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by V. Hadjipavlidis

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TRENT POLYTECHNIC

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being a thesis submitted to

The Council for National Academic Awards

for the degree of

DOCTOR OF PHILOSOPHY

by

Vasilios Hadji-Pavlidis, G.R.S.C.

February 1985

ΟΜΗΡΟΥ ΟΔΥΣΣΕΙΑ

ΡΑΨΩΔΙΑ Α

Προοίμιον

Ἀνδρα μοι ἔννεπε, μοῦσα, πολύτροπον, ὃς μάλα πολλὰ
πλάγχθη, ἐπεὶ Τροίης ἱερὸν πτολίεθρον ἔπερσεν,
πολλῶν δ' ἀνθρώπων ἴδεν ἄστεα καὶ νόον ἔγνω·
πολλὰ δ' ὅ γ' ἐν πόντῳ πάθεν ἄλγεα ὃν κατὰ θυμόν,
ἀρνύμενος ἥν τε ψυχὴν καὶ νόστον ἑταίρων.
ἀλλ' οὐδ' ὡς ἑτάρους ἐρρύσατο, ἱέμενός περ·
αὐτῶν γὰρ σφετέρῃσιν ἀτασθαλίῃσιν ὄλοντο,
νήπιοι, οἳ κατὰ βοῦς Ὑπερίονος Ἠελίοιο
ἤσθιον· αὐτὰρ ὁ τοῖσιν ἀφείλετο νόστιμον ἦμαρ.
τῶν ἁμόθεν γε, θεὰ θύγατερ Διός, εἰπὲ καὶ ἡμῖν.

PREFACE

The work described in this thesis was carried out by the author in the Department of Physical Sciences, Trent Polytechnic, Nottingham, between October 1980 and February 1984. A few compounds were obtained from other workers and acknowledgement is made in the text.

The author wishes to thank Dr. I.G.C. Coutts for his excellent supervision and encouragement throughout the project. Thanks also to Dr. R.W. Turner of ICI Pharmaceuticals for helpful discussions and donation of chemicals, to Mr. M.L. Wood for spectral determinations, and to Mrs. A. Bodill for typing this thesis.

The author is grateful to Trent Polytechnic for the award of a Research Assistant Demonstratorship.

The work described in Section 5.5 has been accepted for publication: I.G.C. Coutts, N.J. Culbert, M. Edwards, J.A. Hadfield, D.R. Musto, V.H. Pavlidis, and D.J. Richards, J.C.S. Perkin I, in press.

Also the work described in Sections 4.3 and 4.4 was presented as a paper at the annual meeting of the Chemical Society, East Midlands Division, at Loughborough University on December 1984.

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TABLE OF CONTENTS

ABBREVIATIONS

Bzl	benzyl
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
ir	infra-red spectroscopy
Pr^i	iso-propyl
LDA	lithium diisopropylamide
Me	methyl
Ms	methanesulphonyl
nmr	^1H nuclear magnetic resonance spectroscopy
Ph	phenyl
Bu^t	tert-butyl
TTFA	thallium trifluoroacetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin-layer chromatography
Ts	toluene-4-sulphonyl

Novel Compounds

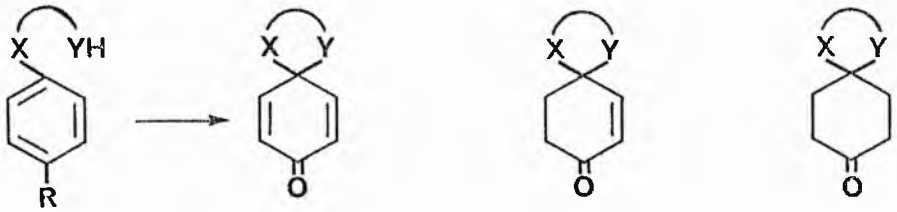
Compounds, the names of which are underlined in both text and experimental sections, have not (to the best of the author's knowledge) been described in the literature.

CHAPTER ONE

INTRODUCTION

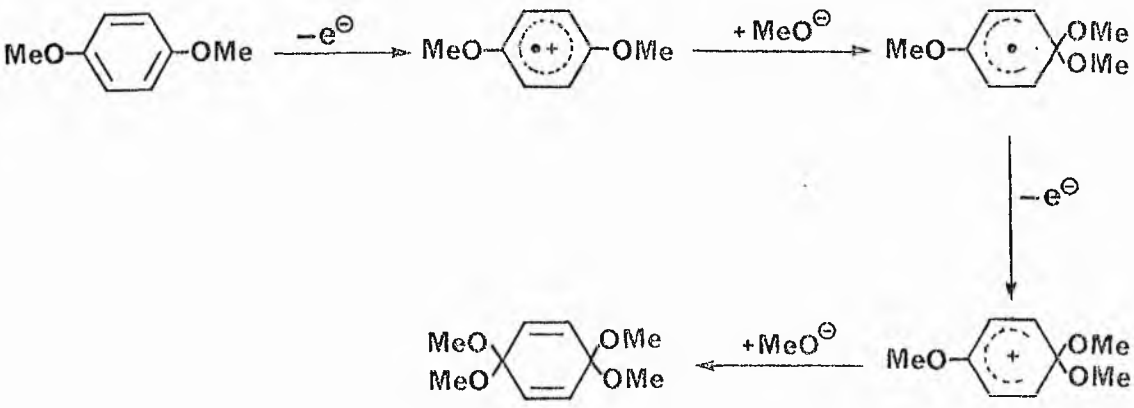
Compounds of the type (2), (3), and (4) are all six-membered cyclic ketones with a spiroheterocyclic system at the 4 position. They have oxidation levels of quinone, enone, and fully saturated ring respectively. Several members of the spirocyclic-enone and-dienone type show useful biological activity (see section 1.5); a study of the synthesis and reactions of such compounds may therefore be both chemically and pharmaceutically rewarding.

Chapters 2, 3, and 4 deal with various synthetic approaches to compounds (2), while in Chapter 5 are discussed attempts to convert compounds (4) into unsaturated systems (3).



(1) (2) (3) (4)

Scheme 1



1.1 Synthetic approaches to spiroheterocyclic quinones

Virtually all established synthetic approaches to compounds of type (2) rely on the oxidation of a substituted benzene (1). The oxidation may be effected by chemical oxidation or by electrooxidation and can occur by radical or radical-cation mechanisms.

1.1.2 Mechanisms of oxidative cyclisations leading to spirocyclohexadienones

Most cyclisations are thought to proceed by one of two complementary mechanisms.

A) Radical cation mechanism

This is the predominant mechanism occuring in anodic oxidation processes, and has been established by many independent studies; a recent book[1] gives an excellent detailed discussion of the field.

A typical mechanistic scheme is that proposed by Pedler[2] for the anodic oxidation of 1,4-dimethoxybenzene in alkaline methanol. In this oxidation (Scheme 1) the aromatic compound is oxidised to a radical cation, which reacts with methoxide ion to give an intermediate product. Further electrochemical oxidation and reaction with methoxide ion gives the tetra-substituted diene. In general, this is known as an ECE mechanism (the letter E symbolises the electrochemical step and C the chemical step).

Although this mechanism is applicable predominantly to electrochemically induced oxidations, a similar mechanism has been proposed by Taylor[3] for the oxidation of electron-rich aryl substrates with thallium (III) trifluoroacetate (see section 1.3.1).

B) Free radical mechanism

For oxidations involving phenolic substrates the initial step involves the removal of one electron by an external oxidant to give a phenoxy radical. Although relatively few phenoxy radicals have been

isolated due to their inherent instability, physical techniques such as esr[4], uv[5], and ir[6] spectrosopy verify their existence.

There are three types of phenoxy radical coupling: (1) direct coupling of two phenoxy radicals, (2) homolytic aromatic substitution and (3) heterolytic coupling preceded by two successive one-electron oxidations. The para coupling of the phenoxy radical from 2,6-dialkylphenol (6) (Scheme 2) illustrates the three modes of a radical coupling.

(1) Homolytic coupling of two phenoxy radicals (6), followed by rapid tautomerisation in protic media gives (10). This route is well established.[7]

(2) Homolytic substitution of a phenoxy radical into another phenol molecule gives the dimeric radical (8), which via (7) leads to (10). Few cases are reported in the literature.[8]

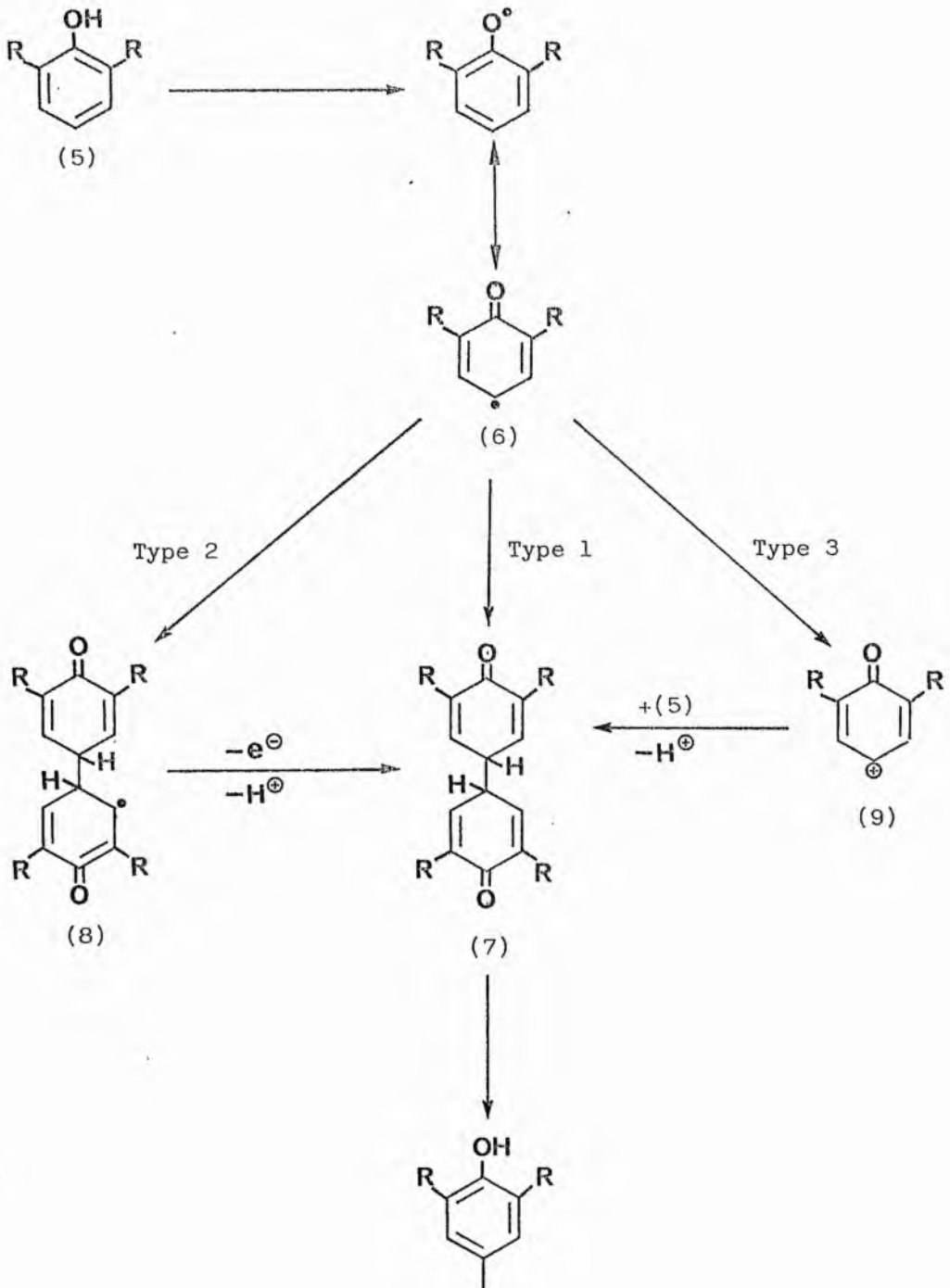
(3) The phenexonium cation (9), generated by further oxidation of the phenoxy radical (6), is capable of electrophilic attack on another phenol molecule to give (7) and hence (10). This route requires extra energy, and is the least favourable of the radical initiated mechanisms.[9]

1.1.3 Phenoxenium ions

Particular interest has been shown recently in phenoxenium ions.[10] The intermediacy of a phenoxenium ion (11) has been suggested in connection with biosynthetic phenolic coupling[11] and with oxidation of phenols by thallium,[12] chromic acid[13] and iodine-Ag.[14] The production of phenoxenium ions has been established through anodic oxidation coupled with potential-sweep measurements,[15] and in some cases, highly resonance stabilised phenoxenium ions have been isolated as crystalline salts.[16]

Aryloxenium ions have been conveniently generated in solution in organic solvents.[17] Intermolecular aryloxylation was observed on

Scheme 2


OH
R
R
(5)
O°
O
(6)
Type 2
Type 1
Type 3
H
$-e^{\ominus}$
$-H^{\oplus}$
+(5)
$-H^{\oplus}$
(8)
(7)
(9)
OH
(10)

thermolysis of N-(aryloxy)-pyridinium tetrafluoroborate (12) in anisole.[17a] Shudo et al[17b] on reacting the N-acyl-p-benzoquinone imine (17) with an excess of phenol found the major product to be the phenyl-4-hydroxyphenyl ether (19), whilst reaction under strongly acidic conditions gave a diphenyl derivative (20). The reaction pathway involves the ionic species (18).

Intermolecular C-C bond formation via aryloxenium ions, produced by elimination of a group from an oxygen atom, is known,[18] although the predominant reaction was ortho substitution (Scheme 3).

Abramovitch et al[19] were able to show intramolecular C-O-C bond formation by preparation of the benzofuran (22) from the phenoxypyridinium salt (21), but no C-C bond formation was observed.

1.1.4 Alternative mechanism for oxidative coupling

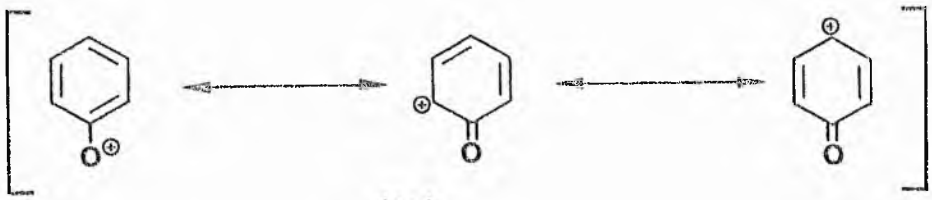
An interesting proposal developed by Hamilton and McDonald[20] obviates the necessity to postulate unpaired electron intermediates. As shown in Scheme 4, a phenol forms a salt with a metal species at the III or IV oxidation level. This by a concerted two-electron flow from a second phenol gives the familiar dimeric products obtained from phenol oxidation.

1.2 Oxidations leading to spirocyclic dienones

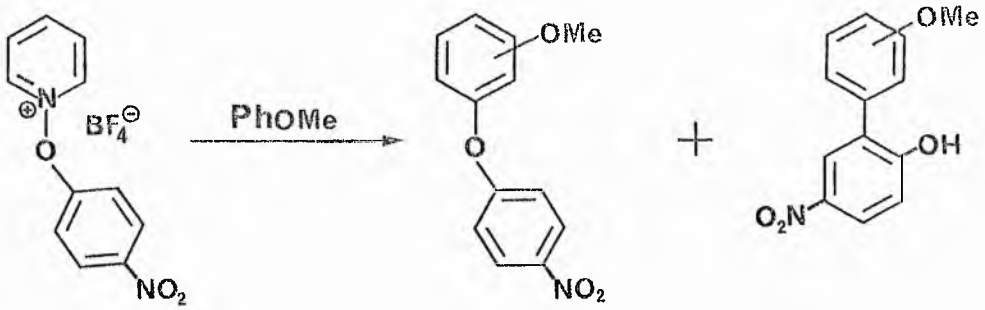
1.2.1 Anodic addition of an alkoxy group

In a pioneering paper Belleau and Weinberg[21] reported that electrochemical oxidation of the 1,4-dimethoxy benzene (23) in methanol gave the hitherto inaccessible benzoquinone bisketal (24); this work was later extended[22] to the formation of spirocyclic bis-ketal (27), formed by the oxidation of bis-hydroxyethoxybenzene (25). A subsequent study[23] established that the formation of compound (27) proceeds via intermediate mixed ketals (26).

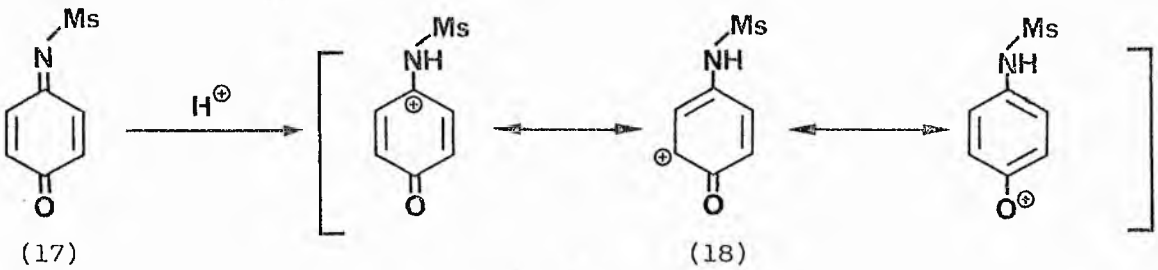
The anodic oxidation of many substituted 1,4-dimethoxybenzenes and



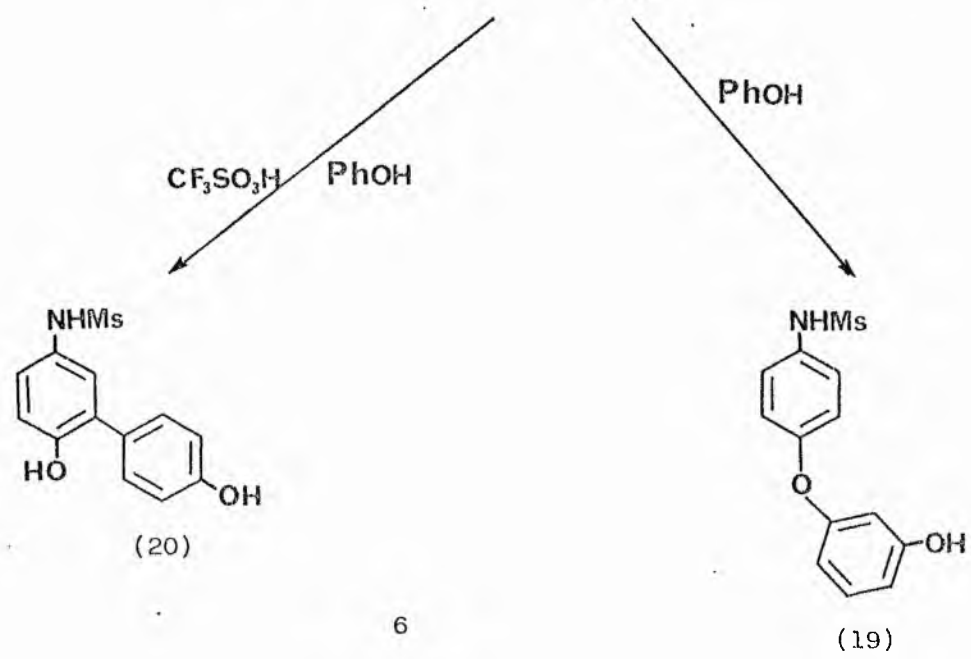
(11)



(12) (13) – o (14) – p (15) – o (16) – p

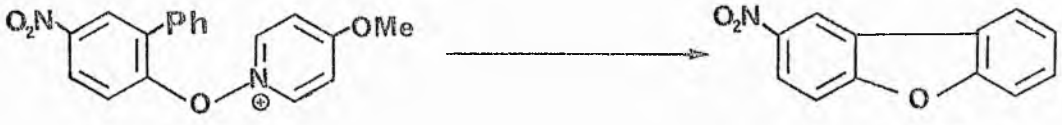


(17) (18)



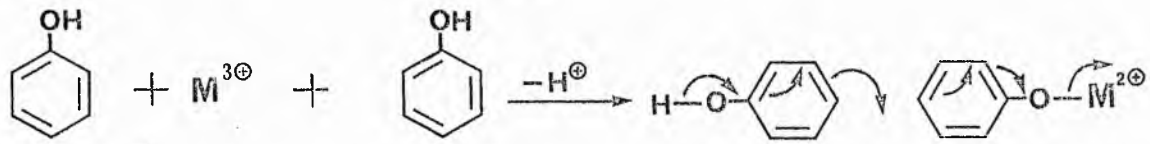
(20) (19)

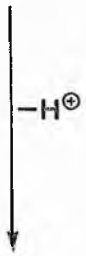
Scheme 3

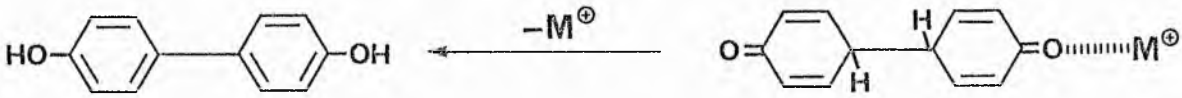


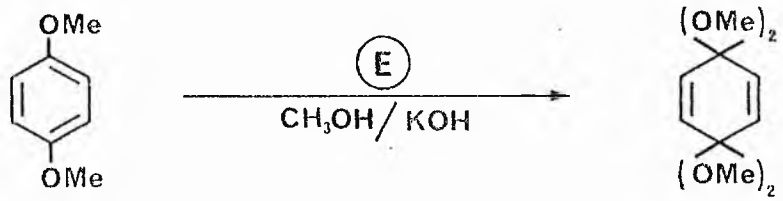
(21) (22)

Scheme 4









(23) (24)

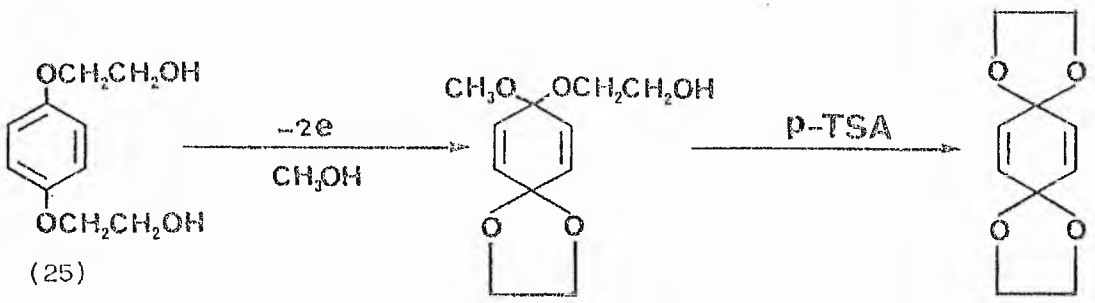
1,4-dimethoxynaphthalenes to their respective quinone bis-ketals has been studied extensively by Swenton.[24-26] The majority of the oxidations were performed in a 2% methanolic potassium hydroxide solution and a single-cell apparatus without accurate potential control was used for compounds which did not have oxidizable or reducible substituent groups. Otherwise, oxidations were carried out in divided cells (anode and cathode compartments separated).

The use of anodic oxidation to form quinone ketals with alcohols other than methanol has not been extensively studied. Anodic oxidation of 1,4-diethoxybenzene in ethanolic potassium hydroxide proceeds in lower yield(63 vs. 88%) than the analogous process in methanolic potassium hydroxide.[24] However, an intramolecular variant of this reaction can be performed[27] conveniently as illustrated in the oxidation of (28) (R=H,Me, or OMe) to give (29).

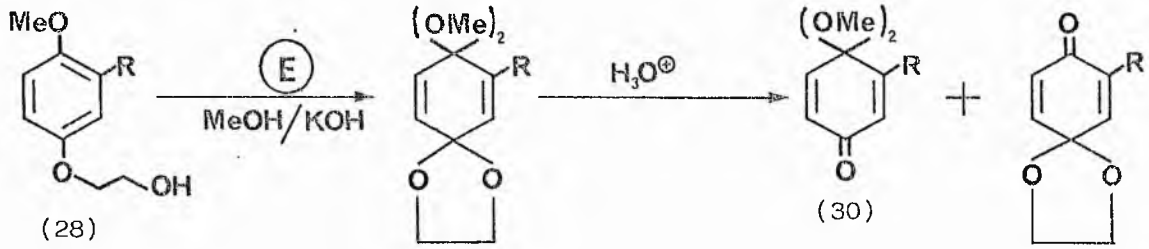
Pedler[2] has recently reported that electrochemical oxidation in methanolic potassium hydroxide of p-diethoxy-, p-di-n-propoxy-,p-di-iso-propoxy-, p-di-butoxy-, p-di-isobutoxy-, and p-di-s-butoxy benzenes gave the corresponding 3,6-dialkoxy-3,6-dimethoxycyclohexa-1,4-dienes in an approximately equimolar mixture of cis-and trans-isomers.

A number of mixed quinone bisacetals have been prepared by Farina et al[28] using electrochemical oxidation in methanolic potassium hydroxide of 1,4-disubstituted alkoxy benzenes.

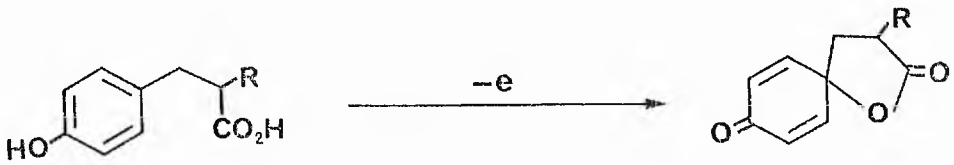
The most important reaction of quinone bisacetals is their selective hydrolysis to the synthetically versatile quinone monoacetals. For both benzoquinone and naphthoquinone bisacetals acid-catalysed monohydrolysis affords the respective quinone monoacetals.[29] The regiospecificity of the monohydrolysis depends on the substituents on the ring. The monohydrolysis of the mixed bisacetals (29) (R=H,Me, or Br) gave the monoacetals (31) in good yield,[27] while (29) (R=OMe) gave (30). Thus,



(25) (26) (27)



(28) (29) (30) (31)



(32) a; R=H
b; R=NHCOOMe

(33)

(34) (35)

the slower rate of hydrolysis of an ethylene ketal allows selective hydrolysis to afford moncketals of the type (31). However, if R is a good electron-donating group (i.e. OMe), the monoketal (30) will result.

Thus far, the anodic oxidation of methoxylated heterocyclic compounds in methanolic potassium hydroxide has yielded synthetically useful results only with benzothiophenes.[30,31]

The electrochemical oxidation of p-xylene in methanol-sodium methoxide has been recently reported[32] to give a 3:1 isomeric ratio of cis- and trans- 3,6 dimethoxy-3,6-dimethyl-1,4-cyclohexadiene.

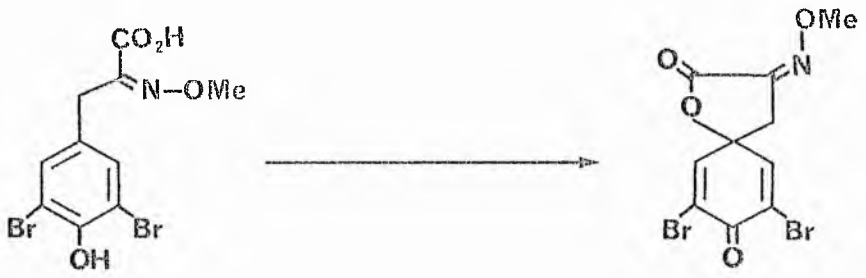
1.2.2 Anodic intramolecular acyloxylation

The electrooxidation of p-hydroxyphenylpropanoic acids in aqueous solution at a platinum anode leads to internal lactonisation products. For example, phloretic acid (32a) affords the dienone lactone (33a) in 20% yield.[33] Under identical conditions, N-methoxycarbonyltyrosine (32b) and cis-p-hydroxycinnamic acid (34)[34] are converted to the spirodienone (33b) and the unsaturated spirolactone (35), respectively, in yields of 15 and 5%. These spirolactones undergo acid-catalysed rearrangements to give coumarins.

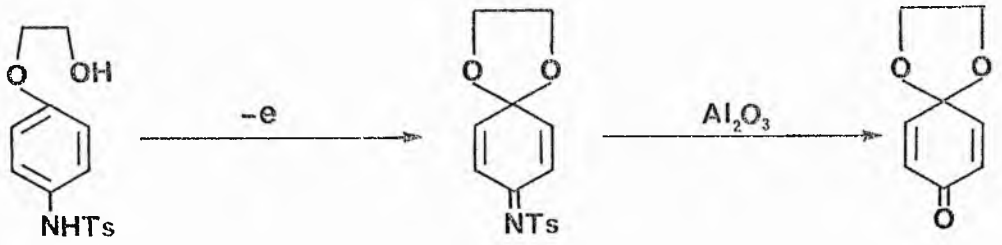
It is of interest that in our hands the anodic oxidation of trans-p-toluenesulphonamido-cinnamic acid gave no spirocyclic product.

Yamamura et al[35] have reported that anodic oxidation in methanol of 3,5-dibromo-4-hydroxyphenylpyruvic acid O-methyloxime(36) gave spirolactone (37) in 27% yield.

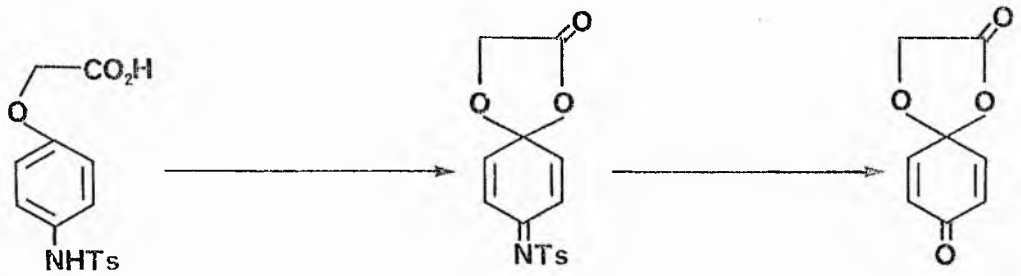
Electrochemical oxidation of N-4-toluenesulphonylanilines bearing appropriate para substituents, e.g. (38), (41), and (44) at a carbon felt anode in acetonitrile gave[36] the N-sulphonylimines (39), (42), and (45) respectively; on passage down a neutral alumina (Grade II activity) the imines were smoothly converted to spirodienones (40), (43), and (46).



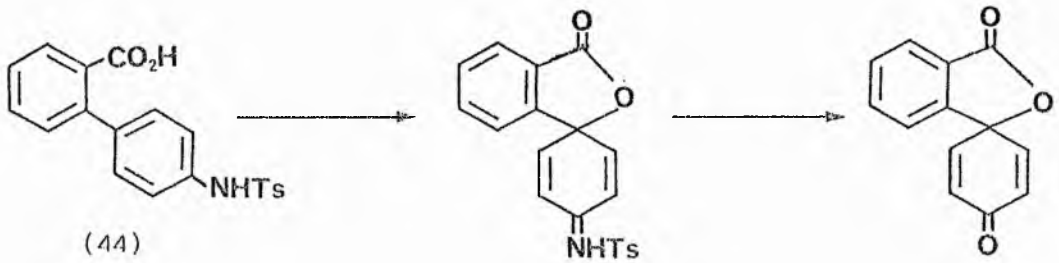
(36) (37)



(38) (39) (40)



(41) (42) (43)



(44) (45) (46)

Anodic oxidation in acetonitrile at graphite electrodes of 4-methoxyphenoxyacetic acids (47) has recently been reported[37] to give the corresponding spirodienone lactones (48).

1.3 Chemical oxidation

1.3.1 Thallium (III) salts

An important advance in synthetic approaches to quinone monoketals was the use by Taylor and McKillop[38] of thallium (III) nitrate as an oxidant. Oxidation of a variety of 4-alkyl- and 4-alkoxyphenols with one equivalent of thallium trinitrate in either methanol or trimethyl orthoformate, gave the 4-alkyl-4-methoxy- and 4,4-dimethoxy-cyclohexa-2,5-dienones in moderate to excellent yield. Mixed monoketals of p-benzoquinone were observed when 4-alkoxy-3,5-disubstituted phenols were oxidised by thallium trinitrate in the appropriate alcohol, e.g. (49) gave (50 a-c).

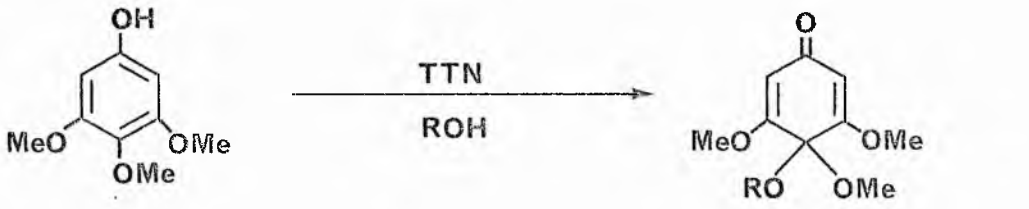
The formation of the cyclohexadienones under these conditions was initially thought[39-40] to proceed by *ipso* thallation, followed by displacement of thallium by methanol. However, a radical mechanism has been postulated[3] more recently (Scheme 5).

Wheeler *et al*[41] prepared the monoacetal of juglone methyl ether (52) from the oxidation of 1,5-naphthalenediol monomethyl ether (51) with thallium trinitrate in a mixture of ethylene glycol and trimethyl orthoformate. The monoacetal (52) is a promising intermediate in the synthesis of daunomycinone.[42]

Thallium (III) trifluoroacetate (TTFA) has been shown to effect electrophilic thallation of a wide variety of aromatic substrates carrying a variety of substituent groups (moderately activating to moderately deactivating). The resulting aryl thallium bis-trifluoroacetates are exceptionally versatile intermediates for the regiospecific intro-

(47) R^1/R^2 = $-(CH_2)_5-$, CH_3, H

(48)

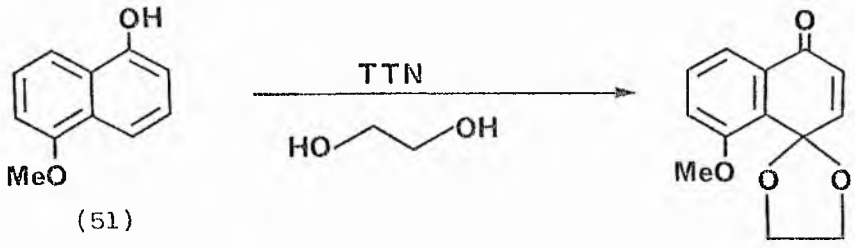


(49)

(50) a; R=C_2H_5

b; R=$CH(CH_3)_2$

c; R=$C(CH_3)_3$



(51)

(52)

duction of new substituents into the aromatic nucleus.

With highly activated aromatic substrates, however, electrophilic thallation is not normally observed; instead, a 1-electron oxidation takes place to generate a radical cation whose subsequent fate is determined by the nature of the reaction medium and the substrate itself. The ability of thallium (III) reagents to act as 1-electron oxidants of highly aromatic substrates is well documented[43,44] and has been exploited for the synthesis of biaryls,[45] including aporphine and homo-aporphine alkaloids[46,47] from nonphenolic precursors.

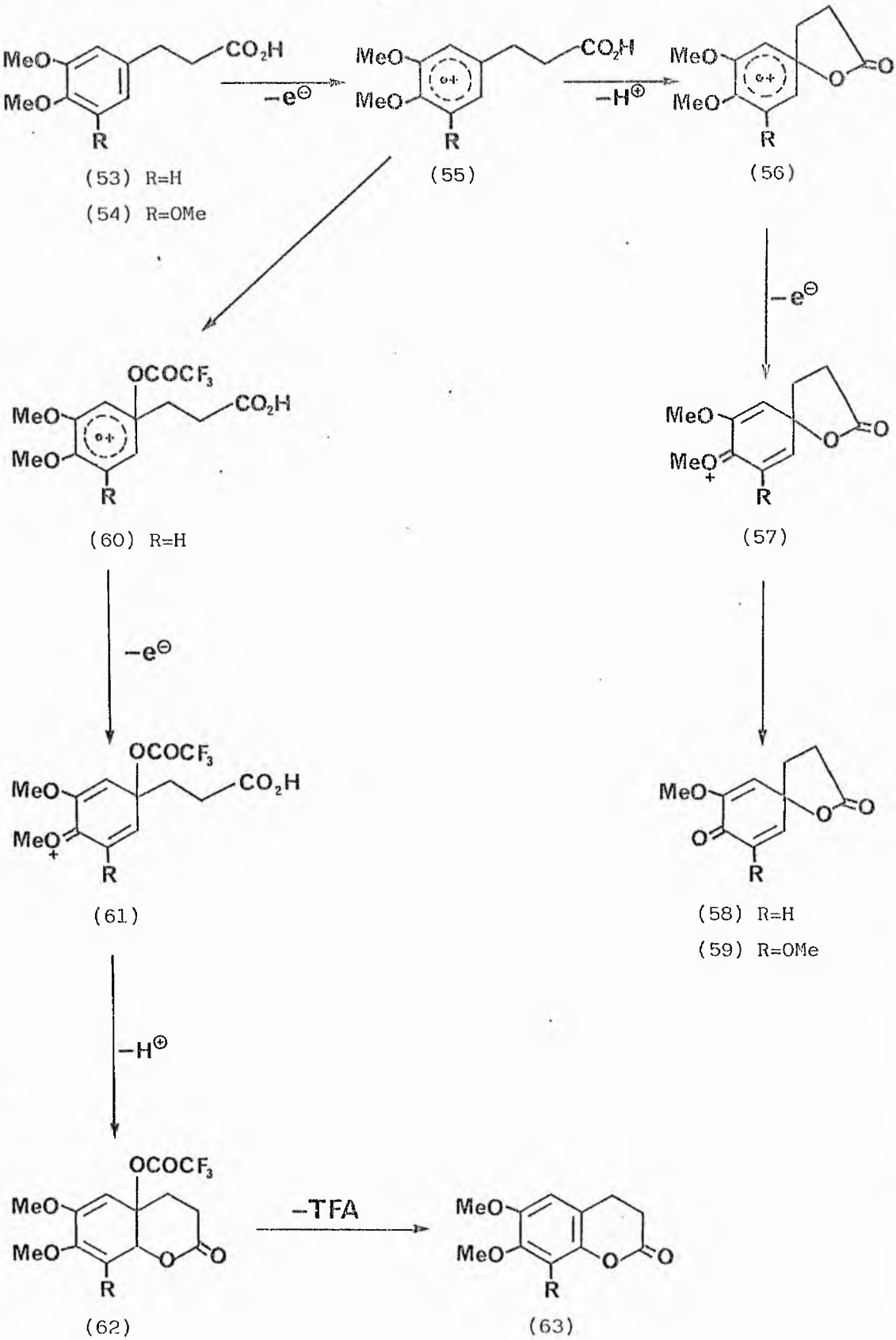
Taylor et al[3,48] found that treatment of electron-rich arylpropionic acids with thallium (III) trifluoroacetate in trifluoroacetic acid containing a small amount of boron trifluoride-etherate resulted in the formation of dihydro-coumarins and spirocyclohexadienone lactones. It was suggested that these products resulted from the initial formation of aromatic radical cations followed by intramolecular cyclisation involving the side-chain carboxyl group, as outlined in Scheme 5. The solvent, trifluoroacetic acid, plays a key role as the demethylating agent. The dihydrocoumarins arise by a competitive pathway involving intermolecular capture of the radical cation (55) by solvent (trifluoroacetic acid). Oxidation of the resulting radical (60), intramolecular Michael addition by the carboxylic group and aromatization then gives the dihydrocoumarin (63) (R=H).

