the situation where the rate-limiting step requires bond-breaking.

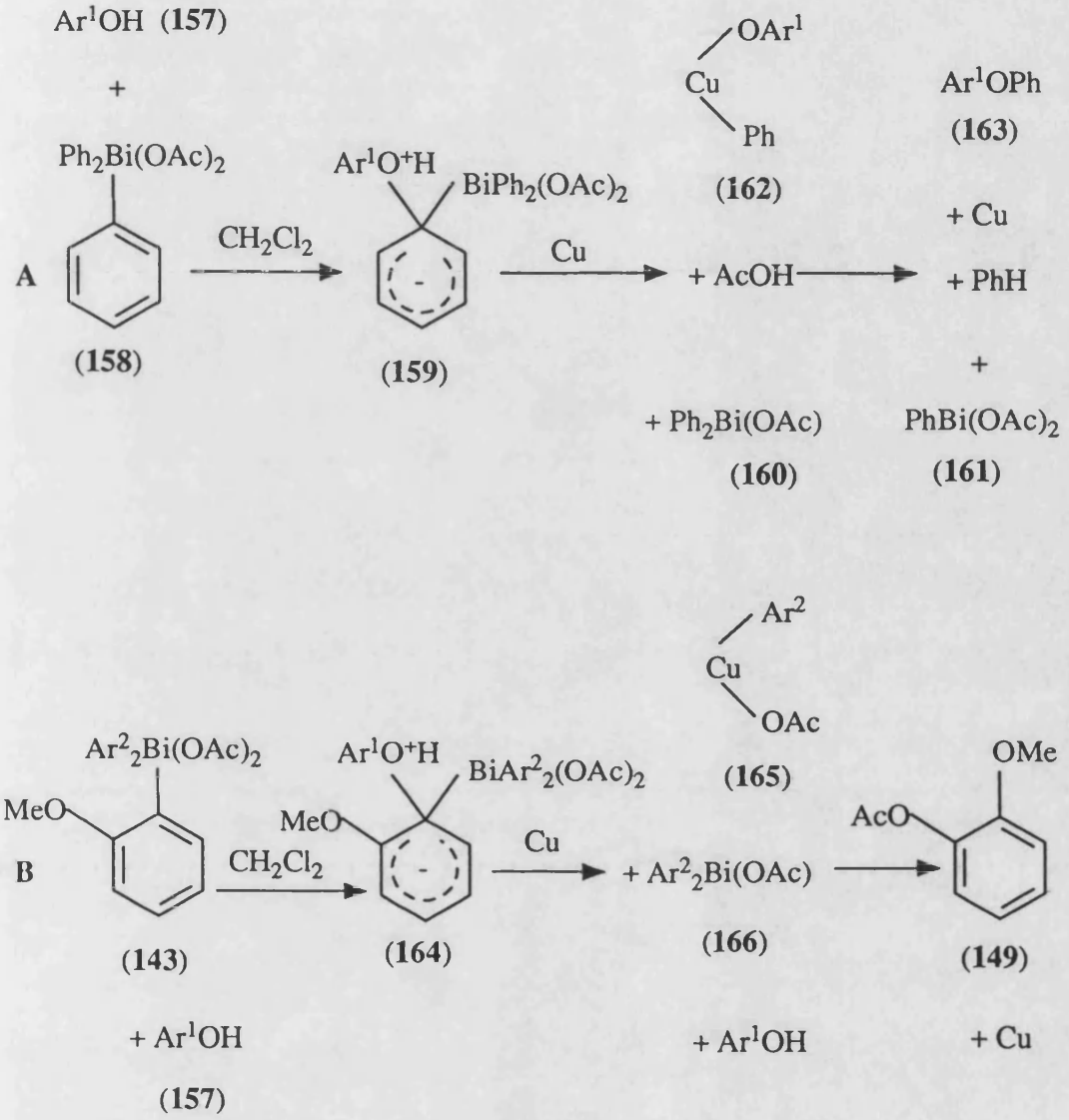
Barton and co-workers proposed that the copper catalysis mechanism

involves formation of a copper-aryl bond.[99] This species would subsequently undergo reductive elimination to form the product. For example, when triphenyl bismuth is treated[99] with palladium (0) catalyst, quantitative formation of biphenyl and the deposition of metallic bismuth is observed.

It seems probable that a similar process is involved in copper catalysis for arylation of phenols, for it might be anticipated that copper mediation indicates a mechanism involving exclusively radical processes. However, in that case it would be expected that diacetate (**143**), containing an *ortho*-methoxy group, would be well activated for the reaction. Perhaps its actual behaviour could be explained by a second, competing, reaction of a radical nature. It is understandable that such a process would be preferred for tri-(2-methoxyphenyl)bismuthine (**143**).

Conversely, were a nucleophilic stage to be involved, the reaction would be disfavoured for diacetate (**143**) which is in line with experiment. Therefore for phenylation of a phenol, we contemplated the possibility that SNAR attack by phenol (**157**) on the bismuthine (**158**) is the *first* step, as shown in Scheme 23A. A possible subsequent step is radical migration of participating species from the transition state (**159**). That reaction would involve insertion of copper into the newly formed C-O bond. Assisted C-Bi bond breaking, with concomitant loss of acetoxy ion from bismuth, would occur. The resulting bismuth species (**160**) is known to react with acid, forming bismuth diacetate (**161**). Copper species (**162**), generated at the same time, would undergo subsequent reductive elimination to give phenylated phenol (**163**). Diacetate (**150**) would react similarly.

In the case of the diacetate (**143**), C-1 certainly appears to be sufficiently electron-deficient to undergo attack by phenol (**157**). However, the resultant transition-state (**164**) would not be favoured, and may be expected to decompose to starting materials. In the presence of copper, a similar reaction to that shown in Scheme 23A could occur. It is feasible that the activated aryl group and an acetyl


Ar1OH (157)
+
Ph2Bi(OAc)2
A
CH2Cl2
(158)
Ar1O+H
BiPh2(OAc)2
(159)
Cu
OAr1
Cu
Ph
(162)
+ AcOH
+ Ph2Bi(OAc)
(160)
Ar1OPh
(163)
+ Cu
+ PhH
+
PhBi(OAc)2
(161)
Ar2
Cu
OAc
(165)
Ar2Bi(OAc)2
MeO
B
CH2Cl2
(143)
Ar1O+H
BiAr2(OAc)2
MeO
(164)
Cu
+ Ar2Bi(OAc)
(166)
OMe
AcO
(149)
+ Ar1OH
(157)
+ Ar1OH
+ Cu
CH2Cl2
Cu
C
Ar3Bi(OAc)2
Ar3Bi + Cu(OAc)2
(143) Ar2 = o-MeOPh
(150) Ar2 = m-MeOPh
(144) Ar2 = o-MeOPh
(151) Ar2 = m-MeOPh

Scheme 23.

migrate to form copper species (**165**), with simultaneous loss of phenol (**157**) from C-1 of aryl, as shown in Scheme 23B.

This idea is attractive because it explains the different course of the reaction in the presence of a phenol. It also explains why starting phenol (**79**) was regenerated. In the absence of any phenol it is the acetoxy groups which migrate, see Scheme 23C. We are unable to explain why the diacetates (**143**) and (**150**) apparently produce copper in differing oxidation states.

More work is needed to test the above speculations, but, in the light of our original objectives, we felt it inappropriate to become more deeply involved in an investigation of these processes. With many competing claims to our time, we turned our attention to the attempted synthesis of the diaryl ether(**68**).

3·3. Experimental.

Assignment of ^{1}H and ^{13}C n.m.r. spectra could generally be made by comparison with values calculated for anisole. Shifts were usually somewhat downfield, due to inductive electron-withdrawal from the Ar_2Bi or Ar_2BiXY substituent. These effects were relatively minor, C-1 excepted (see Discussion). They could often be used unambiguously to assign shifts which would be degenerate in the case of anisole.

Preparation of Tri-(2-methoxyphenyl)bismuth[88] (**145**).——All glassware was oven- or flame-dried. THF (200 ml) was added to oven-dried magnesium turnings (2·85 g, 0·12 mol) in a three-necked round bottomed flask, equipped with a mechanical stirrer, a dropping funnel (100 ml), and a reflux condenser. The stirred mixture was maintained under a constant flow of dry nitrogen gas. 2-Bromoanisole (18·9 g, 0·10 mol), was dissolved in THF (75 ml) and about 15 ml of this solution was added to the reaction mixture, which was heated under reflux. After five minutes, a few crystals of iodine were added to promote the Grignard reaction. The remainder of the aryl bromide was then added, dropwise, to the stirred mixture during the course of about 2 hours. After a further hour, the light-brown mixture was allowed to cool for an hour, and then chilled (ice-bath) for a further 30 minutes. Bismuth trichloride (10·65 g, 33 mmol) was added to the dropping funnel and washed into the rapidly stirred reaction mixture with THF in several aliquots. The colour of the reaction mixture became light-green, grey, orange, and finally green. After 90 minutes, the rate of stirring was slowed to normal and the mixture was allowed to warm to room temperature overnight. The black mixture was concentrated *in vacuo* to a thick slurry. Ice (200 ml), 10% w/v ammonium chloride solution (75 ml), and dilute hydrochloric acid (5 ml) were added, and the stirred mixture was filtered under suction. The residue was dried between room temperature and 70 °C, at 30 mm, in a vacuum oven. The dried

residue (13·85 g) was extracted with chloroform for two days in a soxhlet extractor. The extract was freed of solvent to give the product as a pale yellow solid (10·5 g). This was recrystallised from chloroform to afford tri-(2-methoxyphenyl)bismuth (7·7 g, 43%), m.p. 155-158 °C (lit.,[88] 169-170 °C) (Found: C, 47·2; H, 4·1. Calc. for $C_{21}H_{21}BiO_3$: C, 47·55; H, 4·0%); R_f 0·75, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1575 (C=C), 445 cm^{-1} (C-Bi)(cf. Ph_3Bi, lit.,[100] 435w cm^{-1}); δ_H (270 MHz; $CDCl_3$) 7·45 (3H, dd, *J* 7, 2 Hz, 6-H), 7·32 (3H, qd, *J* 8, 7, 2 Hz, 4-H), 6·99 (3H, dd, *J* 8, <1 Hz, 3-H), 6·86 (3H, td, *J* 7, 1 Hz, 5-H), and 3·75 (9H, s, CH_3); *m/z* (70 eV EI) 530 (M^+, 1%), 423 (M^+-$MeOC_6H_4$, 20), 316 ((MeOPh)Bi, 100), 209 (Bi, 75), 107 ($MeOC_6H_4$, 20).

Tri-(2-methoxyphenyl)bismuth dibromide[88] (**146**).——The bismuthine (**145**)(2·15 g, 4 mmol) was dissolved in tetrachloromethane (10 ml) by gently warming to 45 °C. The solution was stirred under dry nitrogen and approximately 0·2 M bromine solution in tetrachloromethane (29·0 ml) was added dropwise. This lead to progressive precipitation of the yellow product. The end-point was detected by the persistence of an orange colour. The mixture was allowed to stir for 15 minutes and then filtered under suction to yield the pale yellow product, *tri-(2-methoxyphenyl)bismuth dibromide* (2·65 g, 94%), m.p. 94-95 °C (Found: C, 36·1; H, 3·0. $C_{21}H_{21}BiBr_2O_3$ requires C, 36·55; H, 3·05%); R_f 0·0, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1595 (C=C), 440 cm^{-1} (C-Bi); δ_H* (270 MHz; $CDCl_3$-DMSO-D_6) 7·34 (3H, dd, *J* 8, 1 Hz, 6-H), 6·82 (3H, qd,* *J* 8, 7, 2 Hz, 4-H), 6·56 (3H, dd, *J* 7, 1 Hz, 5-H), 6·51 (3H, dd,** *J* 7, 1 Hz, 3-H), 3·13 (9H, s, CH_3); *m/z* (^{i}Bu CI) 585, 583, 581 (M^+-$MeOC_6H_4$, 1, 3, 1), 423 ($(MeOPh)_2Bi$, 50) 331 (40), 214 ($(MeOPh)_2$, 70), 186, 188 (MeOPhBr, 100, 100).

*Spectrum contained signals due to an impurity; presumably arising from reductive elimination.[97] The extra shifts (not listed) were easily identified by their integrals - about 10-20% of those for dibromide (**146**). After standing in solution, resonances due to the decomposition product dominated.

*Overlapping central doublets formed a poorly resolved triplet.

