Aspects of the chemistry of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids and related compounds by J. A. Hadfield

ABSTRACT

The main topic in this investigation is an exploration of routes to spirolactones derived from 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (tetrahydroisoquinaldic acids); by analogy with related cyclohexadienone spiro-γ-lactones, the isoquinaldic acid lactones may be useful intermediates in the synthesis of more complex molecules such as bisbenzylisoquinolines. Previous work had established that oxidation of 1-benzyltetrahydroisoquinaldic acids having oxygen substituents on the 6 or 7 position occurs on the isoquinoline benzene ring and does not lead to spirolactone formation, necessitating the synthesis of acids without such substitution; no such acids have been described. As model compounds, a series of isosteric 1-benzyl-tetrahydronaphthalene-1-carboxylic acids were prepared by reaction of 1-lithiotetrahydronaphthalene carboxylic esters with benzyl halides. On chemical or anodic oxidation, acids with phenolic, methoxy, or sulphonamide functions on the 4'-benzyl position all gave good yields of spirolactones. In a novel synthesis of 1-benzyltetrahydroisoquinaldic acids without 6- or 7- alkoxy substituents, lithiation of N-pivaloyltetrahydroisoquinoline was used to introduce benzyl and carboxyl groups at the 1-position. None of the resulting acids gave spirolactones on chemical or anodic oxidation, but reaction of N-bromosuccinimide with a 4'-hydroxybenzyltetrahydroisoquinaldic acid yielded a brominated cyclohexadienone spirolactone.

A study has been made of the scope of a reaction of 1-benzyltetrahydroisoquinaldic acids with trifluoroacetic anhydride in pyridine, which affords 7,8-dihydroprotoberberines. It has been established that the reaction is synthetically useful only for dimethoxy- or trimethoxybenzyl acids and occurs via a N-trifluoroacetyl acid.

A number of N-sulphonylcyclohexadienimine spirolactones have been prepared and subjected to attack by nucleophiles. Cyanide was successfully inserted into the cyclohexadiene moiety, accompanied by lactone ring opening.

An attempt to prepare a gem-dimethylphenylpyruvic acid was unsuccessful, but 3-thienylpyruvic acid has been prepared.

TRENT POLYTECHNIC

ASPECTS OF THE CHEMISTRY OF 1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXYLIC ACIDS AND RELATED COMPOUNDS

being a thesis submitted to

The Council for National Academic Awards

for the degree of

DOCTOR OF PHILOSOPHY

by

John Anthony Hadfield, B.Sc.

August 1984

PREFACE

The work described in this thesis was carried out by the author in the Department of Physical Sciences, Trent Polytechnic, Nottingham between May 1980 and August 1983. Throughout the duration of this investigation the author has not been registered for any other award of the CNAA nor with any other degree-awarding body; no material contained in this thesis has been used in any other submission for an academic award. Any work not carried out solely by the author is acknowledged in the text.

Part of the work described in Chapters Two and Three was presented at the International Symposium of the Phytochemical Society of Europe on the Chemistry and Biology of Isoquinoline Alkaloids, London, April, 1984. Advanced studies undertaken in connection with this research programme include postgraduate lectures on n.m.r. spectroscopy, microprocessors, and polymers; many local and national lectures and symposia of the Chemical Society have also been attended.

The author wishes to thank Dr I.G.C. Coutts for his excellent supervision throughout the project and Dr P.R. Huddleston for his helpful advice and encouragement. The author also wishes to thank Mr M.L. Wood for carbon-13 n.m.r. spectral determinations.

The author is also indebted to Trent Polytechnic for the position of Research Assistant/Demonstrator and for the provision of research facilities between the above dates.

J. A. Hadfield

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An attempt to prepare a gem-dimethylphenylpyruvic acid was unsuccessful, but 3-thienylpyruvic acid has been prepared.

TABLE OF CONTENTS

ABBREVIATIONS

Ac	acetyl
ar.	aromatic
t-Bu	tert-butyl
n-BuLi	n-butyl-lithium
Bz	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	N,N-dimethylformamide
DMSO	hexadeuterodimethylsulphoxide
Et	ethyl
i.r.	infra-red
LDA	lithium di-isopropylamide
Me	methyl
Ms	methanesulphonyl
n.m.r.	nuclear magnetic resonance
Ph	phenyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
tlc	thin-layer chromatography
TMEDA	tetramethylethylenediamine
Ts	p-toluenesulphonyl
u.v.	ultra-violet

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

1.1 General Introduction

Cyclohexa-2,5-dien-4-ones substituted at position 1 with a spirolactone function, and related compounds, have been isolated as mould metabolites[1] and have been postulated as intermediates in the biosynthesis of some mammalian secondary metabolites[2]. They have become the subject of increasing chemical investigations which will be discussed later.

An early suggestion[3] that 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids have a fundamental role in the biosynthesis of 1-benzylisoquinoline alkaloids (which, in turn are precursors of more complex isoquinoline alkaloids) is supported by feeding experiments and by the isolation of related isoquinoline carboxylic acids from cacti. (Section 1.2).

Very recently it has been shown[4] that conversion of the cyclohexadienone lactone 1 to its mono-epoxide 2, followed by reaction with a nucleophile, forms an addition product 3 in which insertion of the nucleophile into the cyclohexadienone moiety is accompanied by lactone ring opening (Scheme 1).

These observations invite the speculation that tetrahydroisoquinoline carboxylic acids 4 having a p-hydroxybenzyl substituent at position 1 might be capable of forming spirolactone cyclohexadienones 5, which on epoxidation and nucleophilic attack would afford 1-benzylisoquinolines 6,7 substituted in the benzyl residue. Indeed, if the nucleophile were itself a benzylisoquinoline, the predicted product would be a bisbenzylisoquinoline. For example, if the nucleophile were the anion of a 7-hydroxybenzylisoquinoline 8 the expected product would be a "head-to-tail" coupled dimer

6, while attack by the anion of a 4'-hydroxybenzylisoquinoline 9 would yield a "tail-to-tail" coupled bisbenzylisoquinoline 7 (Scheme 2). Even if this were not a genuine biosynthetic route to bisbenzylisoquinoline alkaloids, it would be chemically interesting and might possibly lead to bisbenzylisoquinolines which are otherwise difficult to synthesise (Section 1.5).

In view of the above observations a study has been made of:

(a) possible routes to 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids and the more accessible analogous 1,2,3,4-tetrahydronaphthalene-1-carboxylic acids;

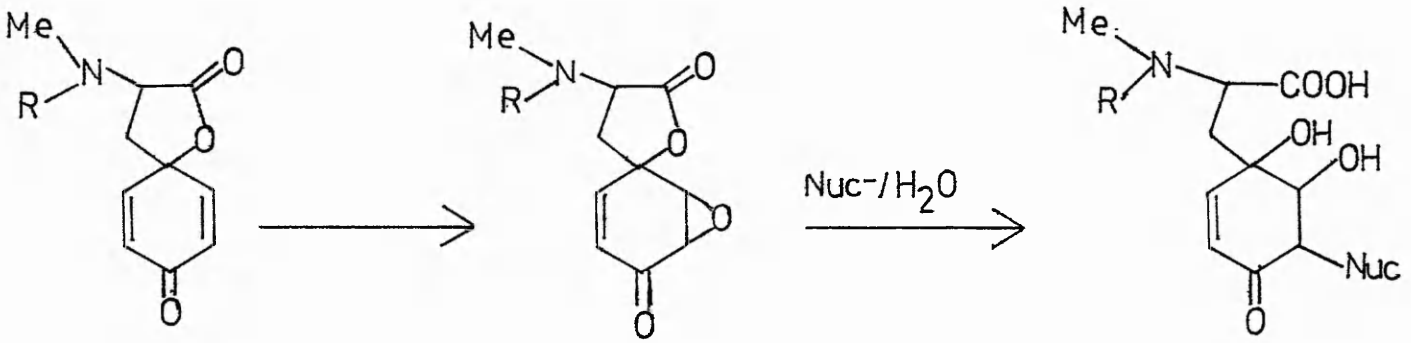
(b) the synthesis of spirolactones by the oxidation of the above acids, and

(c) the reaction of spirolactones with nucleophiles with the long-term objective of forming bisbenzylisoquinolines.

1.2 Isoquinoline-1-carboxylic acids in the biosynthesis of isoquinoline alkaloids

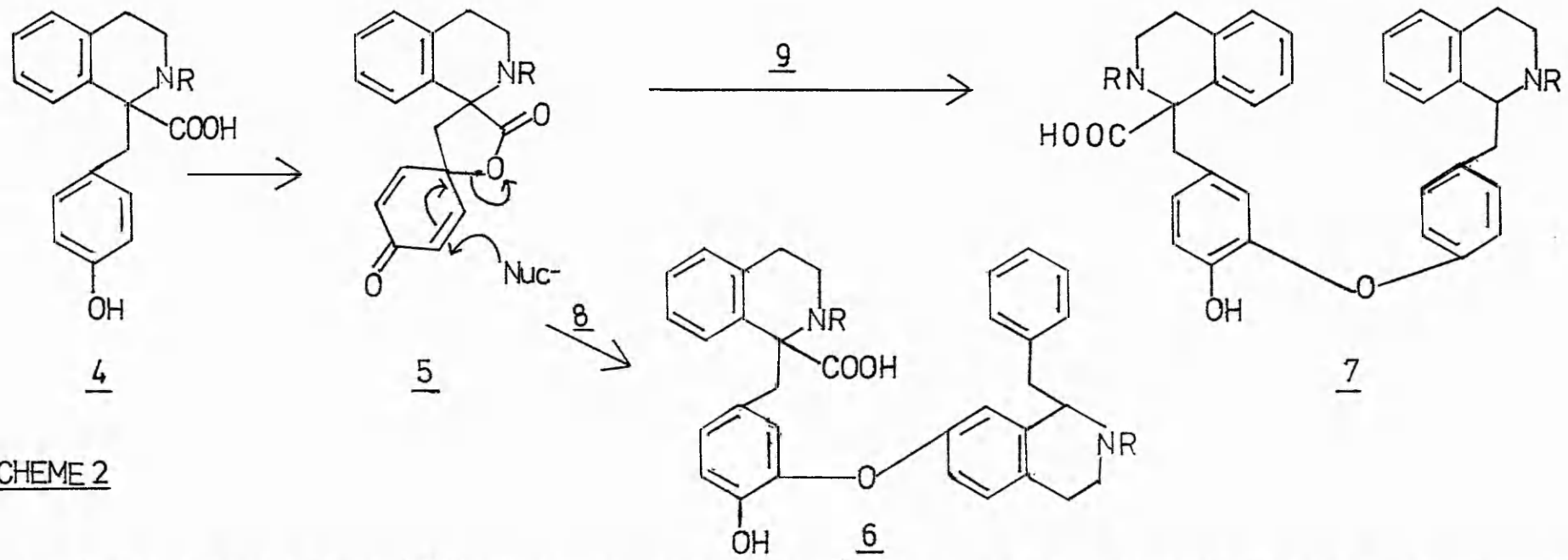
In 1934, Schopf and Bayerle[5] demonstrated that dopamine reacted with various aldehydes at room temperature and neutral pH ("physiological conditions") to afford good yields of 1-monosubstituted tetrahydroisoquinolines. This prompted Hahn to suggest[3] that a key step in the biogenesis of 1-benzylisoquinoline alkaloids involved the condensation of dopamine with appropriate pyruvic acids. In support of this reaction, he prepared 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 10 in 87% yield under biologically plausible conditions. Initially, this theory was rejected owing to the failure of both Hahn[3] and Whalley and Govindachari[6] to decarboxylate this and similar acids under mild "physiological" conditions in vitro.

SCHEME 1



1 2 3

R = $OCOCH_2Ph$



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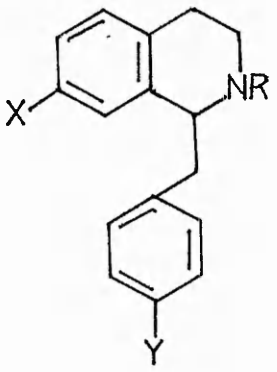
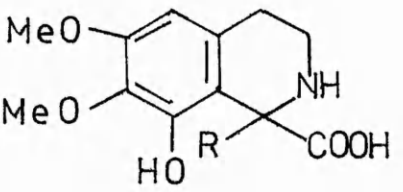


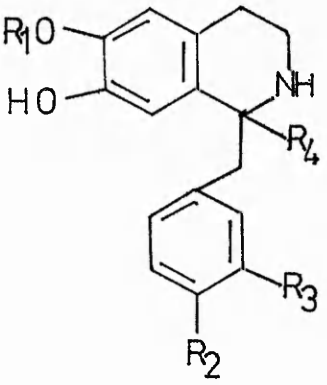
8 X=O⁻, Y=H

9 X=H; Y=O⁻



11 R=H

12 R=Me



10 $R_1=R_2=R_3=H$; $R_4=COOH$

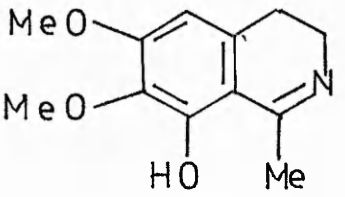
18 $R_1=H$; $R_2=R_3=OH$; $R_4=COOH$

20 $R_1=R_3=H$; $R_2=OH$; $R_4=COOH$

22 $R_1=R_3=R_4=H$; $R_2=OH$

23 $R_1=Me$; $R_2=OH$; $R_3=R_4=H$

28 $R_1=H$; $R_2=OH$; $R_3=OMe$; $R_4=COOH$



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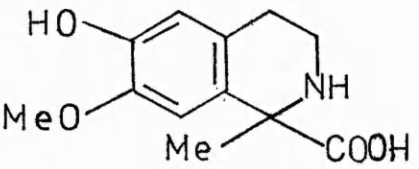

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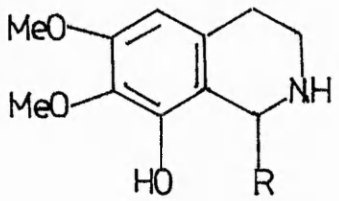
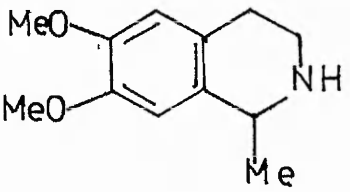


13 R = Me

14 R = H



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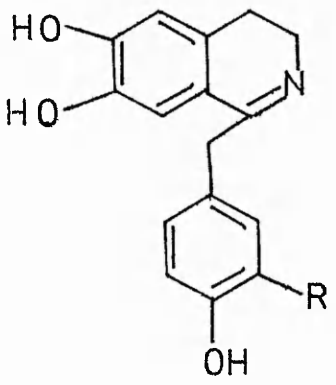
Recently, however, considerable evidence in favour of Hahn's hypothesis has been elicited. Not only have peyoxylic acid 11 and peyoruvic acid 12 been detected[7,8] in peyote cacti, but also their incorporation into the alkaloids anhalonidine 13 and anhalamine 14 has been demonstrated by feeding experiments.[9] Pyruvate has been shown[7,10] to be an efficient precursor of anhalonidine 13, and the 1-methyl acid 16 is a precursor of salsolidine 17 in Echinocercus merkeri.[11] Norlaudanosoline-1- carboxylic acid 18 and its decarboxylation product 19 were both incorporated into morphine[12] and reticuline[13,14] in Papaver somniferum and Litsea glutinosa, respectively. Norcoclaurine-1-carboxylic acid 20, from 21 and 22, has been identified as a precursor of coclaurine 23 in Annona reticulata.[15]

The incubation[9] of the tetrahydro acid 12 with fresh slices of peyote cacti afforded the 3,4-dihydroisoquinoline 15, giving rise to the theory that the decarboxylation of these acids might be of an oxidative nature. The more widely distributed tetrahydroisoquinolines could then be formed by a suitable reduction, probably with NADH or NADPH.

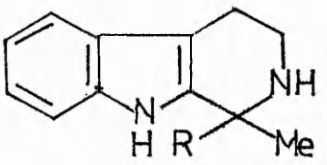
1,2,3,4-Tetrahydro-β-carbolines are analogues of 1,2,3,4-tetrahydroisoquinolines and might be expected to form from the condensation of a tryptamine and an α-keto acid. 1-Methyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid 24 has been established as a precursor of harman 25 in Passiflora edulis and of eleagnine 26 in Eleaginus angustifolia; it is a natural consituent of both these plants and is an eight-fold better precursor of 25 than is N-acetyltryptamine.[16] Pyruvate is incorporated into the β-carboline alkaloid harmine 27[16,17].

The failure of earlier workers (vide supra) to effect the decarboxylation of tetrahydroisoquinoline-1-carboxylic acids has



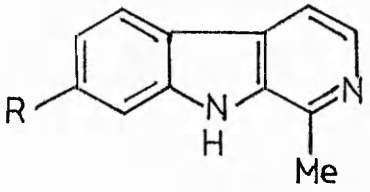
19 R=OH

21 R=H



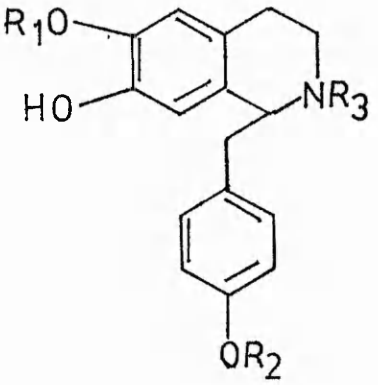
24 R=COOH

26 R=H



25 R=H

27 R=OMe

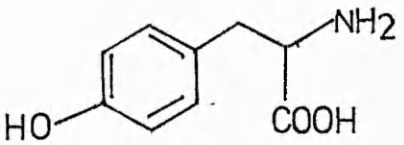


29 R_1=Me; R_2=R_3=H

31 R_1=R_3=Me; R_2=H

35 R_1=R_2=R_3=H

36 R_1=R_2=R_3=Me



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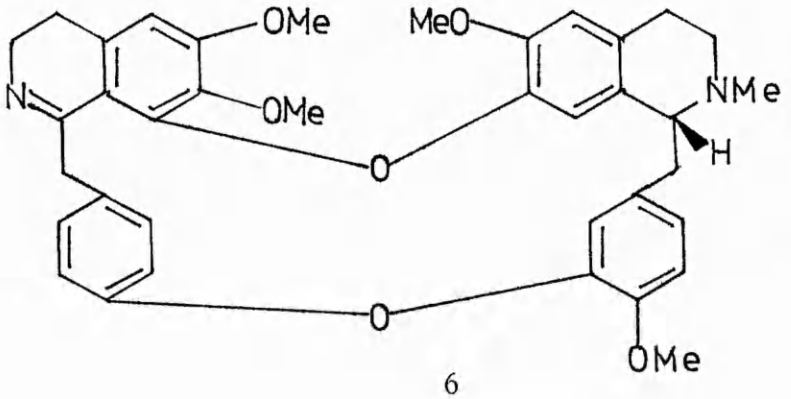


30

been resolved by Bobbitt who established that the decarboxylation of these acids occurred by an oxidative process. He found that the decarboxylation of these acids, which contained a 6- or 7-hydroxy function, by low potential anodic oxidation,[18] or by prolonged aerial oxidation in basic media[19] afforded 3,4-dihydroisoquinolines. In support, it has been shown that these acids can be oxidatively decarboxylated under mild "physiological" conditions by using horse-radish peroxidase or laccase enzymes.[20]

1.3 Isoquinoline-1-carboxylic acids as "mammalian metabolites"

3'-O-Methylnorlaudanosoline-1-carboxylic acid 28 has been detected[21] in the urine of patients suffering from Parkinson's disease who have been treated with L-dopa. The same acid 28 has also been found in the brains and urine of rats fed with labelled L-dopa.

3',4'-Deoxynorlaudanosoline-1-carboxylic acid 10 has been found[22] in the urine of children suffering from phenylketonuria, and has been detected in the urine and brain (cortex and cerebellum) of rats which have been experimentally induced with hyperphenyl-alaninaemia. It is a non-competitive inhibitor of dopamine-β-hydroxylase.

It has been claimed that 1-substituted 4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids[23] or their esters[24] are as effective antitussive agents as is codeine phosphate, but with much lower toxicity and fewer adverse effects on respiration and the gut smooth muscle.

An inspection of Dreiding atomic models of 18 and related acids suggests that these isoquinolines can assume conformations with a juxtaposition of key groups similar to that required for

the opiate activity of morphine and methione-enkephalin, as determined by computer generated models.[25] Following this up, Coscia et al.[26] have elucidated that 18 is a relatively pure opiate agonist; 28 and 10 were opiate agonists but higher concentrations were required.

In another study,[27] the differing efficiency with which isoquinolines and related tetrahydroisoquinoline-1-carboxylic acids inhibited bonding to β-adrenergic receptors was correlated with the relative conformational rigidity of the acids. (Chapter 3).

1.4 Biosynthesis of bisbenzylisoquinolines

1.4.1 Phenol oxidative coupling

Of all the aromatic systems present in nature, phenols are one of the most easily oxidised. Depending on the conditions used, the oxidation products of phenols are often mixtures of dimers, polymers and quinonoidal compounds. Phenol oxidative coupling has long been recognised as a plausible natural reaction mechanism, and many biosynthetic pathways involving such processes have been proposed. Many attempts have been made to produce this natural process in vitro.

In 1925, Robinson[28] suggested that phenol oxidative coupling processes were involved in the biosynthesis of morphine alkaloids from phenolic 1-benzylisoquinolines. However, the significance of phenol coupling in natural product chemistry was not widely appreciated until the publication of a key paper[29] by Barton and Cohen in 1957. In this, they pointed out that the one-electron oxidation of a phenolate ion generates a phenoxyl radical, which carries appreciable spin density at the ortho and para carbon atoms as well as at the oxygen atom. Two such species can, therefore, react together by a radical pairing mechanism to generate new O-O,

O-C, or C-C bonds, but new bonds to carbon atoms should be formed at the ortho and para positions. This mechanism for oxidative phenol coupling has not been proved for any biosynthetic process, but all the evidence gained so far is entirely consistent with such a view. In particular, oxidative coupling between two aromatic rings takes place only when a free phenolic group is located at the appropriate position in both precursor rings.

1.4.2. Biosynthetic studies on bisbenzylisoquinolines

The bisbenzylisoquinolines constitute one of the largest group of isoquinoline alkaloids. They are dimeric bases, and when two or more diphenyl ether linkages are present, a large ring is formed. Two chiral centres are present in these alkaloids (except when one or both of the nitrogen atoms are in the form of an imine) leading to diastereoisomers.

Bisbenzylisoquinolines may be considered to arise in nature by the oxidative dimerisation of simple phenolic 1-benzylisoquinolines. Feeding experiments have been carried out *in vivo* to determine which 1-benzylisoquinolines are indeed precursors of bisbenzylisoquinoline alkaloids.

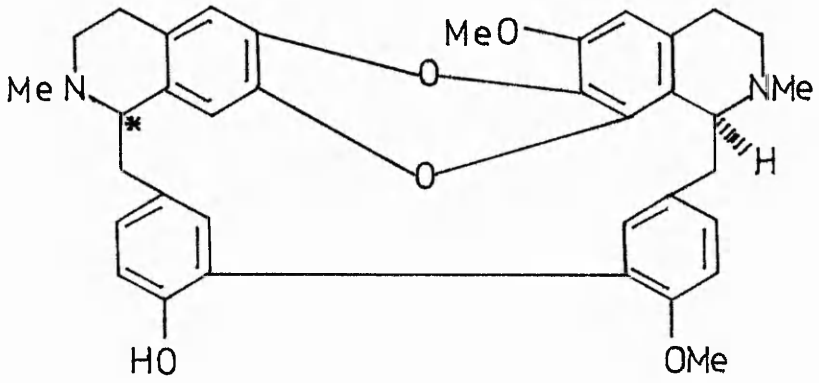
All the published biosynthetic studies on bisbenzylisoquinolines have involved the use of coclaurine 29 or a methylated derivative of coclaurine. The first study, by Barton *et al.*[30] in 1966, showed that epistephanine 30 is derived in *Stephania japonica* exclusively from (-)-N-methylcoclaurine 31, but not from its enantiomer. This confirmed the absolute configuration of the alkaloid and demonstrated that racemisation of the (+)-enantiomer is unimportant in the biosynthesis of 30 in this plant.

The diastereomeric bases tiliacorine 32 and tiliacorinine 33 have been found to incorporate[31] radioactivity from labelled tyrosine 34, norcoclaurine 35, coclaurine 29, and N-methylcoclaurine 31 in Tiliacora racemosa. As expected the methoxylated isoquinoline 36 was not incorporated. Degradation of these alkaloids derived from N-methyl [3',5',8-$^{3}H_{3}$] coclaurine established that they were formed from two units of the precursor 31. Further experiments demonstrated that this base was used with the expected loss of one of the methyl/methoxyl groups from C-6, but without the loss of tritium from C-1. Therefore, the incorporation of the iminium species 37 which was observed must occur through reduction to 31.

Also, the stereochemistry at C-1 of a precursor will be retained on formation of tiliacorine 32 and tiliacorinine 33. It was shown that (+)-(S)-N-methylcoclaurine gave the "left hand" half of tiliacorine 32 whilst the (-)-(R)-isomer gave the "right hand" half. A seventy-fold difference in the incorporation of N-methylcoclaurine 31 isomers into tiliacorinine 33 leads to the conclusion that both of its asymmetric centres are (S); and the (S)-isomer was shown to label both halves of 33, so it is apparent that 32 and 33 are derived from N-methylcoclaurine 31, and that the coupling is stereospecific.

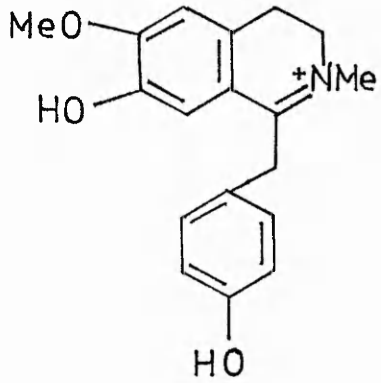
The biosynthesis of cocsulin 38[32] and cocsulinin 39[33] in Cocculus laurifolius has been found to parallel that of tiliacorine 32 and tiliacorinine 33. They are both specifically derived from (S)-N-methylcoclaurine 31 which has also been found to occur naturally C. laurifolius[34].

Similarly, tiliagenine 40 is derived[35] from 31, the (+)-(S)-isomer providing one half of the molecule, with the other half arising from (-)-(R)-N-methylcoclaurine 31. The configurations at C-1 and C-1' are (S) and (R), respectively.



32 * = H

33 * = H



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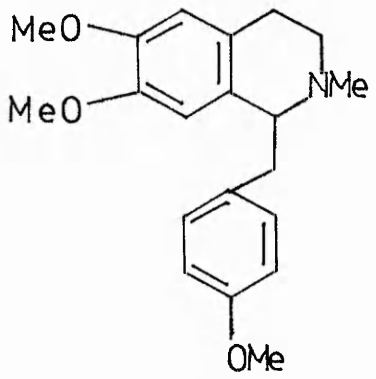

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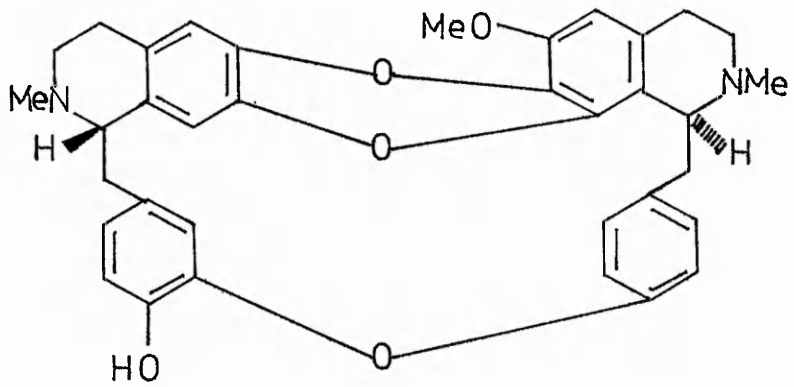

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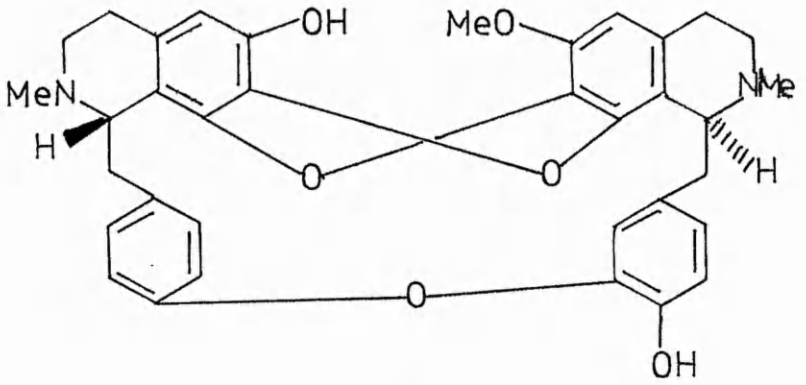
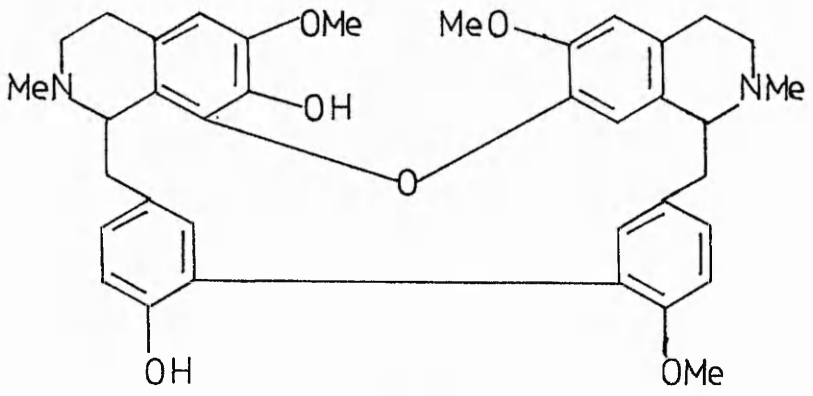
Bhakuni *et al.*[36] have shown that oxyacanthine 41 is derived from norcoclaurine 35, coclaurine, 29 and N-methylcoclaurine 31 in *C. laurifolius*; whilst N,O,O—trimethylcoclaurine 42 was not incorporated into the alkaloid. They also showed that the incorporation of racemic 31 occurred equally into both halves of oxyacanthine 41 without the loss of tritium from C-1. Their results indicated that (R)-N-methylcoclaurine 31 is built into the "right hand" half of the molecule, whilst (S)-N-methylcoclaurine was incorporated into the "left hand" half of the molecule. Also, despite their discovery that 37 is incorporated into oxyacanthine 41, it appears that the stereoisomers of N-methylcoclaurine are not interconvertible (via 37) prior to utilisation for alkaloid biosynthesis, so the incorporation of 37 that is observed is not by a normal pathway.

Isotetrandrine 43 has been shown[37] to arise in *C. laurifolius* from both coclaurine 29 and N-methylcoclaurine 31. The R and S isomers of 31 are not interconverted during biosynthesis. 37 is also efficiently incorporated into isotetrandrine 43 but this does not appear to be a normal biosynthetic pathway for the same reasons as given above.

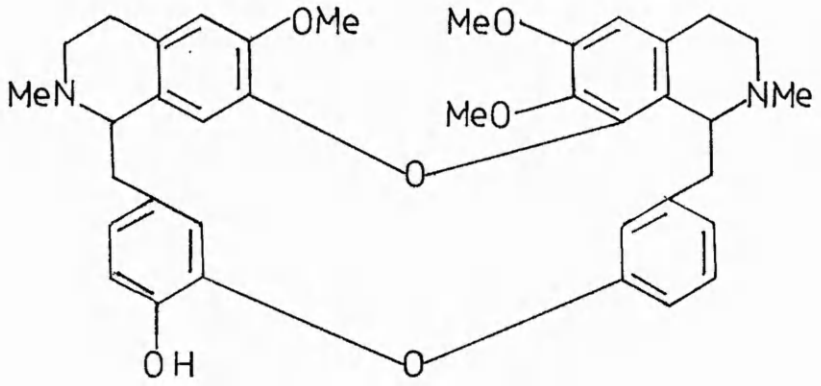
The formation of 30, 32, 33, 38, 39, 40, 41 and 43 from the coclaurine skeleton can be rationalised in terms of phenol oxidative coupling. The coupling is seen at its simplest in 30, 40, 41 and 43 where two such reactions must occur. The formation of 39 is only slightly more complex, formally involving three such coupling steps. In the case of 32, 33 and 38, coupling results in the loss of an oxygen function from C-6 or C-7'. These losses can be interpreted in terms of a radical[29,38] or cationic mechanism.[38,39]


OH
MeO
MeN
H
NMe
H
O
O
O
OH

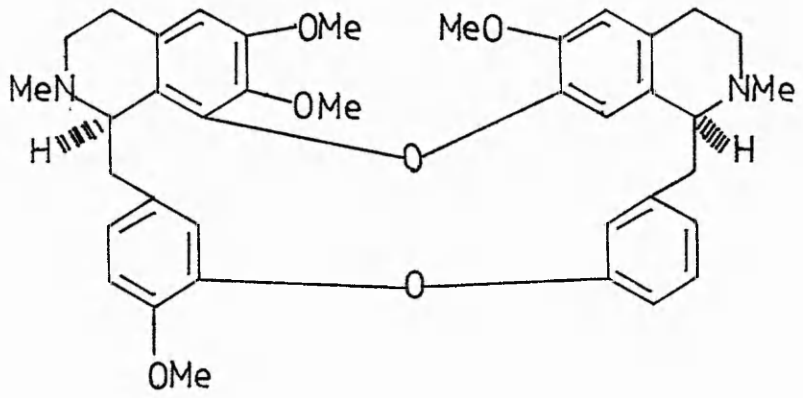
39


OMe
MeO
MeN
OH
NMe
O
OH
OMe

40


OMe
MeO
MeN
MeO
NMe
O
OH
O

41



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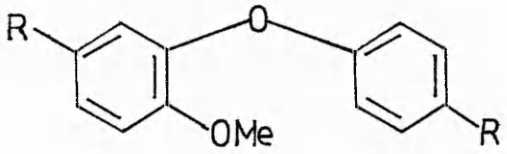
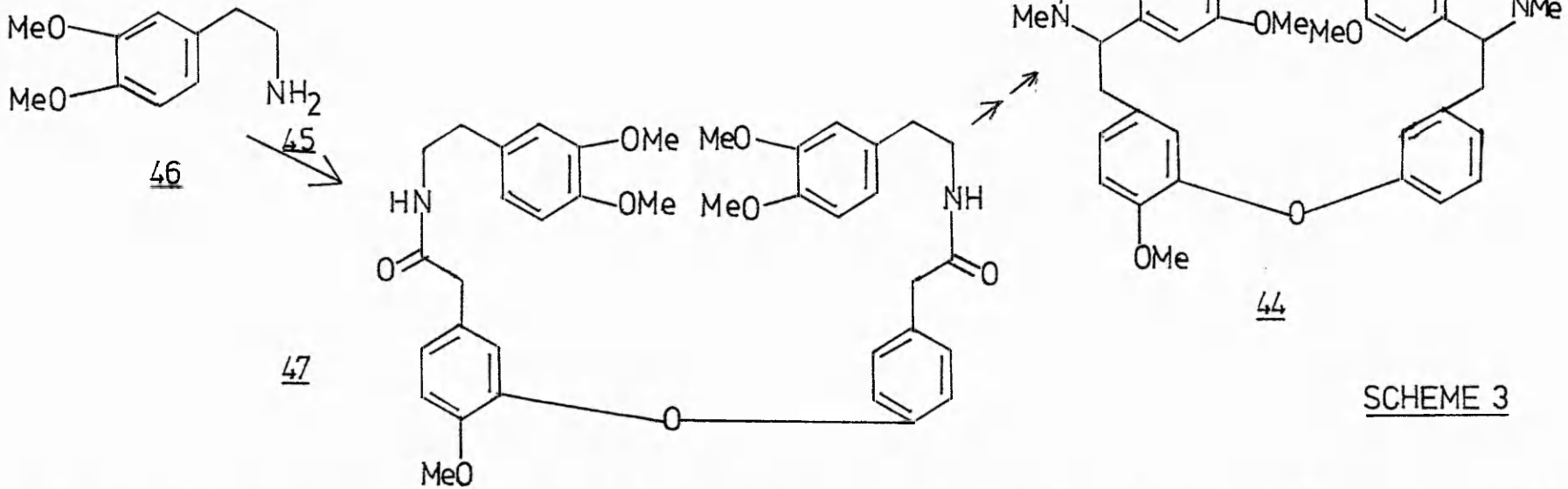


45 R=CH_2COOH

48 R=CH_3CO

49 R=CH=C(SMe)—N O

50 R=CHO



SCHEME 3

1.5 Syntheses of bisbenzylisoquinolines

The successful synthetic routes to bisbenzylisoquinolines fall into two main categories:

(a) synthesis from diphenyl ethers by the addition of an isoquinoline moiety or isoquinoline precursor;

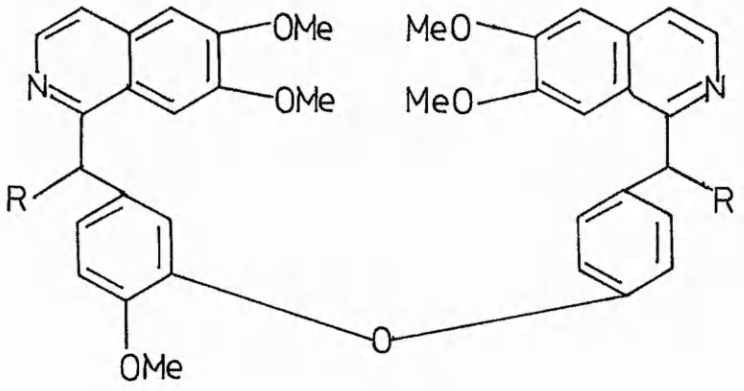
(b) synthesis by coupling together two pre-formed 1-benzylisoquinoline units.

1.5.1. Syntheses using diphenyl ether intermediates

The first laboratory synthesis[40] of the bisbenzylisoquinoline O-methyldauricine 44 involved the condensation of the diphenyl ether bis acid 45 with homoveratrylamine 46 to form the bisamide 47. Cyclisation under Bischler-Napieralski conditions (Chapter 3) yielded a bis-3,4-dihydroisoquinoline which, upon reduction and N-methylation, produced O-methyldauricine 44 (Scheme 3). An alternative synthesis[41,42] involved subjecting the diacetyl compound 48 to the Willgerodt-Kindler reaction and hydrolysing the resulting bis-thiomorpholide to the bisenaminothioether 49. The bisamide 47 was prepared by condensing homoveratrylamine 46 with 49.

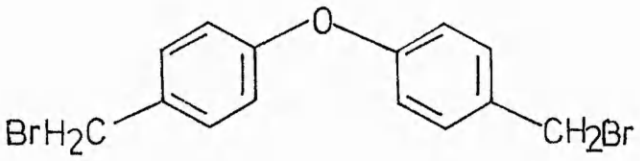
An interesting synthesis of bisbenzylisoquinolines has been developed by Popp.[43] Condensation of the dialdehyde 50 with a Reissert anion (Chapter 3) gave the bisisoquinoline base 51 in 83% yield. 51 was hydrolysed with aqueous alcoholic alkali to the diol 52. Reduction of the carbinol 52, quaternisation of the resulting aromatic isoquinoline with methyl iodide, and further reduction with sodium borohydride afforded O-methyldauricine 44 in an overall yield of 52% (based on Reissert compound).

A more direct approach[44] to bisbenzylisoquinolines using Reissert compounds has been elaborated. The condensation of one mole of

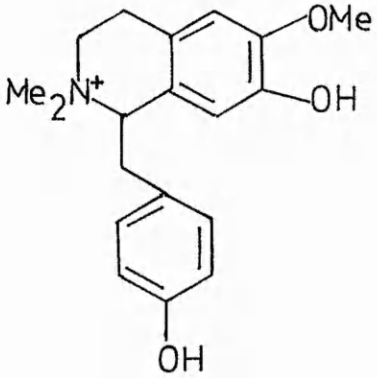


51 R=OCOPh

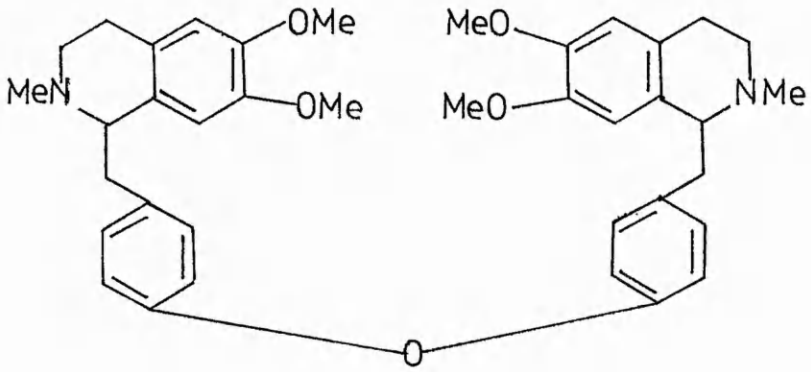
52 R=OH



53



55



54

a bishalomethyldiphenyl ether 53, in place of the dialdehyde 50, with two moles of a Reissert anion afforded, in excellent yield, a bisbenzyl Reissert compound which was converted by standard methods to the bisbenzylisoquinoline 54.

1.5.2. Syntheses using pre-formed isoquinolines

The synthesis of bisbenzylisoquinolines from two pre-formed 1-benzylisoquinoline units has been achieved by using biomimetic phenol oxidation or an Ullman reaction.

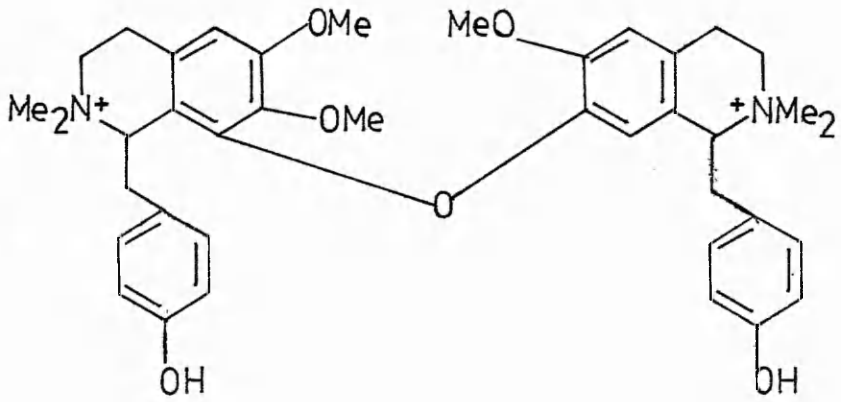
Phenol oxidation

A few attempts have been made to synthesise bisbenzylisoquinolines by routes involving phenol oxidative coupling, similar to those proposed[29] for the biogenesis of various alkaloids.

Franck and his associates[45] reported the first biogenetic-type synthesis of a bisbenzylisoquinoline. Oxidation of magnocurarine methiodide 55, a quaternised benzylisoquinoline, with alkaline potassium ferricyanide afforded the "head-to-head" coupled dimer 56. The similar oxidation of the tertiary amine 4'-O-methyl-N-methylcoclaurine 36 afforded a separable mixture of two racemic and diastereomeric bisbenzylisoquinolines 57 and 58 in a relatively high yield of 15%.[46]

In the dimerisation of benzylisoquinolines, it is usually easier for oxidative coupling to occur on ring A than on ring C of the molecule. A rare instance of dimerisation involving only ring C has been reported by Schofield *et al.*[47] The oxidation of racemic armepavine methiodide 59 with silver oxide afforded a mixture of the C-C linked diastereoisomers 60.

