

TRENT POLYTECHNIC

SYNTHESIS OF SPIROHETEROCYCLES

BY

OXIDATION OF SULPHONAMIDES

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for the degree of

DOCTOR OF PHILOSOPHY

by

Donald Richard Musto B.Sc.

July 1981

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To Cathy

Declaration:- The work described in this thesis was carried out by the author in the Department of Physical Sciences, Trent Polytechnic, Nottingham between February 1977 and April 1980. Throughout the duration of this investigation the author has not been registered for any other award of the CNAAB nor with any other degree awarding body. Parts of this work have already been published (Tetrahedron Letters, 1980, 21, 5055) and also presented at a Symposium of the Chemical Society, Perkin Division, at Loughborough University, December 1980. Compounds, the names of which are underlined in both text and experimental sections, have not (to the best of the author's knowledge) been described in the literature. Advanced studies undertaken in connection with this research programme include post-graduate lectures on biosynthesis, linear free energy relationships, and NMR; many local and national lectures and symposia of the Chemical Society have also been attended.

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Donald Richard Musto
Trent Polytechnic
July 1981

SUMMARY

The oxidation of 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids to isoquinaldic spirodienelactones and the reaction of these with nucleophiles may provide an efficient route to substituted benzylisoquinolines, and to bisbenzylisoquinolines. Accordingly the oxidation of the model compound 3-(4-hydroxyphenyl)-propanoic acid to 1-oxaspirodeca-[4.5]-6,9-diene-2,8-dione was studied in an unsuccessful attempt to improve on published low-yield procedures. The use of acidic sulphonamides as "phenol equivalents" in the oxidative sequence was then considered. N-chloro-sulphonamides derived from p-anisidine on reaction with silver cations in methanol gave chloro-substituted N-sulphonyl-4,4-dimethoxycyclohexa-2,5-dienimines, but anodic oxidation of methanolic solutions of p-anisidine or p-toluidine sulphonamides gave high yields of the desired N-sulphonylimines. Similarly anodic oxidation in acetonitrile of p-sulphonamidophenoxyalkanoic acids or alcohols, or of p-sulphonamidophenylalkanoic acids or alcohols gave fair to excellent yields of the corresponding spirocyclohexadienimines. It appears that 5-membered spiroheterocycles form more readily than do 6-membered, and that phenoxyalkanoic substrates cyclise more efficiently than do the corresponding phenylalkanoic compounds. Oxidation of substrates to spiro products using lead tetraacetate gave more side reactions, but allowed preparation of imines on a larger scale than by electrochemical procedures.

The spiro-imines are smoothly hydrolysed by neutral alumina to the corresponding spirodienones, thus providing a good route to these compounds. Preliminary studies suggest that spiro lactone imines undergo dienone-phenol rearrangements, and that attack by nucleophiles takes place at the ring rather than at the lactone.

An efficient synthesis of a 1-(4-p-tosylamidobenzyl)-tetrahydroisoquinoline-1-carboxylic acid was carried out, and the acid subjected to anodic oxidation under a variety of conditions. No evidence of spiro lactone formation was obtained. The oxidation of 1-(N-sulphonyl-4-aminobenzyl)-isoquinolines in an attempt to prepare aporphines related to glaziovine failed to give the desired products.

ABBREVIATIONS

ar.	aromatic
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
Ether	diethyl ether
IR	infra-red
Me	methyl
NMR	nuclear magnetic resonance
Petroleum	petrol ether b.p. 60-80°
Ph	phenyl
TFA	trifluoroacetic acid
TLC	thin-layer chromatography
UV	ultra-violet

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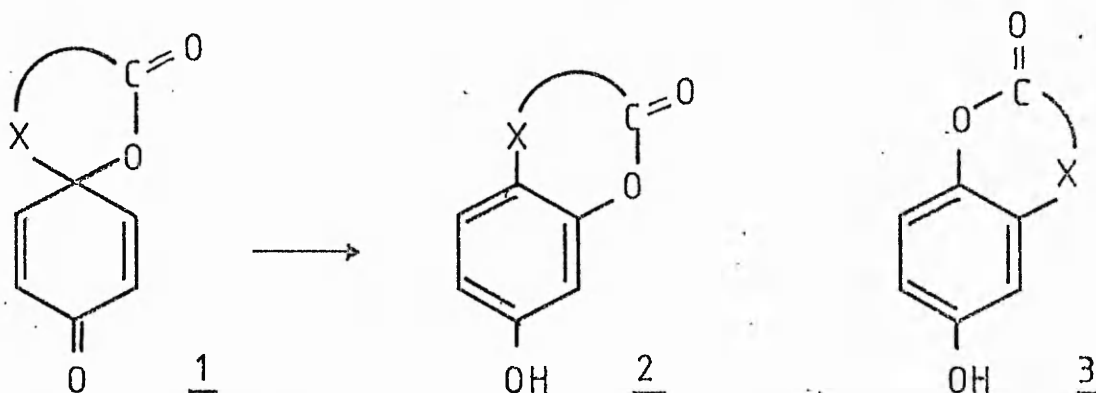
CHAPTER ONE

INTRODUCTION

1.1 General Introduction

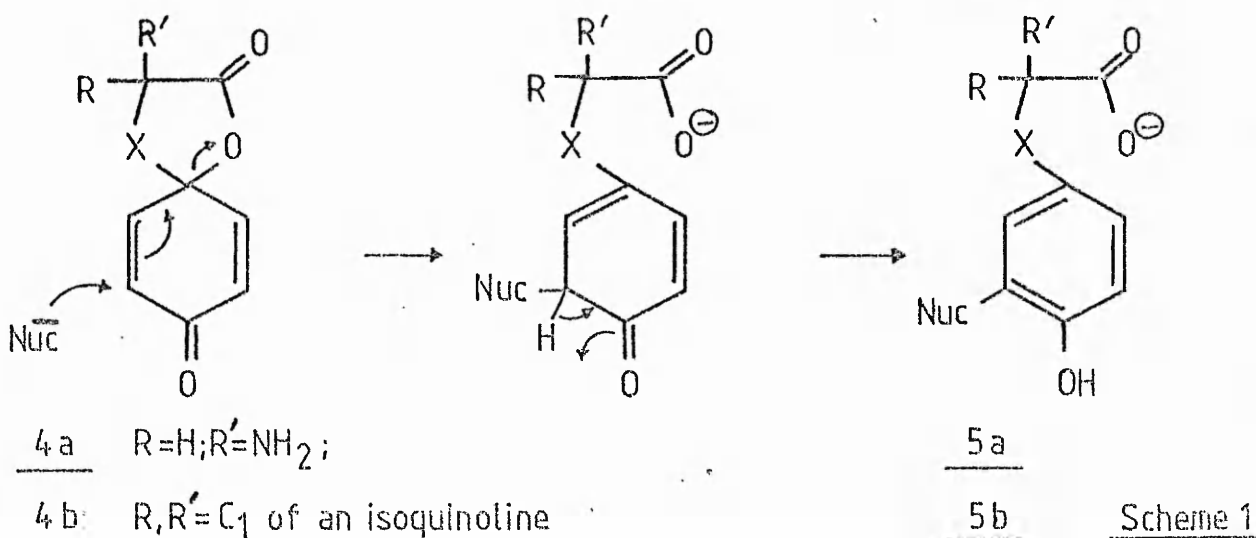
Cyclohexadienespirolactones of the type 1 have a synthetic potential in either of two major reaction pathways.

(i) They may undergo dienone-phenol rearrangements under acidic conditions to give a wide range of the oxygen heterocycles 2 and 3.



General examples of such transformations are discussed in Section 1.3, while the special significance of these schemes to the biogenesis of coumarins and aporphine alkaloids is discussed in Chapters Two and Five respectively.

(ii) Since the carboxylate anion is an excellent leaving group, there exists the possibility that nucleophiles may be induced to react with compounds 4a,b as shown in Scheme 1 to give products 5a,b.



By this route the valuable, but not too accessible compound L-DOPA^{1,2} might be obtainable from L-tyrosine (see Chapter Three). There also exists the possibility that if the spiro lactone 4b could be produced from the corresponding isoquinaldic acid, a novel coupling reaction leading to bis-benzylisoquinolines might occur. This proposal is detailed in Chapter Four.

1.2 Preparation of Cyclohexadienespirolactones

1.2.1 Reactions of Quinones with Ketenes

p-Benzoquinone reacts with diphenylketen³ and dimethylketen⁴ to give the β -lactones 6a and 7. Recently Ogino *et al.*^{5,6} employed the same method to obtain the substituted spiro- β -lactones 6a-e and studied their reactions with nucleophiles (see Section 1.4). This method of preparation of spiro lactones is obviously limited to the β -lactone series.

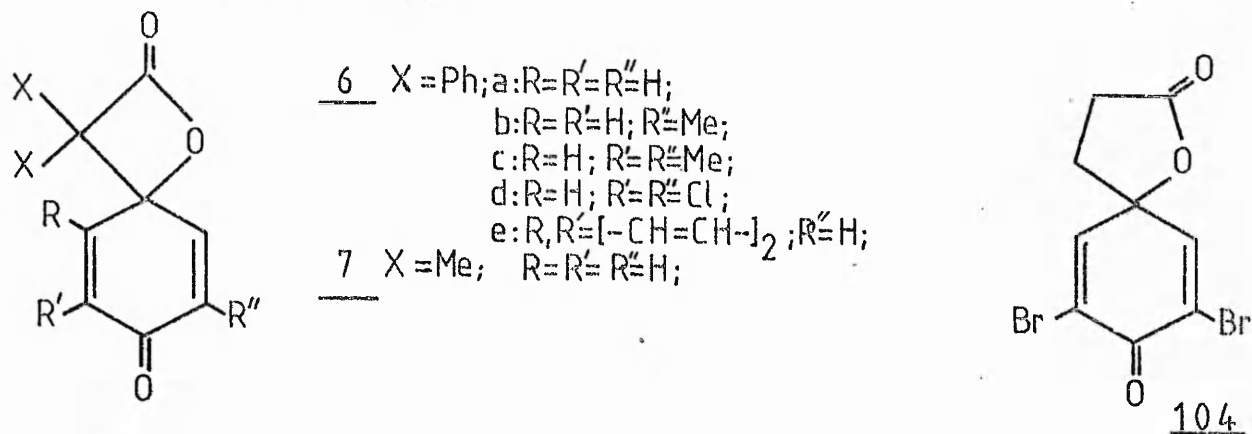
1.2.2 Electrophilic Addition to Benzenoid Compounds

Addition of an electrophile E^{\oplus} to a para-substituted phenol 8 may proceed via the carbocation 9, or via the cyclohexadienone 10, which by nucleophilic displacement of E^{\ominus} from the doubly allylic position gives the spiro compound 11; this requires that E^{\ominus} is a good leaving group (Scheme 2). Thus treatment of 4-hydroxyphenylpropanoic (phloretic) acid 100 with N-bromosuccinimide gives the brominated spiro lactone 104 in high yield. Other examples of this approach to halogenated lactones from 4-hydroxyphenylpropanoic acid 100 are given in Chapter Two.

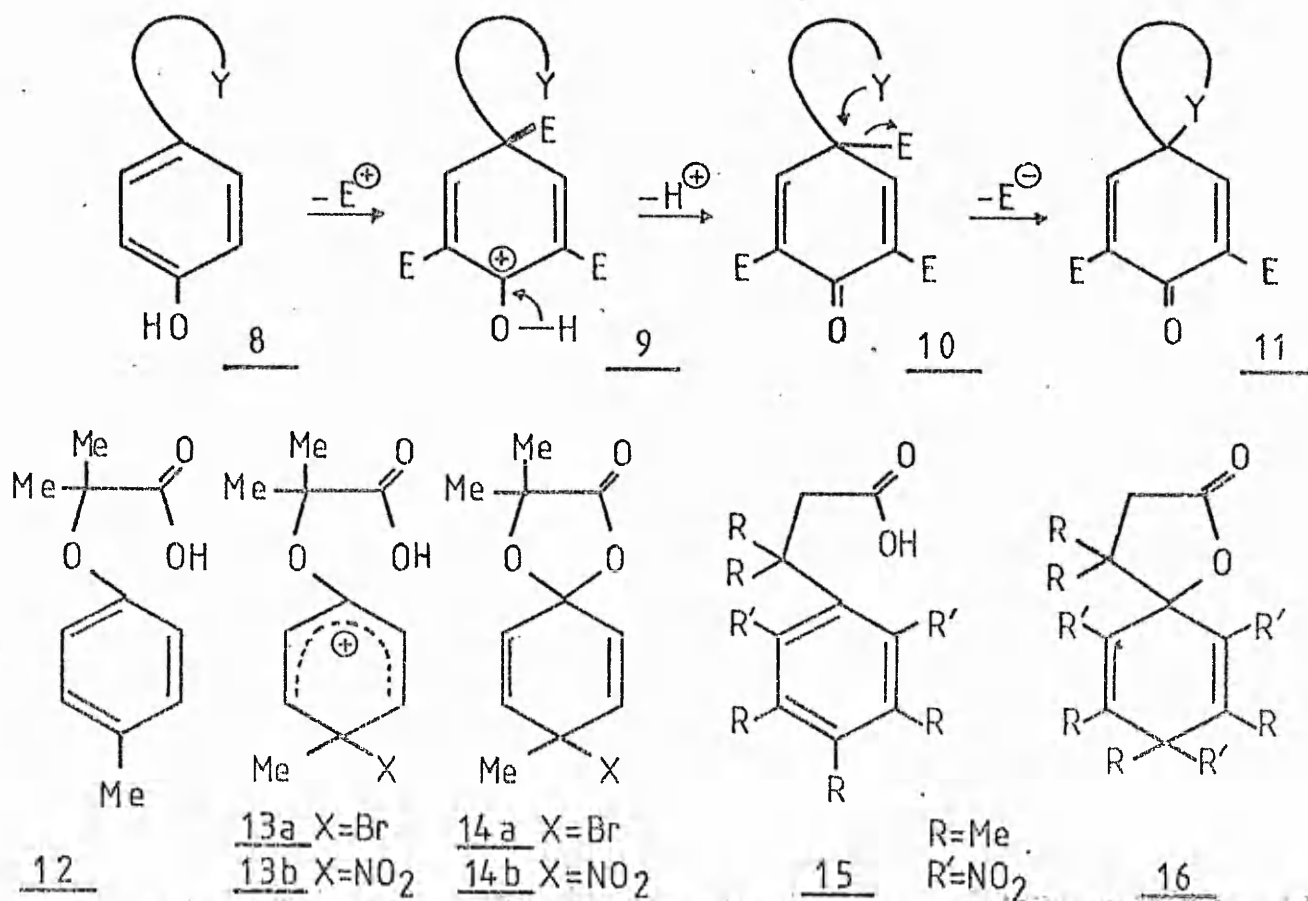
Treatment⁷ of the potassium salt of 2-methyl-2-(4-tolyoxy)-propanoic acid 12 with bromine in aqueous solution gives a good yield of the brominated spiro lactone 14a. Reaction proceeds by electrophilic addition of the bromonium ion para to the alkoxy group, the bulky nature of which enforces ipso^{8,9,10} attack on the methyl substituent rather than

at the free ortho position. Intramolecular nucleophilic addition of the carboxylate anion to the Wheland intermediate 13a may be concerted with, or follow the bromination.

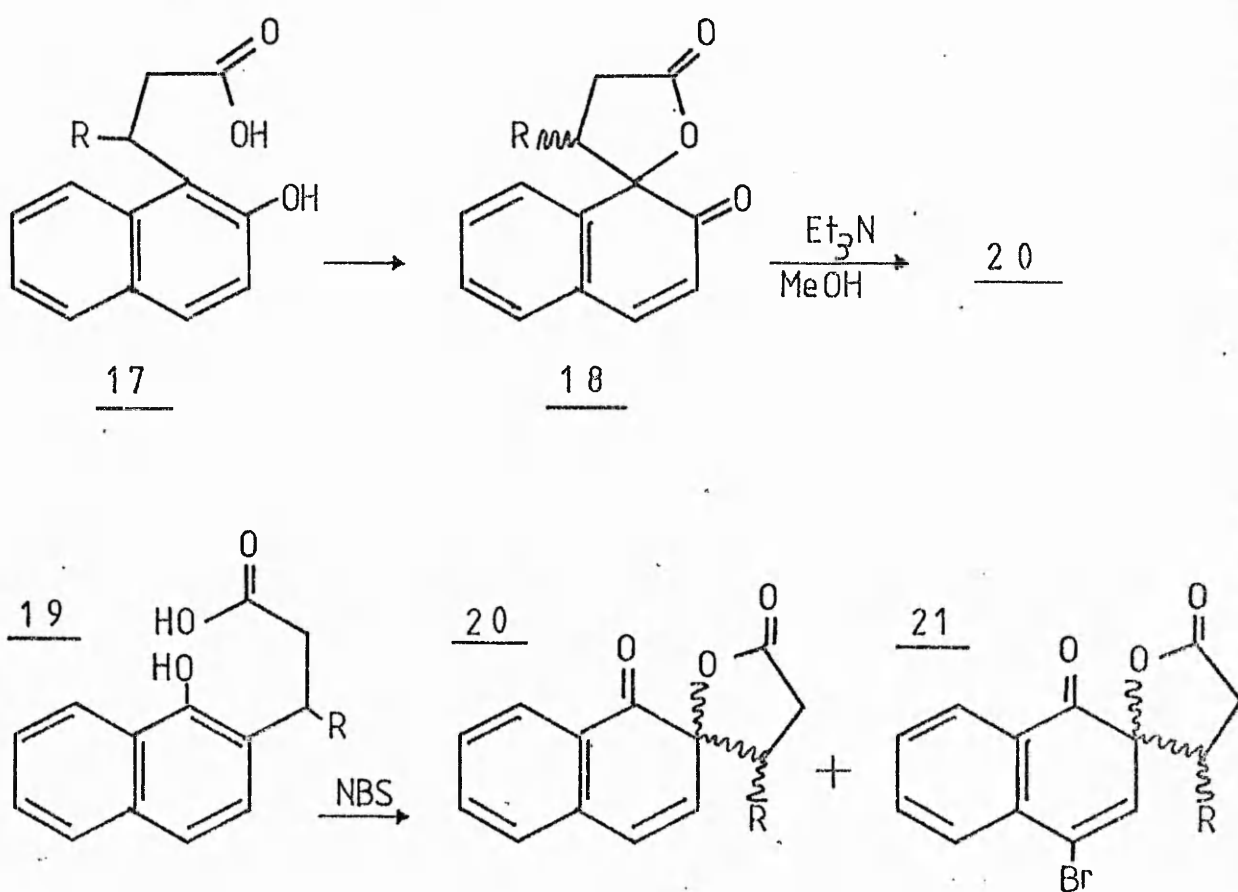
Low temperature nitration¹¹ of 12 in acetic anhydride gave the nitrolactone 14b, presumably via the intermediate 13b, while a related compound 16 has been isolated¹² from the nitration¹³ of the substituted phenylpropanoic acid 15.



Scheme 2

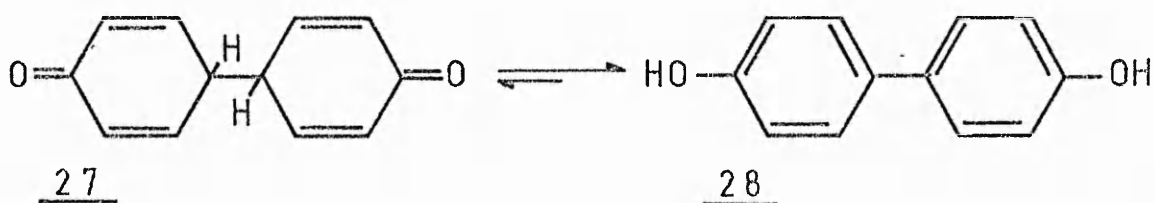
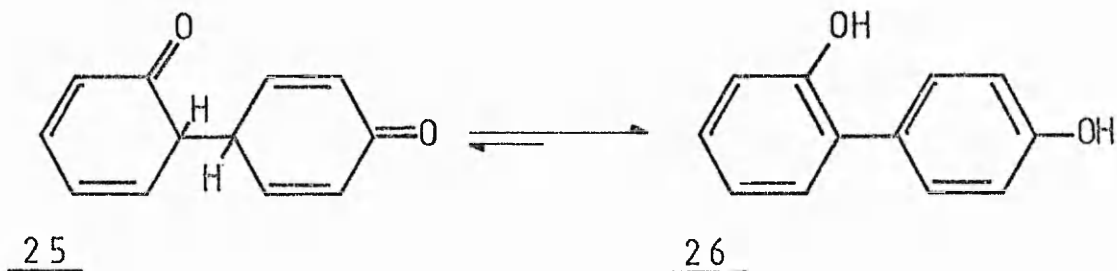
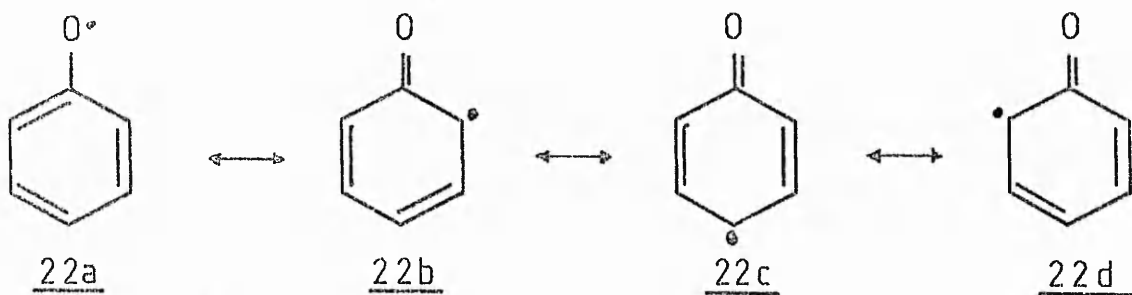


The preparation of a series of naphthalene-derived ortho-spirolactones has been reported by a Swiss group.¹⁴ The reaction of the carboxylate 17 with N-bromosuccinimide gave compounds 18, the proportion of the stereoisomers in the product being dependent on the temperature of the bromination. Similar treatment of the carboxylate 19 gave a mixture of products 20 and 21; on heating under reflux with methanol and triethylamine one of the stereoisomers of 18 underwent an unusual rearrangement to give a stereoisomer of 20.



1.2.3 Intramolecular Oxidative Coupling

Phenolic ring systems occur widely in nature, and are one of the most easily oxidised of organic functional groups. The oxidation



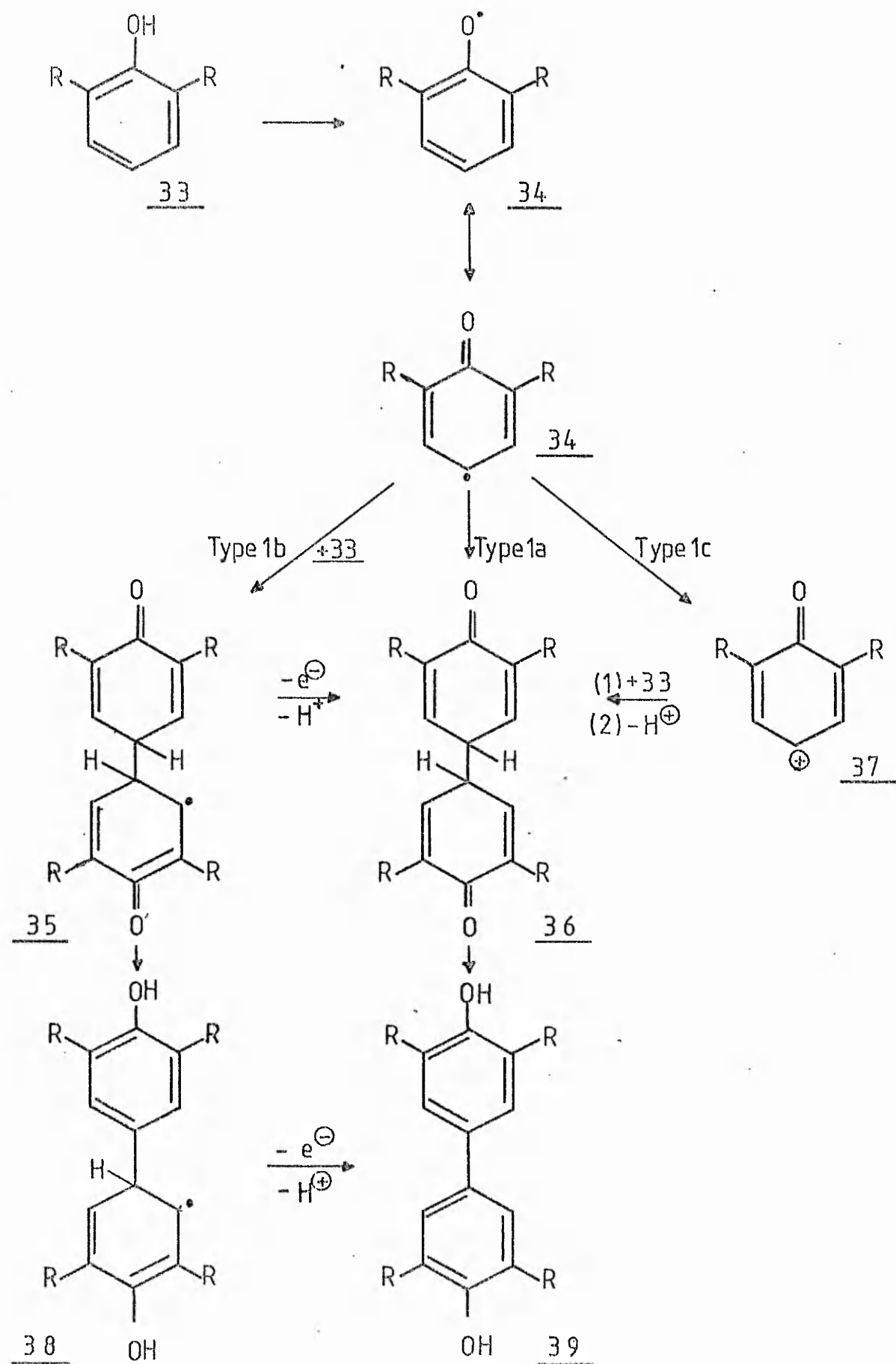
products are often complex mixtures of dimers, polymers and quinonoidal compounds, depending upon the type of oxidant and the reaction conditions used. The importance of oxidative phenolic coupling in the biosynthesis of natural products has long been recognised, and was formalised in an influential paper by Barton and Cohen.¹⁵ These authors rationalised the products of phenol oxidation by suggesting that they arise from the dimerisation of a phenoxy radical (in which the distribution of the unpaired electron is depicted by mesomers 22a-d) to give carbon-carbon or carbon-oxygen-carbon coupled products 23-32.

In general, phenol coupling has been assumed to operate by a radical dimerisation mechanism probably because most of the early investigations involved known one-electron oxidants, e.g. alkaline ferricyanide, ferric chloride, silver oxide and manganese dioxide. Nevertheless, in spite of what appears to be an abundance of evidence in favour of a radical dimerisation mechanism, Barton¹⁶ has suggested that alternative mechanisms may also be involved under certain conditions and should therefore be considered as possible pathways. These include simple coupling of phenoxy radicals in various stages of protonation, phenoxy radical substitution (considered unlikely¹⁷), and the reaction of phenoxonium cations and phenoxonium cation radicals. Much recent work has been concentrated on the identification of these cationic species, (especially phenoxonium cation radicals) due to the dramatic growth of electrochemical methods in organic synthesis.

A recent review¹⁸ divided the more common oxidants into two mechanistic groups, which are further subdivided into several general types:

Group 1:- mechanisms involving free radical intermediates;

a) direct coupling of two phenoxy radicals;



- b) homolytic aromatic substitution;
- c) heterolytic coupling preceded by two successive one-electron oxidations.

Group 2:- mechanisms which do not involve radicals;

- a) heterolytic coupling preceded by a single two-electron transfer;
- b) concerted coupling and electron transfer.

These groups are discussed briefly as follows:

Group 1

There would appear to be indisputable evidence that the initial step in the majority of phenol oxidations involves the removal of one electron by an external oxidant to give a phenoxy radical. Although relatively few phenoxy radicals have been isolated due to their inherent instability, physical techniques such as ESR,¹⁹ UV²⁰ and IR²¹ spectroscopy, redox titration²² curves and polarographs²³ all verify their existence.

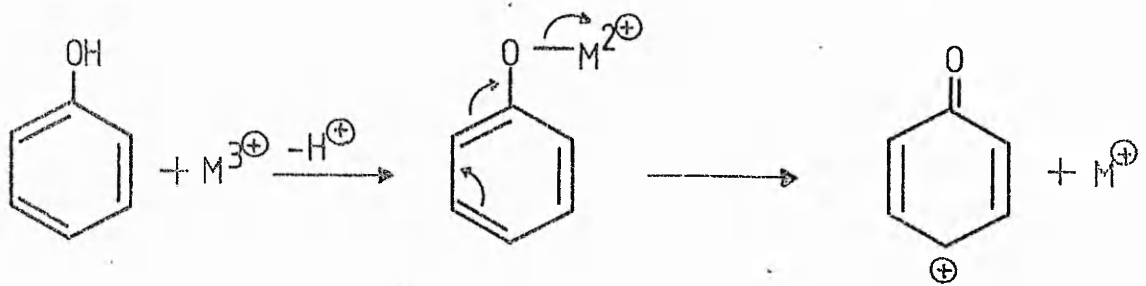
The para coupling of the phenoxy radical from 2,6-dialkylphenol 33 (Scheme 3) illustrates the three modes of radical coupling outlined in Group 1, and is commented on below.

1a Homolytic coupling of two phenoxy radicals 34, followed by rapid tautomerisation in protic media gives 39. This route is well established.²⁴

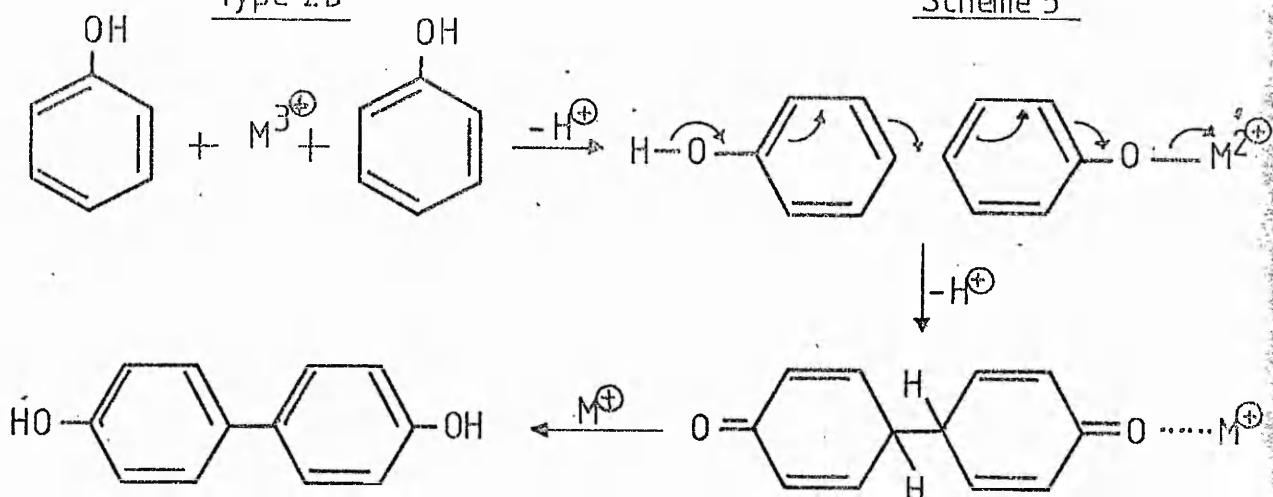
1b Homolytic substitution of a phenoxy radical into another phenol molecule gives the dimeric radical 35, which via either 36 or 38 leads to 39. Few cases are reported in the literature.²⁵

1c The phenoxonium cation 37, generated by further oxidation of the phenoxy radical 34, is capable of electrophilic attack on another

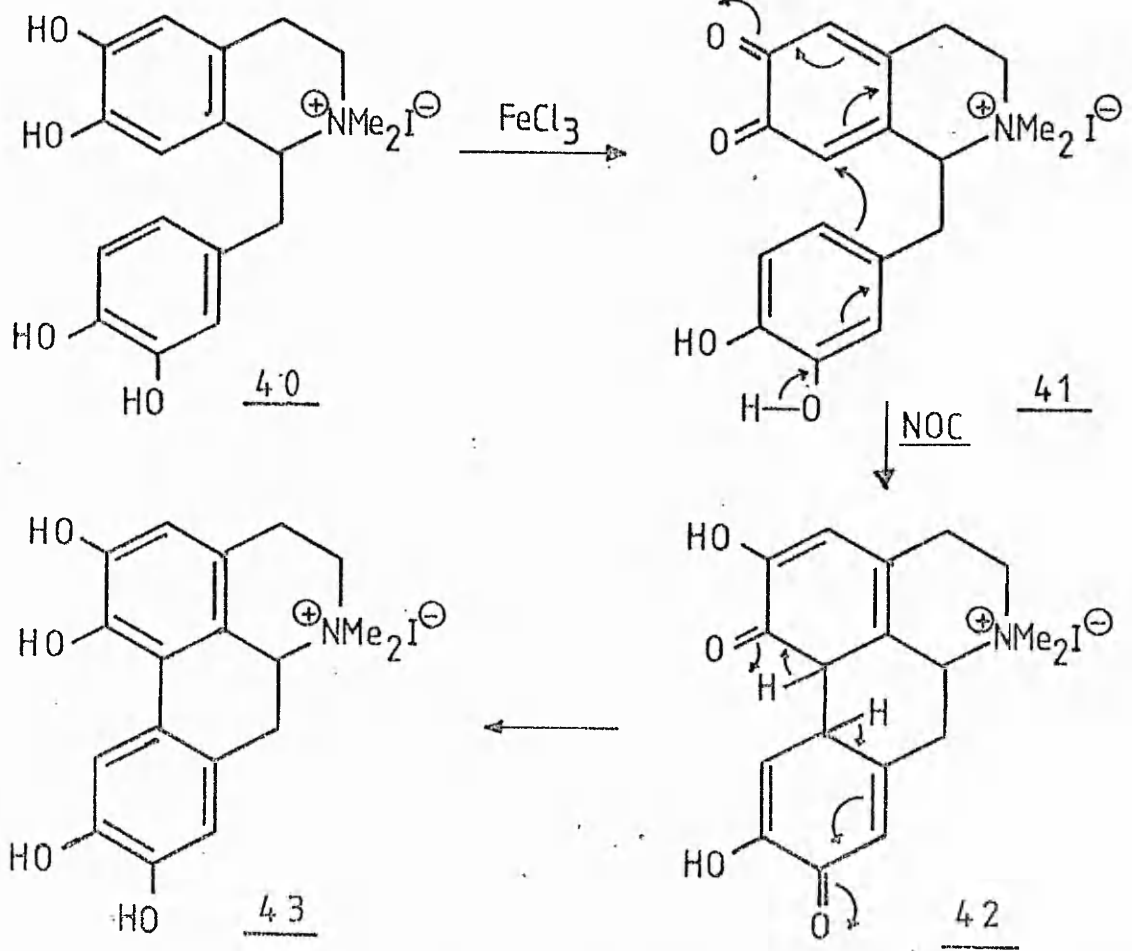
Type 2a



Type 2b



Scheme 6



phenol molecule to give 36 and hence 39. This route requires extra energy, and is therefore the least favourable of the radical initiated mechanisms, but evidence is available for the existence of this species under conditions of strong acid or during anodic oxidations.²⁶

Group 2

Non-radical modes of oxidative coupling are illustrated in Schemes 4, 5 and 6. The oxidant need not be a tripositive species; other metals in different oxidation states or organic compounds can also be involved.

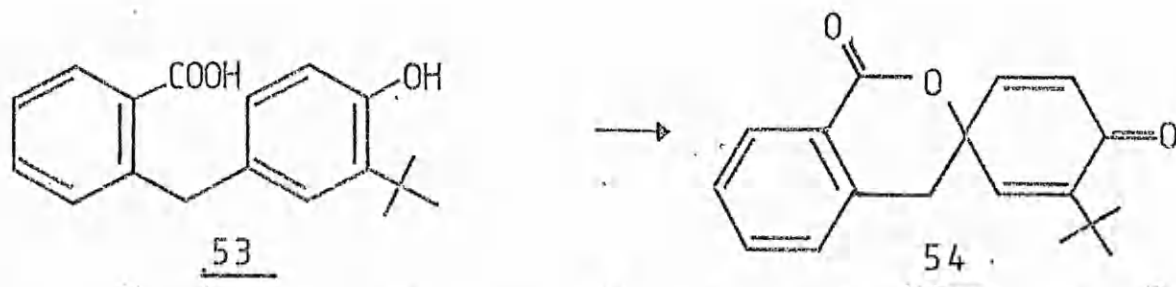
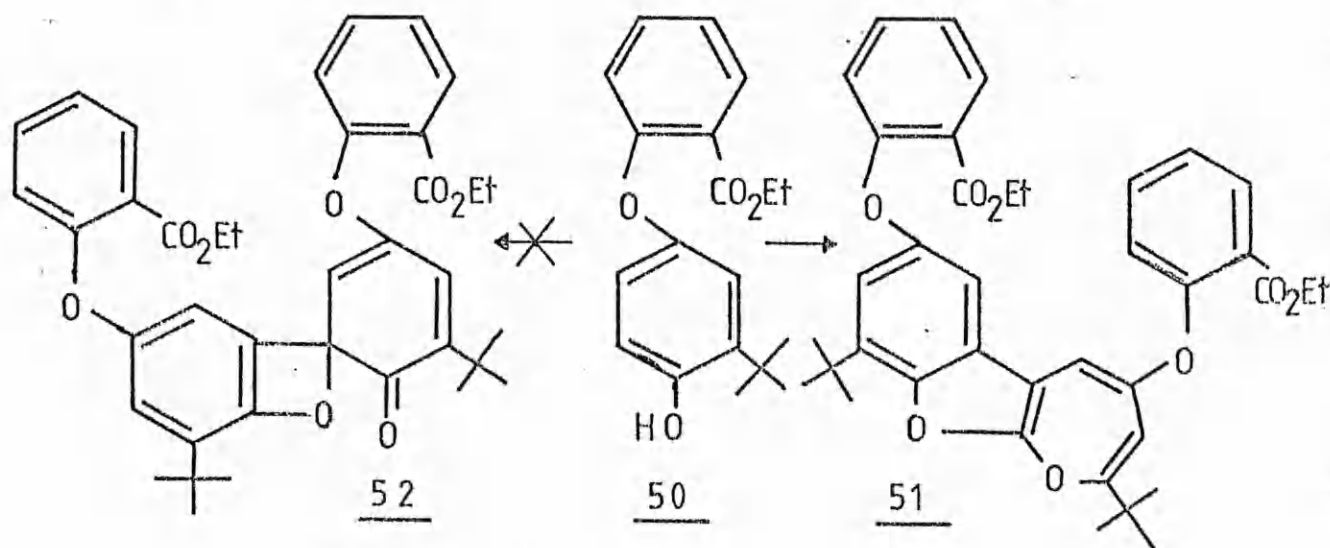
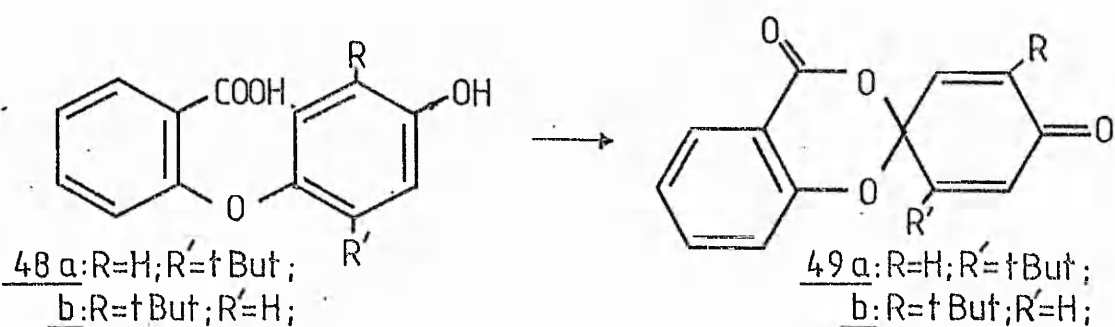
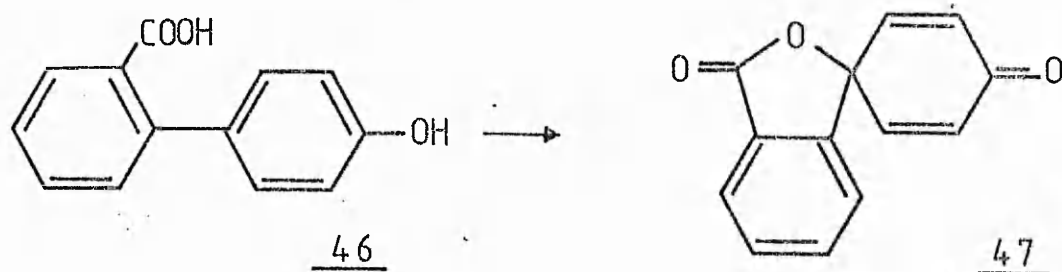
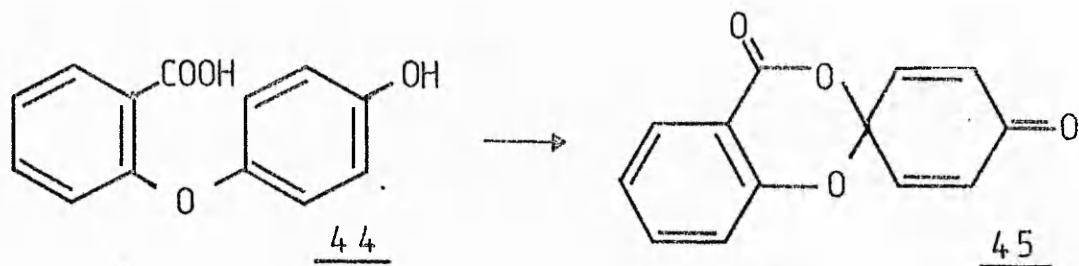
2a The initial phenol-oxidant complex decomposes to give a formally charged cation, electrophilic reactions of which have been described previously, (Scheme 3 Type 1c).

2b This is a concerted two-electron pathway and seems more likely on energetic grounds.

Several metals e.g. Pb (IV),²⁷ V (IV),²⁸ V (V),²⁹ Tl (III),³⁰ and Mn (III),³¹ are known to complex with the hydroxy function of a phenol; the complex may decompose to give a phenoxonium cation or to induce a concerted electron transfer process.

The term "non-oxidative coupling" (NOC) has been coined³² to describe an overall oxidative coupling process which does not involve in the coupling step a radical or cationic species. Thus, the oxidation of laudanosoline 40 with ferric chloride gives the quinone 41, which undergoes³³ Michael addition (i.e. NOC) to yield the aporphine 43. Although the NOC concept distinguishes between such reactions and those utilising charged intermediates, it may be that the terminology is a little misleading since the product of the overall reaction is at a higher oxidation state than that of the starting substance.