**Left doublet unresolved; appeared as a broad singlet.

Tri-(2-methoxyphenyl)bismuth carbonate[92] (**147**).——To a well stirred suspension of the dibromide (**146**)(0·59 g, 0·9 mmol) in acetone (10 ml) was added potassium carbonate (94 mg, 0·7 mmol) dissolved in water (1 ml). A very gradual lightning of the yellow colour of the precipitate was noticed, and the mixture was allowed to stir overnight. Further water (5 ml) was added to the, now cream, mixture. This was concentrated *in vacuo* and filtered, to produce *tri-(2-methoxyphenyl)bismuth carbonate* (0·42 g, 83%) (Found: 45·4; H, 3·9. $C_{22}H_{21}BiO_6$ requires C, 44·75; H, 3·6%); R_f 0·65, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1580 (C=C), 445 cm^{-1} (C-Bi); *m/z* (^{i}Bu CI) 530 (M^+-CO_3, 1%), 423 ($(MeOPh)_2Bi$, 100), 331 (10), 316 ((MeOPh)Bi, 65), 209 (Bi, 40).

Tri-(2-methoxyphenyl)bismuth diacetate (**143**)*: Attempted Synthesis from carbonate* (**147**) *with Acetic Acid.*[87]——The carbonate (**147**)(0·11 g, 0·2 mmol) was stirred with glacial acetic acid (2 ml) and warmed gently (oil bath). At 60 °C, the material dissolved without apparent evolution of carbon dioxide, leaving a colourless solution. The oil bath and stirred solution were allowed to cool for 90 minutes. Water (1 ml) was added, but no precipitation was seen. Addition of more water did not produce so much as

turbidity. The mixture was concentrated *in vacuo* and the residue freeze-dried to leave a white powder. This was tentatively characterised as a mixture of acetoxybismuth oxides (62 mg), m.p. above 300 °C (Found: C, 8·7; H, 1·1. $C_{25}H_{27}BiO_7$ requires C, 46·3; H, 4·2%); $\upsilon_{max.}$ (KBr) 1530s, vbr, 1410s, vbr, 1050w, 1020m, 650m, 615m, 530w, br, 470w cm^{-1}.

Preparation from dibromide (**146**).——The dibromide (**146**)(1·1 g, 1·6 mmol) was added to a round bottomed flask (25 ml) together with acetonitrile (15 ml). The flask was wrapped in foil, and silver acetate (0·82 g, 4·9 mmol) was added to the stirred mixture. After five hours the suspension of yellow silver bromide was filtered through celite, and the filtrate was freed of solvent *in vacuo*, to produce the crude product (0·78 g). This was dissolved in benzene and precipitated with petrol, to yield *tri-(2-methoxyphenyl)bismuth diacetate* (0·64 g, 61%), m.p. 148-150 °C (Found: C, 46·2; H, 4·2. $C_{25}H_{27}BiO_7$ requires C, 46·3; H, 4·2%); R_f 0·0, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1620 (C=O), 1580, 1560 (C=C), 440 cm^{-1}(C-Bi); δ_H* (270 MHz; $CDCl_3$) 8·23 (3H, dd, *J* 8, 2 Hz, 6-H), 7·43 (3H, td, *J* 7, 2 Hz, 4-H), 7·21 (3H, t, *J* 7 Hz, 3-H or 5-H), 7·20 (3H, t, *J* 8 Hz, 3-H or 5-H), 3·88 (9H, s, CH_3), 1·69 (6H, s, O_2CCH_3); δ_C (68 MHz; $CDCl_3$) 175·76 (C=O), 158·28 (C-2), 151·08 (C-1), 133·50 (C-6), 131·46 (C-4), 122·80 (C-5), 112·84 (C-3), 56·01 (CH_3), 22·25 (O_2CCH_3); *m/z* (70 eV EI) 589 (M^+-OAc, 2%), 482 ($(MeOPh)_2Bi(OAc)$, 4), 423 (482-OAc, 15), 375 ((MeOPh)Bi(OAc), 25), 316 ((MeOPh)Bi, 85), 209 (Bi, 100), 124 (30), 107 ($MeOC_6H_4$, 20).

*Partial overlap of some signals seen.

Attempted Synthesis of 3-Benzyloxy-5-(2'-methoxyphenyloxy)benzoic acid methyl ester[59] (**77**).——Metallic copper granules (3 mg) and the diacetate

(143)(70 mg, 0·1 mmol) were added to a stirred solution of 3-benzyloxy-5-hydroxybenzoic acid methyl ester (**79**)(24 mg, 0·1 mmol) in dichloromethane (5-7 ml); the mixture being maintained under dry argon gas. (A reflux condenser was required to prevent evaporation of solvent). T.l.c. indicated that the triarylbismuth diacetate (**143**) was being consumed, and five or six new components were forming; of which two were major. However, the starting phenol did not appear to be reacting at all. After 15 hours the mixture was freed of solvent, and chromatography on silica gel with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:20 to 1:3) as eluant, produced two identifiable components. Chromatography was repeated for the first of these; the impure material was isolated and adequately characterised as 2-methoxyphenyl acetate (11 mg, 61%), M^+ = 166·3277 (Calc. for $C_9H_{10}O_3$: *M*, 166·0692); R_f 0·45, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 1745 (C=O), 1595 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 7·20 (1H, qd, *J* 8, 7, 2 Hz), 7·02 (1H, dd, *J* 8, 2 Hz, 4-H), 6·98 (1H, dd, *J* 5, 2 Hz, 5-H), 6·95 (1H, dd, *J* 4, 1 Hz, 3-H), 3·83 (3H, s, CH_3), 2·32 (3H, s, O_2CCH_3) *m/z* (70 eV EI) 166 (M^+, 8%), 125 (8), 124 (M^++1-COMe, 100), 109 (MeOPh+1, 56), 81 (12), 52 (10), 51 (5) 43 (37), 28 (10) (cf. lit.[96]). The remaining compound was characterised as starting phenol, 3-benzyloxy-5-hydroxybenzoic acid methyl ester (23 mg, 33%), by t.l.c., i.r., ^1H n.m.r. and mass spectrometry.

Treatment of diacetate (**143**) *with Copper Granules.*—— Metallic copper granules (8 mg) were added to a stirred solution of the diacetate (**143**)(0·32 g, 0·5 mmol), in dichloromethane (10 ml). The mixture was stirred under dry argon gas for 24 hours, during which time a dark-green colour developed. As in the similar reaction of the phenol (**79**) and the diacetate (**143**) above, t.l.c. showed the presence of about five components. The mixture was worked-up and purified as

outlined above. The single component recovered was found not to be 2-methoxyphenyl acetate, but was characterised as tri-(2-methoxyphenyl)bismuth (**145**)(38 mg, 15%), m.p. 150-154 °C (lit.,[88] 169-170 °C) (Found: C, 48·6; H, 4·22. Calc. for $C_{21}H_{21}BiO_3$: C, 47·95; H, 4·0. Calc. for $C_9H_{10}O_3$: C, 65·0; H, 6·0%). Infrared, ^1H n.m.r., and mass spectra were identical to those obtained from authentic bismuthine (**143**).

Tri-(3-methoxyphenyl)bismuth[88] (**151**).——Prepared as for bismuthine (**145**), using 3-bromoanisole (20 g, 0·11 mol) in THF (100 ml), magnesium turnings (2·85 g, 0·12 mol), bismuth trichloride (11·25 g, 35·7 mmol), and THF (200 ml). The product recovered from soxhlet extraction was recrystallised from chloroform, to yield *tri-(3-methoxyphenyl)bismuth* (8·3 g, 44%), m.p. 82-85 °C (Found: C, 47·95; H, 4·0. $C_{21}H_{21}BiO_3$ requires C, 47·55; H, 4·0%); R_f 0·5, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1580, 1560 (C=C), 440 cm^{-1} (C-Bi); δ_H (270 MHz; $CDCl_3$) 7·34 (9H, m, 2-H, 5-H, 6-H), 6·82 (3H, m, *J* 6, 3, 3 Hz, 4-H), 3·70 (9H, s, CH_3); *m/z* (^{i}Bu CI) 531 (M^++1, 3%), 423 (M^+-$MeOC_6H_4$, 80), 316 ((MeOPh)Bi, 100), 209 (Bi, 100), 109 (45), 108 (MeOPh, 30).

Tri-(3-methoxyphenyl)bismuth dibromide[88] (**152**).—— Prepared as for dibromide (**146**), using bismuthine (**151**) (1·1 g, 2·0 mmol), 0·2M bromine solution in tetrachloromethane (10·2 ml), and tetrachloromethane (10 ml). On this occasion, the product did not precipitate from the solution during reaction. The reaction mixture was concentrated and the product filtered to yield *tri-(3-methoxyphenyl)bismuth dibromide* (1·3 g, 92%), m.p. 94-97 °C (Found: C, 36·7; H, 3·05. $C_{21}H_{21}BiBr_2O_3$ requires C, 36·55; H, 3·05%); R_f 0·15, ethyl

acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1590, 1545 (C=C), 435br cm^{-1} (C-Bi); δ_H (270 MHz; $CDCl_3$) 8·11 (3H, t, *J* 8 Hz, 6-H), 8·08 (3H, d, *J* 2 Hz, 2-H), 7·56 (3H, t, *J* 8 Hz, 5-H), 7·04 (3H, dd, *J* 5, 2 Hz, 4-H), 3·87 (9H, s, CH_3).

Tri-(3-methoxyphenyl)bismuth carbonate (**153**).[92]—— Prepared as for carbonate (**147**), using dibromide (**152**) (0·47 g, 0·7 mmol), potassium carbonate (95 mg, 0·7 mmol), and acetone (10 ml). Product filtered from the reaction mixture, to yield *tri-(3-methoxyphenyl)bismuth carbonate* (0·31 g, 76%), m.p. 140-146 °C (Found: C, 45·0; H, 3·65. $C_{22}H_{21}BiO_6$ requires C, 44·75; H, 3·6%); R_f 0·5, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1580, 1555br (C=C), 440 cm^{-1} (C-Bi). The product was insoluble in all solvents tried, and this prevented solution n.m.r..

Tri-(3-methoxyphenyl)bismuth diacetate (**150**).——
Method A; from dibromide (**152**). Prepared as for diacetate (**143**), using the dibromide (**152**) (0·45 g, 0·6 mmol), silver acetate (0·27 g, 1·6 mmol), and dioxane (30 ml). The reaction was carried out in the dark, and the product was twice precipitated with light petroleum (b.p. 60——80 °C) from benzene to yield *tri-(3-methoxyphenyl)-bismuth diacetate* (0·28 g, 66%), m.p. 147-149 °C (Found: C, 46·35; H, 4·2. $C_{25}H_{27}BiO_7$ requires C, 46·3; H, 4·2%); R_f 0·05, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ (KBr) 1610sh (C=O), 1590br (C=C), 440 cm^{-1} (C-Bi); δ_H (270 MHz; $CDCl_3$) 7·82 (3H, t, *J* <1 Hz, 2-H), 7·67 (3H, d, *J* 8 Hz, 6-H), 7·51 (3H, t, *J* 8 Hz, 5-H), 7·00 (3H, dd, *J* 8, 3 Hz, 4-H), 3·83 (9H, s, CH_3) 1·85 (6H, s, O_2CCH_3); δ_C (68 MHz; $CDCl_3$) 161·59 (C-3), 131·33 (C-5), 125·60 (C-6), 119·17 (C-2), 116·86 (C-4), 55·56 (CH_3), 22·02 (O_2CCH_3). Shifts for C-1

and C=O are either not visible or coincident.

Method B; from carbonate (**153**) *and Acetic Acid.*[87] Prepared as for the attempt to make diacetate (**143**), using the carbonate (**153**) (0·13 g, 0·2 mmol), and acetic acid (10 ml). The starting material dissolved on warming to about 50 °C, although evolution of carbon dioxide was not observed. The solution was stirred for about 15 minutes. On work-up, a product immediately precipitated as a cream solid. The reaction mixture was filtered and the residue washed with water, before being dried by suction and overnight in a vacuum desiccator. The cream solid was found to be a mixture of the product, tri-(3-methoxyphenyl)bismuth diacetate, and starting carbonate (**153**)(0·11 g), m.p. 125-130 °C (Found: C, 46·6; H, 4·1. Calc. for $C_{25}H_{27}BiO_7$: C, 46·3; H, 4·2%); All other physical data were in good accord with those obtained from the previous reaction.
Additionally, the following chemical shifts were assigned to starting carbonate (**153**); δ_H (270 MHz; $CDCl_3$) 7·34 (9H, d, *J* 7 Hz, 2-H, 5-H, 6-H), 6·83 (3H, m, 4-H), 3·71 (9H, s, OCH_3); δ_C (68 MHz; $CDCl_3$) 129·64 (C-5), 122·93 (C-6), 113·46 (C-2, C-4), 55·01 (OCH_3). Shifts for C-1 and C=O in the diacetate, and C-1, C-3, and CO_3 in the carbonate were either not visible or coincident.