Bobbitt[48] has isolated two dimers 61 and 62 from the electrolytic oxidation of the sodium salt of racemic N-carbethoxy-N-norarmepavine



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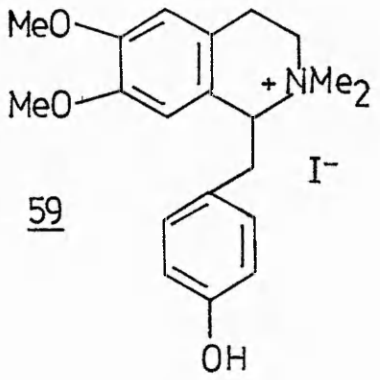

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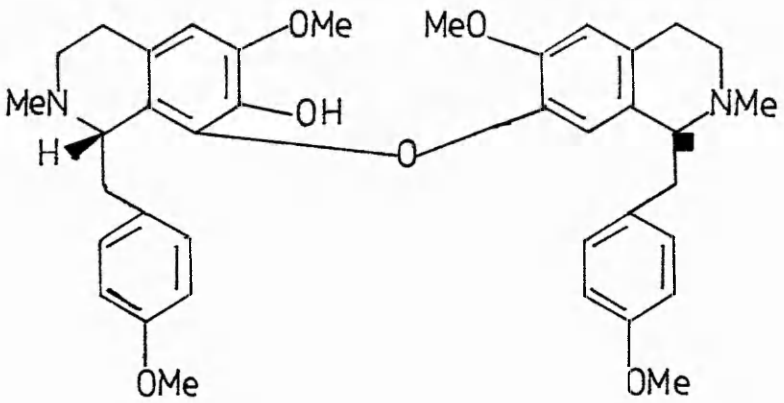
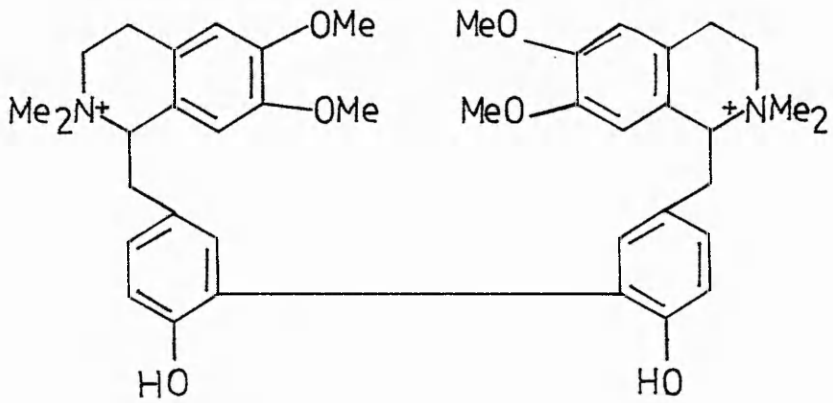


57 ■ = H

58 ■ = H



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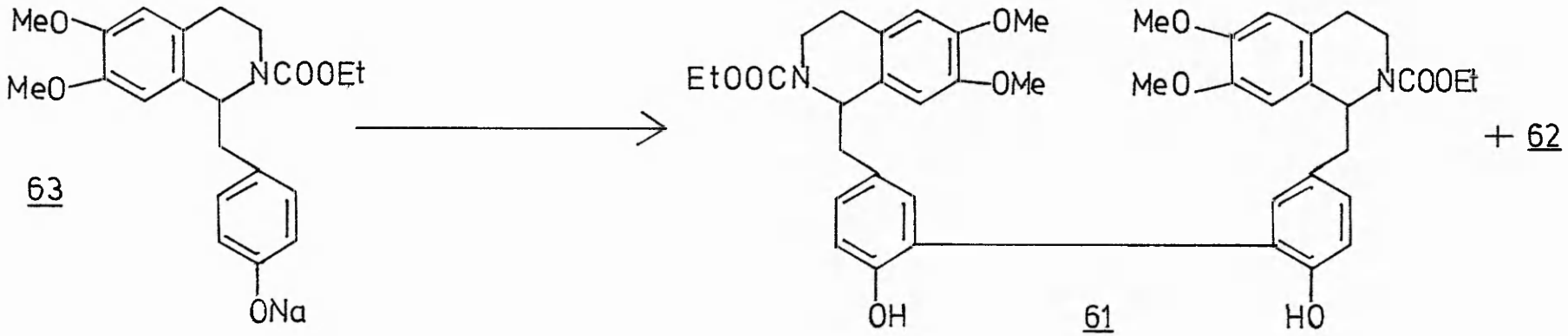
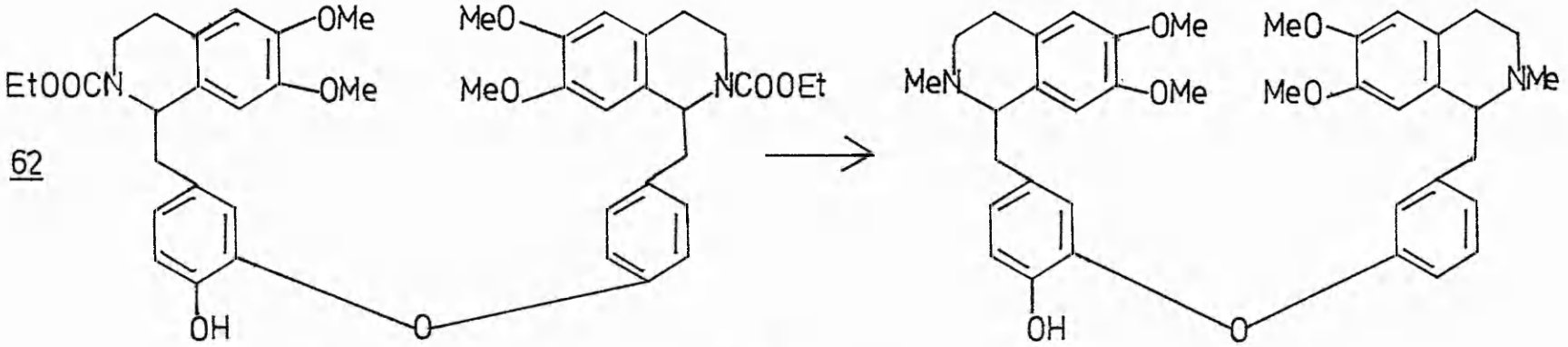


63 61 + 62



62 64

SCHEME 4

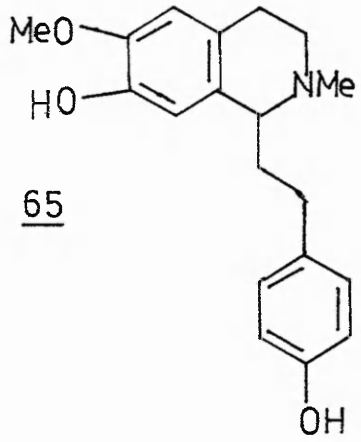
63. 62 was converted, without isolation, into a mixture of dauricine isomers 64 via O-benzylation, reduction and hydrogenolytic debenzylation (Scheme 4). This transformation represents the first preparation of an analogue of a natural bisbenzylisoquinoline by the oxidation of a phenolic monomeric benzylisoquinoline.

The only report of an isoquinoline dimer which possesses a "head-to-tail" ether linkage, without an accompanying link between the C rings, has been published by Kametani.[49] He claims that the enzymic phenol oxidation of 7-hydroxy-6-methoxy-2-methyl-1-(4-hydroxyphenethyl)-1,2,3,4-tetrahydroisoquinoline 65 with homogenised Wasabia japonica in the presence of hydrogen peroxide was found to give, by "head-to-tail" C-O-C coupling, the bisphenethylisoquinoline. 66. The only real evidence for the formation of the dimer 66 was the mass spectrum of its triacetyl derivative 67, so this result must be regarded with some suspicion.

Ullman condensations

The classical Ullman-ether synthesis of a bisbenzylisoquinoline involves the direct coupling of a phenolic 1-benzylisoquinoline with a halogenated benzylisoquinoline in the presence of copper or one of its salts or oxides. The advantage of this approach is that the two halves of the dimer may be prepared separately as pure enantiomers before the final coupling step. However, syntheses of bisbenzylisoquinolines by the Ullman reaction are usually of theoretical interest only owing to the very poor yields obtained.

The condensation[50] of N-methylcoclaurine 31 with 8-bromo-6,7-dimethoxy-2-methyl-1-(3-bromo-4-methoxybenzyl)-1,2,3,4-tetra-



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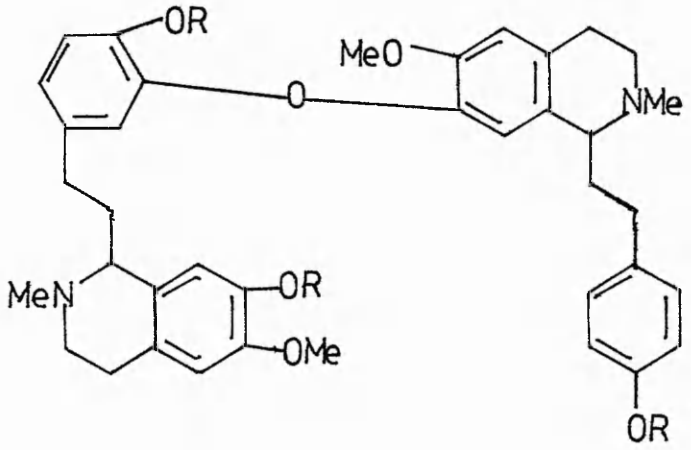
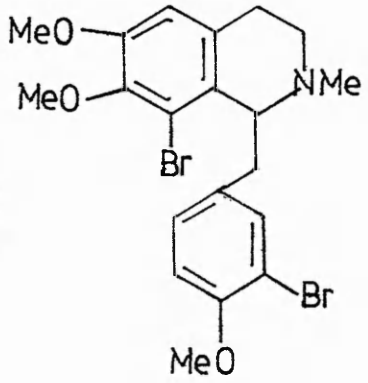


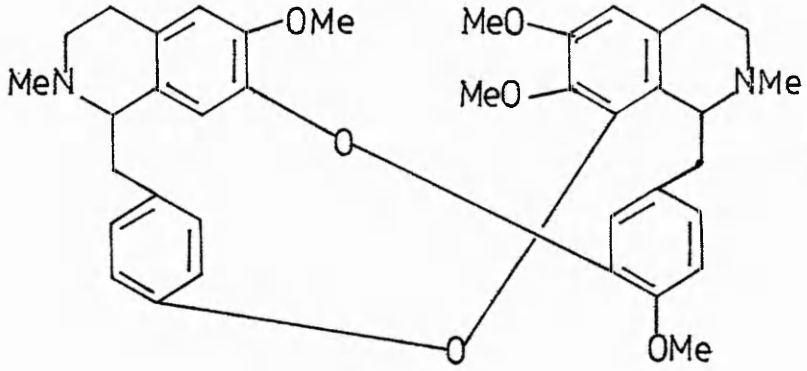
66R=H

67R=Ac



69

+ 31 ⟶



70

SCHEME 5

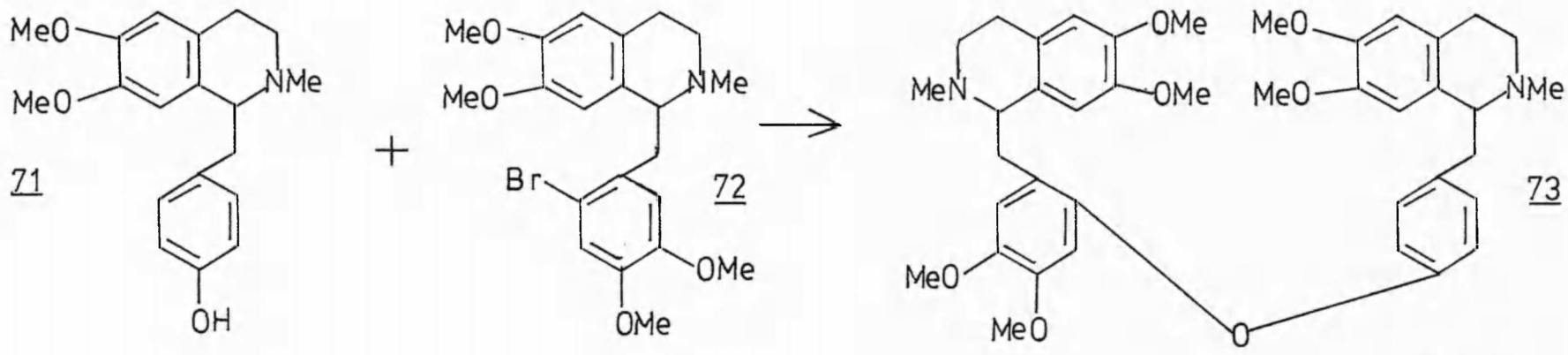
hydroisoquinoline 69 under Ullman conditions afforded, in very low yield, a mixture of bisbenzylisoquinolines including dimethylcurine 70 which contains two "head-to-tail" diphenyl ether linkages (Scheme 5).

In a modification of the Ullman procedure Cava and Afzali[51] have found that the condensation of equimolar amounts of S-(+)-armepavine 71 with S-(+)-6'-bromolaudanosine 72 in pyridine in the presence of pentafluorophenylcopper gave (+)-O-trimethylmagnolamine 73 in 42% yield (Scheme 6). However, expense may have limited the use of this reagent by other workers.

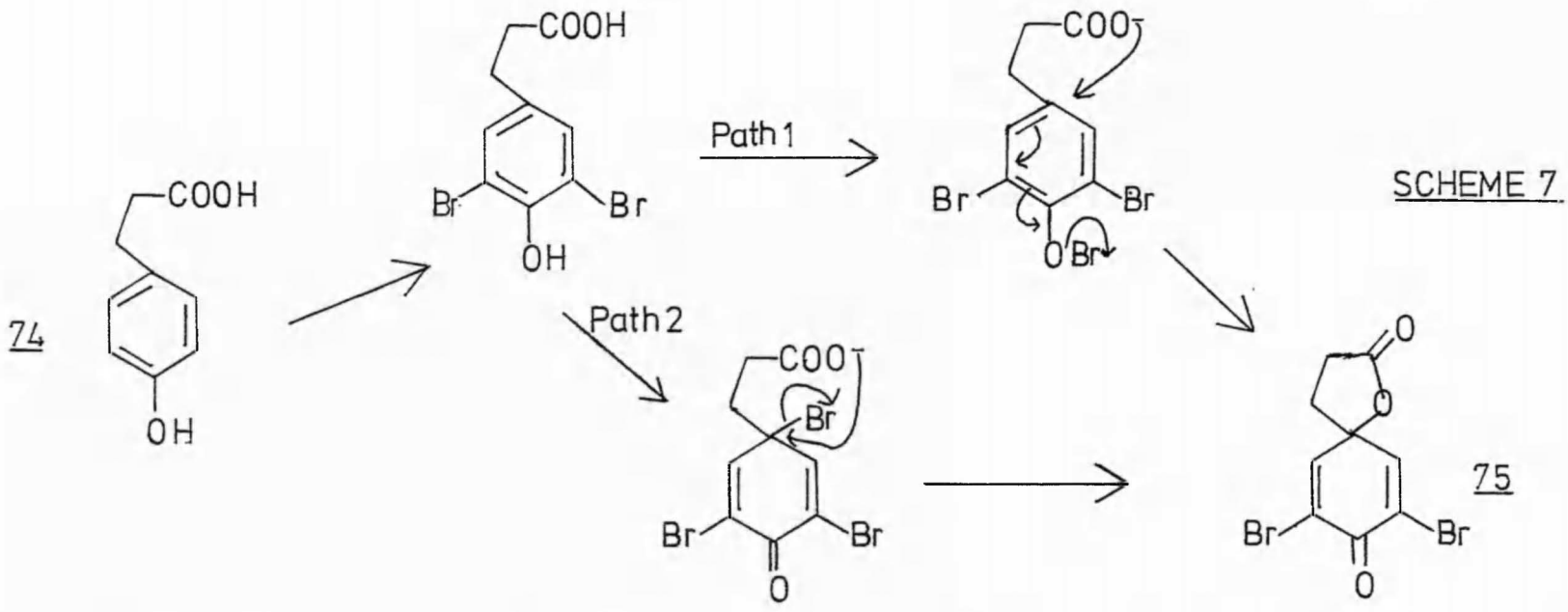
1.6 Synthesis of cyclohexadiene spirolactones

1.6.1 Electrophilic addition

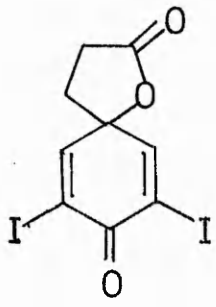
An extensively used method for synthesising cyclohexadiene spirolactones involves the addition of an electrophile to a p-substituted phenol. For example, the treatment of 3-(4-hydroxyphenyl)-propanoic (phloretic) acid 74 with N-bromosuccinimide or bromine affords the brominated spirolactone 75 in good yield.[52,53] Similarly the di-iodospirolactone 76 can be prepared[54] by the action of N-iodosuccinimide on phloretic acid 74. Two possible reaction mechanisms have been postulated[53] (Scheme 7). Path 1 involves the formation of a Br-O bond, nucleophilic attack of the alkanoic side chain on the C-1 position and the subsequent displacement of a bromide ion. Path 2 includes the bromination of the C-1 position, nucleophilic attack of the propanoic acid moiety on C-1, and, again, the displacement of a bromide ion. However, most of the evidence suggests that Path 2 is the probable route. The reaction of phenol with excess bromine affords[55] the tetrabromocyclohexadienone 77, and the treatment[56] of indole-3-propanoic acid 78 with 3 moles



SCHEME 6



SCHEME 7



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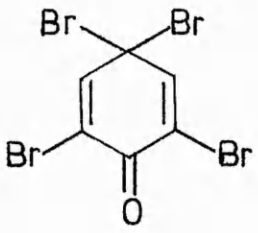

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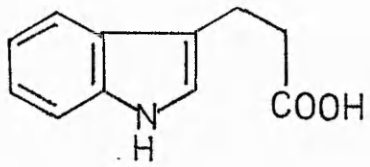

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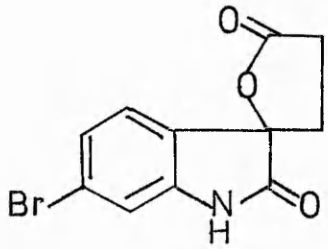

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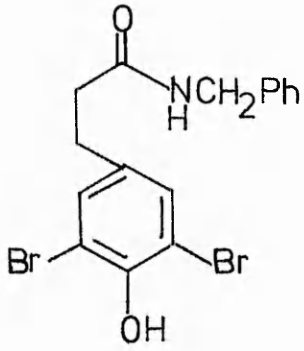

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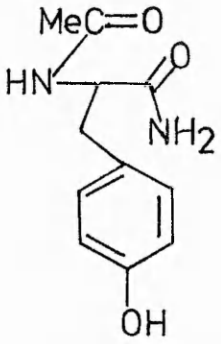

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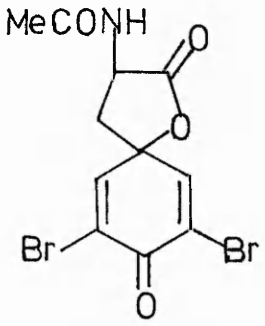

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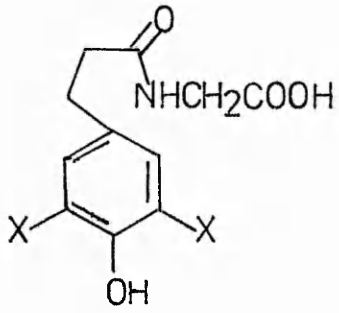
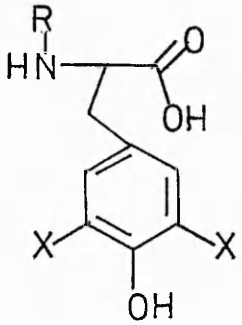


84 X=H

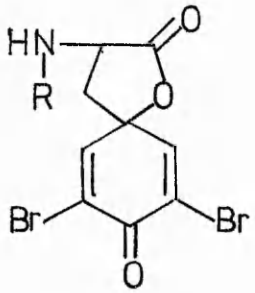
85 X=Br



86 R=OCPh; X=H

87 R=OCMe; X=Br

88 R=OCOCH$_2$Ph; X=Br



89 R=OCPh

90 R=OCMe

91 R=OCOCH$_2$Ph

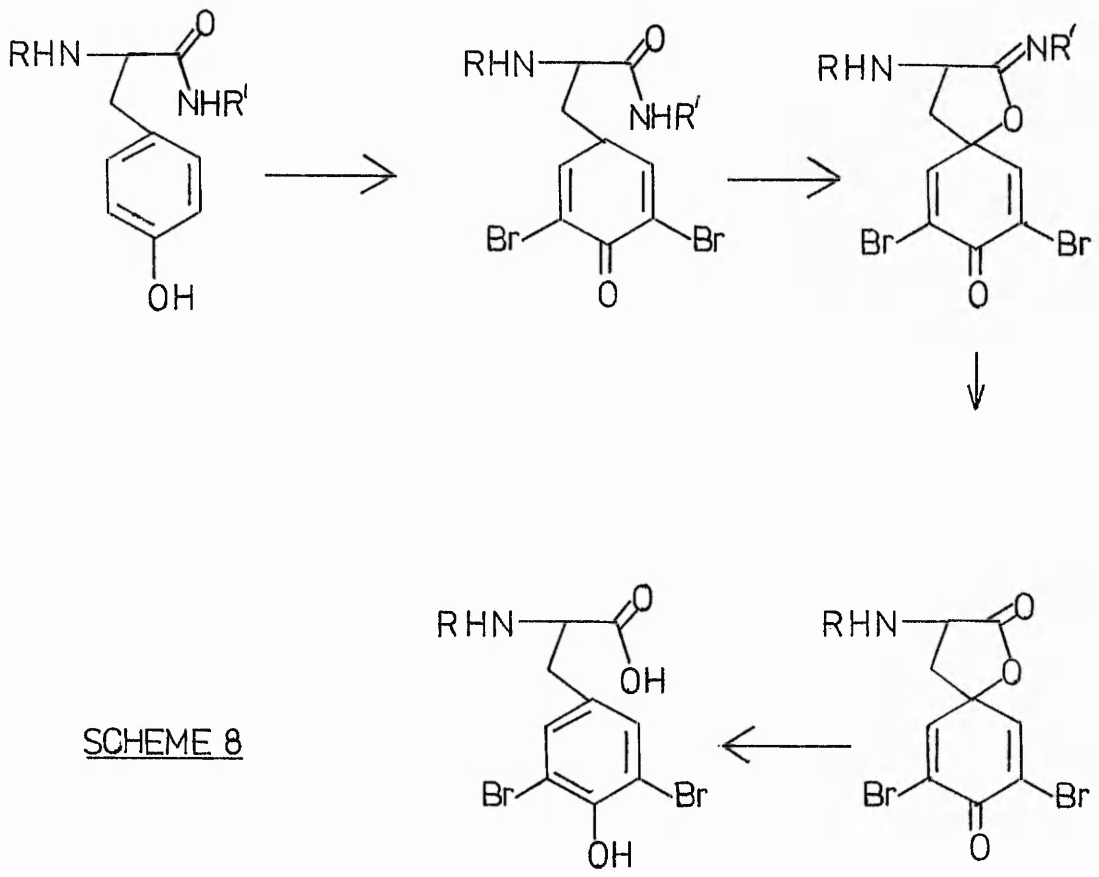
of N-bromosuccinimide yields the brominated spirolactone 79.

Du Vigneaud et al.[57] found that selective cleavage of the polypeptides oxytocin and vasopressin at the amide linkage between the carbonyl of tyrosine and the nitrogen of the attached amino acid occurs during treatment with aqueous bromine. Corey and Haefele[52] followed up this finding and proposed that a spirodienone was an intermediate in the reaction (Scheme 8). N-benzyl-3,5-dibromophloretamide 80 when reacted with bromine under Du Vigneaud's conditions liberated benzylamine with the quantitative formation of the dibromospirolactone 75. Similarly, the reaction of N-acetyltyrosine amide 81 with bromine in aqueous methanol results in the elimination of ammonia and the formation of the dibromospirolactone 82. Reduction of 82 with zinc and acetic acid affords N-acetyl-3,5-dibromotyrosine 83 which can be re-converted to 82 on treatment with bromine.

The amides N-phloretylglycine 84 and 3,5-dibromophloretylglycine 85 react[53] with N-bromosuccinimide to yield both glycine and the dibromolactone 75, while the N-aroyl derivatives of tyrosine 86 and 3,5-dibromotyrosine 87,88 afforded the corresponding halogenated N-aroylspirolactones 89, 90 and 91 in good yield.

The treatment of 3-(4-methoxyphenyl)propanoic acid 92 with N-bromosuccinimide in buffered sodium acetate and acetonitrile afforded[53] a mixture of the dibromolactone 75 and the dihydrocoumarin 93 by way of the cationic intermediate 94 (Scheme 9).

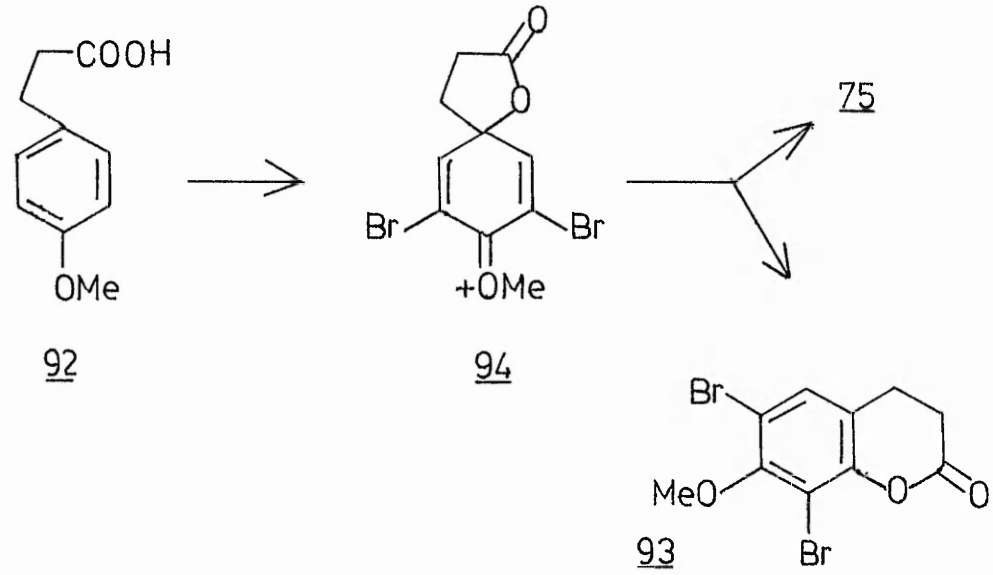
N-Bromosuccinimide has been used to prepare some naphthalene-derived ortho-spirolactones.[59] The treatment of the carboxylate of 95 with N-bromosuccinimide gave the stereoisomers 96 the ratio of which were dependent on the reaction temperature. Similarly the reaction of the carboxylate of 97 afforded two products 98, and 99 with methanol and triethylamine gave 98 as a rearrangement

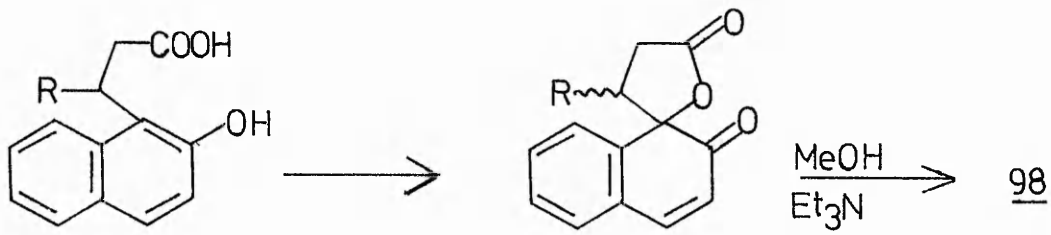


SCHEME 8

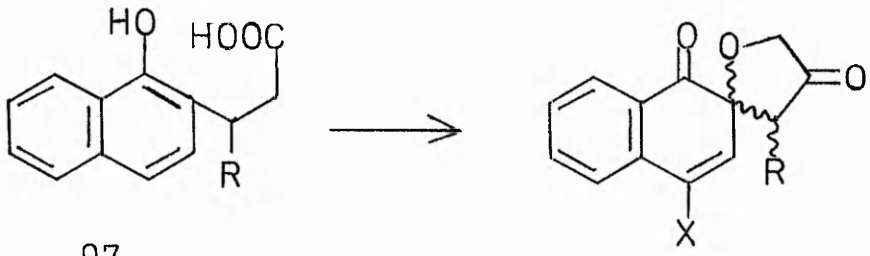
83 R=Ac

SCHEME 9





95 96

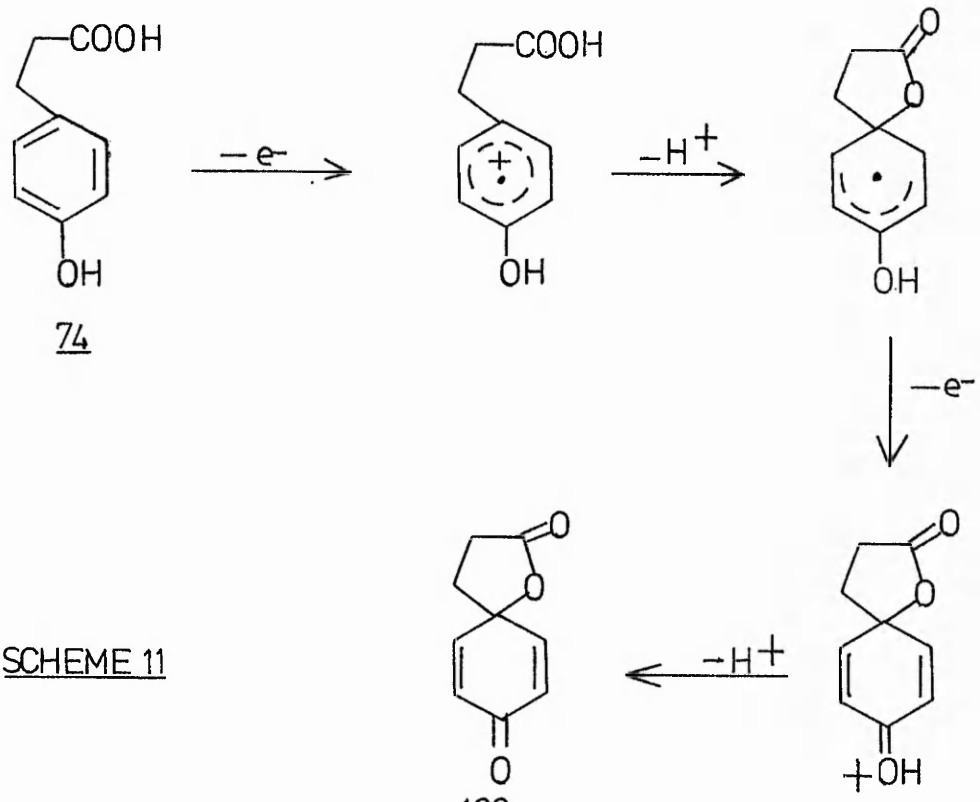


97

98 X = H

99 X = Br

SCHEME 10



74

100

SCHEME 11

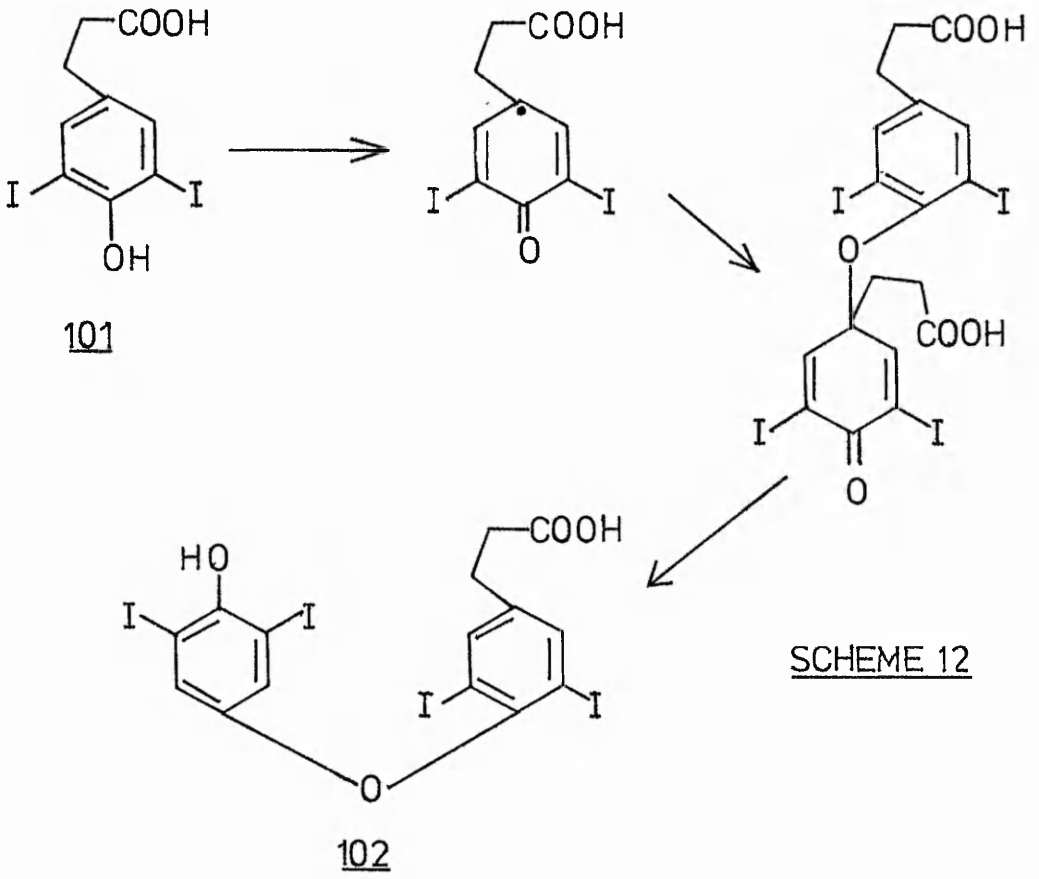
product (Scheme 10).

1.6.2. Oxidation by coupling of p-hydroxyphenylalkanoic acids

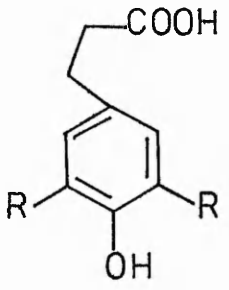
Another synthetic method involves the direct oxidation of phloretic acid 74 and its derivatives. The anodic oxidation of phloretic acid 74 has been studied in detail[60] but yields of greater than 20% of the desired 1-oxaspiro [4.5] deca-6,9-dien-2,8-dione 100 could not be achieved. The oxidation probably occurs via the formation of a radical cation in the aryl ring, capture of this cation by the propanoic acid side chain with the loss of a proton, followed by the further loss of an electron and a proton (Scheme 11).

The reaction of 3,5-di-iodophloretic acid 101 with a series of oxidising agents has been studied by Matsuura et al.[61] In only one instance was an identifiable product obtained, albeit in poor yield; polymers being the usual products. The treatment of 101 with potassium ferricyanide at pH12 afforded the "dimer" 102 by a radical mechanism and a side-chain modification (Scheme 12). However, oxidation with hypochlorite and hydrogen peroxide, as well as photo-oxidation in the presence of a sensitizer yielded the di-iodospirolactone 76; whilst the photo-oxygenation of 3,5-dibromophloretic acid 103 afforded 75. The reaction of 3,5-dichloro-phloretic acid 104 with hypochlorite and hydrogen peroxide gave the dichlorospirolactone 105 in 40% yield. Hydrogen peroxide in acetic acid has been used[2] to oxidise phloretic acid 74 to 100, but only a low yield was obtained.

The phenolic carboxylic acid 106 has been converted[62] to the spirolactone 107 in moderate yield, and the analogous diphenyl ethers 108 and 109 have been oxidised[63] to the spirolactones 110

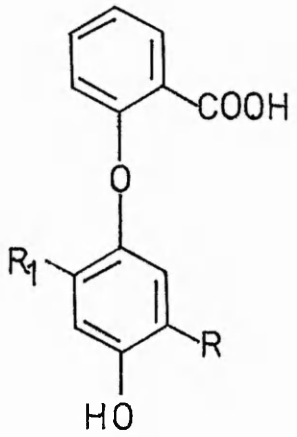


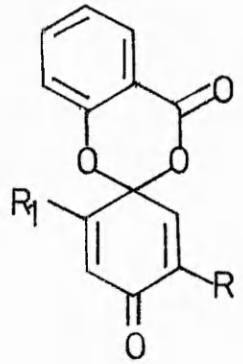
SCHEME 12

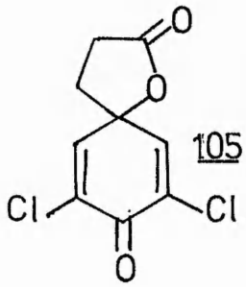


103 R = Br

104 R = Cl







106 R = R_1 = H

108 R = H; R_1 = Bu^t

109 R = Bu^t; R_1 = H

107 R = R_1 = H

110 R = H; R_1 = Bu^t

111 R = Bu^t; R_1 = H

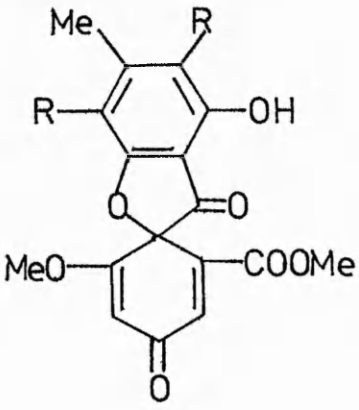
and 111 in 60% yield by using lead dioxide (107 could also be prepared by treating 106 with ceric ammonium sulphate[1a]).

The hydrolysis[64] of geodin 112[65] afforded the carboxylic acid 113 which could be oxidised[1a] by lead dioxide in ether to geodoxin 114[66] in good yield. Similarly the oxidation of asterric acid 115 (obtained from the *in vitro* hydrolysis of 116) afforded[1a] the spirolactone 117 in 70% yield. Interestingly, these dechlorinated analogues 116, 115 and 117 have all been isolated[67] from *oospora sulphurea ochrea*.

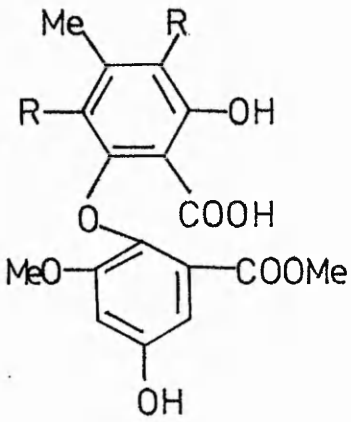
The acid 118 (obtained from the acid hydrolysis of dehydrogriseofulvin 119) could be oxidised with manganese dioxide to dehydrogriseofulvoxin 120 in excellent yield[68] (Scheme 13) whilst the oxidation of the biphenic acid 121 with manganese dioxide in ether[62] gave the cyclohexadienone spirolactone 122 in 25% yield.

1.6.3. Oxidation with thallium salts

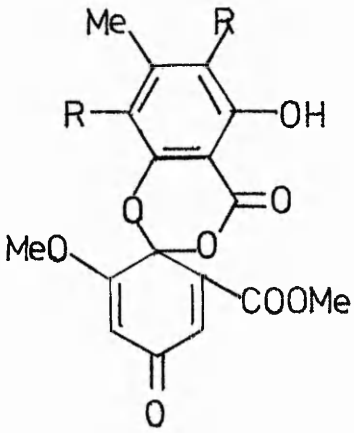
Thallium trifluoroacetate has been shown to effect electrophilic thallation of a wide variety of aromatic substrates carrying a variety of substituent groups (moderately activating to moderately deactivating). The resulting arylthallium bis(trifluoroacetates) are exceptionally versatile intermediates for the regiospecific introduction of new substituents into the aromatic nucleus. With highly activated aromatic substrates, however, electrophilic thallation is not normally observed; instead a one-electron oxidation takes place to generate a radical cation (see earlier) whose fate is determined by the nature of the reaction medium and of the substrate itself. The ability of thallium reagents to act as one-electron oxidants is well documented[69-73] and has been exploited for the synthesis of aporphine and homoaporphine alkaloids[74,75]



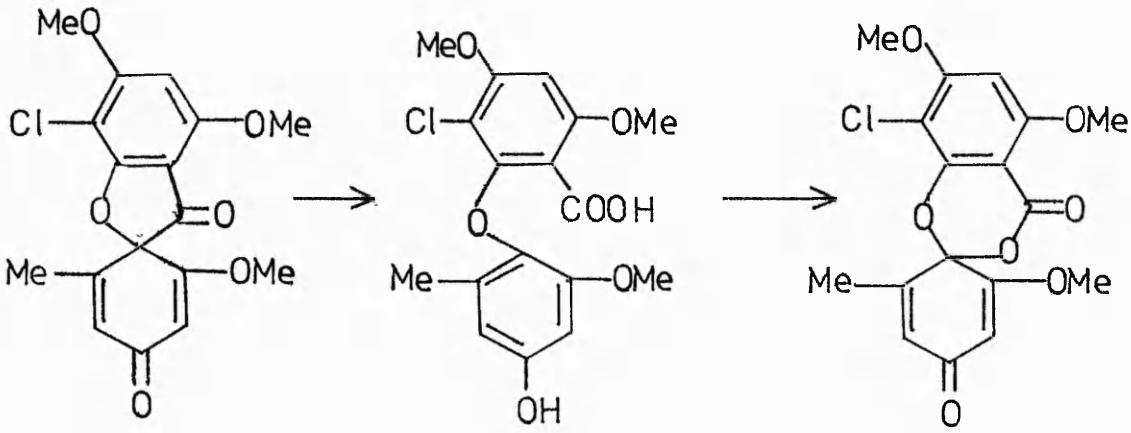
112 R=Cl
116 R=H



113 R=Cl
115 R=H



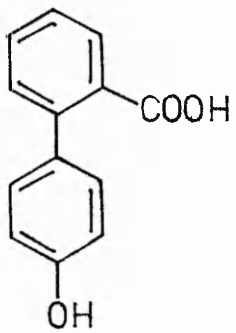
114 R=Cl
117 R=H



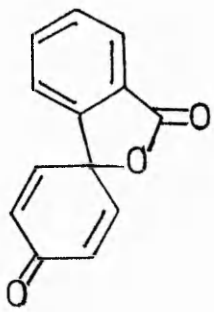
119 118 120

SCHEME 13

121



122



from non-phenolic precursors. These transformations represent capture (both inter- and intramolecular) of the initially generated aromatic radical cation by another aromatic compound acting as a nucleophile.

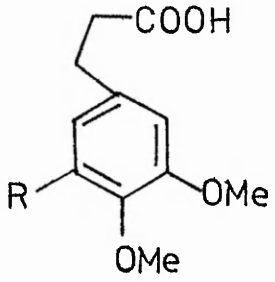
McKillop *et al*[76] have recently described the preparation of cyclohexadienonespirolactones from alkoxylated arylalkanoic acids by using thallium trifluoroacetate. The oxidation of 3-(3,4-dimethoxyphenyl) propanoic acid 123 afforded methyl 3-(2-hydroxy-4,5-dimethoxyphenyl) propanoate 124. This was not a primary oxidation product but a compound formed by acid catalysed ring opening of the initial product, 6,7-dimethoxydihydrocoumarin 125, during the isolation. A second primary oxidation product was identified as the cyclohexadienone spirolactone 126. However, the spirolactone 127 was the only product isolated on oxidation of the trimethoxy acid 128. The absence of dihydrocoumarin formation in this case can be explained by both steric hindrance to ortho- substitution and facile demethylation of the doubly-flanked methoxy group.

Analogously, the methoxynaphthylalkanoic acid 129 was oxidised to the benzo-fused cyclohexadienone spirolactone 130 in excellent yield; whilst the homologous butanoic acid 131 afforded the spirolactone 132 in 35% yield.

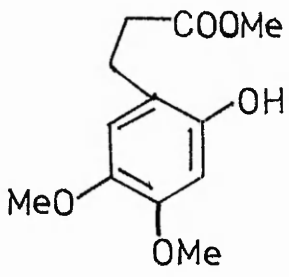
These thallium oxidations presumably occur by a mechanism similar to that described for anodic oxidation (Section 1.6.2), the main difference being the removal of the methyl group by the solvent. (Scheme 14).

1.6.4. Miscellaneous spirolactone syntheses

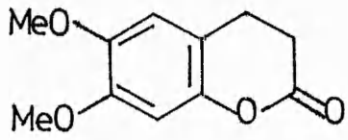
p-Benzoquinone reacts photochemically with one molar equivalent of either diphenylketen[77] or dimethylketen[78] to give the spiro-β-



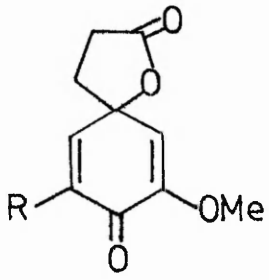
123 R=H
128 R=OMe



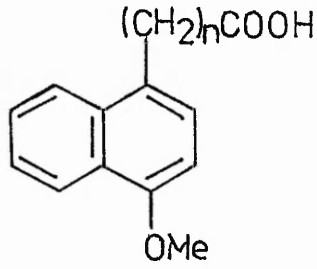
124



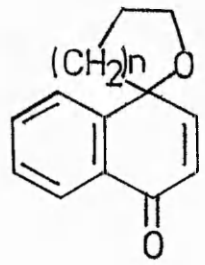
125



126 R=H
127 R=OMe

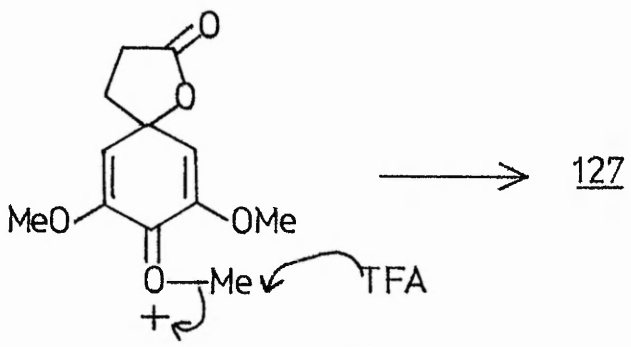


129 n=2
131 n=3



130 n=2
132 n=3

SCHEME 14



lactones 133 and 134 respectively. Ogino et al.[79] have extended this reaction to obtain the analogous spirolactones 135-138 and have studied their reaction with nucleophiles (see Section 1.7). (If two moles of keten are used, the quinodimethane 139 is produced[79] after a decarboxylation step). This synthetic route is of limited value and can only be applied to the synthesis of spiro-β-lactones.

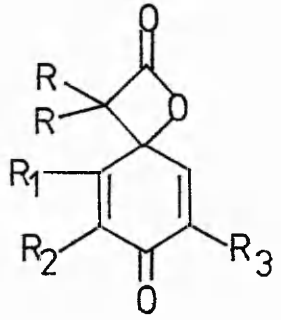
The hydroxylamine 140, prepared from the reduction of 4'-nitrobiphenyl-2-carboxylic acid 141 with zinc and ammonium chloride, has been "oxidised" under acidic conditions[62] to the spirolactone 122 by way of the unstable cyclohexadienimine 142 (Scheme 15).

