CHEMICAL STUDIES OF 1,5-BENZODIOXEPANONES

THESIS

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by

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CONTENTS

Abstract

Chromone and flavanone derivatives were prepared by condensation of the corresponding 2-hydroxyacetophenones (with diethyl oxalate or the appropriate aromatic aldehyde respectively) and cyclisation of the condensation products.

Baeyer-Villiger rearrangement of these flavanones, with MCPBA, resulted in expansion of the C-ring. Spectroscopic techniques have been used to establish the regioselectivity of the rearrangement and hence, the identity of the rearranged products as 1,5-benzodioxepan-4-ones.

The 1,5-benzodioxepan-4-ones were subjected to detailed ^{1}H and ^{13}C n.m.r. analysis and a combination of low and high resolution mass spectrometry has been used to study the mass fragmentation pathways of these ring-expanded products.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Prof. P.T Kaye for his continued guidance, enthusiasm, and patience throughout this investigation, and Sharon Volker, the typist, for the wonderfully fine work she has done.

My wife deserves many thanks for the patience she showed in sacrificing many lonely days during the period of this study. Thank you again.

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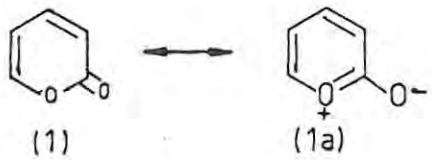
1. INTRODUCTION

Pyrones consist of a six-membered heterocycle containing one oxygen atom and five sp^2 hybridized carbons. Two isomers are possible, *viz.*, the α - and γ - pyrones [(1) and (2) respectively]. Four types of benzanulated pyrones are possible, *viz.*, compounds (3), (4), (5) and (6), compound (5) being relatively rare. The flavones (7), isoflavones (8), and the flavanones (9), are members of a much wider family of natural products called flavanoids. The anthocyanins are derivatives of the flavilium salt (10) and, hence, they also belong to the flavonoid family of natural products, the parent structure of which is flavan (11). The flavanoids are found almost exclusively in the plant kingdom, and most of them are highly coloured and, as a result, play a vital role in the ecology of plants by making the flowers and fruits attractive to insects[1]. Because of the importance of these compounds as drugs and their general propensity towards biological activity, they have been extensively studied.[1,2]

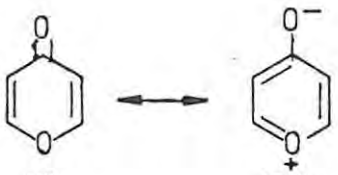
1.1 Survey of structure and biological activity of chromone and flavanone derivatives

In 1924, Arndt suggested that the ether oxygen in γ-pyrone (2) could interact electronically with the carbonyl group and thus modify the properties of the latter[3]. In fact, the carbonyl group of γ-pyrone is devoid of normal ketonic properties, failing to form the hydrazone or oxime derivatives, while with phenylhydrazine, cleavage of the heterocyclic ring occurs;[4] chromone oxime and phenylhydrazone, however, are known. The Diels-Alder reaction may be used to assess the aromaticity in pyran-4-one systems. The failure of pyran-4-one to react with the diene, 2,3-dimethyl-



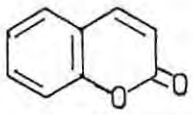
(1) (1a)

α-pyrone



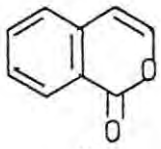
(2) (2a)

γ-pyrone



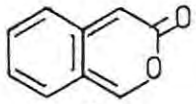
(3)

coumarin

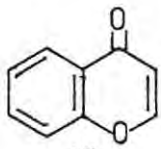


(4)

isocoumarin

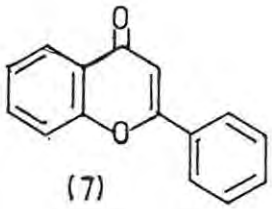


(5)



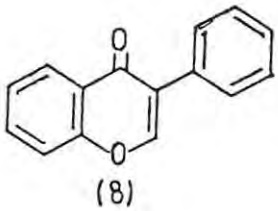
(6)

chromone



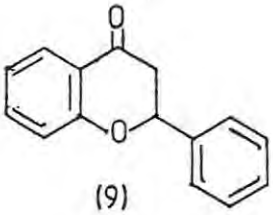
(7)

flavone



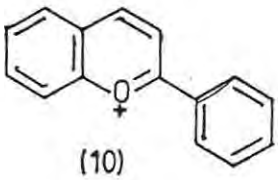
(8)

isoflavone



(9)

flavanone



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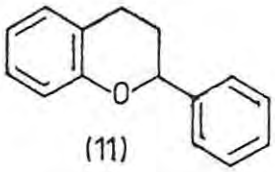
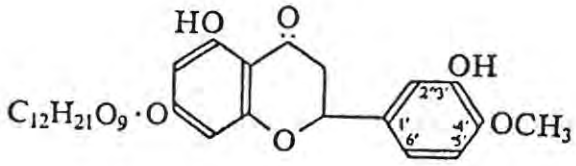


(11)

flavan

1,3-butadiene, to produce a Diels-Alder adduct indicates that pyran-4-one has substantial π-electron delocalization, consistent with the betaine structure (2a)[5]. Generally, the properties of the heterocyclic ring of the chromone nucleus are similar to those of γ-pyrone.

Benzo-fusion of γ-pyrone increases the basicity; the pKa of chromone is 2.0 compared to 0.1 for γ-pyrone. As a result of its basicity, chromone tends to form salts with acids[6]. The spectroscopic properties of chromones are best interpreted in terms of an aliphatic π-system in the heterocyclic ring.[7] I.r. spectroscopy can be used to distinguish chromones from coumarins (3). The carbonyl stretching frequency in the i.r. spectrum of chromone occurs at 1660cm^{-1}, [8] which is much lower than that of coumarins, at 1710cm^{-1}. Numerous i.r. spectra of naturally occuring flavonoids have been recorded[9]. The parent flavanone has a carbonyl absorption band at 1680cm^{-1} while the substituted flavanones, hesperidine (12) and naringin (13) have carbonyl absorption bands at 1639cm^{-1}.



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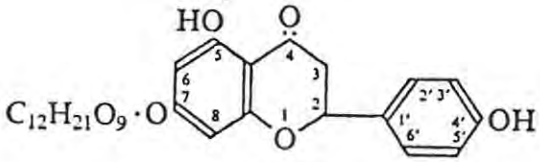


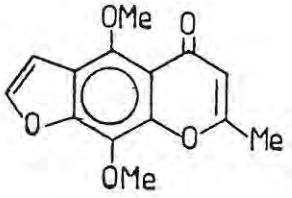
(13)

This shift is evidence of the presence of hydrogen bonding in these flavonoids. Introduction of hydroxyl groups in the 3'- and 4'- positions of unsubstituted flavanone causes the carbonyl frequency to shift to $1665cm^{-1}$.[10] Acetylation of these hydroxyl groups causes a shift back to $1680cm^{-1}$. In the ^{13}C n.m.r. spectra, the chemical shifts of C-2, C-3, and C-4 offer a means of distinguishing the different classes of flavonoids. The carbonyl carbon signals of both flavones and isoflavones appear in the region 174.5 - 178.6ppm[11], but the difference between the C-2 and C-3 signals in the two series permits immediate distinction. In the flavones the C-2 signal is a singlet (in the off-resonance decoupled spectrum) and the C-3 signal a doublet, whereas in the isoflavones the pattern is reversed. In the flavanones the carbonyl carbon signals appear in the region 189.5 - 191.6ppm. (except when a 5-OH group is present), while the C-2 and C-3 resonances appear at 75.0 - 80.3 and 42.8 - 44.6ppm. respectively.

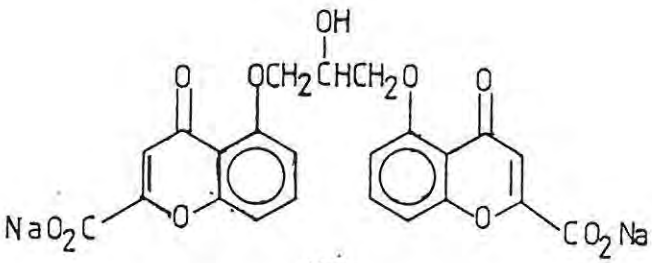
Chromone derivatives occur widely in nature, and many natural and synthetic chromones have biological activities which render them of considerable pharmaceutical interest. Khellin (14), a naturally occuring oxygen heterocycle with vasodilator and smooth muscle relaxing properties, is used clinically in the treatment of angina and bronchial asthma[12]. King *et al.*[12] investigated a series of chromone-2-carboxylic acids which were found to inhibit, in varying degrees, the bronchoconstrictor response. This discovery led to the introduction of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt (disodium cromoglycate) (15) for the treatment of asthma. This drug has been shown to inhibit the liberation of the mediators of immediate type allergic reactions initiated by reagenic

antibody antigen interactions. 2-(5-Tetrazolyl) chromones (16, R^1=R^2=H; R^1=Me, R^2=H; R^1=H, R^2=Me; and R^1=NO_2,R^2=H) were found to exhibit more antiallergic activity than disodium cromoglycate (15)[13].

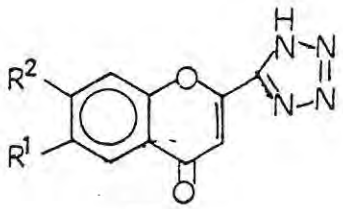
The dried radix of *Scutellaria baicalensis* has been used from ancient times in Chinese medicine as a diuretic or antiallergic drug[14]. Biacalein (17), one of the flavonoids present in this radix, and its water-soluble derivative, sodium baicalein-6-phosphate (18) were shown to posess antianaphylactic activity on experimental animals. Many natural and synthetic flavonoids have been tested for biological activity against a wide range of diseases and disease causing agents. Most of the biologically active flavonoids contain hydroxy or methoxy substituents. Chikao *et al*[15] tested several flavones and flavanones against Hela cells *in vitro* and found them to be antitumor agents with 5,7-dihydroxy-4'-methoxyflavone (19) showing the most potent activity. 5,7-Dihydroxyflavanone (20) was found to inhibit the growth of the bacterium *staphylococcus aureus*[16] by complexing essential metals and by modification of the cell membrane. 7-Hydroxyflavanone (21) partially inhibits the growth of the same bacterium through a different mode of action. The flavanone is throught to be transported into the cytoplasm, where it alters the interior surface of the cell membrane. Flavanones such as compounds (22) and (23) have also tested positive as mucolytics, immunostimulants, and for the treatment of liver diseases[17], their toxicity to fish has also been investigated[18].


OMe
O
O
Me
OMe

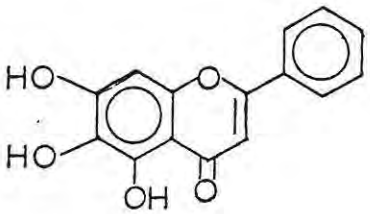
(14)


OH
O
OCH2CHCH2O
O
NaO2C
O
O
CO2Na

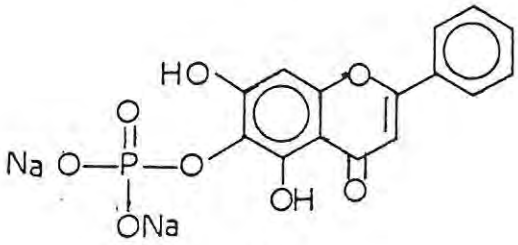
(15)


H
N-N
N-N
R2
R1
O
O

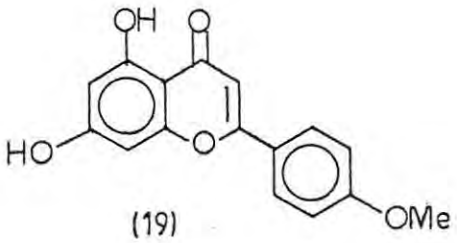
(16)


HO
HO
O
OH
O

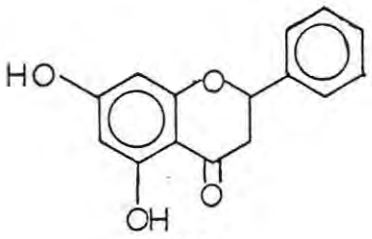
(17)


HO
O
Na O—P—O
ONa
O
OH
O

(18)



(19)



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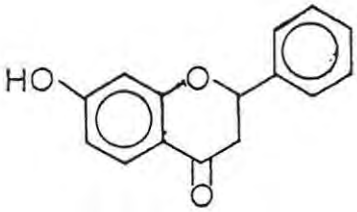
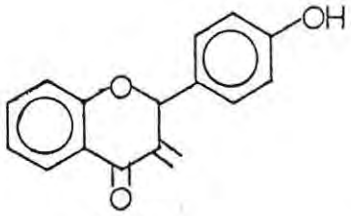
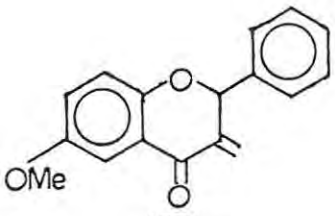


(21)



(22)



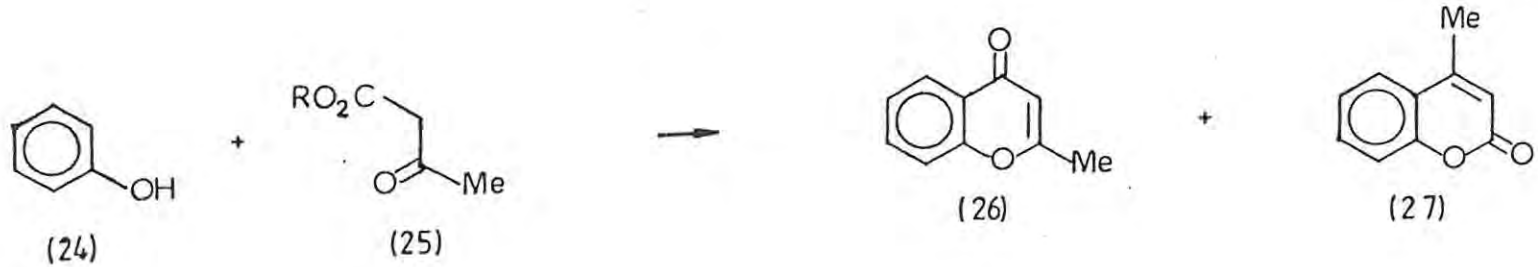
(23)

1.2 Chromone synthesis

There are several established methods for chromone synthesis. In fact, a wide variety of reactants and reaction conditions can be used to prepare chromones and the review by Ellis[19] contains a comprehensive list of examples. Only a brief discussion of some of these reactions will be provided here.

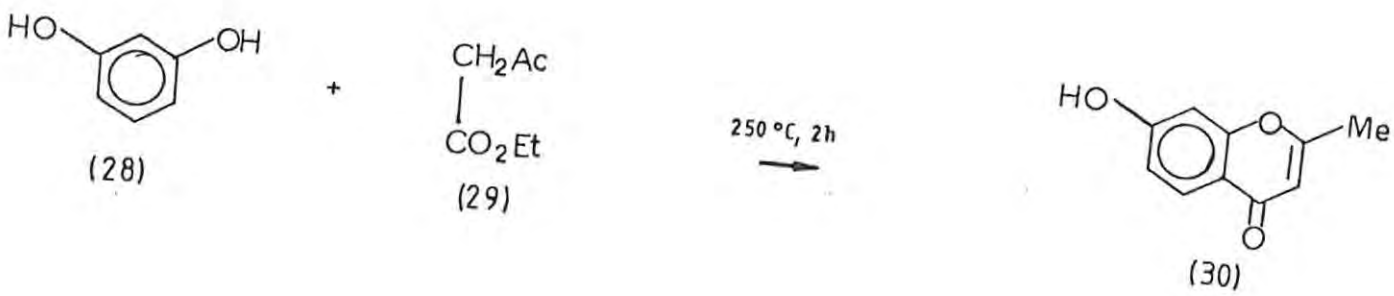
The two most common precursors of chromones are 2-hydroxyacetophenones or phenols. In either case, a side-chain is built on to the substrate and the resulting product is subsequently cyclized. Many syntheses differ only in the source of this side-chain.