3-Benzyloxy-5-(3-methoxyphenyloxy)benzoic acid methyl ester[59] (**93**).——Tri-3-methoxyphenylbismuth diacetate (0·20 g, 0·3 mmol) and metallic copper granules (5 mg) were added to a solution of phenol (**79**) (66 mg, 0·3 mmol) in dichloromethane (15 ml). The mixture was stirred at room temperature, under a flow of dry argon. T.l.c. with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:3) as eluant, after 20 minutes and 2 hours, showed the reaction to be sluggish. The mixture was allowed to stir for 24 hours. T.l.c indicated two major components, a small amount of starting material, and further minor

components; at R_f 0·65, and on the baseline. Solvent was removed *in vacuo* to give the crude mixture as a pale yellow oil. Chromatography on silica gel, using the same eluant as for t.l.c., yielded three components; an uncharacterised bismuth-containing side-product (10 mg, R_f 0·45), a colourless oil (88 mg, R_f 0·40), and starting material (7 mg, R_f 0·15). T.l.c. showed the oil was contaminated by side product, and so chromatography was repeated. This afforded clean separation, and the isolation of another colourless oil. Trituration and two recrystallisations from methanol afforded pure *3-Benzyloxy-5-(3-methoxyphenyloxy)benzoic acid methyl ester* (44 mg, 46%), m.p. 77-78 °C (Found: C, 72·3; H, 5·5. $C_{22}H_{20}O_5$ requires C, 72·5; H, 5·55%); R_f 0·4, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:5); $\upsilon_{max.}$ ($CHCl_3$) 1615s cm^{-1} (C=O); $\lambda_{max.}$ (EtOH) 304, 281, 205 nm; δ_H (270 MHz; $CDCl_3$) 7·40, 7·36-7·25 (8H, m, C_6H_5, 2-H, 6-H, 5'-H), 6·82-6·57 (4H, m, 4-H, 2'-H, 4'-H, 6'-H), 5·06 (2H, s, CH_2Ph), 3·88 (3H, s, CO_2CH_3), 3·77 (3H, s, Me); δ_C (68 MHz; $CDCl_3$) 166·35 (C=O), 160·93 (C-5), 159·79 (C-3'), 158·30 (C-3), 157·49 (C-1'), 136·15 (Ph C-1), 132·36 (C-1), 130·25 (C-5'), 128·60 (Ph C-3, Ph C-5), 128·14 (Ph C-4), 127·56 (Ph C-2, Ph C-6), 112·38, 111·34, 110·44, 110·11 (C-2, C-4, C-6, and C-6'), 109·5 (C-4'), 105·31 (C-2'), 70·32 (CH_2), 55·34 (CO_2CH_3), 52·29 (CH_3); *m/z*(low eV EI) 364 (M^+, 85%), 91 (CH_2Ph, 100).

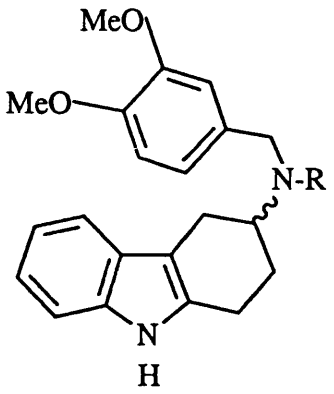
Treatment of diacetate (**150**) *with Copper Granules.*——The procedure was as for the analogous treatment of diacetate (**143**), using the diacetate (**150**)(29 mg, 0·05 mmol), copper granules (3 mg) and dichloromethane (10 ml). After about 18 hours the mixture had become cloudy, and t.l.c. showed five components less polar than starting material. Solvent was removed *in vacuo* and chromatography over silica gel using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:20) as eluant, yielded a single identifiable product. This was

characterised as tri-(3-methoxyphenyl)bismuth (**151**), albeit impure, (7 mg, 28%), m.p. 75-78 °C (Found: C, 58·8; H, 5·5. Calc. for $C_{21}H_{21}BiO_3$: C, 47·55; H, 4·0%); All other physical data were in good accord with those obtained from an authentic sample.

CHAPTER 4.

4. ATTEMPTED SYNTHESIS OF SEROTONINOID ANALOGUES.

4·1. Introduction.

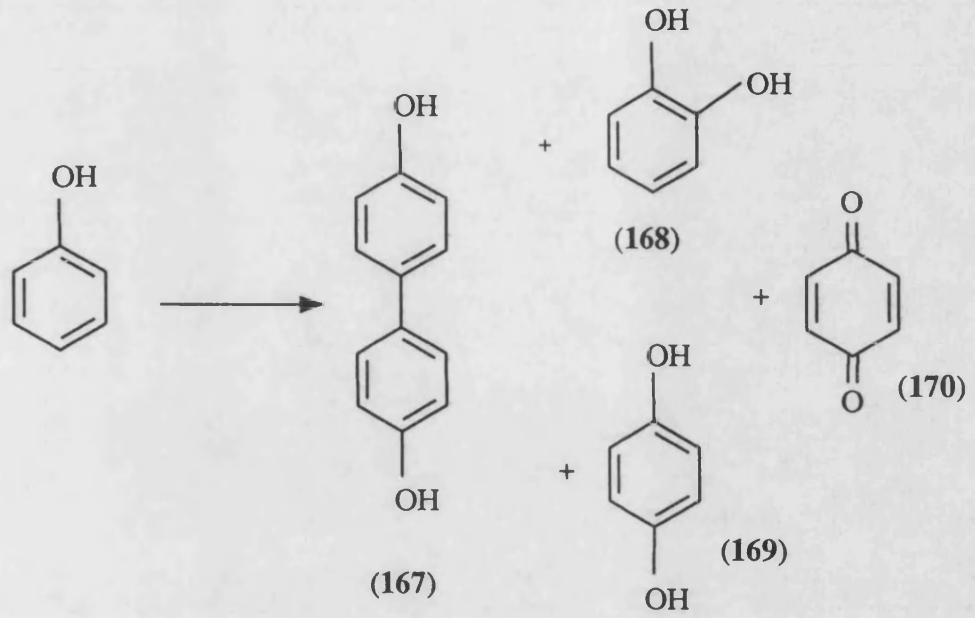


(72)

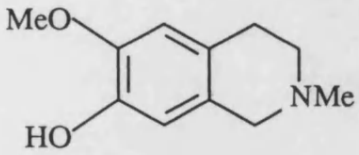
As established in Chapter 1, we wished to investigate the anodic electrochemistry of tetrahydrocarbazole (**72**). In 1912, Fichter and Brunner[48] applied electrolysis to a solution of phenol in dilute sulphuric acid. This resulted in the formation of a little biphenyl (**167**), diphenols (**168**) and (**169**), and *p*-quinone (**170**), as indicated in Scheme 24. Fichter and Dietrich[101] continued this research, but some time passed before the technique was investigated further.

In more recent electro-oxidative studies, Bobbitt and co-workers[102] applied the method to a variety of 6,7-disubstituted-1,2,3,4-tetrahydro-isoquinolines. Their aim was to develop a controllable model process for common biosynthetic oxidations. Amongst the substrates investigated was the alkaloid corypalline (**171**). From the reaction mixture, they isolated dimeric species (**172**).

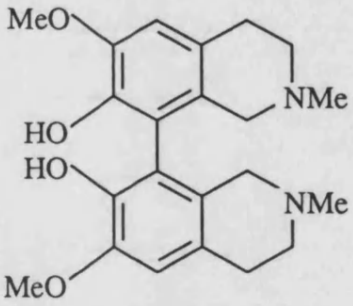
For our purposes, intramolecular anodic coupling, rather than dimerisation, is of more relevance. Ronlán and Parker[103a] together with Hammerich[103b] investigated intramolecular coupling reactions of diaryl alkanes such as bibenzyl (**173**). Phenanthrene (**174**) was isolated, indicating a common



Scheme 24.



(171)

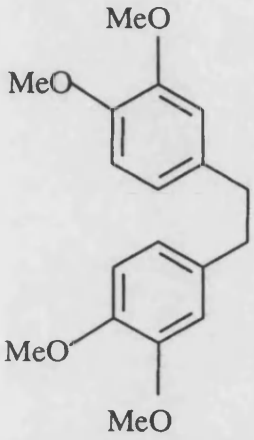


(172)

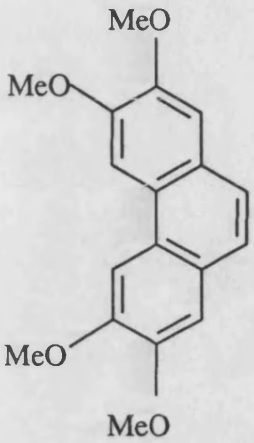
problem associated with anodic oxidation. The intermediate species are often more reactive than the starting materials. Such over-oxidation is usually unwanted.

Ronlán and co-researchers were able to reverse the over-oxidation they observed; by polarity inversion of the reaction cell, or by adding zinc powder.

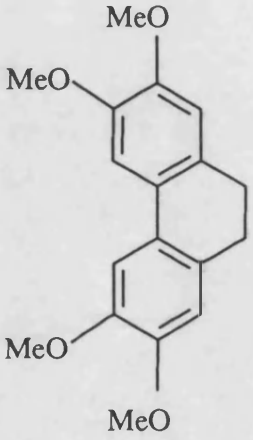
Thus 9,10-dihydrophenanthrathene (**175**) was isolated. These workers[103,104] have also investigated the reaction of homologues of bibenzyl (**173**). The length of linking alkyl chain has been varied from one to sixteen carbon atoms.[49]



(**173**)



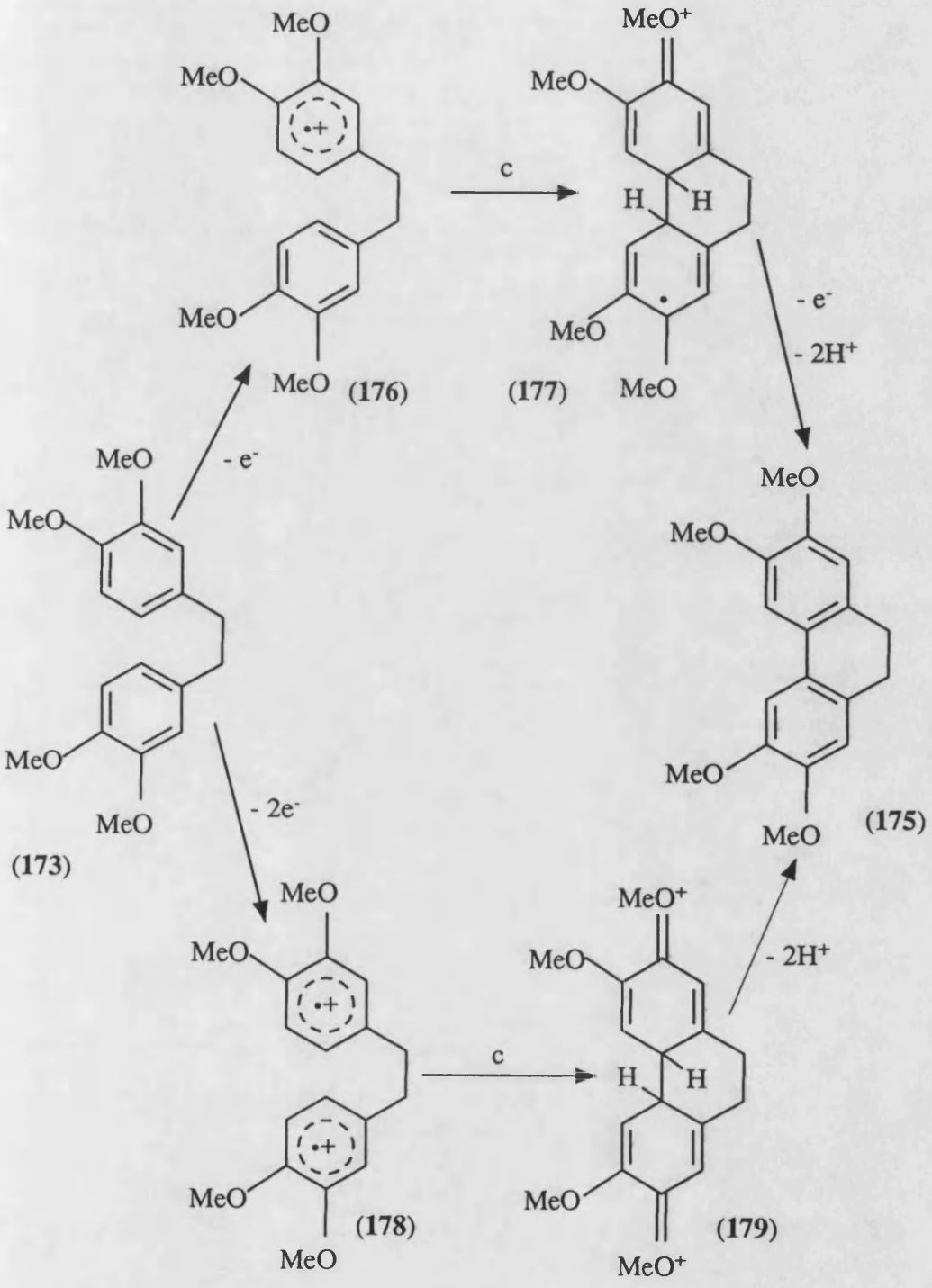
(**174**)



(**175**)

The mechanism of these reactions, still the subject of debate, has been reviewed in some depth by Sainsbury.[49] It may be regarded as a composite of two simplified extremes, which are indicated in Scheme 25. These are defined as *e.c.e.* (*e*lectron loss, *c*hemical reaction, *e*lectron loss), and *e.e.c.* (*e*lectron loss, *e*lectron loss, *c*hemical reaction).

