TRENT POLYTECHNIC

THE CHEMISTRY OF SOME NOVEL NITROGEN-CONTAINING SPIROCYCLOHEXADIENES

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the Council for National Academic Awards
for the degree of
DOCTOR OF PHILOSOPHY

by

Mark Richard Southcott, BSc

November 1987

PREFACE

The work described in this thesis was carried out by the author in the Department of Physical Sciences, Trent Polytechnic, Nottingham, between November 1984 and November 1987. Throughout the duration of this investigation the author has not been registered for any other award of the CNAA nor with any other degree-awarding bodies. No material contained in this thesis has been used in any other submission for an academic award. Any work not carried out solely by the author is acknowledged in the text.

Advanced studies were undertaken in connection with this research programme. These included postgraduate lecture courses at Trent Polytechnic on n.m.r. spectroscopy and on biosynthesis. External lectures attended included local seminars at Fisons plc and the Universities of Nottingham and Loughborough. The author also participated in annual RSC East Midlands Perkin Division meetings, the Third International Symposium of Natural Products at Nottingham University and an RSC workshop on computer aided molecular modelling at Leeds University.

The author wishes to thank Dr I G C Coutts for his excellent supervision and to Dr R W Turner and Dr N F Elmore of ICI Pharmaceuticals Division for their advice and help.

M.R. Southcott

Trent Polytechnic

November 1987

SUMMARY

THE CHEMISTRY OF SOME NOVEL NITROGEN-CONTAINING SPIROCYCLOHEXADIENES

by MARK R SOUTHCOTT

The work described in this thesis involves nitrogen-containing spirocyclohexadienes as isolated products or as reaction intermediates.

In the first Chapter is described the synthesis of a series of 2'-sulphonamido-4-hydroxydiphenylamines. Oxidation of these compounds gave novel N-sulphonylphenazinones rather than anticipated spiro-benzimidazoles, but one bis-dienone based on the latter system was isolated. An attempt was made to elucidate some acid-base reaction of the bis-dienone and related products.

The following Chapter discusses the preparation of several N-aryl-cyclohexadienimine-4-spirolactones and acetals by the anodic or chemical oxidation of 4-anilinophenoxyacetic or hydrocinnamic acids and corresponding alcohols. The stability of the lactones and acetals is strongly influenced by alkyl substituents in the heterocyclic ring.

In Chapter Three there is reported an investigation of the reaction of t-butyl 4-nitrohydrocinnamate with zinc and trifluoroacetic acid to give directly a cyclohexadienone spirolactone, presumably via a dienimine intermediate. Unsuccessful efforts were made to improve yields in this reaction, and to extend it to more complex substrates, including tetrahydroisoquinoline-1-carboxylate esters. However, the preparation of a spirolactone by acid treatment of an aryl azide shows synthetic promise.

The final Chapter describes application of a Smiles rearrangement in the development of a useful general method for converting phenols to primary or secondary anilines. Reaction of a range of phenols, including electron-rich molecules, with bromoisobutyramide gives aryl ethers, which on treatment with sodium hydride in DMF/DMPU rearrange smoothly to anilides, which can be hydrolysed to anilines. Steric and electronic restraints on the reaction were studied. N-substituted aryloxyisobutyramides, obtained by reacting phenols with secondary bromoisobutyramides or derived α-lactams rearranged to give anilides, benzoxazinones, or, surprisingly, N-alkyl anilines directly.

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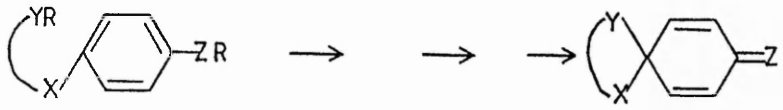
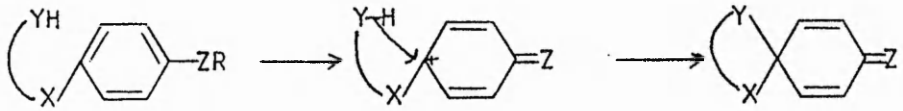
GENERAL INTRODUCTION

Nitrogen-containing spirocyclohexadienes 2 can be formed from precursors 1, where either Y or Z is a nitrogen atom. The conversion of 1 to 2 might occur by two complementary pathways.

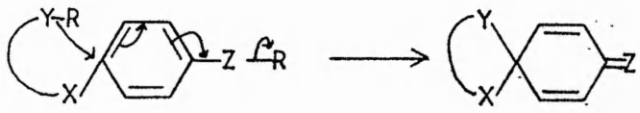


1 2

The first involves initial oxidation on the benzene ring, followed by further proton and electron removal steps: this may be termed as an oxidative pathway.



In the second pathway an ipso attack by a nucleophilic species Y on a benzene ring para to the Z substituent leads to net expulsion of a group R from atom Z.



The nitrogen-containing spirodienes may be capable of isolation as distinct products or may simply occur as reaction intermediates.

In the first Chapter the preparation has been re-examined of a number of spirocyclohexadienes 2, where Y is a sulphonimido group. The synthesis of a novel series of N-arylcyclohexa-2,5-dienimine-4-spirolactones or spiroketals is reported in Chapter Two. Both of these studies are concerned with the formation of spiro compounds by oxidative pathways.

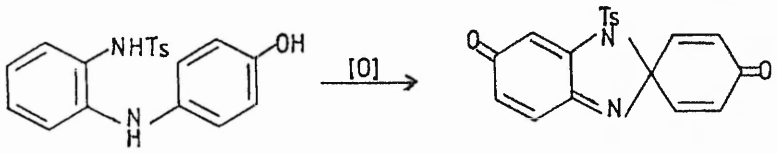
In Chapter Three the direct conversion of nitroarenes to spirocyclohexadienones has been investigated; the reaction may proceed via a hydroxylamine intermediate and be an example of the second pathway outlined above.

The final Chapter discusses the use of a Smiles rearrangement to convert phenols to anilines, a transformation which involves a nitrogen-containing spiro-Meisenheimer intermediate.

CHAPTER ONE

1.1 Introduction

In this Chapter the preparation of the nitrogen-containing spirocyclohexadienone 4 by oxidation of the phenol 3 has been reinvestigated.



3 4

1.1.1 Phenol Oxidation

Oxidation of phenols is one of their most characteristic chemical properties and often leads to complex product mixtures, which may be dimeric, polymeric or quinonoid in nature. Their wide occurrence in nature has led to many biosynthetic pathways involving oxidative coupling being proposed, and to attempts to duplicate the proposed coupling reactions *in vitro*. The field has been reviewed many times.[1-10]

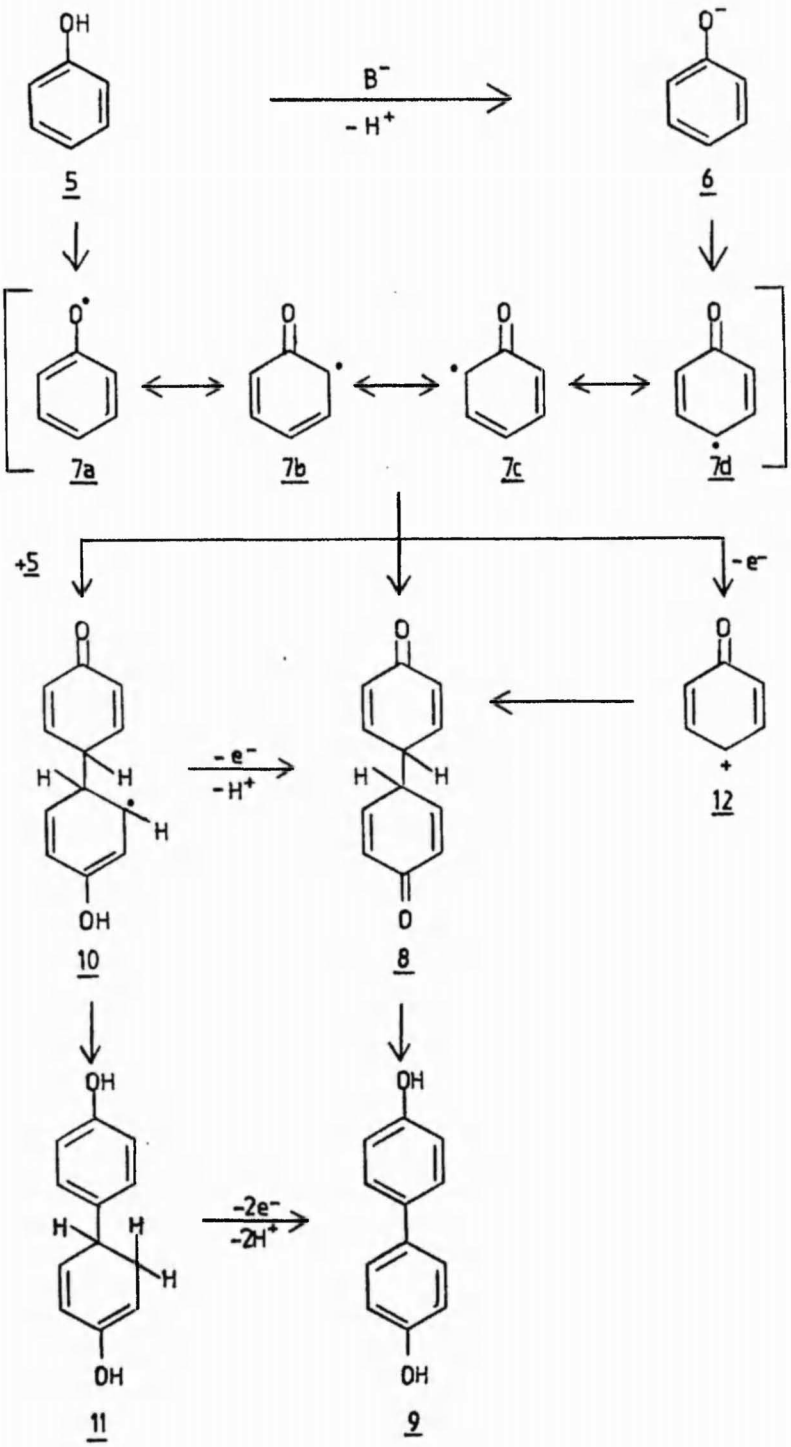
Since earlier oxidants used [eg. silver oxide, cerium(IV) ions, etc.] were of the 'one electron' type, a general mechanism involving generation of a phenoxyl radical by homolytic cleavage of the O-H bond in phenol 5 or by one-electron removal from a phenoxide anion 6 was proposed.

Phenoxyl radicals whose existence has been confirmed by E.S.R. spectroscopy are resonance stabilised and may be depicted by the canonical structures 7a-d. The stabilisation leads to longer half-lives for the phenoxyl radicals than is usual for alkyl or aryl radicals, but in the absence of ortho and para substituents they still undergo further reaction rapidly. Dimerisation occurs more readily than solvent attack or polymerisation.[4,7]

Phenoxyl radicals are stabilised[12] by substituents at positions 2, 4 and 6 which provide either steric hindrance or increased delocalisation of the unpaired electron, and can react by one of three general paths, all leading to the same product.

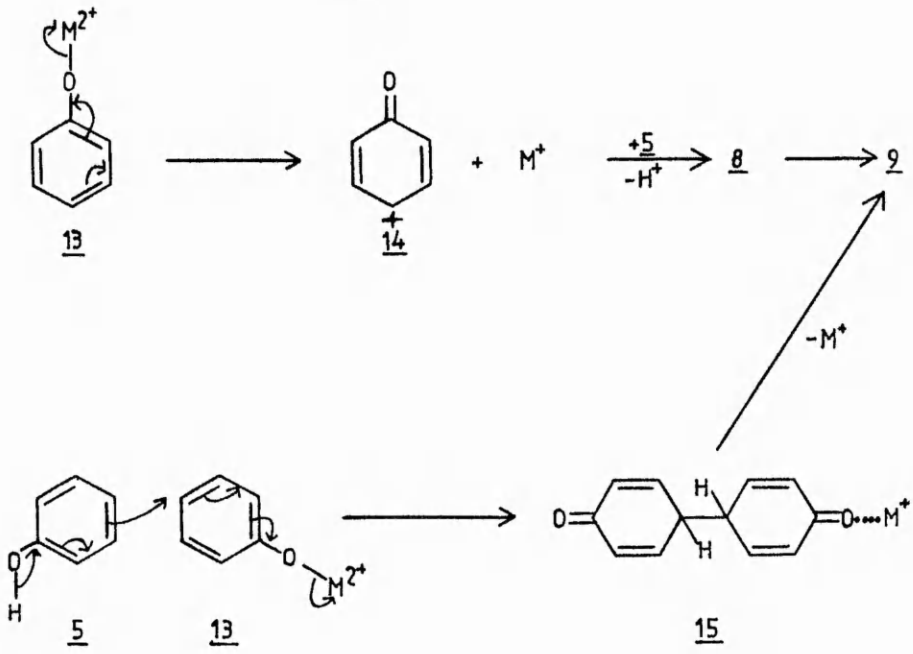
Firstly, the unpaired electrons combine giving bisdienone 8 which can quickly tautomerise to diphenol 9. Secondly, one radical may substitute into another phenol molecule generating the dimeric radical 10, which can either lose an electron and a proton giving bisdienone 8 or disproportionate to the dihydro product 11; structures of the form 11 have not been observed in oxidative coupling reactions. It is thought that the energy gained by rearomatisation favours further oxidation of dihydrophenol 11 to diphenol 9. Finally, an ionic coupling process may occur following the oxidation of a phenoxyl radical 7 to a cation 12. A detailed discussion of the generation of phenoxonium cations is found in Chapter 3.

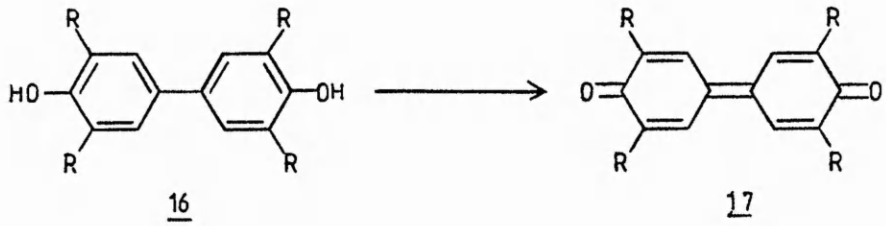
Alternative non-radical oxidation processes have been proposed[13] in which metal oxidants such as manganese dioxide,[10] lead dioxide[10] and mecuric oxide'[10] form initial metal-

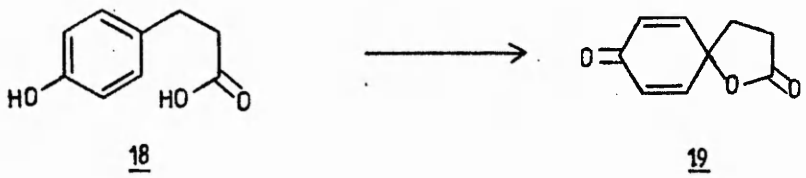

OH
B⁻
- H⁺
O⁻
5
6
7a
7b
7c
7d
+5
-e⁻
- e⁻
- H⁺
10
8
12
-2e⁻
-2H⁺
11
9

phenolate compounds 13. These can decompose into phenoxonium cations 14 with concurrent two-electron reduction of the metal ion. Electrophilic substitution into another phenol leads to the bisdienone 8, which again tautomerises to diphenol 9. Coupling between complex 13 and phenol 5 may also occur by a concerted process to yield bisdienone-metal complex 15 which subsequently tautomerises to diphenol 9. Because it avoids the necessity of a phenoxonium cation it is thought that a concerted electron transfer mechanism is preferred to an electrophilic substitution mechanism, ie. reaction sequence 13 -> 15 -> 9 is preferred to 13 -> 14 -> 8 -> 9. In the case of para - para coupled dimers 16 further oxidation often occurs to give the extended quinones 17.

Although much evidence[10] for the coupling of radicals has been found, there are some cases of oxidative coupling where this mechanism is chemically very unlikely. One such group of reactions is the coupling of aliphatic carboxylic acid groups to phenols, as shown[15,16] by the intramolecular oxidation of phloretic acid 18 to spirolactone 19. It is unlikely that the reaction involves the formation of a carboxyl radical because such acyloxy radicals are known to decompose readily with loss of carbon dioxide to produce aliphatic radicals. It therefore seems likely that coupling occurs via a non-radical process and may occur, for example, by nucleophilic attack of a carbonyl or carboxylate anion on a radical cation, followed by further oxidation.


M2+
O
13
O
14
+ M+
+5
-H+
8
9
-M+
H
O
H
5
O
M2+
13
H
H
O
O M+
15


R
R
HO
OH
R
R
16
R
R
O
O
R
R
17


HO
HO
O
18
O
O
O
19

1.1.2 Electrochemical Oxidation of Phenols

Due to its selectivity and convenience electrochemical oxidation[18] has re-emerged as a useful synthetic technique in organic chemistry recently.[18] There exist two sets of views concerning the mechanism of the primary electrode reaction[19] of phenols.

The first involves the loss of an electron leading to the formation of a phenoxyl radical 7 and calculations have shown[20] that the observed anodic wave function corresponds to the energy needed to transport one electron. The second involves the transference of two electrons in the initial oxidation stage with an intermediate being formed.[21] These correspond to the phenoxyl radicals and phenoxonium cations discussed above.

It has been shown[19] that the stoichiometry of the phenol oxidation process depends on the pH of the electrolyte solution. The oxidation potential of a phenol in alkaline medium is lower by a factor of two than that in acid medium, which suggests that unionised phenols undergo a two-electron process. If the phenol is ionised, a one-electron change occurs.

1.1.3 The Synthesis of nitrogen-containing heterocylic spirocyclohexadienones

In the mechanisms discussed above, the radical or phenoxonium ion generated by oxidation of a phenol can react with a second phenol-derived molecule. A variety of other structural types may arise by reaction of the oxidised species with different nucleophiles; for example, spirolactones may be

formed from carboxylate attaching species (Chapter Two). In this section is discussed the preparation of some nitrogen-containing compounds derived by oxidation of phenols with a nitrogen-containing side-chain. Several types of nitrogen-containing spirocyclohexadienones have been prepared by such processes.

Spirolactams

Hey and his co-workers have shown that the persulphate oxidation[22] of N-methylbiphenyl-2-carboxamide 20 and the corresponding 4-methoxy compound 21 afforded the spirolactam 22. Similarly carboxamide 23 gave both spirolactams 24 and 25 in 45 and 25% yields respectively. The dienol 26 was prepared[23] by photolysis of N-ethyl-2-bromo-4'-hydroxybenzanilide in aqueous alkali in the presence of sodium borohydride; on oxidation with manganese dioxide it afforded dienone 27 in 59% yield. Similarly N-methyl-2-iodo-4'-methoxybenzanilide yielded[24] spirolactam 22 on photolysis in oxygen-free benzene, while the same product was obtained[25] by the oxidation of the appropriate biphenyl-2-carboxamide with t-butyl hypochlorite and iodine.

Spirolactams 22, 24 and 27 have also been prepared[26] by the thermal decomposition of the diazonium sulphates of the aminobenzanilides 28, 29 and 30 respectively, presumably via benzyne intermediates. It was found[27] that these spirolactams could also be formed by treatment of N-alkyl-2- or 3-bromo-4'-hydroxybenzanilides with potassium in liquid ammonia; this is good evidence of a benzyne intermediate. Pyrolysis of dimer 31

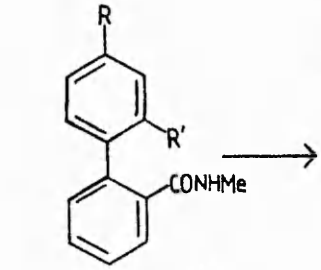
in the presence of iodine as an oxidant also yielded[28] spirolactam 22.

Spiroisoxazolines

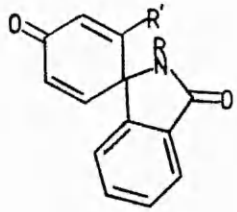
In an investigation[29] into the synthesis of aerothionin, a sponge metabolite, oxidation of a series of 4-hydroxyaryl-propan-2-one oximes 32 with manganese tris(acetylacetonate) in acetonitrile gave spiroisoxazolines 33 in yields of 20-60%. This reaction did not produce dienones from corresponding 2-hydroxyaryl oximes, probably because the phenol and oxime groups were close enough to interact with the manganese. The mechanism is considered unlikely to proceed through a bi-radical but rather by trapping, by the oxime, of an incipient phenoxonium cation produced by heterolysis of the oxygen-manganese bond in the metal-phenol complex. Bromine and sources of positive bromine have also effected this cyclisation, oxime 34 giving spiroisoxazoline 35 in 65% yield with bromine-water, while oxime 36 yielded 72% of dienone 37 on treatment with N-bromosuccinimide. Reaction of the 2-hydroxyaryl oxime 38 with 2,4,4,6-tetrabromocyclohexa-2,5-dienone afforded spiro-2,4-dienone 39, which was also prepared by cyclodehydration of oxime 40 in boiling pyridine.

Miscellaneous syntheses of nitrogen-containing spirocyclohexa-dienones

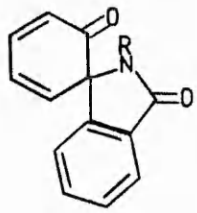
The conversion[30] of benzylamine 41 to the unusual spirodienone 42 is an interesting example of the oxidative coupling of aryl rings using thallium (III) trifluoroacetate.



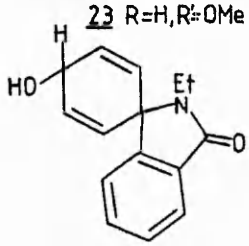
20 R=H, R'=H
21 R=OMe, R'=H
23 R=H, R'=OMe



22 R=Me, R'=H
25 R=Me, R'=OMe
27 R=Et, R'=H



24 R=Me



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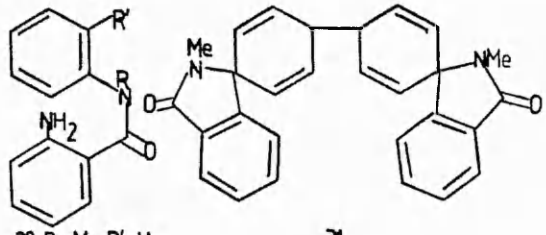
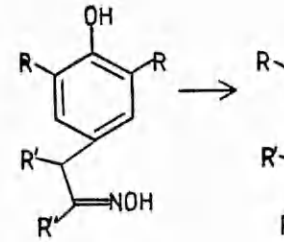
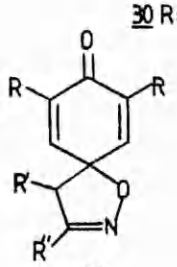


28 R=Me, R'=H
29 R=Et, R'=H
30 R=Me, R'=OMe

31



32 R=H, t-Bu, Br
R'=H, Me; R''=H, Me, COOMe



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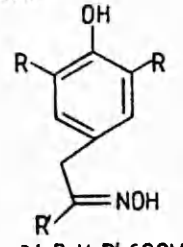
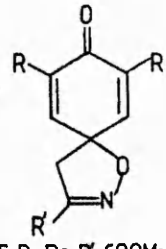
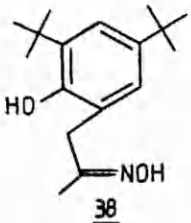


34 R=H, R'=COOMe
36 R=t-Bu, R'=Me



35 R=Br, R'=COOMe
37 R=t-Bu, R'=Me



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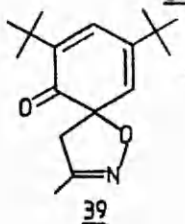

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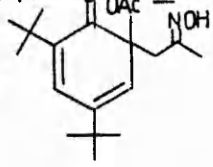

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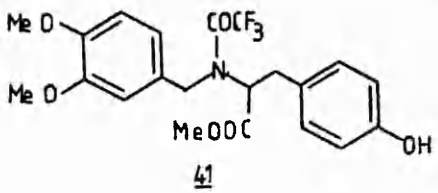

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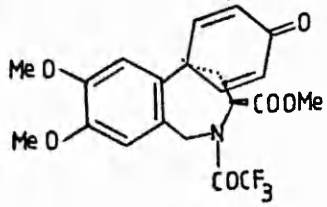


42

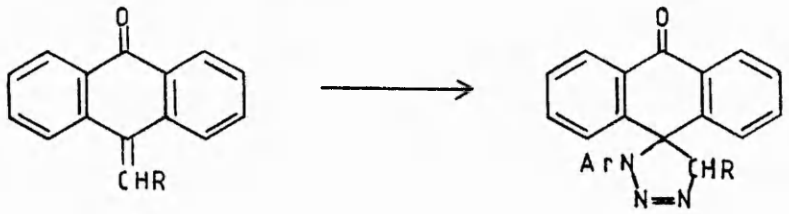
Hirakawa et al reacted 10-methylanthrones 43 with aryl azides to afford the corresponding spiroanthranonetriazolines 44.

Recently the diazonium salt 45 was shown[32] to react with acrylonitrile to give the cyanospirodienone 46.

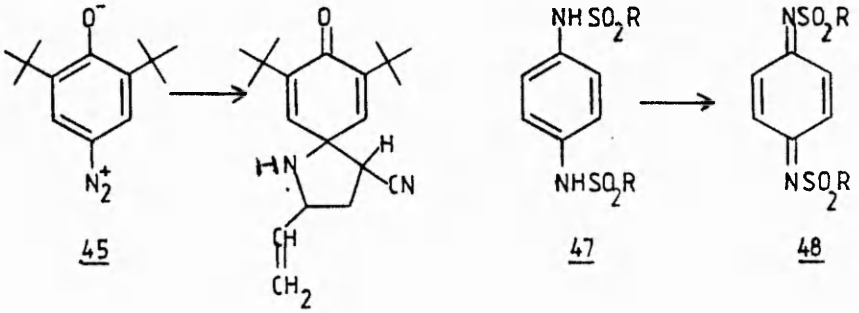
N-Sulphonamido spirocyclohexadienones

As discussed more fully in Chapter Two, extensive studies by Adams and his co-workers[33] established that N-sulphonyl-quinonediimines 48 are formed in high yield by oxidation of 1,4-disulphonamidobenzenes 47. The analogy between this reaction and the oxidation of quinol to p-benzoquinone suggested that N-sulphonylanilines might also replace phenols in oxidative coupling reactions. In confirmation of this, the spirobenzoxazole 50 was prepared by oxidation with active manganese dioxide of either the phenolic N-tosyldiphenylamine[34] 49 or the sulphonamidodiphenyl ether[35] 51; yields of dienone 50 were comparable (approximately 50%) from either route. Further studies showed[35] that bissulphonamide 52 gave dienone 53 in 58% yield, and that trifluoromethyldiphenylether 54 was oxidised[74] to dienone 55 in 31% yield.

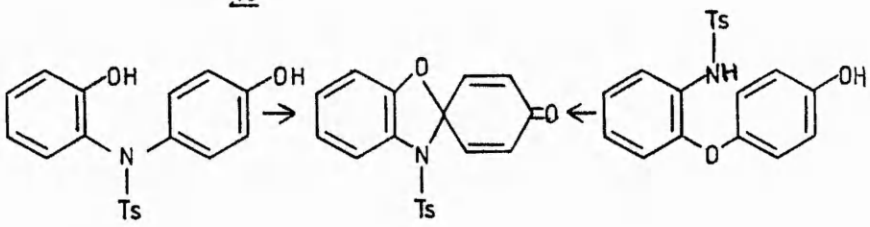
Recently Taylor et al have reported[36] that the major product isolated from treatment of N-tosylisoquinoline 56 with thallium(III) trifluoroacetate is the N-tosylphenethylamine 59. In their suggested mechanism for the reaction, Scheme 1, radical cation 57 is captured by the N-tosyl group and further oxidation gives the aziridinium species 58.



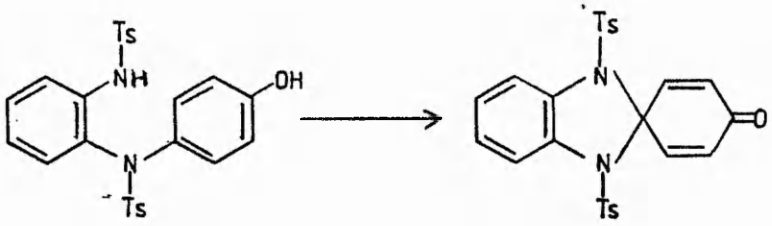
43 44



45 46 47 48



49 50 51



52 53

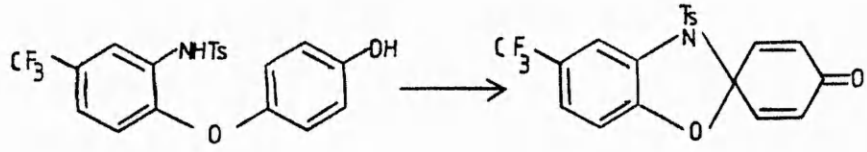
Hamblin,[37] as part of the study of the oxidation of N-sulphonamidodiaryls at Trent Polytechnic, discovered that oxidation by active manganese dioxide of diphenylamine 3 did not give the expected spirodienone 60 but afforded bisquinone 4 in 15% yield. This bisquinone 4 showed unusual physical properties, in that it went blue in base and red in acid. The synthesis and investigation of the unusual properties of bisquinone 4 were the basis of the work undertaken in this Chapter.

1.2 Discussion

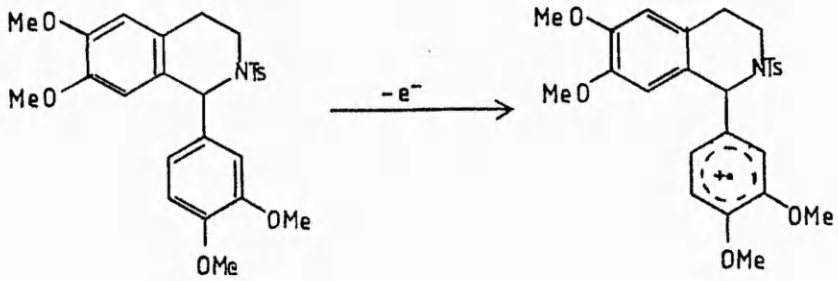
The present study of acid-base chemistry of bisquinone 4 required efficient synthesis of the compound in research quantities. The preparation of precursors 3 and 69 described by Hamblin[37] was therefore reinvestigated.

In general the previous route to 3, outlined in Scheme 2, proved satisfactory, but a significant improvement resulted when the debenzylation of benzyloxydiphenylamine 63 to phenol 3 was carried out with hydrogen bromide in glacial acetic acid rather than the ethanolic hydrochloric acid originally used.

In an attempted alternative synthesis of bisquinone 4 reaction of 2-fluoronitrobenzene with 4-aminophenol in isopropanol gave hydroxydiphenylamine 64 (90%) which yielded 2-amino-4'-hydroxy- diphenylamine 65 (84%) on hydrogenation. Treatment of diphenylamine 65 with toluene-4-sulphonyl chloride in a phosphate buffer[37] gave only a trace of sulphonamide 3, contaminated with the O,N-ditosyl compound 66.

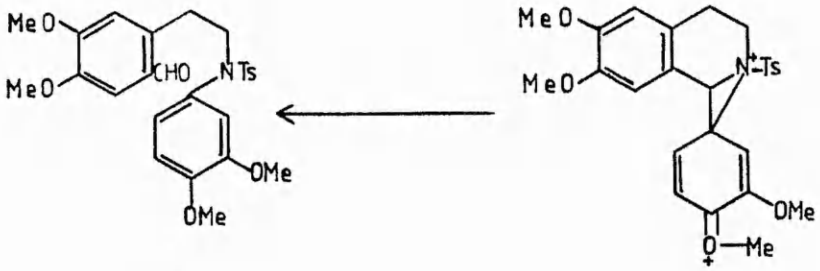


54 55

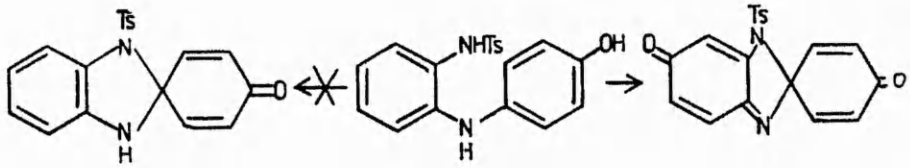


56 57

SCHEME 1



59 58

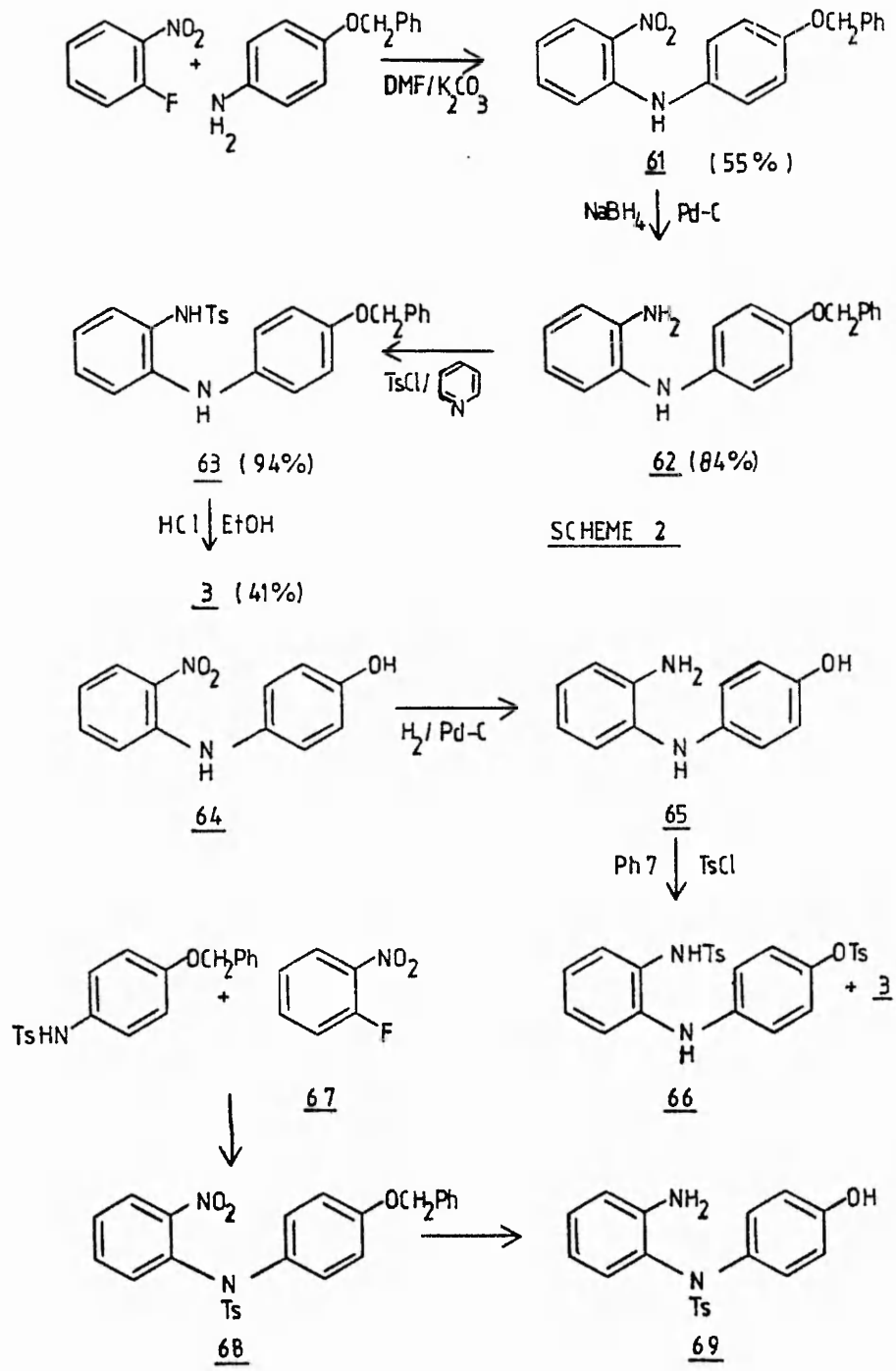


60 3 4

Experiments to repeat the synthesis of 2-amino-4'-hydroxydiphenylamine 69 encountered difficulties. The reported[38] preparation in quantitative yield of N-tosyldiphenylamine 68 by the copper-catalysed reaction of N-tosyl-4-benzyloxyaniline 67 with 2-fluoronitrobenzene now gave a much lower yield of product separated with difficulty from tarry by-products. It proved possible, however, to obtain diphenylamine 68 in 85% yield by the reaction of tosylaniline 67 with 2-fluoronitrobenzene in dimethylformamide (DMF) in the presence of potassium carbonate (K_2CO_3) and tetrabutylammoniumhydrogen sulphate. Catalytic hydrogenation of diphenylamine 68 readily afforded aminodiphenylamine 69 (80%).

In the original investigation the oxidation of sulphonamide 3 to bisquinone 4 in 15% yield was achieved using a large excess of active manganese dioxide, prepared by the method of Franck and Blaschke;[39] the experimental difficulty of making large quantities of this reagent limits the availability of the quinone. A study was therefore undertaken of alternative oxidants, of comparable redox potential and capable of acting as oxygen donors.

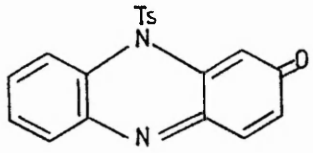
The reactions of sulphonamide 3 were investigated with the commercially available manganese dioxide prepared by the Sedema company and freshly prepared manganese dioxide,[40] lead tetraacetate,[41] silver(II) oxide,[42] silver(II) picolinate,[43] and ceric ammonium sulphate.[44] In each case no bisquinone 4 was formed, the product being a mixture of three components; this same mixture could even be obtained from the reaction of sulphonamido 3 with potassium ferricyanide, which has a lower


NO2
OCH2Ph
F
NH2
DMF/K2CO3
61 (55%)
NaBH4
Pd-C
NHTs
TsCl/
63 (94%)
62 (84%)
HCl
EtOH
3 (41%)
OH
H2/Pd-C
64
65
Ph7
TsCl
TsHN
67
NHTs
OTs
+ 3
66
68
69

SCHEME 2

redox potential.[44] The product mixture consisted of an unstable red compound of high R_f value and a slower-running colourless compound which was contaminated by a yellow component with an identical R_f value. Treatment of the reaction mixture with sodium borohydride ($NaBH_4$) converted the red and yellow compounds to materials of very low R_f value, allowing isolation, in a 10% yield of the colourless compound by flash chromatography.

The i.r. spectrum of this colourless compound contained no N-H or O-H stretch, but had a weak carbonyl band at 1625 cm^{-1}. The proton n.m.r. spectrum showed an aromatic methyl peak and 11 aromatic protons. The ^{13}C n.m.r. spectrum confirmed the presence of methyl and aromatic carbons and showed a resonance at 150.44 δ, which is attributed to a carbonyl group. The mass spectrum with a parent ion at 350 a.m.u., and elemental analysis are in agreement with a molecular formula of $C_{19}H_{14}N_2O_3S$. The structure assigned to this compound is the N-tosylphenazin-2-one 70.



70

The low value for carbonyl stretch in the i.r. spectrum and the ^{13}C n.m.r. resonance at 150.44 δ are attributed to the phenazinone behaving as an enaminone. A review[45] of the i.r.

spectra of such compounds indicates that 1625 cm^{-1} is a typical value for the carbonyl stretch of these systems. It might be thought that the sulphonyl substituent on the enaminone nitrogen would diminish conjugation of the nitrogen lone pair with the enone, but the aromaticity gained by such conjugation may be a dominant factor.

Phenazinones have been prepared by the oxidation of phenazines, intramolecular cyclisations and intermolecular cyclisations.

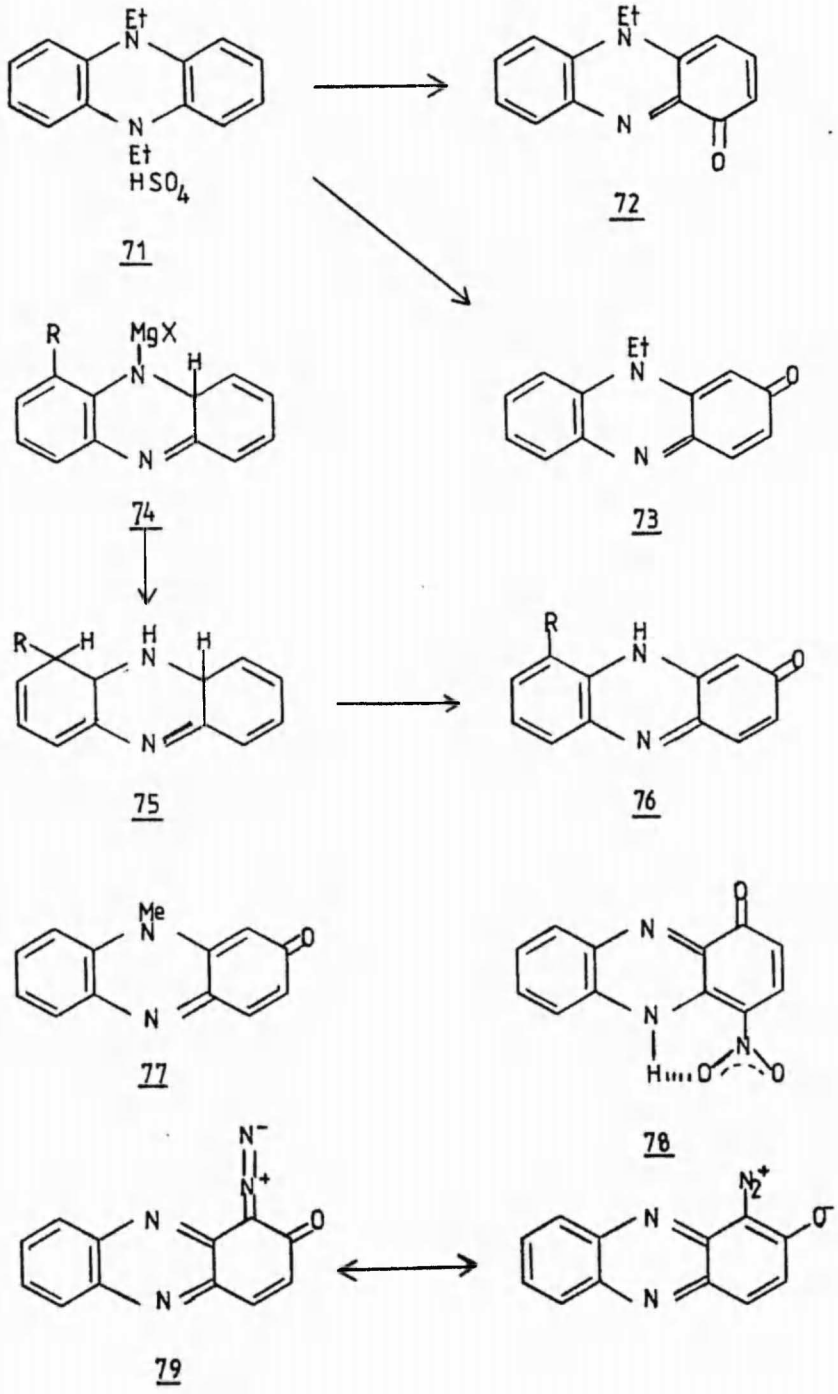
McIlwain in 1937 oxidised[46] phenazine ethosulphate 71 with ferricyanide to obtain 5-ethylphenazin-1-one 72; whereas light catalysed autoxidation yielded the isomeric phenazin-2-one 73. The oxidation of phenazinium salts has been used to prepare many phenazinones.[47-52]

Reaction[53] of phenazine with Grignard reagents gives complex 74 which on hydrolysis to 75 yields 9-alkyl phenazin-2-ones 76.