Naphthylalkanoic acids showed similar reactions. Oxidation of 3-(4-methoxy naphthyl) propionic acid (64) gave the dienone lactone (66) (74% yield) and even 3-(1-naphthyl) propionic acid (65) gave the same lactone (66).

1.3.2. Lead tetraacetate

Lead tetracetate has been used extensively for the oxidation of a range of organic compounds. Phenols in particular react readily with

Scheme 5


MeO
MeO
R
CO2H
−e⊖
−H⊕
(53) R=H
(54) R=OMe
(55)
(56)
−e⊖
OCOCF3
(60) R=H
(57)
−e⊖
(61)
(58) R=H
(59) R=OMe
−H⊕
(62)
−TFA
(63)

lead tetraacetate, usually in acetic acid, to give excellent yields of the corresponding acetoxy cyclohexadienones. Although homolytic pathways were originally postulated for the reaction,[49] more recent work favours either heterolysis of (67)[50] or electrophilic attack by the phenol on lead tetraacetate.[51] Concerted transfer of acetate from lead to carbon (68) can account for the generally encountered predominance of α-acetoxylation.[52]

The application of the reaction to the synthesis of a wide range of isoquinoline alkaloids has been reviewed.[53]

Lead tetraacetate oxidation of phenols carried out in the presence of alcohols gives rise to alkoxydienones.[52] The presence of methoxy groups on the phenolic substrate can lead to predominant formation of quinones.[54]

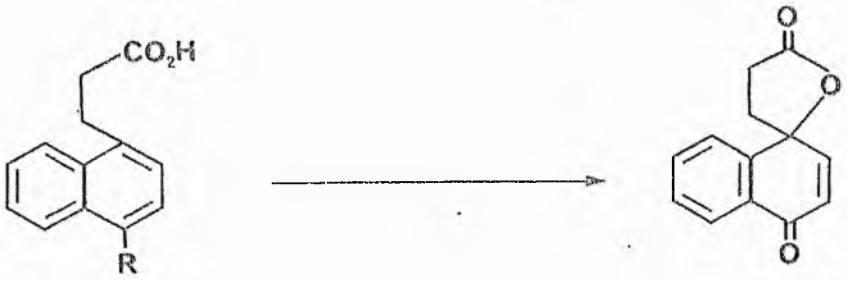
The reaction of phenols with aryl lead (IV) triacetates in chloroform/pyridine produces moderate yields of o- or p-dienones with no acetoxylation occuring.[55]

The reactions of lead tetraacetate with organic substrates have been reviewed several times.[49,56,57]

1.3.3 2,3-Dichloro-5,6-dicyanobenzoquinone

Phenols undergo a wide variety of reactions with 2,3-dichloro-5,6-dicyanobenzoquinone, the initial step being formation of the phenoxyl radical. The oxidation of 2,6-disubstituted phenols with 2,3-dichloro-5,6-dicyanobenzoquinone usually gives diphenoquinones in high yield.

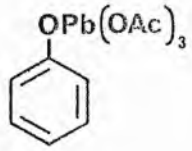
Quinone ketals have been prepared[58] by the oxidation of substituted hydroquinone monoalkyl ethers with 2,3-dichloro-5,6-dicyanobenzoquinone, e.g. (69) gave (70) in 75% yield. Compound (70) was not available by the oxidation of the phenol with thallium trinitrate.



(64) R=OMe

(65) R=H

(66)



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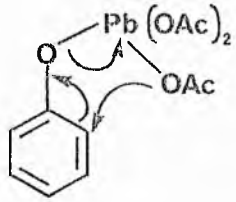

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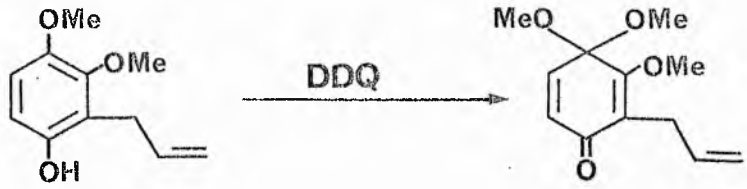

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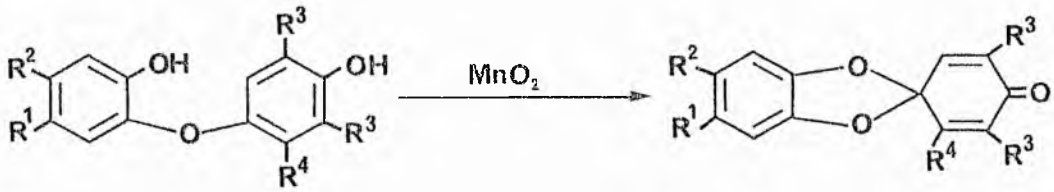

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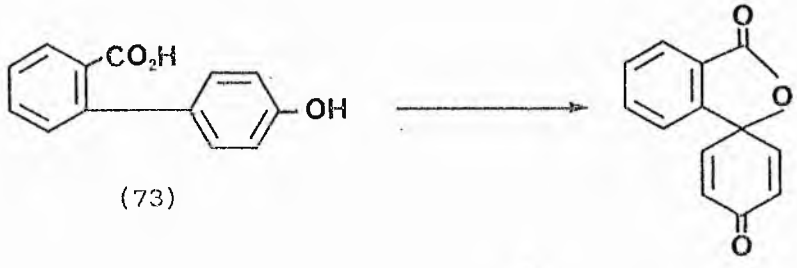


(73)

(74)

1.3.4 Manganese dioxide

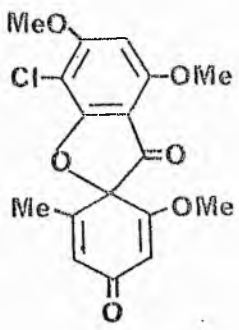
Active manganese dioxide has been widely used as an oxidant in organic chemistry. Phenolic compounds have successfully been converted to spirocyclohexadienones by oxidative coupling using manganese dioxide as the oxidant. Coutts *et al*[59,60] have reported that treatment of 2,4′-dihydroxydiphenyl ethers (71) (R^1=H, Me, or CO_2Me; R^2=H or NO_2; R^3=H or Me; R^4=H, NO_2, or CO_2Me) with active manganese dioxide gave the dienones (72) in low to medium yield.

Oxidation of 4′-hydroxybiphenyl-2-carboxylic acid (73) with manganese dioxide in ether afforded[61] the lactone (74) in 25% yield. The carboxylic acid (76), obtained by the acid hydrolysis of dehydrogriseofulvin (75) has been oxidised[62] to dehydrogriseofulvoxin (77) in 85% yield by manganese dioxide in acetone-ether. Dehydrogriseofulvin (75) has been obtained quantitatively by the oxidation with manganese dioxide of a suitable substituted 2,4′-dihydroxybenzophenone.[63]

A comprehensive review[64] of manganese dioxide as an oxidant in organic chemistry has appeared.

1.3.5 Miscellaneous oxidants

One of the most popular reagents used for phenolic oxidative coupling is potassium ferricyanide, either in alkaline solution or as part of a two-phase system. A number of heterocyclic and carbocyclic spirodienones have been prepared from the oxidative coupling of phenols with potassium ferricyanide, e.g. dehydrogriseofulvin (75)[63] from 2,4′-dihydroxybenzophenone, spirodienone (78)[65] from 2,4′-dehydroxydiphenylethane, and a series of dioxepin spirodienones (79) (R or R^1=Me, Et, *iso*-Pr and Ph) from 2- or 3-substituted-4-methoxyphenols.[66,67] More recently, Sargent and Sala[68] oxidised benzophenones (80) and (81) with potassium ferricyanide for brief periods (30-120 s) and obtained excellent yields of the grisadiendiones (82), which then rearranged under basic and thermal conditions to depsidones (83).[69,70]



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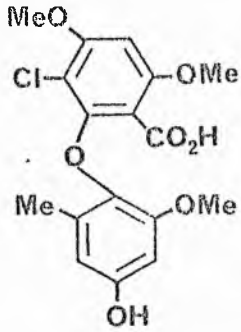

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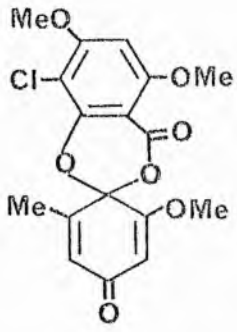

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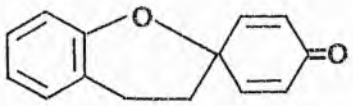

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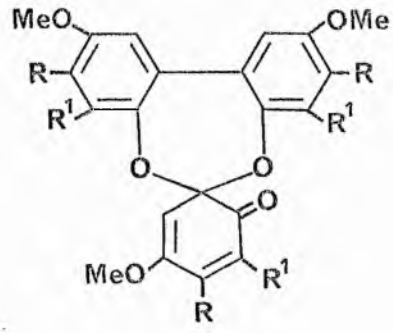

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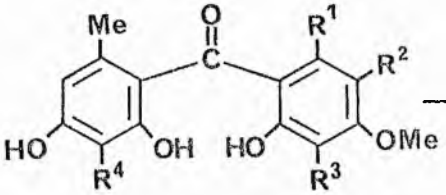
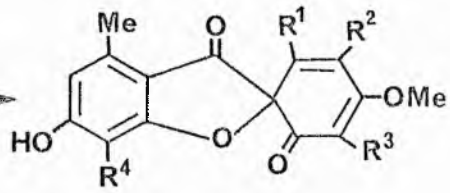


(80) $R^1=R^3=R^4=Me$; $R^2=H$

(81) $R^1=R^3=Me$; $R^2=Cl$; $R^4=H$



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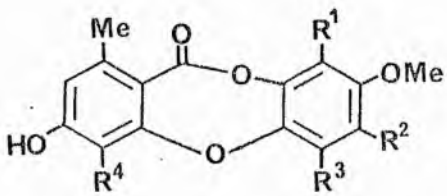


(83)

The phenolic carboxylic acid (84) has been converted in moderate yield to the spirolactone (85) by oxidation[71] with lead dioxide. Treatment of carboxydiphenyl ethers (86) (R^1=H or tert-Bu; R^2=tert-Bu or H) with lead dioxide in ether gave[72] the lactones (87) in 60% yield. The diphenyl methane (88) gave the corresponding spirolactone (89) on oxidation with lead dioxide. Hassall et al[73] reported on the oxidation of dihydroxybenzophenones, in connection with the synthesis of griseofulvin. The spirodienones (90) (R=H or Me) were obtained by lead dioxide oxidation of the corresponding benzophenones in 8 and 70% yields respectively. The carboxylic acids obtained by the hydrolysis of geodin[74] and dechlorogeodin have been oxidised[71] with lead dioxide to geodoxin and dechlorogeodoxin respectively.

Other oxidants which have only been used sporadically to prepare monoacetals of p-benzoquinones in low yield, include copper (II) species, ceric salts, manganese (III) compounds and ferric chloride. Vanadium oxytrihalides are more recently developed reagents, but have been particularly used in the oxidation of non-phenolic or monophenolic compounds rather than diphenols.

1.4 Miscellaneous methods for synthesizing spirocyclic cyclohexadienones

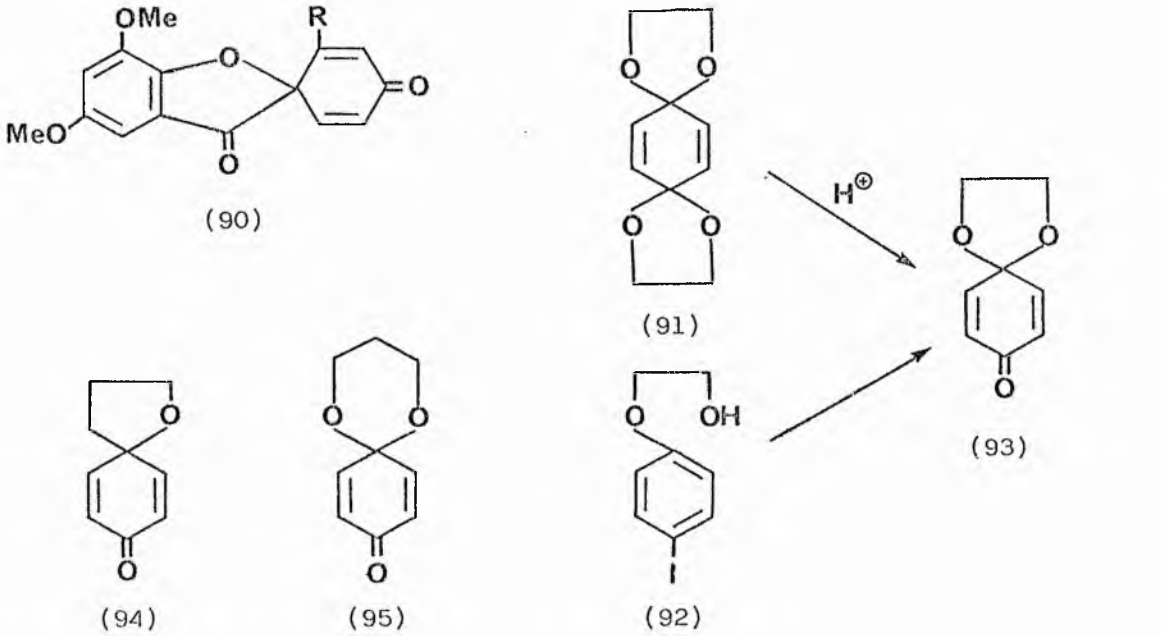
1.4.1 Spiroketals

Two syntheses of one of the simplest spirodienones, 1,4-benzoquinone monoethylene ketal (93) have been reported. The first[75] proceeded from the bis(ethylene ketal) of cyclohexa-1,4-dione which was brominated and dehydrobrominated to give 1,4-benzoquinone-bis (ethylene ketal) (91) which on partial hydrolysis gave 93% of (93). The second synthesis[76] relied on the photochemical cyclisation of 4-iodophenoxyethanol (92) which gave (93) in 84% yield via oxygen-iodine bond cleavage. Spiroketals (94) and (95) were similarly

(84) (85)

(86) (87)

(88) (89)



(90) (91) (93) (94) (95) (92)

prepared[76] from the photochemical cyclisation of 3-phenylpropanol and 3-phenoxypropanol.

1.4.2 Spirolactones

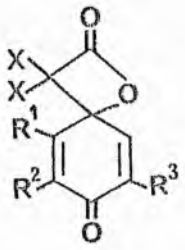
p-Benzoquinone reacts with diphenyl keten[77] and dimethyl keten[78] to give the β-lactones (96) (X=Ph or Me, R^1=R^2=R^3=H). Ogino et al[79] employed the same method to obtain the substituted spiro-β-lactones (96) (X=Ph, R^1=H, R^2=H, Me, or Cl, R^3=H, Me, or Cl). This method of preparation of spirolactones is obviously limited to the β-lactone series.

Electrophilic addition of an electrophile $E^{\oplus}$ to a para-substituted phenol (97) may proceed via the carbocation (98), or via the cyclohexadienone (99), which by nuclephilic displacement of $E^{\ominus}$ from the doubly allylic position gives the spiro compound (100). Treatment of 4-hydroxyphenylpropanoic acid (101) with N-bromosuccinimide gives[80] the brominated spirolactone (102) (R=Br) in high yield, while treatment with N-iodosuccinimide gives (102) (R=I).

Treatment[79] of the potassium salt of 2-methyl-2-(4-tolyloxy) propanoic acid (103) with bromine in aqueous solution gives a good yield of the brominated spirolactone (104) (X=Br). The reaction is assumed to proceed by ipso electrophilic addition of the bromonium ion para to the alkoxy group, followed by intramolecular nucleophilic addition of the carboxylate anion. Low temperature nitration of (103) in acetic anhydride gave[81] the nitrolactone (104) ($X=NO_2$).

1.5 Spirodienones with biological activity

The spirocyclohexadienone structure occurs in two main classes of natural products, fungal metabolites and alkaloids. It also occurs in an oxidation product of vitamin E, which is thought to be a liver metabolite.



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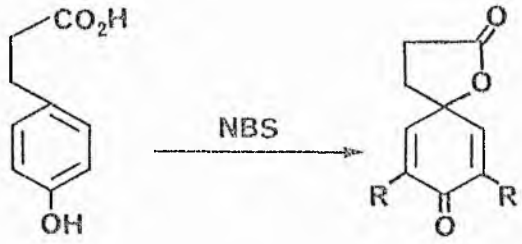
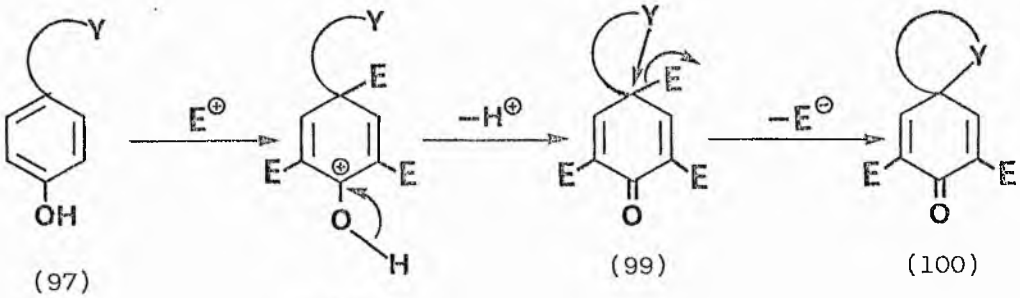
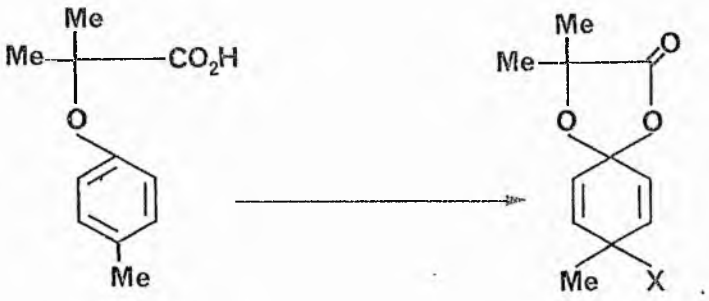


(101) (102)



(97) (98) (99) (100)



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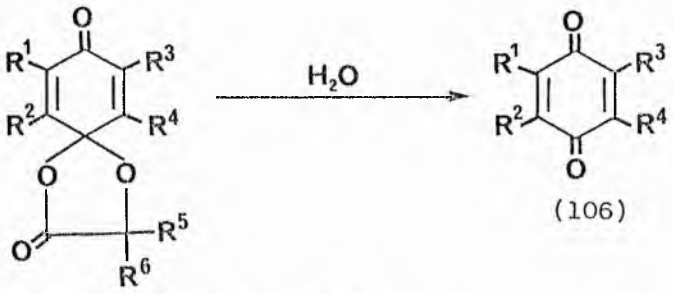


(106)

(105) a; $R^1, R^2, R^3, R^4, R^5, R^6$=H

b; R^1, R^2, R^3, R^4=Cl; R^5, R^6=H

c; R^1, R^2, R^3, R^4=Cl; R^5=CH_3; R^6=H

1.5.1 Spirolactone fungicides related to benzoquinones

Benzoquinones such as p-tetrachlorobenzoquinone (chloranil)[82] and 2,3-dichloronaphthaquinone (dichlone)[83] are active against fungi and bacteria, but their present usage is mainly restricted to seed dressings as these compounds have proved to be too labile for foliar application. The probable reasons for the rapid loss of activity when quinones are sprayed on foliage include, hydrolysis to substances such as chloranilic acid which are only weakly fungitoxic, photolysis causing either reduction or dimer formation, and sublimation at low temperatures.

To overcome the instability of the quinones, the hydrolysis of spirolactones (105 a-c) to benzoquinones (106) was studied,[84] in an attempt to determine the parameters which would make the spirolactones sufficiently resistant towards hydrolysis and release the derived benzoquinones at a steady rate over a prolonged period. It was established[84] that the placing of an alkyl group in the side-chain has a greater effect in reducing the rate of hydrolysis when halogen is present in the quinoid ring than when only hydrogen is present.

All the available evidence suggests[84] that the spirolactones can not, in themselves, prevent spore germination, and that the agent responsible for their apparent activity is the derived benzoquinone.

Benzoquinones are thought to act by two major pathways in their antimicrobial action: (i) addition of thiol and amino groups to the $\alpha\beta$-unsaturated ketonic system;[85] and (ii) interference with biological oxidation-reduction reactions.[86]

The spirolactone system should be unable to undergo reversible reduction owing to the blocking effect of the spiro ring.

1.5.2 Fungal metabolites

Griseofulvin (from Penicillium species)

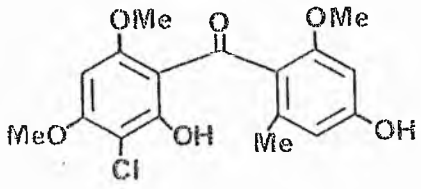
Griseofulvin is one of the few medically important antifungal agents. Its gross structure was determined[87] as (109) and its absolute configuration subsequently established.[88] It is a reduced spirodienone but is easily oxidised to dehydrogriseofulvin (108) by selenium dioxide.[89] Compound (108) has been synthesised from griseophenone (107) by several workers.[63,90] Analogues of griseofulvin have been prepared[90,91] via the oxidation of the appropriate benzophenones to the dehydrogriseofulvins (110) (R^1=H, F, Cl, or Br; R^2=H or Cl; R^3=H or Me; R^4=OMe). The mode of action of griseofulvin is not yet known.

Thelepin (from Thelepus setosus)

This compound, similar to the fungal metabolites, was isolated from a marine annelid, and its structure established[92] as (111). Thelepin shows antifungal activity comparable with that of griseofulvin, and has been recently synthesised.[92a]

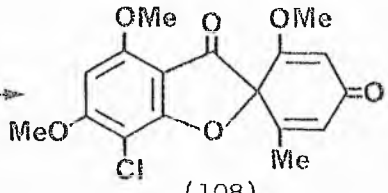
1.5.3 Alkaloids

The spirocyclohexadienone structure is found in a wide range of naturally occuring alkaloids or their synthetic intermediates, e.g. proaporphine,[93] morphinandienone,[94] erythrina,[95] amaryllidaceae,[96] cularine,[97] and phenanthroquinolizidine alkaloids.[98] The field has been reviewed.[99] However, heterocyclic spirocyclohexadienone structures are found in very few naturally occuring alkaloids or their synthetic intermediates, e.g. cularine itself (112) has an oxygen atom in the spiro ring, while some amaryllidaceae alkaloid intermediates typified by (113), have a nitrogen atom in their spiro ring. None of the heterocyclic spirocyclohexadienone alkaloids showsbiological activity.



(107)

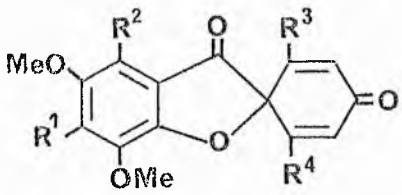
ox



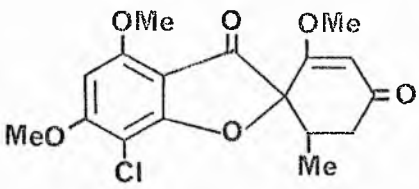
(108)

H_2/Pd

SeO_2



(110)



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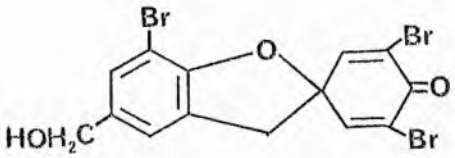

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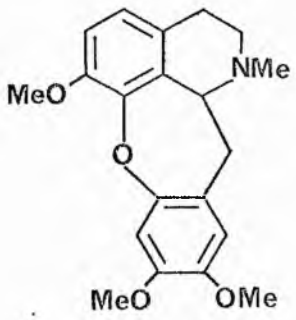

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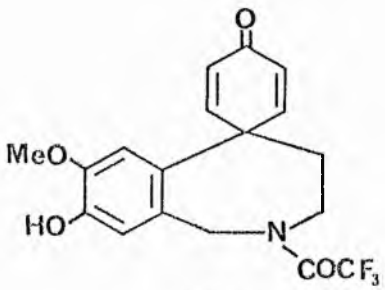


(113)

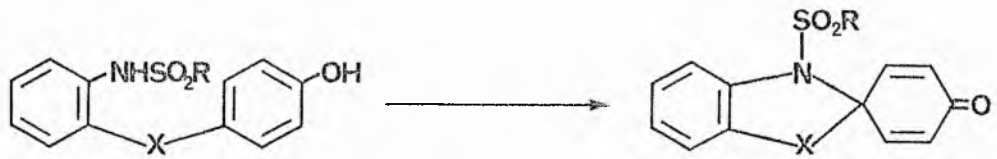
CHAPTER TWO

SYNTHESIS OF NITROGEN CONTAINING SPIROCYCLOHEXADIENONES

2.1 Introduction

Although the oxidation of aromatic sulphonamides to quinone-imides and di-imides has been extensively studied,[100] the use of a sulphonamide substitute as a "phenol equivalent" in an oxidative coupling reaction has received little attention. The successful oxidation with manganese dioxide of secondary aromatic sulphonamides (114) and (119) to give spirobenzoxazole (120) and spirobenzimidazole (121) respectively has recently been reported.[101] The yield of benzoxazole compares favourably with that obtained by oxidation of the isomeric dihydroxydiphenylamine (118), which is more difficult to synthesize.

In this Chapter are discussed attempts to synthesize 5- or 6-membered nitrogen-containing spirocyclic cyclohexadienones (II), using the oxidative coupling of sulphonamides (I) in the formation of the spirocyclic ring.



(I) (II)

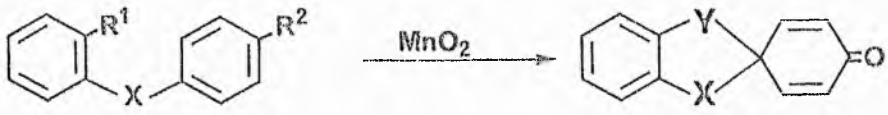
If the X linkage in (I) is a one-carbon unit the resulting spiroheterocycle is an azagrisan which may have useful pharmacological activity.

2.2 Nitrogen containing heterocylic spirodienones

Nitrogen-containing heterocyclic spirodienones are less common than their oxygen-containing analogues. Hey and his co-workers made a study of spirodienone lactams. Compound (123) (R=Me or Et) was first isolated[102] from the decomposition of the aminobenzanilide (122), in 48% yield. The 2-methoxy isomer of (122) gave a low yield of the 2,4-dienone (124). It was later found[103] that the same compounds were formed by treatment of N-alkyl-2-or 3-bromo-4′-hydroxybenzanilides with potassamide in liquid ammonia.

Persulphate oxidation of biphenylcarboxamides gives spirolactams.[104] Compound (123) (R=Me) was formed from N-methylbiphenyl-2-carboxamide and also from the 4′-methoxy analogue. Oxidation of N-methyl-2′-methoxybiphenyl-2-carboxamide gave (124) (R=Me) and (125). The dienol (126) was prepared[105] by photolysis of N-ethyl-2-bromo-4′-hydroxybenzanilide in aqueous alkali in the presence of sodium borohydride; on oxidation by manganese dioxide it gave the dienone (123) (R=Et, 59% yield). Similarly,[106] N-methyl-2-iodo-4′-methoxybenzanilide gave (123) (R=Me) on photolysis in oxygen-free benzene, while the same product was obtained by similar treatment of N-methyl-2-iodobenzanilide in benzene saturated with oxygen. Compounds (123) (R=H, Me or Ph) were obtained[107] by the oxidation of the appropriate biphenyl-2-carboxamides with tert-butyl hypochlorite and iodine. Naphthalene analogues (127) and (128) of these spirolactams have been prepared by decomposition of diazonium salts.[108,109]

The oxidation of phenolic oximes has been studied[110] in an investigation into the synthesis of aerothionin, a sponge metabolite. Reaction of a series of 4-hydroxyarylpropan-2-one oximes (129) with manganese tris (acetylacetonate) in acetonitrile gave spiro-isoxazolines (130) (R^1=H or t-Bu; R^2=H or Me; R^3=H, Me or COOMe) in yields of 20-60%. This



(114) X=O, R^1=NHTs, R^2=OH

(115) X=O, R^1=NO_2, R^2=OBzl

(116) X=O, R^1=NH_2, R^2=OBzl

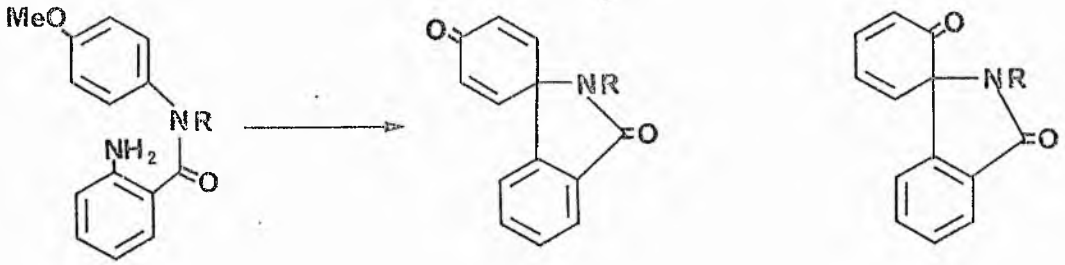
(117) X=O, R^1=NHTs, R^2=OBzl

(118) X=NTs, R^1=R^2=OH

(119) X=NTs, R^1=NTs, R^2=OH

(120) X=O, Y=NTs

(121) X=Y=NTs



(122) (123) (124)

(125) (126)

(127) (128)

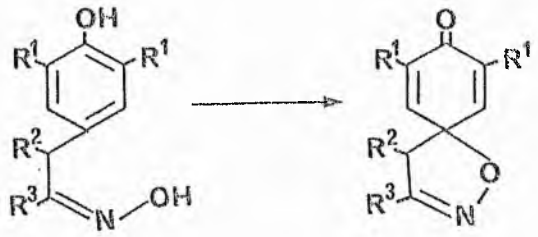
reagent did not produce dienones from the 2-hydroxyaryloximes, probably because the phenol and oxime groups were close enough to interact with the manganese. The mechanism is considered unlikely to proceed through a bi-radical but rather by trapping, by the oxime, of an incipient phenoxenium ion produced by heterolysis of the oxygen-manganese bond in the metal-phenol complex. A similar intermediate has been postulated for the preparation of spiroisoxazole (132) by anodic oxidation of 3,5-dibromo-4-hydroxyphenylpyruvate oxime.[35] Bromine and sources of "positive bromine" also effected the cyclisation; the oxime (131) gave (132) in 65% yield with bromine water while (133) gave (134) in 72% yield on treatment with N-bromosuccinimide.

2.3 Preparation of substrates for oxidation

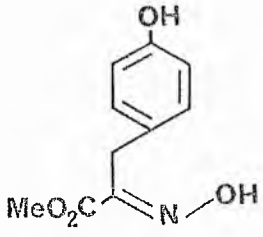
2.3.1 Diphenyl ethers

The successful oxidation with manganese dioxide of a series of 2,4′-dihydroxydiphenyl ethers (71) to the corresponding 1,3-benzodioxole-2-spirocyclohexadien-4′-ones (72) has been reported recently.[60] The dihydroxydiphenyl ethers were prepared in good yields from the reaction of p-substituted phenols with aryl halides in the presence of a copper catalyst.[111]

From the reaction of 1-bromo-2-nitrobenzene with 4-benzyloxyphenol a 41% yield of diphenyl ether (115) was reported,[99] but it has been found in these laboratories that nitro-substituted aryl halides give tars when treated with copper. A reaction between 4-benzyloxyphenol and 1-bromo-2-nitrobenzene in refluxing methyl ethyl ketone and potassium carbonate gave only a 17% yield of (115). On reduction with iron/acetic acid (115) produced the amine (116) in 74% yield. This amine was converted to sulphonamide (117) with 4-toluenesulphonyl-chloride in pyridine and debenzylated with ethanolic hydrochloric acid



(129) (130)



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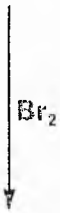
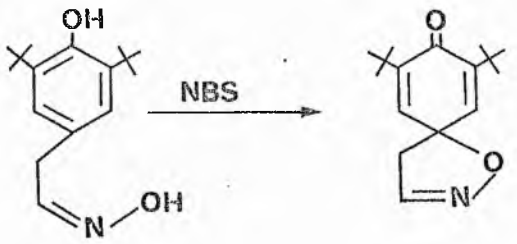
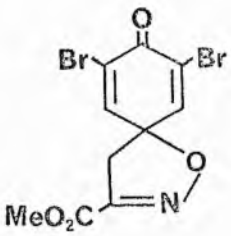




(133) (134)



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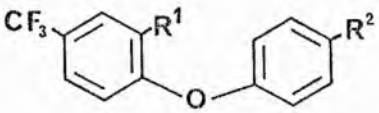
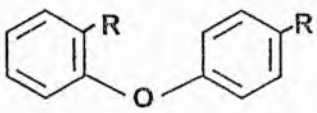


(135) R^1=NO_2, R^2=OBzl
(136) R^1=NH_2, R^2=OBzl
(137) R^1=NHTs, R^2=OBzl
(138) R^1=NHTs, R^2=OH



(139) R=NO_2
(140) R=NH_2
(141) R=NHTs

to give phenol (114).

The low yield obtained from the above reaction was dramatically improved by the use of a more activated aryl halide. Reaction of the sodium salt of 4-benzyloxyphenol with 4-chloro-3-nitrobenzotrifluoride in dimethylformamide at 140°C gave a 57% yield of the nitrodiphenyl ether (135) which, on reduction with iron/acetic acid produced the corresponding amino compound (136). This compound was converted to sulphonamide (137) and debenzylated with ethanolic hydrochloric acid to afford the sulphonamido-phenol (138).

2,4′-Dinitrodiphenyl ether (139) was prepared in 68% yield from the reaction of 4-nitrophenol and 1-fluoro-2-nitrobenzene in dimethylformamide. Catalytic hydrogenation gave the diamine (140) which was converted to bis-sulphonamide (141) in 70% yield.

2.4 Preparation of 2-sulphonamidobenzophenones

The synthesis of naturally occuring grisa-2′,5′-diene-3,4′-diones and their analogues has usually been accomplished by oxidative coupling of 2,4′-dihydroxybenzophenones (see Chapter One). It seemed likely that nitrogen-containing spirocyclohexadienones could be formed from the oxidative coupling of secondary aromatic sulphonamidobenzophenones, which could be obtained from 2-aminobenzophenones.

The use of 2-aminobenzophenones as starting materials for a synthesis of a wide variety of heterocyclic systems is well documented. An early review[112] listed their use in the preparation of fluorenones, acridines, acridones, cinnolines, quinazolines, and indazoles. More recently, 4-arylquinolines,[113] 3-arylindoles,[114] 4-arylquinazolones,[115] and the pharmacologically active 1,4-benzodiazepines[116] have been prepared from 2-aminobenzophenones. Methods for the preparation of 2-aminobenzophenones and their derivatives have been reviewed recently.[117]

From the available methods for the preparation of 2-aminobenzophenones, the methods involving (a) the use of nitroaryl substrates, (b) the addition of a Grignard reagent to a 3,1-benzoxazin-4-one and (c) the Friedel-Crafts reaction of 2-sulphonamidobenzoyl chlorides with anisole were used in this study because of the reported high yields and the availability of the starting materials.

2.4.1 Attempted preparation of aminobenzophenones by Friedel-Crafts acylation

A general approach to the preparation of aminobenzophenones derivatives employs the Friedel-Crafts reaction of a nitroaroyl halide with a substituted benzene; reduction of the intermediate nitrobenzophenone affords the corresponding aminobenzophenone. This method is usually satisfactory for the synthesis of 3- or 4-aminobenzophenone derivatives, but has proved to be less useful for 2-aminobenzophenone derivatives. The 2-nitrobenzyl chlorides are not good substrates for the Friedel-Crafts reaction, probably due to detrimental complexation of the nitro group with the catalyst. Russian workers have reported[118] that the trichlorosilyl group can be used to activate the acid group of 2-nitrobenzoic acid for a Friedel-Crafts reaction. Yields of 50-80% have been claimed, but these results could not be repeated by other workers.[117]

2.4.2 Preparation of aminobenzophenones from morpholineacetonitriles

The use of masked functional groups such as acyl anion equivalents in the formation of carbon-carbon bonds has proved to be a useful strategy in the development of new synthetic methods.[119] For example, Stetter has studied the addition of aryl aldehydes to $\alpha\beta$-unsaturated esters, ketones, and nitriles by the use of anions from intermediate cyanohydrins.[120] The utility of O-alkylated cyanohydrins[121] and O-silyated cyanohydrins in the synthesis of ketones has been reported.[122]

Related masked acyl anion equivalents are those derived from α-aryl-α-(dialkylamino)acetonitriles.[123] Alkylations with benzyl halides have been studied[124] and Leete reported[125] the 1,4-addition of α-(3-pyridyl)-4-morpholineacetonitrile to acrylonitrile.