The conversion of the sulphonamido acid 143 to the cyclohexadienimine 144 has been accomplished in good yield by anodic oxidation[60,80] and in quantitative yield by oxidation at room temperature with lead tetra-acetate.[81] The above anodic oxidation procedure has also been successfully applied to various other sulphonamido acids.[80] Elution of the dienimines on a Brockmann grade II neutral alumina column generally afforded good yields of the corresponding dienones.[80] (e.g. Scheme 16).

1.7 Reaction of cyclohexadienonespirolactones and related compounds with nucleophiles

All the positions of cyclohexa-2,5-dien-4-ones with potential leaving groups on C-1 can accommodate nucleophilic attack at any position on the ring unless the carbon is tertiary [82-7]. This is also true for cyclohexadienonespirolactones which can undergo nucleophilic attack at the lactone carbonyl[79], dienone carbonyl[79], and the carbon-carbon double bond.[60]

It is known that β-propiolactones can react with nucleophiles in either or both of two ways. Cleavage may occur at the carbonyl



133 R = Ph; $R_1 = R_2 = R_3 = H$

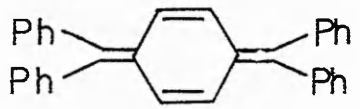
134 R = Me; $R_1 = R_2 = R_3 = H$

135 R = Ph; $R_1 = R_2 = H$; $R_3 = Me$

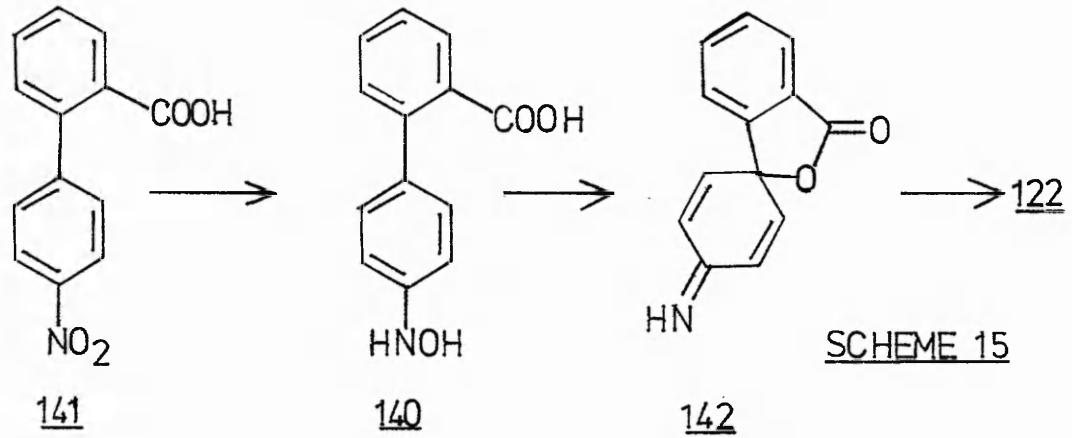
136 R = Ph; $R_1 = H$; $R_2 = R_3 = Me$

137 R = Ph; $R_1 = H$; $R_2 = R_3 = Cl$

138 R = Ph; $R_1, R_2 = (CH=CH)_2$; $R_4 = H$

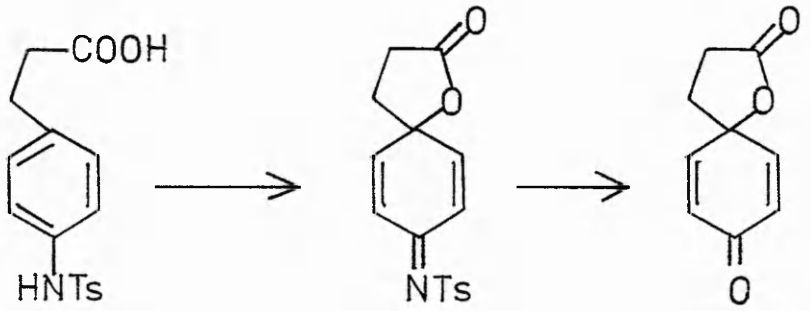


139



141 140 142 122

SCHEME 15



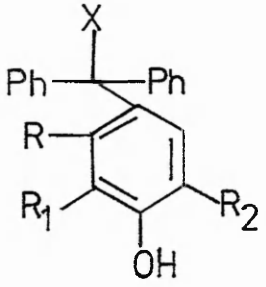
143 144 100

SCHEME 16

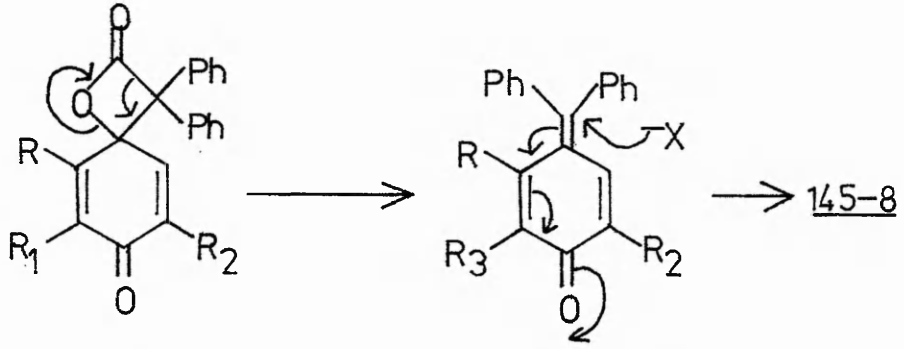
oxygen bond and at the alkyl oxygen bond to give ring opened products.[88] However, in the spiro compounds 133, 135-8 the β-carbon of the β-lactone ring cannot be the reaction centre of a nucleophilic attack because it is blocked by the cyclohexadienone moiety. Ogino et al.[79] have recently studied the reaction of substituted 3,3-diphenyl and 3,3-dimethyl-1-oxaspiro[3.5]nona-5,8-dien-2,7-diones with various nucleophiles. These compounds were expected to have enhanced reactivity toward nucleophiles because of the ring strain in the β-propiolactone moiety. The reaction of 133 with potassium cyanide in acetonitrile afforded an 80% yield of (p-hydroxyphenyl)-diphenylacetonitrile 145. Similar results were obtained from the reactions of 135-8 with potassium cyanide; and in the reaction of 133 the evolution of carbon dioxide was noted. The treatment of 133 with methylmagnesium iodide or methyl-lithium afforded the corresponding diphenylethane 150.

The transient p-quinone diphenylmethide derivatives, 153 and 154 were isolated as orange precipitates immediately after the addition of potassium cyanide to the lactones 136 and 137. On stirring, the orange precipitates disappeared and the normal products (147 and 148) were obtained in good yield.

From these observations, a concerted mechanism for nucleophilic attack on the 3-position with decarboxylation can be excluded, and the reactions of 133, 135-8 with nucleophiles can most reasonably be explained by a mechanism which proceeds through p-quinone diphenylmethides 151-4 as intermediates followed by 1,6-addition of a nucleophile (Scheme 17). This reaction in which nucleophiles attack the carbonyl carbon to cause decarboxylation is the only case reported for β-lactones. This is favoured in view of the energy gain from release of ring strain in the β-lactone moiety and also from formation of the stable p-quinone diphenyl methide



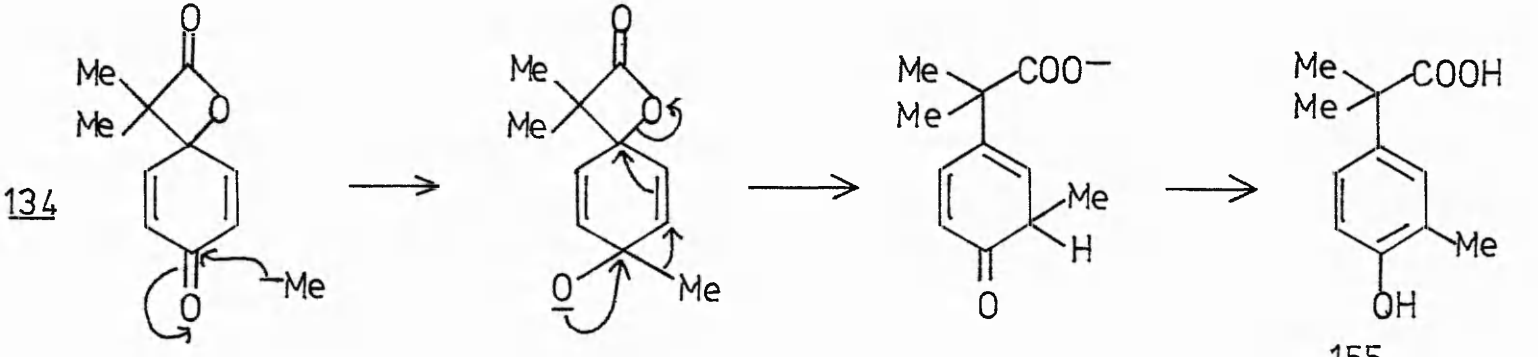
145 X=CN; R=R1=R2=H
146 X=CN; R=R1=H; R2=Me
147 X=CN; R=H; R1=R2=Me
148 X=CN; R=H; R1=R2=Cl
149 X=CN; R,R1=(CH=CH)2; R2=H
150 X=Me; R=R1=R2=H



133, 135-8

151 R=R1=R2=H
152 R=R1=H; R2=Me
153 R=H; R1=R2=Me
154 R=H; R1=R2=Cl

SCHEME 17



134

155

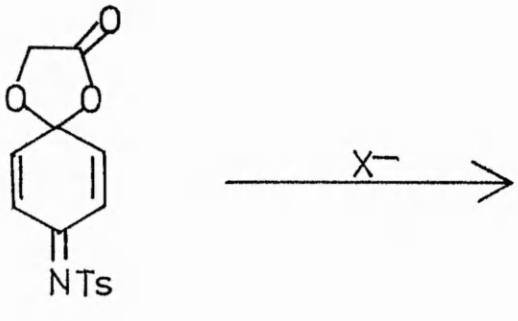
SCHEME 18

derivatives and $XCO_2^{\ominus}$ groups.

The reaction of 134 with methyl-lithium did not give p-tert-butylphenol, the analogue of 145, but gave, instead, α-(4-hydroxy-3-methylphenyl)-α-methylpropanoic acid 155. In this case, the nucleophile attacked the cyclohexadienone moiety as in the reactions of cyclohexadienones. Two mechanisms can be postulated for this reaction. Attack of the methyl anion on the dienone carbonyl group followed by a 1,2-methyl shift would afford 155 (Scheme 18). For spiro-cyclohexadienones, a similar 1,3-addition of a Grignard reagent to the enone has been reported;[86] and Musto[60] has produced evidence for the formation of the ring-opened lactones 156a,b and 157a,b after nucleophilic attack on the cyclohexadienimines 158 and 159 (Scheme 19). However, the two mechanisms[79,86] cannot be distinguished on the basis of the products. In the case of the reaction of the β-spirolactam 160 with methyl-lithium, the carbinol formed with the dienone carbonyl function could be isolated and so the mechanism described in Scheme 18 is certainly plausible.

The different reactivities of the 3,3-diphenyl- and 3,3-dimethyl-spiro compounds 133, 135-8 and 134 can be explained by the relative stabilities of the intermediate p-quinone methides.

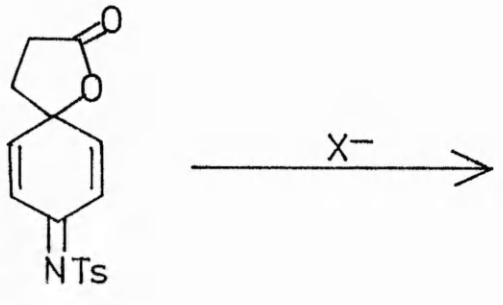
The reactions of p-quinol acetates with nucleophiles are known to effect the allylic displacement of the acetoxy group giving ortho-substituted phenols.[82] Umezawa[87] has extended this reaction to synthesise homo-aporphine, homo-morphinandienone and homo-proaporphine alkaloids by the use of an internal nucleophile. The reaction of the quinol acetate 161 with trifluoroacetic acid afforded (±)-1-hydroxy-2,10,11-trimethoxyhomo-aporphine 162, (±)-1-hydroxy-2,10-dimethoxyhomoproaporphine 163 and a related homo-morphinandienone. The homo-proaporphine 163, which was isolated



158

156a X=CN

b X=I

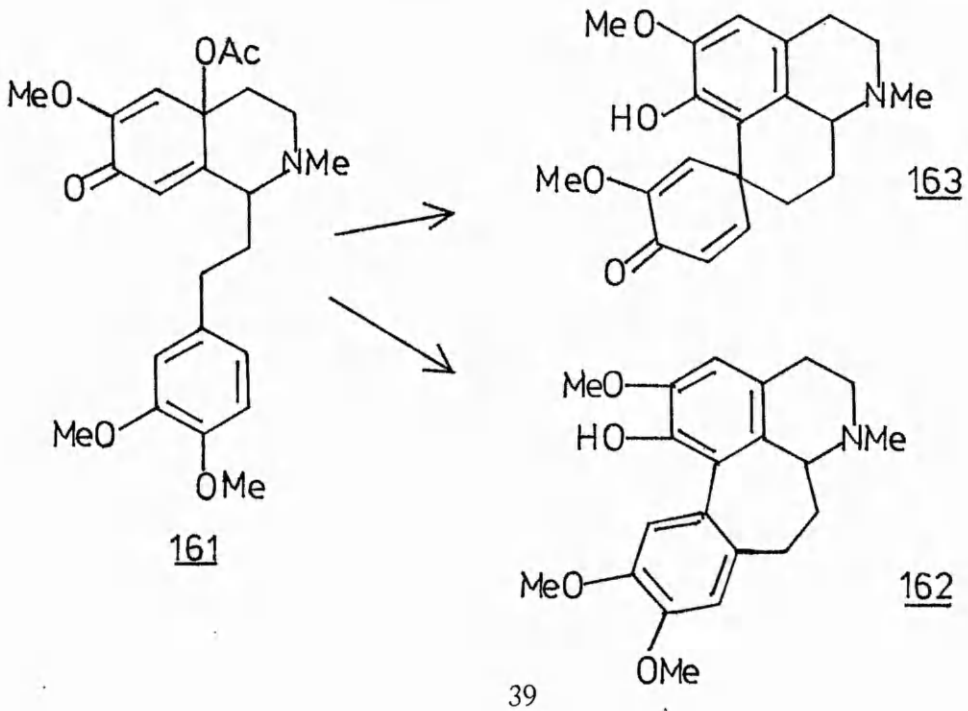


159

157a X=CN

b X=I

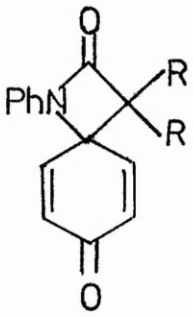
SCHEME 19



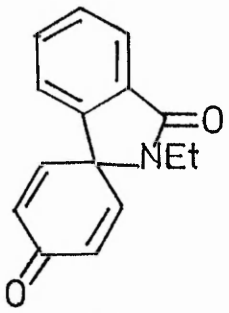
161

163

162

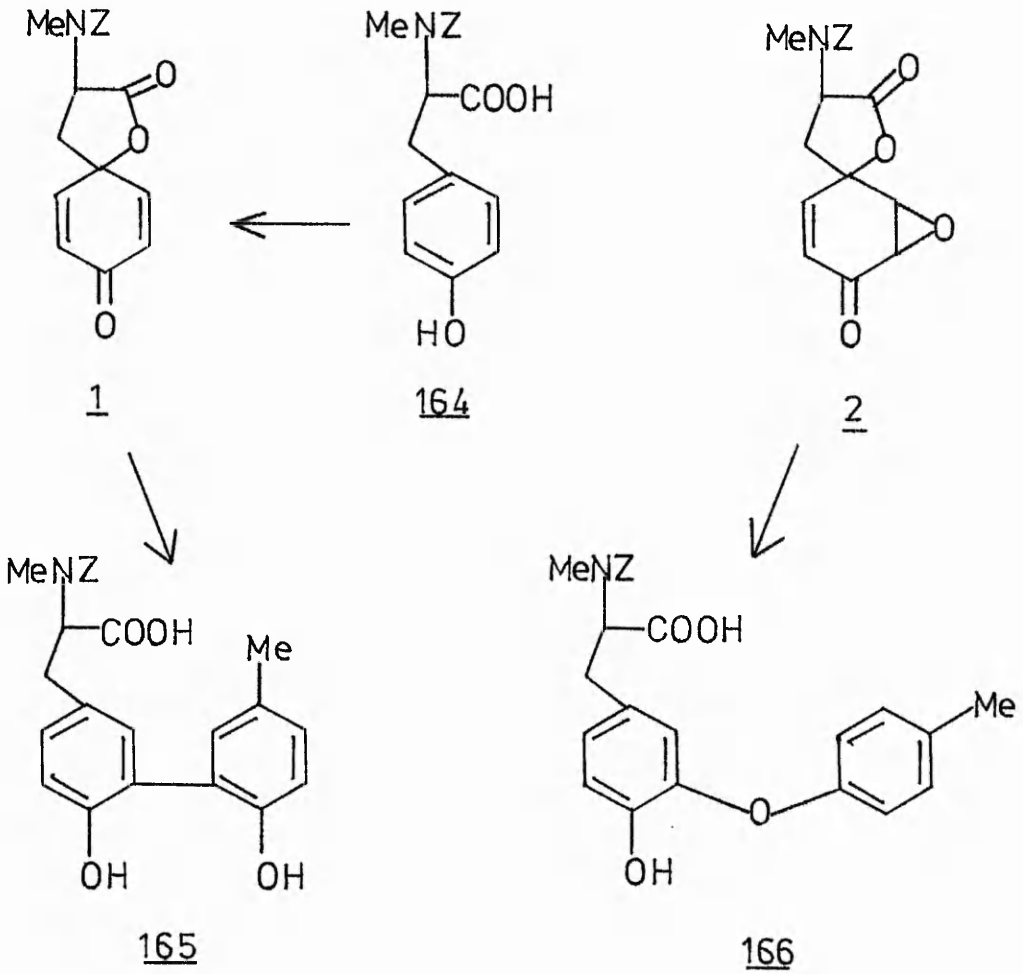


160a R=Me
b R=Ph



170

SCHEME 20 Z = $OCOCH_2Ph$



1 164 2

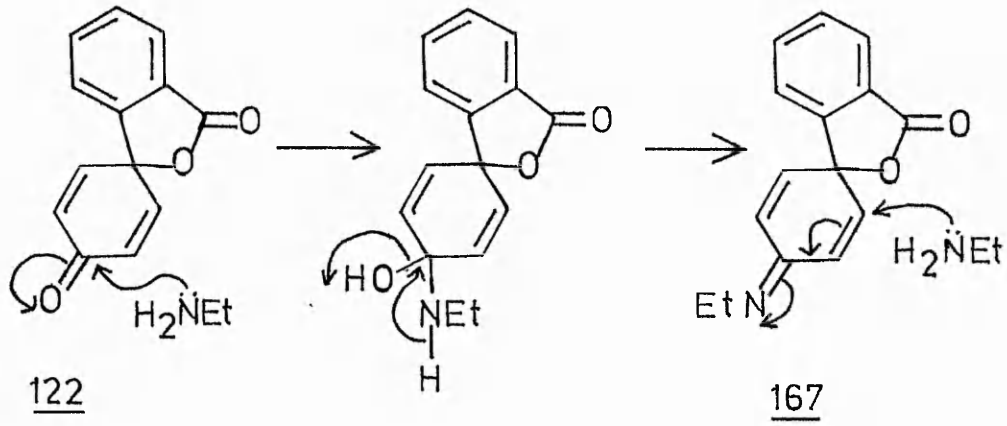
165 166

in low yield, arises from the coupling of the 1' and 8 carbons and the homoaporphine 162 results from the coupling of the 2' and 8 carbons.

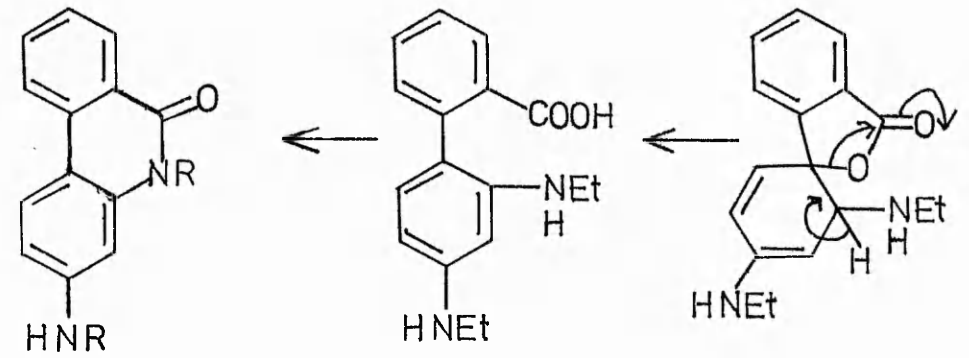
Inoue et al.[4] have prepared the dienone lactone 1 by the oxidation of N-methyl-N-benzyloxycarbonyl-L-tyrosine 164 with thallic nitrate. Attempts at introducing an oxygen nucleophile into the cyclohexadienone ring were all unsuccessful, yielding solely carbon-carbon coupled compounds. For example the reaction of 1 with p-cresol gave the biphenyl 165 which coincides with earlier observations[89] and can be explained by the HSAB theory. However, the dienone mono-epoxide 2, derivable from 1, afforded C-O-C coupled products on treatment with phenoxides. The biphenyl ether 166 was produced in good yield on successive reaction with potassium p-cresolate, diazomethane and zinc in acetic acid (Scheme 20).

Hey et al.[62] have studied the reaction of ethylamine with the cyclohexadienone spirolactone 122 and have noted the formation of 10-ethyl-2-ethylaminophenanthridone 168. Its formation may initially involve attack on the dienone carbonyl group by ethylamine to give the imine 167. Indeed evidence for the existence of 167 has been provided.[62] The subsequent course of the reaction probably involved a 1,4-addition of ethylamine to the imine 167, followed by rearrangement and cyclodehydration to give 168 (Scheme 21). A similar product 169 was formed when ammonia was used as a nucleophile whilst the reaction of the dienone-lactam 170 with ethylamine gave 168 - presumably by a similar mechanism to that shown in Scheme 21.

N-ethyl-2',5'-dihydroxybiphenyl-2-carboxamide 171 is another product from treating 122 with ethylamine. Here the lactone carbonyl function undergoes nucleophilic attack (Scheme 22). The alkaline



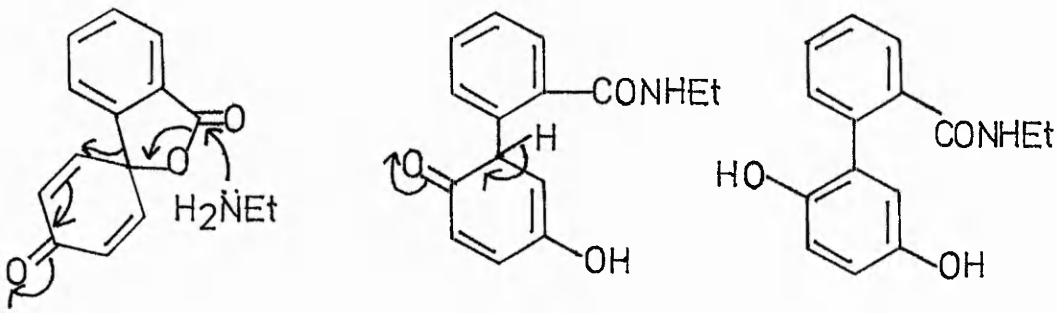
122 167



168 R=Et
169 R=H

SCHEME 21

SCHEME 22

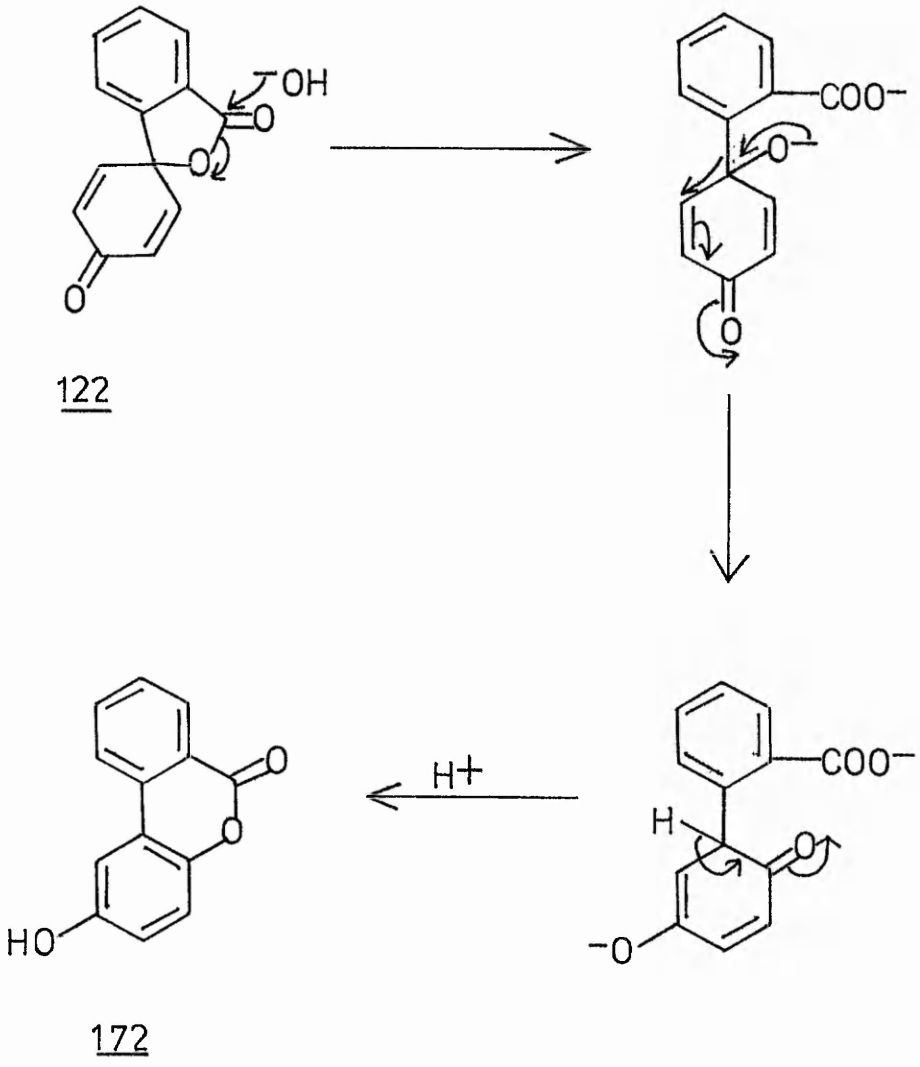


122 171

hydrolysis[62] of 122 also occurs via attack on the lactone carbonyl by hydroxide and yields the benzocoumarin 172 (Scheme 23).

Addendum Recent developments in elucidating the biogenetic role of tetrahydroisoquinoline-1-carboxylic acids

The feeding experiments discussed in Section 1.2 were carried out on whole plants. Pioneering studies by Zenk and coworkers[170] using plant cell cultures have resulted in the isolation of some of the enzymes which mediate alkaloid biosynthesis. In particular an enzyme, S-norlaudanosoline synthase obtained from a number of isoquinoline-producing plants, catalyses the condensation of dopamine with 3,4-dihydroxyphenylacetaldehyde at pH 7.8 to give S-laudanosoline. This enzyme also catalyses with less efficiency the reaction of dopamine with 4-hydroxyphenylacetaldehyde and with phenylacetaldehyde, but does not affect the reaction of dopamine with various phenylpyruvic acids. This appears to prove that for benzylisoquinolines the first biosynthetic step is condensation between dopamine and an aldehyde rather than a pyruvic acid; tetrahydroisoquinoline-1-carboxylic acids may arise as artefacts, being formed by non-enzymatic reaction between dopamine and pyruvic acids. The status of the isoquinoline acids in the biosynthesis of cactus alkaloids is still unresolved.



122

172

SCHEME 23

CHAPTER TWO

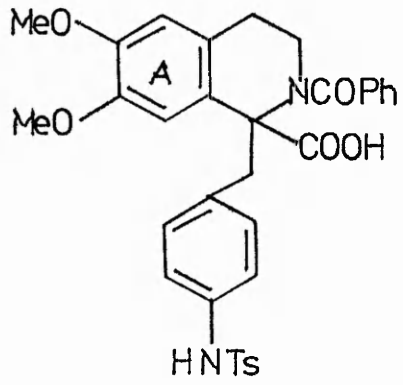
2.1 1,2,3,4-Tetrahydronaphthalene-1-carboxylic Acids

1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acids possessing +M substituents on the A ring have previously been prepared at Trent Polytechnic in order to carry out other investigations.

Preliminary anodic oxidation experiments on the p-toluenesulphonamido acid 173 revealed that no spirolactone was formed, but that oxidation occurred in the electron-rich A ring.

For this reason a series of 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, containing no +M substituents in the A ring were required. Such compounds have not so far been described. In view of this dearth of knowledge concerning the above acids, and of the possible problems involved in the synthesis of the required amino acids (see Chapter 3), a study was made of the synthesis of 1-benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids. These carboxylic acids, as isosteres of the isoquinoline acids were expected to act as "models" for the synthesis of isoquinoline cyclohexadienone spirolactones.

Vejdelek et al.[90,91] utilized a rather circuitous route to some 1-alkyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids (Scheme 24). The reduction of 1-naphthoic acid 174 to the 1,2,3,4-tetrahydro acid 175 was followed by conversion to the amide 176. Dehydration of 176 with phosphorus pentoxide afforded the nitrile 177, effectively a cyclic analogue of phenylacetonitrile. The proton on the carbon atom α to the nitrile was readily removed with sodamide and successfully alkylated with benzyl and allyl bromide. Vigorous alkaline hydrolysis of the 1,1-disubstituted tetrahydronaphthalenes 178a and 178b afforded the acids 179a and 179b (the amide 180 was also isolated as a by-product of the hydrolysis of 178a).



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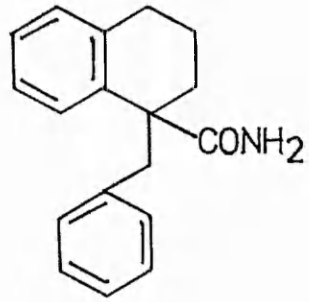
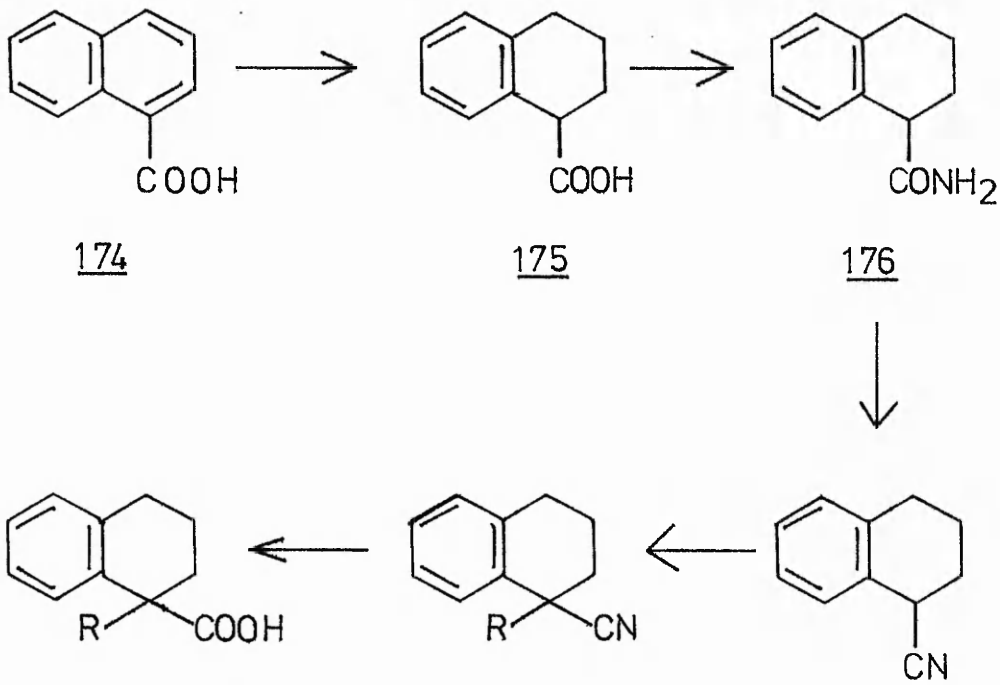


180



174 175 176

177

179a R=CH_2Ph
b R=$CH{=}CH_2$

178a R=CH_2Ph
b R=$CH{=}CH_2$

SCHEME 24

As far as can be ascertained no other synthesis of these 1-substituted tetrahydronaphthoic acids has been described.

2.2 The preparation of 1,2,3,4-tetrahydronaphthalene-1-carboxylic acids

It seemed to us that 1-benzyl-1,2,3,4-tetrahydronaphthoic acids might be synthesised more directly if esters of 175 were used in place of the nitrile 177. These compounds, still possessing an acidic proton at position 1 of the tetrahydronaphthalene should be capable of carbanion formation and alkylation to afford esters which on hydrolysis would give the desired acids.

The parent acid 175 was prepared in excellent yield by reducing 1-naphthoic acid 174 with sodium in boiling ethanol.[92] Esterification of 175 with methanol and sulphuric acid afforded the methyl ester 181 in quantitative yield.

The removal of the proton α to the ester group was effected by using the non-nucleophilic base lithium di-isopropylamide (LDA) at -78° in tetrahydrofuran under a nitrogen atmosphere. The lemon yellow anion 182 was treated with various benzyl halides to give the novel 1-substituted -1,2,3,4-tetrahydronaphthalene-1-carboxylates 183-7 in good to excellent yields. The n.m.r. spectra of the benzylated products from 182 all showed the peaks for the benzylic protons as AB quartets (see Chapter 3).

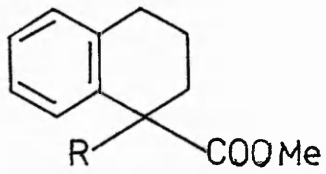
Catalytic hydrogenation of the benzyloxy ester 184 afforded the novel phenolic ester 188 in a yield of 92%. The methyl esters 185-8 were readily saponified with methanolic potassium hydroxide to the corresponding novel carboxylic acids 189-92 in excellent yield. The acid 192 could also be prepared by hydrogenolysis of the benzyloxy acid 193 (see below).

The esters 183 and 184 could not be saponified under the above conditions nor with various concentrations of aqueous potassium or sodium hydroxide. The use of trimethylsilyl chloride and sodium iodide[93] also failed to effect the desired de-esterification. However, the benzyloxy ester 184 could be hydrolysed in almost quantitative yield to the novel benzyloxy acid 193 by using potassium tert-butoxide in ether.[94] Similarly the ester 183 could be converted, albeit in low yield, to the novel nitro acid 194.

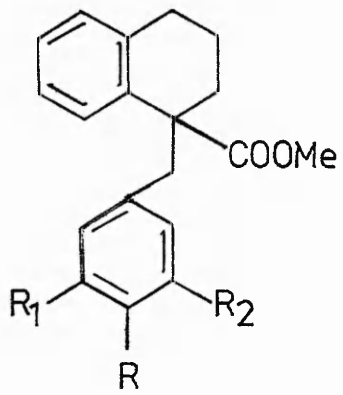
Although the amino ester 195 could be prepared in excellent yield by hydrogenation of the nitro ester 183 in the presence of palladised charcoal, its subsequent saponification afforded an amino acid 196 which could not be satisfactorily recrystallised; it was, however, characterised by conversion to the sulphonamido acid 197. The crude sulphonamido esters 198 and 199 could be prepared by tosylation and mesylation of the ester 195 but neither ester could be saponified to the desired acids 197 and 200. Owing to the problems involved in saponifying the esters 183, 195, 198 and 199, attempts to prepare 1-(4-nitrogensubstitutedbenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids by this route were abandoned.

Since tert-butyl esters can be readily de-esterified under acidic conditions, their use in the preparation of nitrogen substituted benzyl naphthoic acids appeared attractive. There are few cheap methods available for the synthesis of tert-butyl esters, but a modified version of Murphy's[95] procedure seemed a reasonable synthetic approach. The reaction of 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 175 with oxalyl chloride followed by treatment with a mixture of tert-butanol and triethylamine afforded the novel tert-butyl ester 201 in excellent yield.

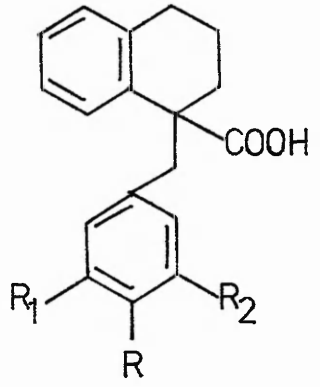
Although it was envisaged that the steric bulk of the t-butyl ester might cause difficulties, it was found that LDA removed the



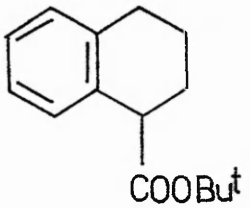
181 R=H
182 R=Li



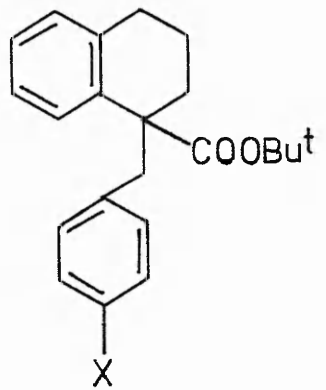
183 $R=NO_2$; $R_1=R_2=H$
184 R=OBz; $R_1=R_2=H$
185 R=OMe; $R_1=R_2=H$
186 $R=R_1=OMe$; $R_2=H$
187 $R=R_1=R_2=OMe$
188 R=OH; $R_1=R_2=H$
195 $R=NH_2$; $R_1=R_2=H$
198 R=NHTs; $R_1=R_2=H$
199 R=NHMs; $R_1=R_2=H$



189 R=OMe; $R_1=R_2=H$
190 $R=R_1=OMe$; $R_2=H$
191 $R=R_1=R_2=OMe$
192 R=OH; $R_1=R_2=H$
193 R=OBz; $R_1=R_2=H$
194 $R=NO_2$; $R_1=R_2=H$
196 $R=NH_2$; $R_1=R_2=H$
197 R=NHMs; $R_1=R_2=H$
200 R=NHTs; $R_1=R_2=H$



201



202 $X=NO_2$
203 $X=NH_2$
204 X=NHTs
205 X=NHMs

α proton from 201, and the resulting yellow anion reacted with p-nitrobenzyl bromide to afford the novel tert-butyl-1-(4-nitrobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 202 in good yield. Catalytic hydrogenation of 202 produced the gummy amino ester 203 which was reacted with p-toluenesulphonyl chloride or with methanesulphonyl chloride to afford the crude novel sulphonamido esters 204 and 205 in good yield. The treatment of these esters 204 and 205 in chloroform with trifluoroacetic acid at room temperature gave the crystalline sulphonamido acids 200 and 197 in quantitative yield.

2.3 The preparation of naphthalene cyclohexadienone spirolactones

Phenylpropanoic acids containing para-hydroxy or methoxy substituents can be oxidised to cyclohexadienone spirolactones under a variety of conditions (see Chapter 1). The tetrahydronaphthalene carboxylic acids 189-92, 197, and 200 are, in effect, 2,2-disubstituted-3-phenylpropanoic acids and, as such, were expected to yield cyclohexadienone spirolactones by using one or more of the oxidative methods previously described.

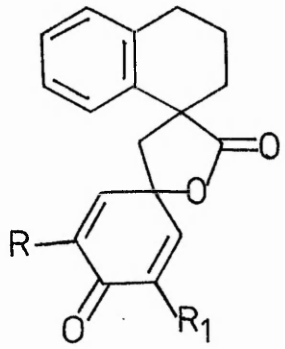
2.3.1 Thallium trifluoroacetate oxidations

Recently McKillop et al.[76] have described the oxidation of some methoxylated phenylpropanoic acids to their corresponding cyclohexadienone spirolactones by the use of thallium trifluoroacetate. The use of this oxidant, therefore, seemed appropriate for the oxidation of the readily available acids 189-91.

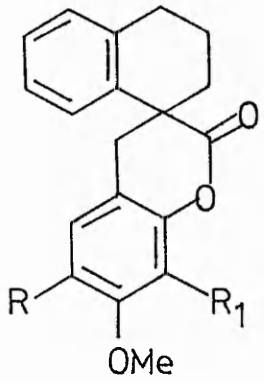
The treatment of the acids 189-91 with thallium trifluoroacetate at -20° in the presence of boron trifluoride - etherate immediately afforded highly coloured complexes. (These coloured complexes

have been described as charge-transfer species.[69]) After thirty seconds the reactions were quenched with tert-butanol and the products isolated as described in the Experimental section. The trimethoxy acid 191 afforded a good yield of a crystalline fawn solid which was identified as the novel spirolactone 206 by (a) the presence of vinylic resonances in its n.m.r. spectrum, (b) high resolution mass spectroscopy which indicated an M-CO_2 ion at m/e 296, and (c) i.r. spectroscopy which showed peaks at 1765, 1685, 1660 and 1620 cm^{-1} in good agreement with published [1,2,76] values of cyclohexadienone spirolactone spectra. There was no evidence in the infra-red spectrum of the presence of the δ-lactone 207 which is a possible primary oxidation product (see later).

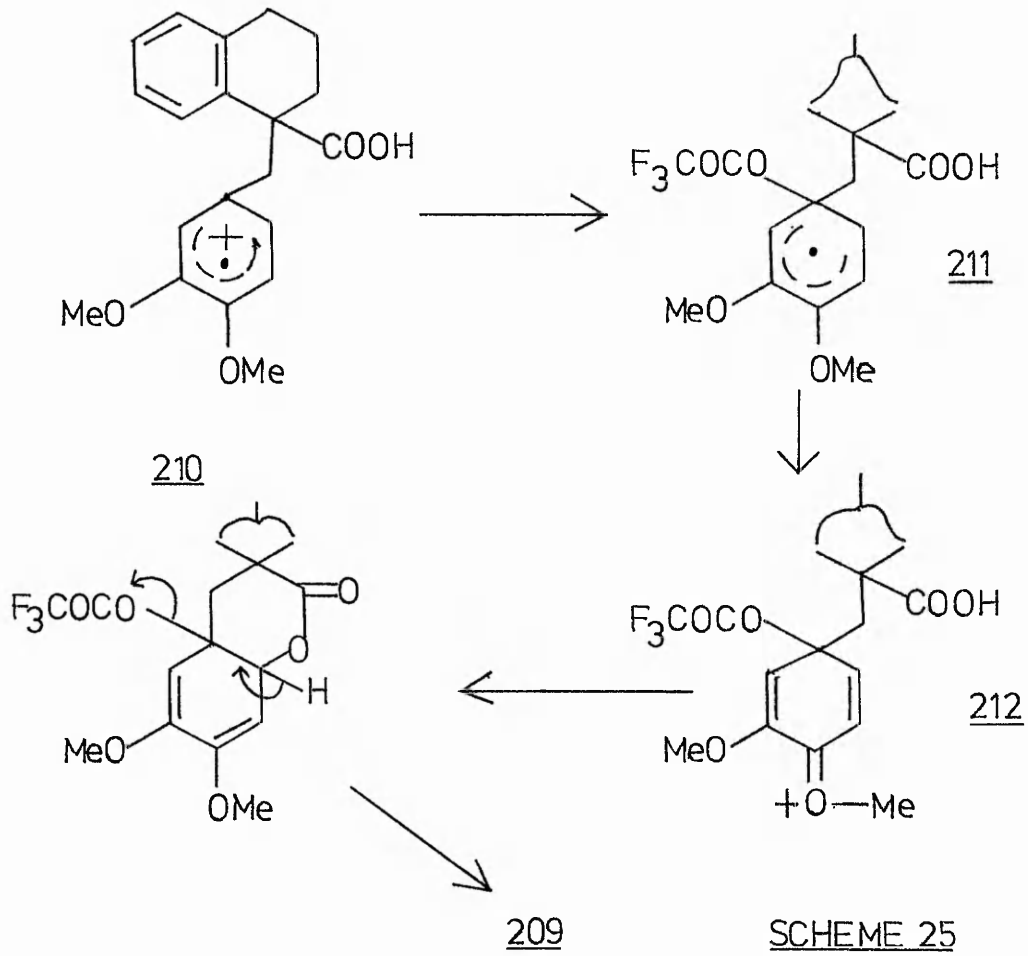
The oxidation of the dimethoxy acid 190 afforded a complex mixture from which only one of the two major components could be separated by flash chromatography. The n.m.r. spectrum of the separated product showed resonances at ca. δ 6.2 and 6.55 indicating the presence of vinylic protons, whilst the i.r. spectrum showed strong peaks at 1770, 1680, 1645 and 1620 cm^{-1} characteristic of a cyclohexadienone spirolactone. The low resolution mass spectrum showed a weak molecular ion at m/e 310 and a slightly stronger M-CO_2 ion at m/e 266. The product was therefore identified as the novel cyclohexadienone spirolactone 208a or 208b. However, the infra-red spectrum of the crude product had a medium strength absorption at 1725 cm^{-1} denoting contamination with another carbonyl containing entity. Possible products are the dihydrocoumarins 209a or 209b which could be formed by the trifluoroacetylation of the radical cation 210 to give the dienone 212 via 211. Attack on 212 by the acid group and the loss of trifluoroacetic acid would lead to 209a or 209b (Scheme 25).