The Simonis reaction involves the condensation of ß-ketoesters with phenols[20] (Scheme 1). Two disadvantages are associated with this synthesis :- (i) yields range from low to moderate; and (ii) cyclisation of the initially formed ester can give rise to chromones (26), to coumarins (27), or to mixtures of the two heterocycles. Chromone formation is favoured when the phenol (24) contains a deactivating substituent, such as chloro-, or when the ß-ketoester is α-substituted. Also, the distribution can often be shifted towards the chromone by use of phosphorus pentoxide as condensing agent. In the absence of a condensing agent, the Simonis condensation requires a higher reaction temperature[19]. It had been reported that only reactive phenols [such as resorcinol (28)] and 2-alkyl- or 2-arylacetoacetates gave chromones, but a low yield of 7-hydroxy-2-methylchromone (30) has, in fact, been obtained by heating resorcinol with ethyl acetoacetate (29) (Scheme 2). It has been suggested[21] that the



(24) (25) (26) (27)

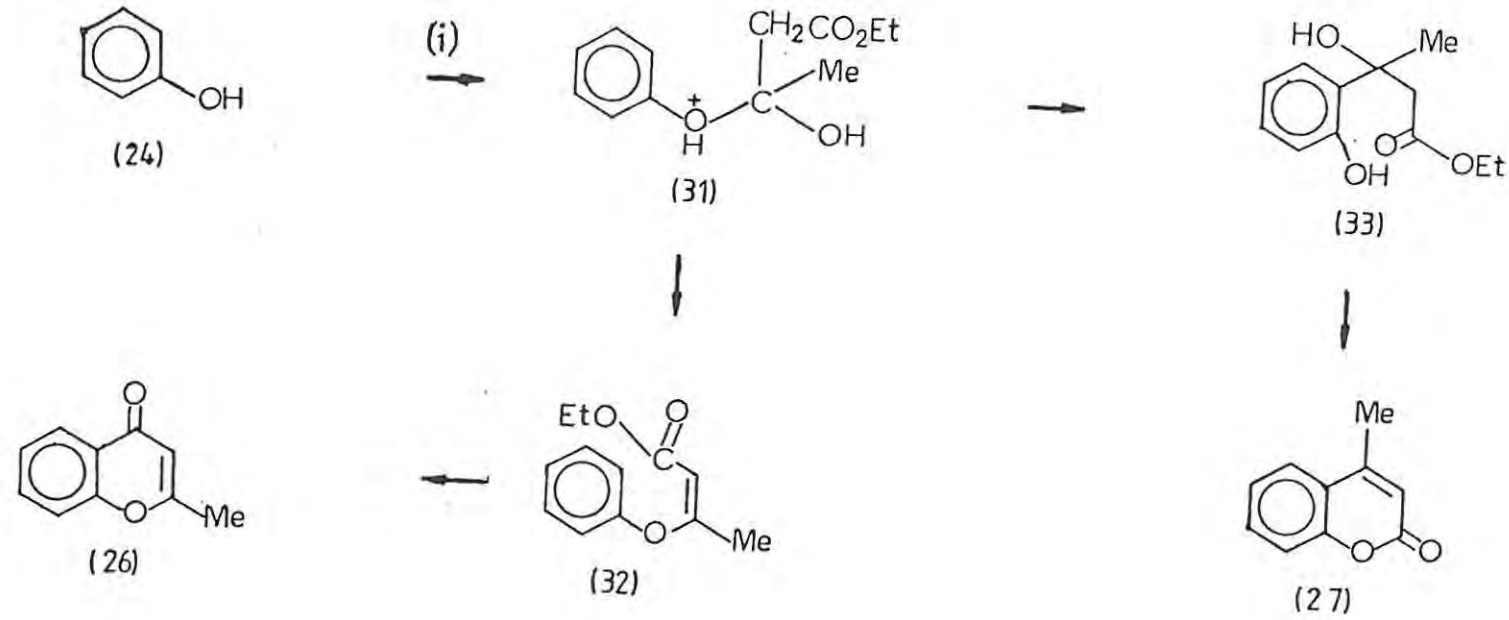
SCHEME 1



SCHEME 2

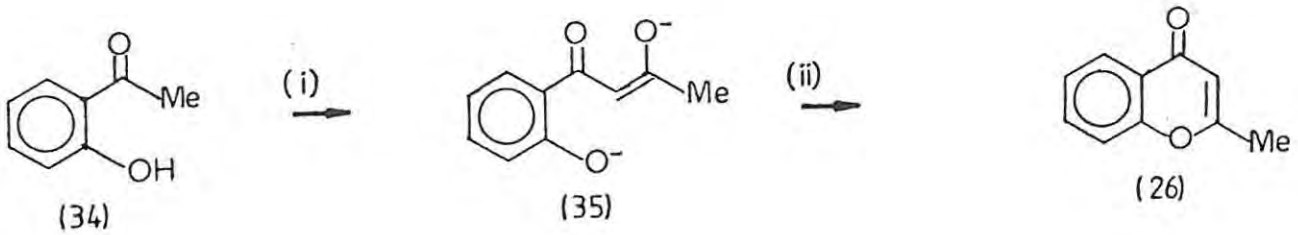
condensation phase of the Simonis reaction proceeds through a common oxonium ion (31). Dehydration to the phenoxyacrylate ester (32) is followed by cyclisation to the chromone, whilst a rearrangement to the substituted phenol (33) subsequently affords the coumarin (Scheme 3).

The Kostanecki-Robinson syntheses of chromones has been frequently used since its first application by Nagai[22] and Tahara[23] in 1892. The basic approach is shown in Scheme 4. An *o*-hydroxyacetophenone (34) is condensed with an acylating agent to form a 1,3-diketone (35), which spontaneously cyclizes to the chromone on acidification in what is, effectively, a reverse of chromone hydrolysis.[24,25] This method is successful in the synthesis of a large number of chromones. Almost any group may be present in the aromatic ring, provided that it does not react under the experimental conditions, and chromones containing alkyl,[26,27] alkoxy,[28,29,30] alkoxycarbonyl,[31,32] cyano,[33] and halogen groups,[34] amongst others, have been synthesized by this route. One problem associated with the Kostanecki-Robinson synthesis of chromones is the simultaneous formation of coumarins, which is sometimes observed, even with simple hydroxy acetophenones[35]. There seems to be no pattern to the extent to which the two benzopyranones are produced; sometimes little or no coumarin is formed, whilst in other cases, it is the major product[36]. The coumarin is probably derived from the initial, acylated hydroxyacetophenone, which in addition to undergoing a Baker-Venkataraman rearrangement (discussed below), may cyclize through an intramolecular aldol condensation and undergo elimination of water to give rise to the coumarin (Scheme 5). In general, the Kostanecki-Robinson reaction may give one or more of the products shown in scheme 6. An *o*-



SCHEME 3

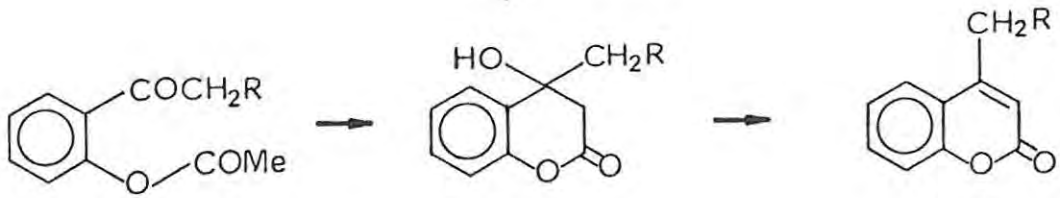
Reagent : (i) $MeCOCH_2CO_2Et$



(34) (35) (26)

SCHEME 4

Reagents : (i) Na, CH_3CO_2Et; (ii) H^+



(36) (37) (38)

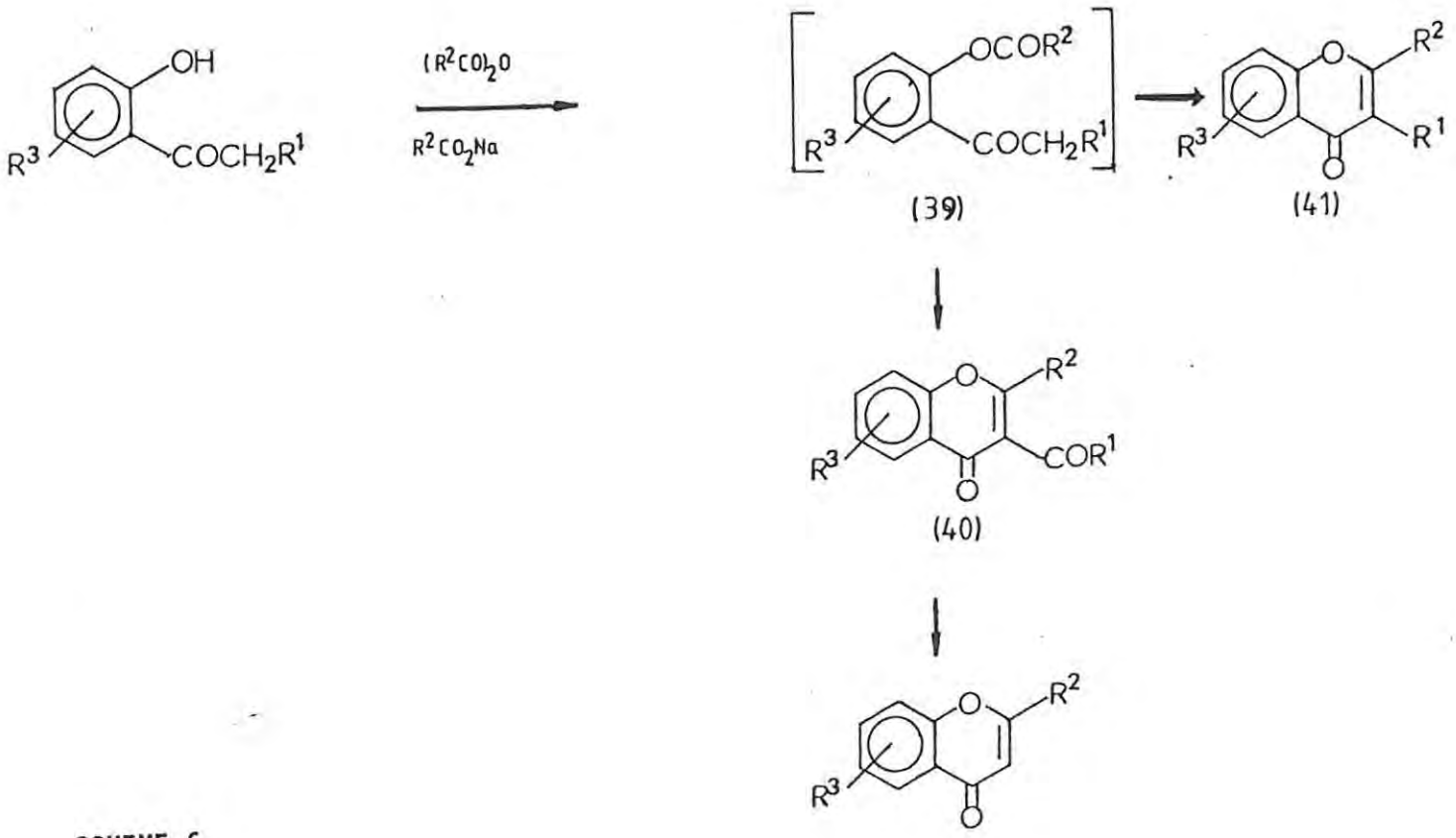
SCHEME 5

acyloxyphenylalkanone (39) is probably an intermediate in the reaction; it may undergo a Baker-Venkataraman rearrangement to yield an *o*-hydroxydiketone that loses water to give a chromone (40) or (41). When R^1 is a substituent, other than hydrogen, the chromone (41) is formed, but when R^1=H, either (40) or (42), or a mixture of both, may be obtained.

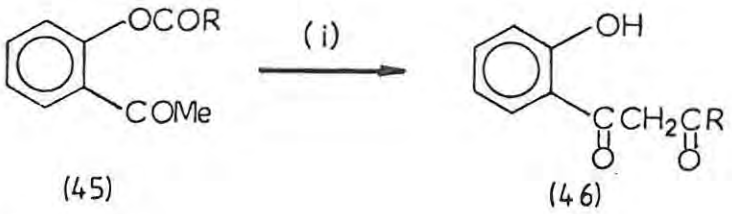
The 1,3-diketones (44) that are formed in the Claisen condensation may also be prepared from *o*-acyloxyacylbenzenes (43) by a transformation called the Baker-Venkataraman rearrangement[37].

(43) (44)

The scope and mechanism of this rearrangement has been extensively studied since it was first described by Baker[38] in 1933. The group R^3 may be either aliphatic or benzenoid, and it is thus possible to prepare chromones or flavones by this route. In addition to potassium carbonate, other catalysts have also been recommended for the Baker-Venkataraman rearrangement; of these, sodium,[39,40] sodium alkoxide,[41] sodium hydride,[42,43] and sodamide[44] are the best known examples. Some of these catalysts are effective under milder conditions and give higher yields than potassium carbonate; for example, sodium ethoxide in ethanol enables the rearrangement to the ester [(45), R= alkyl or aryl, (Scheme 7)] to proceed rapidly at room temperature in almost quantitative yield[41].


OH
R3
COCH2R1
(R2CO)2O
R2CO2Na
OCOR2
R3
COCH2R1
(39)
R2
O
R3
R1
(41)
R2
O
R3
COR1
O
(40)
R2
O
R3
O

SCHEME 6

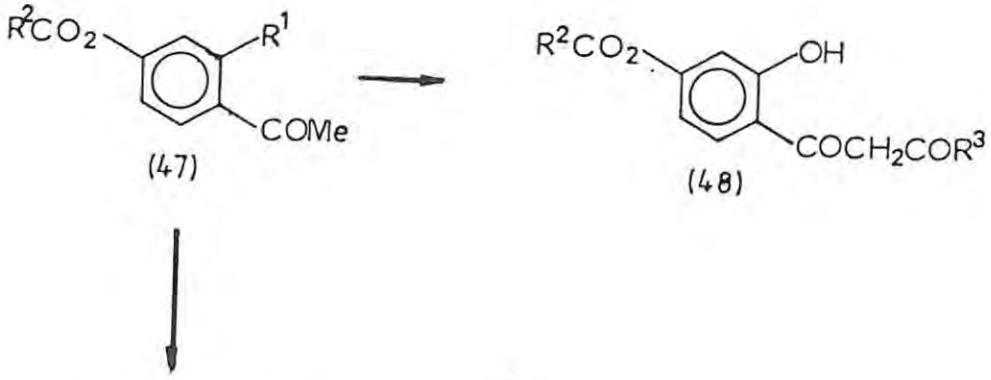


(45) (46)

SCHEME 7

Reagent : (i) NaOEt - EtOH

The machanism of the base-catalysed rearrangement has been shown to be intramolecular. Baker's original work[38] demonstrated that 2,4'-dibenzoylresacetophenone was formed when 4'-acetyloxy-2'-benzoyloxyacetophenone was heated with potassium carbonate in toluene, and that no 1,3-diketone was obtained when 4'-acyloxyacetophenones or 4'-acyloxy-2'-hydroxyacetophenones were similarly treated (Scheme 8).



(47) (48)

No rearrangement

(R^2 and R^3 = alkyl or aryl)

SCHEME 8

$R^1 = OCOR^3$

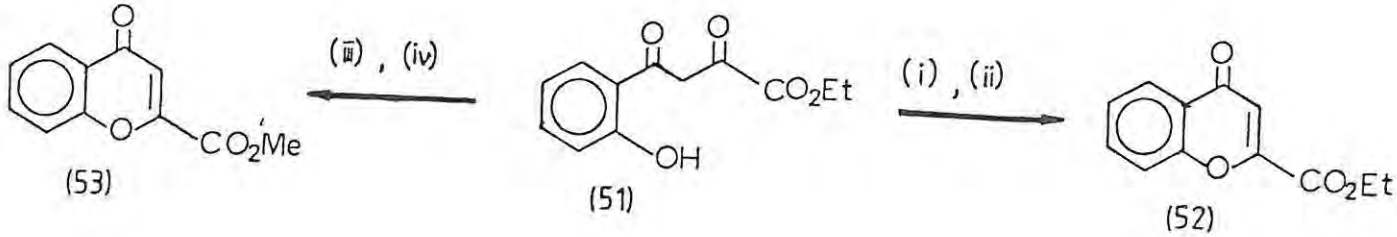
Ellis *et al.*[45] synthesized a number of 3-substituted chromones by converting substituted hydroxyacetophenones into the corresponding chromones by treatment with triethyl orthoformate and perchloric acid at room temperature. Good yields result when an electron withdrawing group is present in the acyl moiety of the ketone. When deuteriated acetic anhydride and sodium acetate are used to cyclize the 1,3-diketone, the deuteriated chromone is formed with >95% incorporation of the isotope.[46] (Scheme 9).

The use of diethyl oxalate offers an added attraction in that the intermediate 1,3-diketo ester readily undergoes transesterification, thereby allowing the synthesis of various chromone-2-carboxylic esters to be achieved from one starting material[47] (Scheme 10).