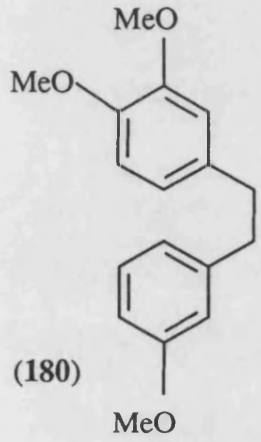
In the first of these cases, proceeding *via* intermediates (**176**) and (**177**), a radical cation is formed by loss of an electron from one aromatic ring. This species then undergoes a chemical bond-forming reaction with the other ring. The second case postulates intermediates (**178**) and (**179**). It requires that both rings


MeO
MeO
MeO
MeO
(176)
c
MeO+
MeO
H
H
MeO
MeO
(177)
- e-
- 2H+
MeO
MeO
MeO
MeO
(175)
- e-
MeO
MeO
MeO
MeO
(173)
- 2e-
MeO
MeO
MeO
MeO
(178)
c
MeO+
MeO
H
H
MeO
MeO+
(179)
- 2H+

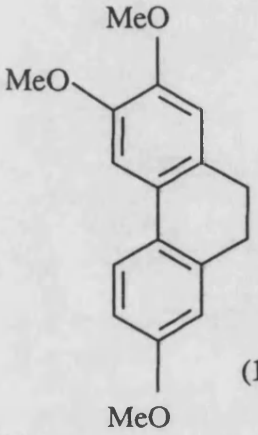
Scheme 25.

form radical cations before the bond-forming reaction occurs.

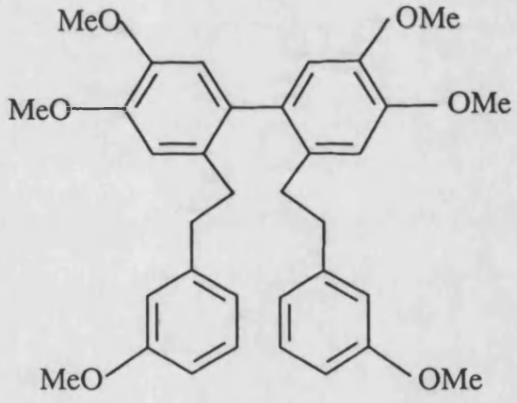
Ronlán and co-workers[103a] were able to draw some conclusions from the electrochemistry of bibenzyl (**180**). Cyclic voltammetry indicated that the monomethoxylated aromatic ring is not oxidised until +1·6 V, whereas the disubstituted ring ionises at only +1·2 V.[49,103a] At potentials sufficient to ionise both rings, they isolated bibenzyl (**181**); however at intermediate voltages their product was dimer (**182**).



(**180**)



(**181**)



(**182**)

They inferred that a diradical cation was required for intramolecular cyclisation. However, Ronlán and co-workers[103b,104] thought both mechanisms may operate, dependent on the length of the linking alkyl chain. Kinetic studies[105] of the reaction indicated that the true situation is probably more complicated than that indicated in Scheme 25. Sainsbury and co-workers[50-54,106]

have investigated several facets of this process, especially in pursuit of natural products.

Cyclic voltammetry is a technique for determining the oxidative potential of starting materials. We used a single cell for this purpose, as illustrated in Figure 5. A ramp voltage generator was used to supply a gradually increasing potential between two electrodes in the cell. Current flowing in the cell could be measured by an ammeter in this circuit. The oxidative potential at the anode may be measured using a standard calomel electrode (s.c.e.).

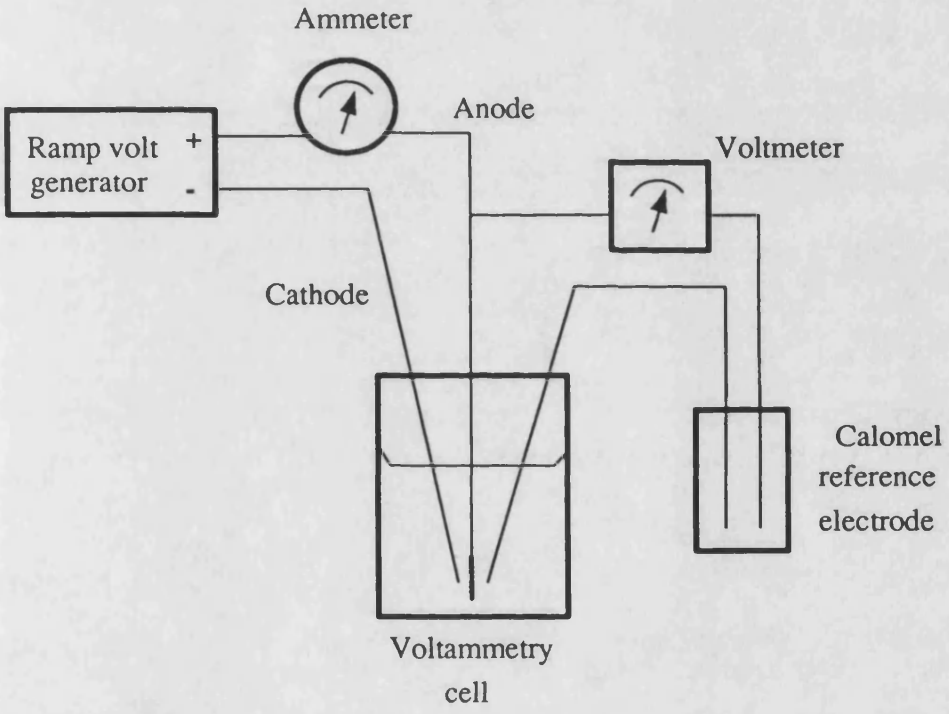


Figure 5.

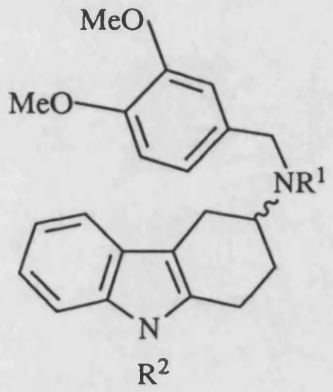
A test substance was added, in a suitable combination of solvent and electrolyte. A linearly increasing potential was applied between anode and cathode, from 0 V to +2 V, and allowed to fall back at the same rate. The resulting potential at the calomel electrode was plotted along the x-axis of a chart recorder. The current, which reaches a maximum when an ionisation is occurring,

was plotted along the y-axis.

This process lead to a cyclical graph, containing peaks at the oxidative potentials of any susceptible functions in the molecule. Oxidative ionisations, in which we were interested, occur on the positive voltage sweep. Reductive reactions occur when the polarity is reversed.

4·2. Discussion.

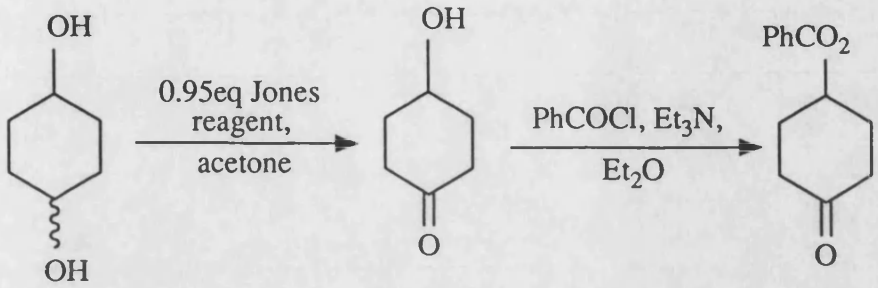
4·2·1. Preparation of 3-(*N*-3,4-dimethoxybenzyl)amino-1,2,3,4-tetrahydrocarbazole.



(**72**) $R^1 = R^2 = H$
(**183**) $R^1 = R^2 = CHO$
(**184**) $R^1 = H{\cdot}HCl$, $R^2 = H$

Our preliminary target compound was the secondary amine (**72**), together with the derivatives, diformamide (**183**) and hydrochloride salt (**184**). Amine (**72**) was easily prepared, *via* imine (**185**), see Scheme 27. Condensation of commercially available 3,4-dimethoxybenzaldehyde with amine[107-109] (**186**) afforded imine (**185**). Starting material, benzoate (**187**), for our synthesis of amine (**186**), was prepared using the method outlined in Scheme 26. Partial oxidation of cyclohexane-1,4-diol (**188**), by the method of Haslanger and Lawton,[110] afforded 4-hydroxycyclohexanone (**189**). This was *O*-benzoylated in ether and pyridine,[111] affording 4-benzoyloxycyclohexanone (**187**).

For the preparation of secondary amine (**186**), we chose the recent route of Bird and Wee,[109] shown in Scheme 27. Fischer indolisation of ketone (**187**)



(188) (189) (187)

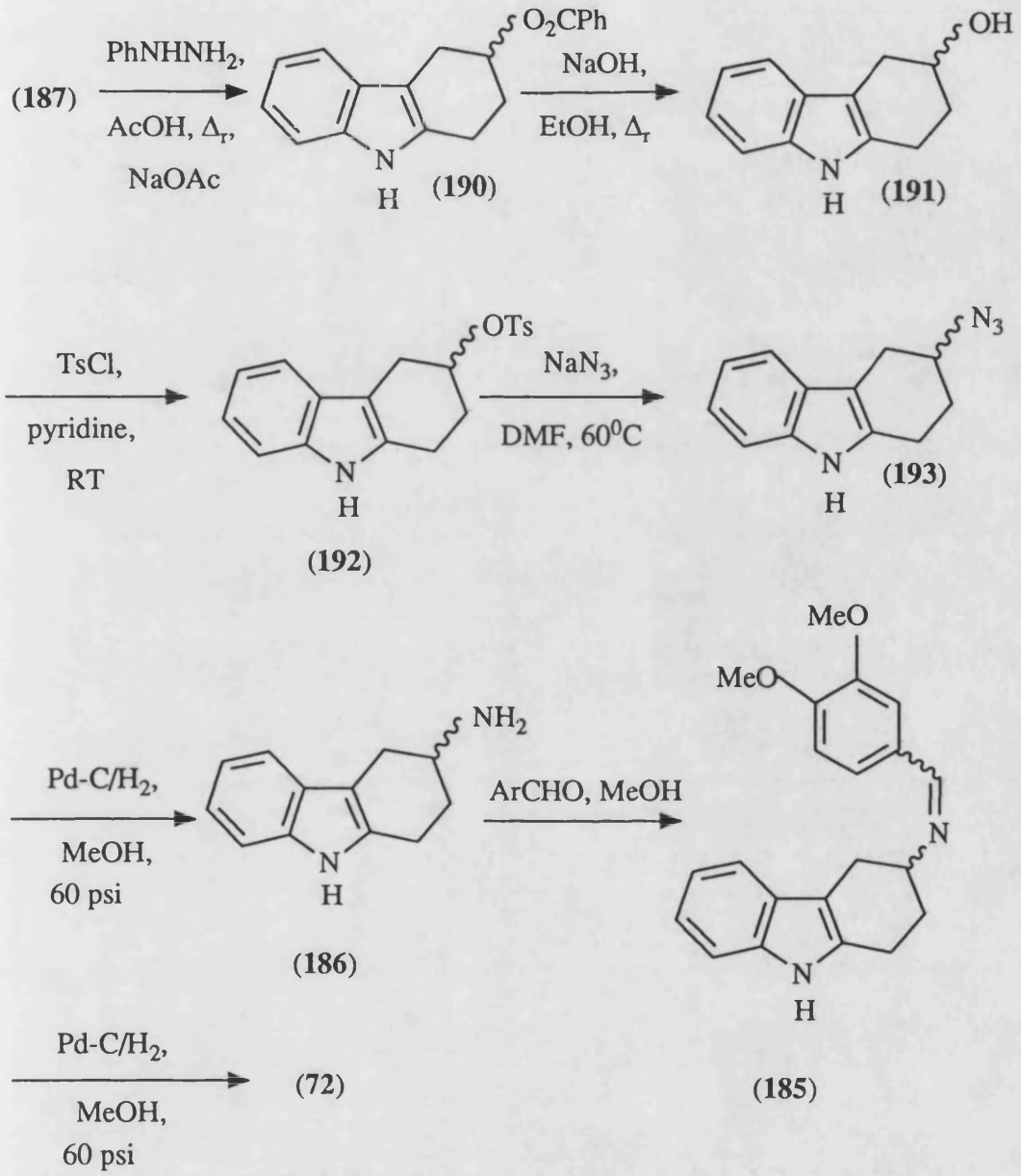
Scheme 26.