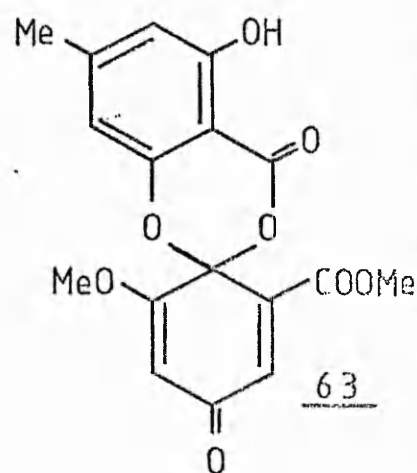
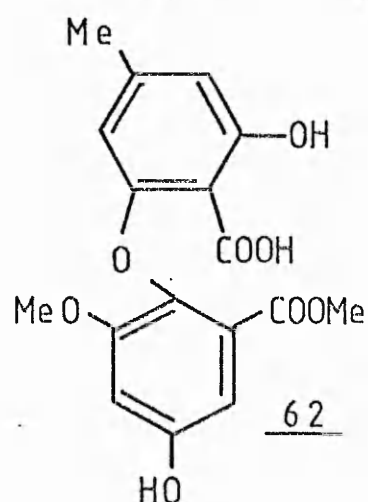
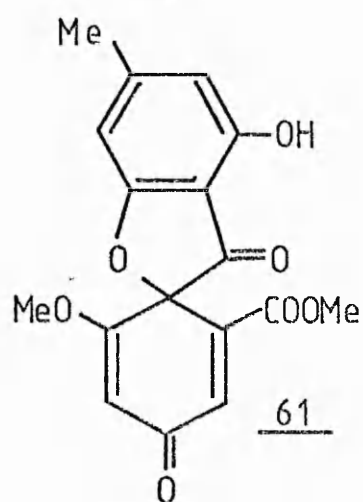
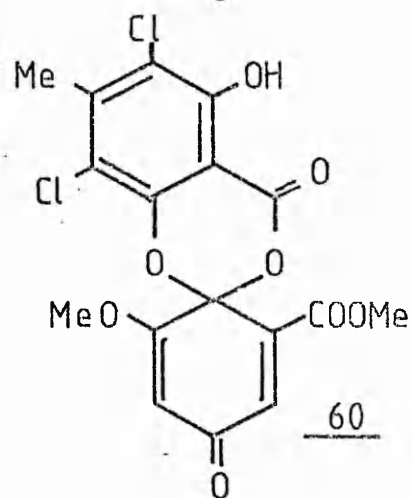
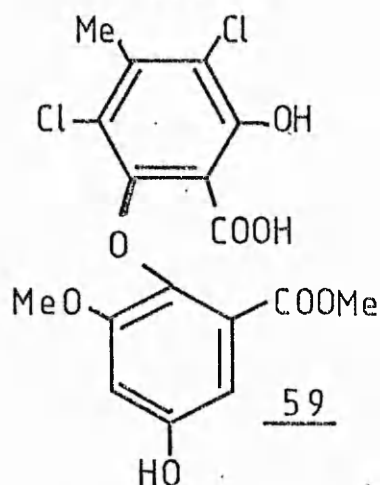
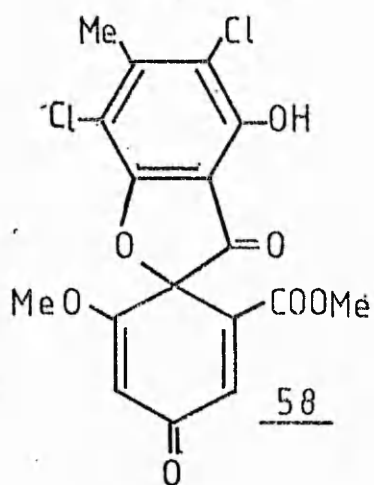
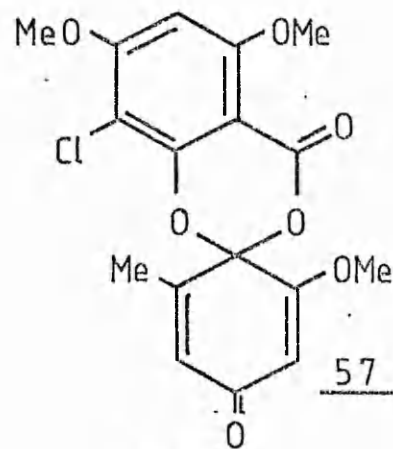
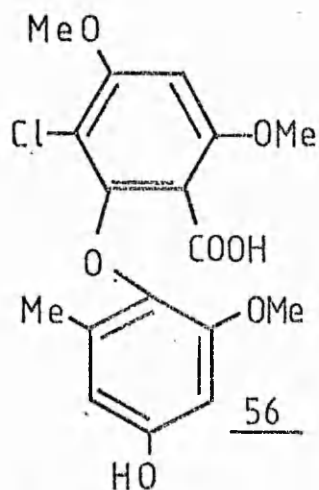
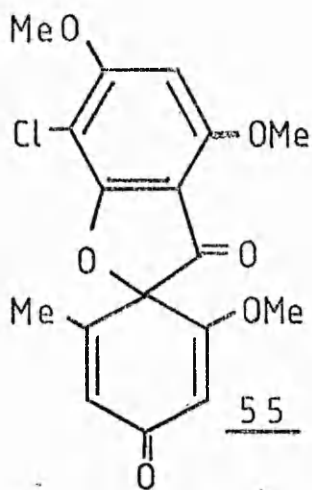
The application of phenol oxidation to the synthesis of spiro-lactones is discussed in the following section.

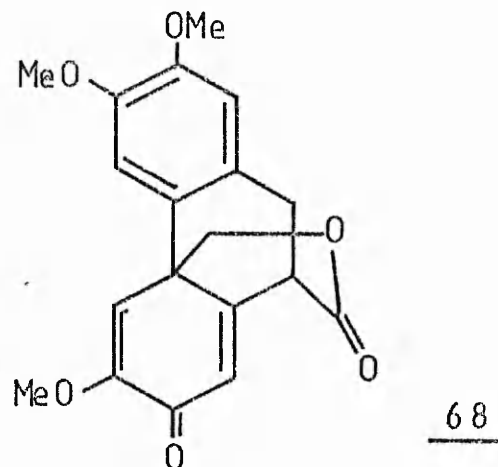
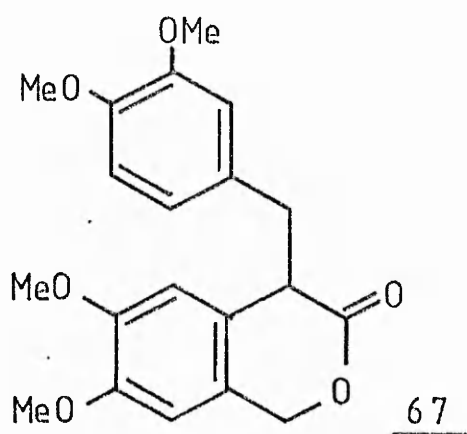
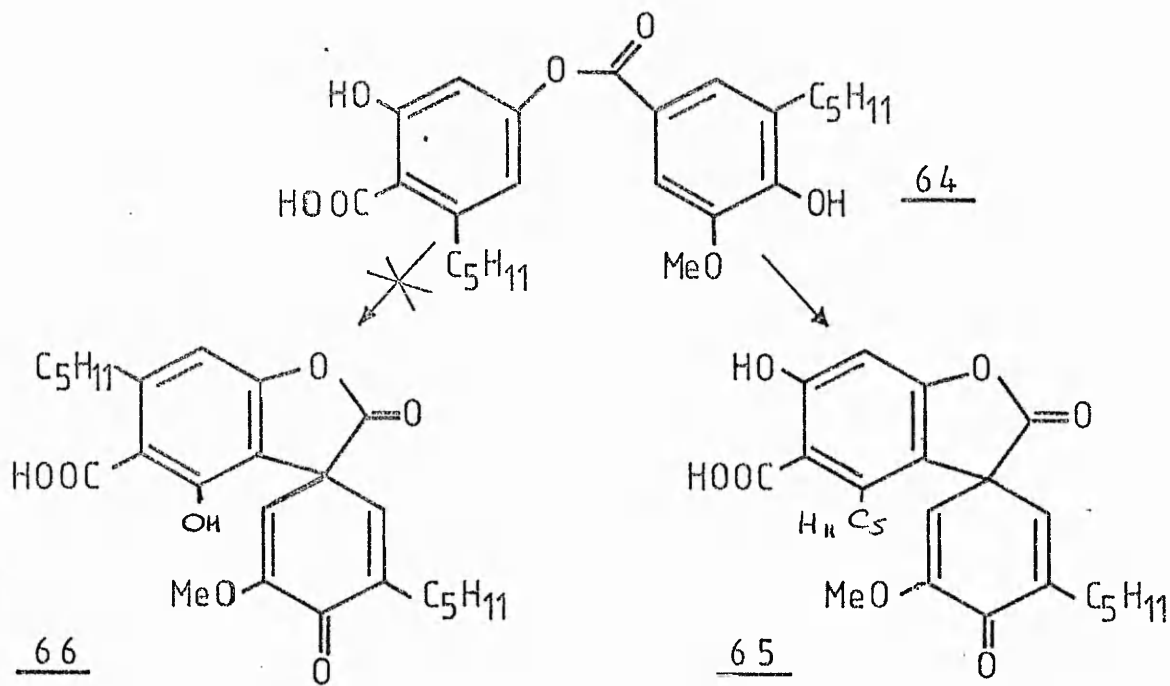


The phenolic carboxylic acid 44 has been converted in moderate yield to the spiro lactone 45 by oxidation³⁴ with ammonium ceric sulphate or lead dioxide. Similarly oxidation³⁵ of 4'-hydroxybiphenyl-2-carboxylic acid 46 with manganese dioxide in ether afforded the lactone 47 in 25% yield. The search³⁶ for phenoxonium ions has yielded new spiro lactones; e.g. the treatment of carboxydiphenyl ethers 48a,b with lead dioxide in ether gave in 60% yield the lactones 49a,b. A recent paper by Rieker et al.³⁷ proposes that the related ester 50 is quantitatively converted to 51, an oxaspirobenzofuran, and not the spirobenzoxet 52, as was originally reported.^{38,39} The corresponding diphenylmethane 53 does, however, give the desired spiro lactone 54 on oxidation.³⁶ The carboxylic acid 56, obtained by the acid hydrolysis of dehydrogriseofulvin 55, has been oxidised⁴⁰ to dehydrogriseofulvoxin 57 in 85% yield by manganese dioxide in acetone-ether. It has not been established whether the griseofulvoxin structure occurs naturally. Similarly acid 59, obtained by the hydrolysis⁴¹ of geodin 58⁴² was oxidised³⁴ in high yield to geodoxin 60⁴³ by lead dioxide in ether. Dechlorogeodin 61, asterriic acid 62, and dechlorogeodoxin 63, have all been isolated⁴⁴ from oospora sulphurea ochrocea. The *in vitro* hydrolysis of 61 into 62, and the subsequent oxidation³⁴ of 62 into 63 in 71% yield using lead dioxide in ether, have also been achieved.

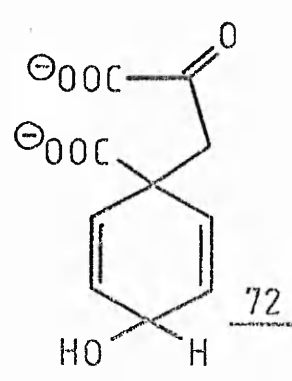
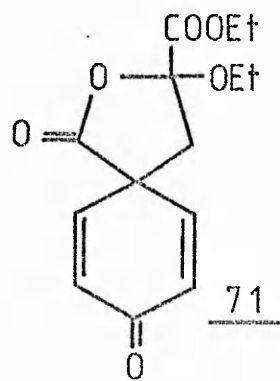
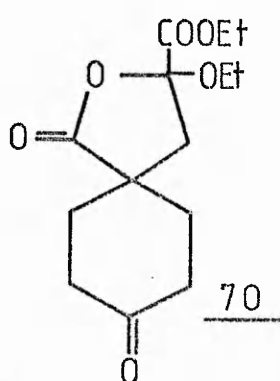
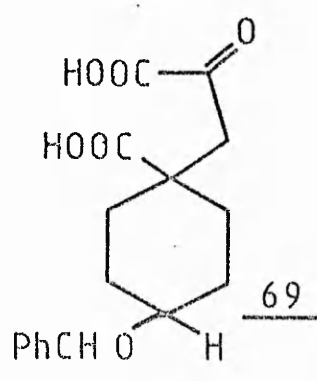
1.2.4 Miscellaneous Cyclohexadienonespirolactones

This section includes some examples of cyclohexadienonespirolactones in which the lactone and cyclohexadienone rings both contain the same





Scheme 7

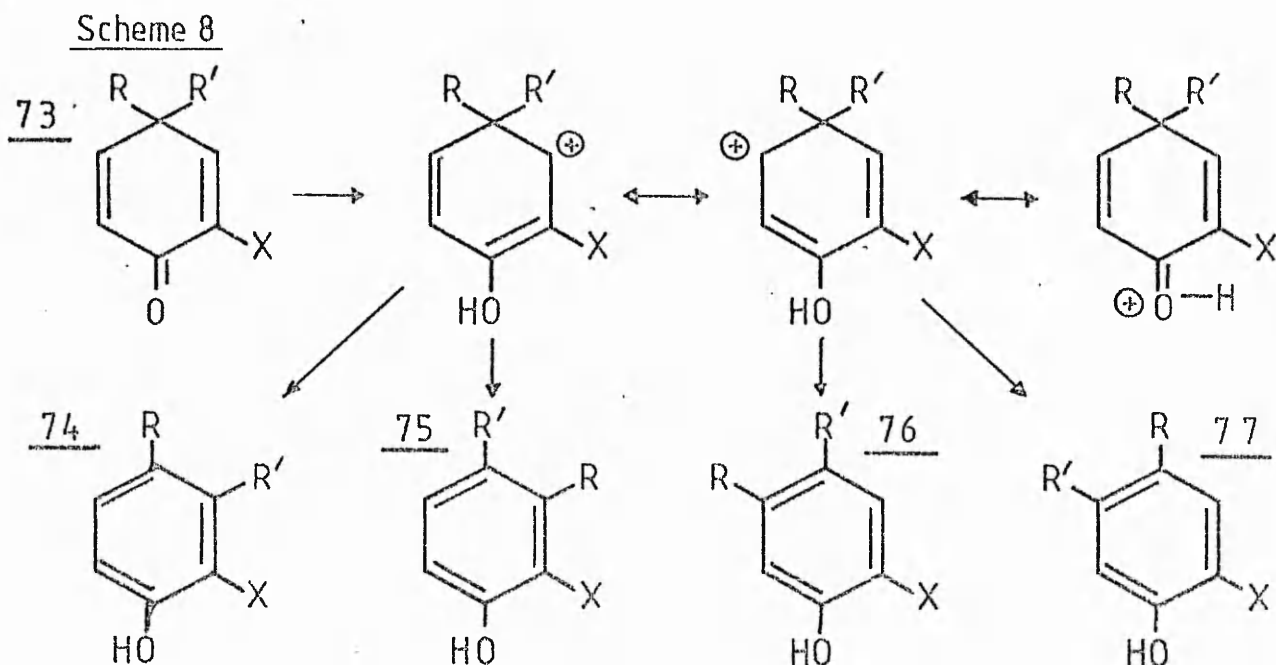


spiro-carbon atom but whose position is other than adjacent to the lactone ring oxygen, and thus these compounds are not of direct relevance to this thesis.

Treatment⁴⁵ of the phenolic ester 64 with an excess of manganese dioxide in benzene gave in 25% yield, picrolichenic acid 65, a metabolite⁴⁶ from *Pertusaria amara*; no trace of *o-p* coupling, to give the isomeric compound 66 was observed. The anodic oxidation⁴⁷ of isochromanone 67 in acetonitrile gave a 55% yield of the bicyclic spiro lactone 68. In a recent communication,⁴⁸ a novel spiro lactone 71 was described as a suitable precursor for prephenate 72, an intermediate in the biosynthesis⁴⁹ of phenylpyruvic acid. Although the gross structure of 72 had been postulated, its *in vitro* synthesis has only recently been achieved 69 → 72 (Scheme 7).⁵⁰

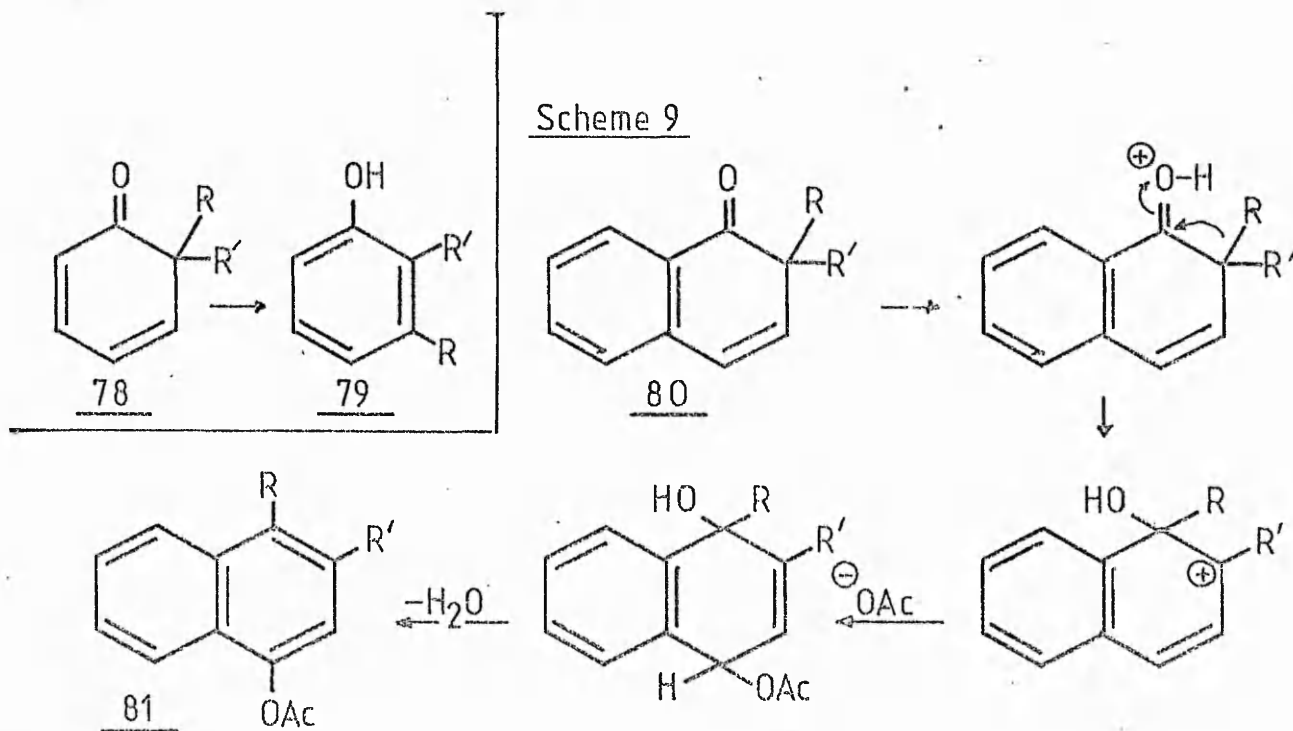
1.3 Dienone-Phenol Rearrangement

This is an acid-catalysed rearrangement of a carbocation in which the nature of both ring substituents and migrating species affects the composition of the final product. For example, the 2-substituted

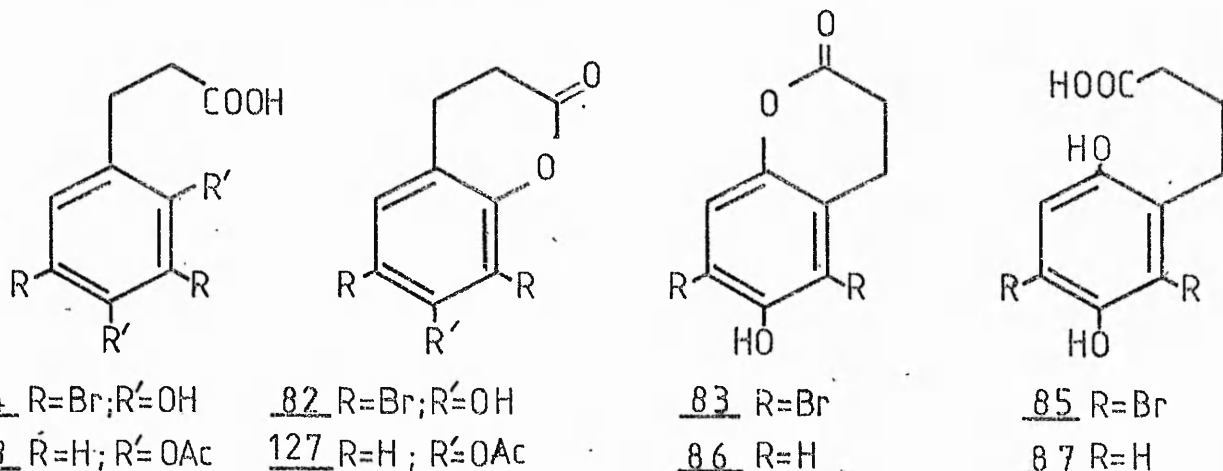


cyclohexa-2,5-dienone 73 could give four possible products 74-77 (Scheme 8). The effect of the 2-substituent can be steric - a tert-butyl group tends to be C₅ rather than C₃ directing - or electrostatic e.g. an electronegative bromine would destabilise an intermediate with a positive charge near it, and so would also be C₅ directing.⁵¹ Usually a more substituted alkyl group migrates in preference to a less substituted one,⁵² and phenyl groups migrate more readily than alkyl groups.⁵³⁻⁶ Electron withdrawing substituents decrease the migratory aptitude of phenyl groups, while electron donating substituents enhance it.⁵⁷ In all cases a carbon bond migrates rather than a heteroatom bond.

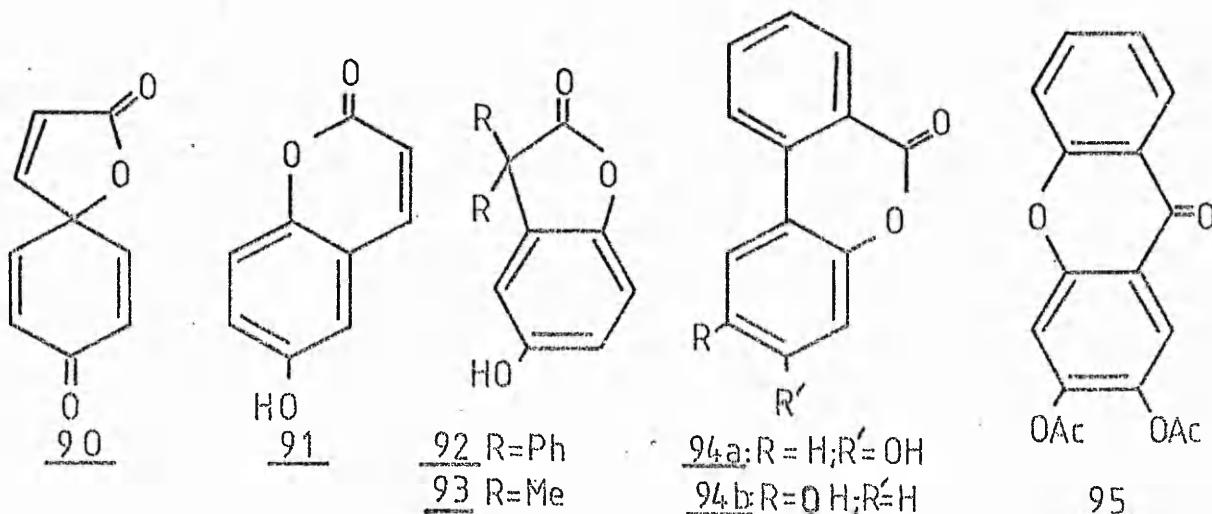
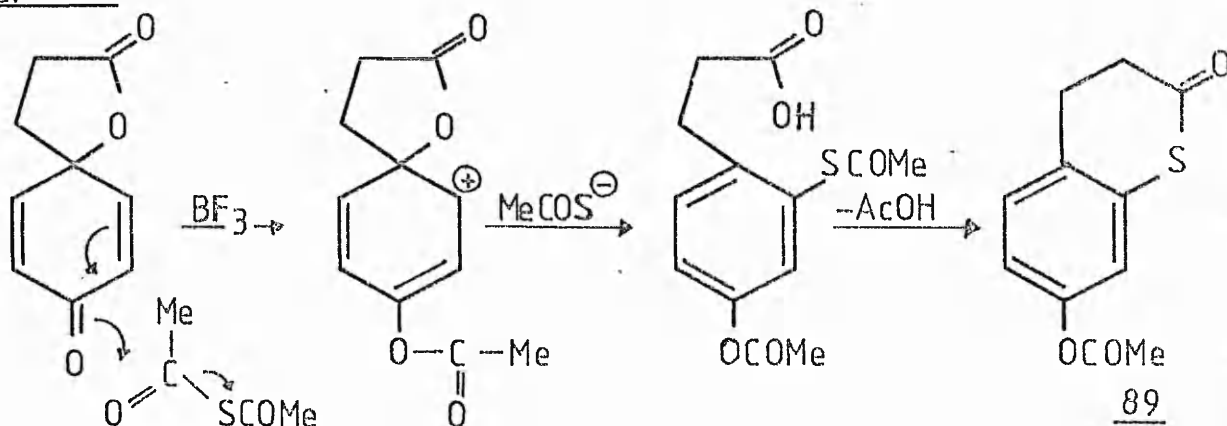
Cyclohexa-2,4-dienones can react in two different ways. Monocyclic compounds 78 react mainly as discussed above, resulting⁵⁸ in normal 6-5 migration 79. However bicyclic naphthalene-type compounds, e.g. 80, rearrange as shown in Scheme 9 with attack of a nucleophile (usually acetate when the rearrangement occurs in acetic anhydride-sulphuric acid) at the 4-position giving 81.⁵⁹



The dienone-phenol rearrangement has been applied to dienone-spirolactones. Thus treatment of the dibromolactone 104 with either 0.5 - 2m sulphuric acid,⁶⁰⁻¹ or 4.5m sulphuric acid in acetonitrile,⁶² gives rise to both 2,4-dihydroxy- and 2,5-dihydroxy-dibromophenylpropanoic



Scheme 10



acids 84 and 85 via hydrolysis of the 7- and 6-hydroxycoumarins 82 and 83 produced by oxygen and carbon migration respectively. The predominant products from this reaction are species derived from oxygen migration.

Rearrangement of lactone 102 with 0.5M sulphuric acid, however, yields⁶¹ only the products 86 and 87, resulting from carbon migration. As 6-hydroxycoumarin 86 is known to hydrolyse to the 2,5-dihydroxy acid 87 under these conditions, whereas cyclisation of acid 87 to give 86 does not occur, evidently 86 was the first product formed by dienone-phenol rearrangement initiated by protonation on the carbonyl carbon of the dienone system. No trace of the products from oxygen migration were detected, thereby refuting earlier claims.⁶² The use⁶¹ of an acetic anhydride-sulphuric acid mixture on 102 gave some 6-acetoxycoumarin, due to the presence of the sulphuric acid, but mainly the 2,4-diacetoxyacid 88 was produced. Experiments involving the use of O¹⁸-labelled acetic anhydride, and also diacetyl sulphide-boron trifluoride, led to the proposal of a mechanism (Scheme 10), in which the products 89 (+ 88) ostensibly arising from oxygen migration, originated in fact from interaction with solvent molecules.

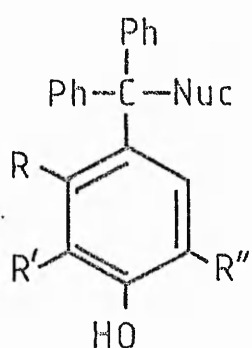
The unsaturated lactone 90 when treated⁶² with 3M sulphuric acid, rearranges in 96% yield to the 6-hydroxycoumarin 91; the substituted β -lactones 6a-e and 7 also undergo⁶³ carbon migration to the benzofuranones 92a-e and 93 in high yields on reacting with a sulphuric acid-acetic acid mixture. Interestingly, 47 in hot sulphuric acid undergoes⁶⁴ oxygen migration to 94a, while 94b is produced under basic conditions. Treatment³⁴ of 45 with acetic anhydride-boron trifluoride yields the xanthone 95.

1.4 Reaction of Cyclohexadienonespirolactones with Nucleophiles

Much of the chemistry of quinones results from Michael-type addition of nucleophiles to the enone moiety contained in the ring. The synthetic utility of these 1,4-addition reactions may be limited by a lack of regioselectivity and also by further transformations of the adduct. Some recent preliminary experiments⁶⁵⁻⁶ have been carried out to determine whether quinone mono- and bis-ketals show greater selectivity in their reactions with nucleophiles, from which the results look promising.

An alternative approach explored by Ogino et al⁶ has been to use a good leaving group para to the cyclohexadienone carbonyl to direct the regioselectivity of the reaction. Substituted 3,3-diphenyl-1-oxaspiro-[3.5]-nona-5,8-diene-2,7-diones 6a-e were chosen as having enhanced reactivity towards nucleophiles because of the ring strain in the β -propiolactone moiety. Although the reactions of α,α -diphenyl- β -propiolactones with nucleophiles are known to occur at the β -carbon with cleavage of either or both the carbonyl-oxygen and alkyl-oxygen bonds,⁶⁷ in spiro compounds 6a-e the α -carbon on the β -lactone ring could not be the reaction centre because it is blocked by the cyclohexadiene moiety.

The reaction of compounds 6a-e in acetonitrile with excess potassium cyanide gave the correspondingly substituted α,α -diphenyl-p-hydroxybenzeneacetonitriles 96a-e (Nuc=CN); in the reaction of 6a with potassium cyanide the evolution of carbon dioxide was established. When potassium cyanide was initially added to the acetonitrile solutions of 6c and 6d, orange precipitates, which were identified as the transient quinone methides 97c and 97d, were immediately formed in 78 and 69% yields respectively. On stirring the orange precipitates disappeared and 96c and 96d (Nuc=CN) were obtained. Halide-(Br⁻ and I⁻)-ion-catalysed decarboxylations of 6a also gave p-quinone diphenylmethides



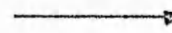
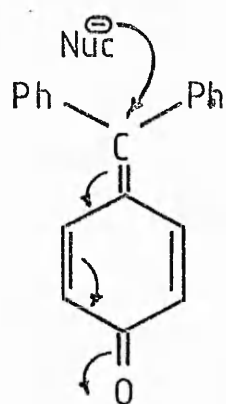
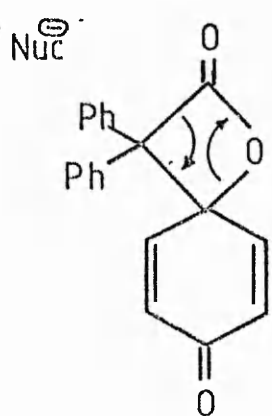
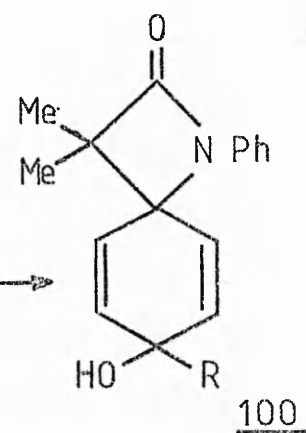
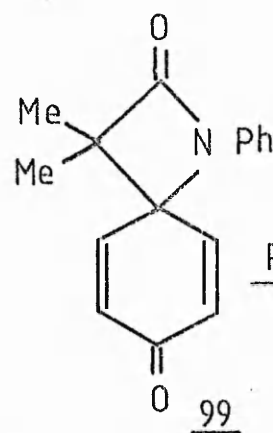
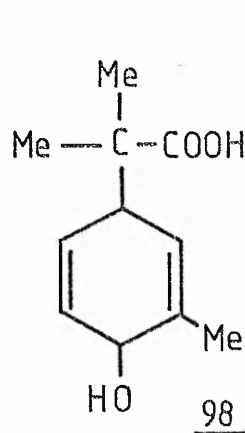
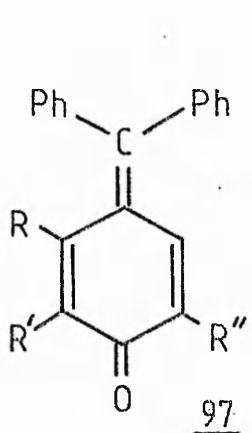
96 a : $R = R' = R'' = H$;

b : $R = R' = H$; $R'' = Me$;

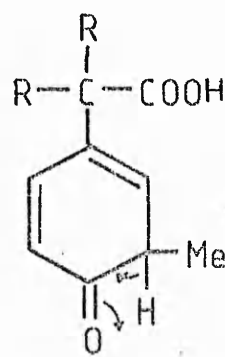
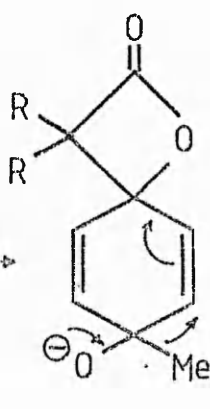
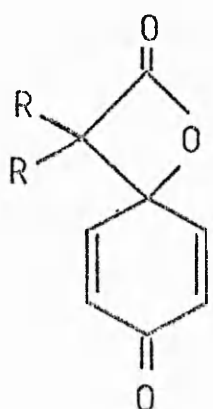
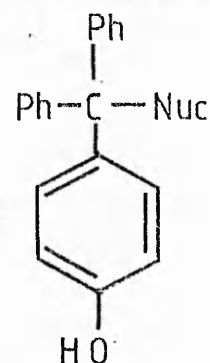
c : $R = H$; $R' = R'' = Me$;

d : $R = H$; $R' = R'' = Cl$;

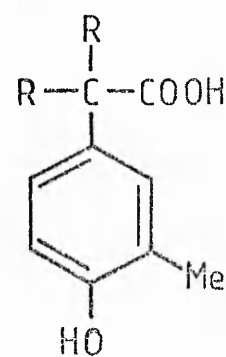
e : $R, R' = [-CH=CH-]_2$; $R'' = H$;



Scheme 11



Scheme 12



97a. Treatment of 6a with methyl magnesium iodide or methyl lithium in ether afforded α -(p-hydroxyphenyl)- α,α -diphenylethane 96a (Nu=Me) in 65 and 27% yields respectively.

The reaction of compounds 6a-e with nucleophiles appears to proceed via attack on the carbonyl carbon of the β -lactone ring, rather than on the cyclohexadiene group, giving decarboxylated p-quinone diphenylmethides 97a-e intermediates, followed by 1,6-addition of the nucleophile to give the final product (Scheme 11). This reaction in which nucleophiles attack the carbonyl carbon to cause decarboxylation is the first case reported for β -lactones.

The reaction of 7 with potassium cyanide was complex and no identifiable compounds were isolated. However, when reacted with methyl lithium, 7 gives α -(4-hydroxy-3-methylphenyl)- α -methylpropanoic acid 98, in rather poor yield, showing that in this case attack of the nucleophile takes place on the cyclohexadiene group. The reaction may occur by methyl anion attack on either the position allylic to the leaving carboxy group, or the diene carbonyl group followed by a vinylogous pinacol rearrangement. The two mechanisms cannot be distinguished on the basis of the products, but from the reaction of the spiro lactam 99 with methyl lithium, the carbinol 100, formed with the dienone-carbonyl function, was isolated; Scheme 12 was therefore proposed. The different reactions of the 3,3-diphenyl- and 3,3-dimethyl-spirolactones can be explained by the relative stabilities of the p-quinone methides.

CHAPTER TWO

Attempted High Yield Synthesis of 1-Oxaspiro-[4.5]-deca-6,9-diene-2,8-dione

2.1.1 Synthesis of 1-Oxaspiro-[4.5]-deca-6,9-diene-2,8-dione

The spirolactone 102 has been implicated in three main biochemical areas *viz* the enzymatic degradation of tyrosine, the specific cleavage of certain peptide bonds, and the biosynthesis of coumarins.

The degradation of tyrosine to acetoacetate in the liver involves the conversion of p-hydroxyphenylpyruvic acid 115 into homogentisic acid 120, the mechanism for which is still unresolved. In 1952 Witkop et al⁶⁸ proposed a mechanism (Scheme 13) via p-quinol-type intermediates, while a later mechanism suggested by Hassall and co-workers⁶¹ involved the formation of spirolactones (Scheme 14). In connection with the latter theory, phloretic acid 101 was oxidised with hydrogen peroxide in glacial acetic acid, peracetic acid, and lead tetraacetate in anhydrous methanol in modest yields (12, 2, 7% respectively) to the corresponding spirolactone 102; under acid conditions this gave β -(2,5-dihydroxyphenyl)-propanoic acid 121 (c.f. 120) via carbon migration. The original Witkop mechanism has recently received support from the finding⁶⁹ that the conversion of 115 to 120 (Scheme 13) is catalysed by the enzyme p-hydroxyphenylpyruvate hydroxylase, and that atmospheric oxygen is incorporated into both the newly formed hydroxy- and side chain carbonyl groups, with liberation of carbon dioxide. Saito et al⁷⁰⁻¹ were able to demonstrate the chemical feasibility of this scheme by isolation of the p-quinol 119 from the dye-sensitised photooxygenation of 115. Also the occurrence of intermediate 118 in the reaction was demonstrated by indirect means. However the participation of singlet oxygen in the chemical reaction means that direct extrapolation of the mechanism to the enzymatically catalysed reaction is questionable. It was during this work that the Japanese

101 R=H; R'=OH;

103 R=Br; R'=OH;

105 R=I; R'=OH;

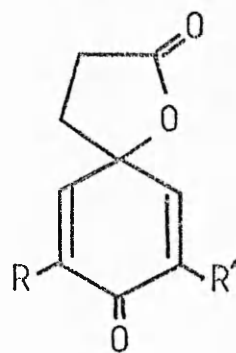
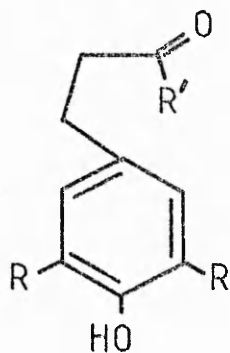
107 R=Cl; R'=OH;

109 R=H; R'=OMe;

111 R=H; R'=NHCH₂COOH;

113 R=Br; R'=NHCH₂C₆H₅;

114 R=Br; R'=NHCH₂COOH;



102 R=R'=H;

104 R=R'=Br;

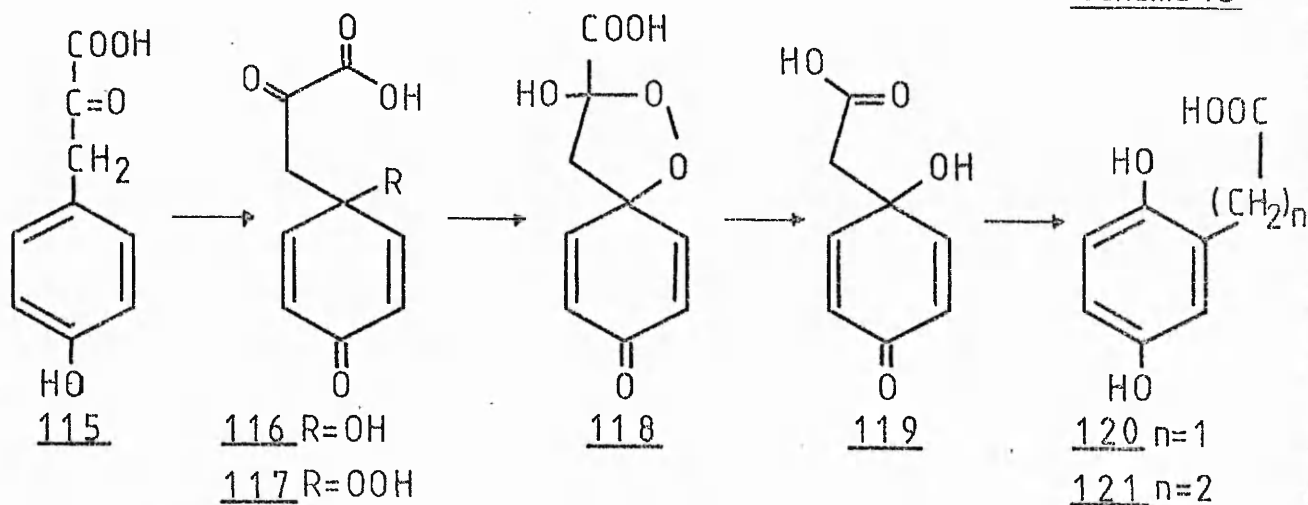
106 R=R'=I;

108 R=R'=Cl;

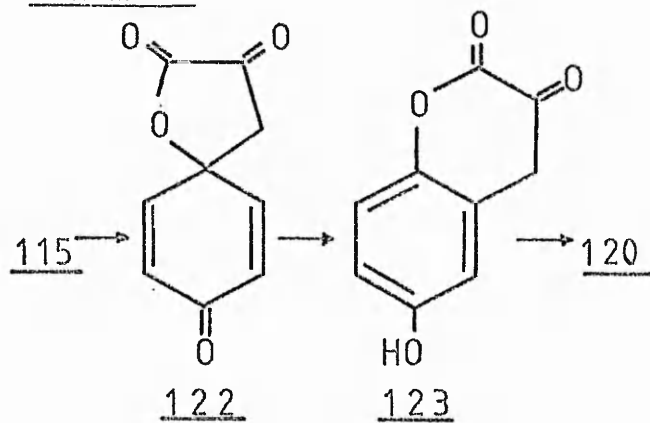
110 R=H; R'=OMe;

112 R=R'=OMe;

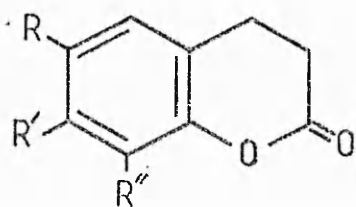
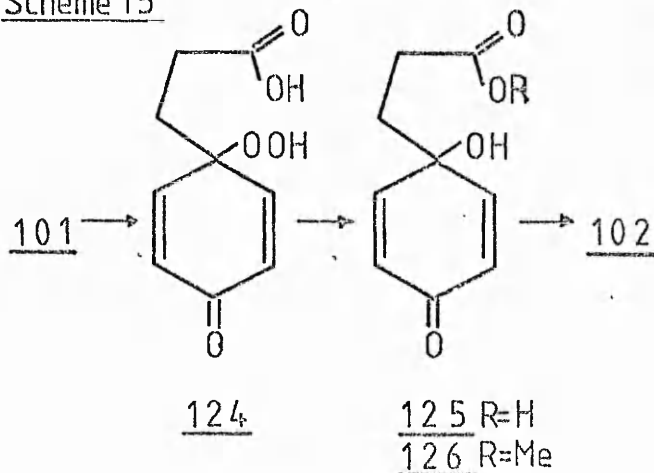
Scheme 13



Scheme 14



Scheme 15



86 R=OH; R'=R''=H;

127 R=R''=H; R'=OH;

128 R=R''=Br; R'=MeO;

129 R=R'=MeO; R''=H;

photooxygenated phloretic acid 101 (in phosphate buffer pH 8.5) to the spiro lactone 102 and the p-quinol 125 in 22 and 50% respectively. Treatment of the p-quinol 125 with N,N -dicyclohexylcarbodiimide gave the spiro lactone 102 in 90% yield (Scheme 15). The p-quinol 119 has been independently synthesised,⁷² but was not detected during enzyme catalysed conversion of p-hydroxyphenylpyruvic acid 115 into homogentisic acid 120. During unsuccessful attempts to produce the p-quinol 116, enzymatic oxidation of the methyl ester of phloretic acid 109 gave the spiro lactone 102 and the p-quinol 126; the latter was stabilised by conversion to the spiro lactone 102 in 27% yield by warming with an acetic acid/hydrochloric acid mixture.

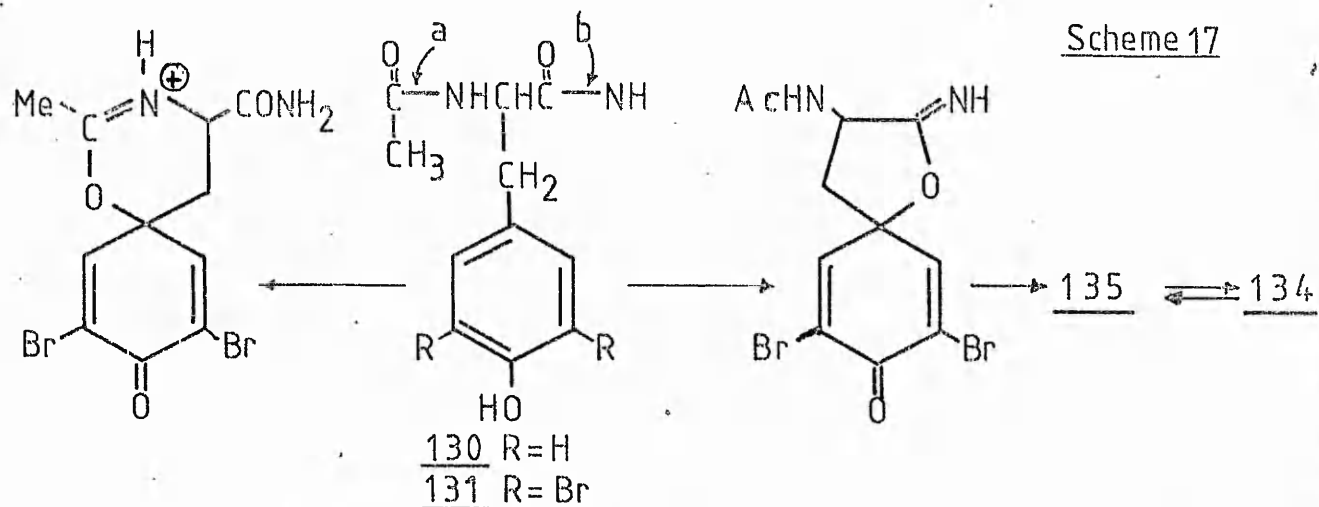
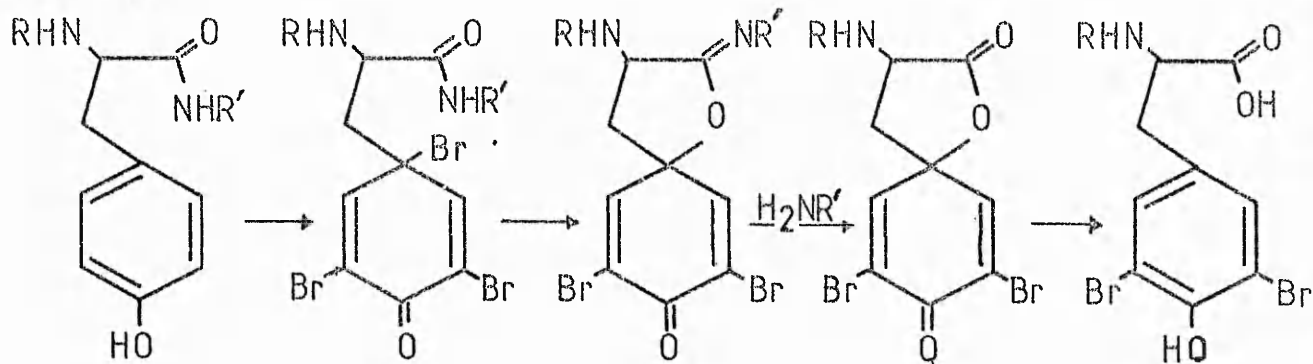
Efforts by Witkop and co-workers⁷³ to increase the selectivity in the non-enzymatic cleavage of tyrosyl-peptide linkages led to the use of electrochemical techniques. Controlled electrode potential anodic oxidation of phloretyl-glycine 111 gave the spiro lactone 102 with the liberation of glycine.