Chromones can also be obtained from chromanones. This method is not usually of great preparative value, because the chromanones are not readily available and because their conversion into chromones is not always achieved in high yield. Five different methods have been used,[19] *viz.*, dehydrogenation or oxidation of chromanones; dehydration of 2-hydroxychromanones; dehydrobromination; nitrosation; and hydrolysis and isomerization of 3-ylidene derivatives (Scheme 11). Other methods for preparing chromones have also been used. Condensation of *o*-acetoxybenzoyl chloride with lithium enolates, obtained by treatment of trimethylsilyl ethers with phenyllithium, gives chromones[48] (Scheme 12); a number of alkyl - and cycloalkanochromones have been prepared by this method. Chromones can also be prepared from other heterocycles like furans, benzofurans,[49] and coumarins,[50,51] and also from enamines.[52,53]

(49) (50)

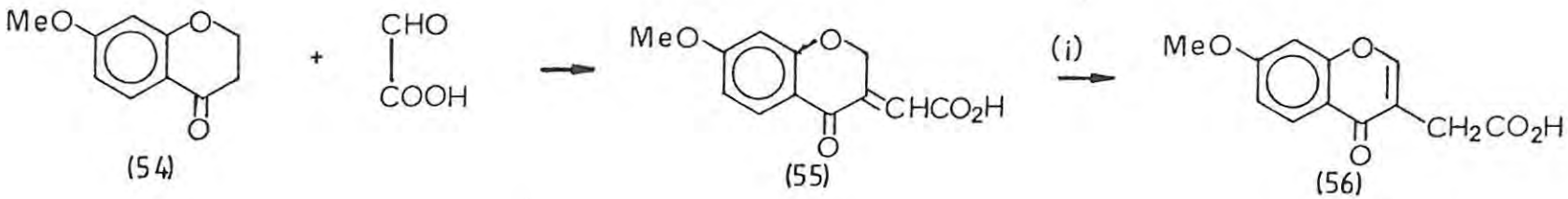
SCHEME 9



(53) (51) (52)

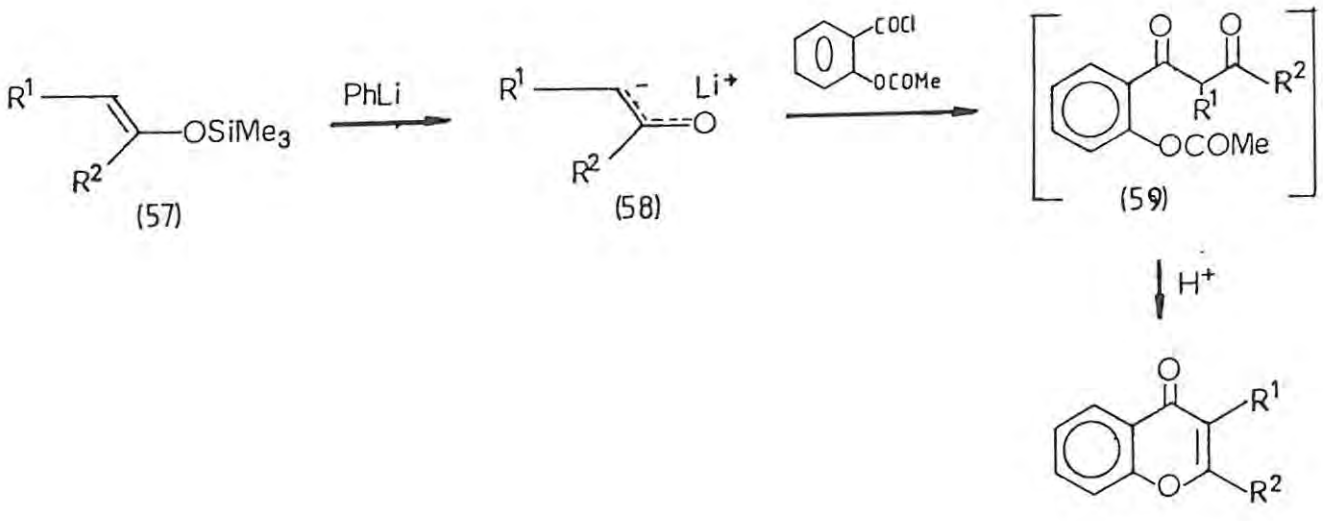
SCHEME 10

Reagents : (i) EtOH; (ii) H_2SO_4; (iii) MeOH, H_2SO_4, 0°C; (iv) MeOH, HCl, boil.



SCHEME 11

Reagent : (i) Ni, xylene.


R1
OSiMe3
R2
(57)
PhLi
R1
Li+
O
R2
(58)
COCl
OCOMe
R1
R2
OCOMe
(59)
H+
O
R1
O
R2

SCHEME 12

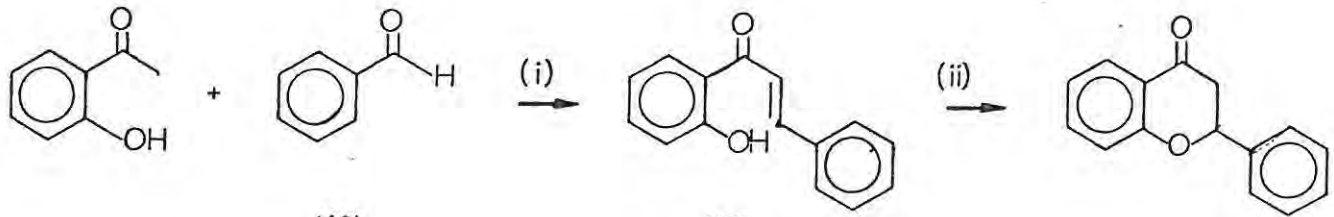
1.3 Flavanone synthesis

Flavanones (9) are synthesized *via* the formation of chalcones (61), which are then cyclized. Common precursors for chalcone formation are 2'-hydroxy-acetophenones [e.g. compound (34)] and substituted benzaldehydes [e.g. compound (60)]. The synthesis begins with the base catalysed aldol condensation of a 2'-hydroxyacetophenone with benzaldehyde to afford the required chalcone, and this condensation is then followed by an acid or base catalysed cyclization to form the flavanone (9) (Scheme 13).

Tomsen and Torssell[54] developed a 3-step synthesis of flavone (Scheme 14). In their synthesis salicylaldoxime (62) is chlorinated to the corresponding hydroxamoyl chloride, which then undergoes cyclo-addition with styrene or phenylacetylene. The isoxazole cycloadducts (63) are reductively cleaved over Raney nickel to ß-hydroxyketones (64) which are cyclised to flavanoids.

Chalcones may also be prepared by *C*-alkylation of phenols with appropriate cinnamoyl systems, either directly or by Fries rearrangement.[55,56] Simonis and Lear[57] prepared chalcones by acylation of phenols with cinnamoyl chloride, but this method is not generally suitable because both the *para*-position and the hydroxyl group of the phenol have to be protected to prevent mixtures of products being formed.

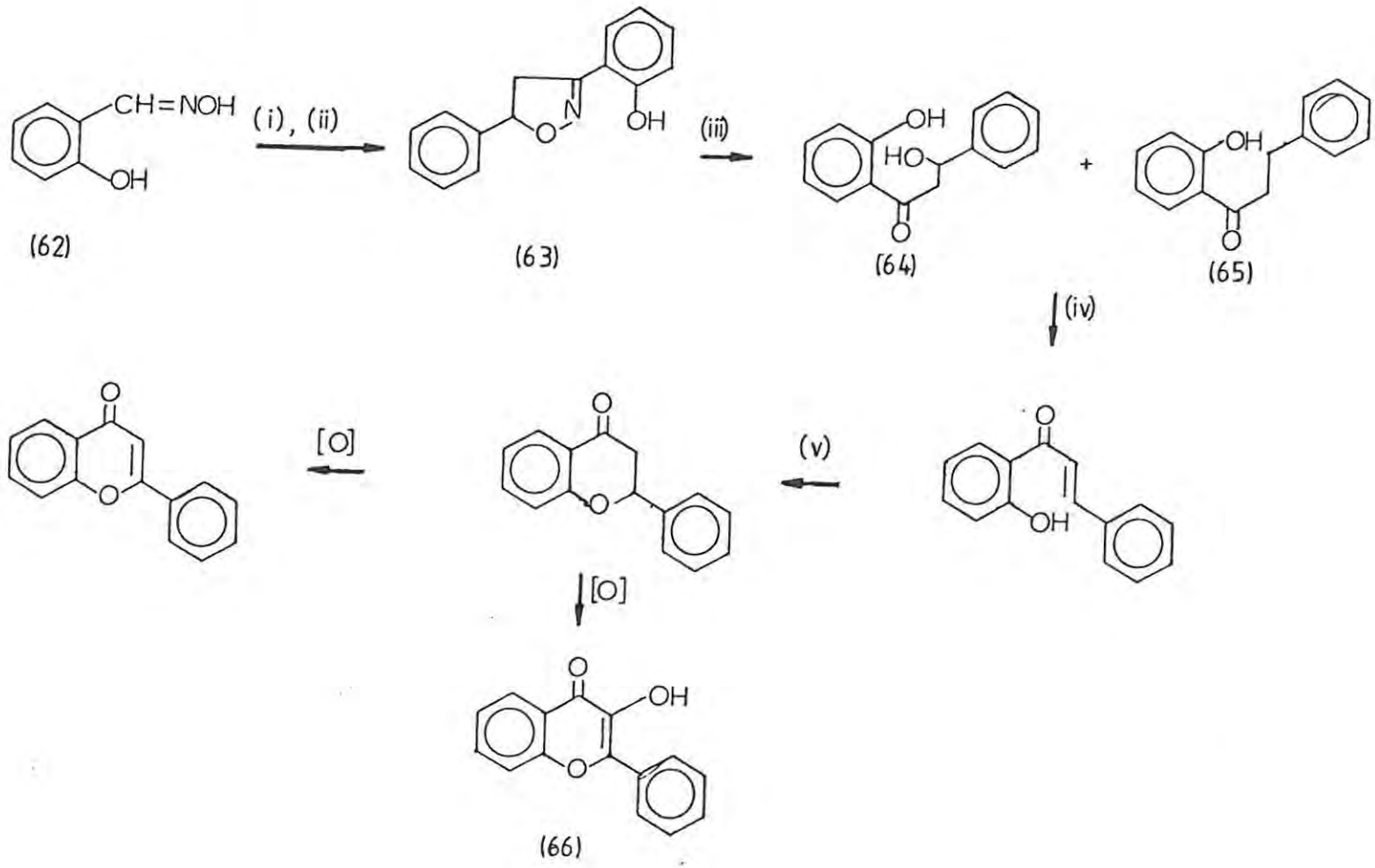
2'-Hydroxychalcones have been prepared[58] by a regio-controlled reaction between bromomagnesium salts of mono - and dihydric phenols and variously substituted cinnamaldehydes, in aprotic non-polar media and in the presence of a suitable basic additive. This method appears to be of general applicability with respect to both mono - and dihydric phenols.



(60) (61)

SCHEME 13

Reagents : (i) base; (ii) acid or base.



SCHEME 14

Reagents : (i) NCS; (ii) Styrene, Δ, Py; (iii) Raney Ni, H_2; (iv) H^+; (v) OH^-.

Széll *et al.*[59,60] have synthesized a number of nitrochalcones from acetophenones and benzaldehydes using sodium hydroxide or hydrochloric acid as catalysts. Using different substituents in the aldehyde component, they concluded that electron donating groups favour condensation by acid catalysts and electron-withdrawing groups favour condensation by bases.

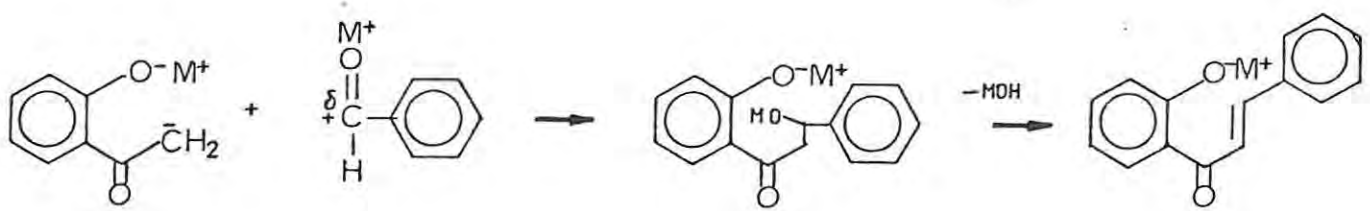
Flavanones can also be obtained[61] as one of the three products resulting from the oxidation of 2'-hydroxychalcones with 2,3-dichloro-5,6-dicyano-4-benzoquinone. This is, obviously, not a suitable method for flavanone synthesis because the yield ranges from 3-13%, but the method is slightly better for the synthesis of flavones with reported yields of up to 42%. Both acids and bases have been employed as catalysts in the cyclisation of chalcones to flavanones. Bases which have been used include butylamine,[62] potassium carbonate,[63] pyridine,[64] and dilute sodium hydroxide.[65] The transition metal complex, Co(salpr) [salpr = *2,4-N*^{1}*N*^{7}-azaheptamethylenebis (salicylideneiminato)] catalyses the conversion of 2'-hydroxychalcones to flavanones in methanol under oxygen.[66] Base catalysis by Co(salpr) (OH) produced *in situ* is responsible for the reaction, which is found to proceed reversibly. Acid catalysts used in the cyclisation step include acetic acid containing a small amount of mineral acid,[67] hydrogen fluoride,[68] and orthophosphoric acid,[69,70] which is the most common reagent used for effecting the cyclisation. The conversion does not occur with dihydroxy derivatives.

The effects of solvent and catalyst concentration on both the condensation of hydroxyacetophenone with benzaldehyde (to produce chalcones), and

cyclisation (to flavanones) have been studied.[69,71] The kinetics and mechanism of ring closure have also been investigated.[72,73,74] The yield of chalcone was found to be highest in EtOH-H_2O (96:4), with the yield being enhanced by changing the catalyst (KOH < NaOH < LiOH) and by increasing the concentration of alkali. This shows that the chalcone is favoured as charge density and concentration of alkali metal cations (M) increase, which means that the cation (M) coordinates with the carbonyl of benzaldehyde as shown in Scheme 15.

It was also discovered[71] that the reaction time for ring closure could be decreased by using a higher boiling solvent. The reaction time was found to decrease with the alcohol (propanol < ethanol < methanol). Alcohols higher than butanol were found to be unsuitable because they promote side reactions. The acid concentration appears to have no influence on the yield of the flavanone.

Flavanones are difficult to obtain in the pure state since they are easily isomerized to chalcones by traces of base. A number of methods of purification have been used, including gas chromatography[75] and column chromatography.[76] The most common and simple method of separating flavanones from chalcones is by evaporating a large portion of the solvent from the reaction mixture and allowing the flavanone to crystallise out.



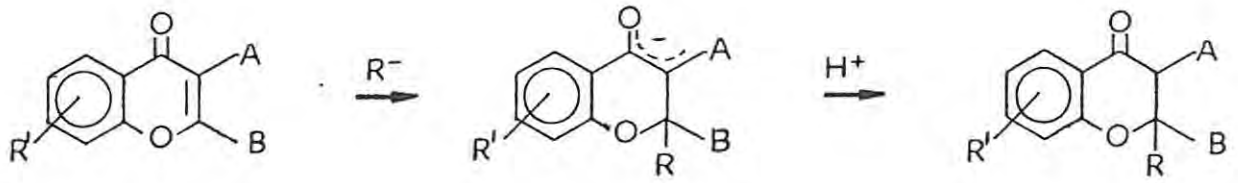
SCHEME 15

1.4 Reactions of chromones with organometallic reagents

The reactions of organometallic reagents with chromones have not been widely researched. A little work appears to have been done on reactions of chromones with lithium dimethylcuprate.[77,78] Chromones activated by carbonyl substituents at *C*-3 have been transformed into the corresponding 2-methyl-4-chromanones by treatment with lithium dimethylcuprate[77] (Scheme 16). In order to develop the above method for synthetic purposes, a means of inducing chirality at *C*-2 was required, hence the examination of the reaction of 3-(arylsulphinyl) chromones (67) with lithium dimethylcuprate.[78] Only two [compounds (68) and (69)] of the four possible diastereoisomeric products were obtained in the ratio 6:1 respectively.

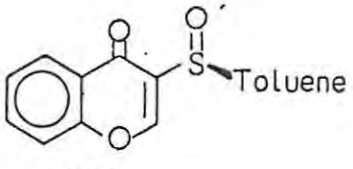
1.5 The Baeyer-Villiger Oxidation reaction

The Baeyer-Villiger reaction has been widely applied in organic synthesis for the conversion of ketones to esters or lactones.[79,80] A general mechanism[81] of the oxidation reaction is shown in Scheme 17. Carbon-14-isotope-effect investigations on acetophenones have indicated that migration of aryl groups takes place in the rate-determining step, and this shows that migration of the migrating group is concerted with departure of $R'CO_2^-$. Amongst alkyl groups, the migratory aptitude is, tertiary > secondary > primary > methyl. Aryl groups migrate in preference to primary alkyl groups. Reddy *et al.*[82] recently reported the oxidation of chromanones (70) to 3,4-dihydro-1,5-benzodioxepin-2-ones (71) with MCPBA (Scheme 18). They proposed that the "exclusive formation of 3,4-dihydro-1,5-benzodioxepin-2-ones, rather than the alternative products, 1,4-benzodioxepin-5-ones, may

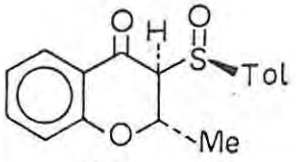


SCHEME 16

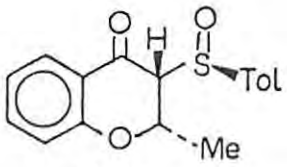
be ascribed to the greater migratory aptitude of an aryl over a methylene group in the Baeyer-Villiger oxidation step". The peracid oxidation of a ketone to an ester was first reported by Baeyer and Villiger[83] in 1899. They found that the cyclohexanone (72) could be oxidized to the lactone (73) as shown in Scheme 18.