206 R=R$_1$=OMe
208a R=H; R$_1$=OMe
b R=OMe; R$_1$=H
213 R=R$_1$=H
219 R=R$_1$=Br



207 R=R$_1$=OMe
209a R=H; R$_1$=OMe
b R=OMe; R$_1$=H



210

209

SCHEME 25

The oxidation of the monomethoxylated acid 189 yielded a product which, after purification on an alumina column afforded in low yield a white solid. The i.r. spectrum of this solid showed a strong absorption at 1780 cm^{-1} and weaker absorptions at 1670, 1640 and 1610 cm^{-1} suggesting that the product was the novel cyclohexadienone spirolactone 213. It was identical to the spirolactone obtained by anodic oxidation of 192 and 189 (see below).

The ester 187 was not oxidised by thallium trifluoroacetate.

2.3.2 Anodic oxidation

The anodic oxidation of the naphthoic acids was carried out in acetonitrile using carbon felt anodes with a calomel electrode as reference electrode (see p.105). The reactions all appeared to be two electron oxidations but current fluctuations made accurate coulometry difficult.

The acid 191 was readily oxidised at 1.5V to give a product from which three compounds were isolated by flash chromatography. The major product was identified as the spirolactone 206 by n.m.r. and i.r. spectroscopy, and by comparison with an authentic sample from the thallium oxidation of 191. The next most abundant product was α-tetralone 214, identified by its n.m.r. and i.r. spectra and by comparison with authentic material. This presumably arose from the oxidative cleavage of the benzyl residue of 191. The third product, a minor component showed a carbonyl peak at 1690 cm^{-1} in the i.r. spectrum, whilst the n.m.r. spectrum indicated the presence of a tetrahydronaphthalene skeleton and the absence of any methoxy groups. The product, however, could not be identified.

The oxidation of 190 followed by elution of the product on an alumina column afforded two non-separable compounds. The

i.r. spectrum of the mixture exhibited strong absorptions at 1770, 1680, 1645 and 1620 cm^{-1} and a weaker absorption at 1725 cm^{-1}. Tlc and mass spectral analysis showed the major product to be the spirolactone 208a or 208b; whilst the other product was tentatively identified as the dihydrocoumarin 209a or 209b.

Oxidation of the mono-methoxy acid 189 gave a very low current. Crystallisation of the complex reaction product from methanol yielded a small quantity of a compound which was identified as the cyclohexadienone spirolactone 213 by comparison with an authentic sample (next paragraph).

In contrast to 189, the phenolic acid 192 gave a high current when oxidised at 1.47V, and chromatographic purification of the initial product afforded the spirolactone 213 as a crystalline solid. Its structure was confirmed by spectroscopy and elemental analysis. The exceptional yield (40%) of 213 as compared to the yield from the anodic oxidation of phloretic acid 74 can be explained by the presence of the tetrahydronaphthalene skeleton which must direct the acid function towards the radical cation (Scheme 11).

The oxidation of the sulphonamido acid 200 at a potential of 1.79V afforded a high yield of a crude solid which exhibited i.r. peaks at 1770 (C=O) and 1550 cm^{-1} (C=N) and which was tentatively identified as the novel imine 215; the oxidation of 197 gave a good yield of an amorphous froth which was identified as the novel methanesulphonamido imine 216 by inspection of its i.r. absorbances at 1775 (C=O) and 1560 cm^{-1} (C=N). Hydrolysis of 215 on a grade II neutral alumina column[80] afforded the dione 213 contaminated with p-toluenesulphonamide, but similar hydrolysis of 216 gave the spirolactone 213 free of methanesulphonamide in an overall yield of 43%.

2.3.3 Other chemical oxidations

Peracetic acid[58] and N-bromosuccinimide[52,53,59] have been used successfully in the oxidation of phloretic acid 74 to the spirodienones 217 and 218. Similar reagents were therefore employed in an attempt to oxidise the analogous tetrahydronaphthalene acid 192.

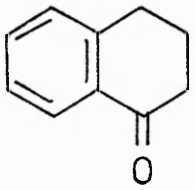
Stirring the acid 192 in a solution of lead tetra-acetate in acetic acid for 2h provided a crude product in 32% yield which had similar spectroscopic properties to the spirolactone 213. However all attempts to recrystallise the sample failed to provide a purer product.

N-Bromosuccinimide in methanol[59] did not react with acid 192 but the treatment of the latter with N-bromosuccinimide in an acetate buffer at pH 4.6 in accordance with Witkop's method[53] afforded an excellent yield of a fawn crystalline solid. The elemental analysis, n.m.r. spectrum, i.r. peaks at 1775 and 1680 cm^{-1}, and the presence in the mass spectrum of a triplet at m/e 392, 394 and 396 ($M-CO_2$) all indicated that the product was the expected novel dibromo-cyclohexadienone spirolactone 219.

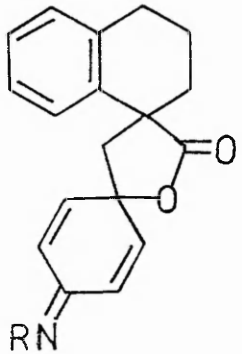
The oxidation of the biphenyl ester 220 with lead tetra-acetate surprisingly afforded the isobenzofuran lactone 221 (Chapter 4), but the application of this method to the crude sulphonamido ester 198 failed to produce a pure sample of the imine 215.

2.4 The attempted preparation of naphthalene-substituted cyclohexadienones containing a six-membered spirolactone ring.

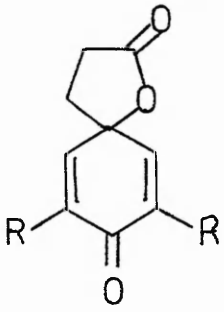
Previous work in the Department has shown that anodic oxidation of 4-(p-hydroxyphenyl)- or 4-(p-tosylamidophenyl)butanoic acids gives little, if any, of the corresponding δ-spirolactones.[60]



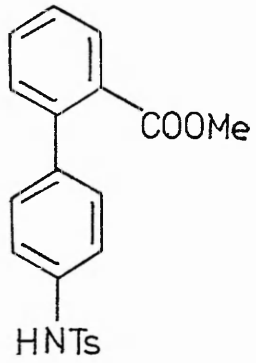
214



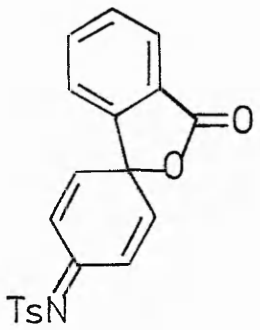
215 R=Ts
216 R=Ms



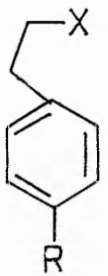
217 R=H
218 R=Br



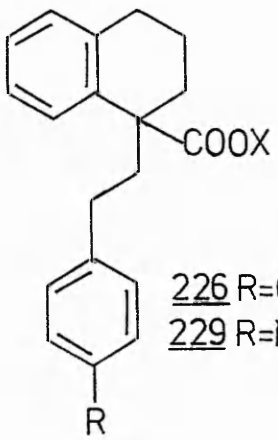
220



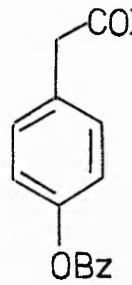
221



222 R=OBz; X=Cl
223 R=NO_2; X=Br
225 R=OBz; X=OH
227 R=OBz; X=I
228 R=OBz; X=OTs



226 R=OBz; X=Me
229 R=NO_2; X=Bu^t



224 X=OH
230 X=Cl

This result is in accord with studies which show that Ar 1-5 cyclisations proceed more readily than do Ar 1-6 reactions.[96] The high yield of spirolactone obtained on the oxidation of acid 192, compared with the lactone yield from the oxidation of phloretic acid 74 (Chapter 1) suggested that the naphthalene system has a beneficial effect on oxidative cyclisation processes. If so, oxidation of homologues of the 1-benzyltetrahydronaphthoic acids might give access to the elusive spiro-δ-lactones. These oxidations would also be useful as model studies on the preparation of spirolactones derived from phenethylisoquinolines.

Various strategies are available for preparing the necessary extended naphthoic acid precursors. The most obvious is to alkylate either of the two esters 181 or 201 with an appropriate 2-phenethyl halide. The first requirement was to obtain the necessary electrophiles viz. 2-(p-benzyloxyphenyl) ethyl chloride 222 and 2-(p-nitrophenyl) ethyl bromide 223. Benzylation of p-hydroxyphenylacetic acid afforded the benzyloxy acid 224 in excellent yield and reduction of 224 with borane methyl sulphide gave a quantitative yield of the phenylethyl alcohol 225. The thionyl chloride treatment of 225 afforded the crystalline alkyl chloride 222. A sample of 223 was available from an earlier investigation.[60] However, the reaction of the anion 182 with 222 under conditions previously described (p.47) failed to produce the desired ester 226 and only starting materials were recovered. Even the use of the alkyl iodide 227 (prepared from 222 by treatment with sodium iodide in acetone) failed to afford 226. Similarly the reaction of the bromide 223 with 201 provided solely starting materials. Since it has already been demonstrated that 182 and the anion of 201 are efficient nucleophiles, the electrophilicities of 222, 223 and 227 are obviously insufficient to allow a reaction to occur.

One possible remedy appeared to be the use of the sulphonate ester 228; but all attempts to convert the alcohol 225 to the sulphonate ester 228 were unsuccessful and this approach to 226 and 229 was abandoned.

A related strategy involved using the acetyl chloride 230 as an electrophile. (The reaction of 230 with two moles of the anion 182 to form a carbinol was deemed unlikely on steric grounds). Treatment of 182 with the acid chloride 230 afforded a crystalline product which was identified by spectroscopy and elemental analysis as the desired novel keto ester 231. Treatment of 231 with sodium borohydride failed to reduce the keto function, and an attempt to prepare a thioketal using ethane-1,2-diol in the presence of boron trifluoride etherate was unsuccessful.

The other possible route to six-membered spirolactones from 193 involved lengthening the carboxylic acid 193 to the acetic acid 232. Two methods seemed useful for this transformation:

(a) The reaction of the benzyloxy acid chloride 233 (prepared by treating 193 with thionyl chloride) with diazomethane afforded an excellent yield of the novel diazoketone 234. However no rearrangement product 232 could be detected when 234 was treated with either silver (I) oxide[97] or copper (I) iodide.[98]

(b) The reduction of the acid 193 to the novel carbinol 235 was accomplished efficiently by using borane-methyl sulphide complex or lithium aluminium hydride. The reaction of 235 with thionyl chloride afforded a good yield of a fawn gum which was identified as the alkyl chloride 236 by n.m.r. and i.r. spectroscopy. However, the nucleophilic displacement of the chloride by cyanide could not be achieved. The fact that the nitrile 237 could not be formed can be explained by the "neopentyl" environment of the chloride 236. It is well known[99] that such nucleophilic displacements

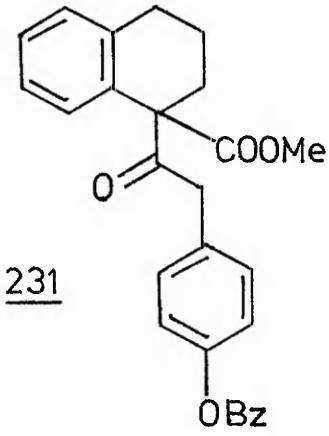
are difficult to effect.

Owing to the failure of the above four methods to produce a homologous acid of 193, no further attempt could be made to synthesise a six-membered cyclohexadienone spirolactone.

2.5 Miscellaneous reactions

The catalytic debenzylation of 235 afforded the novel, phenolic alcohol 238 in quantitative yield. Anodic oxidation of 238 afforded a mixture of the starting material and a compound which showed i.r. peaks at 1665 (C=O) and 1630 cm^{-1} (C=C), a molecular ion of m/e 266 in the mass spectrum and vinylic resonances at ca. δ 6.05 and 6.25. This compound was therefore identified as the novel cyclohexadienone 239, but could not be obtained free from starting material.

Cyclohexadienone mono-epoxide spirolactones are attacked by oxygen nucleophiles[4], a reaction which might be elaborated into a novel synthesis of bisbenzylisoquinolines (Chapter 1). Experimental details of the epoxidation have not yet been published, and preliminary reactions of 213 with hydrogen peroxide gave none of the desired epoxylactone 240.



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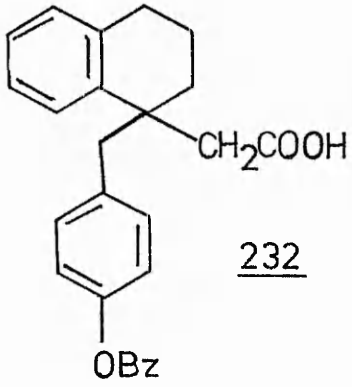

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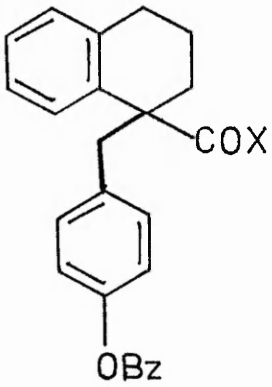
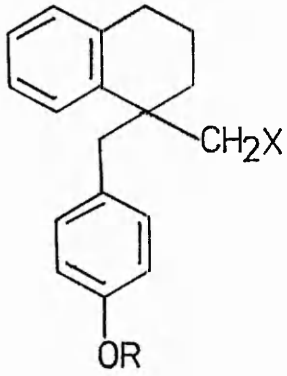
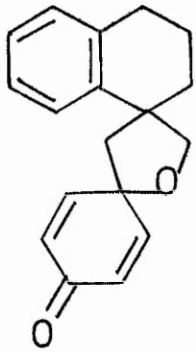


233 X=Cl
234 X=CHN_2



235 R=Bz;X=OH
236 R=Bz;X=Cl
237 R=Bz;X=CN
238 R=H; X=OH



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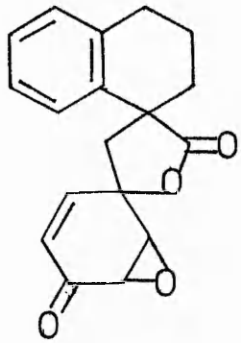

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CHAPTER THREE

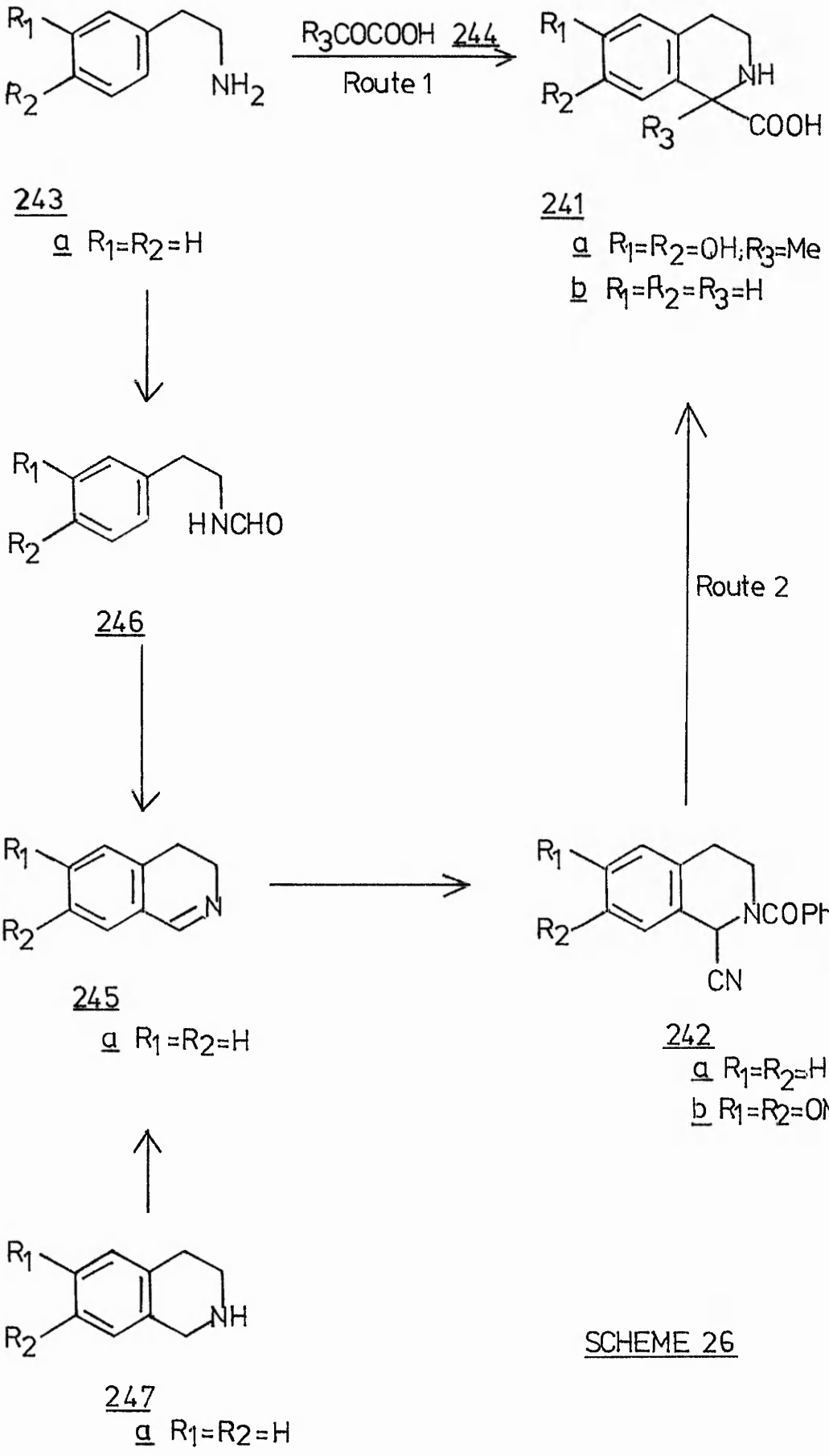
3.1 1,2,3,4-Tetrahydroisoquinoline-1-carboxylic Acids

In principle there are a number of routes available for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids 241. They may be obtained directly by the Pictet-Spengler reaction between a phenylethylamine 243 and a pyruvic acid 244 (Route 1, Scheme 26). Alternatively, hydrolysis of dihydro Reissert compounds 242, the synthesis of which requires a 3,4-dihydroisoquinoline, 245 leads to the desired acids (Route 2, Scheme 26). The 3,4-dihydroisoquinolines can be formed from the cyclodehydration of N-acyl-β-phenylethylamines 246 (the Bischler-Napieralski reaction) or by the partial oxidation of 1,2,3,4-tetrahydroisoquinolines 247.

3.1.1. The Pictet-Spengler Reaction

Although the preparation of 1,2,3,4-tetrahydroisoquinolines by the Pictet-Spengler reaction has been adequately reviewed,[6] the formation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids is mentioned only briefly.

The Pictet-Spengler reaction is a special example of a Mannich reaction where a β-arylethylamine is condensed with a carbonyl compound to form a tetrahydroisoquinoline. In 1911 Pictet and Spengler[100] reacted β-phenylethylamine 243a with formaldehyde dimethyl-acetal in concentrated hydrochloric acid to form the parent 1,2,3,4-tetrahydroisoquinoline 247a. Ring closure occurs because the species 248 has sufficient electrophilicity to undergo intramolecular substitution. Using acetaldehyde as the carbonyl component the intermediate 249 has lost some of its electrophilicity owing to the


R1
R2
NH2
R3COCOOH 244
Route 1
NH
COOH
R3
243
a R1=R2=H
241
a R1=R2=OH; R3=Me
b R1=R2=R3=H
HNCHO
246
Route 2
N
245
a R1=R2=H
NCOPh
CN
242
a R1=R2=H
b R1=R2=OMe
247
a R1=R2=H

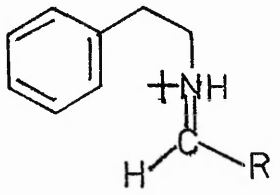
SCHEME 26

+I and hyperconjugative effects of the methyl group. This loss of electrophilicity is sufficient to prevent electrophilic substitution and only the Schiff base 249 is formed. However, if the aromatic ring is activated in the positions ortho or para to cyclisation by a hydroxyl function, isoquinolines will indeed be formed with aldehydes (or with α-keto acids).

In the case of an α-keto acid, the carboxylic group has an electron withdrawing effect and the reactivity of the ketone carbonyl is similar to that of an aldehyde, making cyclisation feasible if the arene is activated.

Hahn[3,101] has claimed that, for reaction with a β-arylethylamine, the α-keto acid must be enolisable. He cites phenylglyoxylic acid 250 and triphenylpyruvic acid 251, neither of which contain a carbonyl carbon with an α-hydrogen atom, as compounds which do not undergo the Pictet-Spengler reaction. In the former case the electron donating effect of the phenyl group may be the difficulty; in the latter steric hindrance is likely to be the problem. More puzzling is the claim[3] that trimethylpyruvic acid 252 will not form a tetrahydroisoquinoline with a β-arylethylamine. A feasible mechanism can be postulated for nucleophilic attack on the keto carbon (Scheme 27); but no similar mechanism is suitable for nucleophilic attack on an enol.

In 1968, Kametani and co-workers[102] published the first synthesis of 1,2,3,4-tetrahydroisoquinolines formed from a phenethylamine and various simple ketones. They claimed that heating 1-(3-hydroxyphenyl)-2-aminoethanol 253 under reflux in acetone (in the absence of an acidic catalyst) afforded 4,6-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline 254 in 79% yield. D'Amico et al. had previously claimed[103] that the product was 5-(3-hydroxyphenyl)-2,2-dimethyloxazolidine 255. Considerably lower yields



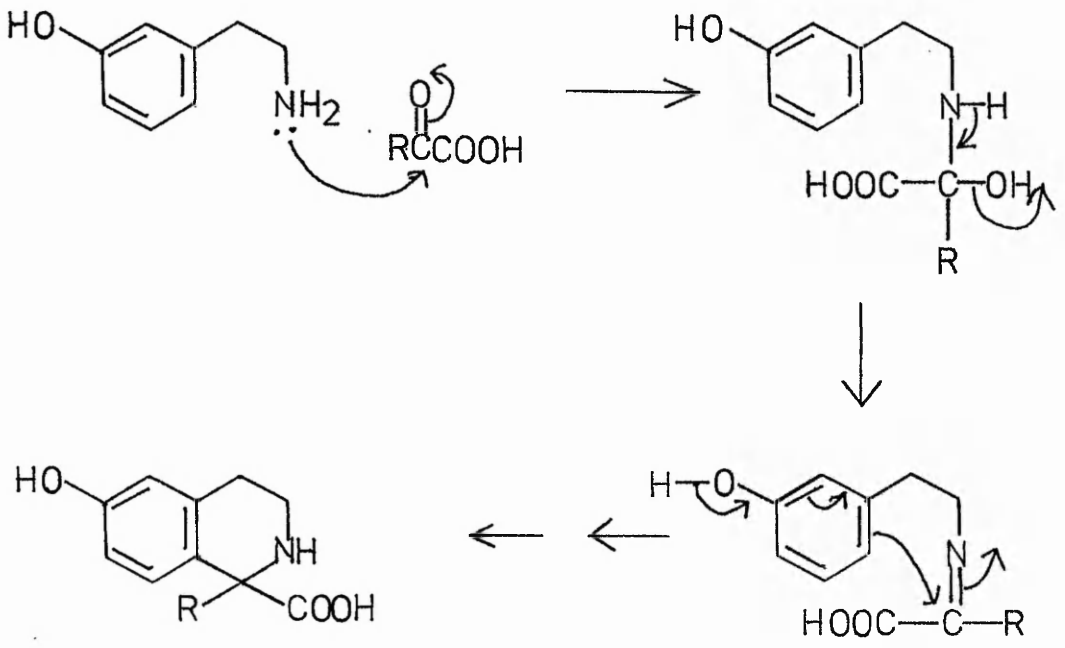
248 R = H
249 R = Me

PhCOCOOH

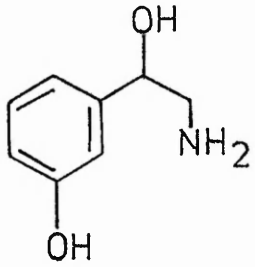
250

$(R)_3CCOCOOH$

251 R = Ph
252 R = Me



SCHEME 27



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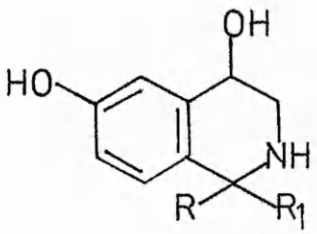


254 R=R1=Me
256 R=Me;R1=Ph
257 R=Me;R1=Et

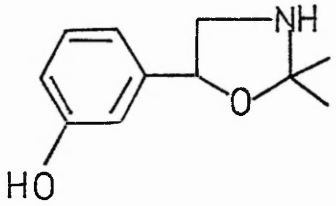
were reported for the isoquinolines obtained from cyclohexanone and acetophenone. Only one isomer of 4,6-dihydroxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline 256 was obtained, from the latter ketone whilst ethyl methyl ketone gave a separable mixture of isomers 257 in a combined yield of 47%. Acetone has been condensed with dopamine[104] 258 and 3-hydroxy-β-phenylethylamine[105] 259 to form the corresponding 1,2,3,4-tetrahydroisoquinolines 260 and 261.

Extraction of the yam with acetone has afforded[106] 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline 260. Various possibilities arise here. 260 could be an artifact produced from dopamine in the yam and the acetone extracting mixture; or it could indeed be a natural product from the in vivo condensation of dopamine and acetone. Other possible biosyntheses of 260 may involve the coupling of dopamine with pyruvic acid or pyruvaldehyde, followed by a biochemical reduction of the resulting acidic or aldehydic function (Section 1.2).

3.1.2 The Bischler-Napieralski Cyclisation

The classical Bischler-Napieralski reaction consists of the cyclodehydration of β-phenylethylamides to 3,4-dihydroisoquinolines by heating to high temperatures with phosphorus pentoxide, phosphorus oxychloride or zinc chloride.[107] (Route 2, Scheme 26). The yields by this method have been improved by the use of milder reaction conditions.

The early mechanistic idea[108] concerning the course of the Bischler-Napieralski reaction involved the protonation of the amide oxygen atom by a trace of hydrogen chloride followed by cyclisation to a 1-hydroxy-tetrahydroisoquinoline and ultimate



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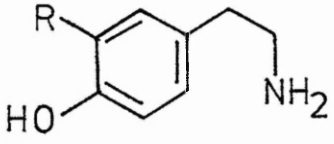
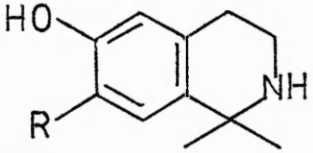
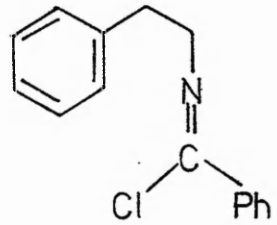


258 R=OH
259 R=H



260 R=OH
261 R=H



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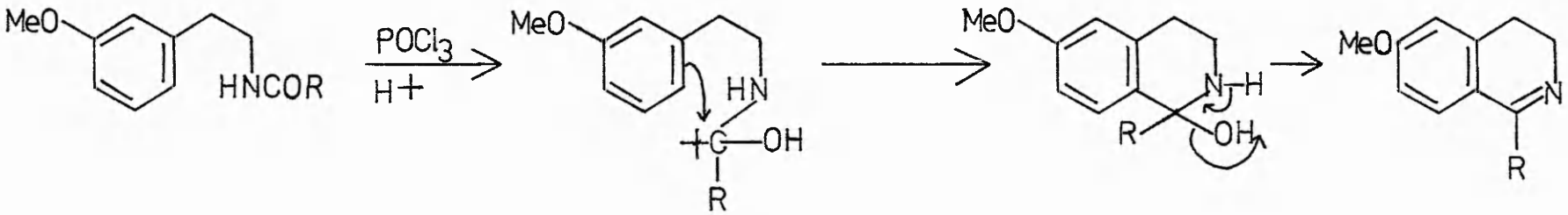
SCHEME 28

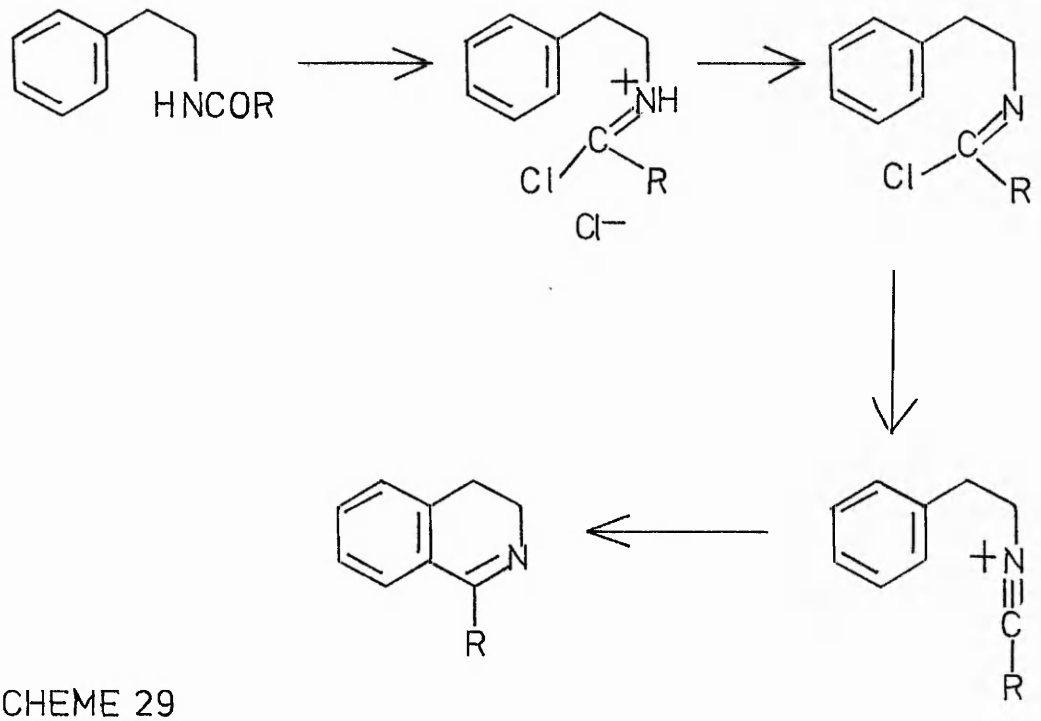


dehydration to a 3,4-dihydroisoquinoline (Scheme 28). A similar mechanism involves the formation of a bond between the carbonyl oxygen atom and phosphorus (from eg. phosphorus pentachloride) followed by the loss of a chlorophosphorous acid.

Recently, however, it has been proved[109] that a variety of β-phenylethylamides yield imidoyl chlorides (eg. 262) or their hydrohalides on treatment under milder conditions with various reagents (phosphorus pentachloride, phosphorus oxychloride, thionyl chloride and carbonyl bromide). These imidoyl chlorides cyclise to yield 3,4-dihydroisoquinolines. Thus it is clear that dehydration or the loss of the carbonyl oxygen atom must precede ring closure. (Unless we are looking at different reactions occurring in the different conditions). The rate of cyclisation can be enhanced by the addition of a Lewis acid catalyst, and this can be explained by the formation of a nitrilium salt (Scheme 29). Indeed in the example of N-(β-phenylethyl)benzimidoyl chloride 262 cyclisation does not occur in the absence of a Lewis acid catalyst.

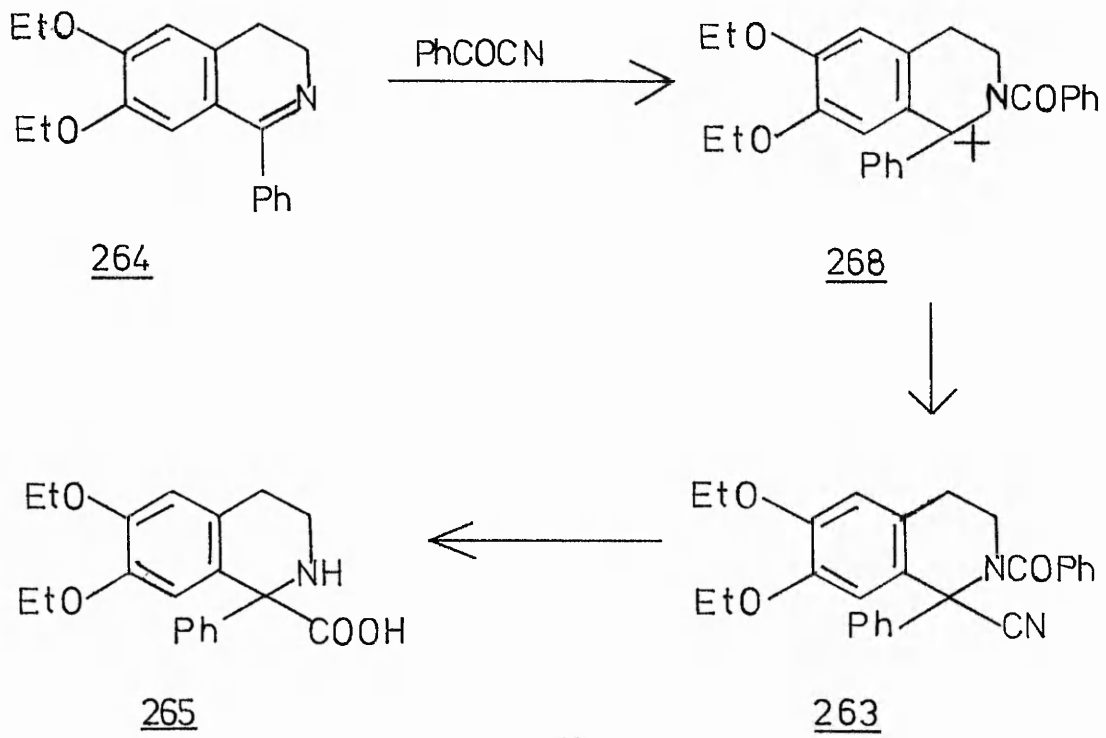
3.1.3 Oxidation of tetrahydroisoquinolines

Another method available for synthesising 3,4-dihydroisoquinolines involves the oxidation of a pre-formed 1,2,3,4-tetrahydroisoquinoline ring, but there are few reports published concerning this conversion.[110,111] A recent method[112] consists of the N-chlorination of a tetrahydroisoquinoline with tert-butyl hypochlorite followed by oxidation with potassium superoxide. For example, the parent 1,2,3,4-tetrahydroisoquinoline 247a can be converted to 3,4-dihydroisoquinoline 245a in 95% yield by this method. Although not of direct relevance to this project, it is of interest to note that reaction of these 3,4-dihydroisoquinolines with nucleophiles yielded 1-substituted and 1,1-disubstituted tetra-



SCHEME 29

SCHEME 30



264 268 265 263

hydroisoquinolines[112]).

3.1.4 Reissert compounds

Although the preparation and alkylation of Reissert compounds is well-documented,[113] there are comparatively few examples of the synthesis and alkylation of 3,4-dihydro Reissert compounds.

The parent dihydro Reissert compound 242a has been prepared,[114] but with difficulty and only in moderate yield, and no alkylation of this compound has been described. Similar compounds containing functions at the C-6 and C-7 positions have been synthesised from the appropriate 3,4-dihydroisoquinolines.[18,20,115-118]

The acidic proton at C-1 of a dihydro Reissert compound may be removed by the use of sodium hydride in DMF,[18,20,116] by LDA and by potassium hydroxide in benzene in the presence of phase transfer catalysts such as dicyclohexyl-18-crown-6 or cetyltrimethyl ammonium bromide.[118] The subsequent insertion of an electrophile generally gives good to excellent yields of 1-alkyl substituted tetrahydroisoquinolines. Hydrolysis of these latter compounds normally yields 1-alkyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids 241. However, in some instances[20,119,120] no amino acid is obtained. In the treatment of dihydro Reissert compounds with hydrochloric acid in acetic acid the cyanide function is hydrolysed in preference to the amide group.[60]

There is one claim that a dihydro Reissert compound 263 can be obtained by the addition of benzoyl cyanide to 6,7-diethoxy-1-phenyl-3,4-dihydroisoquinoline 264. Hydrolysis with potassium hydroxide in amyl alcohol afforded the carboxylic acid 265 (Scheme 30). This preparation by a "reverse-Reissert" approach is perhaps surprising on account of the failure of Popp[113b] to synthesise

a Reissert compound from 1-methylisoquinoline. (He claims that this is a steric effect as neither 2- nor 8-substituted quinolines form Reissert compounds[122]). Similarly the dimethoxy compound 266 could only be prepared[119] in poor yield by a "reverse-Reissert" route. The major product was identified as the amide 267, presumably formed from the hydrolysis of the acylated Schiff base. Nevertheless, the success of forming 263 may be attributed to mesomeric stabilisation of the intermediate 268 by the phenyl group, allowing a cyanide anion to be inserted at C-1.

3.2 Approaches to the synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.

The previous section (3.1) has described the few available methods for the synthesis of 1-substituted-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids. All of these require the presence of an electron donating substituent on the phenyl ring of a β-phenylethylamine to effect efficient cyclisation to an isoquinoline, except when a pre-formed isoquinoline unit is available. In the latter case the only possible route to isoquinoline acids bearing no +M substituents on the A ring involves the use of a "reverse-Reissert" approach.

Only a few 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids or derivatives possessing a non-electron rich A ring have so far been prepared.[123-128] The parent acid 243b has been synthesised by the hydrolysis of the Reissert compound 269 followed by catalytic hydrogenation of the aromatic acid 270.[123] In view of the successful use of tetrahydro-1-naphthoic acid 175 in synthesising 1-benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids the acid 241b appeared to be an attractive starting material for the preparation

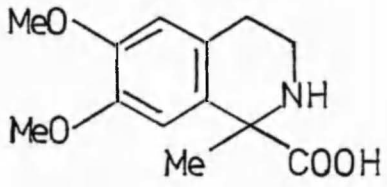
of 1-substituted-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids. However, the reported reduction of 270 involved prolonged hydrogenation and afforded 241b in only moderate yield. Moreover, when the hydrolysis of 269 was attempted at Trent Polytechnic using hydrobromic acid, only the acid hydrobromide 271 could be obtained. Basification of 271 with ammonia failed to afford 270. Treatment of 269 with hydrochloric acid yielded the unwanted novel amide hydrochloride 272.

Another possible approach[114a] involved an attempt to prepare the dihydro Reissert compound 242a. Treatment of 1,2,3,4-tetrahydroisoquinoline 247a with sodium hypochlorite afforded 3,4-dihydroisoquinoline 245a in good yield.[110] However, all efforts to form 242a from 245a resulted in the formation of the benzoyl cyanide dimer 273.[129] On account of these failures, no further attempt was made to prepare 241b and a different strategy was employed in the search for an efficient synthesis of the desired isoquinoline acids.

3.2.1. Metallation of isoquinolines

Protons which are α to electron withdrawing atoms or groups are acidic and are susceptible to removal under basic conditions. This concept was employed successfully in the alkylation of 1,2,3,4-tetrahydronaphthalene-1-carboxylates in the position α to the ester function. (Chapter 2).

The proton on C-1 of a tetrahydroisoquinoline is benzylic, but its acidity is decreased by the effect of the lone pair of electrons on the nitrogen atom. Acylation of the nitrogen atom neutralises the effect of the lone pair of electrons, and also allows the possibility of stabilisation of carbanions by the



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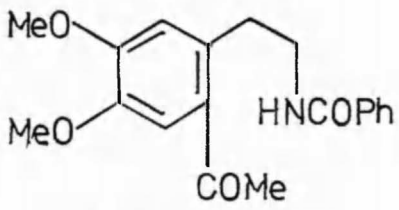

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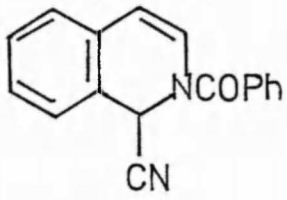

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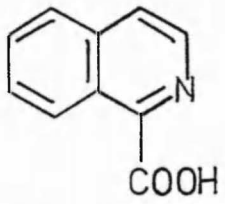

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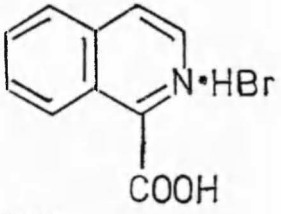

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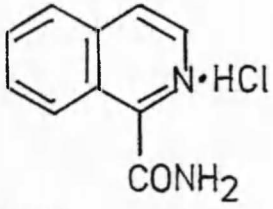

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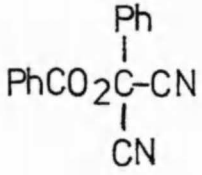

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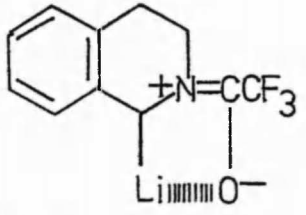

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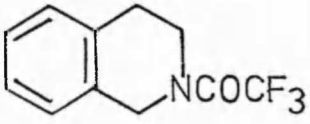

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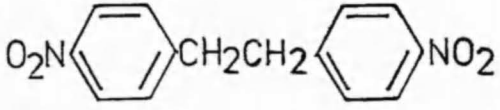

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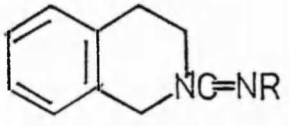


277

formation of a cyclic complex (eg. 274). Similar complexes are found in the ortho- lithiation of a number of benzenoid compounds, a field of growing synthetic importance which has been the subject of two recent excellent reviews.[130,131]

Accordingly, 2-trifluoroacetyl -1,2,3,4-tetrahydroisoquinoline 275 was prepared.[132] However, all attempts at alkylating 275 with various equivalents of n-butyl-lithium, lithium di-isopropyl-amide, methyl-lithium, n-butyl-lithium/TMEDA and p-nitrobenzyl bromide or ethyl chloroformate failed to produce the desired alkylated products. On addition of p-nitrobenzyl bromide to the supposed lithio compound 274 a deep purple colour appeared which may be attributed to a species formed by the abstraction of a benzylic proton from the bromide. The mass spectrum of the reaction products indicated the presence of the p-nitrobenzyl bromide "dimer" 276. Another problem was the instability of the amide 275. Distillation of 275 afforded a homogeneous clear oil which, after standing for 24h, appeared (by tlc) to decompose.

During the attempts to alkylate 275 two papers were published concerning the lithiation of N-substituted -1,2,3,4-tetrahydro-isoquinolines. One[128] described the preparation and alkylation of the formamidine 277. Treatment of 277 with s-butyl-lithium and an electrophile afforded good yields of 1-substituted 1,2,3,4-tetrahydroisoquinolines. Even though an acidic function could be inserted at C-1 (by using ethyl chloroformate as an electrophile), no method was available to remove the formamidine group which would not adversely affect an acid or ester group. As problems with the nitrogen atom of the formamidine group could be envisaged at the oxidation stage the use of 277 was not considered further.

The other[133] described the lithiation and alkylation of N-pivaloyl-1,2,3,4-tetrahydroisoquinoline 278, which appeared the

more attractive compound for our needs. The pivaloyl group would offer little hindrance during the oxidation of the target acids and could be able to coordinate with the lithium atom (cf. 274).

3.3 The preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.

The pivalamide 278 was prepared according to the published procedure[133] in excellent yield. The literature method for the lithiation of 278 involves the use of the highly pyrophoric base tert-butyl-lithium in the presence of TMEDA. These hazardous reaction conditions are undesirable, but fortunately it was discovered that by using n-butyl-lithium or methyl-lithium the red lithio intermediate 279 could be formed. Unfortunately, the only identified product from the reaction of 279 with p-nitrobenzyl bromide was the "dimer" 276. However, the addition of solid carbon dioxide to 279 yielded a fawn gum which upon treatment with diazomethane afforded the crystalline novel ester 280 in an overall yield of 47%. This yield was subsequently improved to 66% by using lithium di-isopropylamide as the lithiating agent. (280 could also be prepared by the successive reaction of 279 with ethyl chloroformate, ethanolic potassium hydroxide and diazomethane).

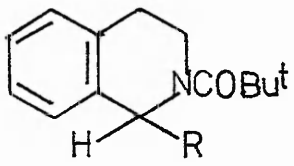
This ester 280 is an isostere of the naphthoic ester 181 and was expected to have a similar reactivity to 181 toward electrophiles. Yet, in practice, the alkylation of 280 was not so easy to accomplish. Only starting materials were returned when 280 was treated with the following range of reagents and electrophiles : methyl-lithium, LDA or n-butyl-lithium/TMEDA with p-benzyloxybenzyl chloride; LDA with p-nitrobenzyl bromide; LDA with 3,4,5, trimethoxybenzyl chloride; and LDA, potassium carbonate

/acetone; potassium carbonate/DMF/tetrabutylammonium hydrogensulphate or sodium hydroxide/benzene/triethylbenzylammonium bromide with methyl iodide. However, the formation of an anion was indicated by the appearance of a yellow colour on addition of 280 to sodium hydride in DMF. The introduction of methyl iodide or ethyl iodide to the anion of 280 afforded the novel 1-substituted esters 281 and 282 respectively in good yields. Yet when 3,4,5-trimethoxybenzyl chloride was used as an electrophile no coupled product was obtained, and in the case of p-nitrobenzyl bromide only a 20% yield of the novel nitro ester 283 was produced. The high yields of the esters 281 and 282 suggest that the anion of 280 has sufficient nucleophilicity to react when the electrophilic reagent contains a good leaving group. To verify this, the three benzyl iodides 284-6 were prepared by treating the corresponding chlorides with sodium iodide in acetone.[134] On reaction of the ester 280/sodium hydride/DMF mixture with the iodide 284 the yield of 283 increased to 40%, and the halides 285 and 286 afforded, in reasonable yield, the novel benzylated isoquinolines 287 and 288 respectively.