Albright and McEvoy[126] have investigated the alkylation of anions of α-aryl-4-morpholineacetonitriles with ethyl bromoacetate, epichlorohydrin, or allyl chloride and also acylations with ethyl chloroformate and benzoyl chlorides. These anions add to ethyl acrylate and acrylonitrile to give 1,4-addition products[127] and, most important of all, they displace halogen on benzene derivatives containing electron-withdrawing groups to give benzophenones.

The α-aryl-4-morpholineacetonitriles are usually prepared from the acid-catalysed reaction of an aromatic aldehyde with an excess of morpholine followed by the addition of potassium cyanide. The anions are usually generated with sodium hydride in dimethylformamide.[126]

The reaction sequence from nitroaryl substrates and acyl anions to give 2-sulphonamidobenzophenones is shown in Scheme 6. Reaction of 4-benzyloxybenzaldehyde with morpholine and potassium cyanide in the presence of 4-toluenesulphonic acid gave a 65% yield of morpholineacetonitrile (142).

Similarly, from 3,4,5-trimethoxybenzaldehyde, morpholine, and potassium cyanide was obtained the known[127] morpholineacetonitrile (143) in 80% yield. The anions of (142) and (143), generated with sodium hydride in dry dimethylformamide, were reacted with 4-chloro-3-nitro-1-trifluoromethyl benzene at 0°C to give adducts (144) and (145) in 71 and 50% yield respectively. When (144) and (145) were heated under reflux in 70% acetic acid, the nitrobenzophenones (146) and (149) were obtained in 75 and 78% yield respectively.

Catalytic reduction with concurrent hydrogenolysis of the benzyl ether of (146) gave a 75% yield of the corresponding aminohydroxybenzophenone (147), which was converted to sulphonamidophenol (148) in 84% yield.

Similarly, the nitro compound (149) was reduced to amine (150) in 70% yield. This amine did not react with 4-toluenesulphonylchloride even after prolonged reflux in chloroform and pyridine, presumably due to steric hindrance. However, it reacted with methanesulphonyl chloride to give a 40% yield of sulphonamide (151).

2.4.3 The addition of a Grignard reagent to a 3,1-benzoxazin-4-one

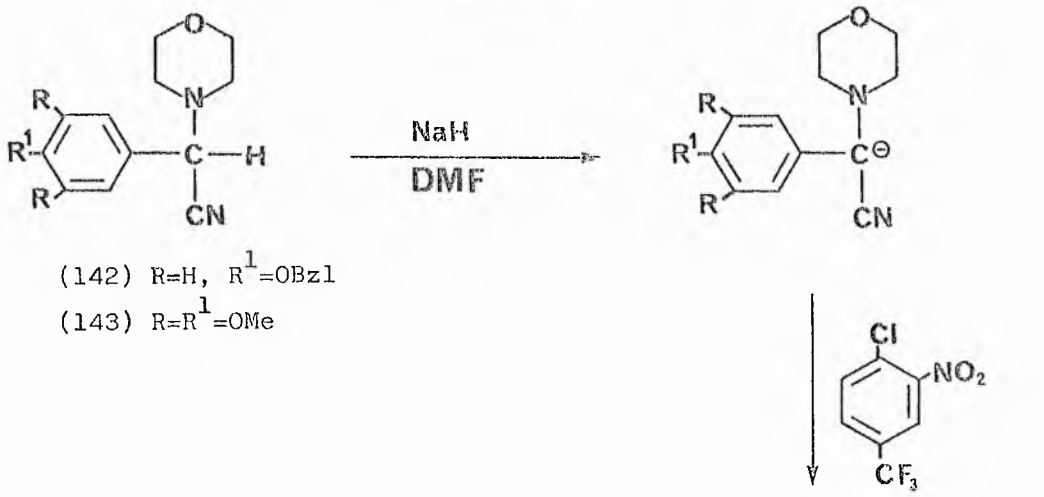
The inverse addition of a Grignard reagent to a 3,1-benzoxazin-4-one is well documented[128] and has been used extensively[129,130] to prepare 2-aminobenzophenones. The yields reported have been in the range of 25-50%, but by control of the temperature and use of an excess of the 3,1-benzoxazin-4-one yields approaching 90% can routinely be obtained. The 3,1-benzoxazin-4-ones are prepared from anthranilic acids and acetic anhydride.

The attempted inverse addition of 4-methoxyphenylmagnesium-bromide to 2-methyl-4H-3,1-benzoxazin-4-one (Scheme 7, R^1 = H and R^2 = p-OMe) failed to give any of the expected amide, perhaps due to insufficient formation of the Grignard; haloanisoles are known[131] to form Grignards with difficulty.

2.4.4 Friedel-Crafts reaction of 2-sulphonamidobenzoyl chloride with anisole

2-(p-Toluenesulphonamido)-4'-methoxybenzophenone (154) was prepared in 63% yield from the Friedel-Crafts reaction of the acid chloride of p-toluenesulphonylanthranilic acid[132] (152) with anisole (see Experimental). This one step high yield synthesis seemed

Scheme 6

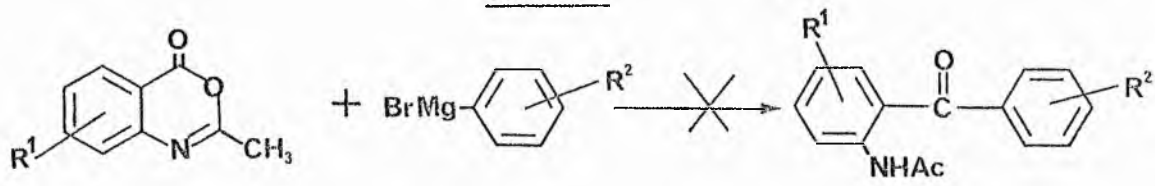


(142) R=H, R^1=OBzl
(143) R=R^1=OMe

(144) R=H, R^1=OBzl
(145) R=R^1=OMe

(146) R=H, R^1=OBzl, R^2=NO_2
(147) R=H, R^1=OH, R^2=NH_2
(148) R=H, R^1=OH, R^2=NHTs
(149) R=R^1=OMe, R^2=NO_2
(150) R=R^1=OMe, R^2=NH_2
(151) R=R^1=OMe, R^2=NHTs

Scheme 7



(152) R=Ts
(153) R=Ms

(154)

promising, but unfortunately all attempts to remove the methyl protecting group in order to obtain the phenol failed. Methyl protecting groups on phenols are generally very difficult to remove and the reagents and conditions used are summarised in Chapter 3.

2.5 Preparation of 2-sulphonamidoanthranilate esters and N,N-diaryl-2-carboxylates

The preparation of five-membered nitrogen-containing spirodienones has been discussed in section 2.2. Compounds of type (113), which contain a nitrogen atom in their seven-membered spiro-ring, have often been implicated in the synthesis of amaryllidaceae alkaloids.[96] However, compounds with six membered nitrogen-containing spirodienones have not been described previously.

One possible route into six membered nitrogen spirodienones is by oxidative coupling of the sulphonamido esters (156) and (158) to give lactones (159) and (160). The esters (155) and (157) were prepared from the reaction of the acid chlorides of 4-toluenesulphonamido-and methanesulphonamidoanthranilic acids (152) and (153) with 4-benzyloxyphenol in refluxing pyridine; the resulting benzyl ethers were cleaved by hydrogenolysis to give good yields of phenols (156) and (158).

The spirolactones (159) and (160) should also be obtainable by oxidative coupling of NN-diarylsulphonamido-2-carboxylates. The preparation of a series of unsymmetrically substituted NN-diaryltolnene-4-sulphonamides from the copper-catalysed reaction of N-arylsulphonamides with aryl bromides has been reported.[133] Unfortunately, this method could not be applied successfully to the synthesis of diarylsulphonamido-carboxylates. Very low (5-11%) yields of diarylsulphonamido-esters were obtained from the reaction of N-toluene-4-sulphonyl-4-benzyloxyaniline or N-methanesulphonyl-4-

benzyloxyaniline with methyl 2-bromobenzoate, methyl 2-fluorobenzoate, methyl 2-bromo-5-nitrobenzoate, and methyl 2-fluoro-5-nitrobenzoate in the presence of copper bronze and anhydrous potassium carbonate.

Scherrer[134] has reported that diphenyliodonium-2-carboxylate reacts readily in copper ion catalysed condensations with a variety of nucleophiles, including anilines and sulphonanilides, to give ortho-substituted benzoic acids. These reactions occur at temperatures of 80-100°C, below those at which benzyne formation and other side reactions become important. The nature of the copper (II) catalysis appears to be different from the more common copper (I) catalysis of diaryliodonium reactions in that high specificity for nucleophilic attack on the carboxylate-bearing ring is observed.

When the sodium salt of N-methanesulphonyl-4-benzyloxyaniline was reacted with an equimolar quantity of diphenyliodonium-2-carboxylate in 1,2-dimethoxyethane with cupric acetate as catalyst, the diphenylamine carboxylic acid (161) was obtained in 50% yield; hyrogenolysis of the benzyl group gave an 86% yield of the corresponding phenolic acid (162).

2.6 Oxidation of substrates

The use of phenol oxidative coupling as a route to spirocyclohexadienones has been discussed in Chapter One. The range of oxidants which has been used is wide, but because of the success achieved in the oxidation of dihydroxydiaryl ethers[60] using manganese dioxide, this reagent was chosen first in the present case. Lead tetraacetate was used for the oxidation of the phenolic benzoic acid (162).

2.6.1 Synthesis of the benzoxazole spirodienones (120) and (163)

2-(4-Toluenesulphonamido)-4′-hydroxydiphenyl ether (114), when heated under reflux in benzene with an excess of manganese dioxide (SEDEMA, "Faradiser M"), afforded the desired spirodienone (120) in 50% yield. The same spirodienone (120) has previously been obtained[101] in similar yield using a different[135] manganese dioxide.

Similarly, oxidation of 2-(4-toluenesulphonamido)-4-trifluoromethyl-4′-hydroxydiphenyl ether (138) with manganese dioxide gave the desired spirodienone (163) as a yellow crystalline solid in 31% yield. Its ir spectrum showed three bands at 1680, 1640 and 1615 cm^{-1}, which coincide with those reported[136] to be the characteristic stretching absorptions of cyclohexa-2,5-dienones (1640-1680, 1615-1650 and 1590-1620cm^{-1}).

The lower yield of spirodienone obtained from this oxidation is perhaps due to the influence of the electron-withdrawing trifluoromethyl group. This presumably reduces the nucleophilicity of the sulphonamide group and diminishes its ability to react with the radical cation formed on the neighbouring phenolic ring.

The oxidation with manganese dioxide of the bis-sulphomanidodiphenyl ether (141) gave a complex mixture of products, from which was isolated by chromatography on alumina a 0.5% yield of benzoxazole (120), identified by t.l.c., ir spectroscopy, and mixed m.p., with the product of oxidation of (114). This benzoxazole presumably arises from the hydrolysis on the alumina column of the intermediate spiroimine. Similar hydrolysis of imine bonds on alumina columns have been utilised for the efficient synthesis of spirodienones (see Chapter 1).

2.6.2 Synthesis of a nitrogen-containing six-membered spirolactone

N-Methanesulphonyl-N-4-hydroxyphenylanthranilic acid (162), when stirred in a suspension of freshly crystallised lead tetraacetate in

glacial acetic acid, afforded the spirolactone (160) in 40% yield. Its ir spectrum showed a characteristic δ-lactone absorption at 1750 cm^{-1}, whilst bands at 1680 and 1640 cm^{-1} were characteristic of a cyclohexa-2,5-dienone.

The spirolactone obtained in 5% yield from the oxidation with manganese dioxide of the ester (158) was identified as (160) by t.l.c., ir spectroscopy, and mixed m.p.

No evidence of spirolactone formation was obtained from the oxidation with manganese dioxide of ester (156). However, a yellow compound, homogenous by t.l.c., with an Rf value different from that of starting material, was obtained almost quantitatively. Its ir spectrum showed a strong absorption at 1700 cm^{-1}, which is identical to the carbonyl absorption of the starting material; it also showed the complete disappearance of the absorption due either to phenol or sulphonmide group. Elemental analysis of this yellow compound gave different results from samples recrystallised from different solvents. No clear identification of this oxidation product of (156) could be made on this evidence.

2.6.3 Oxidation of benzophenones (148) and (151)

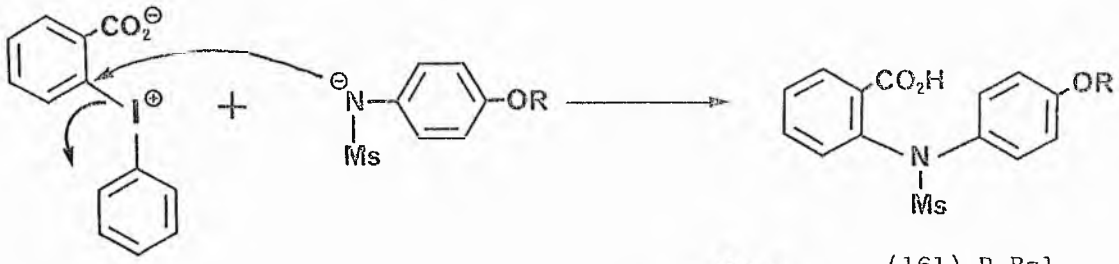
From attempted oxidation of benzophenone (148) with manganese dioxide in benzene, lead tetraacetate in acetic acid, or anodic oxidation in acetonitrile starting material was recovered, with no evidence of dienone formation.

The oxidation of (151) with thallium (III) trifluoroacetate in trifluoroacetic acid under conditions described in the General Introduction gave a high yield of a yellow compound which did not show any characteristic cyclohexa-2,5-dienone absorptions in the ir spectrum. Flame tests established the presence of thallium, which broadened the resonances in the proton nmr spectrum. The properties of the oxidation product of (151) were consistent with a thallated adduct.

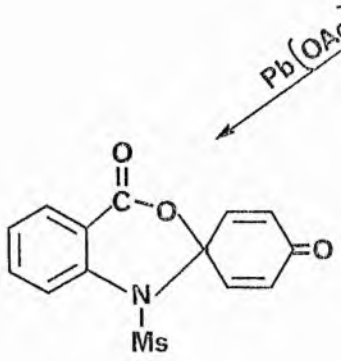
(155) X=CO_2, R^1=NHTs, R^2=OBzl
(156) X=CO_2, R^1=NHTs, R^2=OH
(157) X=CO_2, R^1=NHMs, R^2=OBzl
(158) X=CO_2, R^1=NHMs, R^2=OH

(159) R=Ts

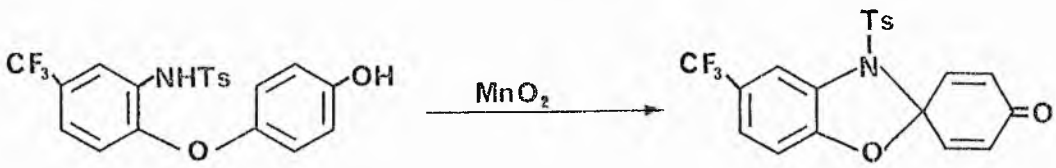
(160) R=Ms



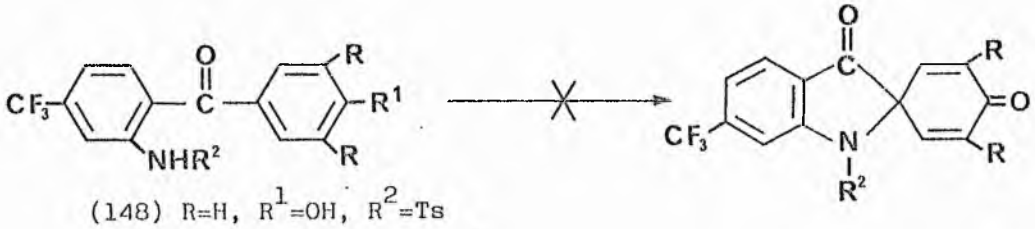
(161) R=Bzl
(162) R=H



(160)



(138) (163)



(148) R=H, R^1=OH, R^2=Ts
(151) R=R^1=OMe, R^2=Ms

CHAPTER THREE

THE GENERATION AND SYNTHETIC UTILITY OF THE DIANION DERIVED FROM 3-FUROIC ACID

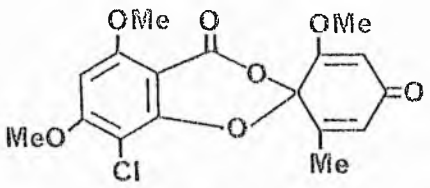
3.1 Introduction

δ-Spirolactones of the type (V) shown in Scheme 8, where Ar is benzene or a five-membered aromatic heterocycle have structures similar to those found in the mould metabolites griseofulvoxin (164) and geodoxin (165), the only difference being the replacement of oxygen by carbon. Such compounds have not, to our knowledge, been prepared. A possible synthetic sequence for compounds of type (V), where Ar is a heterocycle is outlined in Scheme 8.

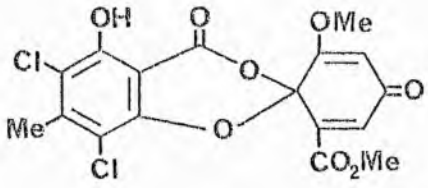
A dianion (I), derived from the ortho lithiation of the carboxylic acid with lithium diisopropylamide is condensed with an aryl aldehyde or ketone, substituted in the 4-position with a protected hydroxyl, to give carbinols (II) (R=alkyl or H). Oxidation of carbinols (II) (R=H) with manganese dioxide to the benzophenones (III) or reduction to the diarylalkanes (IV), and hydrogenolysis of the phenol protecting groups gives substrates ready for oxidation. Finally, oxidation of these substrates with manganese dioxide or lead tetraacetate could lead to cyclisation by intramolecular capture of the radical cation generated on the phenolic ring with carboxylate ion, to give (V).

3.2 Heteroatom facilitated lithiations

Heteroatom facilitated lithiations have proved to be exceptionally useful in the regioselective and very often regiospecific functionalization of carbocyclic and heterocyclic aromatic as well as of olefinic substrates. The term lithiation is here defined as the exchange of a hydrogen atom attached to an sp^2-hybridized carbon atom

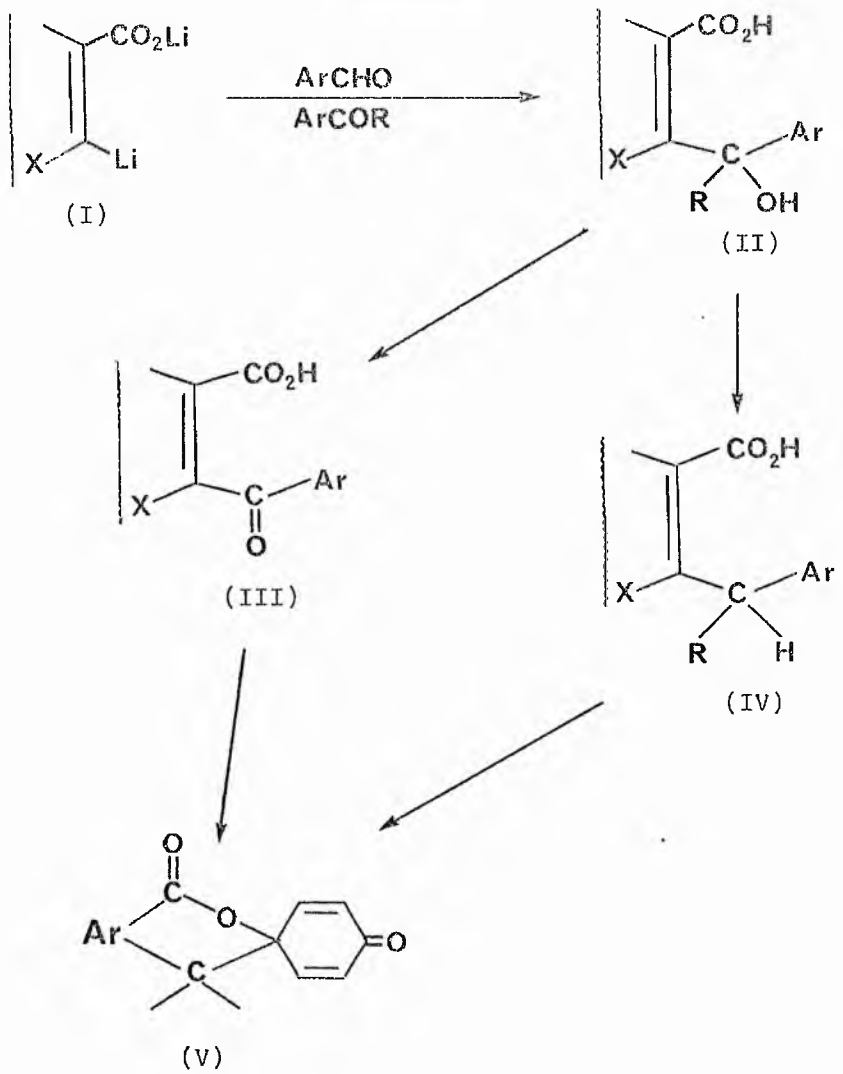


(164)



(165)

Scheme 8



by lithium to form a covalent lithium-carbon bond. Based on the relative position of the heteroatom, such lithiations have been classified into two principal categories: alpha and beta (ortho) lithiations. A schematic illustration of these reactions is shown in Scheme 9. Two excellent reviews[139,140] on heteroatom facilitated lithiations have appeared recently.

Beta or ortho lithiations are reactions in which a heteroatom or group of heteroatoms attached directly or indirectly to an olefinic or aromatic π-system directs the metalating agent to deprotonate the beta or ortho position. Conversely, in alpha lithiations deprotonation occurs on the same sp^2-carbon to which the heteroatom X is attached.

The formation of dianions (166) directly from alkanoic acids and the base lithium diisopropylamide (LDA) was first reported by Creger[141] who demonstrated the considerable synthetic utility of these species. The rather different dianion (167) has been obtained from the corresponding α-bromo acid by metal-halogen exchange.[142]

The metallation of simple heterocycles and the subsequent reactions of the resulting anionic species with electrophiles has long been recognised as an extremely valuable method in heterocyclic synthesis.[139] Although many substituents have been used to control the site of metallation in a variety of heterocycles[139] (e.g. regiometallation at the 2-position of a 3-substituted furan[143] or thiophen), there are few reports of the metallation of heterocyclic acids.

Dean and his co-workers[144] have reported the formation and trapping by carbon dioxide of the dianion (168) derived from benzo [b] furan-2-carboxylic acid and LDA. A more recent paper[145] describes the synthetic utility of (168) and its isomer (169). Davies and Davies[146] have briefly reported that sequential treatment of thiophen-3-carboxylic acid with LDA followed by either deuterium oxide

or trimethylsilyl chloride leads only to the 2-subtituted derivative, implying that dianion (170) can be formed. Subsequently, Knight[147a] has shown that similar treatment of thiophen-2-carboxylic acid leads only to the 5-substituted derivative via dianion (172). In a similar manner, the dianionic species (171) and (173) can be obtained from the corresponding furancarboxylic acid.[147b]

The reactions of the thiophen and furan dianions with a range of electrophiles have been reported. In general, the thiophen dianions (170) and (172) are more stable and less reactive that the corresponding furan dianions (171) and (173). Whereas the latter are rapidly protonated at $-30^{o}C$, compounds (170) and (172) appear to be relatively stable at this temperature. Also notable is the marked difference in reactivity with carbonyl compounds; the furan dianions (171) and (173) appeared to react instantly and virtually quantitatively at $-78^{o}C$ while the thiophens (170) and (172) required much higher temperatures and the condensations generally resulted in lower yields.

Related to (170) and (171), dianionic species (174) and (175) have been obtained from treatment of 3-methylisothiazole-4-carboxylic acid[148] and oxazole-4-carboxylic acid[149] with n-butyllithium. Metal-halogen exchange has been used[150] for the preparation of dianions (176) and (177) from the corresponding 3,4,5-tribromo- and 3-dibromothiophen-2-carboxylic acids, as an alternative to direct metallation (i.e. metal-hydrogen exchange).

In an effort to synthesize six-membered heterocyclic cyclohexadienones, the reactions of (171) with a number of aldehydes and ketones were examined.

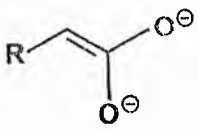
3.3 Generation and reactions of lithium 2-lithiofuran-3-carboxylate (171)

Addition of a solution of furan-3-carboxylic acid in tetrahydrofuran (THF) to lithium diisopropylamide (LDA) (2 equivalents) in THF

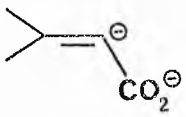
Scheme 9

beta lithiations

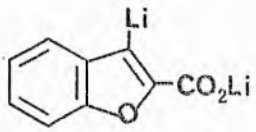
alpha lithiations



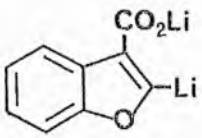
(166)



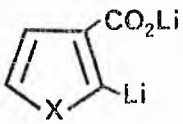
(167)



(168)

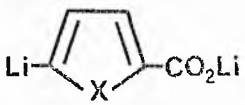


(169)



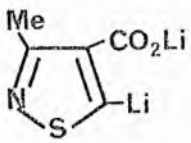
(170) X=S

(171) X=O

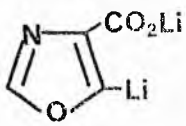


(172) X=S

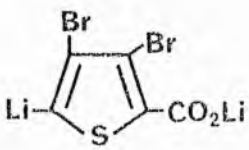
(173) X=O



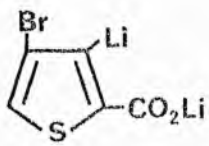
(174)



(175)



(176)



(177)

at -78°C produced a white precipitate which gradually dissolved during 30 min to give a clear, yellow-green solution of (171). Treatment of that solution with the appropriate benzaldehyde or acetophenone gave the alcohols (178)-(185) in excellent yields. Oxidation of the alcohols with manganese dioxide in benzene or acetonitrile gave the corresponding ketones (186)-(191) (Table 1).

Treatment of the acids (178) and (184) with ethereal diazomethane gave the esters (192) and (193), which were oxidised to the ketones (194) and (195) with manganese dioxide (Table 1).

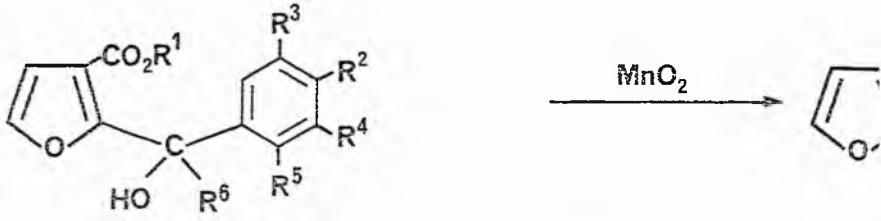
The ir spectra of compounds (186)-(191) showed intense absorptions at 3120 and 1710-1740 cm^{-1}, while carbon-13 nmr spectra showed a single carbonyl absorption at 184 ppm with no absorption at 165 ppm due to the furoic acid carbonyl. Based on the spectroscopic evidence and analysis results it was concluded that all the compounds (186)-(191) exist exclusively as the cyclic lactol tautomer and not the open free acid. The esters (194) and (195) showed ir carbonyl absorptions at 1730 and 1640-1660cm^{-1}.

3.4 Aspects of tautomerism

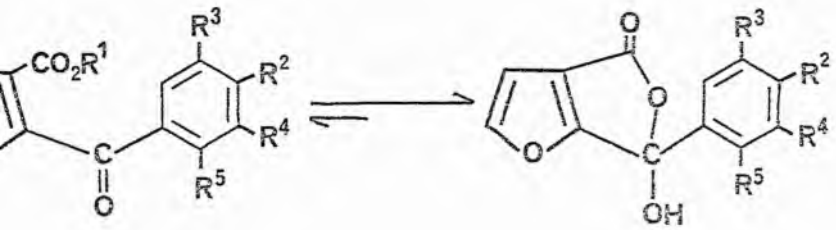
Although ring-chain tautomerism is commonly encountered in diverse groups of compounds, such as carbohydrates, alkaloids, and steroids, and intermediates in their synthesis and degradation, little systematic study of the phenomenon has been reported. In some of the detailed investigations with a large number of related compounds, observed facts have been correlated with steric, electronic, and entropy factors. However, few generalisations of predictive value applicable to more than one group of compounds have emerged.[151,152]

Keto-acid-lactol tautomerism can be regarded as a carbonyl addition equilibrium involving a weakly nucleophilic carboxylate group (eq.1).

TABLE 1



	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	MP(°C)
(178)	H	OBzl	H	H	H	H	82	126
(179)	H	OCH_3	H	H	H	H	81	brown oil
(180)	H	OCH_3	OCH_3	OCH_3	H	H	92	yellow oil
(181)	H	OCH_3	H	H	OCH_3	H	93	yellow oil
(182)	H	OBzl	H	OCH_3	H	H	72	98-100
(183)	H	OCH_3	H	OBzl	H	H	60	103-105
(184)	H	NO_2	H	H	H	H	87	157-159
(185)	H	NO_2	H	H	H	CH_3	66	yellow oil
(192)	CH_3	OBzl	H	H	H	H	88	brown liquid
(193)	CH_3	NO_2	H	H	H	H	85	113-115



	Yield (%)	MP (°C)
(186)	50	166–168
(187)	60	175–177
(188)	60	165–166
(189)	40	198
(190)	30	138–139
(191)	40	159–160
(194)	70	67–69
(195)	71	94–96

A close parallel may be expected between carbonyl reactivity and tautomeric compositions.

(eq.1)

A study[153] using ir spectroscopy of o-benzoylbenzoic acids showed that whereas the acid itself exists in the open form (196) in the solid state, the two forms are in equilibrium [(196)⇌(197)] in polar solvents. Most of the acids with strongly electron-donating substituents in ring A of (196) were entirely in the open form in solution. Conversely, electron-withdrawing groups destabilise the ketonic carbonyl and cause increased preference for the lactol form. The influence of a nitro group on ring B is, however, unexpected. Irrespective of its position, it destabilises the lactol with respect to the open form. Methyl substituents ortho to a carboxyl or carbonyl group in ring B have the opposite effect, i.e. they shift the equilibrium towards the lactol form.

It has been suggested[153] that the unusual influence of the nitro-group in ring B is due to the electronic destabilisation of the lactol group by the nitro-group; this effect must be greater than the similar influence on the ketonic carbonyl of the open form. The reason for the greater susceptibility of the lactol carbonyl group to electronic influences may be that it is the more polar. Also, the greater sensitivity of the lactone carbonyl group might be accounted for by disturbance of the stabilising mesomerism of the lactone group by a nitro-group in ring B due to alternative conjugation.

A recent paper[154] details the preparation of 2-(2-furoyl)benzoic acid (198) by the reaction of 2-lithiofuran with phthalic anhydride. From the values quoted for the infra-red carbonyl absorptions (1686 and

1667 cm^{-1}) of the product it is evident that it exists exclusively in the open form.

This observation, and the earlier studies on benzoylbenzoic acids make it puzzling that even the more electron rich acids such as (181) exist in the lactol form.

3.5 Reduction of carbinols (180) and (185) with sodium borohydride in trifluoroacetic acid

Sodium borohydride in trifluoroacetic acid (TFA) reduces diarylmethanols and triarymethanols to the corresponding diarylmethanes and triarylmethanes.[155] Diarylketones can also be reduced to diarylmethanes.[156] The reaction involves formation in TFA of the stabilised carbocation which is quenched by a hydride species.

The reaction can be carried out by adding the substrate neat or as a dichloromethane solution to a mixture of sodium borohydride pellets and TFA at 15-20°C in an inert atmosphere. Using the commercially available pellets of sodium borohydride provides for the safe, slow release of reducing agent into the medium, since this form of sodium borohydride dissolves relatively slowly in dry trifluoroacetic acid.

This method of reduction was successfully employed to reduce carbinols (180) and (185) to the corresponding diarylmethane (199) and diarylethane (200). The method was not successful in the reduction of compounds with benzyloxy groups on one of the rings, as trifluoroacetic acid is also known effectively to cleave benzyl ethers.[157] Thus, attempted reduction of carbinols (178), (182) and (183) resulted in the formation of complex mixtures of products, which could not be separated.

Catalytic hydrogenation was also used to reduce carbinol (184) directly to the diarylmethane amine (201).

3.6 Oxidation of sulphonamides (203) and (204) with lead tetraacetate and attempted oxidation of (199) with thallium trifluoroacetate

Catalytic reduction of the nitro group in (200) followed by treatment with p-toluenesulphonyl chloride, gave the sulphonamide (203),

which was oxidised with lead tetraacetate to the six-membered spirolactone (205) in 31% yield. The sulphonamide (204) gave spirolactone (206) in only 3% yield.

Thallium trifluoroacetate oxidation[3] of (199) gave a yellow solid, whose spectral properties were consistent with a thallated adduct. There was no evidence of spirolactone formation.

3.6.1 Attempted oxidation of 2-(4-hydrobenzoyl) benzoic acid

2-(4-Methoxybenzoyl)benzoic acid (207) was obtained in 44% yield by the classical method of adding p-methoxyphenylmagnesium bromide to phthalic anhydride.[158] (A more efficient method, which utilises the condensation of (O-lithioaryl)oxazolines with aryl acid chlorides, has subsequently been reported[159]).

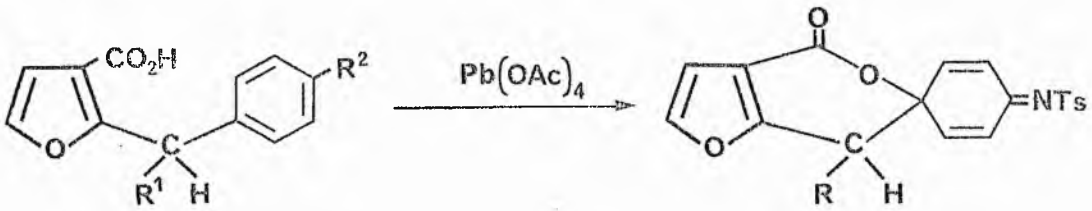
The demethylation of the p-methoxy substituent on the acid to give the 2-(4-hydroxy benzoyl)benzoic acid (208) proved troublesome. Reagents such as hydroiodic acid-acetic acid,[160] borontribromide-dimethyl sulphide complex,[161] pyridinium hydrochloride, and iodotrimethylsilane[162] proved totally ineffective. The demethylation was finally brought about by a mixture of hydrobromic-acetic acid [163] under reflux for 20h, albeit in a low (30%) yield.

The same hydroxy acid was obtained by the action of a 4-trimethylsilyloxyphenylmagnesium bromide[164,165] on phthalic anhydride followed by acid hydrolysis of the adduct, in 30% yield.

Attempted oxidation of 2-(4-hydroxybenzoyl)benzoic acid with manganese dioxide, lead tetraacetate,and anodically produced complex mixtures and tars, whose composition could not be determined.

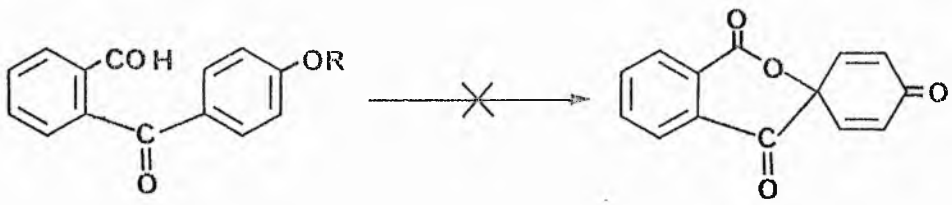
(196) (197)

(198) (199)



(200) R^1=Me; R^2=NO_2
(201) R^1=H; R^2=NH_2
(202) R^1=Me; R^2=NH_2
(203) R^1=Me; R^2=NHTs
(204) R^1=H; R^2=NHTs

(205) R=Me
(206) R=H



(207) R=CH_3
(208) R=H

CHAPTER FOUR

NON-OXIDATIVE APPROACHES TO SPIROCYCLOHEXADIENONES

4.1 Introduction

In previous chapters the preparation of spirocylic dienones by a variety of oxidative routes has been discussed. An alternative route to these compounds might involve the construction of a spiro ring on a six-membered ring already at the quinone level of oxidation. The ready 1,4-addition reactions of simple quinones make these unpromising starting materials for such a synthetic approach, but 2,6-disubstituted benzoquinones, and quinone monoketals seem more suitable synthons. The preparation of spirolactone cyclohexadienes outlined in Scheme 10 exemplifies this approach.

In an alternative annelation strategy, (Schemell) a monoprotected p-quinone might react with a carbanion (I) containing a blocked nucleophile to give quinol (II). Suitable derivatisation of the quinol hydroxyl and removal of the nucleophile protecting group would give (III) which would cyclise to (IV). This approach is applicable to the synthesis of grisans and azagrisans.