Rearrangement[54] of 2-hydroxyphenazine by reaction with basic methyl sulphate afforded 10-methylphenazine-2-one 77, while 1-hydroxy-4-nitrophenazine gave 4-nitrophenazin-1-one 78 by acid treatment.[55]

Diazotisation of phenazines has been shown[58] to lead to phenazinones, with 1-amino-2-ethoxyphenazine giving the interesting phenazin-2-one 79, which was also prepared by the diazotisation of 1-aminophenazine.

The intermolecular cyclisation[57] of N-ethyl-1,2-phenylene-diamine with 2,5-dihydroxy-1,4-benzoquinone by acid catalysis yields 3-hydroxyphenazin-2-one 80. The intermolecular



cyclisation of 1,2-phenylenediamines with benzoquinones has been used[58,59] many times to give phenazinones.

Miyano et al[60,61] developed the intramolecular cyclisation of N-phenylamines 81 with sodium isopropoxide and isopropyl acetate to afford phenazin-1-ones 84 in 60% yields, the mechanism proposed being cyclisation to N-hydroxyoxide 82, dehydration to N-oxide 83 and rearrangement to phenazinone 84.

Recently the ferricyanide oxidation of quinone imines 85 has been shown[62] to yield phenazinones 86 in 60-70% yields.

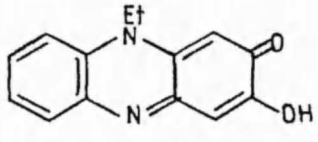
Phenazinones have been reported to be antihypoxics,[63] bacterostatics,[64] fungiostatics,[64] and active against mycobacteria.[65]

No N-sulphonylphenazin-2-ones such as 70 have been previously reported.

1.2.1 Oxidation of N-tosyldiphenylamine 69

The oxidation of N-tosyl-2'-amino-4-hydroxydiphenylamine 69 with either activated or commercially available manganese dioxides yielded bisquinone 4 as the only product, in 11% yield. There was no evidence of any phenazinone formation.

In view of the new efficient route to precursor 69, and its clean oxidation to bisquinone, this latter route to compounds of this type must now be considered the one of choice. Further exploration of the synthesis of related compounds by this method is obviously desirable.



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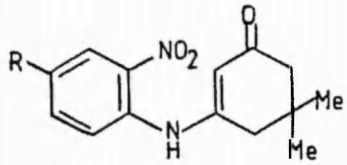

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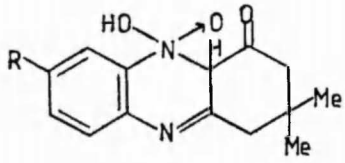

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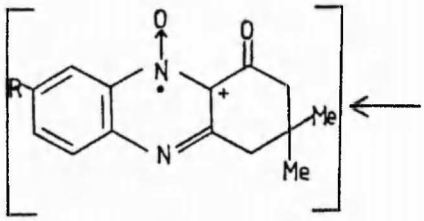

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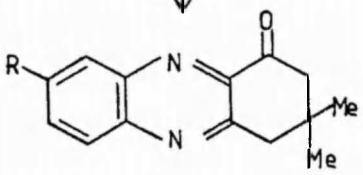

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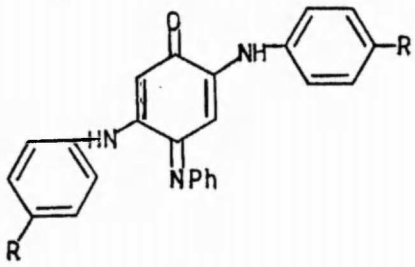

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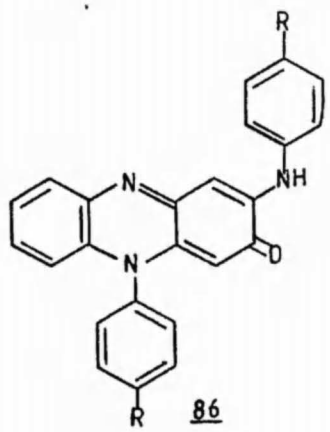


86

1.2.2 Biological activity of bisquinone 4

Since compound 4 contains two linked enone systems, it has the potential to act as a bisalkylating agent and therefore to be potentially useful in antitumour therapy. When assayed by the Institute of Cancer Research it showed inhibitory activity against a variety of cell suspensions, at a concentration of 10^{-6} to 10^{-7} molar. Tests on mice however, showed little therapeutic effect, although the compound was apparently non-toxic.

1.2.3 The acid/base chemistry of an oxidation product from diphenylamine 3

Potassium permanganate coated onto molecular sieves has been recently reported[66] to oxidise monohydric phenols to quinones and is therefore able to act as an oxygen donor to benzene rings. This reagent was stirred with diphenylamine 3 in chloroform in an attempt to prepare bisquinone 4. No bisquinone 4 was formed, but the sole product from the reaction was an unstable yellow compound. On treatment with base this yellow compound yielded red solutions, which on acidification afforded a yellow compound with a different R_f value from that of the original yellow compound. None of these compounds had been detected in any other oxidation of diphenylamine 3. As this oxidation product was easily obtainable, the chemistry of this acid/base change was investigated in the hope that any successful techniques could be applied to the investigation of the similar properties of the less accessible bisquinone 4.

The red anion did not react with dimethyl sulphate or methyl iodide, but treatment, with diazomethane, of the yellow compound obtained by acidification of the red anion, yielded a labile product which decomposed on attempted isolation.

It was therefore concluded that the instability of these coloured intermediate molecules rendered this investigation unproductive.

1.2.4 The preparation and oxidation of a 4-trifluoromethyl analogue of diphenyl-amine 3

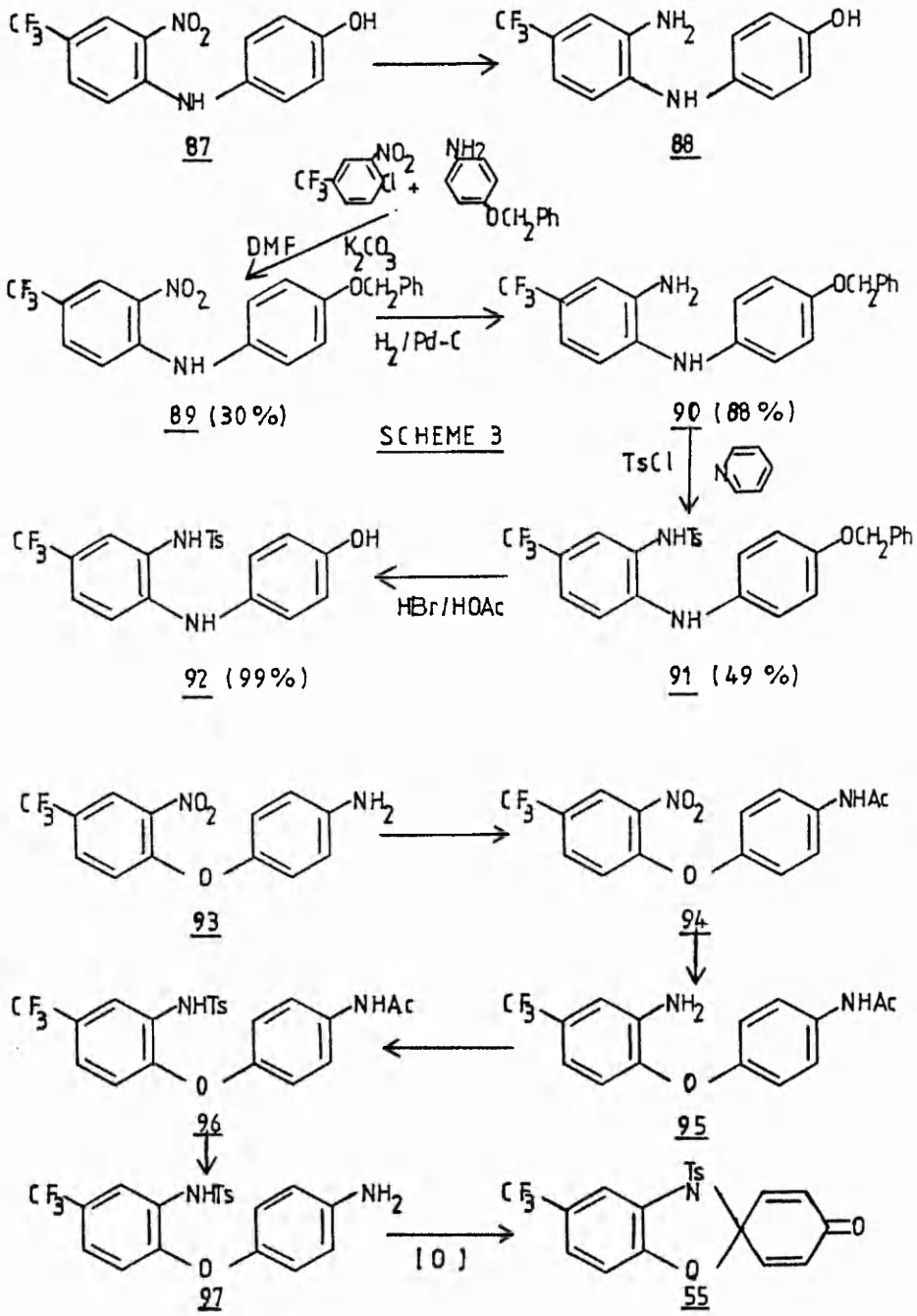
The oxidation of diphenylamine 3 had originally[37] been carried out in an attempt to prepare spirodienone 60 and it is reasonable to assume that bisquinone 4 is formed by further oxidation of this intermediate. To isolate compounds like 60 it is necessary to prevent oxidation on the benzene ring position para to the diphenylamine link. It was thought that the introduction of a trifluoromethyl group at this position, as in sulphonamidodiphenylamine 92, might prevent bisquinone formation, and 92 should be easily prepared from the cheap starting material, 4-chloro-3-nitrobenzotrifluoride.

Following a published procedure[67] the benzotrifluoride was reacted with 4-amino-phenol in propan-2-ol to form the nitro-diphenylamine 87 in 75% yield. Catalytic hydrogenation of 87 gave the corresponding amine 88 which oxidised in solution immediately on contact with air to yield a complex mixture. This instability may perhaps be explained by the capto-dative theory,[68-73] which postulates that the combined action of an electron-withdrawing (captor) and an electron-releasing (donor)

substituent on a radical centre leads to an enhanced stabilisation of the radical. With diphenylamine 88 the captor trifluoromethyl group and the donor hydroxy group could be enhancing free-radical formation on the diphenylamine nitrogen, thus increasing overall instability. The decrease in stability when the 2-nitrodiphenylamine 87 is converted to its corresponding 2-amino compound 88 is unexpected according to this capto-dative theory, as the nitro group is more strongly electron-withdrawing than the amino group; this might be explained by the aminophenol 88 existing as a zwitterion, in which the protonated amine acts as an electron-withdrawing group, which increases diphenylamine free-radical stability.

It was therefore decided to use protected phenols, with benzyl as the O-protecting group leading to diphenylamine 92, as shown in Scheme 3.

Attention was also given to protecting phenolic diphenylamine 87 by O-acetylation prior to reduction of the nitro group. The preparation of diphenylamine 87, described in the literature[67] did not yield a homogeneous product, but gave both diphenylamine 87 and aminodiphenylether 93. Acetylation of this mixture led to the isolation of the acetylated ether 94 in 10% yield. Catalytic hydrogenation afforded diaminodiphenylether 95 in 88% yield, tosylation with toluene-4-sulphonyl chloride in pyridine yielded 39% of sulphonamido 96, which upon saponification gave the 4-amino-2-sulphonamidodiphenylether 97 in 76% as its hydrochloride. Oxidation of diphenylether 97 by manganese dioxide (Sedema) in benzene afforded the previously reported[74] spirodienone 55 in a 14% yield. This route to 55

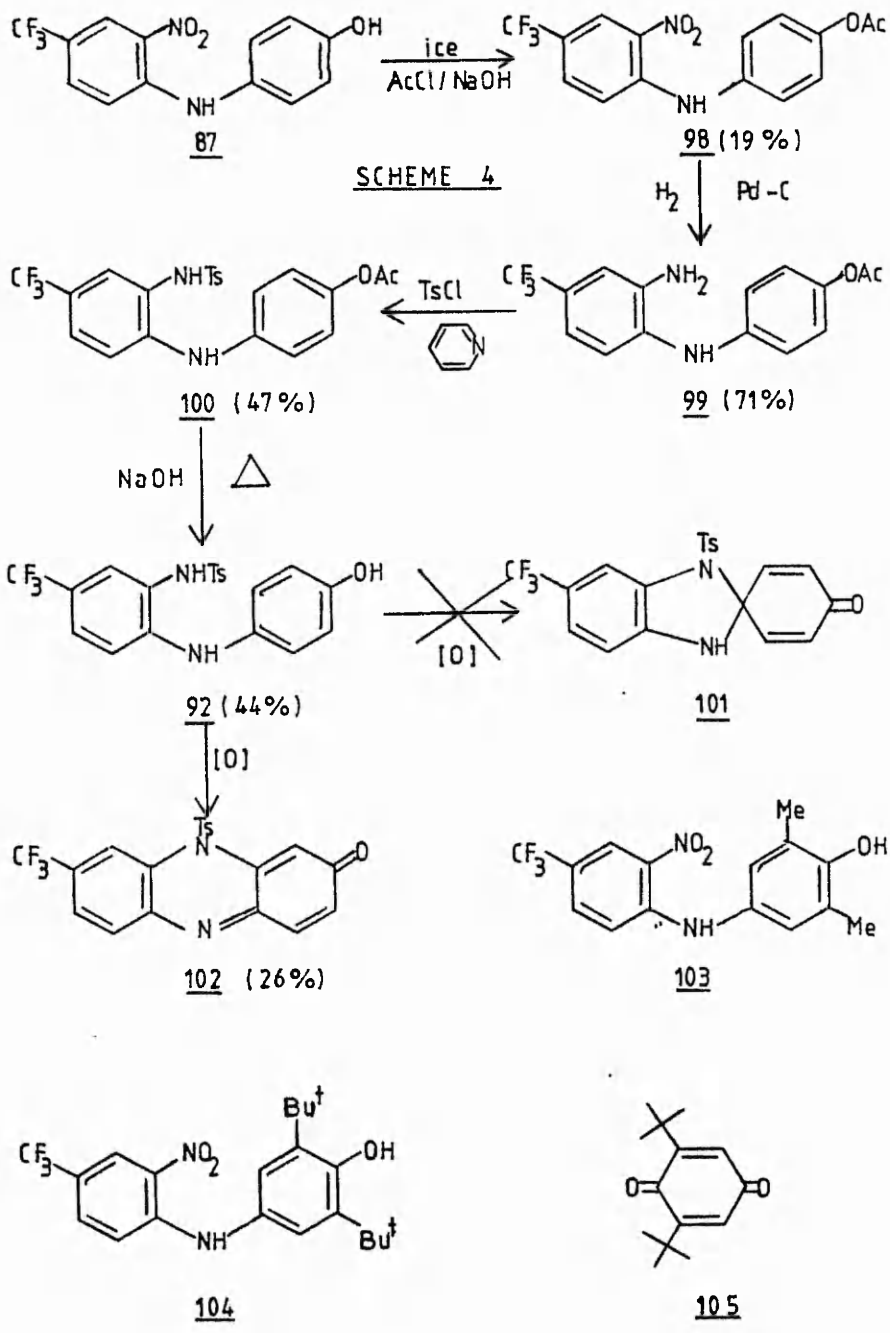

87
88
DMF
K2CO3
H2/Pd-C
89 (30%)
90 (88%)
SCHEME 3
TsCl
HBr/HOAc
92 (99%)
91 (49%)
93
94
95
96
97
[O]
55

was repeated by a separate worker,[75] with N-acetyldiphenylether 94 being prepared directly from the reaction of 4-chloro-3-nitrobenzotrifluoride with p-acetylaminophenol (paracetamol) in butan-2-one and K_2CO_3, in 64% yield. This oxidative route to spirodienones is of great interest as oxidation of an aniline to spirodienones in non-aqueous media has not been reported previously.

In a second preparation of diphenylamine 92 the diphenylether 93 was removed from diphenylamine 87 by acid wash, prior to acetylation. This route led to diphenylamine 92 (Scheme 4) but in lower overall yield than that using benzyl protected phenols discussed earlier.

Oxidation of diphenylamine 92 gave no spirodienone 101 but yielded 26% of the N-tosylphenazin-2-one 102. This same product was obtained from reaction of 92 with both activated and commercially available manganese dioxides.

As an extension to the oxidation of diphenylamines 3 and 92 to phenazinones the preparation of 2,6-dialkyl analogues of diphenylamines 3 and 92 were attempted. The unstable dialkyl diphenylamine 103 was prepared in 54% yield from the reaction of 4-chloro-3-nitrobenzotrifluoride with 4-amino-2,6-dimethylphenol in propan-2-ol. Both 103 and the t-butyl analogue 104 were highly unstable, and with the latter the benzoquinone 105 was isolated from any attempted reaction mixtures. It is presumed that the combination of the previously described capto-dative effect and the free-radical stabilisation[76] due to the steric effects of the dialkyl groups leads to increased diphenylamine instability.



87

98 (19 %)

SCHEME 4

100 (47 %)

99 (71%)

92 (44%)

101

102 (26%)

103

104

105

CHAPTER TWO

2.1 Introduction

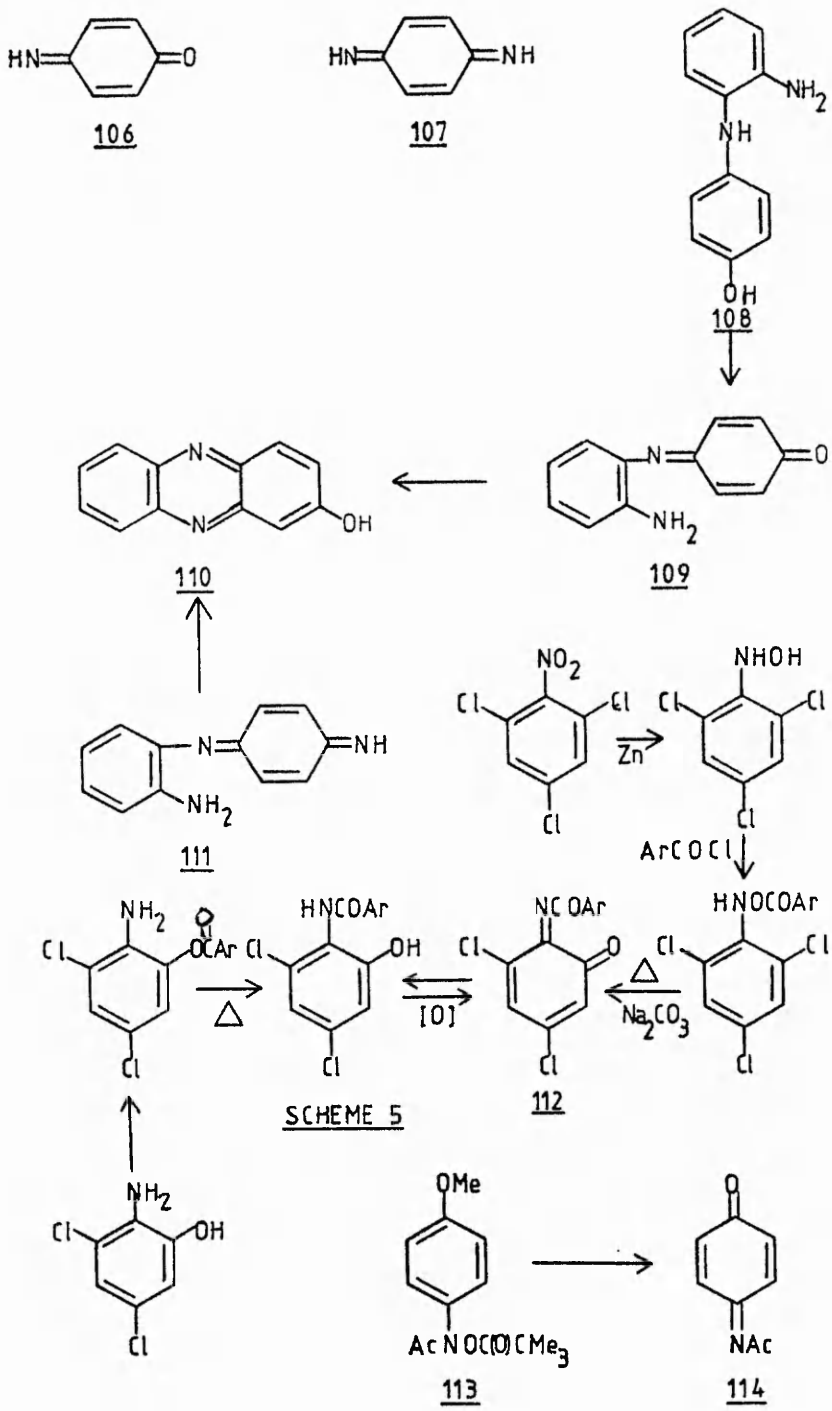
In this Chapter is described the preparation of several novel spirocyclohexadienimine lactones and ketals. The synthesis of cyclohexadienimines is reviewed, but a discussion of their occurrence as reaction intermediates is deferred until Chapter Three.

2.1.1 The synthesis of cyclohexadienimines

In 1904 Willstaetter[77] isolated monoimine 106 and di-imine 107 from the oxidation of p-phenylenediamine; both products were very unstable. He did, however, establish that the imines obtained from the oxidation of N-N'-diaryl-p-phenylenediamines were considerably more stable. The N-aryl mono-imine 109 has been isolated[78] from the reaction of diphenylamine 108 with ferricyanide, but was found to cyclise easily to phenazine 110. The latter compound was also obtained from di-imine 111, presumably by hydrolysis to quinonimine 109.

N-Acyl quinonimines have also been isolated; for example the ortho-quinone-imide 112 was prepared by two separate reaction pathways, shown in Scheme 5. A recent study[79] of the hydrolysis of hydroxamic acid 113, a model for suspected carcinogenic metabolites of phenacetin, led to the isolation of quinonimine 114.

The N-t-butylcyclohexadienimines 115 were synthesised[80] by treatment of their corresponding N-t-butyl-N-chloramines with

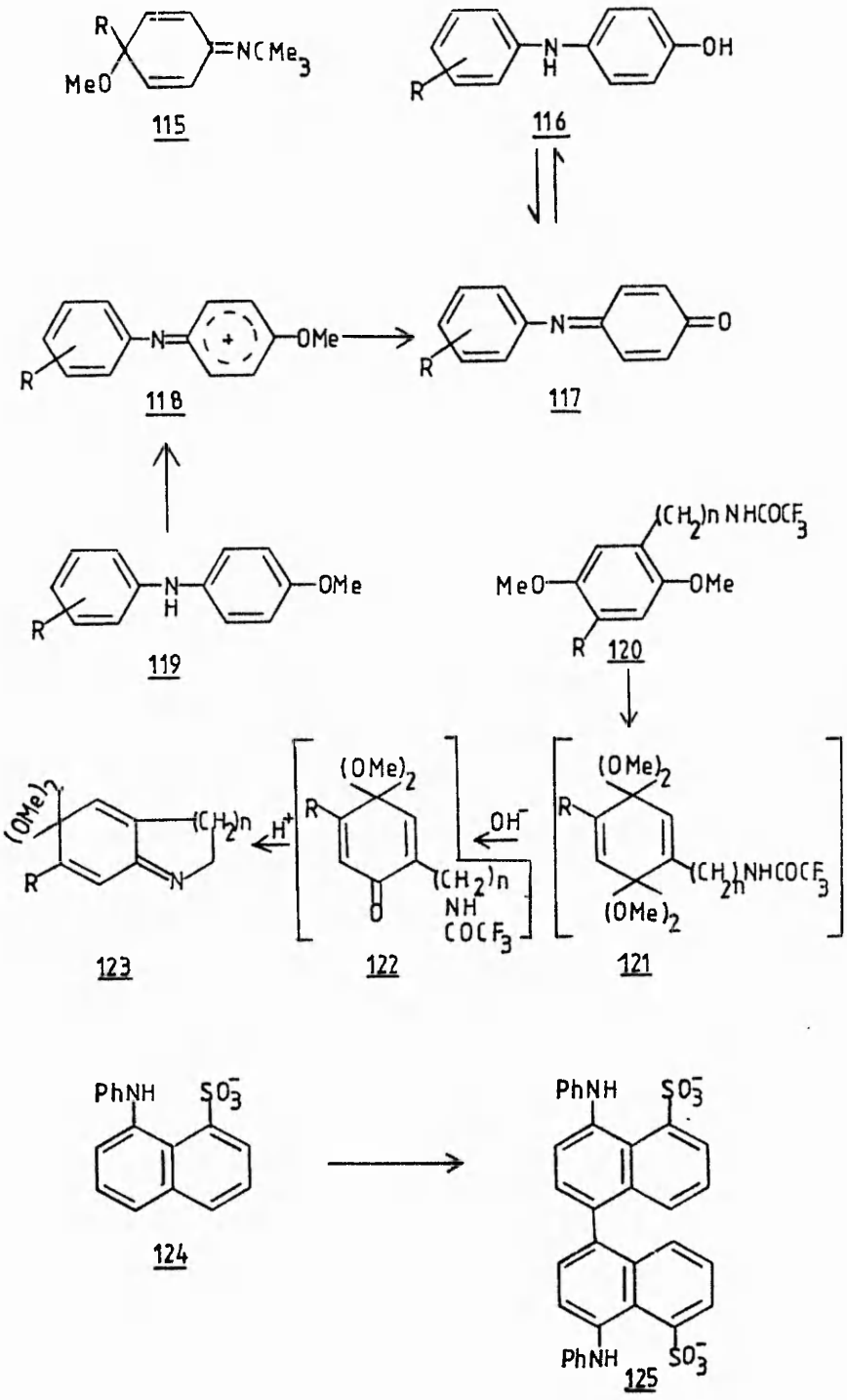

106
107
108
109
110
111
112
113
114
SCHEME 5

silver cation in methanol. This is the only reported preparation of an N-alkyl quinonimine by chemical oxidation.

Electrochemical oxidation has been used by several workers to prepare cyclohexadienimines, and it is now used more extensively than chemical oxidation because it allows greater control of oxidation potential in mild conditions (see Section 1.1.2). Anodic oxidation[81] of diphenylamine 116 at low pH gave the quinonimine 117, which hydrolysed in more alkaline media to p-benzoquinone and aniline. Imine 117 was also obtained by electrochemical oxidation of the appropriate anisidine 118, oxidation giving intermediate 119, which hydrolysed to imine 117. Swenton has used electrochemical oxidation as a route to cyclohexadienimines. Anodic oxidation[82,83] of trifluoroacetamide 120 gave intermediate bisketal 121, which upon base hydrolysis afforded p-quinoneketal 122, acid hydrolysis then yielding cyclic cyclohexadienimineketals 123. The facile synthesis[84] of binaphthyl compounds 125 was achieved by anodic oxidation of 8-anilino-1-naphthalene sulphonates 124.

An exhaustive investigation by Adams and his coworkers showed[85] that oxidation of N-sulphonyl-p-aminophenols or p-phenylenediamines gave stable quinone mono- and di-sulphonimides, the reaction of which paralleled those of corresponding quinones.

Quinonimines have recently attracted attention as possible intermediates in many biological processes. Isolation[86] of the cancerostatic compound agaracine[87] 126 from the toadstool Agaricus xanthoderma attracted other workers to investigate this fungus. The unusual compound 127 was also isolated[88] and



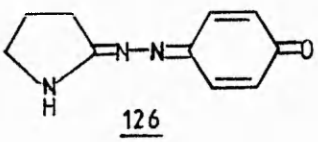
was shown[87] to be a biosynthetic precursor of the antibiotic diazonium salt 128, also found in the toadstool.

French workers investigating the cytotoxic compounds 9-methoxyellipticine 129 and N^2-methyl-9-methoxyellipticine acetate 130 have found[89,90] that peroxidase treatment of ellipticines leads to the quinonimines 131, which reduce easily to 9-hydroxyellipticines 132. This route for the *in vitro* formation of electrophilic derivatives of 9-methoxyellipticine is proposed as the possible metabolic pathway for these cytotoxic drugs. A recent report[90a] on the reaction of quinonimine 131 with primary amines shows that position 10 is the preferred site for nucleophilic attack.

2.1.2 Synthesis of cyclohexadienespirolactones

(a) Electrophilic addition to phenols

An extensively used method for synthesising cyclohexadiene spirolactones involves the addition of an electrophile to a p-substituted phenol. For example, the treatment of 3-(4-hydroxyphenyl)propanoic (phloretic) acid 18 with N-bromosuccinimide or bromine affords the brominated spirolactone 133 in good yield[91,92]; N-iodosuccinimide treatment[93] gave the analogous di-iodospirolactone. Two possible reaction mechanisms have been postulated[92] (Scheme 6), but most of the evidence[92] suggests that path 2 is the more probable route. The reaction of phenol with excess bromine yields[94] dienone 134 and N-bromosuccinimide treatment[95] of indole 135 gives spirolactone 136.



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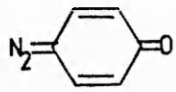

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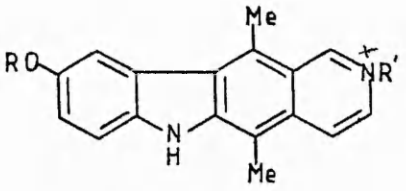
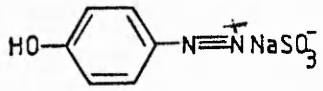


129 R=Me, R'=H

130 R=Me, R'=Me



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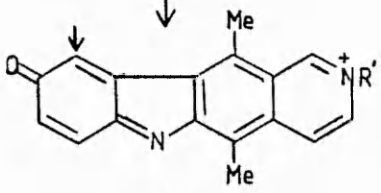

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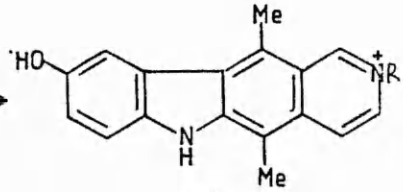

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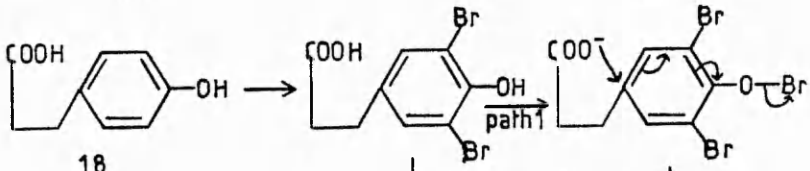
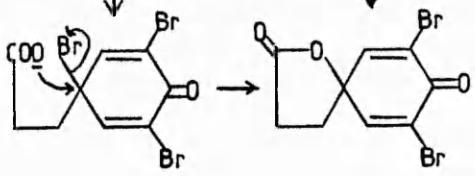


18

SCHEME 6



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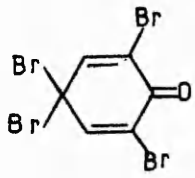


134

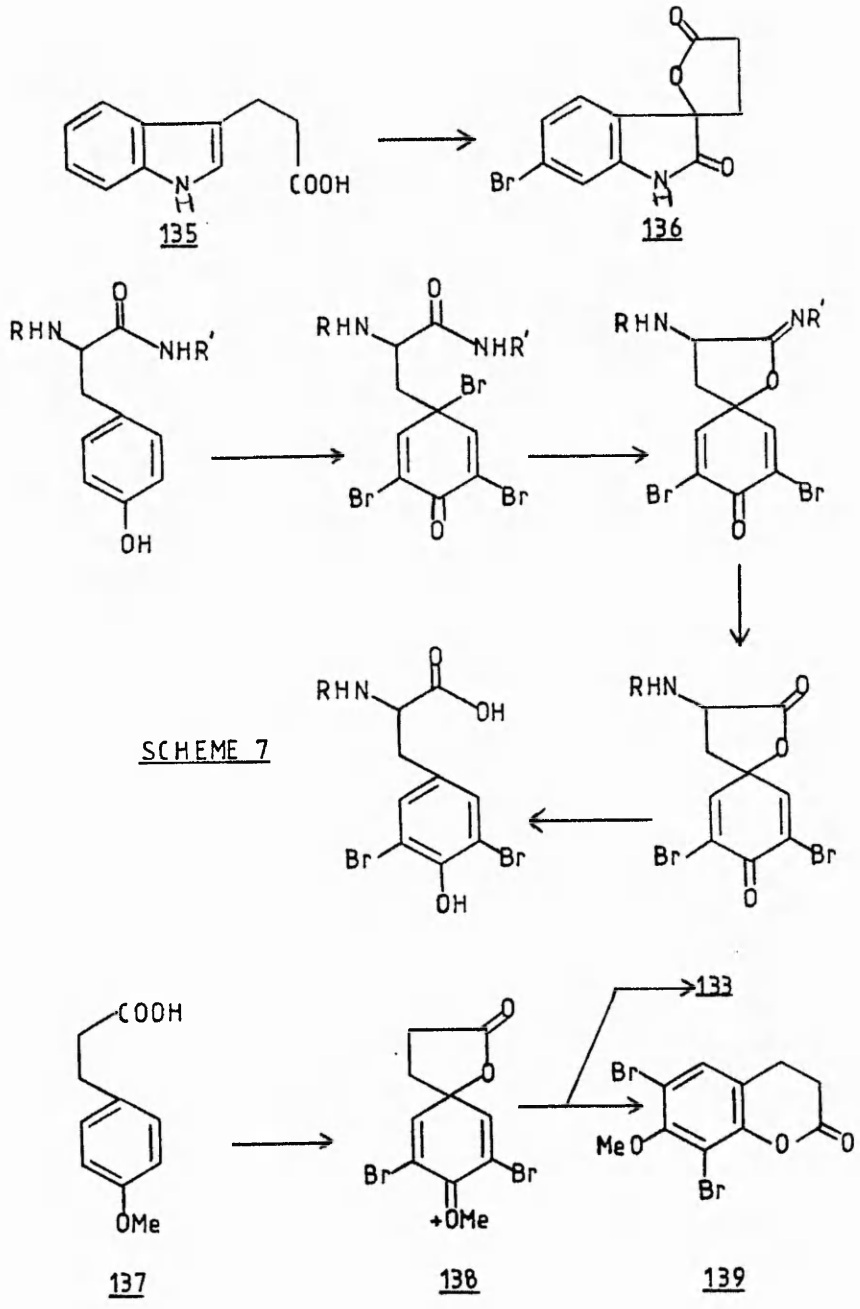
Du Vigneaud et al[95] found that selective cleavage of the polypeptides oxytocin and vasopressin at a tyrosine residue could be achieved by treatment with aqueous bromine. Later workers proposed[91] a mechanism (Scheme 7) and Du Vigneauds conditions were used to obtain several spirolactones. Many other spirolactones have been prepared[92] by bromination of phloretic amides.

N-Bromosuccinimide has been used to prepare a mixture of dibromolactone 133 and dihydrocoumarin 139 by reaction with the methyl ester 137 (Scheme 8) and also to obtain naphthalene derived o-spirolactones[97] (Scheme 9).

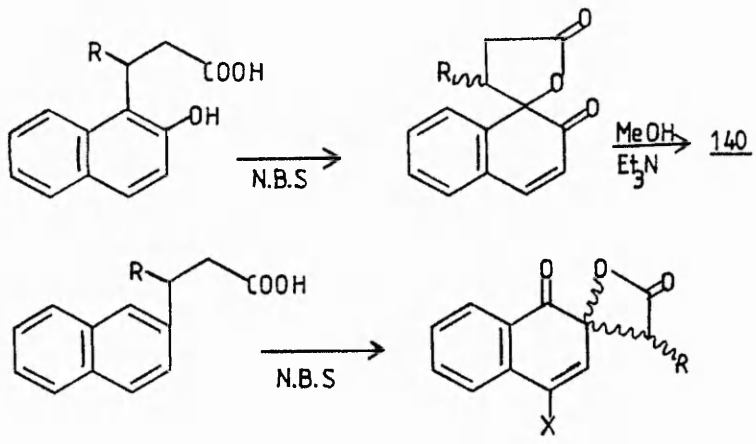
(b) Oxidative cyclisation of p-hydroxyphenylalkanoic acids

Another synthetic route involves the direct oxidation of phloretic acid 18 and its derivatives. The anodic oxidation of phloretic acid 18 has been studied in detail,[98] but yields of greater than 20% of the desired spirodienone 19 have not been achieved. The mechanism of anodic oxidation is discussed in Section 1.1.2.

The reaction of 3,5-di-iodophloretic acid 142 with a series of oxidising agents has been studied by Matsuura et al.[99] In only one instance was an identifiable product obtained, albeit in poor yield, polymers being the usual product (Scheme 10). However, oxidation with either hypochlorite and peroxide or photo-oxidation in the presence of a sensitizer yielded the di-iodospirolactone analogues of 133; the dichloro and dibromo derivatives behaved similarly. Hydrogen peroxide has been used[100] to prepare spirolactone 19

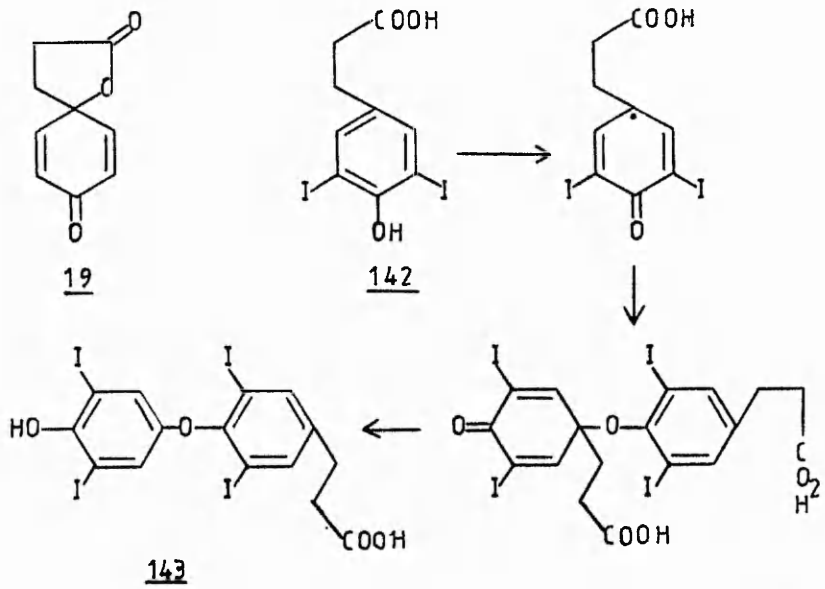

COOH
135
Br
136
RHN
NHR'
OH
Br
O
NR'
SCHEME 7
OH
137
OMe
138
+OMe
133
Me O
139

SCHEME 8

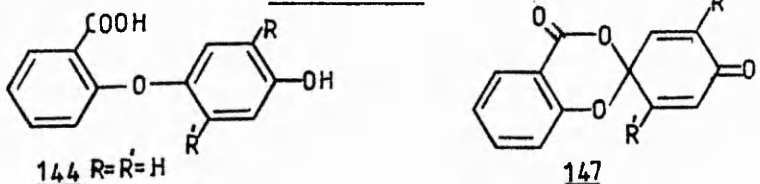


SCHEME 9

140 X = H
141 X = Br



SCHEME 10



144 R = R' = H
145 R = H, R' = CMe_3
146 R = CMe_3, R' = H

147

from phloretic acid 18, but in low yield. The latter is readily accessible by treatment of phloretic acid with N-iodosuccinimide.

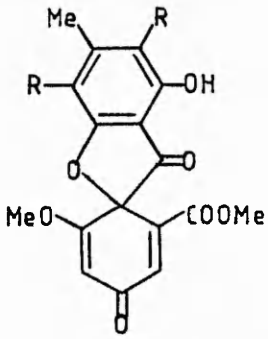
The 2-phenoxybenzoic acids 144-146 were converted[101] to their corresponding spirolactones 147, by treatment with either lead dioxide[102] or ceric ammonium sulphate.[103] Geodin[104] 148 when hydrolysed gives the carboxylic acid 149 which oxidises with lead dioxide[103] to geodoxin[105] 150 in good yield. Compounds 151-153 were all isolated[106] from oospora sulphurea ochrea and the in vitro hydrolysis of quinone 151 to acid 152 followed by oxidation to lactone 153 occurred in 70% yield.

Hydrolysis of dehydrogriseofulvin 154 to acid 155 followed by manganese dioxide oxidation afforded dehydrogriseofulvoxin 156 in excellent yield[107] (Scheme 11), whilst the oxidation of biphenic acid 157 with manganese dioxide in ether[101] gave the cyclohexadienonespirolactone 158 in 25% yield.

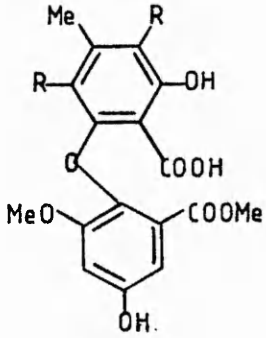
Recently phenyliodosyl bis(trifluoroacetate) has been reported[108] to convert p-hydroxyphenyl acids 159 to spirolactones 160 in 70 to 80% yields.

(c) Oxidation with thallium salts

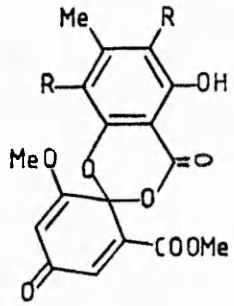
Thallium(III) trifluoroacetate has been shown to effect electophilic thallation of a wide variety of aromatic substrates bearing many different substituent groups (moderately activating to moderately deactivating). The resulting arylthallium bis(trifluoroacetates) are exceptionally versatile intermediates for the regiospecific introduction of new substituents into the aromatic nucleus. With highly



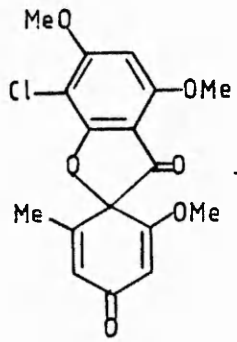
148 R = Cl
151 R = H



149 R = Cl
152 R = H



150 R = Cl
153 R = H



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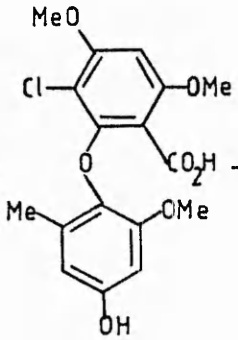

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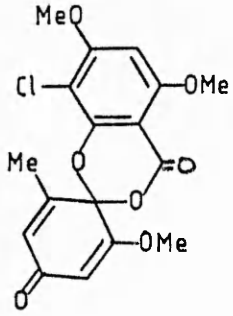

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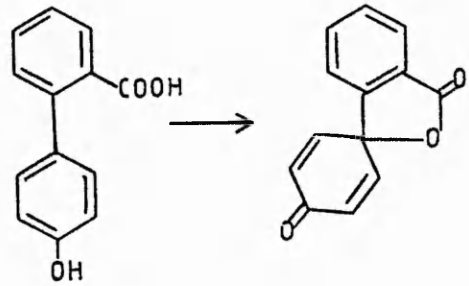
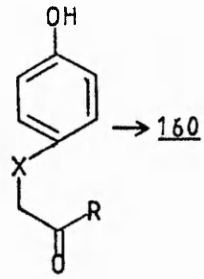
SCHEME 11



157 158



159 X = O or C
R = OH or $NHCH_2Ph$

activated aromatic substrates however, electrophilic thallation is not normally observed; instead a one-electron oxidation takes place to generate a radical cation whose fate is determined by the nature of the reaction medium and of the substrate itself. The ability of thallium reagents to act as one-electron oxidants is well documented[109-113] and has been exploited, for example, in the synthesis of aporphine and homoaporphine alkaloids[114,115] from non-phenolic precursors. These transformations represent capture (both inter and intramolecular) of the initially generated aromatic radical cation by another aromatic compound acting as a nucleophile.