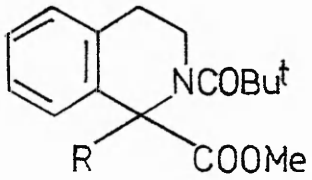
At this stage it appeared that a simple saponification would be sufficient to produce the desired acids. Heating a small quantity of 288 with potassium hydroxide in methanol under reflux for several hours afforded the desired novel acid 289. Unfortunately, this result was not reproducible - other attempted saponifications returned solely starting materials. Similarly no de-esterification of the phenolic ester 290 (prepared from the hydrogenolytic debenzylation of 287) could be achieved under a variety of conditions.

These failures necessitated the employment of other synthetic approaches to the desired acids. Two strategies were considered.

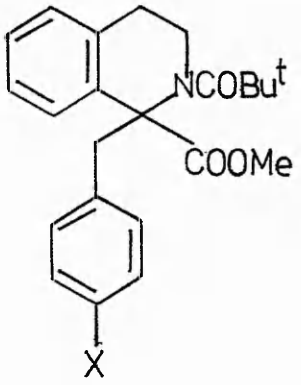
1) The insertion of the acidic function after the mono-alkylation of the 1-position of 278.



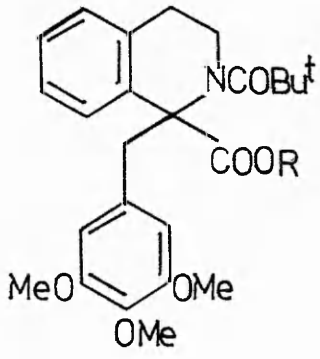
278 R=H
279 R=Li
280 R=COOMe



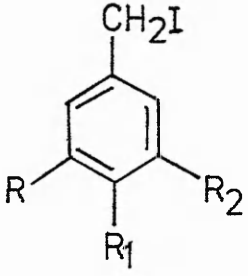
281 R=Me
282 R=Et



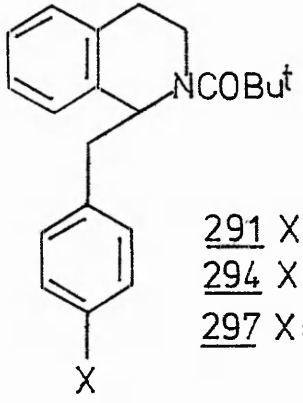
283 X=NO_2
287 X=OBz
290 X=OH



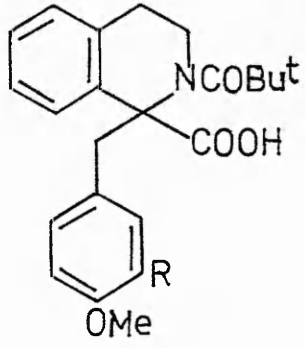
288 R=Me
289 R=H



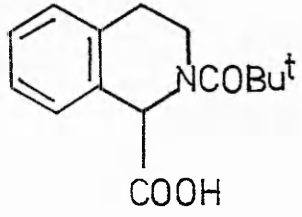
284 R=R_2=H; R_1=NO_2
285 R=R_2=H; R_1=OBz
286 R=R_1=R_2=OMe



291 X=OBz
294 X=OMe
297 X=OH



295 R=OMe
296 R=H



298

2) The use of an ester function which could be removed more readily than a methyl ester.

1) The treatment of 278 with lithium di-isopropylamide produced the characteristic crimson colour of its anion 279. Treatment of this anion with p-benzyloxybenzyl chloride, 3,4,5-trimethoxybenzyl chloride, 3,4-dimethoxybenzyl chloride and 4-methoxybenzyl chloride afforded the novel amides 291-4 respectively, in virtually quantitative yields. The addition of 292-4 to lithium di-isopropyl-amide again afforded red anions which, on addition of solid carbon dioxide, produced the acid 289 and the novel carboxylic acids 295 and 296, albeit in moderate yields. However, no acid was obtained on treating 291 with carbon dioxide in the presence of methyl-lithium, lithium di-isopropylamide, or n-butyl-lithium and TMEDA. Only starting materials were returned when 291 was treated with lithium di-isopropylamide- methyl iodide, or sodium hydride - ethyl chloroformate, or lithium di-isopropylamide - t-butyl bromoacetate. This latter reagent was expected to form an isoquinoline-1-acetic acid which, on oxidation, would hopefully form a six-membered spirolactone.

Catalytic hydrogenation of 291 afforded the novel phenol 297, but only starting material was recovered when carbonation of 297 was attempted. So, although the desired methoxylated acids 289, 295, and 296 had been prepared neither the p-hydroxybenzyl nor the p-nitrogen-substituted benzyl acids could be synthesised by the above methods.

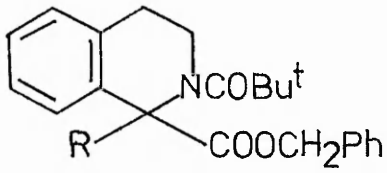
2) After the success in preparing the naphthoic acids 197 and 200 by the use of a t-butyl ester, the same philosophy appeared attractive in the synthesis of the hitherto elusive isoquinoline acids. However, no ester was obtained when the acid 298 was treated

with t-butanol and oxalyl chloride[95] or t-butanol and p-toluene-sulphonyl chloride.[135] This lack of reaction can be perhaps explained by steric hindrance.

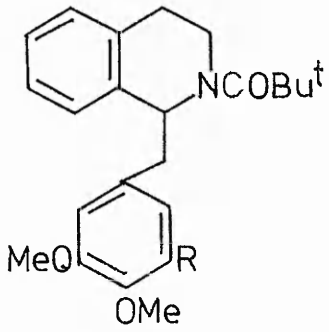
Another possible intermediate would be a benzyl ester. Treatment of 278 with lithium di-isopropylamide and excess benzyl chloroformate produced a mixture of substances, including the starting amide 278; no separation of the products was attempted. Heating the acid 298 under reflux in acetone containing benzyl chloride and potassium carbonate afforded the crystalline novel benzyl ester 299 in reasonable yield. The addition of sodium hydride and methyl iodide to 299 afforded the novel alkylated ester 300 in excellent yield, whilst reaction of 299 with p-benzyl-oxybenzyl iodide 285 produced the novel ester 301 in good yield, albeit as a crude gum. The bisbenzylated isoquinoline 301 gave the novel phenolic acid 302 in good yield on hydrogenolysis. Alkylation of 299 with p-nitrobenzyl iodide 284 afforded the ester 303 as a crude red gum which was converted to the amino-acid 304 upon hydrogenation. Tosylation by standard methods afforded the sulphonamido acid 305 in good yield. Although compounds 303-5 could not be crystallised for analysis, their spectral characteristics indicated that they were the designated compounds. Similarly the isoquinolines 306 and 307 could only be prepared as crude products whose spectral properties were satisfactory. However, as 307 could not be de-esterified, these products have little importance in the general strategy.

3.4 The oxidation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.

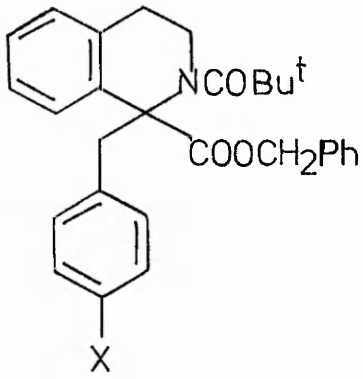
Various attempts[14,18-20] have been made to oxidise isoquinoline-



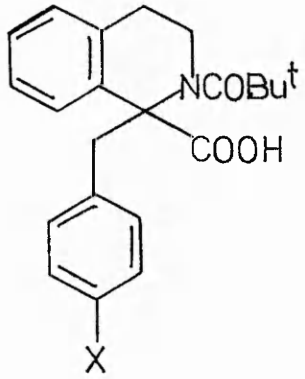
299 R=H
300 R=Me



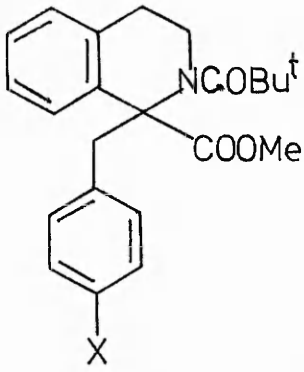
292 R=OMe
293 R=H



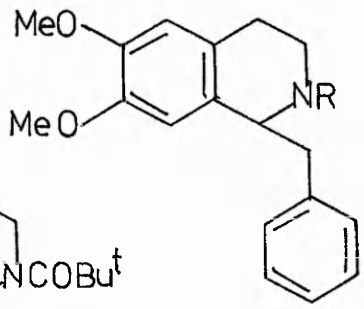
301 X=OBz
303 X=NO$_2$



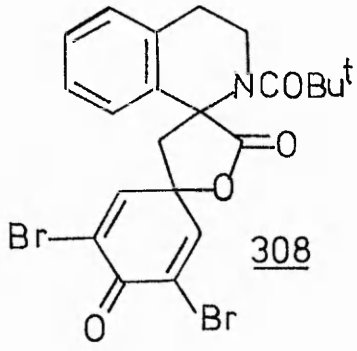
302 X=OH
304 X=NH$_2$
305 X=NHTs



306 X=NH$_2$
307 X=NHTs



309 R=H
310 R=Me



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1-carboxylic acids. Most of these studies have involved the elucidation of the mechanism of their decarboxylation whilst others have tried to apply this oxidation to the formation of intramolecularly coupled 1-benzylisoquinolines.[20,60,119] However, the only previous attempt to prepare a cyclohexadienespirolactone by the oxidation of an isoquinoline acid was unsuccessful[60] (Section 2.1).

After the success of synthesising spirolactones from naphthoic acids (Chapter 2) it seemed that the oxidation of the acids 289, 295, 296, 302 and 305 would readily yield the desired isoquinoline spirolactones. In practice, the story was not so simple.

The neutral product from the thallium trifluoroacetate oxidation of 289 showed no i.r. peaks above 1620 cm^{-1} indicating that no lactone had been formed. The two other methoxylated acids 295 and 296 were not treated with thallium trifluoroacetate as they were now not expected to form spirolactones after the failure to oxidise 289.

The anodic oxidation of the crystalline methoxy acids 289, 295, and 296 yielded dark oils. Only the product from 289 indicated the possible presence of a lactone with an i.r. peak at 1780 cm^{-1}, but mass spectral data did not show either a parent ion or an M-CO_2 peak. Disappointingly neither the phenolic acid 302 nor the sulphonamido acid 305 produced any evidence of lactone formation on anodic oxidation.

The naphthalene dibromospirolactone 219 was readily formed on treating the acid 192 with N-bromosuccinimide (Section 2.3.3). Similarly the addition of N-bromosuccinimide to the isoquinoline acid 302 in an acetate buffer[53] afforded a dark crystalline solid which exhibited i.r. peaks at 1785, 1685 and 1620 cm^{-1}, M+1 and

$M+1-CO_2$ triplets after chemical ionisation mass spectroscopy, and M and $M-CO_2$ triplet ions after electron impact mass spectroscopy. These data indicated that the novel dibromospirolactone 308 had been formed. Similar treatment of the ether 296 with N-bromosuccinimide failed to afford 308.

3.5 The structure of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.

The 1,2,3,4-tetrahydroisoquinoline skeleton can be regarded as a benzene ring fused to a piperidine system. The carbon-carbon bond between C-4a and C-8a is, in essence, a double bond. Therefore the expected stable conformation for the piperidine moiety to adopt is the half-chair - similar to the stable conformation of cyclohexene.

The n.m.r. spectrum of 1-benzyl - 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 309 indicates[136] that ring C exists preferentially in a conformation which permits minimum steric interaction with ring A. In effect, ring C is orientated away from ring A. However, when an N-methyl group is present, as in 310, the n.m.r. spectrum shows the C-8 proton to be appreciably shifted upfield in comparison to the C-8 resonance in the secondary anime 309. Similarly the methoxyl group at C-7 is shifted upfield. The resonances for the C-5 proton and the C-6 methoxyl group are virtually unchanged. This upfield shift of the C-8 proton and the C-7 methoxyl group can be explained as resulting from shielding by ring C which now takes up a preferred conformation underneath ring A. In other words, the N-substituent forces the C ring under the A ring, and the said resonances are shifted upfield by the ring - current effect of the benzyl group.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids are extremely insoluble compounds (< 5 mg/ml, H_3O^+).[137] As a consequence their n.m.r. spectra have scarcely been studied. Bobbitt and Cheng[18] noted that the C-8 proton of 6,7-dioxygenated -1-benzyl acids appears at exceptionally low field, probably on account of the deshielding effect of the carboxyl group.

Another noticeable feature in the n.m.r. spectra of these acids is the appearance of an AB quartet at δ3.0-3.3; these resonances are due to the benzylic protons. One would expect a simple singlet for this resonance, but the appearance of an AB quartet indicates the benzyl residue experiences hindered rotation along the C-1 and C-α bond.

The novel acids 289, 295, 296, and 302 and esters 283, 288, and 290 have the added dimension of a pivaloyl group on the nitrogen. From Cava's work[136] one would expect the pivaloyl group to push the benzyl portion beneath ring A; whilst Bobbitt's theory[138] would suggest that the carboxyl function is near ring A. For the four aforementioned acids the author has noted that the ring A aromatic protons appear as two distinct signals in the n.m.r. spectrum. The resonances at δ7.5-7.8 (which integrate for 1 proton) are shifted downfield with respect to the three other ring A protons. So it appears that the N-pivaloyl group is not able to force the benzyl residue underneath ring A; and that the carboxyl group takes up a position near to the C-8 proton. Again, the benzylic protons appear as an AB quartet indicating restricted rotation.

In the n.m.r. spectrum of the acids 289 and 296 the carboxyl protons appear at δ7.92 and δ8.00 respectively; whilst in the i.r. spectrum the acid carbonyls absorb at 1740 cm^{-1}. The relative upfield position of the acid proton resonances and the relatively high frequency (ca.15 cm^{-1} more than expected for an aliphatic

acid) of the acid carbonyl absorptions imply that no inter or intramolecular hydrogen bonding is occurring. The acidic proton resonance of the dimethoxy acid 295 is not discernible, but the appearance of the acid carbonyl absorption at 1735 cm^{-1} again indicates an absence of hydrogen bonding. These data indicate that the acids 289, 295, and 296 exist as monomers.

In contrast, however, the acid carbonyl absorption of the phenolic acid 302 appears at 1700 cm^{-1} indicating that some hydrogen bonding is occurring. No conformation of 302 allows an intramolecular hydrogen bond between the phenolic and acidic functions - so the hydrogen bonding must be of an intermolecular nature. The acid carbonyl group of one molecule is therefore hydrogen bonded to either the acidic proton or phenolic proton of another molecule of 302.

CHAPTER FOUR

Discussion

This chapter contains several topics which were studied during this project, but which do not merit individual chapters.

4.1 Studies on the formation of some 7,8-dihydroprotoberberines

A previous investigation[20,119] in the Department required the synthesis of N-acyl derivatives of the tetrahydroisoquinoline-1-carboxylic acid 311. This compound proved to be unreactive under mild conditions toward a range of acylating agents, and, in an attempt to prepare a trifluoroacetamide, was heated under reflux in pyridine with trifluoroacetic anhydride (TFAA). From the dark reaction mixture was isolated in reasonable yield a yellow crystalline solid to which the unexpected 7,8-dihydroprotoberberine structure 312 was assigned on spectral and analytical evidence.[119] Since the reaction seemed to offer a convenient route to unusually substituted protoberberines, its application to a number of isoquinoline carboxylic acids with varying oxygenation patterns was studied.

4.1.1 Preparation of phenolic 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids by the Pictet-Spengler reaction

6-Hydroxy and 6,7-dihydroxy substituted isoquinoline-1-carboxylic acids can be prepared by the condensation of a β-phenylethylamine with a pyruvic acid (Section 3.1.1). Various methods are available for the synthesis of α-keto acids and their synthesis has been the subject of a recent review.[138] 3-Hydroxy-4-methoxy-β-phenylethylamine 313 was prepared from isovanillin (see below) while

3,4-dihydroxyphenylethylamine (dopamine) 314 is commercially available.

Pyruvic Acids

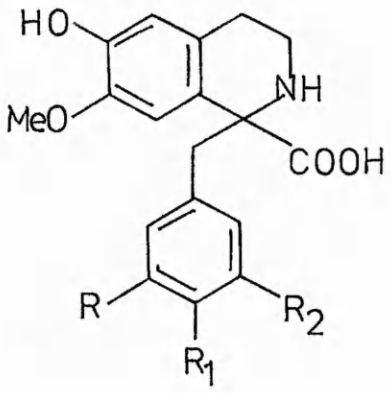
Of the methods available for the preparation of α-keto acids, the synthesis from a benzaldehyde via an azlactone seemed to be the most attractive. Heating 3,4,5-trimethoxybenzaldehyde with hippuric acid afforded the yellow crystalline azlactone 315 in good yield. Hydrolysis of 315 with aqueous sodium hydroxide and treatment of the resulting basic solution with sulphur dioxide precipitated out benzoic acid. Acidification and boiling of the residual solution afforded the crystalline α-keto acid 316. The dimethoxy analogue 317 was prepared by the same method. The acids 318, 319, and 320 were available from another investigation.[139]

The novel isoquinoline acid 321 and the known[139] acid 322 were prepared in moderate yield from the condensation of dopamine 314 and the pyruvic acids 317 and 318 respectively. The dihydroxy acids 323-5 were already available in the Department.

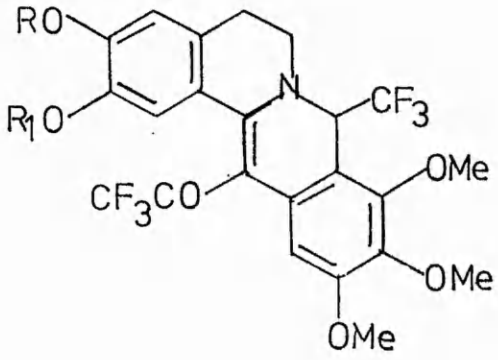
3-Hydroxy-4-methoxy-β-phenylethylamine 313

Isovanillin was benzylated with benzyl chloride to give benzyl-isovanillin 326 in good yield. The treatment of the aldehyde 326 with nitromethane in the presence of ammonium acetate afforded the nitrostyrene 327 which was smoothly converted to the amine 328 on reduction with lithium aluminium hydride. Debenzylation of 328 with ethanolic hydrochloric acid yielded the desired phenolic amine 313.

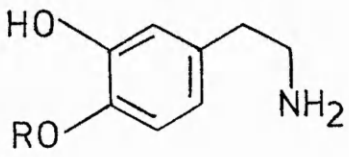
The condensation at pH6 of 313 with the pyruvic acids 317 and 319 yielded the novel isoquinoline acids 329 and 330 respectively, whilst its condensation with 316 and 320 afforded the known[18,119] acids 311 and 331.



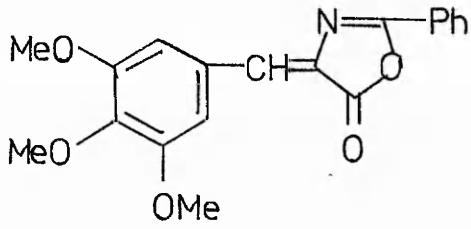
311 R=R1=R2=OMe
329 R=R1=OMe; R2=H
330 R, R1=OCH2O; R2=H
331 R=R2=H; R1=OMe



312 R=H; R1=Me
340 R=R1=H
341 R=R1=Me



313 R=Me
314 R=H



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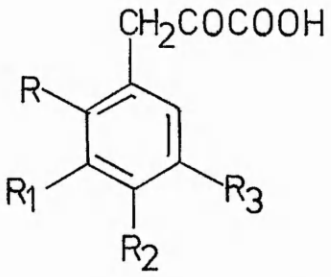
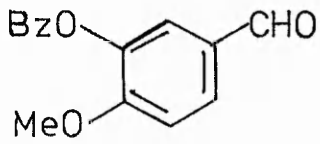


316 R=H; R1=R2=R3=OMe
317 R=R1=H; R2=R3=OMe
318 R=R2=R3=OMe; R1=H
319 R=R3=H; R1, R2=OCH2O
320 R=R1=R3=H; R2=OMe



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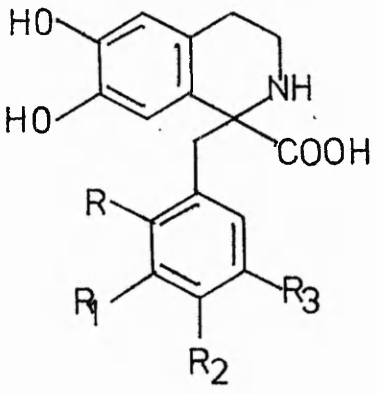
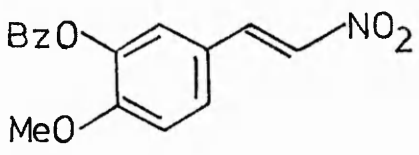


321 R=R1=H; R2=R3=OMe
322 R=R2=R3=OMe; R1=H
323 R=H; R1=R2=R3=OMe
324 R=R1=H; R2,R3=OCH2O
325 R=R1=R3=H; R2=OMe



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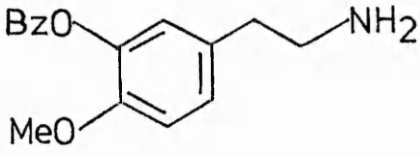

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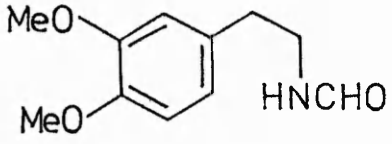

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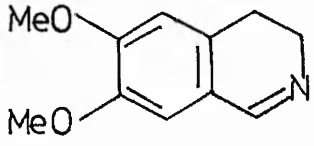

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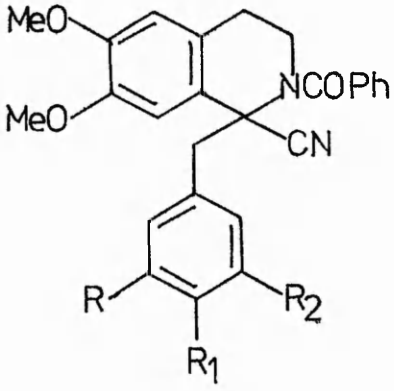
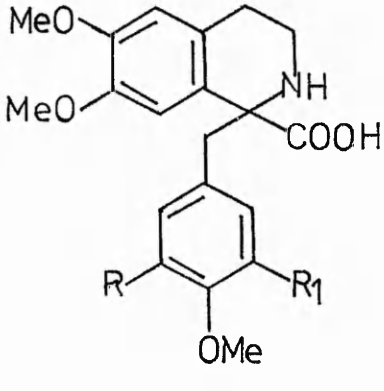


334 R=H; R1,R2=OCH2O
335 R=R1=R2=OMe
336 R=R1=OMe; R2=H
337 R=R2=H; R1=OMe



338 R=R1=OMe
339 R=OMe; R1=H

4.1.2 Preparation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids

The thermal condensation of 3,4-dimethoxy-β-phenylethylamine 46 with formic acid afforded the amide 332 which was cyclised to the dihydroisoquinoline 333 by heating under reflux in toluene containing phosphorus oxychloride. From the isoquinoline 333 by treatment with benzoyl chloride and potassium cyanide was obtained in reasonable yield the dihydro Reissert compound 242b. This yielded the known[116] amido-nitrile 334 and novel analogues 335-7 by reaction with either sodium hydride in DMF or with aqueous sodium hydroxide and cetyltrimethylammonium bromide in benzene followed by treatment of the resulting carbanion with the appropriate benzyl chlorides. Hydrolysis of the nitriles 335 and 336 with phosphoric acid[116] gave the new acids 338 and 339.

4.1.3 The reaction of 6,7-dihydroxy, 6-hydroxy-7-methoxy, and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids with trifluoroacetic anhydride

Heating the trimethoxy acid 323 in pyridine containing TFAA for 30 min afforded after chromatographic purification bright yellow crystals whose i.r. and n.m.r. spectra indicated that the novel dihydroxy-dihydroprotoberberine 340 had been formed (30% yield). The structure of 340 was confirmed by methylation to the known[119] pentamethoxy protoberberine 341. (Another product isolated from this reaction was identified by n.m.r., i.r., high resolution mass spectroscopy, and elemental analysis as the novel amido ester 342 which suggests that N-trifluoroacetylation is the first step in the formation of the protoberberine 340). Similar treatment of 321 with TFAA followed by methylation of the product with diazomethane

afforded a yellow crystalline solid whose u.v. and high resolution mass spectra indicated that the tetramethoxyprotoberberine 343a or 343b had been formed in 20% yield. The product from treating the methylenedioxybenzyl acid 324 with the above reagents yielded a yellow gum which could not be induced to crystallise. However, by comparing the extinction coefficient (ε) in the u.v. spectrum of the product at ca. 430 nm with that of 341, it could be deduced that the protoberberine 344a or 344b had been formed in a yield of approximately 10%. No protoberberine could be identified from heating either the monomethoxy acid 325 or the trimethoxy acid 322 with TFAA.

In the 6-hydroxy-7-methoxy series, the preparation of the pentamethoxy protoberberine 341 was repeated successfully from 311 in 50% isolated yield, as was the protoberberine 343a or 343b in moderate yield. Only a crude yellow gum could be obtained from the treatment of 330 with TFAA and diazomethane. The ε from its u.v. spectrum at ca. 430 nm showed that a small amount of protoberberine 344a or 344b had been formed. No protoberberine could be identified from the reaction of 331 with TFAA.

The isolation of pure protoberberines from the hydroxylated acids was hampered by the presence of impurities which gave extra carbonyl peaks in the i.r. spectra of the crude products. Initially these extra peaks were attributed to O-trifluoroacetylation of the phenolic products, but treatment with sodium bicarbonate failed to remove these unwanted peaks. In spite of this a cleaner reaction was thought probable if non-phenolic acids were used. Indeed the pentamethoxy acid 338 was smoothly converted to 341 in good isolated yield on treatment with TFAA in pyridine, but, inexplicably, no yellow chromophore was visible in the u.v. spectrum of the product obtained from heating 339 with TFAA.

4.1.4 Miscellaneous attempts to prepare 7,8-dihydroprotoberberines and analogous compounds

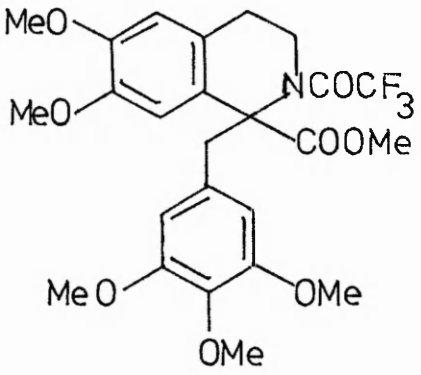
In order to test the speculation that N-trifluoracetylation is the first step in protoberberine formation from isoquinoline-1-carboxylic acids, the known[20] amido acid 345 and the novel compound 346 were prepared by treating the amino acids 311 and 330 with TFAA and triethylamine at room temperature. Heating 345 in pyridine containing TFAA followed by methylation produced the crystalline tetracycle 341 in good yield; but similar treatment of 346 produced only a small quantity of the protoberberine 344a or 344b (the presence of which was shown by a weak yellow chromophore in the u.v. spectrum of the reaction product).

Heating the acid 323 with TFAA in 2,6-lutidine or triethylamine in place of pyridine failed to afford a protoberberine. Similar results were obtained when 323 was heated with acetic anhydride and when the acetamide 347 (prepared by treating 311 with acetic anhydride in the presence of 4-N,N-dimethylaminopyridine[140]) was treated with TFAA in pyridine.

In conclusion, it appears that the formation of 7,8-dihydroprotoberberines from isoquinoline acids is restricted to electron rich 1-benzyl acids. Furthermore, the more electron-rich the benzyl ring, the greater the yield (and purity) of the protoberberine. An intermediate is an N-trifluoroacetyl isoquinoline-1-carboxylic acid.

4.1.5 3-Thienylpyruvic acid 348

One possible application of the TFAA-pyridine route to protoberines could involve the synthesis of a 1-thenyl-1,2,3,4-tetrahydro-



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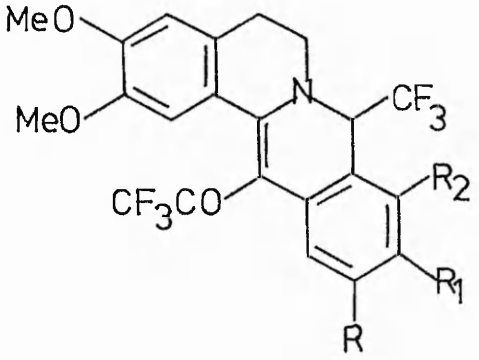
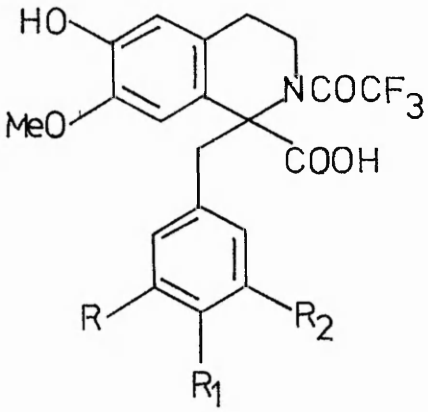


343a R=R1=OMe;R2=H

b R=H;R1=R2=OMe

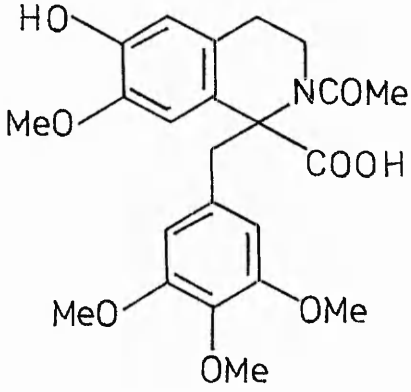
344a R,R1=OCH2O;R2=H

b R=H;R1,R2=OCH2O



345 R=R1=R2=OMe

346 R,R1=OCH2O;R2=H



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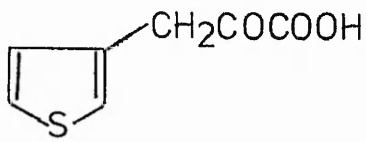

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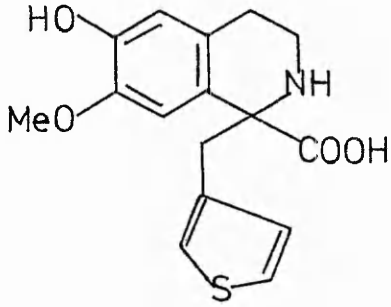


349

isoquinoline-1-carboxylic acid and its subsequent reaction to form a benzo[a]thieno[2,3-g]quinolizine; only one example of this ring system has so far been described.[141] To prepare the 1-thenyl acid 349 the single reported[142] synthesis of 3-thienylpyruvic acid was followed. Side-chain bromination of 3-methylthiophene with N-bromosuccinimide afforded 3-thienyl bromide 350 in good yield. Treatment of 350 with potassium cyanide in acetone gave the nitrile 351 which on condensation with diethyl oxalate under basic conditions yielded the cyano ester 352. Cagniant[142] claimed that heating 352 in the presence of hydrochloric acid afforded 3-thienylpyruvic acid 348. When this latter reaction was attempted, bright yellow crystals with the same m.p. as described previously[142] were obtained; however elemental analysis indicated the presence of nitrogen. High resolution mass spectroscopy showed a molecular formula of $C_8H_5NO_3S$. ^{13}C n.m.r. spectroscopy again indicated the presence of eight carbon atoms, including a peak at 104.6 p.p.m. which showed the presence of a nitrile, although no nitrile peak was present in the i.r. spectrum. These data indicated that the product of this latter reaction was the cyanopyruvic acid 353 (Scheme 31).

Although there are several syntheses of α-keto acids described in the literature,[138] most of these methods involve steps which are incompatible with a thiophene nucleus. Nevertheless a method has been found[143] to synthesise 2-thienyl pyruvic acid; and this was applied to the preparation of 348. The condensation of thiophene-3-carboxaldehyde 354 with the ester 355 in the presence of sodium hydride afforded the novel amino ester 356 in good yield. Basic hydrolysis then gave the desired 3-thienylpyruvic acid 348 (Scheme 32).

The Pictet-Spengler condensation of the β-phenylethylamine 313 and 348 afforded the 1-thenyl isoquinoline carboxylic acid

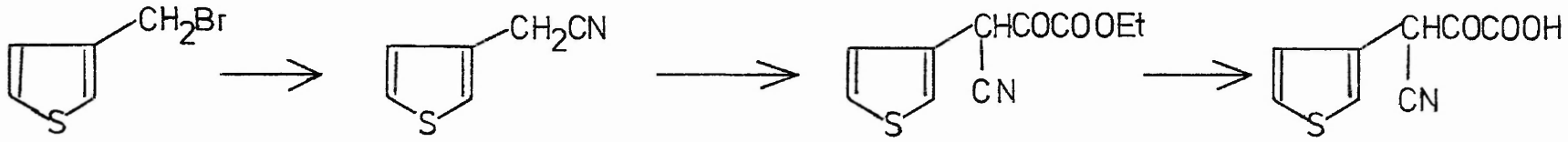
349. This acid gave no yellow product when heated with TFAA in pyridine.

4.2 Cyclohexadienimine spirolactones and related compounds

The main aim of the investigation had been to synthesise spirolactones from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, and to explore their reaction with nucleophiles. Since spirolactones having no substituent alpha to the dienone carbonyl had proved difficult to prepare in the isoquinoline series, some attention was given to obtaining research quantities of simpler cyclohexadienones. As discussed in Section 1.6 such compounds may be quite difficult to obtain, and one of the more efficient routes to them appears to be by the hydrolysis of corresponding N-sulphonyl cyclohexadienimines. Therefore studies were undertaken to extend and improve the earlier findings in this Department on the utility of this method of synthesing dienones.

4.2.1 Preparation of 3-(p-sulphonamido)phenyl propanoic acids as oxidation substrates

The preparation of the sulphonamido acid 357 was carried out by a previously described method.[60] Nitration of 3-phenylpropanoic acid 358 gave the nitro-substituted acid 359 which on catalytic hydrogenation afforded the amino acid 360 in excellent yield; subsequent treatment with p-toluenesulphonyl chloride yielded the sulphonamido acid 357 (Scheme 33). Reaction of 360 with pentafluorophenylsulphonyl chloride produced, after crystallisation of the initial product form ethanol, the novel ethyl ester 361. No sulphonamide could be isolated from treating 360 with 2,4,6-triisopropylbenzenesulphonyl chloride, whilst its treatment with

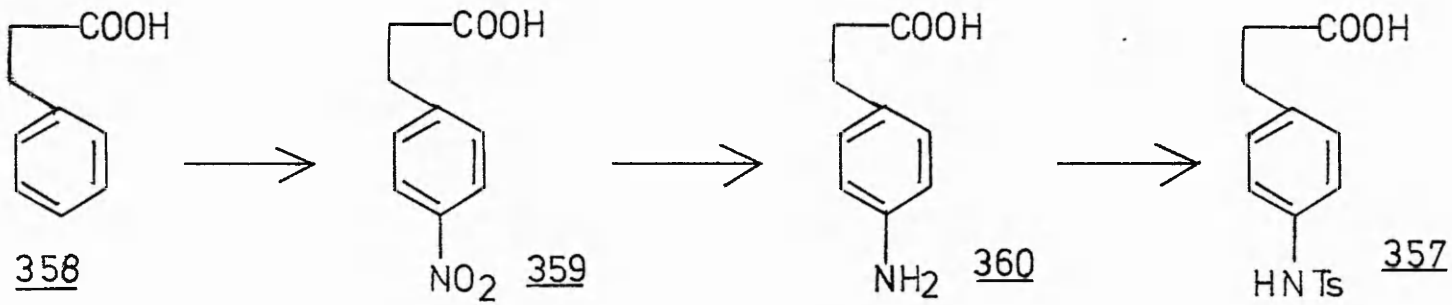


350 351 352 353

SCHEME 31

354 356 348

SCHEME 32

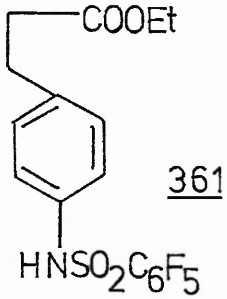


358 359 360 357

SCHEME 33

methane sulphonyl chloride gave inconsistent yields of the new sulphonamido acid 362. This last reaction proved difficult to handle because of the insolubility of 362, and an ester was thought more simple to handle; a tert-butyl ester was chosen because it would cause no deblocking problems. Accordingly, the nitro ester 363 was prepared in good yield by treating the acid 359 with tert-butanol and p-toluenesulphonyl chloride in pyridine.[135] Catalytic hydrogenation of 363 produced the crystalline amino ester 364 in excellent yield, which, in turn, afforded the novel sulphonamido ester 365 upon treatment with methanesulphonyl chloride. The acid 362 was prepared by either heating 365 at 100° for 1h or by treating it with trifluoroacetic acid.

The initial attempt to prepare the tert-butyl ester 363 involved treating the nitro acid 359 with oxalyl chloride and tert-butanol in the presence of triethylamine.[95] However, the product of this reaction, a bright orange solid, exhibited two carbonyl peaks in its i.r. and ^{13}C n.m.r. spectra. The ^{1}H n.m.r. spectrum showed a ratio of nine t-butyl protons to seven other aliphatic hydrogens to eight aromatic protons, and elemental analysis gave an empirical formula of $C_{22}H_{24}N_2O_7$. A possible structure for this compound which accommodates the analytical and spectral data is the keto ester 366. A feasible reaction mechanism would involve dehydrochlorination of the acid chloride 367 to the ketene 368, followed by dimerisation of the latter to 369. Nucleophilic attack of tert-butanol on 369 leads to 366 (Scheme 34). However, the structure 366 cannot account for the fact that reaction of the orange compound with trifluoroacetic acid yields two equivalents of the acid 359 when the expected product would be the symmetrical ketone 370. (Unless this is an unexpected novel reaction of a β-keto ester with trifluoroacetic acid).



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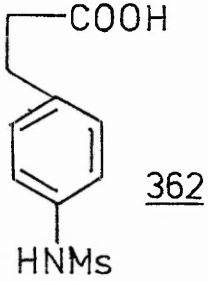

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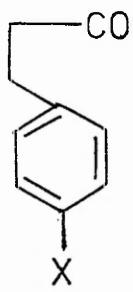
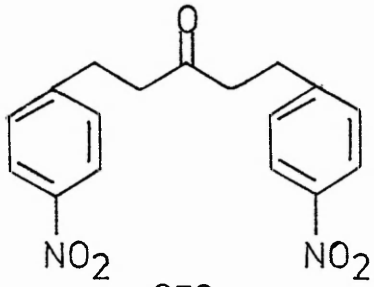


363 X=NO_2
364 X=NH_2
365 X=NHMs



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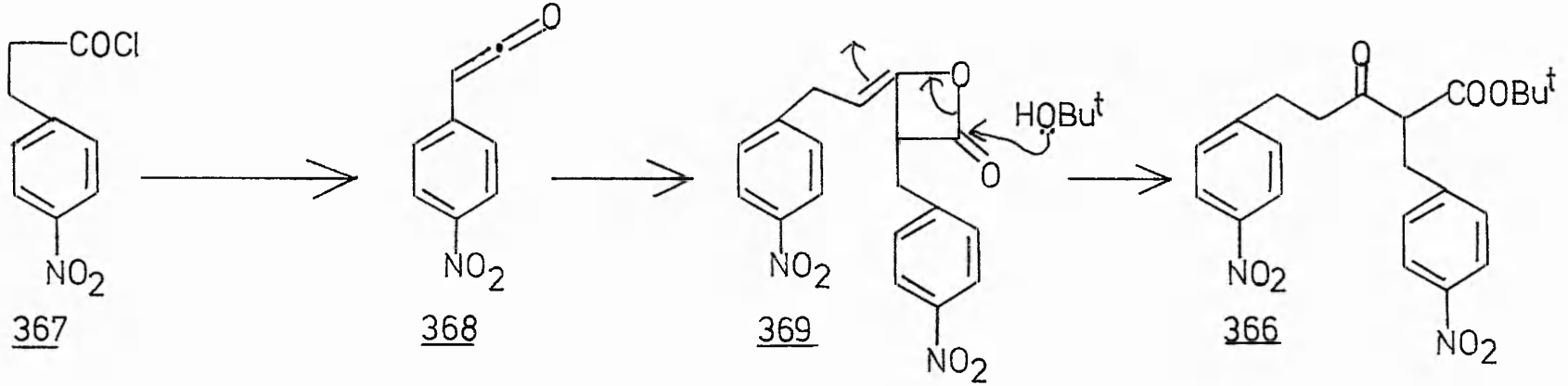
SCHEME 34



367 368 369 366

The spirolactone 371 has been prepared[62a] in low yield by a Bamberger reaction of 372 and in 25% yield by the manganese dioxide oxidation[62b] of the phenolic acid 373, the synthesis of which is laborious. A study of the synthesis of 371 by the cyclohexadienimine method seemed appropriate and the sulphonamido acid 374 was prepared by the following route. Biphenyl-2-carboxylic acid 375 was nitrated with concentrated nitric acid to give the nitro acid 376 in low yield. (The major product was the unwanted 2'-nitro isomer. This latter product results from anchimeric assistance[144] by the acid function which directs the nitronium ion into the 2'-position when one would expect substition to occur in the sterically less hindered 4'-position). Esterification of 376 with methanol afforded the crystalline methyl ester 377 which, upon hydrogenolysis, yielded the amino ester 378 characterised as its hydrochloride salt. Tosylation of 378 by standard methods gave the novel sulphonamido ester 379 in excellent yield, and its subsequent saponification afforded the new sulphonamido acid 374.

4.2.2. The preparation of cyclohexadienimine spirolactones

Various methods have been employed to oxidise appropriately substituted 3-phenylpropanoic and similar acids to their corresponding cyclohexadienimine spirolactones (Section 1.6). Some of these methods were applied to the above sulphonamides in an attempt to obtain good yields of cyclohexadienimines.

4.2.2.1. Anodic oxidation

The anodic oxidation at 1.4V of the toluenesulphonamido acid 357 was repeated[60] and afforded the imine 380 in good yield. Although

spectroscopy and tlc showed 380 to be virtually pure, recrystallisation considerably reduced the yield of product. Similar oxidation of the methanesulphonamido acid 362 gave the novel imine 381, but in widely varying yields (0-70%). On oxidation the biphenic acid 374 produced the novel imine 382 in good yield. No spirolactone was obtained from the anodic oxidation of the amino acid 360, and since the ethyl ester 361 could not be saponified its oxidation was not attempted.

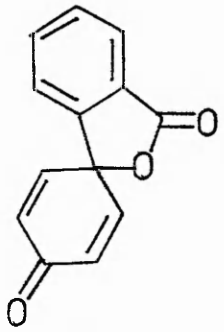
4.2.2.2. Chemical oxidations

Lead tetra-acetate has been used to prepare cyclohexadienone spirolactones[60,81] including the naphthalene spirolactone 213 described in Section 2.3.3. Heating the sulphonamide 357 to reflux in acetic acid containing lead tetra-acetate yielded a mixture which was identified by tlc and i.r. spectroscopy as containing the imine 380 as well as its hydrolysis products - p-toluenesulphonamide and the dienone 100. However, as the total yield of products was very poor no separation of the mixture was attempted. The treatment of the mesyl acid 362 with lead-tetra-acetate at room temperature [81] afforded the imine 381, but again in low yield. The amino acid 360 provided the dienone 100 in a yield of 12% after treatment with lead-tetra-acetate and elution on an alumina column. Surprisingly the reaction of the methyl ester 379 with lead tetra-acetate afforded a 25% yield of the imine 382; the ester 383 produced only a small quantity of the imine 380.

4.2.3. Reactions of N-sulphonyl cyclohexadienimine spirolactones

4.2.3.1. Hydrolysis

Spirodienones have been prepared[80] by the hydrolysis of the



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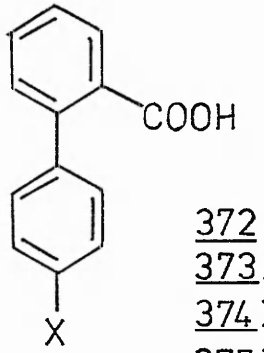
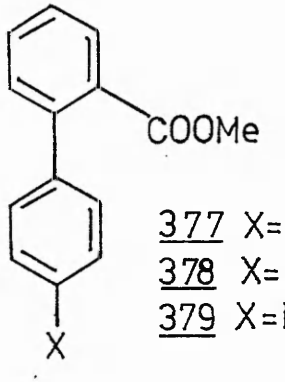
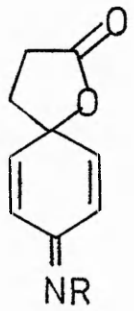


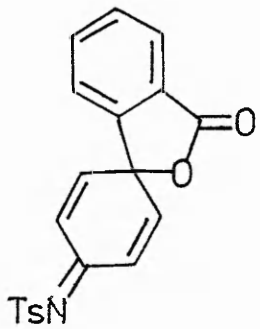
372 X=NHOH
373 X=OH
374 X=NHTs
375 X=H
376 X=NO_2



377 X=NO_2
378 X=NH_2
379 X=NHTs



380 R=Ts
381 R=Ms



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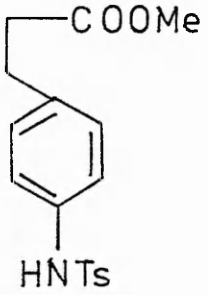

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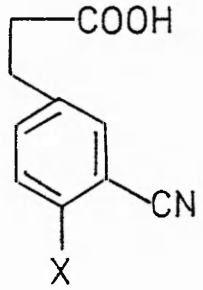
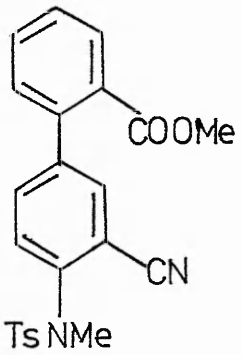


384 X=NHTs
385 X=NHMs



386

corresponding N-sulphonyl cyclohexadienimines (including 380) on elution down a Brockmann grade II neutral alumina column. On repetition of this, we found that all the solvents used to elute 380 yielded a mixture of the desired dienone 100 and p-toluenesulphonamide. In order to resolve this difficulty, the synthesis and hydrolysis of other similar spirolactones was attempted; but only the two acids 362 and 374 could be prepared. On elution from an alumina column with various solvents the mesyl imine 381 yielded a mixture of the dienone 100 and methanesulphonamide. Chromatographic separation of the latter from 100 was rendered difficult by the fact that methanesulphonamide is not visible on tlc. Elution of 381 on basic alumina resulted in the preferential hydrolysis of the lactone ring and the isolation of the sulphonamido acid 362. However, on chromatography the biphenyl dienone 371 could be obtained from 382 in good yield free from p-toluenesulphonamide (cf. Section 2.3.2).