Scott *et al*⁶² used anodic oxidation of phloretic acid 101 to produce the spiro lactone 102, a possible intermediate in the biosynthesis of coumarins. The 1% aqueous solution of substrate gave a 20% yield of spiro lactone 102. It was noted that the methyl ester 109 did not react under these conditions. The spiro lactone 102 was supposedly rearranged to both 6- and 7-hydroxydihydrocoumarins 86 and 127 when heated under reflux in acid media, although there is now some doubt⁶¹ of the authenticity of these claims.

2.1.2 Synthesis of Halogenated 1-Oxaspiro-[4.5]-deca-6,9-diene-2,8-diones

The dibromospiro lactone 104 has been employed during studies on oxidative tyrosyl-peptide cleavages and coumarin biosynthesis, whilst the

Scheme 16



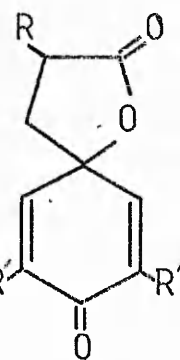
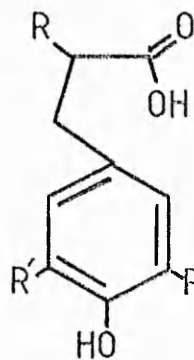
132 $\text{R}=\text{PhCONH}$; $\text{R}'=\text{H}$;

134 $\text{R}=\text{MeCONH}$; $\text{R}'=\text{Br}$;

136 $\text{R}=\text{PhCH}_2\text{OCONH}$; $\text{R}'=\text{Br}$;

138 $\text{R}=\text{MeOCONH}$; $\text{R}'=\text{H}$;

140 $\text{R}=\text{NH}_2$; $\text{R}'=\text{I}$;



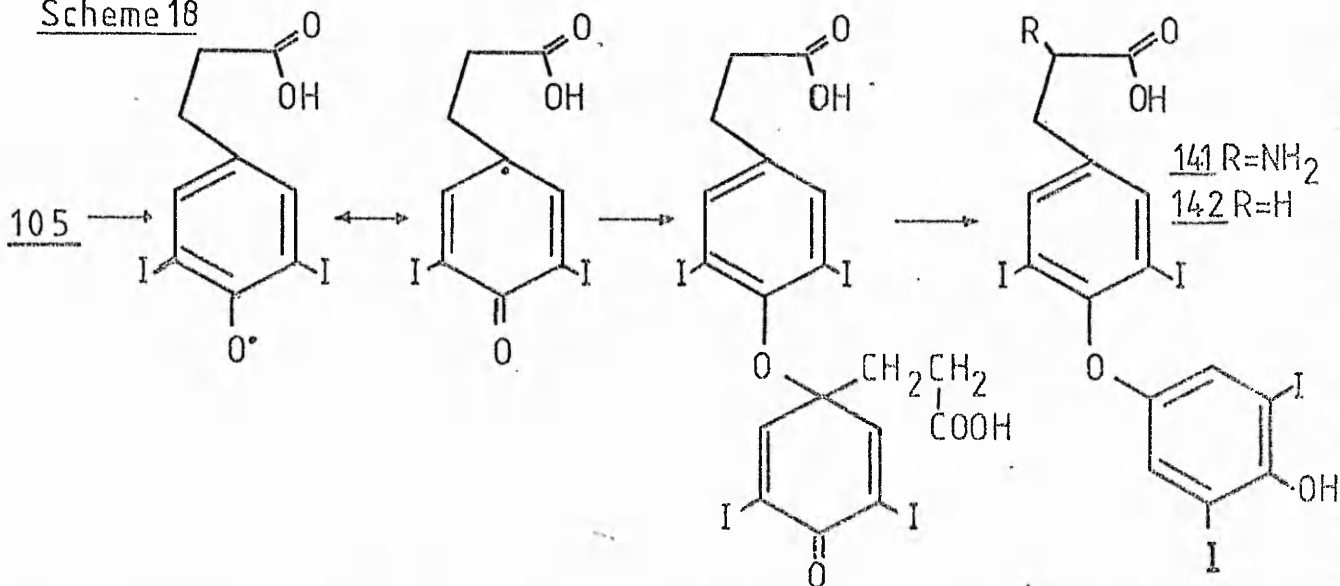
133 $\text{R}=\text{PhCONH}$; $\text{R}'=\text{Br}$;

135 $\text{R}=\text{MeCONH}$; $\text{R}'=\text{Br}$;

137 $\text{R}=\text{PhCH}_2\text{OCONH}$; $\text{R}'=\text{Br}$;

139 $\text{R}=\text{MeOCONH}$; $\text{R}'=\text{H}$

Scheme 18



diiodospirolactone 106 and to a lesser extent the dichlorospirolactone 108 were produced during elucidation of the biosynthesis of thyroxine.

Du Vigneaud and co-workers⁷⁴ found that treatment with aqueous bromine causes selective cleavage of the polypeptides oxytocin and vasopresin at the amide linkage between the carbonyl of tyrosine and the nitrogen of the attached amino acid. Further investigation by Corey and Haefele⁷⁵ led to the proposal of a mechanism (Scheme 16). N-benzyl-3,5-dibromophloretamide 113 when reacted with bromine under Du Vigneaud conditions, liberated benzylamine with the quantitative formation of the halogenated spiro lactone 104. The reaction of phloretic acid 101 and 3,5-dibromophloretic acid 103 with aqueous bromine,⁶⁰ or NBS,⁷⁵ also gives the halogenated spiro lactone 104 in good yield. Similarly, the reaction of N-acetyltyrosine amide 130 with bromine in aqueous methanol (Scheme 17) results in the liberation of ammonia and the formation of the halogenated spiro lactone 135. N-acetyl-3,5-dibromotyrosine 134, produced by the zinc/acetic acid reduction of 135, is readily converted back into its lactone form 135 on treatment with bromine. The cleavage of the tyrosyl-amino linkage 131a and not the acetyl-amino linkage 131b demonstrates the preferential formation of five rather than six membered spiro rings, a result in accordance with previous findings.^{76,77}

The two dipeptides, N-phloretylglycine 111 and 3,5-dibromophloretylglycine 114 react⁶⁰ with NBS to give the halogenated spiro lactone 104 and glycine liberation. Analogous transformations were effected when N-acyl derivatives of tyrosine, 132 and 3,5-dibromotyrosine 134, 136 were treated with NBS yielding the corresponding halogenated N-acylspiro lactones 133, 135, 137 in high yield.

During studies on the biosynthesis of coumarins, it was found⁶² that p-methoxyphenylpropanoic acid 146 reacted with NBS in buffered (NaOAc and

MeCN) solution to give a mixture of the dibromospirolactone 104 and the hydrocoumarin 128 by way of the intermediate 143, of sufficient life-time to generate the brominated spirolactone 104 by hydrolysis.

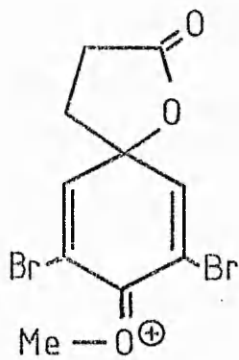
Matsuura and co-workers,⁷⁸ in an effort to elucidate the biosynthesis of thyroxine 141 from 3,5-diiodotyrosine 140, have investigated the reaction of 3,5-diiodophloretic acid 105 with a series of oxidising agents. The modified dimer 142, from the proposed radical mechanism and side-chain modification (Scheme 18) was found in only one case ($K_3Fe(CN)_6$: pH 12), and even then in very small yield, polymers being the usual products. However photooxidation in the presence of a sensitizer, as well as oxidation with hypochlorite and hydrogen peroxide, or NBS, gave neither dimer nor polymer, but the iodospirlactone 106, while photooxygenation of 3,5-dibromophloretic acid 103 yielded the dibromolactone 104. The iodolactone 106 can also be produced⁷⁹ by the action of N-iodosuccinimide on phloretic acid 101.

During the above work on thyroxine, 3,5-dichlorophloretic acid 107 was treated⁷⁸ with hypochlorite and hydrogen peroxide giving a 40% yield of the expected dichlorospirlactone 108.

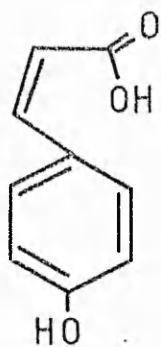
2.1.3 Synthesis of Other Related Spirolactones

Miscellaneous substituted spirolactones have been produced during investigation of coumarin formation.

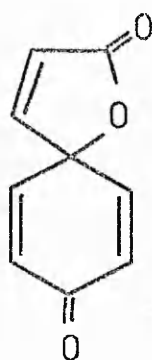
The unsaturated lactone 90 obtained⁶² in 15% yield by anodic oxidation of p-hydroxycinnamic acid 144, can be rearranged on treatment with mineral acid to a separable mixture of 6-hydroxycoumarin 91 and, it is claimed, some umbelliferone 145. Anodic oxidation of N-carbo-methoxytyrosine 138 yielded the substituted spirolactone 139, a possible intermediate in the biogenesis of novobiocin. Thallium (III) trifluoroacetate in trifluoroacetic acid oxidised⁸⁰ 3-(3,4-dimethoxyphenyl)-



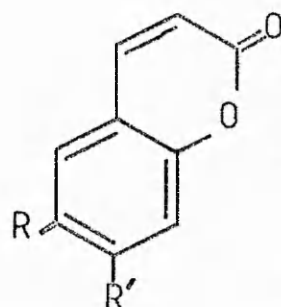
143



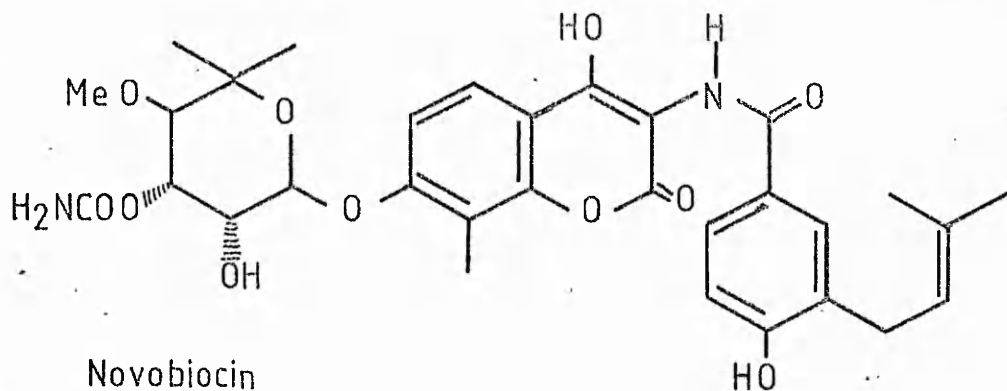
144



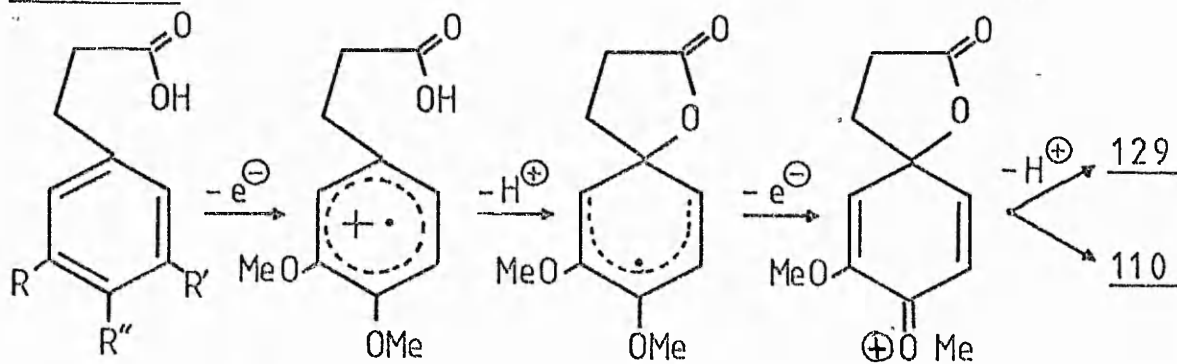
90



91 R=OH; R'=H;
145 R=H; R'=OH;



Scheme 19



146 R=R'=H; R''=OMe;

147 R=R''=OMe; R'=H;

148 R=R'=R''=OMe;

propanoic acid 147 to a 3:1 mixture (57% recovery) of the dihydro-coumarin 129 and the spirolactone 110; the proposed mechanism is shown in Scheme 19. Analogous conversion of 3-(3,4,5-trimethoxyphenyl)-propanoic acid 148 almost exclusively to the spirolactone 112 in 37% yield was also achieved.

2.2 Conclusion

From the results surveyed in the preceding sections it is obvious that the dihalogenated lactones 104, 106 and 108, can be formed much more readily than the parent lactone 102, but that these compounds, being substituted in the position ortho to the dienone carbonyl are not suitable for the synthetic pathways outlined in Scheme 1. Attempts to dehalogenate the bromolactone 104 to 102 have been unsuccessful,⁸¹ and the photooxygenation route to 102, although a good yield process, is a small scale method of some experimental difficulty.

The most promising approach to the spirolactone 102 appears to be the use of anodic oxidation of phloretic acid 101 at a controlled electrode potential (unlike the early electrochemical studies where a constant cell voltage was employed) or by trying the newer range of chemical oxidants.

2.3.1 Synthesis of Spirolactones by Anodic Oxidation

The potentiostatically controlled oxidation of phloretic acid 101 at a carbon felt anode was investigated, with variation of solvent, anode potential, and rate of addition of substrate; some of these experiments are summarised in Table I.* In no case could the yield be increased to greater than the previously reported⁶² 20%. It was thought that intermolecular phenol coupling on the anode surface might be a

* (Experimental Section, Page 81)

major competing reaction, but the low yield of bromolactone 104 from anodic oxidation of dibromophloretic acid 103 makes this unlikely. Use of a two-compartment cell did not improve the yield of spirolactones 102 and 104; authentic samples of these compounds were in any case resistant to cathodic reduction.

2.3.2 Synthesis of Spirolactones by Chemical Oxidants

Treatment of phloretic acid 101 with chemical oxidants *viz* manganese dioxide, manganese tris acetylacetonate, DDQ (in methanol and benzene), silver oxide, and lead dioxide, all failed to produce any spirolactone 102 at all. Attempts made to improve the known low-yield oxidation of phloretic acid 101 to the lactone 102 by lead tetraacetate, by variation of solvent systems, quantity of oxidant, and temperature, failed to give yields greater than 5%.

None of the above oxidants produced the unsaturated lactone 90 from *p*-hydroxycinnamic acid 144; therefore anodic oxidation remains the only means of effecting this transformation.

2.4 Conclusion

The above results indicate that direct oxidation of phloretic acid 101 to the spirolactone 102 in high yield is unlikely. Although the use of substituted precursors increase the yields, these cannot then be transformed to desired spirolactone 102. Therefore alternative routes to this compound must be considered.

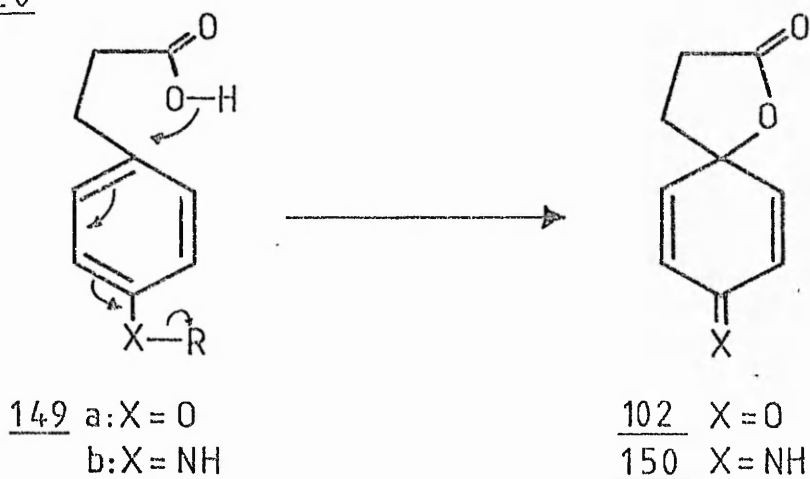
CHAPTER THREE

The Preparation and Properties of Cyclohexadienimines

3.1 Introduction

The poor yields of spiro lactone 102 obtained by intramolecular oxidative coupling of phloretic acid 101 (Chapter Two) necessitated an investigation of alternative synthetic approaches to the lactone. One attractive route to 102 would be to use reactions (Scheme 20) in which the lactone is formed by expulsion of a leaving group from the para position of a phenylpropanoic acid 149a,b with synchronous nucleophilic attack by the side-chain carboxyl substituent.

Scheme 20

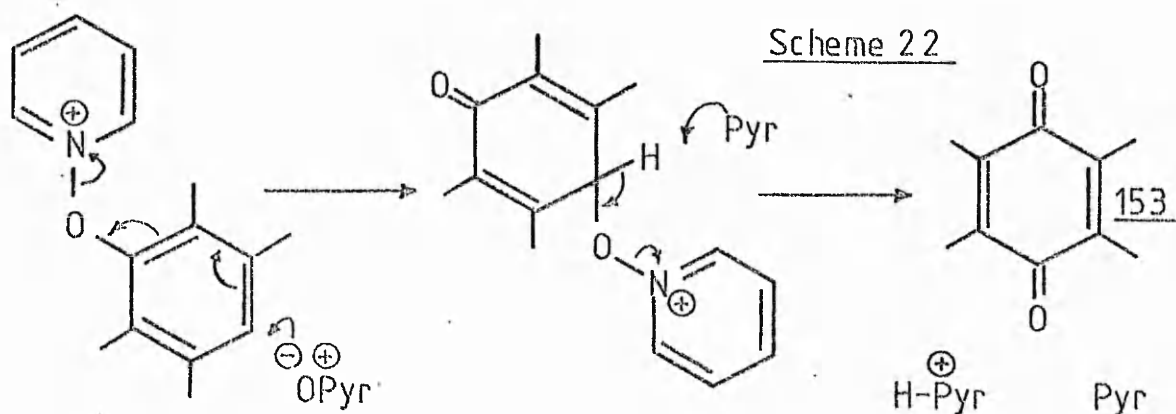
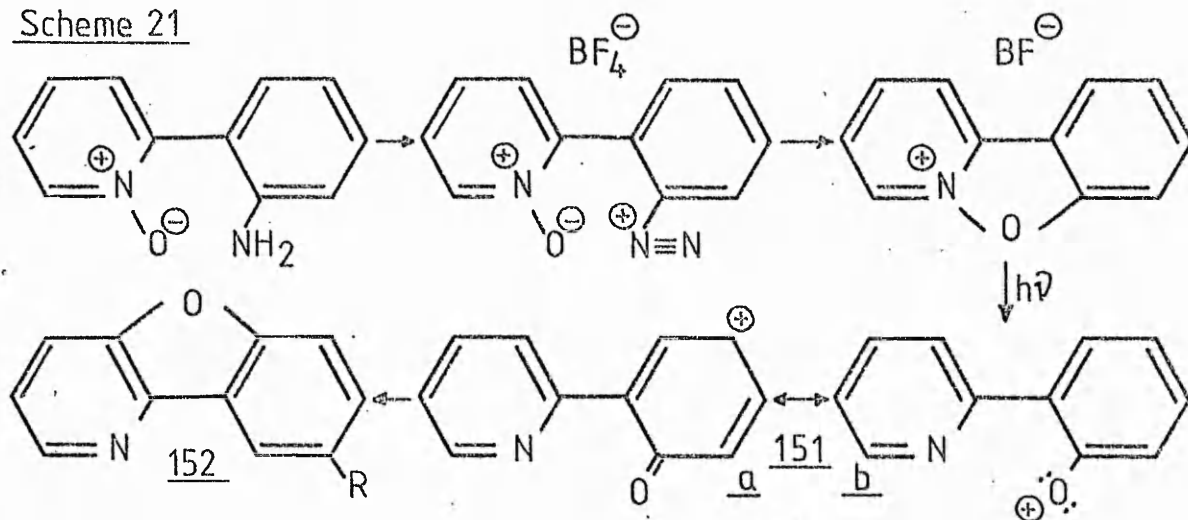


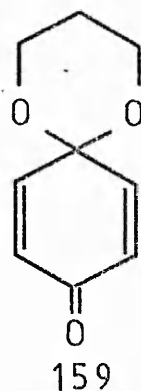
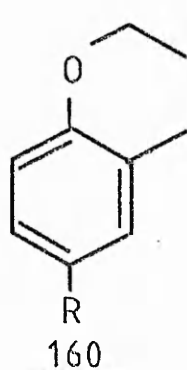
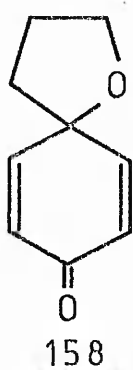
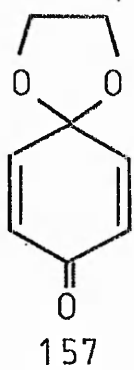
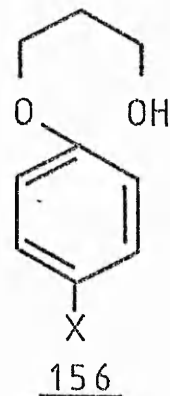
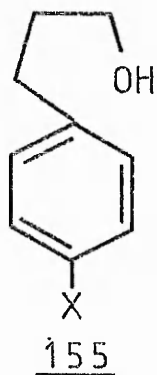
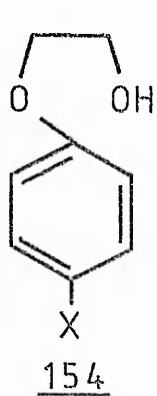
For direct formation of a dienone, compounds of the type 149a would be desirable, but suitable phenol derivatives 149a containing leaving groups leading to the incipient or full phenoxonium species are not readily accessible.

In the search for aryloxonium ions, recent studies by Abramovitch and co-workers^{82,83,84} have centred around the thermolysis and photolysis of N-aryloxypyridinium salts. It was proposed that these experimental conditions produced⁸³ a phenoxonium ion 151 which underwent an internal nucleophilic

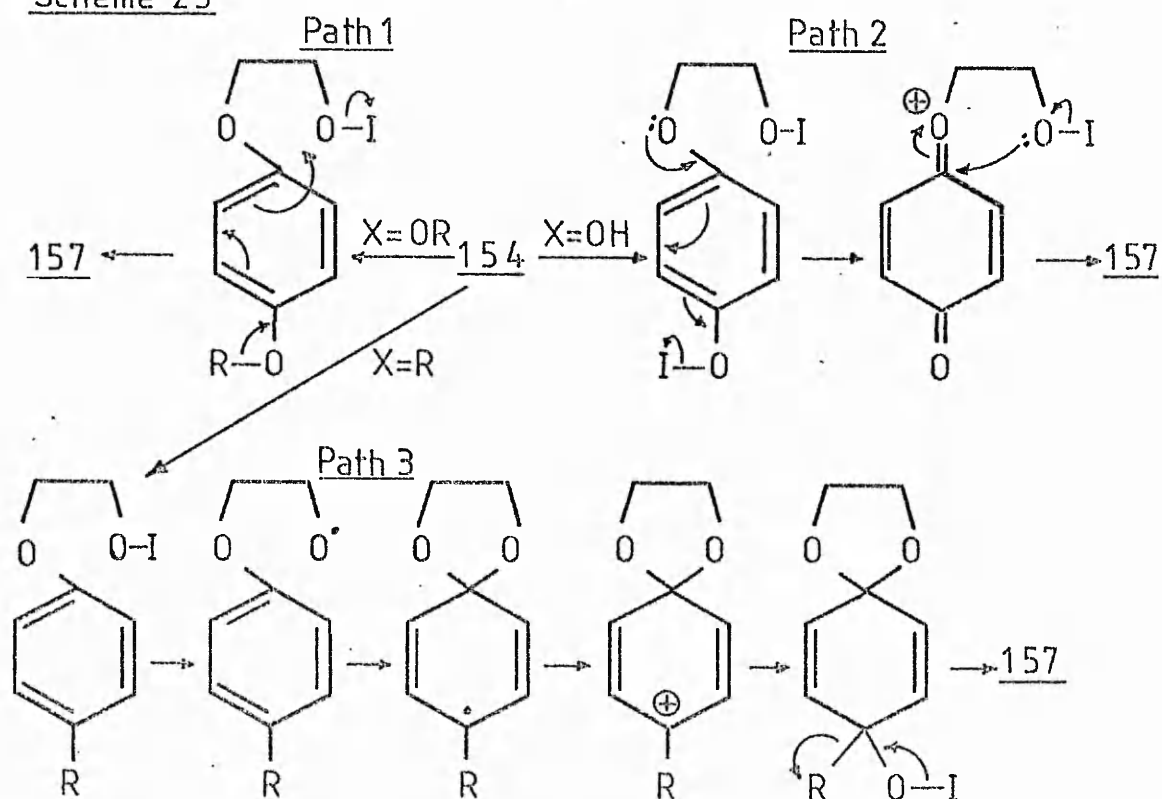
attack by the β -carbon of the pyridine ring to give 152 (Scheme 21); in support of this mechanism it was found that electron-withdrawing substituents para to the phenolic oxygen enhanced the product yield, presumably by increasing the electrophilicity of the oxygen anion 151a, and reducing the contribution made by the mesomer 151b to the overall charge distribution. Earlier work⁸² had also involved the use of pyridine as a leaving group; one example of this is shown in Scheme 22, where the proposed concerted mechanism

Scheme 21





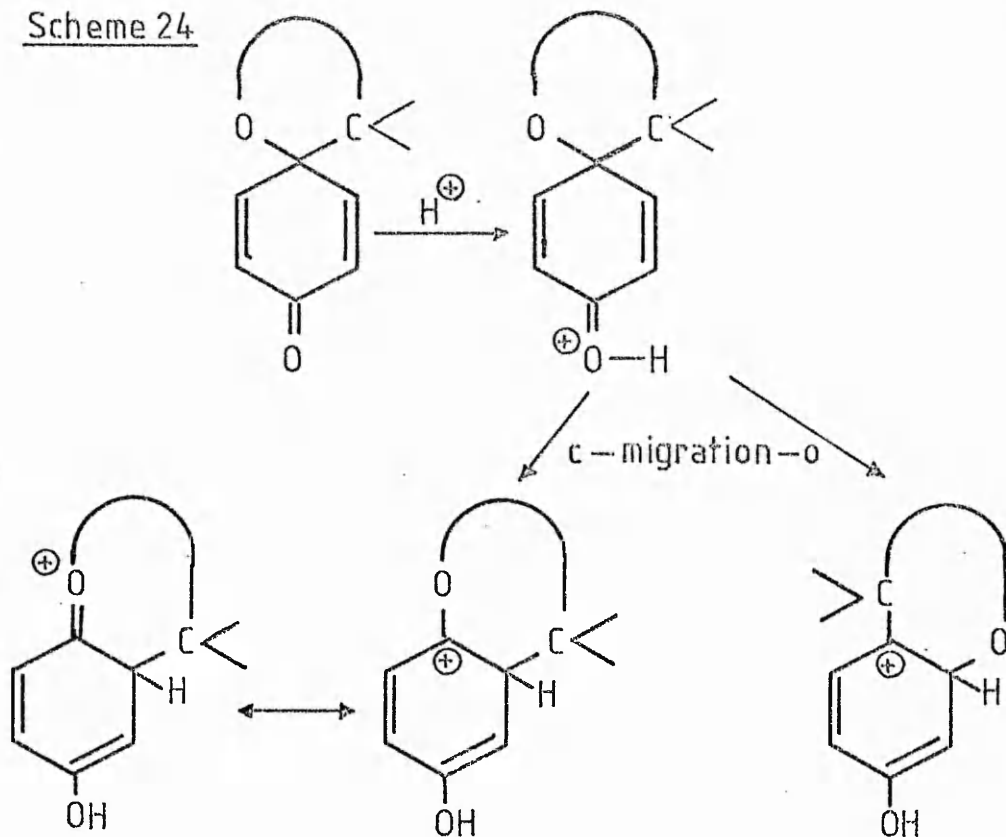
Scheme 23



results in the production of substituted quinones 153. However the relatively small scale, modest yield, and complexity of both starting materials and side reactions suggest this to be a somewhat unfavourable approach to cyclohexadienones.

Goosen et al⁸⁵ have recently shown that the reaction of a number of p-substituted 2-phenoxyethanols 154, 3-phenylpropan-1-ols 155, and 3-phenoxypropan-1-ols 156, with mercury (II) oxide and iodine gives the spirodienones 157, 158 and 159, as products. Electron-donating substituents promoted intramolecular cyclisations of 154 and 155 by an Ar₁-5 mechanism to give 157 and 158, whilst Ar₁-6 cyclisation occurred (albeit less readily) with 156. Less activated systems gave nuclear iodinated products, and when a deactivating substituent (e.g. X=NO₂) was present the substrate was relatively inert. Interestingly, three different reaction mechanisms for these cyclisations were proposed. In the dark reactions, the phenoxyethanol series was thought to give a hypoiodite species and hence the monoketal 157 (Scheme 23 Path 1); this reaction was successful only for substrates with an oxygen moiety (RO-) in the para position. In the specific case of p-hydroxyphenoxyethanol 154 (X=OH), a sequence involving the production of a phenoxy-iodide was proposed, which by an aryl assisted expulsion of iodide gave a charged quinonoid species (formally analogous to quinone methides formed in certain phenol oxidations⁸⁶); this then collapses to 157 (Scheme 23 Path 2). For reactions involving photolysis, a radical intermediate was postulated, which underwent further oxidation to a carbocation, and then to the spirodienone 157 (Scheme 23 Path 3). The Ar₂-6 cyclisation products 160 from 3-phenylpropan-1-ols 155 have been shown to arise by rearrangement of Ar₁-5 intermediates 158 in which carbon migrates in preference to oxygen⁶¹ due to stabilisation of the cationic intermediate afforded by the heteroatom remaining in the para-position (Scheme 24- see also Section 1.3).

Scheme 24

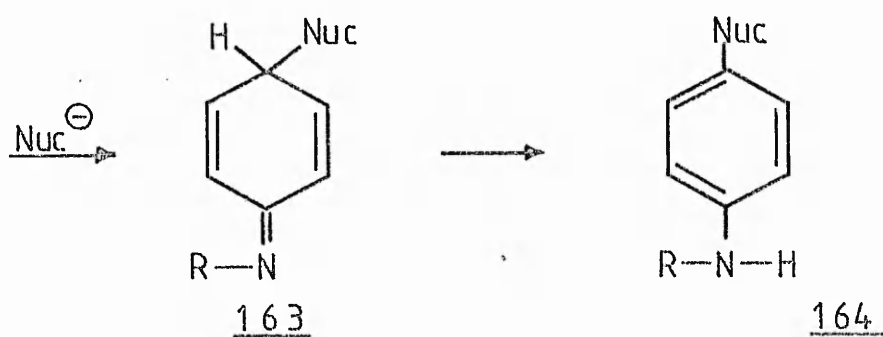
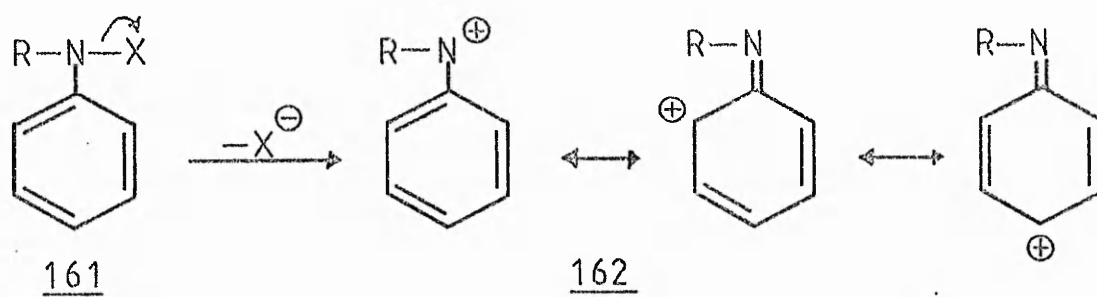


The use of nitrogen species 149b in Scheme 20 is a potentially more promising approach than one involving phenolic precursors, since there is evidence, discussed in the following section, to suggest that nitrenium intermediates may be available by the process shown in Scheme 25, and that they undergo ready nucleophilic attack on the aromatic ring. The resulting azomethine 150 should be susceptible to hydrolysis to yield the desired dienone 102.

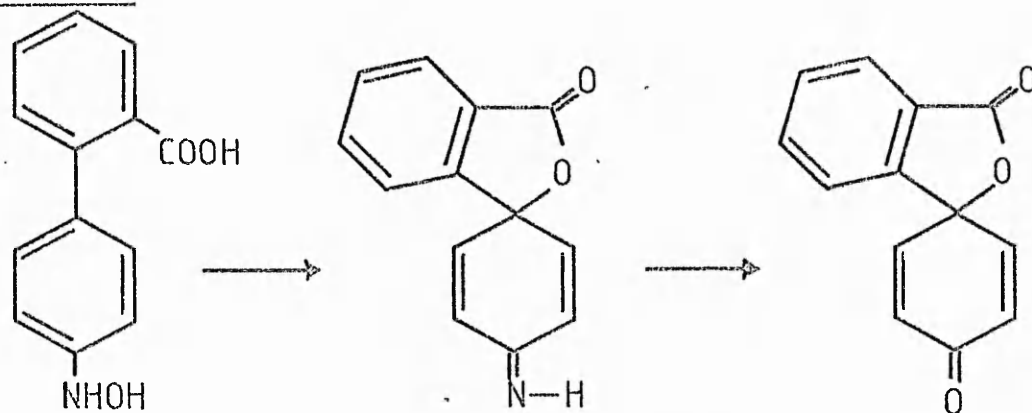
3.2.1 Routes to Dienones Involving Nitrogen Precursors

Although nucleophilic aromatic substitution is generally limited to

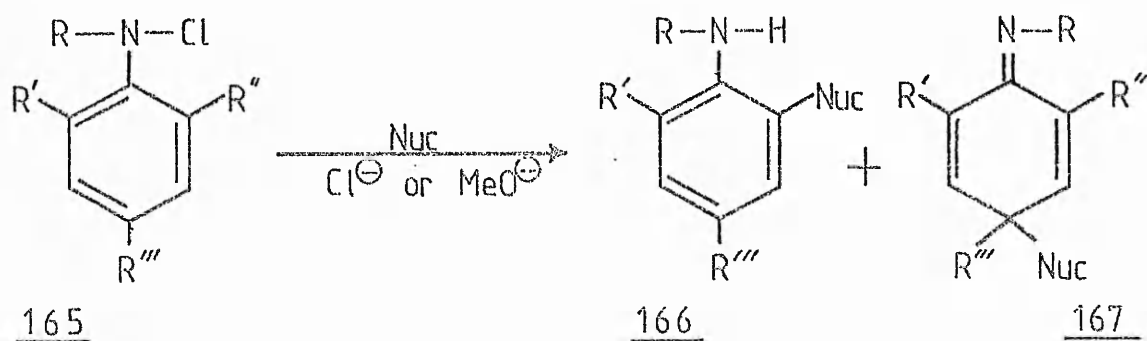
Scheme 25



Scheme 26

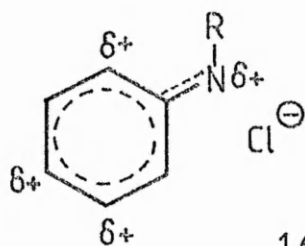


Scheme 27



aromatic systems with strongly electron withdrawing substituents, the acid catalysed rearrangements of hydroxylamines to aminophenols (Bamberger reaction Scheme 25 X = OH) show that the presence of a suitable leaving group on the heteroatom can result in generation of an anilinium cation which can undergo subsequent nucleophilic addition; if tautomerisation of 163 is blocked, cyclohexadienimines or the corresponding dienones can be isolated⁶⁴ (Scheme 26).

A systematic investigation has been undertaken by Gassman and co-workers⁸⁷ of this type of substitution, in which the anilinium ion is generated by treatment of N-chloroanilines with silver trifluoroacetate in methanol. Consideration of the relative electronegativities of nitrogen and carbon indicate that considerable charge delocalisation into the aromatic nucleus would occur in these electron-deficient species, rendering the ring very susceptible to nucleophilic attack. Thus from the N-chloroanilines 165 were obtained mixtures of products (Scheme 27) arising by mono-chlorination or mono-methoxylation of the substrates ortho or para to the nitrogen function. The initial product (e.g. 167 R^{'''} = H) from nucleophilic attack in the para position on compounds unsubstituted at this site, undergo tautomerism to the corresponding aromatic amine. The product ratio was found to be relatively independent of temperature, but the course of the nucleophilic addition is controlled by the nature of the aniline substituents. N-chloroanilines with electron-donating substituents undergo nucleophilic attack by the solvent as the major reaction pathway leading to methoxylated products. As the substituents on the aromatic ring become increasingly more electron-withdrawing, incorporation of the solvent in a nucleophilic reaction decreases up to a point where, in the case of p-carboethoxy- and p-nitro-substituents no solvent incorporation occurs at all. Formation of ring chlorinated products appears to involve the anilinium ion and the chloride ion forming a "tight ion pair" 168. As substituents on the ring become more electron-withdrawing, the



stability of the anilium ion decreases, thus forming a tighter ion complex, which in extreme cases, would appear to collapse into ring chlorinated products, to the exclusion of the nucleophilic attack by the solvent. Further studies⁸⁸ on nitrenium ions have involved the thermal rearrangement of N-chloroanilines in ethanol, to give ring chlorinated products. The synthesis of the spirodienone glaziovine from an N-chloro-amine precursor¹⁶⁶ is discussed in Chapter Five.

Extensive experimental studies on nitrogen radicals have shown the similarity⁸⁹ between carboxamidyl ($\text{RCO}\dot{\text{N}}\text{R}$) and sulphonamidyl⁹⁰ ($\text{RSO}_2\dot{\text{N}}\text{R}$) radicals, and their collective dissimilarity⁹¹ to aminium radicals ($\text{R}\dot{\text{N}}\text{R}$). All three types of nitrogen radicals have been generated by photolysis and thermolysis of the corresponding N-halogeno-derivative, and, once produced, have been used almost exclusively in the formation of new nitrogen-carbon bonds. The possible intermediacy of amino radicals in the silver ion promoted and non-catalysed solvolysis of N-chloroamines in methanol has also been investigated by Gassman,⁹² who found the products from N-chloroderivatives of bicyclic amines with rigid geometry occurring via the proposed nitrenium ion, to be quite different from those formed under radical conditions. No direct evidence for a radical-induced mechanism of the type required for the conversion of 149b to 150 has been obtained, and thus a nitrogen radical approach involving aryl participation to cyclohexadienimines appears unlikely.

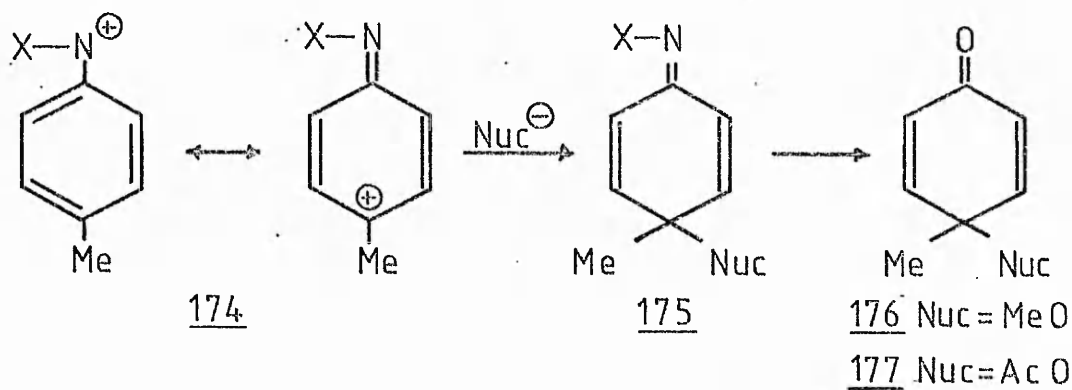
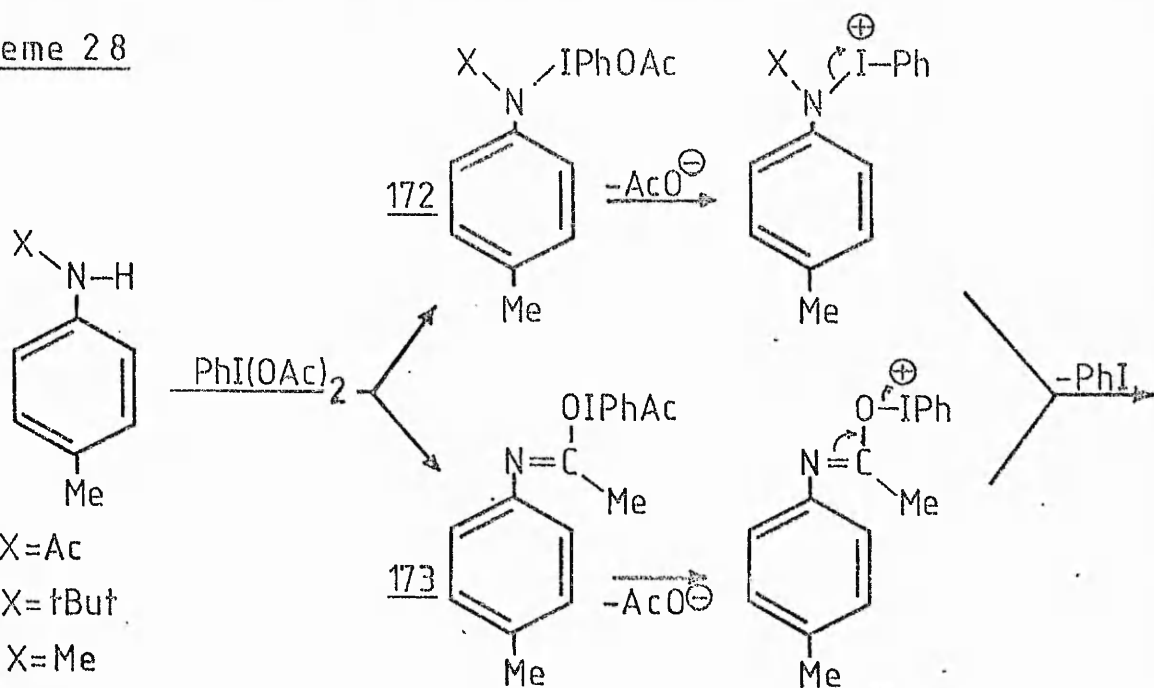
The reaction⁹³ of phenyliodosoacetate in acetic acid with acetanilides having electron-donating substituents such as MeO- or Me- in the para position gives good yields of meta-acetoxyated products and is now thought⁹⁴ to proceed via an intermediate anilinium cation. The process was found to be catalysed by mineral acids, and no evidence for a radical mechanism has been obtained;⁹⁵ it was also noted that N-methylacetanilides did not react under these conditions. Recent⁹⁴ investigations have shown that phenyliodoso acetate in methanol reacts with N-substituted-4-toluidines, 169, 170 and 171, to give 4-methoxy-4-methylcyclohexa-2,5-dienone 176 in good yield. Changing the reaction solvent to acetic acid gave the corresponding acetoxydienone 177 in slightly lower yields; the reaction of 171 under these conditions also produced some of the disubstituted compound 179, and a mechanism (Scheme 29) has been proposed for this. All these results suggest a common ionic mechanism (Scheme 28) in which initial attack by the phenylacetoxyiodonium ion on the amino or acetamido function of the substrate gives the iodoso intermediates 172 or 173, followed by cleavage to iodobenzene and the resonance stabilised nitrenium ion 174. Reaction of 174 with solvent leads to the dienimines 175 which hydrolyse during isolation to the corresponding dienones 176-177. With acetic acid as the reaction medium, the dienimine 180 underwent further reaction to the meta-acetoxyated derivative 181 (Scheme 30).

A recent investigation⁹⁶ of the oxidation of substituted N-alkylanilines with lead tetra-acetate in acetic acid showed products resulting from N-acetylation, nuclear acetoxylation, and N-dealkylation of the starting material. The discussion of these results favours the intermediacy of an aryl nitrenium ion rather than of an aminium radical.