McKillop et al[116] described the use of thallium(III) trifluoracetate to prepare cyclohexadienonespirolactones from alkoxylated aryl alkanoic acids; for example, acid 161 gave propanoate 162, via acid catalysed ring-opening of one of the initial oxidation products, coumarin 163 or spirolactone 164. Oxidation of the analogous methoxy compound 165 yielded the spirolactone 166 only, steric hindrance to ortho-substitution and facile demethylation of the doubly-flanked methoxy group preventing coumarin formation.

These thallium oxidations presumably occur by a mechanism similar to that described for anodic oxidations (see Section 1.1.2), the main difference being the removal of the methyl group by the solvent (Scheme 12).

(d) Miscellaneous spirolactone syntheses

p-Benzoquinone reacts photochemically with one molar equivalent of either diphenylketene[117] or dimethylketene[118] to

give spiro-β-lactones 167 and 168. Ogino et al[119] extended this to prepare spirolactones 169-172 and have studied their reaction with nucleophiles (if two moles of ketene are used, the quinodimethane 173 is produced[119] after a decarboxylation step). This synthetic route is of limited value as it can only be applied to the preparation of spiro-β-lactones.

The preparation of spirolactones from hydroxylamines and aromatic azides is discussed in Chapter Three.

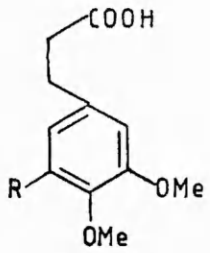
2.1.3 Cyclohexadiene spiroketals

Cyclohexadiene spiroketals have been synthesised by the methods described for spirolactone preparation and therefore only representative examples will be cited.

An example of intermolecular oxidative coupling is the preparation[120] of spiroketal 174 by oxidation of 3-t-butyl-4-methoxyphenol with ferricyanide, lead dioxide or silver dioxide. Intramolecular oxidative coupling with manganese dioxide, of dihydroxydiphenylether 175 leads[121] to the isolation of spiroketal 176 in low yield.

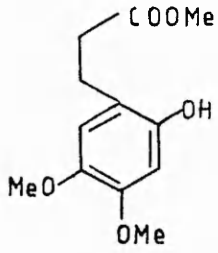
Tetrahalo-1,2-benzoquinones react with α-tetralones or naphthols in refluxing benzene to produce spiro-2,4-dienone ketals,[122] such as compound 177. A further example of an electrophilic addition reaction is the iodination[123] of 2-phenoxyethanol giving iodoethanol 178, which when irradiated yields 84% of spiroketal 179.

Although monocyclic cyclohexadienimine spiroketals have been prepared (see Section 2.1.1), no cyclohexadienimine spiroketals 180 have been reported.



161 R=H

165 R=OMe



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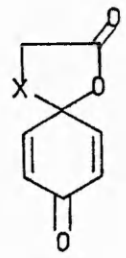

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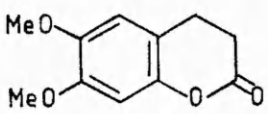

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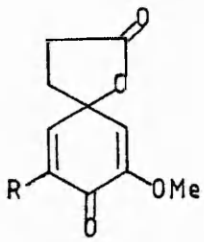
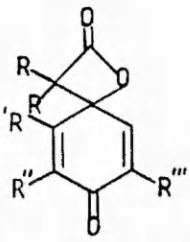


164 R=H

166 R=OMe



167 R= Ph, R'= R''= R'''=H

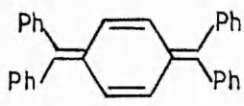
168 R= Me, R'= R''= R'''= H

169 R=Ph, R'= R''= H, R'''=Me

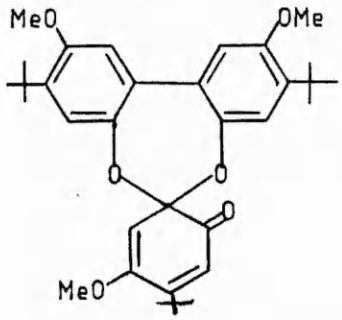
170 R= Ph, R'= H, R''= R'''= Me

171 R=Ph, R'=H, R''= R'''=Cl

172 R=Ph, R' R''=(CH=CH)$_2$ R'''=H



173



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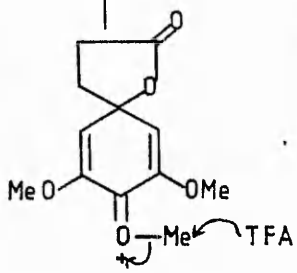
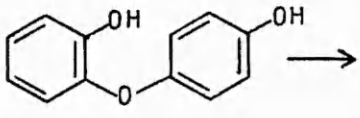


SCHEME 12



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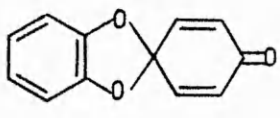


176

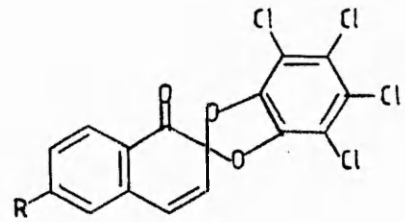
2.2 Discussion

Having discussed N-substituted quinonimines and cyclohexadiene spirolactones and ketals, molecules combining these two structural features will be considered.

Apart from a recent paper by Swenton,[124] in which he describes the one-step conversion of p-methoxyamides 181, by anodic oxidation in methanolic lithium perchlorate containing mild base, to N-acyl quinonimine ketals 183, via intermediate 182, the only examples of these compounds are from work carried out in this department.

Anodic oxidation[125] of sulphonamide 184 yielded the stable N-tosylcyclohexadiene spirolactone 185, which was hydrolysed on alumina to cyclohexadienone 186. Several sulphonamides 187-191 were treated in this way and a later paper[126] cites the preparation of 2-substituted-N-sulphonylcyclohexadienimines 193, by anodic or lead tetraacetate oxidation of the sulphonamides 192; several of the dienimines prepared were shown to undergo Diels-Alder type cyclisations with 2,3-dimethylbutadiene giving adducts such as 194.

The compounds synthesised were made as analogues of spirolactones of known[127] antifungal activity. This activity is linked to the rates of absorption and of hydrolysis of the compounds, and none of the N-sulphonyldienimines prepared at Trent showed significant fungicidal properties. It was thought that this might be due to the poor absorption of the relatively polar sulphonyl group, and the present investigation was concerned with the replacement of this group by a more lipophilic aryl substituent, as in compound 195. Alteration of



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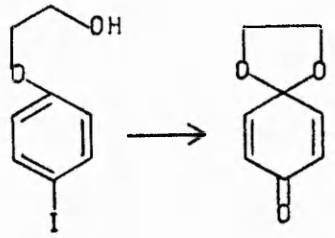
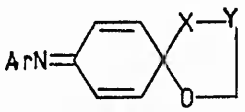


178 179



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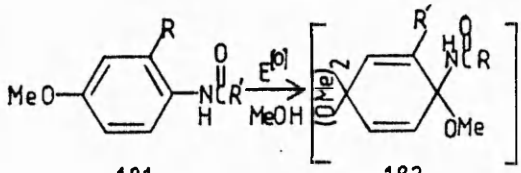
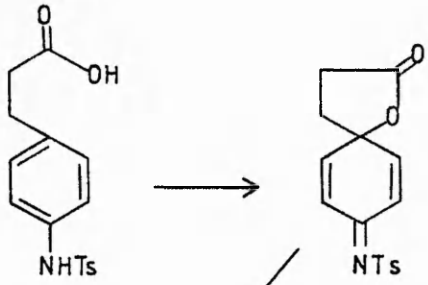
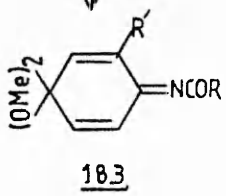


181 182



184 185



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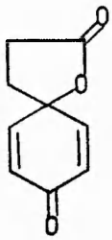

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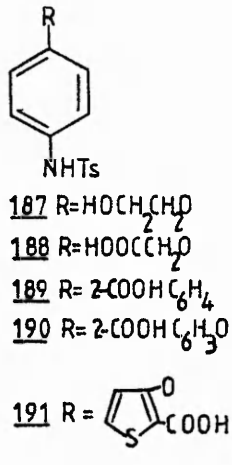
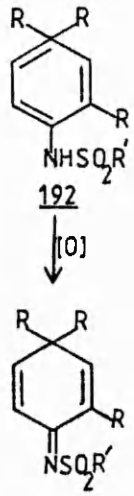


187 R=$HOCH_2CH_2O$
188 R=$HOOCCH_2O$
189 R= 2-$COOHC_6H_4$
190 R= 2-$COOHC_6H_3O$
191 R =



192

193

the X and Y units in these molecules would also significantly change the hydrolytic behaviour of the resulting spirolactones and ketals.

The aryl group initially used was 2-nitro-4-trifluoromethylphenyl, which is readily introduced using inexpensive 4-chloro-3-nitrobenzotrifluoride and which is resistant to oxidation.

It was decided to prepare spirolactones of the type 195 in which X = O or CR_2 by oxidative cyclisation of either 4-arylaminohydrocinnamic acids or 4-arylaminophenoxyacetic acids 196. The acids could also be reduced to the analogous ethanols, oxidation of which would yield novel spiroketals 180 (X = O or CR_2).

2.2.1 Synthesis of substrates

(a) 4-Arylaminophenoxyacetic acids

The phenoxy acids 196 were prepared by one of the two general routes:

(I) by initial formation of a 4-aminophenoxyacetic acid, followed by N-arylation yielding the desired diphenylamine;

(II) by elaboration of the phenolic group of a 4-hydroxydiphenylamine.

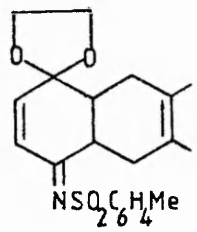
The 2-phenoxypropanoic acid 198 was synthesised via route II. The previously reported[67] preparation of the ethyl ester 197 was undertaken by reacting 4-hydroxy-2'-nitro-4'-trifluoromethyldiphenylamine 87 (see Chapter One) with ethyl 2-bromopropionate yielding 99% of ester 197, saponification giving the desired acid 198 in 60% yield.

Initial preparation of 2-phenoxyethanoic acid 200 was attempted using the procedure described above for acid 198. However, the ethyl ester 199, isolated from the reaction of ethylchloroacetate with diphenylamine 87, yielded a complex mixture upon saponification. Treatment of the analogous t-butyl ester 201, (prepared quantitatively from t-butylbromoacetate and diphenylamine 87), with trifluoroacetic acid at room temperature afforded the desired acid 200 in 50% yield.

Finally, the synthesis of 2-phenoxy-2-methylpropanoic acid 202 was studied. Following route I the 4-nitrophenoxypropanoic acid 203 was prepared by reaction of 4-nitrophenol with sodium hydroxide, acetone and chloroform. Hydrogenation yielded amino acid 204 which existed as a zwitterion and was resistant to N-arylation even in the presence of added base. Attempted synthesis of the ethyl ester of acid 204 did not yield a clean product. Acid 202 was successfully obtained in 32% yield by treating diphenylamine 87 with sodium hydroxide, acetone and chloroform.

(b) 4-Arylaminohydrocinnamic acids

The attempted synthesis of 4-anilinohydrocinnamic acid 206 by N-arylation of zwitterion 205 failed and its methyl ester gave a complex mixture. It was thought that the benzylic protons of these compounds were assisting free-radical formation, thus leading to product degradation; it was therefore decided to try the preparation of 3,3-dimethylhydrocinnamic acid 208, in which no benzylic protons were present.



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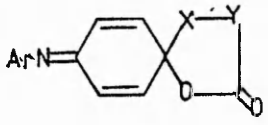

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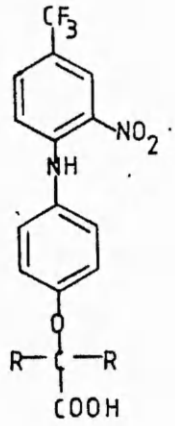

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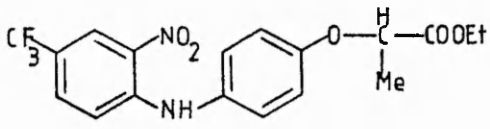

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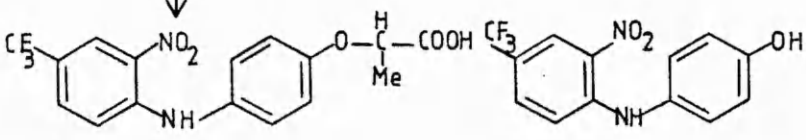
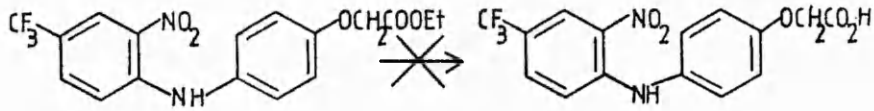
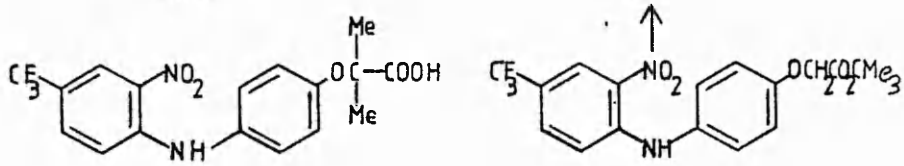


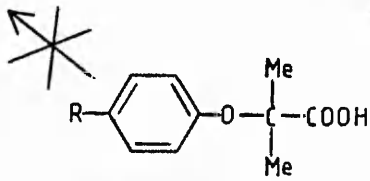
198 87



199 200



202 201



203 R = NO_2

204 R = NH_2

The synthesis of acid 208 proceeded smoothly in moderate to good yields and is shown in Scheme 13.

The N-tosyl acid 210 was prepared in 60% yield by reaction of amino ester 209 with p-toluenesulphonyl chloride, as comparative oxidation studies with the previously reported[74] hydrocinnamic acid 211 were thought to be valuable.

(c) 4-Arylaminophenoxyethyl and hydrocinnamyl alcohols

The previously described 4-arylaminophenoxyacetic and hydrocinnamic acids were all easily converted to their corresponding alcohols 212-215, in good yields by treatment with borane-methyl sulphide complex.[128]

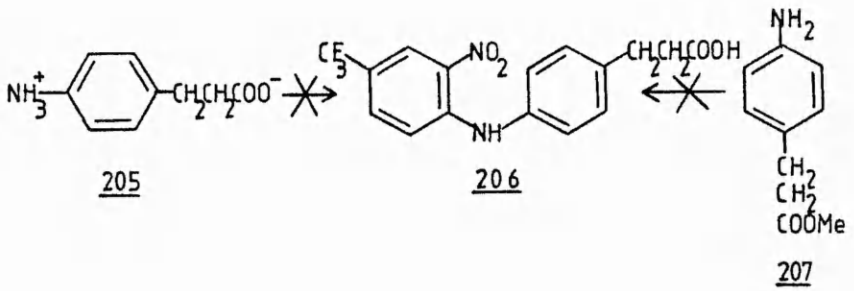
(d) 4-perfluoroarylaminohydrocinnamic acids

As an extension of the study of these systems it was decided to attempt the preparation of spirolactones in which the nitroaryl group was replaced with a biologically more inert perfluoroaryl substituent. Octafluorotoluene was reacted with aniline in DMF/K_2CO_3, yielding diphenylamine 216; similarly amino ester 209 gave diphenylamine 217. Both perfluoroaryl compounds were found to be unstable.

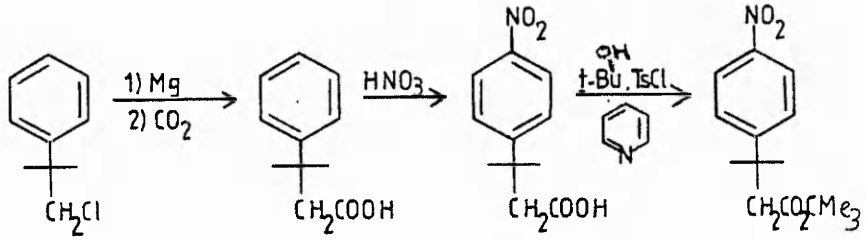
2.2.2 Oxidation of substrates

(a) 4-Arylaminophenoxyacetic acids and alcohols

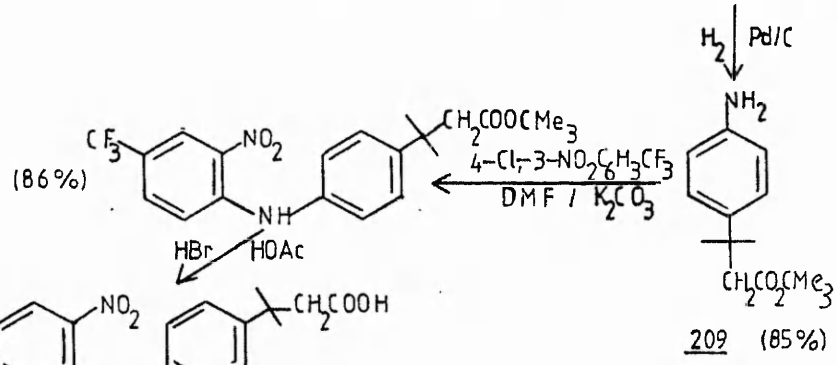
Oxidation of the parent acid 200, with lead tetraacetate in glacial acetic acid, manganese dioxide or electrochemically yielded a complex product mixture, the i.r. spectrum of which showed no lactone carbonyl band. However, by oxidation of the



205 206 207



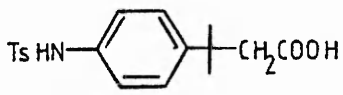
(76%) (36%) (76%)



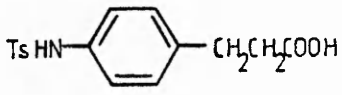
(86%) 209 (85%)

208 (67%)

SCHEME 13



210



211

derived ethanol 212 was obtained in moderate yield the spiroketal 218, which when stored in a glass tube exposed to sunlight decomposed slowly over a period of approximately one week to a complex mixture.

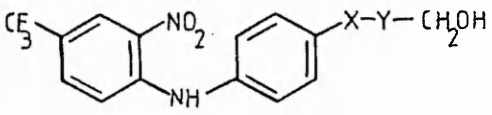
The corresponding monomethyl acid 198 yielded, by chemical or anodic oxidation the spirolactone 219, which when left standing decomposed over a one month period to quinonimine 220; this was independently prepared by the manganese dioxide oxidation of diphenylamine 87.

Dimethyl substituted acid 202, when oxidised at the anode or by lead tetraacetate, gave the stable spirolactone 221.

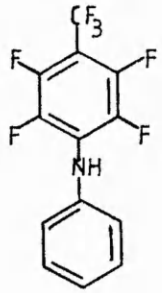
Chemical oxidation of ethanols 213 and 214 was complicated by the presence in the product of a small amount of the corresponding spirolactones 219 and 221, which were presumably formed by oxidation of the ethanols to their acids, which then gave the spirolactones. The mixture of spirolactone and spiroketal was difficult to separate due to their similar R_f values and solubilities. However, alcohols are resistant to anodic oxidation and when compounds 213 and 214 were thus treated they were converted smoothly to spiroketals 222 and 223, without any sign of spirolactone formation. This illustrates an advantage of electrochemistry in organic synthetic chemistry. Both spiroketals were unstable over a short period of time.

(b) 4-Arylaminohydrocinnamic acids and related alcohols

Oxidation of the dimethylhydrocinnamic acid 208 by lead tetraacetate yielded 46% of the spirolactone 224, while anodic



212 X= O, Y= CH_2
213 X= O, Y= CHMe
214 X= O, Y= $C(Me)_2$
215 X= $C(Me)_2$, Y= CH_2



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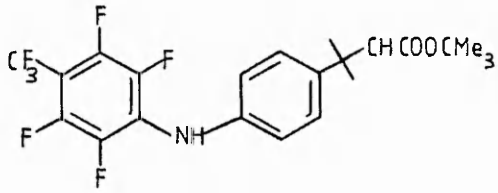

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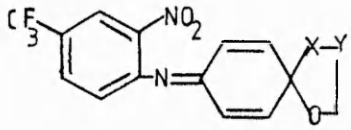
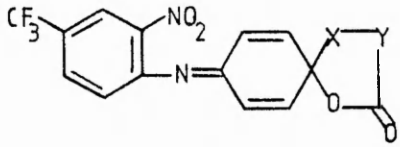
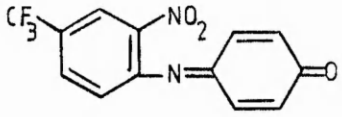


218 X= O, Y= CH_2
222 X= O, Y= CHMe
223 X= O, Y= $C(Me)_2$



219 X= O, Y= CHMe
221 X= O, Y= $C(Me)_2$
224 X= $C(Me)_2$, Y= CH_2



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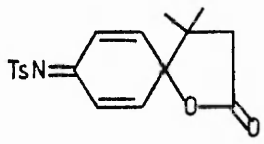

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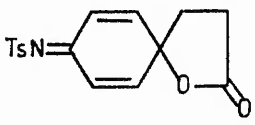
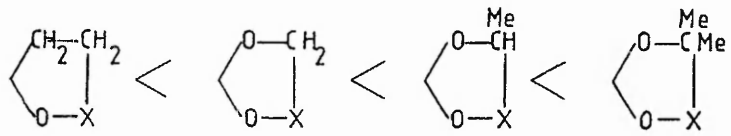


226

oxidation gave almost quantitative conversion; the lactone decomposed over a 1h period when exposed to the atmosphere.

2.2.3 Hydrolytic stability of spirolactones and spiroketals

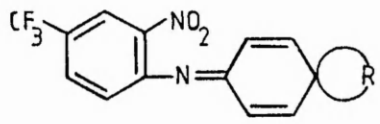
Table 1 summarises the yields and the approximate stabilities found for the spirolactones and spiroketals isolated. It is seen that lactones derived from phenoxyacetic acids are more stable than those from hydrocinnamic acids. Both spirolactones and spiroketals are more stable when the C-2 position (see below) in the spiro-ring is alkylated; gem-dialkyl compounds are more stable than monoalkyl compounds, and are formed in better yield.

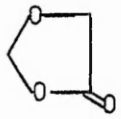
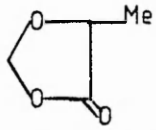
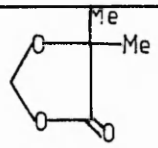
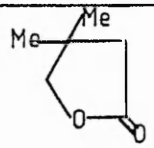
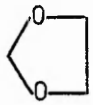
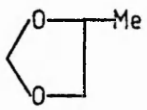
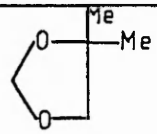


increasing stability

This increase in ring stability is perhaps explained by the Thorpe-Ingold (gem dialkyl) effect,[129-133] which might be summarised[134] as follows: the diminution of the internal angle in a small ring leads to a spreading apart of the external angle. This in turn relieves steric compression between substituents attached to one and the same carbon, thus favouring the ring form over the open-chain form.

TABLE 1



R Unit	% Yield by oxidation		Shelf life
	lead tetraacetate	anodic	
	0	0	—
	17	56	1 month
	20	55	2 Yr
	46	80	1h
	49	56	1 week
	mixture with corresponding lactone	50	1 week
	mixture with corresponding lactone	60	1 week

The anomolous result in the series is the instability of compounds derived from α,α-dimethylphenylpropanoic acids or phenylpropanols. Lactone 224 decomposes immediately, and no spiroketal is obtained from the oxidation of alcohol 215. This could perhaps be attributed to the ring strain in the compounds, but this argument should also apply to sulphonamide 225 which forms readily in yields higher than the lactone 226 without methyl groups and is perfectly stable.

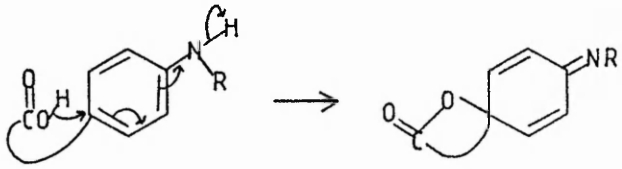
Spiroketal 223 was found to give the starting ethanol 214, when reduced by sodium borohydride.

CHAPTER THREE

3.1 Introduction

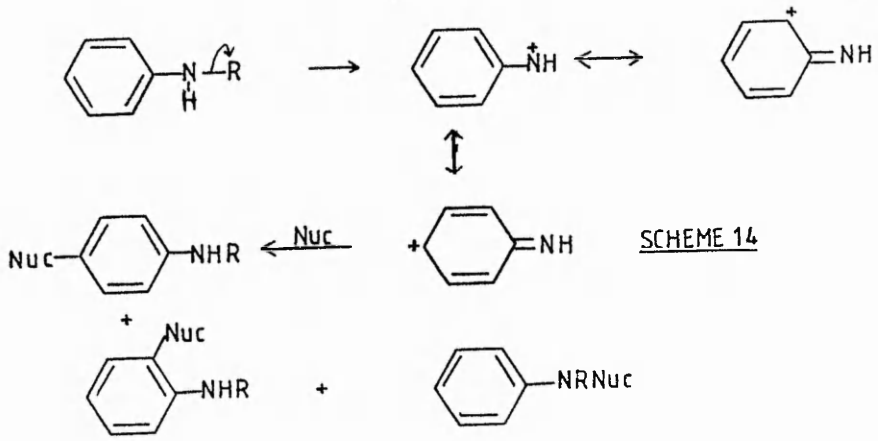
In Chapter Two was described the preparation of a series of N-aryl-cyclohexa-2,5-dienimines containing a 4-spirolactone function. The syntheses of spirolactones reviewed in the previous Chapter are, in the main, low yielding processes and there is still a need for efficient preparative methods for these compounds, the synthetic potential of which is discussed later in this Chapter.

A logical extension of the earlier work to this problem is to use the pathway outlined in Chapter One



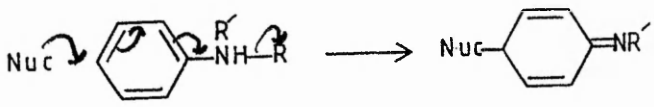
Although there appears to be few examples of this reaction reported, the attack by nucleophiles on species generated by expulsion of a leaving group from the nitrogen of a N-aryl intermediate is rather better demonstrated.

Two processes can lead to dienone formation. In the first the expulsion of a leaving group from nitrogen leads to a positively charged nitrenium intermediate, which then undergoes ortho or para attack by a nucleophile.



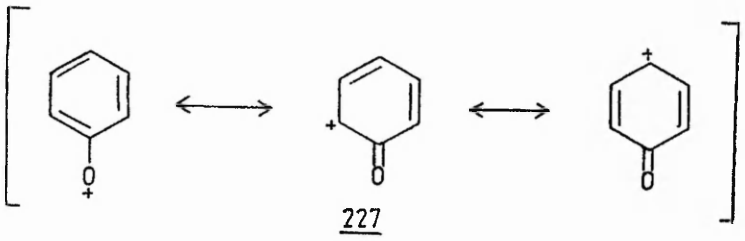
SCHEME 14

A second mechanism (Scheme below) involves concerted attack by a nucleophile and expulsion of a leaving group without the formation of the high-energy nitrenium species.



The dienimines formed will readily hydrolyse to dienones, and this approach to dienones parallels the synthesis of such compounds from phenoxonium intermediates.

It is obvious that phenoxonium ions 227, due to the charge distribution shown below, could be useful in nucleophilic aromatic substitution reactions.



227

Phenoxonium ions have been suggested as possible intermediates in biosynthetic phenolic coupling reactions[8,13] and in the oxidation of phenols by thallium salts,[135] chromic acid[136] and iodine/silver.[137] The production of phenoxonium ions has been achieved by anodic oxidation, with their existence confirmed by potential-sweep measurements,[138] and in some cases have been isolated as crystalline salts.[17] Aryloxonium ions have also been generated conveniently in solution in organic solvents.[139]

Further evidence for phenoxonium ion formation comes from the intramolecular aryloxylation of tetrafluoroborate 228 which gives compounds 229-231 when heated in anisole.[140] Similarly the addition of phenol to quinonimine 232 gives[141] the hydroxyphenol ether 233 when reacted in mild acid and derivative 234 in the stronger trifluoroacetic acid.

Intermolecular carbon-carbon bond formation via such intermediates, prepared by elimination of a nucleofugal group

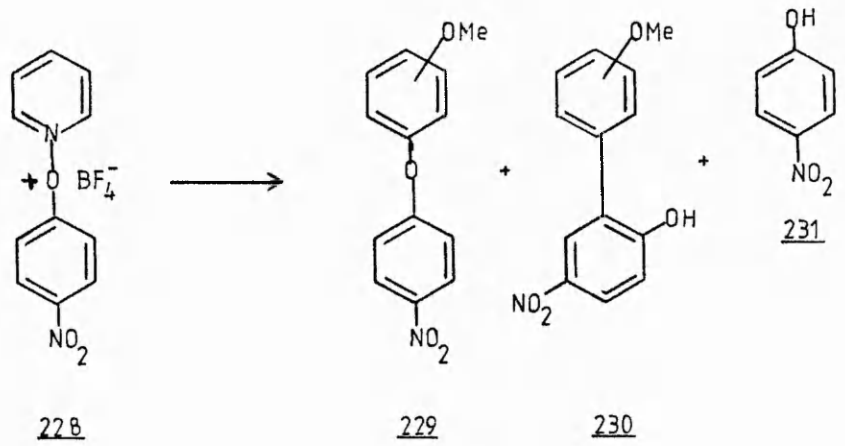
from the oxygen atom, is known although, as with tosylate 235; ortho substitution to give biphenyl 236 predominates over para attack to derivative 237. In fact Shudo has reported[140] that attack of the intermediate resulting from treatment of hydroxaminic acid 238 with acid occurs only at the ortho positions yielding biphenyl 239 and triphenyl 240.

Abramovich et al showed[142] that the phenoxypyridinium salt 241 underwent ether and not carbon-carbon bond formation to yield benzofuran 242. It was suggested that the oxygen atom ortho to the α-aryl cation centre imposes a rotational conformation in which the aryloxy group is geometrically unlikely to undergo cation attack. Further support for this postulate comes from the observation[143] that the thermal decomposition of tetrafluoroborate 243, with no oxygen atom ortho to the α-aryl cation centre, undergoes carbon-carbon bond formation giving derivatives 244 and 245.

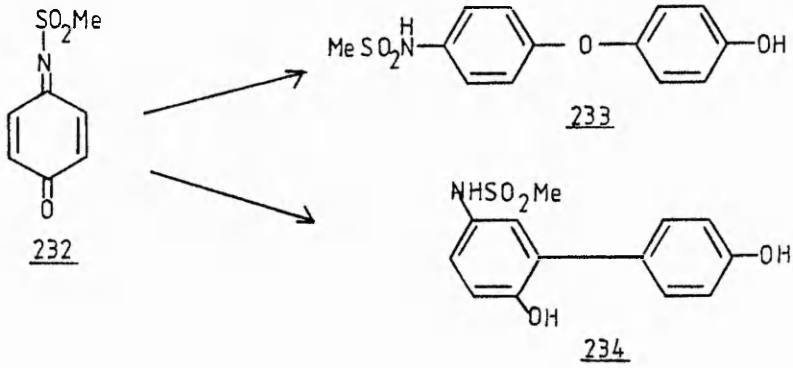
Since phenoxonium ions have been shown to undergo nucleophilic attack, it might be assumed that the analogous nitrenium ions could undergo similar reactions.

3.1.1 Formation and reactions of nitrenium cations

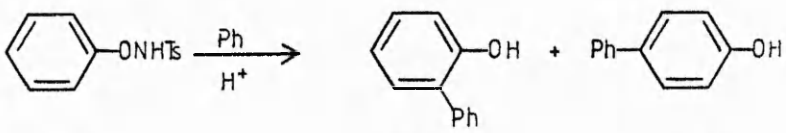
Nitrenium ions have received considerable attention in recent years, although they have not been isolated[144] as distinct species. They have been generated by treatment of azides[145] or arylhydroxylamines[146,147] with strong acids or by the solvolysis of N-chloroanilines.[148]



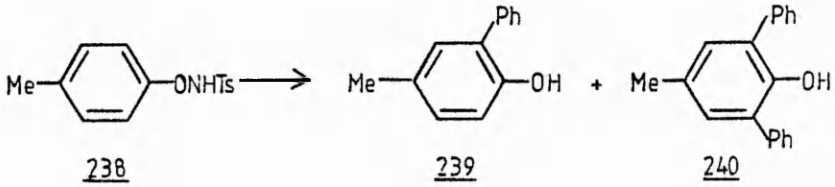
228 229 230 231



232 233 234



235 236 237



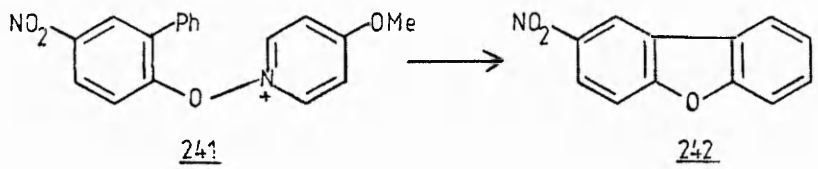
238 239 240

3.1.2 Bamberger Rearrangement

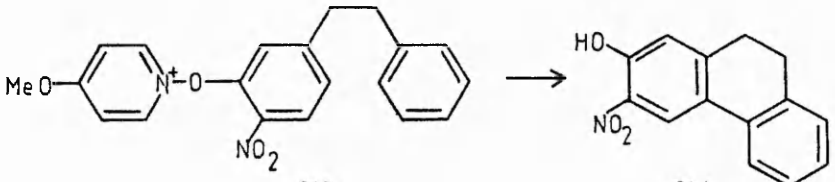
The most intensely studied reaction considered to involve nitrenium intermediates is the rearrangement of hydroxylamines to p-aminophenols, discovered by Bamberger[146] and which bears his name. The mechanism[149] involves protonation of the hydroxylamine oxygen, dehydration, nucleophilic attack by water para to the nitrogen atom and deprotonation (Scheme 15).

Adaption of this reaction using nucleophiles other than water and by blocking tautomerism of the arylnitrenium ion, has led[101(a)] to the preparation of spirodienone 248, by acid rearrangement of hydroxylamine 246, via intermediate 247.

More recently, the formation of a resonance stabilised ion by loss of nitrogen from the conjugate acid of an azide has been proposed[153] as an alternative source of the nitreneum ion. Reaction of a nucleophile with the nitrenium ion would then yield either ortho or para substituted amines. Alternatively, attack by the nucleophile and elimination of nitrogen could be synchronous[145(b)] (Scheme 16). Both inter- and intra-molecular nucleophilic attack of nitreneum ions have been reported with nucleophiles such as methanol,[154] halide ions,[145(b)] benzene and toluene.[155]

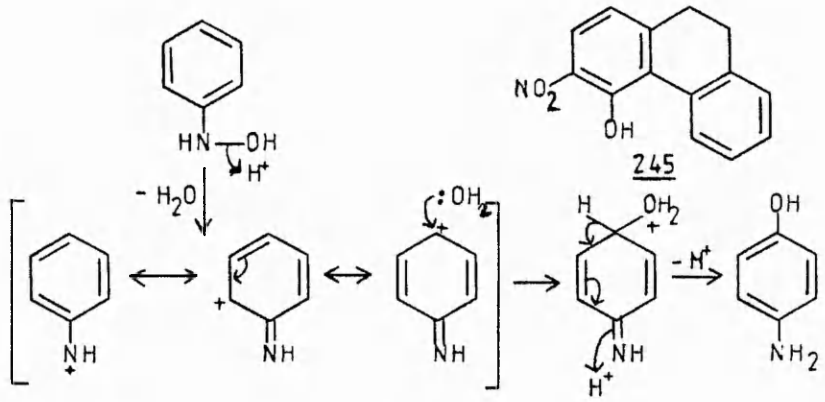


241 242



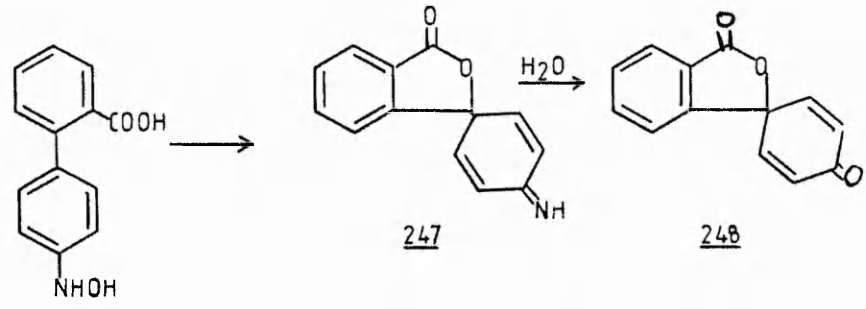
243 244

+



245

SCHEME 15



246 247 248

3.1.3 Nucleophilic substitution of aryl azides

The protic acid-catalysed decomposition of aryl azides was first observed by Greiss[156] who reported that the decomposition of phenyl azide in hydrochloric acid gave a mixture of ortho- and para-chloroanilines, while in the presence of concentrated sulphuric acid, p-aminophenol was formed.[157]

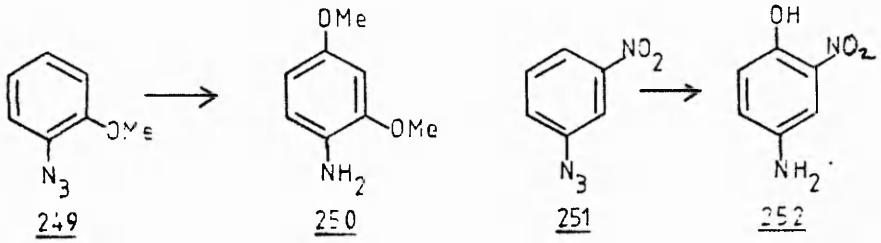
Solvent attack, both ortho and para, of aryl azides has been used extensively, eg. the 4-amino cresol 250 was formed from o-tolylazide 249 in the presence of methanol; similarly nitroazide 251 yielded aminophenol 252 in aqueous solutions.

The decomposition[158] of azide[159] 253 in a TFA/TFSA mixture gave phenanthrene 254 as the major product, together with a lower yield of the 4-amino isomer 255. A related cyclisation is the conversion by acid treatment of trans-m-azidocinnamate 256 to phenanthrene. The cis-isomer 258 gave C-O bonded coumarin 259, while azido acetic acid 260 gave coumarin 261. Since the latter compound was also obtained from amide 262 it can be assumed that the carbonyl oxygen acts as the nucleophile to trap the nitrenium ion.

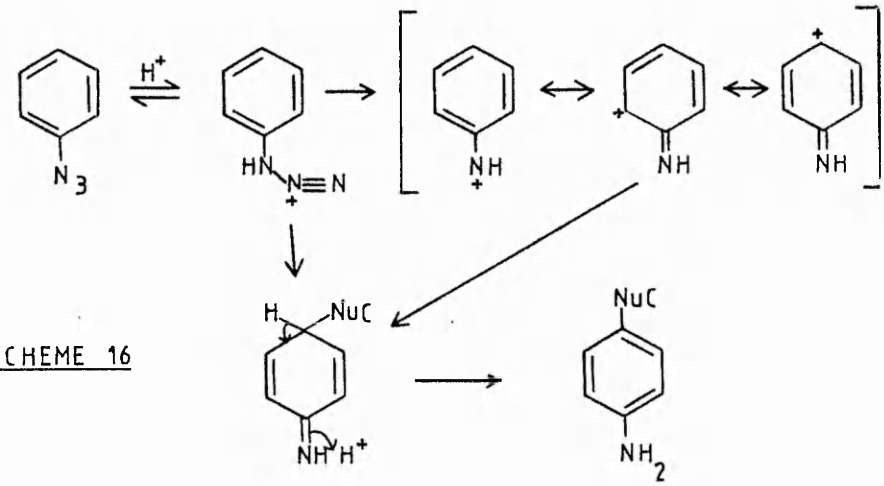
Takeuchi and his co-workers have reported[160] the formation of a nitrenium ion by treatment of phenyl azides with trifluoroacetic acid; subsequent trapping by benzene gave compounds 263-265, while toluene yielded only two products, 266 and 267, by attack at the nitrogen atom only. This work was extended[162] to the trapping of nitrenium species by olefins.

3.1.4 Nucleophilic substitution of N-chloroanilines

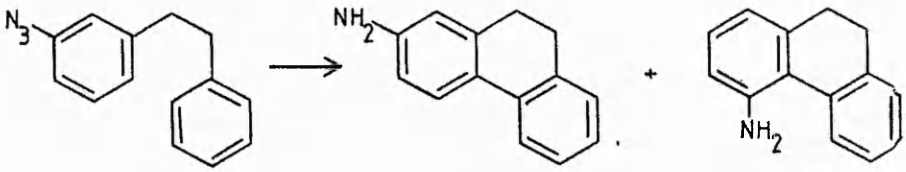
N-Chloroamines have been proposed as intermediates in the chlorination of aromatic amines[142] and the formation of



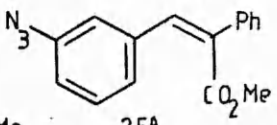
249 250 251 252



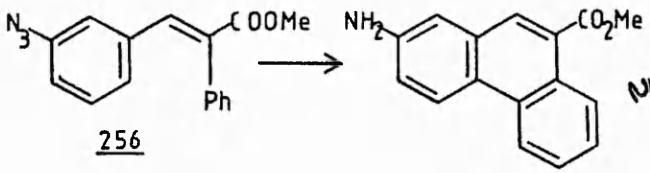
SCHEME 16



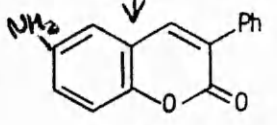
253 254 255



258



256 257



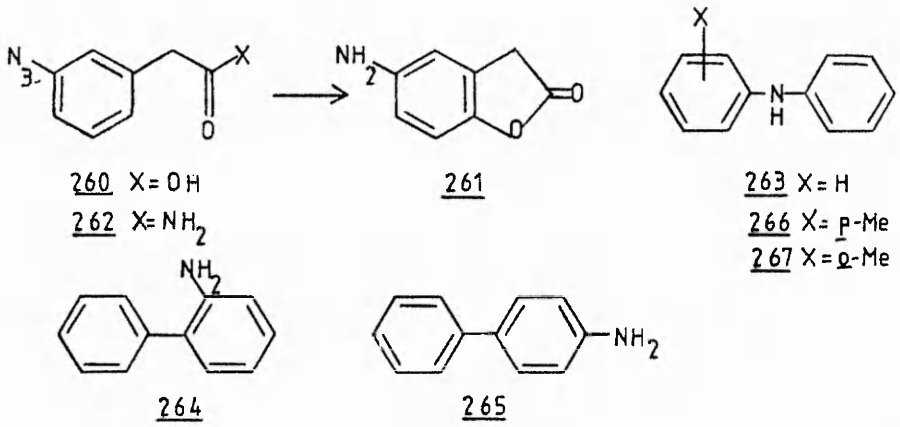
259

nitrenium ions using chloride ion as a leaving group has been studied.[80] The presence of silver trifluoroacetate left the initially generated cation susceptible to nucleophilic attack by solvent and indeed the major product from reaction in methanol resulted from para-methoxylation. A suggested mechanism[163] involved hydrogen migration as the ultimate step (Scheme 17); similarly aniline 268 gave imine 115 (see Chapter Two).