4.2.3.2. Reactions with nucleophiles

Preliminary studies[79] on the attack by nucleophiles of spiro-β-lactones have indicated that the nucleophile can be inserted either into the lactone or dienone functions.

The reactions of 380 with methyl-lithium, phenyl-lithium, p-sodium thiocresolate, sodium p-tert-butyl phenoxide, sodium methoxide, sodium 2,6-dimethoxyphenoxide and lithium-acetylide all furnished inconclusive results. In all cases no nucleophile could be detected by n.m.r. in the product. Surprisingly, however, the acid 357 seemed to be the most abundant acidic product isolatable from the reaction of 380 with the above sodium salts. This is unusual as the isolation of 357 from 380 requires a change in the

oxidation state of 380. This must mean that either 380 is acting as an oxidising agent or that it is being reduced by one of the supposed nucleophiles. No coupled product from p-tert-butyl phenoxide nor from 2,6-dimethoxyphenoxide could be identified from their reaction with 380; thus the former hypothesis appears to be invalid. A tentative suggestion is that the reduction of 380 is being effected by residual sodium hydride contaminating the added nucleophiles, but sodium hydride is usually regarded as a poorly nucleophilic base.

The reaction of imines 380-82 with potassium cyanide in DMF was more successful. The product from 380 was identified by elemental analysis, i.r. spectroscopy and ^{13}C n.m.r. as the cyano acid 384. Imine 381 gave a bicarbonate soluble oily product which from i.r. and mass spectroscopy was assigned as the novel acid 385. The crude acidic product from the cyanide attack on imine 382 was treated with diazomethane to give the ester 386.

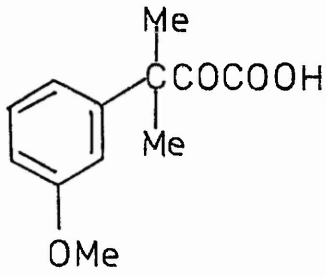
These last results prove that nucleophilic attack can indeed occur alpha to the diene moiety of a cyclohexadienimine spiro-γ-lactone and that this attack leads to the opening of the lactone ring. Thus, if an isoquinoline spirolactone can be formed, the speculation that this may be a possible route to bisbenzylisoquinolines becomes more promising (Section 1.1).

4.3 Attempted preparation of 3-methyl-(m-methoxyphenyl)-2-oxo-butanoic acid

As the benzylic position 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids tends to undergo oxidation,[19,20,119] an attempt was made to replace the labile benzylic protons with less easily

removed methyl groups. In order to achieve this it was necessary to prepare a gem-dimethylphenylpyruvic acid, such as 387. A previous attempt in the department to synthesise such an acid had been unsuccessful.[119] A recent paper has described the preparation of the propanoic acid 388 which by conversion to its acid cyanide 389 and hydrolysis would yield the keto acid 387.

The synthesis of 388 was repeated in excellent yield by treating the carboxylate 390 with two successive equivalents on n-butyl-lithium followed by the addition of two successive equivalents of methyl iodide. The treatment of the acid chloride 391 with copper (I) cyanide[145,146] failed to afford the nitrile 389, but its treatment with sodium cyanide in acetone afforded a low yield of an oil which was assumed to be the new acyl cyanide 389 on the basis of i.r., n.m.r., and mass spectral data. An attempt to improve the yield of 389 by allowing a longer reaction time afforded a pale yellow oil with different spectral characteristics to those of 389. An inspection of the i.r., ^{1}H and ^{13}C n.m.r. spectra of this latter product showed that the acid chloride 391 had coupled with the reaction solvent to yield the novel cyano ester 392. An attempt to hydrolyse the acyl cyanide 389 with hydrochloric acid failed to yield 387. After this synthesis was attempted two new methods[147,148] of preparing acyl cyanides were published and perhaps use of these could lead to the successful preparation of 389.



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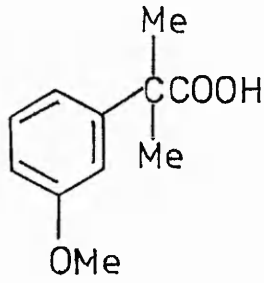

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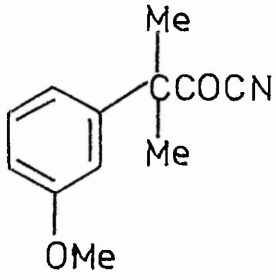

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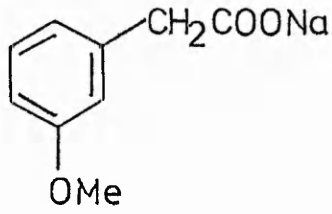

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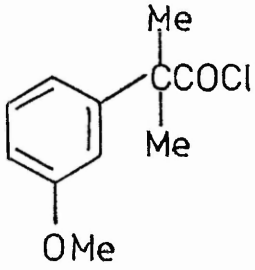

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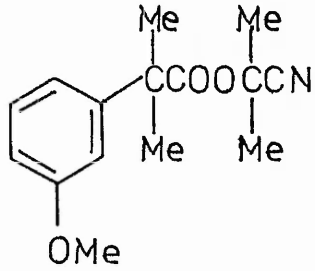

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EXPERIMENTAL SECTION

General

Infra-red spectra were recorded as potassium bromide discs (unless otherwise stated) using either a Perkin Elmer 137 or 683 grating spectrophotometer both calibrated with polystyrene film. Ultra-violet absorption spectra and absorbance measurements were determined using a Perkin Elmer 402 u.v.-visible spectrophotometer. Proton magnetic resonance spectroscopy was performed using either a JEOL JNM C-60 HL 60 MHz or a Hitachi Perkin Elmer R24B 60 MHz spectrometer both with tetramethylsilane as the internal standard in deuterochloroform as solvent (unless otherwise indicated). Carbon-13 n.m.r. spectra were recorded on a JEOL JNM FX60Q 60 MHz Fourier Transform spectrometer. Low resolution mass spectrometry was carried out by the Department of Chemistry, Leicester Polytechnic, and high resolution mass spectroscopic determinations were performed by The Boots Company, Nottingham. Elemental analyses were determined by the analytical section of Imperial Chemical Industries, Alderley Park, Macclesfield. Melting points were measured in degrees centigrade 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. Thin-layer chromatography was carried out using pre-spread plates (5 x 20 cm; Polygram SIL G/UV_{254} and Polygram ALOX N/UV_{254} from Camlab, Cambridge). Column chromatography was performed using Fison silica-gel (60-120 mesh) and BDH neutral alumina. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh ASTM). All solvents for chromatographic work were redistilled. Ether, benzene and toluene

were dried over sodium wire, THF was dried over calcium hydride, chlorinated solvents were dried over calcium chloride, and pyridine was dried over potassium hydroxide pellets. Other solvents were dried using 5A molecular sieves. Light petroleum used had b.p. 60-80° unless otherwise indicated.

General anodic oxidation procedure

Anodic oxidations were carried using either a Wenking potentiostat model 70 TS1 or model LB 75 and standard calomel electrode with a graphite felt anode (5 x 3 cm) and a platinum anode (3 x 2 cm). The one compartment cell (a 250 ml beaker) contained a solution of tetraethylammonium perchlorate (2g) in acetonitrile (150 ml) and was stirred magnetically. The oxidations were carried out in air at room temperature. Substrates were added in one portion to an equilibrated, pre-electrolysed anodic cell, at an anodic potential which allowed a current of 20-60 mA to pass. The current was monitored until either the current dropped to background level or until tlc indicated that no starting material remained. The cell solution was filtered and evaporated to dryness on a rotary evaporator. The residues were partitioned between methylene chloride (50 ml) and water (50 ml), and the organic layer separated. The methylene chloride solution was further washed with water (2 x 20 ml), saturated sodium bicarbonate solution (2 x 20 ml) and water (20 ml), dried over magnesium sulphate, filtered, and rotary evaporated to dryness.

WORK DESCRIBED IN CHAPTER TWO

Preparation of Oxidation Subtrates and their Intermediates

1,2,3,4-Tetrahydronaphthalene-1-carboxylic acid 175

Sodium metal (59.5g, 2.59M) was added as quickly as possible to a solution of 1-naphthoic acid 174 (17g, 98.8 mM) in boiling ethanol (450 ml). The mixture was heated under reflux until all the sodium had dissolved and then allowed to cool to a solid mass. Dilution with water (40 ml) and treatment with 10N sulphuric acid (170 ml) yielded a precipitate of sodium sulphate after cooling overnight at 4°. After filtering off the sodium sulphate, the ethanol was distilled off and the aqueous residue was acidified with excess 10N sulphuric acid. The precipitated colourless oil solidified overnight at 4°. Recrystallisation from either ethyl acetate or light petroleum afforded the title acid 175 (15.81g, 91%) as colourless plates m.p. 84-5° (lit.[92] m.p. 84-6) ν_{max} : 3300-2100 (H-bonded OH); 1680 cm^{-1} (C=O). δ : 1.53-2.20 (4H, m, 2-CH_2, 3-CH_2); 2.70 (2H, t, J = 4Hz, 4-CH_2); 3.75 (2H, t, J = 5Hz, 1-CH); 7.04 (4H, s, aromatics); 12.25 (1H, s, exchanges with D_2O, CO_2H).

Methyl 1,2,3,4-tetrahydronaphthalene-1-carboxylate 181

A solution of the acid 175 (5g, 28.4 mM) in methanol (100 ml) containing conc. sulphuric acid (5 ml) was heated under reflux for 1.5 hours. After the removal of most of the methanol by rotary evaporation, the residue was poured into water (100 ml) and extracted into ether (3 x 20 ml). The ether extracts were combined and washed with saturated sodium bicarbonate (20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Removal of solvent yielded the methyl ester as a tan oil (5.2g, 96%) b.p. 96-8°/0.5mm) (lit.[149] b.p. 106-7°/1mm) ν_{max} 1735 cm^{-1} (C=O). δ : 1.62-2.20 (4H, m, 2-CH_2, 3-CH_2); 2.70 (2H, t, J = 6Hz, 4-CH_2); 3.57 (3H, s, OCH_3); 3.76 (1H, t, J =

5Hz, 1-CH); 7.00 (4H, s, aromatics).

4-Benzyloxyphenylacetic acid 224

4-Hydroxyphenylacetic acid (14g, 92 mM) was dissolved in hot ethanol (120 ml) containing potassium hydroxide (14.5g). Benzyl chloride (14.5g, 115 mM) was added to the solution and the mixture was heated under reflux with stirring for 5h. The solvent was removed and the residue dissolved in water (100 ml) and washed with ether (30 ml). The aqueous layer was acidified and the resultant precipitate filtered off, and washed thoroughly with water. Recrystallisation from benzene afforded the title ether 224 as colourless plates (18.07g, 81%) m.p. 122-3° (lit.[150] m.p. 114°).

2-(4-Benzyloxyphenyl)-ethanol 225

Prepared from the acid 224 (1g, 4.13 mM) and borane methyl sulphide (0.5 ml, 5 mM) by the method described for the alcohol 235 (p. 120) Evaporation of the solvent afforded the title alcohol 225 as white plates (0.84g, 89%) m.p. 85-7° (lit.[151] m.p. 83-5°)(from light petroleum). (Found C, 79.4; H, 7.3. Calculated for $C_{15}H_{16}O_2$ C, 78.9; H, 7.0%). δ : 1.18 (1H, s, exchanges with D_2O, O$\underline{H}$); 2.67 (2H, t, J = 6Hz, HO-CH_2-C$\underline{H}_2$); 3.65 (2H, t, J = 6Hz, HO-C$\underline{H}_2$); 4.90 (2H, s, OC$\underline{H}_2$); 6.78 (2H, d, J = 9Hz, ar. ortho to O); 7.00 (2H, d, J = 9Hz, ar. meta to O); 7.23 (5H, s, aromatics).

2-(4-Benzyloxyphenyl)-ethyl chloride 222

A solution of the alcohol 225 (1g, 4.39 mM) in thionyl chloride (5 ml) was heated under reflux for 1.5h. Evaporation of the thionyl chloride afforded the title alkyl chloride 222 as white crystals (1.08g, 100%) m.p. 52-3° (from petroleum b.p. 40-60°). (Found C, 72.1; H, 5.9. Calculated for $C_{15}H_{15}$C10 C, 73.0; H, 6.1%). δ : 2.82 (2H, t, J = 7Hz, Cl-CH_2-C$\underline{H}_2$); 3.48 (2H, t, J = 7Hz, Cl-C$\underline{H}_2$); 4.88 (2H, s, OC$\underline{H}_2$); 6.78 (2H, d, J = 9Hz, ar. ortho to O); 7.00

(2H, d, J = 9Hz, ar. meta to O); 7.24 (5H, s, aromatics).

This compound has been described in the patent literature.[152]

4-Benzyloxyphenylacetyl chloride 230

The acid 224 (1g, 4.42 mM) was dissolved in thionyl chloride (3 ml) and left at room temperature for 24h. Evaporation of the thionyl chloride afforded the title acid chloride 230 as a white solid (0.95g, 82%) ν_{max} : 1790 cm^{-1} (C=O).

General Preparation of Methyl 1-benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxylates

Methyl 1-lithio-1,2,3,4-tetrahydronaphthalene-1-carboxylate 182

n-Butyl-lithium (3.6 ml of a 1.6M solution in hexane, 5.78 mM) was added by syringe to stirred di-isopropylamine (0.81 ml, 5.78 mM) at -10° under a steady flow of dry nitrogen. After 15 minutes the resulting white gum was diluted with dry tetrahydrofuran (20 ml), the mixture was cooled to -78° and a solution of the ester 181 (1g, 5.26 mM) in tetrahydrofuran (10 ml) added in one portion.

To a stirred solution of the lithio compound 182 (5.26 mM) in tetrahydrofuran (30 ml) at -78° under a flow of nitrogen was added in one portion an electrophile (5.26 mM) in tetrahydrofuran (5 ml). After one hour this mixture was allowed to warm up to room temperature, quenched with water (20 ml), and extracted into ether (3 x 20 ml). The combined ether extracts were washed with 2M hydrochloric acid (20 ml), saturated brine (3 x 20 ml), water (20 ml) and dried ($MgSO_4$). The ether was rotary evaporated to dryness and the crude product purified as detailed below.

By this method were prepared the following compounds.

Methyl 1-(4-nitrobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 183.

From 4-nitrobenzylbromide (1.14g, 5.27 mM) the product was a fawn oil which on trituration with ether and crystallisation from methanol afforded the title ester 183 as white crystals (1.14g, 67%) m.p. 112-3°. (Found : C, 70.4; H, 6.1; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.2; H, 5.8; N, 4.3%). ν_{max} : 1722 cm^{-1} (C=O). δ : 1.72-2.10 (4H, m, 2-CH_2, 3-CH_2); 2.58-2.78 (2H, broad t, 4-CH_2); 3.45{2H, ABq, J = 14Hz, benzylic CH_2 [partially hidden by 2.69 (3H, s, OCH_3)]} 7.00-7.55 (6H, m, aromatics); 8.06 (2H, d, J = 9Hz, ar. ortho to N).

Methyl 1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 184.

From 4-benzyloxybenzyl chloride (9.8g, 42.2 mM) and the lithiated intermediate 182 (42.1 mM) was obtained the title ester 184 as white crystals (10.73g, 66%) m.p. 112-113° (from methanol). (Found C, 81.0; H, 7.0. $C_{26}H_{26}O_3$ requires C, 80.8; H, 7.0%). ν_{max} : 1730 cm^{-1} (C=O). δ : 1.32-1.92 (4H, m, 2-CH_2 3-CH_2); 2.46 (2H, broad t, 4-CH_2); 3.10 {2H, ABq, J = 13Hz, benzylic CH_2 [partially obscured by 3.43 (3H, s, CO_2CH_3)]}; 6.60 (2H, d, J = 8Hz, ar. ortho to OCH_2Ph); 6.78 (2H, d, J = 8Hz, ar. meta to OCH_2Ph); 6.90-7.52 (9H, m, aromatics).

Methyl 1-(4-methoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 185.

From 4-methoxybenzyl chloride (1.65g, 10.5 mM) and the lithiated intermediate 182 (10.5 mM) the title ester 185 was obtained as a yellow oil. Trituration with a little ether afforded a white solid (3.06, 94%) m.p. 55.5-56.5° (methanol) (Found : C, 77.7,

H, 7.1%). ν_{max} : 1730 cm^{-1} (C=O). δ : 1.35-1.85 (4H, m, 2-CH_2, 3-CH_2); 2.30 (2H, broad t, 4-CH_2); 2.94 (2H, ABq, J = 14Hz, benzylic CH_2); 3.25 (3H, s, OCH_3); 3.31 (3H, s, CO_2CH_3); 6.37 (2H, d, J = 9Hz, ar. ortho to OCH_3); 6.63 (2H, d, J = 9HZ, ar. meta to OCH_3); 6.72-7.30 (4H, m, aromatics).

Methyl 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 186

From 3,4-dimethoxybenzyl chloride (3.24g, 17.4 mM) and the lithiated ester 182 (17.4 mM) the title ester 186 was obtained as colourless crystals (3.45g, 58%) m.p. 85-6° (ether-petroleum b.p. 40-60°). (Found : C, 73.6; H, 7.1. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%). ν_{max} : 1730 cm^{-1} (C=O). δ : 1.64-2.06 (4H, m, 2-CH_2, 3-CH_2); 2.59 (2H, broad t, 4-CH_2); 3.26 (2H, ABq, J = 16Hz, benzylic CH_2); 3.60 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 3.80 (3H, s, CO_2CH_3); 6.32 (1H, s, 2'-ar.); 6.65 (2H, s, 5',6'-ar.); 7.09-7.57 (4H, m, aromatics).

Methyl 1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 187.

From 3,4,5-trimethoxybenzyl chloride (2.28g, 10.5 mM) and the lithiated intermediate 182 (10.5 mM) the title ester 187 was obtained as colourless needles (1.99g, 51%) m.p. 90.5-91° after repeated recrystallisation from methanol. (Found : C, 71.4; H, 7.0. $C_{22}H_{26}O_5$ requires C, 71.2; 7.0%). ν_{max} : 1720 cm^{-1} (C=O). δ : 1.42-2.00 (4H, m, 2-CH_2, 3-CH_2); 2.46 (2H, broad t, 4-CH_2); ca. 3.4 [2H, ABq, J = 11 Hz, benzylic CH_2 partially hidden by 2.51 (9H, s, 3 x OCH_3)]; 2.64 (3H, s, CO_2CH_3); 6.00 (2H, s, ar. ortho to OCH_3); 7.10-7.45 (4H, m, aromatics).

Methyl 1-(4-benzyloxyphenylacetyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate. 231

From the acid chloride 230 (p. 108) (3g, 12.1 mM) and the lithiated intermediate 182 (11.6mM) was obtained a yellow oil. Prolonged trituration with petroleum and recrystallisation from methanol afforded the title ester 231 as colourless plates (2.97g, 62%) m.p. 90.5-92.5°. (Found : C, 78.5; H, 6.3. $C_{27}H_{26}O_4$ requires C, 78.3; H, 6.3%). ν_{max} : 1730 cm^{-1} (C=O, ester); 1705 cm^{-1} (C=O). δ_H : 1.70-2.00 (2H, m, 3-CH_2); 2.20-2.50 (2H, m, 2-CH_2); 2.80 (2H, t, J = 6Hz, 4-CH_2); 2.59 (2H, s, CH_2-C=O); 2.72 (3H, s, CO_2CH_3); 5.01 (2H, s, OCH_2); 6.90 (4H, s, aromatics ortho and meta to CH_2-C=O); 7.19 (4H, s, naphthalene aromatics); 7.44 (5H, s, aromatics). δ_C : 19.7; 29.2; 29.6; 44.6; 52.6; 65.3; 70.0; 114.7; 125.8; 126.4; 127.3; 127.9; 128.5; 129.7; 130.5; 131.7; 137.0; 137.8; 157.7; 172.0; 205.0.

Methyl 1-(4-hydroxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 188.

The benzyloxy ester 184 (6.4g, 16.7 mM) was hydrogenated in ethyl acetate (120 ml) containing 5% palladium on charcoal at atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate evaporated to yield the title phenolic ester 188 as colourless crystals (4.54g, 92%) m.p. 130-1° (from methanol). (Found : C, 76.0; H, 6.7. $C_{19}H_{20}O_3 \cdot \frac{1}{4}H_2O$ requires C, 75.9; H, 6.8%). ν_{max} : 3600-3200 (OH); 1725 cm^{-1} (C=O); δ : 1.42-2.12 (4H, m, 2-CH_2 3-CH_2); 2.65 (2H, broad t, 4-CH_2); 3.24 (2H, ABq, J = 14Hz, benzylic CH_2); 3.63 (3H, s, CH_3); 5.18 (1H, broad s, exchanges with D_2O, OH); 6.56 (2H, d, J = 8Hz, ar. ortho to OH); 6.82 (2H, d, J = 8Hz, ar. meta to OH); 7.00-7.56 (4H, m, aromatics).

Methyl 1-(4-aminobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 195.

The nitro ester 183 (8g, 24.6 mM) was hydrogenated in tetrahydrofuran (500 ml) using 5% palladium on charcoal (2g) as described for the ester 188. Removal of the organic solvent afforded a brown oil which crystallised from methanol as a fawn powder (6.68g, 92%) m.p. 89-91°. (Found : C, 76.6; H, 7.4; N, 4.7. $C_{19}H_{21}NO_2 \cdot \frac{1}{4}H_2O$ requires C, 76.1; H, 7.2; N, 4.7%). ν_{max} : 3460, 3370 (NH_2); 1725 cm^{-1} (C=O). δ : 1.55-2.04 (4H, m, 2-CH_2, 3-CH_2); 2.60 (2H, broad t, 4-CH_2); 3.18 (2H, ABq, J = 14Hz, benzylic CH_2); 3.30 (2H, s, exchanges with D_2O, NH_2); 3.54 (3H, s, CH_3); 6.38 (2H, d, J = 8Hz, ar. ortho to NH_2); 6.73 (2H, d, J = 8Hz, ar. meta to NH_2); 6.92-7.58 (4H, m, aromatics).

Methyl 1-[4-(p-toluenesulphonamido)benzyl]-1,2,3,4-tetrahydronaphthalene-1-carboxylate 198.

p-Toluenesulphonyl chloride (0.5g, 2.62 mM) was added in portions to a stirred solution of the amino ester 195 (0.68g, 2.31 mM) in chloroform (50 ml) containing pyridine (1 ml) at 0°C. The mixture was allowed to reach room temperature overnight and then poured into 4M hydrochloric acid (50 ml). The organic layer was separated, washed with 4M hydrochloric acid (50 ml), water (2 x 50 ml), and dried ($MgSO_4$). The solvent was removed to afford the title ester 190 as an orange gum (0.88g, 85% which failed to crystallise. ν_{max} (film) : 3260 (NH); 1725 (C=O); 1160 cm^{-1} (SO_2N). δ : 1.30-1.95 (4H, m, 2-CH_2, 3-CH_2); 2.10 (3H, s, aromatic CH_3); 2.35 (2H, broad t, 4-CH_2); 3.00 (2H, ABq, J = 13Hz, benzylic CH_2); 3.40 (3H, s, CO_2CH_3); 6.50-7.67 (13H, m, aromatics and NH).

Methyl 1-(4-methanesulphonamidobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 199.

Prepared from the amino ester 195 (0.5g, 1.69 mM) and methanesulphonyl

chloride (0.22g, 1.9 mM) according to the procedure for the sulphonamide 198. The product was isolated as the title sulphonamide 199 as a red-brown gum (0.52g, 85%) which failed to crystallise. ν_{max} (film) : 3260 (NH); 1725 (C=O) 1155 cm^{-1} (SO_2N).

tert-Butyl 1,2,3,4-tetrahydronaphthalene-1-carboxylate 201.

To a stirred solution of the naphthoic acid 175 (5g, 28.4 mM) in dry dichloromethane (100 ml) containing DMF (0.75 ml) at 0° under a flow of nitrogen was added oxalyl chloride (4.3 ml, 49.3 mM) in benzene (10 ml) dropwise over 10 mins. After dilution with dichloromethane (50 ml) this mixture was added to a solution of tert-butanol (50 ml) in dichloromethane (150 ml) containing triethylamine (8 ml) over a period of 1.5h. The dichloromethane was removed in vacuo at room temperature, the residue dissolved in ethyl acetate (200 ml), washed with 2M hydrochloric acid (25 ml), saturated sodium bicarbonate solution (4 x 25 ml), water (25 ml), brine (25 ml) and dried ($MgSO_4$). Removal of the solvent and distillation yielded the title ester 201 as a colourless oil (5.79g, 88%) b.p. 84-6°/0.2 mm. (Found : C, 77.1; H, 8.8. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%). ν_{max} (film) : 1730 cm^{-1} (C=O). δ : 1.44 (9H, s, 3 x CH_3); 1.67-2.20 (4H, m, 2-CH_2, 3-CH_2); 2.63-2.82 (2H, m, 4-CH_2), 3.65 (1H, t, J = 5Hz, 1-CH); 7.00 (4H, m, aromatics).

tert-Butyl 1-(4-nitrobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 202.

The tert-butyl ester 201 (2g, 8.62 mM) was added to lithium di-isopropylamide [prepared from n-butyl-lithium (5.56 ml of a 1.55M solution in hexane, 8.62 mM) and di-isopropylamine (1.2 ml, 8.62 mM)] at -10° in dry tetrahydrofuran (40 ml) under a flow of nitrogen. The temperature was lowered to -78°and 4-nitrobenzyl bromide

(1.88g, 8.70 mM) in tetrahydrofuran (10 ml) was added to the above mixture in one portion. After stirring for 1h the mixture was allowed to reach room temperature and was quenched with water (20 ml). The mixture was extracted into ether (3 x 20 ml), washed with 2M hydrochloric acid (20 ml), water (2 x 20 ml), brine (20 ml) and dried ($MgSO_4$). Removal of the solvent and trituration with a little ether yielded the title ester 202 as yellow flakes (2.25g, 71%) m.p. 74-75.5° (from methanol). (Found : C, 71.8; H, 6.9, N, 3.9. $C_{22}H_{25}NO_4$ requires C, 71.9; H, 6.8; N, 3.8%). ν_{max} : 1720 (C=O); 1520, 1350 cm^{-1} (NO_2). δ : 1.58 (9H, s, 3 x CH_3); 1.57-2.03 (4H, m, 2-CH_2, 3-CH_2); 2.60 (2H, broad t, 4-CH_2); 2.37 (2H, ABq, J = 13Hz, benzylic CH_2); 7.07-7.50 (6H, m, aromatics); 7.98 (2H, d, J = 9Hz, ar. ortho to NO_2).

tert-Butyl 1-(4-aminobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 203.

The nitro ester 202 (5.05g, 1.38 mM) was hydrogenated in methanol (500 ml) as described for the ester 188. The product, a yellow oil, was identified as the title amine 203 (4.4g, 95%) b.p. 175-82°/0.2 mm. ν_{max} (film) : 3460, 3380 (NH_2); 1715 cm^{-1} (C=O). δ : 1.37 (9H, s, 3 x CH_3); 1.54-2.16 (4H, m, 2-CH_2, 3-CH_2); 2.58 (2H, broad t, 4-CH_2); 3.13 {2H, ABq, J = 14Hz, benzylic CH_2 [partially obscured by 3.4 (2H, broad s, exchanges with D_2O, NH_2)]}; 6.34 (2H, d, J = 8Hz, ar. ortho to NH_2); 6.72 (2H, d, J = 8Hz, ar. meta to NH_2); 6.98-7.56 (4H, m, aromatics).

tert-Butyl 1-[4-(p-toluenesulphonamido)benzyl]-1,2,3,4-tetrahydronaphthalene-1-carboxylate 204.

Prepared from the amino ester 203 (2.68g, 7.95 mM) and p-toluenesulphonyl chloride (1.54g, 8.08 mM) by the method described for

the sulphonamide 198 as a white gum (3.39g, 87%) after treatment with activated charcoal. ν_{max} (film) : 3260 (NH); 1715 (C=O); 1160 cm^{-1} (SO_2N). δ : 1.34 (9H, s, 3 x CH_3); 1.50-1.94 (4H, m, 2-CH_2, 3-CH_2); 2.31 (3H, s, ar-CH_3); 2.50 (2H, broad t, 4-CH_2); 3.15 (2H, ABq, J = 13Hz, benzylic CH_2); 6.81-7.18 (10H, m, aromatics); 7.27 (1H, s, exchanges with D_2O, NH); 7.59 (2H, d, J = 8Hz, ar. ortho to S). Fully characterised by conversion to the acid 200 (p. 117)

tert-Butyl 1-(4-methanesulphonamidobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate 205

Prepared from the amino ester 203 (0.92g, 2.73 mM) and methanesulphonyl chloride (0.4g, 3.49 mM) according to the method described for the sulphonamide 198 as an orange solid (1.03g, 91%) which failed to recrystallise. ν_{max} (film) : 3270 (NH); 1715 cm^{-1} (C=O) δ : 1.38 (9H, s, 3 x CH_3); 1.58-2.10 (4H, m, 2-CH_2, 3-CH_2); 2.40-2.80 (2H, m, 4-CH_2); 2.89 (3H, s, SCH_3); 3.20 (2H, ABq, J = 14 Hz, benzylic CH_2); 6.10-6.70 (1H, broad s, exchanges with D_2O, N-H); 6.91-7.55 (8H, m, aromatics). Fully characterised by conversion to the acid 197 (p. 118)

General Preparation of 1-Benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acids.

1-(3,4,5-Trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 191.

The ester 187 (0.2g, 0.54 mM) was heated under reflux for 3.5h in methanol (20 ml) containing potassium hydroxide (1g). After removal of the methanol the resultant solid residue was dissolved in water (20 ml), washed with ether (10 ml), acidified with concentrated hydrochloric acid, extracted with dichloromethane (3 x 20 ml) and

dried ($MgSO_4$). Evaporation of the solvent afforded the title acid 191 as colourless plates (0.18g, 94%) m.p. 137-9° (chloroform-light petroleum). (Found : C, 69.8; H, 6.7. $C_{21}H_{24}O_5.\frac{1}{4}H_2O$ requires C, 69.9; H, 6.8%). ν_{max} : 3200-2300 (H-bonded O-H); 1690 cm^{-1} (C=O). δ : 1.34-2.02 (4H, m, 2-CH_2, 3-CH_2); 2.52 (2H, broad t, 4-CH_2); 3.16 (2H, broad s, benzylic CH_2); 3.48 (6H, s, 2 x OCH_3); 3.66 (3H, s, OCH_3); 6.01 (2H, s, ar. ortho to OCH_3; 6.98-7.52 (4H, m, aromatics); 11.68 (1H, s, exchanges with D_2O, CO_2H).

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 190.

The title acid 190 was prepared from the ester 186 (3.1g, 9.12 mM) according to the above procedure. The product was isolated as white crystals (2.8g, 94%) m.p. 155-7° (from chloroform-light petroleum). (Found : C, 73.3; H, 6.8. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.7%). ν_{max} : 3200-2300 (H-bonded O-H; 1690 cm^{-1} (C=O). δ_H : 1.50 - 2.13 (4H, m, 2-CH_2, 3-CH_2); 2.58 (2H, broad t, 4-CH_2); 3.26 (2H, ABq, J = 13Hz, benzylic CH_2); 3.51 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 6.33 (1H, s, 2'-ar.); 6.62 (2H, s, 2',3'-ar.); 7.08-7.64 (4H, m, aromatics); 10.90 (1H, s, exchanges with D_2O, CO_2H). δ_C : 19.7; 30.0; 31.3; 45.3; 50.2; 55.6; 110.4: 113.1; 122.7; 125.7; 126.7; 128.9; 129.7; 136.2; 138.2; 147.5; 148.1; 182.5.

1-(4-Methoxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 189.

From the ester 185 (2.8g, 9.0 mM), the title acid 189 was prepared as for the acid 191. The product was isolated as a yellow oil. Trituration with petroleum b.p. 40-60° and recrystallisation from chloroform-light petroleum afforded the title acid 189 as colourless needles (2.16g, 80%) m.p. 120.5-121°. (Found : C, 76.8; H, 6.9. $C_{19}H_{20}O_3$ requires (C, 77.0; H, 6.8). ν_{max} : 3300-2200 (H-bonded

O-H); 1690 cm^{-1} (C=O). δ : 1.45-2.12 (4H, m, 2-CH_2, 3-CH_2); 2.61 (2H, broad t, 4-CH_2); 3.22 (2H, ABq, J = 13Hz, benzylic CH_2); 3.63 (3H, s, OCH_3); 6.57 (2H, d, J = 8Hz, ar. ortho to OCH_3); 6.86 (2H, d, J = 8Hz, ar. meta to OCH_3); 7.00-7.60 (4H, m, aromatics); 11.59 (1H, s, exchanges with D_2O, CO_2H).

1-(4-Hydroxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 192.

From the phenolic ester 188 (0.2g, 0.675 mM), the title acid 192 was prepared by the same method as for the acid 191. The product was isolated as colourless crystals (0.17g, 89%) m.p. 168-9° (from chloroform-light petroleum). (Found : C, 76.4; H, 6.4. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%). ν_{max} : 3600-2000 (H-bonded O-H); 1690 cm^{-1} (C=O). $\delta_H(CDCl_3/DMSO)$: 1.65-2.08 (4H, m, 2-CH_2, 3-CH_2); 2.64 (2H, m, 4-CH_2); 3.10 (2H, ABq, J = 13Hz, benzylic CH_2); 6.49 (2H, d, J = 8Hz, ar. ortho to OH); 6.76 (2H, d, J = 8Hz, ar. meta to OH); 6.93-7.55 (4H, m, aromatics); 8.55-9.90 (1H, broad s, exchanges with D_2O, CO_2H). $\delta_C(CDCl_3/DMSO)$: 19.9; 30.2; 31.0; 45.2; 50.3; 114.9; 125.6; 129.0; 129.1; 131.4; 137.6; 137.8; 155.3; 178.8.

Catalytic debenzylation of the ether 193 (3g, 8.06 mm) in tetrahydrofuran (100 ml) also yielded the above phenolic acid 192 (1.82g, 80%).

1-[4-(p-Toluenesulphonamido)benzyl]-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 200.

The tert-butyl ester 204 (1g, 2.04 mM) was stirred in chloroform (50 ml) at 0° whilst trifluoroacetic acid (10 ml) was added in one portion. The solution was allowed to reach room temperature overnight and the organic solvents were removed in vacuo to yield a yellow froth. Careful recrystallisation from either aqueous methanol or chloroform-light petroleum afforded the title acid

200 as a fawn solid (0.17g, 96%) m.p. 174-5°. (Found : C, 66.9; H, 5.6; N, 3.0. $C_{25}H_{25}NO_4S.\frac{3}{4}H_2O$ requires C, 66.9; H, 5.9; N, 3.1%). ν_{max} : 3600-2300 (H-bonded OH); 1695 (C=O); 1330, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$)/DMSO) : 1.45-2.08 (4H, m, 2-CH_2, 3-CH_2); 2.30 (3H, s, CH_3); 2.59 (2H, broad t, 4-CH_2); 3.22 (2H, ABq, J = 14Hz, benzylic CH_2); 6.82-7.38 (10H, m, aromatics); 7.60 (2H,d, J = 8Hz, ar. ortho to S); 8.80 (1H, broad s, exchanges with D_2O, CO_2H).

1-(4-Methanesulphonamidobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 197

Prepared from the tert-butyl ester 205 (0.2g, 0.482 mM) according to the method for the sulphonamido acid 200. The product was isolated as a fawn powder (0.17g, 98%) m.p. 180-180.5 (from aqueous methanol). (Found : C, 63.1; H, 5.9; N, 3.7. $C_{19}H_{21}NO_4S$ requires C, 63.5; H, 5.8; N, 3.9%). ν_{max} : 3500-2400 (H-bonded O-H); 3250 (NH); 1695 (C=O); 1335, 1155 cm^{-1} (SO_2N). δ ($CDCl_3$/DMSO) : 1.50-2.04 (4H, m, 2-CH_2, 3-CH_2); 2.59 (2H, broad t, 4-CH_2); 2.86 (3H, s, CH_3); 3.25 (2H, ABq, J = 13Hz, benzylic CH_2); 6.80-7.60 (8H, m, aromatics); 9.06, 9.98 (2H, 2 broad s, exchange with D_2O, NH, CO_2H).

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 193.

To a stirred suspension of potassium tert-butoxide (24g, 0.21M) in dry ether (400 ml) at 0° was added water (1.04 ml). After 5 mins the ester 184 (10g, 25.9 mM) was added in one portion and the mixture stirred overnight. The reaction mixture was poured into water (1000 ml), the ethereal layer discarded and the aqueous layer washed with ether (50 ml), acidified with concentrated hydrochloric acid, and continuously extracted into dichloromethane. Removal of the solvent afforded the title acid 193 as colourless

prisms (9.24g, 96%) m.p. 179-81° (from glacial acetic acid). (Found : C, 80.8; H, 6.7. $C_{25}H_{24}O_3$ requires C, 80.6; H, 6.4%). ν_{max} : 3300 - 2300 (H-bonded O-H); 1690 cm^{-1} (C=O). δ (DMSO) : 1.30-1.76 (4H, m, 2-CH_2, 3-CH_2); 2.40 (2H, broad t, 4-CH_2); 2.97 (2H, ABq, J = 13Hz, benzylic CH_2); 5.01 (2H, s, OCH_2Ph); 6.42-7.45 (13H, m, aromatics).

1-(4-Nitrobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 194.

Prepared from the nitro ester 183 (0.5g, 1.54 mM) and potassium tert-butoxide (0·266g, 2.6 mM) by the same method as for the benzyloxy acid 193. The title acid 194 was isolated as fawn cubes (0.13g, 27%) m.p. 171-3° (from methanol). (Found : C, 69.3; H, 5.6; N, 4.6. $C_{18}H_{17}NO_4$ requires C, 69.5, H, 5.5; N, 4.5%). ν_{max} : 3600-2200 (H-bonded O-H); 1700 cm^{-1} (C=O). δ ($CDCl_3$/DMSO) : 1.36-2.09 (4H, m, 2-CH_2, 3-CH_2); 2.55 (2H, broad t, 4-CH_2); 3.30 (2H, ABq, J = 14Hz, benzylic CH_2); 6.98-8.02 (8H, m, aromatics).

1-(4-Aminobenzyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid 196.

The amino ester 195 (0.5g, 1.69 mM) was stirred for two days in methanol (20 ml) and 2M sodium hydroxide (20 ml). After removal of the methanol the aqueous portion was brought to pH 7 by the careful addition of concentrated hydrochloric acid. The resulting precipitate was filtered off and identified as the title amino acid 196 (0.2g, 42%). ν_{max} : 3600-2200 (salt bands); 1695 cm^{-1} (C=O). δ : 1.48-2.15 (4H, m, 2-CH_2, 3-CH_2; 2.64 (2H, broad t, 4-CH_2); 3.20 (2H, ABq, J = 14Hz, benzylic CH_2); c.a. 5.5-6.9 (2H, broad s, exchanges with D_2O, NH_2); 6.42 (2H, d, J = 8Hz, ar. ortho to NH_2); 6.78 (2H, d, J = 8Hz, ar. meta to NH_2); 7.03-7.60 (4H, m, aromatics). Fully characterised by conversion to the N-mesyl

acid 197 (p. 118).

Preparation of Miscellaneous 1,1-Disubstituted-1,2,3,4-tetrahydronaphthalenes.

1-(4-Benzyloxybenzyl)-1-(2-diazocetyl)-1,2,3,4-tetrahydronaphthalene 234.

The benzyloxy acid 193 (1g, 2.69 mM) was added to thionyl chloride (5 ml). After standing overnight the thionyl chloride was distilled off to yield the crude acid chloride 233 as a pink solid (1.02g, 97%). ν_{max} : 1780 cm^{-1} (C=O).

The acid chloride 233 (4.08g, 10.4 mM) in dry benzene (30 ml) was added dropwise to a stirred solution of diazomethane in dry ether at 0°C. The mixture as allowed to attain room temperature and after 1h the excess diazomethane was destroyed by the dropwise addition of glacial acetic acid. Removal of the organic liquids afforded the title diazoketone 234 as yellow cubes (3.9g, 94%) m.p. 108-9° (from methanol). (Found : C, 79.3; H, 6.2; N, 6.7. $C_{26}H_{24}N_2O_2$ requires C, 78.8; H, 6.1; N, 7.1%). ν_{max} : 2100 (N≡N); 1620 cm^{-1} (C=O). δ : 1.37-2.27 (4H, m, 2-CH_2 3-CH_2); 2.54 (2H, t, J = 6Hz, 4-CH_2); 3.24 (2H, s, benzylic CH_2); 4.78 (1H, s, CHN_2); 4.87 (2H, s, OCH_2Ph); 6.66-7.23 (13H, m, aromatics).

1-(4-Benzyloxybenzyl)-1-hydroxymethyl-1,2,3,4-tetrahydronaphthalene 235.

Borane-methyl sulphide (0.16 ml, 1.68 mM) was added to a stirred solution of the benzyloxy acid 193 (0.5g, 1.34 mM) in dry tetrahydrofuran (5 ml). After 2h methanol (10 ml) was added dropwise. Removal of the organic solvents afforded a white gum which was identified as the title alcohol 235 by crystallisation from ether as white crystals (0.43g, 89%) m.p. 94-6°. (Found : C, 83.6; H, 7.2. $C_{25}H_{26}O_2$

requires C, 83.8; H, 7.3%). ν_{max} : 3640-3230 cm^{-1} (H-bonded O-H). δ : 1.54 (1H, s, exchanges with D_2O, OH); 1.56-2.00 (4H, m, 2-CH_2, 3-CH_2); 2.62 (2H, broad t, 4-CH_2); 2.86 (2H, s, HO-$\underline{CH}_2$); 3.60 (2H, ABq, J = 11Hz, benzylic CH_2); 4.93 (2H, s, OCH_2Ph); 6.65-7.41 (13H, m, aromatics).

This alcohol was also obtained by the following procedure.

To a stirred suspension of lithium aluminium hydride (1g, 26.3 mM) in dry ether (30 ml) under a flow of dry nitrogen was added a solution of the benzyloxy ester 184 (6.5g, 16.8 mM) in tetrahydrofuran (50 ml) dropwise). The mixture was stirred for 1h and quenched successively with 10% aqueous THF (20 ml), 20% aqueous THF (20 ml), 50% aqueous THF (20 ml) and water (20 ml). The inorganic salts were filtered off, the filtrate separated and the organic layer dried ($MgSO_4$). Removal of the organic solvents afforded a tan oil (5.9g, 98%). Recrystallisation from ether yielded the title alcohol 235 which had spectral characteristics identical with those of an authentic sample.

1-(4-Hydroxybenzyl)-1-hydroxymethyl - 1,2,3,4-tetrahydronaphthalene 238.

The benzyl ether 235 (4.34g, 12.1 mM) in tetrahydrofuran (200 ml) was catalytically hydrogenated according to the procedure for the phenol 188. The product was identified as the title phenol 238 as pale pink crystals (3.1g, 95%) m.p. 130-2° (from toluene). (Found : C, 81.0; H, 7.6. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%). ν_{max} : 3600-3100 cm^{-1} (H-bonded O-H). δ : 1.30-1.82 (4H, m, 2-CH_2, 3-CH_2); 1.92 (1H, broad s, exchanges with D_2O, CH_2-$\underline{OH}$); 2.50 (2H, broad t, 4-CH_2); 2.70 (2H, s, $\underline{CH}_2$-OH); 3.50 (2H, ABq, J = 11Hz, benzylic CH_2); 6.44 (2H, d, J = 8Hz, ar. ortho to OH); 6.66 (2H, d, J =

8Hz, ar. meta to OH); 6.82-7.27 (4H, m, aromatics).

1-(4-Benzyloxybenzyl)-1-chloromethyl-1,2,3,4-tetrahydronaphthalene 236.