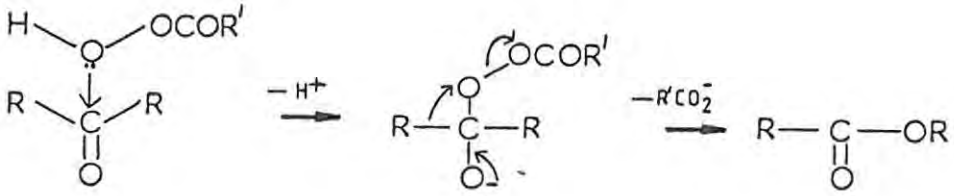
(67)



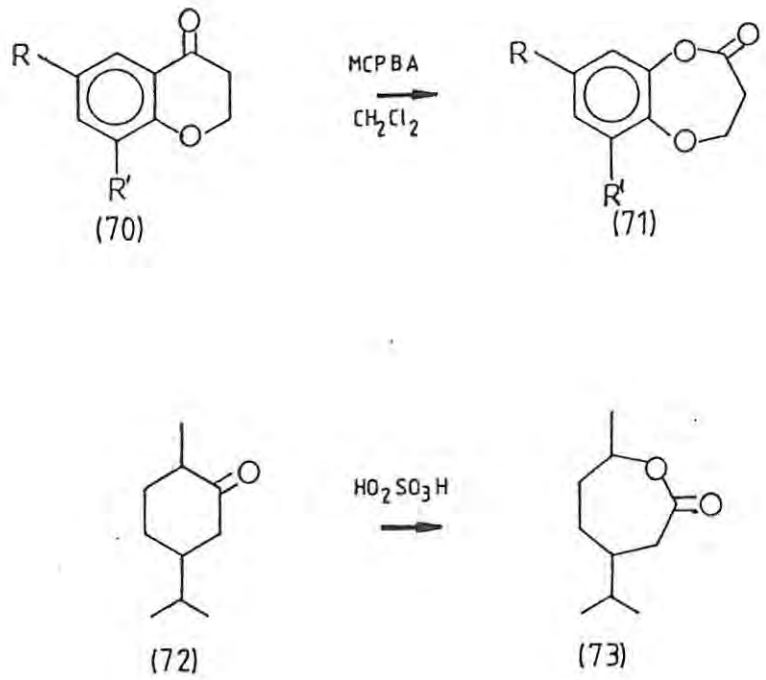
(68)



(69)



SCHEME 17



SCHEME 18

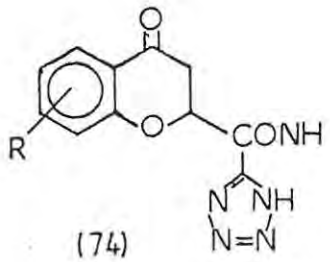
A number of reagents have been used to effect the oxidation.[79] Amongst these are :- persulfuric acid; peracetic acid; monoperphthalic acid; hydrogen peroxide; *meta*-chloroperbenzoic acid (MCPBA),[84,85] which has been widely used despite the fact that very long reaction times are often required; and bis (trimethylsilyl) peroxide,[86] which directs the oxidation specifically to the carbonyl function, leaving carbon-carbon double bonds unaffected. Magnesium monoperoxyphthalate hexahydrate (MMPP) is a newly developed reagent which promises to be a useful replacement for the somewhat unstable MCPBA.[87]

Certain difficulties have been observed when MCPBA is used. These include the incompatibility of some substrates with the reagent,[88,89] and the complete inertness of other ketones.[89] Koch and Chamberlin,[90] consequently, modified the conditions for efficient Baeyer-Villiger oxidation with MCPBA. They found that a mixture of trifluoroacetic acid (TFA) and MCPBA oxidizes both cyclic and acyclic ketones in much shorter times and in higher yields than with MCPBA alone. Some Baeyer-Villiger oxidations of ketones with MCPBA proceed much faster and with higher yields in the solid state than in solution.[91] Baeyer-Villiger reactions may be carried out with a variety of solvents, the choice of which is determined, largely, by the solubilities of the reactants and products. Rate studies have shown that the raction is favoured by polar solvents.[92] The oxidation can be carried out either at room temperature or by refluxing for the required time. The Baeyer-Villiger oxidation of aromatic aldehydes and ketones by peroxy acids provides a useful, additional approach to the synthesis of phenols. Such oxidation may be carried out by using reagents such as peroxyacetic acid,[93] trifluoroperoxyacetic acid,[94,95,96] 4-nitro- and 3,5-dinitroperoxybenzoic

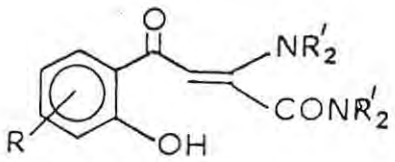
acid,[97,98] and, most frequently, MCPBA.[85,99,100]

1.6 Previous studies, within the group, on chromones and flavanones.

A range of chromone-2-carboxylic acids was prepared[101] for oximation and subsequent (in the event, unsuccessful) ring expansion to 1,5-benzoxazepin-4-ones. An i.r. conformational analysis of the chromone-2-carboxylate ester analogues, involving variable solvent and variable temperature techniques was also performed. A current project[102] has been concerned with the synthesis and conformational analysis of chromone-2-carboxamides modelled on biologically active compounds such as the tetrazolyl chromone (74). Exploration of the possible interaction of proteins with chromone systems has involved kinetic studies of ring-opening reactions which afford enamines (75).



(74)



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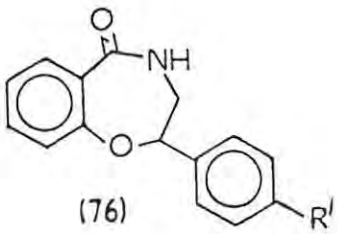


(76)

A series of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-ones (76), which bear certain structural similarities to the benzodiazepines, have been prepared[103] by ring expansion of the corresponding flavanones *via* the Schmidt reaction, and the mass fragmentation patterns of these and related compounds have also been investigated.

1.7 Aims of the present investigation

The aims of the present study have been :-

(i) synthesis of a range of chromone-2-carboxylate esters and flavanone derivatives;

(ii) ring expansion of the heterocyclic systems by Baeyer-Villiger oxidation techniques;

(iii) investigating the regioselectivity in reactions of chromone derivatives with organometallic reagents; and

(iv) detailed spectroscopic analysis of the various products.

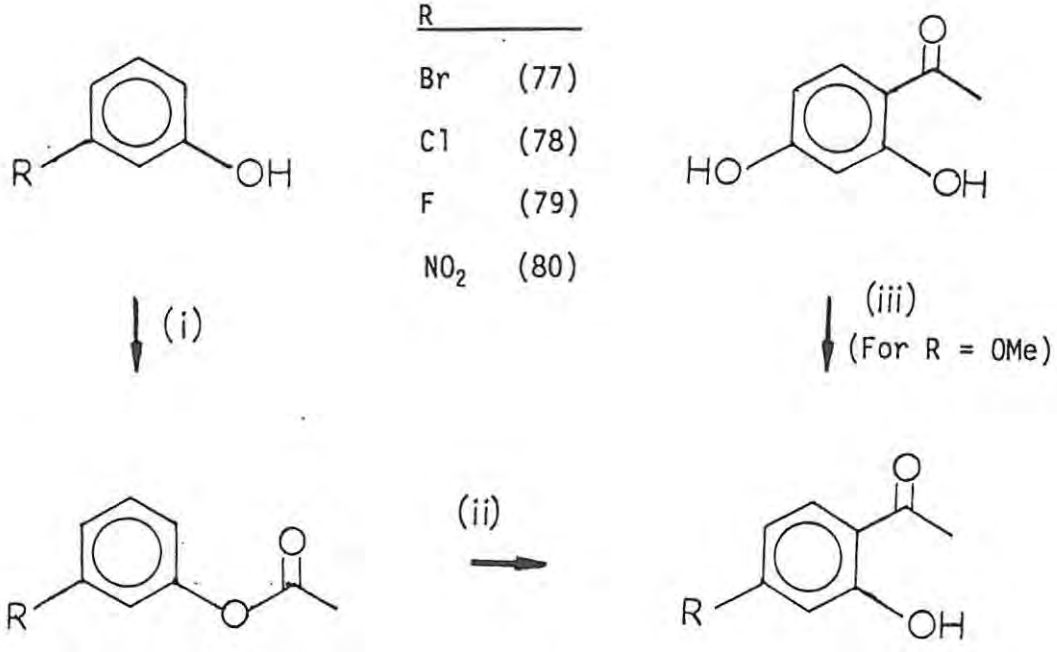
2. DISCUSSION

2.1 Synthesis of Chromone derivatives

Chromones are usually prepared by the condensation of *o*-hydroxyacetophenones with diethyl oxalate. In this study, a number of chromone derivatives have been prepared by this general method. The preparation of the *o*-hydroxyacetophenone precursors, *via* Fries rearrangement of *m*-halogenophenyl acetates, or methylation of resacetophenone (2,4-dihydroxyacetophenone), is discussed in Section 2.1.1, while condensation with diethyl oxalate and subsequent cyclisation is covered in Section 2.1.2.

2.1.1 Preparation of *o*-hydroxyacetophenones

The *o*-hydroxyacetophenones (86-90) were prepared as shown in Scheme 19. The *meta*-substituted phenols (77, 78, 79 and 80) were acetylated with acetic anhydride and the resulting phenyl acetates (82, 83, 84, and 85) subjected to Fries rearrangement, by heating in the presence of anhydrous aluminium trichloride, to give the required *o*-hydroxyacetophenones (86, 87, 88, and 89). The crude phenyl acetates, [usually obtained in good yield (84-97%)] appeared to be pure by ^{1}H n.m.r. spectroscopy, although the i.r. spectra of 3-bromo-(82), 3-chloro- (83) and 3-fluorophenylacetate (84) showed hydroxyl bands indicating the presence of some starting material. These acetate esters [(82), (83), and (84)] were distilled in the hope of eliminating the contaminants, but the i.r. hydroxyl bands were still present after distillation. Consequently, these compounds [(82), (83), and (84)] were used without further purification. All of the hydroxyacetophenones, with the exception of 2-hydroxy-4-nitroacetophenone (89), were obtained in good



R		
Br	(77)	
Cl	(78)	
F	(79)	
NO_2	(80)	

R		
(82)	Br	(86)
(83)	Cl	(87)
(84)	F	(88)
(85)	NO_2	(89)
	MeO	(90)

SCHEME 19

Reagents : (i) aq.NaOH - Ac_2O, 0°C; (ii) $AlCl_3$, Δ; (iii) Me_2SO_4.

yields (65-85%) by Fries rearrangement of the corresponding *m*-halogenophenyl acetates.

The series of compounds, phenols, phenyl acetates, and hydroxyacetophenones (Scheme 19), can readily be distinguished from one another by means of their ^1H n.m.r. spectra (Fig.1). Thus, for example, the acetyl methyl^1H signal of *m*-fluorophenyl acetate (84) resonates at 2.25ppm., while in 4-fluoro-2-hydroxyacetophenone (88) the corresponding signal is shifted upfield to 2.61ppm.; this signal of course, is absent in the phenolic precursor (79).

The Fries rearrangement reactions were followed by TLC and were found to be complete after 2-3 hours. On addition of aqueous acid, a vigorous exothermic reaction occurs due to the reaction of excess $AlCl_3$ with water. After work-up and distillation, the oily products were shown to be pure by ^1H n.m.r. analysis. 2-Hydroxy-4-nitroacetophenone (89) was not easy to prepare. A mixture of *m*-nitrophenyl acetate (85), $AlCl_3$, and dry nitrobenzene was heated for 8 hours. steam-distillation and work-up gave a low yield (22%) of the required compound (89) - despite the comparatively long reaction time. Drews[101] used the same method without drying the nitrobenzene and obtained an even lower yield (7.5%). The problem associated with this low yield is that, for a multistep synthesis, a large quantity of starting material has to be used or the reaction has to be repeated several times. 2-Hydroxy-4-methoxyacetophenone (90) was prepared by methylation of resacetophenone (81) by using dimethyl sulphate.

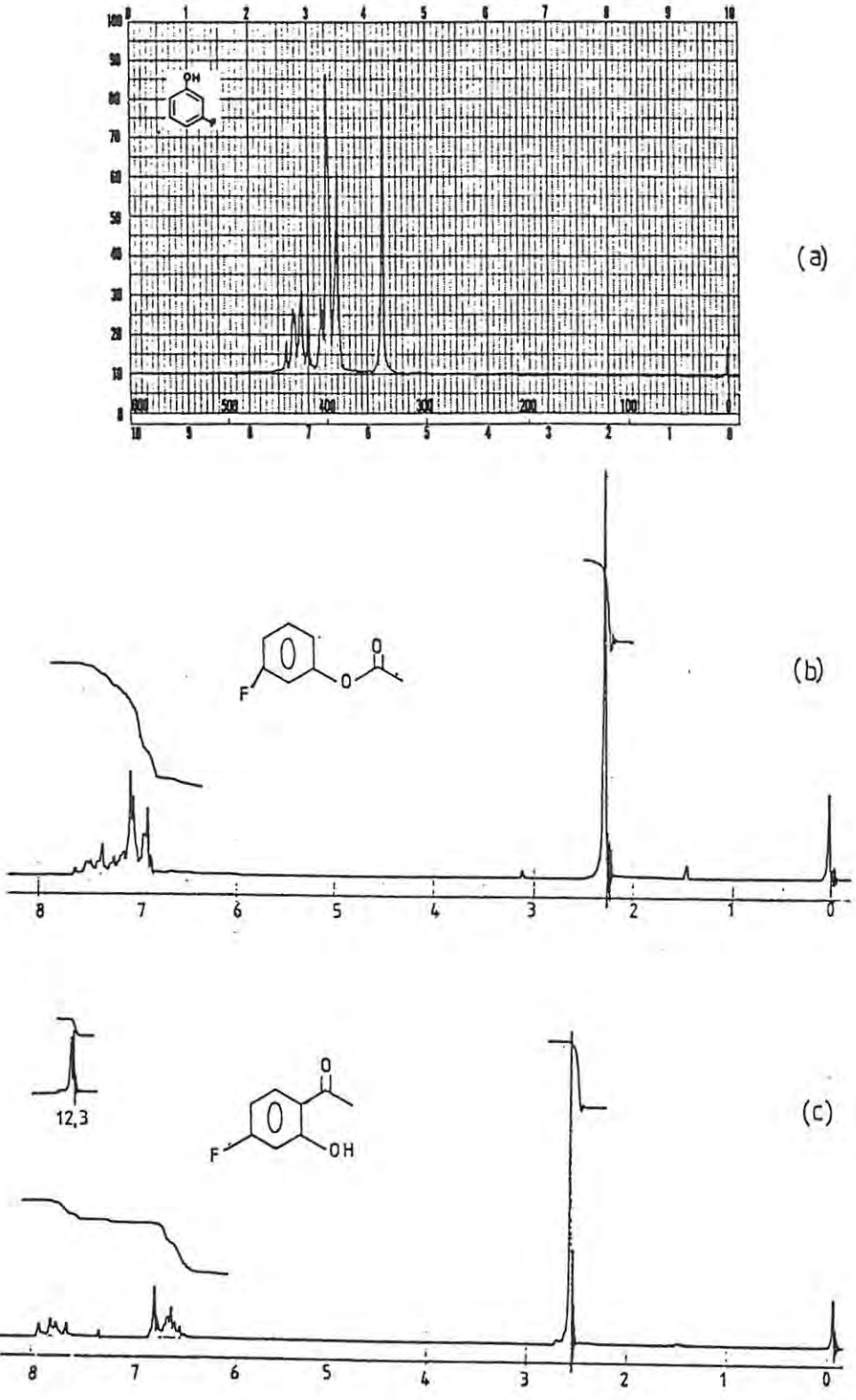


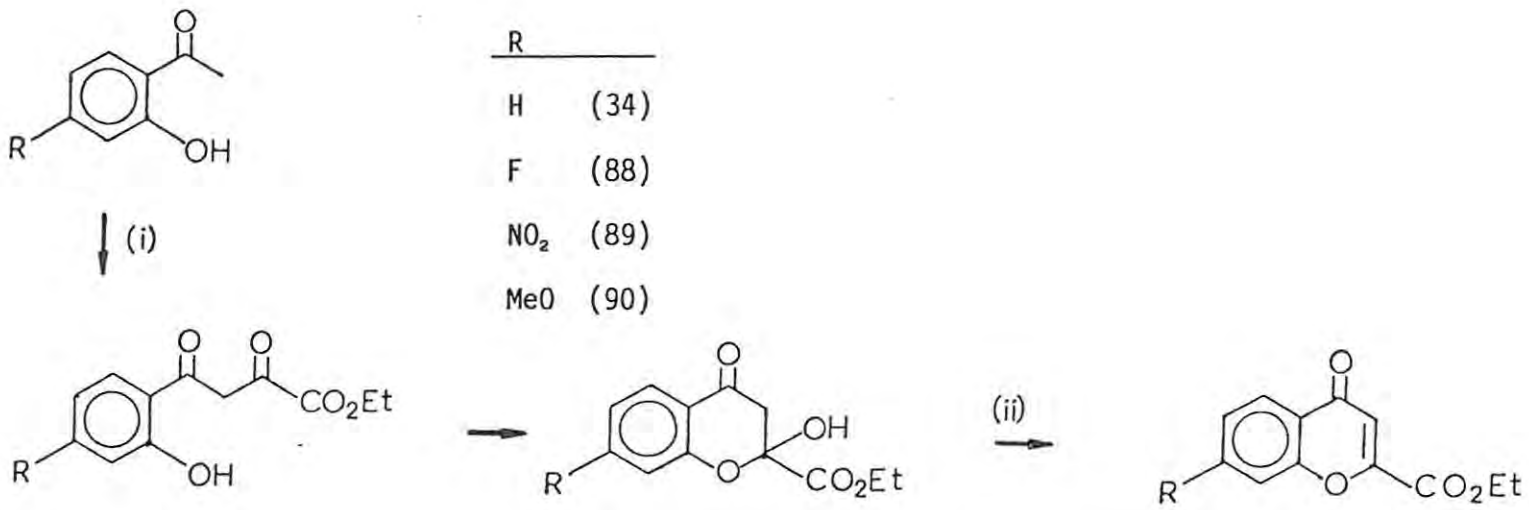
FIGURE 1 : ^{1}H n.m.r. spectra of (a) *m*-fluorophenol, (b) *m*-fluorophenyl acetate, and (c) 3-fluoro-2-hydroacetophenone.