3.1.5 Nucleophilic substitution of N-arylhydroxylamines

Shudo et al proposed[165] the intermediacy of nitrenium ions when hydroxylamines are treated with strong acids. The TFA-catalysed reaction of N-arylhydroxylamines 269 with benzene gave the nitrogen coupled diphenylamine 270. Using the stronger trifluoromethane sulphonic acid (TFSA)[165] the carbon coupled isomers 271 and 272 were isolated. The presence of an iminium-benzenium ion intermediate was supported by the reaction of p-substituted arylhydroxylamines 273 with TFA; three products were isolated, the expected ortho-aniline 274 and compounds 275 and 276, which were probably formed by rearrangement of the intermediate 277. The low regioselectivity of the latter reaction suggests that the intermediate 277 may be a highly reactive[166] di-cation, rather than a protonated nitrenium ion (Scheme 18).

Nucleophilic substitution reactions of hydroxylamines using phosphorus oxychloride as a leaving group have been reported,[167] eg. hydroxylamine 278 was reacted with phosphorus



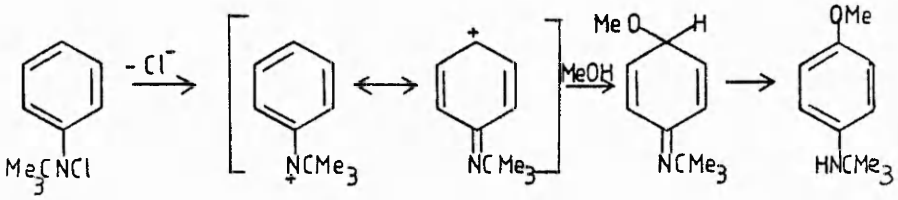
260 X = OH
262 X = NH_2

261

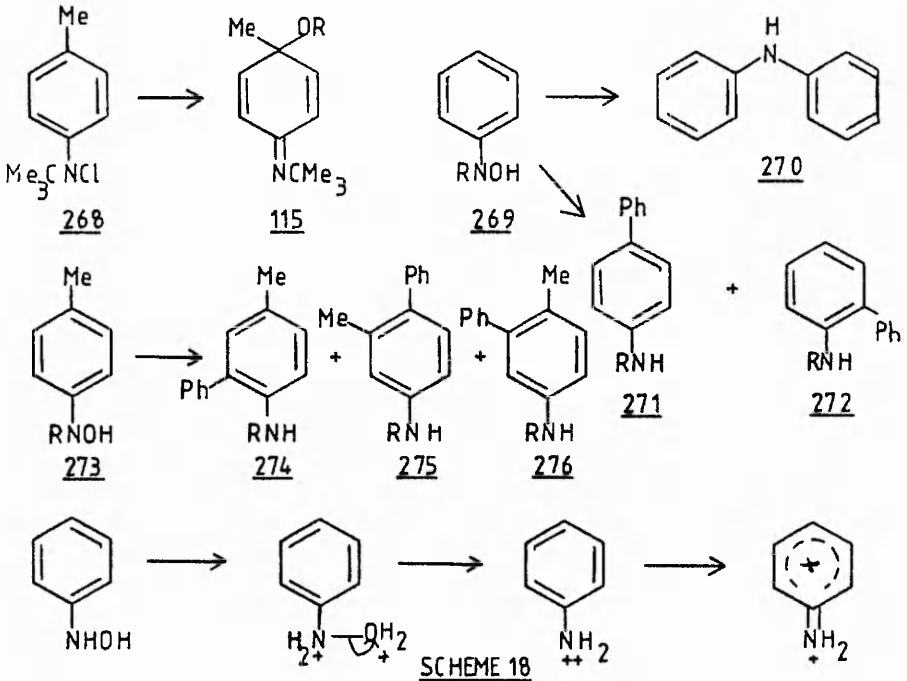
263 X = H
266 X = p-Me
267 X = o-Me

264

265



SCHEME 17



SCHEME 18

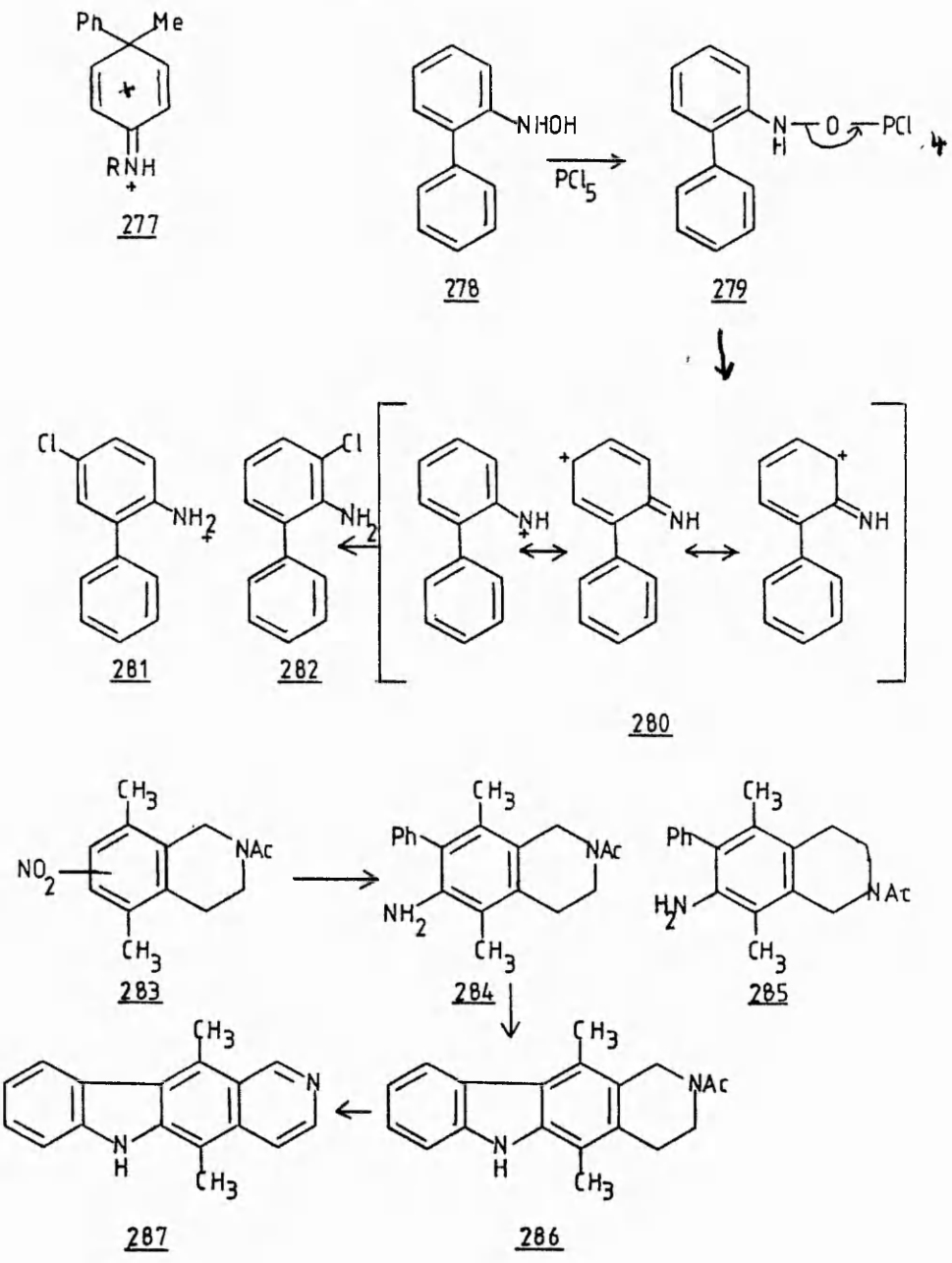
pentachloride giving complex 279, which after expulsion of oxychloride, yielded nitrenium intermediate 280, subsequent para and ortho attack affording both compounds 281 and 282.

Recently Shudo and his co-workers have combined the known production of hydroxylamines by metal-acid reduction of nitroarenes with the nucleophilic attack on nitrenium ion.[168] Nitrobenzene when reduced with metal in TFA and benzene gave both 4- and 2-biphenylamine, via reduction to hydroxylamine, nitrenium ion formation and nucleophilic attack by benzene. Treatment[169] of nitroisoquinolines 283 with iron pentacarbonyl in TFA gave isomers 284 and 285 in a 2:1 ratio. Isolation of isomer 284 followed by diazotisation and thermal rearrangement yielded N-acetylellipticine 286, dehydrogenation giving ellipticine 287 itself (see Chapter Two). Similarly the benzylisoquinolines 288 were converted by reduction in TFA to aporphines 289 in good yield.

It has been found[170] that phenylselenyl chloride promotes the rearrangement of N-arylhydroxamic acids 290 under mild conditions to give p-hydroxybenzanilides 291, quinonimines 292 and quinolimines 293. The product obtained was dependent on the structure of the hydroxamic acids and the reaction conditions.

3.1.6 Cyclohexadienespirolactones

Cyclohexadienespirolactones of the type 294 have synthetic potential in two major pathways.

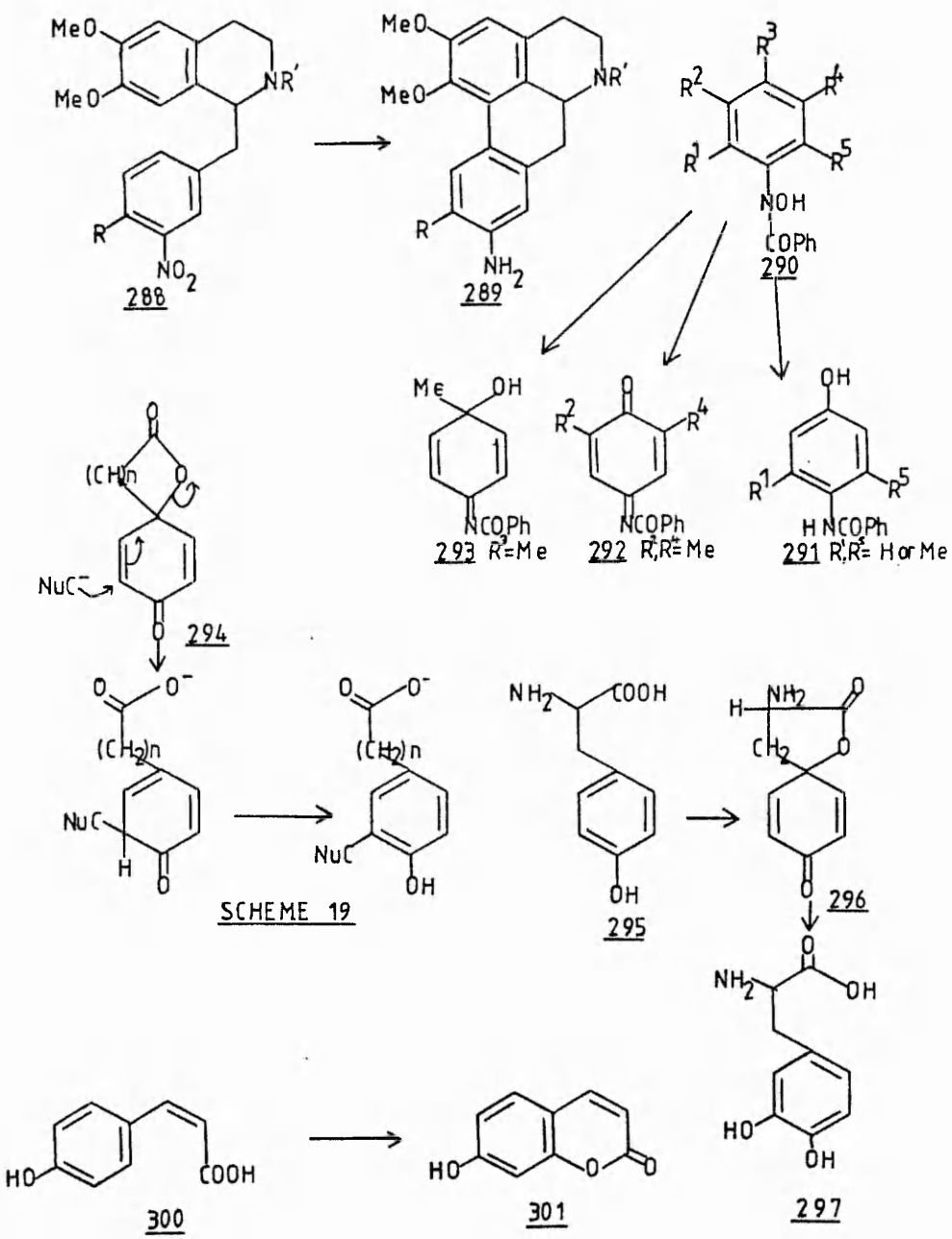

Ph
Me
RNH
277
NHOH
PCl5
278
N
H
O
PCl
279
Cl
NH2
281
Cl
NH2
282
NH
NH
NH
280
CH3
NO2
NAc
CH3
283
CH3
Ph
NAc
NH2
CH3
284
CH3
Ph
H2N
NAc
CH3
285
CH3
N
H
CH3
287
CH3
NAc
N
H
CH3
286

(a) Due to the ability of the carboxylate anion to act as a leaving group, it is possible that suitable nucleophiles may be introduced directly into the position adjacent to the cyclohexadienone carbonyl (Scheme 19). By such a route, for example, L-dopa[171] 297 could be prepared from L-tyrosine 295, by oxidation to lactone 296, followed by attack with base.

(b) Cyclohexadienespirolactones can undergo dienone-phenol rearrangements[100] to give a wide variety of oxygen heterocycles, including coumarins.

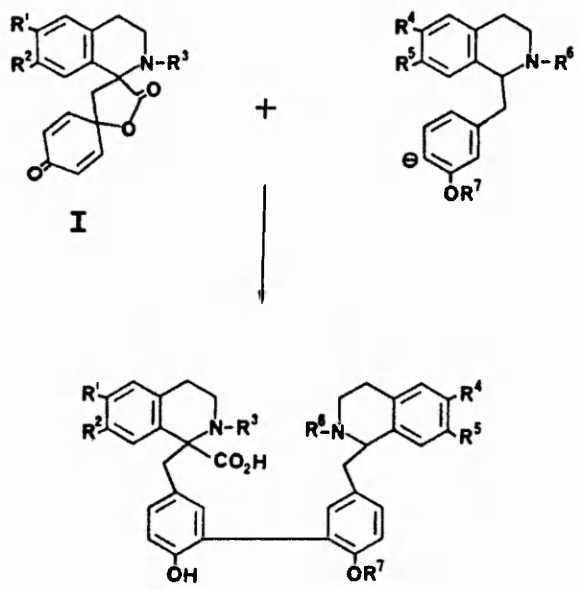
(I) The synthesis of bis-benzylisoquinolines

In striking contrast to other 1,2,3,4-tetrahydro-isoquinolines, the tetrahydroisoquinoline-1-carboxylic acids (tetrahydroisoquinaldic acids) have attracted little chemical attention. An early suggestion[172] that they were key intermediates in the biosynthesis of isoquinoline alkaloids appeared to gain support from whole-plant feeding experiments,[173] and from investigations[174-176] into their oxidative decarboxylation to dihydroiso-quinolines. More recent studies,[177] using enzymes isolated from plant cell cultures, suggest that the isoquinaldic acids are artefacts, arising from Pictet-Spengler condensation of dopamine and α-keto acids, without enzyme mediation.

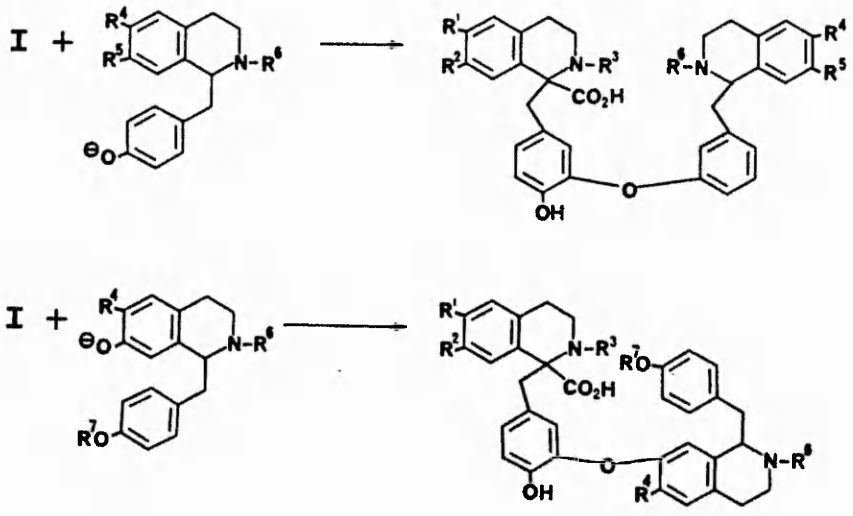

MeO
MeO
NR'
R
NO2
288
NH2
289
R1
R2
R3
R4
R5
NOH
COPh
290
Me
OH
NCOPh
293 R²=Me
291 R¹,R⁵= H or Me
(CH2)n
NuC
294
SCHEME 19
NH2
COOH
OH
295
296
HO
300
301
297

However, they still have synthetic potential. It has been demonstrated[178] that nucleophilic attack on cyclohexadienone γ-lactones derived from phenylpropanoic acids leads to lactone ring opening, with incorporation of the nucleophile into the dienone ring; carbon nucleophiles react readily with the dienone itself, but with oxygen nucleophiles prior formation of a cyclohexadienone epoxide is advantageous. Spirolactones formed from tetrahydroisoquinaldic acids might thus be useful intermediates in the synthesis of bisbenzylisoquinolines, the preparation[179] of which still relies on inefficient Ullmann syntheses, or on capricious oxidative coupling of phenols. Reaction of a negatively charged 3'-carbon of a benzylisoquinoline with a tetrahydroisoquinaldic acid-derived lactone would give a carbon-carbon linked dimer (Scheme 20), while attack by the oxygen anions of phenolic benzylisoquinolines on lactones (or their epoxy derivatives) would yield bisbenzylisoquinolines containing "head-to-tail" or "tail-to-tail" ether links (Scheme 21).

The synthesis of a spirolactone from a 1-benzyltetraisoquinaldic acid presents problems. A systematic study by Bobbitt & Cheng[174] of the anodic oxidation of a large number of these acids showed that they undergo fragmentation or oxidation at the α-carbon of the benzyl substituent if this group contains a free phenolic function in the para position. The acids are also decarboxylated at low oxidation potentials if they have a hydroxyl on the 6



SCHEME 20



SCHEME 21

or 7 position of the isoquinoline portion of the molecule; this precludes the use of the most convenient route to 1-benzyltetrahydroisoquinaldic acids, the condensation of phenylpyruvic acids with 3-hydroxyphenylethylamines, which results in a 6-hydroxyisoquinaldic acid. Furthermore, the amine nitrogen of the acids is a potential nucleophile and is sensitive also to oxidation; the neutralisation of the nitrogen lone pair electrons by acylation or quaternisation of necessity introduces steric hindrance to the desired γ-lactone formation.

The most promising oxidation precursors for the formation of spirolactones, therefore, appear to be N-acylated isoquinaldic acids without hydroxy or alkoxy groups at the 6 or 7 position. Since classic routes to tetrahydroisoquinolines rely on electrophilic cyclisation onto electron rich phenylethylamines, such acids are virtually unknown.

(II) The synthesis of coumarins

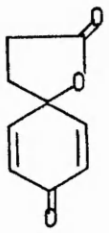
Spirolactone 19 (see Chapters One and Two) is implicated in three main biochemical areas: enzyme degradation of tyrosine, specific cleavage of certain peptide bonds[180] and biosynthesis of coumarins.[181] As will be seen later, this spirolactone is produced easily from a nitroarene and thus its biosynthetic role is of interest in this discussion.

Haworth proposed[182] that natural 7-hydroxycoumarin 301 may be formed oxidatively from 4-hydroxycinnamic acids 300, the evidence being that such transformations have been achieved[183] easily in the laboratory, their frequent co-occurrence[184] and the results of tracer studies which showed[185] that labelled caffeic acid 303 and scopoletin 304 are both formed when labelled phenylalanine 302 was fed to Nictonia tabacum. However, it was not clear[186] if the oxidative cyclisation of cinnamic acids involved a quinol 306 or dienone 307 intermediate (Scheme 22).

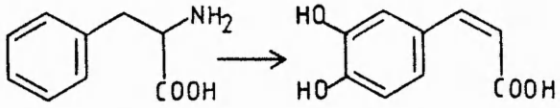
The quinol intermediate mechanism was supported by Witkop[187] during his study of the degradation of tyrosine to acetoacetate in the liver. It was proposed that pyruvic acid 308 gave homogentisic acid 311 via a cyclic peroxide intermediate 309 (Scheme 23). Further evidence comes from the oxidative cleavage of tyrosyl-peptide bonds by N-bromosuccinimide, as described in Chapter Two.

Saito et al[188] were able to prepare a mixture of the quinol 310 and the spirolactone 19 by anodic oxidation of phloretic acid. The quinol was converted into lactone 19 in 90% yield by treatment with N,N'-dicyclohexylcarbodiimide (DCC), whereas at higher pH quinol 310 yielded[123] both 3,4-dihydro-6-hydroxycoumarin and β-(2,5-dihydroxyphenyl)propionic acid 312.

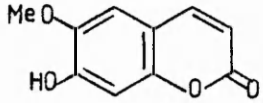
Further examples of spirolactone involvement in coumarin syntheses have already been discussed in Chapter Two.



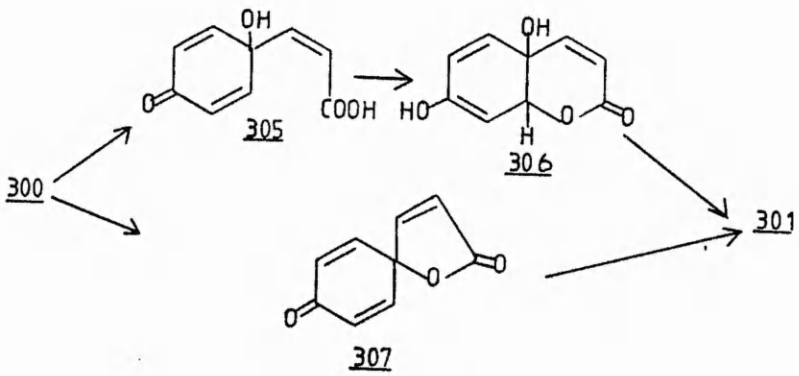
19



302 303



304



SCHEME 22

3.2 Discussion

Several years ago a project student[189] applying the ideas discussed above reacted 4-nitrohydrocinnamoate 313 with TFA/zinc and got spirolactone 19 in 12% yield. A possible reaction mechanism is shown in Scheme 24.

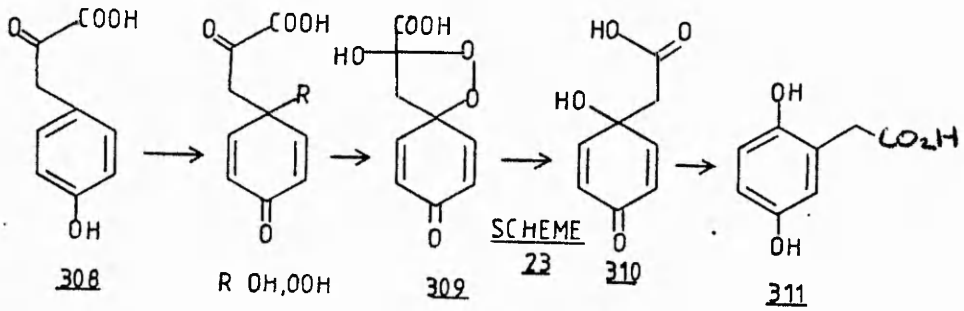
The nitroarene to cyclohexadienonespirolactone conversion is of great synthetic interest and it was decided to exploit this reaction further by optimising the reaction conditions, preparing possible intermediates for further reaction and attempting the conversion on more complex substrates.

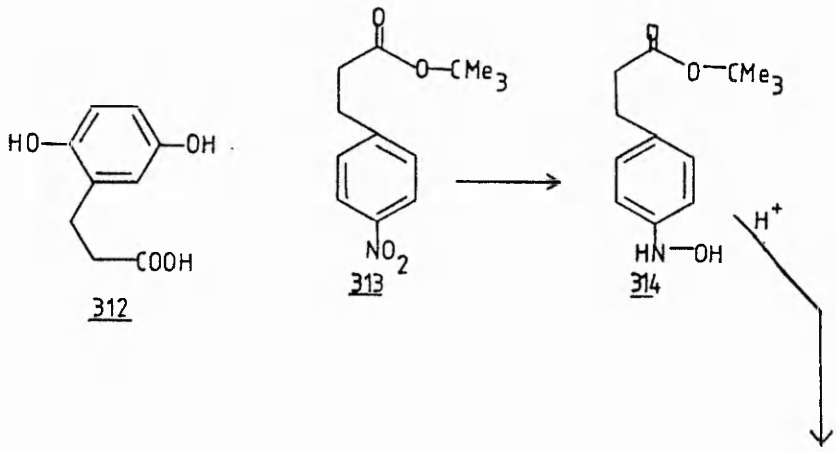
3.2.1 Optimisation of the rearrangement of nitroarene to spirocyclohexadienone

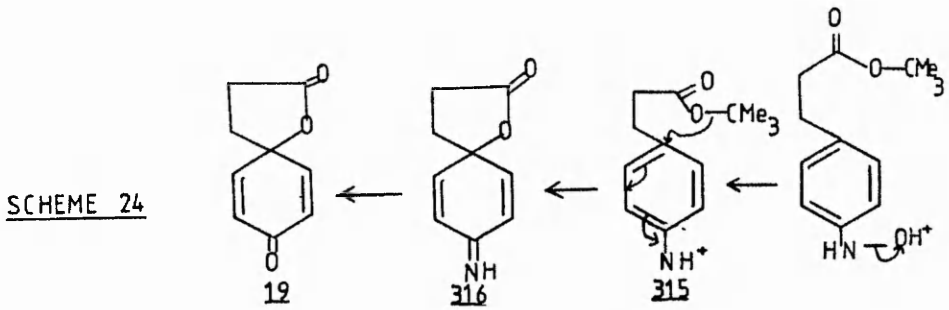
It was decided to use the previously reported[189] conversion of hydrocinnamoate 313 to lactone 19 as the model for optimisation studies. The ester 313 was prepared easily in 86% yield by the toluene-4-sulphonyl chloride catalysed reaction of 4-nitrohydrocinnamic acid with t-butanol in pyridine.

(a) Modification of reaction conditions

The reaction originally developed involved dissolving the ester 313 in TFA at 0-5^{o} and adding zinc with stirring, after which an exotherm was noted. The product was isolated in organic solvent from a sodium hydrogen carbonate solution and separated from lower R_f value material by passing the product down a silica column. The following modifications were made in an attempt to improve upon the moderate yield of spirolactone 19.


COOH
OH
308
R OH,OOH
309
HO
310
SCHEME
23
311
CO2H


HO
OH
COOH
312
CMe3
NO2
313
HN—OH
314
H+


SCHEME 24
19
NH
316
NH+
315
OH+

(I) Nature of reducing metal

Replacement of commercially available zinc powder with activated zinc powder[190] showed an improved 18% yield of lactone 19. Zinc amalgam,[191] however, yielded a complex mixture in which no lactone could be detected by i.r. spectroscopy.

The use of iron, tin and aluminium led to no reaction occurring; but magnesium powder did yield 16% of lactone 19. Attempts to maximise this magnesium reduced conversion by using granular and chipped magnesium failed to give any lactone 19.

It was therefore concluded that activated zinc would be the reducing metal of choice in this conversion.

(II) Temperature of reaction

The temperature range that could be investigated was determined by the melting point of TFA, -15^{o}, and its boiling point of 72^{o}. The reaction was carried out at 10^{o} intervals within this range, with all the reaction products being isolated. The exact temperatures were maintained by careful use of ice/water-baths.

At temperatures from -10 to $+10^{o}$ only the de-esterified acid 317 was isolated in moderate yield. At 20^{o} lactone 19 was obtained in 15% yield as well as 20% of acid 317. At 30^{o} the ratio of lactone to acid was 18% to 20%, whereas at 40^{o} and 50^{o} just the desired lactone 19 was formed in 18% yield, with no accompanying acid. Higher temperatures led to complex product mixtures.

It was decided that the best temperature range was $30-50^{o}$.

(III) Addition sequence

Modification of the reaction sequence by adding a solution of the ester 313 in TFA to a stirred suspension of zinc in TFA under nitrogen gave a lower (9%) yield of lactone 19.

(IV) Dilution of the reaction with inert solvents

As discussed earlier, any solvent that can act as a nucleophile would be unsuitable as it could react with the nitrenium ion intermediate. Three inert solvents, carbon tetrachloride, hexafluorobenzene and chlorotrifluoromethane (Freon 11) were used to dilute the reaction medium in the hope that it would lead to greater yields of lactone 19. The nitroester was recovered unchanged from all these reactions.

(V) Using acids other than TFA

Trifluoromethylsulphonic acid (TFSA), as reported earlier, has been used as the acid catalyst in Bamberger rearrangement reactions. The attempted replacement of TFA by both neat TFSA and mixtures of the two acids showed no improvement in the 18% yield of lactone 19 that was obtained in neat TFA. Due to the greater expense and the highly corrosive nature of TFSA, it was decided to use neat TFA in any subsequent reactions.

(IV) Reaction time

The reaction was quenched by adding sodium hydrogen carbonate solution to the acid mixture at various time intervals. It was concluded that the best time to stop the reaction was immediately after the exotherm had ceased.

(b) Reaction of other nitrohydrocinnamoates with zinc/trifluoroacetic acid

Since reaction of the parent acid 317 with zinc/TFA yielded a complex mixture, it was concluded that esterification of the acid was necessary for lactone formation. It was, however, decided to attempt this conversion with esters other than the previously used t-butyl group. The methyl and ethyl esters 318 and 319 were obtained easily by the Fischer-Speir method, but preparation of the benzyl ester 320 proved to be more difficult. Treatment of acid 317 with benzyl chloride under Schotten-Bauman conditions, or in the presence of K_2CO_3 and phase-transfer catalyst, failed to produce any ester 320, as did reaction of benzyl chloride with the sodium salt of acid 317 in p-dioxan. Initial attempts to react the acid with dicyclohexylcarbodiimide (DCC) and benzyl alcohol failed, but the use of 4-dimethylamino-pyridine[192] as a catalyst led to the production of ester 320 in moderate yield.

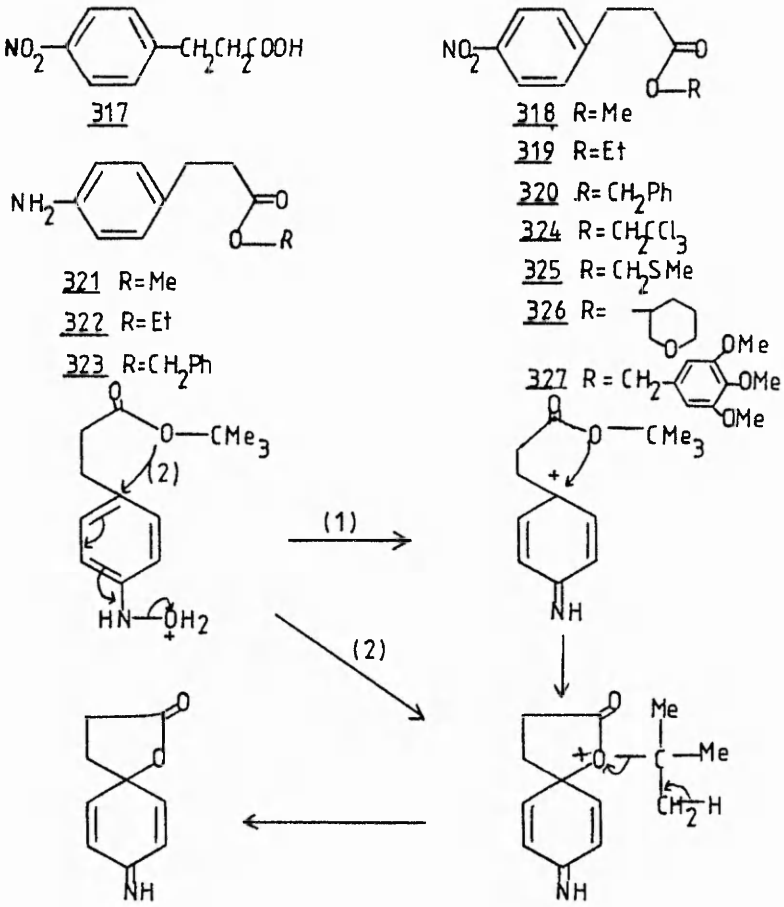
Treatment of esters 318-320 with zinc/TFA produced no lactone 19, but gave the corresponding anilines 321-323,

the novel benzyl aniline 323 being independently prepared for comparison by reduction of ester 320 in iron and acetic acid.

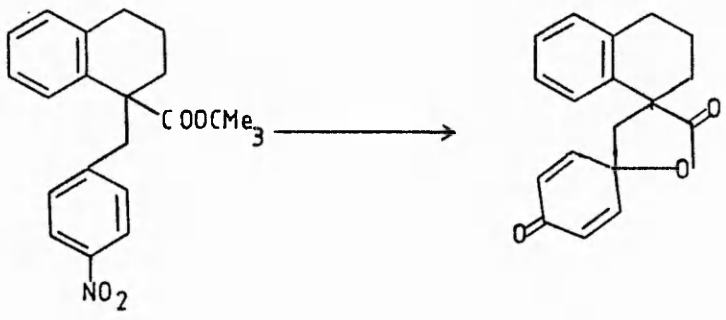
Consideration of the experimental results so far obtained suggested that the t-butyl ester was uniquely suitable for lactone formation. A possible mechanism to account for this is shown in Scheme 25, and involves the intermediacy of a protonated hydroxylamine and expulsion of 2-methylpropene after lactone formation. Both benzyl and t-butyl esters of 4-nitrohydrocinnamic acid are stable in cold TFA; addition of water cleaves the t-butyl but not the benzyl ester, which indicated that the latter might be too stable for efficient cyclisation.

A study of other acid-labile esters was therefore undertaken. Esters chosen were trichloroethyl, methylthiomethyl, tetrahydropyran and 3,4,5-trimethoxybenzyl. All these esters 324-327 were prepared easily, in good yields, by methods reported in the literature[193-195] and had expected spectroscopic properties. However, due to their instability, microanalysis was not possible except for trimethoxy ester 327.

Treatment of esters 324-327 with zinc/TFA under the optimised conditions led to complex product mixtures making t-butyl the only ester group useful in this conversion.


NO2
CH2CH2COOH
317
NH2
O
O—R
321 R=Me
322 R=Et
323 R=CH2Ph
318 R=Me
319 R=Et
320 R=CH2Ph
324 R=CH2CCl3
325 R=CH2SMe
326 R=
327 R=CH2
OMe
OMe
OMe
O—CMe3
(2)
(1)
(2)
HN—OH2
NH
Me
Me
CH2H

SCHEME 25


COOCMe3
NO2
328
329

3.2.2 The attempted conversion of more complex nitroarene substrates

Although the conversion of t-butylhydrocinnamoate to spirolactone can only be performed in moderate yield it still represents a synthesis of spirolactones under reducing conditions, and application of the reaction to more complex molecules was therefore still considered worthwhile. Most attention was focussed on the isoquinoline series, but model experiments were carried out on the more accessible isosteric tetrahydronaphthoic ester 328.

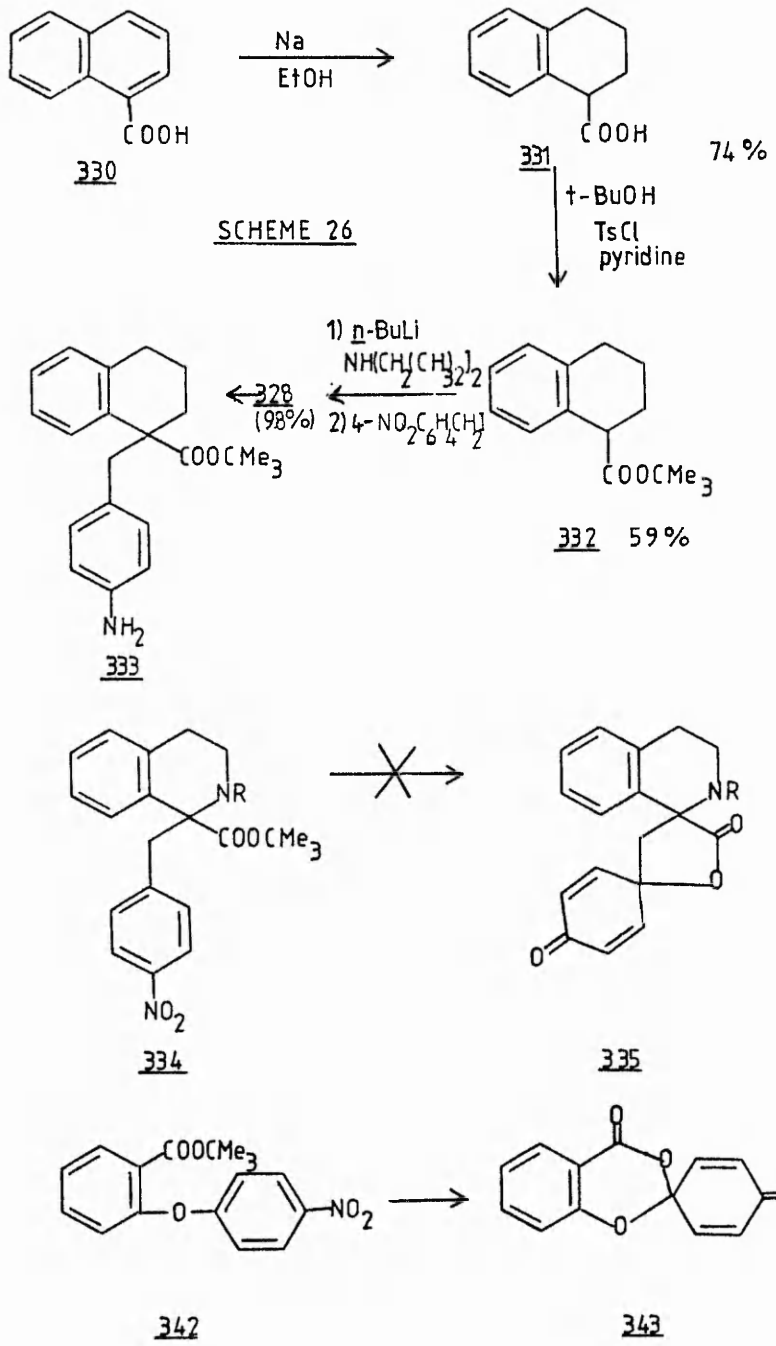
(a) Naphthoic ester 328

The preparation of naphthoic ester 328 is outlined in Scheme 26. Treatment of ester 328 with TFA/zinc yielded the corresponding amine 333 as the only isolated product.

(b) Isoquinoline 334

As discussed in Section 3.1.1(a) the preparation of benzyl isoquinoline spirolactones, such as 334, is desirable as they might be of value in the synthesis of bis-benzylisoquinolines.

The preparative route to isoquinoline 334 is outlined in Scheme 27. The pivaloyl group was chosen as a blocking group since it was easily added to the isoquinoline nitrogen and acted as an activator to lithiation. However, attempts to prepare the t-butyl ester of N-pivaloylisoquinoline-1-carboxylic acid 337 failed due, it was thought, to steric crowding effects of the t-butyl and pivaloyl groups.


Na
EtOH
COOH
330
COOH
331
74 %
t-BuOH
TsCl
pyridine
SCHEME 26
1) n-BuLi
NH(CH2CH)32
2) 4-NO2C6H4CH2
328
(98%)
COOCMe3
COOCMe3
332 59%
NH2
333
NR
COOCMe3
NO2
334
NR
335
COOCMe3
O
NO2
342
343

It was therefore decided to prepare the known[196] benzyl ester of the acid, 339. It was hoped that the benzyl group could be replaced by a t-butyl group at a later synthetic stage after removal of the pivaloyl group. The benzyl ester 339 was prepared successfully by reaction of acid 337 with benzyl chloride in acetone and potassium carbonate. Reaction with sodium hydride followed by the addition of p-nitrobenzyl iodide led to isolation, in 99% yield, of the 1-benzylisoquinoline 340. It was hoped that acid treatment of ester 340 would yield an amino acid 341 that could be esterified with t-butanol. However, amino acid 341 appeared to exist as a zwitterion and was resistant to esterification by reaction with DCC and t-butanol. This work was terminated due to the difficulties encountered and the great amount of time already spent upon it.

(c) Diphenylether 342

The diphenylether 344, available in the laboratory from a previous investigation was converted to the t-butyl ester 342 by reaction with t-butanol and n-butyl lithium. Treatment of ester 342 with zinc/TFA gave a complex mixture containing no lactone; it did however prove possible to prepare this lactone from an azide (see later).