and phenylhydrazine hydrochloride, in refluxing acetic acid, resulted in a high yield of tetrahydrocarbazole (**190**). Ethanolysis of the benzoate function afforded the alcohol (**191**), which was *p*-tosylated by the corresponding sulphonyl chloride, in pyridine. Reaction of tosylate (**192**) with sodium azide afforded alkyl azide (**193**).

Some modification of Bird and Wee's conditions[109] for azide formation proved necessary. We found hydrogenation of azide (**193**) ineffective if it had been prepared in dimethylsulphoxide. Catalyst poisoning by traces of that solvent may be to blame. An excellent alternative solvent was *N,N*-dimethylformamide, and we also lowered reaction temperature from 100 °C to 60 °C.

We were thus able to isolate and characterise crystalline azide (**193**) in a pure state. It was then possible to obtain primary amine (**186**), in good yield and purity - provided the following procedure was used. Rigorous degassing, of both ethanolic reaction solution and the suspension of catalyst, was found to be *essential*. Similarly, following reduction, the Parr hydrogenation apparatus must be flushed and charged with nitrogen gas prior to work-up.

Rapid filtration through celite, followed by removal of solvent *in vacuo*, afforded a colourless or pale yellow oil. Immediate trituration, with methanol produced an off-white solid, which could easily be recrystallised from methanol



Ar = 3,4-dimethoxyphenyl

Scheme 27.

in good yield. Deviation from this procedure resulted in formation of a gummy solid, which rapidly darkened in colour. The product would not then crystallise, and purification by sublimation[109] is necessary. When used, this resulted in some

decomposition and lower yields.

Formation of the Schiff's base (**185**) was achieved by stirring amine (**186**) and 3,4-dimethoxybenzaldehyde in methanol. Reaction overnight resulted in imine (**185**) precipitating from solution. The imine was recovered, and then redissolved in ethanol or methanol. Conditions similar to those outlined above, for hydrogenation and work-up, allowed recovery of the desired amine (**72**).

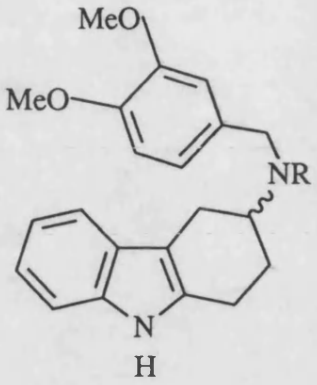
We were now in a position to begin investigation of the anodic electrochemistry of amine (**72**). However, in practice, we first had two problems to contend with. It has been shown[49] that unprotected secondary amines tend to give rise to N-C coupled by-products, under anodic oxidation conditions. Secondary amine protection, for tetrahydrocarbazole (**72**), was thus an essential prerequisite.

More serious is the tendency of indoles to undergo facile oxidation. It is known[49] that indolic rings are oxidised more easily (*ca.* +0.8 V) than methoxylated benzene rings (*ca.* +1.2 to +1.6 V). This can result in undesirable dimerisations taking place, *via* the heterocyclic nucleus in indoles (or tetrahydrocarbazoles). Such processes tend to compete successfully with aryl coupling reactions.

We were therefore interested in preparing derivatives of partially unsaturated carbazole (**72**). Diformamide (**183**) was of prime interest in this respect; *N*-formylation of an indole ought to lessen its electron density, and hence ease of oxidation. However, we did not want to risk complete deactivation of the substrate. Therefore a more easily oxidised compound, such as hydrochloride salt (**184**), was also an attractive substrate.

We applied, to amine (**72**), Sheehan and Yang's[112] method for formylation of amino acids. Overnight reaction resulted in formation of diformamide (**183**). Shorter reaction times produced the formate salt (**194**), instead of the anticipated monoformamide (**195**). We also prepared hydrochloride

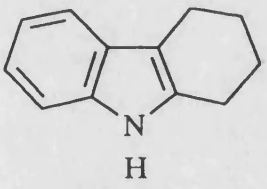
salt (**184**), by passing hydrogen chloride gas through a methanolic solution of amine (**72**). The desired product precipitated after about an hour.



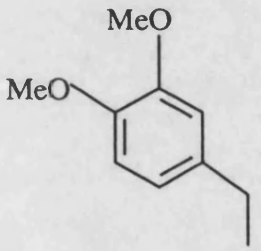
(**194**) R = $H_2^+ HCO_2^-$

(**195**) R = CHO

4·2·2. Anodic oxidation of several derivatives of 3-(*N*-3,4-dimethoxybenzyl)-amino-1,2,3,4-tetrahydrocarbazole.



(**196**)



(**197**) NH_2

The results of cyclic voltammetry, for diformamide (**183**), formate (**194**), and for hydrochloride (**184**), are detailed in Table 1. Values for tetrahydrocarbazole (**196**) and 3,4-dimethoxybenzylamine (**197**) were also determined for comparative purposes.

		Oxidation potential peaks (V)			
Compound	Solvent	O1	O2	O3	O4
(183)	MeCN	--	+1·22	+1·41	+1·54
(183)	TFA-CH_2Cl_2	--	--	+1·43	+1·60
(184)	MeCN	+0·97	+1·18	+1·47	+1·53
(184)	TFA-CH_2Cl_2	+0.94	+1·22	+1·49	+1·61
(194)	MeCN	+0·97	+1·20	+1·49	+1·56
(194)	TFA-CH_2Cl_2	+0·89	--	+1·47	+1·53
(196)	MeCN	+0·77	+0·93	--	--
(197)	MeCN	--	--	+1·32	+1·48
(197)	TFA-CH_2Cl_2	--	--	--	+1·54

Table 1.

These results were broadly as we had expected, and suggested that diformamide **(183)** may be a good substrate for anodic ring-closure. Electrochemistry was performed on all the above derivatives of amine **(72)**. We used a twin cell reaction set-up, the cells being separated by a sinter, as detailed in Figure 6. The electrolytic solvent was either 4% sodium perchlorate in acetonitrile, or trifluoroacetic acid-dichloromethane (1:4).

We started our investigation using diformamide **(183)**, acetonitrile-sodium perchlorate, and an open cell (illustrated in Figure 6), at room temperature. Reaction was allowed to proceed until the theoretical amount of charge had passed through the cell. That value was calculated from the following equation.

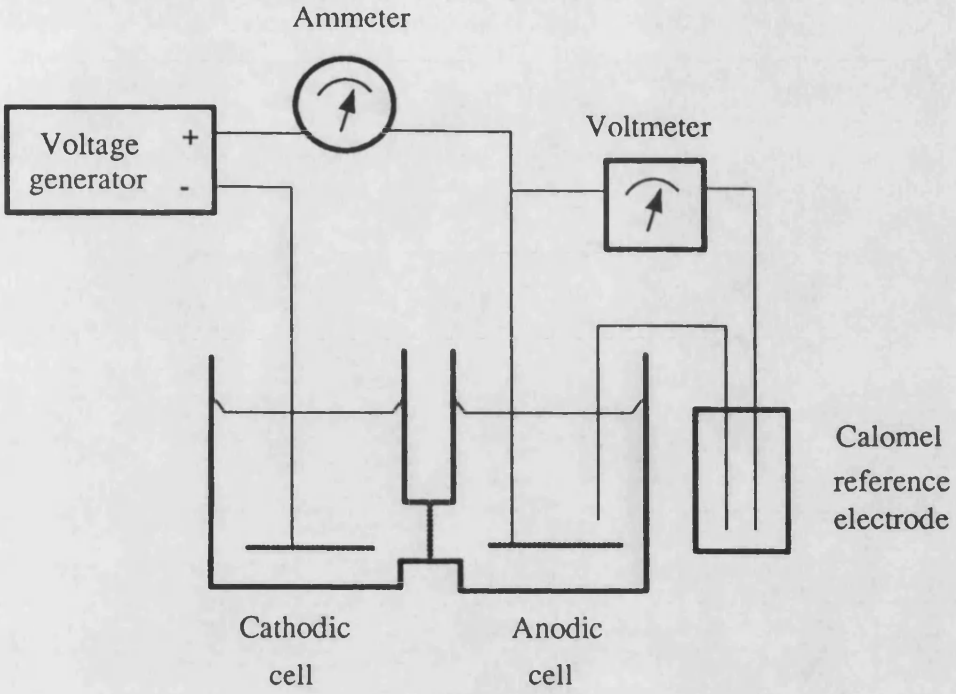


Figure 6.

$$t_{reac} = \frac{n \cdot m \cdot F}{I}$$, where;

t_{reac} = time of reaction in seconds,

n = number of moles of compound,

m = number of moles of electrons per mole of compound,

F = Faraday constant (96, 487),

I = current in Amps.

Current through the cell was adjusted to maintain the oxidative potential below +1.6 V. Work-up involved decanting the contents of the cells into two beakers and stirring them with zinc powder. Results were not encouraging; t.l.c. indicated

that the crude product was a very complex mixture. We were unable to determine the outcome in more detail.

We next started trying to optimise the variables involved. Firstly, we repeated the process for the two other substrates, amine salts (**184**) and (**194**). These results were not significantly different. Similarly ineffective was stopping the reaction prematurely, after monitoring by t.l.c. The intent had been to isolate starting material and products, prior to possible over-oxidation of the latter.

Our next change was of solvent; from the acetonitrile system to trifluoroacetic acid-dichloromethane (1:4). Ronlán, Hammerich and Parker[103a] indicate that intermediate diradical cations are much more stable in the latter solvent. This was a pertinent point in cases where we suspected the indole unit may be undergoing premature oxidation. We required any intermediates so formed to remain stable long enough for the dimethoxy ring to become involved. However, the change of solvent lead to no visible alteration in outcome of the reaction.

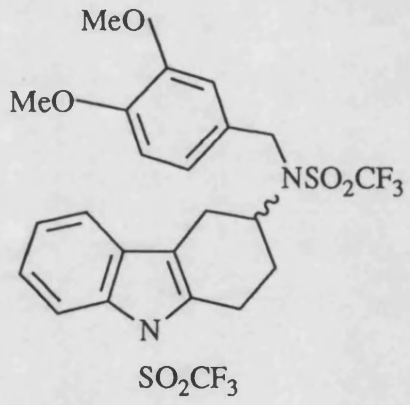
Other factors we altered, in an attempt to influence the reaction, were the use of a closed cell, and of lower temperature. The former case was to investigate the effect of exclusion of moisture, since water is known[49] to undergo reaction with some radical cationic intermediates. Because oxygen gas is a biradical, we also speculated on the possibility of its involvement with the probable radical cationic intermediates. We therefore degassed the solution before and during reaction.

Use of such a closed cell system did not allow insertion of a calomel electrode (this would, in any case, have been a source of moisture). Therefore, we applied conditions of Ronlán and co-workers[103b] in which current density at the anode was kept constant. Reaction was deemed to be over after the theoretical charge had passed through the cell. A less complex mixture appeared to result, but even so we were unable to separate or characterise it.