2.1.2 Preparation of chromone-2-carboxylate esters

The chromone-2-carboxylate esters were prepared as shown in Schemes 20 and 21. For the condensation of the *o*-hydroxyacetophenones [(34), (88), (89), and (90)], dry ethanol was used for efficient formation of sodium ethoxide. The intermediates in these reactions were not isolated except in the case of the raction of 2-hydroxy-4-methoxyacetophenone (90). In this case, material isolated prior to dehydration was shown by ^{1}H n.m.r. analysis to be a mixture of comounds (91) and (92). Dehydration of the chromanone esters with acid gave the corresponding chromone derivatives. All the chromones were isolated as chromone-2-carboxylate esters, except compound (93) which was isolated as a carboxylic acid.

This compound, chromone-2-carboxylic acid (93), was obtained by using equal quantities of acetic acid and hydrochloric acid in the dehydration step, while the other chromonone-2-carboxylate esters were obtained by using a trace of hydrochloric acid and excess acetic acid. Ethyl 7-nitrochromone-2-carboxylate (95) was obtained in poor yield (34%). This is probably due to the deactivating effect of the electron withdrawing nitro-group. Attempts to completely purify ethyl 7-fluorochromone-2-carboxylate (94) were unsuccessful, but the compound was shown to be almost pure by ^{1}H n.m.r. spectroscopy and gave a satisfactory combustion analysis.

Ethyl chromone-2-carboxylate (52) and methyl chromone-2-carboxylate (53) were prepared by acid catalysed esterification of chromone-2-carboxylic acid (93) with ethanol and methanol respectively (Scheme 21).

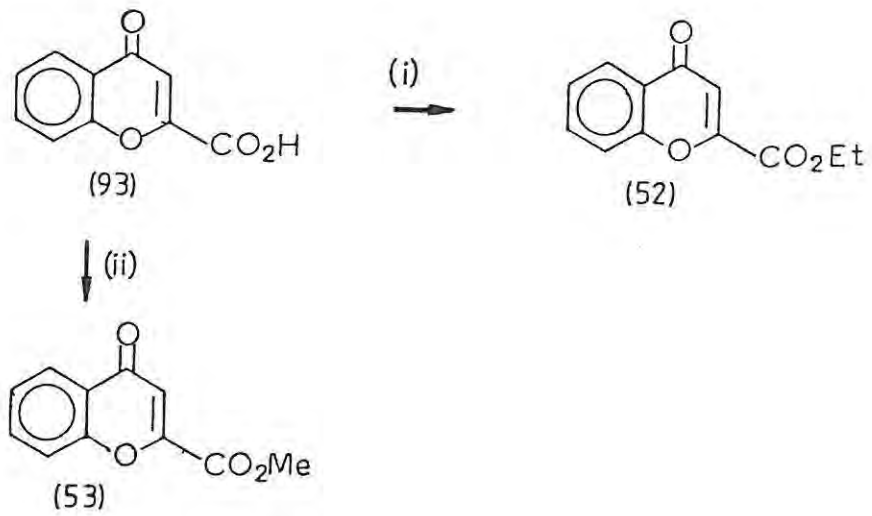


R			
H	-[a]	-[a]	(93)[b]
F	-[a]	-[a]	(94)
NO_2	-[a]	-[a]	(95)
MeO	(91)	(92)	(96)

[a] Intermediates were not isolated. [b] Isolated as carboxylic acid.

SCHEME 20

Reagents: (i) NaOEt-EtOH, $(CO_2Et)_2$; (ii) H^+, Δ.



SCHEME 21

Reagents : (i) EtOH, H^+, Δ; (ii) MeOH, H^+, Δ.

2.2 Synthesis of flavanone derivatives

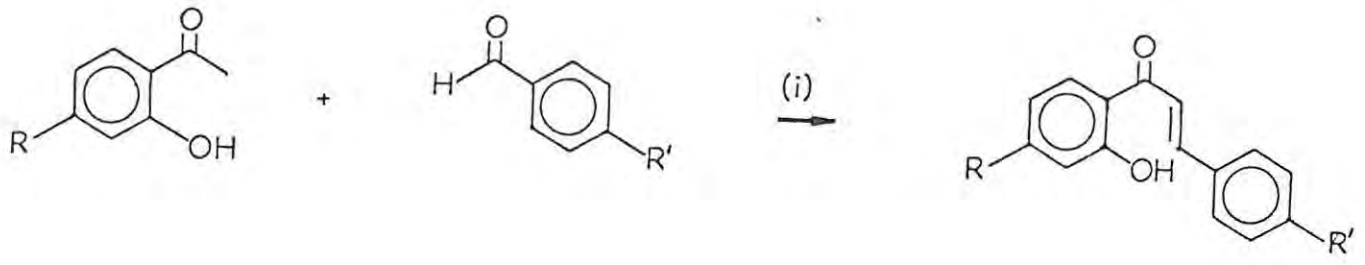
Flavanones were synthesized in two steps using hydroxyacetophenones as starting materials. The first step involved condensation of hydroxyacetophenones with benzaldehyde to give the corresponding chalcones, which were then cyclized to the corresponding flavanones. The condensation of hydroxyacetophenones is discussed in section 2.2.1, while the cyclization of chalcones to flavanones is covered in section 2.2.2.

2.2.1 Preparation of 2'-hydroxychalcones

2'-Hydroxychalcones were prepared as shown in Scheme 22. All of the chalcones with exception of 2'-hydroxy-4'-methoxychalone (100) were prepared by condensation of hydroxyacetophenones with benzaldehyde in ethanol, using potassium hydroxide as a catalyst. The reactions were performed at *ca.*0°C for 2-4 days. All the chalcones were readily precipitated by dilution (with water) and acidification of the reaction mixture. These chalcones were recrystallized from ethanol, except in the ase of the relatively insoluble 2'-hydroxy-4'-nitrochalcone (101) which was used without further purification.

A slightly different method was used to prepare 2'-hydroxy-4'-methoxychalcone (100). Sodium hydroxide was used (instead of potassium hydroxide) as a catalyst for the condensation reaction which was performed at room temperature (instead of at *ca.*0°C) for 24 hours.

All the required chalcones were shown to be pure by ^{1}H n.m.r. analysis except compound (101) which was shown to contain some impurities.



R		R'	R		R'
H		H	H	(61)	H
Br	(86)	H	Br	(97)	H
Cl	(87)	H	Cl	(98)	H
F	(88)	H	F	(99)	H
OMe	(90)	H	OMe	(100)	H
NO_2	(89)	H	NO_2	(101)	H
H		Cl	H	(102)	Cl
H		F	H	(103)	F

SCHEME 22

Reagents : (i) EtOH, base, 0°C.

2.2.2. Preparation of substituted flavanones

The flavanones were prepared by cyclisation of the corresponding chalcones in an ethanolic medium using phosphoric acid as a catalyst for the reaction (Scheme 23). The chalcone solutions were refluxed for at least 48 hours before work-up to afford mixtures of the chalcones and corresponding flavanones. Pure flavanones were not readily obtained since they easily isomerize to chalcones. Recrystallisation could not be used to separate the flavanones from the chalcones because they both crystallize from the same solvent. The best method for separation was to evaporate a large quantity of the reaction solvent and allow the less soluble flavanone to crystallize out. The crude flavanones, which were yellow because of chalcone impurities, were recrystallized from ethanol-hexane (1:3) and colourless flavanones were obtained . When ethanol alone was used for recrystallisation, several recrystallisations were necessary before the pure flavanones were obtained.

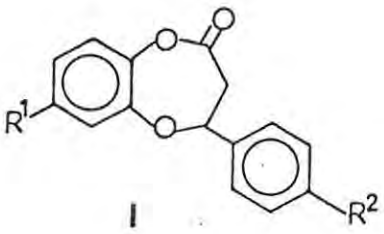
R		R′	R		R′
H	(61)	H	H	(9)	H
Br	(97)	H	Br	(105)	H
Cl	(98)	H	Cl	(106)	H
F	(99)	H	F	(107)	H
OMe	(100)	H	OMe	(108)	H
NO_2	(101)	H	NO_2	(109)	H
H	(102)	Cl			
H	(103)	F	H	(110)	Cl
H	(104)	Br	H	(111)	F

SCHEME 23

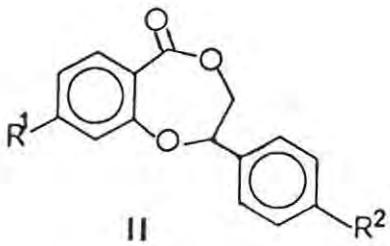
Reagents : (i) EtOH, H_3PO_4, reflux.

2.3 Baeyer-Villiger oxidation of flavanones

The Baeyer-Villiger oxidation of flavanones converts them to the corresponding lactones. In principle, either one or both of the isomeric products (I or II below) are possible.



I



II

In this investigation, the lactones of type I were proved to be the products of MCPBA oxidation. The structures of the 1,5-benzodioxepan-4-ones (I)* were confirmed by the following evidence: (a) a reported[82] Baeyer-Villiger oxidation of chromanone derivatives which gave products corresponding to isomer I (Scheme 17); (b) ^1H n.m.r. chemical shifts (page 53); and (c) MS fragmentation patterns (page 49). The oxidation of flavanones by MCPBA in dry dichloromethane gave the 1,5-benzodioxepan-4-ones detailed in Scheme 24. The yields of the products varied in the range 17-78%. All the 1,5-benzodioxepan-4-ones were prepared by refluxing the corresponding flavanones with MCPBA in dichloromethane for 16 hours or longer. The residue which was obtained after evaporation of the solvent was dissolved in ethyl acetate and the resulting solution was washed with aq. $NaHCO_3$ (to remove unreacted MCPBA and *m*-chlorobenzoic acid) and then with water.

Different methods of purification were applied. 2-Phenyl-1,5-benzodioxepan-4-one (113), which was prepared by the oxidation of flavanone (9), was

* The numbering system used for the 1,5-benzodioxepanone products in this thesis follows the numbering in the flavanone precursors rather than the more systematic numbering. Thus, compound (113) is named 2-phenyl-1,5-benzodioxepan-4-one rather than 4-phenyl-1,5-benzodioxepan-2-one.

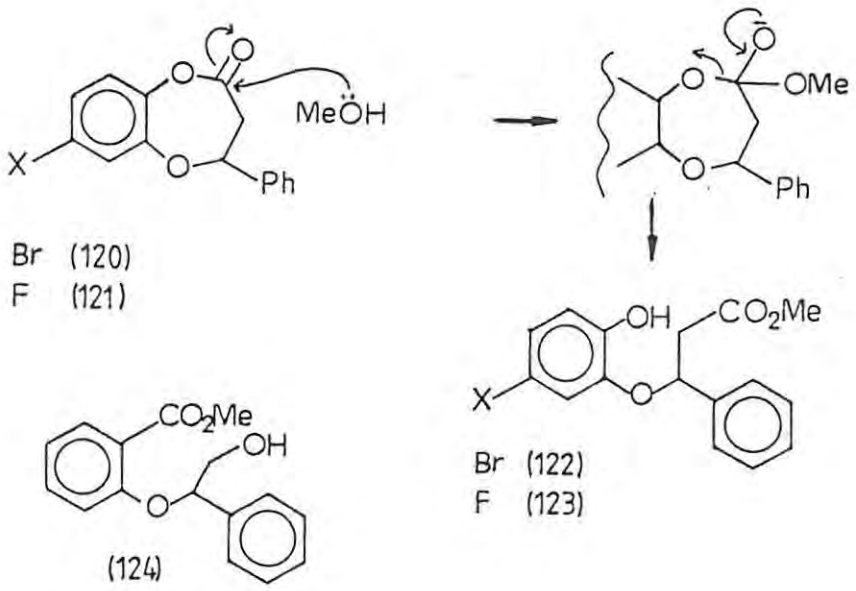
R		R'	R		R'
H	(9)	H	H	(113)	H
Cl	(98)	H	Cl	(114)	H
OMe	(100)	H	OMe	(115)	H
H	(105)	Br	H	(116)	Br
H	(106)	Cl	H	(117)	Cl
H	(107)	F	H	(118)	F
H	(108)	OMe	H	(119)	OMe

SCHEME 24

Reagents : (i) CH_2Cl_2, MCPBA, reflux.

purified by sublimation and recrystallisation from methanol; 8-chloro-2-phenyl-1,5-benzodioxepan-4-one (114) and 2-(4-bromophenyl)-1,5-benzodioxepan-4-one (116) were purified by flash chromatography; 8-methoxy-2-phenyl-1,5-benzodioxepan-4-one (115), was purified by flash chromatography and recrystallisation from methanol; and the rest of the compounds were purified by recrystallisation from methanol.

Although methanol was successfully used for recrystallisation of some of the above products, its use may be accompanied by nucleophilic opening of the C-ring of 1,5-benzodioxepan-4-ones. This complicating transesterification was observed in the case of the bromo compound (120) [and the fluoro analogue (121)] as shown below:



^{1}H And ^{13}C n.m.r. spectroscopy confirmed the structures of compounds (122) and (123). These compounds also confirm that the products of the Baeyer-Villiger oxidation of flavanones correspond to isomer I.

If the products corresponded to the second isomer (II), then the methyl ester and hydroxyl group would be interchanged as in structure (124). The ^1H n.m.r. chemical shift observed for the 3-methylene protons (δ 2.93) is consistent with structures (122) and (123). In the case of structure (124) these protons are calculated[127] to resonate at δ 3.88. A recently developed alternative to MCPBA, *viz*, magnesium monoperoxyphthalate was used in several unsuccessful attempts to expand the C-ring in flavanones (9), (100), (106), and (108).

2.3.1 Mass-spectrometric studies of the benzodioxepanones

A combination of low-and high-resolution mass spectometry has been used to study fragmentation patterns in the mass spectra of 1,5-benzodioxepan-4-ones. Pathways for possible fragmentation patterns in the spectra of these compounds (Scheme 25) were facilitated by high resolution analysis of significant peaks in the mass spectrum of the parent system (113) (Figure 2) together with low resolution analysis of the monosubstituted analogues (114-119).

Ring opening of the molecular ion **a** (Scheme 25) to the acyclic analogue **b** leads to a resonance stabilized conjugated acylium carbocation **c**, which is responsible for the base peak. Loss of ketene from the molecular ion (**a**) gives the odd electron species **d** containing both A- and B-rings. Loss of H· from **d** gives an even electron species **e**, while loss of a phenyl radical gives another carbocation **f** containing the A-ring. Elimination of $C_7H_4O_3$ (possibly as the carbonate diester illustrated in Shceme 25) from the molecular ion yields the styryl radical cation **g** which, in turn, undergoes loss of H· to give an even electron species, $C_8H_7^+$ (**h**).