(d) Biphenyl 345

It has been reported[101a] that 4'-hydroxyamino-2-biphenylcarboxylic acid 246 when heated with acid yields spirodienone 248 (see earlier). It was therefore decided

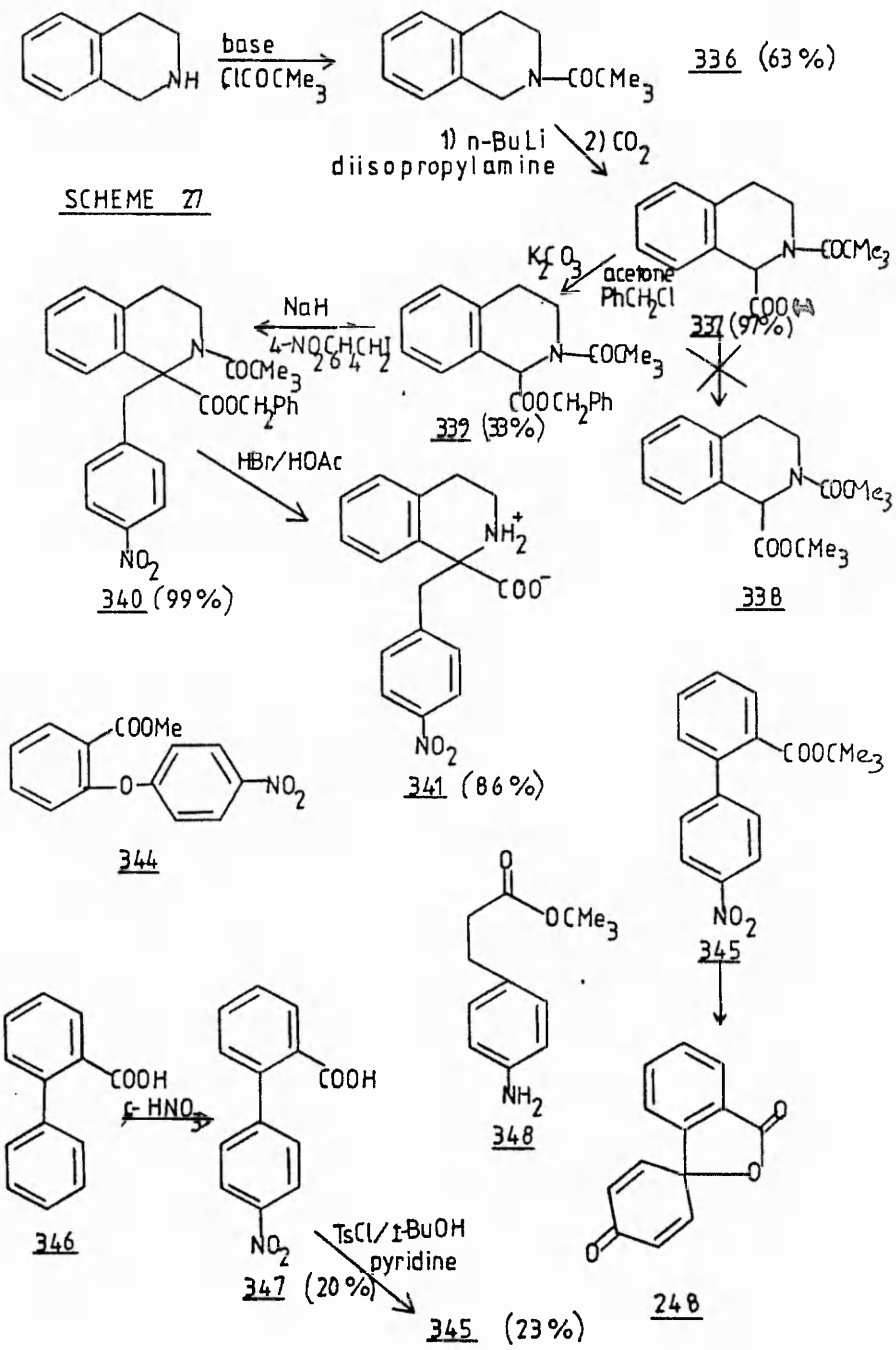
to attempt the conversion of the analogous nitroarene 345 to lactone 248, since a successful reaction would lead support to a hydroxylamine intermediacy. Ester 345, was prepared by a separate worker[198] as shown in Scheme 28. Again, treatment with zinc/TFA led to a complex mixture.

Although it seems likely that zinc/TFA reaction proceeds via a hydroxylamine reaction, the failure of the last reaction suggested that an examination of the behaviour of appropriately substituted hydroxylamines might shed light on the mechanism and perhaps lead to improved syntheses of dienones.

3.2.3 The attempted isolation of possible intermediates

As outlined in Scheme 24, it was thought that reduction of a nitroarene in TFA would lead to nitrenium ion formation via a hydroxylamine. It therefore seemed a natural extension to this investigation to prepare hydroxylamine 314; subsequent treatment with acid should yield lactone 19. If an efficient conversion was found, it could then be used as a route to prepare more complex lactones.

The preparation of hydroxylamine 314 was initially attempted by the reduction of nitro compound 313 with zinc in a near neutral solution of aqueous ammonium chloride and by a more recent[199] method using selenium as the reducing metal. Both gave no hydroxylamine. Compound 314 was finally prepared in a 57% yield by the Raney nickel reduction[200] of nitroester 313 in the presence of hydrazine hydrate. Attempts to prepare


base
ClCOCMe3
336 (63%)
1) n-BuLi
diisopropylamine
2) CO2
SCHEME 27
K2CO3
acetone
PhCH2Cl
337 (97%)
NaH
4-NO2C6H4CH2Cl
339 (33%)
HBr/HOAc
340 (99%)
338
341 (86%)
344
345
348
346
347 (20%)
TsCl/t-BuOH
pyridine
345 (23%)
248
SCHEME 28

a N-benzoyl derivative of 314 for analysis, by a two phase reaction[200] with benzoyl chloride gave no product, as did reaction of 314 with toluene-4-sulphonyl chloride and with DCC and benzoic acid. This failure of hydroxylamine 314 to react under a variety of conditions is puzzling, as it was homogeneous by t.l.c. and had expected spectroscopic properties.

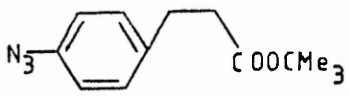
Treatment of hydroxylamine 314 with TFA or TFSA gave a complex mixture whose i.r. spectrum showed no lactone stretch. Milder mineral acids induced no change in the hydroxylamine.

As the parent hydroxylamine 314 did not yield spirolactone 19 by acid treatment, preparation of more complex hydroxylamines was not attempted.

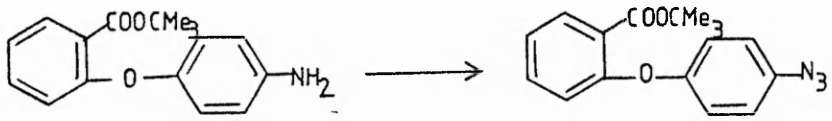
3.2.4 An alternative route to spirolactones via phenyl azides

Catalytic hydrogenation of nitroester 313 to novel amino-ester 348 (82%) followed by diazotisation and addition of sodium azide gave the parent azide 349 in 87% yield. Reaction with TFA did yield 14% of lactone 19, as the only product.

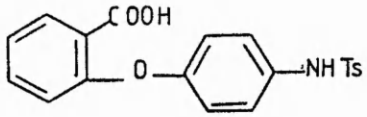
Azide 351 was then prepared in 75% yield by the same method, from amine 350. Treatment of this azide with TFA yielded a mixture, which on t.l.c. appeared to be a major component and two minor products. However, the R_f value and solubilities of these components were very similar, thus preventing separation. The i.r. spectrum of the reaction product was identical with that of an authentic sample of lactone 343 prepared by the anodic oxidation[121] and subsequent alumina treatment of sulphonamide 352.



349



350 351



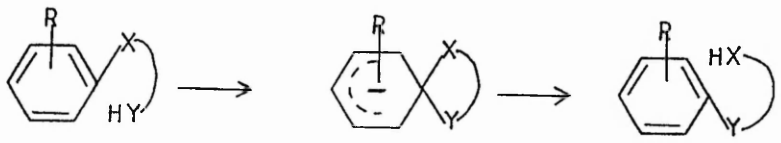
352

This route from nitroarene to spirolactone *via* an azide shows promise, but further work was prevented by lack of time.

CHAPTER FOUR

4.1 Introduction

In a Smiles rearrangement[201-204] a compound 353 is converted to an isomeric compound 355 via a spirocyclic intermediate 354.



353 354 355

Because of the charge accumulation in the Meisenheimer intermediate 354, such rearrangements have usually been described only for molecules in which the aromatic ring bears electron-withdrawing substituents.

Recently however a group of ICI chemists[205] have reported Smiles rearrangements involving electron-rich substrates. The phenols 356 were converted to phenoxyisobutyramides 357, which underwent Smiles rearrangement via the nitrogen-containing spirocyclohexadiene intermediate 358 to give anilides 359. Acid hydrolysis then afforded anilines 360, thus representing an overall conversion of phenols to anilines.

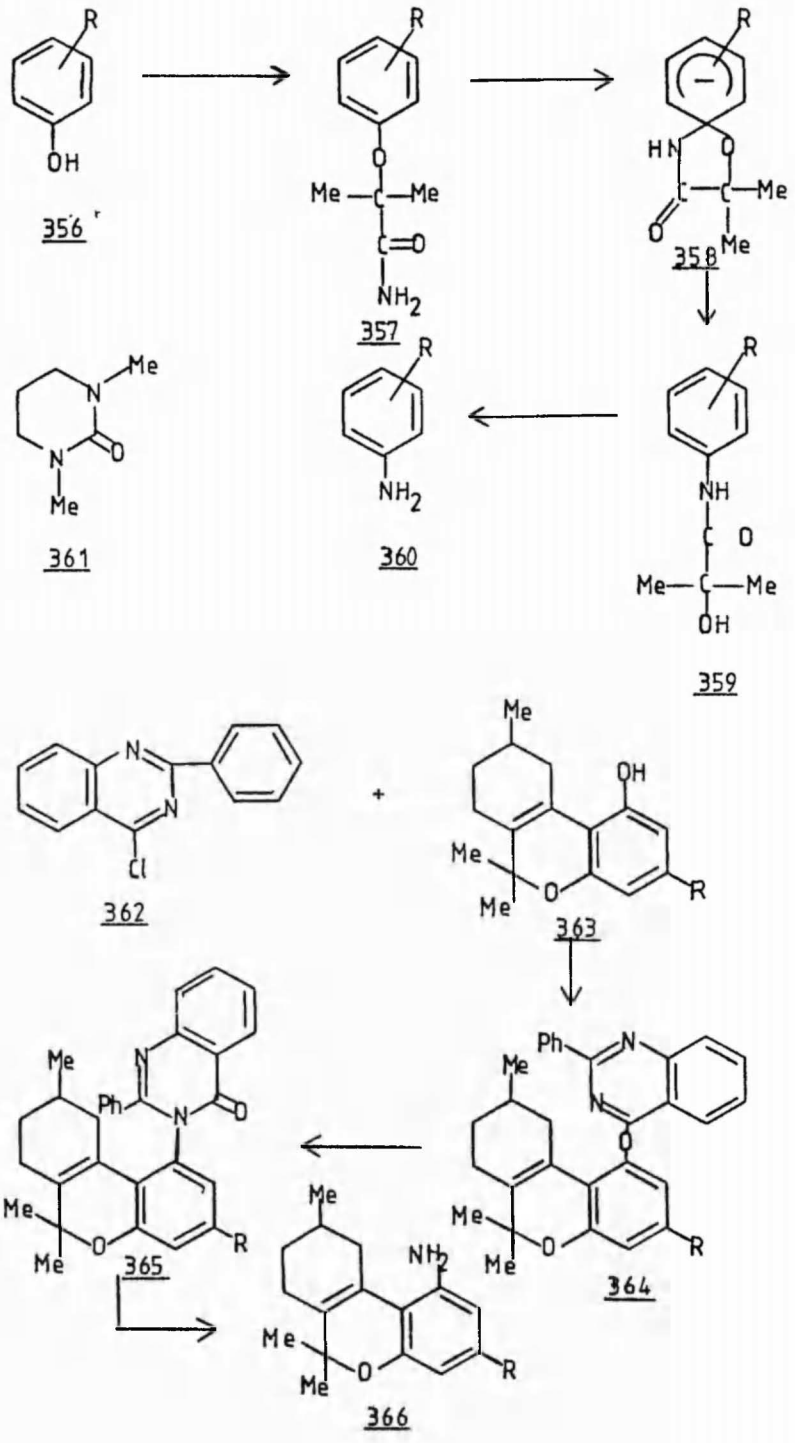
Clearly this transformation is dependent on the ease of formation of the intermediate Meisenheimer complex. It has been shown[206] that the rate constants for Meisenheimer complex formation are much greater for five-membered rings, as in 358,

than for their six or seven membered counterparts. Intermediate 358 is also stabilised by the Thorpe-Ingold or gem-dialkyl effect of the sidechain methyl groups, as discussed in Chapter Two.

The Smiles rearrangements studied by the ICI group[205] used the highly toxic hexamethylphosphoric triamide (HMPA) as a solvent. This compound is one of the best dipolar aprotic solvents for enhancing the nucleophilicity of reagents. However, Seebach recently reported[207,208] that the non-toxic 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) 361 can reproduce the effects of HMPA very closely. With the possibility of a safe replacement for HMPA in this phenol to aniline conversion it was decided to investigate this work further.

4.1.1 The conversion of phenols to anilines

Scherrer and Beatty have explored[209] the use of 4-chloro-2-phenylquinazoline ("AM-ex-OL") 362 as a reagent for transforming phenols to anilines. A published example[210] of its use is the conversion of cannabinoid 363 to its corresponding amino derivative 366. The sodium salt of phenol 363 was reacted with "AM-ex-OL" 362 in DMF at 150^{o} to give, in 62% yield, ether 364, which was heated at 330^{o} over N_2 yielding 69% of the rearranged quinazoline 365. From saponification of 365 with potassium hydroxide at 150^{o} was obtained 73% of the desired aniline 366. Although the yields in this example are reasonable, the high temperature required and strongly basic conditions make this an unsuitable procedure for many compounds. The quinazoline 362 is also expensive.


R
OH
356
Me
Me
O
NH2
357
HN
O
Me
Me
358
Me
N
O
N
Me
361
NH2
360
NH
O
Me
Me
OH
359
N
N
Cl
362
Me
OH
Me
O
Me
R
363
Ph
N
Me
N
O
Me
O
Me
R
364
Me
N
Ph
N
O
Me
O
Me
R
365
Me
NH2
Me
O
Me
R
366

That this has become one of the most popular routes from phenols to anilines reflects the limitations of other methods of effecting the transformation.

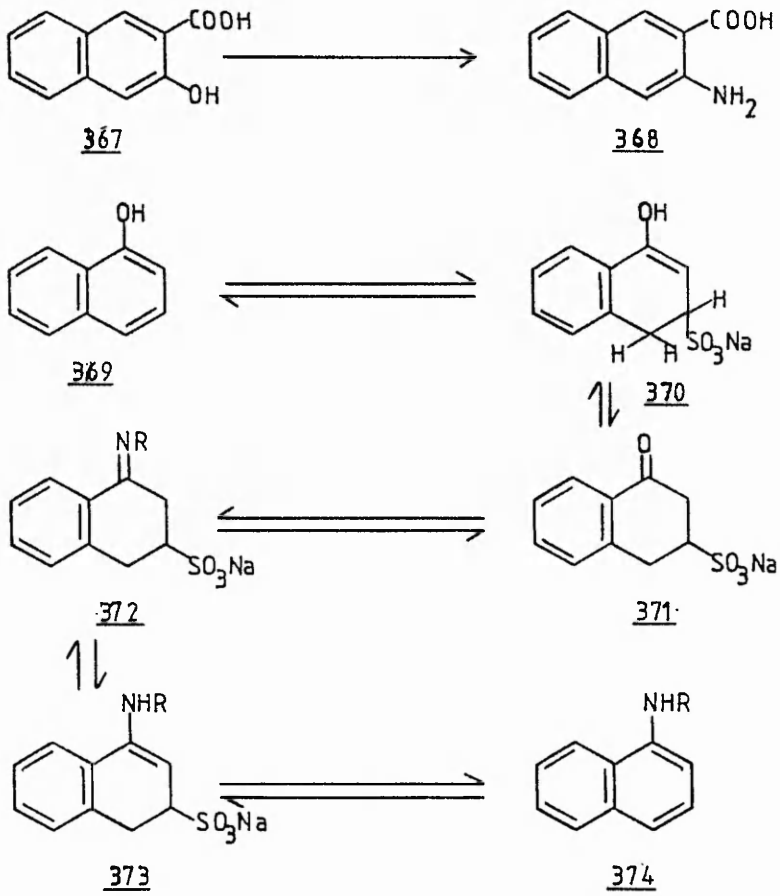
The direct reaction of phenols with ammonia over alumina or silica catalysts at 425^{o} has been reported,[211-214] while the phenol 367 is converted[215] to amine 368 by reaction with ammonia over zinc chloride at 195^{o} and 400lb pressure.

Another method for the conversion of phenols to anilines or N-alkylanilines is the Bucherer reaction[216], which is limited to phenols that can undergo keto-enol tautomerisation. The mechanism,[217] as shown for 1-naphthol 369, involves the reaction with sodium bisulphite to give enol 370, tautomerisation to ketone 371 followed by formation of Schiff base 372, which tautomerises to aminosulphate 373 and desulphonates giving amine 374. This process is reversible and has been used in aminoisoquinoline synthesis.[218]

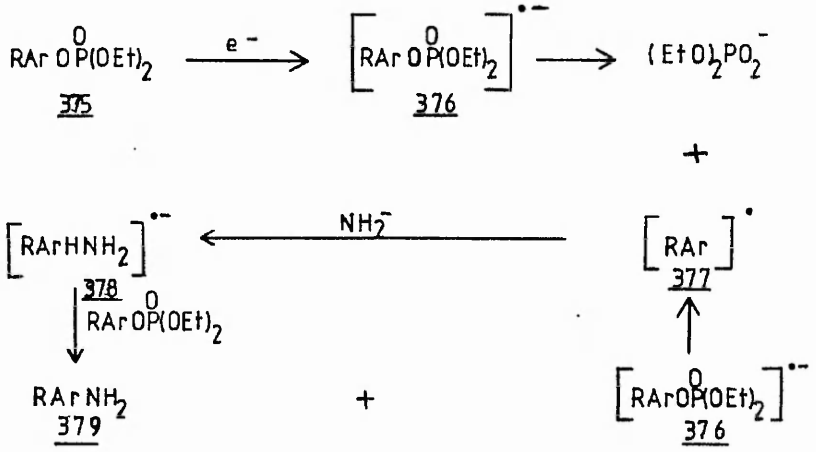
Hydroxy groups in benzene rings can be replaced by amino groups if they are first converted[219] to their aryl diethyl phosphates 375 by reaction with the highly toxic diethyl chlorophosphate. Treatment with potassium in liquid ammonia is conjectured to lead to electron capture forming the anion radical 376, which ruptures to afford an aryl radical 377. This reacts with an amide anion forming radical anion 378, which in a propagation step gives aniline 379 and another radical anion 376.

4.2 Discussion

In this study of the conversion of phenols to anilines via a Smiles rearrangement of phenoxyisobutyramides, the following



367 368 369 370 372 371 373 374



375 376 378 377 379 376

objectives were identified:

(a) to determine if the rearrangement of unactivated substrates would occur efficiently in solvents less toxic than HMPA;

(b) to optimise the preparation of the phenoxyisobutyramides 357 from phenols 356 and to determine steric or other factors limiting their formation or rearrangement;

(c) to extend the investigation to include the formation and rearrangement of secondary amides 380;

(d) to investigate the hydrolysis of anilides 359 to anilines 360;

(e) to apply the conversion to more complex phenols.

4.2.1 Alternative solvents for the Smiles rearrangement

When the amide 381 in DMPU was reacted with one equivalent of sodium hydride, and heated on the steambath for one hour, anilide 382 was isolated in 80% yield. The same result was obtained when the experiment was carried out using a 10% solution of DMPU in DMF as solvent. This latter mixture was used in all further rearrangements since removal of the DMPU from ethyl acetate solutions of the product by aqueous washing was achieved more quickly than when using neat DMPU, which is also expensive.

4.2.2 Factors affecting the formation and rearrangement of phenoxyisobutyramides

In the original investigation,[205] two methods were employed to convert phenols to the phenoxyisobutyramides 383-389. The first, which has been published,[205] involves

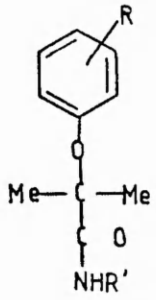
formation of an aryloxy-2-methyl propanoic acid 390 by reaction of a phenol with acetone, sodium hydroxide and chloroform. Treatment of the acids with thionyl chloride and then ammonia gave the amides 383-389. In the second method,[220] the aryloxy anion 391, generated by treatment of a phenol with sodium hydride in p-dioxan was reacted with bromoisobutyramide 392.

Amide 392 is obtained by the reaction of ammonia with bromoisobutyryl bromide, the preparation[221] of which on a large scale is unpleasant. It has, however, recently become available commercially at reasonable cost from several sources, and the generally mild conditions of this second route to phenoxyisobutyramides makes it the preferred one.

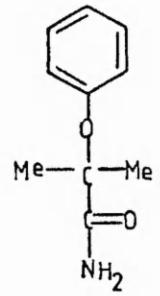
Using this method, previously reported amides 387, 389 and novel compounds 393-407 were prepared. Yields were moderate to good, with the poorest results for compounds 401 and 402 caused by difficulties in crystallisation. The low (31%) yield of amide 405 from 8-hydroxyquinoline may be due to steric hindrance from the neighbouring nitrogen lone pair.

No amides were formed from the attempted reaction of the bromoisobutyramide 392 with 2,6-dimethyl, di-t-butyl or diphenyl phenols, again probably for steric reasons.

Bromoisobutyramide 392 did not react with the anions of 4-hydroxybenzaldehyde, methyl salicylate, methyl 4-hydroxybenzoate or umbelliferone 408. In all of these anions the negative charge is in conjugation with a carbonyl group, reducing the nucleophilicity of the intermediates. Significantly the sodium salts of methyl 3-hydroxybenzoate and of dihydroumbelliferone 409 in which this conjugation is absent, reacted readily to give butyramides 406 and 407.



380



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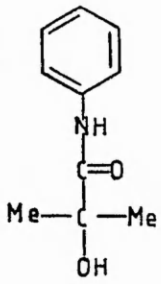
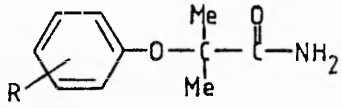


382



383 R = 4-NO_2

384 R = 3-CF_3, 4-NO_2

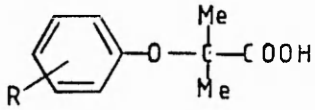
385 R = 4-PhCO

386 R = 2-PhCO, 4-Cl

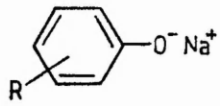
387 R = 4-Cl

388 R = 2-Me

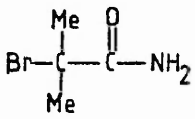
389 R = 4-OMe



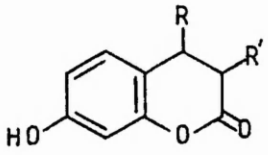
390



391



392

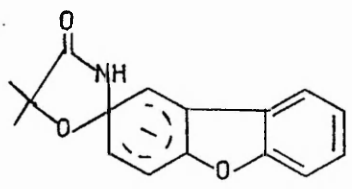


408 R,R' = bond

409 R=R' = H

In general, the rearrangement of aryloxybutyramides to anilines proceeded smoothly in satisfactory (60-98%) yields (see Table 2). However, from the reaction of the dihydro-umbelliferone derivative 407 with sodium hydride in DMF/DMPU was obtained a complex mixture. This may be due to abstraction of benzylic protons from 407, or to attack by nucleophiles on the lactone carbonyl; the lower reactivity of the aromatic ester 406 might account for its successful conversion to 425 but further studies are required.

Rearrangement of dibenzofuran derivative 404 proceeded extremely slowly and in poor (21%) yield. This was attributed to steric strain in the Meisenheimer intermediate 426 and molecular modelling calculations kindly carried out by Dr D Gilmore of ICI Pharmaceuticals Division tend to support this explanation. Using a basic CNDO programme there appears to be a markedly greater (~ 26 kcal/mol) binding energy in intermediate 426 than in a similar structure which lacks the carbon-carbon biaryl bond. The assumptions of a CNDO calculation make these results only of indicative value, but from a more refined AMPAC computation the heat of formation of 426 was again higher (1.7 kcal/mol) than that of a corresponding structure without the aryl-aryl bond. The second calculation ignores solvation, which should however be very similar for both intermediates and again gives credence to the steric strain hypothesis.

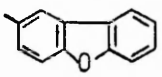
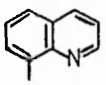
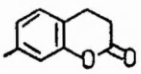


426

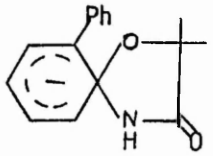
TABLE 2

Ar $OC(Me_2)C(O)NH_2$ ⟶ Ar $NHC(O)C(Me_2)OH$

357 359

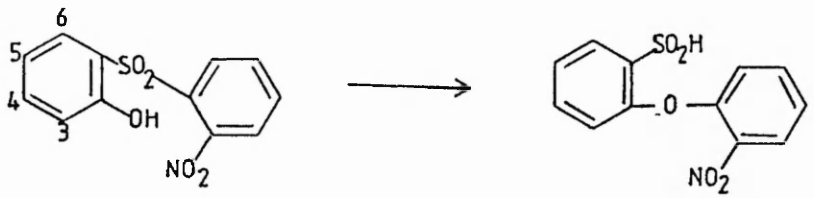
		% Yield of amide 357		% Yield of anilide 359
387	Ar = 4-Cl-C_6H_4	75	410	98
389	Ar = 4-MeO-C_6H_4	85	411	68
393	Ar = 4-Ph-C_6H_4	98	412	87
394	Ar = 1-naphthol	98	413	81
395	Ar = 2-naphthol	92	414	93
396	Ar = 5,6,7,8-tetrahydro-2-naphthol	83	415	81
397	Ar = 4-Me-C_6H_4	82	416	72
398	Ar = 2-OMe-C_6H_4	49	417	31
399	Ar = 2-F-C_6H_4	75	418	62
400	Ar = 2-Cl-C_6H_4	69	419	54
401	Ar = 2-Br-C_6H_4	40	420	96
402	Ar = 2-I-C_6H_4	48	421	87
403	Ar = 2-Ph-C_6H_4	77	422	45
404	Ar = 	45	423	21
405	Ar = 	31	424	60
406	Ar = 3-COOMe-C_6H_4	63	425	62
407	Ar = 	51		—

In contrast to the sluggish reaction of 404, the Smiles rearrangement of the 2-phenylphenoxyisobutyramide 403 proceeded instantaneously in the mixed DMPU/DMF solvent system, and was complete after 15 minutes in neat DMF only. This increased rate of rearrangement is attributed to the steric strain encountered in the intermediate Meisenheimer complex 427. The bulk effect of the 2-phenyl group increases the steric strain on 427, thus increasing the rate of ring opening to anilide 422.



427

This result is in accord with the work of Bunnett and Okamoto,[222] who found that the Smiles rearrangement of 2-hydroxy-2'-nitrodiphenyl sulphones 428 to 2-(o-nitrophenoxy)-benzenesulphinic acids 429 was accelerated by bulky substituents at 3- and 6- positions.



428 429

4.2.3 The formation and rearrangements of secondary phenoxypropanamides 380

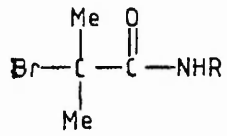
With the successful development of this conversion of phenols to anilines, it seemed logical to extend the investigation to the preparation of secondary anilines from phenols. As discussed in Section 4.1.1 only the Bucherer reaction may be used at present to transform phenols to secondary anilines and this requires high temperatures. Since the direct N-alkylation of anilines also involves harsh conditions and a large excess of alkylating agent, a mild conversion of phenols to secondary anilines is clearly desirable.

The preparation of secondary bromoisobutyramides 430-441 was carried out by reacting bromoisobutyrl bromide with the relevant amine under Schotten-Baumann conditions. All the bromoamides, except the N-allyl amide 441, were formed in moderate yields. The reaction of allylamine with bromoisobutyryl bromide in the presence of aqueous sodium hydroxide gave a product, the i.r. spectrum of which showed two carbonyl bands, at 1730 and 1650 cm^{-1}. The relative intensity of the 1730 cm^{-1} band increased when the reaction was carried out in chloroform in the presence of anhydrous sodium hydrogen carbonate. The product, homogeneous by t.l.c., was shown by g.l.c. to consist of at least two components. Although it proved possible with much effort to separate these compounds by H.P.L.C., only minute quantities of each was obtained. The fraction showing the carbonyl at 1650 cm^{-1} also had an NH

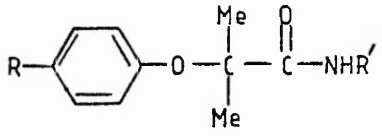
stretching frequency at 3285 cm^{-1}, and is probably the desired N-allyl bromoisobutyramide 441. The other product, with the absorption at 1730 cm^{-1}, had no absorption above 3100 cm^{-1} and gave a negative Beilstein bromine test. Lack of time prevented further study of this unusual compound.

Unexpected difficulties were encountered in the attempted preparation of phenoxyamides 442-447 by the reaction of appropriate phenols and bromoisobutyramides with sodium hydride in dioxan. Product yields were low (17-51%) and t.l.c. examination of the reaction mixtures showed incomplete reaction even after prolonged periods. It was initially suspected that this might be due to the low solubility of some of the sodium phenolates in dioxan, but substitution of dioxan by tetrahydrofuran, diglyme or even DMPU gave no improvement.

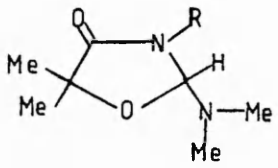
When DMF was tried as a solvent, interesting results were obtained. From the reaction in DMF of N-phenyl bromoisobutyramides 435 and 439 with sodium phenolate or sodium hydride the oxazolidin-4-ones 450 and 451 were obtained in 48 and 26% yields respectively, as the only products. The base-promoted reactions of 2-bromocarboxamides has been studied extensively by D'Angeli[223-228] and his co-workers who have reported[223] the room temperature formation of oxazolidin-4-ones when bromoisobutyramides are reacted with sodium hydride and DMF. The mechanism postulated[225] involves the non-concerted cycloaddition of zwitterions 452, possibly arising through the conjugate anion of a 2-bromocarboxamide, onto the carbonyl group of DMF to produce the intermediate betaine 453, which cyclises to oxazolidin-4-one 454. Further evidence for this mechanism came from the reaction of DMF with both α-lactam 455,



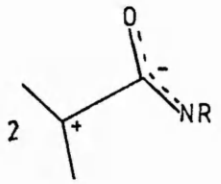
430 R = Me
431 R = Et
432 R = adamantyl
433 R = CMe_3
434 R = C_6H_{11}
435 R = Ph
436 R = CH_2CMe_3
437 R = CH_2Ph
438 R = 3,5-$(CF_3)_2C_6H_3$
439 R = 4-$MeOC_6H_4$
440 R = 2,4-$(MeO)_2C_6H_3$
441 R = $-CH_2CH=CH_2$



442 R = Cl ; R' = Me
443 R = Cl ; R' = CH_2Ph
444 R = Ph ; R' = Me
445 R = Ph ; R' = CH_2Ph
446 R = Ph ; R' = 3,5-$(CF_3)_2C_6H_3$
447 R = Ph ; R' = 2,4-$(MeO)_2C_6H_3$
448 R = H ; R' = Ph
449 R = H ; R' = 4-$MeOC_6H_4$ — erroneous
461 R = H ; R' = adamantyl
462 R = H ; R' = CMe_3
466 R = H ; R' = Me
467 R = H ; R' = Et
468 R = H ; R' = C_6H_{11}
469 R = H ; R' = CH_2CMe_3



450 R = Ph
451 R = 4-$OMeC_6H_4$



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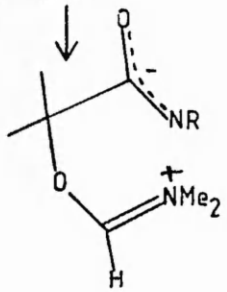
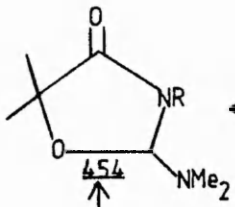


453



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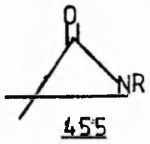

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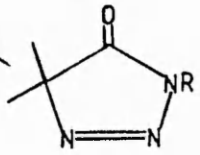


456

which is thought to be in conjunction with zwitterion 452 and triazolinone 456, which was expected to yield the zwitterion 452 by irreversible loss of nitrogen, to afford oxazolidin-4-ones 454. Electrochemical reduction of 2-bromo-carboxamides in DMF has also been shown[228] to yield oxazolidin-4-ones.

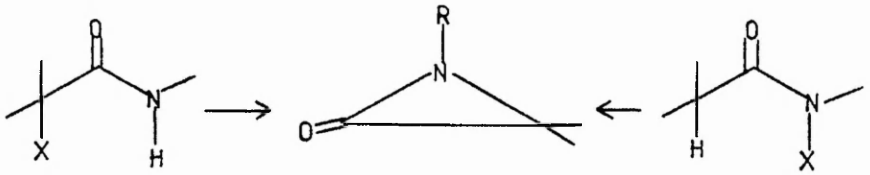
This led us to suspect that α-lactam formation, from the reaction of secondary bromoisobutyramides and sodium hydride could be a competing reaction in the attempted preparation of secondary phenoxyisobutyramides.

α-Lactams (azirinones) have been prepared[229] by dehydrohalogenation of either 2,2-disubstituted-2-halogenoethanamides 457 or 2,2-disubstituted-N-halogenoethanamides 458; the milder conditions required for deprotonation in the former route make it the method of choice. A review[230] of the subject discusses the stabilisation of α-lactams by bulky substituents at positions C-1 and N-3, which is partly due to the resulting steric inhibition of nucleophilic attack on the carbonyl. Adamantyl and t-butyl groups have been favourite substituents.

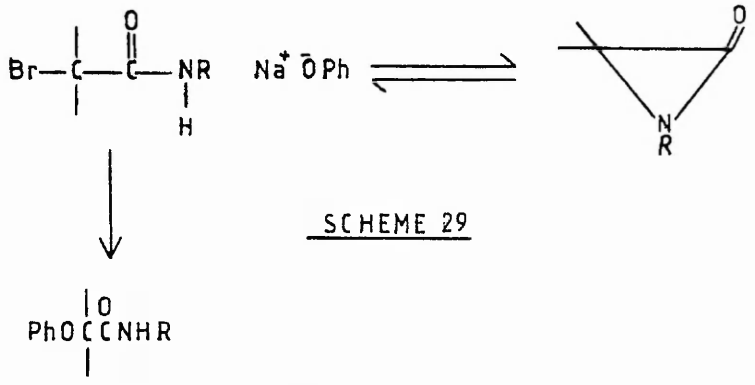
Aziridinones were reported[230-232] to undergo cleavage of the acyl-nitrogen bond exclusively upon treatment with ionic, aprotic nucleophiles (salts) and cleavage of the alkyl-nitrogen bond exclusively or mainly by non-ionic, protic nucleophiles. Such a simple explanation of selectivity in ring-opening reactions of aziridinones has been recently challenged by Talaty[233] who has shown the position of attack on α-lactams to be more complicated. However, it was decided to determine whether phenoxybutyramides 380 might be more efficiently obtained by the reaction of phenols on preformed

α-lactams. The previously prepared[234] stable adamantyl and t-butyl-α-lactams 459 and 460 were isolated in 42 and 80% yields respectively by treatment of the corresponding secondary bromoisobutyramides 432 and 433 with sodium hydride in tetrahydrofuran (THF) at 0^{o}. Reaction of these α-lactams with phenol at 0^{o} in THF gave the desired secondary phenoxyisobutyramides 461 and 462 in 51 and 90% yields respectively. Extension of this method to the synthesis of secondary phenoxyisobutyramides 466-469 was undertaken as follows. The appropriate bromoamide was stirred, at temperatures ranging from -20 to -40^{o}, with sodium hydride in THF, and quantitative α-lactam formation was confirmed by the total disappearance of starting amide, detected by t.l.c. and by the absence of the amide carbonyl stretching frequency in the i.r. spectrum of the reaction mixture. When aziridinone formation was complete phenol was added giving the isobutyramides in moderate to good yield (55-96%). The preparation of an α-lactam from N-neopentylisobutyramide met an unexpected difficulty, since the compound was totally inert to sodium hydride. The reason for this is not apparent, since the related trifluoroacetamide reacted smoothly with hydride. When amide 436 was treated with sodium phenoxide in dioxan, a quantitative yield of phenoxyamide 469 was obtained, which again implies that α-lactam formation is a competing reaction lowering the yield of N-substituted aryloxybutyramides (see Scheme 29).

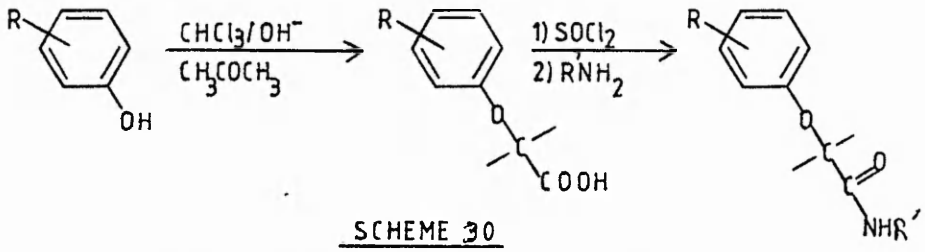
The route to secondary phenoxyisobutyramides from substituted phenols, using preformed α-lactams was then explored. Mono-substituted phenoxyisobutyramides 470-475 were



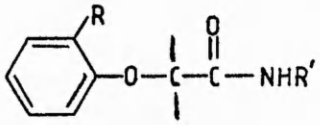
457 459 R = adamantyl 458
460 R = CMe_3
463 R = Me
464 R = Et
465 R = C_6H_{11}



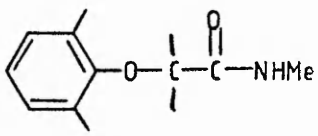
SCHEME 29



SCHEME 30



470 R=Cl, R'=Me
471 R=I, R'=Me
472 R=Me, R'=Me
473 R=F, R'=adamantyl
474 R=OMe, R'=adamantyl



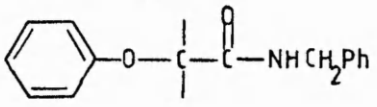
475

prepared from the reaction of the appropriate phenol with a preformed α-lactam, in 80-98% yields. Phenols disubstituted in the 2 and 6 positions with phenyl, chloro or methoxy groups did not react with the lactam, but surprisingly 2,6-dimethylphenol gave a 54% yield of amide 475.

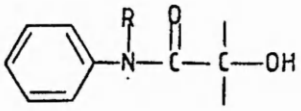
A third possible route to secondary isobutyramides is simply an extension of the original ICI synthesis of primary isobutyramides, in which phenols are converted to aryloxy-isobutyric acids and then to the corresponding amides (see Scheme 30). By this method were prepared amides 466, 467 and 448 in reasonable yield, while amide 478 was obtained quantitatively from the dicyclohexylcarbodiimide-mediated coupling of 2-phenoxy-2-methylpropanoic acid with benzylamine.

The Smiles rearrangement of secondary aryloxyisobutyr-amides has produced interesting results. The treatment of N-phenyl and N-(3,5-bistrifluoromethylphenyl) amides 448 and 446 with sodium hydride in DMF/DMPU, gave the expected anilides 479 and 480 in 31 and 56% yields respectively. However, the Smiles rearrangement of N-alkyl substituted amides 446 (N-Me); 467 (N-Et); 478 (N-CH_2Ph); 442 (N-Me); 443 (N-CH_2Ph); 444 (N-Me); 445 (N-CH_2Ph) all led to the isolation of the corresponding secondary ANILINES 481-487 in 50-98% yields.

A tentative explanation of this unexpected and useful result is as follows. After formation of the Meisheimer intermediate 488 ring opening may lead to the alcoholic anion 489. It can be assumed that if the nitrogen is not substituted (ie. R=H) proton transfer from the nitrogen to the oxygen will occur giving resonance stabilised anion 490, which on treatment

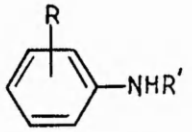


478



479 R = Ph

480 R = 3,5$(CF_3)_2C_6H_3$



481 R = H, R′ = Me

482 R = H, R′ = Et

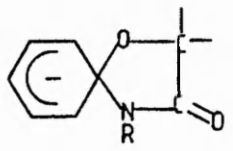
483 R = H, R′ = CH_2Ph

484 R = 4-Cl, R′ = Me

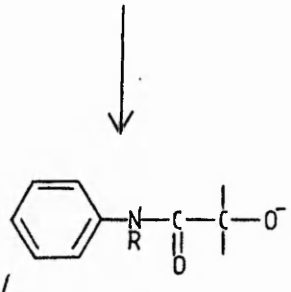
485 R = 4-Cl, R′ = CH_2Ph

486 R = Ph, R′ = Me

487 R = Ph, R′ = CH_2Ph



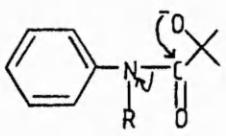
488

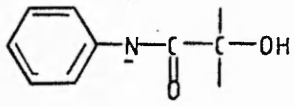


489

if R ≠ H or Ar

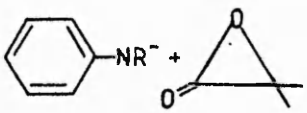
R = H

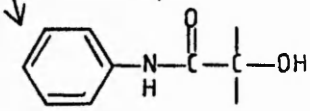




R = Ar

490





492 493 491

SCHEME 31

with water will yield the expected anilide 491. However, if the nitrogen is substituted (ie. R≠H) the alcoholic anion could attack the carbonyl forming the oxiranone 493 and the secondary amine 492. It might be argued that anions 489, in which the R substituent is aryl will be extensively delocalised and thus good leaving groups, but compounds such as 446 and 448 gave anilides rather than anilines in the Smiles rearrangement. However, intramolecular attack by the alcohol anion on the carbonyl group in 448, R=Ph is obviously subject to severe steric crowding, perhaps preventing oxiranone formation.

Oxiranones[232] have been postulated as short-lived intermediates in a variety of reactions.[235] Only low temperature ozonolysis[236] of di-t-butylketene 494 and low temperature photolysis of 1,2-dioxolane-3,5-diones[237] 496 has furnished oxiranones 495 and 497, which were characterised by n.m.r. and i.r. spectroscopy and found to be stable up to -20^{o} and room temperature respectively.

Steric crowding prevented the Smiles rearrangements of several secondary phenoxyisobutyramides; the 2,6-dimethylphenoxyamide 475 and compounds 446, 461, 462, 474 and 468 all with bulky nitrogen substituents were recovered unchanged from reaction with hydride in DMF/DMPU.

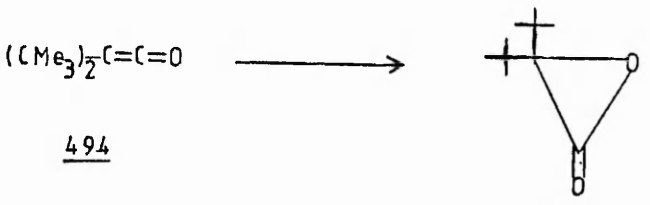
As mentioned previously the N-neopentylamide 436 was resistant to proton abstraction and this, rather than steric considerations, may be the reason that the N-neopentylphenoxyisobutyramide 469 also failed to rearrange.

It was reported in Section 4.2.2 that the Smiles rearrangement of 2-halogenated primary phenoxyisobutyramides

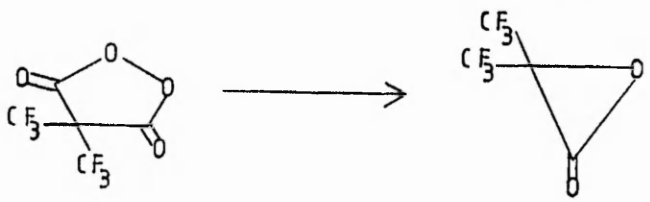
498 gave the expected anilides 499. It was now decided to investigate the Smiles rearrangement of corresponding N-substituted amides 500 as the greater steric restraint to intermediate Meisenheimer formation might lead to alternate attack at the ortho-halogenated position on the aromatic ring, giving 1,4-benzoxazin-3-ones 501. Indeed, reaction in DMF/DMPU with sodium hydride of 2-halogenated amides 470 and 471 gave N-methylbenzoxazinone 502, while amide 473 afforded N-adamantylbenzoxazinone 503, both reactions proceeding quantitatively. However, as expected, the 2-methoxy and 2-methyl groups of amides 472 and 474 could not be displaced to form benzoxazinones.