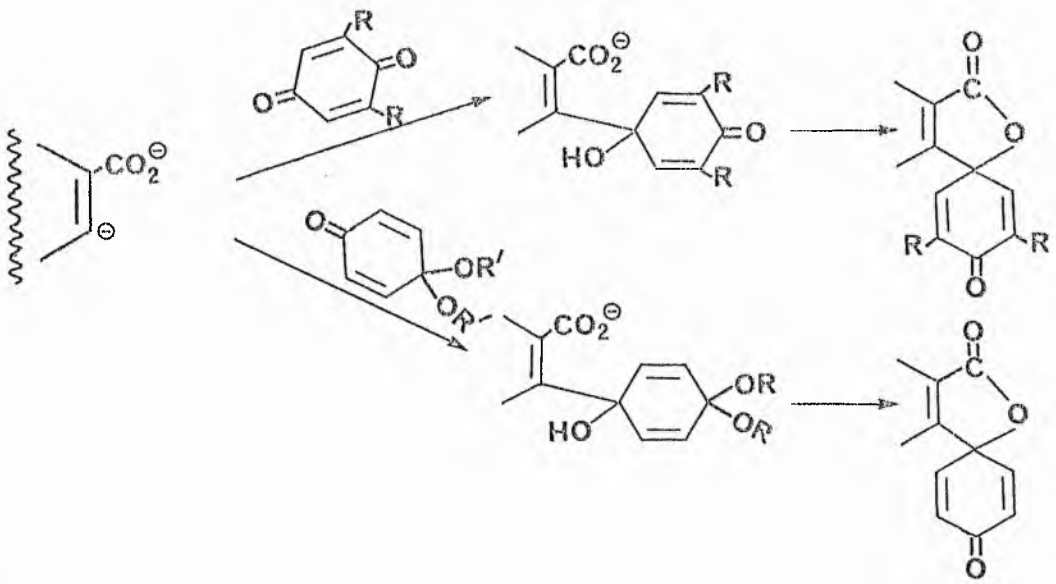
The addition reactions of quinone monoketals are discussed in Section 4.1.

As shown in Scheme 12 related quinol derivatives (V) on treatment with base might yield methides of protected quinones (VI). These are of interest as potential fungicides, and attempts to follow Scheme 12 are discussed in Section 4.5.

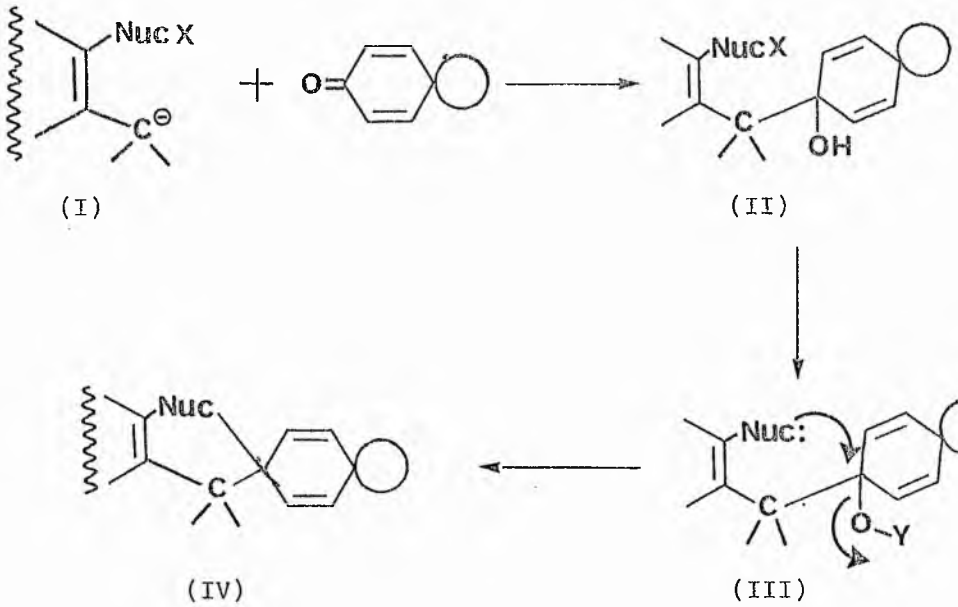
4.2 Reactions of quinone monoketals

The chemistry of quinone monoketals can be divided into three general sections: transformations at the carbonyl group, 1,4-addition reactions, and Lewis acid-catalyzed reactions.[167]

Scheme 10



Scheme 11



(I) (II) (III) (IV)

Scheme 12

(V) (VI)

4.2.1 Reactions at the carbonyl group

One of the earlier systematic studies of quinone monoketal reactivity dealt with the reaction of the monoketal of benzoquinones with ammonia derivatives (Scheme 13).[168] While such transformations have not yet been used extensively in synthesis, they allow for the replacement of the quinone monoketal carbonyl group by the nitroso, azo, or amino groups, or a hydrogen atom with production of an aromatic system.

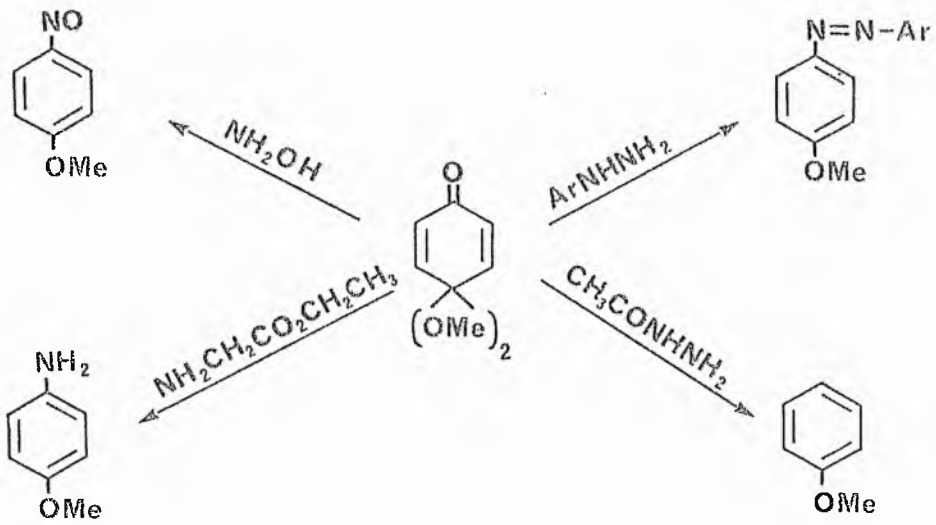
Sodium borohydride reduction of quinone monoketals affords labile alcohols (Scheme 14).[29] With monosubstituted systems, sodium borohydride reduction yields alcohols that usually eliminate on standing to form the corresponding p-methoxyphenol. However, when the quinone monoketal is more substituted, the alcohols are reasonably stable.

A major synthetic use of quinone monoketals is the addition reactions of organometallic reagents to the carbonyl group. A main advantage here is the unambiguous regiochemical outcome of the reaction relative to the quinone. Furthermore, the quinone monoketals seem less susceptible to electron-transfer-mediated reduction processes than do the corresponding quinones.

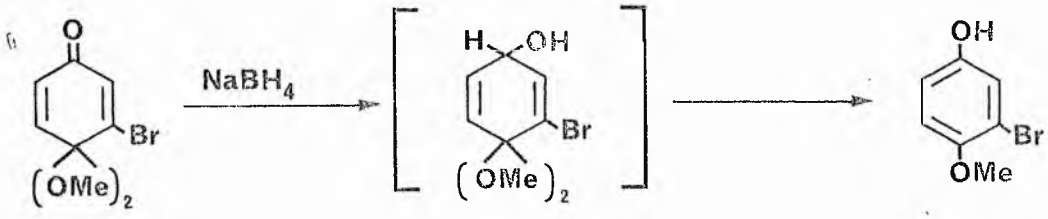
A number of organolithium and Grignard reagents react with quinone monoketals to give the corresponding protected p-quinols. Evans et al[169] used the reaction sequence outlined in Scheme 15 in a general approach to the synthesis of phenanthrenoid compounds; as an alternative to oxidative phenolic coupling. The functionalized phenethyl carbanions were prepared by deprotonation with LDA or n-butyllithium.

Reactions between lithiated N,N-dimethyl α-trimethylsilylacetamide[170] and quinone monoketals have been reported to yield protected quinone methides (Scheme 16). This approach was utilized by Evans[171] in the synthesis of the alkaloid cherylline.

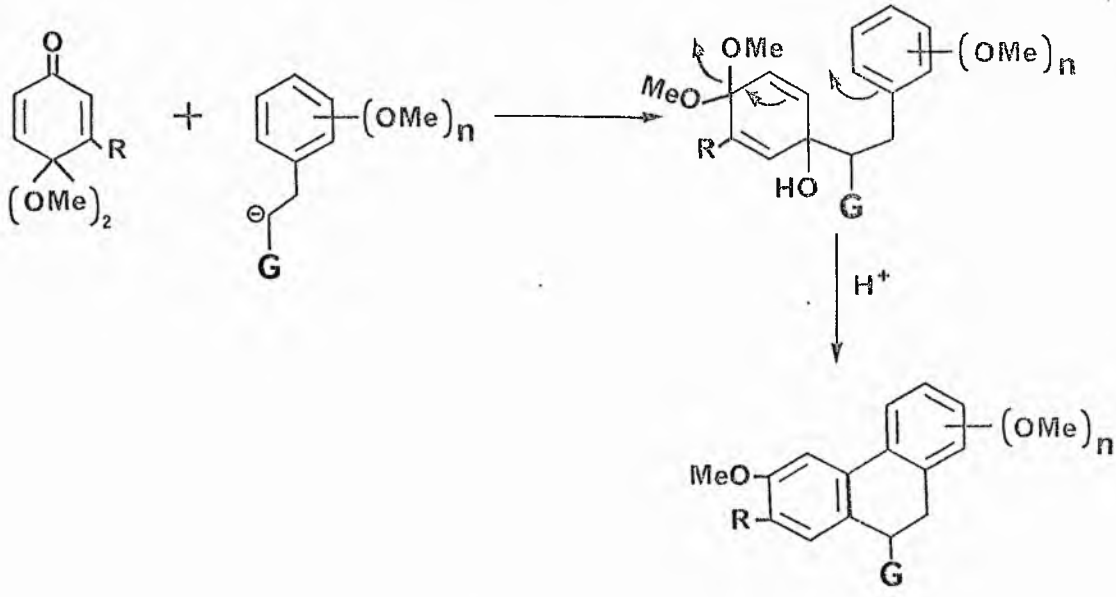
Scheme 13



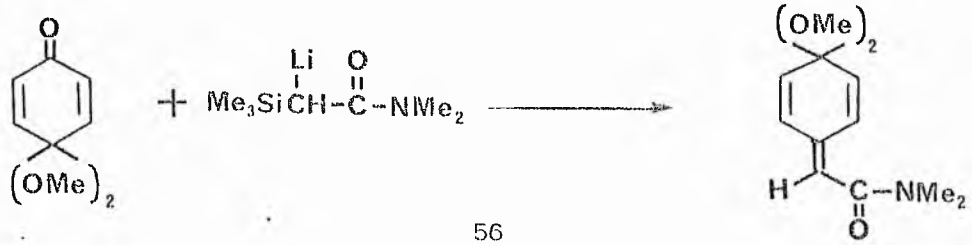
Scheme 14



Scheme 15



Scheme 16



Some of the reaction pathways followed by Grignard reagents and quinone monoketals are illustrated in Scheme 17.[29] While methylmagnesium bromide reacts to form the normal addition product, the tert-butyl Grignard gives reduction of the monoketal, and allyl Grignard gives ring-alkylated products.

An unusual 1,3-addition reaction of methylmagnesium iodide with spirocyclohexadienones has been reported[172] to give diphenylethers and diphenylamines as the only products (Scheme 18). More recently[79] doubt has been cast on this mechanism and one involving a vinylogous pinacol rearrangement has been proposed; it is however difficult to explain the formation of the dimethylated products by this proposal.

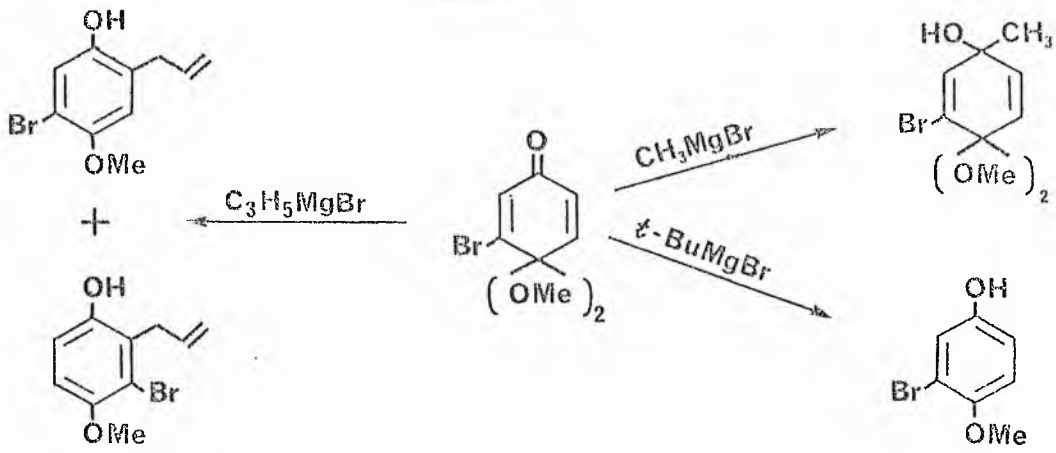
4.2.2 1,4-Addition reactions

Michael additions to quinone monoketals are quite general. Simple monoketals react with dimethylsulfoxonium methylide to give the corresponding mono- or bis-cyclopropyl ketones.[173] A total synthesis of the alkaloid (±)-colchicine has utilized the reaction of dimethylsulfoxonium methylide and 3,4,4-trimethoxycyclohexa-2,5-dien-1-one for the introduction of the tropolone moeity in the compound.[174]

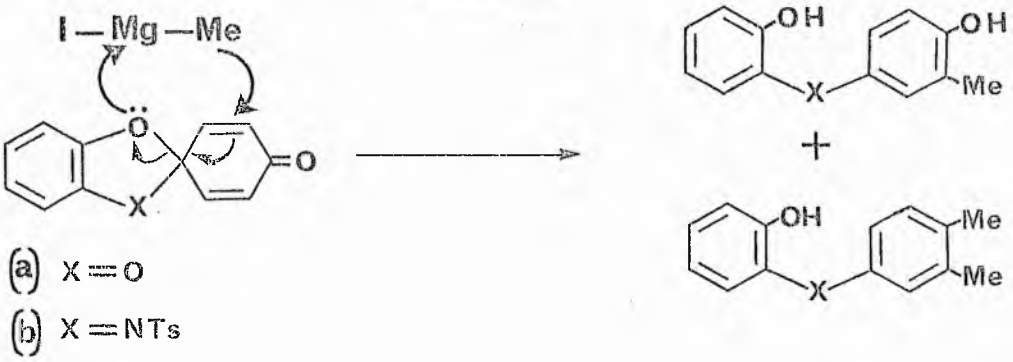
Addition of diethyl malonate to a series of benzoquinone monoacetals gave 1,4-adducts which were subsequently aromatized. The same sequence applied to ethyl acetoacetate resulted in substituted benzofurans.[175] The 1,4-addition of the benzylidine derivative of ethyl glycine to the enone system of a quinone monoacetal and subsequent aromatization has provided a high yield preparation of intermediates for the synthesis of isoquinoline quinones.[176]

Scheme 19 illustrates the general strategy for the utilization of quinone monoketals in regiospecific annelation reactions; here, 1,4-addition is followed by a second intramolecular nucleophilic attack leading to polycyclic systems. Since highly functionalized monoketals are readily available via the anodic oxidation-hyrdolysis route (see

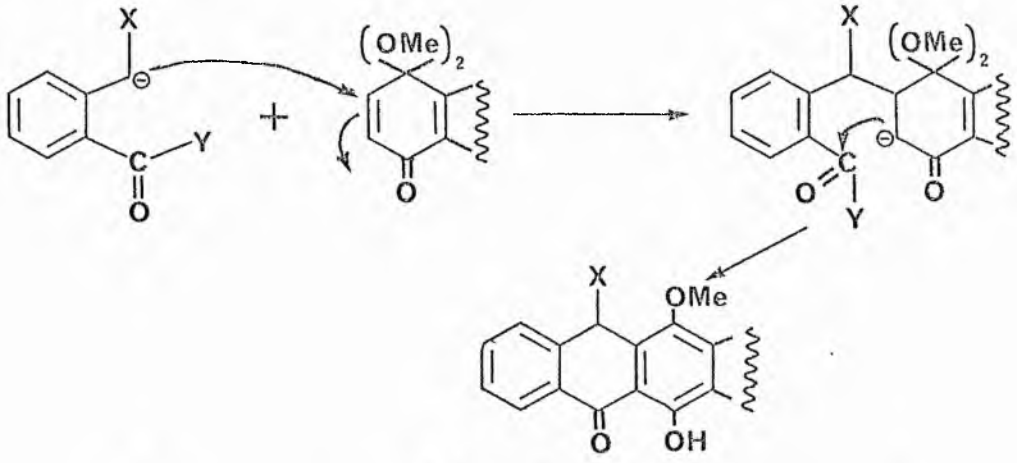
Scheme 17



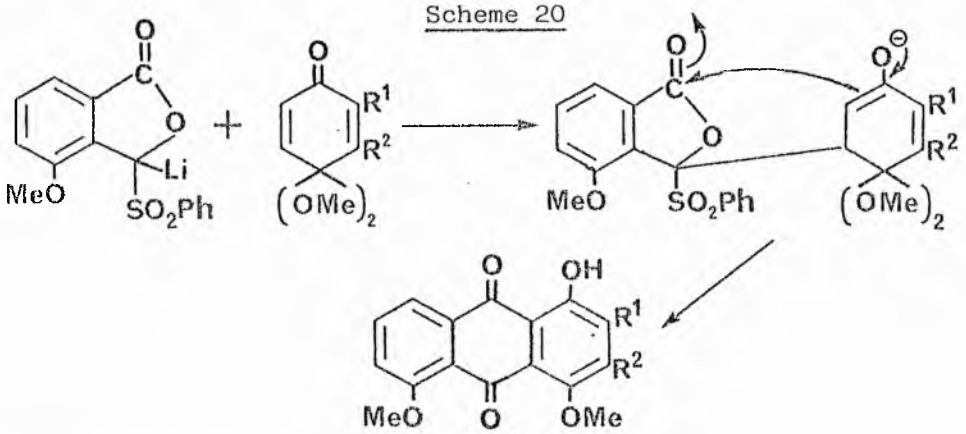
Scheme 18



Scheme 19



Scheme 20



Chapter 1), this is an especially attractive route to linearly fused natural products. Two particular reagents have been successfully employed in synthesizing such systems. Reactions of dimethylhomophthalate (x=CO_2CH_3, y=OCH_3, Scheme 19) with quinone monacetals in the presence of base afforded anthrone derivatives.[177]

The reactions of the anion of 4-(or 7)-methoxy-3-phenyl-sulphonylphthalide with variously substituted quinone monoacetals has given anthraquinones with total regioselectivity(Scheme 20).[178] This annelation reaction has been useful for regiospecific construction of anthracyclinone ring systems,[179] leading to an efficient synthesis of racemic daunomycinone.[180] More recently,[181] a high-yielding enantiospecific synthesis of (-)-7-deoxydaunomycinone has been achieved.

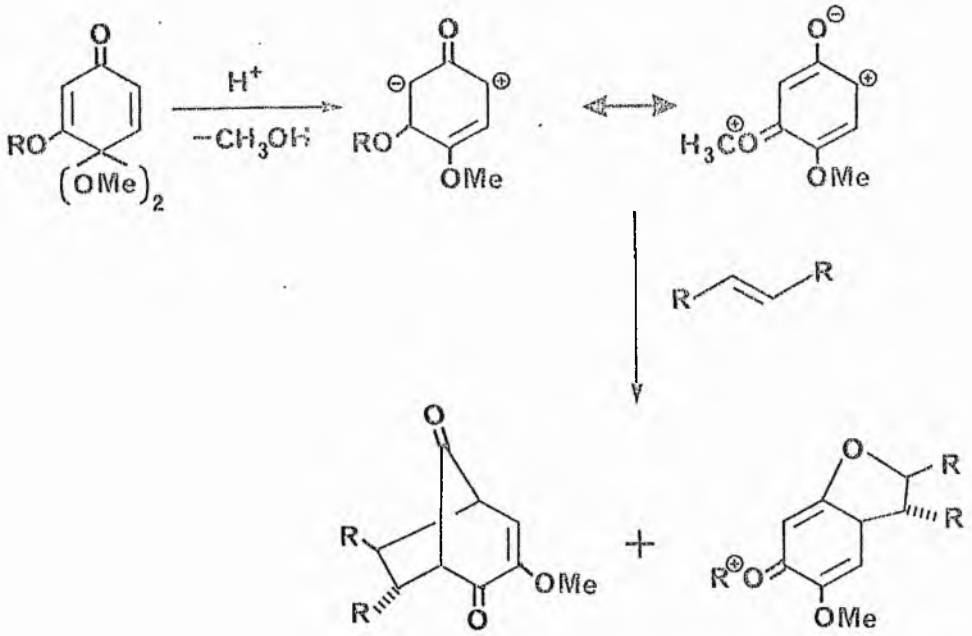
4.2.3 Quinone ketals as 1,3-dipole intermediates

A second class of annelation reactions consists of Lewis acid-catalyzed reactions of oxygen-substituted monoketals with olefins. In this reaction the ketal eliminates alcohol to afford a 1,3-dipolar species which leads to bicyclic products (Scheme 21). This type of reaction has been used to obtain key intermediates for elaboration of neolignan-type natural products guianin,[182] burchellin,[182] futoenone[182] and megaphone.[183] A new synthesis of substituted tropolones[184] and a synthesis of gymnomitrol[185] have also employed this acid-catalyzed reaction.

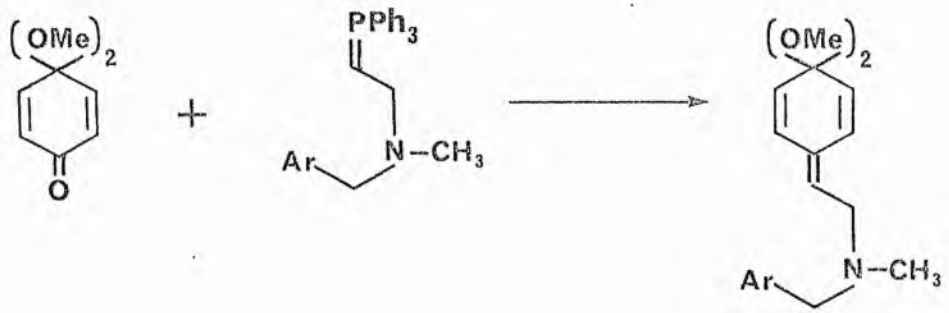
4.3 A novel one step synthesis of γ-spirolactones

The utility of the reactions of the dianion (171), obtained from 3-furoic acid on treatment with LDA, with a series of aldehydes and ketones has been described in Chapter 3. The high yields of the carbinols thus obtained makes this particular dianion useful in our strategy for the non-oxidative approach to spirolactones (Scheme 10).

Scheme 21



Scheme 22



When a solution of ketal (209) or (210) in THF was added to a solution of the dianion (171) at -78°C, the corresponding carbinols were obtained in 80 and 85% yield respectively as stable solids. Attempts to dehydrate these carbinols with p-toluenesulfonyl chloride in pyridine gave reaction mixtures which, although showing characteristic γ-lactone absorptions at 1770 cm^{-1} in the ir spectra, were contaminated with impurities which could not be removed by repeated recrystallisations or chromatography. Similar problems were encountered when cyclisation of these carbinols was attempted using benzoyl chloride in triethylamine. The use of N,N -dicyclohexylcarbodiimide also failed to induce cyclisation.

It was therefore decided to isolate the p-quinol benzoates of the carbinols and use these to form the spirolactones. Surprisingly, when an equimolar amount of benzoyl chloride was added to the reaction mixture at -78°C, the only products isolated after workup were the spirolactones (212) and (213) in 33 and 32% yield respectively. It may be that the benzoyl chloride reacts with the furoic acid anion to give a mixed anhydride which undergoes nucleophilic attack by the quinol oxygen to form the spirolactones (Scheme 23).

When the same reaction sequence was applied to quinone monoketal (211) no spirolactone was obtained, presumably because of the known[181] tendency of LDA to react destructively with dimethoxydienones. The only product, isolated in good yield, was N,N-diisopropylbenzamide

This reaction indicated that the diisopropylamine liberated from the LDA/furoic acid reaction was a scavenger for benzoyl chloride, possibly affecting the yield in the cyclisation of the lithiated carbinol. However, when 3 moles of benzoyl chloride was used in the cyclisation, no improvement in overall yield of lactone was obtained. This may be because the lactone and diisopropylamide have very similar Rf values and

the mixture is difficult to separate.

The possibility of hydrolysing the lactone ketals to the corresponding lactone dienones was then examined briefly. The phenylene ketal in (213) proved very stable to hydrolysis attempts with p-toluenesulphonic acid even on prolonged heating. The hydrolysis of the ethylene ketal in (212) seemed more promising. However, the difficulty to obtain substantial amounts of the lactone allowed only for t.l.c. scale reactions, from which the desired dienone could not be isolated.

4.4 Synthesis of novel γ-spirolactones from 1,2-addition reactions of organometallic reagents with sterically hindered 1,4-benzoquinones

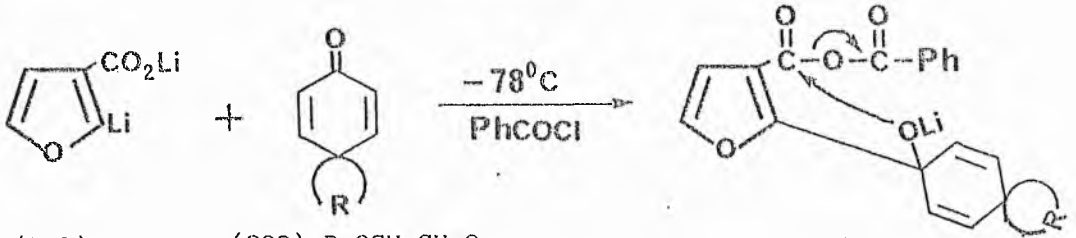
4.4.1 Reactions of benzoquinones with organometallic reagents

It has been reported[186] recently that at low temperatures alkyl lithiums add to unprotected benzoquinones to give excellent yields of cyclohexa-2,5-dienones. A simple synthetic route to 2,5-disubstituted 1,4-benzoquinones has also involved the 1,2-addition to the carbonyl group of organolithium reagents.[187] Liotta et al[188] have shown that additions of carbanions to unsymmetrical 1,4-benzoquinones can be achieved at either carbonyl carbon by a choice of reaction conditions.

4.4.2 Ortho lithiation

As defined in Chapter 3, beta (ortho) lithiation consists of the replacement of a hydrogen atom bonded to an sp^2 hybridised carbon by lithium at the position beta to a functional group with non-bonding electrons. The designation "ortho lithiation", which is a type of beta lithiation, is used in this chapter to denote: (1) the deprotonation of the position adjacent to the directing atom or functional group attached to carbocyclic aromatic systems and (2) the lithiation by metal-halogen exchange of aromatic systems with halogen substituents ortho to the directing atom or functional group. The reaction itself is characterized by its high degree of regioselectivity, as, with very

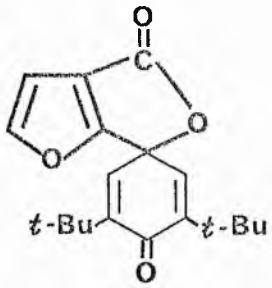
Scheme 23



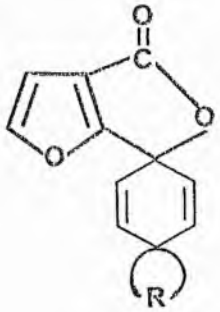
(171) (209) R=OCH_2CH_2O

(210) R=OC_6H_4O

(211) R=$(OCH_3)_2$



(214)

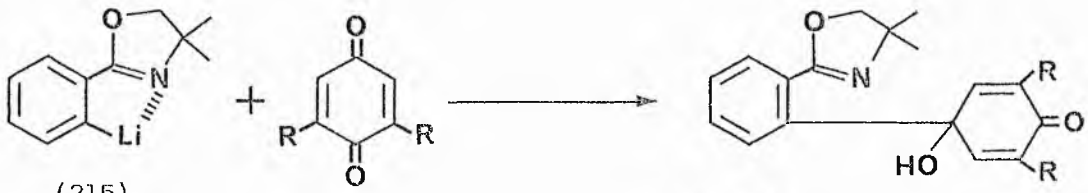


(212) R=OCH_2CH_2O

(213) R=OC_6H_4O

Scheme 24

Scheme 25



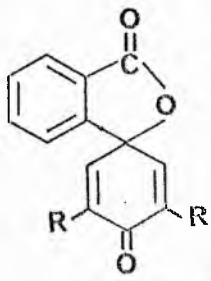
(215)

(216) R=Bu^t

(217) R=Pr^i

(218) R=Me

$H^+/EtOH$



(219) R=Bu^t

(220) R=Pr^i

(221) R=Me

few exceptions, no other carbon atoms are deprotonated. The reaction is shown in Scheme 24, where X represents a heteroatom and n may vary from 0 to 2. Metalations of this type are observed with a variety of groups in which X may be nitrogen, oxygen, sulphur, halogen, selenium, or phosphorus. Two excellent reviews on ortho lithiations have appeared recently.[139,140]

As we were interested in compounds with masked nucleophiles α-to the lithiated carbon atom, attention was turned to the useful carboxylic acid protecting group 4,4-dimethyl-2-oxazoline, which also happens to be an ortho-directing group.

Meyers and his co-workers[189] have taken advantage of the inertness of the oxazoline derived from bromobenzoic acids towards Grignard and hydride reagents, to elaborate or functionalize carboxylic acid derivatives.

The ortho lithiation of 2-aryloxazolines with n-butyllithium proceeds readily even at low temperatures. The ortho-metalated intermediates react with numerous electrophiles.[190-193] On para-methoxy substituted benzoic acids lithiation occurs regioselectively in the position ortho to the oxazoline ring,[190] showing the strong directing influence of this substituent. This directing capacity is so high that it can compete successfully with the alpha metalation of the thiophene nucleus, one of the most readily lithiated substrates known.[194] Moreover, despite the susceptibility of the pyridine nucleus to attack by nucleophilic metalating agents, the oxazoline derived from pyridine-4-carboxylic acid can successfully be lithiated in the 3 position.[195-197]

4.4.3 1,2-Addition reactions of benzoquinones

Liotta[198] has recently reported a simple, inexpensive procedure for the large-scale production of alkyl quinones. The method is a modified two-phase Jones oxidation procedure (ether/aqueous chromic acid)

of alkyl substituted phenols. The symmetrical 2,6-dimethyl, 2,6-diisopropyl, and 2,6-di-tert-butyl-1,4-benzoquinones were prepared by this method and were used in the following reaction.

When a solution of 2-(2-bromopheny)-4,4-dimethyl-2-oxazoline (215) in THF was metalated with n-butyllithium at -78°C, and was then quenched by the addition of a solution in THF of 2,6-di-tert-butylbenzoquinone, 2,6-diisopropylbenzoquinone, or 2,6-dimethylbenzoquinone, the carbinols (216), (217), and (218) were obtained in 50, 66, and 58% yield respectively (Scheme 25). The reactions were not very efficient and the products had to be separated from by-products by flash chromatography. Gschwend[190] has commented on the relative unreactivity of oxazolinolithiums towards aldehydes and ketones.

The hydrolysis with ethanolic sulphuric acid of the oxazoline protecting group on the di-tert-butyl and di-isopropyl carbinols (216) and (217) proceeded smoothly to give the expected spirolactones (219) and (220) in 75 and 67% yield as stable crystalline solids.

In the case of dimethyl carbinol (218) however, the hydrolysis product was not homogeneous and could not be purified by flash chromatography or by crystallisation. The ir spectrum showed a strong absorption at 1720cm^{-1} and the mass spectrum gave an m/z of 314 (25%) and 240 (100%). The nmr spectrum, although showing weak signals due to an impurity, was consistent with a δ-lactone structure (222) or its isomer (223), thought to be the dienone-phenol rearrangement product of the intermediate γ-lactone (221).

The hydrolysis of (218) was followed by withdrawing aliquots from the reaction mixture and examining their ir spectra. After 1h, a strong absorption at 1770cm^{-1} indicated the formation of the intermediate γ-lactone (221), which rearranged very rapidly under the reaction conditions to give either (222) via oxygen migration or (223) via carbon migration.

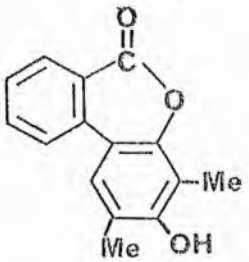
The impurity present in the hydrolysis product of (218) was accidentally isolated when the suspected δ-lactone (222) or (223) was treated with ethereal diazomethane in an attempt to isolate its methyl ether. Spectroscopic evidence as well as elemental analysis results identified the impurity as the ester (224), most probably arising from transketalisation of a γ-lactone.

4.4.4 Synthesis of spirolactone (214)

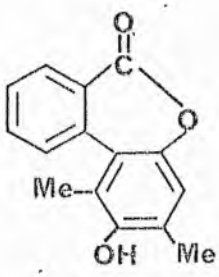
The reaction of the furoic acid dianion (171) with 2,6-di-tert-butyl-1,4-benzoquinone using the benzoyl chloride method employed for the synthesis of spirolactones (212) and (213), gave a 20% yield of the spirolactone (214) which was characterised by spectroscopy and chemical analysis. It was, however, unstable, decomposing at room temperature over a period of three days.

4.4.5 Dienone-Phenol rearrangement

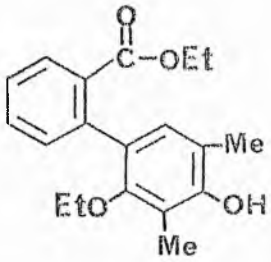
This is an acid-catalysed rearrangement of a carbocation in which the nature of both ring substituents and migrating species affects the composition of the final product. For example, the 2-substituted cyclohexa-2,5-dienone (225) could give four possible products (226) - (229) (Scheme 26). The effect of the 2-substituent can be steric - a tert-butyl group tends to be C_5 rather than C_3 directing - or electrostatic, e.g. an electronegative bromine would destabilise an intermediate with a positive charge near it, and so would also be C_5 directing.[199] Usually a more substituted alkyl group migrates in preference to a less substituted one,[200] and phenyl groups migrate more readily than alkyl groups.[201-203] Electron withdrawing substituents decrease the migratory aptitude of phenyl groups, while electron donating substituents enhance it.[204] In all cases a carbon bond migrates rather than a heteroatom bond.



(222)

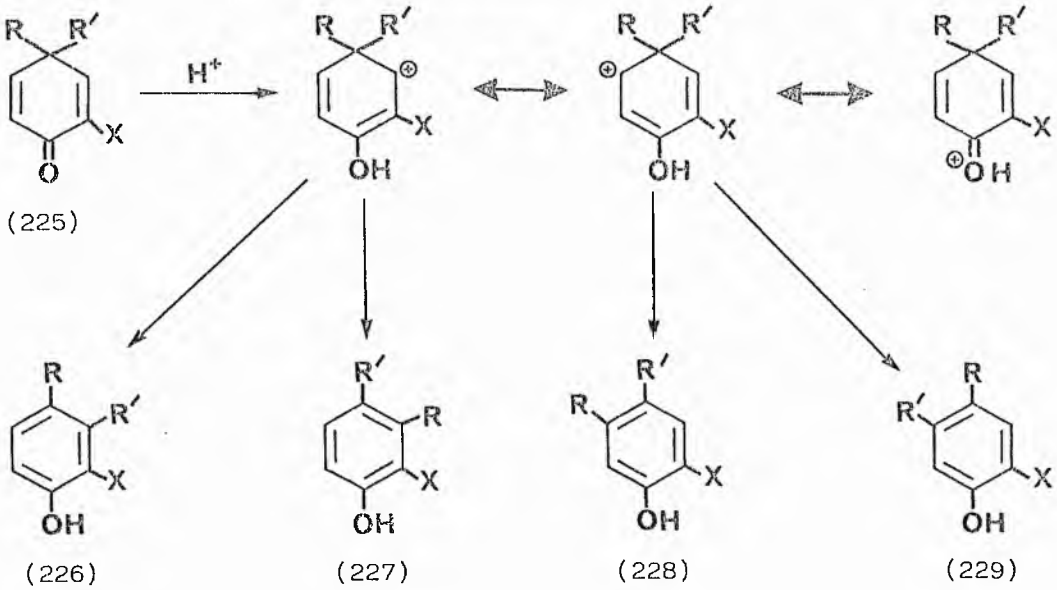


(223)

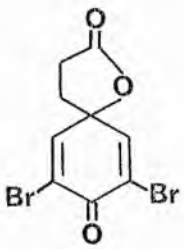


(224)

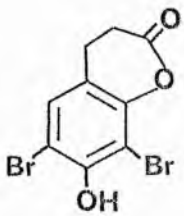
Scheme 26



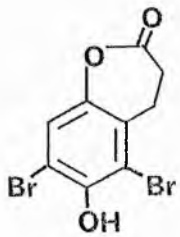
(225) (226) (227) (228) (229)



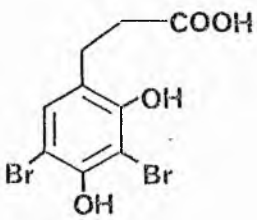
(230)



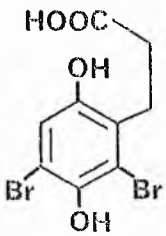
(231)



(232)



(233)



(234)

The dienone-phenol rearrangement has been applied to dienone-spirolactones. Thus treatment of the dibromolactone (230) with either 0.5 - 2M sulphuric acid,[80] or 4.5M sulphuric acid in acetonitrile,[205] gives rise to both 2,4-dihydroxy- and 2,5-dihydroxy-dibromophenylpropanoic acids (233) and (234) via hydrolysis of the 7- and 6-hydroxycoumarins (231) and (232) produced by oxygen and carbon migration respectively. The predominant products from this reaction are species derived from oxygen migration.