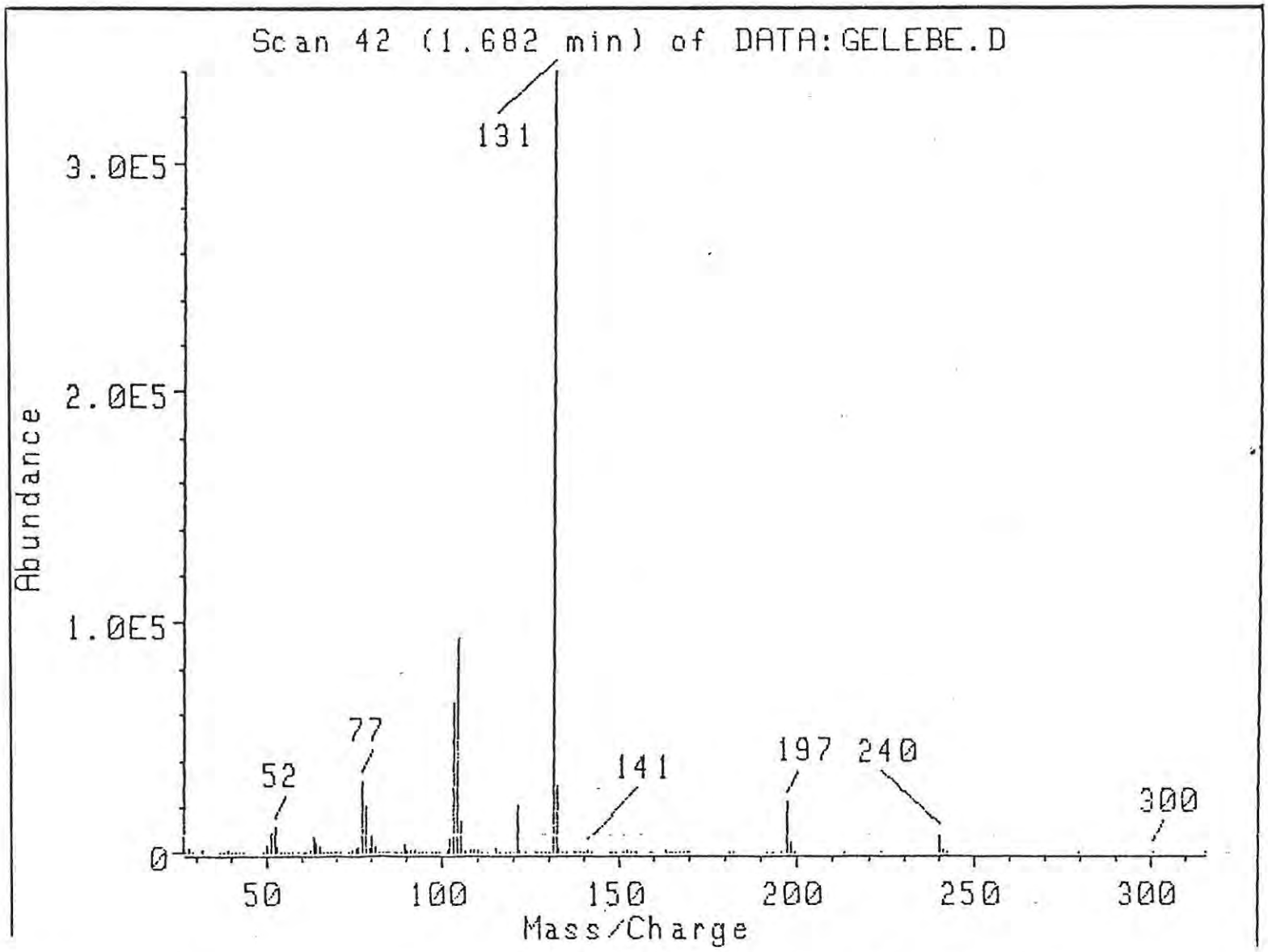
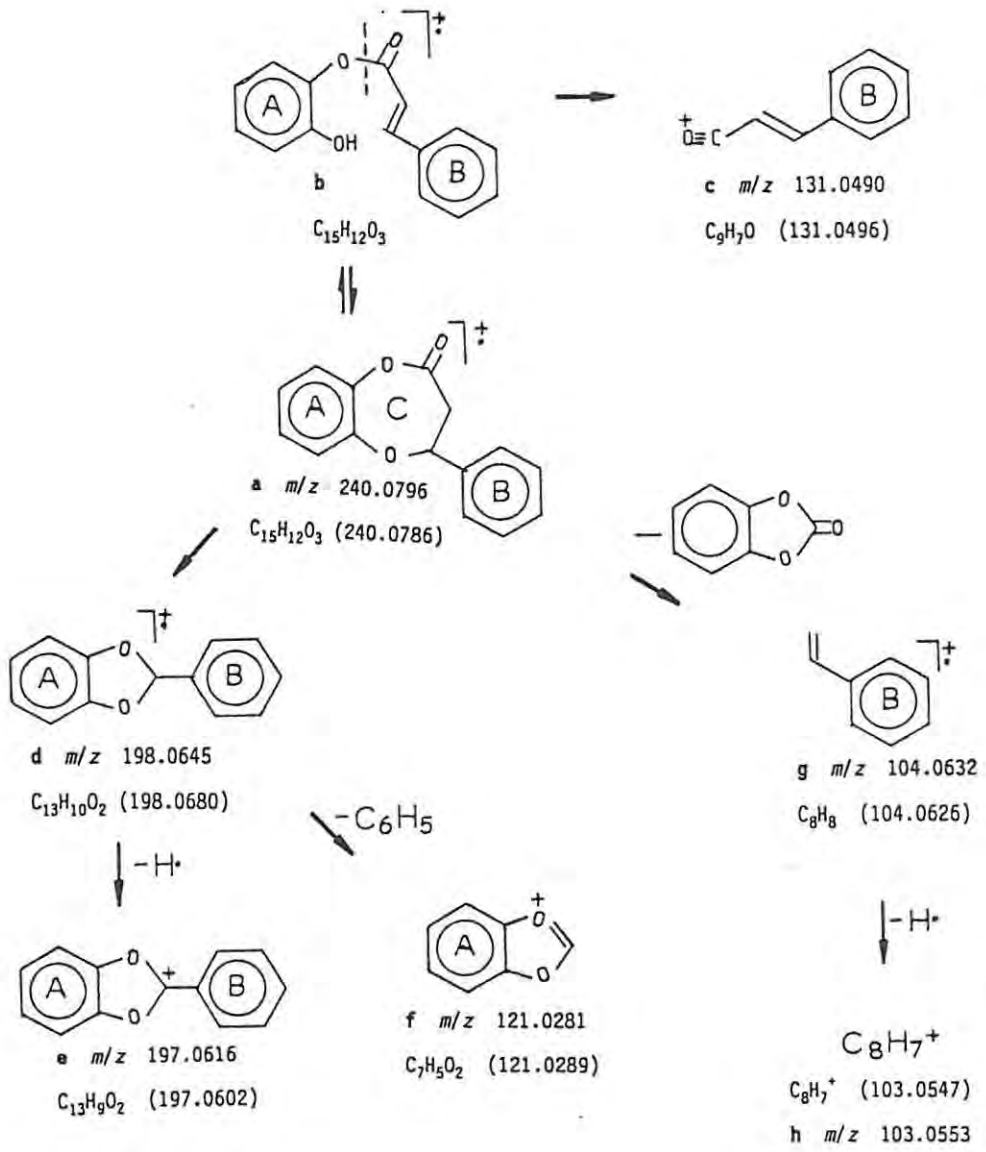
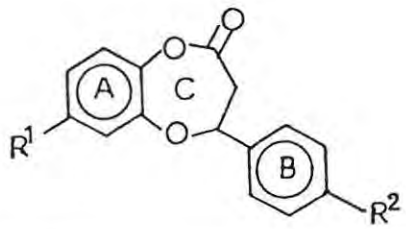


FIGURE 2 : Low resolution mass spectrum of 2-phenyl-1,5-benzodioxepan-4-one.



SCHEME 25 MS fragmentation patterns for 1,5-benzodioxepan-4-one (**a**). The high resolution masses (*m/z*) determined for individual ions is followed, in parentheses, by calculated formula masses.



Nominal mass peaks (m/z) for fragment types (a-h)

Cpd.	R^1	R^2	a	c	d	e	f	g	h
(113)	H	H	240	131	198	197	121	104	103
(114)	Cl	H	276[a]	131	234[a]	233[a]	156[a]	104	103
(115)	OMe	H	270	131	229	228	152	104	103
(116)	H	Br	318[b]	210[b]	277[b]	276[b]	121	183[b]	182[b]
(117)	H	Cl	276[a]	166[a]	234[a]	232[a]	121	139[a]	138[a]
(118)	H	F	258	150	216	215	121	123	122
(119)	H	OMe	270	161	228	227	121	134	133

Table 1. Nominal masses (m/z) of selected peaks in the spectra of 1,5-benzodioxepanones. [a]m/z values correspond to ^{35}Cl. [b]m/z values correspond to ^{79}Br.

From the mass contributions of the 4'-and 8-halogeno- and methoxy-substituents (Table 1) it may be concluded that ion types **f** are A-ring fragments, ions of type **c**, **g**, and **h** are B-ring fragments, and ion types **d** and **e** involve both A- and B-rings (the ring assignments following flavanoid conventions).

2.3.2 N.m.r. spectroscopic studies of the benzodioxepanones

The ^{1}H and ^{13}C n.m.r. spectra of the 1,5-benzodioxepan-4-ones (113)-(119) were examined in some detail. In the ^{1}H n.m.r. spectra [illustrated for compound (117) - Figure 3], the symmetrically split signals at *ca.*δ3.1 are due to couplings of the non-equivalent diastereotopic 3-H nuclei with each other and with the adjacent methine proton [this coupling is also shown by the COSY spectra of 2-phenyl-1,5-benzodioxepan-4-one (113) in Figure 4(a)]. In some cases [as with 2-(4-methoxyphenyl)-1,5-benzodioxepan-4-one (119)] these signals were not fully resolved, and, hence the coupling constants could not always be measured. However, such measurements were possible in the case of 2-(4-chlorophenyl)-1,5-benzodioxepan-4-one (117) and the splitting pattern and coupling constants are shown in Figure 3. The multiplet (an overlapping doublet of doublets which appears as a triplet) at *ca.*δ5.7 corresponds to the 2-H nucleus, which couples with the two diastereotopic protons at C-3 as already mentioned. the aromatic proton signals occur in the region between δ6.5 and 7.6, and is more complex in the compounds with aromatic substituents.

The ^{13}C n.m.r. spectra of these compounds were also studied. The expected chemical shifts for the carbon nuclei in all of the compounds examined were calculated using methods of additive increments.[127] The observed signals were assigned on the basis of these values and the results are summarised in Table 2.

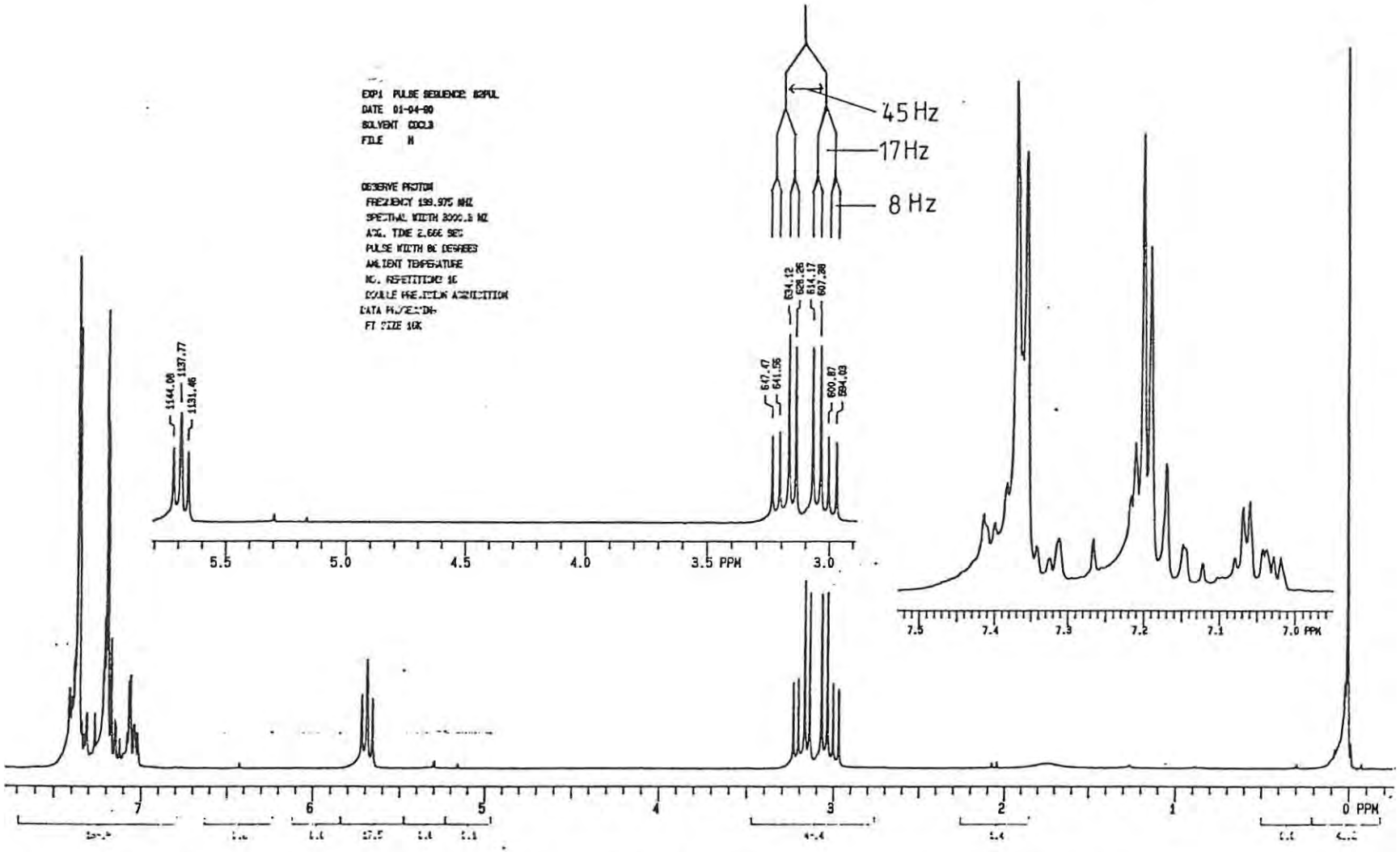
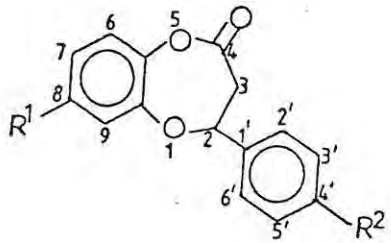


FIGURE 3 : ^{1}H N.m.r. spectrum of 2-(4-chlorophenyl)-1,5-benzodioxepan-4-one.



R′	R²	C-2	C-3	C-4	C-5a	C-6	C-7	C-8	C-9	C-9a	C-1′	C-2′ C-6′	C-3′ C-5′	C-4′
H	H	(84.0)	(39.9)	(172.0)	(137.1)	(123.1)	(122.1)	127.2)	(115.4)	(152.5)	(148.8)	(126.6)	(128.6)	(126.1)
		83.4	38.4	167.3	138.5	125.6	124.1	128.7	120.4	145.6	145.1	126.5	129.0	126.1
OMe	H	(84.0)	(39.9)	(172.0)	(129.4)	(123.4)	(107.7)	(158.6)	(101.0)	(154.5)	(148.8)	(126.6)	(128.6)	(126.1)
		83.6	38.6	168.5	139.1	121.0	119.8	158.2	109.8	146.2	139.5	129.1	129.4	126.5
Cl	H	(84.0)	(39.9)	(172.0)	(135.2)	(124.4)	(122.5)	(133.4)	(116.0)	(154.8)	(148.8)	(126.6)	(128.6)	(126.1)
		79.2	42.2	176.5	138.4	123.6	118.4	126.6	116.4	146.5	144.6	126.4	129.1	125.0
H	Br	(84.0)	(39.9)	(172.0)	(137.1)	(123.1)	(122.1)	(127.2)	(115.4)	(153.5)	(146.9)	(127.9)	(129.0)	(132.3)
		82.7	38.4	167.1	132.0	124.0	123.1	125.9	120.5	145.0	137.5	126.6	127.8	132.0
H	Cl	(84.0)	(39.9)	(172.0)	(137.1)	(123.1)	(122.1)	(127.2)	(115.4)	(153.5)	(146.9)	(127.9)	(129.0)	(132.3)
		82.7	38.4	167.1	137.0	125.9	124.0	126.6	120.5	145.6	145.0	127.5	129.0	134.9
H	F	(84.0)	(39.9)	(172.0)	(137.1)	(123.1)	(122.1)	(127.2)	(155.4)	(153.5)	(146.9)	(127.9)	(129.0)	(132.3)
		83.1	38.6	167.8	143.9	124.5	120.7	126.3	115.9	146.8	145.5	128.3	116.1	163.4
H	OMe	(84.0)	(39.9)	(172.0)	(137.1)	(123.1)	(122.1)	(127.2)	(115.4)	(153.5)	(141.1)	(128.9)	(114.2)	(157.5)
		83.5	38.5	168.2	131.0	126.0	124.8	126.8	120.6	146.2	145.4	128.0	144.4	160.0

Table 2. Observed and calculated[a] ^{13}C chemical shift data for 1,5-benzodioxepan-4-ones.

[a] These values are given in parenthesis and were calculated following the method in reference 127.

2.4 Reactions of chromones with organolithium reagents.

The chromone esters have more than one electrophilic centre where attack by a nucleophile could, in principle, take place. This may lead to the formation of more than one product, depending on the ratio of the nucleophile to the chromone ester. The range of possible primary products arising from reaction of an alkyllithium with ethyl 7-chromone-2-carboxylate (52) is illustrated in Scheme 26. Subsequent reaction of these primary products with the alkyllithium to give secondary products is possible.

In this preliminary regioselectivity study, butyllithium was reacted with a series of chromone esters [(52), (94)-(96)] and products, shown to be complex mixtures by TLC, were obtained. These results suggest that several of the reaction pathways outlined in Scheme 26 are, in fact, followed. Complex mixtures were also obtained when the ratio of butyllithium to chromone ester was increased. Methods of purification which were attempted include flash chromatography, preparative chromatography, recrystallisation, and high performance liquid chromatography (HPLC). Chromatography of the product mixture obtained from the reaction of ethyl 7-chromone-2-carboxylate (52) afforded a number of fractions, one of which was sufficiently pure for complete analysis. (Further separation of the complex mixture was beyond the scope of the present study and may be the subject of future research).