1,4-Benzoxazin-3-ones have been prepared previously by either reductive cyclisation of 2-nitrophenoxyacetic acids or by cyclisative elimination reactions of 3-chloroacetylamino-phenols. The first reported[238] preparation involved the reaction of 5-chloroacetylaminoeugenol 504 with pyridine and triethylamine followed by acidification to give 1,4-benzoxazin-3-one 505. This method has been used to prepare[239] many 4-substituted 1,4-benzoxazin-3-ones.

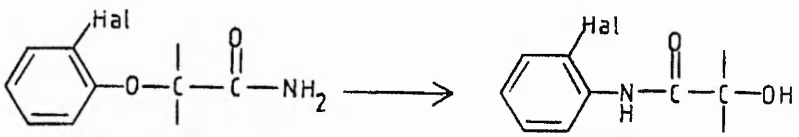
Geigy reported[240] the preparation of 4-hydroxy-1,4-benzoxazin-3-one 507 by the reduction of 2-nitrophenoxyacetic ester 506 with zinc in ammonium chloride. Many studies[241,242] on 4-hydroxy-1,4-benzoxazin-3-ones have been undertaken due to their antifungal activity,[243] antimetabolic properties in corn[244] and anti-reproductive potency in aphids.[245] Benzylation of the parent 1,4-benzoxazin-3-one with benzyl



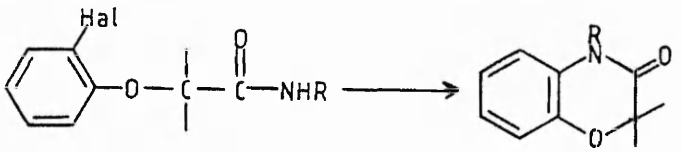
494 495



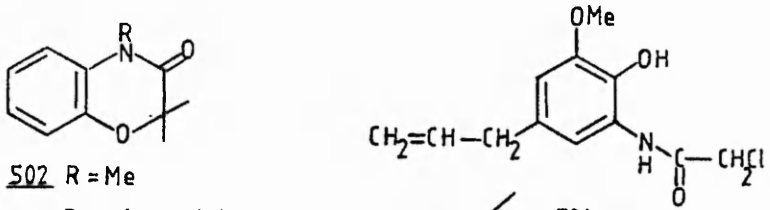
496 497



498 499



500 501



502 R = Me

503 R = adamantyl

504

505

chloride and potassium carbonate yielded[246] the anti-spasmodic[247] compound 508.

The novel preparation of 1,4-benzoxazin-3-ones described by the author compares favourably with the methods previously reported and thus offers a new route to these compounds.

1,4-Benzoxazin-3-ones have been shown to be amphetamine antagonists,[249] anticataleptics,[248] analgesics,[249] anti-flamatory agents,[241] sedatives,[250] sympatholytics,[250] anti-cholesteremics,[250] dopamine receptor antagonists,[251] broncho-dilators,[253] uterus muscle relaxants,[253] and vasodilators,[253] to bind[252] covalently with the guanine of DNA and to have protease activity.[254]

4.2.4 The hydrolysis of anilides 359 to anilines 360

The hydrolysis of the parent anilide 382, the final step in the phenol to aniline conversion was re-examined. However, it was found that refluxing in either 50% sodium hydroxide solution or 5N sulphuric acid, the conditions developed by Turners groups,[205] could not be improved upon. With the discovery that N-alkyl substituted phenoxyisobutyramides rearrange to their secondary anilines directly, a milder route to anilines may be via N-benzylisobutyramides. The N-benzyl anilines resulting from Smiles rearrangement can obviously be readily debenzylated.

4.2.5 The conversion of more complex phenols to anilines

It was decided to attempt the preparation of amino-oestrones as previous syntheses were limited and were not effected in good yield.

Morrow and Hofer, using the method developed by Scherrer (see Section 4.1), claim[255] to have converted oestrone 509 to amino analogue 510 in 52% yield by reaction of 509 with 4-chloro-2-phenylquinazoline followed by pyrolysis and saponification. Later workers, however, report yields of 10%[256] and 34%[257] for this reaction.

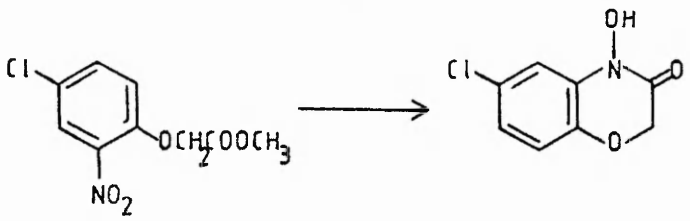
In a series of patents Pappo[258] describes the synthesis of 3-aminooestrones by the acid catalysed cyclisation of 2-methyl-2-(6-amino-1-naphthyliden)ethylcyclopentane-1,3-diones 511, but no yields are quoted. 3-Aminooestrones have also been prepared[259] by reaction of the corresponding oestra-3,17-diones 512 with the appropriate amine and acetic acid; again no yields are reported.

Italian workers described[260] the synthesis of 2-cyano-3-aminooestrone acetates 514 by reaction of the analogues oestrone-3-one-17-acetates 513 with ammonium formate, catalytic reduction giving aminooestrones 514 in 46% yield.

Condensation[261] of 10,17-β-dihydroxyoestra-1,4-dien-3-one 515 with 2,4-dinitrophenylhydrazine has led to aminooestrones. The azo product 516 was reduced by sodium hydrosulphate to the diamino azo compound 517. Further treatment with sodium hydrosulphate gives the aminooestrone 518, with no yields quoted.

The attempted synthesis of 3-aminooestrones from oestrone was undertaken to display the flexibility of the phenol to aniline conversion under development in this study.

The preparation of 3-isobutyroxyamidooestrone 519 and β-oestradiolamide 520 was achieved by reaction of the phenols, oestrone or β-oestradiol, with sodium hydride followed by



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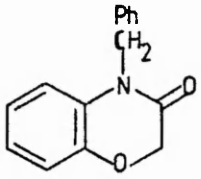

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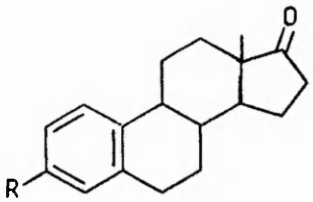
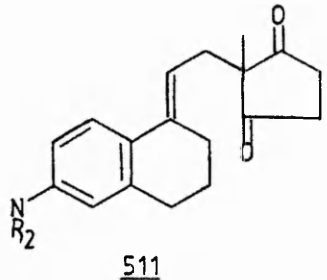


509 R=OH
510 R = NH_2



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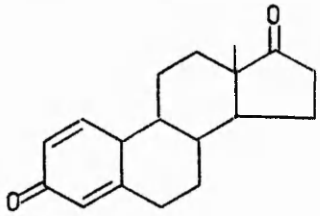

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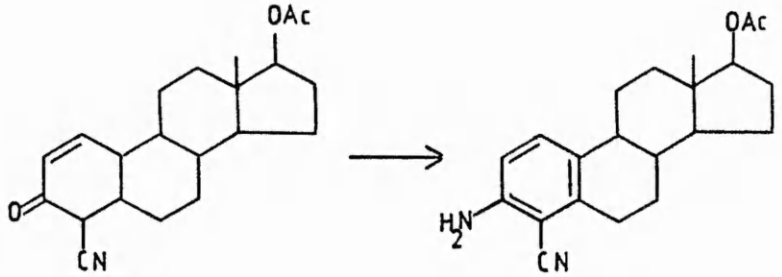
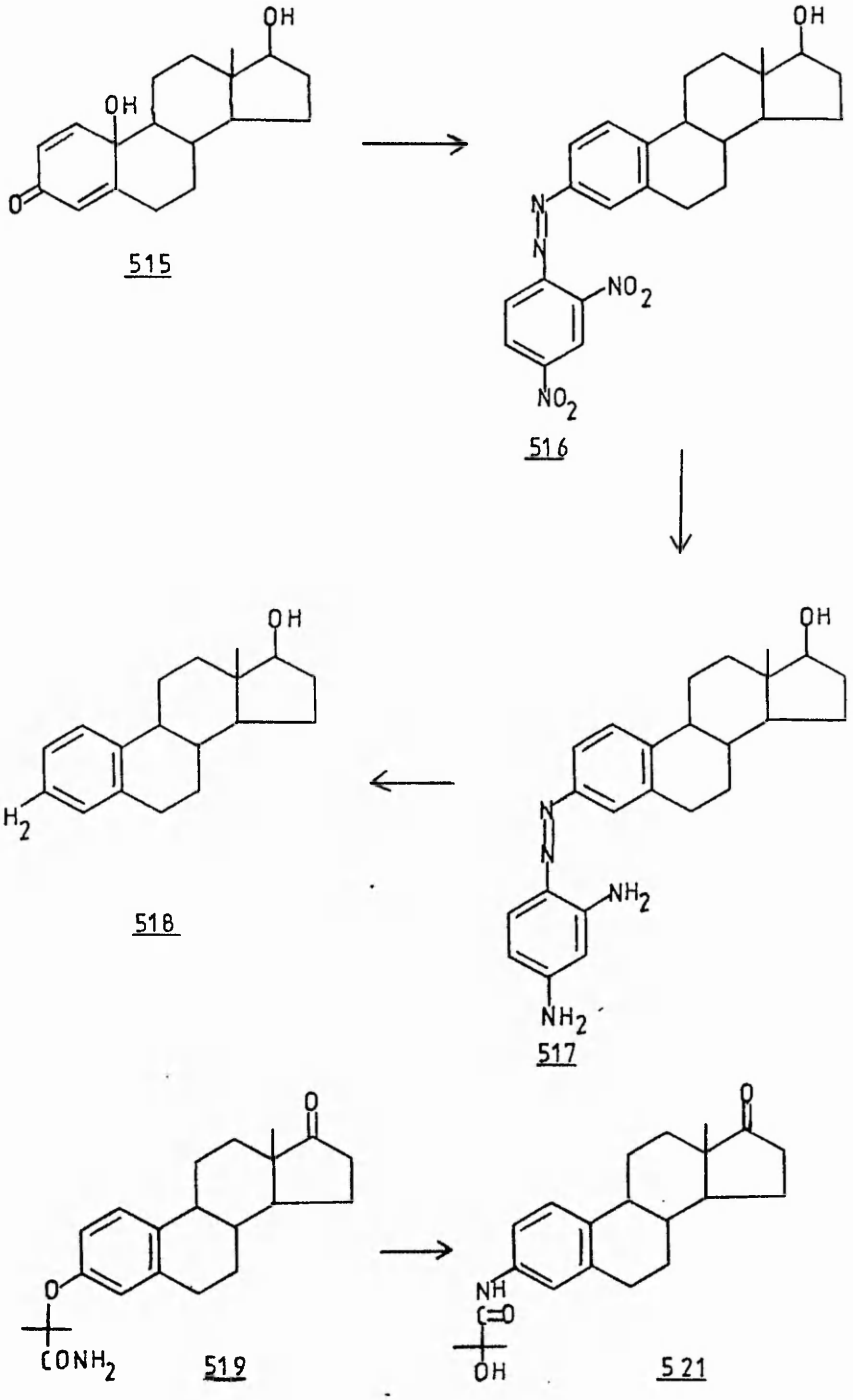


513 514

heating in dioxan with bromoisobutyramide 392, to give 77 and 88% yields respectively. Smiles rearrangement of the amides yielded 94 and 88% of anilides 521 and 522 respectively.

However, when the sodium salt of oestrone was reacted with N-methylbromoamide 430 in dioxan, a complex mixture was obtained. It is thought that because of competing α-lactam formation, the reaction proceeds slowly, thus allowing the 17-keto position of oestrone to be subjected to attack by nucleophiles in the reaction mixture. This idea was supported by the preparation of the N-methylamidooestradiol 523 in 88% yield, by the same reaction. The N-methyl amidooestrone 524 was however obtained in 82% yield by reaction of oestrone with N-methylα-lactam 463. Smiles rearrangement of N-methyl-oestradiol 523 gave novel 3-methylaminooestradiol 525, isolated as its hydrochloride in 60% yield. But rearrangement of the N-methyloestrone 524 yielded a complex mixture of products, base attack at C-17 probably causing degradation. Attempts to protect the C-17 position by acetal formation, failed as acetal 527 when treated with DMPU/DMF and hydride afforded a complex mixture.

It appears that there is scope for applying this efficient phenol-aniline conversion to many complex substrates, provided attack by base or base-generated species does not give rise to significant competing reactions.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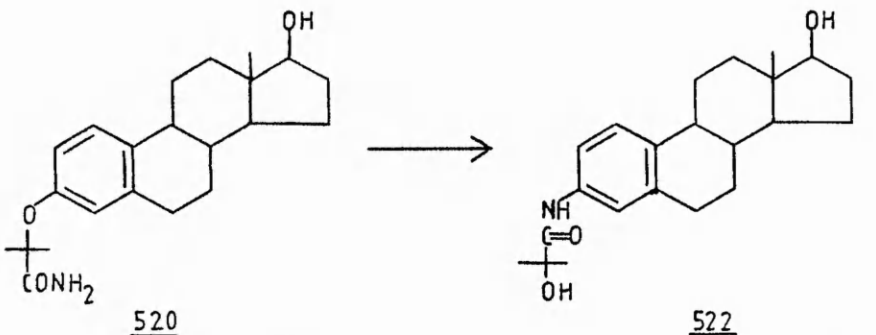
CONH2
519
O
NH
C=O
OH
521



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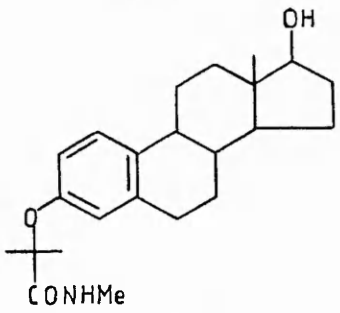

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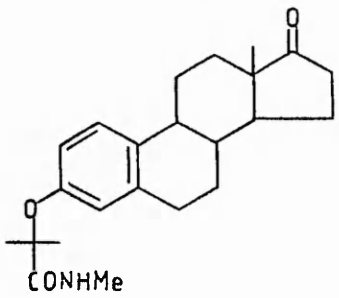

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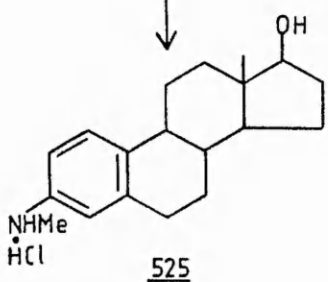

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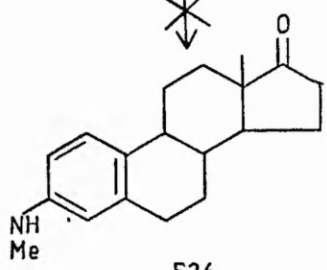

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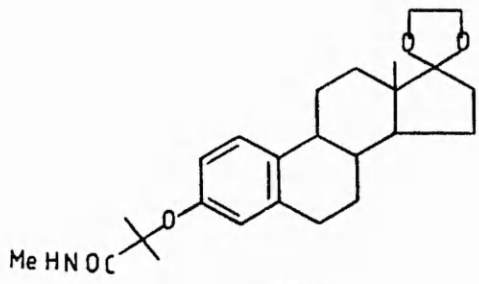

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EXPERIMENTAL SECTION

Novel Compounds

Compounds, the names of which are underlined in this section, have not (to the best of the Author's knowledge) been described in the literature.

Experimental Details

Infra-red spectra were recorded using a Perkin Elmer 683 grating spectrophotometer. Proton magnetic resonance spectroscopy was performed using a Hitachi Perkin Elmer R24B 60 MHz spectrometer with tetramethylsilane as the internal standard. Carbon-13 n.m.r. spectra were recorded on a JOEL JNM FX60Q 60 MHz Fourier Transform spectrometer. Low resolution mass spectrometry was carried out by the Department of Chemistry, Leicester Polytechnic. Elemental analyses were determined by the analytical sections of either ICI Pharmaceuticals Division or Nottingham University. Melting points were measured in degrees centigrade using open capilliaries in an electrically heated Gallenkamp melting point apparatus and are not corrected. Hydrogenations were performed using the medium pressure apparatus of Chas W Cook and Sons, Birmingham, and also a standard atmospheric pressure hydrogenation apparatus. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh ASTM). All solvents for chromatography were redistilled. HPLC work was carried out using a Pye Unicham PU401D pump, a Pye Unicham LCXP gradient programmer and a Perkin Elmer LC55 UV detector with a 8 μL flowcell. Gas chromatography was performed on a Perkin Elmer F33 machine.

Ether, benzene and toluene were dried over sodium wire, THF over calcium hydride, pyridine over potassium hydroxide pellets. Other solvents were dried using 5A molecular sieves. Petroleum has b.p. 60-80^{o} unless otherwise stated.

Work described in Chapter One

General method for preparation of toluene-4-sulphonamides

The amine (1 mol eq) and toluene-4-sulphonyl chloride (1 mol eq) were heated in pyridine (80 ml/10 g of amine) on a steambath for 30 min. The mixture was poured onto ice/HCl (500 ml, 4M) and the solid was filtered off to give the desired N-toluene-4-sulphonyl compound, which was purified by crystallisation.

General method for catalytic hydrogenation

The compound was dissolved in either ethyl acetate or ethanol and hydrogenated in the presence of palladised charcoal (5% Pd on C, 1 g/5 g substrate) until all the hydrogen had been taken up. The catalyst was filtered off, the solvent evaporated and the residue recrystallised.

Preparation of phenolic sulphonamide 3

4-Benzyloxyaniline hydrochloride (50 g, 0.25 mol) was heated under reflux with 2-fluoronitrobenzene (26 ml, 0.25 mol) anhydrous K_2CO_3 (60 g), tetrabutylammonium hydrogen sulphate (5 g) and dry DMF (400 ml), for 6 h. The reaction mixture was poured into water (1 L), the resulting precipitate filtered off, the filtrate extracted with $CHCl_3$ (3 x 300 ml), the organic layer dried ($MgSO_4$) and evaporated.

Crystallisation of the combined solids from chloroform/ethanol gave 4-benzyloxy-2'-nitrodiphenylamine 61 (52.9 g, 67%). m.p. 83-84° (lit[37] m.p. 83.5-84.5°). ν_{max}^{KBr}: 3320 cm^{-1} (NH). δ_H ($CDCl_3$): 8.2 (1H, d, exchangeable with D_2O, NH); 6.5-7.4 (13H, m, ArH); 5.1 (2H, s, $PhCH_2O$).

To absolute ethanol (100 ml) under nitrogen was added palladised charcoal (5% Pd, 2 g), sodium borohydride (10 g) and then dropwise with stirring a solution of diphenylamine 61 in dry toluene (200 ml). After leaving overnight the reaction was poured into water (400 ml), extracted with ethyl acetate (2 x 150 ml), the organic layers dried (Na_2SO_4) and evaporated. Recrystallisation from petroleum (b.p. 80-100°) of the residual solid gave 4-benzyloxy-2'-aminodiphenylamine 62 (11.3 g, 83%). m.p. 109-110° (lit[37] m.p. 109-110°). ν_{max}^{KBr}: 3420, 3310 cm^{-1} (NH_2 and NH). δ_H ($CDCl_3$): 6.6-7.4 (13H, m, ArH); 4.9 (2H, s, $PhCH_2O$); 3.4 (2H, broad s, exchangeable with D_2O, NH_2).

The aminodiphenylamine 62 (10 g, 22 mmol) was reacted with toluene-4-sulphonyl chloride as described earlier, giving 4-benzyloxy-2'-(toluene-4-sulphonamido)diphenylamine 63 (14.5 g, 95%). m.p. 161-162° (from ethanol) (lit[37] m.p. 161.5-162°). ν_{max}^{KBr}: 3360, 3130 cm^{-1} (2 x NH). δ_H ($CDCl_3$): 6.7-7.7 (17H, m, ArH); 6.5 (1H, s, exchangeable with D_2O, NH); 5.0 (2H, s, $PhCH_2O$); 2.4 (3H, s, $C_6H_4CH_3$).

Debenzylation of sulphonamide 63

(a) The tosyldiphenylamine 63 was dissolved in a solution of HBr in glacial acetic acid (33% HBr, 30 ml) and small aliquots were analysed by t.l.c. (ethylacetate/hexane 1:1). After 0.5 h all 63 had been debenzylated. Water (100 ml) was added, the

precipitated solid filtered and recrystallised (ethyl acetate-petroleum) to give 4-hydroxy-2'-(toluene-4-sulphonamido)diphenylamine 3 (2.1 g, 85%) m.p. 170-171° (lit[37] m.p. 170-171°). ν_{max}^{KBr}: 3420, 3240 cm^{-1} (2 x NH and OH). δ_H (d_6 DMSO): 9.0 (1H, broad s, exhangeable with D_2O, OH); 7.6-6.4 (12H, m, ArH); 3.2 (2H, broad s, exchangeable with D_2O, 2 x NH); 2.3 (3H, s, $C_6H_4CH_3$).

(b) Compound 63 (3 g, 6.7 mmol) was heated under reflux with ethanol (250 ml) and conc. HCl (250 ml), for 4 h. The solvent was evaporated and the solid recrystallised to give compound 3 (1 g, 41%). m.p. 170-171°.

(c) Compound 63 (3 g) was dissolved in ethyl acetate (100 ml) and hydrogenated with palladised charcoal as described earlier, to give compound 3 (1.8 g, 76%). m.p. 170-171°.

Preparation of aminophenol 69

To a solution of 4-benzyloxyaniline (9.3 g, 47 mmol) in dry pyridine (100 ml) was added toluene-4-sulphonyl chloride (8.8 g, 47 mmol) as described earlier to give N-(toluene-4-sulphonyl)-4-benzyloxyaniline (13.1 g, 79%). m.p. 154-155° (from ethanol) (lit[37] m.p. 157°). ν_{max}^{KBr}: 3250 cm^{-1} (NH). δ_H ($CDCl_3$): 6.7-7.9 (17H, m, ArH); 5.0 (2H, s, $PhCH_2O$); 2.6 (3H, $C_6H_4CH_3$).

(a) N-(toluene-4-sulphonyl)-4-benzyloxyaniline (10 g, 28 mmol) was reacted with 2-fluoronitrobenzene (4.0 g, 28 mmol) using the same conditions as for compound 61 affording 4-benzyloxy-2'-nitro-N-(toluene-4-sulphonyl)-diphenylamine 69 (3.0 g, 22%). m.p. 147-148° (from ethanol) (lit[37] m.p. 147-148°). δ_H ($CDCl_3$): 6.3-7.9 (17H, m, ArH); 5.0 (2H, s, $PhCH_2O$); 6.4 (3H, s, $C_6H_4CH_3$).

(b) The sulphonamide (10 g, 28 mmol) was mixed with 2-fluoronitrobenzene (4.8 g, 34 mmol), anhydrous K_2CO_3 (4.7 g) and copper bronze (2 g) and heated at 180° for 6 h; during the heating the mixture was swirled periodically. The excess 2-fluoronitrobenzene was distilled off under vacuum. The residue was triturated in water and extracted with $CHCl_3$ (3 x 50 ml). The combined extracts, after filtration through celite were washed with sodium hydroxide solution (1M, 100 ml portions) until the secondary sulphonamide was no longer extracted, then with water (2 x 100 ml) and dried (Na_2SO_4). Evaporation gave a black gum which was dissolved in benzene, treated repeatedly with activated charcoal and crystallised yielding compound 69 (3.0 g, 22%). m.p. 147-148°.

Attempted alternative preparation of diphenylamine 3

A solution of 4-aminophenol (30 g, 0.27 mol) and 2-fluoronitrobenzene (30 g, 0.21 mol) in propan-2-ol (250 ml) was heated under reflux for 12 h. The solvent was evaporated, the residue dissolved in benzene (100 ml), filtered, and the filtrate evaporated to give 4-hydroxy-2'-nitrodiphenylamine 64 (55.9 g, 90%). m.p. 89-90° (from toluene) (lit[265] m.p. 89°). ν_{max}^{KBr}: 3350, 3300 cm^{-1} (NH and OH). δ_H ($CDCl_3$): 6.3-7.2 (9H, one exchangeable with D_2O, m, 8ArH and 1OH); 9.7-9.0 (1H, broad s, exchangeable with D_2O, NH).

Nitrophenol 64 (9.4 g, 41 mmol) was catalytically hydrogenated as described earlier giving 2'-amino-4-hydroxydiphenylamine 65 (7.4 g, 84%). m.p. 149-150° (from ethanol) (lit[265] m.p. 149.5). ν_{max}^{KBr}: 3370, 3300, 3120 cm^{-1} (NH_2, NH and OH). δ_H ($CDCl_3/d_6$ DMSO): 3.1-7.3 (1H, s very broad, exchangeable with D_2O, OH); 6.3-7.0 (10H, 2 exhangeable with D_2O, 8ArH and NH_2); 6.0 (1H, s, exchanges with D_2O, NH).

Amine 65 (7.2 g, 33 mmol) was added to toluene-4-sulphonyl chloride (6.35 g, 33 mmol) and pH 7 phosphate buffer solution (100 ml). The solution was heated on a steambath for 1 h, hydrochloric acid (4M, 1L) was added, the resulting solids filtered off, dissolved in $CHCl_3$ (200 ml), the solution washed with water (3 x 100 ml), the organic layer dried ($MgSO_4$) and evaporated. T.l.c. (ethylacetate/hexane 1:1) showed the product to contain two components which were separated by flash chromatography (eluent chloroform/light petroleum 1:1). The first product isolated was 4-(toluene-4-sulphoxy-2'-(toluene-4-sulphonamido)diphenylamine 66 (0.62 g, 4%). m.p. 100-101°. (Found: C, 59.5; H, 4.8; N, 5.0 $C_{26}H_{24}N_2S_2O_5$ H_2O requires: C, 59.3; H, 5.0; N, 5.3%). ν_{max}^{KBr}: 3250 cm^{-1} (NH). δ_H ($CDCl_3$): 6.0-8.0 (18H, m, 16ArH and 2 x NH exchangeable with D_2O); 2.3 (6H, d, 2 x CH_3). The second product was diphenylamine 3 (0.4 g, 3%), identical with previously prepared material.

Attempted preparation of a methanesulphonyl analogue of diphenylamine 3

Aminodiphenylamine 62 (13 g, 45 mmol) was dissolved in dry CH_2Cl_2 (150 ml), methanesulphonyl chloride (3.7 ml, 48 mmol) and triethylamine (5 ml) were added and the mixture stirred for 2 h. Evaporation and recrystallisation from ($CHCl_3$/toluene) yielded the unstable 4-benzyloxy-2'-methanesulphonamidodiphenylamine (9.6 g, 74%). m.p. 143-144°. (Found: C, 64.8; H, 5.4; N, 7.5 $C_{20}H_{20}N_2O_3S$ requires: C, 65.2; H, 5.4; N, 7.6%). ν_{max}^{KBr}: 3320, 3090 cm^{-1} (2 x NH). δ_H ($CDCl_3$/d6 DMSO): 8.7 (1H, s, exchanges with D_2O, NH); 6.8-7.5 (18H, m, 17ArH and NH exchanges with D_2O); 5.0 (2H, s, $PhC\underline{H}_2O$); 2.9 (3H, s, $C_6H_4C\underline{H}_3$).

The above sulphonamide (9.4 g) was refluxed in ethanol (250 ml) and conc. HCl (250 ml) for 0.25 h to give a product shown by t.l.c. (ethyl acetate/hexane 1:1) to be a complex mixture.

Preparation of sulphonamide 92

4-Chloro-3-nitrobenzotrifluoride (48 g, 0.21 mol) was reacted with 4-benzyloxyaniline hydrochloride (50 g, 0.21 mol), as described previously for the preparation of diphenylamine 62, to give 4-benzyloxy-2'-nitro-4'-trifluoromethyldiphenylamine 89 (24.3 g, 30%). m.p. 134.5-135.5° (from $CHCl_3$/ethanol) (lit[67,74] m.p. 134-135°). ν_{max}^{KBr}: 3350 cm^{-1} (NH). δ_H ($CDCl_3$): 9.6 (1H, s, exchangeable with D_2O, NH); 7.1-8.5 (12H, m, ArH); 5.2 (2H, s, $PhC\underline{H}_2O$).

Catalytic hydrogenation of compound 89 yielded 2'-amino-4-benzyloxy-4'-trifluoromethyldiphenylamine 90 (12.2 g, 88%). m.p. 119-120° [from petroleum (b.p. 80-100°)]. ν_{max}^{KBr}: 3440, 3350 cm^{-1} (NH and NH_2). δ_H ($CDCl_3$): 6.8-7.35 (12H, m, ArH); 5.2 (1H, s, exchangeable with D_2O, NH); 5.0 (2H, s, $PhC\underline{H}_2O$); 3.6 (2H, s, exchanges with D_2O, NH_2).

Reaction of amine 90 with toluene-4-sulphonyl chloride, as described earlier, gave 4-benzyloxy-2'-(toluene-4-sulphonamido)-4'-trifluoromethyldiphenylamine 91 (3.5 g, 40%). m.p. 180-181° (from ethanol) (lit[67,74] m.p. 180-181°). ν_{max}^{KBr}: 3390, 3360 cm^{-1} (2 x NH). δ_H ($CDCl_3$): 9.3 (1H, s, exchangeable with D_2O, NH); 6.75-7.5 (17H, m, 16ArH and NH); 5.0 (2H, s, $PhC\underline{H}_2O$); 3.2 (3H, s, $C_6H_4C\underline{H}_3$).

(a) The benzyloxyamine 91 was dissolved in a solution of HBr in glacial acetic acid (33% HBr, 20 ml). After 1 h, water (100 ml) was added, the resulting solid filtered off and

recrystallised from ethanol to give 4-hydroxy-2'-(toluene-4-sulphonamido)-4'-trifluoromethyldiphenylamine 92 (2.4 g, 99%). m.p. 206-207°. (Found: C, 56.8; H, 3.9; N, 6.2 $C_{20}H_{17}F_3N_2O_3S$ requires: C, 56.9; H, 4.0; N, 6.6%). M^+, 422. ν_{max}^{KBr}: 3380, 3370, 3260 cm^{-1} (OH and 2 x NH). δ_H ($CDCl_3$): 9.4 (1H, s, exchangeable with D_2O, NH); 6.8-7.8 (13H, m, 11ArH, 1NH and 1OH); 2.5 (3H, s, $C_6H_4CH_3$).

(b) The benzyloxy compound 91 (3 g, 6 mmol) was heated under reflux in a mixture of ethanol (250 ml) and conc. HCl (250 ml), for 4 h. Solvent evaporation and recrystallisation of the residue from ethanol gave diphenylamine 92 (0.34 g, 14%). m.p. 206-207°.

Second attempted preparation of sulphonamide 92

4-Aminophenol (12 g, 0.11 mol) was dissolved in propan-2-ol (120 ml), 4-chloro-3-nitrobenzotrifluoride (12 g, 53 mmol) was added and the mixture was heated at reflux for 12 h. The solvent was evaporated, the residue dissolved in benzene, filtered, the benzene evaporated yielding 4-hydroxy-2'-nitro-4'-trifluoromethyldiphenylamine 87 (11.9 g, 75%). m.p. 133-124° (from $CHCl_3$/hexane) (lit[67] m.p. 134-135°). ν_{max}^{KBr}: 3410 cm^{-1} (OH); 3360 cm^{-1} (NH). δ_H ($CDCl_3$): (1H, s, exchangeable with D_2O, NH); 6.4-7.9 (7H, m, ArH); 4.0 (1H, broad s, exchangeable with D_2O, OH).

Compound 87 (10 g) was catalytically hydrogenated yielding a clear solution which turned deep red after 10 sec in air. T.l.c. showed 9 products.

Attempted preparation of diphenylamine 92 using phenol protection

The mixture of diphenylamine 87 and diphenylether 93, obtained by reaction of 4-chloro-3-nitrobenzotrifluoride with 4-aminophenol (29 g, 97 mmol) was dissolved in ethanol (40 ml); water (40 ml), sodium hydroxide (8 g), ice and acetic anhydride (13 ml, 0.14 mol) were added. The mixture was shaken until a precipitate was formed. The solid was filtered off and recrystallisation from carbon tetrachloride gave 4-acetamido-2'-nitro-4'-trifluoromethyldiphenylether 94 (20 g, 60%). m.p. 143-144°. (Found: C, 52.8; H, 3.0; N, 7.8 $C_{15}H_{11}F_3N_2O_4$ requires: C, 52.9; H, 3.2; N, 8.2%). ν_{max}^{KBr}: 3350 cm^{-1} (NH); 1670 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.0-8.3 (8H, m, 7ArH and NH); 2.2 (3H, s, $C\underline{H}_3$).

Compound 94 was catalytically hydrogenated as described earlier giving 4-acetamido-2'-amino-4'-trifluoromethyldiphenyl ether 95 (14.9 g, 88%). m.p. 120-121° (from CCl_4). (Found: C, 58.1; H, 4.2; N, 8.9 $C_{15}H_{13}F_3N_2O_2$ requires: C, 58.1; H, 4.2; N, 9.0%). ν_{max}^{KBr}: 3490, 3300 cm^{-1} (NH_2 and NH). δ_H (d6 DMSO): 9.9 (1H, s, exchanges with D_2O, NH); 6.7-7.7 (7H, m, ArH); 5.0 (2H, s, exchanges with D_2O, NH_2); 2.0 (3H, s, $C\underline{H}_3$).

Amine 95 (14 g, 45 mmol) was reacted with toluene-4-sulphonyl chloride as described earlier giving 4-acetamido-2'-(toluene-4-sulphonamido)-4'-trifluoromethyldiphenyl ether 96 (9.2 g, 39%). m.p. 223-224° (from ethanol). (Found: C, 56.6; H, 3.9; N, 6.1 $C_{22}H_{18}F_3N_2O_4S$ requires: C, 56.9; H, 4.1; N, 6.0%). ν_{max}^{KBr}: 3320, 3200 cm^{-1} (2 x NH); 1685 cm^{-1} (C=O). δ_H (d6 DMSO): 10.0 (1H, s, exchangeable with D_2O, NH); 6.5-7.7 (12H, m, 11ArH and NH); 2.3 (3H, s, $C_6H_4C\underline{H}_3$); 2.0 (3H, s, $C\underline{H}_3CO$).

Compound 96 (8.5 g, 18 mmol) was dissolved in ethanol (50 ml); water (50 ml) and sodium hydroxide (10 g) were added. The solution was heated at reflux for 1 h, acidified with HCl (4M), the resulting solid filtered off, yielding 4-amino-2'-(toluene-4-sulphonamido)-4'-trifluoromethyldiphenyl ether hydrochloride 97 (5.7 g, 76%). m.p. 187-188° (from ethanol). (Found: C, 52.9; H, 3.9; N, 5.8 $C_{20}H_{18}ClF_3N_2O_3S$ requires: C, 52.3; H, 3.9; N, 6.1%). ν_{max}^{KBr}: 3270-2600 cm^{-1} (NH_3^+ and NH). δ_H ($CDCl_3$/d6 DMSO): 6.5-7.8 (12H, m, 11ArH and NH); 5.1 (3H, s, exchanges with D_2O, NH_3^+); 2.4 (3H, s, $C_6H_4CH_3$).

Attempted preparation of diphenylamine 92 from diphenylamine 87

Purified diphenylamine 87 (55 g, 0.18 mol) was dissolved in ethanol (75 ml); water (75 ml), sodium hydroxide (15 g), ice and acetic anhydride (28 ml, 0.28 mol) were added and the mixture shaken until a precipitate formed. The solid was filtered off to give 4-acetoxy-2'-nitro-4'-trifluoromethyldiphenylamine 98 (11.7 g, 19%). m.p. 106-107° (from cyclohexane). (Found: C, 52.7; H, 3.2; N, 7.8, M^+, 340 $C_{15}H_{11}F_3N_2O_4$ requires: C, 52.9; H, 3.2; N, 8.2%, M^+, 340.) ν_{max}^{KBr}: 3340, 3300 cm^{-1} (2 x NH); 1750 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.6 (1H, s, exchangeable with D_2O, NH); 8.5 (1H, s, ArH); 7.1-7.6 (6H, m, ArH); 2.3 (3H, s, $COCH_3$).

Acetoxy compound 98 (11.7 g, 34 mmol) was reduced by catalytic hydrogenation giving 4-acetoxy-2'-amino-4'-trifluoromethyldiphenylamine 99 (7.6 g, 71%). m.p. 131-132° (from $CHCl_3$/cyclohexane). (Found: C, 57.8; H, 4.1; N, 8.7, M^+, 310 $C_{15}H_{13}F_3N_2O_2$ requires: C, 58.1; H, 4.2; N, 9.0%, M^+, 310). ν_{max}^{KBr}: 3420 cm^{-1} (NH); 3320 cm^{-1} (NH_2); 1750 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.7-7.2 (8H, m, 7ArH and NH); 4.7 (2H, s, exchanges with D_2O, NH_2); 2.2 (3H, s, $COCH_3$).

Amine 99 (7.6 g, 25 mmol) was reacted with toluene-4-sulphonyl chloride, giving 4-acetoxy-2'-(toluene-4-sulphonamido)-4'-trifluoromethyldiphenylamine 100 (5.3 g, 47%). m.p. 207-208° (from $CHCl_3$). (Found: C, 56.9; H, 3.9; N, 5.6; M^+, 464 $C_{22}H_{19}F_3N_2O_4S$ requires: C, 56.9; H, 4.1; N, 6.0%; M^+, 464).ν_{max}^{KBr}: 3360, 3240 cm^{-1} (2 x NH); 1750 cm^{-1} (C=O). δ_H ($CDCl_3$/d6 DMSO): 9.4 (1H, s, exchanges with D_2O, NH); 6.6-7.6 (12H, m, 11ArH and NH); 2.2 (6H, s, 2 x CH_3).

Sulphonamide 100 was refluxed in a solution of ethanol (50 ml), water (50 ml) and sodium hydroxide (10 g) for 1 h. After neutralisation with HCl (4M), the mixture was extracted with $CHCl_3$ (3 x 50 ml), the organic layers dried ($MgSO_4$) and the solvent evaporated to give sulphonamide 92 (2 g, 44%). m.p. 206-207° (from ethanol).

The attempted preparation of 2,6-dialkyl analogues of diphenylamines 3 and 92

(a) A solution of 4-amino-2,6-dimethylphenol (10 g, 73 mmol) and 4-chloro-3-nitrobenzotrifluoride (16.4 g, 73 mmol) in propan-2-ol (200 ml) was heated under reflux for 12 h. T.l.c. (ethyl acetate/hexane 1:1) of the reaction mixture showed the presence of only one product. However the red solid obtained by evaporation of the solvent was demonstrated by t.l.c. to consist of several compounds of similar R_f values. Although the spectral properties of this mixture were consistent with it being mainly 4-hydroxy-2,6-dimethyl-2'-nitro-4'-trifluoromethyldiphenylamine 103 (12.9 g, 54%).ν_{max}^{KBr}: 3250 cm^{-1} (OH); 3360 cm^{-1} (NH). δ_H ($CDCl_3$): 9.5 (1H, s, exchanges with D_2O,

NH); 6.8-8.4 (5H, m, ArH); 4.8 (1H, s, exchangeable with D_2O, OH); 2.2 (6H, s, 2 x CH_3), it rapidly (approx. 1 h) decomposed.

The attempted acetylation of 103 under Schotten-Baumann conditions led to a complex mixture.

(b) 2,6-Di-t-butylphenol (103 g, 0.5 mol) was dissolved in hexane (200 ml) and under N_2 was added a 50% aqueous solution of concentrated nitric acid (200 ml). The mixture was stirred for 12 h at 20^{o} and the resulting solid was filtered off. Recrystallisation from ethanol yielded 2,6-di-t-butyl-4-nitrophenol (80 g, 64%). m.p. 155-156^{o} (lit[265] m.p. 155.5^{o}).

The above nitrophenol (80 g) was catalytically hydrogenated giving 2,6-di-t-butyl-1,4-benzoquinone 105 (50 g, 71%). m.p. 67-68^{o} (from $CHCl_3$/hexane) (lit[265] m.p. 67-68^{o}). ν_{max}^{KBr}: 1650 cm^{-1} (p-quinone). δ_H ($CDCl_3$): 6.5 (2H, s, 2 vinylics); 1.3 (18H, s, 6 x CH_3).

Preparation of bisquinone 4

(a) Sulphonamidophenol 3 (5 g, 14 mmol), manganese dioxide, prepared by the method of Franck and Blaschke,[39] (50 g) and benzene (200 ml) were heated with stirring under reflux for 2 h. The solids were filtered off, washed with hot benzene (3 x 100 ml), the filtrates evaporated and the residue recrystallised (benzene) to yield bisquinone 4 (0.78 g, 15%). m.p. 195-197^{o} (lit[37] m.p. 196-197^{o}). (M^+ required 366, M^+ found 366). ν_{max}^{KBr}: 1680, 1630, 1605 cm^{-1} (cyclohexa-2,5-dien-4-one). δ_H ($CDCl_3$): 7.3-8.1 (4H, quartet, ArH); 6.2-6.8 (7H, m, vinylics); 3.5 (3H, s, $C_6H_4\underline{CH_3}$). δ_C ($CDCl_3$/d6 DMSO): 21.23

(CH_3); 92.13, 103.82 (4 vinylics); 127.72, 129.60, 130.18, 130.96, 134.34, 136.94, 141.22, 146.03, 161.68 (6ArC, 4 vinylics and 2-C-N); 183.75, 185.63 (2C=O).

(b) Aminosulphonamide 69 (5 g, 14 mmol) manganese dioxide (Sedema "FARADISER M", 10 g) and benzene were heated with stirring under reflux for 2 h. The solvent was evaporated and the residual solid was extracted in a soxhlet apparatus with acetone for 8 h. After evaporation of the extract, recrystallisation gave bisquinone 4 (0.58 g, 11%) (from benzene), m.p. 195-197°.

Preparation of N-tosylphenazinone 70

Sulphonamide 3 (5 g, 14 mmol) was oxidised by the following methods:

(a) Heating under reflux with stirring with manganese dioxide (Sedema "FARASIDER M" or prepared by the method of Attenborough et al[40], 25 g) in benzene (200 ml) for 2 h. The solid was filtered off and the solvent evaporated.

(b) Stirring in glacial acetic acid (50 ml) and lead tetra-acetate (5 g) for 2 h. The solution was poured into water (100 ml), extracted with $CHCl_3$ (2 x 50 ml), the organic layer dried ($MgSO_4$) and the solvent evaporated.

(c) Stirring with potassium ferricyanide (2.5 g), hydrogen peroxide (5 g, 30% aqueous solution) and glacial acetic acid (50 ml) for 2 h, pouring into water (50 ml), extraction with chloroform (2 x 50 ml), the organic layer dried ($MgSO_4$) and the solvent evaporated.

(d) Heating under reflux with stirring in benzene (200 ml) containing silver(II) oxide (20 g) for 2 h. The solution was filtered and the filtrate evaporated.

(e) Heating under reflux with stirring with silver picolinate (50 g) and benzene (200 ml) for 2 h, followed by filtration and evaporation.

(f) Stirring with 20% ceric ammonium nitrate[44] on silica (60-120 mesh, 100 g) in CH_2Cl_2 (200 ml) for 1 h, filtration and evaporation.