4.5 Preparation of p-quinol benzoates as potential precursors of grisan derivatives

As outlined in Scheme 11, reactions of suitably substituted benzylic anions with dienone ketals and the trapping of the intermediates by benzoyl chloride at low temperatures could give potential precursors of grisan derivatives.

Dimethyl homophthalate has been shown[177] to react with quinone monoacetals in the presence of base to afford polycyclic ring systems. A recent review[180] of the 1,4-dipolar reactions leading to annelation discusses the uses of dimethylhomophthalate.

Homophthalic acid esters (235) and (236) could form the basis for our strategy by providing the latent nucleophile (carboxyl group) for the formation of spirolactones.

The reactions of homophthalic acid with methanol or ethanol under acid catalysis did not give the desired esters, but these were obtained in excellent yield when homophthalic anhydride was treated with the appropriate alcohol.

The reactivity of the benzylic anion derived from esters (235) or (236) and LDA (2 molar equivalents) in THF at -78°C was tested by quenching the anion with methyl iodide, cyclohexanone, and 4-nitro-acetophenone. In the first case a low yield (10%) of the methylated

product was obtained, whereas in the latter two cases no product formation was evident.

Similarly, the attempted reaction of the lithiated anion with ketal (210) did not give any p-quinol, the starting materials being recovered almost quantitatively. When the solvent was changed to diethyl ether and the reaction temperature lowered to $-100^{\circ}C$ there was still no evidence of product formation. Unfortunately, since there was only a small formation of the anion this effort was abandoned.

Attention was next turned to benzylic anions derived from suitably protected o-hydroxyphenylacetate esters. Although there exists an abundance of reagents which can be used for the protection of hydroxyl groups,[206] a blocking group which combines stability to organometallic reagents, reducing agents, base, amd mildly acidic reagents, with susceptibility to facile removal by a highly specific reagent is rare; the dimethyl-tert-butylsilyl group satisfies these criteria. Corey and co-workers[207] have shown that in the presence of imidazole as catalyst and dimethylformamide as solvent dimethyl-tert-butylchlorosilane is an effective reagent for the conversion of a variety of alcohols to dimethyl-tert-butylsilyl ethers in high yield under mild conditions. Removal of the silyl protecting group can be accomplished using lithium tetrafluoroborate,[208] and tetra-n-butylammonium fluoride either in THF or supported on silica gel.[207]

When methyl-o-hydroxyphenyl acetate (237) was treated with dimethyl-tert-butylchlorosilane in the presence of imidazole and dry dimethylformamide at room temperature for 70h, the silyl ether (238) was obtained in 72% yield. A solution of this ether in THF was treated with LDA at $-83^{\circ}C$ followed by the addition of a solution of ketal (210) in THF. The mixture was finally quenched by the addition of benzoyl chloride and allowed to reach ambient temperature (Scheme 27).

Examination of the reaction product by t.l.c. showed it to be a complex mixture and no attempt was made to isolate any of the components. Instead, the mixture was treated with tetra-n-butylammonium fluoride in THF for 30 min. and then diluted with water. Again, t.l.c. examination showed a number of spots and all attempts to isolate homogeneous products by chromatography for spectroscopic examination failed.

The same reaction was repeated several times using diethyl ether as solvent and different reaction temperatures (-78°C, - 24°C, 0°C) but in each case the same complex mixtures were encountered. This line of investigation was therefore abandoned.

4.6 Quinone methides

Ortho- and para- quinone methides constitute a class of highly electrophilic molecules that are frequently encountered in natural product chemistry.[204-211] A large number of quinone methides have been isolated as fungal metabolites,[209] wood pigments,[209] and insect pigments.[212] In addition, quinone methides have been implicated as intermediates in oxidative phosphorylation,[209] in the biosynthesis of chromans,[209] lignin,[213] and the alkaloids cephalotaxine,[214] spirobenzylisoquinolines,[215] oberylline,[216] and isopavines.[217] It has also been suggested that some quinonoid substances that exhibit anti-tumor properties may be activated in vivo by conversion to quinone methides.[218]

There are no general methods for preparing p-quinone methides from quinonoid precursors. In principle, olefination of a quinone carbonyl group offers the most direct route from a quinone to a quinone methide.[219] Although several Wittig reactions on quinone substrates have been reported, this method has yet to be established as a generally effective approach to the synthesis of quinone methides.[220]

Hyatt[240] (Chapter 5.3.1) has recently reported two new stable quinone methides of type (239), where X = Y = CN or X = CN, Y = CO_2Et, obtained from the oxidation with manganese dioxide of the corresponding cyclohexanone olefins.

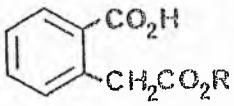
Nakayama et al[221] have prepared stable quinone methide imines by deprotonation with base of 2-aryl-1,3-dithiolylium salts.

The conversion of p-quinone monoketals into p-quinone methide ketals has recently been utilised by Evans[171] in the synthesis of the alkaloid cherylline (Scheme 16). Quinones monoprotected as their (trimethylsilyl)oxy cyanide derivatives have been used in the synthesis of p-quinols[222-224] and p-quinol benzoates.[225] Treatment of those p-quinol benzoates with base afforded[225] stable quinone methides of type (239), where X = CO_2R and Y = Ar. It has been observed that o- and p-electron-donating substituents on group Y can confer stability on those quinone methides.

In the absence of electron-donating substituents, the expulsion of the trimethylsilyl cyanide blocking group was accompanied by aromatisation. However, the use of more stable quinone protecting groups such as the phenylene ketal would afford more stable intermediates and would lead to novel quinone methide ketals.

4.6.1 Preparation of p-quinol benzoates as precursors of quinone methide ketals

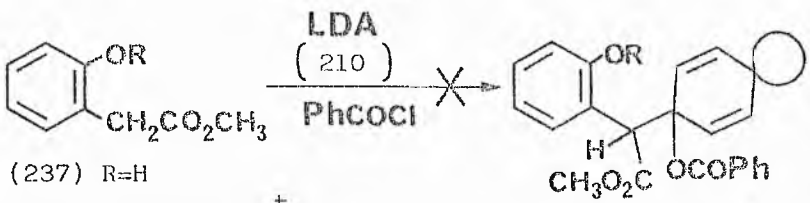
When a solution of ketal (210) in THF was added to the anion derived from methoxyphenyl ester (240) or nitrophenyl ester (241) and LDA at -78°C, and the resulting lithio-quinol was trapped by benzoyl chloride at -78°C, the p-quinol benzoates (242) and (243) were obtained in 50% and 37% yield respectively. Both benzoates showed ir absorptions for aliphatic and aromatic ester. The benzylic proton appeared as a singlet in the nmr spectrum. Both benzoates analysed correctly.



(235) R=CH_3

(236) R=CH_2CH_3

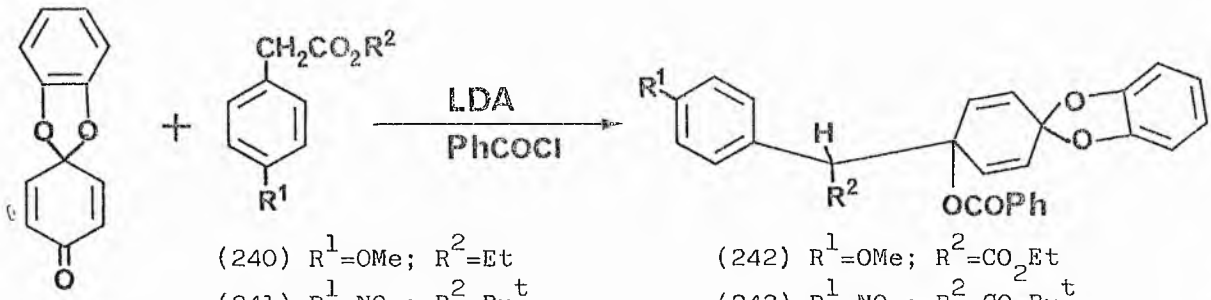
Scheme 27



(237) R=H

(238) R=$Si(Me)_2Bu^t$

R=$Si(Me)_2Bu^t$



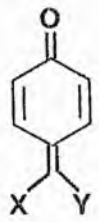
(210)

(240) R^1=OMe; R^2=Et

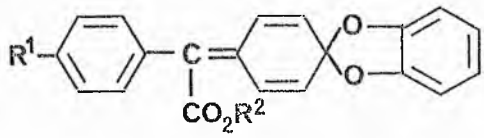
(241) R^1=NO_2; R^2=Bu^t

(242) R^1=OMe; R^2=CO_2Et

(243) R^1=NO_2; R^2=CO_2Bu^t

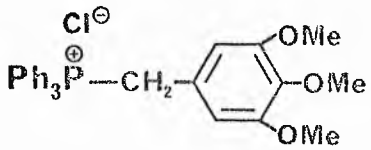


(239)

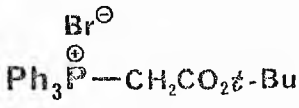


(244) R^1=OMe; R^2=Et

(245) R^1=NO_2; R^2=Bu^t



(246)



(247)

A solution of benzoate (242) or (243) in toluene was treated with 1,8-diazobicyclo[5.4.0]undec-7-ene at room temperature for 3h and then with water and a few drops of acetic acid. The crude products were partially purified by chromatography and crystallisation. Their ir spectra showed a hydroxy absorption at 3400cm^{-1} and a total abesence of the aromatic ester carbonyl absorption at 1710cm^{-1};. elemental analysis also supported the presence of an extra hydroxyl group.

The use of a different base (sodium hydride) to abstract the acidic benzylic proton yielded quinone methides (244) and (245), identical to those previously obtained. The incorporation of a hydroxy group into the products was again evident from the ir spectra.

Therefore, despite the ease of formation of p-quinols, the corresponding quinone methides seem to be susceptible to nucleophilic attack by water. All attempts to isolate the quinone methides directly from the reaction mixture using flash chromatography, gave compounds which were shown by t.l.c. and ir to be indentical to those previously obtained.

4.6.2 Attempted preparation of quinone methides by Wittig reactions on quinone monoketals

Wittig reactions on quinone monoketals have been reported[171] to yield protected quinone methides (Scheme 22), and sterically hindered 1,4-benzoquinones react with phosphorus ylides to give quinone methides.[226]

As mentioned in section 4.6, o- and p-electron donating substituents on the aryl group of the olefin and an electron withdrawing substituent on the other group confer stability on quinone methides of type (239). The synthesis of protected quinone methides by reactions of phosphorus ylides with quinone monoketals, required ylides suitably substituted to stabilise the quinone methides. Accordingly, 3,4,5-trimethoxybenzyltriphenylphosphonium chloride (246) was prepared in 84% yield from 3,4,5-trimethoxybenzyl chloride and triphenylphosphine in refluxing

o-chlorobenzene, and tert-butyl-triphenylphosphonium acetate bromide (247) was prepared in 87% yield from tert-butylbromoacetate and triphenylphosphine in refluxing benzene.

When a solution of the phosphonium chloride (246) in dimethylsulfoxide was treated with sodium hydride followed by the addition of ketal (210) at room temperature, t.l.c. examination of the mixture showed the presence of the starting ketal as well as some product. Chromatographic separation of the components of the mixture gave ketal (80% recovery), a small amount of a brown solid and finally a small amount of a colourless solid which was identified as triphenylphosphine oxide from its mp and ir spectrum. The ir spectrum of the brown solid (8% overall yield) showed absorptions at 1640 and 1590cm^{-1}, which could be attributed to an alkenic double bond. However, analysis results and mass determination were not consistent with the expected quinone methide product.

Similarly, treatment of the phosphonium bromide (247) with sodium ethoxide followed by the addition of ketal (210) gave a mixture, from which was recovered starting ketal (75%), triphenylphosphine oxide and an amorphous solid, the spectral properties of which were not consistent with a quinone methide.

It has therefore been established that quinone monoketal (210) reacts very inefficiently with phosphorus ylides and that the small amounts of quinone methides which might have been produced are very labile and difficult to isolate.

CHAPTER FIVE

ATTEMPTED SYNTHESIS OF SPIROCYCLOHEXENONES

5.1 Introduction

Spirocyclohexanone ketals of the type (249-254) have been used occasionally as starting materials in the synthesis of natural products (see section 5.3). A useful transformation of compounds of this type would be oxidation to compounds of type (248), which have a cyclohexenone type structure similar to that found in griseofulvin.

In this chapter are described attempts to synthesise spirocyclohexenones using either oxidation of compounds (250) and (254), or cycloaddition reactions of benzoquinone-type compounds with various butadienes. Catalytic hydrogenation of cyclohexadienones with selective reduction of one of the alkenic bonds could also lead to compounds (248), but in our laboratory this approach led to ring opening and aromatisation of the substrates.

5.2 A review of methods of synthesis of cyclohexanone monoketals

Some utility in the synthesis of natural products has been demonstrated for the ethylene monoketal (249) of 1,4-cyclohexadione and some of its functional equivalents (250-254) (see section 5.3).

Access to the useful monoketal (249) has not been easy. Routes employing partial reaction of 1,4-cyclohexanedione with ethylene glycol gave low (up to 30%) yields of (249) after a difficult (extraction/derivatization or chromatographic) workup.[234,235] A route based on cyclohexanone ring formation gave a 20% yield of (249).[236] A process involving partial oxidation of 1,4-cyclohexanediol with Jones reagent to give

4-hydroxycyclohexanone followed by ketalization with ethylene glycol and further oxidation with chromium trioxide-pyridine gave[237] (249) in 30% yield.

Marshall and Flynn[238] have recently described a high-yielding (88%) preparation of (250) from hydroquinone mono-methyl ether. Although efficient and suitable for mole-scale operation, the three-step sequence involves a dissolving-metal reduction followed by a two-day period of ammonia evaporation before the workup. Also large quantities of toxic chromium (VI) are used in the final step.

A more recent convenient preparation of (250) has been described by Babler and Spina,[239] in which the ketal is obtained in 85% yield by the continuous extraction with hexane of an aqueous solution of 1,4-cyclohexanedione containing 2,2-dimethyl-1,3-propanediol in molar excess and sulfuric acid as a catalyst. This ketal, though expensive, is now commercially available.

Hyatt recently reported[240] that treatment of 1,4-cyclohexanedione with one equivalent of 1,4-butanediol under standard ketalization conditions surprisingly afforded a product mixture containing 80% of monoketal (254), whereas similar reactions using ethylene glycol or 2,2-dimethyl-1,3-propanediol gave the expected statistical mixture of starting material, monoketal, and bisketal. Most of the undesired crystalline bisketal was removed by filtration, and the monoketal (254) was obtained in 40 - 60% yield by vacuum fractional distillation. It is not clear why ketalization of 1,4-cyclohexanedione gives more monoketal with 1,4-butanediol than with other diols, but a suggestion has been made[240] that the flexibility of the seven-membered ring in (254) allows orientations of the oxygen lone electron pairs that are precluded for the rigid five- and six-membered-ring ketals.

Monoketals (250), (251) (252), and (253) have been prepared in high yields from the oxidation of 4-hydroxycyclohexanone monoketal by the 3,5-dimethylpyrazole modification of the Collins oxidation.[241]

5.3 Reactions of cyclohexanone monoketals

Cyclohexanone monoketals undergo two types of reactions: (a) transformations at the carbonyl group and (b) reactions at the α-carbon atom. There are only a few reports in literature of either type of reaction.

5.3.1 Transformations at the carbonyl group.

Knoevenagel reactions of (254) with malononitrile and with ethyl cyanoacetate, followed by ketal hydrolysis, gave the keto olefins (255) and (256); oxidation of these keto olefins with active manganese dioxide gave[240] the stable quinone methides (257) and (258).

Treatment of ketals (249) - (253) with dimethylamine hydrochloride and potassium cyanide in aqueous dimethylamine gave the aminonitriles (259). The displacement of the cyanide group by the tetrahydropyranyl ether of m-hydroxyphenyl-magnesium bromide gave 4-aryl-4-(dimethylamino) cyclohexanone ketals (260), a number of which showed narcotic antagonist activity.[242]

5.3.2 Reactions at the α-carbon atom

Marshall and Flynn[243] used monoketal (250) as the starting material in the stereoselective synthesis of an isomer of the sesquiterpene vernolepin. The main steps in this synthesis were bis-alkylation of (250) with 1,3-dichloro-2-propene in the presence of sodium iodide, reduction of the ketone group to the alcohol, hydrolysis of the ketal, and further functionalization on the α-carbon atom.

The enolate anion of (250), generated with lithium diisopropylamide in the presence of an equimolar amount of hexamethylphosphoramide was

(248)

(249) R=CH_2CH_2

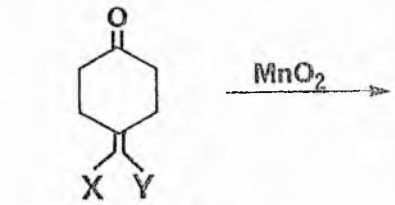
(250) R=$CH_2C(CH_3)_2CH_2$

(251) R=$CH_2CH(C_6H_5)CHCH_2$

(252) R=$(CH_2)_3$

(253) R=$CH_2CH(CH_2CH{=}CH_2)CH_2$

(254) R=$(CH_2)_4$

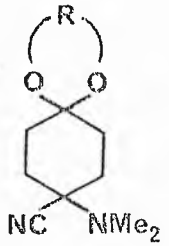


(255) X=Y=CN

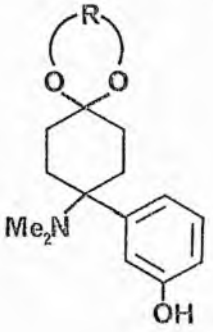
(256) X=CN; Y=CO_2Et

(257)

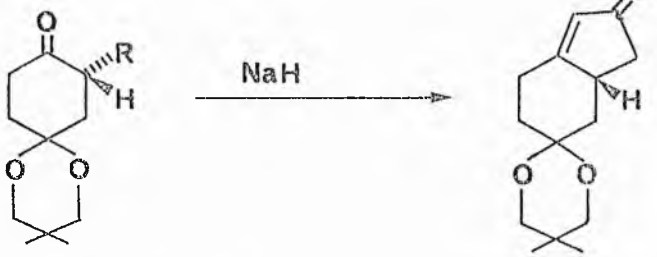
(258)



(259)



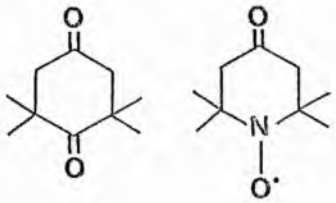
(260)



(261) R=$CH_2C(OEt){=}CHP(O){=}(OMe)_2$

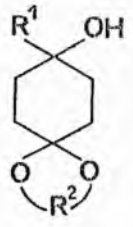
(262) R=$CH_2C(=O)CH_2P(=O)(OMe)_2$

(263)



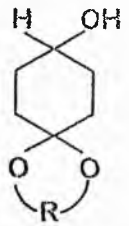
(264)

(265)



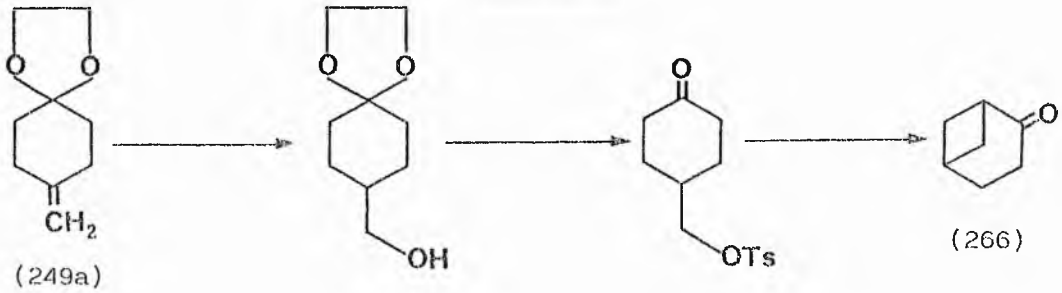
(267) R^1=Bu^n; R^2=$CH_2C(CH_3)_2CH_2$

(268) R^1=Ph; R^2=$CH_2C(CH_3)_2CH_2$



(269) R=$(CH_2)_4$

Scheme 28



(249a)

(249b)

(249c)

(266)

monoalkylated with dimethyl 3-bromo-2-ethoxypropenylphosphonate to give (261), which after mild acid hydrolysis afforded the diketo phosphonate (262). When compound (262) was treated with sodium hydride in dimethoxyethane the corresponding 2-cyclopenten-1-one (263) was obtained.[244]

Alkylation of the enolate anion of (250) (generated with sodium hydride in dimethyl ether at 25°C) with methyl iodide followed by acid hydrolysis of the ketal gave 2,2,6,6-tetramethyl-1,4-cyclohexanedione (264), a diamagnetic analogue of the nitroxide spin label 4-oxo-2,2,6,6-tetramethylpiperidinyl-N-oxy (265).[245]

Finally, Nicolaou et al[246] used monoketal (249) as starting material in the synthesis of bicyclo[3.1.1]-heptan-2-one (266). In this synthesis, outlined in Scheme 28, the monoketal (249) was converted to 4-methylenecyclohexanone ketal (249a) with methylenetriphenylphosphorane, which gave the hydroxy ketal (249b) on treatment with diisoamylborane. Hydrolysis of the ketal and protection of the hydroxy group as the tosylate gave (249c), which was converted to (266) with dimsylpotassium (KCH_2SOCH_3). Compound (266) is a key intermediate in the total synthesis of carbocyclic thromboxane A_2.

5.4 1,2-Addition reactions of cyclohexanone monoketals

The monoketals (250) and (254) were used in this study. The monoketal (254) was prepared by the method described by Hyatt,[240] whereas the monoketal (250) was purchased from Aldrich Chemicals Co.

A solution of monoketal (250) or (254) in THF was added to the dianion (171) derived from 3-furoic acid and lithium diisopropylamide under conditions similar to those described in Chapter 3. Surprisingly, the monoketals were recovered unchanged in quantitative yield, and even the presence of tetramethylethylenediamine (4 molar excess) or variation in the reaction temperature (0°C, -24°C, -78°C, -100°C) did not have any effect in promoting the reaction.

The monoketals (250) and (254) did not react either with the carbanion generated from ethyl-(4-methoxyphenyl)acetate (240) and lithium diisopropylamide in the THF at 0°C, -78°C or -100°C. This carbanion reacted very efficiently with cyclohexadienone monoketals (see Chapter 4).

This anomalous behaviour of the monoketals with the lithiated carbanions could be either due to solvent effects, or the electronic influence of the oxygen lone pairs of electrons in the complexing of the lithium reagent.

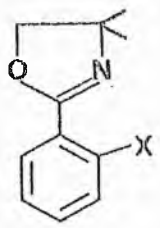
When a solution of (250) in diethyl ether was added to n-butyllithium at 0°C, no reaction took place, but when the reaction temperature was lowered to -78°C, the cyclohexanol (267) was obtained in almost quantitative yield. It is obvious from this reaction that the solvent and the reaction temperature play a critical role in determining the path of the complex equilibria that exist.

Internally co-ordinated lithium anions, e.g. (271) (see Chapter 4), reacted with (250) and (254) in THF at -78°C to give carbinols (272) and (273) in good yields. Simultaneous hydrolysis of the oxazoline and the ketal in refluxing ethanol-sulfuric acid, gave the spirolactone (274) in 69% yield (Scheme 29).

The behaviour of the monoketals (250) and (254) with Grignard reagents was examined next. Phenylmagnesium bromide, prepared in ether, added to (250) to give the cyclohexanol (268) in almost quantitative yield. The oxazolino-Grignard (270) gave the carbinols (272) and (273), identical to those obtained from the lithium anion (271), albeit in lower yield. Hydrolysis of the oxazoline and the ketal gave the spirolactone (274), identical to that obtained previously.

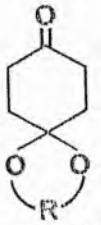
Finally, sodium borohydride reduction of (254) in ethanol, gave the cyclohexanol (269).

Scheme 29



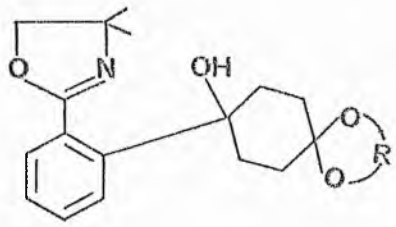
(270) X=MgBr

(271) X=Li



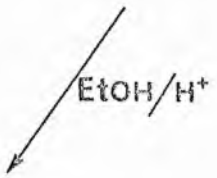
(250)

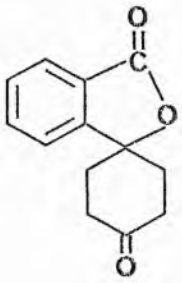
(254)



(272) $R=CH_2C(CH_3)_2CH_2$

(273) $R=(CH_2)_4$





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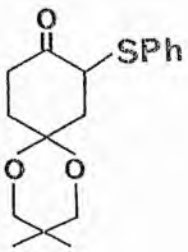
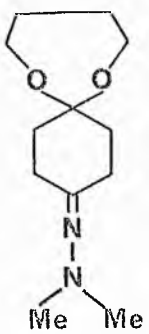


(275)



(276)

5.4.1 Attempts to convert cyclohexanone ketals to cyclohexenone ketals

Introduction of a double bond α- to a carbonyl group can proceed either by hydride ion abstraction (an ionic mechanism) or abstraction of a hydrogen aton or an electron (a free-radical mechanism). Hydrogen can be removed from the saturated compound either catalytically or chemically. Catalytic dehydrogenation over a metal catalyst (e.g. platinum, palladium etc.) is extensively used in industry. Chemical dehydrogenation can be achieved by the use of sulphur, selenium, bromine, high-potential quinones, lead tetraacetate, manganese dioxide etc.

5.4.2 Use of organoselenium and organosulphur compounds as dehydrogenating agents

One of the major applications of organoselenium chemistry is based on the fact that phenyl alkyl selenides can be converted into olefins under very mild conditions.[247] This constitutes a standard method for making $\alpha\beta$-unsaturated carbonyl compounds and is carried out in three steps: (a) introduction of a benzeneseleno group (PhSe-) alpha to the carbonyl, (b) oxidation of the resulting selenide to the selenoxide level, and (c) fragmentation of the selenoxide.

The usual method for introducing the PhSe- group is by reaction of a lithium enolate, generated at low temperature in THF, with diphenyldiselenide, benzeneselenyl chloride, or benzeneselenyl bromide.[248] The most common reagents employed for the oxidation of the α-selenenylated carbonyl compounds are sodium periodate, peracids (usually m-chloroperbenzoic acid), ozone, and hydrogen peroxide. The selenoxide thus formed can be allowed to fragment by warming to room temperature.

This method of dehydrogenation was attempted with monoketals (250) and (254). A solution of the ketal (250) or (254) in THF was treated with lithium diisopropylamide at $-78^{\circ}C$, followed by addition of benzeneselenyl bromide (prepared from diphenyldiselenide and bromine). After

workup of the reaction mixture, only starting materials were recovered. The failure of the reaction is possibly due to the anomalous behaviour of the ketals with the lithium reagent, which was also observed during attempted 1,2-addition reactions reported earlier.

A closely related method for making $\alpha\beta$-unsaturated carbonyl compounds introduced by Trost,[249,250] uses dimethyldisulphide or diphenyldisulphide to produce the corresponding α-sulphenylated products. Oxidation to the sulphoxide, followed by thermolysis leads to the $\alpha\beta$-unsaturated systems.

When a solution of (250) in ether was added to a suspension of sodium hydride and an equimolar amount of diphenyldisulphide in ether at $0^{\circ}C$, a yellow oil, thought to be (275) was obtained in 80% yield. Several attempts to oxidise this oil to the corresponding sulphoxide with hydrogen peroxide or with m-chloroperbenzoic acid failed.

5.4.3 α-Functionalisation of (254) via its N,N-dimethylhydrazone

Corey et al[251] have shown that N,N-dimethylhydrazones can be efficiently metallated at the α-carbon atom, that these reagents participate in a variety of useful carbon-carbon bond forming reactions, and that hydrolysis of the hydrazones to carbonyl compounds may be accomplished under mild conditions using aqueous sodium periodate or cupric ion. The metallation of the N,N-dimethylhydrazones is effected by lithium diisopropylamide in tetrahydrofuran at $0^{\circ}C$.

This method of metallation, which leads to α-functionalisation, was attempted with N,N-dimethylhydrazone (276), derived from cyclohexanone monoketal (254) and N,N-dimethylhydrazine. When a solution of (276) in THF was added to lithium diisopropylamide at $0^{\circ}C$ and the mixture was quenched after 10h by the addition of diphenyldisulphide, only starting materials were recovered after workup. Several attempts using different reaction temperatures and duration of metallation also failed. This could again be due to the anomalous behaviour of the ketal with the lithiated reagent.

5.5 Diels-Alder reactions of spiroketal and spirolactone cyclohexadienones and cyclohexadienimines

5.5.1 Introduction

Another way to obtain cyclohexendione ketals and lactones is to perform cycloaddition reactions on corresponding cyclohexadienone and cyclohexadienimine substrates.

Thus far, the thermal addition reactions of quinone monoketals have been limited to Diels-Alder chemistry. The benzoquinone monoketals undergo Diels-Alder reaction with 1-methoxybutadiene, isoprene, and 2-methoxybutadiene[28,252] (Scheme 30). The cycloaddition with 1-methoxybutadiene is highly regiospecific, giving only the 'ortho' adduct. The cycloadditions with isoprene and 2-methoxybutadiene show virtually no regioselectivity.

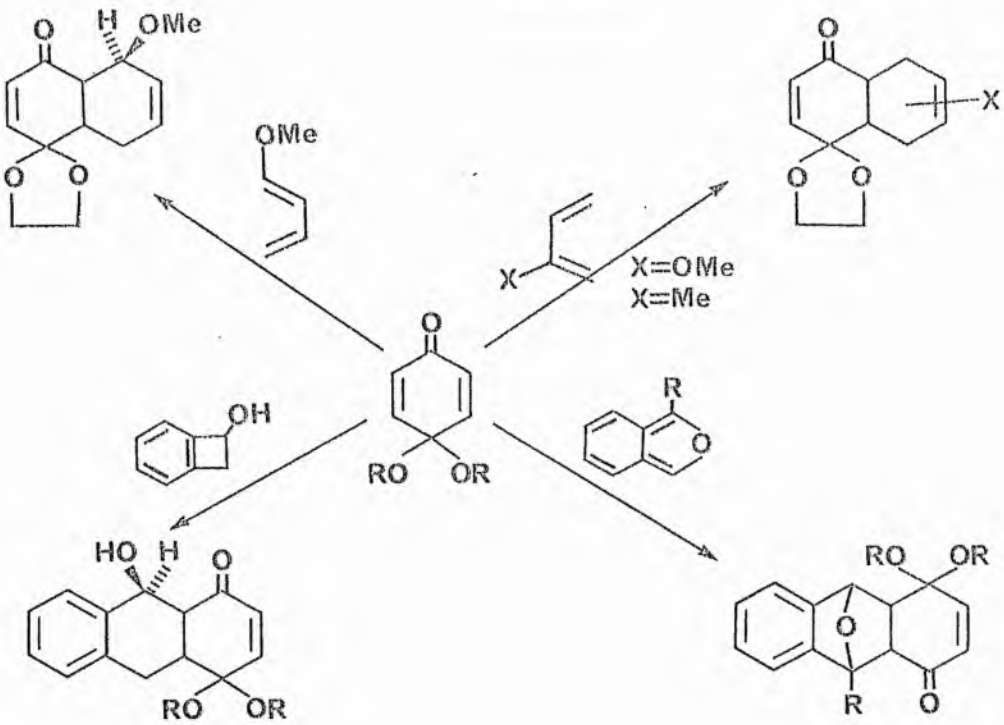
Diels-Alder reactions with benzocyclobutenol[28] and isobenzofurans[253] have also been reported in connection with projected routes to anthracyclinone natural products.[254]

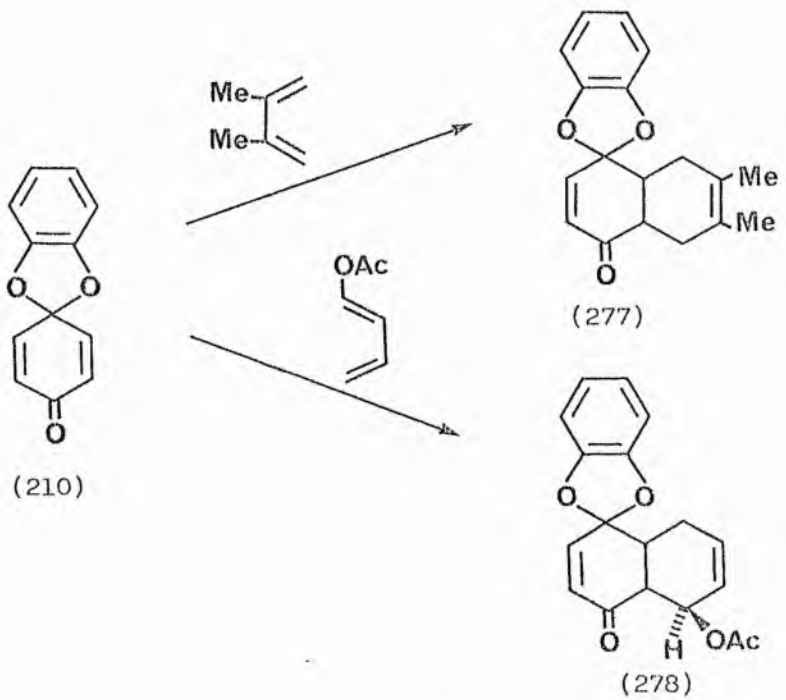
The cycloadditions of quinone imines with dienes was studied by Adams and co-workers,[100] but the regio- and stereochemistry of the adducts were not determined. A more recent investigation[255] with the objective of determining the influence of the benzenesulphonimide group on the regiochemistry of the cycloaddition as well as the relative dienophile double bond reactivity established that : (1) the regiochemistry of the cycloadditions is exclusively controlled by the benzenesulphonimide group, and (2) the double bond in the quinone imine which is syn to the benzenesulphonimide is the more activated dienophilic position.

5.5.2 Cycloaddition reactions

The reaction of cyclohexadienone ketal (210) with 2,3-dimethyl-1,3-butadiene in refluxing benzene afforded after 50h the adduct (277) in 50% yield. Ketal (210) also added to trans-1-acetoxy-1,3-butadiene

Scheme 30


H
OMe
O
O
O
OMe
X
X=OMe
X=Me
OH
R
O
RO
OR
HO
H
RO
OR
RO
OR
O
R
O


Me
Me
O
O
O
Me
Me
O
(277)
OAc
O
O
O
(210)
O
O
O
H
OAc
(278)

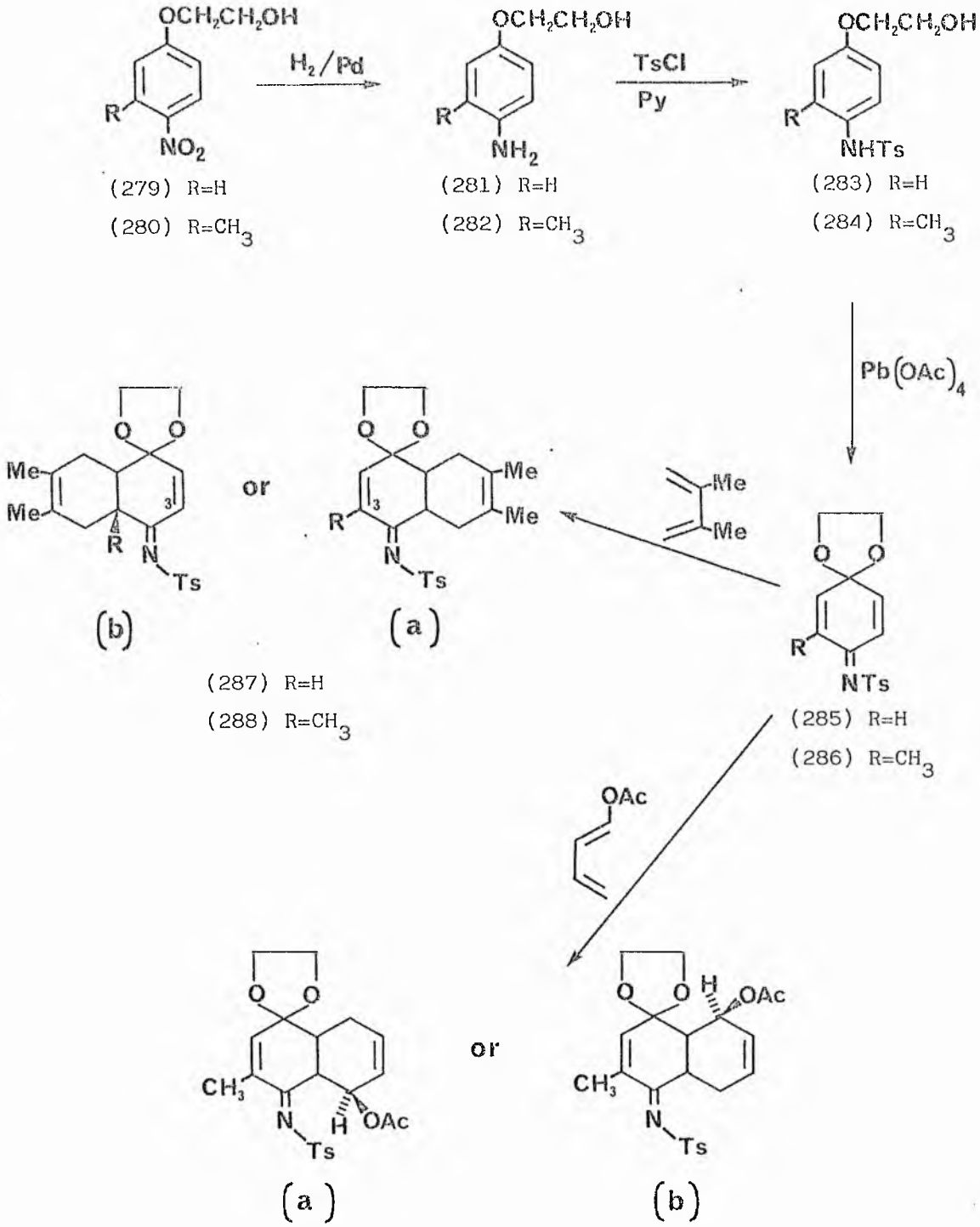
in refluxing toluene to give an adduct (278) in 70% yield. Unfortunately, proton nmr studies on this compound were prevented by the fact that it is extremely insoluble in most deuterated solvents, but the assignment to it of structure (278) was made in accordance with the expected regioselectivity on steric grounds.[28]

Cycloaddition of the imine ketal (285) to 2,3-dimethyl-1,3-butadiene in refluxing benzene afforded the adduct (287a) or (287b) in 50% yield.