In order to obtain the successfully purified product [compound (130)], the nucleophile has to attack the chromone ester at C-2, as shown in Scheme 26. The chromone C-2 attack by nucleophiles is

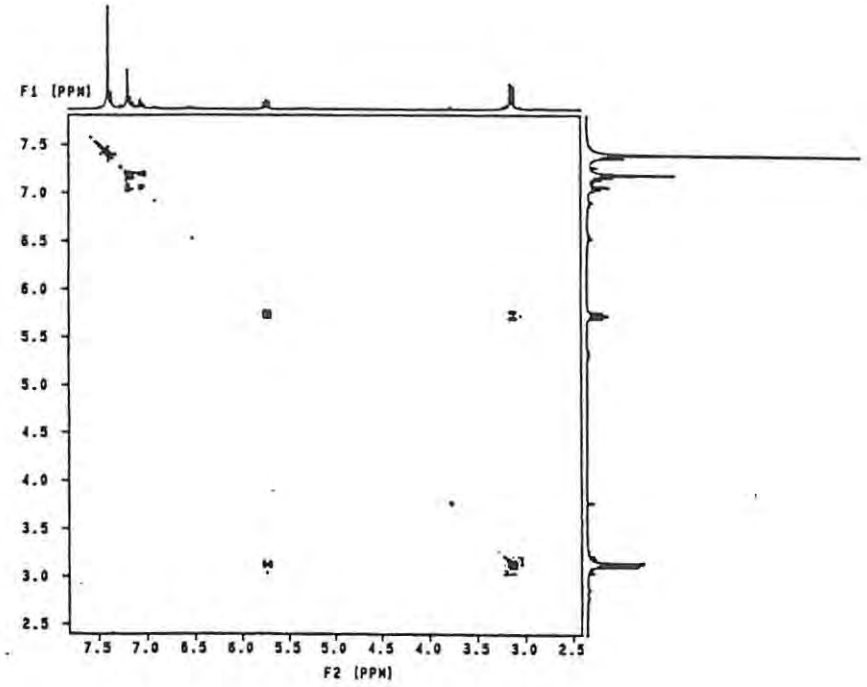


FIGURE 4 : COSY n.m.r. spectrum of 2-phenyl-1,5-benzodioxepan-4-one.

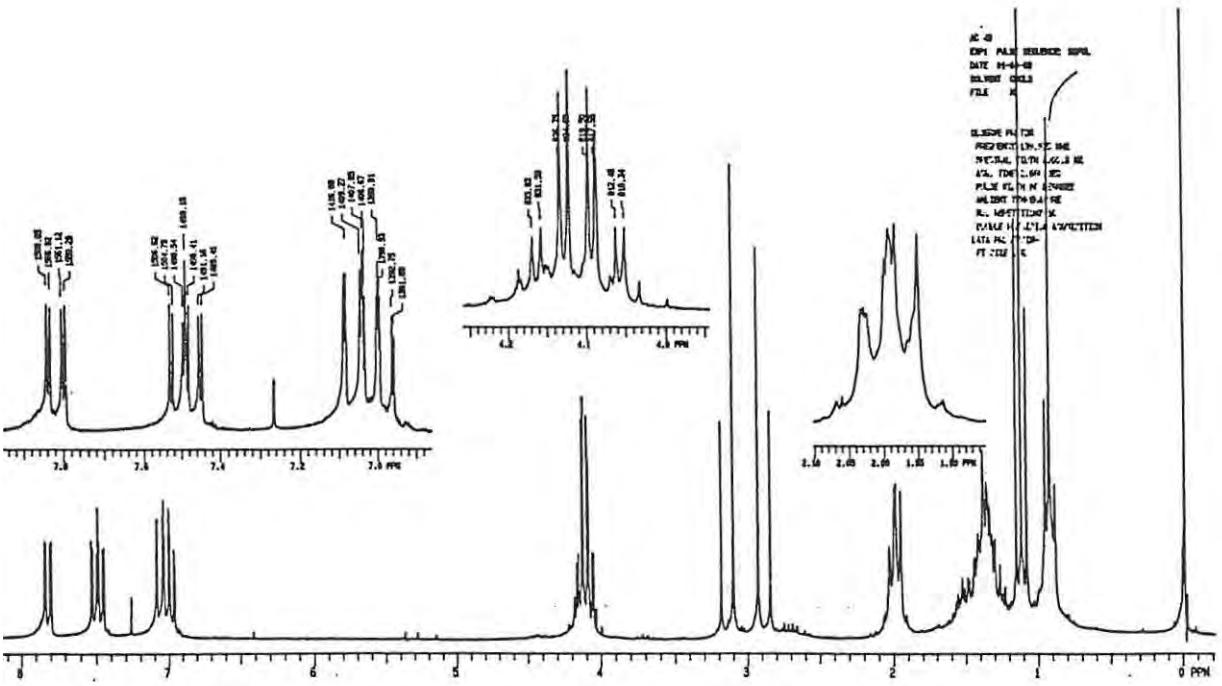
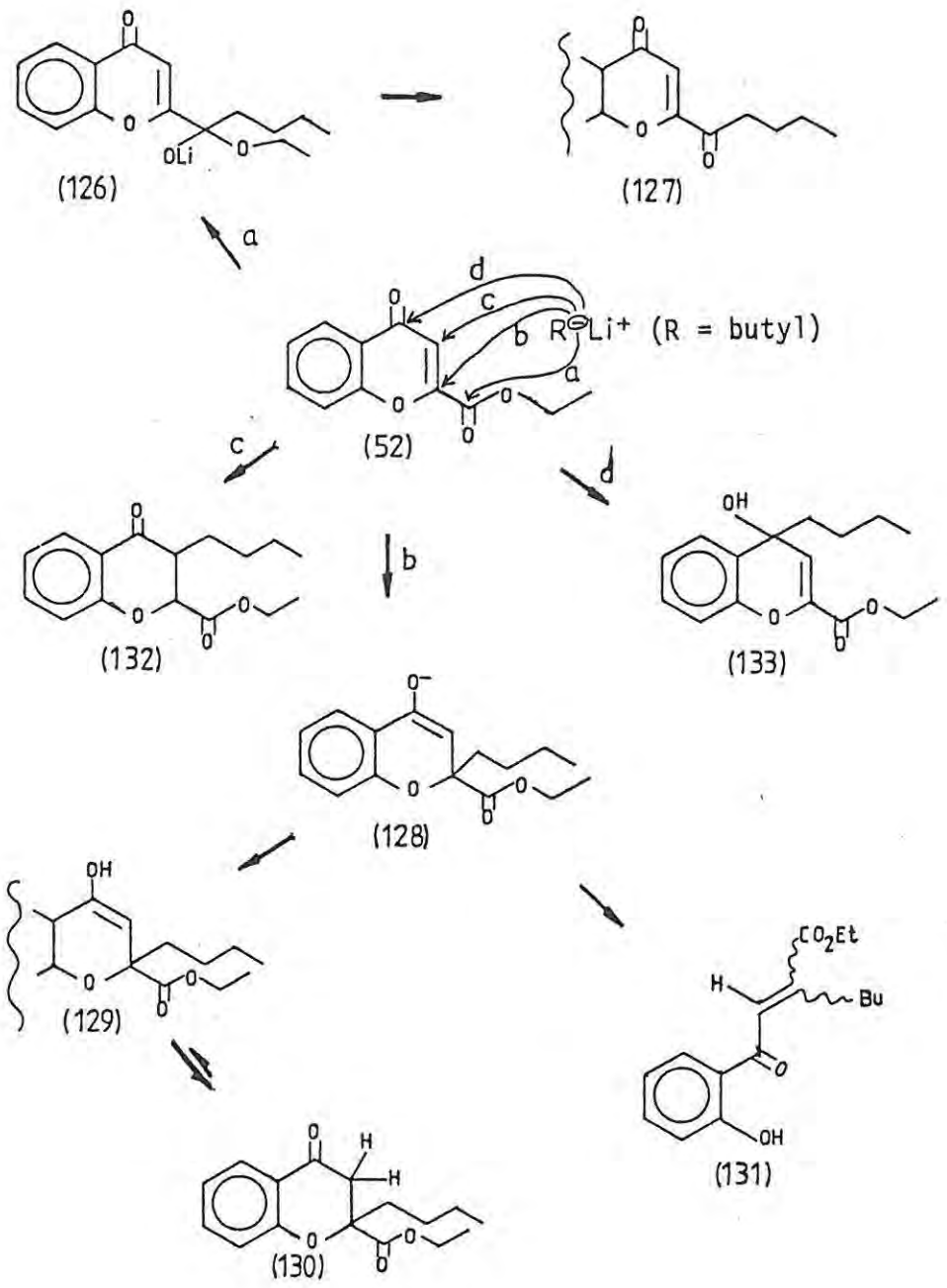


FIGURE 5 : ^{1}H N.m.r. spectrum of 2-butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one.

common. Typically intermediates such as (128) undergo ring-opening to compound (131), but in this case protonation (presumably on work-up) and tautomerism affords product (130)- effectively a Michael addition product. The isolated product was identified as 2-butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one (130) by means of high resolution mass spectroscopy and ^{1}H and ^{13}C n.m.r. data.

High resolution mass spectroscopy analysis of what was taken to be the molecular ion (*m/z*), indicated a molecular formula of $C_{16}O_4H_2O$ - a result which indicates the introduction of a single butyl group.

In the ^{1}H n.m.r. spectrum (Figure 5), the presence of the two proton doublet of doublets at *ca.*δ3.0 and the absence of a vinylic proton signal at *ca.*δ7.0 are particularly significant. The primary products, (127), (131) and (133) all contain a vinylic proton (3-H) and may thus be excluded, while the 2-H nucleus in product (132) is calculated to resonate at *ca.*δ2.53 and may also be excluded. The doublet of doublets at *ca.*δ3.0 is however, consistent with the diastereotopic 3-H nuclei in product (130) which has a chiral centre at C-2. The further splitting of the methylene quartet at *ca.*δ4.1 is also due to the diastereotopic nature of these protons. The ^{13}C spectrum (Figure 6) is also consistent with the proposed product.



SCHEME 26 : Primary products of nucleophilic attack on ethyl 7-chromone-2-carboxylate.

2.5 Conclusion

During the course of this research :-

(i) ranges of flavanone and chromone-2-carboxylate esters have been prepared;

(ii) Baeyer-Villiger rearrangement of the flavanones to the 1,5-benzodioxepan-4-ones has been achieved by MCPBA;

(iii) these ring expanded products have been subjected to detailed n.m.r. (^{1}H and ^{13}C) and mass spectroscopic analysis; and

(iv) a study of the reactions of butyllithium with chromone-2-carboxylate esters has been initiated and one of the products successfully identified.

Future research related to the present study may include :- detailed investigations of the regioselectivity of the reactions of arganometallics with chromone esters and the chemical properties of the novel benzodioxepanones; and pharmacological studies on benzodioxepanones to explore their biological potential.

3. EXPERIMENTAL

Melting points were determined on a Kofler hotstage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 180 spectrometer using KBr discs unless otherwise stated. 60MHz ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R12 n.m.r. spectrometer using tetramethylsilane as internal standard. High field ^{1}H and ^{13}C n.m.r. spectra were recorded on Varian Gemini 200MHz or Bruker WM500. Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer and high resolution spectra on Varian MAT212 mass spectrometer.

TLC analysis was performed on MERCK Silica gel $60F_{254}$ precoated plastic plates and flash chromatography was carried out with MERCK Silica gel 60 [particle size 0.040-0.063mm (230-400 mesh ASTM)].

3-Bromophenyl acetate (82).[104] - Ac_2O (5.8ml, 0.06mol) was added dropwise to a stirred solution of 3-bromophenol (6.6g, 0.038mol) and NaOH (2.4g, 0.06mol) in H_2O (*ca.*46ml), at 0°C. The resulting mixture was sitrred for 1 hour at *ca.*0°C and was then extracted with Et_2O (2 x 30ml). The combined extracts were washed (20ml aq. $NaHCO_3$ and then 20ml H_2O), dried (anhyd. $MgSO_4$), and evaporated to afford an oil which was distilled to give 3-bromophenyl acetate (82) (6.87g, 84%), b.p. 124-128°C/13-15mmHg (lit.[105] 149°C/40mmHg); δ_H (60MHz; $CDCl_3$) 2.21 (3H, s, CH_3) and 6.9 - 7.45 (4H, m, ArH); υ_{max} (Thin film) 1775cm^{-1} (CO).

3-Chlorophenyl acetate (83).[104] The experimental procedure employed for the synthesis of 3-bromophenyl acetate (82) was followed, using Ac_2O (14ml, 0.148mol), 3-chlorophenol (13.3g, 0.104mol), and NaOH (5.85g, 0.146mol) in H_2O (100ml). Work-up afforded 3-chlorophenyl acetate (83) (15.39g, 87%), b.p. 103-105°C/13-15mmHg (lit.[104] 105-107/13mmHg); δ_H (60MHz; $CDCl_3$) 2.21 (3H, s, CH_3) and 6.9-7.4 (4H, m, ArH); υ_{max} (Thin film) 1775cm^{-1} (CO).

3-Fluorophenyl acetate (84).[104] - Ac_2O (14.7ml. 0.156mol) was added dropwise to a stirred solution of 3-fluorophenol (12.4g, 0.11mol) and NaOH (6.24g, 0.156mol) in H_2O (106ml), maintaining the termperature between 0 and 5°C by means of an ice-salt bath. The solution was stirred for a further 1 hour at the same temperature. After warming to room temperature, the organic layers were combined, washed with 5% aq. $NaHCO_3$ (2 x 30ml) and brine (1 x 50ml), dried (anhyd. $MgSO_4$), and the solvent was evaporated to give an oil which was distilled *in vacuo* to afford 3-fluorophenyl acetate (84)

(15.05g, 89%) b.p. 79-80°C/*ca*.15mmHg (lit.[106] 77-78°C, 13mmHg); δ_H (60MHz; $CDCl_3$) 2.3 (3H, s, CH_3) and 6.9-7.5 (4H, m, ArH); υ_{max} 1770cm^{-1} (CO).

3-Nitrophenyl acetate (85).[104] - Ac_2O (21,86g, 0.23mol) was added dropwise to a stirred, cooled (ice-salt bath) solution of 3-nitrophenol (20.6g, 0.144mol) and NaOH (9.28g, 0.23mol) in H_2O (200ml), maintaining the temperature at *ca*.0°C and the resulting mixture was stirred at this temperature for 1 hour. The reaction mixture was then extracted with Et_2O (3 x 100ml). The combined extracts were washed with 5% aq. $NaHCO_3$ (60ml), dried (anhyd. $MgSO_4$), and the solvent was evaporated to afford crude 3-nitrophenyl acetate (85) (25.26g, 97%). m.p. 52-54°C (lit.[107] 55-56°C); δ_H (60MHz, $CDCl_3$) (3H, s, OCH_3) and 7.5-8.3 (4H, m, ArH).

4-Bromo-2-hydroxyacetophenone (86).[108] - A mixture of 3-bromophenyl acetate (82) (10.85g, 0.051mol) and $AlCl_3$ (22.3g, 0.167mol) was heated at 175-180°C for 3 hours. After cooling, 2M-HCl (*ca* 100ml) was added to the reaction mixture, which was then steam distilled. The distillate was extracted with $CHCl_3$ (3 x 50ml) and the combined extracts were re-extracted with 0.5M - KOH (3 x 50ml). The combined alkaline extracts were washed with $CHCl_3$ (2 x 40ml), acidified and extracted with $CHCl_3$ (3 x 30ml). The organic layer was dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford crude 4-bromo-2-hydroxyacetophenone (86) (7g, 65%), m.p. 41-42°C (lit.[108] 42-43°C); δ_H (60MHz; $CDCl_3$) 2.59 (3H, s, CH_3), 6.9-7.2 (2H, m, 5-H, 6-H), 7.5-7.7 (1H, m, 3-H), and 12.4 (1H, s, OH); υ_{max} *ca*.3600-2500 (OH) and 1640cm^{-1} (CO).

4-Chloro-2-hydroxyacetophenone (87).[108] - The experimental procedure employed for the synthesis of 4-bromo-2-hydroxyacetophenone (86) was followed, using 3-chlorophenyl acetate (83) (10g, 0.059mol) and $AlCl_3$ (18.6g, 0.140mol). Work-up afforded 4-chloro-2-hydroxyacetophenone (87) (6.78g, 68%), b.p. 119-121°C/*ca.* 13mmHg (lit.[108] 121-124°C/15mm); δ_H (60MHz; $CDCl_3$) 2.6 (3H, s, CH_3), 6.75-7.0 (2H, 5-H and 6-H), 7.5-7.75 (1H, m, 3-H), and 12.45 (1H, s, OH); υ_{max}. *ca.*3400 - 2700 (OH) and 1640cm^{-1} (CO).