To a solution of the alcohol 235 (1g, 2.79 mM) in benzene (30 ml) was added thionyl chloride (3 ml) followed by pyridine (0.4 ml) dropwise. The mixture was heated under reflux for 2 hours, cooled, and the solvents evaporated. The residue was dissolved in dichloromethane (30 ml), washed with water (2 x 10 ml) 2M hydrochloric acid (2 x 10 ml), water (2 x 10 ml), and dried ($MgSO_4$). Removal of the solvent, extraction into light petroleum and treatment with charcoal yielded the crude alkyl chloride 236 as a fawn gum (0.72g, 68%). δ : 1.50-2.30 (4H, m, 2-CH_2, 3-CH_2); 2.62-2.78 (2H, m, 4-CH_2); 2.95 (2H, s, CH_2Cl); 3.20-3.48 (2H, m, benzylic CH_2); 4.92 (2H, s, OCH_2Ph); 6.78-7.42 (13H, m, aromatics).

Oxidation of 1-benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids

3,5-Dimethoxy-3",4"-dihydrodispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H),1"(2"H)-naphthalene]-4,5'-dione 206

Thallium(III) trifluoroacetate (0.6g, 1.1 mM) was dissolved in trifluoracetic acid (5 ml) and diluted with dichloromethane (20 ml). Boron trifluoride etherate (0.5 ml) was added and the temperature was adjusted to -20° under a stream of dry nitrogen. To this mixture was added a solution of the acid 191 (0.356g, 1 mM) in dichloromethane (5 ml) in one portion. After 30s the mixture was quenched with tert-butanol (10 ml), allowed to reach room temperature, washed with water (4 x 25 ml), saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation of the solvent afforded the title lactone 206 as fawn needles (0.19g, 56%) m.p.

(168-9° from chloroform-light petroleum). (Found : C, 69.5; H, 5.9. M^+, 296.1401. $C_{20}H_{20}O_5$ requires C, 70.6; H, 5.9%. M-CO_2 requires 296.1407). ν_{max} : 1765 (γ-lactone); 1685, 1660 (ketone); 1620 cm^{-1} (C=C). δ : 1.86-2.26[4H, m, C(3)H_2, C(4)H_2]; 2.74(2H, s, benzylic CH_2); 2.85[2H, broad t, C(2)H_2]; 3.70 (6H, s, 2 x OCH_3); 5.80 (2H, s, alkenics); 7.14 (4H, s, aromatics).

Anodic oxidation of the acid 191 (0.5g, 1.4 mM) at 1.41V by the method described (p. 105) afforded three products which were separated by flash chromatography (chloroform-ether eluant). The fraction with an Rf value of 0.55 was isolated as a fawn solid (0.16g, 34%) m.p. 174-6° (methanol) which had spectral and tlc characteristics identical with those of the title lactone 206. The fraction with Rf value (0.72) corresponding to that of α-tetralone gave a colour test with 2,4-dinitrophenylhydrazine and had n.m.r. and i.r. spectra identical with γ-tetralone. The fraction with an Rf value of 0.77 was not identified.

3",4"-Dihydrodispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H), 1"(2"H)-naphthalene]-4,5'-dione 213

The phenolic acid 192 (0.5g, 1.77 mM) was oxidised at 1.47V as described in the general anodic oxidation procedure to yield an orange froth (0.27g, 54%). Elution of the froth on a alumina column (Brockmann activity II) with ethyl acetate afforded the title lactone 213 as colourless crystals (0.2g, 40%) m.p. 146-7° (from methanol). (Found : C, 74.8; H, 5.7. $C_{18}H_{16}O_3 \cdot \frac{1}{2}H_2O$ requires C, 74.7; H, 5.9%). ν_{max} : 1775 (γ-lactone); 1675 (ketone); 1635 cm^{-1} (C=C). δ : 1.90-2.45[4H, m, C(3) H_2, C(4) H_2]; 2.63 (2H, s, benzylic CH_2); 2.74-2.94[2H, m, C(2)H_2]; 6.20(2H, d, J = 11Hz, vinylic); 6.85-7.28 (6H, m, aromatic and vinylic). m/z 280 (M^+, 2%); 236 (6); 174 (42); 130 (100); 128 (19); 107 (27); 44 (23).

Anodic oxidation of the methyl ether 189 (0.5g, 1.7 mM) afforded a multitude of products one of which was identified by tlc and reaction with 2,4-dinitrophenylhydrazine as 4-methoxybenzaldehyde. Recrystallisation of the mixed products from methanol afforded the above lactone 213 as a fawn powder (0.02g, 4%) which had spectral properties identical to those already described for the lactone.

Anodic oxidation of the methanesulphonamido acid 197 (0.5g, 1.39 mM) by the method described (p. 105) afforded the imine 216 as a fawn froth (0.4g, 80%). ν_{max} : 1775 (C=O); 1560 cm^{-1} (C=N). Elution of this froth with ethyl acetate on a alumina column (Brockmann activity II) afforded the lactone 213 (0.17g, 54%) which had identical spectral properties to those already described.

Anodic oxidation of the p-toluenesulphonamido acid 200 (0.5g, 1.15 mM) by the method described (p. 105) afforded the amide imine 215 as a fawn froth (0.41g, 82%). ν_{max} : 1780 (C=O); 1555 cm^{-1} (C=N). Hydrolysis of this froth on an alumina column in ethyl acetate afforded a mixture of p-toluenesulphonamide and the lactone 213. Recrystallisation of the mixture from methanol yielded the title lactone 213 as fawn crystals (0.15g, 56%) which had spectral properties identical to those previously described.

3",4"-Dihydrodispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H), 1"(2"H)-naphthalene]-4-one 239

The alcohol 238 (0.5g, 1.87 mM) was oxidised at 1.4V according to the method described in the general anodic oxidation procedure. The removal of the acetonitrile afforded a yellow gum which was passed down an alumina column in ethyl acetate. Evaporation of the solvent yielded a mixture of the starting alcohol 238 and

the title dienone 239 (0.21g). ν_{max} : 1665 (C=O); 1630 cm^{-1} (C=C). m/z 266 (M^+, 0.5%); 144 (80); 130 (100); 116 (29); 107 (24).

3,5-Dibromo-3",4"-dihydrodispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H),1"(2"H)-naphthalene]-4,5'-dione 219

To a solution of the phenolic acid 192 (0.2g, 0.71 mM) in acetonitrile (10 ml) and acetate buffer (0.2M, pH 4.6, 20 ml) was added a solution of N-bromosuccinimide (0.4g, 2.25 mM) in the same solvent mixture (10 ml). The mixture was left at room temperature overnight, extracted into ethyl acetate (3 x 10 ml), washed with saturated sodium bicarbonate solution (4 x 10 ml), water (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded the title dibromo lactone 219 as tan needles (0.26g, 83%) m.p. 177-9° (from ethanol). (Found : C, 49.7; H, 3.2. $C_{18}H_{14}Br_2O_3$ requires C, 49.3; H, 3.2%). ν_{max} : 1775 (γ-lactone); 1680 cm^{-1} (ketone). δ : 1.85-2.30 [4H, m, $C(3)H_2$, $C(4)H_2$]; 2.70 (2H, s, benzylic CH_2); 2.69-2.94 [2H, m, $C(2)H_2$]; 6.98-7.35 (6H, m, aromatics and alkenics). m/z 436 (M^+, 3%); 392 (3%); 174 (42); 129 (100); 44 (51).

x-Methoxy-3",4"-dihydrodispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H),1"(2"H)-naphthalene]-4,5'-dione 208a or 208b

The reaction of the acid 190 (0.326g, 1 mM) and thallium (III) trifluoroacetate (0.6g, 1.1 mM) by the method described (p.122) afforded a multispot product. Flash chromatography (chloroform eluant) afforded the crude title lactone 208a or 208b as a purple solid (0.1g, 32%) which failed to recrystallise. ν_{max} : 1760 (γ-lactone); 1680, 1650 (ketone); 1620 cm^{-1} (C=C). m/z 310 (M^+, 1%) 266 (26); 130 (83); 118 (34); 44 (100).

Anodic oxidation of the acid 190 (0.5g, 1.53 mM) at 1.51V by the

method described (p. 105) afforded the crude title lactone 208a or 208b as a pale gum (0.15g, 32%) which had i.r. and tlc characteristics similar to those described previously for lactone 208a or 208b. The i.r. spectrum of the product showed an extra absorption at 1730 cm^{-1} indicating the possible presence of the chromanone 209a or 209b.

WORK DESCRIBED IN CHAPTER THREE

2-Benzoyl-1-cyano-1,2,-dihydroisoquinoline 269

To a stirred mixture of potassium cyanide (75.5g, 1.16M) in water (480 ml) and isoquinoline (50g, 0.388M) at 0°C was added benzoyl chloride (109g, 0.779M) dropwise over 2.5h. After stirring for a further 1h the mixture was left at 4° overnight and a solid precipitated out. The product was filtered off washed with water (80 ml), 2N hydrochloric acid (80 ml), water (100 ml) and dried in a vacuum desiccator. Recrystallisation from chloroform-light petroleum afforded the title dihydroisoquinoline 269 as white crystals (46.1g, 46%) m.p. 124-5° (lit.[153] m.p. 125-6°). ν_{max} : 2220 (C≡N); 1665 (C=O); 1630 cm^{-1} (C=C).

Isoquinoline-1-carboxylic acid hydrobromide 271

The dihydroisoquinoline 269 (1.5g, 5.77 mM) was heated under reflux for 30 min. in glacial acetic acid (15 ml) and hydrobromic acid 1.5 ml, 48%). On cooling the reaction mixture solidified. Filtration of the mixture and washing the product with light petroleum (5 ml) and ether (5 ml) afforded the title acid 271 as orange crystals (1.07g, 73%) m.p. 198-200° (lit.[154] m.p. 202-3°). ν_{max} : 3600-2200 (salt bands); 1730 cm^{-1} (C=O).

Isoquinoline-1-carboxylic acid amide hydrochloride 272

The dihydroisoquinoline 269 (1g, 3.85 mM) was stirred for 3h in glacial acetic acid (10 ml) containing concentrated hydrochloric acid (2.5 ml). Evaporation of the solvents afforded the title amide hydrochloride 272 as white crystals (0.26g, 32%) m.p. 220-2° (from methanol). (Found : C, 57.5; H, 4.3; N, 13.5. $C_{10}H_8N_2O.HCl$ requires C, 57.6; H, 4.3; N, 13.4%). ν_{max} : 3660-2020 (salt bands); 1675 (C=O).

3,4-Dihydroisoquinoline 245a

Sodium hypochlorite (11 ml of a 2.2M solution, 24.2 mM) was added dropwise over 1h to a stirred solution of 1,2,3,4-tetrahydroisoquinoline 247a (2.66g, 20 mM) at 0°. After standing the mixture at room temperature overnight the precipitated sodium chloride was filtered off and the filtrate was heated under reflux with sodium hydroxide (5g) for 45 min. The methanol was evaporated and the residue extracted into ether (3 x 10 ml) and dried (Na_2SO_4). The ethereal solution was treated with crushed carbon dioxide and the precipitated carbonate was filtered off. Evaporation of the filtrate afforded 3,4-dihydroisoquinoline 245a as a colourless oil (1.68g, 64%) b.p. 100-5°/1 mm (lit.[110] b.p. 69-72°/2 mm). Picrate m.p. 172-3° (lit.[155] m.p. 174-6°) from ethanol. ν_{max} : 1575 cm^{-1} (C=N). δ : 2.40-3.95 (4H, m, $\underline{CH}_2$-$\underline{CH}_2$); 7.00-7.20 (4H, m, aromatics); 7.23 (1H, t, J = 2Hz, N = $\underline{CH}$).

2-Trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline 275

To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (5g, 37.6 mM) in dry chloroform (100 ml) at 0° was added trifluoroacetic anhydride (5.5 ml, 42.9 ml) in one portion. After stirring for 3h the organic solvent was evaporated, the residue dissolved in ether (30 ml) and washed with saturated sodium bicarbonate (5 x 10 ml), 2N hydrochloric acid (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the ether afforded the title amide 275 as a colourless oil (7.03g, 82%) b.p. 79-80°/0.1 mm (lit.[132] b.p. 136-8°/13 mm). (Found : C, 57.1; H, 4.4; N, 6.0. Calculated for $C_{11}H_{10}F_3NO$ C, 57.6; H, 4.4; N, 6.1%). ν_{max} (film) : 1690 cm^{-1} (C=O). δ : 2.87 [2H, t, J = $6H_2$, C(4)H_2]; 3.80[2H, t, J = $6H_2$, C(3)H_2]; 4.71[2H, s, C(1)H_2]; 7.14 (4H, s, aromatics).

2-Trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 278

To a stirred solution of 1,2,3,4 - tetrahydroisoquinoline (20.4g, 0.153 M) in dry ether (200 ml) containing triethylamine (20g) was added dropwise a solution of trimethylacetyl chloride (20g, 0.166M) in dry ether (200 ml). After 2h the precipitated triethylamine hydrochloride was filtered off and washed with ether. The filtrate was washed with 2N hydrochloric acid (2 x 100 ml), water (3 x 100 ml) and dried ($MgSO_4$). Removal of the solvent afforded the title amide 278 as white platelets (30.3g, 91%) m.p. 64-5° (lit.[133] m.p. 65°) (from aqueous methanol or light petroleum). ν_{max} : 1620 cm^{-1} (C=O). δ : 1.30 (9H, s, 3 x CH_3); 2.84 [2H, t, J = $6H_2$, C (4)H_2]; 3.81[2H, t, J = $6H_2$, C(3)H_2]; 4.70[2H, s, C(1)H]; 7.05 (4H, s, ar.).

1-Lithio-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 279

n-Butyl-lithium (3.27 ml, 1.55M solution in hexane, 5.07 mM) was added by syringe to stirred di-isopropylamine (0.71 ml, 5.07 mM) at -10° under a flow of dry nitrogen. After 15 min the lithium di-isopropylamide formed as a white gum and was diluted with tetrahydrofuran (15 ml). The temperature was lowered to -78° and a solution of the amide 278 (1g, 4.61 mM) in tetrahydrofuran (10 ml) was added in one portion to produce the crimson lithiated intermediate 279.

General Preparation of 1-Benzyl-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinolines

To a stirred solution of the lithiated intermediate 279 (4.61 mM) in tetrahydrofuran (25 ml) at -78° under a flow of nitrogen was added in one portion a solution of the appropriate benzyl halide (4.61 mM) in tetrahydrofuran (10 ml). Stirring was continued for 1h at -78° and the mixture was allowed to reach room temperature. The mixture was quenched with water (30 ml) and extracted with

ether (3 x 20 ml). The combined ether extracts were washed with 2N hydrochloric acid (2 x 20 ml), water (3 x 20 ml), brine (20 ml) and dried ($MgSO_4$). The solvent was removed and the product purified as detailed below.

1-(4-Benzyloxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 291

From 4-benzyloxybenzyl chloride (1.08g, 4.65 mM) and the lithiated intermediate 279 (4.61 mM) the title amide 291 was isolated as colourless crystals (1.65g, 86%) m.p. 121-22.5 after trituration with a little ether and recrystallisation from methanol. (Found : C, 80.9; H, 7.6; N, 3.4. $C_{28}H_{31}NO_2$ requires C, 81.3; H, 7.6; N, 3.4%). ν_{max} : 1620 cm^{-1} (C=O). δ : 1.27 (9H, s, 3 x CH_3); 2.64-3.54 [4H, m, benzylic CH_2, and C(4)H_2]; 4.00-4.30 [2H, m, C(3)H_2]; 4.97(2H, s, OCH_2); 5.75 [1H, t, J = 7Hz C(1)H]; 6.70-7.30 (13H, m, aromatics).

1-(3,4,5-Trimethoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 292

From the 3,4,5-trimethoxybenzyl chloride (2g, 9.24 mM) and the lithiated intermediate 279 (9.22 mM) the title amide 292 after trituration with petroleum b.p. 40-60° and recrystallisation from ether or methanol was isolated as colourless prisms (3.39g, 93%) m.p. 139.5- 40.5. (Found : C, 72.9; H, 8.1; N, 3.5. $C_{24}H_{31}NO_4$ requires C, 72.5; H, 7.8; N, 3.4%). ν_{max} : 1610 cm^{-1} (C=O). δ : 1.25 (9H, s, 3 x CH_3); 2.67-3.54[4H, m, benzylic CH_2 and C(4)H_2]; 3.72 (6H, s, 2 x OCH_3); 3.81 (3H, s, OCH_3); 3.87-4.30[2H, m, C(3)H_2)]; 5.85[1H, t, J = 7Hz, C(1)H]; 6.28 (2H, s, ar. ortho to OCH_3); 6.80-7.28 (4H, m, aromatics).

1-(3,4-Dimethoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 293

From 3,4-dimethoxybenzyl chloride (2.85g, 15.3 mM) and the lithiated

intermediate 279 (15.2 mM) the title amide 293 was obtained as colourless crystals (5.0g, 90%) m.p. 149-50° (from methanol). (Found : C, 75.3; H, 8.0, N, 3.7. $C_{23}H_{29}NO_3$ requires C, 75.2; H, 7.9; N, 3.8%). ν_{max} : 1620 cm^{-1} (C=O). δ : 1.21 (9H, s, 3 x CH_3); 2.60-3.48[4H, m, benzylic CH_2 and C(4) H_2]; 3.70 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 3.96-4.26[2H, m, C(3)H_2]; 5.75[1H, t, J = 7Hz, C(1)H]; 6.51-7.07 (7H, m, aromatics).

1-(4-Methoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 294.

From 4-methoxybenzyl chloride (7.3g, 46.6 mM) and the lithiated intermediate 279 (46.1 mM) the title amide 294 was isolated as colourless prisms (15.1g, 97%) m.p. 111-3° (from methanol). (Found : C, 78.7; H, 8.2; H, 4.0. $C_{22}H_{27}NO_2$ requires C, 78.3, H, 8.0; N, 4.2%). ν_{max} : 1620 cm^{-1} (C=O). δ : 1.20 (9H, s, 3 x CH_3); 2.64-3.56 [4H, m, benzylic CH_2 and C(4)H_2]; 3.72 (3H, s, OCH_3; 4.02-4.30[2H, m, C(3)H_2]; 3.74[1H, t, J = 7Hz, C(1)H]; 6.72 (2H, d, J = 9Hz, ar. ortho to OCH_3); 6.91-7.10 (6H, m, aromatics).

Methyl 2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 280.

To the stirred lithiated intermediate 279 (4.61 mM) in tetrahydrofuran (20 ml) at -78° under a flow of nitrogen was added excess crushed carbon dioxide. After 1h the cooling bath was removed, the mixture allowed to reach room temperature and quenched with water (20 ml). The aqueous layer was collected and the organic layer was extracted with saturated sodium bicarbonate solution (3 x 10 ml). The aqueous fractions were combined, carefully acidified with concentrated hydrochloric acid, extracted with dichloromethane (3 x 20 ml), and the bulk extracts were dried ($MgSO_4$). Evaporation of the solvent

afforded crude 2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 298 as a tan gum (0.8g, 67%). ν_{max} (film) : 3500-2300 (H-bonded OH); 1710 (C=O, acid); 1630 cm^{-1} (C=O, amide).

The crude acid 298 (0.8g, 3.07 mM) in dichloromethane (10 ml) was added to a solution of diazomethane in ether. After 3h the excess diazomethane was destroyed by the dropwise addition of glacial acetic acid (2 ml). The mixture was washed with saturated sodium bicarbonate solution (2 x 10 ml), water (3 x 10 ml), brine (10 ml) and dried ($MgSO_4$). Removal of the solvent afforded the title methyl ester 280 as a white solid (0.84g, 66% overall) b.p. 136°/0.08 mm m.p. 162-3.5°. (Found : C, 69.5; H, 7.6; N, 5.2. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.6; N, 5.1%). ν_{max} : 1740 (C=O, ester); 1630 cm^{-1} (C=O, amide). δ_H : 1.29 (9H, s, 3 x CH_3); 2.88[2H, t, J = 6Hz, C(4)H_2]; 3.65 (3H, s, OCH_3); 3.84-4.08[2H, m, C(3)H_2)]; 5.77[1H, s, C(1)H_2]; 7.07-7.58 (4H, m, aromatics). δ_C : 28.0; 29.0; 38.7; 43.0; 52.3; 58.1; 126.5; 127.5; 128.2; 130.5; 134.8; 171.5; 177.8.

Benzyl-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 299.

A stirred mixture of the crude acid 298 (2.5g, 9.58 mM), benzyl chloride (1.22g, 9.64 mM), potassium carbonate (1.33g, 9.64 mM) and sodium iodide (50 mg) in dry acetone (50 ml) was heated under reflux for 48h. The mixture was cooled, filtered and the acetone removed in vacuo to yield a brown oil. Extraction of the oil into light petroleum, and treatment with activated charcoal afforded the title benzyl ester 299 as colourless needles (1.92g, 57%) m.p. 91-2° (from light petroleum). (Found : C, 74.8; H, 7.1; N, 4.0. $C_{22}H_{25}NO_3$ requires C, 75.2; H, 7.1; N, 4.0%). ν_{max} : 1745 (C=O,

ester); 1620 cm^{-1} (C=O, amide). δ_H : 1.30 (9H, s, 3 x CH_3); 2.89[2H, t, J = 6Hz, C(4)H_2]; 3.85-4.10[2H, m, C(3)H_2]; 5.12(2H, s, CH_2Ph); 5.87[1H, s, C(1) H]; 7.12-7.67 (9H, m, aromatics). δ_C : 28.0; 29.2; 38.8; 43.0; 58.3; 67.1; 126.5; 127.7; 128.0; 128.4; 130.5; 134.9; 135.7; 170.8; 177.8.

General Method for the Alkylation of the Benzyl and Methyl Esters 280, 299.

To a stirred solution of the ester 280,299 (0.727 mM) in DMF (10 ml) under a flow of nitrogen at 0° was added sodium hydride (5 mM); a yellow colour appeared. After stirring the mixture for 30 min the appropriate electrophile (0.73 mM) was added neat or in DMF (10 ml). The mixture was stirred for a further 30 min, poured into ice-water (10 ml), and extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water (3 x 10 ml), dried over magnesium sulphate and the solvent removed under reduced pressure, the resulting crude product purified as detailed below.

Methyl 1-methyl-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 281.

From the methyl ester 280 (1g, 3.64 mM) and methyl iodide (0.65g, 4.58 mM) the title isoquinoline 281 was obtained as colourless crystals (0.7g, 67%) m.p. 133-4° (from methanol). (Found : C, 70.4; H, 8.0; N, 5.1. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8%). ν_{max} : 1730 (C=O, ester); 1625 cm^{-1} (C=O, amide). δ : 1.32 {9H, s, [C-$(CH_3)_3$]}; 1.79 [3H, s, C(1) CH_3]; 2.78-3.10[2H, m, C(4)H_2]; 3.54 (3H, s, OCH_3); 4.00-4.44 [2H, m, C(3)H_2]; 7.09-7.24 (4H, m, aromatics).

Methyl 1-ethyl-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 282.

From the methyl ester 280 (0.2g, 0.727 mM) and ethyl iodide (excess)

the title isoquinoline 282 was obtained as white crystals (0.2g, 91%) m.p. 105-7° (from aqueous methanol). (Found : C, 70.2; H, 8.3; N, 4.3. $C_{18}H_{25}NO_3.\frac{1}{4}H_2O$ requires C, 70.2; H, 8.3; N, 4.6%). ν_{max} : 1735 (C=O, ester); 1630 cm^{-1} (C=O, amide). δ : 0.66 (3H, t, J = 6Hz, $CH_2\underline{CH_3}$); 1.32 (9H, s, 3 x CH_3); 2.15-2.98 [4H, m, $CH_3\underline{CH_2}$ and C(4) H_2]; 3.48 (3H, s, OCH_3); 3.90-4.36[2H, m, C(3) H_2]; 7.06-7.36 (4H, m, aromatics).

Methyl 1-(4-nitrobenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 283.

From the methyl ester 280 (0.2g, 0.727 mM) and 4-nitrobenzyl iodide 284 (0.2g, 0.76 mM) the title benzylisoquinoline 283 was obtained as orange crystals (0.12g, 40%) m.p. 153-4° (from methanol). (Found : C, 66.3; H, 6.2; N, 6.7. $C_{23}H_{26}N_2O_5.\frac{1}{2}CH_3OH$ requires C, 66.2; H, 6.6; N, 6.6%). ν_{max} : 1740 (C=O, ester); 1635 (C=O, amide); 1520, 1350 cm^{-1} (NO_2). δ : 1.30 (9H, s, 3 x CH_3); 2.60-3.04[2H, m, C(4)H_2]; 3.60 (3H, s, OCH_3); ca. 3.60-3.94[2H, m, C(3)H_2]; 3.95 (2H, ABq, J = 13Hz, benzylic CH_2); 6.74 (2H, d, J = 9Hz, ar. meta to NO_2); 6.94-7.70 (4H, m, aromatics); 7.82 (2H, d, J = 9Hz, ar. ortho to NO_2).

Methyl 1-(3,4,5-trimethoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 288.

From the methyl ester 280 (1g, 3.64 mM) and 3,4,5-trimethoxybenzyl iodide 285 (1.07g, 3.66 mM) the title benzylisoquinoline 288 was obtained as colourless cubes (0.8g, 48%) m.p. 145-7° (from methanol). (Found : C, 69.1; H, 7.3; N, 3.2. $C_{26}H_{33}NO_6$ requires C, 68.6; H, 7.3; N, 3.1%). ν_{max} : 1735 (C=O, ester); 1625 cm^{-1} (C=O, amide). δ : 1.33 (9H, s, 3 x CH_3); 2.70-3.06 [2H, m, C(4) H_2]; 3.44-4.16 [4H, m, benzylic CH_2 and C(3) H_2]; 3.54, 3.60, 3.75 (12H, 3s, 4 x OCH_3); 5.85 (2H,s, ar. ortho to OCH_3); 7.13-7.74 (4H, m, aromatics).

4-Benzyloxybenzyl iodide 285.

Thionyl chloride (8.6g, 86.4 mM) was added dropwise to a stirred solution of 4-benzyloxybenzyl alcohol (10g, 46.7 mM) in dry benzene (30 ml). The mixture was heated under reflux for 2h and treated with activated charcoal. The removal of the solvent afforded 4-benzyloxybenzyl chloride (10.6g, 98%) as tan crystals m.p. 76-77° (lit.[156] m.p. 75-77°).

To a solution of 4-benzyloxybenzyl chloride (2g, 8.6 mM) in dry acetone (20 ml) was added sodium iodide (1.5g, 10 mM). After heating the mixture at 100° for 10 min the precipitated sodium chloride was filtered off and the acetone removed in vacuo at room temperature. The residue was extracted with light petroleum and the soluble benzyl iodide 285 was used without further purification.

Methyl 1-(4-benzyloxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 287.

From the methyl ester 280 (3g, 10.9 mM) and 4-benzyloxybenzyl iodide 285 (3.6g, 11.1 mM) the title benzylisoquinoline 287 was obtained as a gum (2.69g, 52%) which failed to crystallise. ν_{max} (film) : 1740 (C=O, ester); 1630 cm^{-1} (C=O, amide). δ : 1.29 (9H, s, 3 x CH_3); 2.59-2.95 [2H, m, C(4)H_2]; 3.56(3H, s, OCH_3); 3.40-4.20 [4H, m, benzylic CH_2 and C(3)H_2]; 4.93 (2H, s, OCH_2); 6.60-7.70 (13H, m, aromatics). The ester 287 was fully characterised by debenzylation to the hydroxy ester 290 (see later).

Benzyl 1-methyl-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 300.

From the benzyl ester 299 (0.2g, 0.57 mM) and methyl iodide (excess) the title isoquinoline 300 was obtained as colourless crystals (0.17g, 82%) m.p. 95-6° (from light petroleum). (Found : C, 75.5;

H, 7.4, N, 3.9. $C_{23}H_{27}NO_3$ requires C, 75.6; H, 7.4; N, 3.8%). ν_{max} : 1740 (C=O, ester); 1625 cm^{-1} (C=O, amide). δ : 1.24 (9H, s, 3 x CH_3); 1.81 (3H, s, CH_3); 2.82-4.43 (4H, m, CH_2-CH_2); 4.95 (2H, ABq, J = 13Hz, CH_2Ph); 7.08-7.24 (9H, m, aromatics).

Benzyl 1-(4-benzyloxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate 301.

From the benzyl ester 299 (1g, 2.85 mM) and 4-benzyloxybenzyl iodide 285 (0.93g, 2.87 mM) the crude title benzylisoquinoline 301 was obtained as a white gum (1.31g, 84%). ν_{max} (film) : 1735 (C=O, ester); 1630 cm^{-1} (C=O, amide). The benzyloxy ester 301 was fully characterised by hydrogenation to the phenolic acid 302 (see later).

Methyl 1-(4-hydroxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate 290.

Prepared by the catalytic hydrogenation of the benzyl ether 287 (2.69g, 5.71 mM) in methanol (80 ml) as previously described for the phenol 188. Evaporation of the solvent afforded the title phenolic ester 290 as colourless crystals (1.2g, 55%) m.p. 205.5-6° (from chloroform-light petroleum). (Found : C, 72.4; H, 7.2; N, 3.7. $C_{23}H_{27}NO_4$ requires C, 72.4; H, 7.1; N, 3.7%). ν_{max} : 3260 (OH); 1730 (C=O, ester); 1595 cm^{-1} (C=O, amide). δ : 1.28 (9H, s, 3 x CH_3); 2.02-3.00 (4H, m, CH_2-CH_2); 3.50 (3H, s, OCH_3); 3.68 (2H, m, ABq, benzylic CH_2); 6.30-6.65 (4H, m, ar. ortho and meta to OH); 6.70 (1H, s, exchanges with D_2O, OH); 6.80-7.56 (4H, m, aromatics).

Methyl 1-(4-aminobenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate 306.

Prepared by the catalytic hydrogenation of the nitro ester 283 (0.5g, 1.22 mM) in methanol (100 ml) as previously described for

the phenol 188. Evaporation of the solvent afforded the crude title amino ester 306 as a fawn solid (0.37g, 80%)) which could not be recrystallised. ν_{max} : 3540, 3460 (NH_2); 1735 (C=O, ester); 1625 cm^{-1} (C=O, amide). δ : 1.26 (9H, s, 3 x CH_3); 2.58-2.95[2H, m, C(4)H_2]; 3.36-4.14[4H, m, benzylic CH_2 and C(3)H_2]; 3.54 (3H, s, OCH_3); 6.42-7.59 (10H, m, aromatics and NH_2).

Methyl 1-[4-(p-toluenesulphonamido)benzyl]-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 307.

Prepared from the crude amino ester 306 (0.28g, 0.737 mM) by the method described for the sulphonamide 198. The title sulphonamide 307 was obtained as a yellow froth (0.35g, 89%) which failed to crystallise. ν_{max} : 3300 (NH); 1750 (C=O, ester); 1620 (C=O, amide); 1170 cm^{-1} (SO_2N). δ : 1.23 (9H, s, 3 x CH_3); 2.34 (3H, s, ar.-CH_3); 2.42-2.73[2H, m, C(4)H_2]; 3.57 (3H, s, OCH_3); 3.35-4.18 4H, m, benzylic CH_2 and C(3)H_2 ; 6.39-7.75(12H, m, aromatics).

1-(4-Hydroxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline 297.

Prepared by the catalytic hydrogenation of the benzyl ether 291 (2.68g, 6.48 mM) in ethyl acetate (100 ml) as previously described for the phenol 188. Evaporation of the solvent afforded the title phenol 297 as colourless plates (0.43g, 21%) m.p. 225-7°. (Found : C, 77.9; H, 7.8, N, 4.3. $C_{21}H_{25}NO_2$ requires C, 78.0; H, 7.7; N, 4.3%). ν_{max} : 3290 (OH); 1610 cm^{-1} (C=O).

1-(3,4,5-Trimethoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid 289.

The amide 292 (1g, 2.52 mM) was lithiated with lithium di-isopropyl-amide [prepared from methyl-lithium (1.98 ml, 1.4M solution, 2.77 mM and di-isopropylamine (0.39 ml, 2.77 mM)] and was reacted with

carbon dioxide as described for acid 298. It was obtained as colourless platelets (0.52g, 47%) m.p. 204-6° from chloroform-light petroleum). (Found C, 67.8; H, 7.1; N, 3.2. $C_{25}H_{31}NO_6$ requires C, 68.0; H, 7.0; N, 3.2%). ν_{max} : 3420-3140 (O-H); 1735 (C=O, acid); 1620 cm^{-1} (C=O, amide). δ ($CDCl_3$/DMSO) : 1.30 (9H, s, 3 x CH_3); 2.50-2.97 [2H, m, C(4)H_2]; 3.72{2H, ABq, J = 14Hz, benzylic CH_2 partially obscured by 3.52(6H, s, 2 x OCH_3), 3.67 (3H, s, OCH_3) and ca. 3.6[2H, m, C(3)H_2]}; 5.86 (2H, s, ar. ortho to OCH_3); 6.90-7.76 (4H, m, aromatics); 7.93 (1H, s, shifts to 7.49 with D_2O, CO_2H).

1-(3,4-Dimethoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 295

Prepared from the amide 293 (1g, 2.72 mM) by the method described for the acid 298 as white platelets (0.5g, 45%) m.p. 191-2° (from chloroform-light petroleum). (Found C, 70.0; H, 7.2; N, 3.4. $C_{24}H_{29}NO_5$ requires C, 70.1; H, 7.1; N, 3.4%). ν_{max} : 3500-2500 (H-bonded O-H); 1735 (C=O, acid); 1620 cm^{-1} (C=O, amide). δ ($CDCl_3$/DMSO) : 1.28 (9H, s, 3 x CH_3); 2.40-2.76[2H, m, C(4)H_2]; 3.67{2H, ABq, J = 14Hz, benzylic CH_2 partially obscured by 3.37 (3H, s, OCH_3), 3.66 (3H, s, OCH_3); and ca. 3.5[2H, m, C(3)H_2]}; 5.96 [1H, s, ar. (2')H]; 6.24[1H, d, J = 8Hz, ar.(5')H]; 6.66 [1H, d, J = 8Hz, ar.(6')H]; 6.95-7.75(4H, m, aromatics).

1-(4-Methoxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 296.

Prepared from the amide 294 (8g, 23.7 mM) by the method described for the acid 298 as white platelets (4g, 44%) m.p. 240-3° (from chloroform-light petroleum). (Found : C, 71.9; H, 7.1; N, 3.5. $C_{23}H_{27}NO_4$ requires C, 72.4; H, 7.1; N, 3.7%). ν_{max} : 3600-2500 (H-bonded O-H); 1740 (C=O, acid); 1615 cm^{-1} (C=O, amide). δ (DMSO) :

1.08 (9H, s, 3 x CH_3); 2.12-2.60[2H, m, C(4)H_2]; 3.42 (3H, s, OCH_3); ca. 3.48 [2H, m, C(3)H_2 hidden by 3.48 (2H, ABq, J = 14Hz, benzylic CH_2)]; 6.34 (4H, s, ar. ortho and meta to OCH_3); 6.75-7.63 (4H, m, aromatics); 7.99 (1H, s, CO_2H).

1-(4-Hydroxybenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 302.

The benzyl ester 301 (1.3g, 2.38 mM) was hydrogenated in tetrahydrofuran by the method described for the phenol 188. Evaporation of the solvent afforded the title phenolic acid 302 as colourless crystals (0.6g, 69%) m.p. 222° (from acetone). [Found : C, 71.2; H, 7.1; N, 3.8. $C_{22}H_{25}NO_4.\frac{1}{2}(CH_3)CO$ requires C, 71.2; H, 7.1; N, 3.5%]. ν_{max} : 3600-2000 (H-bonded OH); 1705 (C=O, acid); 1605.cm^{-1} (C=O, amide). δ (DMSO) : 1.24 (9H, s, 3 x CH_3); 2.14-2.64 (4H, m, CH_2-CH_2) 3.65 (2H, ABq, J = 13Hz, benzylic CH_2); 3.67 (1H, s, exchanges with D_2O, ar. OH); 6.34 (4H, s, ar. ortho and meta to OH); 7.00-7.62 (4H, m, aromatics); 8.42-9.60 (1H, broad s, exchanges with D_2O, CO_2H).

1-[4-(p-Toluenesulphonamido)benzyl]-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 305.

From the benzyl ester 299 (1.5g, 4.27 mM) and 4-nitrobenzyl iodide (1.13g, 4.3 mM) was obtained benzyl 1-(4-nitrobenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 303 as a red gum (0.9g, 43%) which could not be crystallised. ν_{max} (film) : 1740 (C=O, amide); 1630 (C=O, amide); 1520, 1340 cm^{-1} (NO_2).

The above benzylisoquinoline 303 (0.9g, 1.85 mM) was hydrogenated in tetrahydrofuran by the method described for the phenol 188 to yield crude 1-(4-aminobenzyl)-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 304 as yellow solid (0.52g, 77%).

ν_{max} : 3600-2200 (salt bands); 1725 (C=O, acid); 1620 cm^{-1} (C=O, amide). δ : 1.26 (9H, s, 3 x CH_3); 2.45-4.03 (6H, m, benzylic CH_2 and $\underline{CH_2}$-$\underline{CH_2}$); 6.20 (2H, s, exchanges with D_2O, NH_2); 6.36 (4H, s, ar. ortho and meta to NH_2); 6.95-7.70 (4H, m, aromatics).

The above amino acid 304 (0.5g, 1.49 mM) was treated with p-toluenesulphonyl chloride (0.29g, 1.52 mM) by the method described for the sulphonamide 198 to yield 1-[4-(p-toluenesulphonamido)benzyl]-2-trimethylacetyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 305 as an orange froth (0.52g, 73%). ν_{max} : 3600-2300 (salt bands); 1705 (C=O, acid); 1625 (C=O, amide), 1155 cm^{-1} (SO_2N). δ : 1.23 (9H, s, 3 x CH_3); 2.33 (3H, s, ar.-CH_3); 2.45-4.12 (6H, m, benzylic CH_2 and $\underline{CH_2}$-$\underline{CH_2}$); 6.38 (12H, m, aromatics).

Reaction between acid 302 and N-bromosuccinimide

3,5-Dibromo-3",4"-dihydro-2"-pivaloyldispiro[cyclohexa-2,5-diene-1,2'(3'H)-furan-4'(5'H),1"(2"H)-isoquinoline]-4,5'-dione 308.

The title compound 308 was prepared from the phenolic acid 302 (0.2g, 0.54 mM) and N-bromosuccinimide (0.31g, 1.74 mM) by the method described for the naphthalene analogue 219 with THF (10 ml) as a co-solvent. The product was isolated as a purple solid (0.17g, 60%) m.p. 204-6° (methanol). ν_{max} : 1785 (γ-lactone); 1685 (ketone); 1620 cm^{-1} (C=C). δ : 1.37 (9H, s, 3 x CH_3); 2.27-3.85 (6H, m, N-$\underline{CH_2}$-$\underline{CH_2}$, and $\underline{CH_2}$); 7.23-7.36 (6H, m, aromatics and vinylics). m/z (EI) 521 (M^+, 1%); 477 (M-CO_2, 2); 392(7); 57(100); 44(48). m/z (CI) 522 (M^+ + H, 0.5%); 478 (M + H-CO_2, 40); 396(40); 132(100).

WORK DESCRIBED IN CHAPTER FOUR

Preparation of 1,2,3,4-Tetrahydroisoquinoline-1-carboxylic Acids

3,4,5-Trimethoxyphenylpyruvic acid 316

A solution of 3,4,5-trimethoxybenzaldehyde (25.9g, 132 mM), hippuric acid (40g) and anhydrous sodium acetate (13g) in acetic anhydride (70 ml) was heated at 100° for 2h. After cooling overnight at 4° the precipitated azlactone 315 (38g, 88%) was filtered off, washed with water and aqueous ethanol, and air-dried m.p. 163-4° (lit.[157] m.p. 165-6°).

A solution of the azlactone 315 (38g, 116 mM) in aqueous sodium hydroxide (38g in 300 ml) was heated at 100° for 3h. Sulphur dioxide was bubbled through the cooled solution and the precipitated benzoic acid filtered off. The filtrate was made strongly acidic with 4M hydrochloric acid and boiled to precipitate the title acid 316 as fawn crystals (23.1g, 68%) m.p. 116-7° (lit.[157] m.p. 168-9°) (from acetic acid). ν_{max} : 3400 (enol OH); 3260 (salt band); 1700 cm^{-1} (acid).

3,4-Dimethoxyphenylpyruvic acid 317

Prepared by the method described for the acid 316 from 3,4-dimethoxybenzaldehyde (20.8g, 0.125M) as fawn crystals (17.5g, 62%) m.p. 182-3° (lit.[158] 187°) (from acetic acid). ν_{max} : 3400 (enol OH); 3280 (salt band); 1695 cm^{-1} (acid). δ ($CDCl_3$/DMSO) : 3.80 (6H, s, 2 x OCH_3); 6.40 (1H, s, C=C-H); 6.80-7.45 (3H, m, aromatics); 9.20-10.60 (1H, broad s, exchanges with D_2O, CO_2H).

Benzylisovanillin 326

To a stirred solution of isovanillin (55.9g, 368 mM) in ethanol (250 ml) was added potassium hydroxide (21g) in water (60 ml) and benzyl chloride (50.5g, 400 mM). The mixture was heated under

reflux for 4h and cooled overnight. The liquid phase was decanted and reduced to low volume in vacuo. The residues were poured into alkaline water (2l). The aqueous layer was decanted and more alkaline water (3l) was added. The aqueous layer was decanted and the solid residue was recrystallised from ethanol to give benzylisovanillin 326 as tan crystals (67.7g, 76%) m.p. 63-4° (lit.[159] m.p. 63°. ν_{max} : 1680 cm^{-1} (C=O). δ : 3.90 (3H, s, OCH_3); 5.10 (2H, s, OCH_2); 6.8-7.35 (8H, m, aromatics); 9.77 (1H, s, CHO).

3-Benzyloxy-4-methoxy-ω-nitrostyrene 327

A solution of benzylisovanillin 326 (60g, 0.25M), ammonium acetate (18g, 0.25M) and nitromethane (90 ml) in glacial acetic acid (180 ml) was heated under reflux for 1.5h and cooled overnight at 4°. The crystalline product was filtered off, washed with ether (300 ml) and recrystallised from ethanol to give bright yellow flakes of the title nitrostyrene 327 (54g, 76%) m.p. 124-7° (lit.[160] m.p. 125-7°). ν_{max} : 1625 (C=C); 1510, 1335 cm^{-1} (NO_2). δ : 3.90 (3H, s, OCH_3); 5.10 (2H, s, OCH_2); 6.83-7.98 (10H, m, aromatics and vinylics).

3-Benzyloxy-4-methoxy-β-phenylethylamine hydrochloride 328

To a stirred slurry of lithium aluminium hydride (30g, 0.4M) in dry THF (1l) was added a solution of the styrene 327 (66g, 0.23M) in dry THF (1l) dropwise under a flow of dry nitrogen. After this addition the mixture was stirred for a further hour and the excess lithium aluminium hydride destroyed by the successive addition of 20% aqueous THF (100 ml), and 50% aqueous THF (100 ml). A solution of sodium hydroxide (65g) in water (200 ml) was added dropwise to afford a granular precipitate of inorganic salts and a clear organic layer which was decanted off. The precipitate was washed with more THF (3 x 100 ml) and the THF portions were combined and

evaporated to yield a brown oil. The brown oil was dissolved in ether (1l) and heated under reflux for 1h. The solution was filtered and the filtrate washed with water (2 x 500 ml) and dried (K_2CO_3). The ethereal solution was treated with small portions of ethanolic hydrogen chloride and the resulting white precipitate was filtered off and washed with ether. Recrystallisation from ethanol-ether afforded the title hydrochloride 328 as white crystals (46.4g, 68%) m.p. 163-4° (lit.[161] m.p. 166°). δ : 3.00 (4H, s, $\underline{CH_2}$-$\underline{CH_2}$); 3.78 (3H, s, OCH_3); 5.03 (2H, s, OCH_2); 6.75-7.90 (11H, m, aromatics and $\underline{NH_2}.\underline{HCl}$).

3-Hydroxy-4-methoxy-β-phenylethylamine hydrochloride 313

A solution of the benzyl ether hydrochloride 328 (10g, 34 mM) in ethanol (100 ml) containing conc. hydrochloric acid (50 ml) was heated under reflux for 9h. Evaporation of the solvent afforded the title phenolic hydrochloride 313 as tan crystals (5.6g, 80%) m.p. 203° (lit.[162] m.p. 204-6°) (from methanol-ether). ν_{max} : 3340 (OH); 3200-2500 cm^{-1} (salt bands).

N-formyl-β-(3,4-dimethoxyphenyl)-ethylamine 332

Formic acid (5.6 ml, 148 mM) was added dropwise to a solution of homoveratrylamine 46 (26.6g, 147 mM) in ether (250 ml). The precipitated white crystals were heated at 180° for 2h to afford the title amide 332 as a tan oil (26.1g, 85%). ν_{max} (film) : 3360 (NH); 1675 cm^{-1} (C=O).

6,7-Dimethoxy-3,4-dihydroisoquinoline 330

Phosphoryl chloride (55 ml) was added dropwise to a solution of the amide 332 (36.3g, 174 mM) in toluene (250 ml) at 0°. The mixture was heated under reflux for 1.5h and poured into light petroleum (800 ml). The petroleum was decanted, the residue dissolved in

2M hydrochloric acid (300 ml) and basified with 4M sodium hydroxide. Extraction with ether (3 x 100 ml) and evaporation of the solvent afforded the title imine 333 as a tan oil (24.6g, 74%). ν_{max} (film) : 1580 cm^{-1} (C=N). δ : 2.40-2.70 (2H, m, N-CH_2-CH_2); 3.50-3.85 (8H, m, 2 x OCH_3, N-CH_2); 6.60, 6.75 (2H, 2s, aromatics); 8.15 (1H, broad t, N=C-H).