Moore et al[255] have reported that the cycloaddition of 1-methoxy-1,3-butadiene to 1,4-benzoquinone monobenzenesulphonimide (290) yields a mixture of regioisomers (291) and (292) in 2:1 ratio (Scheme 31). The stereochemistry of the adducts was readily assigned from the observation that the nmr absorption for the vinyl proton at position 3 in the minor product (292) is deshielded relative to the analogous absorption in (291). These appear respectively at δ8.1 and δ6.7. That the deshielded absorption is due to the syn-vinyl proton (with respect to the benzenesulphonyl group) is based upon the observation that the chemical shift of the syn-vinyl proton in the quinone imine (290) appears at δ8.1. Therefore, it is apparent that the proton on the syn double bond is experiencing a deshielding anisotropy effect of the benzenesulphonyl group.

If the above argument is true for benzoquinone-imines, it can then be extended to benzoquinone ketal-imines. The nmr spectrum of adduct (287) shows an absorption for the vinyl proton at position 3, at δ6.2. That vinyl proton is clearly not syn to the p-toluenesulphonyl group because it is not experiencing a deshielding effect, and it can therefore be safely assumed that adduct (287) is the regioisomer (287a).

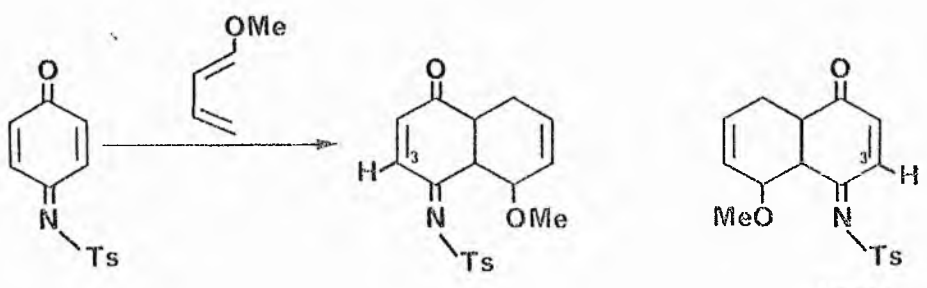
Similarly, the imine ketal (286) added to 2,3-dimethyl-1,3-butadiene in refluxing benzene to give (288a) or (288b) in 80% yield. The nmr spectrum of the adduct shows a vinyl proton absorption corresponding to



(279) R=H
(280) R=CH_3
(281) R=H
(282) R=CH_3
(283) R=H
(284) R=CH_3
(287) R=H
(288) R=CH_3
(285) R=H
(286) R=CH_3

(289)

Scheme 31



(290) (291) (292)

only one proton, i.e. the regioisomer (288a) is favoured. The regioisomer (288b) should show vinyl proton absorptions corresponding to two protons. Also, the electron-donating effect of the methyl substituent on the double bond anti to the p-toluenesulphonyl group renders that bond even less reactive a dienophile, thus favouring the regioisomer (288a).

The cycloaddition of imine ketal (286) and trans-1-acetoxy-1,3-butadiene in refluxing toluene gave the adduct (289a) or (289b). Under the reaction conditions, the imine decomposed extensively. Although the 'ortho' adduct structure (289a) is favoured both on steric grounds and effective regiocontrol by the p-toluenesulphonyl group,[255] the nmr spectrum of the product in which the methylene protons of the ketal appear as two triplets would appear to favour structure (289b). The significance of the nmr results is not clear, however, as the methylene protons of the symmetrical adduct (288a) also appear as a multiplet.

Imine lactones[256] (293) and (294) added to 2,3-dimethyl-1,3-butadiene in refluxing benzene to give adducts (295) and (296) in 50% yield. The assignments were again based on the nmr absorption of the vinyl proton at position 3, which is at δ6.8 for (295) and δ6.2 for (296).

An interesting observation was made when an attempt was made to speed the cycloaddition of imine lactone (294) to 2,3-dimethyl-1,3-butadiene using a Lewis acid catalyst, aluminium chloride. The only product isolated in 50% yield was the adduct (297), in which the imine bond had hydrolysed to the quinone. So far, the only method available for that hydrolysis is passage of the imine down an alumina column.[36]

A preliminary investigation showed that treatment of imine ketal (285) with aluminium chloride in methylene chloride at room temperature produced a complex mixture. Infra-red examination showed the characteristic dienone absorption pattern at 1690, 1640, and 1610cm^{-1} and the

total loss of absorbance at 1550cm^{-1} (C = N). Time did not allow any further elaboration on that observation.

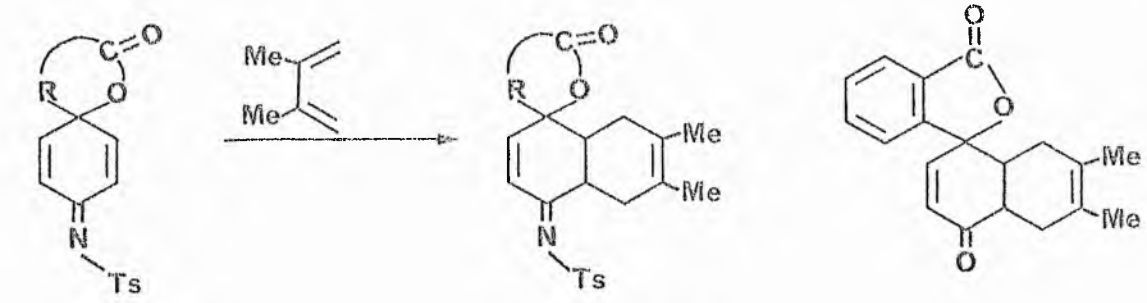
Reduction with sodium borohydride in ethanol of the C = N bond in adduct (288a) gave a 75% yield of the corresponding sulphonamide (298). This reaction indicated that Diels-Alder adducts such as (288a) behave differently from the starting spiro-imines which usually undergo 1,4-addition reactions with nucleophiles followed by opening of the spiro-ring and subsequent aromatisation.

5.5.3 Siloxy dienes in cycloaddition reactions

A valuable extension of Diels-Alder methodology in organic synthesis has been the use of siloxy-dienes pioneered by Danishefsky and his co-workers.[257] Thus, reaction of trans-4-methoxybut-3-en-2-one with trimethylchlorosilane in the presence of zinc chloride gives trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene. This compound undergoes cycloadditions with a variety of dienophiles, and when the resulting adducts are subjected to acid, hydrolysis of the silyl ether back to the enone occurs with concurrent expulsion of the methoxy group as methanol (Scheme 32). This synthetic sequence has been used in syntheses of vernolepin,[258] pentalenolactone,[259] and prephenic acid.[260]

Cycloaddition of trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene on to p-benzoquinone has been reported[261] but the adduct could not be isolated, presumably because of β-elimination of methanol and disproportionation of the resultant dihydronaphthoquinone derivative. Accordingly, the resultant mixture was acylated with pyridine and acetic anhydride to afford 1,4,7-triacetoxynaphthalene.

It has been recently noted[262] that Diels-Alder cycloadducts of unsymmetrical electron-rich dienes and methyl- or methoxy-benzoquinones or naphthoquinones produce adducts in which the more nucleophilic diene



(293) R=CH_2CH_2

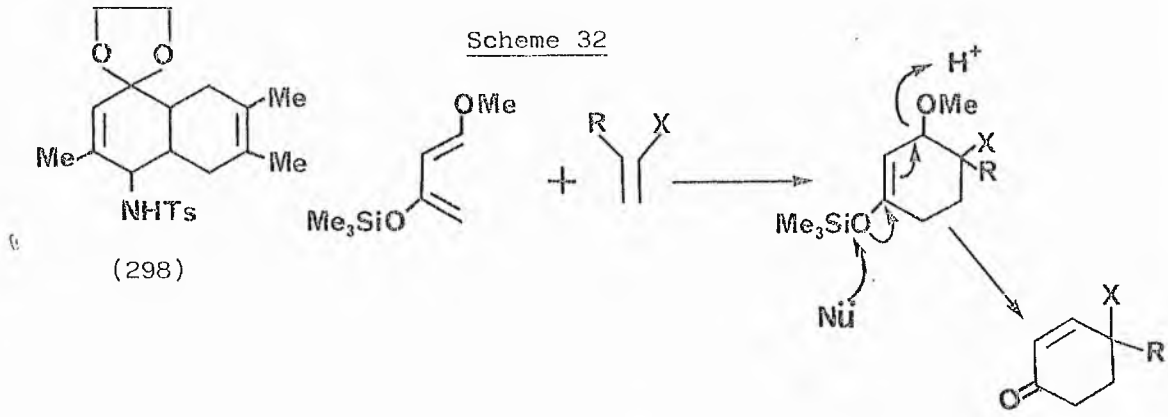
(294) R=C_6H_4

(295) R=CH_2CH_2

(296) R=C_6H_4

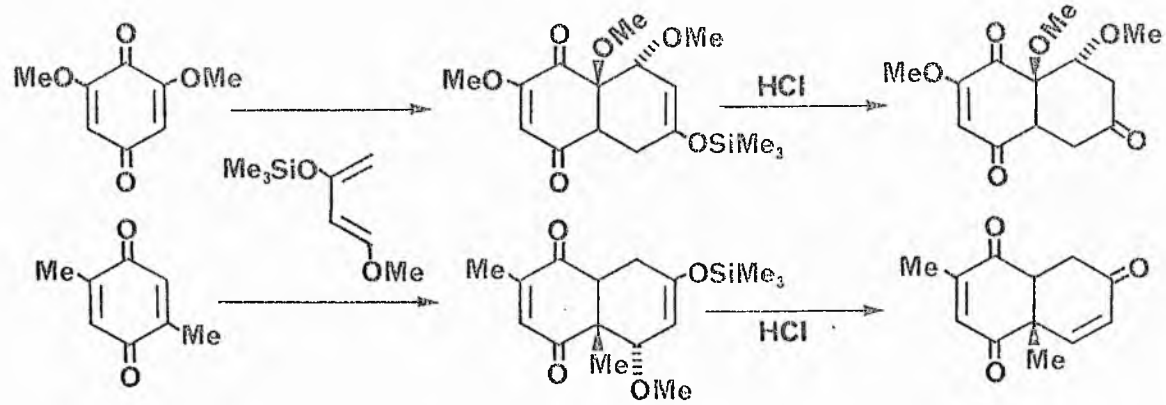
(297)

Scheme 32

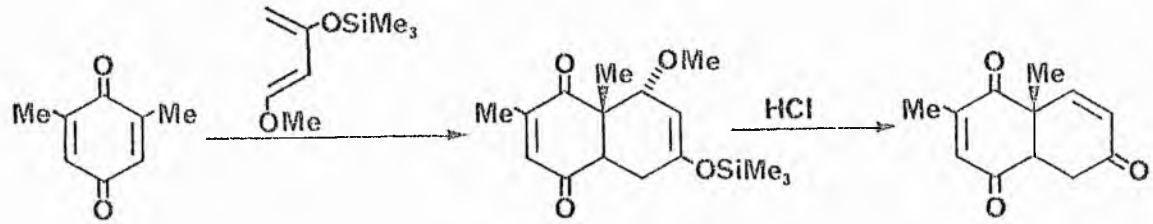


(298)

Scheme 33



Scheme 34



(299)

(300)

terminus becomes bonded to the non-methylated or non-methoxylated carbon. Thus, 2,6-dimethoxybenzoquinone and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene give the ortho, para adduct, which on acid hydrolysis yields the ketone, with retention of the methoxy group (Scheme 33). Similarly, the unsymmetrical 2,5-dimethylbenzoquinone gives the ortho, para adduct which hydrolyses further to the conjugated ketone (Scheme 33). With both 2-methyl and 2-methoxynaphthoquinones, similar results were obtained. The attack of the most nucleophilic terminus of the electron-rich diene on the less substituted terminus of the dienophile has been attributed to repulsive effects,[262] which may be specific secondary orbital repulsive effects between the diene nucleophilic terminus and substituent orbitals.

The cycloaddition reaction between the symmetrical 2,6-dimethyl-benzoquinone and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene gave the adduct (300) in 30% yield, via intermediate (299) (Scheme 34). The assignment of structure (300) to this adduct was given in accordance with the observations made by other workers,[262] and was supported by spectroscopic and analysis data.

EXPERIMENTAL SECTION

General Introduction

Infra-red spectra were recorded using a Perkin Elmer 157 G spectrophotometer calibrated with polystyrene film. Proton magnetic resonance spectra were recorded on a Hitachi-Perkin Elmer 24B (60 MHz) spectrophotometer, and carbon-13 on a JEOL JNM-FX 60Q spectrophotometer with tetramethylsilane as the internal standard in the solvent indicated. Low resolution mass spectroscopy determinations were carried out by Leicester Polytechnic. Elemental microanalyses for C, H, N and S were carried out by the analytical section of Imperial Chemical Industries plc., Alderley Edge, Macclesfield. Melting points were determined using open capillaries in an electrically heated Gallenkamp melting point apparatus and are uncorrected.

Hydrogenations were performed using the medium pressure apparatus of Chas. W. Cook and Sons, Birmingham, and also a standard atmospheric pressure hydrogenation apparatus. Column chromatography was carried out using a Fison silica-gel MFC (80-200 mesh) and neutral alumina Brockman Activity II. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). All solvents for chromatographic work were redistilled. Other solvents were dried using molecular sieves (except ether, THF, and benzene, which were dried over sodium). Petroleum used has b.p. 60-80^{o}.

General electrochemical oxidation procedure

All anodic oxidations were carried out using a Wenking potentiostat model 70 TS 1 and standard calomel reference electrode, with a graphite felt anode (5 x 3cm) and a platinum cathode (3 x 2cm). The one compart-

ment cell (a 250ml beaker) contained a solution of tetraethylammonium perchlorate (2.5g) in either methanol or acetonitrile (150ml) and was stirred magnetically. The oxidations were carried out in air at room temperature. Substrates were added in solution of the cell solvent to an equilibrated, pre-electrolysed anodic cell, at a predetermined anodic potential, and the current monitored with time until either the current dropped to the background level or until all starting material was shown by t.l.c. examination to have reacted. The cell solution was decanted and filtered and the solvent was evaporated off in vacuo. The residues were partitioned between methylene chloride and water, and the organic layer separated. When the starting materials were acidic an additional wash with saturated sodium bicarbonate solution was employed. The organic layers were dried and evaporated to dryness.

Oxidation of sulphonamides using lead tetraacetate
General procedure

To a solution of the sulphonamide (10 mmol) in glacial acetic acid (50ml) was added lead tetraacetate (3g) and the mixture was stirred overnight at room temperature. The mixture was poured into water, extracted with ether, the ether extract was washed with saturated sodium bicarbonate solution, dried, and the ether was evaporated off in vacuo.

Oxidation of phenols with manganese dioxide
(SEDEMA, "Faradiser M")

To a solution of the phenol (5 mmol) in benzene (50ml) was added manganese dioxide (3g) and the mixture was heated under reflux with stirring for 3h. After cooling, the solution was filtered and the benzene was evaporated off in vacuo. The products were purified by chromatography on silica gel.

Oxidation of electron-rich aryl compounds
with thallium (III) trifluoroacetate

To a solution of thallium (III) trifluoroacetate (0.6g/mmol of substrate) in trifluoroacetic acid (5ml) and methylene chloride (20ml)

was added boron trifluoride-etherate (0.5ml) and the mixture was cooled to -20°C with vigorous stirring. A solution of the appropriate substrate (1 mmol) in methylene chloride (5ml) was added and the mixture was quenched with tert-butyl alcohol (10ml) after 30 sec, and allowed to come to room temperature. The mixture was washed with water, aqueous sodium bicarbonate solution, dried, and the methylene chloride was evaporated off *in vacuo*. The residue was chromatographed on silica gel.

Catalytic reduction of nitro compounds and hydrogenolysis of benzylic ethers

To a solution of the nitro compound or the benzylic ether (10 mmol) in ethanol or ethyl acetate (100ml) was added a slurry of palladium (5 or 10% on charcoal, 1g) in water (3ml) and the mixture was shaken under hydrogen until uptake of gas ceased. The catalyst was removed by filtration and the solvent was evaporated off *in vacuo*. The product was recrystallised from an appropriate solvent.

Preparation of sulphonamides. General procedure

To a solution of the amine (10 mmol) in chloroform (50ml) and pyridine (5ml) was added freshly recrystallised p-toluenesulphonyl chloride (11 mmol) or methanesulphonyl chloride (11 mmol) and the mixture was heated under reflux until t.l.c. examination showed the disappearance of the starting materials. The mixture was poured into hydrochloric acid (4M), the organic layer was separated and washed with hydrochloric acid, water, dried, and evaporated to dryness. The solids obtained were recrystallised from appropriate solvents.

2-Nitro-4-trifluoromethyl-4′-benzyloxydiphenyl ether (135)

To a solution of 4-benzyloxyphenol (5.0g), 0.025M) in dry DMF (50ml) was added sodium hydride (0.72g, 0.025M) over 30 min, followed by 4-chloro-3-nitrobenzotrifluoride (5.6g, 0.025M) in dry DMF (10ml), and the mixture was heated at 140°C for 6h. The mixture was poured into water and extracted with chloroform. The extract was washed with 2M sodium hydroxide solution, water, dried, and evaporated to dryness, to give (135) (5.5g, 57%) as yellow crystals, m.p. 76-7°C (from petroleum). (Found : C, 61.7; H, 3.3; N, 3.2. $C_{20}H_{14}F_3NO_4$ requires C, 61.7; H, 3.6; N, 3.6%). ν_{max} : 1520 and 1330 cm^{-1} (NO). δ_H : 5.0 (2H, s, CH_2) and 7.0 - 8.0 (12H, m, arom.).

Similarly, from 4-benzyloxyphenol and o-bromonitrobenzene was obtained 2-nitro-4′-benzyloxydiphenyl ether (115) (17%), m.p. 75°C (lit.,[137] 77°C).

2-Amino-4-trifluoromethyl-4′-benzyloxydiphenyl ether (136)

The nitro compound (135) (7.6g, 0.02M), iron powder (3.5g), acetic acid (8.4g) and absolute ethanol (50ml) were heated under reflux for 3h, cooled and poured into water. The aqueous mixture was extracted with chloroform (150ml) and ether (150ml), and the combined extract was dried and evaporated to dryness to give (136) (3.5g, 50%), as a brown crystalline solid, m.p. 98 - 9°C (from ethanol). (Found : C, 66.8; H, 4.3; N, 3.4. $C_{20}H_{16}F_3NO_2$ requires C, 66.8; H, 4.4; N, 3.9%). ν_{max} : 3400 and 3330cm^{-1} (NH_2). δ_H : 4.0 (2H, br s, exchanges with D_2O, NH_2), 5.0 (2H, s, CH_2), and 6.9-7.4 (12H, m, arom.).

Similarly, from ether (115) was obtained 2-amino-4′-benzyloxydiphenyl ether (116) (74%), m.p. 147-8°C (lit.,[101] 148-9°C).

2-(p-Toluenesulphonamido)-4-trifluoromethyl-4′-benzyloxydiphenyl ether (137)

The title sulphonamide was prepared from amine (136) (3.5g, 0.01M) and p-toluenesulphonyl chloride (1.9g, 0.01M) as colourless crystals (3.0g, 60%), m.p. 138-9°C, (from ethanol). (Found : C, 62.9; H, 4.0; N, 2.3. $C_{27}H_{22}F_3NO_4S$ requires C, 63.2; H, 4.3; N, 2.7%). ν_{max} : 3250cm^{-1} (NH). δ_H : 2.4 (3H, S, CH_3), 5.0 (2H, s, CH_2), and 6.6-8.0 (16H, m, arom.).

Similarly, from amine (116) was obtained 2-p-toluenesulphonamido-4′-benzyloxydiphenyl ether (117) (66%), m.p. 148- 50°C (lit.,[101] 150-1°C).

2-(p-Toluenesulphonamido)-4-trifluoromethyl-4′-hydroxydiphenyl ether (138)

A solution of sulphonamide (137) (2.5g, 5mmol) in ethanol (25ml) and concentrated hydrochloric acid (25ml) was heated under reflux for 3h, cooled and reduced to low bulk in vacuo, to give (138) (1.9g, 89%) as a colourless amorphous solid, m.p. 168- 70°C (from aqueous ethanol). (Found : C, 56.6; H, 3.6; N, 3.1. $C_{20}H_{16}F_3NO_4S$ requires C, 56.7; H, 3.8; N, 3.3%). ν_{max} : 3460 (OH) and 3250cm^{-1} (NH). δ_H : 2.4 (3H, s, CH_3), 6.5-7.6 (11H, m, arom.), and 9.2 (1H, br s, exchanges with D_2O, NH).

Similarly, from sulphonamide (117) was obtained 2-p-toluenesulphonamido-4′-hydroxydiphenyl ether (114), (76%), m.p. 164-6°C (lit.,[101] 167-8°C).

Spirooxazoles (163) and (120) from the oxidation of sulphonamides (138) and (114)

The sulphonamides were oxidized with 'active' manganese dioxide as described in the general introduction to give after chromatography an alumina: (i) spirooxazole (163) as a yellow crystalline solid (31%), m.p. 120°C (from petroleum). (Found : C, 56.8; H, 3.7; N, 3.0. $C_{20}H_{14}F_3NO_4S$ requires C, 57.0; H, 3.3; N, 3.3%). ν_{max} : 1680 (CO) and 1640cm^{-1} (C=C). δ_H : 2.4 (3H, s, CH_3), 6.2 and 6.6 (4H, 2d, vinylic)

and 6.8-7.6 (7H, m, arom.). (ii) spirooxazole (120) as yellow prisms (50%), m.p. 170-1°C (lit.,[101] 172-3°C). ν_{max} : 1682, 1645, and 1613cm^{-1}.

2,4′-Dinitrodiphenyl ether (139)

To a solution of 4-nitrophenol (13.9g, 0.1M) in DMSO (30ml) was added potassium fluoride (8.7g, 0.15M) and o-fluoronitrobenzene (14.1g, 0.1M), and the mixture was heated on a steam bath for 30 min. After cooling, the mixture was poured into water and the precipitate was filtered and air dried. The title ether was obtained as a yellow crystalline solid (18g, 68%), m.p. 98-100°C (from ethanol), (lit.,[138] 100-3°C). ν_{max} : 1520 and 1350cm^{-1} (NO).

2,4′-Diaminodiphenyl ether (140)

Catalytic hydrogenation of 2,4′-dinitrodiphenyl ether (5.2g, 0.02M) as described in the general introduction yielded the title amine (3.9g, 95%) as a brown crystalline solid, m.p. 78-80°C (from ethanol), (lit.,[138] 78-80°C). ν_{max} : 3400, 3320 and 3220cm^{-1} (NH).

2,4′-bis-(p-Toluenesulphonamido)diphenyl ether (141)

The title sulphonamide was prepared from 2,4′-diaminodiphenyl ether (2.0g , 0.01M) and p-toluenesulphonyl chloride (3.8g, 0.02M) by the method described in the general introduction as a pale pink crystalline solid (3.5g, 70%), m.p. 169-71°C (from toluene-petroleum). (Found : C, 61.0; H, 4.7; N, 5.3; S, 12.6. $C_{26}H_{24}N_2O_5S_2$ requires C, 61.4; H, 4.7; N, 5.5; S, 12.5%). ν_{max} : 3250 (N H), 1350 and 1150cm^{-1} (SO_2N). δ_H : 2.3 (3H, s, CH_3), 2.4 (3H, s, CH_3) and 6.8-7.7 (18H, m, 2H's exchange with D_2O, arom. and NH).

Oxidation of sulphonamide (141) with lead tetraacetate and manganese dioxide

A) The sulphonamide (141) was oxidised with lead tetraacetate by the usual procedure, to a red gum which was not t.l.c. homogeneous.

B) Oxidation of the sulphonamide (141) with manganese dioxide (SEDEMA) gave a red solid, which was chromatographed on a neutral alumina column with toluene as eluant, to give the known benzoxazole (120)(0.5%), identified by t.l.c., ir spectrum, and mixed m.p., with the product of oxidation of (114).

α-(4-Benzyloxyphenyl)-4-morpholineacetonitrile (142)

A mixture of 4-benzyloxybenzaldehyde (21.2g, 0.1M) in dry THF (250 ml), freshly distilled morpholine (17.4g, 0.2M) and 4-toluenesulphonic acid (19.0g, 0.1M) was heated under reflux for 1h. After cooling, a solution of potassium cyanide (6.5g, 0.1M) in water (10ml) was added and reflux resumed for a further 10h. The solution was reduced in bulk and partitioned between chloroform (100ml) and aqueous sodium carbonate (100ml). The chloroform layer was washed with sodium bisulphite, water, dried, and evaporated to dryness. The acetonitrile (142) was obtained as colourless crystals (20.0g, 65%), m.p. 90°C (from ethanol). (Found : C, 74.2; H, 6.9; N, 8.5. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.0%). ν_{max} : 2220 (C≡N). δ_H : 2.5 (4H, dt, CH_2NCH_2), 3.6 (4H, dt, CH_2OCH_2), 4.7 (1H, s, CH-CN), 5.0 (2H, s, CH_2) and 7.0-7.4 (9H, m, arom.).

α-(3,4,5-Trimethoxyphenyl)-4-morpholineacetonitrile (143)

From, 3,4,5-trimethoxybenzaldehyde (19.6g, 0.1M), morpholine (17.5g, 0.2M), 4-toluenesulphonic acid (19.0g, 0.1M) and potassium cyanide (6.5g, 0.1M) was obtained acetonitrile (143) (23.5g, 80%), by the same procedure as for (142), as colourless crystals, m.p. 137-8°C (from benzene-petroleum (lit.,[127] 137-9°C). ν_{max} : 2210 (C≡N). δ_H : 2.5 (4H, dt, CH_2NCH_2), 3.7 (4H, dt, CH_2OCH_2), 3.75 (3H, s, OMe), 3.8 (6H, s, 2 x OMe), 4.8 (1H, s, CH-CN) and 6.7 (2H, s, arom.).

α-(4-Benzyloxyphenyl)-α-(2-nitro-4-trifluoromethylbenzene)-4-morpholineacetonitrile (144)

To sodium hydride (1.15g, 50% dispertion in oil, 0.025M) in dry DMF

(50ml) was added the morpholineacetonitrile (142) (4.5g, 0.015M) with stirring. The mixture was cooled to 0°C after 1h, and a solution of 4-chloro-3-nitro-1-trifluoromethylbenzene (3.38g, 0.015M) in DMF (10ml) was added under nitrogen. Stirring at room temperature was resumed for a further hour, after which the mixture was poured into ice containing 4M acetic acid (5ml). The solid which precipitated was filtered and air dried to give (144) (5.3g, 71%) as yellow needles, m.p. 162-4°C (from ethanol). (Found : C, 62.7; H, 4.7; N, 7.8; $C_{26}H_{22}F_3N_3O_4$ requires C, 62.7; H, 4.4; N, 8.3%). ν_{max} : 2220 (C≡N), 1520 and 1330cm^{-1} (NO). δ_H : 2.5 (4H, dt, CH_2NCH_2), 3.7 (4H, dt, CH_2OCH_2), 5.1 (2H, s, CH) and 7.0-8.4 (12H, m, arom.).

From morpholineacetonitrile (143) (5.84g, 0.02M) and 4-chloro-3-nitro-1-trifluoromethylbenzene (4.50g, 0.02M) was obtained α-3,4,5-trimethoxyphenyl)-α-(2-nitro-4-trifluoromethylbenzene)-4-morpholinoacetonitrile (145) (4.50g, 50%), by the method described for (144), as yellow needles, m.p. 174-6°C (from ethanol). (Found : C, 54.5; H, 4.7; N, 8.5. $C_{22}H_{22}F_3N_3O_6$ requires C, 54.8; H, 4.6; N, 8.7%). ν_{max} : 2215 (C≡N), 1540 and 1350cm^{-1} (NO). δ_H : 2.5 (4H, dt, CH_2NCH_2), 3.7 (4H, dt, CH_2OCH_2), 3.8 (3H, s, OMe), 3.9 (6H, s, 2 x OMe), 6.9 (2H, s, arom.), and 8.3 (1H, d, arom.).

2-Nitro-4-trifluoromethyl-4′-benzyloxybenzophenone (146)

A solution of morpholineacetonitrile (144) (4.97g, 0.01M) in glacial acetic acid (100ml) was heated under reflux for 1h, then cooled and diluted with ice-water. The solid which precipitated out was filtered and washed repeatedly with water. The benzophenone (146) was obtained as yellow crystals (3.0g, 75%), m.p. 155-7 °C (from ethanol). (Found : C, 62.9; H, 3.7; N, 2.9. $C_{21}H_{14}F_3NO_4$ requires C, 62.8; H, 3.5; N, 3.4%). ν_{max} : 1660 (CO), 1550 and 1330cm^{-1} (NO). δ_H : 5.0

(2H, s, CH_2), and 7.1-8.1 (12H, m, arom.).

From morpholineacetonitrile (145) (4.81g, 0.01M) in glacial acetic acid (100ml) was obtained 2-nitro-4-trifluoromethyl-3′,4′,5′-trimethoxybenzophenone (149) (3.0g, 78%), by the method described for (146), as yellow needles, m.p. 141-3°C (from ethanol). (Found : C, 52.8; H, 3.6; N, 3.1. $C_{17}H_{14}F_3NO_6$ requires C, 53.0; H, 3.6; N, 3.6%). ν_{max} : 1660 (CO), 1530 and 1350cm^{-1} (NO). δ_H : 3.8 (6H, s, 2 x OMe), 3.9 (3H, s, OMe), 7.0 (2H, s, arom.), 7.6 (1H, d, arom.), 8.0 (1H, d, arom.), and 8.5 (1H, s, arom.).

2-Amino-4-trifluoromethyl-4′-hydrobenzophenone (147)

A solution of benzophenone (146) (1.2g, 3mmol) in ethyl acetate (100ml) was hydrogenated using palladium (10% on carbon, 0.5g) as described in the general introduction, to yield the title benzophenone (147) (0.6g, 75%), as a colourless amorphous solid, m.p. 119- 20°C (from aqueous ethanol). (Found : C, 59.4; H, 3.9; N, 4.5. $C_{14}H_{10}F_3NO_2$ requires C, 59.8; H, 3.6; N. 5.0%). ν_{max} : 3400 (OH), 3330 (NH), 1615cm^{-1} (CO). δ_H : 6.7-7.4 (9H, m, arom. plus NH_2), and 9.9 (1H, s, exchanges with D_2O,OH).

From benzophenone (149) (1.9g, 5mmol) was obtained 2-amino-4-trifluoromethyl-3′,4′,5′-trimethoxybenzophenone (150) (1.3g, 70%), by the method described for (147), as colourless crystals, m.p. 112-4 °C (from aqueous ethanol). (Found : C, 57.3; H, 4.6; N, 3.8. $C_{17}H_{16}F_3NO_4$ requires C, 57.4; H, 4.5; N, 3.9%). ν_{max} : 3450 and 3340 (NH), and 1635cm^{-1} (CO). δ_H : 3.9 (6H, s, 2 x OMe), 3.95 (3H, s, OMe), 6.0 (2H, br s, exchanges with D_2O,NH_2), 6.6 (1H, d, arom.), 7.0 (2H, s, arom.), 7.1 (1H, d, arom.) and 7.6 (1H, d, arom.).

2-(p-Toluenesulphonamido)-4-trifluoromethyl-4′-hydroxybenzophenone (148)

To a phosphate buffer (2M, pH 7.0, 10ml) was added aminobenzophenone (147) (1.4g, 5mmol) followed by p-toluenesulphonyl chloride (0.95g,

5mmol) and the mixture was heated on a steam bath for 30 min. After cooling the solution was poured into 4M hydrochloric acid (50ml) and filtered to give (148) (1.85g, 84%), as a colourless amorphous solid, m.p. 180-2°C (from aqueous ethanol). (Found : C, 58.2; H, 4.2; N, 2.9. $C_{21}H_{16}F_3NO_4S$ requires C, 57.9; H, 3.7; N, 3.2%). ν_{max} : 3400 (OH), 3200 (NH) and 1615cm^{-1} (CO). δ_H : 2.3 (3H, s, CH_3), 7.0-7.8 (11H, m, arom.) and 9.7 (1H, br s, exchanges with D_2O,NH).

2-Methanesulphonamido-4-trifluoromethyl-3′,4′,5′-trimethoxybenzophenone (151)

To a solution of amine (150) (1.8g, 5mmol) in chloroform (30ml) and pyridine (5ml) was added methanesulphonyl chloride (0.57g, 5mmol) and the mixture was heated under reflux for 15h. After cooling, the mixture was poured into 4M hydrochloric acid and the organic layer was separated and washed with water, dried, and evaporated to dryness. Sulphonamide (151) (0.9g, 40%) was obtained as colourless crystals, m.p. 143-5°C (from methanol). (Found : C, 50.1; H, 4.0; N, 3.5. $C_{18}H_{18}F_3NO_6S$ requires C, 49.9; H, 4.1; N, 3.2%). ν_{max} : 3250 (NH) and 1670cm^{-1} (CO). δ_H : 3.1 (3H, s, CH_3), 3.9 (6H, s, 2 x OMe), 3.95 (3H, s, OMe), 7.0 (2H, s, arom.), 7.4 (1H, d, arom.), 7.8 (1H, d, arom.), 8.0 (1H, s, arom.), and 9.7 (1H, br s, exchanges with D_2O,NH).

2-Methyl-4H-3,1-benzoxazine-4-one

A mixture of anthranilic acid (3.0g, 0.21M) and acetic anhydride (100ml) was heated under reflux for 1h, cooled, and concentrated under vacuo to give 2-methyl-4H-3,1-benzoxazine-4-one (28g, 79%), as colourless needles, m.p. 75-7°C (lit.,[117] 76-8°C).

N-Methanesulphonylanthranilic acid (153)

The title acid was prepared from anthranilic acid (27.4g, 0.2M) and methanesulphonyl chloride (23g, 0.2M), as a brown solid (21g, 50%),

m.p. 125°C (from ethanol). ν_{max} : 1660 (CO_2H), 1330 and 1150cm^{-1} (SO_2N). δ_H : 3.0 (3H, s, CH_3), 6.6-7.9 (5H, m, one H exchanges with D_2O, arom. and NH).

p-Toluenesulphonylanthranilic acid (152)

The title acid was prepared from anthranilic acid (27.4g, 0.2M) and p-toluenesulphonyl chloride (40g, 0.21M), as a colourless amorphous solid (40g, 80%), m.p. 228-30°C (from aqueous ethanol), (lit.,[132] 229-30°C). ν_{max} : 1680 (CO_2H), 1380 and 1150cm^{-1} (SO_2N).

2-(p-Toluenesulphonamido)-4′-methoxybenzophenone (154)

p-Toluenesulphonylanthranilic acid (5.8g, 0.02M), anisole (20ml) and phosphorus pentachloride (4.2g, 0.021M) were heated to 50°C for 20 min., then cooled to 0°C and aluminium chloride (10.6g, 0.08M) was added in small portions. The mixture was stirred for 4h at room temperature and then poured into ice/conc. hydrochloric acid. Anisole was removed by vacuum distillation and the crude product was washed with dilute hydrochloric acid, water, and a 5 % solution of sodium carbonate. The title benzophenone (154) was obtained as colourless needles (63%), m.p. 138-40°C (from ethanol). (Found : C, 66.2; H, 5.1; N, 3.8. $C_{21}H_{19}NO_4S$ requires C, 66.1; H, 5.0; N, 3.7%). ν_{max} : 1640 (CO), 1350 and 1150cm^{-1} (SO_2N). δ_H : 2.3 (3H, s, CH_3), 3.8 (3H, s, OMe), and 6.8-7.8 (13H, m, one H exchanges with D_2O, NH and arom.).

2-Methanesulphonamidobenzoyl chloride

The title acid chloride was obtained from N-methanesulphonylanthranilic acid (10.7g, 0.05M) and thionyl chloride (20ml) as a colourless amorphous solid (8.0g, 70%), m.p. 300°C (from carbon tetrachloride). ν_{max} : 3280 (NH) and 1750cm^{-1} (CO). δ_H : 3.1 (3H, s, CH_3) and 7.1-8.1 (5H, m, arom. and NH).

2-p-Toluenesulphonamidobenzoyl chloride

The title acid chloride was obtained from p-toluenesulphonylanth-

ranilic acid (11.6g, 0.04M) and thionyl chloride (20ml) as a colourless amorphous solid (9.7g, 79%), m.p. 126-8°C (from carbon tetrachloride), (lit.,[132] 128-9°C). ν_{max} : 3250 (NH) and 1740cm^{-1} (CO).

4-Benzyloxyphenyl -2-methanesulphonamido benzoate (157)

To 2-methanesulphonamidobenzoyl chloride (3.5g, 0.015M) in dry pyridine (70ml) was added 4-benzyloxyphenol (3.0g, 0.015M) and the mixture was heated under reflux for 4h, cooled, and poured into ice/hydrochloric acid. The precipitate was filtered, washed with water and recrystallised from aqueous methanol (charcoal) to afford (157) (3.0g 50%), m.p. 145-7°C. (Found : C, 63.6; H, 4.9, N, 3.3. $C_{21}H_{19}NO_5S$ requires C, 63.5; H, 4.8; N, 3.5%). ν_{max} : 3220 (NH), 1700 (CO), 1330 and 1140cm^{-1} (SO_2N). δ_H : 3.1 (3H, s, CH_3), 5.1 (2H, s, CH_2), 7.1-8.3 (14H, m, one H exchanges with D_2O, arom. and NH).