We adopted these closed-cell conditions as the most optimised so far, and repeated this reaction at -30 °C. The substrate in the majority of these experiments was the amine hydrochloride (**184**), because it was easy to obtain in a pure crystalline state. The latest reaction conditions made very little difference to the results previously observed.

Taking our results as a whole, we were able to speculate on the fate of some of the starting material. In many cases, there were peaks in the mass spectra which indicated that dimerisation may have occurred; even in the case of diformamide (**183**). From reaction of amine hydrochloride (**184**), we were able to isolate an oily component, which appeared to be mostly 3,4-dimethoxybenzaldehyde.

Clearly, some decomposition of the secondary amine had occurred. This implied that protonation of amine was not sufficient to prevent oxidation of its electron lone-pair, even under acidic conditions. We therefore tried, without success, to synthesise the *N*-triflate (**198**). Starting amine (**72**) appeared very reactive when treated with trifluoromethanesulphonic anhydride, low temperature notwithstanding.

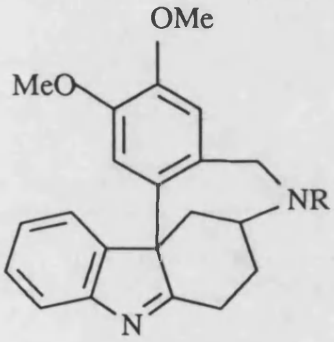


(**198**)

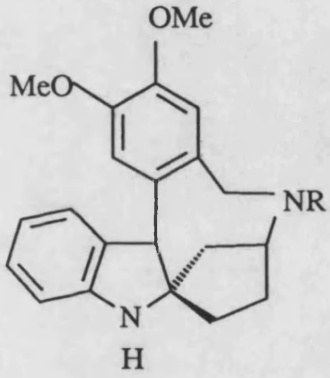
Since diformamide (**183**) apparently failed to undergo intramolecular

reaction, more than electronic factors may be at work. It is well known that successful reaction requires the formation of a suitable geometric transition state.[49] Examination of the ^{1}H n.m.r. data of our electrolysis substrates supplied some evidence that this may not occur with derivatives of amine (**72**).

Azide (**193**) is perhaps the only compound in the series, shown in Scheme 27, not to exhibit a fixed cyclohexenyl ring conformation. Amine (**72**) serves to illustrate the rigidity of the remaining tetrahydrocarbazoles. Its ^{1}H n.m.r. spectrum included a multiplet at δ 3·06 (C-3), and two doublets of doublets; at δ 2·86, J = 15 and 5 Hz, and δ 2·28, J = 15 and 9 Hz (C-4). That indicates that cyclohexyl ring-flip does not occur, and so the two C-4 protons are not degenerate.



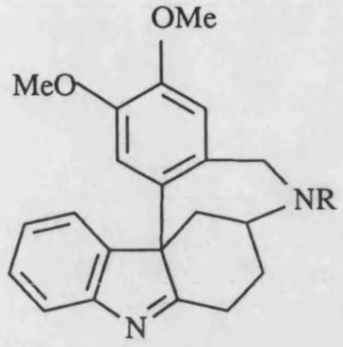
(**73**)



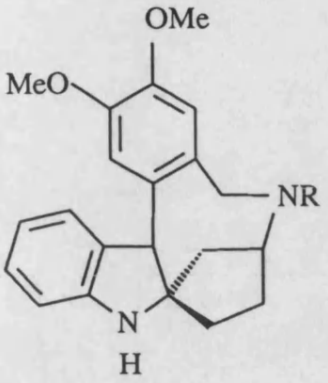
(**74**)

It is most probable that the cyclohexenyl ring would be locked in a conformation with its amino substituent in the equatorial position. This would fail to allow a favourable transition state to form. The two rings to be coupled would not get close enough for the desired reaction to occur. Therefore, we concluded, anodic oxidation is not a suitable method for synthesis of compounds such as pentacycles (**73**) or (**74**). Furthermore, such geometry of (**72**) may prevent its cyclisation by any other means. We lacked the time to investigate a synthesis of

novel serotoninoid analogues using a different approach.



(73)



(74)

4·3. Experimental.

Preparation of 4-Hydroxycyclohexanone[110] **(189).**—— In a three-necked round-bottomed flask (5000 ml), equipped with a mechanical stirrer, a thermometer, and a dropping funnel (100 ml), cyclohexane-1,4-diol (59·9 g, 0·5 mol) was dissolved in Analar acetone (2500 ml). This vigorously stirred solution was kept between 0 °C and 5° (ice-bath) and freshly prepared, ice-cold, Jones Reagent (60·8 ml; 0·95 eq) was added over a 50 minute period. The Jones Reagent was prepared as follows: to chromium trioxide (26·8 g) at ice-bath temperature, concentrated sulphuric acid (23 ml) was added slowly, with stirring, and allowed to cool. The resultant solution was made up to 100 ml with water, added slowly, with stirring. After addition of Jones Reagent, the green suspension was allowed to warm to room temperature, with stirring, over a 20 minute period. The chromium salts were allowed to settle, and the acetone solution was decanted and filtered through a bed of celite under reduced pressure. Acetone was removed *in vacuo* to yield a pale green oil. Chromatography on silica gel, using ethyl acetate-hexane (2:5) as eluant, yielded a nearly colourless oil, 4-hydroxycyclohexanone (24·4 g, 41%); b.p. 95-97 °C/0·3 mm (lit.,[111,113] 97-98 °C/0·5 mm, 83-85 °C/0·6 mm)(Found:* C, 61·9; H, 10·0. Calc. for $C_6H_{10}O_2$: C, 63·15; H, 8·85%); R_f 0·35, methanol-chloroform (1:9); υ_{max} (film) 3410br (OH), 1695s cm^{-1} (C=O); δ_H(270 MHz; DMSO-D_6) 4·85 (1H, br s, OH), 3·94 (1H, m, *J* 8, 8, 4, 4 Hz, 4-H), 2·38 (2H, m, *J* 14, 8, 6 Hz, 2-H, 6-H), 2·22 (2H, m, *J* 14, 8, 6 Hz, 2-H, 6-H), 1·90 (2H, m,* 3-H, 5-H), 1·73 (2H, m, *J* 14, 7, 7, 6 Hz, 3-H, 5-H); *m/z* (low eV EI) 114 (M^+, 100%), 73 (C_4H_9O, 30), 68 (C_5H_8, 40), 60 (30), 55 (C_3H_3O, 30).

*The oil appears to be hygroscopic.

*Insufficiently resolved for determination of coupling constants.

4-Benzoyloxycyclohexanone (**187**).——Alcohol (**189**) (23·75 g, 0·2 mol) was stirred overnight in ether (500 ml), together with pyridine (100 ml), and benzoyl chloride (26·5 ml, 0·25 mol). The mixture was diluted with ether (250 ml) and washed with 2M sulphuric acid (4x250 ml), saturated sodium hydrogen carbonate solution (2x250 ml), brine (250 ml), and dried (sodium sulphate). Solvent was removed *in vacuo* to provide a pale yellow oil. This was stirred and warmed with light petroleum (b.p. 40——60 °C), and ether was added to the refluxing mixture until the oil dissolved. The crude product precipitated on cooling. Crystallisation from pentane-ether (5:1) afforded 4-benzoyloxycyclohexanone (30·55 g, 67%), m.p. 62·5-63·5°C (lit.,[111] 63 °C) (Found: C, 71·8; H, 6·5. Calc. for $C_{13}H_{14}O_3$: C, 71·55; H, 6·45%); R_f 0·3, methanol-chloroform (1:9); $\upsilon_{max.}$ (KBr) 1709s cm^{-1} (C=O); δ_H (200 MHz; $CDCl_3$) 8·05 (2H, dd, *J* 8, 2 Hz, 2'-H, 6'-H), 7·57 (1H, tt, *J* 7, 7, 2, 2 Hz, 4'-H), 7·45 (2H, td, *J* 8, 8, 2 Hz, 3'-H, 5'-H), 5·43 (1H, m, *J* 8, 8, 4, 4 Hz, 4-H), 2·67 (2H, m, *J* 14, 8, 6 Hz, 2-H, 6-H), 2·46 (2H, m, *J* 14, 7, 7 Hz, 2-H, 6-H), 2·23 (4H, m, *J* 14, 7, 7, 7 Hz, 3-H, 5-H); *m/z* (EI) 218 (M^+, 2%), 123 ($PhCO_2H$+1, 5) 113 (M^+-PhCO, 1), 105 (PhCO, 100), 96 (C_6H_8O, 60), 77 (Ph, 35), 68 (C_5H_8, 20).

3-Benzoyloxy-1,2,3,4-tetrahydrocarbazole[108] (**190**).—— A solution of the ketone (**187**)(29·7 g, 0·15 mol), in glacial acetic acid (600 ml), was stirred under reflux for one hour, together with sodium acetate (12·3 g, 0·15 mol) and phenylhydrazine hydrochloride (21·6 g, 0·15 mol). The solution was allowed to cool to room temperature and filtered. The residue was dissolved in minimum refluxing THF, and filtered hot through celite. This cooled filtrate was freed of solvent *in vacuo*, and the resultant residue was crystallised from minimum ethanol to yield 3-benzoyloxy-1,2,3,4-tetrahydrocarbazole (32·5 g, 82%), 193-194 °C (lit.,[114] 193°C) (Found: C, 78·2; H, 5·85; N, 4·8. Calc. for

$C_{19}H_{17}NO_2$: C, 78·35; H, 5·9; N, 4·8%); R_f 0·3, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:4); $\upsilon_{max.}$ (KBr) 3366s (NH), 1702s cm^{-1} (C=O); δ_H (200 MHz; DMSO-D_6) 10·70 (1H, s, NH), 7·96 (2H, dd, *J* 8, 2 Hz, 2'-H, 6'-H), 7·64 (1H, tt, *J* 8, 8, 2, 2 Hz, 4'-H), 7·51 (2H, tt, *J* 8, 8, 2, 2 Hz, 3'-H, 5'-H), 7·36 (1H, dt, *J* 8, 2, 2 Hz, 5-H), 7·28 (1H, dt, *J* 8, 2, 2 Hz, 8-H), 7·03 (1H, td, *J* 8, 8, 2 Hz, 7-H), 6·94 (1H, td, *J* 8, 8, 2 Hz, 6-H), 5·47 (1H, m, *J* 6 Hz, 3-H), 3·20* (1H, dd, *J* 15, 5 Hz, 4-H), 2·93* (2H, t, *J* 6 Hz, 1-H), 2·87* (1H, dd *J* 15, 5 Hz, 4-H), 2.10 (2H, q, *J* 6 Hz, 2-H); δ_C (23 MHz; DMSO-D_6) 165·39 (C=O), 136·30 (C-8a), 133·16 (C-4', C-4b), 130·18 (C-1'), 129·07 (C-2', C-6'), 128·62 (C-3', C-5'), 127·15 (C-9a), 120·38 (C-6), 118·21 (C-5), 117·13 (C-7), 110·73 (C-8), 104·99 (C-4a), 70·64 (C-3), 27·52 (C-4), 26·87 (C-2), 19·99 (C-1); *m/z* (EI) 291 (M^+, 2%), 186 (M^+-PhCO, 1), 169 (M^+-$PhCO_2H$, 100%), 167 (carbazole, 15), 154 (169-NH, 5), 143 (169-C_2H_2, 10), 128 (154-C_2H_2, 5), 115, (143-C_2H_4, 5), 105 (PhCO, 10), 77 (Ph, 20).

*Partially obscured by water signal.

*Signals partially overlap.