2-Benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 242b

Benzoyl chloride (1.2g, 8.5 mM) was added dropwise to a stirred mixture of the dihydroisoquinoline 333 (0.35g, 1.8 mM) in dichloromethane (10 ml) and potassium cyanide (1g, 15.3 mM) in the minimum of water. The mixture was stirred for 3h and poured into 2M sodium hydroxide (15 ml). The organic layer was washed with 2M sodium hydroxide (15 ml), 2M hydrochloric acid (2 x 15 ml) water, (3 x 15 ml), and dried ($MgSO_4$). Evaporation of the solvent afforded the title amide 242b as white crystals (0.3g, 51%) m.p. 214-5° (lit.[115] m.p. 212-3°) (from chloroform-light petroleum). ν_{max} : 1630 cm^{-1} (C=O). δ : 2.75-3.50 (4H, m, CH_2-CH_2); 3.90 (6H, s, 2 x OCH_3); 6.25 (1H, s, N-C-H); 6.65, 6.75 (2H, 2s, ar. ortho to O); 7.45 (5H, s, aromatics).

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline 334

3,4-Methylenedioxybenzyl chloride (1.1g, 6.45 mM) was added in portions to a mixture of the Reissert compound 242b (2g, 6.2 mM) and sodium hydride (0.4g) in dry DMF (20 ml) under nitrogen. The mixture was stirred for 2h, poured onto crushed ice (30g) and extracted with chloroform (3 x 20 ml). The combined extracts were washed with 2M hydrochloric acid (2 x 20 ml), 2M sodium hydroxide (2 x 20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Evaporation

of the solvent afforded the title benzyl Reissert compound 334 as colourless crystals (2.3g, 81%) m.p. 189.5-190.5° (lit.[116] m.p. 191-2°). (Found : C, 70.8; H, 5.4; N, 6.1. Calculated for $C_{27}H_{24}N_2O_5$ C, 71.1; H, 5.3; N, 6.1%): ν_{max} : 1655 cm^{-1} (C=O). δ : 1.96-2.35 (2H, m, N-CH_2-CH_2); 3.19-4.39 (4H, m, N-CH_2, benzylic CH_2); 3.82, 3.85 (6H, 2s, 2 x OCH_3); 5.80 (2H, s, O-CH_2-O); 6.04, 6.17, 6.20, 6.47, 6.60, 7.05, 7.37 (10H, 7s, aromatics).

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline 335

The title compound 335 was prepared by the method described for the benzyl Reissert compound 334 from 3,4,5-trimethoxybenzyl chloride (1.4g, 6.47 mM) and the Reissert compound 242b (2g, 6.2 mM) as white crystals (2.2g, 71%) m.p. 197-8° (from methanol). (Found : C, 69.0; H, 6.1; N, 5.5. $C_{29}H_{30}N_2O_6$ requires C, 69.3; H, 6.0; N, 5.6%). ν_{max} : 1640 cm^{-1} (C=O). δ : 3.50-4.45 (21H, m, N-CH_2-CH_2, benzylic (CH_2, 5 x OCH_3); 5.75 (2H, s, ar. 2',6'); 6.45, 7.10, 7.20, 7.40 (7H, 4s, aromatics).

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline 336

To a stirred mixture of the Reissert compound 242b (2g, 6.2 mM), 3,4-dimethoxybenzyl chloride (1.2g, 6.4 mM) and cetyltrimethylammonium bromide (20 mg) in toluene (50 ml) under nitrogen was added 50% aqueous potassium hydroxide (1.5 ml) in one portion. The mixture was stirred overnight, acidified to pH6 with 2M sulphuric acid, extracted with toluene (3 x 20 ml) and the extracts dried ($MgSO_4$). Evaporation of the solvent afforded the title benzyl Reissert compound 336 as white crystals (1.8g, 61%) m.p. 161-3° (from methanol-ether). (Found : C, 70.5; H, 6.0; N, 5.8. $C_{28}H_{28}N_2O_5$ requires C, 71.2;

H, 5.9; N, 5.9%). ν_{max} : 1655 cm^{-1} (C=O). δ : 3.20-4.48 (18H, m, N-CH_2-CH_2, benzylic CH_2, 4 x OCH_3); 6.00-7.40 (10H, m, aromatics).

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline 337

Prepared by the method described for the benzyl Reissert compound 336 from 4-methoxybenzyl chloride (0.5g, 3.19 mM) and the Reissert compound 242b (1g, 3.1 mM) as white crystals (0.55g, 40%) m.p. 166-8° (from chloroform-light petroleum). (Found : C, 72.8; H, 5.8; N, 6.2. $C_{27}H_{26}N_2O_4$ requires C, 73.3; H, 5.9; N, 6.3%). ν_{max} : 1650 cm^{-1} (C=O). δ : 3.15-4.45 (15H, m, N-CH_2-CH_2, benzylic CH_2, 3 x OCH_3); 6.50, 6.60, 7.10, 7.45 (11H, 4s, aromatics).

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 339

A mixture of the benzyl Reissert compound 336 (0.5g, 1.06 mM) and 88% phosphoric acid (8 ml) was heated at 100° for 1h under a stream of nitrogen. The mixture was poured into water, the precipitated benzoic acid was filtered off and the filtrate adjusted to pH7 with concentrated aqueous ammonia. The solution was kept at 4° for 24h and the resulting precipitate was filtered off, washed with water and acetone to afford the title acid 339 as a fawn powder (0.2g, 49%) m.p. 236-8° (d). (Found : C, 64.6; H, 6.4; N, 3.8. $C_{21}H_{25}NO_6$ requires C, 65.1; H, 6.5; N, 3.6%). ν_{max} : 3080-2100 (salt bands); 1620 cm^{-1} (C=O).

6,7-Dimethoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 338

Prepared by the method described for acid 339 from the benzyl Reissert compound 335 (1.5g, 3 mM) as a fawn powder (1.04g, 77%). m.p. 235-8°. Recrystallisation from methanol-hydrochloric acid - ether afforded

the title acid hydrochloride 338 as white crystals m.p. 254-60(d). (Found : C, 57.5; H, 6.8; N, 3.4. $C_{22}H_{27}NO_7.HCl$ requires C, 58.2; H, 6.2; N, 3.1%). ν_{max} : 3160-2420 (salt bands); 1715 cm^{-1} (C=O).

6-Hydroxy-7-methoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid 311

To a solution of 3,4,5-trimethoxyphenylpyruvic acid 316 (5.08g, 20 mm) in water (20 ml) containing a few drops of ammonium hydroxide was added a solution of the amine hydrochloride 313 (4.06g, 20 mm) in water (40 ml). The pH was adjusted to 6 and the mixture was heated at 100° for 5 mins and left to cool overnight. The resulting solid (3.98g, 50%) was filtered off and a small portion was recrystallised from concentrated hydrochloric acid-methanol-ether to afford the title amino acid hydrochloride 311 as white crystals m.p. 250-2°(d) (lit.[20] m.p. 252-4°).

6-Hydroxy-7-methoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid 329

Prepared by the method described for acid 311 from 3,4-dimethoxy-phenylpyruvic acid 317 (1.05g, 4.9 mM) and the amine hydrochloride 313 (1g, 4.9 mM) as fawn crystals (0.98g, 53%) m.p. 233-5°(d) (lit.[102] m.p. 99-100°) (from acetic acid - water). (Found : C, 63.6; H, 6.3; N, 3.6. Calculated for $C_{20}H_{23}NO_6.\frac{1}{4}H_2O$ C, 63.6; H, 6.2; N, 3.7%). ν_{max} : 3500-3300 (OH); 3200-2500 (salt bands); 1625 cm^{-1} (C=O).

6-Hydroxy-7-methoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid 330

Prepared by the method described for the acid 311 from 3,4-methylene-dioxyphenylpyruvic acid 319 (4.16g, 20 mM) and the amine hydrochloride 313 (4.06g, 20 mM) as a fawn solid (3.53g, 52%) m.p. 273-8°(d). A small portion was recrystallised from concentrated hydrochloric

acid - methanol - ether to give the title acid hydrochloride 330 m.p. 273-5°(d). (Found : C, 54.8; H, 5.5; N, 3.4. $C_{19}H_{20}NO_6Cl.1\frac{1}{4}H_2O$ requires C, 54.8; H, 5.4; N, 3.4%). ν_{max} : 3500-2300 (salt bands); 1710 cm^{-1} (C=O). ν_{max} (free acid) : 3460 (OH); 3150-2300 (salt bands); 1630 cm^{-1} (C=O).

6-Hydroxy-7-methoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 331

Prepared by the method described for acid 311 from 4-methoxyphenylpyruvic acid 320 (1.2g, 6.2 mM) and the amine hydrochloride 313 (1.23g, 6.0 mM) as a fawn solid (1.41g, 68%). A small portion was crystallised from concentrated hydrochloric acid - methanol - ether to give the title acid hydrochloride 331 as white crystals m.p. 257-9°(d) (lit.[18] m.p. 258-61°d).

2-Trifluoroacetyl-6-hydroxy-7-methoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 345.

To a stirred suspension of the amino acid 311 (0.5g, 1.25 mM) in dry chloroform (15 ml) containing triethylamine (0.7 ml) was added trifluoroacetic anhydride dropwise until the acid just dissolved. The mixture was stirred for a further 3h, washed with water (3 x 5 ml), 2M hydrochloric acid (2 x 5 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded the title amide 345 as light brown cubes (0.48g, 80%) m.p. 192-3° (lit.[20] m.p. 191-2.5°) (from aqueous ethanol). ν_{max} : 3540 (OH); 3400-2400 (H-bonded OH); 1715 (acid); 1690 cm^{-1} (amide). δ ($CDCl_3$/DMSO) : 1.75-3.10 (4H, m, N-CH_2-CH_2); 3.25-3.98 (14H, m, 4 x OCH_3, benzylic CH_2); 5.6(1H, s, exchanges with D_2O, OH); 5.80 (2H, s, ar-2',6'); 6.42[1H, s, C(8)]; 6.98[1H, s, C(5)].

2-Trifluoroacetyl-6-hydroxy-7-methoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 346

The title compound 346 was prepared by the method described for

amide 345 from the amino acid 330 (1.5g, 4.2 mM) as tan crystals (1.3g, 68%) m.p. 188-90° (from aqueous ethanol). (Found : C, 55.7; H, 4.1; N, 3.0. $C_{21}H_{18}F_3NO_7$ requires C, 55.6; H, 4.0; N, 3.1%). ν_{max} : 3420 (OH); 1715 (acid); 1690 cm^{-1} (amide). δ : 2.40-2.95 (2H, m, N-CH_2-CH_2); 3.42-4.00 (7H, m, OCH_3, benzylic CH_2, N-CH_2); 5.86 (2H, s O-CH_2-O); 6.10-7.12 (5H, m, aromatics); 7.30-8.60 (1H, broad s, exchanges with D_2O, CO_2H).

2-Acetyl-6-hydroxy-7-methoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 347

To a stirred solution of the acid 311 (0.25g, 0.62 mM) in dry dichloromethane (5 ml) containing 4-N,N-dimethylaminopyridine (50 mg) was added acetic anhydride (2 ml) dropwise. The mixture was stirred overnight, diluted with dichloromethane (50 ml) and washed with 0.5M hydrochloric acid (5 x 20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded a tan solid (0.3g, 99%) which recrystallised from methanol as the title amido acid 347 as colourless needles m.p. 219-20.5. (Found : C, 59.3; H, 6.3; N, 2.6. $C_{23}H_{27}NO_8.H_2O$ requires C, 59.6; H, 6.3; N, 3.0%). ν_{max} : 3540 (OH); 1730 (acid); 1650 cm^{-1} (amide).

6,7-Dihydroxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 321

Prepared by the method described for acid 311 from 3,4-dimethoxyphenylpyruvic acid 317 (1.6g, 7.14 mM) and dopamine hydrochloride 314 (1.35g, 7.16 mM) as fawn crystals (1.68g, 65%) m.p. 209-12°. (Found : C, 54.9; H, 6.6; N, 3.4. $C_{19}H_{21}NO_6.3H_2O$ requires C, 55.2; H, 6.5; N, 3.4%). ν_{max} : 3580 (OH); 3520-2200 (salt bands); 1630 cm^{-1} (C=O).

3-Thenyl bromide 350

A solution of 3-methylthiophene (44g, 0.45 M) and benzoyl peroxide

(0.8g) in dry benzene (140 ml) was heated under reflux with stirring while a mixture of N-bromosuccinimide (80g, 0.45M) and benzoyl peroxide (0.8g) was added in small portions. The heating was continued until no more foaming occurred (ca. 5h). After cooling the solid succinimide was filtered off and the filtrate evaporated to afford the title bromide 350 as a colourless oil (59g, 74%) b.p. 46-60°/ 0.06 mm (lit.[163] b.p. 75-8°/1 mm).

3-Thiopheneacetonitrile 351

To a solution of potassium cyanide (6.5g, 100 mM) in water (10 ml) was added a solution of 3-thenyl bromide 350 (14.77g, 83.4 mM) in acetone (40 ml) over a period of 10 minutes. The mixture was heated under reflux for 4h and the resulting potassium bromide was filtered off. The acetone was removed in vacuo and the organic layer separated. Distillation of the organic layer afforded the title nitrile 351 as a colourless oil (4.91g, 48%) b.p 75-6°/0.5 mm (lit.[142] b.p. 116°/16 mm). ν_{max} (film) : 2260 cm^{-1} (C≡N).

Ethyl 3-cyano-2-oxo-3-(3-thienyl) propanoate 352

A mixture of 3-thiopheneacetonitrile 351 (10g, 81.3 mM) and diethyl oxalate (6.75g, 46.2 mM) was added dropwise to a stirred solution of sodium (1.1g, 47.8 mM) in ethanol (15 ml) at 0°. The mixture was allowed to reach room temperature overnight and poured into 2M hydrochloric acid to reach pH1. After 6h the precipitated title ester 352 was filtered off and recrystallised to give fawn flakes (11.4g, 63%) m.p. 109-10° (lit.[142] m.p. 110°) (from benzene-light petroleum). ν_{max} : 3310 (OH, enol); 2225 (C≡N); 1695 cm^{-1} (ester). δ_H : 1.85 (3H, t, J = 7Hz, CH_2-$\underline{CH}_3$); 4.45 (2H, q, J = 7Hz, CH_3-$\underline{CH}_2$). 7.20-7.95 (4H, m, aromatics and enol $\underline{OH}$). δ_C : 14.0; 64.9; 93.4; 117.2; 126.0; 128.0; 128.4; 132.0; 147.3; 163.7.

3-Cyano-2-oxo-3-(3-thienyl)-propanoic acid 353

The cyano ester 352 (4.5g, 20.2 mM) was heated under reflux in glacial acetic acid (22 ml) containing concentrated hydrochloric acid (9ml) for 1.5h. The mixture was cooled and the precipitated solid filtered off and washed with acetic acid. Recrystallisation of the solid from ethanol afforded the title α-keto acid 353 as yellow needles (2.67g, 78%) m.p. 252-3° (lit.[142] m.p. 249°). (Found : C, 49.5; H, 2.6; N, 7.2; S,15.8. M^+, 194.9982. $C_8H_5NO_3S$ requires C, 49.2; H, 2.6; N, 7.2; S, 16.4%; M, 194.9989). ν_{max} : 3280 (enol. OH); 1710 cm^{-1} (C=O). δ_H (DMSO) : 7.60-7.78 (2H, m, ar. 3-H, 4-H); 7.99-8.02 (1H, m, ar. 2-H); 11.98 (1H, exchanges with D_2O, CO_2H). δ_C (DMSO) : 104.5; 123.7; 126.0; 126.5; 129.7; 151.0; 168.2; 172.0

Ethyl 2-(N,N-dimethylamino)-3-(3-thienyl)-prop-2-enoate 356

Thiophene-3-carboxaldehyde 354 (1.12g, 10 mM) and N,N-dimethylglycine ethyl ester 355 (4.0g, 30 mM) were added in one portion to a mixture of sodium hydride (0.48g, 20 mM), in dry ether (10 ml) containing ethanol (0.1 ml) at 0°C. The mixture was stirred overnight, poured into ice-water (10 ml) and the ether layer washed with water (3 x 10 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded the title amino ester 356 as a colourless oil (2.07g, 92%). b.p. 102-8°/0.1 mm. (Found : C, 58.5; H, 6.6; N, 6.3. $C_{11}H_{15}NO_2S$ requires C, 58.7; H, 6.7; N, 6.2%). ν_{max} : 1710 (C=O) : 1615 cm^{-1} (C=C).

3-Thienylpyruvic acid 348

A solution of the amino ester 356 (9.21g, 40.9 mM) was heated under reflux in 2M sodium hydroxide (130 ml) for 2h and treated with charcoal. The mixture was acidified to pH 2-3 with 2M hydrochloric acid and heated under reflux for 5 mins. The cooled mixture was extracted with chloroform (3 x 50 ml) and dried ($MgSO_4$). Evaporation of the

solvent yielded the title pyruvic acid 348 as yellow flakes m.p. 171.5-3° (from chloroform). (Found : C, 48.8; H, 3.5. $C_7H_6O_3S$ requires C, 49.4; H, 3.5%). ν_{max} : 3470 (OH, enol); 3300-2000 (H-bonded OH), 1680 cm^{-1} (acid). δ(DMSO) : 6.51 (1H, s, ar. -CH); 7.15-7.70 (3H, m, aromatics); 9.1-10.2 (2H, broad s, exchanges with D_2O, CO_2H and OH).

6-Hydroxy-7-methoxy-1-(3-thenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid 349

Prepared by the method described for acid 311 from the amine hydrochloride 313 (2.4g, 11.8 mM) and 3-thienylpyruvic acid 348 (2g, 11.8 mM) as a fawn powder m.p. 250-2°(d). (Found : C, 59.5; H, 5.2; N, 4.1. $C_{16}H_{17}NO_4S.\frac{1}{4}H_2O$ requires C, 59.4; H, 5.4; N, 4.1%). ν_{max} : 3420 (OH); 3160-2300 (salt bands); 1620 cm^{-1} (C=O).

Reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids with trifluoroacetic anhydride

13-Trifluoroacetyl-8-trifluoromethyl-3-hydroxy-2,9,10,11-tetramethoxy-7,8-dihydroprotoberberine 312

A solution of the amino acid 311 (0.1g, 0.2 mM) in pyridine (25 ml) containing trifluoroacetic anhydride (2 ml) was heated under reflux for 10 mins. The cooled solution was diluted with chloroform (50 ml) and washed with 4M hydrochloric acid (5 x 20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded the title protoberberine 312 as yellow crystals (55 mg, 50%). Methylation with diazomethane afforded the methyl ether analogue 341 as orange needles (76 mg, 68%) m.p. 205-6° (lit.[119] m.p. 205-6°) (from meths). (Found : M^+, 547.1457. Calculated for $C_{25}H_{23}F_6NO_6$ M,547.1430). This compound had i.r., u.v. and t.l.c. characteristics identical with those of an authentic sample.

Methyl 2-trifluoroacetyl-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 342

The title ester 342 was isolated as a by-product from a heated solution of the 6,7-dihydroxy acid 323 in pyridine and trifluoroacetic anhydride. Treatment of the crude by-product with diazomethane afforded the title ester 342 as white cubes m.p. 147-8°(from methanol). (Found : C, 56.6; H, 5.3; N, 2.7. M^+ 527.1751. $C_{25}H_{28}F_3NO_8$ requires C, 56.9; H, 5.3; N, 2.7%, M, 527.1759). ν_{max} : 1740 (ester); 1690 cm^{-1} (amide). δ : 2.10-2.85 (2H, m, N-CH_2-CH_2); 3.40-4.10 (19H, m, N-CH_2, benzylic CH_2, 5 x OCH_3); 5.85 (2H, s, ar. 2',6'); 6.53[1H, s, C(8)H]; 7.05[1H, s, C(5)H].

13-Trifluoroacetyl-8-trifluoromethyl-2,3-dihydroxy-9,10,11-trimethoxy-7,8-dihydroprotoberberine 340

Prepared by the method described for the protoberberine 312 from the dihydroxy acid 323 (2g, 5.1 mM) as yellow flakes (0.77g, 29%) m.p. 180-1°. ν_{max} : 3400 (OH); 1580 cm^{-1} (C=O). δ : 2.50-3.65 (4H, m, N-CH_2-CH_2); 3.30, 3.40, 3.45 (9H, 3s, 3 x OCH_3); 5.45 (1H, q, J = 7.5 Hz, CF_3-C-H); 6.70, 6.95, 7.90 (3H, 3s, aromatics). λ_{max} neutral : 263, 293, 353, 425 nm; pH 14 : 256, 364, 403 nm. Further characterised by treatment with diazomethane to form the permethylated analogue 341 to which it had identical i.r., u.v. and t.l.c. characteristics.

13-Trifluoroacetyl-8-trifluoromethyl-2,3,10,x-tetramethoxy-7,8-dihydroprotoberberine 343a or 343b

Prepared from the dihydroxy acid 321 (0.5g, 1.39 mM) by the method described for the pentamethoxy protoberberine 341 as a crude yellow solid (0.5g, 69%). [Found : M^+, 517.1350, M-CF_3, 448.1398, 100%]. $C_{24}H_{21}F_6NO_5$ requires 517.1318; $C_{23}H_{21}F_3NO_5$ requires 448.1366. λ_{max} (ethanol) 434 nm (ε, 1630 dm^3 mol^{-1} cm^{-1}). Yield calculated from

u.v. absorption spectrum = 20%.

13-Trifluoroacetyl-8-trifluoromethyl-2,3-dimethoxy-x,10-methylenedioxy-7,8-dihydroprotoberberine 344a or 344b

Prepared from the dihydroxy acid 324 (0.26g, 0.76 mM) by the method described for the pentamethoxy protoberberine 341 as a deep yellow gum (0.18g, 47%). λ_{max} (ethanol) 435 nm (ε, 763). Yield calculated from u.v. absorption spectrum = 9%.

Preparation and reactions of sulphonamides

3-(4-Nitrophenyl)-propanoic acid 359

To a well-stirred solution of 3-phenylpropanoic acid (50g, 0.33M) in glacial acetic acid (50 ml) was carefully added dropwise fuming nitric acid (100g) over a period of one hour. The reaction mixture was kept at 20-25° during the addition, allowed to stand at room temperature for 3h with occasional stirring, and poured into cold water (1l). The precipitated yellow solid was filtered off, washed with water, and air-dried to afford, after repeated recrystallisation from ethanol, the nitro acid 359 (34g, 52%) m.p. 163-4° (lit.[164] m.p. 163-4°).

3-(4-Aminophenyl)-propanoic acid 360

To a suspension of the nitro acid 359 (20g, 0.103M) in methanol (200 ml) was added 5% palladium on charcoal (1g) as a slurry in water (1 ml). The suspension was shaken under hydrogen (at 1-4 atmospheres) until uptake ceased. The catalyst was removed by filtration and the filtrate was evaporated to yield the title compound 360 as colourless flakes (15.6g, 92%), m.p. 131-2° (lit.[165] m.p. 131°)(from chloroform or water).

tert-Butyl 3-(4-nitrophenyl)-propanoate 363

To a solution of the nitro acid 359 (1.95g, 10 mM) in dry pyridine (20 ml) containing t-butanol (0.95 ml, 10 mM) was added p-toluene-sulphonyl chloride (1.91g, 10 mM). After being heated on a steam bath for 2 hrs the dark mixture was poured into ice-cold water (50 ml) and extracted into dichloromethane (3 x 20 ml). The combined organic extracts were washed with 2M sodium hydroxide (2 x 20 ml), ice-cold 2M hydrochloric acid (20 ml) and dried ($MgSO_4$). Removal of solvent in vacuo resulted in a brown oil which solidified on cooling. Recrystallisation from methanol yielded the title ester 363 as fawn plates (2.19g, 87%) m.p. 53-4°. (Found : C, 61.9; H, 6.9; N, 5.2. $C_{13}H_{17}NO_4$ requires C, 62.2; H, 6.8; N, 5.6%). ν_{max} : 1725 (C=O), 1520, 1345 cm^{-1} (NO_2). δ : 1.41 (9H, s, 3 x CH_3); 2.59-3.63 (4H, m, CH_2CH_2); 7.37 (2H, d, J = 8Hz, ar. meta to N); 8.15 (2H, d, J = 8Hz, ar. ortho to N).

tert-Butyl 3-(4-aminophenyl)-propanoate 364

The nitro ester 363 (37.55g, 0.15M) in p-dioxan (200 ml) was hydrogenated using 10% palladium on charcoal (3g) as for the phenol 188. Removal of the organic solvent gave a dark oil which solidified on cooling. Distillation produced the title amino ester 364 as a white solid (31.2g, 94%) b.p. 120-4°/0.2 mm, m.p. 59-60°. (Found : C, 70.5; H, 8.5; N, 6.1. $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.6; N, 6.3%). ν_{max} (chloroform) : 3465, 3375 (NH_2); 1720 cm^{-1} (C=O). δ : 1.40 (9H, s, 3 x CH_3) : 2.25-2.94 (4H, m, CH_2CH_2); 6.52 (2H, d, J = 8Hz, ar. meta to N); 6.88 (2H, d, J = 8Hz, ar. ortho to N); 3.82 (2H, s, exchanges with D_2O, NH_2).

tert-Butyl 3-(4-methanesulphonamidophenyl)-propanoate 365

Prepared from the amino ester 364 (2.21g, 10 mM) and methanesulphonyl chloride (0.8 ml, 10.3 mM) by the method described for the sulphonamide

198 as a brown gum (2.54g, 85%) which could not be induced to solidify. ν_{max} (film) : 3260 (NH); 1725 (C=O); 1150 cm^{-1} (SO_2N). δ : 1.41 (9H, s, 3 x CH_3); 2.33-3.05 (4H, m, CH_2-CH_2); 2.94 (3H, s, S-CH_3); 7.13 (4H, s, aromatics); 7.36 (1H, s, exchanges with D_2O, NH).

3-[4-(p-Toluenesulphonamido)phenyl]-propanoic acid 357

Prepared from the amino acid 360 (6g, 36 mM) and p-toluenesulphonyl chloride (7.2g, 38 mM) by the same method as for sulphonamide 198. Best yields were obtained by heating the reaction mixture under reflux in chloroform for 3h. The title sulphonamide was isolated as colourless needles (9.11g, 78%) m.p. 160-1° (lit.[60] m.p. 161-2°) (from aqueous methanol). δ_H (DMSO) : 2.30 (3H, s, CH_3); 2.40-2.90 (4H, m, CH_2CH_2); 7.00 (4H, s, ar. ortho to N and CH_2); 7.26 (2H, d, J = 8Hz, ar. meta to S); 7.61 (2H, d, J = 8Hz, ar. ortho to S); 10.00 (1H, s, exchanges with D_2O, CO_2H). δ_C ($CDCl_3$/DMSO) : 19.7; 28.3; 33.9; 118.9; 125.1; 127.2; 127.9; 134.3; 135.0; 135.4; 141.4; 172.1.

Ethyl 3-(4-pentafluorobenzenesulphonamido)phenylpropanoate 361

Prepared by the method described for sulphonamide 198 from the amino acid 360 (3.1g, 18.8 mM) and pentafluorobenzenesulphonyl chloride (5g, 18.8 mM). Evaporation of the solvent and extraction of the residue into ether (3 x 50 ml) afforded tan crystals (2.93g, 38%). Recrystallisation from aqueous ethanol yielded the title ethyl ester 361 as white needles m.p. 118.5-9°. (Found : C, 48.1; H, 3.6; N, 3.1. $C_{17}H_{14}F_5NO_4S$ requires C, 48.2; H, 3.3; N, 3.3%). ν_{max} : 3220 (NH); 1710 cm^{-1}) C=O). δ : 1.20 (3H, t, J = 7Hz, CH_2-CH_3); 2.40-3.05 (4H, m, CH_2-CH_2); 4.10 (2H, q, J = 7Hz, Ch_3-CH_2); 7.08 (4H, s, aromatics); 7.90 (1H, s, exchanges with D_2O, NH).

3-(4-Methanesulphonamidophenyl)-propanoic acid 362

Methanesulphonyl chloride (1.5g, 13.1 mM) was added dropwise to a stirred suspension of the amino acid 360 (2g, 12.1 mM) in methylene chloride (50 ml) containing pyridine (2 ml) at 0°. The mixture was allowed to reach room temperature overnight and then poured into 4M hydrochloric acid (100 ml). The organic layer was separated, washed with 4M hydrochloric acid (100 ml), water (2 x 100 ml) and dried over magnesium sulphate. The solvent was removed to afford the title sulphonamide 362 as white crystals (1.6g, 54%) m.p. 151-2° (from methanol). (Found : C, 49.6; H, 5.5; N, 5.5. $C_{10}H_{13}NO_4S$ requires C, 49.4; H, 5.3; N, 5.8%). ν_{max} : 3500-2500 (H-bonded OH); 3230 (NH); 1695 (C=O); 1330, 1155 cm^{-1} (SO_2N). δ_H (DMSO) : 2.52-2.80 (4H, m, CH_2-CH_2); 2.94 (3H, s, CH_3); 7.15 (4H, s, aromatics); ca 7.9-8.4 (1H, s, exchanges with D_2O, NH); 9.50 (1H, s, exchanges with D_2O, CO_2H). δ_C ($CDCl_3$/DMSO) : 30.0; 35.5; 38.8; 120.8; 129.0; 136.0; 136.9; 174.1.

The above acid was also prepared in 95% yield by heating the tert-butyl ester 365 at 100° for 1h or by treating 365 with trifluoroacetic acid according to the method described for the acid 200 in 97% yield.

Methyl 3-[4-(p-toluenesulphonamido)-phenyl]-propanoate 383

The sulphonamido acid 357 (2g, 6.27 mM) in methanol (50 ml) containing concentrated sulphuric acid (2 ml) was heated under reflux for 5 hours. The cooled mixture was poured into water (100 ml) and extracted with ether (2 x 20 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution (3 x 20 ml), water (3 x 20 ml) and dried ($MgSO_4$). Removal of the solvent yielded the title ester 383 as fawn crystals (1.8g, 86%) m.p. 93-5° (lit.[166] m.p. 83-5°) (from aqueous methanol). ν_{max} : 3240 (NH); 1730 (C=O);

1340, 1160 cm^{-1} (SO_2N). δ : 2.35 (3H, s, ar.-CH_3); 2.4-3.1 (4H, m, CH_2CH_2); 3.65 (3H, s, OCH_3); 7.00 (4H, m, ar. ortho to N and CH_2); 7.20 (2H, d, J = 9Hz, ar. ortho to CH_3); 7.65 (2H, d, J = 9Hz, ar. ortho to S); 7.4 (1H, broad s, exchanges with D_2O, NH).

Reaction of 3-(4-nitrophenyl)propanoic acid 359 with oxalyl chloride, triethylamine and tert-butanol

To a stirred solution of the nitro acid 359 (10g, 51.3 mM) in dichloromethane (180 ml) containing DMF (1.36 ml) at 0° under a flow of nitrogen was added oxalyl chloride (7.8 ml, 89.4 mM) dropwise over 10 mins. The above mixture was dripped into a mixture of tert-butanol (90 ml), triethylamine (15 ml) and dichloromethane (270 ml) at 0°C over a period of 2h. The dichloromethane was removed in vacuo at room temperature, and the residue dissolved in ethyl acetate (150 ml) and washed with 2M hydrochloric acid (30 ml), saturated sodium bicarbonate solution (3 x 30 ml), brine (30 ml) and dried ($MgSO_4$). Evaporation of the ethyl acetate afforded the supposed keto ester 366 as orange crystals m.p. 122-3° (from methanol). (Found : C, 61.6; H, 5.7; N, 6.7. $C_{22}H_{24}N_2O_7$ requires C, 61.7; H, 5.6; N, 6.5%). ν_{max} : 1730 (ester); 1650 cm^{-1} (ketone). δ_H : 1.34 (9H, s, 3 x CH_3); 2.91-3.71 (7H, m, CH_2-CH and CH_2-CH_2); 7.31 (4H, d, J = 8Hz, ar. meta to N); 8.12 (4H, d, J = 8Hz, ar. ortho to N). δ_C : 27.8; 29.0; 33.4; 43.1; 60.8; 82.9; 123.6; 129.2; 129.7; 146.0; 146.9; 148.2; 167.2; 202.0.

4'-Nitrobiphenyl-2-carboxylic acid 376

To stirred concentrated nitric acid (1850 ml) was added biphenyl-2-carboxylic acid 375 (100g, 505 mM) in one portion. After 2h the mixture was poured into water (4l) and the resulting precipitate was filtered off and washed thoroughly with water (2l). Recrystallisa-

tion from ethanol afforded the title acid 376 as colourless crystals (20.6g, 17%) m.p. 233-5° (lit.[167] m.p. 222-5°).

Methyl 4'-nitrobiphenyl-2-carboxylate 377

A solution of the acid 376 (9.55g, 29.3 mM) in methanol (500 ml) containing concentrated sulphuric acid (6 ml) was heated under reflux for 12h. The methanol was evaporated to low volume, poured into water (500 ml), extracted with ether (3 x 50 ml), and dried ($MgSO_4$). Evaporation of the ether afforded the title ester 377 as yellow crystals (9.49g, 94%) m.p. 75-6° (lit.[168] m.p. 75-6°) (from methanol). ν_{max} : 1720 cm^{-1} (C=O) δ : 3.56 (3H, s, OCH_3); 7.16-8.24 (8H, m, aromatics).

Methyl 4'-aminobiphenyl-2-carboxylate 378

The nitro ester 377 (9.49g, 36.9 mM) was hydrogenated in methanol (400 ml) by the method described earlier for phenol 188. Evaporation of the solvent afforded the title amino ester 378 as a colourless oil (8.0g, 95%). δ_{max} (film) : 3460, 3370 (NH_2); 1730 cm^{-1} (C=O). δ : 3.60 (5H, s, OCH_3 and NH_2); 6.58 (2H, d, J = 8Hz, ar. ortho to N); 7.02 (2H, d, J = 8Hz, ar. meta to N); 7.20-7.70 (4H, m, aromatics). Further characterised as the title amine hydrochloride 378 m.p. 186-9°. (Found : C, 62.8; H, 5.3; N, 4.9. $C_{14}H_{14}ClNO_2 \cdot \frac{1}{4}H_2O$ requires C, 62.7; H, 5.4; N, 5.2%). ν_{max} : 3200-2400 (salt bands); 1730 cm^{-1} (C=O).

Methyl 4'-(p-toluenesulphonamido)-biphenyl-2-carboxylate 379

Prepared from the amino ester 378 (3g, 13.2 mM) and p-toluenesulphonyl chloride (2.52g, 13.2 mM) by the method described for sulphonamide 198. Recrystallisation from chloroform - light petroleum afforded the title sulphonamide 379 as white cubes (4.63g, 92%) m.p. 113.5-115°. (Found : C, 66.3; H, 5.1; N, 3.7. $C_{21}H_{19}NO_4S$ requires C, 66.1;

H, 5.0; N, 3.7%). ν_{max} : 3240 (NH); 1720 cm^{-1} (C=O). δ : 2.35 (3H, s, ar.-CH_3); 3.54 (3H, s, OCH_3); 7.08-7.80 (9H, m, aromatics and NH).

4'-(p-Toluenesulphonamido)-biphenyl-2-carboxylic acid 374

A solution of the ester 379 (5g, 13.1 mM) in 2M sodium hydroxide (100 ml) was heated on a steam bath for 4h. The cooled solution was washed with ether (20 ml), acidified with concentrated hydrochloric acid, extracted into dichloromethane and dried over magnesium sulphate. Evaporation of the solvent afforded the title sulphonamido acid 374 as white needles (4.34g, 90%) m.p. 185-7° (from ether). (Found : C, 65.2; H, 4.7; N, 3.4. $C_{20}H_{17}NO_4S$ requires C, 65.4; H, 4.6; N, 3.8%). ν_{max} : 3270 (NH); 3100-2200 (H-bonded O-H); 1690 cm^{-1} (C=O). δ : 2.20 (3H, s, CH_3); 7.00-8.02 (13H, m, aromatics and NH); 8.55 (1H, s, CO_2H).

N-(p-Toluenesulphonyl)-1-oxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 380

The sulphonamido acid 357 (0.5g, 1.57 mM) was oxidised at an anode potential of 1.4V as described in the general anodic oxidation procedure to yield a brown oil (0.3g, 60%) which solidified on cooling. Recrystallisation from ethanol produced the title imine 380 as fawn needles m.p. 148° (lit.[60] m.p. 146-8°). ν_{max} : 1785 (C=O); 1655 (C=C); 1550 (C=N); 1320, 1160 cm^{-1} (SO_2N). δ : 2.45 (3H, s, CH_3); 2.4-3.0 (4H, m, CH_2CH_2); 6.1-8.0 (8H, m, aromatics and vinylics).

N-(Methanesulphonyl)-1-oxaspiro-[4.5]-deca-6,9-dien-2-one-8-imine 381

The sulphonamido acid 362 (0.5g, 2 mM) was oxidised at an anode potential of 1.4V as described in the general anodic oxidation procedure. The product was a fawn powder 381 (0.34g, 69%) m.p. 186-8° (ethyl acetate-ether). (Found : C, 49.7; H, 4.6; N, 5.7;

$C_{10}H_{11}NO_4S$ requires C, 49.8; H; 4.6; N, 5.8%). ν_{max} : 1770 (C=O); 1660 (C=C); 1558 (C=N); 1295, 1135 cm^{-1} (SO_2N). δ : 2.10-2.80 (4H, m, CH_2CH_2); 3.02 (3H, s, CH_3); 6.14-7.35 (4H, m, vinylics).

4-p-Tolylsulphonyliminospiro [cyclohexa-2,5-diene-1,1'(3'H)-isobenzofuran]3'-one 382

The sulphonamido acid 374 (0.5g, 1.36 mM) was oxidised at an anode potential of 1.4V as described in the general anodic oxidation procedure. Recrystallisation from methanol afforded the title spirolactone 382 as a yellow powder (0.35g, 70%) m.p. 158-62°. (Found : C, 65.6; H, 4.2; N, 3.9; S, 8.8. $C_{20}H_{15}NO_4S$ requires C, 65.8; H, 4.1; N, 3.8; S, 8.8%). ν_{max} : 1775 (C=O); 1655 (C=C); 1560 cm^{-1} (C=N). δ : 2.45 (3H, s, ar-CH_3); 6.52-8.15 (12H, m, aromatics and vinylics).

The above spirolactone was also prepared in 25% yield by treating the sulphonamido ester 379 with lead tetra-acetate in glacial acetic acid.

Spiro [cyclohexa-2,5-diene-1',1(3'H)-isobenzofuran]-3',4-dienone 371

The spirodienimine 382 (0.2g, 0.548 mM) was dissolved in ethyl acetate (1 ml) and eluted down a grade II alumina column. Evaporation of the eluent afforded the title spirodienone 371 as white crystals (0.087g, 75%) m.p. 182-3° (lit.[62] m.p. 189°) (from ethanol). ν_{max} : 1770 (γ-lactone); 1670 (dienone); 1630 cm^{-1} (C=C). δ ($CDCl_3$/DMSO) : 6.40, 6.78 (4H, 2d, J = 9Hz, vinylics); 7.26-7.98 (4H, m, aromatics).

3-[3-Cyano-4-(p-toluenesulphonamido)phenyl]-propanoic acid 384

Potassium cyanide (42 mg, 0.64 mM) was added to a solution of the tosyl imine 380 (0.2g, 0.63 mM) in DMF (5 ml) under a nitrogen atmosphere. The mixture was stirred overnight, the solvent removed in vacuo and the residue partitioned between ether (50 ml) and

saturated bicarbonate solution (50 ml). The aqueous layer was separated, acidified with concentrated hydrochloric acid, extracted into dichloromethane (4 x 20 ml), and dried ($MgSO_4$). Evaporation of the solvent afforded the title acid 364 as white crystals (60 mg, 28%) m.p. 68-70° (from chloroform - light petroleum). (Found : C, 59.2; H, 4.9; N, 7.6. $C_{17}H_{16}N_2O_4S$ requires C, 59.3; H, 4.7; N, 8.1%). ν_{max} : 3240 (NH); 3060-2400 (H-bonded OH); 2220 (C≡N); 1710 cm^{-1} (C=O). δ_C ($CDCl_3$/DMSO) : 21.3; 28.6; 34.1; 112.4; 117.1 (CN); 123.4; 124.5; 126.7; 129.4; 130.1; 136.4; 136.7; 139.5; 143.4; 173.4.

3-(3-Cyano-4-methanesulphonamidophenyl)-propanoic acid 385

Prepared by the method described for acid 384 from the mesyl imine 381 (0.2g, 0.83 mM) and potassium cyanide (60 mg, 0.92 mM) as a fawn gum (90 mg, 41%) which solidified on treatment with hot chloroform. ν_{max} : 3240 (NH); 2220 (C≡N); 1710 cm^{-1} (C=O). m/z 268 (M^+, 15%); 222 (83); 209 (20); 144 (100); 143 (85); 131 (50); 116 (29); 44 (44).

Methyl 3'-cyano-N-methyl-4'-(p-toluenesulphonamido) biphenyl-2-carboxylate 386

The imine 382 (200 mg, 0.55 mM) was treated with potassium cyanide (40 mg, 0.62 mM) by the method described for acid 384. To the crude acidic product was added a solution of diazomethane (excess) in ether (50 ml) and the mixture was left at room temperature overnight. The ethereal solution was treated with glacial acetic acid (1 ml), washed with saturated sodium bicarbonate solution (3 x 20 ml), water (2 x 20 ml), brine (20 ml) and dried (Na_2SO_4). Evaporation of the solvent afforded the title ester 386 as a fawn gum (100 mg, 43%) b.p. 235-40°/0.5 mm. (Found : C, 65.4; H, 4.8; N, 6.0. $C_{23}H_{20}N_2O_4S$ requires C, 65.7; H, 4.8; N, 6.7%).

ν_{max} (film) : 2220 (C≡N); 1720 cm^{-1} (C=O). δ : 2.48 (3H, s, ar. $-CH_3$); 3.15 (3H, s, $N-CH_3$); 3.67 (3H, s, OCH_3); 7.10-8.05 (11H, m, aromatics).

Attempted preparation of a gem-dimethylphenylpyruvic acid α-(3-Methoxyphenyl)-α-methyl-propanoic acid 388

To a slurry of sodium hydride (3g) in oil and di-isopropylamine (9 ml) in dry tetrahydrofuran (200 ml) was added 3-methoxyphenylacetic acid (10g, 60.2 mM) under a flow of nitrogen. The mixture was heated under reflux, cooled to 0° and n-butyl-lithium (4g, 62.5 mM) was added by syringe. After warming to 30° to complete metallation and cooling to 0°, methyl iodide (9g, 63.4 mM) was added dropwise and the mixture stirred for 2h at 30°. The mixture was cooled to 0°, n-butyl-lithium (4g, 62.5 mM) added and the temperature raised to 30° for 5 mins. Methyl iodide (9g, 63.4 mM) was added to the mixture dropwise at 0° and stirred at 30° for 3h. Water (250 ml) was added and the organic layer was discarded. The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether (3 x 50 ml) and the combined extracts dried (Na_2SO_4). Evaporation of the ether afforded the title acid 388 as white flakes (10g, 86%) m.p. 47-8° (lit.[169] m.p. 48-50°) (from aqueous methanol). δ : 1.56 (6H, s, 2 x CH_3); 3.71 (3H, s, OCH_3); 6.65-7.30 (4H, m, aromatics); 10.54 (1H, s, exchanges with D_2O, CO_2H).

α-(3-Methoxyphenyl)-α-methyl-propanoyl cyanide 389

The gem-dimethyl acid 388 (2g, 10.3 mM) was left in thionyl chloride (3 ml) for 24h. Removal of the thionyl chloride afforded the acid chloride 391 (2.35g, 100%). ν_{max} (film) : 1800, 1775 cm^{-1} (C=O). δ : 1.56 (6H, s, 2 x CH_3); 3.73 (3H, s, OCH_3); 6.67-7.37 (4H, m, aromatics).

The above acid chloride 391 (2g, 8.75 mM) was heated under reflux in acetone (20 ml) containing sodium cyanide (0.51g, 10.4 mM) for 6h. The acetone was removed in vacuo, the residue dissolved in ether (20 ml) and washed with water (3 x 5 ml), saturated sodium bicarbonate solution (3 x 5 ml), brine (5 ml) and dried ($MgSO_4$). Evaporation of the ether afforded the title acyl cyanide 389 as an almost colourless oil (0.48g, 27%) b.p. 100-8°/0.05 mm. ν_{max} (film) : 2220 (C≡N); 1710 cm^{-1} (C=O). δ : 1.60 (6H, s, 2 x CH_3); 3.78 (3H, s, OCH_3); 6.80-7.48 (4H, m, aromatics). m/z 203 (M^+, 5%) 149 (100); 121 (21); 109 (22).

2-Cyano-2-propyl -(3-methoxyphenyl)-α-methylpropanoate 392

Prepared by the method described for the acyl cyanide 389 from the acid chloride 391 (1g, 4.38 mM) by heating under reflux for 72h. Distillation of the product afforded the title ester 392 as a pale yellow oil (0.2g, 18%) b.p. 140-2°/1 mm. ν_{max} (film) : 1740 cm^{-1} (C=O). δ_H : 1.55, 1.63 (12H, 2s, 4 x CH_3); 3.76 (3H, s, OCH_3); 6.70-7.34 (4H, m, aromatics). δ_C : 26.2; 26.6; 46.8; 55.2; 68.4; 111.7; 111.9; 117.8; 119.2; 129.5; 145.4; 159.7; 174.4.

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