The organic residues from all these oxidations were shown by t.l.c. (hexane/ethyl acetate 1:1) to consist of five products, with two components dominating the mixture; a red compound of high R_f value and a colourless lower R_f value compound. The residues were combined, dissolved in ethanol (20 ml) and sodium borohydride (excess) was added. After stirring for 0.5 h t.l.c. (same solvents) showed only baseline material and the colourless compound remaining. The colourless compound was isolated by flash chromatography (eluent petroleum/ethyl acetate 1:1) as 10-(toluene-4-sulphonyl)phenazin-2-one 70, m.p. 162-163°. (Found: C, 64.7; H, 4.2; N, 7.8; M^+, 350 $C_{19}H_{14}SO_3N_2$ requires: C, 65.1; H, 4.0; N, 8.0%; M^+, 350). ν_{max}^{KBr}: 1630 cm^{-1} (C=O, weak). δ_H ($CDCl_3$): 7.2-8.3 (11H, m, 3 vinylics and 8ArH); 2.5 (3H, s, $C_6H_4CH_3$). δ_C ($CDCl_3$): 21.69 (CH_3); 120.64, 126.81, 128.40, 129.73, 129.99, 128.53, 130.83, 131.16, 131.42, 132.30, 141.81, 143.76, 145.83, (12Ar, 4 vinylics and 1 C=N); 150.44 (C=O).

Preparation of phenazinone 102

Sulphonamide 92 (1 g, 2.4 mmol) was dissolved in benzene (50 ml); manganese dioxide (Sedema "FARADISER M", 19 g) was added and

the mixture heated at reflux, with stirring, for 1 h. T.l.c. (hexane/ethyl acetate 1:1) showed one predominating product with several minor contaminants. The solids were filtered off, the filtrate evaporated and the residue dissolved in ethanol (20 ml). $NaBH_4$ (5 g) was added and the mixture stirred for 0.5 h. The solvent was evaporated, the residue partitioned between ether and water, the organic layer dried ($MgSO_4$) and evaporated. Crystallisation from hexane/$CHCl_3$ gave 8-trifluoromethyl-10-(toluene-4-sulphonamido)phenazin-2-one 102 (0.26 g, 26%). m.p. 136-137°. (Found: C, 57.0; H, 3.4; N, 6.8; M^+, 418 $C_{20}H_{13}F_3N_2O_3S$ requires: C, 57.4; H, 3.1; N, 6.7; M^+, 418).)) ν_{max}^{KBr}: 1675 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.4-8.7 (10H, m, 7ArH and 3 vinylics); 2.5 (3H, s, CH_3).

Oxidation of amine hydrochloride 97 to dienone 55

Amine hydrochloride 97 (2 g) in benzene (100 ml) was heated under reflux with stirring with active manganese dioxide (25 g) for 2 h. The solids were filtered off and the filtrate evaporated to give spirodienone 55 (0.35 g, 14%). m.p. 175-176° (from $CHCl_3$/hexane) (lit[37] m.p. 175-176°).)) ν_{max}^{KBr}: 1680 cm^{-1} (C=O); the i.r. spectrum was identical with that of an authentic sample. δ_H ($CDCl_3$): 6.2-7.9 (12H, m, 7ArH, 1NH and 4 vinylics); 2.5 (3H, s, $C_6H_4CH_3$).

The acid/base chemistry of an oxidation product from diphenylamine 3

Compound 3 was dissolved in CH_2Cl_2 (150 ml) and to this was added molecular sieves (13X, 25 g) onto which had been evaporated an aqueous solution of potassium permanganate (3 g). The reaction mixture after 12 h stirring was shown by t.l.c. (ethyl acetate/hexane

1:1) to consist of a high R_f value red component and a lower R_f value yellow compound; the latter turned red in ammonia fumes and back to yellow in HCl fumes. Attempted separation by flash chromatography of the mixture led to degradation of both products. It was noted that when the mixture was dissolved in base (yellow compared to red) upon reacidification the yellow compound obtained (Y_2) had a higher R_f than that of the original yellow compound (Y_1). The solvent was decanted and evaporated, giving Y_2 as a light red solid. This solid was dissolved in $CHCl_3$ (50 ml) and extracted with NaOH (2M, 50 ml), and divided into three aliquots.

(a) To one aliquot was added dimethyl sulphate (1 g). After overnight stirring the product was extracted with $CHCl_3$ (2 x 50 ml), washed with NaOH (2M, 2 x 50 ml), the organic layer dried ($MgSO_4$) and evaporation gave a complex mixture of products.

(b) To the second aliquot was added methyl iodide (3 g) in CH_2Cl_2 (30 ml). No reaction occurred after 10 h stirring.

(c) The third aliquot was acidified with HCl (2M), extracted with CH_2Cl_2 (5 x 50 ml). The organic layers were combined, dried ($MgSO_4$), filtered and diazomethane (excess) was added and stirred for 1 h. T.l.c. (hexane/ethyl acetate 1:1) showed 1 red product present only. The solvent was evaporated to give a highly unstable product, which decomposed to a complex mixture after only a few seconds.

Work carried out in Chapter Two

General method for anodic oxidation

Anodic oxidations were carried out using either a Wenking potentiostat model 70TSI or model 30TSI and a standard calomel electrode with a graphite felt anode (5 x 3 cm) and a platinum anode (3 x 2 cm). The one compartment cell (a 250 ml beaker) contained a solution of tetraethylammonium perchlorate (2 g) in acetonitrile (150 ml) and was stirred magnetically. The oxidations were carried out under nitrogen at room temperature. Substrates were added in one portion to an equilibrated, pre-electrolysed anodic cell, at an anodic potential which allowed a current of 20-60 mA to pass. The current was monitored until either the current dropped to background level or until t.l.c. examination indicated that no starting material remained. The cell solution was filtered and evaporated, the residues partitioned between methylene chloride (50 ml) and water (50 ml). The organic layer was washed with water (50 ml), saturated sodium hydrogencarbonate solution (2 x 20 ml) (ie. the starting material was a carboxylic acid) and water (20 ml), dried over $MgSO_4$, filtered and evaporated.

Preparation of 4-arylaminophenoxyacetic acids

To a solution of 4-hydroxy-2'-nitro-4'-trifluoromethyldiphenylamine 87 (7 g, 23 mmol) in dry butanone (80 ml) was added anhydrous K_2CO_3 (3.5 g) and ethyl 2-bromopropanoate (4.6 g, 25 mmol) and the mixture was heated under reflux for 5 h. The solution was poured into water (200 ml) and extracted with ethyl acetate (3 x 100 ml), the organic layers combined, washed with water (2 x 100 ml) and dried

($MgSO_4$). Evaporation yielded ethyl 2-[4-(2'-nitro-4'-trifluoromethylanilino)phenoxy]propanoate 197 (9.3 g, 99%). m.p. 61-62° (from $CHCl_3$/petroleum) (lit[67] m.p. 61-63°). ν_{max}^{KBr}: 3360 cm^{-1} (NH); 1740 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.6 (1H, s, exchangeable with D_2O, NH); 8.4 (1H, s, ArH); 6.8-7.8 (6H, m, ArH); 4.6-5.0 (1H, q, OC<u>H</u>-Me); 3.9-4.4 (2H, q, C<u>H</u>$_2$-CH_3); 1.0-1.4 (6H, m, CH_2-<u>Me</u> and CH-<u>CH_3</u>).

Ester 197 (9.4 g, 23 mmol) was dissolved in methanol (75 ml), 20% aqueous NaOH solution (75 ml) was added and the solution heated under reflux for 1 h. When cool, the solution was acidified with HCl (4M), the resulting solid filtered off to give 2-[4-(2'-nitro-4'-trifluoromethylanilino)phenoxy]propanoic acid 198 (5.2 g, 60%). m.p. 160-161° (from $CHCl_3$/petroleum) (lit[67] m.p. 158-161°). ν_{max}^{KBr}: 3340 cm^{-1} (NH); 3500-2500 (broad OH); 1700 cm^{-1} (C=O). δ_H ($CDCl_3$/d_6 DMSO): 9.6 (1H, s, exchanges with D_2O, OH); 8.8 (1H, s, NH); 8.4 (1H, s, ArH); 6.9-8.0 (6H, m, ArH); 4.5-4.8 (1H, q, OC<u>H</u>-Me); 1.5-1.7 (3H, d, C<u>H</u>$_3$-CH).

<u>4-(2'-Nitro-4'-trifluoromethylanilino)phenoxyacetic acid 200</u>

A mixture of diphenylamine 87 (16 g, 53 mmol), dry butanone (300 ml), anhydrous K_2CO_3 (30 g) and t-butyl bromoacetate (10.4 g, 53 mmol) was heated under reflux for 4 h. The solvent was evaporated and the product partitioned between water (100 ml) and ethyl acetate (100 ml), the organic layer dried ($MgSO_4$) and evaporated to give crude t-butyl ester 201 (22.1 g, 99%). ν_{max}^{film}: 3350 cm^{-1} (NH); 1750 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.5 (1H, s, NH); 7.1-8.5 (7H, m, ArH); 4.5 (2H, s, OC<u>H</u>$_2$); 1.3 (9H, s, 3 x CH_3).

The crude ester 201 (91.7 g, 48 mmol) was dissolved in TFA (20 ml) and left at room temperature for 15 min. Water (50 ml) was

added and the solid filtered off and washed with water. Recrystallisation from ethyl acetate yielded the title acid 200 (8.5 g, 50%). m.p. 148-150° (Found: C, 50.4; H, 3.0; N, 7.6 $C_{15}H_{11}F_3N_2O_5$ requires: C, 50.6; H, 3.1; N, 7.9%). ν_{max}^{KBr}: 3490, 3340 cm^{-1} (OH and NH); 1740 cm^{-1} (C=O). δ_H ($CDCl_3$/d6 DMSO): 9.7 (1H, s, NH); 8.4 (1H, s, ArH); 6.9-7.7 (6H, m, ArH); 6.5 (1H, s, exchangeable with D_2O, OH); 4.65 (2H, s, CH_2-O).

2-Methyl-2-[4-(2'-nitro-4'-trifluoromethylanilino)phenoxy]propanoic acid 202

(a) To a solution of 4-nitrophenol (50 g, 36 mmol) in acetone (360 ml) was added, slowly, ground NaOH (77 g, 1.9 mol) in portions, so that the temperature stayed below 35°. The mixture was brought to reflux and dry $CHCl_3$ (54 ml, 0.67 mol) was added at a rate to maintain reflux, which was continued for a further 4 h. The acetone was evaporated, the residue dissolved in water and extracted with ether (200 ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in boiling saturated sodium hydrogen carbonate (200 ml), charcoal added, boiled for 5 min and filtered. After several charcoal treatments, the basic solution was acidified and the resulting precipitate filtered off to give 2-methyl-2-(4-nitrophenoxy)-propanoic acid 203 (19.37 g, 21%). m.p. 121-123° (from water) (lit[205] m.p. 121-122°). ν_{max}^{KBr}: 2500-3500 cm^{-1} (broad OH); 1720 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-8.2 (4H, ABq, ArH); 1/4 (6H, s, 2 x CH_3).

Nitroacid 203 (10 g, 44 mmol) dissolved in ethyl acetate (100 ml) was catalytically hydrogenated, giving 2-methyl-2-(4-aminophenoxy)propanoic acid 204 (2.2 g, 25%). m.p. 217-219°

(from water) (lit[205] m.p. 217°). ν_{max}^{KBr}: 2000-3100 cm^{-1} (salt bands NH_3^+). δ_H (d6 DMSO): 6.3-6.6 (7H, m, 4ArH and NH_3^+); 2.4 (6H, s, 2 x CH_3).

Amino acid 203 (2 g, 10 mmol) was dissolved in dry THF (100 ml); anhydrous K_2CO_3 (2 g), tetrabutylammonium hydrogen sulphate (0.1 g) and 4-chloro-3-nitrobenzotrifluoride (2.25 g, 10 mmol) were added and heated at reflux, under a stream of nitrogen. No reaction occurred. Replacement solvents of DMF and acetone showed no improvement.

(b) 4-Nitrophenol (40 g, 0.29 mol), dry butanone (400 ml), anhydrous K_2CO_3 (25 g) and ethyl 2-bromo-2-methylpropanoate (56.5 g, 0.29 mol) were heated together under reflux for 6 h. The solids were filtered off and the solvent evaporated. T.l.c. (hexane/$CHCl_3$ 1:1) showed two products which did not separate on distillation. Flash chromatography (eluent petroleum/ethyl acetate 1:1) gave the product of higher R_f value, the other product decomposing on the silica column. Evaporation of the solvent afforded ethyl 2-methyl-2-(4-nitrophenoxy)propanoate (1.7 g, 1.8%). b.p. 133° at 15 mm Hg (lit[205] b.p. 132-166° at 0.4 mm Hg). ν_{max}^{film}: 1750 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-8.2 (4H, ABq, ArH); 4.0-4.4 (2H, q, $C\underline{H}_2$-Me); 1.6 (6H, s, 2 x CH_3); 1.1-1.3 (3H, t, $C\underline{H}_3$-CH_2). Repeat preparation in which butanone was replaced by DMF, acetone and THF, all gave similar results.

(c) 4-Hydroxy-2'-nitro-4'-trifluoromethyldiphenylamine 87 (56 g, 0.19 mol) was reacted with acetone, $CHCl_3$ and NaOH as described for acid 203, giving 2-methyl-2-[4-(2'-nitro-4'-trifluromethylanilino)phenoxy]propanoic acid 202 (23.4 g, 32%).

m.p. 109-110° (from cyclohexane). (Found: C, 53.4, H, 3.9; N, 6.9 $C_{17}H_{15}F_3N_2O_5$ requires: C, 53.1; H, 3.9; N, 7.3%). ν_{max}^{KBr}: 3320 cm^{-1} (NH); 3100 (broad OH); 1705 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.55 (1H, s, exchangeable with D_2O, NH); 8.4 (1H, s, ArH); 7.0-7.6 (7H, m, 6ArH and OH, exchanges with D_2O); 1.6 (6H, s, 2 x CH_3).

4-Arylaminohydrocinnamic acids

(a) Attempted preparation by N-arylation of 4-aminohydrocinnamic acid

To a stirred solution of hydrocinnamic acid (50 g, 0.33 mol) in glacial acetic acid (50 ml) was added fuming nitric acid (100 g) dropwise over a period of 1 h at a temperature of 20-25°. After 3 h at room temperature the mixture was poured into water (1 L), the solid filtered off to give 4-nitrohydrocinnamic acid (25.8 g, 40%). m.p. 162-163° (from ethanol) (lit[265] m.p. 164-165°). ν_{max}^{KBr}: 2500-3300 cm^{-1} (broad OH); 1700 cm^{-1} (C=O). δ_H (d6 DMSO): 9.6 (1H, s, exchangeable with D_2O, OH); 7.3-8.3 (4H, ABq, ArH); 2.4-3.2 (4H, m, $C\underline{H}_2$ $C\underline{H}_2$).

The above acid (10 g, 55 mmol) was hydrogenated yielding 4-aminohydrocinnamic acid 205. m.p. 133-134° (from $CHCl_3$) (lit[265] m.p. 135°). ν_{max}^{KBr}: 2200-3100 cm^{-1} (broad salt NH_3^+); 1630 cm^{-1} (broad COO^-). δ_H ($CDCl_3$/d6 DMSO): 6.5-7.1 (4H, ABq, ArH); 6.5 (3H, s, exchangeable with D_2O, NH_3^+); 2.4-3.0 (4H, m, $C\underline{H}_2$ $C\underline{H}_2$).

(b) Aminoacid 205 (1 g, 6mmol) anhydrous K_2CO_3 (2 g), tetrabutylammonium hydrogen sulphate (0.1 g), dry DMF (50 ml) and 4-chloro-3-nitrobenzotrifluoride (0.13 g, 6 mmol) were refluxed for several hours. No reaction occurred.

3-Methyl-3-[4-(2'-nitro-4'-trifluoromethylanilino)phenyl]butanoic acid

1-Chloro-2-methyl-2-phenylpropane (50 g, 0.29 mol) was added slowly to magnesium (7.4 g) in dry diethyl ether (110 ml) over a 4 h period. The mixture was poured onto solid CO_2 and allowed to warm up to room temperature. The solvent was evaporated and distillation of the residue (180^o at 0.1 mm Hg) gave 3-methyl-3-phenylbutanoic acid (40.3 g, 76%). m.p. 57-58^o (lit[262] m.p. 57^o). ν_{max}^{film}: 2500-3500 cm^{-1} (broad OH); 1700 cm^{-1} (C=O). δ_H ($CDCl_3$): 10.2 (1H, s, exchangeable with D_2O, OH); 6.9 (5H, s, ArH); 2.2 (2H, s, CH_2); 1.1 (6H, s, 2 x CH_3).

The above acid (40.3 g, 0.23 mol) was added to stirred fuming nitric acid (71 ml) at -30^o over 1 h. The temperature of the solution was allowed to rise to 5^o over 1 h and stirring was continued between 0-5^o for 2 h. The mixture was poured onto ice and the solid filtered off, washed with water to yield 3-methyl-3-(4-nitrophenyl)butyric acid (18.0 g, 36%). m.p. 173-174^o (from ethanol/toluene) (lit[263] m.p. 172-174^o). ν_{max}^{KBr}: 2500-3100 cm^{-1} (broad OH); 1700 cm^{-1} (C=O). δ_H ($CDCl_3$/ d6 DMSO): 7.5-8.2 (4H, ABq, ArH); 2.7 (2H, s, CH_2); 1.5 (6H, s, 2 x CH_3).

The above nitroacid (10 g, 45 mmol) was dissolved in dry pyridine (100 ml) containing t-butanol (14.6 ml, 45 mmol). Toluene-4-sulphonyl chloride (9.14 g, 48 mmol) was added and the mixture heated

on a steambath for 2 h. The mixture was poured into ice/water (100 ml), extracted with methylene chloride (3 x 100 ml), the organic layer washed with water (2 x 100 ml), aqueous sodium hydroxide (2M, 3 x 200 ml), hydrochloric acid (2M, 3 x 100 ml), water (100 ml) and dried ($MgSO_4$). Evaporation yielded t-butyl 3-methyl-3-(4-nitrophenyl)butanoate (9.5 g, 76%). m.p. 36-38^{o} (from methanol). (Found: C, 64.6; H, 7.6; N, 5.1 $C_{15}H_{21}NO_4$ requires: C, 64.5; H, 7.5; N, 5.0%).ν_{max}^{KBr}: 1720 cm^{-1} (C=O).δ_H ($CDCl_3$): 7.2-7.9 (4H, ABq, ArH); 2.3 (2H, s, CH_2); 1.2 (6H, s, 2 x CH_3); 1.0 (9H, s, 3 x CH_3).

Nitroester (9.5 g, 34 mmol) was catalytically hydrogenated giving t-butyl 3-methyl-3-(4-aminophenyl)butanoate 209 (7.2 g, 85%). The product decomposed upon heating and chromatography also led to degradation. The low resolution mass spectrum showed a parent ion at 249 a.m.u.ν_{max}^{film}: 3450 and 3360 cm^{-1} (NH_2); 1720 cm^{-1} (C=O).δ_H ($CDCl_3$): 6.5-7.3 (4H, ABq, ArH); 3.5 (2H, s, exchangeable with D_2O, NH_2); 2.4 (2H, s, CH_2); 1.3 (6H, s, 2 x CH_3); 1.2 (9H, s, 3 x CH_3).

Aminoester 209 (7.0 g, 28 mmol), anhydrous K_2CO_3 (4 g), tetrabutylammonium hydrogen sulphate (1 g), 4-chloro-3-nitrobenzotrifluoride (6.3 g, 28 mmol) and dry DMF (150 ml) were heated at reflux for 4 h. The solvent was evaporated and the residue treated several times with charcoal in hot $CHCl_3$ (50 ml). Evaporation gave a gum which was dissolved in hexane and left at 0^{o} for 2 months, yielding orange crystals of t-butyl 3-methyl-3-[4-(2'-nitro-4'-trifluoromethylanilino)phenyl]butanoate (10.6 g, 86%). m.p. 79-80^{o}. (Found: C, 60.4; H, 5.7; N, 6.1 $C_{22}H_{25}F_3N_2O_4$ requires: C, 60.3; H, 5.7; N, 6.4%, M^+, 438.)ν_{max}^{film}: 3340 cm^{-1} (NH); 1720 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.6 (1H, s, exchangeable with D_2O, NH); 8.4 (1H, s, ArH); 7.1-7.6 (6H, m, ArH); 2.3 (2H, s, CH_2); 1.3 (6H, s, 2 x CH_3); 1.0 (9H, s, 3 x CH_3).

The above ester (1.9 g, 4 mmol) was dissolved in TFA (10 ml). After 15 min, water (50 ml) was added and the solid filtered off to give 3-methyl-3-[4-(2'-nitro-4'-trifluoromethylanilino)phenyl]butanoic acid 208 (1.1 g, 67%). m.p. 123-124° (from cyclohexane). (Found: C, 56.7; H, 4.5, N, 6.9 $C_{18}H_{17}F_3N_2O_4$ requires: C, 56.5; H, 4.4; N, 7.3%). M^+, 382.) ν_{max}^{KBr}: 3360 cm^{-1} (NH); 2800-3500 cm^{-1} (broad OH); 1700 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.7 (1H, s, exchanges with D_2O, NH); 8.5 (1H, s, ArH); 7.1-7.6 (6H, m, ArH); 2.7 (2H, s, CH_2); 1.6 (6H, s, 2 x CH_3).

3-Methyl-3-(4'-toluene-4-sulphonamidophenyl)butanoic acid 210

Amino ester 209 (9.0 g, 47 mmol) was treated with TFA (50 ml) as described for acid 208 and tosylated at pH7 giving the title acid 210 (9.7 g, 60%). m.p. 154-155° (from $CHCl_3$/hexane). (Found: C, 62.3; H, 6.0; N, 4.0 $C_{18}H_{21}NO_4S$ requires: C, 62.2; H, 6.1; N, 4.0%).) ν_{max}^{KBr}: 3240 cm^{-1} (NH); 2500-3300 cm^{-1} (broad OH); 1700 cm^{-1} (C=O). δ_H($CDCl_3$/d_6 DMSO): 9.5-9.0 (2H, 2s, both exchangeable with D_2O, OH and NH); 7.0-7.7 (8H, m, ArH); 2.7 (2H, s, CH_2); 2.4 (3H, s, CH_3 Ar); 1.5 (6H, s, 2 x CH_3).

General method for reduction of acids to alcohols

To a solution of the acid (5 g) in dry toluene (50 ml), borane methyl sulphide complex (2M in THF, 2 molar equivalents) was added and the mixture was stirred for 1 h. Methanol (50 ml) was added dropwise, the solvents were evaporated and the residue recrystallised.

By this method were prepared the following alcohols:

2-[4-(2'-nitro-4'-trifluoromethylanilino)phenoxy]ethanol 212 (61%). m.p. 103-104° (from cyclohexane/$CHCl_3$). (Found: C, 52.6; H, 3.7; N, 7.8 $C_{15}H_{13}F_3N_2O_4$ requires: C, 52.6; H, 3.8; N, 8.2%), M^+, 342. ν_{max}^{KBr}: 3360 cm^{-1} (NH); 3200-3600 cm^{-1} (broad OH). δ_H ($CDCl_3$): 9.6 (1H, s, exchanges with D_2O, NH); 8.5 (1H, s, ArH); 6.9-7.4 (6H, m, ArH); 4.0-4.2 (4H, m, $C\underline{H}_2$-$C\underline{H}_2$); 2.0 (1H, s, exchangeable with D_2O, OH).

2-[4-(2'-Nitro-4'-trifluoromethylanilino)phenoxy]propanol 213 (98%). m.p. 80-81° (from toluene/petroleum). (Found: C, 54.2; H, 4.0; N, 7.7% $C_{16}H_{15}F_3N_2O_4$ requires: C, 54.0; H, 4.2; N, 7.8%). ν_{max}^{KBr}: 3350 cm^{-1} (NH); 3200-3600 cm^{-1} (broad OH). δ_H ($CDCl_3$): 9.6 (1H, s, exchangeable with D_2O, NH); 8.5 (1H, s, ArH); 6.9-7.6 (6H, s, ArH); 4.4-4.6 (1H, q, C$\underline{H}$-Me); 3.6-3.7 (2H, d, $C\underline{H}_2$-CH); 2.3 (1H, s, exchanges with D_2O, OH); 1.2-1.4 (3H, d, $C\underline{H}_3$-CH).

2-Methyl-2-[4-(2'-nitro-4'-trifluoromethylanilino)phenoxy]-propanol 214 (85%). m.p. 66-68° (from toluene/petroleum). (Found: C, 55.1; H, 5.0; n, 7.2 $C_{17}H_{17}F_3N_2O_4$ requires: C, 55.1; H, 4.6; N, 7.6%). ν_{max}^{KBr}: 3340 cm^{-1} (NH); 3200-3700 cm^{-1} (broad OH). δ_H ($CDCl_3$: 9.6 (1H, s, exchangeable with D_2O, NH); 8.5 (1H, s, ArH); 7.0-7.6 (6H, m, (ArH); 3.6 (2H, s, $C\underline{H}_2$); 2.8 (1H, s, exchanges with D_2O, OH); 1.4 (6H, s, 2 x CH_3).

3-Methyl-3-[4-(2'-nitro-4'-trifluoromethylanilino)phenyl]-butanol 215 (30%) as a gum. The product contained a small quantity of impurity of very similar R_f value which prevented successful elemental analysis. M^+, 368. ν_{max}^{film}: 3350 cm^{-1} (NH); 3200-3600 cm^{-1} (broad OH). δ_H ($CDCl_3$): 9.7 (1H, s, exchangeable with D_2O, NH); 8.5 (1H, s, ArH); 7.1-7.6 (6H, m, ArH); 3.4-3.6 (2H, t, CH_2-$C\underline{H}_2$-C); 2.2 (1H, s, exchanges with D_2O, OH); 1.8-2.1 (2H, t, CH_2-$C\underline{H}_2$-O); 1.35 (6H, s, 2 x CH_3).

4-N-Perfluoroarylaminohydrocinnamic acids

Aniline (0.35 g, 4 mmol) was refluxed with octafluorotoluene (1.0 g, 4 mmol) in dry CH_2Cl_2 (10 ml), anhydrous K_2CO_3 (1 g) and tetrabutylammonium hydrogen sulphate (0.1 g) for 4 h as described by Jarman and McCague.[264] T.l.c. (hexane/$CHCl_3$ 1:1) showed one product spot only. The solvent was evaporated and the product separated between ether (100 ml) and water (100 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The t.l.c. of the mixture after 2 h showed several product spots.

Ester 209 (7.0 g, 28 mmol) was reacted with octafluorotoluene (3.99 ml, 28 mmol) as described above. Similar results were given.

General procedure for oxidation with lead tetraacetate

To a solution of acid or alcohol (1 g) in glacial acetic acid (10 ml) was added lead tetraacetate (2 g) and the mixture stirred for 1 h. Water (50 ml) was added and the reaction was extracted with ether (3 x 20 ml), the combined ether layer washed with saturated sodium hydrogencarbonate solution until effervescence ceased, then with water (2 x 30 ml), dried ($MgSO_4$) and evaporated. Recrystallisation yielded the pure spiro-lactone or ketal.

General method for manganese dioxide oxidations

The acid or alcohol (1 g) was dissolved in benzene (20 ml) and heated under reflux with manganese dioxide (Sedema "FARADISER M", 5 g) for 1 h. The solids were filtered off and the solvent evaporated. Recrystallisation yielded the spiro-lactone or ketal.

Using one of the oxidatative methods the spirodienones listed in TABLE 3 were prepared.

TABLE 3

Starting Material	Product	% Yield $Pb(OAc)_4$	% Yield MnO_2	Anode	m.p.	$\nu_{cm^{-1}}$	δ_H
212	218	49	-	90	132-133° (cyclohexane/$CHCl_3$)	-	8.4, 7.8-7.9, 6.9-7.0, 6.4, 4.1
198	219	17	-	56	113-114° (hexane/$CHCl_3$)	1810	8.3, 7.7-7.9, 6.8-7.0, 6.4, 4.0-4.8, 1.5-1.6
202	221	20	-	55	123-124° (toluene/hexane)	1805	8.3, 7.7-7.9, 6.8-7.0, 6.4, 1.6
213	222	mixture	-	50	-	-	8.3, 7.7-7.8, 6.9-7.1, 6.4, 4.1-4.5, 3.5-3.7, 1.3-1.4
214	223	mixture	-	60	-	-	8.3, 7.7-7.9, 6.9-7.1, 6.4, 1.2
208	224	46	-	80	-	1790	8.3, 6.9-7.9, 6.5, 2.6, 1.1
210	225	90	90	50	166-167° (hexane/$CHCl_3$)	1790	6.3-8.0, 2.6, 2.45, 1.1

Compound (Molecular Formula)		Found (%) C	H	N	Required (%) C	H	N
218	($C_{15}H_{11}F_3N_2O_4$)	52.9	3.2	7.7	52.9	3.2	8.2
219	($C_{16}H_{11}F_3N_2O_5$)	52.7	2.7	7.6	52.2	3.0	7.6
221	($C_{17}H_{13}F_3N_2O_5$)	53.5	3.5	7.1	53.4	3.4	7.3
225	($C_{18}H_{18}NO_4S$)	62.4	5.2	3.8	62.6	5.5	4.1

222, 223 and 224 were too unstable for analysis.

Hydrolysis of spirolactone 219

After standing for two weeks lactone 219 was shown by i.r. and proton n.m.r. spectroscopy to be identical with quinonimine 220 (which was prepared independently in 20% yield by manganese dioxide oxidation of diphenylamine 87). m.p. 113-114^{o} (from petroleum). (Found: C, 52.5; H, 2.1; N, 9.8 $C_{15}H_7F_3N_2O_3$ requires: C, 52.7; H, 2.4; N, 9.5%). ν_{max}^{KBr}: 1650 cm^{-1} (quinone). δ_H ($CDCl_3$): 8.4 (1H, s, ArH); 6.5-8.2 (6H, m, 2ArH and 4 vinylics).

Reduction of a spiroketal

Spiroketal 223 (1 g, 3 mmol) was dissolved in dry ethanol (10 ml), $NaBH_4$ (2 g) was added and the reaction was stirred for 1 h. Water (50 ml) was added and the product extracted into ether (2 x 50 ml), washed with water and dried ($MgSO_4$). Evaporation and recrystallisation gave alcohol 214 (91%), the i.r. spectrum of which was superimposable with that of a previously prepared sample.

Work carried out in Chapter Three

Optimisation of the conversion of nitroarene to spirocyclohexadienone

To a solution of 4-nitrohydrocinnamic acid (28.5 g, 0.15 mol) in dry pyridine (280 ml) was added t-butanol (13.8 ml, 0.15 mol) and toluene-4-sulphonyl chloride (27.7 g, 0.15 mol) and the reaction was heated overnight on a steambath. The mixture was poured onto ice/HCl (4M, 200 ml), the product extracted into CH_2Cl_2 (2 x 300 ml), washed with NaOH (2M, 2 x 300 ml), HCl (2M, 2 x 300 ml), dried ($MgSO_4$). evaporation gave t-butyl 4-nitrohydrocinnamate 313 (30.2 g, 86%). m.p. 53-54° (from methanol) (lit[198] m.p. 53-54°). ν_{max}^{KBr}: 1735 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.5-8.3 (4H, ABq, ArH); 3.05 (2H, t, CH_2-Ar); 2.6 (2H, t, CH_2CO); 1.4 (9H, s, 3 x CH_3).

Modification of reaction conditions

Nature of metal

To hot (100°) conc. H_2SO_4 (200 ml) containing 3 drops of conc. HNO_3 was added cautiously zinc powder (100 g). After the addition, mechanical stirring was continued for 10 minutes, the acid decanted off and distilled water was added and allowed to stand for 30 minutes. The solid was filtered off under argon, dried in a vacuum desiccator and stored under argon.

Ester 313 (1 g, 4 mmol) was dissolved in TFA (5 ml) under N_2 at 5°. With stirring the activated zinc powder (0.6 g, 9 mmol) was added at such a rate that the temperature did not rise above 20°. The mixture was stirred for 1 h then poured into saturated sodium hydrogen carbonate solution (200 ml) and extracted with ethyl acetate (2 x 100 ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in

CH_2Cl_2 (10 ml) and passed down a silica column (5 g, 60-120 mesh). Evaporation of the solvent, followed by trituration in propan-2-ol gave spirodienone 19 (0.12 g, 18%). m.p. 100° (lit[189] m.p. 100°). ν_{max}^{KBr}: 1770 cm^{-1} (C=O, lactone); 1675 cm^{-1} (C=O, dienone). δ_H: ($CDCl_3$); 6.95 (2H, d, vinylics); 6.25 (2H, d, vinylics); 2.8 (2H, t, CH_2-vinylics); 2.4 (2H, t, CH_2COO).

The above experiment was repeated, with the zinc being replaced by other metals (0.9 mmol). After the extraction with ethyl acetate the hydrogencarbonate solution was neutralised with dilute hydrochloric acid, and the precipitated 4-aminohydrocinnamic acid 317 collected.

Metal	Zinc Amalgam	Iron powder	Tin powder	Aluminium powder	Magnesium powder	Magnesium granular
% Yield of acid 317	complex mixture	72	75	68	-	74

Magnesium powder yielded lactone 19 (0.1 g, 16%). m.p. 106°.

Reaction temperature

Ester 313 (1 g, 4 mmol) was reacted with active zinc (0.6 g, 9 mmol) and TFA (5 ml) as described previously, at various temperatures.

Temp °C	-10	0	10	20	30	40-50	60-70
% Yield lactone 19	0	0	0	15	18	18	complex mixture
% Yield acid 317	67	70	61	30	20	0	-

Addition sequence

To stirred dry active zinc (0.6 g), 9 mmol under N_2 at 30^o was added, in one aliquot, a solution of ester 313 (1 g, 4 mmol) in TFA (5 ml) and the mixture was stirred for 1 h. After treatment as described previously the reaction gave lactone 19 (0.6 g, 9%), m.p. 106^o.

With inert solvents

To a stirred solution of ester 313 (1 g, 4 mmol) in dry CCl_4 (5 ml) was added TFA (5 ml) followed by active zinc (0.6 g, 9 mmol), the temperature being kept at 30^o by the use of an ice-bath. The products were isolated as described previously, to give a complex mixture. Similar results were obtained by using hexafluorobenzene or refluxing chlorotrifluoromethane in place of CCl_4.

Variation in acid

Ester 313 (1 g, 4 mmol) was dissolved in TFSA (5 ml) and active zinc (0.6 g, 9 mmol) was added under N_2. The reaction was stirred, at 30^o, for 1 h to give lactone 19 (0.12 g, 18%), m.p. 106^o. Mixtures of TFA/TFSA gave identical results.

Reaction time

Ester 313 (1 g, 4 mmol) was reacted with TFA/zinc, with the reaction being stopped at various times.

Time/min	2	immediately after exotherm ceased	30	60
% Yield of lactone 19	10	18	18	18

Reaction of other 4-nitrohydrocinnamates with zinc/TFA

Methyl, ethyl and benzyl esters of 4-nitrohydrocinnamic acid

A solution of 4-nitrohydrocinnamic acid 317 (10 g, 0.05 mol) in methanol (100 ml), that had been saturated with HCl gas, was stirred for 1 h, the solvent evaporated to give methyl 4-nitrohydrocinnamate 318 (3.24 g, 30%), m.p. 76-77° (from ethanol) (lit[263] m.p. 76-77°). ν_{max}^{KBr}: 1730 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.2-8.2 (4H, ABq, ArH); 3.5 (3H, s, CH_3-O); 3.1 (2H, t, CH_2-Ar); 2.7 (2H, t, CH_2COO). Similarly was prepared ethyl 4-nitrohydrocinnamate 319 (1 g, 9%), m.p. 33-34° (from ethanol) (lit[265] m.p. 33°). ν_{max}^{KBr}: 1735 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.1-8.0 (4H, ABq, ArH); 3.1 (2H, q, CH_2-CH_3); 2.6 (2H, t, CH_2-Ar); 3.0 (2H, t, CH_2-COO); 2.2 (3H, t, CH_3-CH_2).

Acid 317 (10 g, 0.05 mol) in CH_2Cl_2 (100 ml) was added to dicyclohexylcarbodiimide (10.55 g, 0.05 mol) and the mixture was stirred for 1 h. Benzyl alcohol (5.5 ml, 0.05 mol) and 4-dimethylaminopyridine (0.62 g, 5 mmol) were added and stirring was continued for 12 h. The precipitated urea was filtered off and filtrate was washed with water (3 x 100 ml) acetic acid solution (5%, 3 x 100 ml) and water (3 x 100 ml). Drying ($MgSO_4$) and evaporation gave benzyl 4-nitrohydrocinnamate 320 (8.0 g, 57%), m.p. 55-56° (from ethanol). (Found: C, 67.4; H, 5.3; N, 4.9 $C_{16}H_{15}NO_4$ requires: C, 67.4; H, 5.3; N, 4.9%). ν_{max}^{KBr}: 1730 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.1-8.1 (9H, m, ArH); 5.05 (2H, s, CH_2-Ph); 2.5-3.2 (4H, m, CH_2CH_2).

Esters 318, 319, 320 were reacted with zinc/TFA, as described previously, to give the corresponding amino esters:

Starting Ester	Product	% Yield	m.p.	lit[265] m.p.	KBr max	H
318	321	23	56-57°	56-57°	3425, 3320, 1730	6.5-7.0, 3.6,3.5, 2.4-2.9
319	322	29	33-34°	34°	3420 3320 1725	6.4-6.8, 3.8,3.45 2.4-2.9, 1.7-1.8
320	323	contam-inated product			superimposable on spectrum of an authentic sample	

Preparation of authentic benzyl amino ester 323

Iron filings (1.7 g, 30 mmol) and water (1.2 ml) were heated together on a steambath. Ester 320 (2 g, 7.2 mmol) and glacial acetic acid (1.74 ml, 30 mmol) were added and the mixture was stirred for 1 h. A solution of NaOH (1.3 g) in water (1 ml) was added and the solution filtered. The iron filings were boiled in benzene (10 ml) and filtered. The filtrates were combined, extracted with ether (3 x 20 ml), the organic layers combined and dried ($MgSO_4$). Evaporation and distillation gave benzyl 4-aminohydrocinnamate 323 (0.38 g, 21%), b.p. 131-132° at 0.5 mm Hg. (Found: C, 75.2; H, 6.6; N, 5.0 $C_{16}H_{17}NO_2$ requires: C, 75.3; H, 6.6; N, 5.5%). ν_{max}^{Film}: 3450 and 3380 cm^{-1} (NH_2); 1725 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.2 (5H, s, benzyl ArH); 6.5-7.0 (4H, ABq, ArH); 5.1 (2H, s, CH_2-Ph); 3.5 (2H, s, exchanges with D_2O, NH_2); 2.4-2.9 (4H, m, CH_2-CH_2).

Reaction of ester 313 with TFA

Ester 313 (1 g, 4 mmol) was dissolved in TFA (5 ml). T.l.c. (ethyl acetate/hexane 1:2) after 24 h showed no change. Water (10 ml) was added giving acid 317 (0.78 g, 96%).

Preparation of esters 324-327

The following esters were prepared by reaction with acid 317:

Ester	% Yield	Preparative reference	ν_{max} cm^{-1}	δ_H	M^+
324	68	193	1740	7.35-8.2, 4.8, 2.6-3.4	326
325	77	194	1735	7.3-8.2, 5.1, 2.5-3.2, 2.1	255
326	34	195	1740	7.3-8.1, 2.4-4.2	279

The reaction of acid 317 with 3,4,5-trimethoxybenzyl alcohol in the presence of DDQ, as described for ester 323, gave 3,4,5-trimethoxybenzyl 4-nitrohydrocinnamate 327 (43%), m.p. 72-73° (from ethanol). (Found: C, 61.3; H, 5.7; N, 3.7 $C_{19}H_{21}NO_7$ requires: C, 60.8; H, 5.6; N, 3.7%). ν_{max}^{KBr}: 1725 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.3-8.25 (4H, ABq, ArH); 6.6 (2H, s, benzyl ArH); 5.0 (2H, s, $ArCH_2$); 3.9 (9H, s, 3 x CH_3O); 2.6-3.4 (4H, m, CH_2CH_2).

Reaction of esters 324-327 with TFA/zinc

Esters 324-327 were treated with active zinc/TFA as described previously, giving complex mixtures, in which lactone 19, could not be identified by t.l.c. or infra-red spectroscopy.

Reaction of more complex esters

Naphthoic acid 328

Sodium metal (35 g, 1.52 mol) was added as quickly as possible to a solution of 1-naphthoic acid (10 g, 58 mmol) in boiling ethanol (260 ml). After the addition, heating was continued until all the sodium dissolved. After cooling, water (23 ml) and H_2SO_4 (10 N, 100 ml) were added and the reaction was left at 4^o overnight. The precipitated sodium sulphate was filtered off and the filtrate concentrated. The aqueous residue was acidified with excess H_2SO_4 (10 N) and left overnight. The solid was collected to give 1,2,3,4-tetrahydro-1-naphthoic acid 331 (7.5 g, 74%), m.p. 84-85^o (from ethyl acetate) (lit[196] m.p. 84-85^o). ν_{max}^{KBr}: 3300-2100 (broad OH); 1680 cm^{-1} (C=O). δ_H ($CDCl_3$): 12.25 (1H, s, exchangeable with D_2O, OH); 7.05 (4H, s, ArH); 3.75 (1H, t, 1-CH); 2.7 (2H, t, 4-CH_2); 1.55-2.2 (4H, m, 2-CH_2, 3-CH_2).

Acid 331 (10 g, 61 mmol), toluene-4-sulphonyl chloride (10.8 g, 56 mmol), t-butanol (5.75 ml, 61 mmol) and dry pyridine (200 ml) were mixed together and heated on a steambath for 8 h. The mixture was poured onto ice/HCl (4M, 400 ml) and extracted with CH_2Cl_2 (3 x 200 ml). The organic layers were washed with NaOH (2M, 3 x 200 ml), HCl (2M, 3 x 200 ml) and water (2 x 200 ml) and dried ($MgSO_4$). Evaporation and distillation afforded t-butyl 1,2,3,4-tetrahydro-1-naphthoic acid 332 (7.8 g, 59%), b.p. 132^o at 2.0 mm Hg (lit[196] b.p. 84-86^o at 0.2 mm Hg). ν_{max}^{Film}: 1730 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.0 (4H, m, ArH); 3.65 (1H, t, 1-CH); 2.65-2.8 (2H, m, 4-CH_2); 1.7-2.2 (4H, m, 2-CH_2, 3-CH_2); 1.44 (9H, s, 3 x CH_3).

To diisopropylamine (5.2 ml, 51 mmol) under dry N_2 was added n-butyl lithium (2.5M in hexane, 12.4 ml, 51 mmol) and the mixture was stirred for 1 h at 0^{o}. The gummy solid was diluted with dry THF (100 ml) and it was added to a solution of ester 332 (8 g, 34 mmol) in dry THF (100 ml) at -78^{o}. After stirring for 10 min a solution of 4-nitrobenzyl iodide (9.2 g, 34 mmol) in dry THF (100 ml) was added and the mixture was stirred for 1 h. The temperature of the reaction was allowed to rise to ambient, water (300 ml) was added and the mixture was extracted with ether (3 x 200 ml). The ether layer was separated, washed with water (3 x 300 ml), dried ($MgSO_4$) and evaporated to give t-butyl 1,2,3,4-tetrahydro-1-(4-nitrobenzyl)-1-naphthoate 328 (12.4 g, 98%), m.p. 74-75^{o} (from methanol) (lit[196] m.p. 74-75^{o}). ν_{max}^{KBr}: 1720 cm^{-1} (C=O); δ_H ($CDCl_3$): 8.0-8.2 (2H, d, ArH ortho to NO_2); 7.1-7.5 (6H, m, ArH); 2.6 (2H, broad t, 4-CH_2); 2.4 (2H, ABq, benzyl CH_2); 1.6-2.0 (4H, m, 2-CH_2, 3-CH_2); 1.6 (9H, s, 3 x CH_3).