3-Hydroxy-1,2,3,4-tetrahydrocarbazole[108] (**191**).——To a solution of benzoate (**190**)(21·3 g, 73·1 mmol), was added a solution of sodium hydroxide (5·85 g, 0·15 mol). The reaction mixture was stirred at reflux for 2 hours, during which time a large volume of sodium benzoate precipitated. Sufficient water to dissolve the white solid was added, and the resultant pale brown solution was concentrated *in vacuo*. The crude product separated, and was collected. Crystallisation from ethanol-water afforded 3-hydroxy-1,2,3,4-tetrahydro-carbazole (12·85 g, 94%), m.p. 151-152 °C (lit.[108,114] 149-150 °C from water and ethanol-water) (Found: C, 77·4; H, 7·1; N, 7·4. Calc. for $C_{12}H_{13}NO$: C, 77·0; H, 6·95; N, 7·5%); R_f 0·4, methanol-dichloromethane (1:20); $\upsilon_{max.}$ (KBr) 3387s

(NH), 3339m, br cm^{-1} (OH); δ_H (200 MHz; DMSO-D_6) 10·59 (1H, s, NH), 7·33 (1H, dd, *J* 8, 2 Hz, 5-H), 7·25 (1H, dd, *J* 8, 2 Hz, 8-H), 7·00* (1H, dt, *J* 8, 8, 2 Hz, 7-H), 6·93* (1H, dt, *J* 8, 8, 2 Hz, 6-H), 4·84 (1H, d, *J* 4 Hz, OH), 4·03 (1H, br m,* 3-H), 2·95 (1H, dd, *J* 10, 6 Hz, 4-H), 2·79 (2H, br m, 1-H), 2·50 (1H, dd, *J* 14, 7 Hz, 4-H), 2·01, 1·82 (2H, br m, 2-H); δ_C (23 MHz; DMSO-D_6) 136·30 (C-8a), 133·59 (C-4b), 127·42 (C-9a), 119·97 (C-6), 117·99 (C-5), 117·02 (C-7), 110·52 (C-8), 106·45 (C-4a), 66·36 (C-3), 31·53 (C-4), 30·34 (C-2), 20·86 (C-1); *m/z* (EI) included 187 (M^+, 40%), 169 (M^+-H_2O, 10), 167 (carbazole, 25), 156 (169-CH, 1) 143 (169-C_2H_2, 100), 138 (1), 130 (167-C_3H, 10), 115 (143-C_2H_4, 10), 99 ($C_6H_{11}O$, 1).

*Signals partially overlap.

*Poorly resolved.

3-p-Toluenesulphonyloxy-1,2,3,4-tetrahydrocarbazole[109] **(192).**—— *p*-Toluenesulphonyl chloride (16·75 g, 87·8 mmol) was added to a solution of alcohol (**191**)(10·3 g, 54·9 mmol), dissolved in pyridine (100 ml). The mixture was stirred overnight, during which time a white precipitate of pyridinium hydrochloride separated, then diluted with ether. The mixture was worked-up as for the benzoate (**187**), and removal of solvent afforded the crude solid. Crystallisation from chloroform afforded 3-*p*-toluenesulphonyloxy-1,2,3,4-tetrahydrocarbazole (12·35 g, 66%), m.p. 147-149 °C (dec.) (lit.,[109] 151-152 °C (dec.) from toluene) (Found: C, 66·8; H, 5·6; N, 4·1; S, 9·5. Calc. for $C_{19}H_{19}NO_3S$: C, 66·85; H, 5·6; N, 4·1; S, 9·4%); R_f 0·4, dichloromethane; $\upsilon_{max.}$ (KBr) 3394s (NH), 1379, 1189s cm^{-1} (SO_2); δ_H (200 MHz; DMSO-D_6) 10·79 (1H, s, NH), 7·84 (2H, d, *J* 8 Hz, 2'-H, 6'-H), 7·47 (2H, d, *J* 8 Hz, 3'-H, 5'-H), 7·29 (1H, d, *J* 6 Hz, 5-H), 7·23 (1H, d, *J* 6 Hz, 6-H), 7·01 (1H, td, *J* 8, 8, 2 Hz, 7-H), 6·92 (1H, td, *J* 8, 8, 2 Hz, 6-H), 4·99 (1H, br m, 3-H), 2·94 (1H, dd, *J* 15, 6

Hz, 4-H), 2·77* (2H, t, *J* 6 Hz, 1-H), 2·75* (1H, dd, *J* 15, 6 Hz, 4-H), 2·23 (3H, s, CH_3), 2·00 (2H, br m, 2-H); δ_C (23 MHz; DMSO-D_6) 144·65 (C-1'), 136·14 (C-8a), 133·76 (C-4'), 132·73 (C-4b), 130·02 (C-3', C-5'), 127·31 (C-2', C-6'), 126·82 (C-9a), 120·48 (C-6), 118·26 (C-5), 117·02 (C-7), 110·68 (C-8), 103·91 (C-4a), 78·77 (C-3), 27·79 (C-4), 27·47 (C-2), 19.29 (C-1); *m/z* (EI) included 341 (M^+, 10), 186 (M^+-$MePhSO_2$, 2), 169 (186-OH, 65), 167 (carbazole, 35), 154 (169-NH, 5) 143 (169-C_2H_2, 15), 128 (154-C_2H_2, 5), 115 (143-C_2H_4, 5), 91 (MePh, 10), 77 (Ph, 2), 28 (C_2H_4, 100).

*Signals partially overlap.

3-Azido-1,2,3,4-tetrahydrocarbazole[109] (**193**).——A solution of tosylate (**192**)(11·65 g, 34·1 mmol) in DMF (200 ml), together with sodium azide (3·3 g, 51·1 mmol), was stirred behind a blast screen for 15 hours at 60 °C. The cooled dark brown solution was poured into ice-water (1 L), and extracted with ether (3x300 ml). The combined organic phase was washed with brine (250 ml), and dried (sodium sulphate). Removal of solvent *in vacuo* and chromatography over silica gel, with ethyl acetate-light petroleum (b.p. 60——80 °C) (1:4), yielded 3-azido-1,2,3,4-tetrahydrocarbazole (5·1 g, 70%), m.p. 80·5-81 °C (Found: C, 68·0; H, 5·6; N, 26·3. Calc. for $C_{12}H_{12}N_4$: C, 67·9; H, 5·7; N, 26·4%); R_f 0·4, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:4); $\upsilon_{max.}$ (KBr) 3395s (NH), 2099s cm^{-1} (N_3); δ_H (270 MHz; DMSO-D_6) 7·31 (1H, d, *J* 8 Hz, 5-H), 7·26 (1H, d, *J* 8 Hz, 8-H), 7·01 (1H, td, *J* 8, 8, <2 Hz, 7-H), 6·93 (1H, td, *J* 8, 8, <2 Hz, 6-H), 4·06 (1H, br m, 3-H), 3·02 (1H, dd, *J* 15, 5 Hz, 4-H), 2·81 (2H, t, *J* 6 Hz, 1-H), 2·66 (1H, dd, *J* 16, 8 Hz, 4-H), 2·10 (1H, m, *J* 12, 6, 6, 3 Hz, 2-H), 1·95 (1H, m, *J* 16, 8, 8, 7 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 136·13 (C-8a), 132·43 (C-4b), 127·29 (C-9a), 121·47 (C-6), 119·41 (C-5), 117·66 (C-7), 110·55 (C-8), 106·80 (C-4a), 57·35 (C-3), 28·02 (C-4), 26·79 (C-2), 20·84 (C-1); *m/z* (NH_3 CI)

213 (M^++1, 70%), 212 (50), 185 (100), 184 (M^+-N_2, 80), 170 (M^+-N_3, 35), 169 (30), 167 (carbazole, 15), 156 (169-CH, 90), 154 (169-NH, 15), 143 (169-C_2H_2, 100), 130 (30), 115 (15), 77 (5).

3-Amino-1,2,3,4-tetrahydrocarbazole[109] (**186**).——A solution of the azide (**193**)(3·0 g, 14·2 mmol) was dissolved in methanol (50 ml) and the solution was thoroughly degassed, by a stream of nitrogen gas, for 20 minutes. A suspension of palladium on charcoal (10%) was similarly degassed and added to the reaction mixture. This was hydrogenated at a pressure of 60 psi for 24 hours. The bomb was evacuated and pressurised with nitrogen for 20 minutes, before the mixture was filtered through celite. Evaporation of solvent *in vacuo* and trituration and crystallisation from methanol afforded 3-amino-1,2,3,4-tetrahydrocarbazole (1·95 g, 74%), m.p. 181-182 °C (lit.,[109] 176-177 °C) (Found: C, 77·1; H, 7·6; N, 15·0. Calc. for $C_{12}H_{14}N_2$: C, 77·4; H, 7·6; N, 15·05%); R_f 0·05, ethyl acetate-light petroleum (b.p. 60——80 °C) (1:1); $\upsilon_{max.}$ (KBr) 3351, 3326s (free NH), 3200-2300 cm^{-1} (H-bonded NH); δ_H (270 MHz; DMSO-D_6) 10·65 (1H, s, NH), 7·31 (1H, d, *J* 8 Hz, 5-H), 7·23 (1H, d, *J* 8 Hz, 8-H), 6·97 (1H, td, *J* 8, 8, <2 Hz, 7-H), 6·90 (1H, td, *J* 8, 8, >2 Hz, 6-H), 3·06 (1H, br m, 3-H), 2·86 (1H, dd, *J* 15, 5 Hz, 4-H), 2·74 (2H, br m, 1-H), 2·28 (1H, dd, *J* 15, 9 Hz, 4-H), 1·94* (1H, br m, 2-H), 1·69-1·52* (1H, m, 2-H); δ_C (68 MHz; DMSO-D_6) 136·26 (C-8a), 133·86 (C-4b), 127·37 (C-9a), 120·04 (C-6), 118·03 (C-5), 117·09 (C-7), 110·32 (C-8), 107·32 (C-4a), 47·87 (C-3), 32·85 (C-4), 31·00 (C-2), 21·60 (C-1); *m/z* (EI) 186 (M^+, 60%), 169 (10), 167 (15), 156 (5), 154 (5), 143 (100), 130 (5), 128 (5), 115 (10), 77 (10).

*These signals were superimposed upon a very broad (0·5 ppm) singlet, corresponding to NH_2. The total signal integrated to four protons, and to two protons after shaking with D_2O.

3-(N-3,4-Dimethoxybenzylimino)-1,2,3,4-tetrahydro-carbazole (**185**).——The amine (**186**)(1·6 g, 8·5 mmol), was suspended in a solution of 3,4-dimethoxybenzaldehyde (1·4 g, 8·5 mmol) in methanol (20 ml) and stirred overnight. The voluminous precipitate of imine was collected to yield *3-(N-3,4-dimethoxybenzylimino)-1,2,3,4-tetrahydro-carbazole* (2·1 g, 75%), m.p. 185-186 °C (Found: C, 75·8; H, 6·65; N, 8·4. $C_{21}H_{22}N_2O_2$ requires C, 75·4; H, 6·65; N, 8·4%); $\upsilon_{max.}$ ($CHCl_3$) 3475m (NH), 1640m cm^{-1} (C=N); δ_H (270 MHz; $CDCl_3$) 8·35* (1H, s, NH), 7·99 (1H, s, CH=N), 7·46* (2H, dd, *J* 10, 2 Hz, 5'-H, 2'-H), 7·27* (1H, dd, *J* 7 Hz, 5-H), 7·19 (1H, dd, *J* 8, 2 Hz, 8-H), 7·12** (1H, td, *J* 8, 8, 1 Hz, 7-H), 7·07** (1H, td, *J* 8, 8, 1 Hz, 6-H), 6·88 (1H, d, *J* 8 Hz, 6'-H), 3.91, (3H, s, CH_3), 3.89 (3H, s, CH_3), 3·71 (1H, br m, 3-H), 2·94 (2H, d, *J* 8 Hz, 1-H), 2·88 (2H, dd *J* 10, 5 Hz, 4-H), 2·28-2·01 (2H, m, 2-H); δ_C (68 MHz; $CDCl_3$) 159·29 (C=N), 152** (C-3'), 149** (C-4'), 136·16 (C-8a), 133·34 (C-4b), 129·64 (C-1'), 127·63 (C-9a), 122·99 (C-6'), 121·11 (C-6), 119·17 (C-5), 117·67 (C-7), 110·44 (C-2'), 109·08 (C-8), 108·43 (C-4a), 66·88 (C-3), 55·89 (CH_3), 31·08 (C-4), 29·13 (C-2), 21·96 (C-1); *m/z* (^{i}Bu CI) 335 (M^++1, 100%), 334 (55), 186 (5), 169 (30), 167 (80).

*Assigned on the assumption that H-bonding with the imine nitrogen is responsible for the upfield shift.

*Poorly resolved signals. In the case of the resonance at δ 7·27, the second coupling constant was unresolved.