4-Benzyloxyphenyl-2-p-toluenesulphonamido benzoate (155)

Prepared from 2-(p-toluenesulphonamido)benzoyl chloride (3.1g, 0.01M) and 4-benzyloxyphenol (2.0g, 0.01M) by the method described for (157), the title sulphonamide was obtained as colourless crystals (3.6g, 76%), m.p. 158-60°C (from chloroform-ethanol). (Found : C, 68.5; H, 4.8; N, 3.1. $C_{27}H_{23}NO_5S$ requires C, 68.5; H, 4.9; N, 2.9%). ν_{max} : 3180 (NH), 1710 (CO), 1340 and 1150cm^{-1} (SO_2N). δ_H : 2.4 (3H, s, CH_3), 5.1 (2H, s, CH_2) and 7.1-8.1 (18H, m, one H exchanges with D_2O, arom. and NH).

4-Hydroxyphenyl-2-methanesulphonamido benzoate (158)

Catalytic hydrogenation of the benzyloxy benzoate (157) (2.0g, 0.05M) as described previously, gave the title phenol (1.0g, 75%), m.p. 134-5°C (from aqueous ethanol). (Found : C, 54.6; H, 4.3; N, 4.5. $C_{14}H_{13}NO_5S$ requires C, 54.7; H, 4.2; N, 4.5%). ν_{max} : 3400 (OH), 3160 (NH), 1700 (CO), 1350 and 1150cm^{-1} (SO_2N). δ_H : 3.1 (3H, s, CH_3), 3.4 (1H, br s, exchanges with D_2O, NH), 6.9-7.3 (5H, m, arom), 7.7 (2H, d, arom.), 8.2 (1H, d, arom.), and 9.6 (1H, br s, exchanges with D_2O,OH).

4-Hydroxyphenyl-2-p-toluenesulphonamido benzoate (156)

Catalytic hydrogenation of the benzyloxy benzoate (155) (9.4g, 0.02M) as described previously, gave the title phenol (6.6g. 87%), m.p. 148-50°C (from aqueous ethanol). (Found : C, 62.4; H, 4.6; N, 3.4. $C_{20}H_{17}NO_5S$ requires C, 62.6; H, 4.4; N, 3.6%). ν_{max} : 3440 (OH), 3230 (NH), 1705 (CO), 1340 and 1150cm^{-1} (SO_2N). δ_H : 2.4 (3H, s, CH_3), 7.0-8.2 (12H, m, arom.), 9.6 (1H, br s, NH) and 10.4 (1H, br s, OH).

N-Methanesulphonyl-4-benzyloxyaniline

The title sulphonamide was prepared from 4-benzyloxyaniline hydrochloride (23.5g, 0.1M) and methanesulphonyl chloride (11.4g, 0.1M) as described in the general introduction, as a brown crystalline solid (26g, 93%), m.p. 163-5°C (from methanol). (Found : C, 60.4; H, 5.4; N, 4.8. $C_{14}H_{15}NO_3S$ requires C, 60.6; H, 5.4; N, 5.0%). ν_{max} : 3280 (NH), 1320 and 1150cm^{-1} (SO_2N). δ_H : 2.8 (3H, s, CH_3). 5.0 (2H, s, CH_2), 6.9 (2H, d, arom.), 7.2 (2H, d, arom.), 7.4 (5H, s, arom.) and 9.1 (1H, s, exchanges with D_2O,NH).

N-Methanesulphonyl-N-(4-benzyloxyphenyl)anthranilic acid (161)

To a solution of N-methanesulphonyl-4-benzyloxyaniline (2.77g, 0.01M) in 1,2-dimethoxyethane (70ml) was added sodium hydride (0.3g, 0.01M) under an atmosphere of nitrogen, with stirring. Diphenyliodonium-2-carboxylate (3.25g, 0.01M) and cupric acetate (0.2g) were added and the mixture was heated under reflux for 30h, cooled, and treated with water and a 4M aqueous solution of sodium hydroxide. The solution was filtered through celite and the filtrate was acidified with concentrated hydrochloric acid. The title acid was obtained as a colourless amorphous solid (2.0g, 50%), m.p. 160-2°C (from benzene). (Found : C, 63.6; H, 4.7; N, 3.4. $C_{21}H_{19}NO_5S$ requires C, 63.5; H, 4.8; N, 3.5%). ν_{max} : 1720 (CO_2H), 1335 and 1150cm^{-1} (SO_2N). δ_H : 3.1 (3H, s, Me), 5.0 (2H, s, CH_2), 7.0 (2H, d, arom.), 7.3 (5H, s, arom.), 7.36 (4H, s, arom.), and 7.45 (2H, d, arom.).

N-Methanesulphonyl-N-(4-hydroxyphenyl)anthranilic acid (162)

To a solution of the acid (161) (2.0g, 5mmol) in ethyl acetate (100 ml) was added a slurry of palladium (5% on carbon, 1.0g) in water (3ml) and the mixture was shaken under hydrogen until uptake of gas ceased. The catalyst was removed by filtration and the solvent was evaporated off to yield the acid (1.3g, 86%) as a colourless amorphous solid, m.p. 163-5°C (from aqueous methanol). (Found : C, 54.7; H, 4.3; N, 4.5. $C_{14}H_{13}NO_5S$ requires C, 54.7; H, 4.2; N, 4.5%). ν_{max} : 3400 (OH), 1700 (CO_2H), 1310 and 1140cm^{-1} (SO_2N). δ_H : 3.1 (3H, s, Me), 6.8 (2H, d, arom.) and 7.3-7.5 (7H, m, one H exchanges with D_2O, arom. and OH).

Oxidation of (162) with lead tetraacetate

The acid (162) (300mg, 1mmol) was oxidised with lead tetraacetate by the method described in the general introduction to yield the novel spirolactone (160) (120mg, 40%) as colourless srystals, m.p. 138-40°C (from ethanol). (Found : C, 54.8; H, 4.0; N, 3.9. $C_{14}H_{11}NO_5S$ requires C, 55.0; H, 3.6; N, 4.5%). ν_{max} : 1750 (δ-lactone), 1680 (CO), 1360 and 1160cm^{-1} (SO_2N). δ_H : 3.2 (3H, s, Me), 6.3 (2H, d, vinylic), 7.2 (2H, d, vinylic) and 7.5-7.8 (4H, m, arom.).

WORK DESCRIBED IN

CHAPTER THREE

Generation and reactions of lithium 2-lithiofuran-3-carboxylate (171); General procedure

n-Butyllithium (21.4ml of a 1.65M solution in hexane, 30mmol) was added to diisopropylamine (4.2ml, 30mmol, freshly distilled from solid KOH) with stirring at $-10^{\circ}C$ under nitrogen. After 15 minutes, the resulting viscous oil was diluted with THF (50ml), cooled to $-78^{\circ}C$ and a solution of furan-3-carboxylic acid (1.68g, 15mmol) in THF (15ml) was added. The mixture was stirred at $-78^{\circ}C$ for 30 minutes, then treated with an electrophile, which was added neat if liquid or, if solid, in THF (ca. 1ml $mmol^{-1}$). After the reaction period (usually one hour) the mixture was allowed to reach ambient temperature, then diluted with water and washed with ether (2 x 50ml). The aqueous portion was acidified with 10% aqueous hydrochloric acid and extracted with ether (3 x 50ml). The combined ether extracts were washed with saturated brine (100ml), dried and evaporated *in vacuo*.

The following acids were prepared from the dianion (171) and appropriate carbonyl compound.

2-(Hydroxy (4-benzyloxyphenyl)methyl) furan-3-carboxylic acid (178)

From 4-benzyloxybenzaldehyde (3.18g, 15mmol) was obtained the title acid (3.91g, 82%), as a colourless amorphous solid, m.p. 125-6°C (from ether-petroleum). (Found : C, 70.5; H, 5.1. $C_{19}H_{16}O_5$ requires C, 70.3; H, 4.9%). ν_{max} : 1690cm^{-1} (CO_2H). δ_H : 5.0 (2H, s, CH_2), 6.3 (1H, s, CH), 6.8 (1H, d, 4-H) and 7.0-7.3 (11H, m, arom.). δ_C : 68.3, 69.8, 114.5, 127.4, 127.6, 127.8, 128.5, 134.0, 136.9, 141.0, 146.6, 158.1, 160.3, 162.1, 166.3.

2-(Hydroxy(4-methoxyphenyl)methyl)furan-3-carboxylic acid (179)

From 4-methoxybenzaldehyde (2.0g, 15mmol) was obtained the title acid (179) (3.0g, 81%), as a brown oil. ν_{max} : 1680cm^{-1} (CO_2H). δ_H : 3.8 (3H, s, OMe), 6.4 (1H, s, CH), 6.8 (1H, d, 4-H) and 7.4- 78 (6H, m, arom.).

2-(Hydroxy(3,4,5-trimethoxyphenyl)methyl)furan-3-carboxylic acid (180)

From 3,4,5-trimethoxybenzaldehyde (5.9g, 30mmol) was obtained the title acid (180) (8.5g, 92%), as a yellow oil. ν_{max} : 1700cm^{-1} (CO_2H). δ_H : 3.7 (3H, s, Me), 3.8 (6H, s, 2 x Me), 6.4 (1H, s, CH), 6.8 (1 H, d, 4-H) and 7.3-7.8 (4H, m, arom.).

2-(Hydroxy(2,4-dimethoxyphenyl)methyl)furan-3-carboxylic acid (181)

From 2,4-dimethoxybenzaldehyde (2.5g, 15mmol) was obtained the title acid (181) (3.9g, 93%), as a yellow oil. ν_{max} : 1700cm^{-1} (CO_2H). δ_H : 3.6 (3H, s, OMe), 3.65 (3H, s, OMe), 6.4 (1H, s, CH), 6.8 (1H, d, 4-H) and 7.4-7.9 (5H, m, arom.).

2-(Hydroxy(4-benzyloxy-3-methoxyphenyl)methyl)furan-3-carboxylic acid (182)

From 4-benzyloxy-3-methoxybenzaldehyde (7.26g, 30mmol) was obtained the title acid (182) (7.60g, 72%), as a colourless amorphous solid, m.p. 98-100°C (from ether). (Found : C, 67.6; H, 4.8. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%). ν_{max} : 1680cm^{-1} (CO_2H). δ_H : 3.8 (3H, s, OMe), 5.0 (2H, s, CH_2-ar), 6.2 (1H, s, CH-ar), 6.6 (1H, d, 4-H), 6.8 (1H, br s, exchanges with D_2O, OH) and 7.0-7.4 (9H, m, arom.). δ_C : 55.9, 67.9, 70.9, 110.6, 111.4, 113.9, 114.7, 118.8, 127.6, 128.0, 128.7, 135.2, 137.4, 141.5, 147.7, 149.7, 161.9, 165.9.

2-(Hydroxy(3-benzyloxy-4-methoxyphenyl)methyl)furan-3-carboxylic acid (183)

From 3-benzyloxy-4-methoxybenzaldehyde (7.26g, 30mmol) was obtained the title acid (183) (6.0g, 60%), as a pale yellow amorphous solid, m.p.

103–5°C (from ether-petroleum). (Found : C, 67.3; H, 5.0. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%). ν_{max} : 1680cm^{-1} (CO_2H). δ_H : 3.8 (3H, s, OMe), 5.0 (2H, s, CH_2), 6.3 (1H, s, CH), 6.6 (1H, br s, exchanges with D_2O, OH), 6.8 (1H, d, 4-H) and (7.1–7.4 (9H, m. arom.). δ_C : 55.4, 68.1, 70.3, 110.9, 111.8, 114.0, 118.7, 127.6, 127.9, 133.5, 136.4, 140.5, 146.0, 147.4, 148.6, 161.2, 165.0.

2-(Hydroxy(4-nitrophenyl)methyl)furan-3-carboxylic acid (184)

From 4-nitrobenzaldehyde (4,5g, 30mmol) was obtained the title acid (184) (6.9g, 87%), as yellow crystals, m.p. 150–2°C (from ether).(Found : C, 54.4; H, 3.6; N, 4.9. $C_{12}H_9NO_6$ requires C, 54.7; H, 3.4; N, 5.3%). ν_{max} : 1690 (CO_2H), 1520 and 1350cm^{-1} (NO). δ_H : 6.5 (1H, s, CH), 6.7 (1H, s, exchanges with D_2O, OH), 6.8 (1H, d, 4-H), 7.3–8.2 (6H, m,arom.). δ_C : 66.3, 111.0, 119.7, 123.0, 127.0, 143.2, 148.6, 159.8, 164.4, 165.3.

2-(1-Hydroxy-1-(4-nitrophenyl)ethyl)furan-3-carboxylic acid (185)

From 4-nitroacetophenone (5.0g, 30mmol) was obtained the title acid (185) (5.5g, 66%), as a yellow oil. (Found : C, 56.0; H, 4.0; N, 4.8. $C_{13}H_{11}NO_6$ requires C, 56.3; H, 4.0; N, 5.0%). ν_{max} : 1690 (CO_2H), 1520 and 1350cm^{-1} (NO). δ_H : 1.2 (3H, s, Me), 6.8 (1H, d, 4-H), 7.0 (2H, d, arom.), 7.4 (1H, d, 5-H), 8.0 (2H, d, arom.) and 9.8 (1H, br s, OH).

Oxidation of hydroxy acids using manganese dioxide

General procedure

To a solution of the hydroxy acid (10mmol) in benzene or acetonitrile (50ml) was added 'active' manganese dioxide (SEDEMA, "Faradiser M") (6g) and the mixture was heated under reflux with stirring for 3h. The mixture was then filtered and the solvent was evaporated off in vacuo.

The following keto-acids were prepared by the general procedure.

2-[Oxo-(4-benzyloxyphenyl)]furan-3-carboxylic acid (186)

From the hydroxy acid (178) (3.24g, 10mmol) was obtained the ketone

(186) (1.6g, 50%), as colourless needles, m.p. 166-8°C (from ethanol). (Found : C, 71.0; H, 4.4. $C_{19}H_{14}O_5$ requires C, 70.8; H, 4.3%). ν_{max}: 3120 (OH) and 1720cm^{-1} (CO). δ_H : 5.2 (2H, s, CH_2), 6.8 (1H, d, 4-H), 7.0-7.4 (9H, m. arom.) and 7.6 (1H, d, 5-H). δ_C : 68.0, 113.5, 114.6, 126.4, 127.2, 127.6, 128.3, 134.0, 136.6, 142.0, 145.8, 159.0, 160.2, 161.9, 184.2.

2-[Oxo(4-methoxyphenyl)]furan-3-carboxylic acid (187)

From the hydroxy acid (179) (2.48g, 10mmol) was obtained the ketone (187) (1.47g, 60%), as colourless needles, m.p. 175-177°C (from ethanol). (Found : C, 63.1; H, 4.0. $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.0%). ν_{max}: 3130 (OH) and 1740cm^{-1} (CO). δ_H : 3.7 (3H, s, OMe), 6.8 (1H, d, 4-H), 6.9 (2H, m, arom.), 7.5 (1H, d, 5-H) and 8.0 (2H, m, arom.).

2-[Oxo-(3,4,5-trimethoxyphenyl)]furan-3-carboxylic acid (188)

From the hydroxy acid (180) (3.0g, 10mmol) was obtained the ketone (188) (1.8g, 60%), as yellow needles, m.p. 165-6°C (from ethanol). (Found : C, 58.4; H, 4.5. $C_{15}H_{14}O_7$ requires C, 58.8; H, 4.5%). ν_{max}: 3120 (OH) and 1735cm^{-1} (CO). δ_H : 3.9 (6H, s, 2 x Me), 4.0 (3H, s, Me), 7.0 (1H, d, 4-H), 7.5 (2H, s, arom.) and 7.8 (1H, d, 5-H). δ_C : 56.4, 61.1, 108.8, 117.0, 129.2, 130.4, 144.6, 146.0, 148.3, 152.9, 160.7, 184.2.

2-[Oxo-(2,4-dimethoxyphenyl)]furan-3-carboxylic acid (189)

From the hydroxy acid (181) (2.78g, 10mmol) was obtained the ketone (189) (1.1g, 40%), as yellow needles, m.p. 198°C (from methanol). (Found : C, 61.2; H, 4.6. $C_{14}H_{12}O_6$ requires C, 60.8; H, 4.4%). ν_{max} : 3120 (OH) and 1720cm^{-1} (CO). δ_H : 3.8 (3H, s, OMe), 4.0 (3H, s, OMe), 6.8 (1H, d, 4-H) and 7.0-7.8 (4H, m, arom.). δ_C : 55.0, 55.7, 95.5, 97.0, 98.5, 110.9, 121.3, 129.6, 140.3, 156.2, 157.6, 159.2, 162.0, 184.0.

2-[Oxo-(4-benzyloxy-3-methoxyphenyl)]furan-3-carboxylic acid (190)

From the hydroxy acid (182) (3.54g, 10mmol) was obtained the ketone (190) (1.0g, 30%), as yellow needles, m.p. 138-9°C (from ethanol). (Found : C, 67.8, H, 4.2. $C_{20}H_{16}O_6$ requires C, 68.2; H, 4.5%). ν_{max} : 3140 (OH) and 1720cm^{-1} (CO). δ_H : 3.9 (3H, s, OMe), 5.3 (2H, s, CH_2), 7.0-7.7 (10H, m, arom.). δ_C : 56.3, 71.6, 112.5, 113.5, 117.1, 127.1, 127.5, 128.9, 129.0, 136.0, 146.0, 148.4, 150.0, 154.7, 161.2, 183.8.

2-[Oxo(3-benzyloxy-4-methoxyphenyl)]furan-3-carboxylic acid (191)

From the hydroxy acid (183) (3.54g, 10mmol) was obtained the ketone (191) (1.4g, 40%), as yellow needles, m.p. 159-60°C (from ethanol). (Found : C, 67.9; H, 4.3. $C_{20}H_{16}O_6$ requires C, 68.2; H, 4.5%). ν_{max}: 3140 (OH) and 1745cm^{-1} (CO). δ_H : 3.9 (3H, s, OMe), 5.2 (2H, s, CH_2-ar), 7.0-7.9 (10H, m, arom.). δ_C : 56.4, 71.3, 111.1, 115.8, 117.0, 127.6, 128.4, 129.0, 130.2, 136.6, 146.0, 148.4, 150.0, 156.2, 161.3, 183.7.

Preparation of methyl esters of 3-furoic acid carbinols.

General Procedure

To a solution of the hydroxy acid (5mmol) in ether (20ml) was added an excess of ethereal diazomethane. The solution was allowed to stand overnight and the excess diazomethane was destroyed with glacial acetic acid. The ether layer was washed with saturated sodium bicarbonate solution, dried, and ether evaporated off *in vacuo*.

The following esters were obtained:

Methyl 2-(hydroxy(4-benzyloxyphenyl)methyl)furan-3-carboxylate (192)

From the hydroxy acid (178) (1.6g, 5mmol) was obtained ester (192) (1.5g, 88%), as a brown liquid. ν_{max} : 3400 (OH) and 1725cm^{-1} (CO). δ_H: 3.6 (3H, s, OMe), 5.1 (2H, s, CH_2), 6.2 (1H, s, CH), 6.8-7.9 (12H, m, arom.).

The hydroxy ester (192) (1.7g, 5mmol) in benzene (50ml) was oxidised with 'active' manganese dioxide as described previously to give methyl 2-[oxo-(4-benzyloxyphenyl)]furan-3-carboxylate (194) (1.2g, 70%), as colourless needles, m.p. 67-9 °C (from ether-petroleum). (Found : C, 71.1; H, 5.1. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%. ν_{max} : 1730 (ester) and 1640cm^{-1} (ketone). δ_H : 3.6 (3H, s, OMe), 5.1 (2H, s, CH_2), 6.9-7.9 (11H, m, arom.).

Methyl 2-(hydroxy-(4-nitrophenyl)methyl)furan-3-carboxylate (193)

From the hydroxy acid (184) (1.3g, 5mmol) was obtained ester (193) (1.2g, 85%), as yellow crystals, m.p. 113-5°C (from aqueous methanol). (Found : C, 56.4; H, 3.7; N, 4.9. $C_{13}H_{11}O_6$ requires C, 56.3; H, 3.9; N, 5.0%). ν_{max} (KBr) : 3400 (OH) and 1730cm^{-1} (CO). δ_H : 3.4 (1H, br s, exchanges with D_2O, OH), 3.9 (3H, s, OMe), 6.4 (1H, s, CH), 6.7 (1H, d, 4-H), 7.4 (1H, d, 5-H), 7.7 (2H, d, arom.), and 8.2 (2H, d, arom.).

The hydroxy ester (193) (1.4g, 5mmol) in benzene (50ml) was oxidised with 'active' manganese dioxide as described previously to give methyl 2-[oxo-(4-nitrophenyl)]furan-3-carboxylate (195) (1.0g, 71%), as yellow needles, m.p. 94-6°C (from aqueous methanol). (Found : C, 56.3; H, 3.4; N, 5.2. $C_{13}H_9NO_6$ requires C, 56.7; H, 3.3; N, 5.1%. ν_{max} : 1730 (ester) and 1660cm^{-1} (ketone). δ_H : 3.7 (3H, s, OMe), 6.9 (1H, d, 4-H), 7.6 (1H, d, 5-H), 8.0 (2H, d, arom.), and 8.3 (2H, d, arom.).

Reduction of hydroxy acids with sodium borohydride-trifluoroacetic acid. General procedure

To trifluoroacetic acid (50ml) cooled to 0°C in an ice bath was added with stirring under nitrogen sodium borohydride (10 pellets, 4.0g) over 30 min. A solution of the hydroxy acid (10mmol) in methylene chloride (30ml) was added and the mixture was stirred overnight at room

temperature. The mixture was diluted with water, reduced to low bulk *in vacuo*, dissolved in chloroform and extracted with saturated sodium bicarbonate solution. The extract was acidified with 10% hydrochloric acid, extracted with ether, the ether was dried, and evaporated off *in vacuo*.

The hydroxy acid (180) (3.1g, 10mmol) gave 2-[(3,4,5-trimethoxyphenyl)methane]furan-3-carboxylic acid (199) as colourless needles (2.2g, 75%), m.p. 108-10°C (from aqueous methanol). (Found : C, 61.8; H, 5.6. $C_{15}H_{16}O_6$ requires C, 61.6; H, 5.5%). ν_{max}: 1680cm^{-1} (CO_2H). δ_H : 3.8 (9H, s, 3 x OMe), 4.3 (2H, s, CH_2), 6.5 (2H, s, arom.), 6.7 (1H, d, 4-H) and 7.3 (1H, d, 5-H).

The hydroxy acid (185) (2.77g, 10mmol) gave 2-[1-(4-nitrophenyl)ethane]furan-3-carboxylic acid (200) (2.0g, 76%), as a yellow amorphous solid, m.p. 100-2°C (from petroleum). (Found : C, 59.9; H, 4.0; N, 5.7. $C_{13}H_{11}NO_5$ requires C, 59.8; H, 4.2; N, 5.4%). ν_{max}: 1690 (CO), 1520 and 1350cm^{-1} (NO). δ_H : 1.6 (3H, d, $CHCH_3$), 5.0 (1H, q, CH CH_3), 6.7 (1H, d, 4-H), 7.3 (1H, d, 5-H), 7.4 (2H, d, arom.) and 8.0 (2H, d, arom.).

2-[(4-Aminophenyl)methane]furan-3-carboxylic acid (201)

The nitro acid (184) (2.63g, 10mmol) in ethyl acetate (100ml) was reduced catalytically as described in the general introduction to give the amine (201) (1.8g, 83%), as yellow crystals, m.p. 160-2°C (from chloroform-petroleum). (Found : C, 66.2; H, 5.2; N, 6.2. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.0; N, 6.4%). ν_{max}: 3420, 3350, 3200 (NH) and 1690cm^{-1} (CO). δ_H : 4.2 (2H, s, CH_2), 4.8 (2H, br s, exchanges with D_2O, NH_2), 6.6-7.3 (6H, m, arom.).

2-[1-(4-Aminophenyl)ethane]furan-3-carboxylic acid (202)

Similarly, from the nitro acid (200) was obtained the amine (202), (2.0g, 87%) as a brown oil. ν_{max} : 3450, 3370 (NH) and 1700cm^{-1} (CO).

δ_H : 1.6 (3H, d, $CHC\underline{H}_3$), 5.0 (1H, q, $\underline{CH}CH_3$), 6.5-7.2 (8H, m, 2 H's exchange with D_2O, arom. and NH_2).

2-[1-(4-Toluenesulphonamido phenyl)ethane]furan-3-carboxylic acid (203)

To the amino acid (202) (2.31g, 10mmol) in chloroform (50ml) and pyridine (5ml) was added p-toluenesulphonyl chloride (2.0g, 11mmol), and the solution was heated under reflux for 4h, then cooled and poured into ice-cooled hydrochloric acid (4N). The organic layer was separated and washed with hydrochloric acid, water, dried, and evaporated to dryness. Trituration of the product with petroleum gave (203) (1.8g, 47%), as a colourless amorphous solid, m.p. 130-2°C (from benzene-petroleum). (Found : C, 62.7; H, 5.3; N, 3.4. $C_{20}H_{19}NO_5S$ requires C, 62.3; H, 4.9; N, 3.6%). ν_{max} : 3240 (NH), 1680 (CO), 1330 and 1150cm^{-1} (SO_2N). δ_H : 1.5 (3H, d, $CHC\underline{H}_3$), 2,3 (3H, s, CH_3), 5.0 (1H, q, $\underline{CH}CH_3$), 6.6 (1H, d, 4-H), 7.0-7.6 (9H, m, arom.) and 9.3 (1H, br s, exchanges with D_2O, NH).

Similarly, from amino acid (201) (2.17g, 10mmol) was obtained 2-[4-(4-toluenesulphonamido phenyl)methane]furan-3-carboxylic acid (204) as a brown crystalline solid (1.8g, 50%), m.p. 122-3°C (from ether-petroleum). (Found : C, 61.0; H, 4.3; N, 3.5. $C_{19}H_{17}NO_5S$ requires C, 61.4; H, 4.6; N, 3.7%). ν_{max} : 3250 (NH), 1680 (CO), 1330 and 1150cm^{-1} (SO_2N). δ_H : 2.4 (3H, s, CH_3), 4.2 (2H, s, CH_2), 6.6 (1H, d, 4-H), 7.0-7.7 (10H, m, arom.).

Oxidation of sulphonamides with lead tetraacetate

Using the general procedure outlined in the introduction, sulphonamide (203) (1.9g, 5mmol) gave the imine-lactone (205) as a red gum. Chromatography on silica gel with chloroform as eluant gave pure imine (0.6g, 31%), as brown crystals, m.p. 148-50°C (from ethanol). (Found : C, 62.2; H, 4.4; N, 3.5. $C_{20}H_{17}NO_5S$ requires C, 62.6; H, 4.4; N, 3.6%). ν_{max} : 1745 (δ-lactone), 1660 (C=C), 1560 (C=N), 1330 and 1150cm^{-1} (SO_2N).

δ_H : 1.6 (3H, d, $CH\underline{CH}_3$), 2,3 (3H, s, CH_3), 5.0 (1H, q, $\underline{CH}CH_3$), 6.6 (1H, d, 4-H), and 7.0-7.7 (9H, m, arom. and vinylic).

Similarly, from the oxidation of sulphanamide (204) (1.8g, 5mmol) was obtained a red gum which was shown to be a complex mixture by t.l.c. Chromatography on silica gel with chloroform as eluant gave the imine (206) (60mg,3%) as brown crystals, m.p. 157-9°C (from ether-petroleum). ν_{max} : 1745 (δ-lactone), 1660 (C=C), 1560 (C=N), 1320 and 1150cm^{-1} (SO_2N).

2-(4-Methoxybenzoyl)benzoic acid (207)

To magnesium turnings (3.0g, 0.125M) in dry ether (400ml) was added a solution of 4-bromoanisole (18.6g, 0.1M) in dry THF (100ml) with stirring. When all the magnesium turnings were consumed, the reagent was syringed off and added gradually to a solution of phthalic anhydride (13.4g, 0.09M) in boiling dry benzene (100ml), and the mixture was refluxed for two hours. The mixture was hydrolysed with ice-concentrated sulphuric acid and the organic layer was separated and extracted with a 10% solution of sodium carbonate. The basic extracts were acidified with concentrated hydrochloric acid and extracted with ether, the ether was washed with water, dried, and evaporated of in vacuo. The acid (207) was obtained (10.0g, 44%), as colourless needles, m.p. 145-7°C (from 4M acetic acid), (lit.,[158] 144-6°C). ν_{max} : 1690 (acid) and 1660cm^{-1} (ketone). δ_H : 3.8 (3H, s, OMe), 7.3-8.0 (8H, m, arom.) and 10.4 (1H, s, OH).

2-(4-Hydroxybenzoyl)benzoic acid (208)

A solution of the acid (207) (2.5g, 10mmol) in hydrogen bromide-acetic acid (20ml) was heated under reflux for 10h, cooled, and poured into cold water. The mixture was extracted with chloroform, the extract was washed with water, dried, and evaporated to dryness. The hydroxy acid (208) was obtained (0.7g, 30%), as a colourless amorphous solid,

m.p. 208-10°C (from water) (lit.,[166] 212-3°C). ν_{max} : 1690 (acid), 1645 (ketone) and 3400cm^{-1} (OH). δ_H : 6.8 (2H, d, arom.), 7.3-7.6 (6H, m, arom.) and 9.8 (1H, br s, exchanges with D_2O, OH).

The same hydroxy acid (208) was obtained by the action of 4-trimethylsilyloxyphenylmagnesium bromide[165] (20mmol, prepared from 4-trimethysilyloxyphenyl bromide[164] (4.9g, 20mmol) and MeMgI) on phthalic anhydride (3.0g, 20mmol). Hydrolysis of the silyl ether with 2M hydrochloric acid gave the acid (1.5g, 30%), m.p. 206-8°C (from water), which had ir and nmr spectra identical to those of the previously prepared acid.

WORK DESCRIBED IN

CHAPTER FOUR

2,4′-Dimethoxydiphenyl ether

The ether was prepared from p-bromoanisole and 2-methoxyphenol as described in the literature,[227] m.p. 75°C (lit.,[228] 77°C). 2,4′-dihydroxydiphenyl ether was prepared from the dimethoxy ether by the method described in the literature,[227] m.p. 164°C.

1,3-Benzodioxole-2-spirocyclohexadien-4′-one (210)

To a solution of 2,4′-dihydroxydiphenyl ether (10g, 0.05M) in toluene (300ml) was added manganese dioxide (30g) and the mixture was heated under reflux for 4h, then cooled and filtered through celite. The solvent was evaporated off *in vacuo* and the residue was extracted with petroleum to give the dienone (2.0g, 20%) as yellow prisms, m.p. 140-2°C (from petroleum),(lit.,[227] 144-5°C). ν_{max} : 1680 (CO) and 1640cm^{-1} (C=C). δ_H : 6.2 (2H, d, vinylic), 6.9 (2H, d, vinylic), and 6.8 (4H, s, arom.).

N-(p-Toluenesulphonyl)-4,4-dimethoxycyclohexa-2,5-dienimine

A solution of N-(p-toluenesulphonyl)-4-anisidine (1.38g, 5mmol) in methanol (50ml) was oxidised at a cell potential of 1.0v as described in the general electrochemical procedure to give the title imine as colourless needles (1.0g, 66%), m.p. 145-7°C (from toluene-petroleum), lit.,[229] 149°C). ν_{max} : 1660 (C=C), 1540 (C=N), 1310 and 1150cm^{-1} (SO_2N). δ_H : 2.4 (3H, s, CH_3), 3.3 (6H, s, 2 x OMe), 6.3 (1H, d, vinylic), 6.6-6.9 (2H, m, vinylic), 7.3 (2H, d, arom.), 7.6 (1H, d, vinylic), and 7.9 (2H, d, arom.).

A solution of the dienimine (1.5g, 0.05M) in toluene was passed down a neutral alumina column (30g), to give 4,4-dimethoxycyclohexa-2,5-

dienone (211) (0.7g, 95%) as a yellow oil. ν_{max} : 1690 (CO) and 1640 (C=C). δ_H : 3.35 (6H, s, 2 x OMe), 6.2 (2H, d, vinylic) and 6.8 (2H, d, vinylic).

A solution of the imineketal(39) (1.5g, 0.05M) in toluene was passed down a neutral alumina column to give the dienone (209) (0.35g, 50%) as colourless needles, m.p. 48-9°C (lit.,[75] 51-3°C). ν_{max} : 1675 (CO) and 1640cm^{-1} (C=C). δ_H : 4.1 (4H, s, CH_2CH_2), 6.1 and 6.6 (4H, 2d, vinylic).

Preparation of spirolactones (212) and (213)

To lithium 2-lithio-furan-3-carboxylate (171) (5mmol, prepared as described in Chapter 3) was added a solution of dienone ketal (209) or (210) (5mmol) in THF (5ml) at -78°C under nitrogen. The mixture was stirred for 30 min. and then quenched by the addition of benzoyl chloride (1.16ml, 10mmol) and allowed to reach ambient temperature. The mixture was extracted with ether, the ether extract was washed with saturated sodium chloride solution, dried, and evaporated to dryness.

From dienone ketal (210) (1.0g, 5mmol) was obtained spirolactone (213) (0.5g, 33%) as colourless needles, m.p. 210°C (from ethanol). (Found : C, 69.5; H, 3.4. $C_{17}H_{10}O_5$ requires C, 69.4, H, 3.4%). ν_{max}: 1770cm^{-1} (γ-lactone). δ_H: 6.1 (2H, d, vinylic), 6.5 (2H, d, vinylic), 6.8 (1H, d, 4-H), 6.9 (4H, s, arom.), 7.8 (1H, d, 5-H).

From dienone ketal (209) (0.75g, 5mmol) was obtained spirolactone (212) (0.4g, 32%) as colourless needles, m.p. 200°C (from methanol). (Found : C, 63.0; H, 4.1. $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.0%). ν_{max} : 1770cm^{-1} (γ-lactone). δ_H : 4.1 (4H, s, OCH_2CH_2O), 5.9 (2H, d, vinylic), 6.1 (2H, d, vinylic), 6.6 (1H, d, 4-H), 7.6 (1H, d, 5-H).

Preparation of spirolactone (214)

From lithium 2-lithiofuran-3-carboxylate (171) (5mmol) and 2,6-ditert-

butyl-1,4-benzoquinone (1.1g, 5mmol), following the same procedure as described for spirolactone (213), was obtained a brown oil, which was purified by flash chromatography with ethyl acetate as eluant to yield a yellow crystalline solid (0.2g, 20%), m.p. 145-7°C (from petroleum). (Found : C, 72.0; H, 7.0%; M^+, 324. $C_{19}H_{22}O_4$ requires C, 72.5; H,7.0%, M, 324). ν_{max} : 1775 (γ-lactone), 1670, 1650 and 1610cm^{-1} (dienone). δ_H : 1.3 (18H, s, 6 x Me), 6.3 (2H, s, vinylic), 6.8 (1H, d, 4-H), 7.6 (1H, d, 5-H).

Preparation of 2,6-dimethyl-1,4-benzoquinone and 2,6-diisopropyl-1,4-benzoquinone

A solution of the phenol (0.25M) in ether (350ml) was oxidised with 150g of Jones' reagent at room temperature for 24h. The solution was washed with ether, ether washed with saturated sodium bicarbonate solution and water, dried, and ether evaporated in vacuo.

2,6-Dimethyl phenol (30g, 0.25M) gave 2,6-dimethyl-1,4-benzoquinone (25g, 74%) as yellow needles, m.p. 45-7°C (lit.,[198] 45-7°C). ν_{max} : 1650 (C=O) and 1610cm^{-1} (C=C). δ_H : 2.0 (6H, s, 2 x Me), 6.5 (2H, s, vinylic).

2,6-Diisopropyl phenol (44.5 g, 0.25M) gave 2,6-diisopropyl-1,4-benzoquinone (12g, 25%) as a yellow liquid, b.p. 110°C/1.7mmHg, (lit.,[230] 130°C/5mmHg). ν_{max}: 1650 (C=O) and 1600cm^{-1} (C=C). δ_H : 1.1 (12H, d, 4 x Me), 3.0 (2H, m, $\underline{CH}CH_3$), 6.4 (2H, s, vinylic).

N-(2,2-Dimethyl-3-hydroxypropyl)-2-bromobenzamide

To 2-bromobenzoic acid (25g, 0.125M) was added thionyl chloride (45g, 0.375M) and the mixture was stirred at 25°C for 24h. Thionyl chloride was removed and the residue was distilled under reduced pressure to yield a colourless liquid (21.0g, 77%), b.p. 130°C/12mmHg, (lit.,[189] 118°C/10 mmHg). ν_{max} : 1780cm^{-1} (CO).

To a solution of 2-amino-2-methyl-1-propanol (16.2g, 0.182M) in methylene chloride (100ml) cooled in an ice-bath, was added a solution of 2-bromobenzoyl chloride prepared above (20.0g, 0.091M) in methylene chloride (50ml) dropwise, over 1h. The colourless crystals which separated from the solution were filtered and dried to give the hydroxy amide (25.0g, 100%) m.p. 140-2°C, (lit.,[189] 140°C). ν_{max} : 3400 (OH) and 1640cm^{-1} (CONH).

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline (215)

Thionyl chloride (36g, 0.3M) was added dropwise to N-(2,2-dimethyl-3-hydroxy propyl)-O-bromobenzamide (25.0g, 0.092M) with stirring. When the vigorous reaction has subsided, the yellow solution was poured into dry ether (150ml) and the crystals which separated from the solution were filtered, neutralized with 20% aqueous sodium hydroxide solution and extracted with ether. The extract was dried, the ether was evaporated off *in vacuo* and the oil which resulted was distilled under reduced pressure to afford the oxazoline as a colourless liquid (15.0g, 64%), b.p. 63°C/0.2mmHg, (lit.,[189] 63°C/0.2mmHg). ν_{max} : 1660cm^{-1} (C=N). δ_H : 1.4 (6H, s, 2 x Me), 4.0 (2H, s, CH_2), 7.3 (2H, m, arom.), and 7.6 (2H, m, arom.).