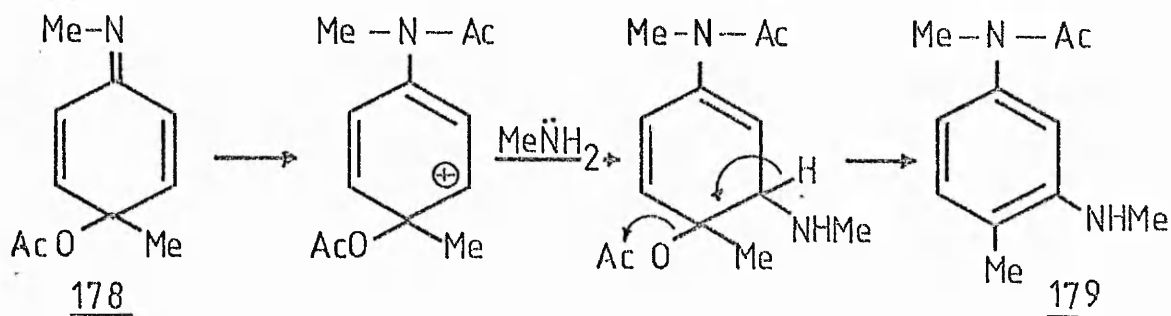
The novel dienimine 182 was shown⁹⁷ to undergo easy hydrolysis to the dienone 183, which had previously been prepared⁹⁸ by the action of diaroyl peroxides on phenols. The thermal rearrangement of 182, 183 and 184, (the

Scheme 28

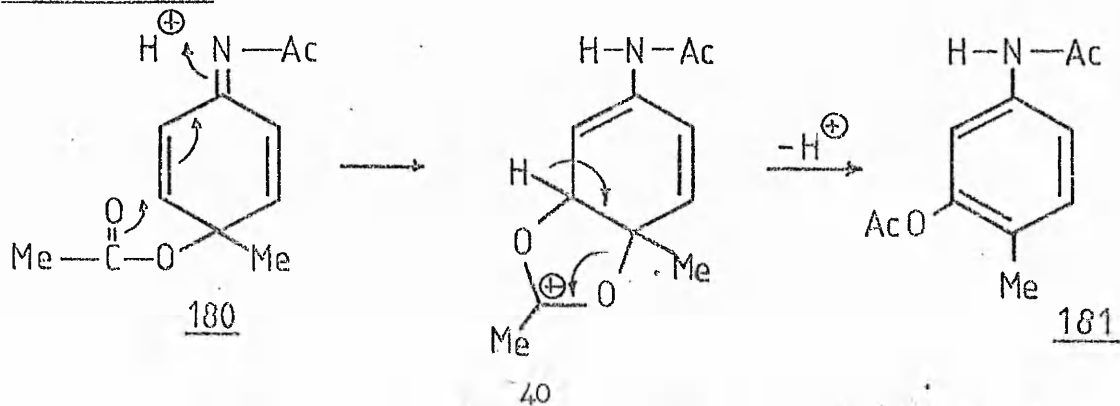
- 169 X=Ac
170 X=tBut
171 X=Me



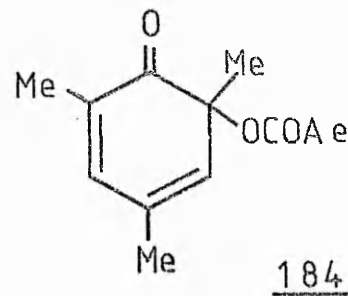
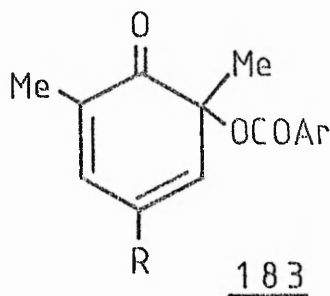
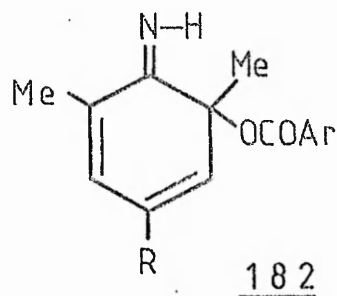
Scheme 29



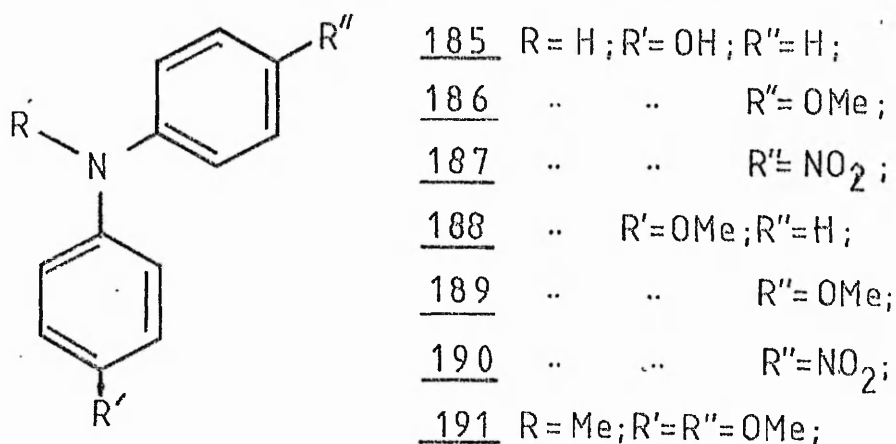
Scheme 30



last formed by the action of lead tetraacetate on N-benzenesulphonyl-2,4,6-trimethylaniline⁹⁹), is postulated to proceed to para-acyloxy species via a transient cation intermediate.



Anilinium cations have also been implicated in a study¹⁰⁰ of the anodic oxidation of diphenylamines. The aminophenols 185-190 all underwent two-electron oxidation to give quinone-imines, with subsequent hydrolysis to



p-benzoquinone and anilines. The N-methyl derivative 191 was observed to give an initial one electron oxidation to a primary cation radical, followed by a loss of another electron to yield a quinone-iminium cation, which was rapidly hydrolysed to the quinone and N-methylanisidine.

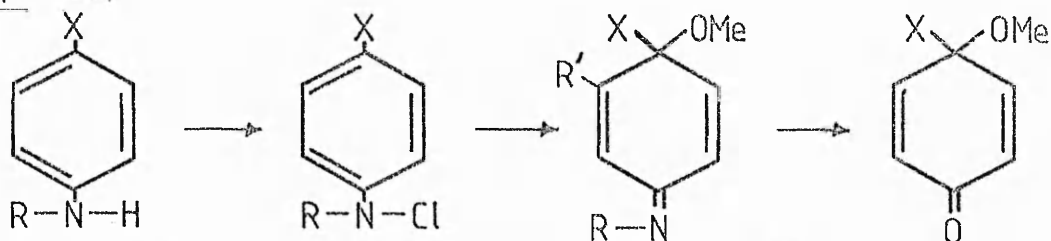
The synthesis and reactions of quinone mono- and di-imines have been well

reviewed.¹⁰¹ Unsubstituted species are prepared using silver oxide in dry ether, but are unstable to light, and in acid solutions are easily hydrolysed to the corresponding p-benzoquinone. By the use of N-acyl, N-aroyl, or best of all N-sulphonyl derivatives, far more stable products are formed, including diimides from substituted and unsubstituted o-phenylenediamine, 1,2-, 1,4-, and 2,6-naphthalenediamines and benzidines. The sulphonamides are highly crystalline, and are prepared using a range of oxidants such as lead tetraacetate, red lead (Pb_3O_4), lead dioxide, silver oxide, chromium trioxide, sodium or potassium dichromate, bromine in pyridine, and sodium bismuthate, whereas N-acyl compounds require more specific conditions. Nearly all the mono- and di-imides studied underwent addition reactions much more easily than does benzoquinone.

3.2.2 Preparation of a Series of Nitrogen-substituted Cyclohexadienimines

A series of N-substituted anisidines and toluidines 192-203 were prepared, and treated in dichloromethane solution with tert-butyl hypochlorite and then with silver trifluoroacetate in methanol. The N-tosyl-p-anisidine 192 gave a crystalline product, the infra-red spectrum of which showed peaks at 1660 and 1550cm^{-1} , considered characteristic of cyclohexadienimines, together with sulphonamide absorption at 1310 and 1155cm^{-1} . However NMR spectroscopy and analytical data pointed to the mono-chlorinated structure 207 for this product, rather than 204 (see Experimental). Similarly analytical and spectral data for the product from the reaction of tert-butyl hypochlorite and silver trifluoroacetate in methanol with N-tosyl-p-toluidine 193 indicated the formation of a dichlorinated cyclohexadienimine. The N-mesyl derivatives of p-anisidine 194 and p-toluidine 195 proved even more of a problem under these conditions. The IR spectrum of the product from the former indicated the presence of an imine, although analytical and mass spectral data suggested dichlorination had occurred; the reaction of 195 gave a mixture of products which could not

Scheme 31



192: X=MeO; R= Ts;

193: X= Me ; R= Ts;

194: X=MeO; R= Ms;

195: X= Me ; R= Ms;

196: X=MeO; R= Ns;

197: X= Me O; R= Ac;

198: X= Me O; R= PhCO;

199: X= Me O; R= CF₃ CO;

204: X=MeO; R= Ts; R'= H;

208 X=MeO

205: X=MeO; R= Ms; R'= H;

206: X= Me O; R= Ns; R'= H;

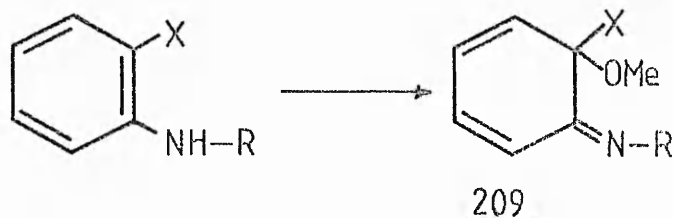
207: X= Me O; R= Ts; R'= Cl;

200: X=MeO; R=Ts;

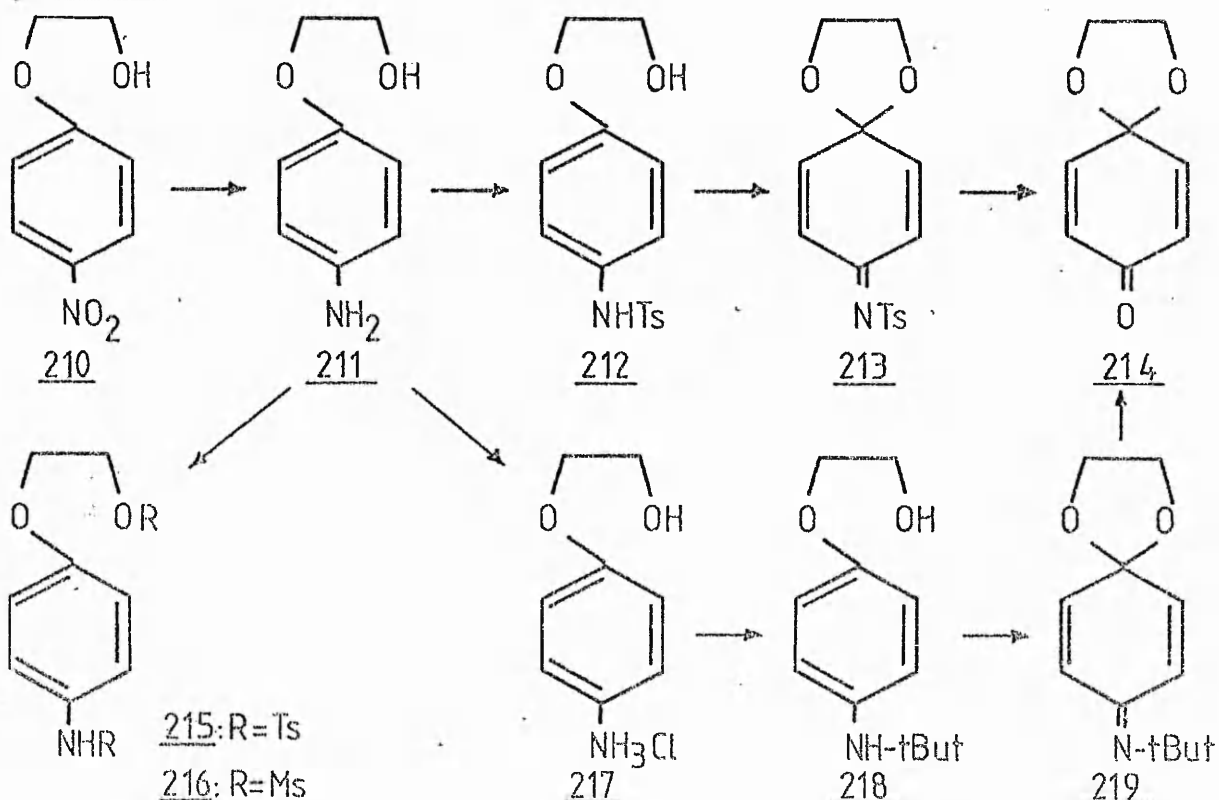
201: X=MeO ; R=Ms;

202: X= Me ; R= Ts;

203: X= Me ; R= Ms;



Scheme 32



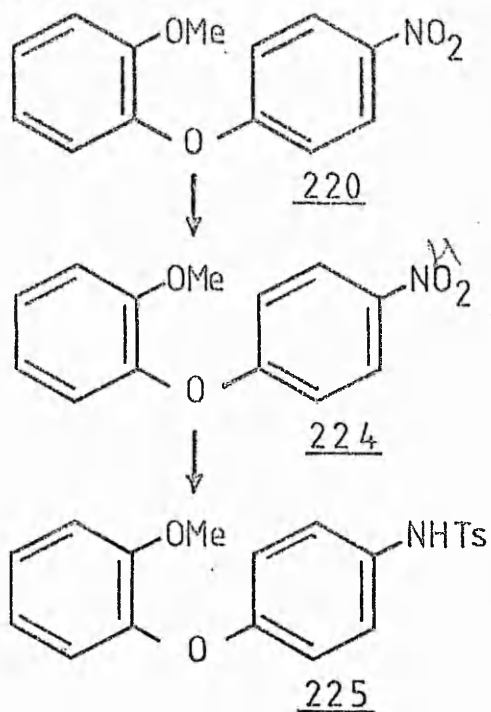
be separated. The N-(2-nitrobenzenesulphonyl)-p-anisidine 196 formed an intractable tar when reacted with hypochlorite, and there was also no evidence of imine formation from the N-sulphonyl derivatives of o-toluidine and o-anisidine (200 - 203), nor from the three amides 197, 198 and 199.

As N-tosyl-p-anisidine 192 had given the most encouraging results from the intermolecular reactions, N-tosyl-4-aminophenoxyethanol 212 should, in a non-nucleophilic solvent, undergo intramolecular attack due to the presence of the side-chain alcohol acting as an internal nucleophile, to yield the cyclic ketal structure 213 (Scheme 32). Preparation of 212 involved the reaction of sodium nitrophenoxide with 2-chloroethanol to give 210, catalytic hydrogenation to the amine 211, followed by preparation of the mono-sulphonyl-derivative 212 under weakly basic conditions. Some of the bis-sulphonyl product 215 was also isolated. Hypochlorite treatment of 212 gave the expected product 213 in 30% yield, although some evidence for the presence of a small amount of chlorinated products was also found. Several attempts to produce the mono-N-mesyl analogue of 212, always resulted in the bis-product 216.

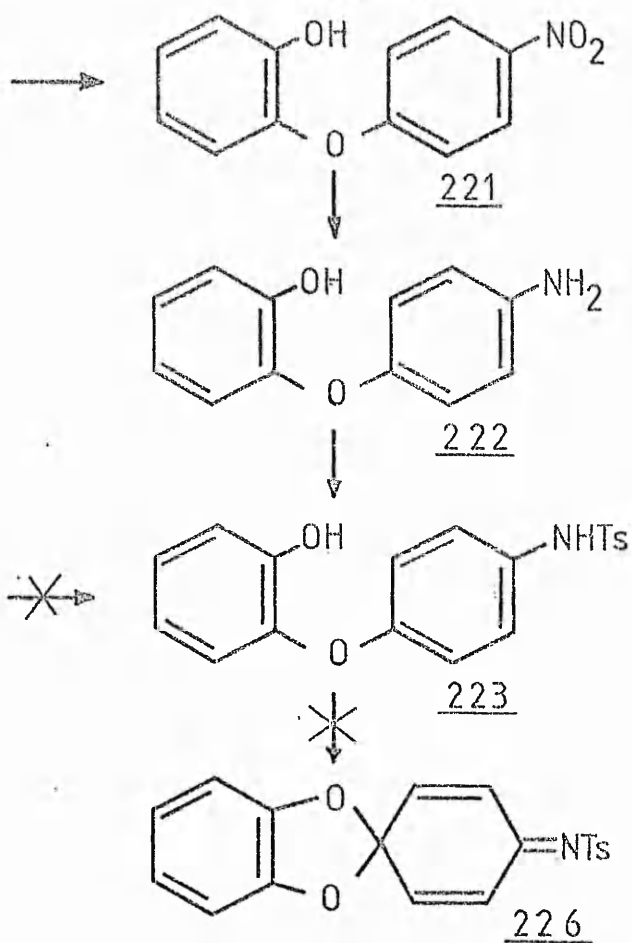
In the diphenyl ether 223 there is the possibility of using an internal phenolic nucleophile to create the novel tricyclic product 226. The reaction (Scheme 33 Path 1) under Ullman conditions of 2-methoxyphenol and 4-nitro-bromobenzene gave ether 220 which by demethylation to 221 and hydrogenation yielded 222; this reacted with tosyl chloride to give the mono-sulphonamide 223. The alternative route (Scheme 33 Path 2) failed when 225 could not be demethylated to the free phenol 223. The reaction of 223 with hypochlorite gave a black tar, composed largely of starting material. No evidence of cyclisation was observed.

Since the action of an internal carboxylic acid nucleophile was also of interest, the N-tosyl-p-aminophenoxyacetic acid 234 was synthesised in a manner similar to 212 (Scheme 34), starting from sodium nitrophenoxide and ethyl chloroacetate. Hydrolysis of the ester 229 gave the desired acid 234.

Scheme 33

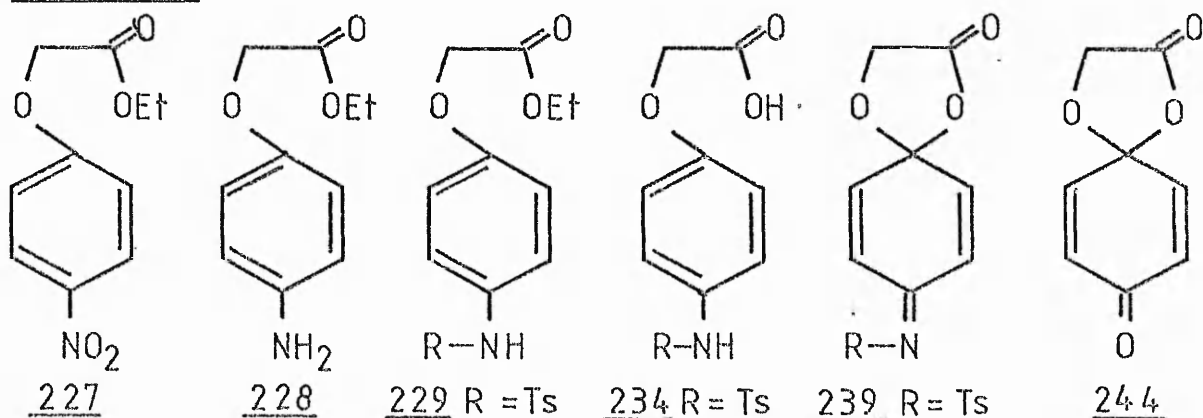


Path 1



Path 2

Scheme 34



230 R = Ms 235 R = Ms 240 R = Ms

231 R = Bs 236 R = Bs 241 R = Bs

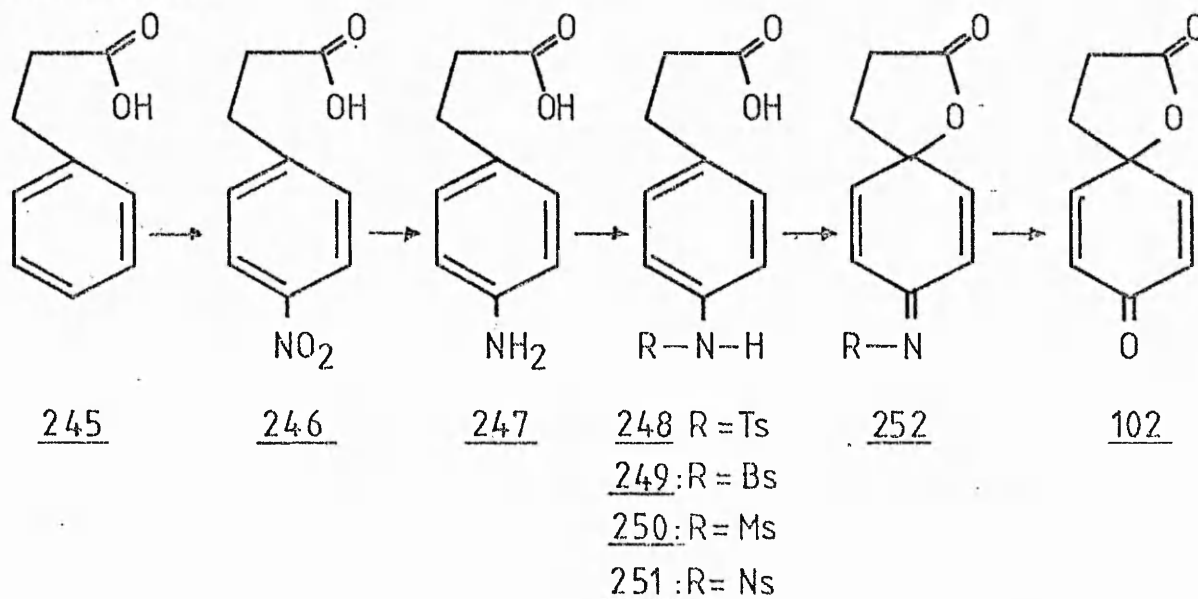
232 R = Ns 237 R = Ns 242 R = Ns

233 R = Piv 238 R = Piv 243 R = Piv

in high yield. Treatment of 234 with hypochlorite gave a small quantity of product 239, which although homogeneous by T.L.C. failed to crystallise; the IR spectrum showed a lactone carbonyl at 1800cm^{-1} and characteristic diene, imine and sulphonyl peaks, although some acid starting material peaks were also observed.

Of greatest interest in this series, was the possible lactone formation from the phenylpropanoic acid 248 (Scheme 35). It was synthesised by nitration of phenylpropanoic acid 245 with fuming nitric acid to give 246; catalytic hydrogenation produced the amino acid 247, followed by a high yield conversion to sulphonamide 248. After treatment with hypochlorite only a small amount of solid product 252 was isolated. The IR spectrum showed a lactone carbonyl at 1785cm^{-1} and also diene, imine and sulphonyl absorptions.

Scheme 35



Consideration of the success achieved by Gassman and co-workers⁸⁷ using N-tert-butyl-derivatives suggested that these might lead to enhanced imine yields compared with those obtained from the N-sulphonyl series. However attempts to produce 2-(N-tert-butyl-p-aminophenoxy)-ethanol 218 from the

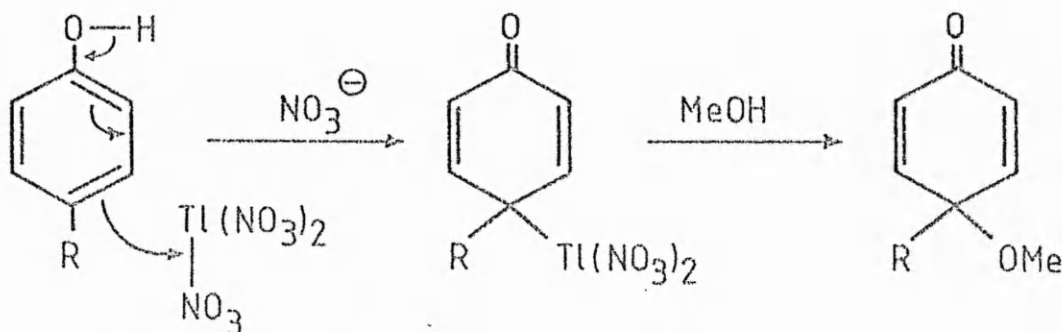
corresponding amino hydrochloride 217 and tert-butanol in a pressurised steel bomb, gave a mixture, which proved impossible to separate. This entire approach was abandoned. Several experiments using phenyliodoso acetate⁹⁴ on 212 also resulted in an intractable mixtures of products, and the use of this reagent was not pursued further.

3.3.1 Review of Methods for the Preparation of Cyclohexadienones

Although the nitrenium approach to cyclohexadienimines (3.2.2) has produced reasonable yields of this class of compound, competing reactions leading to chlorinated products made it desirable to seek new synthetic strategies. Since the first report of the formation of a quinone ketal 279 by Belleau and Weinberg¹⁰² in 1963, there has been an upsurge of interest in this class of compound, and two main methods of synthesis, by chemical or electrochemical oxidation, are favoured at present.

Thallium (III) nitrate has been employed extensively by McKillop *et al*¹⁰³ to produce a wide variety of 4,4-disubstituted cyclohexa-2,5-dienones from the corresponding phenols. A proposed mechanism involving *ipso* thallation of the phenol, followed by nucleophilic attack at the developing electrophilic centre created by heterolysis of the weak carbon-thallium bond, is outlined in Scheme 36. DDQ has also been used extensively to produce p-quinone ketals in good yield.¹⁰⁴ Oxidation of phenols with other reagents¹⁰⁵ including copper (II)

Scheme 36



species, ceric salts, silver oxide and manganese dioxide has given quinone ketals, albeit in low yield.

The preparation of quinone ketals by electrochemical oxidation of 1,4-dialkoxybenzenes has been studied by Swenton¹⁰⁶ and co-workers, who, by extending the methods of Weinberg,¹⁰⁷ have devised synthetic routes to large quantities of quinone bis-ketals; examples have been reported in the benzene, naphthalene and benzothiophene series. Selective hydrolysis of the bis-ketals yields the corresponding mono-ketal derivative. A direct electrochemical synthesis¹⁰⁸ of 208 from 4-methoxyphenol has been reported.

Since the most efficient route to the dienone 102 was by anodic oxidation of phloretic acid 101 (see Chapter Two) it was thought possible that electrochemical oxidation of the para-substituted-N-sulphonyl derivatives used in the hypochlorite reactions in Section 3.2.2 might produce the corresponding dienimine species.

3.3.2 Electrochemical Preparation of Cyclohexadienimines

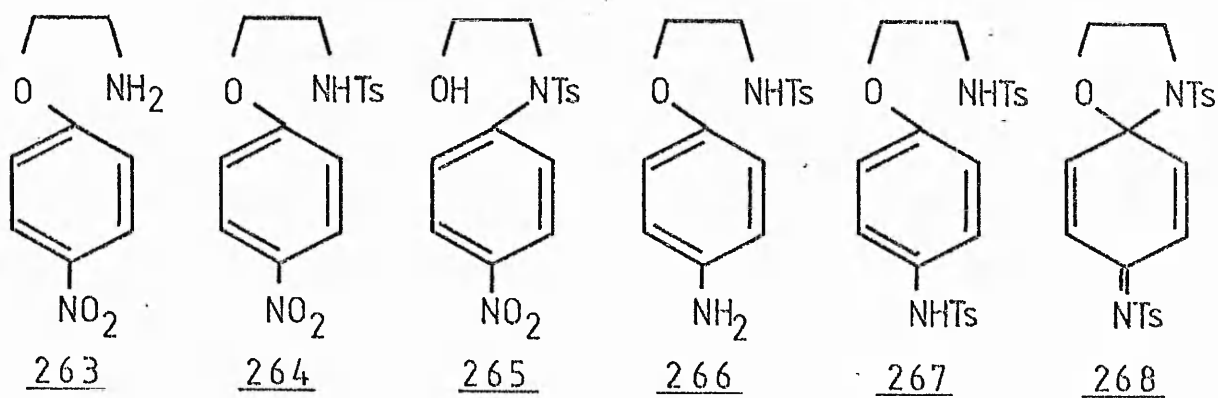
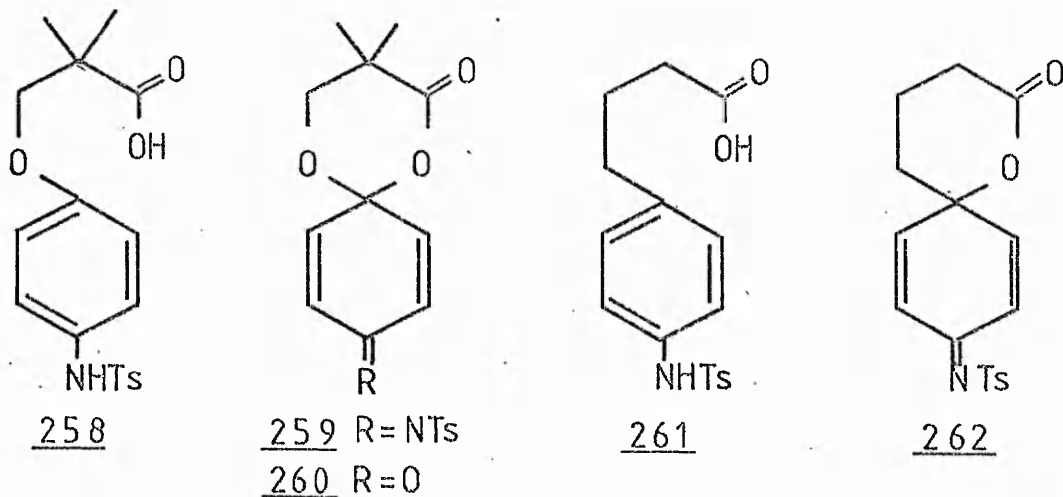
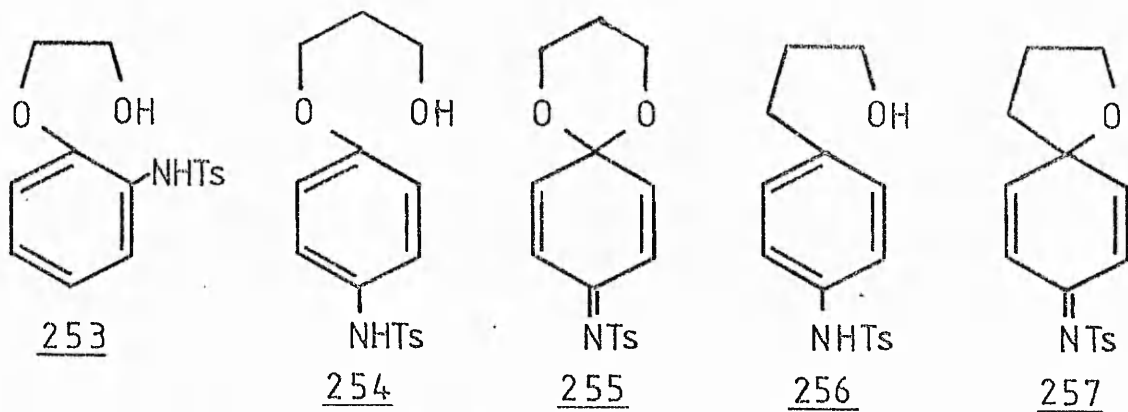
The N-sulphonyl-p-anisidines 192, 194 and 196 were anodically oxidised in methanol to the corresponding N-sulphonyl-4,5-dimethoxycyclohexa-2,5-dienimines 204, 205 and 206 in good (70-75%) yield. (N.B. Subsequent studies on the hydrolysis of 205 (3.5.2) to the more stable dienone 208, showed a quantitative conversion to the imine during the electrochemical procedure.) Although considerable loss of product occurred in isolating pure crystalline compounds from the rather gummy oxidation materials obtained initially, chromatographic and spectral evidence later suggested these to be almost pure imines. Oxidation of the p-toluidines 193 and 195 yielded mixtures, and although purification failed, IR spectra of the crude products showed characteristic imine absorptions. The N-tosyl derivatives of o-anisidine and o-toluidine 200 and 202, yielded intractable tars on oxidation. The attempted

anodic methoxylation of the N-acyl-p-anisidines 197, 198 and 199 gave mainly starting material, contaminated with a little tar.

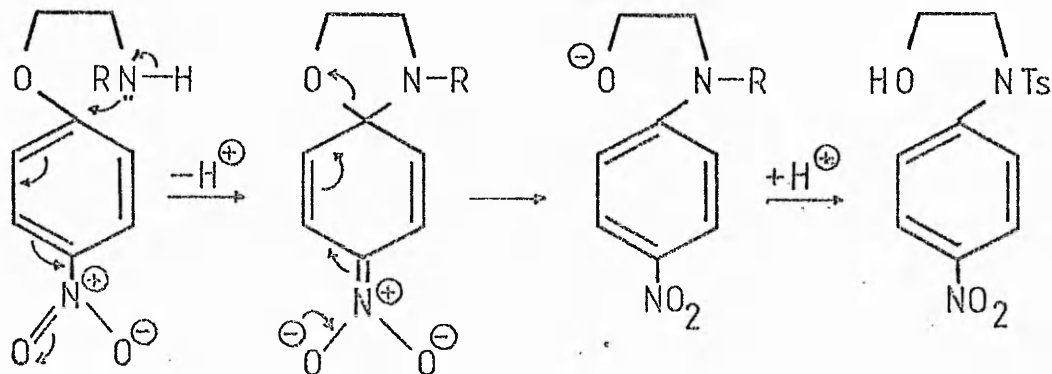
Anodic oxidation of the phenoxyethanol 212 gave a product homogeneous by TLC and with spectral properties consistent with the cyclic ketal 213, but which could not be obtained as a crystalline solid in a satisfactory yield. Attempted oxidation of the ortho isomer 253 gave only starting material contaminated with tar. The phenoxypropanol 254 yielded the desired product 255 after column chromatography, in 32% yield, but this imine soon decomposed at room temperature. Reduction of the propanoic acid 248 in THF with borane-methyl sulphide gave the corresponding propanol 256, which could not be induced to crystallise; anodic oxidation of this material gave a product homogeneous by TLC, but the IR spectrum of which indicated it to be the imine 257 contaminated with starting alcohol. Efforts to obtain pure imine failed. From the anodic oxidation of the phenolic sulphonamide 223, only starting material was isolated in spite of a high initial cell current; this was probably indicative of phenolic oxidation.

A series of phenoxyacetic acids 234 - 238 produced by standard methods (Scheme 34), were subjected to anodic oxidation at 1.4v and all except the pivaloyl derivative 238 cyclised smoothly to the corresponding spirolactones 239 - 242 in good yields. The amide 238 gave a red oil, the IR spectrum of which contained both lactone bands at 1800cm^{-1} and an amide peak at 3460cm^{-1} . Oxidation of the phenoxy-2,2-dimethylpropanoic acid 258 at the lower potential of 1.0v gave a negligible coulometric titration, and starting material was recovered.

The sulphonamidopropanoic acid 248 at a potential of 1.4v gave on average better than a 60% yield of sulphonimine 252 as a gum, but conversion of this to a crystalline solid with acceptable spectral and analytical properties lowered the overall yield to less than 20%. The corresponding sulphonyl derivatives 249, 250 and 251, returned starting material when oxidised at 1.0v.



Scheme 37



The sulphonamidobutanoic acid 261 produced a yellow oil, homogeneous by TLC, the IR spectrum of which indicated the presence of the desired product 262. However although a good yield was achieved, no crystalline solid could be formed.

The synthesis of the bis-sulphonamide 267 was attempted by several routes (see Experimental), the most successful being the method of Knipe et al.¹⁰⁹ Reaction of 2-aminoethanol with dimsyl anion, followed by addition of 4-nitrobromobenzene gave the phenoxyethylamine 263, but as attempts at purification of this failed, the substance was reacted in its crude state with tosyl chloride. However analysis of the product by NMR spectroscopy showed the desired product 264 often to be contaminated with the isomeric aniline derivative 265, produced by a Smiles rearrangement (Scheme 37); this type of rearrangement is well documented.¹¹⁰ The nitro ether 264 was easily reduced to the amine 266 which was converted to the bis-sulphonamide 267. Anodic oxidation of 267 at 1.2v gave a low yield of amorphous solid, which was shown by IR, NMR and mass spectroscopy to be the desired product 268 contaminated with a little unreacted starting material 267.

3.3.3 Conclusions from the Electrochemical Preparations of Cyclohexadienimines (3.3.2)

The following conclusions have been drawn from the work done in the preceding section (3.3.2) on the electrochemical preparation of a series of cyclohexadienimines.

(i) N-sulphonyl derivatives of para-substituted anilines can yield cyclohexadienimines under anodic oxidation conditions, and of the sulphonamides tested, those derived from 4-toluenesulphonic acid gave the best results. No evidence for analogous imine formation from N-acyl anilines was obtained.

(ii) Formation of 2,5-cyclohexadienimines occurs readily, but preparation of the corresponding 2,4-isomers from ortho-substituted anilines could not be achieved. This parallels the difficulty in preparing 2,4-dienones from

catechol derivatives.¹¹¹

(iii) The presence of an alkoxy-substituent para to the sulphonamide gives enhanced yields. This is consistent with the findings by Goosen⁸⁵ and is discussed in Section 3.1.

(iv) Compounds containing 5-membered spiro rings form more readily than those containing 6-membered rings. Similar results have been noted by Winstein⁷⁷ in his classic work on Ar_1-n reactions, in studies on spiro-Meisenheimer complexes,¹¹² and in work on the Smiles rearrangement.¹¹⁰

(v) Compounds which oxidised readily at a carbon felt anode to the corresponding imine failed to react at a platinum anode; a similar result has been observed in the oxidation of phenols.¹¹³

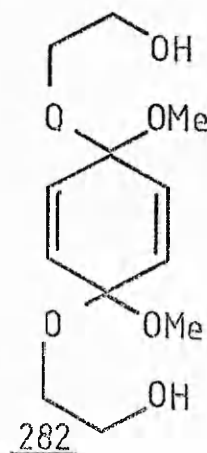
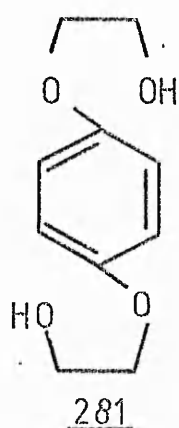
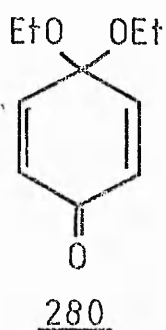
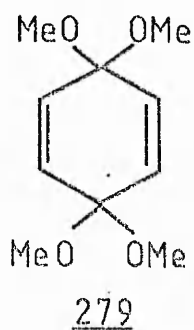
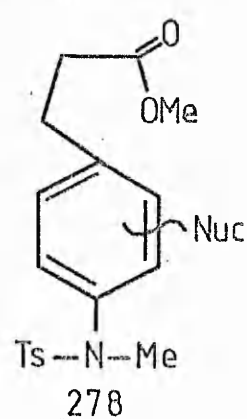
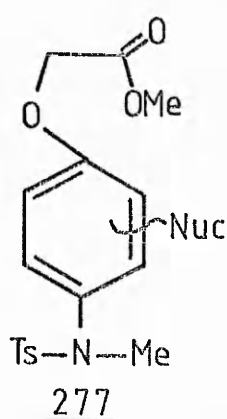
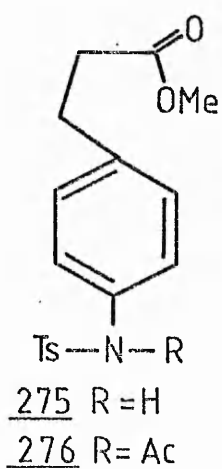
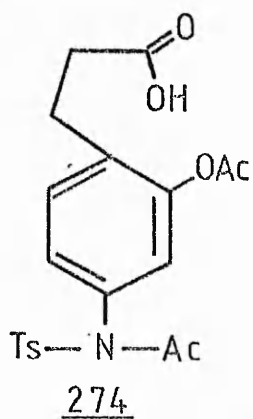
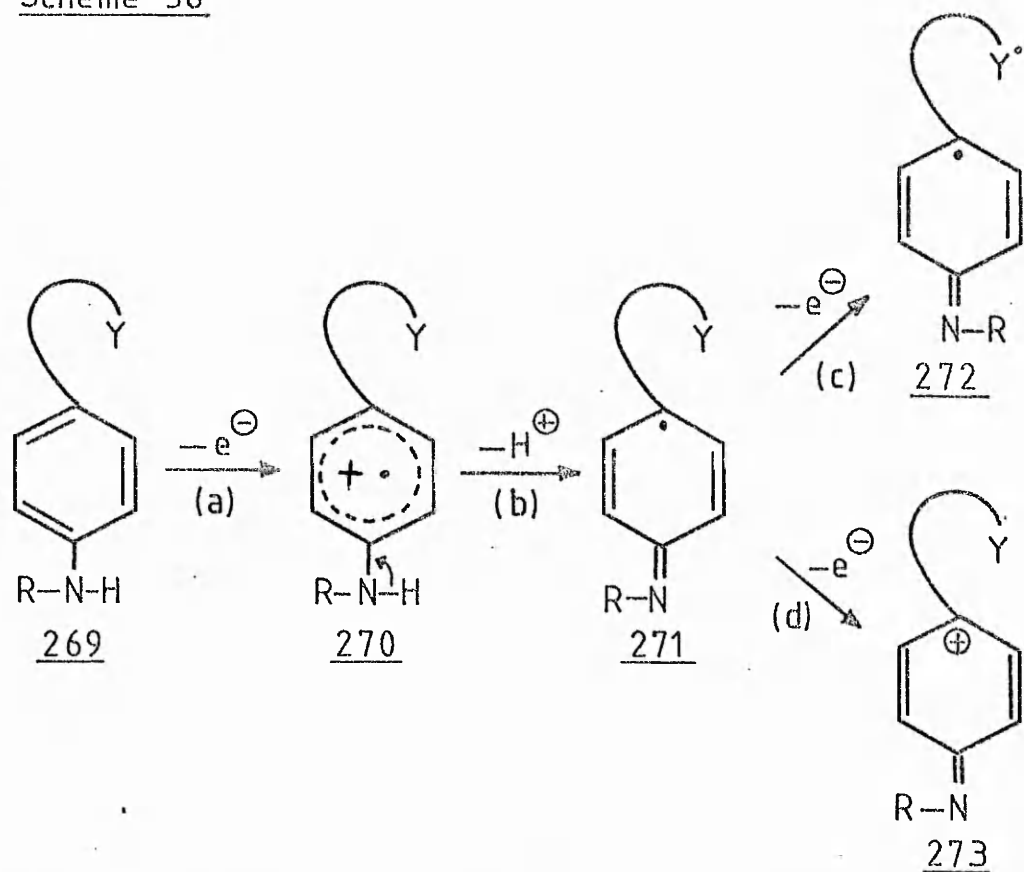
3.3.4 Mechanistic Discussion of the Preparation of Cyclohexadienones by Anodic Oxidation

The proposed mechanism for the electrochemical preparation of cyclohexadienimines is shown in Scheme 38 and is based on the following considerations.

(a) The mechanism for the oxidative methoxylation of phenols under anodic conditions has been elucidated in excellent work by Ronlan and co-workers.¹¹³ Using current-potential curves, it was shown that although methanol and phenol have somewhat similar discharge potentials, the rate of phenoxy radical formation far exceeds that of methoxy radicals, thought to be due to preferential adsorption of the unsaturated compounds onto the anode surface, so that there is a very low concentration of methanol in the double layer. The charge transfer from methanol to the anode is also much slower. Thus the first step in the anodic oxidation of phenols in the presence of nucleophiles involves the formation of a radical cation by the loss of one electron to the anode, and by analogy, this is also thought to be true for sulphonamides 269 giving the anilinium radical cation 270.

(b) With methanol acting as a base, deprotonation of the strongly acidic phenoxy radical cation is rapid and methoxylation of the cation is discounted.

Scheme 38



The sulphonamide radical cation 270 would also be expected to lose a proton under these circumstances to yield the radical 271. The removal of another electron from the cation 270 to give a dicationic species could only occur if higher potentials are being used, due to the extra energy required.

(c) An alternative route to a spirodienimine involves concurrent oxidation of both aromatic nucleus and side chain to give a diradical 272 which can then undergo intramolecular dimerisation. However, no product was obtained from 223 which contains the easily oxidised phenolic hydroxyl in the side-chain, while side-chain substituents such as alcohol and carboxylic acid, which do not oxidise at the anode potentials employed, give high yields of products. This route is therefore thought improbable.

(d) Thus the likelihood is that the uncharged radical 271 is anodically oxidised further to the full cation 273, and on repulsion from the double layer undergoes nucleophilic attack to give the imine products found.

3.4 Preparation of Spirocyclohexadienimines by Chemical Oxidation

Since the phenoxyethanol 212 had been converted in high yield by anodic oxidation to the spiroimine 213, it seemed a suitable substrate for investigating the possibility of the formation of such systems by chemical oxidation. Treatment of the ethanol 212 with several oxidants viz DDQ in methanol or benzene, iron/dimethylformamide complex,¹¹⁴ iron/dimethylsulphoxide complex,¹¹⁴ potassium ferricyanide, active manganese dioxide in toluene, gave virtually unchanged starting material. However reaction with lead tetraacetate in acetic acid at room temperature led to an almost quantitative yield of the desired imine. Lead tetraacetate was also effective in the production of 239 from the phenoxy acid 234. The dimethylpropanoic acid 258, which had not previously given the imine 259 on anodic oxidation, when treated with one molar equivalent of lead tetraacetate in acetic acid gave a product, the IR

spectrum of which indicated it to be a mixture of starting material 258, dienimine 259, and dienone 260; separation of this material was not attempted. The conversion of the phenylpropanoic acid 248 to the spiro lactone 252 in 40% yield was achieved after some initial difficulties. The butanoic acid 261 proved even more difficult to oxidise, confirming earlier findings that 5-membered spirocyclic rings are more easily produced than 6-membered ones; and although some spiro lactone 262 was found, it was heavily contaminated with starting acid. The action of lead tetraacetate on the bis-sulphonamide 267 also gave some spiroimine 268, but the yield was low and the presence of imine 268 in the reaction was deduced by IR and NMR spectroscopy.