**Signals overlap.

**Low intensity signals not recognised by the computer. Quoted to the nearest p.p.m.

3-(N-3,4-Dimethoxybenzylamino)-1,2,3,4-tetrahydro-carbazole (**72**).——The imine (**185**)(1·5 g, 4·5 mmol) was reduced by the same procedure used for preparation of amine (**186**), to yield *3-(N-3,4-dimethoxy-benzylamino)-1,2,3,4-tetrahydrocarbazole* (1·1 g, 72%), m.p. 151-152 °C (Found: C, 73·9; H, 7·15; N, 8·1. $C_{21}H_{24}N_2O_2$ requires C, 74·95; H, 7·2; N, 8·35%); R_f 0·5, methanol-dichloromethane (1:9); $\upsilon_{max.}$ (Nujol) 3360 cm^{-1} (NH); δ_H (270 MHz; DMSO-D_6) 10·64* (1H, s, NH), 7·32 (1H, d, *J* 8 Hz, 5-H), 7·22 (1H, d, *J* 8 Hz, 8-H), 7·04-6·81 (5H, m, 7-H, 6-H, 6'-H, 5'-H, 2'-H), 3·78 (2H, s, Ar*CH*$_2$NRH), 3·74 (3H, s, CH_3), 3·71 (3H, s, CH_3), 3·35 (1H, br m, 3-H), 3·02-2·60 (3H, m, 1-H, 4-H), 2·38 (1H, dd, *J* 16, 8 Hz, 4-H), 2·07 (1H, br m, 2-H), 1·65 (1H, br m, 2-H); *m/z* (70 eV EI) 336 (M^+, 30%), 186 (10), 185 (M^+-151, 50), 169 (15), 167 (5), 151 ($(MeO)_2PhCH_2$, 45), 143 (100).
*Removed by shaking with D_2O.

9,N-Diformyl-3-(N-3,4-dimethoxybenzylamino)1,2,3,4-tetrahydrocarbazole (**183**).——Amine (**72**) (0·51 g, 1·5 mmol) was dissolved in 98% formic acid (3·2 ml) to which was added acetic anhydride (1·1 ml).[112] The mixture was allowed to stir overnight. Work-up, addition of 5 ml ice-water and concentration *in vacuo*, afforded a crude gum - in contrast to the literature[112] process. Chromatography over silica gel with ethyl acetate-light petroleum (b.p. 60——80 °C) (4:1) yielded *9,N-diformyl-3-(N-3,4-dimethoxybenzylamino)-1,2,3,4-tetrahydrocarbazole*, a pale yellow waxy solid (0·30 g, 50%) which would not crystallise from a variety of solvents, m.p. 80-84 °C (Found: C, 69·1; H, 6·4; N, 6·8. $C_{23}H_{24}N_2O_4$ requires C, 70·4; H, 6·15; N, 7·15%); $\upsilon_{max.}$ ($CHCl_3$) 1695br, 1655br cm^{-1} (NCHO); δ_H* (270 MHz; $CDCl_3$) 9·05, 8·47 (1H, s, E/Z $ArCH_2NRCHO$), 8·38 (1H, s, NCHO), 7·29 (4H, d, *J* 8 Hz, 5-H, 6-H, 7-H, 8-H), 6·89 (1H, s, 2'-H), 6·82 (1H, s, 6'-H), 6·75 (1H, s, 5'-H), 4·69, 4·57 (1H, d, *J* 13

Hz, E-ArCH_2NRCHO), 4·45 (1H br s, Z-ArCH_2NRCHO), 3·88 (6H, br s, CH_3), 3·48 (1H, dd, *J* 18, 9 Hz, 4-H), 2·91 (3H, br m, 4-H, 1-H), 2·10 (2H, br m, 2-H); (70eV EI) 392 (M^+, 1%), 376 (M^+-O, 2), 364 (M^+-CHO, 1), 349 (376-CO, 1), 334 (364-CHO, 1), 307 (3), 293 (3), 279 (3), 225 (2), 211 (2), 197 (M^+-195, 100), 195 ($(MeO)_2PhCH_2NCHO$, 10), 169 (30), 167 (20), 151 (40), 149 (40).

*Spectrum quite poorly resolved.

3-(N-3,4-Dimethoxybenzylamino)-1,2,3,4-tetrahydrocarbazole formate (**194**).——The procedure used in the preparation of diformamide (**183**) was applied to amine (**72**)(0·60 g, 1·8 mmol). The mixture was worked-up after 1 hour, producing a dark brown residue (0·49 g). Trituration in hot ethyl acetate yielded a white crystalline solid, *3-(N-3,4-dimethoxybenzylamino)-1,2,3,4-tetrahydrocarbazole formate* (0·37 g, 54%), m.p. 184-186 °C (Found: C, 68·8; H, 6·8; N, 7·25. $C_{22}H_{25}N_2O_4$ requires C, 69·1; H, 6·85; N, 7·3%); $\upsilon_{max.}$ (KBr) 3650-2100 ($R_2NH_2^+$), 1570 cm^{-1} (HCO_2^-); δ_H (270 MHz; DMSO-D_6) 10·79 (1H, s, NH), 8·36 (1H, s, HCO_2^-), 7·36 (1H, d, *J* 8 Hz, 5-H), 7·26 (1H, d, *J* 8 Hz, 8-H), 7·22 (1H, d, *J* 2 Hz, 2'-H), 7·03 (2H, m, 6'-H, 5'-H), 6·96 (2H, m, 7-H, 6-H), 6·5-4·75 (2H,* s, Ar$CH_2NH_2^+$R); 4·13, 4·06 (2H, d, *J* 13 Hz, Ar$CH_2NH_2^+$R), 3·77 (3H, s, CH_3), 3·74 (3H, s, CH_3), 3·26 (1H, br m, 3-H), 3·16 (2H, dd, *J* 14, 9 Hz, 4-H), 2·81 (2H, br m, 1-H), 2·67 (1H, dd, *J* 14, 9 Hz, 4-H) 2·31 (1H, br m, 2-H), 1·89 (1H, br m, 2-H); *m/z* (70 eV EI) identical to spectrum obtained from starting material (**72**).

*Integrates to rather more than 2H. Probably an averaged shift of amine and water protons.

3-(N-3,4-Dimethoxybenzylamino)-1,2,3,4-tetrahydro-carbazole hydrochloride (**184**).——Amine (**72**)(0·50 g, 1·4 mmol) was dissolved in minimum boiling methanol, and remained in solution on cooling to ice-bath temperature. Dry hydrogen chloride gas was bubbled through the stirred solution for 1 hour, during which time the mixture became pale yellow. On scraping the flask walls, *3-(N-,3,4-dimethoxybenzylamino)-1,2,3,4-tetrahydro-carbazole hydrochloride* (0·45 g, 90%) separated, m.p. 245-253 °C (Found: C, 67·4; H, 6·7; N, 7·4. $C_{21}H_{25}ClN_2O_2$ requires C, 67·65; H, 6·75; N, 7·5%); $\upsilon_{max.}$ (Nujol) 3245br cm^{-1} ($R_2NH_2^+$); δ_H (270 MHz; DMSO-D_6) 10·86* (1H, s, NH), 9·49* (1H, br s, $R_2NH_2^+$), 9·39* (1H, br s, $R_2NH_2^+$), 7·41 (1H, d, *J* 2 Hz, 2'-H), 7·39 (1H, d, *J* 7 Hz, 5-H), 7·27 (1H, d, *J* 7 Hz, 8-H), 7·14 (1H, dd, *J* 8, 2 Hz, 6'-H), 7·03 (1H, td, *J* 7, 7, 1 Hz, 7-H), 6·99 (1H, d, *J* 8 Hz, 5'-H), 6·97 (1H, td, *J* 7, 7, 1 Hz, 6-H), 4·06, 4·04 (2H, d, *J* 13, Hz, Ar$CH_2NH_2R_2$), 3·80 (3H, s, CH_3), 3·76 (3H, s, CH_3), 3·43 (1H, br m, 3-H), 3·26 (1H, dd, *J* 14, 6 Hz, 4-H), 2·83 (3H, br m, 4-H, 1-H), 2·44 (1H, br m, 2-H), 2·02 (1H, br m, 2-H); *m/z* (70 eV EI) identical to spectrum obtained from starting material amine (**72**).

*Removed by D_2O.

Typical procedures for electrolysis.——

In acetonitrile with sodium perchlorate. Starting material (ca. 0·5 mmol), dissolved in electrolysis solvent (4% sodium perchlorate electrolyte in acetonitrile) was added to the anodic cell of the electrolysis apparatus (see Figure 6, Discussion). The reaction solution was generally made about 10 mMolar. No attempt was made to exclude air or atmospheric moisture. Current was passed through the cells, and the measured voltage was kept below 1·6 Volts. This required periodic adjustment of the current; there was a tendency for the voltage

to rise. Reaction was monitored by comparison with the theoretical total charge required, and by t.l.c. The latter rapidly showed development of a streak on the plate, in addition to starting material. In all cases the colour of the solution gradually became deep green, orange, or red. In most cases, reaction was stopped with starting material still present in an attempt to reduce over-oxidation. The contents of the cells were poured into two beakers, a small volume of water was added, and acetonitrile was removed *in vacuo*. The residue was diluted with water, and extracted with ether or ethyl acetate. Removal of solvent *in vacuo* produced dark brown residues, the crude products. Attention was focussed on the solutions from the anodic cell. However, some solutions from the cathodic cell were worked-up and shown to contain only a small amount of material; this was very impure and could not be characterised.

In dichloromethane with trifluoroacetic acid. Similar conditions to those above were used, but with several modifications. Dry trifluoroacetic acid-dichloromethane (1:3) was used as electrolyte and solvent. Glassware was oven dried and assembled under a flow of nitrogen, and the cells were stoppered. Solvents were degassed, by a flow of dry nitrogen, in order to remove oxygen, prior to the introduction of substrate. No calomel electrode was used, and therefore it was not possible to monitor the voltage between the cells (*cf.* Figure 6, Discussion). Instead, current was applied at a constant current density[103b] of 0·16 mA cm^{-2}, until the theoretical charge had been passed. Work-up was similar to that in the previous procedure; however excess zinc powder was added to the anodic solution, with stirring for 1 hour. This was in order to reduce the effects of over-oxidation. After filtration, work-up was continued as previously. In general, zinc reduction lead to lightening of the colouration. Frequently pale yellow solutions were produced. Removal of solvent *in vacuo* afforded the crude products.

Results of electrolysis experiments.—— The above procedures were applied to diformamide (**183**), formate (**194**), and hydrochloride (**184**). In every case, the crude products contained very many components. Employment of various eluants, and silica and alumina stationary phases, did not afford separation in any case. Physical data were collected for the various impure chromatographic fractions, but none could be unambiguously characterised. However, the presence of several components in some of the chromatographic fractions could be inferred.

Electrolysis of 3-(N-3,4-Dimethoxybenzyl)amino-1,2,3,4-tetrahydrocarbazole formate (**194**). $\upsilon_{max.}$ (KBr) 1670sh cm^{-1}; *m/z* (+F.A.B.) 672 (60%), 671 (95), 670 (20, various dimers of amine (**72**)), 522 (20), 521 (40), 520 (20, various isomers between amines (**72**) and (**186**)).

Electrolysis of 3-(N-3,4-Dimethoxybenzyl)amino-1,2,3,4-tetrahydrocarbazole hydrochloride (**184**).——

Fraction A. m/z (^{i}Bu CI) 414 (371+C_3H_7, 3%), 399 (371+CO, <1), 373 (20) 371 (dimers of (**186**), 80).

Fraction B. Shown to be predominantly 3,4-dimethoxybenzaldehyde, δ_H (270 MHz; $CDCl_3$) 9·86* (1H, s, CHO), 7·47 (1H, dd, *J* 8, 2 Hz, 6-H), 7·27 (1H, d,* *J* 2 Hz, 2-H), 6·99 (1H, d, *J* 8 Hz, 5-H), 3·98 (3H, s, CH_3), 3·95 (3H, s, CH_3); *m/z* (^{i}Bu CI) 373 (1%), 371 (4), 167 (M^+, 100), 166 (35).

*Unaffected by D_2O.

*Partially obscured by chloroform signal.

Attempted preparation of 9,N-*di-(trifluoromethanesulphonyl)-3-(*N-*3,4-dimethoxybenzylamino)-1,2,3,4-tetrahydro-carbazole* (**198**).——Trifluorosulphonic anhydride was added to a solution of amine (**72**) (0·35 g, 1·0 mmol) at -78 °C (see preparation of sulphonamide (**121**), Chapter 2). The stirred mixture was left to warm, and was worked-up as previously. The resultant crude material (0·30 g) was shown by t.l.c. (various eluants) to contain a large number of components, which could not be separated by chromatography with methanol-dichloromethane (1:99) as eluant. Physical data collected on chromatography fractions did not allow characterisation.

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