Preparation of carbinols (216), (217) and (218)

General Procedure

To a solution of 2-(2-bromophenyl)-4,4-dimethyl-2-Oxazoline (1.3g, 5mmol) in dry THF (20ml) was added butyllithium (4.35ml of a 1.55M solution in hexane, 5.5mmol) with stirring under nitrogen at -78°C. After 1h, the solution was quenched with the appropriate benzoquinone (5mmol) in dry THF (5ml), stirred at -78°C for another 30 min. and then allowed to reach ambient temperature. The solution was reduced to low bulk *in vacuo*, treated with water and extracted with chloroform (3 x 50ml). The chloroform extracts were dried and evaporated to dryness. The resulting mixture was purified by flash chromatography with ethyl acetate-petroleum (1:3) as eluant.

From 2,6-ditert-butyl-1,4-benzoquinone (1.1g, 5mmol) was obtained carbinol (216) (1.0g, 50%) as colourless crystals, m.p. 100-2°C (from pentane). (Found : C,75.9; H, 8.4; N, 3.5. $C_{25}H_{33}NO_3$ requires C, 75.9; H, 8.3; N, 3.5%). ν_{max} : 3400 (OH), 1670 (CO) and 1640cm^{-1} (C=N). δ_H : 1.2 (18H, s, 6 x Me), 1.5 (6H, s, 2 x Me), 4.2 (2H, s, CH_2O), 4.0 (1H, s, exchanges with D_2O, OH), 6.5 (2H, d, vinylic), 7.2-7.7 (4H, m, arom.).

From 2,6-diisopropyl-1,4-benzoquinone (0.96g, 5mmol) was obtained carbinol (217) (1.2g, 66%) as a brown oil. ν_{max} : 3400 (OH), 1670 (CO), and 1640cm^{-1} (C=N). δ_H : 1.0 (12H, d, 4 x Me), 1.4 (6H, d, 2 x Me), 3.0 (2H, m, $\underline{CH}CH_3$), 4.0 (2H, m, CH_2O), 3.3 (1H, s, exchanges with D_2O,OH), 6.2 (2H, s, vinylic), 7.2-.7.7 (4H, m, arom.).

From 2,6-dimethyl-1,4-benzoquinone (0.7g, 5mmol) was obtained carbinol (218) (0.9g, 58%) as yellow crystals, m.p. 141-3°C (from petroleum). (Found : C, 73.5; H, 6.9; N, 4.3. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.7; N, 4.5%). ν_{max}: 3400 (OH), 1670 (CO) and 1650cm^{-1} (C=N). δ_H : 1.4 (6H, d, 2 x Me), 1.9 (6H, d, 2 x Me), 3.4 (1H, s, exchanges with D_2O, OH), 3.9 (2H, m, CH_2O), 6.4 (1H, s, vinylic), 6.6 (1H, s, vinylic), 7.1-7.6 (4H, m, arom.).

Preparation of spirolactones (219), (220) and phenol (222) from carbinols

General procedure

A solution of the carbinol (2.5mmol) in ethanol (20ml) and concentrated sulphuric acid (1ml) was refluxed for 18h, cooled, and reduced to low bulk in vacuo. The residue was dissolved in chloroform (50ml), washed with water (3 x 50ml), dried, and evaporated to dryness. The resulting mixture was purified by flash chromatography with ethyl acetate-petroleum (1:4) as eluant.

Carbinol (216) (1.0g, 2.5mmol) gave spirolactone (219) (0.6g, 75%) as a yellow amorphous solid, m.p. 95°C (sublimed). (Found : C, 77.7; H, 7.5. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.4%). ν_{max} : 1780 (γ-lactone),

1665, 1640 and 1600cm^{-1} (dienone). δ_H : 1.3 (18H, s, 6 x Me), 6.3 (2H, s, vinylic), 7.2-7.7 (4H, m, arom.).

Carbinol (217) (0.9g, 2.5mmol) gave spirolactone (220) (0.5g, 67%) as colourless crystals, m.p. 120-2°C (from petroleum). (Found : C, 77.3; H, 6.9. $C_{19}H_{20}O_3$ requires C, 77.0; H, 6.8%). ν_{max} : 1765 (γ-lactone), 1670, 1650 and 1610cm^{-1} (dienone). δ_H : 1.0 (12H, d, 4 x Me), 3.0 (2H, m, $\underline{CH}CH_3$), 6.3 (2H, s, vinylic), 7.1-8.0 (4H, m, arom.).

Carbinol (218) (0.77g, 2.5mmol) gave phenol (222), the dienone-phenol rearrangement product, as colourless crystals (0.4g, 66%), m.p. 100-2°C (from petroleum), contaminated with an impurity and could not be purified by repeated recrystallisations or chromatography. (Found : C, 73.7; H, 5.7%; $\underline{M}^+$ 314 (25%), 240 (100%). $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%, $\underline{M}$ 240. ν_{max} : 3400 (OH) and 1710cm^{-1} (δ-lactone). δ_H : 2.1 (6H, d, 2 x Me), 6.8 (1H, s, arom.), 7.3-7.8 (5H, m, one H exchanges with D_2O, arom. plus OH).

Treatment of phenol (222) (0.24g, 1mmol) with ethereal diazomethane gave the yellow crystalline solid (224) (0.12g, 38%), m.p. 121-3°C (from petroleum). (Found : C, 72.8; H, 6.9%; $\underline{M}^+$, 314. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.0%; $\underline{M}$, 314). ν_{max} : 3400 (OH), and 1700cm^{-1} (ester). δ_H : 1.0 (6H, dt, 2 x $CH_2\underline{CH_3}$), 2.1 (6H, d, 2 x Me), 3.3 (2H, q, $O\underline{CH_2}CH_3$), 4.1 (2H, q, $O\underline{CH_2}CH_3$), 4.8 (1H, br s, exchanges with D_2O, OH), 6.8 (1H, s, arom.), 7.3-7.8 (4H, m, arom.).

Homopthalic anhydride

Homopthalic acid (5.4g, 30mmol) and acetic anhydride (6ml) were heated under reflux for 30 min., cooled and poured into a porcelain dish The solid which formed was washed with dry ether to yield a colourless crystalline solid (4.0g, 82%) m.p. 141-3°C (lit.,[231] 140-2°C).

Methyl 2-carboxyphenyl acetate

A solution of homopthalic anhydride (1.62g, 10mmol) in methanol (30ml)

was heated under reflux for 2h, cooled and reduced to low bulk *in vacuo*. Ester (235) was obtained as colourless crystals (1.8g, 94%), m.p. 94-6°C (from petroleum), (lit.,[231] 96-8°C). ν_{max} : 3000-2500(OH), 1720 (ester) and 1680cm^{-1} (acid). δ_H : 3.6 (3H, s, OCH_3), 4.1 (2H, s, CH_2), 7.3-8.0 (4H, m, arom.).

Preparation of ethyl 2-carboxyphenyl acetate (236)

A solution of homopthalic anhydride (3.24g, 20mmol) in ethanol (50 ml) was heated under reflux for 2h, cooled and reduced to low bulk *in vacuo*. Ester (236) was obtained as colourless crystals (3.1g, 75%), m.p. 103-5°C (from petroleum) (lit.,[231] 107-8°C). ν_{max} : 3000-2500 (OH), 1720 (ester) and 1680cm^{-1} (acid). δ_H : 1.2 (3H, t, $CH_2\underline{CH_3}$), 4.0 (2H, s, CH_2), 4.1 (2H, q, $\underline{CH_2}CH_3$), 7.2-7.9 (4H, m, arom.), and 11.2 (1H, s, exchanges with D_2O, OH).

Preparation of methyl 2-hydroxyphenyl acetate (237)

A solution of O-hydroxyphenylacetic acid (1.52g, 10mmol) in methanol (30ml) and concentrated sulphuric acid (1ml) was heated under reflux for 3h, cooled and reduced to low bulk *in vacuo*. The residue was poured into water and extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution, dried, and evaporated to dryness to give (237), (1.2g, 75%) as colourless needles, m.p. 71-3°C (from petroleum), (lit.,[232] 71-2°C). ν_{max}: 3400 (OH) and 1725cm^{-1} (ester). δ_H : 3.6 (5H, d, CH_2 and OMe), and 6.7-7.2 (5H, m, one H exchanges with D_2O, arom. and OH).

Methyl 2-(dimethyl-tert-butylsilyoxyphenyl) acetate (238)

A mixture of hydroxy ester (237) (0.84g, 5mmol), imidazole (0.98g, 10mmol), dimethyl-tert-butysilyl chloride (0.82g, 5.5mmol) and dry DMF (10ml) was stirred at room temperature for 70h. The mixture was poured into water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to dryness. Distillation under

reduced pressure gave (238) (1.0g, 72%) as a clear liquid, b.p. 116°C/0.1mmHg. (Found : C, 64.2; H, 8.4. $C_{15}H_{24}O_3Si$ requires C, 64.3; H, 8.6%). ν_{max} : 1740cm^{-1} (ester). δ_H : 0.2 (6H, s, 2 x Me), 1.0 (9H, s, 3 x Me), 3.5 (5H, s, OCH_3 and CH_2), and 6.6-7.1 (4H, m, arom.).

Ethyl (4-methoxyphenyl)acetate (240)

The ester was prepared from 4-methoxyphenylacetic acid (16.6g, 0.1M) in ethanol (150ml) and concentrated sulphuric acid (5ml) under reflux as a colourless liquid (14.0g, 73%), b.p. 108-9°C/0.6mmHg (lit.,[233] 140°C/5mmHg). ν_{max} : 1735cm^{-1} (CO). δ_H : 1.2 (3H, t, $CH_2\underline{CH_3}$), 3.5 (2H, s, CH_2), 3.7 (3H, s, OMe), 4.1 (2H, q, $\underline{CH_2}CH_3$), 6.7 and 7.2 (4H, 2d, arom.).

tert-Butyl-2-(4-nitrophenyl)acetate (241)

To a solution of 4-nitrophenylacetic acid (1.81g, 10mmol) in pyridine (20ml) was added 4-toluenesulphonyl chloride (2.8g, 15mmol) at room temperature. Tert-butanol (0.74g, 10mmol) was added and the mixture was allowed to stand overnight, then poured into water and extracted with methylene chloride (4 x 50ml). The extract was washed with saturated sodium bicarbonate solution and 2M hydrochloric acid, dried, and evaporated to dryness. Ester (241) was obtained as a yellow amorphous solid (1.5g, 65%), m.p. 38-9°C (from petroleum). ν_{max} : 1730 (CO), 1520 and 1350cm^{-1} (NO). δ_H : 1.4 (9H, s, 3 x Me), 3.6 (2H, s, CH_2), 7.4 and 8.1 (4H, 2d, arom.).

Quinone-ketal benzoates (242) and (243)

To a solution of lithium diisopropylamide (10mmol , prepared by adding a 1.55 molar solution (6.45ml, 10mmol) of butyllithium in hexane to a solution of diisopropylamine (1.41ml, 10mmol) in dry THF (15ml) at 0°C) was added a solution of ester (240) or (241) (10mmol) in dry THF (5ml) at -78°C under nitrogen. After 30 min., a solution of the quinone ketal (210) (2.0g, 10mmol) in dry THF (10ml) was added to the anion and the mixture was stirred for a further 30 min. and then quenched by the

addition of benzoyl chloride (1.16ml, 10mmol). The mixture was kept at -78°C for a further 30 min., then allowed to reach ambient temperature. The mixture was diluted with dry ether (100ml), filtered and the solvent removed under vacuo.

From ester (240) (1.94g, 10mmol) was obtained the benzoate (242) (2.5g, 50%), as colourless needles, m.p. 115-7°C (from ethanol). (Found : C, 72.6; H, 5.2. $C_{30}H_{26}O_7$ requires C, 72.3; H, 5.2%). ν_{max}: 1735 (aliph. ester), and 1710cm^{-1} (arom. ester). δ_H : 1.3 (3H, t, $CH_2\underline{CH_3}$), 3.8 (3H, s, OMe), 4.2 (2H, dq, $\underline{CH_2}CH_3$), 4.25 (1H, s, CH), and 6.3-8.0 (17H, m, arom. and vinylic).

From ester (241) (2.37g, 10mmol) was obtained the benzoate (243) (2.0g, 37%), as yellow needles, m.p. 77°C (from petroleum). (Found : C, 68.2; H, 5.3; N, 2.8. $C_{31}H_{27}NO_8$ requires C, 68.7; H, 5.0; N, 2.6%). ν_{max} : 1740 (aliph. ester), 1710 (arom. ester), 1520 and 1350cm^{-1} (NO). δ_H : 1.4 (9H, d, 3 x Me), 5.3 (1H, CH), 6.7-8.2 (17H, m, arom and vinylic).

Attempted preparation of quinone ketal methides (244) and (245)

To a solution of the benzoate (1mmol) in dry toluene (5ml) was added dry 1,8-diazobicyclo (5.4.0)undec-7-ene (1.0g, 6.5mmol) under nitrogen and the mixture was stirred at room temperature for 3h and then diluted with toluene (15ml). The solution was washed with water (3 x 25ml), water containing two drops of acetic acid, saturated sodium bicarbonate solution, dried, and evaporated to dryness. The crude product was purified by flash chromatography with ethyl acetate-toluene (1:1) as eluant.

From benzoate (242) (0.5g, 1mmol) was obtained the quinone methide (244) (0.2g, 50%) as a yellow amorphous solid, m.p. 125-30°C (from ethanol). (Found : C, 70.4; H, 5.3. $C_{23}H_{20}O_5$ (plus OH) requires C, 70.2; H, 5.3%). ν_{max} : 3400 (OH), 1725 (CO), and 1600cm^{-1} (C=C).

From benzoate (243) (0.54g, 1mmol) was obtained the quinone methide (245) (0.18g, 43%) as a yellow solid, m.p. 135-7°C (from ethanol). (Found : C, 66.3; H, 5.3; N, 2.7. $C_{24}H_{21}NO_6$ (plus OH) requires C, 66.0; H, 5.0; N, 3.2%). ν_{max} : 3400 (OH), 1730 (CO), 1620 (C=C), 1520 and 1380cm^{-1} (NO).

3,4,5-Trimethoxybenzyltriphenylphosphonium chloride (246)

A mixture of triphenylphosphine (2.62g, 10mmol), 3,4,5-trimethoxybenzyl chloride (2.16g, 10mmol) and dry o-chlorobenzene (5ml) was heated under reflux for 10 min. and then cooled in ice. A colourless crystalline solid precipitated out, which was filtered and washed with dry ether to give (246) (4.0g, 84%), m.p. 210-2°C. δ_H : 3.5 (6H, s, 2 x OMe), 3.8 (3H, s, OMe), 5.5 (2H, d, CH_2), 6.5 (2H, s, arom.) and 7.6 (15H, s, 3 x Ph).

tert-Butyl-triphenylphosphonium bromide acetate (247)

A mixture of triphenylphosphine (2.62g, 10mmol), tert-butyl bromo acetate (1.95g, 10mmol) and benzene (10ml) was heated under reflux for 60 min. and then cooled in ice. A colourless crystalline solid precipitated out, which was filtered and washed with ether to give (247) (4.0g, 87%), m.p. 223-5°C. δ_H : 1.2 (9H, s, 3 x Me), 5.1 (2H, d, CH_2) and 7.7 (15H, s, 3 x Ph).

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CHAPTER FIVE

7,12-Dioxaspiro[5,6]dodecan-3-one (254)

A mixture of 1,4-cyclohexanedione (56g, 0.5M), p-toluenesulfonic acid (0.2g) and toluene (500ml) was stirred at reflux under a Dean-Stark water separator. 1,4-Butanediol (45g, 0.5M) was added dropwise over 3h, during which 9ml (100%) of water was evolved. The mixture was cooled, washed with saturated sodium bicarbonate solution, dried, and the toluene was evaporated off *in vacuo*. The yellow oily residue was triturated with ethyl acetate and cooled in ice. After filtration, the filtrate was stripped of ethyl acetate and distilled through a 12-inch Vigreaux column to give the monoketal (54g, 59%) as a clear liquid, b.p. 90-1°C/0.5mmHg, (lit.,[240] 109-14°C/2.7mmHg). ν_{max} : 1720cm^{-1} (CO). δ_H : 1.7 (4H, m), 2.0 (4H, t), 2.4 (4H, t) and 3.8 (4H, m).

Carbinols (272) and (273) from lithiated oxazoline (271)

A solution of ketal (254) (0.92g, 5mmol) in dry THF (10ml) was added to the lithiated oxazoline (271) (5mmol , prepared by the procedure described in Chapter 4) with stirring at -78°C under nitrogen. After 30 min. the mixture was allowed to reach ambient temperature and was diluted with water. The aqueous solution was extracted with ether, the ether extract was dried, and evaporated to dryness. Carbinol (273) was obtained as a crystalline solid (1.0g, 55%), m.p. 154-5°C (from petroleum). (Found : C, 69.8; H, 8.2; N, 4.1. $C_{21}H_{29}NO_4$ requires C, 70.2; H, 8.1; N, 3.9%). ν_{max} : 3520 (OH) amd 1680cm^{-1} (C=N). δ_H : 1.4 (6H, s, 2 x Me), 1.7-2.1 (12H, m, aliph.), 3.1 (1H, br s, exchanges with D_2O, OH), 3.4 (2H, s, OCH_2), 3.8 (4H, m, CH_2CH_2) and 7.3-7.7 (4H, m, arom.).

From ketal (250) (1.0g, 5mmol) and lithiated oxazoline (271) (5mmol), was obtained carbinol (272) (1.1g, 57%) as a crystalline solid, m.p. 125-7°C (from petroleum). (Found : C, 71.2; H, 8.4; N, 3.9. $C_{22}H_{31}NO_4$ requires C, 70.8; H, 8.4; N, 3.7%). ν_{max} : 3500 (OH) and 1680cm^{-1} (C=N). δ_H : 1.0 (6H, s, 2 x Me), 1.4 (6H, s, 2 x Me), 1.9-2.4 (8H, m, aliph.), 3.2 (1H, br s, exchanges with D_2O,OH), 3.4 (2H, s, OCH_2), 3.6 (4H, d, CH_2CH_2) and 7.3-7.8 (4H, m, arom.).

Carbinols (272) and (273) from Grignard (270)

To the Grignard (270) (5mmol, prepared from 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (1.3g, 5mmol) and triply sublimed magnesium (0.2g) in dry THF (10ml), see also Chapter 4) was added a solution of ketal (250) or (254) (5mmol) in THF (5ml) over 5 min. and the mixture was heated under reflux for 4h. After cooling, the mixture was treated with a 4M aqueous solution of ammonium hydroxide and extracted with ether. The ether extract was dried, and evaporated to dryness.

From ketal (254) (0.92g, 5mmol) and Grignard (270) was obtained carbinol (273) (0.5g, 28%), identical to that obtained from lithiated oxazoline.

From ketal (250) (1.0g, 5mmol) and Grignard (270) was obtained carbinol (272) (0.4g, 21%), identical to that obtained from lithiated oxazoline.

Benzospirolactone (274) from carbinols (272) and (273)

A solution of carbinol (272) or (273) (2mmol) in ethanol (20ml) and concentrated sulphuric acid (1ml) was heated under reflux for 10h. After cooling, the ethanol was evaporated off *in vacuo* and the residue was dissolved in chloroform. The chloroform was washed with saturated salt solution, dried, and evaporated to dryness.

From carbinol (273) (0.72g, 2mmol) was obtained the benzospirolactone (274) (0.3g, 69%), as colourless crystals, m.p. 140-3°C (from petro-

leum). (Found : C, 71.6; H, 5.4. $C_{13}H_{12}O_3$ requires C, 72.1; H,5.5%). ν_{max} : 1760 (γ -lactone) and 1710cm^{-1} (ketone). δ_H : 2.1-2.6 (8H, m, aliph.) and 7.0-7.5 (4H, m, arom.).

The spirolactone obtained in 62% yield from carbinol (272) had spectral properties identical to those of (274).

N,N,-Dimethyl-7,12-dioxaspiro[5,6]dodecan -3-hydrazone (276)

The ketal (254) (1.84g, 10mmol) and N,N -dimethylhydrazine (1.8g, 30mmol) were heated under reflux for 12h, cooled and distilled under reduced pressure. A brown liquid was obtained (2.2g, 100%), b.p. 116°C/ 0.1 mmHg. ν_{max}: 1640cm^{-1} (C=N). δ_H : 1.7-2.0 (8H, m, aliph.), 2.5 (6H, s, 2 x Me), 2.3-2.8 (4H, m, aliph.) and 3.8 (4H, m, CH_2CH_2).

7,12-Dioxaspiro[5,6]dodecan-3-ol (269)

To a suspension of sodium borohydride (1.0g) in absolute ethanol (15ml) was added ketal (254) (0.92g, 5mmol) dropwise, and the mixture was allowed to stand overnight. Water was added and the mixture was extracted with chloroform. The extract was dried and evaporated to dryness. The alcohol (269) was obtained (0.72g, 80%) as a colourless viscous oil. (M^+, 186). ν_{max} : 3400cm^{-1} (OH). δ_H : 1.5-1.8 (12H, m, aliph.), 2.0 (1H, s, CH), 2.3 (1H, s, exchanges with D_2O,OH) and 3.7 (4H, m, CH_2CH_2).

3,3-Dimethyl-1,5-dioxaspiro[5.5]-9-phenylundecan-9-ol (268)

A solution of the ketal (250) (1.0g, 5mmol) in dry ether (15ml) was added dropwise to phenylmagnesium bromide (10mmol, prepared from magnesium (1.0g) and bromobenzene (1.57g) in ether) and the mixture was heated under reflux for 2h. After cooling, the mixture was quenched with ammonium chloride solution and extracted with ether. The ether was dried and evaporated to dryness. The residue was triturated with petroleum to yield the alcohol (268) (1.0g, 71%) as colourless crystals, m.p. 105-7°C (from petroleum). (Found : C, 74.0; H, 8.7. $C_{17}H_{24}O_3$

requires C, 73.9; H, 8.7%). ν_{max} : 3460cm^{-1} (OH). δ_H : 1.0 (6H, s, 2 x Me), 1.7-2.2 (9H, m, one H exchanges with D_2O, aliph. plus OH), 3.6 (4H, d, OCH_2) and 7.3-7.5 (5H, m, arom.).

9-n-Butyl-3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-ol (267)

To n-butyllithium (4.0ml of a 1.55M solution in hexane, 5mmol) cooled to -78°C, was added a solution of the ketal (250) (1.0g, 5mmol) in ether (10ml) and the mixture was allowed to reach ambient temperature after 1h. The mixture was treated with water and extracted with ether. The ether extract was dried and evaporated to dryness to give alcohol (267) (0.7g, 54%) as colourless needles, m.p. 71°C (from petroleum). (Found : C, 69.9; H, 11.0. $C_{15}H_{28}O_3$ requires C, 70.3; H, 10.9%). ν_{max}: 3500cm^{-1} (OH). δ_H : 1.0 (6H, s, 2 x Me), 1.1-1.9 (18H, m, one H exchanges with D_2O, aliph. plus OH), and 3.5 (4H, d, CH_2CH_2).

3,3-Dimethyl-1,5-dioxaspiro[5.5]-8-thiophenylundecan-9-one (275)

To a suspension of sodium hydride (0.2g, 7mmol) in dry ether (20ml) was added diphenyldisulphide (1.3g, 6mmol) at 0°C. A solution of the ketal (250) (1.0g, 5mmol) in dry ether (10ml) was then added and the mixture was stirred overnight. Water was added, followed by extraction with ether. The extract was washed with water, dried, and evaporated to dryness. The mixture which resulted was purified by flash chromatography with ethyl acetate-petrol (1:4) as eluant to give ketone (275) (1.2g, 80%) as a yellow oil. ν_{max}: 1720cm^{-1}(CO). δ_H : 1.0 (6H, d, 2 x Me), 2.3-2.8 (7H, m, aliph.), 3.6 (4H, m, CH_2CH_2), and 7.2-7.4 (5H, m, arom.).

2-(3-Methyl-4-nitrophenoxy)ethanol (280)

To a mechanically stirred solution of 3-methyl-4-nitrophenol (30.6g, 0.2M) in dry DMF (100ml) cooled to 0° was added sodium hydride (8.0g of an 80% suspension in oil, 0.25M) over 0.5h. 2-Chloroethanol (16g, 0.2M) was added and the mixture was heated under reflux for 5h, cooled,

and poured into 2M sodium hydroxide solution (1,000ml). The resulting yellow precipitate was filtered off, washed with water and dried, to give the title ethanol (21g, 53%) as yellow crystals, m.p. 86-8°C (from toluene). (Found : C, 54.4; H, 5.6; N, 7.1. $C_9H_{11}NO_4$ requires C, 54.8; H, 5.6; N, 7.1%). ν_{max} : 3300cm^{-1} (OH). δ_H : 2.6 (3H, s, CH_3), 4.0 (4H, m, CH_2CH_2), 4.5 (1H, br s, exchanges with D_2O,OH), 6.8 (2H, m, arom.) and 8.0 (1H, s, arom.).

Similarly, from 4-nitrophenol (35.0g, 0.25M) and chloroethanol (20g, 0.25M) was obtained 2-(4-nitrophenoxy)ethanol (279) (30.0g, 66%), m.p. 88-90°C (lit.,[264] 92°C).

2-(3-Methyl-4-aminophenoxy)ethanol (282)

A solution of the nitroethanol (280) (19.7g, 0.1M) in ethyl acetate (300ml) was reduced catalytically as described in the general introduction to give the title amine (15.2g, 91%), as brown crystals. m.p. 64-6°C (from chloroform-petroleum). (Found : C, 64.7; H, 7.8; N, 8.4. $C_9H_{13}NO_2$ requires C, 64.7; H, 7.8; N, 8.4%). ν_{max} : 3190, 3300 and 3460cm^{-1} (NH_2 and OH). δ_H : 2.0 (3H, s, CH_3), 3.8 (7H, br s, 3 H's exchange with D_2O, NH_2, OH and CH_2CH_2), and 6.6 (3H, s, arom.).

Similarly, from nitroethanol (279) was obtained amine (281) (91%) as brown crystals, m.p. 72-3°C (lit.,[229] 71-2°C).

2-(3-Methyl-4-(p-toluenesulphonamido)phenoxy)ethanol (284)

A solution of the amine (282) (16.7g, 0.1M) in methylene chloride (100ml) and pyridine (5ml) was tosylated with p-toluenesulphonyl chloride (19.2g, 0.1M) as described in the general introduction to give the title sulphonamide (24g, 75%), as colourless crystals, m.p. 96-8°C (from chloroform-petroleum). (Found : C, 59.9; H, 5.8; N, 3.9. $C_{16}H_{19}NO_4S$ requires C, 59.8; H, 5.9; N, 4.3%). ν_{max} : 3500 (OH) and 3200cm^{-1}(NH). δ_H : 2.0 (3H, s, CH_3), 2,3 (1H, s, exchanges with D_2O,OH), 2.4 (3H, s,

CH_3), 4.0 (4H, s, CH_2CH_2), 6.7 (2H, m, arom.), 7.1 (1H, s, arom.), 7.2 and 7.6 (4H, 2d, arom.).

Similarly, from amine (281) was obtained sulphonamide (283) (85%) as pink crystals, m.p. 124°C (lit.,[229] 124°C).

Oxidation of sulphonamides (283) and (284)

A solution of sulphonamide (284) in glacial acetic acid was oxidised with lead tetraacetate as described in the general introduction to give the ethyleneketal of 4-(p-toluenesulphonimido)-3-methyl-cyclohexa-2,5-diene-1-one (286) (40%) as brown crystals, m.p. 167-9°C (from toluene-petroleum). (Found : C, 59.9; H, 5.3; N, 4.0. $C_{16}H_{17}NO_4S$ requires C, 60.1; H, 5.3; N, 4.4%). ν_{max} : 1660 (C=C), 1540 (C=N), 1310 and 1150cm^{-1} (SO_2N). δ_H : 1.9 (3H, s, Me), 2.4 (3H, s, Me), 4.1 (4H, s, CH_2CH_2), 6.3 (1H, m, vinylic), 6.6 (1H, m, vinylic), 7.3 and 7.8 (4H, 2d, arom.), and 7.6 (1H, m, vinylic).

Similarly, from sulphonamide (283) was obtained the ethyleneketal of 4-(p-toluenesulphonimido)-cyclohexa-2,5-diene-1-one (285) (60%), m.p. 130°C (lit.,[229] 129°C).

Diels-Alder adducts. General procedure

To a solution of the imine ketal or imine lactone or cyclohexadienone (5mmol) in dry benzene (50ml) was added 2,3-dimethyl-1,3-butadiene (0.82g, 10mmol) or trans-1-acetoxy-1,3-butadiene (1.12g, 10mmol) and the mixture was heated under reflux for 50h. The solvent was evaporated off *in vacuo*, and the residue was flash chromatographed with ethyl acetate-petroleum (1:4) and recrystallised from an appropriate solvent.

From imine-ketal (285) (1.5g, 5mmol) and 2,3-dimethyl-1,3-butadiene was obtained adduct (287a) (0.9g, 46%) as colourless crystals, m.p. 105-7°C (from petroleum). (Found : C, 65.2; H, 6.5; N, 3.6%; M^+, 387. $C_{21}H_{25}NO_4S$ requires C, 65.1; H, 6.5; N, 3.6%; M, 387). ν_{max} : 1620

(C=C), 1580 (C=N), 1310 and 1150cm^{-1} (SO_2N). δ_{II} : 1.5 (6H, s, 2 x Me), 2.0-2.2 (6H, m, aliph.), 2.4 (3H, s, Me), 4.0 (4H, s, CH_2CH_2), 6.2 (1H, d, vinylic), 7.2 (3H, d, 2 x arom. plus 1 x vinylic) and 7.7 (2H, d, arom.).

From imine-ketal (286) (1.6g, 5mmol) and 2,3-dimethyl-1,3-butadiene was obtained without chromatography adduct (288a) (1.6g, 80%), as colourless crystals, m.p. 145-7°C (from ether-petroleum). (Found : C, 66.2; H, 6.5; N, 3.6%; M^+, 401. $C_{22}H_{27}NO_4S$ requires C, 65.8; H, 6.7; N, 3.5%; M, 401). ν_{max} : 1570 (C=N), 1310 and 1150cm^{-1} (SO_2N). δ_H : 1.6 (6H, s, 2 x Me), 1.8 (3H, s, Me), 2.0-2.6 (6H, m, aliph.), 2.4 (3H, s, Me), 4.0 (4H, m, CH_2CH_2), 6.2 (1H, s, vinylic), and 7.3, 7.8 (4H, 2d, arom.).

From imine-ketal (286) (1.6g, 5mmol) and trans-1-acetoxy-1,3-butadiene (refluxing toluene, 100h) was obtained adduct (289) (0.6g, 28%), as a colourless amorphous solid, m.p. 136-7°C (from ethyl acetate-petroleum). (Found : C, 61.6; H, 5.7; N, 3.1%; M^+, 431. $C_{22}H_{25}NO_6S$ requires C, 61.3; H, 5.8; N, 3.2%; M, 431). ν_{max} : 1740 (CO) and 1600cm^{-1} (C=N). δ_H : 2.1, 2.2 (6H, 2s, 2 x Me), 2.4 (3H, s, Me), 2.0-2.4 (5H, m, aliph.), 4.4 (4H, dt, CH_2CH_2), 6.5 (1H, s, vinylic) and 7.0-7.6 (6H, m, arom. plus 2 vinylic).

From imine-lactone (293) (1.6g, 5mmol) and 2,3-dimethyl-1,3-butadiene was obtained adduct (295) (1.0g, 50%), as a yellow crystalline solid, m.p. 154-5°C (from ether-petroleum). (Found : C, 65.8; H, 6.1; N, 3.5%; M^+, 399. $C_{22}H_{25}NO_4S$ requires C, 66.1; H, 6.2; N, 3.5%; M, 399). ν_{max} : 1770 (γ-lactone), 1625 (C=C), and 1570cm^{-1} (C=N). δ_H : 1.4 (6H, s, 2 x Me), 2.4 (3H, s, Me), 1.5-3.0 (10H, m, aliph.), 6.8-7.7 (6H, m, arom. plus vinylic).

From lactone-imine (294) (1.8g, 5mmol) and 2,3-dimethyl-1,3-butadiene was obtained adduct (296) (1.0g, 47%), as colourless crystals,

m.p. 152-4°C (from ether-petroleum). (Found : C, 69.6; H, 5.7; N,3.0%; M^+, 447. $C_{26}H_{25}NO_4S$ requires C, 69.8; H, 5.6; N, 3.1%; M, 447). ν_{max}: 1780 (γ-lactone), 1620 (C=C), and 1580cm^{-1} (C=N). δ_H . 1.5 (6H, s, 2 x Me), 2.4 (3H, s, Me), 2.0-2.3 (6H, m, aliph.), 6.2 and 6.5 (2H, 2d, vinylic), and 7.3-8.0 (8H, m, arom.).

From spirocyclohexadienone (210) (1.0g, 5mmol) and 2,3-dimethyl-1,3-butadiene was obtained adduct (277) (0.7g, 50%), as a crystalline solid, m.p. 110-112°C (from petroleum). (Found : C, 76.4; H, 6.5%; M^+, 282. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%; M, 282). ν_{max} : 1690 (CO) and 1640cm^{-1} (C=C). δ_H : 1.6 (6H, s, 2 x Me), 2.2-3.2 (6H, m, aliph.), 6.1 (1H, d, vinylic), 6.6 (1H, d, vinylic), and 6.8 (4H, s, arom.).

From spirocyclohexadienone (210) (1.0g, 5mmol) and trans-1-acetoxy-1,3-butadiene (refluxing toluene, 30h) was obtained adduct (278) (1.1g, 70%) as colourless needles, m.p. 190-1°C (from ethyl acetate). (Found : C, 69.1; H, 5.2%; M^+, 312. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%; M, 312). ν_{max} : 1720 (ester) and 1700cm^{-1} (ketone).

To a solution of lactone-imine (294) (0.9g, 2.5mmol) and 2,3-dimethyl-1,3-butadiene in methylene chloride at 0°C was added powdered aluminium chloride (0.5g) and the mixture was allowed to reach room temperature over 1h. Water was added, the organic layer was separated and washed with water, dried, and the methylene chloride was evaporated off *in vacuo*. A colourless solid (297) was obtained (0.4g, 53%), m.p. 115-7°C (from ether-petroleum). (Found : C, 78.0; H, 6.1. $C_{19}H_{18}O_3$ requires C, 77.6; H, 6.1%). ν_{max}: 1770 (lactone) and 1685cm^{-1}(ketone). δ_H : 1.5 (6H, s, 2 x Me), 2.0-2.4 (6H, m, aliph.), 6.2 (1H, d, vinylic), 6.5 (1H, d, vinylic), and 7.2-7.6 (4H, m, arom.).

Sodium borohydride reduction of adduct (288a)

Adduct (288a) (0.4g, 1mmol) was added to a suspension of sodium borohydride (0.5g) in ethanol (20ml) and the mixture was stirred overnight

at room temperature. The mixture was then diluted with water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to dryness. Sulphonamide (298) was obtained as a colourless amorphous solid (0.3g, 75%), m.p. 151-3°C (from ether-petroleum). (Found : C, 65.5; H, 7.3; N, 3.6. $C_{22}H_{29}NO_4S$ requires C, 65.5; H, 7.2; N, 3.5%). ν_{max}: 3300 (NH), 1600 (C=C), 1330 and 1150cm^{-1} (SO_2N).

trans-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene

To a suspension of anhydrous powdered zinc chloride (1.0g) in triethylamine (55g, 0.5M) was added a solution of trans-4-methoxy-but-3-ene-2-one (20g, 0.2M) in dry benzene (75ml) with stirring at room temperature. Trimethylchlorosilane (43.2g, 0.4M) was then added, and the temperature was raised to 40°C and stirring continued overnight. After cooling, the reaction mixture was added to ether (500ml) and filtered. The filtrate and combined ether washings were concentrated *in vacuo* to give a brown oil. Distillation through a Vigreux column gave the butadiene (22g, 58%), as a clear liquid, b.p. 56-7°C/5mmHg, (lit.,[263] 54-5°C/5mmHg. ν_{max} : 1656, 1618, 1597, 1567cm^{-1}. δ_H : 0.23 (9H, s, 3 x Me), 3.6 (3H, s, OMe), 4.1 (2H, br s, CH_2), 5.4 and 6.8 (2H, 2d, vinylic).

Adduct (300)

To a solution of 2,6-dimethyl-1,4-benzoquinone (1.36g, 10mmol) in benzene (30ml) was added trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (1.72g, 10mmol), and the mixture was heated under reflux for 20h. After cooling to room temperature, the solution was stirred rapidly with 20ml of 4:1 THF -0.1 N aqueous HCl for 30 min. and then poured into 5% aqueous sodium bicarbonate solution (20ml). The mixture was extracted with chloroform, the extract was dried, and evaporated to dryness. The resulting mixture was flash chromatographed with ethyl acetate-petroleum (1:3) and the first fraction yielded a colourless crystalline solid

(0.6g, 30%), m.p. 124-6°C (from ether). (Found : C, 70.6; H, 5.9%; $\underline{M}^+$, 204. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9% $\underline{M}$, 204). ν_{max} : 1675cm^{-1} (broad, CO). δ_H : 1.6 (3H, s, Me), 2.1 (3H, d, Me), 2.5-3.2 (3H, m, aliph.), 6.0 (1H, d, vinylic), and 6.7 (2H, dd, vinylic). δ_C : 16.5, 24.3, 36.2, 50.0, 53.0, 129.5, 136.8, 148.9, 150.1, 194.1, 196.5, and 199.4.

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