3.5.1 Attempted "dienone-phenol" Rearrangement of 252

Although treatment of the imine 252 with 0.5M sulphuric acid led to an inseparable mixture of products, the use of acetic anhydride-boron trifluoride⁶¹ gave an acidic yellow oil, homogeneous by TLC, which was shown by IR and NMR spectroscopy to be the bis-acetylated compound 274, analogous to products obtained by the rearrangement⁶¹ of 102 (see Section 1.3). In support of this structure, the corresponding methyl ester 275 was shown to become N-acetylated in high yield to the amide 276 when treated with acetic anhydride-boron trifluoride.

3.5.2 Hydrolysis of N-Sulphonylimines to the Corresponding Dienones

Attempts to hydrolyse imine 252 to the dienone 102 by heating in a variety of water-solvent mixtures gave inconclusive results. However when 213 was passed down a Grade III alumina column in toluene, the crystalline dienone 214 was eluted in 68% yield; further elution with ether gave 4-toluenesulphonamide. When this hydrolysis technique was applied to the spiro lactone 239, only benzoquinone was isolated. This is doubtless because the initially

formed spirodienone 244 is very susceptible to hydrolysis.¹¹⁵ The hydrolysis of imine 252 by alumina was carried out in chloroform; using this solvent toluene-4-sulphonamide eluted cleanly before the dienone 102 which could then be obtained free from contamination. Similar treatment of N-mesyl derivative 205 gave a quantitative conversion to the dienone 208.

3.5.3 Reaction of Spirodieniminolactones with Nucleophiles

In preliminary experiments to test the validity of the Schemes 1 and 40 the two iminolactones 239 and 252 were each treated in DMF solution with one equivalent of potassium iodide or potassium cyanide, and the bicarbonate soluble fraction of the crude products reacted with diazomethane. Examination of the resulting gums by mass spectroscopy showed that in all four cases the nucleophile (cyanide or iodide) had attacked the diene system, with expulsion of the carboxylate leaving group, and that rearomatisation of the ring had occurred leading, after diazomethane, to products 277 and 278. However due to the lack of time no further spectral data or purification was achieved.

3.5.4 Attempted Selective Reduction of the Imine Bond

Attempted selective reduction of the imine bond in the spiroketal 213 by sodium borohydride in ethanol, aqueous sodium dithionite, or zinc and acetic acid led in every case to a reductive hydrolysis of the ketal 213 to the starting phenoxyethanol 212.

3.5.5 Attempted Transketalisation of Dimethoxycyclohexadienimines

It has been shown that reaction of the dimethyl ketal 208 with thallium (III) nitrate¹⁰³ in ethanol leads to the corresponding diethoxy derivative 280, while Margaretha and Tissot¹¹⁶ have demonstrated the formation from 281 of the bis-ketal 283 in methanol proceeds via the mixed ketal 282 followed

by transketalisation. However treatment of the dimethoxysulphonylimine 204 with ethanediol containing boron trifluoride at room temperature, yielded only p-anisidine 192. No trace of the desired cyclic species 213 was obtained.

CHAPTER FOUR

Attempted Synthesis of Spirolactones from Tetrahydroisoquinoline-1-carboxylic Acids

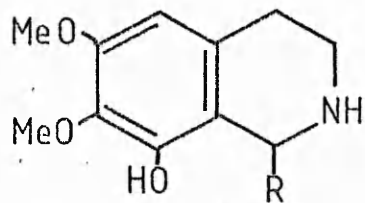
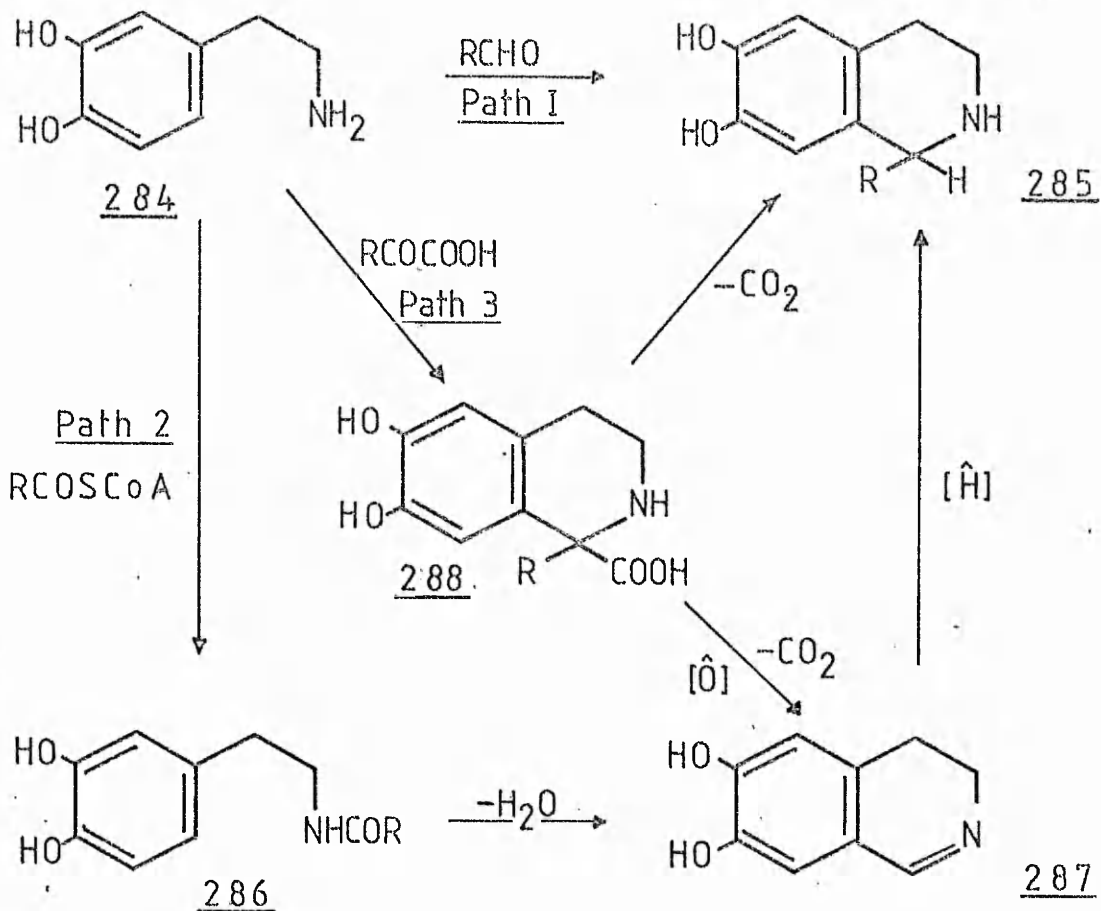
4.1 The Significance of Isoquinoline-1-carboxylic Acids in the Biosynthesis of Isoquinoline Alkaloids

A key step in the in vivo formation of isoquinoline alkaloids^{117,118} is the condensation of a β -phenethylamine derived from either L-tyrosine or L-dopa, with the appropriate carbonyl compound. The exact nature of this carbonyl moiety is uncertain and three different theories have been proposed (Scheme 39).

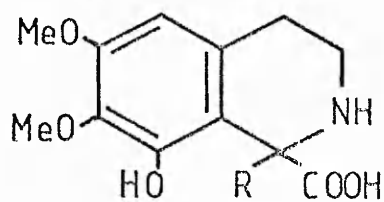
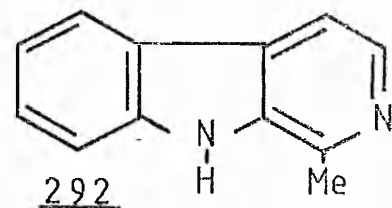
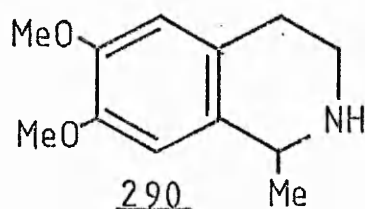
In 1911, Pictet and Spengler¹¹⁹ suggested that the source of the C₁ atom of tetrahydroisoquinolines was a simple aldehyde (Scheme 39 Path 1 284-285). Under physiological conditions β -phenethylamines were condensed with formaldehyde to give anhalamine-type 289 alkaloids,¹¹⁹ with acetaldehyde to give salsolidine-type 290 alkaloids,¹²⁰ and with substituted phenylacetaldehydes to give 1-benzylisoquinolines.¹²¹ However aldehydes are generally regarded as being too reactive to be readily available in plants, and thus there is little evidence¹²² in support of this mechanism. It has also been shown¹²³⁻¹²⁵ that dopa is only incorporated in the phenethylamine half of 1-benzylisoquinolines, but if the necessary phenylacetaldehyde was derived from dopa via dopamine and a deamination reaction, incorporation into the bottom half of the molecule should also occur.

A second mechanism¹²⁶ involving initial acylation of β -phenylethylamine 284 followed by cyclisation of the resulting amide 286 to give dihydroisoquinoline 287 has also been proposed (Scheme 39 Path 2 284-287). With acetylcoenzyme A as the acylating agent, salsolidine-type alkaloids 291 would result, but only one example¹²⁷ has so far been recorded. There is also accumulating evidence¹²⁸⁻¹³¹ of deacylation prior to cyclisation in several other alkaloids, which casts increasing doubt on this mechanism.

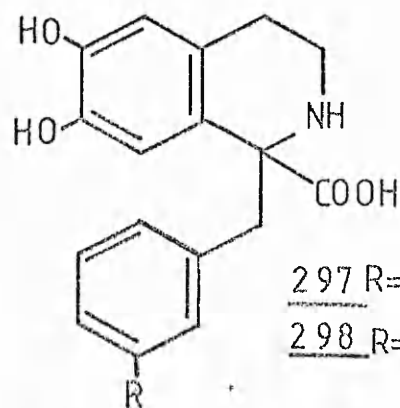
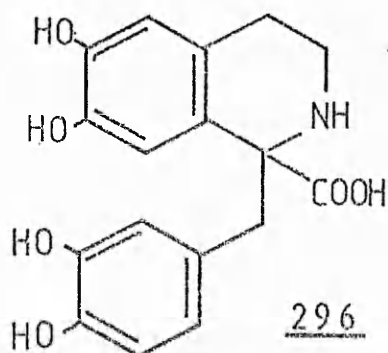
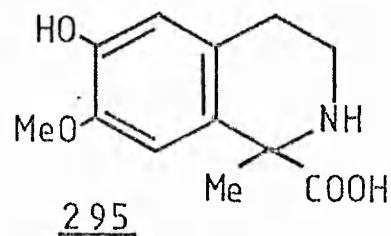
Scheme 39



291 R=Me



294 R=Me



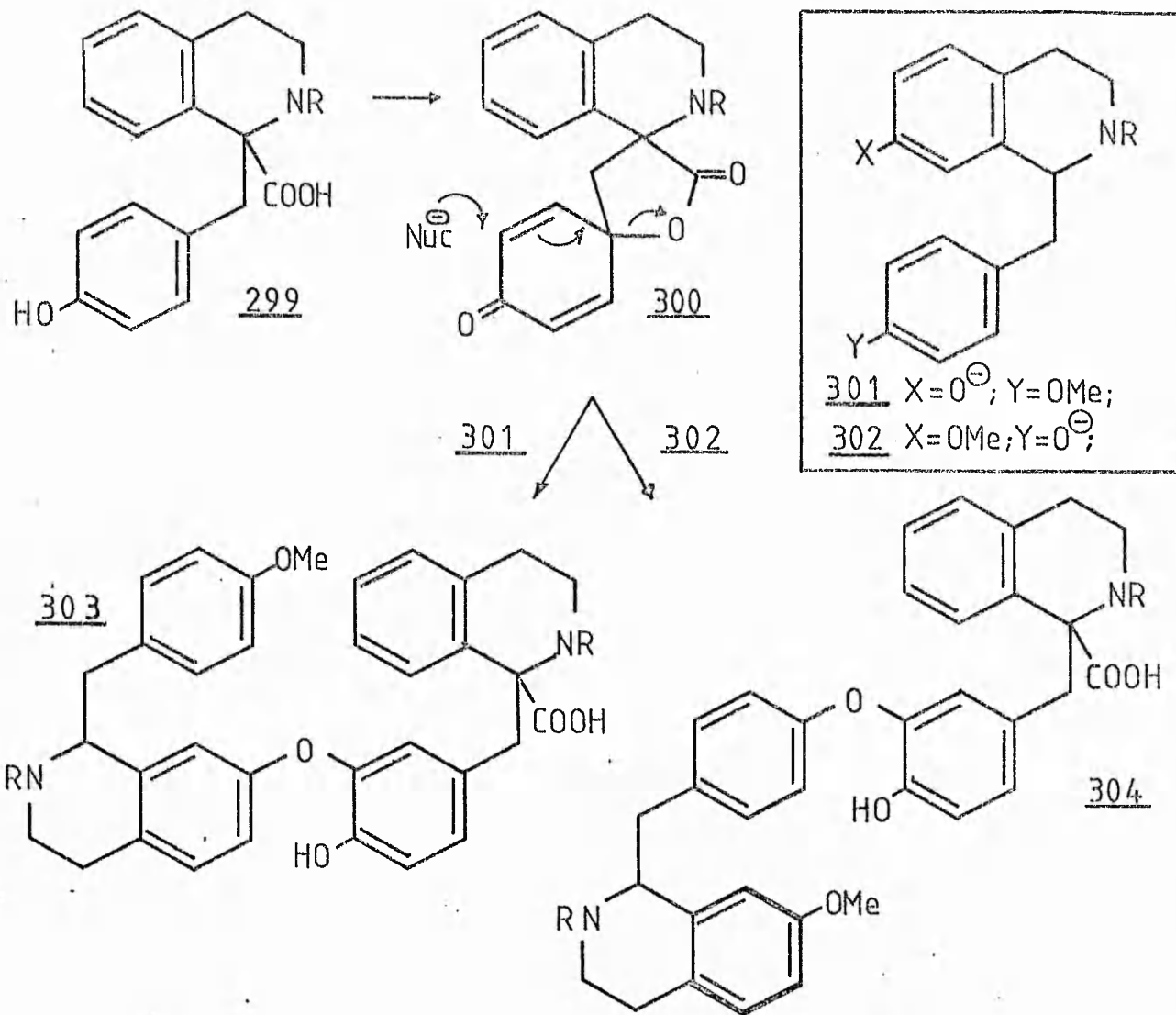
298 R=OMe

A third, and currently most favoured theory, was proposed by Hahn.¹³² He suggested (Scheme 39 Path 3) that the condensation of a β -phenethylamine 284 with an α -ketoacid gave an intermediate tetrahydroisoquinoline-1-carboxylic acid 288 which, depending on the type of decarboxylation, would lead to either di- or tetrahydroisoquinolines 287 or 285. This mechanism was originally rejected^{132,133} due to failure to decarboxylate the acid *in vitro* under mild (physiological) conditions. However it has recently been demonstrated that these acids can readily be decarboxylated to the corresponding 3,4-dihydroisoquinolines by low potential anodic oxidation,¹³⁴ by prolonged aerial oxidation in basic media,¹³⁵ and by the enzymes horseradish peroxidase and laccase.¹³⁶ Other evidence includes the fact that pyruvate is an efficient precursor of both the peyote alkaloid^{126,129} anhalonidine 291, and the β -carboline alkaloid^{137,138} harmine 292. Peyoxylic 293 and peyoruvic acids 294 have been detected^{126,139} in peyote cacti and have been shown¹²⁸ to be precursors of alkaloids anhalonidine 289 and anhalamine 291. Also the isoquinoline-1-carboxylic acid 295 is a precursor^{130,131} of salsolidine 290, whilst acid 296 is incorporated into norlaudanosoline,¹⁴⁰ morphine,¹⁴¹ and reticuline.¹²⁵

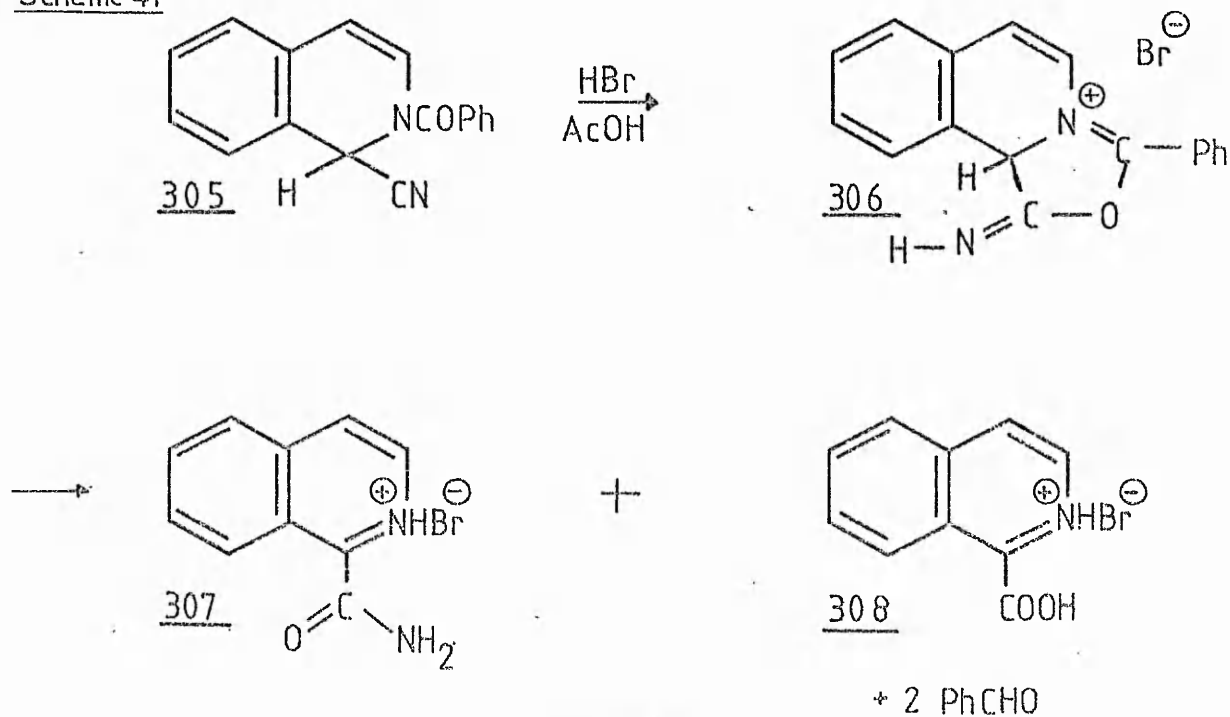
It is of interest that patients suffering from Parkinsonism, who have been treated¹⁴² with L-dopa, accumulate 3'-O-methylnorlaudanosolinecarboxylic acid 298, in their urine, while children with the metabolic disorder phenylketonurea secrete urine containing 3',4'-deoxynorlaudanosolinecarboxylic acid 297.

Since isoquinoline-1-carboxylic acids are now proven intermediates in the biogenesis of benzylisoquinolines, there is the possibility that they are also implicated in the formation of bisbenzylisoquinolines. It may be that acids 299 bearing a 4-hydroxyl substituent on the benzyl residue can oxidise to the spirolactone 300 which could perhaps undergo nucleophilic attack as proposed in Schemes 1 and 40. If the nucleophile were the anion of a 4'-hydroxybenzylisoquinoline 302, the product would be a "tail-to-tail" coupled dimer, 304, while attack by the anion of a 7-hydroxybenzylisoquinoline 301

Scheme 40



Scheme 41



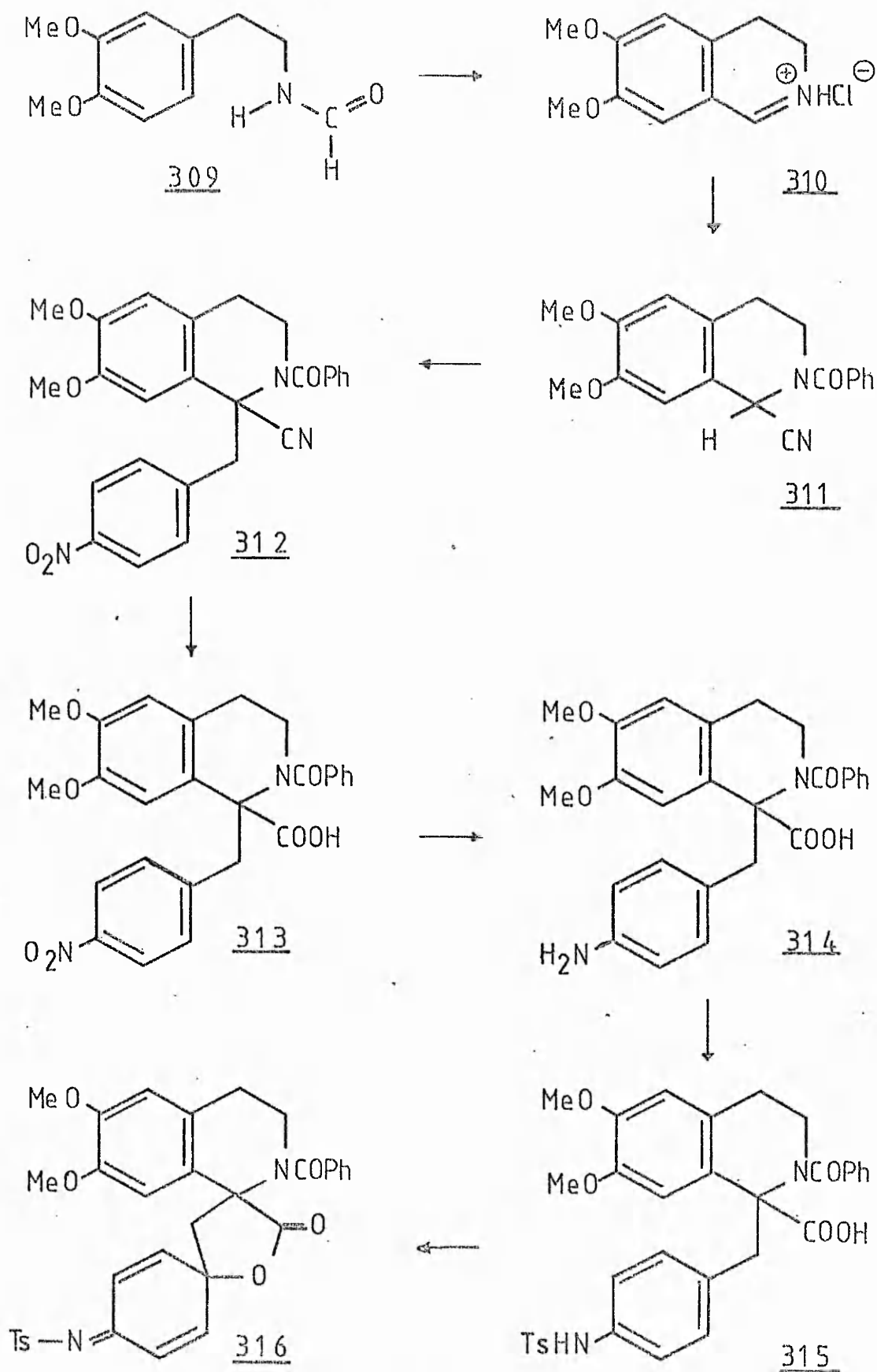
would result in the formation of a "head-to-tail" product 303. Even if this route to dimeric isoquinolines proves not to be biosynthetically significant, it offers an alternative NOC approach to molecules at present difficult to synthesise. Oxidative coupling of benzylisoquinolines leads preferentially to "head-to-head" linkage of the isoquinoline moieties by 7-8 ether bonds, and is well documented.³² The coupling of isoquinolines via 1-benzyl residues is more difficult to bring about by phenol oxidation,¹⁴³ while the only report of "head-to-tail" coupling,¹⁴⁴ involving the enzymatic oxidation of a 1-phenethyl-isoquinoline, relies on rather flimsy spectroscopic evidence.^{145a} Compounds of the type 303 and 304 are usually prepared by rather laborious Ullmann procedures.^{145b}

4.2 Synthesis of Isoquinaldic Acids 315 and 321

The synthetic sequence leading to the isoquinaldic acid 315 is shown in Scheme 42. Pyrolysis of the formate salt of β -3,4-dimethoxyphenylethylamine¹⁴⁶ gave the formamide 309 which could not be induced to crystallise but which had the expected spectral properties. Bischler-Napieralski cyclisation¹⁴⁷ of the amide 309 with phosphorus oxychloride in toluene produced the dihydroisoquinoline 310 in moderate yield; the use of phosphorus pentachloride in the cyclisation gave an unidentified compound rather than the required isoquinoline.

Reaction of the amine 310 with potassium cyanide and benzoyl chloride in a two-phase (water/methylene chloride) system^{148,149} afforded the dihydro Reissert compound 311 in 55% yield, but attempts to produce Reissert compounds on a large scale were not successful. Alkylation of 311 with 4-nitrobenzyl-bromide under phase-transfer conditions¹⁵⁰ gave the substituted Reissert 312 in excellent yield. Although it has been reported¹⁴⁸ that dihydro Reissert compounds heated with 85% phosphoric acid produce isoquinaldic acids, compound 312 gave a complex mixture of products under these conditions. However treatment of 312 in glacial acetic acid with concentrated hydrochloric acid¹⁵¹

Scheme 4.2



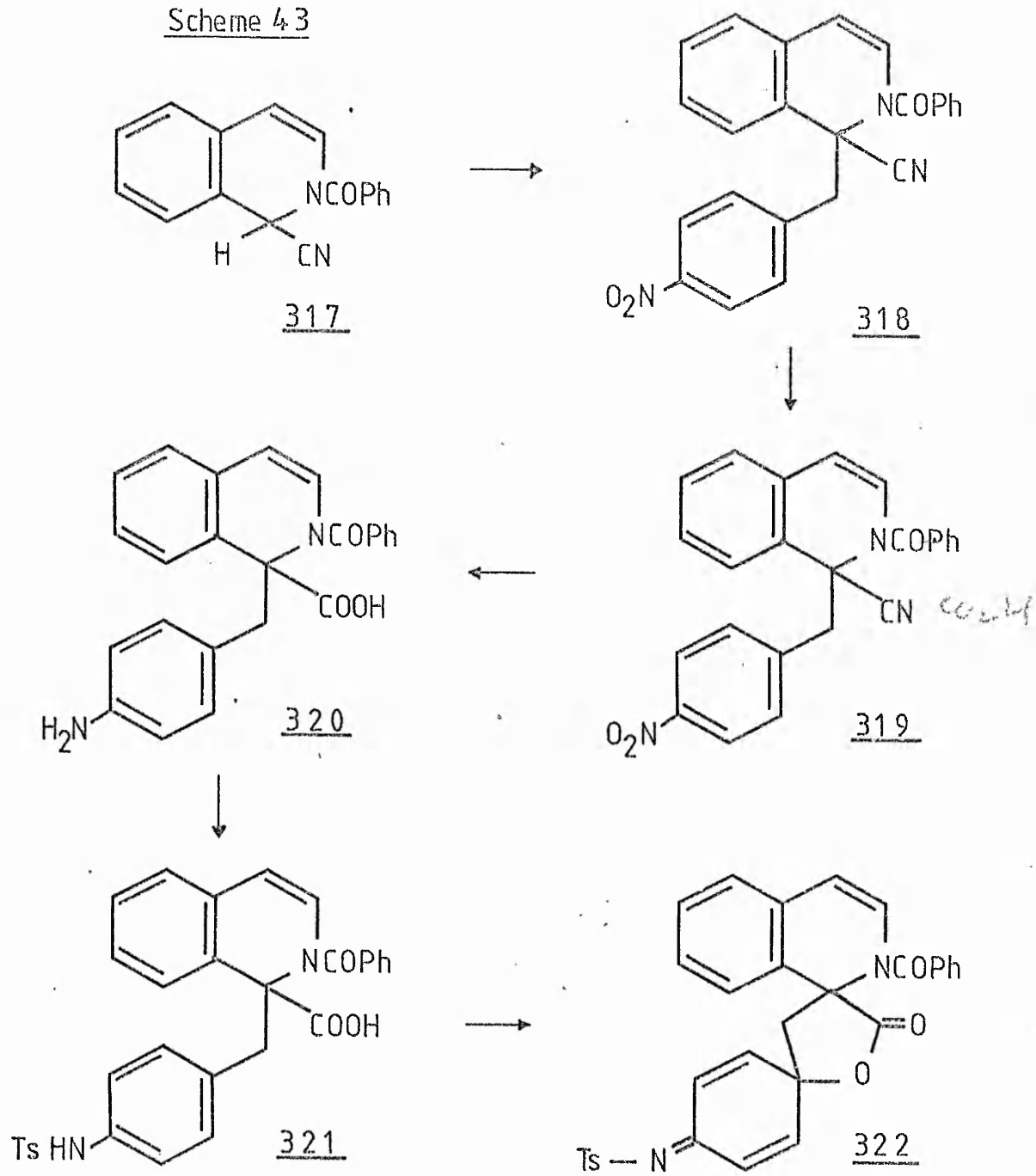
caused preferential hydrolysis of the nitrile to the amido-acid 313. This fortuitous result is particularly surprising since it is reported¹⁵² that reaction of dihydro Reissert compounds with hydrobromic acid in acetic acid yields the iminium bromide 306 which undergoes further hydrolysis to the amide hydrobromide 307 and acid hydrobromide 308, (Scheme 41). The nitro group in 313 was smoothly reduced by room temperature reaction with zinc dust in glacial acetic acid under a nitrogen atmosphere to the amino acid 314. Since purification of the amino acid 314 proved difficult, it was used in its crude state to prepare the dimethoxysulphonamide 315 which recrystallised from methanol.

The attempted synthesis of the unsaturated acid 321 from isoquinoline followed the same pathway (Scheme 43). Conversion of isoquinoline to its Reissert derivative 317 with subsequent phase-transfer alkylation to 318 and hydrolysis to 319 proceeded as for the dihydro compound, but it proved impossible to purify either the amine 320 obtained from reduction of the nitro compound 319, or the sulphonamide 321 derived from 320 (See experimental).

4.3 Oxidation of Isoquinaldic Acid 315

The initial attempts at anodic oxidation of the dimethoxy-acid 315 were undertaken in acetonitrile, using a carbon felt anode, platinum cathode, and TEAP as added electrolyte. At the lower potentials of 1.0v an approximate two electron oxidation appeared to be occurring, with a good recovery of fawn solid. Increasing the potential to 1.4v gave a larger current, and an approximate four electron oxidation, yielding a brown solid. Examination of both sets of products by TLC revealed them to be mixtures, but with some discrete higher R_f material in the case of the 1.0v oxidation. NMR spectra of the crude products showed little detail, and attempts to obtain pure products failed. Mass spectra of some of these products showed only breakdown fragments, with a large peak at m/e 311 common to all. The oxidation products

Scheme 43



regularly showed several IR peaks in the 1750-1630 carbonyl region, but these tended to be broad and ill defined. However the low potential product did, on one occasion, show a medium 1550cm^{-1} peak, but little or no 1800cm^{-1} absorption characteristic of the lactone carbonyl.

Anodic oxidation of 315 in methanolic solution at 1.3v gave a mixture which could not be separated nor characterised.

Only starting material was obtained from the attempted oxidation of 315 with lead tetraacetate.

4.4 Conclusions

Clearly the oxidation of 315 does not proceed smoothly to the corresponding spiro lactone 316. The many IR carbonyl absorptions of the product from the higher potential oxidations may indicate either benzylic oxidation or the formation of a dienone-type system from the methoxylated benzene ring. However conflicting data resulting from the presence of more than one product made identification impossible. The anodic oxidations in methanol, carried out in the hope that benzylic oxidation would yield the dimethyl ketal instead of the carbonyl function, gave a complex mixture of products and proved useless. The only encouraging indication of sulphonylimine production came from the low potential, low current, anodic oxidation in acetonitrile, where an IR peak at 1550cm^{-1} was detected in the spectrum of the crude product.

A repeat of this work using the less bulky, potentially more reactive N-methanesulphonyl derivative may prove more productive.

Due to the failure to produce any isoquinoline spiro lactones, the nucleophile work planned could not be carried out.

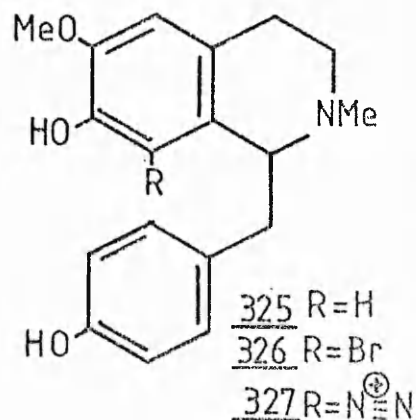
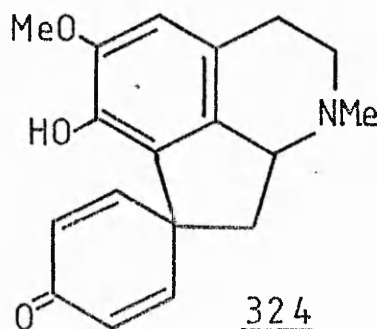
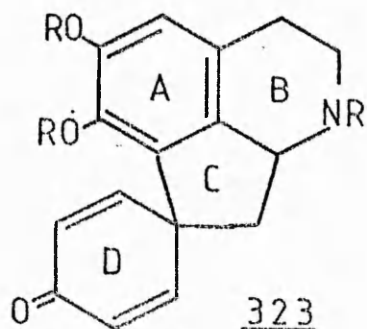
CHAPTER FIVE

Attempted Synthesis of a Proaporphine Related to Glaziovine

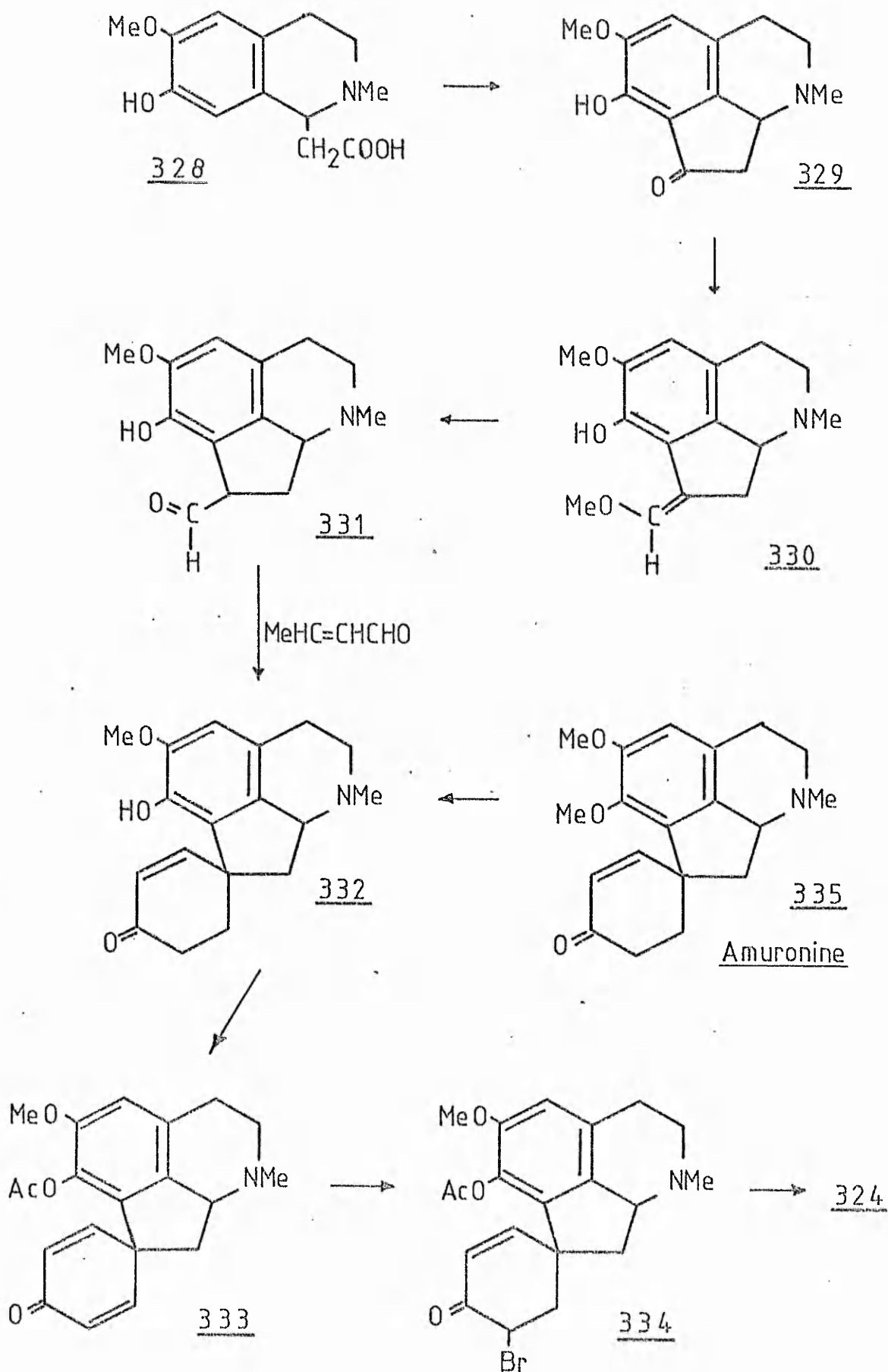
5.1 The Alkaloid Glaziovine

The proaporphine¹⁵³⁻¹⁵⁸ alkaloids 323 are precursors of the pharmaceutically and chemically interesting aporphine alkaloids, and have been isolated from an increasing number of plant species. The general formula and numbering is shown in 323, although ring D may occur in a variety of oxidation states. Synthetic efforts in the proaporphine series have mainly concentrated on efficient ways of obtaining (+) glaziovine 324 which has a promising potential as a tranquillizer.¹⁵⁹

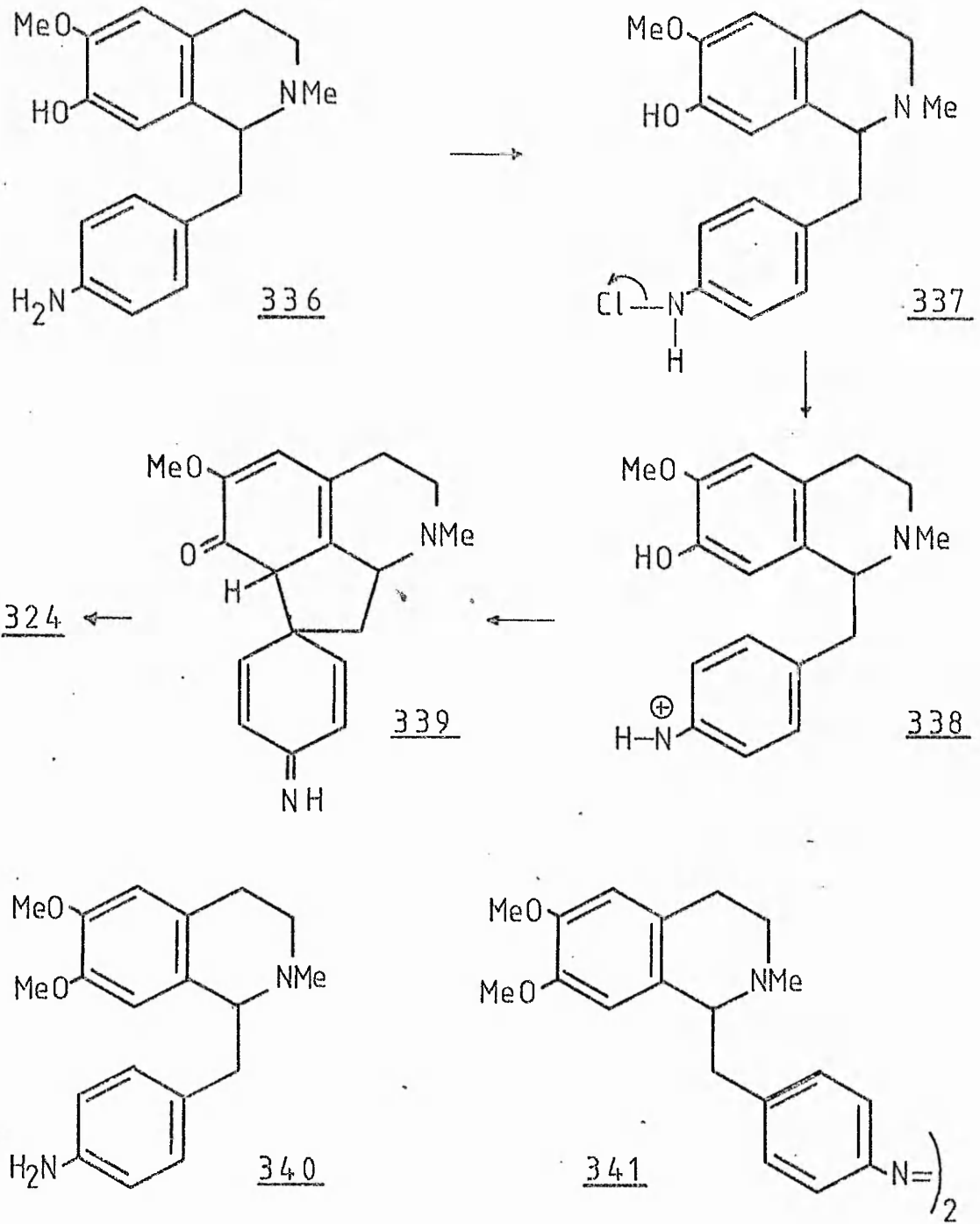
Glaziovine 324 was proposed by Barton and Cohen¹⁵ as an intermediate in the oxidation of N-methylcoclaurine 325 to the corresponding aporphine, several years before its isolation.⁵⁶ Attempts¹⁶⁰ at in vitro phenolic coupling of 325 to 324 have given a very low (1-2%) yield of proaporphine, and better results are achieved by photolysis of the 8-bromo^{161,162} or 8-diazo¹⁶² isoquinolines, 326 and 327, giving proaporphine yields of 26 and 45% respectively.



Scheme 44



Scheme 45



An alternative approach to 324 involves¹⁶³ building the fourth D ring onto a tricyclic ketone by a Bernauer-type¹⁶⁴ synthesis (Scheme 44), giving 11,12-dihydroglaziovine 332. O-acetylation to 333, followed by selective bromination gave 334, which on dehydrobromination and deacetylation yielded glaziovine 324 in 60-64% yield. In a modification¹⁶⁵ of this scheme, the intermediate 332 is obtained by selective demethylation of amurone 335, which is more readily prepared by the Bernauer method.

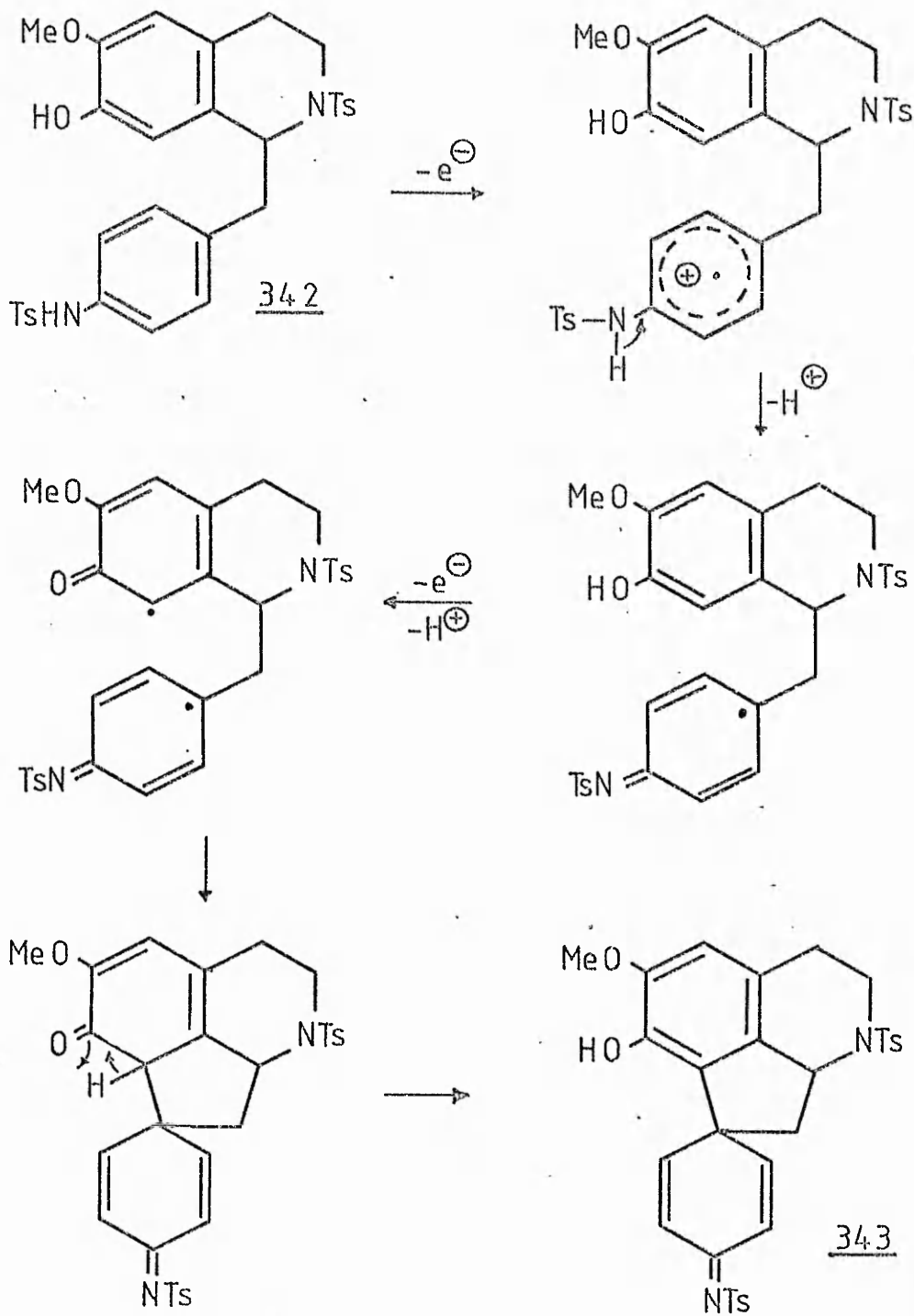
A novel approach by Kametani *et al*¹⁶⁶ involved the use of a benzylisoquinoline in which the 4'-hydroxy substituent of N-methylcoclaurine 325 is replaced by an amino group 336. It was envisaged that use of sodium hypochlorite might generate the N-chloro derivative 337, and hence the nitrenium cation 338, which would undergo C₈-C₁ coupling (Scheme 45). Although no trace of the imine 339 was found, a small amount (1%) of glaziovine 324 was detected; when the dimethoxy analogue 340 was used only the azo compound 341 was isolated.