Reaction of naphthoate 333 (1 g, 3 mmol) with TFA/zinc yielded t-butyl 1-(4-aminobenzyl)-1,2,3,4-tetrahydro-1-naphthoate 333 (0.37 g, 40%), b.p. 180-185^{o} at 0.3 mm Hg (lit[196] b.p. 175-182^{o} at 0.2 mm Hg). ν_{max}^{Film}: 3460 and 3360 cm^{-1} (NH_2); 1720 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.0-7.6 (4H, m, ArH); 6.7 (2H, d, ArH meta to NH_2); 6.35 (2H, d, ArH ortho to NH_2); 3.4 (2H, broad s, exchangeable with D_2O, NH_2); 3.15 (2H, ABq, benzyl CH_2); 1.4 (9H, s, 3 x CH_3).

Isoquinoline 334

Benzyl ester 339 (5 g, 14 mmol), prepared by the route described by Hadfield,[196] was dissolved in dry DMF (200 ml) under dry N_2 at 0^{o}. Sodium hydride (80% in oil, 2.9 g, 97 mmol) was added and

the mixture was stirred for 30 min. A solution of 4-nitrobenzyl iodide (3.8 g, 14 mmol) in dry DMF (50 ml) was added and stirring was continued for 30 min. The mixture was poured onto ice/water (200 ml), extracted with ethyl acetate (3 x 200 ml), the organic layers combined, washed with water (2 x 200 ml), dried ($MgSO_4$) and evaporated. Purification by flash chromatography (eluent petroleum/ethyl acetate 3:1) gave benzyl 2-trimethylacetyl-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 340 (6.8 g, 99%) as a red gum. (Found: C, 71.3;, H, 6.4; N, 5.6 $C_{29}H_{30}N_2O_5$ requires: C, 71.6; H, 6.2; N, 5.8). $M^+ - CH_2-C_6H_4NO_2$, 350. ν_{max}^{Film}: 1735 cm^{-1} (C=O ester); 1630 cm^{-1} (C=O amide). δ_H ($CDCl_3$): 6.7-7.9 (13H, m, ArH); 3.5-5.3 (4H, m, $C\underline{H}_2Ph$ and $C(3)H_2$); 2.5-2.7 (2H, t, $C(4)H_2$); 1.15 (9H, s, 3 x CH_3).

Ester 340 (2 g, 4 mmol) was refluxed in 33% HBr in glacial acetic acid (10 ml) for 2 h, poured onto ice/water (20 ml), neutralised with saturated sodium hydrogen carbonate solution and filtered, giving insoluble amino acid 1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 341 (1.1 g, 86%). ν_{max}^{KBr}: 2100-3600 cm^{-1} (salt bands NH_2^+); 1620 cm^{-1} (broad C=O). δ_H (TFA): 7.4-8.3 (10H, broad m, 8ArH, NH_2^+); 4.2 (2H, s, $C\underline{H}_2Ph$); 3.9 (2H, broad m, C(3)H); 3.3 (2H, broad m, C(4)H).

Acid 341 would not react to form a t-butyl ester.

Diphenylether 342

To t-butanol (1.86 ml, 19 mmol) dissolved in dry THF (40 ml) at 0^o was added with stirring under N_2 ester 345 (5 g, 18 mmol) followed by n-butyl lithium (1.6 M in hexane, 12.35 ml, 19 mmol) and the mixture was left overnight at 0^o. The product was partitioned between

ether (100 ml) and water (100 ml), the ether layer dried ($MgSO_4$). Evaporation and flash chromatography (eluant ethyl acetate/petroleum 1:7) gave t-butyl 4'-nitrodiphenylether-2-carboxylate 342 (2.84 g, 49%), m.p. 105-106° (from ethanol). (Found: C, 65.1; H, 5.5; N, 4.4 $C_{17}H_{17}NO_5$ requires: C, 64.8; H, 5.4; N, 4.4%). M^+, 3.15. ν_{max}^{KBr}: 1715 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-8.2 (8H, m, ArH); 1.3 (9H, s, 3 x CH_3).

Reaction of 342 and 345 with TFA/zinc

Both esters 342 and 345 when reacted with TFA/zinc gave complex product mixtures.

Hydroxylamines and azides derived from hydrocinnamic acid

To a solution of nitroester 313 (1 g, 4 mmol) in ethanol (5 ml) and CH_2Cl_2 (5 ml), cooled to 0°. Raney nickel (W4, 0.025 g) was added, followed dropwise by hydrazine hydrate (0.32 ml, 4 mmol). After 40 minutes stirring the catalyst was filtered off, the solvent evaporated to give t-butyl 4-hydroxyaminohydrocinnamate 314 (0.53 g, 57%) as an orange gum. ν_{max}^{Film}: 3100-3700 cm^{-1} (broad NHOH), 1730 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.7-7.5 (4H, ABq, ArH); 4.9 (1H, s, exchangeable with D_2O, OH); 2.5-3.0 (5H, m, broad NH, CH_2CH_2); 1.5 (9H, s, s x CH_3).

Reaction of hydroxylamine 314 with benzoyl chloride in a two-phase system of benzene and saturated sodium hydrogen carbonate, failed to give any product. Similarly, toluene-4-sulphonyl chloride and DCC/benzoic acid gave no product.

Ester 313 (11 g, 46 mmol) was catalytically hydrogenated at 3 atm H_2 to give t-butyl 4-aminohydrocinnamate 348 (7.84 g, 82%), m.p. 59-60° from petroleum (lit[189] m.p. 59-60°). ν_{max}^{KBr}: 3450, 3370 cm^{-1} (NH_2); 1725 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.6-7.2 (4H, ABq, ArH); 3.8 (2H, s, exchangeable with D_2O, NH_2); 2.5-3.1 (4H, m, CH_2CH_2); 1.5 (9H, s, 3 x CH_3).

Amino ester 348 (5 g, 22 mmol) was dissolved in HCl (1M, 100 ml) and cooled to 0°. After 5 min a white precipitate was observed. A solution of sodium nitrite (1.7 g, 24 mmol) in water (25 ml) was added in portions, the mixture was stirred for 30 min and sodium azide (1.6 g, 24 mmol) in water (25 ml) was added. After 5 min stirring $CHCl_3$ (25 ml) was added and the mixture stirred for a further 1 h. More $CHCl_3$ (100 ml) was added and the organic layer isolated, dried (Na_2SO_4) and evaporated. The crude t-butyl 4-azidohydrocinnamate 349 (5.1 g, 87%) was stored at 4° until needed. ν_{max}^{Film}: 2130 cm^{-1} (N_3); 1740 cm^{-1} (C=O).

Reactions of hydroxylamine 314 and azide 349

Hydroxylamine 314 when reacted with TFA/zinc or TFSA/zinc gave a complex product mixture. No reaction occurred when hydroxylamine 314 was reacted with conc. H_2SO_4.

Azide 349 was reacted with zinc/TFA giving lactone 19 (14%), m.p. 106°

t-Butyl 4'-azidodiphenylether-2-carboxylate 351

Ester 342 (3 g, 9.5 mmol) was catalytically hydrogenated, yielding t-butyl 4'-aminodiphenylether-2-carboxylate 350 (1.86 g, 69%), m.p. 88-89° (from cyclohexane). (Found: C, 71.7; H, 6.7; N, 4.7

$C_{17}H_{19}NO_3$ requires: C, 71.6; H, 6.7; N, 4.9%) M^+, 285. ν_{max}^{KBr}: 3420 and 3360 cm^{-1} (NH_2), 1680 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-7.9 (8H, m, ArH); 3.45 (2H, s, exchangeable with D_2O, NH_2); 1.5 (9H, s 3 x CH_3).

Amine 350 was reacted with sodium azide, as described for azide 349, giving crude t-butyl 4'-azidodiphenylether-2-carboxylate 351 (1.47 g, 75%) as a gum. ν_{max}^{Film}: 2105 cm^{-1} (N_3); 1710 cm^{-1} (C=O).

Azide 351 (1 g, 3.2 mmol) was reacted with zinc/TFA giving a product mixture (0.13 g) which was shown by t.l.c. (ethyl acetate/hexane 1:1) to consist of a major component and two minor byproducts of similar R_f value. ν_{max}^{KBr}: 1750 cm^{-1} (lactone C=O); 1680 cm^{-1} (dienone C=O).

4-(Toluene-4-sulphonamido)diphenylether-2-carboxylic acid 352 was anodically oxidised, and the crude oxidation product hydrolysed by passage down an alumina column, giving spirolactone 343. The infra-red spectrum of the product contained peaks at 1750 cm^{-1} (lactone) and 1680, 1640 cm^{-1} (dienone) and was identical with that of the crude product from acid treatment of azide 351.

Work described in Chapter Four

Preparation of 2-methyl-2-phenoxypropanamide 381

2-Methyl-2-phenoxypropanoic acid (10 g, 55 mmol) was heated under reflux with thionyl chloride (80 ml) for 1 h. The excess thionyl chloride was distilled off, the crude acid chloride dissolved in dry p-dioxan (100 ml) and cooled. Excess ammonia (d 1.88) in p-dioxan was added and the mixture was stirred at room temperature for 5 h. Evaporation and recrystallisation of the residue gave the title amide 381 (6.85 g, 63%), m.p. 112-113^{o} (from toluene/hexane) (lit^{205} m.p. 112-113^{o}). ν_{max}^{KBr}: 3450, 3250 cm^{-1} (NH_2); 1660 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.5-7.3 (7H, m, 5ArH and NH_2 which exchanges with D_2O); 1.5 (6H, s, 2 x CH_3).

Smiles rearrangement of amide 381

To a solution of amide 381 (2.0 g, 10 mmol) in DMPU (20 ml) was added sodium hydride (80% in oil, 0.4 g, 11 mmol) and the mixture was heated on a steambath for 1 h. The solution was poured into water (500 ml) and extracted with ethyl acetate (500 ml). The organic layer was washed with water (3 x 500 ml), dried ($MgSO_4$) and evaporated to give N-phenyl-2-hydroxy-2-methylpropanamide 382 (1.6 g, 80%), m.p. 131-133^{o} (from toluene) (lit^{205} m.p. 131-133^{o}). ν_{max}^{KBr}: 3240 cm^{-1} (OH, NH); 1650 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.1 (1H, s NH); 7.0-7.7 (5H, m, ArH); 5.3 (1H, s, exchangeable with D_2O, OH); 1.5 (6H, s, 2 x CH_3).

General method for the Smiles rearrangement of aryloxyamides

To a solution of the aryloxyamide (1 g) in dry DMPU (1 ml) and dry DMF (10 ml), was added sodium hydride (1.1 mol eq.) and the

mixture was heated on a steambath for 1 h. The solution was poured into water (400 ml) and extracted with ethyl acetate (400 ml), the organic layer washed with water (3 x 500 ml), dried ($MgSO_4$) and evaporated. Recrystallisation or distillation yielded pure anilide.

Preparation of 2-bromo-2-methylpropanamide 392

To bromoisobutyryl bromide (11 ml, 89 mmol) in petroleum (250 ml) at 0^{o} was added ammonia (d 0.88, 40 ml) and the mixture was stirred for 30 min. The petroleum was evaporated and the product partitioned between ethyl acetate (100 ml) and the aqueous residue. The organic layer was dried ($MgSO_4$) and evaporated giving the title bromoamide 392 (7.1 g, 48%), m.p. 147-148^{o} (from $CHCl_3$/petroleum) (lit[205] m.p. 147-148^{o}).

Preparation of phenoxypropanamides 387, 389, 393 - 407, 519 and 520

The appropriate phenol (2 g) was stirred in dry p-dioxan (20 ml) with sodium hydride (80% in oil, 1.1 mol eq.) for 1 h. Bromoisobutyramide 392 (1.0 mol eq.) was added and the reaction mixture heated on a steambath for 4 h. After cooling the precipitated sodium bromide was filtered off and the filtrate evaporated. To the residue was added ice/water (20 ml) and NaOH (1M, 20 ml). Trituration, filtration and recrystallisation gave the following amides:

2-methyl-2-(4-chlorophenoxy)propanamide 387

2-methyl-2-(4-methoxyphenoxy)propanamide 389

2-methyl-2-(4-phenylphenoxy)propanamide 393

2-methyl-2-(1-naphthoxy)propanamide 394

2-methyl-2-(2-naphthoxy)propanamide 395

2-methyl-2-(5,6,7,8-tetrahydro-2-naphthoxy)propanamide 396

2-methyl-2-(4-methylphenoxy)propanamide 397

2-methyl-2-(2-methoxyphenoxy)propanamide 398

2-methyl-2-(2-fluorophenoxy)propanamide 399

2-methyl-2-(2-chlorophenoxy)propanamide 400

2-methyl-2-(2-bromophenoxy)propanamide 401

2-methyl-2-(2-iodophenoxy)propanamide 402

2-methyl-2-(2-phenylphenoxy)propanamide 403

2-methyl-2-(2-dibenzofuranoxy)propanamide 404

2-methyl-2-(8-quinolinoxy)propanamide 405

2-methyl-2-(3-carbomethoxyphenoxy)propanamide 406

7-Hydroxycoumarin (10 g, 62 mmol) was catalytically hydrogenated at 90 p.s.i. with palladised charcoal (5% pd, 3 g) in ethyl acetate (100 ml) at 100° to give 3,4-dihydro-7-hydroxycoumarin (9.8 g, 97%), m.p. 131-132° (from cyclohexane) (lit[265] m.p. 133°). ν_{max}^{KBr}: 3280 cm^{-1} (OH); 1750 and 1740 cm^{-1} (C=O hydrogen bonded to OH). δ_H ($CDCl_3$): 8.1 (1H, s, exchanges with D_2O, OH); 6.5-7.1 (3H, m, ArH); 2.7-2.8 (4H, m, 2 x CH_2).

The dihydrocoumarin was reacted with bromoamide 392 giving

2-methyl-2-(3,4-dihydro-7-coumarinoxy)propanamide 407

2-methyl-2-(estra-1,3,5(10)-triene-17-one-3-oxy)propanamide 519

2-methyl-2-(estra-1,3,5(10)-trien-17 -ol-3-oxy)propanamide 520

Amide (Formula)	% Yield	m.p.	Found % (required) C	H	N	$\delta_H(CDCl_3)$
387 ($C_{10}H_{12}ClNO_2$)	75	120-122 (toluene) lit[205] m.p. 120-121°				6.8-7.3,6.6, 1.5
389 ($C_{11}H_{15}NO_3$)	85	89-90 (cyclohexane) lit[205] m.p. 89-90				6.8-7.3,6.7, 3.7,1.5
393 ($C_{16}H_{17}NO_2$)	98	183-185 (toluene)	75.3 (75.3)	6.7 (7.0)	5.5 (5.4)	6.8-7.5,1.5
394 ($C_{14}H_{15}NO_2$)	98	119-120 (toluene)	73.4 (73.8)	6.6 (6.6)	6.1 (5.9)	6.8-8.3,6.5, 1.6
395 ($C_{14}H_{15}NO_2$)	92	118-119 (toluene)	73.4 (73.2)	6.6 (6.7)	6.1 (6.0)	7.0-7.8,6.6, 1.6
396 ($C_{14}H_{19}NO_2$)	83	113-114 (toluene)	72.2 (72.1)	8.4 (8.2)	5.9 (6.0)	7.0-7.5,6.5, 3.25,2.3,1.5
397 ($C_{11}H_{15}NO_2$)	82	147-148 (toluene)	68.8 (68.4)	8.0 (7.8)	7.2 (7.2)	6.5-7.2,2.2, 1.5
398 ($C_{11}H_{15}NO_3$)	49	133-134 (toluene)	63.3 (63.1)	7.4 (7.2)	6.5 (6.7)	7.3,7.1,3.8, 1.4
399 ($C_{10}H_{12}FNO_2$)	75	93-94 (toluene)	M^+,	197 (197)		6.5-7.2,1.5
400 ($C_{10}H_{12}ClNO_2$)	69	89-90 (toluene)	56.2 (56.2)	5.8 (5.6)	6.3 (6.5)	7.1-7.6,1.6
401 ($C_{10}H_{12}BrNO_2$)	40	78-80 (cyclohexane)	46.6 (46.5)	4.8 (4.6)	5.5 (5.4)	7.0-7.8,1.5
402 ($C_{10}H_{12}INO_2$)	48	101-102 (toluene)	39.4 (39.3)	4.2 (3.9)	4.7 (4.6)	6.6-7.8,1.5
403 ($C_{16}H_{17}NO_2$)	77	96-97 (toluene)	75.0 (75.3)	7.0 (6.7)	5.5 (5.5)	7.1-7.4,6.5 1.5
404 ($C_{16}H_{15}NO_3$)	45	154-155 (toluene)	71.4 (71.4)	5.6 (5.7)	5.2 (4.8)	7.0-8.0,1.5
405 ($C_{13}H_{14}N_2O_2$)	31	178-179 (toluene)	67.8 (67.8)	6.0 (6.1)	12.0 (12.2)	7.2-9.0,1.5

Amide (Formula)	% Yield	m.p.	Found % (required) C	H	N	$\delta_H(CDCl_3)$
406 ($C_{12}H_{15}NO_4$)	63	142-143 (toluene)	60.8 (60.9)	6.3 (6.4)	5.9 (5.9)	7.1-7.7,3.9, 1.5
407 ($C_{13}H_{15}NO_4$)	51	153-154 (toluene)	M^+,	249 (249)		6.3-7.2,2.8, 2.0
519 ($C_{22}H_{29}NO_3$)	77	167-168 (ethanol)	74.3 (73.9)	8.2 (8.2)	3.9 (3.5)	6.6-7.2,6.3, 0.9-3.0
520 ($C_{22}H_{30}NO_3$)	88	198-200 (ethanol/ cyclohexane)	74.2 (74.4)	8.4 (8.2)	3.9 (3.4)	6.4-6.7,6.8, 5.0,0.9-3.0

The infra-red spectra of all the amides showed an NH_2 asymmetric stretch at 3490-3420 and 3200-3900 cm^{-1} and a carbonyl stretching band at 1630-1680 cm^{-1}.

In the mass spectra of new compounds the parent ions corresponded to the calculated RMM of the compounds.

Smiles rearrangement of amides 387, 389, 393 - 407, 519 and 520

See following table.

Smiles rearrangement of amides 387, 389, 393 - 407, 519 and 520

Starting Amide	Product anilide	% Yield	m.p./b.p.	Found % (required) C	H	N	$\delta_H(CDCl_3)$
387	410	98	135-137 (cyclohexane) (lit[205] m.p. 135-137)		-		9.6,7.25-7.9, 5.7,1.5
389	411	68	136-137 (cyclohexane) (lit[205] m.p. 136-137)		-		9.0,6.8-7.6, 5.4,3.8,1.5
393	412	87	167-168 (cyclohexane)	74.9 (75.3)	6.7 (6.7)	5.4 (5.5)	9.35,7.1-7.8, 5.6,1.4
394	413	81	161-162 (cyclohexane)	73.7 (73.3)	6.8 (6.5)	6.1 (6.1)	9.6,7.2-8.0, 5.8,1.5
395	414	93	159-160 (cyclohexane)	73.2 (73.3)	6.6 (6.5)	6.0 (6.1)	9.6,7.2-8.5, 5.8,1.5
396	415	81	97-98 (toluene)	71.9 (72.1)	8.2 (8.1)	5.6 (6.0)	8.9,6.0-7.2, 2.8,1.8,1.5
397	416	72	83-84 (toluene)	68.5 (68.4)	8.4 (7.8)	6.9 (7.3)	6.8-7.3,2.3, 1.5

Starting Amide	Product anilide	% Yield	m.p./b.p.	Found % (required) C	H	N	$\delta_H(CDCl_3)$
398	417	31	143-144 (toluene)	M^+, 209 (209)			6.6-7.5,3.8, 1.5
399	418	62	140° @ 0.02 mm	61.0 (60.9)	6.0 (6.1)	7.0 (7.1)	9.25,8.3-8.5, 7.0-7.1,1.5
400	419	54	161° @ 0.6 mm	56.5 (56.2)	5.2 (5.6)	6.6 (6.5)	9.5,8.4-8.5, 7.0-7.5,4.0,1.5
401	420	96	150° @ 0.3 mm	46.8 (46.5)	5.2 (4.6)	5.7 (5.4)	9.6,8.3-8.5, 4.3,1.5
402	421	87	174° @ 0.2 mm	39.7 (39.3)	4.4 (3.9)	4.4 (4.6)	9.4,6.8-8.3, 4.4,1.5
403	422	45	148-149 (cyclohexane)	75.5 (75.3)	6.8 (6.7)	5.5 (5.5)	9.2,8.4-8.5, 7.2-7.5,5.0,1.4
404	423	21	165-166 (cyclohexane)	71.1 (71.4)	5.7 (5.6)	5.2 (5.2)	9.5,7.3-8.5, 4.4,1.5
405	424	60	123-124 (cyclohexane)	68.2 (67.8)	6.2 (6.1)	11.9 (12.2)	7.2-8.9,3.6, 1.6
406	425	62	124-125 (toluene/ ethanol)	60.9 (60.8)	6.4 (6.3)	5.7 (5.9)	9.1,7.2-8.2 4.0,3.8,1.5

Starting Amide	Product anilide	% Yield	m.p./b.p.	Found % (required) C	H	N	$\delta_H(CDCl_3)$
407	complex mixture						
519	521	94	133-134 (cyclohexane/ ether)	M^+,	355 (355)		6.7-7.3,6.3, 0.9-3.0
520	522	87	203-204 (ethanol/ cyclohexane)	73.9 (74.2)	8.8 (8.4)	3.8 (3.9)	6.3-7.2,3.2, 0.4-2.3

The i.r. spectra of all anilides showed a NH asymmetric stretching frequency at 3380-3590 and 3190-3380 and a carbonyl stretching band at 1660-1680 cm^{-1}. In the mass spectra of new compounds the parent ion corresponded to the calculated RMM.

Preparation of secondary bromoisobutyramides

To bromoisobutyryl bromide (11 ml, 89 mmol) in $CHCl_3$ (100 ml) at 0^o was added with stirring a mixture of the amine (89 mmol) and sodium hydroxide solution (1M, 100 ml). After stirring for 0.5 h the layers were separated, the organic layer dried ($MgSO_4$) and evaporated. Recrystallisation or distillation yielded the following N-substituted amides.

Product	Substituent on amide nitrogen	% Yield	m.p.	ν_{max}	δ_H ($CDCl_3$)
430	Me	52	59-60 ($CHCl_3$/petrol) (lit[266] m.p. 58-60)	3310, 1670	-
431	Et	84	57-59 ($CHCl_3$/petrol) (lit[266] m.p. 57-58)	3310, 1670	-
432	adamantyl	86	77-79 (petrol) (lit[266] m.p.77)	3315, 1650	6.6,1.6-2.1
433	t-butyl	41	84-86 (hexane) (lit[234] m.p. 85-86)	3400, 1650	6.5,1.8,1.2
434[a]	cyclohexyl	42	107-108 (cyclohexane)	3340 1640	6.5-6.9,2.0, 1.0-2.1
435	Ph	20	83-84 ($CHCl_3$/petrol) (lit[265] m.p.83)	3350 1650	-

Product	Substituent on amide nitrogen	% Yield	m.p.	ν_{max}	δ_H ($CDCl_3$)
436[b]	CH_2CMe_3	58	91-92 (petrol)	3370, 1660	7.2,3.0-3.1, 2.0,0.9
437	benzyl	70	71-73 (cyclohexane) (lit[234] m.p.71)	3300, 1650	7.1,4.2-4.4, 1.9
438[c]	$3,5-(CF_3)_2C_6H_3$	15	122-123 (cyclohexane)	3300, 1670	8.7,8.0,7.6, 2.0
439[d]	$4-MeOC_6H_4$	20	87-88 (cyclohexane)	3320, 1650	8.4,6.8-7.5, 3.8,2.0
440	$2,4-(MeO)_2C_6H_3$	95	gum	3330, 1650	-

a: Found: C, 48.5; H, 7.3; N, 5.5. $C_{10}H_{18}BrNO$ requires: C, 48.4; H, 7.2; N, 5.6 %

b: Found: C, 45.7; H, 7.8; N, 5.9. $C_9H_{18}BrNO$ requires: C, 45.7; H, 7.6; N, 5.9 %

c: Found: C, 38.5; H, 2.6; N, 3.7. $C_{12}H_{10}BrF_6NO$ requires: C, 38.1; H, 2.6; N, 3.7 %

d: Found: C, 48.2; H, 5.2; N, 5.1. $C_{11}H_{14}BrNO_2$ requires: C, 48.5; H, 5.1; N, 5.1%

The i.r. spectrum of the crude product obtained from the reaction of allyl amine with bromoisobutyryl bromide contained two peaks at 1735 and 1660 cm^{-1}. Examination of the product by G.L.C. (15% apiezon column, FID detector, column temperature 150^{o}, injection temperature 200^{o}) showed it to consist of two components. Separation

of the mixture on an analytical HPLC column (silica support, eluent hexane/chloroform 10:1) provided small quantities of the pure compounds. The i.r. spectrum of the slower running component had absorbances of 3285 and 1650 cm^{-1}, consistent with the compound being the desired N-allyl amide 441. The i.r. spectrum of the other component had a very strong band at 1730 cm^{-1} and no absorption above 3100 cm^{-1}. The identification of this intriguing contaminant awaits its isolation in larger quantities.

Preparation of secondary phenoxyisobutyramides 442, 444 to 447

Phenol (2 g) was reacted with sodium hydride and the appropriate secondary isobutyramide (1 mol eq.) as described earlier, giving the following isobutyramides.

N-methyl-2-methyl-2-(4-chlorophenoxy)propanamide 442

(1.67 g, 50%), m.p. 63-64° (from hexane). (Found: C, 58.0; H, 6.2; N, 6.0; Cl, 16.0. $C_{11}H_{14}ClNO_2$ requires: C, 58.0; H, 6.1; N, 6.1; Cl, 15.6%). M^+, 227. ν_{max}^{KBr}: 3380 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.7-7.3 (5H, ABq, and s, 4ArH and NH); 2.8-2.9 (3H, d, CH_3-NH).

N-methyl-2-methyl-2(4-phenylphenoxy)propanamide 444

(0.51 g, 17%), m.p. 160-161° (from ethyl acetate). (Found: C, 75.7; H, 7.0; N, 5.0. $C_{17}H_{19}NO_2$ requires: C, 75.8; H, 7.0; N, 5.2%). M^+, 269. ν_{max}^{KBr}: 3380 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.9-8.1 (4OH, m, 9ArH and NH); 2.3-2.4 (3H, d, CH_3-NH); 1.5 (6H, s, 2 x CH_3).

N-benzyl-2-methyl-2-(4-phenylphenoxy)propanamide 445

(2.07 g, 51%), m.p. 106-107° (from cyclohexane). (Found: C, 80.3; H, 6.7; N, 4.0. $C_{23}H_{23}NO_2$ requires: C, 80.0; H, 6.7; N, 4.1%). M^+, 345. ν_{max}^{KBr}: 3380 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-7.6 (15H, m, 14ArH and NH); 4.45-4.55 (2H, d, CH_2-NH); 1.5 (6H, s, 2 x CH_3).

N,(3,5-bistrifluoromethylphenyl)-2-methyl-2-(4-phenylphenoxy)propanamide 446

(3.63 g, 66%), m.p. 138-139° (from cyclohexane). (Found: C, 61.6; H, 4.2; N, 2.9. $C_{24}H_{19}F_6NO_2$ requires: C, 61.7; H, 4.1; N, 3.0%). M^+, 467. ν_{max}^{KBr}: 3380 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-7.8 (13H, m, 12ArH and NH); 1.5 (6H, s, 2 x CH_3).

N-(2,4-dimethoxyphenyl)-2-methyl-2-(4-phenylphenoxy)propanamide 447

(2.45 g, 51%), m.p. 101-102° (from cyclohexane). (Found: C, 73.6; H, 6.2; N, 3.6. $C_{24}H_{25}NO_4$ requires: C, 73.6; H, 6.4; N, 3.6%). M^+, 391. ν_{max}^{KBr}: 3390 cm^{-1} (NH); 1680 cm^{-1} (C=O). δ_H ($CDCl_3$): 9.0 (1H, s, NH); 6.4-8.3 (12H, m, ArH); 3.25 (6H, d, 2 x OMe); 1.6 (6H, s, 2 x Me).

Reaction of N-substituted 2-methylpropanamides in N,N-dimethylformamide

When amides 435 or 439 were reacted by the standard method with phenol in dioxan, t.l.c. of the reaction mixture after 1 h showed the presence of both starting materials as well as some product. Replacement of the p-dioxan by bis 2-methoxyethyl ether (diglyme), butan-2-one or dimethylsulphoxide showed no change from the reaction in p-dioxan. When DMF (50 ml) was used as solvent, t.l.c. showed one product together with phenol. The precipitated sodium bromide was filtered off and the solvent evaporated. Trituration of the residue with NaOH (1M, 100 ml) filtration and recrystallisation from hexane yielded the following compounds:

2-dimethylamino-3-phenyl-5,5-dimethyloxazolidin-4-one 450

(8.4 g, 63%), m.p. 100-101° (from hexane) (lit[224] m.p. 101-102°). ν_{max}^{KBr}: 1710 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.2-7.5 (5H, m, ArH); 6.1 (1H, s,

CH); 2.3 (6H, s, 2 x CH_3 at C5); 1.3-1.4 (6H, d, 2 x CH_3-N). (Identical results were obtained from the reaction of sodium hydride in DMF with 345 in the absence of phenol.)

2-(dimethylamino)-3-(4-methoxyphenyl)-5,5-dimethyloxazolidin-4-one 451 (3.6 g, 26%), m.p. 89-90° (from hexane). (Found: C, 64.0; H, 7.7; N, 10.3. $C_{14}H_{20}N_2O_3$ requires: C, 63.6; H, 7.6; N, 10.6%). M^+, 264. ν_{max}^{KBr}: 1700 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-7.4 (4H, ABq, ArH); 6.05 (1H, s, CH); 3.8 (3H, s, OMe); 2.4 (6H, s, 2 x Me at C5); 1.5-1.6 (6H, d, 2 x Me-N).

General Method for α-lactam formation

To the N-substituted amide (5 g) in dry THF (50 ml) at a controlled temperature was added sodium hydride (1 mol eq.) and the mixture was stirred. At regular intervals aliquots were removed and examined by liquid cell i.r. spectroscopy and by t.l.c. (chloroform/hexane 1:1). The product was either isolated or reacted directly with phenol. Isolation of the α-lactam was achieved by filtration, evaporation and recrystallisation.

From bromoamide 432 was obtained 1-adamantyl-3,3-dimethylazirinone 459 (2.8 g, 42%), m.p. 90-91° (lit[234] m.p. 90-91°) (from hexane). ν_{max}^{KBr}: 1830 cm^{-1} (C=O).

From bromoamide 433 was isolated 1-t-butyl-3,3-dimethylazirinone 460 (2.55 g, 80%), m.p. 22-23° (from hexane) (lit[234] m.p. 22-24°). ν_{max}^{KBr}: 1840 cm^{-1} (C=O).

Direct reaction of the α-lactam without isolation was undertaken by adding the appropriate phenol (1 mol eq.) and stirring for 4 h at the temperature of α-lactam formation. The solution was allowed to reach room temperature and filtered. Evaporation and

recrystallisation gave the following N-substituted phenoxybutanamides.

Starting Bromo-amide	Butan-amide product	Reaction temp. (°C)	% Yield	m.p./b.p.	ν_{max}^{KBr}	$\delta_H(CDCl_3)$
432	461	0	51	80-81 (hexane)	3350, 1660	7.0-7.6,6.5, 1.2-2.1
433	462	0	90	150 @ 0.1	3420, 1680	7.0-7.5,6.6, 1.5,1.4
430	466	-40	96	150 @ 0.3	3350, 1670	6.8-7.1, 2.7-2.8,1.5
431	467	-40	84	160 @ 0.2	3340, 1670	6.8-7.1,2.9-3.4,1.4,0.8-1.1
434	468	-20	55	95-96 (hexane)	3300, 1640	6.9-7.4,6.6, 3.8,1.0-2.0
430	475	-40	54	115-116 (cyclo-hexane)	3320, 1650	7.0-7.1,2.8-3.0,2.2,1.5
430	470	-40	84	135 @ 0.3	3320, 1660	7.0-7.6,2.9-3.0,1.6
430	471	-40	92	180 @ 0.2	3300, 1660	6.8-7.9,2.9-3.0,1.5
430	472	-40	91	120 @ 1.8	3400, 1690	6.8-7.4,2.2-2.4,2.1,2.0
432	473	0	81	180 @ 0.2	3410, 1680	6.8-7.5,0.9-2.1
432	474	0	87	150 @ 0.2	3370, 1680	6.8-7.3,3.8, 1.0-2.1
430	524	-40	82	95-96	3360, 1740	9.1,6.5-8.0, 3.4,0.6-3.0

Amide (Molecular Formula)	Found (%) C	H	N	Required (%) C	H	N
461 ($C_{20}H_{28}NO_2$)	76.4	8.5	3.9	76.4	8.9	4.4
462 ($C_{14}H_{21}NO_2$)	71.7	9.5	5.9	71.5	8.9	5.9
466 ($C_{11}H_{15}NO_2$)	68.3	8.3	7.2	68.4	7.8	7.2
467 ($C_{12}H_{17}NO_2$)	69.2	8.1	6.4	69.6	8.2	6.8
468 ($C_{16}H_{23}NO_2$)	M^+, 261			M^+, 261		
475 ($C_{13}H_{19}NO_2$)	70.7	8.5	6.2	70.6	8.6	6.3
470 ($C_{11}H_{14}ClNO_2$)	58.0	6.2	6.2	58.2	6.3	6.1
471 ($C_{11}H_{14}INO_2$)	42.0	4.6	4.3	41.4	4.4	4.4
472 ($C_{20}H_{27}FNO_2$)	M^+, 331			M^+, 331		
473 ($C_{21}H_{30}NO_3$)	M^+, 343			M^+, 343		
474 ($C_{21}H_{30}NO_2$)	M^+, 207			M^+, 207		
524 ($C_{23}H_{31}NO_3$)	74.4	8.6	3.8	74.8	8.5	3.8

Preparation of secondary phenoxybutanamides 469 and 523

From the reaction of the appropriate phenols and N-substituted bromoisobutyramide in p-dioxin were obtained:

N-(2,2-dimethylpropyl)-2-methyl-2-phenoxypropanamide 469 (90%), m.p. 86-87° (cyclohexane). (Found: C, 72.5; H, 9.5; N, 5.6.

$C_{15}H_{23}NO_2$ requires: C, 72.3; H, 9.2; N, 5.6%). M^+, 249. ν_{max}^{KBr}: 3290 cm^{-1} (NH); 1655 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.9-7.4 (6H, m, 5ArH and NH); 3.1-3.2 (2H, d, CH_2-NH); 1.6 (6H, s, 2 x CH_3); 0.7 (9H, s, 3 x CH_3).

N,2-dimethyl-2-(oestra-1,3,5(10)trien-17 -ol-3-oxy)propanamide 523

(88%), m.p. 139-140 (from cyclohexane/ethyl acetate). (Found: C, 74.3; H, 9.0; N, 3.7. $C_{23}H_{32}NO_3$ requires: C, 74.6; H, 8.6; N, 3.8%). ν_{max}^{KBr}: 3380 cm^{-1} (OH); 3340 cm^{-1} (NH); 1660 and 1650 cm^{-1} (C=O -H-bonded to OH). δ_H ($CDCl_3$): 6.8-7.2 (3H, m, ArH); 6.0 (1H, s, NH); 3.3 (1H, s, exchanges with D_2O, OH); 0.5-2.5 (28H, m, 16H estrone and 4 x CH_3).

Preparation of N-methyl, ethyl and phenyl-phenoxybutanamides 466, 467, and 448

Reaction of 2-methyl-2-phenoxypropanoic acid (15 g, 83 mmol) with thionyl chloride and the appropriate amines as described earlier gave:

N-methyl-2-methyl-2-phenoxypropanamide 466

(7.3 g, 45%), b.p. 150° @ 0.3 mm, i.r. spectrum identical with that of a previously made sample.

N-ethyl-2-methyl-2-phenoxypropanamide 467

(12.9 g, 75%), b.p. 145° @ 0.4 mm, i.r. spectrum superimposable with that of an authentic sample.

N-phenyl-2-methyl-2-phenoxypropanamide 448

(11.22 g, 53%), b.p. 154° at 0.35 mm. (Found: C, 75.5; H, 6.9; N, 5.9. $C_{16}H_{17}NO_2$ requires: C, 75.3; H, 6.7; N, 5.5 %). M^+, 255. ν_{max}^{Film}: 3380 cm^{-1} (NH); 1690 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.8-7.2 (11H, m, 10ArH and NH); 1.5 (6H, s, 2 x CH_3).

Preparation of N-benzyl-2-methyl-2-phenoxypropanamide 478

To a stirred solution of 2-methyl-2-phenoxypropanoic acid (5 g, 28 mmol) in dry CH_2Cl_2 (50 ml) was added DCC (5.72 g, 28 mmol), followed after 10 min by benzylamine (2.97 g, 28 mmol). After overnight stirring the solids were filtered off, the filtrate evaporated and the residue distilled giving the title amide 478 (7.0 g, 94%), b.p. 150° at 0.5 mm. (Found: C, 75.6; H, 7.6; N, 5.7. $C_{17}H_{19}NO_2$ requires: C, 75.8; H, 7.2; N, 5.3%). M^+, 269. ν_{max}^{KBr}: 3340 cm^{-1} (NH); 1660 cm^{-1} (C=O). δ_H ($CDCl_3$): 6.9-7.3 (11H, m, 10ArH and NH); 4.4-4.5 (2H, d, CH_2-NH). 1.5 (6H, s, 2 x CH_3). When the reaction was repeated replacing benzylamine by methylamine no product was obtained.

Smiles rearrangement of secondary phenoxybutanamides

Starting Amide	Anilide (Yield %)	Aniline	m.p./b.p.	ν_{max}	δ_H ($CDCl_3$)
448	479[a]/(31)		102-103° (cyclohexane)	3260, 1670	8.5,6.9-7.6, 6.0-8.0,1.5
446	480[b]/(56)		141-142° (cyclohexane)	3260, 1680	8.9,8.1,6.9-7.6,1.6
466		481/(55)	196-198° (lit[265] 196°)	3405	6.3-7.2,3.3, 2.5
467		482/(46)	204-205° (lit[265] 205°)	3400	6.4-7.3,3.3, 2.7-3.2,0.9-1.1
478		483/(94)	35-36° (lit[265] 35-36°)	3420	6.6-7.4,4.0, 3.6
442		484/(96)	47-49° (lit[265] 47°)	3410	6.2-7.1,4.2, 4.0

Starting Amide	Anilide Yield	Aniline (%)	m.p./b.p.	ν_{max}	δ_H ($CDCl_3$)
444		486/(91)	38-40° (lit[265] 38°)	3405	6.4-7.5,3.6, 2.6
445		487/(88)	85-86° (lit[267] 85-86°)	3400	6.3-7.3,4.1, 3.9
523		525[c]/(60) (as hydro-chloride)	258-260° (water/ ethanol)	2500-3600	6.3-7.2,3.4, 0.5-2.6

a: Found: C, 75.6; H, 6.7; N, 5.4. $C_{16}H_{17}NO_2$ requires: C, 75.3; H, 6.7; N, 5.4%

b: Found: C, 61.6; H, 4.2; N, 3.0. $C_{24}H_{18}F_6NO_2$ requires: C, 61.7; H, 4.0; N, 3.0%

c: Found: C, 70.7; H, 8.9; N, 4.2. $C_{19}H_{27}ClNO$ requires: C, 71.1; H, 8.4; N, 4.4%

Preparation of benzoxazinones

Smiles rearrangement of both amides 470 and 471 gave 2,2,4-trimethyl-1,4-benzoxazin-3(4H)-one 502 (98%), b.p. 110° @ 0.5 mm. (Found: C, 69.2; H, 6.6; N, 6.8. $C_{11}H_{13}NO_2$ requires: C, 69.1; H, 6.8; N, 7.3%). M^+, 191. ν_{max}^{Film}: 1670 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.0 (4H, s, ArH); 3.3 (3H, s, CH_3-N); 1.5 (6H, s, 2 x Me). δ_C ($CDCl_3$): 23.96 (CH_2-C); 28.57 (CH_3-N); 77.92 (C-Me_2); 114.08, 117.52, 122.20, 123.69 (4ArC); 130.05 (ArC-N); 143.50 (ArC-O); 168.95 (C=O).

Amide 473 gave 4-adamantyl-2,2-dimethyl-1,4-benzoxazin-3(4H)-one 503 (0.93 g, 98%), b.p. 180° at 0.2 mm. (Found: C, 76.9; H, 8.3; N, 4.3. $C_{20}H_{25}NO_2$ requires: C, 77.2; H, 8.0; N, 4.5%). M^+, 311.

ν_{max}^{Film}: 1680 cm^{-1} (C=O). δ_H ($CDCl_3$): 7.1 (4H, s, ArH); 1.4-3.0 (21H, m, 15 adamantyl H, and 2 x Me).

Hydrolysis of anilide 382

Anilide 382 (1 g, 5.6 mmol) after heating under reflux in 10, 20, 30 and 40% aqueous sodium hydroxide solutions was recovered unchanged. Standing in TFA or refluxing in sulphuric acid (1N, 2N and 3N) showed no change.

Heating the acid under reflux in 50% sodium hydroxide solution or 5N H_2SO_4 for 1 h followed by basification with sodium hydroxide (4M) extraction into ethyl acetate, the organic layer dried ($MgSO_4$), evaporated and distillation gave aniline (0.48 g, 96%), b.p. 184-186^{o} (lit[265] b.p. 184^{o}). ν_{max}^{Film}: 3500, 3400 cm^{-1} (NH_2). δ_H ($CDCl_3$): 6.3-7.3 (4H, m, ArH); 3.35 (2H, s, NH_2).

Attempted preparation of acetal 527

Amide 524 (0.35 g, 0.9 mmol) was dissolved in dry benzene (50 ml) and added to toluene-4-sulphonic acid (0.05 g) and ethylene glycol (0.06 ml, 0.9 mmol) and refluxed in a Dean and Stark apparatus until all the by-product water had been collected. The benzene was evaporated, the residue separated between NaOH (1M, 100 ml) and ethyl acetate (100 ml). The organic layer was dried ($MgSO_4$) and evaporated giving the unstable ethylene ketal 527 (0.31 g, 79%). M^+, 413. ν_{max}^{Film}: 3380 cm^{-1} (NH). δ_H ($CDCl_3$): 6.5-7.2 (4H, m, 3ArH and NH); 3.9 (3H, s, CH_3-N); 0.8-3.8 (28H, m, 15 estrone H, 2 x CH_2 and 2 x Me).

Smiles rearrangement of 527 gave a complex mixture.

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