5.2 Synthesis of the 4-Tosylamidobenzylisoquinolines 365 and 342

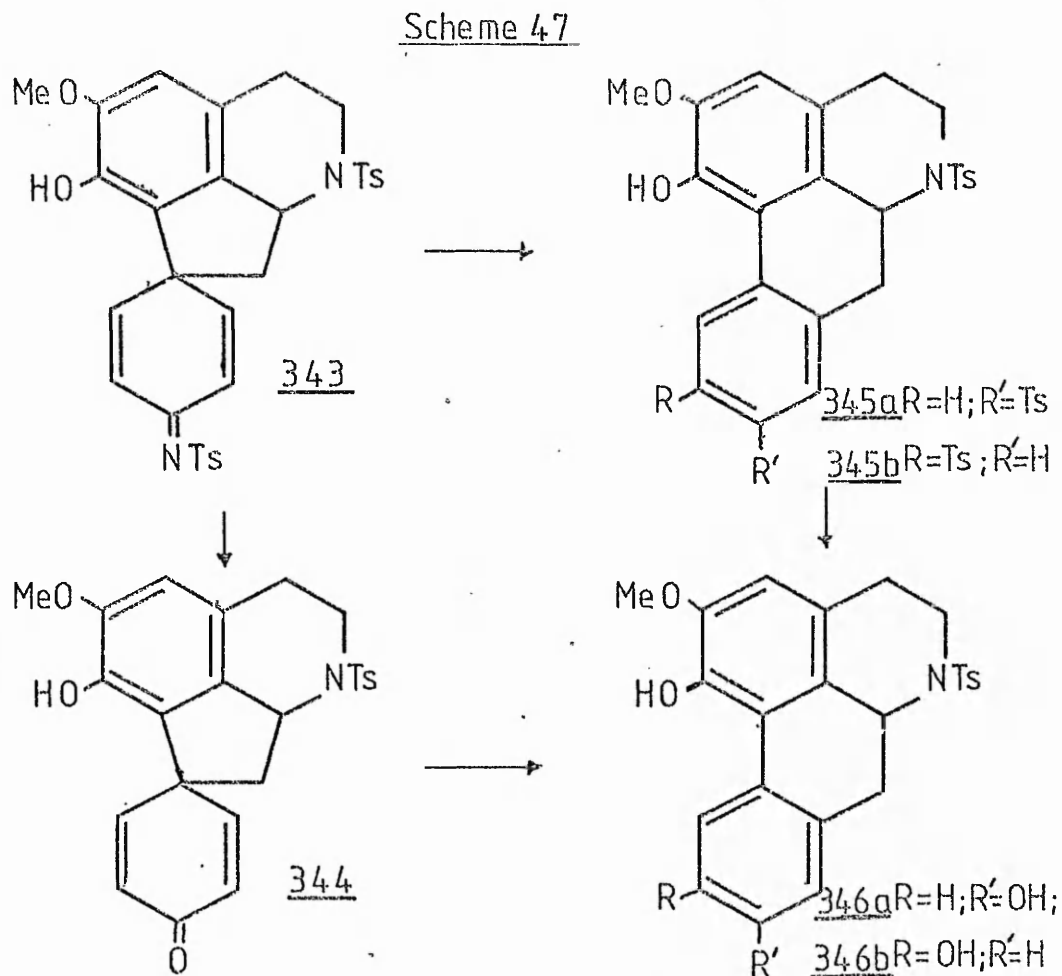
Although the results of the nitrenium approach to glaziovine were disappointing,¹⁶⁶ the lack of good routes to this compound, and the promising results obtained by oxidation of sulphonamides (Chapter Three) prompted an investigation of the approach to the proaporphine outlined in Scheme 46. The use of tert-butyl hypochlorite and silver trifluoroacetate to generate the nitrenium ions favoured by Kametani, was not thought promising due to low yields and chlorinated impurities produced during previous studies (3.2.2).

Although unsuccessful attempts had already been made to oxidise a sulphonamidobenzene moiety in the presence of a phenolic oxygen nucleophile (Chapter Three), it was hoped that the hitherto untried nucleophile, a carbon *ortho* to a phenolic hydroxyl, might undergo C₈-C₁ coupling (Scheme 46):

Scheme 46

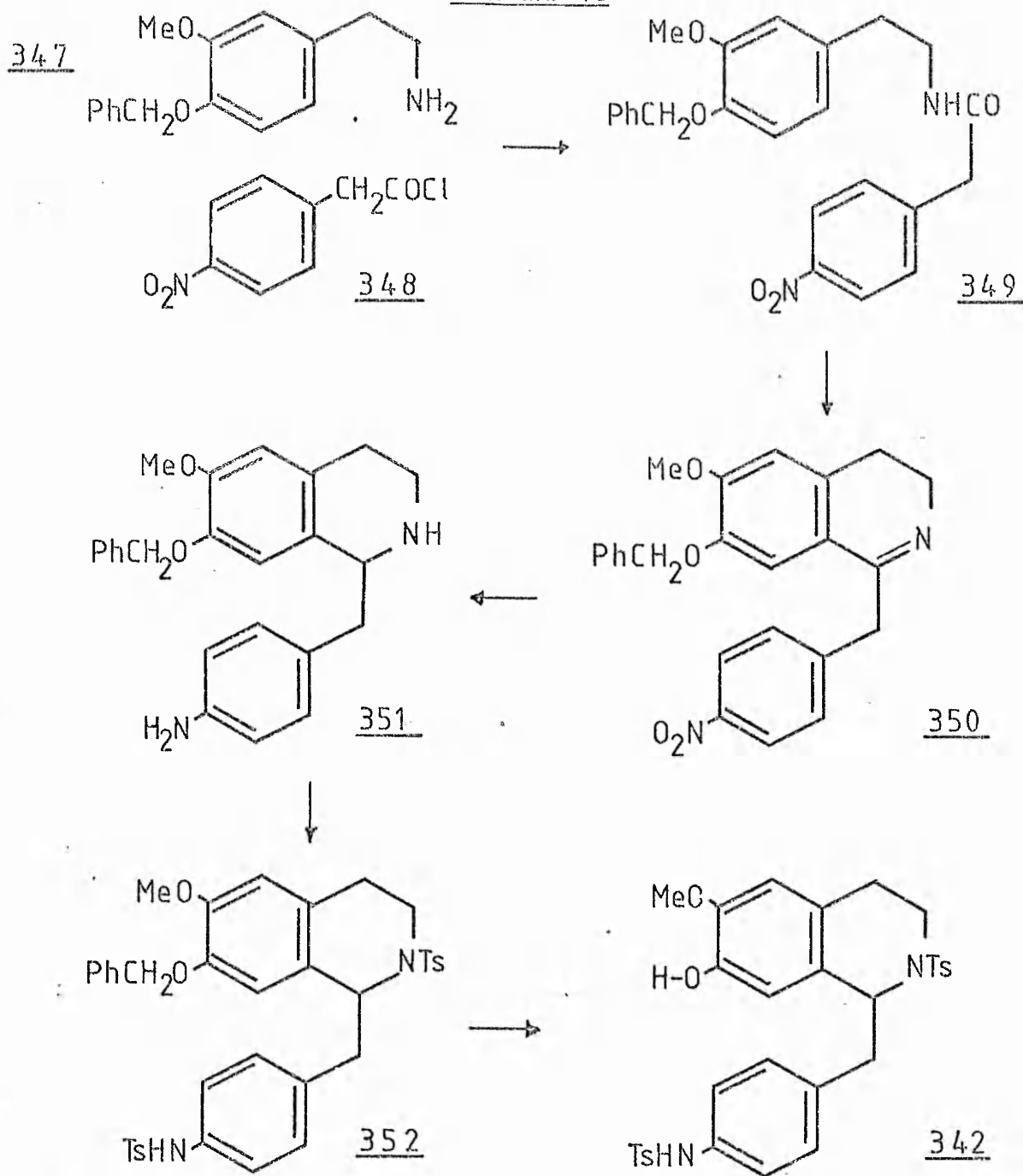


Should this oxidation occur then hydrolysis of the 'proaporphine-type' sulphonylimine 343 (3.5.2) would yield a glaziovine-type dienone 344 which should rearrange to the aporphine 346. Initial rearrangement of 343 to 345 followed by hydrolysis could also be considered as a route to 346 (Scheme 47).

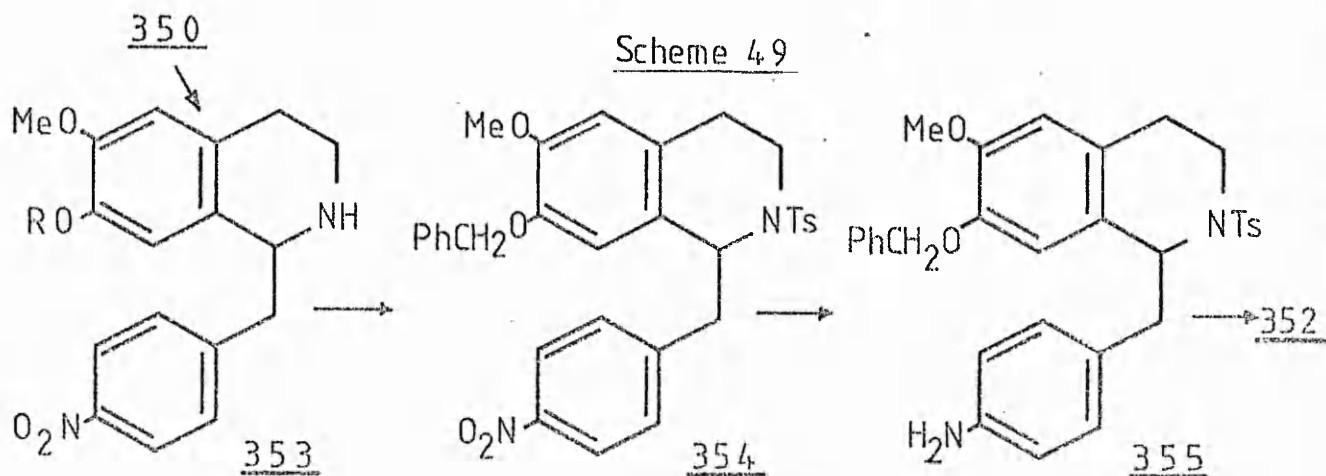


The use of the dimethoxyisoquinoline 365 as a glaziovine precursor was also considered, as it would not undergo intermolecular phenolic coupling, but might be efficient in intramolecular coupling processes; the use of alkoxybenzenes in such reactions is well documented. ¹⁶⁷⁻¹⁷³

Scheme 48



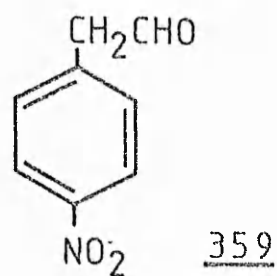
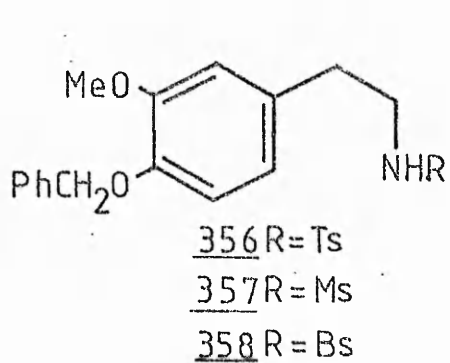
Scheme 49



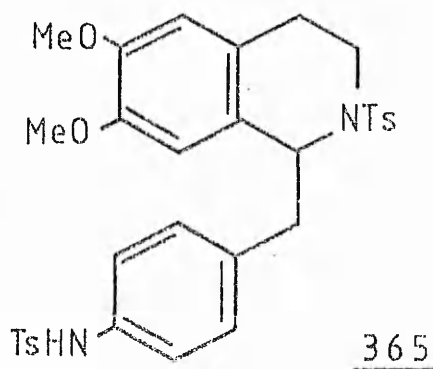
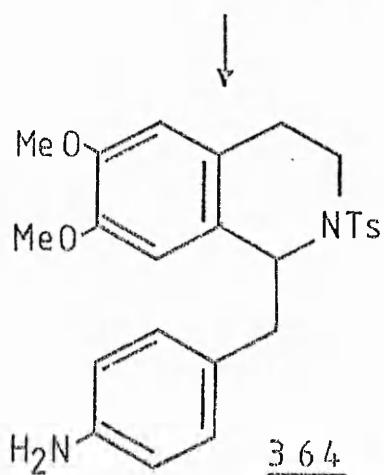
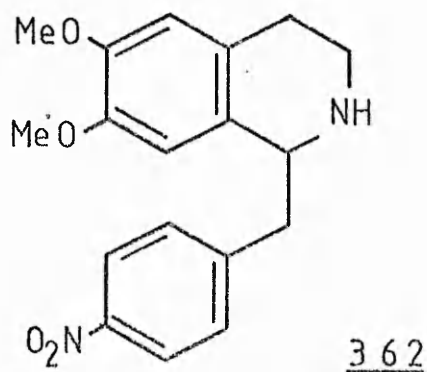
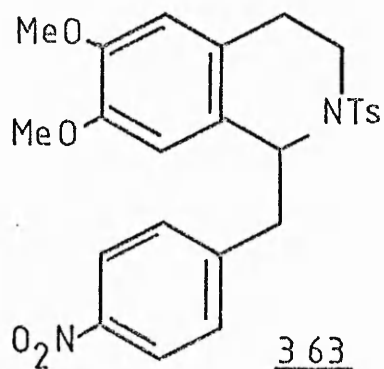
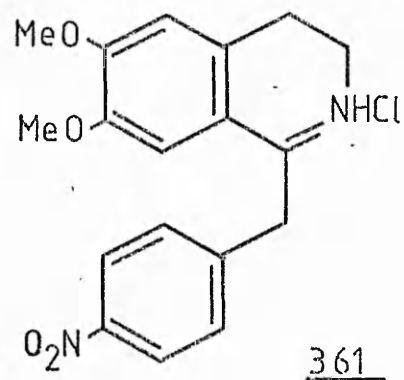
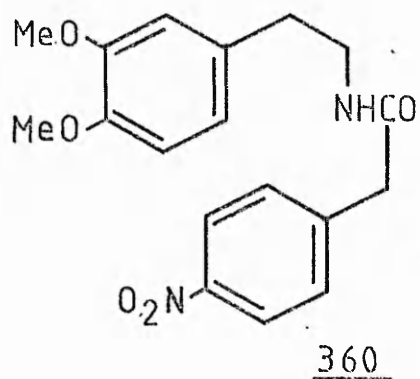
The initial route to 342 is shown in Scheme 48. β -(7-Benzyloxy-6-methoxyphenyl)ethylamine 347 was coupled under basic conditions with 4-nitrophenylacetyl chloride 348, to give the corresponding amide 349 which by Bischler-Napieralski cyclisation with phosphorus pentachloride afforded the hydrochloride of the dihydroisoquinoline 350 in good yield. Several attempts at concurrent reduction of both nitro and imine groups using zinc-acetic acid under a nitrogen atmosphere yielded a brown solid, TLC and spectral examination of which indicated that although the nitro group had been reduced to the desired primary amino function, reduction of the imine was incomplete. All attempts at purification failed and this route to 342 was abandoned.

Smooth selective reduction of the imine 350 with sodium borohydride gave in good yield the tetrahydroisoquinoline 353, which was converted to the sulphonamide 354 (Scheme 49). The easy reduction of the nitro group with zinc and acetic acid, gave high yields of the amine 355, which although homogeneous by TLC, was impossible to recrystallise, and in crude form was reacted with tosyl chloride. Recrystallisation of the bis-sulphonamide 352 also failed, even though TLC and spectral data indicated a fairly pure product. An analytical sample prepared by column chromatography gave poor results. Debenzylation also proved difficult, but by using 10% palladium on charcoal weight for weight with the substrate, effective debenzylation to the free phenol 342 was finally achieved. Although recrystallisation of 342 also failed, TLC and spectral data was in accord with the desired product; an analytical sample prepared by column chromatography gave satisfactory results.

A recently reported variation¹⁷⁴ of the Pictet-Spengler condensation, involving N-sulphonylphenylethylamines and aldehydes, seemed a convenient route to the nitrobenzylisoquinoline 354. The sulphonamides 356, 357 and 358 were readily prepared as crystalline solids, but the preparation of



Scheme 50



4-nitrophenylacetaldehyde 359, presented problems. Oxidation of 4-nitrostyrene with lead tetraacetate in trifluoroacetic acid¹⁷⁵ gave only a low yield of the aldehyde, which proved difficult to purify, and although it condensed in high yield with the sulphonamide 356 to give 354, this approach to N-sulphonyl-isoquinolines was not pursued.

The dimethoxyisoquinoline 365 was synthesised by the path shown in Scheme 50, which closely follows the successful route to 342.

5.3 Oxidation of the Sulphonamidoisoquinolines 342 and 365

The phenolic isoquinoline 342 was anodically oxidised at potentials between 0.9-1.1 volts in both acetonitrile and methanolic solutions. In acetonitrile the lower potential oxidation products were fawn in colour, turning dark purple as the potential increased; a good recovery of solid product was always achieved. Examination by TLC of the 1.0v oxidation product of 342 showed mainly two spot material, but attempted isolation of these components by preparative-layer chromatography was not successful. The IR spectrum of the crude product showed peaks at 1740, 1640, 1630 cm^{-1} , indicating the presence of a variety of carbonyl functions. The mass spectral results showed a mass ion at 577 (possibly a demethylated species derived from the proposed imine 343), together with a complex pattern of less intense peaks. The NMR spectra of such impure and complex material were uninformative. Coulometric determinations indicate oxidations occurring of between two and four electrons. No conclusive evidence of imine formation was found.

The dimethoxyisoquinoline 365 gave cleaner results on oxidation than either 342 or the isoquinaldic acid 315. Close approximation to four electron oxidations of 365 were achieved at potentials of 1.25v in acetonitrile and 1.2v in methanol. TLC of the products from oxidations in acetonitrile showed mainly baseline material even when fairly polar solvents were employed.

Although attempts at purification failed, the IR spectra of crude product showed strong absorptions in the $1700\text{-}1600\text{cm}^{-1}$ carbonyl region, but no imine peak at 1550cm^{-1} was observed. The NMR spectrum again proved of little value, while the mass spectrum showed a large peak at 332, but as the parent ion for the proposed imine should have a mass number of 606, the breakdown patterns were meaningless. The oxidations in methanol proved very complex yielding mixtures which could not be separated and was thus abandoned.

5.4 Conclusions

The two main problems appear to be the impurity and complexity of the starting materials, and the presence of a phenolic group in the isoquinoline.

Although the N-4-toluenesulphonyl derivatives of the low molecular weight anisidines gave optimum results in the preparation of N-sulphonylimines (Chapter Three), the more reactive methanesulphonyl moiety might prove a more suitable derivative for the higher molecular weight isoquinolines. The reduction in both size and molecular weight should allow recrystallisation of intermediates leading to homogeneous starting materials thus reducing the possible side reactions. The NMR spectra of products would be greatly simplified in the aromatic region, facilitating their identification.

The oxidation of the phenolic isoquinoline 342 gave a complex mixture, from which little could be deduced. Oxidation did occur but species other than the desired product formed, leading to material, the IR spectrum of which showed absorption in the carbonyl region. The dimethoxyisoquinoline 365 underwent a four electron oxidation in acetonitrile, but again a proaporphine was not produced, although carbonyl-containing compounds did appear to be formed.

The use of anodic oxidation in methanol for both substrates in an attempt to produce the dimethyl acetal of any benzylic oxidation product, gave only a complex mixture of inseparable products and proved useless.

EXPERIMENTAL SECTION

General

Infrared spectra were recorded using a Perkin Elmer 137 grating spectrophotometer calibrated with a polystyrene film. Proton magnetic resonance spectra were recorded on a JEOL JNM C-60 HL 60 MHz spectrophotometer with tetramethylsilane as the internal standard in the solvent indicated. Low resolution mass spectroscopy determinations were carried out by the analytical section of Imperial Chemical Industries Ltd., Alderley Edge, Macclesfield, as were microanalyses for C, H, Cl, N and S. Melting points were determined using open capillaries in an electrically heated Gallenkamp melting point apparatus and are corrected.

Hydrogenations were performed using the medium pressure apparatus of Chas. W. Cook and Sons, Birmingham, and also a standard atmospheric pressure hydrogenation apparatus. Thin-layer chromatography was carried out using pre-spread plates (5 x 20cm; Polygram SIL G/UV₂₅₄ and Polygram ALOX N/UV₂₅₄ from Camlab, Cambridge). Preparative TLC (thick-layer) was performed on pre-spread (20 x 20cm; Anachem Uniplate, silica-gel G.F.). Column chromatography was carried out using Fison silica-gel MFC (80-200 mesh) and Fison alumina (100-250 mesh). All solvents for chromatographic work were redistilled. Other solvents were dried using molecular sieves (except ether, THF, and benzene, which were dried over sodium). Petroleum used had b.p. 60-80°.

General Anodic Oxidation Procedure

All anodic oxidations (unless stated otherwise) were carried out using a Wenking potentiostat model 70 TS 1 and standard calomel reference electrode, with a graphite felt anode (5 x 3cm) and a platinum cathode (3 x 2cm). The one compartment cell (a 250ml beaker) contained a solution of tetraethylammonium perchlorate (2.5g) in either methanol or acetonitrile (150ml) and

was stirred magnetically. The oxidations were carried out in air at room temperature. Substrates were added in solution of the cell solvent to an equilibrated, pre-electrolysed anodic cell, at a predetermined anodic potential, and the current monitored with time until either the current dropped to the background level or until all starting material was shown by TLC examination to have reacted. The cell solution was decanted, the shredded anode washed with further solvent, and the combined organic solvents filtered, then evaporated to dryness on a rotary evaporator at room temperature. The residues were partitioned between methylene chloride or ether and water, and the organic layer separated. When the starting materials were acidic an additional wash with saturated sodium bicarbonate solution was employed. The organic layers were dried over magnesium sulphate, filtered, then rotary evaporated to dryness at room temperature.

WORK DESCRIBED IN CHAPTER TWO

Preparation of Substrates

3-(3,5-dibromo-4-hydroxyphenyl)-propanoic acid 103. The title compound was prepared⁷⁵ by mixing a solution of bromine in acetic acid with an acetic acid solution of 4-hydroxyphenylpropanoic acid 101, and was obtained as colourless needles which recrystallised from toluene (74%) m.p. 106° (lit.⁷⁵ m.p. 108°).

Disodium salt of 3-(3,5-dibromo-4-hydroxyphenyl)-propanoic acid. Metallic sodium (0.55g 0.024 mol) was dissolved in methanol (50ml) and 3-(4-hydroxyphenyl)-propanoic acid (2.0g 0.012 mol) added. The solution was evaporated to dryness and the residue used in the following electrolyses.

Anodic Oxidation of Phloretic Acid and its Derivatives

The general oxidation procedure outlined earlier was employed on commercially available 3-(4-hydroxyphenyl)-propanoic acid 101(A), 3-(3,5-dibromo-4-hydroxyphenyl)-propanoic acid 103(C), and on their respective disodium salts (B) and (D). The substrates (in acetonitrile solution) were either added dropwise (Dr) or as a bulk addition (Bk). In each case the electrolyte was T.E.A.P. (2g) and the cell solvent acetonitrile (150ml). The electrodes were either platinum (Pt), lead (Pb), or carbon felt (CF) which was sometimes changed several times during the oxidation process (CCF). Some of the results obtained are given in the table below; the weight of product shown is a crude yield prior to recrystallisation.

Table I

SUBST.	Wt S.M. (mg)	P.D. (volts)	I(max) (mA)	Time (Hrs)	Add'n Type	Electrode		Wt P. (mg)	Yield %
						+	-		
A	150	1.0	40	1.25	Bk	CF	Pt	7	5
A*	500	1.2	4	2.00	Dr	Pt	Pt	6	1
A	300	2.0	18	2.00	Dr	Pt	Pt	7	2
A	300	1.2	40	4.50	Dr	CCF	Pt	57	19
A	500	1.2	96	2.00	Dr	CCF	Pt	30	6
A	300	2.0	27	0.35	Bk	Pt	Pb	10	3
B	500	0.5	54	16.00	Bk	CF	Pt	20	5
B	500	0.5	40	1.75	Dr	CCF	Pt	25	6
C	500	1.0	12	1.30	Bk	CF	Pt	33	7
C	500	1.0	38	1.20	Dr	CCF	Pt	52	11
D	700	0.5	24	1.75	Bk	CCF	Pt	32	5
D	700	0.5	39	2.25	Dr	CCF	Pt	28	4

* Oxidation run in acetic acid (22ml) and water (150ml).

Chemical Oxidation of 3-(4-hydroxyphenyl)-propanoic acid 101

(i) The oxidation of phloretic acid 101 was effected⁶¹ with hydrogen peroxide and glacial acetic acid to give the lactone 102 which recrystallised from chloroform as colourless needles (6%) m.p. 105° (lit.⁶¹ m.p. 106°).

ν_{\max} : 1780 cm⁻¹ (lactone C=O); 1690 cm⁻¹ (C=O); 1640 cm⁻¹ (C=C). δ (CDCl₃) : 2.1 - 3.0 (4H, m, CH₂CH₂); 6.25, 6.85 (4H, 2d, J=11 Hz, diene).

(ii) The title acid 101 (1.0g 0.0072 mol) was stirred with a suspension of lead tetraacetate (3.2g 0.0072 mol) in acetic acid (10ml) at room temperature for two hours. The dark reaction mixture was poured into water (300ml) and extracted into methylene chloride (2 x 100ml). The combined organic layers were washed with water (8 x 100ml) until the pH of the aqueous phase had fallen from 3 to 7. The organic solution was dried over sodium sulphate, and solvent removed to leave a yellow oil. Trituration with ether gave a white solid 40mg (4%) with m.p. and spectral properties identical to those of the above lactone 102.

WORK DESCRIBED IN CHAPTER THREE

Preparation of Substrates

General Preparation of 4-nitrophenyl Derivatives

To a mechanically stirred solution of 4-nitrophenol (35g 0.25mol) in dry DMF (100ml) was cautiously added sodium hydride (80% suspension in oil, 8.0g 0.25 mol) over a 30 min. period with initial cooling in an ice/water bath. The alkyl halide (0.25 mol) was added and the mixture refluxed for 5h., then cooled slightly and poured into 2M aqueous sodium hydroxide solution (11):

Either (i) the precipitate was filtered off, washed with water, then air dried, or (ii) the aqueous reaction mixture was extracted with ether (5 x 200ml), the combined organic layers washed with dilute base (2 x 200ml) and water (2 x 200ml), then dried over magnesium sulphate, filtered, and solvent removed on a rotary evaporator.

By this method were prepared the following compounds:-

2-(4-nitrophenoxy)-ethanol 210. From 2-chloroethanol as pale yellow needles (66%) from toluene m.p. 94-6° (lit.¹⁷⁶ m.p. 92°). ν_{\max} : 3280 cm⁻¹ (OH). δ (CDCl₃): 3.9 - 4.3 (4H, m, CH₂CH₂); 7.00 (2H, d, J=9Hz ar. ortho to O); 8.30 (2H, d, J=9Hz ar. ortho to N); 2.4 (1H, s, exchanges with D₂O, OH).

2-(2-nitrophenoxy)-ethanol. From 2-nitrophenol and 2-chloroethanol, fawn needles from ethyl acetate-petroleum (69%) m.p. 32 - 5° (lit.¹⁷⁷ m.p. 35 - 6°). ν_{\max} : 3220 cm⁻¹ (OH). δ (CDCl₃): 3.95, 4.20 (4H, 2t, J=3Hz, CH₂CH₂); 6.8 - 8.0 (4H, m, aromatics); 2.8 (1H, broad s, exchanges with D₂O, OH).

3-(4-nitrophenoxy)-propan-1-ol. From 3-chloropropan-1-ol as pale yellow needles from toluene-petroleum (51%) m.p. 43 - 44° (lit.¹⁷⁸ m.p. 48-9°).

ν_{\max} : 3515 cm^{-1} (OH). δ (CDCl_3): 1.7-2.3 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$); 3.85 (2H, t, $J=7\text{Hz}$, CH_2OH); 4.15 (2H, t, $J=7\text{Hz}$, PhOCH_2-); 6.85 (2H, d, $J=9\text{Hz}$, ar. ortho to O); 8.05 (2H, d, $J=9\text{Hz}$, ar. ortho to N); 2.6 (1H, broad s, exchanges with D_2O , OH).

Ethyl 4-nitrophenoxyacetate 227. From ethyl chloroacetate as yellow needles from toluene-petroleum or ethanol (94%) m.p. 75-6° (lit.¹⁷⁹ m.p. 76°).

ν_{\max} : 1750 cm^{-1} (C=O). δ (CDCl_3): 1.30 (3H, t, $J=7\text{Hz}$, CH_3); 4.20 (2H, q, $J=7\text{Hz}$, OCH_2CH_3); 4.70 (2H, s, OCH_2CO_2); 6.90 (2H, d, $J=9\text{Hz}$, ar. ortho to O); 8.10 (2H, d, $J=9\text{Hz}$, ar. ortho to N).

Ethyl 2,2-dimethyl-3-(4-nitrophenoxy)-propanoate. From ethyl 2,2-dimethyl-3-chloropropanoate as pale yellow needles (petroleum) (38%) m.p. 87-90°. ν_{\max} : 1735 cm^{-1} (C=O). δ (CDCl_3): 1.20 (3H, t, $J=7\text{Hz}$, CH_2CH_3) superimposed on 1.35 (6H, s, $\text{C}(\text{CH}_3)_2$); 4.05 (2H, s, $\text{OCH}_2\text{C}(\text{Me})_2$) superimposed on 4.15 (2H, q, $J=7\text{Hz}$, CH_2CH_3); 6.90 (2H, d, $J=9\text{Hz}$, ar. ortho to O); 8.10 (2H, d, $J=9\text{Hz}$, ar. ortho to N).

3-(4-Nitrophenyl)-propanoic acid 246. To a mechanically stirred solution of phenylpropanoic acid 245 (50g 0.33 mol) in glacial acetic acid (50 ml) was cautiously added dropwise fuming nitric acid (100g) over a period of one hour. The reaction mixture was maintained at 20-25° by means of a cold water bath during the addition, then allowed to stand at room temperature for 3 hrs. with occasional stirring, before being poured into cold water (11). The yellow solid was filtered off, washed with water, and air dried, yielding after repeated recrystallisation from ethanol the nitro acid 32g (50%) m.p. 162° (lit.¹⁷⁹ m.p. 164-5°). ν_{\max} : 1705 cm^{-1} (C=O). δ (DMSO): 2.4-3.2 (4H, m, CH_2CH_2); 7.30 (2H, d, $J=9\text{Hz}$, ar. ortho to C); 8.05 (2H, d, $J=9\text{Hz}$, ar. ortho to N).

General Preparation of 4-Aminophenyl Derivatives

To an organic solution (approx. 200 ml) of the nitro compound (0.03 - 0.1 mol) was cautiously added a slurry of 5% palladium on charcoal (0.5g) in water (1 ml) under an atmosphere of nitrogen. The suspension was either shaken under hydrogen (at 1-4 atmos.) or stirred rapidly under hydrogen at atmospheric pressure, until uptake ceased. The catalyst was removed by filtration through celite, the filtrate evaporated to dryness and the residue recrystallised from the solvent indicated.

By this method were prepared the following compounds:-

2-(4-Aminophenoxy)-ethanol 211. Hydrogenation solvent-ethyl acetate. Colourless needles from chloroform-petroleum (81%) m.p. 69-71° (lit.¹⁷⁶ m.p. 71-72°). ν_{\max} : 3460, 3290, 3190 cm^{-1} (NH_2 , OH). δ (CDCl_3): 3.7-4.1 (4H, m, CH_2CH_2); 6.4-6.9 (4H, m, aromatics); 3.2 (3H, broad s, exchanges with D_2O , NH_2 , OH). The amine hydrochloride 217 was precipitated by bubbling hydrogen chloride gas through an ethanolic solution of above amine 211, and was obtained as salmon pink plates m.p. 205° (lit.¹⁷⁶ m.p. 200-5°).

2-(2-Aminophenoxy)-ethanol. Hydrogenation solvent-ethanol. Colourless needles from chloroform (86%) m.p. 87-90° (lit.¹⁸⁰ m.p. 90-2°). ν_{\max} : 3380, 3320, 3220 cm^{-1} (NH_2 , OH). δ (CDCl_3): 3.7-4.2 (4H, m, CH_2CH_2); 6.6-6.9 (4H, m, aromatics); 3.7 (3H, broad s, exchanges with D_2O , NH_2 , OH).

3-(4-Aminophenoxy)-propan-1-ol. Hydrogenation solvent-ethanol. Colourless needles from chloroform (91%) m.p. 86-88°. ν_{\max} : 3350, 3290, 3120 cm^{-1} (NH_2 , OH).

Ethyl 4-aminophenoxyacetate 228. Hydrogenation solvent-ethyl acetate. Fawn needles from petroleum (84%) m.p. 56-58° (lit.¹⁷⁹ m.p. 58°). ν_{\max} : 3450, 3340 cm^{-1} (NH_2); 1750 cm^{-1} (C=O). δ (CDCl_3): 1.25 (3H, t, $J=7\text{Hz}$, CH_3); 4.20 (2H, q, $J=7\text{Hz}$, OCH_2CH_3); 4.50 (2H, s, OCH_2CO_2); 6.3-6.8 (4H,

m, aromatics); 3.3 (2H, broad s, exchanges with D₂O, NH₂).

Ethyl 2,2-dimethyl-3-(4-aminophenoxy)-propanoate. Hydrogenation solvent-ethyl acetate. Colourless needles from chloroform (69%) m.p. 64°.

3-(4-Aminophenyl)-propanoic acid 247. For the hydrogenation the nitro acid 246 was suspended in methanol. Colourless needles from chloroform or water (97%) m.p. 130° (lit.¹⁷⁹ m.p. 131-2°). ν_{\max} : 3420, 3330 cm⁻¹ (NH₂); 1720 cm⁻¹ (C=O). δ (DMSO): 2.3-2.9 (4H, m, CH₂CH₂); 6.50 (2H, d, J=9Hz, ar. ortho to CH₂); 6.90 (2H, d, J=9Hz, ar. ortho to N); 6.3 (2H, broad s, exchanges with D₂O, NH₂).

4-(4-aminophenyl)-butanoic acid. Hydrogenation solvent-methanol. Colourless needles from water (96%) m.p. 128° (lit.¹⁷⁹ m.p. 130-1°). ν_{\max} : 2500 (broad) cm⁻¹ (salt bands).

General Preparation of Arylsulphonamides

To a stirred ice-cooled solution of the primary aromatic amine (0.05 mol) in methylene chloride (100 ml) containing pyridine (5 ml) was added the sulphonyl chloride (0.05 mol). The mixture was allowed to warm to room temperature overnight, then was poured into 4M hydrochloric acid (200 ml) and extracted into methylene chloride (3 x 200 ml). The combined organic layers were washed with 2M hydrochloric acid (200 ml), and water (2 x 200 ml), dried over magnesium sulphate, filtered and the solvent removed by evaporation. Any discolouration was removed by boiling a chloroform solution of the product with activated charcoal.

By this method were prepared the following compounds.

Compound	Yield %	m.p.	lit. m.p.	Recrystallisation Solvent	Ref
192	85	112°	114°	Ethanol (Toluene)	181
193	63	195°	193-4°	Toluene/ Petroleum	182
194	62	114-6°	116°	Ethanol (Toluene)	179
195	82	100°	102-4°	Toluene/ Petroleum	182-183
197	55	130-1°	130-2°	Water	179
198	60	150-4°	153-4°	Ethanol	179
199	78	112-4°	113-5°	Petroleum 80-100°	184
200	87	124°	126°	Ethanol	185
201	64	115°	115-6°	Ethanol	182
202	50	180-3°	185-6°	Methanol	179
203	82	98-9°	103°	Methanol	182

4-(2-Nitrobenzenesulphonyl)-aniline 196. Yellow needles (37%) m.p. 102-3° (toluene-petroleum). (Found: C, 50.6; H, 3.8; N, 9.0. $C_{13}H_{12}N_2O_5S$ requires C, 50.6; H, 3.9; N, 9.1%). ν_{max} : 3260 cm^{-1} (NH); 1360, 1330, 1170 cm^{-1} (SO_2N). δ ($CDCl_3$): 3.75 (3H, s, OCH_3); 6.75, 7.10 (4H, 2d, $J=9Hz$, ar. ortho to O and NH); 7.5-8.0 (4H, m, aromatics); 7.1 (1H, broad s, exchanges with D_2O , NH).

2-[4-(p-Toluenesulphonamido)-phenoxy]-ethanol 212. Pink plates (79%) m.p. 126-8° (toluene-petroleum). (Found: C, 58.5; H, 5.5; N, 4.4. $C_{15}H_{17}NO_4S$ requires C, 58.5; H, 5.5; N, 4.6%). ν_{max} : 3480 cm^{-1} (OH); 3180 cm^{-1} (NH); 1330, 1160 cm^{-1} (SO_2N). δ (DMSO): 2.40 (3H, s, CH_3); 3.9-4.2 (4H, m, CH_2CH_2); 6.85 (2H, d, $J=9Hz$, ar. ortho to NH); 7.20 (2H, d, $J=9Hz$, ar. ortho to O); 7.35 (2H, d, $J=9Hz$, ar. ortho to CH_3); 7.85 (2H, d, $J=9Hz$, ar. ortho to SO_2).

When an excess of sulphonyl chloride was used in the above preparation an additional compound of higher Rf than that of the desired product was isolated by column chromatography (silica gel, chloroform-ether 1/1) and identified as 2-[4-(p-toluenesulphonamido)-phenoxy]-ethyl p-toluenesulphonate 215. Colourless needles m.p. 132° (toluene-petroleum). (Found: C, 57.2; H, 4.9; N, 2.9. $C_{22}H_{23}NO_6S$ requires C, 57.3; H, 5.0; N, 3.0%). ν_{\max} : 3220 cm^{-1} (NH); 1320, 1140 cm^{-1} (SO_2N). δ (d_6 -DMSO): 2.40 (3H, s, CH_3); 2.45 (3H, s, CH_3); 4.0-4.5 (4H, m, CH_2CH_2); 6.90 (2H, d, $J=9H_z$, ar. ortho to O); 7.20 (2H, d, $J=9H_z$, ar. ortho to N); 7.4-8.2 (8H, m, ar. ortho to S and C).

2-[4-(Methanesulphonamido)-phenoxy]-ethyl methanesulphonate 216 was the only product isolated in the attempted preparation of the methanesulphonamide analogue of 212 and was obtained as white needles (18%) m.p. 132-4° (toluene). (Found: C, 39.1; H, 4.9; N, 4.3. $C_{10}H_{15}NO_6S_2$ requires C, 38.8; H, 4.8; N, 4.5%). ν_{\max} : 3250 cm^{-1} (NH); 1315, 1140 cm^{-1} (SO_2N). δ ($CDCl_3$): 3.00 (3H, s, CH_3); 3.20 (3H, s, CH_3); 4.2-4.8 (4H, m, CH_2CH_2); 7.05 (2H, d; $J=9H_z$, ar. ortho to O); 7.50 (2H, d, $J=9H_z$, ar. ortho to N).

2-[2-(p-Toluenesulphonamido)-phenoxy]-ethanol 253. Fawn needles (85%) m.p. 144-6° (toluene-petroleum). ν_{\max} : 3350, 3160 cm^{-1} (OH, NH); 1330, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.30 (3H, s, CH_3); 3.85 (4H, s, CH_2CH_2); 6.5-7.8 (8H, m, aromatics); 3.4; 8.0 (2H, 2 broad s, OH, NH).

3-[4-(p-toluenesulphonamido)-phenoxy]-propan-1-ol 254. Colourless needles (55%) m.p. 138-9° (toluene). (Found: C, 59.8; H, 5.8; N, 4.3. $C_{16}H_{19}NO_4S$ requires C, 59.8; H, 5.9; N, 4.4%). ν_{\max} : 3510 cm^{-1} (OH); 3150 cm^{-1} (NH); 1330, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$ /DMSO): 1.90 (2H, t, $J=7H_z$, $CH_2CH_2CH_2$); 2.35 (3H, s, CH_3); 3.5-3.8 (2H, m, CH_2OH); 3.95 (2H, t, $J=7H_z$, ar- OCH_2); 6.60 (2H, d, $J=9H_z$, ar. ortho to O); 6.90 (2H, d, $J=9H_z$, ar. ortho to N); 7.10 (2H, d, $J=9H_z$, ar. ortho to C); 7.55 (2H, d, $J=9H_z$, ar. ortho to S).

Ethyl 4-(p-toluenesulphonamido)-phenoxyacetate 229. The reaction mixture was heated under reflux for 2 hrs. Colourless needles (95%) m.p. 90-92° (toluene-petroleum). (Found: C, 58.4; H, 5.4; N, 4.0. $C_{17}H_{19}NO_5S$ requires C, 58.1; H, 5.6; N, 3.9%). ν_{\max} : 3290 cm^{-1} (NH); 1760 cm^{-1} (C=O); 1330, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.20 (3H, t, $J=7Hz$, CH_2CH_3); 2.30 (3H, s, ar- CH_3); 4.15 (2H, q, $J=7Hz$, CH_2CH_3); 4.45 (2H, s, OCH_2CO_2); 6.60 (2H, d, $J=9Hz$, ar. ortho to N); 6.85 (2H, d, $J=9Hz$, ar. ortho to O); 7.05 (2H, d, $J=9Hz$, ar. ortho to C); 7.50 (2H, d, $J=9Hz$, ar. ortho to S).

Ethyl 4-methanesulphonamidophenoxyacetate 230. The reaction mixture was heated under reflux for 1 hr. Colourless plates (80%) m.p. 78-80° (toluene-petrol). (Found: C, 48.3; H, 5.6; N, 5.2. $C_{11}H_{15}NO_5S$ requires C, 48.3; H, 5.5; N, 5.1%). ν_{\max} : 3200 cm^{-1} (NH); 1740 cm^{-1} (C=O); 1330, 1150 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.30 (3H, t, $J=7Hz$, CH_2CH_3); 2.95 (3H, s, SO_2CH_3); 4.25 (2H, q, $J=7Hz$, CH_2CH_3); 4.60 (2H, s, OCH_2CO_2); 6.85 (2H, d, $J=9Hz$, ar. ortho to N); 7.20 (2H, d, $J=9Hz$, ar. ortho to O); 7.0 (1H, broad s, exchanges with D_2O , NH).

Ethyl 4-(p-bromobenzenesulphonamido)-phenoxyacetate 231. The reaction mixture was heated under reflux for 1 hr. Colourless plates (60%) m.p. 110-112° (toluene-petroleum). (Found: C, 46.3; H, 3.8; N, 3.2. $C_{16}H_{16}BrNO_5S$ requires C, 46.4; H, 3.9; N, 3.4%). ν_{\max} : 3260 cm^{-1} (NH); 1720 cm^{-1} (C=O); 1330, 1165 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.25 (3H, t, $J=7Hz$, CH_3); 4.20 (2H, q, $J=7Hz$, CH_2CH_3); 4.55 (2H, s, OCH_2CO_2); 6.70 (2H, d, $J=9Hz$, ar. ortho to N); 6.95 (2H, d, $J=9Hz$, ar. ortho to O); 7.50 (4H, s, aromatics); 7.3 (1H, broad s, exchanges with D_2O , NH).

Ethyl 4-(o-nitrobenzenesulphonamido)-phenoxyacetate 232. The reaction mixture was heated under reflux for 1 hr. Yellow prisms (64%) m.p. 92-4° (toluene-petroleum). (Found: C, 50.4; H, 4.2; N, 7.3. $C_{16}H_{16}N_2O_7S$

requires C, 50.5; H, 4.2; N, 7.4%). ν_{\max} : 3280 cm^{-1} (NH); 1750 cm^{-1} (C=O); 1355, 1165 cm^{-1} (SO_2N). δ (CDCl_3): 1.25 (3H, t, $J=7\text{Hz}$, CH_3); 4.20 (2H, q, $J=7\text{Hz}$, OCH_2CH_3); 4.55 (2H, s, OCH_2CO_2); 6.75 (2H, d, $J=9\text{Hz}$, ar. ortho to O); 7.10 (2H, d, $J=9\text{Hz}$, ar. ortho to N); 7.2-8.0 (4H, m, aromatics); 7.3 (1H, broad s, exchanges with D_2O , NH).

3-[4-(p-Toluenesulphonamido)-phenyl]-propanoic acid 248. Colourless needles (86%) m.p. 161-2° (aqueous methanol). (Found: C, 60.1; H, 5.4; N, 4.2. $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S}$ requires C, 60.2; H, 5.3; N, 4.4%). ν_{\max} : 3240 cm^{-1} (NH); 1720 cm^{-1} (C=O); 1330, 1160 cm^{-1} (SO_2N). δ ($\text{NaOD/D}_2\text{O}$): 2.15 (3H, s, CH_3); 2.2-2.8 (4H, m, CH_2CH_2); 6.95 (4H, s, ar. ortho to N and CH_2); 7.10 (2H, d, $J=9\text{Hz}$, ar. ortho to CH_3); 7.70 (2H, d, $J=9\text{Hz}$, ar. ortho to S).

4-[4-(p-toluenesulphonamido)-phenyl]-butanoic acid 261. The reaction mixture was heated under reflux for 2 hrs. Colourless needles (90%) m.p. 125-6° (aqueous methanol). (Found: C, 57.5; H, 5.6; N, 3.9. $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}$ (+ H_2O) requires C, 58.1; H, 5.0; N, 4.0%). ν_{\max} : 3280 cm^{-1} (NH), 1700 cm^{-1} (C=O); 1330, 1160 cm^{-1} (SO_2N).

Hydrolysis of Ethyl Esters

The ethyl ester (0.025 mol) was dissolved in 2M sodium hydroxide solution (120 ml) and heated under reflux for 2 hr. The reaction mixture was then cooled in ice and made acidic by the dropwise addition of concentrated hydrochloric acid. The colourless precipitate was filtered off, washed with water, and dried in an oven at 100°.

By this method were prepared the following compounds:-

4-(p-Toluenesulphonamido)-phenoxyacetic acid 234. Colourless needles from aqueous ethanol (93%) m.p. 185° (lit.¹⁸⁶ m.p. 187°). (Found: C, 56.0;

H, 4.7; N, 4.3. Calc. for $C_{15}H_{15}NO_5S$ C, 56.0; H, 4.7; N, 4.4%. ν_{\max} :
3280 cm^{-1} (NH); 1725, 1710 cm^{-1} (C=O); 1330, 1155 cm^{-1} (SO_2N). δ (NaOD/D₂O):
2.25 (3H, s, CH_3); 4.30 (2H, s, CH_2); 6.60 (2H, d, J=9Hz, ar. ortho to O);
6.85 (2H, d, J=9Hz, ar. ortho to N); 7.20 (2H, d, J=9Hz, ar. ortho to C);
7.65 (2H, d, J=9Hz, ar. ortho to S).

4-Methanesulphonamidophenoxyacetic acid 235. Colourless needles (97%)
m.p. 205-7° (aqueous ethanol). (Found: C, 43.8; H, 4.5; N, 5.6.

$C_9H_{11}NO_5S$ requires C, 44.1; H, 4.5; N, 5.7%. ν_{\max} : 3250 cm^{-1} (NH);
1740 cm^{-1} (C=O); 1330, 1145 cm^{-1} (SO_2N). δ (NaOD/D₂O): 2.90 (3H, s,
 CH_3); 4.45 (2H, s, CH_2); 6.8-7.2 (4H, m, aromatics).

4-(p-Bromobenzenesulphonamido)-phenoxyacetic acid 236. Colourless
needles (99%) m.p. 221-3° (aqueous ethanol). (Found: C, 43.3; H, 3.1;
N, 3.5. $C_{14}H_{12}BrNO_5S$ requires C, 43.5; H, 3.1; N, 3.6%). ν_{\max} : 3280 cm^{-1}
(NH); 1730, 1710 cm^{-1} (C=O); 1335, 1160 cm^{-1} (SO_2N). δ (NaOD/D₂O):
4.35 (2H, s, CH_2); 6.75 (2H, d, J=9Hz, ar. ortho to O); 7.00 (2H, d,
J=9Hz, ar. ortho to N); 7.40 (2H, d, J=7Hz, ar. ortho to Br); 7.75
(2H, d, J=7Hz, ar. ortho to S).

4-(o-Nitrobenzenesulphonamido)-phenoxyacetic acid 237. Colourless
needles (97%) m.p. 157-9° (aqueous ethanol). (Found: C, 47.8; H, 3.4;
N, 7.9. $C_{14}H_{12}N_2O_7S$ requires C, 47.7; H, 3.4; N, 7.9%). ν_{\max} : 3340 cm^{-1}
(NH); 1730, 1710 cm^{-1} (C=O); 1355, 1170 cm^{-1} (SO_2N); 1355, 1170 cm^{-1}
(SO_2N). δ (NaOD/D₂O): 4.40 (2H, s, CH_2); 6.75 (2H, d, J=9Hz, ar. ortho
to O); 6.90 (2H, d, J=9Hz, ar. ortho to N); 7.3-8.2 (4H, m, aromatics).

4-Trimethylacetamidophenoxyacetic acid 243. Colourless needles

(94%) m.p. 174-6° (aqueous ethanol). (Found C, 62.2; H, 6.9; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%). ν_{\max} : 3340 cm^{-1} (NH); 1710 cm^{-1} (C=O); 1650 cm^{-1} (C=O). δ (NaOD/D₂O): 1.30 (9H, s, C(CH₃)₃); 4.45 (2H, s, CH₂); 6.90 (2H, d, J=9Hz, ar. ortho to O); 7.25 (2H, d, J=9Hz, ar. ortho to N).

2,2-Dimethyl-3-[4-(p-toluenesulphonamido)-phenoxy]-propanoic acid

258. Colourless needles (88%) m.p. 152-4° (aqueous methanol). (Found:

C, 59.1; H, 5.5; N, 3.4. $C_{18}H_{21}NO_5S$ requires C, 59.5; H, 5.8; N, 3.8%).

ν_{\max} : 3240 cm^{-1} (NH); 1700 cm^{-1} (C=O); 1330, 1160 cm^{-1} (SO₂N). δ (CDCl₃):

1.25 (6H, s, C(CH₃)₂); 2.30 (3H, s, ar-CH₃); 3.85 (2H, s, CH₂); 6.65 (2H, d, J=9Hz, ar. ortho to O); 6.90 (2H, d, J=9Hz, ar. ortho to N); 7.15 (2H, d, J=9Hz, ar. ortho to C); 7.55 (2H, d, J=9Hz, ar. ortho to S).

Preparation of 2-Hydroxy-4'-(p-toluenesulphonamido)-diphenyl Ether 223

2-Methoxy-4'-nitrodiphenyl ether 220 was prepared by the reaction¹⁸⁷ of 2-methoxyphenol in DMF solution with sodium hydride and 4-nitrobromobenzene in a yield of 45% and was obtained as yellow needles from toluene-petroleum 80-100°, m.p. 103-4° (lit.¹⁸⁷ m.p. 106°). ν_{\max} : 1600, 1500, 1350, 1105, 850, 740 cm^{-1} . Demethylation was achieved by either of two methods. (a) The methoxy compound 220 (1.0g 0.004 mol) was added to a solution of hydrogen bromide in acetic acid (20 ml) and the mixture was heated under reflux for

6 hr. The solvent was removed on a rotary evaporator, the residue taken up in 2M sodium hydroxide solution (20 ml), washed with ether (2 x 20 ml), and the aqueous phase made acid by the dropwise addition of concentrated hydrochloric acid. The precipitated 2-hydroxy-4'-nitrodiphenyl ether 221 was filtered off, air dried, and recrystallised from petroleum yielding the nitrophenol 221, 390 mg (41%) m.p. 107° (lit.¹⁸⁷ m.p. 109°). ν_{\max} : 3400 cm⁻¹ (OH); 1585, 1480, 1340 cm⁻¹. Alternatively (b) a mixture of concentrated hydrochloric acid (18 ml) and pyridine (16 ml) was distilled until the still head temperature reached 210°, the residue was then cooled to approx. 140° and the methoxy compound 220 (5.0g 0.02 mol) added. The reaction mixture was heated to 180° for 1 hr., cooled slightly, then poured into water (100 ml). The aqueous solution was acidified with hydrochloric acid, extracted with ether (4 x 50 ml) and the combined organic layers extracted with 2M sodium hydroxide solution (3 x 100 ml). The aqueous base was acidified with concentrated hydrochloric acid, the precipitate filtered off, air dried, and recrystallised from petroleum to yield 2.7g (57%) of the nitro-phenol 221 m.p. 106-108°. Reduction to the amine 222 was effected by the cautious addition under nitrogen to ethanol (12 ml) of 5% palladium on charcoal (120 mg) followed by sodium borohydride (1.2g) and to the stirred reaction mixture was added dropwise a solution of the nitro-phenol 221 (1.15g 0.005 mol) in dry benzene (25 ml). After stirring under nitrogen for 3 hr., the mixture was filtered, the filtrate partitioned between water (60 ml) and ethyl acetate (60 ml), the organic layer separated, washed with water (2 x 60 ml), dried over sodium sulphate, filtered, and the solvent removed by rotary evaporation to yield 650 mg (65%) of 4-amino-2'-hydroxy-diphenyl ether 222 as a brown solid which recrystallised from ethanol, m.p. 170-5° (lit.¹⁸⁸ m.p. 174-5°). ν_{\max} : 3380, 3290 cm⁻¹ (NH₂); 2700 cm⁻¹ (broad salt bands). The above amino-phenol 222, p-toluenesulphonyl chloride

and pyridine were reacted in chloroform solution at room temperature as described earlier to give 2-hydroxy-4'-(p-toluenesulphonamido)-diphenyl ether 223 as colourless needles in 96% yield from aqueous ethanol m.p. 159-160°. (Found: C, 63.7; H, 4.8; N, 3.8. $C_{19}H_{17}NO_4S$ requires C, 64.2; H, 4.8; N, 3.9%). ν_{\max} : 3440 cm^{-1} (OH); 3200 cm^{-1} (NH); 1330, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.40 (3H, s, CH_3); 6.7-7.9 (14H, m, aromatics, OH, NH).

The following compounds were produced in the alternative preparation of 223 (Scheme 33 Path II). Reduction of the nitro compound 220 with sodium borohydride was accomplished in an analogous fashion to 221, and yielded 4-amino-2'-methoxydiphenyl ether 224 as colourless needles from aqueous methanol in 85% yield m.p. 92-96° (lit.¹⁸⁷ m.p. 97°). ν_{\max} : 3400, 3310 cm^{-1} (NH_2). Reaction of the above amine 224 with 4-toluenesulphonyl chloride by the method described previously, gave 2-methoxy-4'-(p-toluenesulphonamido)-diphenyl ether 225 which recrystallised from aqueous ethanol as colourless needles in 15% yield, m.p. 147-8°. (Found: C, 64.7; H, 5.1; N, 3.6. $C_{20}H_{19}NO_4S$ requires C, 65.0; H, 5.1; N, 3.8%). ν_{\max} : 3230 cm^{-1} (NH); 1330, 1150 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.40 (3H, s, ar- CH_3); 3.85 (3H, s, OCH_3); 6.9-7.9 (13H, m, aromatics, NH). Attempts to demethylate the above methoxy sulphonamide 225 with hydrogen bromide in acetic acid, or with pyridine hydrochloride failed to yield any trace of the desired phenolic sulphonamide 223.

Preparation of N-(p-toluenesulphonyl)-2-[4-(p-toluenesulphonamido)-phenoxy]-ethylamine 267

2-(4-Nitrophenoxy)-ethylamine 263. Prepared by reacting¹⁰⁹ 4-nitrochlorobenzene with 2-aminoethanol in the presence of dimsyl anion. Although the product obtained from several preparations differed greatly in overall composition, and usually consisted of mixtures of compounds, in one case

the predominant product, (presumably from a Smiles rearrangement of the initially formed phenoxyethylamine) was N-(2-hydroxyethyl)-4-nitroaniline. δ (CDCl₃): 3.40, 3.85 (4H, 2t, J=5Hz, CH₂CH₂); 6.55 (2H, d, J=9Hz, ar. ortho to NH); 8.00 (2H, d, J=9Hz, ar. ortho to NO₂). In another preparation 2-(4-nitrophenoxy)-ethylamine 263 was obtained as a yellow oil, which although homogeneous by TLC failed to solidify, and therefore could not be recrystallised.¹⁰⁹ (lit.¹⁰⁹ m.p. 29-30°). $\bar{\nu}$ _{max}: 3400 (broad NH₂). δ (CDCl₃): 3.25, 4.10 (4H, 2t, J=5.3H_z); 7.00 (2H, d, J=9H_z, ar. ortho to O); 8.20 (2H, d, J=9H_z, ar. ortho to N); 1.7 (2H, NH₂).

Unsuccessful attempts to produce the above amine 263 in pure form included the reaction under reflux of 4-nitrophenol and sodium hydride in DMF solution with 2-chloroethylamine, which resulted in an inseparable mixture of products. Another approach involved the initial preparation of 2-(4-nitrophenoxy)-1-chloroethane, by heating under reflux a solution of 2-(4-nitrophenoxy)-ethanol 210 (10g 0.055 mol) in thionyl chloride (80 ml). When excess solvent had been removed by distillation, the residue was triturated with and recrystallised from petroleum to yield the chloroethane as colourless solid 10.1 g (92%) m.p. 52° (lit.¹⁸⁹ m.p. 47-8°). $\bar{\nu}$ _{max}: 1340 cm⁻¹ (conj. NO₂); absence of OH peak. However when this alkyl halide was stirred with concentrated ammonia in an attempted substitution reaction, only the hydrolytic cleavage of 4-nitrophenol resulted; no trace of the desired amine was observed.

N-(p-toluenesulphonyl)-2-(4-nitrophenoxy)-ethylamine 264

The title sulphonamide was prepared from the almost pure sample of 2-(4-nitrophenoxy)-ethylamine in the usual manner, with triethylamine as the base in the reaction with sulphonyl chloride, and was obtained as yellow cubes (52%) m.p. 146-7° (toluene-petroleum). (Found: C, 53.3; H, 4.8; N, 8.3. C₁₅H₁₆N₂O₅S requires C, 53.6; H, 4.8; N, 8.3%). $\bar{\nu}$ _{max}: 3270 cm⁻¹ (NH); 1340, 1160 cm⁻¹ (SO₂N). δ (CDCl₃): 2.40 (3H; s, CH₃); 3.40, 4.10 (4H, 2t,

J = 5Hz, CH₂CH₂); 6.85 (2H, d, J = 9Hz, ar. ortho to O); 7.30 (2H, d, J = 9Hz, ar. ortho to C); 7.75 (2H, d, J = 9Hz, ar. ortho to S); 8.15 (2H, d, J = 9Hz, ar. ortho to N); 5.3 (1H broad s, NH).

Attempted preparation of the title compound from a less pure sample of starting amine produced not only the desired product 264, but also the isomeric compound N-(4-nitrophenyl)-2-aminoethyl p-toluenesulphonate 265. By subtracting the peaks belonging to 264 from the NMR spectrum of this mixture, the following shift values were observed for 265. δ (CDCl₃): 2.40 (3H, s, CH₃); 3.3-3.7, 4.0-4.4 (4H, 2m, CH₂CH₂); 6.50 (2H, d, J = 9Hz, ar. ortho to NH); 7.30 (2H, d, J = 9Hz, ar. ortho to C); 7.80 (2H, d, J = 9Hz, ar. ortho to S); 8.00 (2H, d, J = 9Hz, ar. ortho to NO₂); c.a. 5.0 (1H, broad s, exchanges with D₂O, NH). These results accord closely with shift values calculated for the proposed structure. No attempt at separation was made.

Failed attempts to produce the title sulphonamide included the reaction of 2-(4-nitrophenoxy)-ethyl chloride with p-toluenesulphonamide, benzene and 50% potassium hydroxide solution under phase transfer conditions, which produced 4-nitrophenol as the only isolated product. When the experiment was repeated, using cetyltrimethylammonium bromide and 50% sodium hydroxide, only starting materials were recovered. The reaction of p-toluenesulphonamide with 2-(4-nitrophenoxy)-ethyl chloride in the presence of potassium carbonate and acetone, also produced mainly 4-nitrophenol, while heating the same two starting materials under reflux with 80% sodium hydride in DMF solution gave an intractable tar.

N-(p-toluenesulphonyl)-2-(4-aminophenoxy)-ethylamine 266. The nitrosulphonamide 264 was hydrogenated in an ethanolic solution as described earlier to give the amine 266 as colourless plates (77%) m.p. 141-143^o (by evaporation of a solution of the amine in Analar chloroform). (Found:

C, 57.1; H, 5.9; N, 8.9. $C_{15}H_{18}N_2O_3S$ requires C, 58.8; H, 5.9; N, 9.1%.

ν_{\max} : 3320, 3390 cm^{-1} (NH_2); 3100 cm^{-1} (NH); 1320, 1150 cm^{-1} (SO_2N).

δ ($CDCl_3$ /DMSO): 2.40 (3H, s, CH_3); 3.30, 3.95 (4H, 2t, $J=5Hz$, CH_2CH_2): 6.70 (4H, s, ar. ortho to NH_2 and O); 7.35 (2H, d, $J=9Hz$, ar. ortho to C); 7.85 (2H, d, $J=9Hz$, ar. ortho to S).

Attempts to produce the amino compound 266 by a zinc and acetic acid reduction of 264 yielded an inseparable mixture of compounds.

N-(p-toluenesulphonyl)-2-[4-(p-toluenesulphonamido)-phenoxy]-ethylamine 267. Reaction of the above amine 266 with p-toluenesulphonyl chloride as described earlier gave the bis-sulphonamide 267 as colourless needles (61%) m.p. 139-141 $^{\circ}$ (ethyl acetate-petroleum). (Found: C, 57.2; H, 5.2; N, 6.0.

$C_{22}H_{24}N_2O_5S_2$ requires C, 57.4; H, 5.2; N, 6.1%). ν_{\max} : 3280 cm^{-1} (NH); 3260 cm^{-1} (NH); 1340, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.40 (6H, s, 2 CH_3); 3.30, 3.90 (4H, 2t, $J=5Hz$, CH_2CH_2); 6.65 (2H, d, $J=9Hz$, ar. ortho to O); 7.00 (2H, d, $J=9Hz$, ar. ortho to N); 7.2-7.9 (8H, m, ar. ortho to C and S).

Preparation of Alcohols 256, 254, 218 and Ester 233

3-[4-(p-toluenesulphonamido)-phenyl]-propan-1-ol 256. To a magnetically stirred solution of the sulphonamido-propanoic acid 248 (1.0g 0.0031 mol) in dry THF (20 ml) under a nitrogen atmosphere, was injected borane methyl sulphide complex (0.8 ml 0.0085 mol) and the solution left for 1 hr. before being poured into ice cooled methanol and allowed to warm to room temperature over a period of 1 hr. Rotary evaporation of the solvent yielded the propanol as a colourless gum which although homogeneous by TLC failed to solidify. ν_{\max} : 3500 cm^{-1} (OH); 3240 cm^{-1} (NH); 1325, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.6-1.8 (2H, m, $CH_2CH_2CH_2$); 2.25 (3H, s, CH_3); 2.4-2.7 (2H, m, ar- CH_2); 3.4-3.7 (2H, m, CH_2O); 7.00 (4H, s, ar. ortho to N and CH_2); 7.10 (2H, d, $J=9Hz$, ar. ortho to CH_3); 7.65 (2H, d, $J=9Hz$, ar. ortho to S); 2.8

8.0 (2H, 2s, OH, NH).

3-[4-[N-(p-toluenesulphonyl)-N-methanesulphonyl]-aminophenyl]-propyl methanesulphonate. Prepared as an analytical derivative of the above alcohol 256 by reacting it with excess methanesulphonyl chloride in the presence of triethyl amine as described earlier. Colourless needles (40%) m.p. $94-5^{\circ}$ (aqueous ethanol). (Found: C, 47.1; H, 5.1; N, 2.7. $C_{18}H_{23}NO_7S_3$ requires C, 46.8; H, 5.0; N, 3.0%). ν_{\max} : 1375, 1350, 1330, 1180, 1160 (SO_2N). δ ($CDCl_3$): 1.8-2.2 (2H, m, $CH_2CH_2CH_2$); 2.45 (3H, s, ar- CH_3); 2.5-2.8 (2H, m, ar- CH_2); 2.95 (3H, s, SO_2CH_3); 3.45 (3H, s, SO_2CH_3); 4.20 (3H, t, $J=6Hz$, OCH_2); 7.00 (2H, d, $J=9Hz$, ar. ortho to CH_2); 7.20 (2H, d, $J=9Hz$, ar. ortho to N); 7.25 (2H, d, $J=9Hz$, ar. ortho to CH_3); 7.70 (2H, d, $J=9Hz$, ar. ortho to S).

4-[4-(p-toluenesulphonamido)-phenyl]-butan-1-ol 254. Prepared in analogous fashion to the above alcohol 256 by the reduction of the sulphonamido-butanoic acid 261 with borane methyl sulphide complex, the butanol was obtained as colourless needles from toluene (95%) m.p. 81° . (Found: C, 63.8; H, 6.6; N, 4.3. $C_{17}H_{21}NO_3S$ requires C, 64.0; H, 6.6; N, 4.4%). ν_{\max} : 3500 cm^{-1} (OH); 3260 cm^{-1} (NH); 1330, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.4-1.7 (4H, m, $CH_2CH_2CH_2CH_2$); 2.35 (3H, s, CH_3); 2.4-2.7 (2H, m, CH_2O); 3.5-3.8 (2H, m, ar- CH_2); 6.90 (4H, s, ar. ortho to CH_2 and N); 7.15 (2H, d, $J=9Hz$, ar. ortho to CH_3); 7.70 (2H, d, $J=9Hz$, ar. ortho to S); 0.9, 5.3 (2H, 2s, OH, NH).

2-(N-t-Butyl-4-aminophenoxy)-ethanol 218. In an attempt to produce the title alcohol in an analogous fashion to that described by Gassman,⁸⁷ 2-(4-aminophenoxy)-ethanol hydrochloride 217 (50g 0.26 mol) and t-butyl alcohol (100 ml) were sealed in a steel bomb and heated to 115° for 24 hr. However the reaction product proved to be a mixture which even extensive column chromatography failed to separate into pure components.

Ethyl 4-trimethylacetamidophenoxyacetate 233. The amino-ester 228 (7.0g 0.037 mol), pivaloyl chloride (7.0g 0.036 mol) and triethylamine (7g) in chloroform solution (80 ml) were heated under reflux for 2 h., cooled, then poured into 2M hydrochloric acid (150 ml). The crude product was extracted into methylene chloride solution, and after drying and solvent removal, was recrystallised from toluene-petroleum to yield 8.4g (84%) of the amide as colourless needles, m.p. 105-8°. (Found: C, 64.4; H, 7.8; N, 5.1. $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.5; N, 5.0%). ν_{\max} : 3240 cm^{-1} (NH); 1730 cm^{-1} (C=O); 1330, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 1.0-1.5 (9H, m, CH_2CH_3 ; $C(CH_3)_2$); 2.30 (3H, s, ar- CH_3); 3.85 (2H, s, ar- OCH_2); 4.10 (2H, q, $J=7Hz$, OCH_2CH_3); 6.65 (2H, d, $J=9Hz$, ar. ortho to O); 6.95 (2H, d, $J=9Hz$, ar. ortho to N); 7.10 (2H, d, $J=9Hz$, ar. ortho to C); 7.60 (2H, d, $J=9Hz$, ar. ortho to S); 7.5 (1H, broad s, exchanges with D_2O , NH).

Reaction of Substituted N-Aryl Sulphonamides with t-Butyl Hypochlorite/Silver Trifluoroacetate

t-Butyl hypochlorite, made by the reaction of sodium hypochlorite with t-butanol,¹⁹⁰ was stored at 0° in dark bottles. Silver trifluoroacetate was obtained by dissolving silver oxide in trifluoroacetic acid,¹⁹¹ and was stored at room temperature in the dark.

General Reaction Procedure

To a solution of the sulphonamide (0.002 mol) in methylene chloride (10 ml) cooled in an ice bath, was added t-butyl hypochlorite (1 ml), followed 1 h. later by a solution of silver trifluoroacetate (2g) in methanol (50 ml). The reaction mixture was stirred and allowed to warm to room temperature over a period of 1h., filtered, and the filtrate stirred with lithium chloride (3g) for 15 mins. The precipitate was filtered off and the filtrate evaporated to yield a gum. This was partitioned between ether (150 ml) and water (150 ml), the organic layer separated, dried over magnesium sulphate, and evaporated.

The residue was purified as indicated in the specific accounts below.

The following compounds were reacted with t-butyl hypochlorite-silver trifluoroacetate as detailed above:-

N-(p-Toluenesulphonyl)-4-anisidine 192. The product, a gum homogeneous by TLC, gave on trituration with ether, a solid which recrystallised from toluene-petroleum as colourless needles, (120 mg) m.p. 149°. (Found: C, 54.7; H, 5.0; N, 4.1; $C_{15}H_{17}NO_4S$ requires C, 58.6; H, 5.5; N, 4.6. $C_{15}H_{16}ClNO_4S$ requires C, 52.8; H, 4.7; N, 4.1%). ν_{max} : 1660 cm^{-1} (C=C); 1550 cm^{-1} (C=N); 1310, 1150 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.45 (3H, s, ar. CH_3); 3.35 (6H, s, $(OCH_3)_2$); 6.30 (0.5H, d, J=9Hz, vinyl H at C_2); 6.6-7.0 (2H, m, vinyl H at C_3, C_6); 7.30 (2H, d, J=9Hz, ar. ortho to C); 7.60 (2H, d, J=9Hz vinyl at C_5); 7.95 (2H, d, J=9Hz, ar. ortho to S). However examination of this solid by TLC indicated that it contained two substances, which were separated by column chromatography (silica gel, chloroform/ether 1:1), to afford two crystalline products. The higher Rf fraction, colourless needles m.p. 170-2° (toluene-petroleum) was identified as 2-chloro-N-(4-toluenesulphonyl)-4,4-dimethoxycyclohexa-2,5-dienimine 207. (Found: C, 53.1; H, 4.7; N, 4.0; Cl, 10.2. $C_{15}H_{16}ClNO_4S$ requires C, 52.8; H, 4.7; N 4.0; Cl, 10.4%). Found m/e = 341. calc for $C_{15}H_{16}ClNO_4S$, 341. ν_{max} : 1650 cm^{-1} (C=C); 1550 cm^{-1} (C=N); 1310, 1145 cm^{-1} (SO_2N). δ (DMSO): 2.45 (3H, s, ar CH_3); 3.40 (6H, s, $(OCH_3)_2$); 6.8-8.1 (7H, m, vinyl and aromatics). The lower Rf material gave conflicting analytical and spectral data, and was assumed to be an inseparable mixture of products.

N-Methanesulphonyl-4-anisidine 194. The reaction product was shown to be homogeneous by TLC and crystallised on trituration with ether to yield x,y-dichloro-4-hydroxy-N-methanesulphonyl-4-methoxycyclohexa-2,5-dienimine as colourless needles (140 mg) m.p. 158° (toluene-petroleum). (Found: C, 33.5; H, 2.9; N, 4.7; m/e 285. $C_8H_9Cl_2NO_4S$ requires C, 33.7; H, 3.2; N, 4.9% m/e 285). ν_{max} : 3200 cm^{-1} (broad OH); 1655, 1630, 1600 cm^{-1} ; 1330, 1165 cm^{-1}

(SO₂N). δ (CDCl₃): 3.05 (3H, s, SCH₃); 3.30 (3H, s, OCH₃); 5.40 (1H, broad s, OH); 6.60 (2H, s, vinylic). TLC examination of this substance after several days indicated that it had decomposed to a mixture of compounds, the structures of which could not be elucidated.

N-(4-Toluenesulphonyl)-4-toluidine 193. Trituration of the oily product with ether yielded x,y-dichloro-4-methoxy-4-methyl-N-(p-toluenesulphonyl)-cyclohexa-2,5-dienimine yellow crystals (21%) homogeneous by TLC m.p. 168° (toluene-petroleum). (Found: C, 51.0; H, 4.1; N, 4.1. C₁₅H₁₅Cl₂NO₃S requires C, 50.0; H, 4.2; N, 4.1%). ν_{\max} : 1640, 1590, 1545 cm⁻¹; 1320, 1150 cm⁻¹ (SO₂N). δ (CDCl₃): 2.50 (6H, s, (ar-CH₃)₂); 3.25 (3H, s, OCH₃); 6.5-8.3 (6H, m, vinylic and aromatics). TLC examination of the product after several days showed considerable decomposition had occurred. Attempts to identify the components of this mixture failed.

Compounds 195, 196, 197, 198, 199, 200, 201, 202 and 203 were all treated as described in the general reaction procedure. The products from these reactions were either inseparable mixtures or yielded a small amount of starting material. In none of these cases were any spectral indications of imine formation observed.

In the following examples, in which the substrate contains an internal nucleophile, the silver trifluoroacetate was added in toluene solution.

2-[4-(p-Toluenesulphonamido)-phenoxy]-ethanol 212. The final gum, on trituration with ether, gave a colourless crystalline compound, homogeneous by TLC, identified as the ethylene ketal of 4-(p-toluenesulphonimido)-cyclohexa-2,5-diene-1-one 213 (30%) m.p. 131-3° (toluene-petroleum). (Found: C, 57.9; H, 4.8; N, 4.4. C₁₅H₁₅NO₄S requires C, 59.0; H, 4.9; N, 4.6%). ν_{\max} : 1655 cm⁻¹ (C=C); 1550 cm⁻¹ (C=N); 1315, 1150 cm⁻¹ (SO₂N). δ (CDCl₃): 2.40 (3H, s, CH₃); 4.15 (4H, s, CH₂CH₂); 6.4-8.2 (8H, m, vinylic and aromatic).

4-(p-Toluenesulphonamido)-phenoxyethanoic acid 234. The product from 1.0g acid was an oil (0.12g) which could not be induced to crystallise. The infra red spectrum $\left[\begin{array}{l} \text{Thin Film} \\ \text{max} \end{array} \right]$: 1820, 1800 cm^{-1} (C=O); 1665 cm^{-1} (C=C); 1570 cm^{-1} (C=N); 1330, 1155 cm^{-1} (SO_2N) indicated that some formation of an imine lactone 239 had occurred.

3-[4-(p-Toluenesulphonamido)-phenyl]-propanoic acid 248. Similarly this product (0.08g) from 1.0g acid remained as an oil, the infra red spectrum of which $\left[\begin{array}{l} \text{Thin Film} \\ \text{max} \end{array} \right]$: 1785 cm^{-1} (C=O); 1655 cm^{-1} (C=C); 1560 cm^{-1} (C=N); 1310, 1160 cm^{-1} (SO_2N) also indicated imine lactone 252 formation.

Electrochemical Oxidation of Substituted N-Aryl Sulphonamides

Solutions of the following compounds (approx. 0.002 mol dissolved in the minimum amount of methanol) were treated as described in the general electrochemical oxidation procedure.

N-(p-Toluenesulphonyl)-4-anisidine 192. At a cell potential of 1.0v, the product was a brown oil, TLC homogeneous, which on trituration with petroleum and ether yielded N-(p-toluenesulphonyl)-4,4-dimethoxycyclohexa-2,5-dienimine 204 as colourless needles (77%) m.p. 149° (toluene-petroleum). (Found: C, 58.2; H, 5.5; N, 4.4. $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{S}$ requires C, 58.6; H, 5.5; N, 4.6%). ν_{max} : 1660 cm^{-1} (C=C); 1540 cm^{-1} (C=N); 1310, 1150 cm^{-1} (SO_2N). δ (CDCl_3): 2.40 (3H, s, ar- CH_3); 3.30 (6H, s, $(\text{OCH}_3)_2$); 6.30 (1H, d, J=9Hz, vinyl at C_2); 6.6-6.9 (2H, m, vinylic H at C_3, C_6); 7.30 (2H, d, J=9Hz, ar. ortho to C); 7.60 (2H, d, J=9Hz, vinyl H at C_5); 7.90 (2H, d, J=9Hz, ar. ortho to S).

N-(o-Nitrobenzenesulphonyl)-4-anisidine 196. The brown solid, produced from an oxidation at 1.0v, recrystallised from toluene-petroleum to yield N-(o-nitrobenzenesulphonyl)-4,4-dimethoxycyclohexa-2,5-dienimine 206 as yellow needles (73%) m.p. 116-8° (Found: C, 49.7; H, 3.8; N, 8.0).

$C_{14}H_{14}N_2O_6S$ requires C, 49.7; H, 4.1; N, 8.3%. ν_{max} : 1660 cm^{-1} (C=C); 1540 cm^{-1} (C=N); 1325, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$): 3.40 (6H, s, $(OCH_2)_2$); 6.1-8.3 (8H, m, vinyl and aromatics).

N-Methanesulphonyl 4-anisidine 194. The cell potential during the oxidation was 1.0v and the product, an oil homogeneous by TLC, was induced to crystallise by cooling to 0° overnight m.p. 79-80. Although attempts at further purification were unsuccessful, the infra red spectrum of the crude material (ν_{max} : 1665 cm^{-1} (C=C); 1560 cm^{-1}) indicated the formation of a dienimine 205. Further evidence for this product is given in the following section on hydrolyses of sulphonylimines.

When compounds 193, 195, 197, 198, 199, 200 and 202 were treated in an analogous fashion to that described above, the recovered product was either unchanged starting material, or an intractable tar.

In the following examples, in which the substrate contains an internal nucleophile, the solvent system was changed to acetonitrile.

2-[4-(p-Toluenesulphonamido)-phenoxy]-ethanol 212. The anodic oxidation, carried out at 1.0v, yielded a red oil, which on trituration with ethanol, although dissolving much of the material, gave colourless crystals of the ethylene ketal of 4-(p-toluenesulphonimido)-cyclohexa-2,5-diene-1-one 213 (16%) m.p. 126° (toluene-petroleum). (Found: C, 58.1; H, 4.9; N, 4.6. $C_{15}H_{15}NO_4S$ requires C, 59.0; H, 4.9; N, 4.6%). The spectral data were identical to those described earlier for this compound. [P100]

3-[4-(p-Toluenesulphonamido)-phenoxy]-propan-1-ol 254. With an anode potential of 1.0v the oxidation product was a dark oil, which was purified by column chromatography (silica gel, eluted with chloroform/ether 1:1), as attempts at recrystallisation failed. Colourless needles (32%) of the propylene ketal of 4-(p-toluenesulphonimido)-cyclohexa-2,5-diene-1-one 255

were obtained m.p. 114-6°. ν_{\max} : 1550 cm^{-1} (C=N), 1320, 1155 cm^{-1} (SO_2N). δ (CDCl_3): 1.6-2.1 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.40 (3H, s, CH_3); 4.00 (4H, t, $\text{J} = 5\text{H}_z$, $(\text{OCH}_2)_2$); 5.9-7.9 (8H, m, vinyl and aromatic).

4-(p-Toluenesulphonamido)-phenoxyacetic acid 234. The electrode potential was 1.4v and the resulting reaction product, an oil, on trituration with petroleum, gave N-(p-toluenesulphonyl)-1,4-dioxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 239 as colourless needles (68%) m.p. 144° (toluene-petroleum). (Found: C, 55.9; H, 4.2; N, 4.3. $\text{C}_{15}\text{H}_{13}\text{NO}_5\text{S}$ requires C, 56.4; H, 4.1; N, 4.4 %). ν_{\max} : 1820, 1800 cm^{-1} (C=O); 1565 cm^{-1} (C=N); 1310, 1150 cm^{-1} (SO_2N). δ (CDCl_3): 2.40 (3H, s, CH_3); 4.45 (2H, s, CH_2); 6.3-8.0 (8H, m, vinylic and aromatics).

4-(Methanesulphonamido)-phenoxyacetic acid 235. Using a cell potential of 1.0v, a crude gum was isolated, which on trituration with petroleum and ether yielded colourless needles of N-methanesulphonyl-1,4-dioxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 240 (60%) m.p. 156-7° (chloroform-petroleum). (Found: C, 44.5; H, 3.7; N, 5.8. $\text{C}_9\text{H}_9\text{NO}_5\text{S}$ requires C, 44.4; H, 3.7; N, 5.8%). ν_{\max} : 1820, 1800 cm^{-1} (C=O); 1565 cm^{-1} (C=N); 1310, 1140 cm^{-1} (SO_2N). δ (CDCl_3): 3.25 (3H, s, CH_3); 4.50 (2H, s, CH_2); 6.2-7.6 (4H, m, vinylic).

4-(p-Bromobenzenesulphonamido)-phenoxyacetic acid 236. The crude product from an anodic oxidation at 1.2v was purified by column chromatography (silica gel eluted with chloroform-ether 1:1) to give N-(p-bromobenzenesulphonyl)-1,4-dioxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 241 as yellow needles (46%) m.p. 141-3° (chloroform-petroleum). (Found: C, 44.0; H, 2.5; N, 3.6. $\text{C}_{14}\text{H}_{10}\text{BrNO}_5\text{S}$ requires C, 43.7; H, 2.6; N, 3.6%). ν_{\max} : 1820, 1800 cm^{-1} (C=O); 1570 cm^{-1} (C=N); 1330, 1160 cm^{-1} (SO_2N). δ (CDCl_3): 4.50 (2H, s, CH_2); 6.2-8.0 (8H, m, vinylic and aromatic).

4-(o-Nitrobenzenesulphonamido)-phenoxyacetic acid 237. The anodic oxidation, at 1.1v, yielded an oil, which on trituration with petroleum gave

N-(o-nitrobenzenesulphonyl)-1,4-dioxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 242 as yellow needles (38%) m.p. 167-8° (chloroform-petroleum). (Found: C, 47.4; H, 2.8; N, 7.6. $C_{14}H_{10}N_2O_7S$ requires C, 48.0; H, 2.9; N, 8.0%). ν_{\max} : 1820, 1800 cm^{-1} (C=O); 1565, 1535 cm^{-1} (C=N); 1330, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 4.50 (2H, s, CH_2); 6.3-8.5 (8H, m, vinylic and aromatic).

3-[4-(p-Toluenesulphonamido)-phenyl]-propanoic acid 248. From 0.5g starting acid and an anode potential of 1.4v, was produced a brown oil (0.3g), homogeneous by TLC, which on trituration with ethanol, and subsequent washing with a little ether, yielded a crystalline solid, identified as N-(p-toluenesulphonyl)-1-oxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 252. Colourless needles (19%) m.p. 146-8° (ether). (Found: C, 61.2; H, 5.0; N, 4.1. $C_{16}H_{15}NO_4S$ requires C, 60.6; H, 4.7; N, 4.4%). ν_{\max} : 1785 cm^{-1} (C=O); 1655 cm^{-1} (C=C); 1550 cm^{-1} (C=N); 1320, 1160 cm^{-1} (SO_2N). δ ($CDCl_3$): 2.45 (3H, s, CH_3); 2.4-3.0 (4H, m, CH_2CH_2); 6.1-8.0 (8H, m, vinylic and aromatic).

4-[4-(p-Toluenesulphonamido)-phenyl]-butanoic acid 261. When 0.5g starting acid was oxidised at a cell potential of 1.3v a yellow oil (0.27g), homogeneous by TLC, was isolated, but attempts at purification failed. However the infra red spectrum of the crude gum $\left[\nu_{\max}^{\text{Thin film}}: 1800-1700 \text{ cm}^{-1} \text{ (C=O)}; 1660 \text{ cm}^{-1} \text{ (C=C)}; 1550 \text{ cm}^{-1} \text{ (C=N)}; 1330, 1160 \text{ cm}^{-1} \text{ (SO}_2\text{N)} \right]$ indicated some formation of the lactone-imine 262 had occurred.

3-[4-(p-Toluenesulphonamido)-phenyl]-propan-1-ol 256. The alcohol 0.75g was oxidised at 1.2v, yielding an oily mixture of compounds. Purification by column chromatography (silica gel eluted with chloroform-ether 1:1) separated the higher Rf material, as a colourless oil which failed to crystallise. The infra red spectrum $\left[\nu_{\max}^{\text{Thin film}}: 3500 \text{ cm}^{-1} \text{ (weak, OH)}; 3260 \text{ cm}^{-1} \text{ (weak NH)}; 1720 \text{ cm}^{-1} \text{ (w)}; 1650 \text{ cm}^{-1} \text{ (C=C)}; 1550 \text{ cm}^{-1} \text{ (C=N)}; 1330, 1160 \text{ cm}^{-1} \text{ (SO}_2\text{N)} \right]$ of this gum indicated a mixture of starting material and cyclised imine 257.

4-(Trimethylacetamido)-phenoxyacetic acid 238. Oxidised at 1.1v, a mixture was recovered (30% by weight) which could not be purified. The crude oil gave an infra red spectrum $\left[\begin{array}{l} \text{Thin film: } 3460 \text{ cm}^{-1} \text{ (bread); } 1820, \\ \text{max} \end{array} \right]$ 1800 cm^{-1} (C=O); 1680, 1660, 1515 cm^{-1} which suggested some lactone 243 formation had occurred.

N-(p-Toluenesulphonyl)-2-[4-(p-toluenesulphonamido)-phenoxy]-ethylamine 267. Using a cell potential of 1.2v, an oil was recovered which could not be induced to crystallise. The spectroscopic data listed below indicate a mixture of starting material, and product imine 268. Found m/e 460 and 458 (2:1) $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ requires m/e 460 $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$ requires m/e 458. $\left[\begin{array}{l} \text{Thin film:} \\ \text{max} \end{array} \right]$ 3280 cm^{-1} (weak NH); 1650 cm^{-1} (C=C); 1560 cm^{-1} (C=N); 1320, 1160 cm^{-1} (SO_2N). δ (CDCl_3): 2.45 (6H, s, $(\text{CH}_3)_2$); 3.1-4.1 (4H, m, CH_2CH_2); 6.1-8.1 (approx. 12H, m, vinyl and aromatic).

From the attempted oxidation of the diphenyl ether 223 at an electrode potential of 1.4v, although a high initial current was recorded (in excess of 100 mA), only starting material was recovered contaminated with a little tar. The sulphonamido-alcohol 253 and acids 249, 250, 251 and 258 all failed to oxidise; however in the case of the acids this is probably due to an insufficiently high anode potential.

Reaction of Substituted N-Aryl Sulphonamides with Lead Tetraacetate

General reaction procedure

A suspension of lead tetraacetate (6.5g 0.15 mol) in glacial acetic acid (30 ml) was added to a stirred solution of the substrate (0.07 mol) in glacial acetic acid (50 ml). The reaction mixture was stirred at room temperature for 1 hr., poured into water (300 ml) and extracted into ether (3 x 100 ml). The combined ethereal extractions were washed with water (2 x 150 ml), saturated sodium bicarbonate solution (2 x 150 ml - or until

effervescence ceased) and water (150 ml), dried over magnesium sulphate, filtered, and the solvent removed by rotary evaporation. Details of purification of the residue are given in the results listed below.

2-[4-(p-Toluenesulphonamido)-phenoxy]-ethanol 212. The initial product, a yellow oil, on trituration with petroleum, yielded the ethylene ketal of 4-(p-toluenesulphonimido)-cyclohexa-2,5-diene-1-one 213 as colourless needles (83%) m.p. 124° (toluene-petroleum), the infra red and NMR spectra of which were identical with those of the imine obtained by anodic oxidation.

4-(p-Toluenesulphonamido)-phenoxyacetic acid 234. The reaction product, a colourless crystalline solid, was shown to be N-(p-toluenesulphonyl)-1,4-dioxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 239 (98%) m.p. 144° (toluene-petroleum), as the infra red and NMR spectra of this material were the same as those recorded from the imine produced by anodic oxidation.

3-[4-(p-Toluenesulphonamido)-phenyl]-propanoic acid 248. Using the reaction conditions detailed above, a yellow/brown oil was obtained, which on trituration with ethanol-ether gave N-(p-toluenesulphonyl)-1-oxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 252 (10%) m.p. $146-8^{\circ}$, the spectral properties of which were identical to those of the spiro lactone produced by anodic oxidation. The yield of lactone 252 could be increased to 40% by heating the reaction mixture under reflux for several hours.

2,2-Dimethyl-3-[4-(p-toluenesulphonamido)-phenoxy]-propanoic acid 258. Although the crude product showed evidence of imine formation $\left[\begin{array}{l} \text{Thin Film} \\ \text{max} \end{array} \right]$: 1785 cm^{-1} (C=O); 1660 cm^{-1} (C=O); 1650 cm^{-1} (C=C); 1550 cm^{-1} (C=N); $1330, 1150 \text{ cm}^{-1}$ (SO_2N), the complex reaction mixture could not be separated into its components.

4-[4-(p-Toluenesulphonamido)-phenyl]-butanoic acid 261 The reaction product, an oil, was shown by TLC to be a mixture, although the infra red

spectrum $\left[\nu_{\text{max}}^{\text{Thin Film}}: 3250 \text{ cm}^{-1} (\text{NH}); 1800-1700 \text{ cm}^{-1} (\text{C=O}); 1655 \text{ cm}^{-1} (\text{C=C}); 1550 \text{ cm}^{-1} (\text{C=N}); 1320, 1160 \text{ cm}^{-1} (\text{SO}_2\text{N}) \right]$ indicated considerable spiro lactone 262 formation had occurred.

N-(p-Toluenesulphonyl)-2-[4-(p-toluenesulphonamido)-phenoxy]-ethylamine 267. When trituration with petroleum failed to yield a crystalline material from the oily reaction product, column chromatography (silica gel eluted with chloroform-ether 1:1) was employed to give an amorphous solid (15% by weight) which was shown to be a mixture of starting material and the cyclised imine 268. $\nu_{\text{max}}: 1560 \text{ cm}^{-1} (\text{C=N}); 1320, 1160 \text{ cm}^{-1} (\text{SO}_2\text{N})$.
{cyclised imine 268. $\nu_{\text{max}}: 1560 \text{ cm}^{-1} (\text{C=N}); 1320, 1160 \text{ cm}^{-1} (\text{SO}_2\text{N})$.
 $\delta (\text{CDCl}_3): 2.45 (6\text{H}, \text{s}, (\text{CH}_3)_2); 3.6-4.4 (4\text{H}, \text{m}, \text{CH}_2\text{CH}_2); 6.1-8.1 (\text{approx.})$

Attempted Dienone-Phenol Rearrangement of 252

(i) The spiro lactone 252 (0.2 g 0.0006 mol) was heated under reflux for 2 hrs with 0.5M sulphuric acid (30 ml), then extracted into ether (5 x 30 ml). On removal of the organic solvent, the resulting oil, although apparently homogeneous by TLC, could not be crystallised. The sample was dissolved in methylene chloride (100 ml), washed with saturated sodium bicarbonate (2 x 100 ml) and water (100 ml), dried, and solvent removed to yield a solid, which by comparison with the infra red and NMR spectra of authentic material was identified as p-toluenesulphonamide.

(ii) The spiro lactone 252 (0.2g 0.0006 mol) was dissolved in acetic anhydride (10 ml), boron trifluoride-etherate (5 drops) added, and the mixture left at room temperature for 2 h. The solvent was removed by rotary evaporation, the residue partitioned between ether (100 ml) and saturated sodium bicarbonate solution. The separated aqueous layer was acidified with concentrated hydrochloric acid, the white precipitate extracted into methylene chloride (3 x 100 ml), dried over magnesium

sulphate, filtered, and the solvent removed under reduced pressure to yield 3-[4-(N-acetyl-p-toluenesulphonamido)-2-acetoxyphenyl]-propanoic acid 274 as a yellow oil (38%). ν_{\max} : 1765 cm^{-1} ($\text{CH}_3\text{CO}_2\text{Ar}$); 1740 cm^{-1} (CO_2H); 1710 cm^{-1} (CH_3CON); 1365, 1170 cm^{-1} (SO_2N). δ (CDCl_3): 1.90 (3H, s, CH_3CON); 2.30 (3H, s, ar- CH_3); 2.45 (3H, s, CH_3COOAr); 2.65, 2.90 (2H, 2t, $J = 6\text{H}_z$, CH_2CH_2); 7.00 (1H, s, aromatic); 7.1-7.5 (4H, m, aromatics); 7.90 (2H, d, $J = 9\text{Hz}$, ar. ortho to S).

Methyl 3-[4-(p-toluenesulphonamido)-phenyl]-propanoate 275. A solution of 3-[4-(p-toluenesulphonamido)-phenyl]-propanoic acid 248 (1.0g 0.003 mol) in methanol (50 ml) containing acetyl chloride (0.5 ml) was heated under reflux for several hours, the solvent removed on a rotary evaporator, and the cooled residue triturated with petroleum to yield the title ester as colourless needles (82%) m.p. 98° (toluene-petroleum).

ν_{\max} : 3240 cm^{-1} (NH); 1730 cm^{-1} (C=O); 1330, 1155 cm^{-1} (SO_2N). δ (CDCl_3): 2.35 (3H, s, ar- CH_3); 2.4-3.1 (4H, m, CH_2CH_2); 3.65 (2H, s, OCH_3); 7.00 (4H, m, ar. ortho to CH_2 and N); 7.20 (2H, d, $J = 9\text{Hz}$, ar. ortho to CH_3); 7.65 (2H, d, $J = 9\text{Hz}$, ar. ortho to S); c.a. 7.4 (1H, broad s, exchanges with D_2O , NH).

Methyl 3-[4-(N-acetyl-p-toluenesulphonamido)-phenyl]-propanoate 276. A solution of the preceding ester 275 (0.8g 0.0024 mol) in acetic anhydride (30 ml) containing boron trifluoride-etherate (5 drops) was left at room temperature for 3 h., before the solvent was removed by evaporation. The residual gum was dissolved in ether (100 ml), washed with water (100 ml), saturated sodium bicarbonate (100 ml), and water (100 ml), dried over magnesium sulphate, filtered, and the solvent removed to yield the title N-acylsulphonamide 276 as colourless needles (70%) m.p. $111-112^\circ$ (methanol).

(Found: C, 60.5; H, 5.7; N, 3.7. $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}$ requires C, 60.8; H, 5.6; N, 3.7%). ν_{\max} : 1740 cm^{-1} (C=O); 1700 cm^{-1} (C=O); 1360, 1170 cm^{-1} (SO_2N). δ (CDCl_3): 1.85 (3H, s, CH_3CON); 2.40 (3H, s, ar- CH_3); 2.5-3.2 (4H, m, CH_2CH_2); 3.65 (3H, s, CH_3O); 7.0-7.5 (6H, m, aromatics); 7.90 (2H, d, $J = 9\text{H}_z$,

ar. ortho to S).

Hydrolysis of N-Sulphonylimines to the Corresponding Dienones

Hydrolysis of the imine bond contained in the sulphonyl imine 213 (100 mg) to the corresponding dienone 214 was attempted using the following aqueous solutions:-

(i) Water (10 ml) with enough THF to effect solution, heated under reflux for 2 h.

(ii) As (i) except the water was buffered to pH 7.

(iii) As (i) plus 2M hydrochloric acid (5 drops).

(iv) As (i) plus trifluoroacetic acid (5 drops).

Little, if any, hydrolysis was observed to have occurred under the above experimental conditions. However when a solution of the imine 213 (400 mg) in toluene was passed down a neutral alumina column Brockman Activity II (12g), removal of the eluate gave the dienone 214 as colourless needles (68%) m.p. 48-9° (lit.¹⁹² m.p. 51-3°. $\bar{\nu}_{\max}$: 1675 cm⁻¹ (C=O); 1640 cm⁻¹ (C=C). δ (CDCl₃): 4.10 (4H, s, CH₂CH₂); 6.10, 6.60 (4H, 2d, J=10Hz, vinyl). Further elution with ether gave p-toluenesulphonamide (45%) as colourless needles m.p. 112-4° (lit.¹⁷⁹ m.p. 105 or 137°).

N-Methanesulphonyl-4-anisidine 194 (300 mg 0.0015 mol) in methanol (150 ml) was oxidised at 1.0v until TLC examination indicated no starting material present. After removal of the solvent by rotary evaporation the residue was washed onto an Activity II neutral alumina column (10g) and eluted with toluene to yield 4,4-dimethoxycyclohexa-2,5-dienone¹⁰⁸ 208 (98%) as a yellow oil. $\bar{\nu}_{\max}$ Thin Film: 2830 cm⁻¹ (MeO); 1690 cm⁻¹ (C=O); 1640 cm⁻¹ (C=C). δ (CDCl₃): 3.35 (6H, s, (OCH₃)₂); 6.20, 6.80 (4H, 2d, J=10Hz, vinyl).

Reaction of Spirodieniminelactones with Nucleophiles

The two iminolactones 239 and 252 (200 mg 0.0006 mol) were each treated in DMF solution (5 ml) with one equivalent of either potassium iodide (105 mg) or potassium cyanide (42 mg) at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between saturated sodium bicarbonate (100 ml) and ether (100 ml). The aqueous layer was acidified using concentrated hydrochloric acid, the precipitate extracted into methylene chloride (4 x 100 ml), the combined extracts dried over magnesium sulphate, filtered, and the solution rotary evaporated to dryness. Examination by TLC of the product showed a mixture of material, which was dissolved in dry ether and reacted with diazomethane. The organic solution was washed with saturated sodium bicarbonate (100 ml) and water (100 ml), dried over magnesium sulphate, filtered, evaporated and the dark residue examined by mass spectroscopy. The following compounds were identified:-

Methyl x-iodo-4-(N-methyl-p-toluenesulphonamido)-phenoxyacetate 277
(NUC=I). Found m/e 475. Calc. for $C_{17}H_{18}NO_5S$ = 475.

Methyl x-cyano-4-(N-methyl-p-toluenesulphonamido)-phenoxyacetate 277
(NUC=CN). Found m/e 374. Calc. for $C_{18}H_{18}N_2O_5S$ = 374.

Methyl 3-[x-iodo-4-(N-methyl-p-toluenesulphonamido)-phenyl]-propanoate 278 (NUC=I). Found m/e 473. Calc. for $C_{18}H_{20}NO_4S$ = 473.

Methyl 3-[x-cyano-4-(N-methyl-p-toluenesulphonamido)-phenyl]-propanoate 278 (NUC=CN). Found m/e 372. Calc. for $C_{19}H_{20}N_2O_4S$ = 372.

Attempted Selective Reduction of the Imine Bond

Reduction of the sulphonyl dienimine 213 was attempted as follows:-

(i) The imine (100 mg) was added in portions to a solution of sodium

borohydride (1g) in ethanol (10 ml), the reaction mixture stirred at room temperature overnight, poured into water (50 ml), extracted with ether (3 x 50 ml), the combined ethereal layers washed once with water (100 ml), dried over magnesium sulphate, filtered, and the solvent removed to yield 2-[4-(p-toluenesulphonamido)-phenoxy]-ethanol 212 (66%) as a grey oil, the IR spectrum of which was identical to that of authentic alcohol.

(ii) The imine 213 (100 mg) in methanolic solution (10 ml) was added to a solution of sodium dithionite (1g) in water (10 ml), the solution left overnight and worked up as above to yield a colourless solid identified as the sulphonamido-ethanol 212 (83%).

(iii) The imine 213 (100 mg) was added to a mixture of powdered zinc (1g) in glacial acetic acid (10 ml), stirred overnight, filtered, and the residue washed thoroughly with ether and fresh acetic acid. The combined filtrate was washed with water (2 x 100 ml), saturated sodium bicarbonate (2 x 100 ml), and water (100 ml), dried over magnesium sulphate, filtered, then rotary evaporated to yield a yellow solid shown to be the sulphonamido-ethanol 212 (95%).

Attempted Transketalisation of Dimethoxycyclohexadienimines

The dimethyl ketal 204 (100 mg) was stirred overnight with ethanediol (10 ml) containing boron trifluoride-etherate (3 drops), then poured into water (100 ml) and extracted into methylene chloride (3 x 100 ml). The combined organic layers were dried and evaporated to yield a crude oil identified by infra red spectroscopy and comparative TLC as N-(p-toluene-sulphonyl)-4-anisidine 192.

WORK DESCRIBED IN CHAPTER FOUR

Preparation of the 6,7-Dimethoxyisoquinaldic Acid 315

6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride 310. The formate salt, produced from commercially available 2-(3,4-dimethoxyphenyl)-ethylamine and formic acid, on pyrolysis at 180° for 1.5h. gave the N-formamide 309 m.p. 38-40° (lit.¹⁴⁶ m.p. 40-2°). ν_{\max} : 3330 cm⁻¹ (NH); 1655 cm⁻¹ (C=O).

Cyclisation of the amide with phosphoryl chloride afforded the isoquinoline 310 as pale yellow needles, m.p. 110-2°.¹⁴⁶ ν_{\max} : 1630 cm⁻¹ (C=N).

2-Benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 311.

The isoquinoline hydrochloride 310 was dissolved in water, made basic with sodium hydroxide solution, and the precipitate extracted into methylene chloride. The organic solution of the free amine was reacted¹⁴⁹ with potassium cyanide (dissolved in the minimum quantity of water) and benzoyl chloride; the reaction temperature was maintained between 20-30° by means of an ice bath. The title Reissert compound 311 was isolated and recrystallised from methanol as colourless needles (63%) m.p. 212° (lit.¹⁴⁸ m.p. 215-6°). ν_{\max} : 1650 cm⁻¹ (C=O).

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline 312. The above 1-alkyl Reissert compound 312 was prepared by a phase-transfer reaction according to the method of Skiles and Cava,¹⁵⁰ from the Reissert compound 311, 4-nitrobenzyl bromide, cetyltrimethylammonium bromide and benzene stirred rapidly in the presence of 50% potassium hydroxide solution, under an atmosphere of nitrogen. The product, a crude yellow oil, on trituration with methanol, gave the title isoquinoline 312 as colourless needles (82%) m.p. 216-219° (chloroform-petroleum). (Found: C, 67.8; H, 5.0; N, 9.0. C₂₆H₂₃N₃O₅ requires C, 68.3; H, 5.0; N, 9.2%). ν_{\max} : 1650 cm⁻¹ (C=O). δ (CDCl₃): 1.6-2.4, 2.8-3.6 (4H, 2m, CH₂CH₂); 3, 5.0,

4.55 (2H, 2d, $J=12\text{Hz}$, ar- CH_2); 3.90 (6H, s, $(\text{OCH}_3)_2$); 6.45, 7.05 (2H, 2s, ar. at C_5, C_8); 6.70, 7.90 (4H, 2d, $J=9\text{Hz}$, ar. ortho to CH_2 and N); 7.35 (5H, s, ar-CO).

2-Benzoyl-6,7-dimethoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 313. A solution of the benzyl Reissert compound 312 (3.5g 0.0077 mol) in glacial acetic acid (80 ml) containing concentrated hydrochloric acid (6 ml) was stirred at room temperature overnight.¹⁵¹ The resulting colourless precipitate was filtered off, washed with a little water, and recrystallised from aqueous acetic acid to yield the isoquinaldic acid 313 in 98% yield, m.p. $244-8^\circ$. (Found: C, 65.0; H, 5.0; N, 5.9. $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_7$ requires C, 65.5; H, 5.0; N, 5.9%). ν_{max} : 1740 cm^{-1} (C=O); 1635 cm^{-1} (C=O). δ (DMSO): 1.6-2.8 (4H, m, CH_2CH_2); 3.30, 4.25 (2H, 2d, $J=12\text{Hz}$, ar- CH_2); 3.70, 3.80 (6H, 2s, $(\text{OCH}_3)_2$); 6.55, 7.10 (2H, 2s, ar. at C_5, C_8); 6.95, 7.95 (4H, 2d, $J=9\text{Hz}$, ar. ortho to CH_2 and N); 7.35 (5H, s, ar-CO).

1-(4-Aminobenzyl)-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 314. The nitro compound 313 (3.0g 0.0063 mol) was reduced with powdered zinc metal (3g) and glacial acetic acid (40 ml) stirred under a nitrogen atmosphere at room temperature for 2h. The reaction mixture was filtered and the residue washed repeatedly with glacial acetic acid. The combined filtrates were evaporated under reduced pressure to leave a yellow oil which, on trituration with ether, gave a pale yellow crystalline solid 2.7g (96%). Although further purification was not successful, the infrared spectrum [ν_{max} : $3450, 3380\text{ cm}^{-1}$ (NH_2); 1720 cm^{-1} (C=O); 1620 cm^{-1} (C=O)] indicated that reduction of the nitro group had been achieved.

2-Benzoyl-6,7-dimethoxy-1-[4-(p-toluenesulphonamido)-benzyl]-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 315. The amino acid 314 (2.7g 0.006 mol), 4-toluenesulphonyl chloride (1.2g 0.006 mol) and pyridine (10 ml)

in chloroform solution (50 ml) were refluxed for 2 hr. After washing with acid and removal of solvent, as described in the previous section, trituration of the residual gum with petroleum, yielded the sulphonamido $\text{C}_{33}\text{H}_{32}\text{N}_2\text{O}_7\text{S}$ requires C, 66.0; H, 5.3; N, 4.7%. ν , 65.3; H, 5.4; N, 4.3. $\text{C}_{33}\text{H}_{32}\text{N}_2\text{O}_7\text{S}$ requires C, 66.0; H, 5.3; N, 4.7%. ν max: 3260 cm^{-1} (NH); 1730 cm^{-1} (C=O); 1620 cm^{-1} (broad C=O); $1340, 1165\text{ cm}^{-1}$ (SO_2N). δ ($\text{D}_2\text{O}/\text{NaOD}$): 1.5-3.0 (2H, m, CH_2N); 2.35 (3H, s, arCH_3); 3.1-4.1 (4H, m, PhCH_2CH_2 ; PhCH_2C); 3.95, 4.25 (6H, 2s, $(\text{OCH}_3)_2$); 6.5-8.0 (approx. 15H, m, aromatic).

Attempted Preparation of the Dihydroisoquinaldic Acid 321

2-Benzoyl-1-cyano-1,2-dihydroisoquinoline 317. The above Reissert compound 317 was prepared from commercially available isoquinoline, potassium cyanide, and benzoyl chloride, by the method described for compound 311. The resulting colourless needles crystallised from ethanol to yield the title compound 317 in 53%, m.p. $123-4^\circ$ (lit.^{193;194} m.p. 128°). ν max: 1660 cm^{-1} (C=O); 1635 cm^{-1} (C=C).

2-Benzoyl-1-cyano-1-(4-nitrobenzyl)-1,2-dihydroisoquinoline 318. Using the Reissert compound 317, 4-nitrobenzyl bromide, cetyltrimethylammonium bromide in benzene and 50% sodium hydroxide solution, the title isoquinoline 318 was prepared in analogous fashion to compound 312 in 86% yield as colourless needles from either ethanol or chloroform-petroleum m.p. $194-6^\circ$ (lit.¹⁹⁴ m.p. $203-4^\circ$). (Found: C, 72.5; H, 4.6; N, 10.2; $\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_3$ requires C, 72.9; H, 4.3; N, 10.6%). ν max: 1680 cm^{-1} (C=O); 1635 cm^{-1} (C=N). δ (CDCl_3): 3.55, 3.85 (2H, 2d, $J=12\text{H}_z$, CH_2); 5.55, 6.35 (2H, 2d, $J=8\text{H}_z$, $\text{CH}=\text{CH}$); 6.8-8.1 (approx. 13H, m, aromatics).

2-Benzoyl-1-(4-nitrobenzyl)-1,2-dihydroisoquinoline-1-carboxylic

acid 319. The alkylated Reissert compound 318 (1.0g 0.0025 mol) was hydrolysed using glacial acetic acid (30 ml) and concentrated hydrochloric acid (2 ml) stirred at room temperature for 3 hr., then poured into cold water. The precipitate was filtered off, washed with distilled water and air dried, yielding the isoguinaldic acid 319 as colourless needles (76%) m.p. 183-4° (aqueous acetic acid). (Found: C, 69.1; H, 4.3; N, 6.3. $C_{24}H_{18}N_2O_5$ requires C, 69.5; H, 4.3; N, 6.7%). ν_{\max} : 1750, 1715 cm^{-1} (C=O); 1670 cm^{-1} (C=O); 1640 cm^{-1} (C=C); δ ($CDCl_3$): 3.40, 4.20 (2H, 2d, J=12Hz, CH_2); 5.00, 6.10 (4H, 2d, J=8Hz, CH=CH); 6.75, 7.85 (4H, 2d, J=9Hz, ar. ortho to CH_2 and N); 7.0-7.3 (4H, m, ar. at C_{5-8}); 7.4 (5H, broad s, superimposed, $PhCO$).

1-(4-Aminobenzyl)-2-benzoyl-1,2-dihydroisoquinoline-1-carboxylic acid

320. Reduction of the preceding nitro acid 319 with zinc metal and glacial acetic acid was effected as described for compound 314, with trituration of the residual oil with ether resulting in a pale yellow solid, m.p. 155-160°. Although further purification was not achieved, the infra red spectrum [ν_{\max} : 3440, 3380 cm^{-1} (NH_2); 1630 cm^{-1} (broad C=O and C=C)] showed that the amino acid 320 had been produced in a crude yield of 58%.

2-Benzoyl-1-[4-(p-toluenesulphonamido)-benzyl]-1,2-dihydroisoquinoline-

1-carboxylic acid 321. The crude amino acid 320 (3.0g 0.0078 mol), p-toluenesulphonyl chloride (1.5g 0.0079 mol) and pyridine (6 ml) in chloroform solution (30 ml) were left overnight at room temperature. After washing with acid as described in the previous section, and removal of the organic solvent by rotary evaporation, the product, a froth, could not be induced to crystallise. Notwithstanding evidence from the infra red spectrum [ν_{\max} : 3240 cm^{-1} (NH); 1730 cm^{-1} (C=O); 1670 cm^{-1} (C=O); 1630 cm^{-1} (C=C); 1350, 1160 cm^{-1} (SO_2N)] indicating the desired sulphonamido acid 321 had

been produced, as further purification could not be achieved, the sample was considered unsuitable for oxidation experiments.

Oxidation of the 6,7-Dimethoxyisoquinaldic Acid 315.

Anodic oxidations of the above sulphonamido acid 315 in acetonitrile solution, using the previously described conditions, were carried out at potentials between 1.0 and 1.4v. At the lower voltage of 1.0v an approximate two electron oxidation appeared to be occurring and a recovery of 80% by weight of a fawn solid was achieved. With the anode potential set at 1.4v, a larger current corresponding to a four electron oxidation was passed, yielding a dark brown solid. Examination of all isolated products by TLC showed complex mixtures to be present, and although NMR spectroscopy proved useless on such impure material, the infra red spectrum of the sample from the 1.4v oxidation [ν_{max} : 3600-2500 cm^{-1} (salt bands); 1730, 1670, 1640, 1555, 1340, 1160 cm^{-1}] showed a peak corresponding to imine formation. The increased absorption in the carbonyl region, coupled to an m/e value of 311 obtained by mass spectroscopy indicates the possible formation of 2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-1-one; similar compounds have been isolated¹⁹⁵ from autoxidation studies carried out in these laboratories.

Repeating these oxidations in methanolic solution also produced a mixture which proved impossible to separate. The infra red. spectra [ν_{max} : 1720, 1640, 1580 cm^{-1}] again showed increased absorption in the carbonyl region, but gave no indication of imine formation. Mass spectroscopy was of little value, as a high degree of fragmentation was observed m/e = 429, 401, 369, 355, 345, 343.

Attempted oxidation of the sulphonamido acid 315 with lead tetraacetate, as described previously, produced a mixture of products, from which only starting material could be isolated. No indication of imine formation was observed.

WORK DESCRIBED IN CHAPTER FIVE

Preparation of the 7-Hydroxy-6-Methoxy-1-Benzylisoquinoline 342

4-Nitrophenylacetyl chloride 348 was made by the action¹⁹⁶ of thionyl chloride on commercially available 4-nitrophenylacetic acid. Trituration of the crude residue with petroleum yielded the acid chloride 348 as pale yellow plates from petroleum (86%) m.p. 46° (lit.¹⁷⁹ m.p. 47°). ν_{max} : 1790 cm^{-1} (C=O).

4-Benzyloxy-3-methoxyphenethylamine 347 was produced by the benzylation of vanillin¹⁹⁷ to give benzylvanillin, its condensation with nitromethane¹⁹⁸ to yield 4-benzyloxy-3-methoxy-*w*-nitrostyrene, which was reduced with lithium aluminium hydride¹⁹⁹ to the amine 347 hydrochloride m.p. 162 (lit.²⁰⁰ m.p. 164-166°).

N-(4-Benzyloxy-3-methoxyphenethyl)-4-nitrophenylacetamide 349. The above amine 347 hydrochloride was dissolved in water and concentrated ammonia solution added until precipitation ceased. The mixture was extracted into ether, separated, and after removal of the organic solvent, trituration of residual oil with petroleum gave the amine 347 as a fawn solid (90%), which together with the acid chloride 348 and triethylamine was left in chloroform solution overnight.²⁰¹ The reaction mixture was washed with dilute aqueous acid, saturated sodium bicarbonate, and water, and the solvent evaporated to yield the title amide 349 which recrystallised from methanol or aqueous ethanol as yellow needles (81%) m.p. 134 (lit.²⁰¹ m.p. 134-6°). ν_{max} : 3310 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ (CDCl_3): 2.65 (2H, t, $J=6\text{H}_z$, ar $\text{CH}_2\text{CH}_2\text{N}$); 3.2-3.7 (4H, m, ar CH_2CO ; ar $\text{CH}_2\text{CH}_2\text{N}$); 3.80 (3H, s, CH_3O); 5.00 (2H, s, ar CH_2O); 6.2-6.8, 7.1-7.5 (10H, 2m, aromatic); 8.00 (2H, d, $J=9\text{H}_z$, ar. ortho to NO_2); c.a. 5.5 (1H, broad s, NH).

7-Benzyloxy-6-methoxy-1-(4-nitrobenzyl)-3,4-dihydroisoquinoline 350 hydrochloride. A solution of the amide 349 (1.0g 0.0024 mol) in chloroform

(20 ml) was left standing overnight with phosphorus pentachloride (2g). The solvent was removed by rotary evaporation, and on addition of methanol (20 ml) to the residue, an exothermic reaction occurred, followed by the formation of yellow needles. The solid was washed with a little ether to give the dihydroisoquinoline 350 hydrochloride (78%) m.p. 201-5° (lit.²⁰¹ m.p. 206-7°) (methanol-ether). (Found: C, 66.2; H, 5.3; N, 6.1. Calc. for $C_{24}H_{23}ClN_2O_4$: C, 65.7; H, 5.2; N, 6.4%). ν_{\max} : 2650 cm^{-1} (broad, salt bands); 1655, 1605, 1570, 1520, 1510 cm^{-1} . δ (D_2O): 2.9-3.1 (4H, m, CH_2 CH_2); 3.8 (3H, s, CH_3O); 4.1 (2H, s, ar CH_2C); 4.95 (2H, s, ar CH_2O); 6.3-8.0 (11H, m, aromatic).

Attempted preparation of 7-benzyloxy-6-methoxy-1-[4-(p-toluenesulphonamido)-benzyl]-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 351 by the zinc and acetic acid reduction of the dihydroisoquinoline 350 (810 mg 0.0018 mol) resulted in an oil which on trituration with petroleum gave a brown solid (500 mg). The infra red and NMR spectra indicated a product in which only the nitro group had been reduced. ν_{\max} : 3430, 3360 cm^{-1} (NH_2); 1630 cm^{-1} (C=N); 1610, 1575, 1520 cm^{-1} . δ ($CDCl_3$): 2.5-2.8, 3.6-4.0 (4H, 2m, CH_2CH_2); 3.80 (3H, s, CH_3O); 4.9 (2H, m, ar CH_2C); 5.00 (2H, s, ar CH_2O); 6.4-7.5 (11H, m, aromatics). Purification of the above crude amine by preparation of the mono- and/or bis-sulphonamide, using the method described in the previous sections, produced only an inseparable mixture.

7-Benzyloxy-6-methoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline 353. To a stirred solution of the dihydroisoquinoline 350 hydrochloride (1.0g 0.0023 mol) in ethanol (30 ml) was added sodium borohydride (700 mg). After stirring overnight, the reaction mixture was poured into 4M sodium hydroxide (50 ml) and extracted into methylene chloride (3 x 50 ml). The combined organic layers were washed once with water (100 ml), dried over potassium carbonate, and the solvent removed to yield a brown gum, which on cooling, and trituration with petroleum, gave a pale orange solid 730 mg

(79%) identified as the tetrahydroisoquinoline 353. ν_{\max} : 1600, 1510 cm^{-1} . δ (CDCl_3): 2.3-3.1 (6H, m, CH_2CH_2 ; ar CH_2C); 3.70 (3H, s, CH_3O); 3.90 (1H, m, ar CH_2CH); 4.85 (2H, s, ar CH_2O); 6.30, 6.40 (2H, 2s, ar. at C_5 and C_8); 6.9-7.3 (7H, m, PhCH_2O ; ar. ortho to CH_2); 7.95 (2H, d, $J=9\text{Hz}$ ar. ortho to N), c.a. 1.4 (1H, broad s, exchanges with D_2O , NH). This material could not be purified further for elemental analysis.

7-Benzyloxy-6-methoxy-1-(4-nitrobenzyl)-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 354. The title sulphonamide 354 was prepared by the method described previously, from the isoquinoline 353, p-toluenesulphonyl chloride and pyridine in chloroform solution heated under reflux for 2 hr. Trituration of the resulting gum yielded the above sulphonamide 354 as pale yellow needles (94%) m.p. 209-210° (methanol). (Found: C, 66.8; H, 5.4; N, 4.9. $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_6\text{S}$ requires C, 66.7; H, 5.4; N, 5.0%). ν_{\max} : 1350, 1150 cm^{-1} (SO_2N). δ (CDCl_3): 2.30 (3H, s, ar. CH_3); 2.3-2.6; 3.2-3.7 (4H, 2m, CH_2CH_2); 3.10 (2H, d, $J=6\text{Hz}$, ar CH_2CH); 3.80 (3H, s, CH_3O); 5.0 (3H, m, PhCH_2O ; ar CH_2CH); 6.35; 6.40 (2H, 2s, ar. at C_5 and C_8); 6.8-7.6 (11H, m, aromatic); 7.95 (2H, d, $J=9\text{Hz}$, ar. ortho to N).

1-(4-Aminobenzyl)-7-benzyloxy-6-methoxy-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 355. A solution of the nitrobenzylisoquinoline 354 in glacial acetic acid was stirred with powdered zinc under an atmosphere of nitrogen, in an analogous fashion to 351. Trituration with ether of the residual oil yielded an off-white solid (87%) m.p. 103-6° which by spectral analysis was identified as the aminobenzylisoquinoline 355. ν_{\max} : 3460, 3380 cm^{-1} (NH_2); 1330, 1160 cm^{-1} (SO_2N). δ (CDCl_3): 2.30 (3H, s, ar CH_3); 2.2-2.6; 3.2-3.7 (4H, 2m, CH_2CH_2); 2.8-3.0 (2H, m, ar CH_2CH); 3.75 (3H, s, CH_3O); 4.8-5.1 (3H, m, PhCH_2O ; ar CH_2CH); 6.10; 6.30 (2H, 2s, ar. at C_5 and C_8); 6.40; 6.65 (4H, 2d, $J=9\text{Hz}$, ar. ortho to CH_2 and N); 7.25 (5H, s,

PhCH_2O); 7.00; 7.40 (4H, 2d, $J = 8\text{Hz}$, ar. ortho to CH_3 and S). 3.4(2H, broad m, exchanges with D_2O , NH_2). No further purification of this compound was achieved.

7-Benzyloxy-6-methoxy-1-[4-(p-toluenesulphonamido)-benzyl]-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 352. The aminobenzylisoquinoline 355 was reacted with p-toluenesulphonyl chloride and pyridine in chloroform at room temperature in the manner described in the previous section. Trituration of the product, an oil, with petroleum gave a yellow solid (74%) m.p. $103-7^\circ$. Recrystallisation attempts were unsuccessful, and even column chromatography (silica gel eluted with chloroform/ether 1:1) failed to afford an analytically pure sample. However spectroscopic evidence identified the material as the title isoquinoline 352. ν_{max} : 3260 cm^{-1} (NH); $1350, 1165\text{ cm}^{-1}$ (SO_2N). δ (CDCl_3): 2.30 (6H, s, $(\text{arCH}_3)_2$); 2.3-3.6 (6H, m, CH_2CH_2 ; ar CH_2CH); 3.75 (3H, s, CH_3O); 4.8-5.1 (3H, m, PhCH_2O ; ar CH_2CH); 6.30, 6.35 (2H, 2s, ar. at C_5 and C_8); 6.6-7.7 (approx. 16H, m, aromatic and NH).

7-Hydroxy-6-methoxy-1-[4-(p-toluenesulphonamido)-benzyl]-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 342. A solution of the benzyloxy-isoquinoline 352 (1.5g 0.0022 mol) in methanol (200 ml) containing 10% palladium on charcoal (1.5 g) was hydrogenated until uptake ceased. The reaction mixture was filtered, the residue washed carefully with methanol (200 ml) and the combined filtrates rotary evaporated to yield 1.25 g (96%) pale pink solid, m.p. $96-99^\circ$. As recrystallisation failed, column chromatography was employed (silica gel eluted with chloroform/ether) to give a pure sample of the phenolic isoquinoline 342. (Found: C, 60.1; H, 5.5; N, 4.3. $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_6\text{S}_2 \cdot 1\frac{1}{2}\text{H}_2\text{O}$ requires C, 60.1; H, 5.7; N, 4.5%). ν_{max} : 3460 cm^{-1} (OH); 3260 cm^{-1} (NH); $1330, 1160\text{ cm}^{-1}$ (SO_2N). δ (CDCl_3): 2.30 (6H, s, $(\text{arCH}_3)_2$); 2.3-3.6 (6H, m, CH_2CH_2 ; ar CH_2CH); 3.75 (3H, s, CH_3O); 4.95 (1H,

t, $J=6\text{Hz}$, ar CH_2CH); 6.35 (2H, 2s, ar. at C_5 and C_8); 6.6-7.9 (approx. 12H, m, aromatic); 5.7 (1H, broad s, exchanges with D_2O , NH/OH).

Alternative Preparation of the Nitrobenzylisoquinoline 354

Preparation of N-sulphonylphenethylamines

The following three sulphonamides 356, 357 and 358 were prepared¹⁷⁴ by reacting the phenethylamine 347 with the corresponding sulphonyl chloride in the presence of pyridine at room temperature in chloroform solution, as detailed in the previous section.

N-(p-Toluenesulphonyl)-2-(4-benzyloxy-3-methoxyphenyl)ethylamine 356.

Using p-toluenesulphonyl chloride, the title compound 356 was produced as colourless needles (80%) m.p. $110-111^\circ$ (aqueous ethanol). (Found: C, 67.2; H, 6.0; N, 3.2. $\text{C}_{23}\text{H}_{25}\text{NO}_4\text{S}$ requires C, 67.1; H, 6.1; N, 3.4%). ν_{max} : 3280 cm^{-1} (NH); $1325, 1160\text{ cm}^{-1}$ (SO_2N). δ (CDCl_3): 2.40 (3H, s, ar CH_3); 2.65, 3.10 (4H, 2t, $J=6\text{Hz}$, CH_2CH_2); 3.80 (3H, s, CH_3O); 5.10 (2H, s, PhCH_2O); 6.40, 6.75 (2H, 2d, $J=7\text{Hz}$, ar. at C_5 and C_6); 6.55 (1H, s, ar. at C_2); 7.20, 7.65 (4H, 2d, $J=8\text{Hz}$, ar. ortho to CH_3 and S); 7.35 (5H, s, PhCH_2O); c.a. 4.5 (1H, broad s, exchanges with D_2O , NH).

N-Methanesulphonyl-2-(4-benzyloxy-3-methoxyphenyl)-ethylamine 357.

Prepared using methanesulphonyl chloride, the colourless product 357 was recrystallised from aqueous ethanol in 55% yield m.p. $140-2^\circ$. (Found: C, 60.9; H, 6.4; N, 4.0. $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{S}$ requires C, 60.9; H, 6.3; N, 4.2%). ν_{max} : 3260 cm^{-1} (NH); $1315, 1145\text{ cm}^{-1}$ (SO_2N). δ (CDCl_3): 2.75 (3H, s, CH_3SO_2); 2.75, 3.35 (4H, 2t, $J=6\text{Hz}$, CH_2CH_2); 3.85 (3H, s, CH_3O); 5.10 (2H, s, PhCH_2O); 6.5-6.9 (3H, m, aromatic); 7.2-7.5 (5H, m, PhCH_2O); 4.4 (1H, broad s, exchanges with D_2O , NH).

N-(p-Bromobenzenesulphonyl)-2-(4-benzyloxy-3-methoxyphenyl)-ethylamine

358. Prepared with p-bromobenzenesulphonyl chloride, the title compound 358 was produced in 81% yield as pink needles m.p. 113-4° (aqueous ethanol). (Found: C, 55.6; H, 4.7; N, 2.8 C₂₂H₂₂BrNO₄S requires C, 55.5; H, 4.6; N, 2.9%). $\bar{\nu}_{\max}$: 3290 cm⁻¹ (NH); 1325, 1160 cm⁻¹ (SO₂N). δ (CDCl₃): 2.65, 3.10 (4H, 2t, J=6Hz, CH₂CH₂); 3.80 (3H, s, CH₃O); 5.10 (2H, s, PhCH₂O); 6.4-6.9 (3H, m, ar. at C₂, C₅, C₆); 7.2-7.7 (9H, m, PhCH₂O; ar. ortho to Br and S); 4.7 (1H, broad s, exchanges with D₂O, NH).

4-Nitrophenethyl bromide. Prepared under standard conditions²⁰² by the addition of fuming nitric acid to a solution of phenethyl bromide in glacial acetic acid and acetic anhydride, yielding the nitro bromide as pale yellow needles from petroleum (60%), m.p. 68° (lit.²⁰² m.p. 69-70°). $\bar{\nu}_{\max}$: 1610, 1600, 1530, 1510, 1350, 850 cm⁻¹.

4-Nitrostyrene. The crude distillate from the steam distillation of a mixture of 4-nitrophenethyl bromide, triethylamine, and water, was extracted into ether, dried, and the organic solvent evaporated to leave the nitrostyrene as a yellow oil (65%) which could not be induced to crystallise at room temperature (lit.²⁰³ m.p. 20-2°). $\bar{\nu}_{\max}$: 1600, 1510, 1340, 855 cm⁻¹.

4-Nitrophenylacetaldehyde 359. Oxidation of the above nitrostyrene in methylene chloride solution was effected using lead tetraacetate¹⁷⁵ dissolved in trifluoroacetic acid. Extraction of the residual gum into petroleum gave only a low yield of the title aldehyde (21%), m.p. 82° (lit. 85-6°)¹⁷⁵. $\bar{\nu}_{\max}$: 1740 cm⁻¹ (C=O); 1345 cm⁻¹ (conj. NO₂).

7-Benzyloxy-6-methoxy-1-(4-nitrobenzyl)-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 354. Prepared by a modified¹⁷⁴ Pictet-Spengler condensation of the N-sulphonylphenethylamine 356 (0.5g 0.0012 mol) and

4-nitrophenylacetaldehyde 359 (0.3g 0.0018 mol) in methylene chloride solution (30 ml) containing boron trifluoride-etherate (1 ml) stirred at room temperature overnight. The title isoquinoline 354 was isolated as pale orange needles (91%) m.p. 197-9° (chloroform-petroleum) the infra red and NMR spectra of which compared exactly with those of the compound prepared by the previous route.

Due to the problems in handling the aldehyde 359 this alternative route to sulphonylisoquinolines similar to 354 was not pursued further.

Preparation of 6,7-Dimethoxy-1-benzylisoquinolines

N-(3,4-Dimethoxyphenethyl)-4-nitrophenylacetamide 360. The above acetamide 360 was prepared²⁰⁴ in an analogous fashion to 349 from commercially available 3,4-dimethoxyphenethylamine, triethylamine and 4-nitrophenylacetyl chloride 348 in chloroform solution. Trituration of the crude gum with petroleum produced an orange solid, which recrystallised from methanol to yield the title acetamide 360 as pale yellow needles (74%) m.p. 119° (lit.²⁰⁴ m.p. 120°). ν_{\max} : 3300 cm⁻¹ (NH); 1655 cm⁻¹ (C=O).

6,7-Dimethoxy-1-(4-nitrobenzyl)-3,4-dihydroisoquinoline hydrochloride 361. The above isoquinoline hydrochloride was prepared by the method described for 350 from the acetamide 360 cyclised using phosphorus pentachloride in chloroform. Addition of methanol caused the exothermic reaction as before, but on cooling no crystallisation occurred; the solution was warmed, ether added, and on re-cooling yellow crystals of title hydrochloride 361 formed, (63%) m.p. 123° (lit.²⁰⁴ m.p. 126-8°) (methanol). ν_{\max} : 2600 cm⁻¹ (broad salt bands); 1645, 1605, 1555, 1520 cm⁻¹.

6,7-Dimethoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline 362. The dihydroisoquinoline hydrochloride 361 was reduced²⁰⁵ with sodium borohydride

hydride in ethanol solution by the method described for 353. The product, a crude gum, gave the tetrahydroisoquinoline 362 on trituration with petroleum and ether in 86% yield, m.p. 122-4°. ν_{\max} : 3330 cm^{-1} (NH); 1600, 1510 cm^{-1} . δ (CDCl_3): 2.5-3.5 (6H, m, CH_2CH_2 ; ar CH_2CH); 3.85 (6H, s, $(\text{CH}_3\text{O})_2$); 4.0-4.3 (1H, m, ar. CH_2CH); 6.6 (2H, s, ar. at C_5 and C_8); 7.40, 8.20 (4H, 2d, $J=9\text{Hz}$, ar. ortho to CH_2 and N); c.a. 1.7 (1H, broad s, exchanges with D_2O , NH). Hydrochloride m.p. 201-4° (lit.²⁰⁵ m.p. 209°) from dilute hydrochloric acid.

6,7-Dimethoxy-1-(4-nitrobenzyl)-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 363. The title compound was produced from the tetrahydroisoquinoline 362, p-toluenesulphonyl chloride and pyridine in chloroform solution heated under reflux for 2 hr. as described in the previous section. The crude gum, when triturated with petroleum, ether and ethyl acetate eventually yielded the sulphonamide 363 as a solid, which recrystallised from ethanol as yellow needles (65%), m.p. 131-4°. (Found: C, 62.4; H, 5.6; N, 5.4. $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_6\text{S}$ requires C, 62.2; H, 5.4; N, 5.8%). ν_{\max} : 1600, 1515 cm^{-1} ; 1340, 1155 cm^{-1} (SO_2N). δ (CDCl_3): 2.35 (3H, s, ar CH_3); 2.4-3.7 (6H, m, CH_2CH_2 ; ar CH_2CH); 3.75, 3.85 (6H, 2s, $(\text{CH}_3\text{O})_2$); 5.15 (1H, t, $J=12\text{Hz}$, ar CH_2CH); 6.35, 6.45 (2H, 2s, ar. at C_5 and C_8); 7.0-8.2 (8H, m, aromatics).

1-(4-Aminobenzyl)-6,7-dimethoxy-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 364. Reduction of the nitrobenzylisoquinoline 363 was achieved using powdered zinc metal and acetic acid as described for 314. The crude product, an oil, on trituration with ether gave a yellow solid (85%) m.p. 95-9°, which although it was not purified further, was identified as the title amine 364 by infra red and NMR spectroscopy. ν_{\max} : 3450, 3380 cm^{-1} (NH_2); 1330, 1155 cm^{-1} (SO_2N). δ (CDCl_3): 2.30 (3H, s, ar CH_3); 3.65, 3.75 (6H, 2s (OCH_3)₂); 6.0-7.7 (aromatic).

6,7-Dimethoxy-1-[4-(p-toluenesulphonamido)-benzyl]-2-(p-toluenesulphonyl)-1,2,3,4-tetrahydroisoquinoline 365. The above aminobenzylisoquinoline 364,

p-toluenesulphonyl chloride and pyridine were heated under reflux for 3 hr in chloroform solution, as detailed in an earlier section. Trituration of the crude product with ether yielded a yellow solid (65%) m.p. 108-112° which again proved impossible to purify, but was identified spectroscopically as the desired sulphonamide 365. ν_{\max} : 3250 cm^{-1} (NH); 1330, 1160 cm^{-1} (SO_2N). δ (CDCl_3): 2.40 (6H, s, $(\text{arCH}_3)_2$); 2.2-3.7 (6H, m, CH_2CH_2 ; arCH_2CH); 3.55, 3.75 (6H, 2s, $(\text{OCH}_3)_2$); 5.00 (1H, t, $J=6\text{Hz}$, arCH_2CH); 6.10, 6.35 (2H, 2s, ar. at C_5 and C_8); 6.7-7.7 (approx. 12H, m, aromatic).

Oxidation of the 7-Hydroxy-6-methoxyisoquinoline 342

The electrochemical oxidation of the above phenolic isoquinoline 342 in acetonitrile solution was undertaken at anode potentials of between 0.9 and 1.1v. At the lower voltage, although coulometry showed a two electron oxidation to be occurring, only starting material could be isolated from the reaction cell. At 1.4v four electron oxidations occurred, which resulted in mixtures of products, the infra red spectra of which showed absorption in the carbonyl ($1750\text{-}1600\text{ cm}^{-1}$) region. Attempts at separating these mixtures were unsuccessful, and on such impure material, NMR spectroscopy proved useless. Also little information was gained from mass spectroscopy, which showed only a meaningless fragmentation pattern. No evidence of imine formation was observed.

Oxidation of the 6,7-Dimethoxyisoquinoline 365

The dimethoxy isoquinoline 365 was subject to electrochemical oxidations at potentials between 1.0 and 1.4v in acetonitrile solution. At 1.25v a

reproducible four electron oxidation was found to be occurring, but examination of the product by TLC showed it to be a mixture. Although further purification failed, the infra red spectrum [ν_{max} : 3280, 1680, 1340, 1160 cm^{-1}] showed the probably presence of starting material together with substances having an increased absorption in the carbonyl region. The NMR spectrum again revealed little, and even though the mass spectrum showed a strong peak at m/e 332, no useful deductions could be made.

When the cell solvent was changed to methanol another four electron oxidation was achieved at 1.2v, again leading to a mixture of products. The infra red spectrum [ν_{max} : 3280, 1740, 1680, 1650, 1340, 1160 cm^{-1}] showed the likely presence of starting material, plus an increase in absorption in the carbonyl region; the NMR spectrum could not be identified, and no evidence for imine formation was found.

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