4-Fluoro-2-hydroxyacetophenone (88).[108] - A mixture of 3-fluorophenyl acetate (84) (6.0g, 0.041mol) and $AlCl_3$ (12.39g, 0.093mol) was heated at 175-180°C for 2 hours. After cooling, 2M - HCl (*ca.* 107ml) was added to the reaction mixture, which was then steam distilled. The distillate was extracted with $CHCl_3$ (3 x 50ml) and the combined extracts were re-extracted with 0.5M - KOH (3 x 50ml). The combined alkaline extracts were acidified and extracted with $CHCl_3$ (2 x 50ml). The organic layer was dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford crude 4-fluoro-2-hydroxyacetophenone (88) (5.33g, 85%), m.p. 21-22°C (lit.[106] 24°C); δ_H (60MHz; $CDCl_3$) 2.6 (3H, s, CH_3), 6.4-6.8 (2H, m, 5-H, 6-H), 7.6-8.0 (1H, m, 3-H), and 12.6 (1H, s, OH); υ_{max}. *ca.* 3500-2500 (OH) and 1640cm^{-1} (CO).

2-Hydroxy-4-nitroacetophenone (89).[109] - A mixture of 3-nitrophenyl acetate (85) (10.03g, 0.055mol), $AlCl_3$ (14.04g, 0.106mol), and dry nitrobenzene (50ml) was heated at 140°C for 8 hours. After cooling, a mixture of ice (40g) and conc. HCl (16ml) was added, and the resulting mixture was steam distilled. The distillate was extracted

with EtOAc (3 x 80ml) and the combined organic extracts were extracted with 0.5M - NaOH (4 x 80ml). The aqueous alkaline solution was acidified with 2M - HCl and then extracted with EtOAc (2 x 80ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated to give 2-hydroxy-4-nitroacetophenone (89) (2.13g, 21%), m.p. 60-61°C (lit.[110] 67°C); δ_H (60MHz; $CDCl_3$) 2.75 (3H, s, CH_3), 7.5-8.1 (3H, m, ArH), and 12.4 (1H, s, OH).

2-Hydroxy-4-methoxyacetophenone (90).[111] - A mixture of resacetophenone (9.8g, 0.065mol), dry acetone (100ml) and Me_2SO_4 (6ml. 0.066mol) was boiled under reflux, over K_2CO_3 (10g, 0.072mol), for 6 hours. After cooling, the solvent was evaporated off and excess Me_2SO_4 destroyed by addition of a 25% NH_3-ice mixture to the residue. The resulting mixture was extracted with Et_2O (4 x 60ml). The ethereal solution was dried (anhyd. $MgSO_4$) and evaporated to give crude 2-hydroxy-4-methoxyacetophenone (90) (6.66g, 67%), m.p. 46-48°C (lit.[111] 48°C); δ_H (60MHz; $CDCl_3$) 2.55 (3H, s, $COCH_3$), 3.85 (3H, s, OCH_3), 6.35-6.6 (2H, m, 3-H and 5-H), 7.6-7.75 (1H, d, *J* 9Hz, 6-H), and 12.85 (1H, s, OH).

Ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (91) and ***ethyl 2-hydroxy-7-methoxychromanone-2-carboxylate*** (92).[101] - A solution of 2-hydroxy-4-methoxyacetophenone (90) (5.0g, 0.030mol) in diethyl oxalate (6.0ml, 0.045mol) was added to a solution of NaOEt (1.03g, 0.045mol) in EtOH (50ml). The stirred mixture was boiled under reflux for 40min. After cooling, the reaction mixture was poured into Et_2O (250ml). The precipitated solid was filtered off, washed (Et_2O), and acidified with 2M - HCl. The resulting mixture

was extracted with Et_2O (4 x 60ml). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated to afford ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (91) and ethyl 2-hydroxy-7-methoxychromanone-2-carboxylate (92) (4.39g) which was used without further purification. δ_H (60MHz; $CHCl_3$/DMSO-d_6) 1.4 (3H, t, *J* 6.7Hz, CH_2CH_3), 3.0 and 3.2 (2H, dd, *J* 13Hz, CH_2CO), 3.9 (3H, s, OCH_3), 4.45 (2H, q, *J* 6.7Hz, CH_2CH_3), and 6.5-8.3 (4H, m, 5-H, 6-H, 8-H, and OH).

Chromone-2-carboxylic acid (93).[114,115] - Diethyl oxalate (30.0ml, 0.22mol) and *o*-hydroxyacetophenone (24ml, 0.20mol) were added to an ethanolic solution of NaOEt [generated *in situ* by adding sodium metal (13.8g, 0.6mol) to dry EtOH (400ml)]. The resulting solution was boiled under reflux for 45min. After cooling, the reaction mixture was poured into Et_2O (600ml) and allowed to stand for 30min. The precipitated yellow solid was filtered off, washed (Et_2O), dissolved in 2M - HCl (400ml), and the resulting solution extracted with Et_2O (4 x 100ml). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated to give ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate. This diketone, together with conc. HCl (80ml) and AcOH (80ml), was boiled under reflux for 40min. The reaction mixture was cooled and the precipitated solid was filtered off, washed (cold AcOH), and recrystallised from EtOAc to afford chromone-2-carboxylic acid (93) (30g, 79%), m.p. 248-249°C (lit.[114] 250-251°C); δ_H (60MHz; DMSO-d_6) 7.05 (1H, s, CO.CH=C), 7.3-8.3 (4H, m, ArH), and 10.29 (1H, s, CO_2H); υ_{max}. 3200-2100 (CO_2H), 1740 (CO), and 1610cm^{-1} (CO_2H).

Ethyl chromone-2-carboxylate (52).[112] - A solution of chromone-2-

carboxylic acid (93) (10g, 0.053mol), EtOH (100ml), and conc. H_2SO_4 (1ml) was boiled under reflux for 2.5 hours. After cooling, the reaction mixture was poured into an ice-water mixture (160ml) and basified (5% aq. $NaHCO_3$) and the resulting mixture was extracted with EtOAc (3 x 50ml). The organic extracts were combined and dried (anhyd. $MgSO_4$), and the solvent was evaporated to afford ethyl chromone-2-carboxylate (52) (5.7g, 50%), m.p. 71-72°C (lit.[112] 72°C); δ_H (60MHz; $COCl_3$) 1.45 (3H, t, *J* 8Hz, CH_3), 4.5 (2H, q, *J* 7Hz, CH_2), 7.2 (1H, s, 3-H), and 7.3-8.0 (4H, m, ArH); υ_{max} 1750 (CO.O) and 1660cm^{-1} (CO).

Methyl chromone-2-carboxylate (53).[101] - Chromone-2-carboxylic acid (93) (5g, 0.026mol) was added to a solution of MeOH (50ml) and conc. H_2SO_4 (2ml). The resulting mixture was refluxed for 24 hours. Once cool, the reaction mixture was poured into a mixture of ice and H_2O (80ml), basified with aq. $NaHCO_3$, and extracted with Et_2O (3 x 50ml). The ether extracts were combined, dried (anhyd. $MgSO_4$), and evaporated. The residue was then recrystallised from MeOH to give methyl chromone-2-carboxylate (53) (3.92g, 73%), m.p. 119-121°C (from MeOH) (lit.[113] 122-123°C); δ_H (60MHz;$CDCl_3$) 4.05 (3H, s, CH_3), 7.2 (1H, s, 3-H), and 7.4-8.4 (4H, m, ArH); υ_{max} 1650 (CO.O) and 1750cm^{-1} (CO).

Ethyl 7-fluorochromone-2-carboxylate (94).[101] - A solution of 4-fluoro-2-hydroxyacetophenone (88) (2g, 0.013mol) in diethyl oxalate (9.81ml, 0.072mol) was added to a solution of NaOEt [generated *in situ* by adding sodium metal (1.205, 0.052mol) to dry EtOH (30ml)]. The stirred mixture was boiled under reflux for 40min. After

cooling, EtOH (54ml) was added to the reaction mixture. The precipitated solid was filtered off and then added to 2M - HCl (72ml). The resulting mixture was extracted with Et_2O (3 x 20ml). The combined organic layers were dried (anhyd. $MgSO_4$) and the solvent was evaporated to give a residue which was refluxed in a mixture of glacial acetic acid (10.8ml) and conc. HCl (0.5ml) for 1.5 hours. After cooling, H_2O (20ml) was added and the crude ethyl 7-fluorochromone-2-carboxylate (94) was collected at the pump (2.21g, 72%) m.p. 100-102°C; (Found: C, 59.16, H; 3.70. $C_{12}H_9O_4F$ requires: C, 61.02; H, 3.84%); δ_H (60MHz; $CDCl_3$) 1.45 (3H, t, *J* 6.7Hz, CH_3), 4.5 (2H, q, *J* 6.7Hz, CH_2), 7.1-7.35 (3H, m, 3-H, 5-H, and 6-H), and 8.15-8.3 (1H, m, 8-H); υ_{max} 1750 (CO.O) and 1660cm^{-1} (CO).

Ethyl 7-nitrochromone-2-carboxylate (95).[116,117] - A solution of 2-hydroxy-4-nitroacetophenone (89) (2.08g, 0.011mol) and diethyl oxalate (15.6ml, 0.129mol) was added to a solution of NaOEt [generated *in situ* by adding sodium metal (0.84g, 0.036mol) to dry EtOH (26ml)]. The resulting solution was boiled under reflux for 45min. After cooling, the yellow slurry was poured into Et_2O (156ml) and allowed to stand for 30min. The yellow solid was filtered off, washed (Et_2O), dissolved in 2M - HCl (104ml), and the resulting solution was extracted with Et_2O (3 x 40ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated to give a residue which was boiled under reflux with AcOH (26ml) and conc. HCl (5 drops) for 45min. After cooling, H_2O (52ml) was added to precipitate the solid fully. The precipitated solid was filtered off and dissolved in Et_2O (156ml). The resulting solution was washed (70ml H_2O, 80ml 5% aq. $NaHCO_3$, 70ml H_2O) and dried (anhyd. $MgSO_4$),

and the solvent was then evaporated to afford ethyl 7-nitrochromone-2-carboxylate (95) (1.03g, 34%), m.p. 133-134°C (lit.[116] 135-137°C); δ_H (60MHz; $CDCl_3$) 1.5 (2H, t, *J* 6.7Hz, CH_3) 4.55 (2H, q, *J* 6.7Hz, CH_2), 7.2 (1H, s, 3-H), and 8.3-8.6 (3H, m, 5-H, 6-H, 8-H); υ_{max} 1740 (CO.O) and 1660cm^{-1} (CO).

Ethyl 7-methoxychromone-2-carboxylate (96).[118] - A mixture of ethyl 2-hydroxy-7-methoxychromanone-2-carboxylate (92) and ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (91) (3.89g, 0.0146mol), conc. HCl (0.25ml), and AcOH (28.6ml) was boiled under reflux for 2.5 hours. After cooling, the soltuion was poured into a mixture of ice and H_2O (180ml), and the resulting mixture basified with aq. $NaHCO_3$ and extracted with EtOAc (3 x 100ml). The organic extracts were dried (anhyd. $MgSO_4$) and evaporated to give crude ethyl 7-methoxychromone-2-carboxylate (96) (3.85g, 57%), m.p. 118-120°C (lit.[119] 122-123°C); δ_H (60MHz; $CDCl_3$) 1.4 (3H, t, *J* 6.7Hz, CH_3), 3.9 (3H, s, OCH_3), 4.5 (2H, q, *J* 6.7Hz, CH_2), 6.9-7.2 (3H, m, 6-H, 8-H, CH = CH), and 8.1 (1H, d, *J* 9Hz, 5-H); υ_{max} 1730 (CO.O) and 1670cm^{-1} (CO).

2'-Hydroxychalcone (61).[108] - A cooled solution of KOH (26.28g, 0.468mol) in H_2O (150ml) was added to a cooled solution of *o*-hydroxyacetophenone (26.5nml. 0.220mol) and benzaldehyde (44.5ml. 0.439mol) in EtOH (300ml). The mixture was then kept at 0°C for 4 days with occasional shaking. The reaction mixture was diluted with H_2O (200ml) and acidified with 2M-HCl. The precipitated chalcone was collected at the pump and recrystallised from EtOH to give yellow crystals of 2'-hydroxychalcone (61) (25.42g, 51%), m.p. 84-85°C

(lit.[61] 88-89°C); δ_H (60MHz; $CHCl_3$) 6.8-8.2 (11H, m, ArH) and 12.9 (1H, s, OH); υ_{max} 1645 (CO) and 1595cm^{-1} (CH = CH).

4'-Bromo-2'-hydroxychalcone (97).[108] - A cooled solution of 60% aq. KOH (20ml) was added to a cooled mixture of 4-bromo-2-hydroxyacetophenone (86) (1.8g, 0.008mol) and benzaldehyde (1.44g, 0.014mol) in EtOH (22ml). The resulting mixture was kept at *ca.* 0°C for 2 days with occasional shaking. The reaction mixture was then diluted with H_2O (20ml) and acidified with 2M-HCl. The precipitated chalcone was collected at the pump and recrystallised from EtOH to give bright yellow cristals of 4'-bromo-2'-hydroxychalcone (97) (2.17g, 85%), m.p. 110-112°C (lit.[108] 115-116°C), δ_H (60MHz; $CDCL_3$) 7.15-7.3 (2H, 2 x br s, CH = CH), 7.4-7.9 (8H, m, ArH), and 13.0 (1H, s, OH); υ_{max} 1650cm^{-1} (CO).

4'-Chloro-2'-hydroxychalcone (98).[108] - The experimental procedure employed for the preparation of 4'-bromo-2'-hydroxyacetophenone (87) was followed using 4-chloro-2-hydroxyacetophenone (5g, 0.029mol), benzaldehyde (4g, 0.038mol), 60% KOH (55ml), and EtOH (60ml). Work-up afforded 4'-Chloro-2'-hydroxychalcone (98) (4.33g, 56.9%), m.p. 119-121°C (lit.[108] 124-125°C); δ_H (60MHz; $CDCl_3$) 6.9-7.15 (2H, m, CH = CH), 7.4-8.0 (8H, m, ArH), and 13.05 (1H, s, OH); υ_{max} 1650cm^{-1} (CO).

4'-Fluoro-2'-hydroxychalcone (99).[108] - A cooled solution of 60% aq. KOH (22ml) was added to a cooled mixture of 4'-fluoro-2'-hydroxychalcone (88) (2g, 0.013mol) and benzaldehyde (1.6g, 0.015mol) in EtOH (24ml). The resulting mixture was kept at *ca.* 0°C

for 2 days with occasional shaking. The reaction mixture was then diluted with H_2O (30ml) and acidified with 2M-HCl, The precipitated chalcone was collected at the pump and recrystallised from EtOH to give yellow crystals of 4'-fluoro-2'-hydroxychalcone (99) (2.19, 70%), m.p. 102-104°C; δ_H (60MHz; $CDCl_3$) 6.69 and 6.84 (2H, 2 x br s, CH = CH), 7.3-8.1 (8H, m, ArH), and 13.25 (1H, s, OH); υ_{max} 1650cm^{-1} (CO).

2'-Hydroxy-4'-methoxychalcone (100).[120] - Benzaldehyde (6.7ml, 0.066mol) and a 50% solution of NaOH (10ml) were added to a solution of 2'-hydroxy-4'-methoxyacetophenone (90) (5g, 0.030mol) in EtOH (50ml). The resulting mixture was shaken and allowed to stand for 1 day at room temperature. The reaction mixture was acidified with 2M-HCl, extracted with Et_2O (3 x 50ml), and the combined extracts were washed with $NaHCO_3$ (1 x 30ml). The combined ether extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford a crude product which was recrystallised from EtOH to give 2'-hydroxy-4'-methoxychalcone (100) (5.39g, 70%), m.p. 100-101°C (lit.[121] 105-6°C); δ_H (60MHz; $CDCl_3$) 3.85 (3H, s, CH_3), 6.4-6.7 (2H, m, CH = CH), 7.3-8.1 (8H, m, ArH), and 13.0 (1H, s, OH); υ_{max} 1630 (CO) and 1570cm^{-1} (CH = CH).

2'-Hydroxy-4'-nitrochalcone (101).[108] - To a cooled mixture of 2-hydroxy-4-nitroacetophenone (80) (0.37g, 0.002mol) and benzaldehyde (0.38ml, 0.0004mol) in EtOH (93ml) was added a cooled solution of KOH (0.63g) in H_2O (19ml). The mixture was kept at 0°C for 4 days with occasional shaking, after which it was diluted with H_2O (100ml) and acidified with 2M-HCl. The precipitated 2'-hydroxy-4'-nitrochalcone (101) was filtered (0.5g, 98%), m.p. 187-189°C (lit.[60] 188-190°C); υ_{max} 1650cm^{-1} (CO).

4-Chloro-2'-hydroxychalcone (102).[108] - A cooled solution of 60% aq. KOH (33ml) was added to a cooled mixture of 2-hydroxyacetophenone (3g, 0.022mol) and 4-chlorobenzaldehyde (2.4g, 0.017mol) in EtOH (36ml). The resulting mixture was kept at *ca.* 0°C for 2 days with occasional shaking. The reaction mixture was then

diluted with H_2O (36ml) and acidified with 2M-HCl. The precipitated chalcone was collected at the pump and recrystallised from EtOH to give yellow needles of 4-chloro-2'-hydroxychalcone (102) (2.44g, 55%), m.p. 145-147°C (lit.[122] 150°C); δ_H (60MHz; $CDCl_3$) 6.98 - 7.12 (2H, 2 x br s, CH = CH), 7.4-8.0 (8H, m, ArH), and 12.8 (1H, s, OH); υ_{max} 1650cm^{-1} (CO).

4-Fluoro-2'-hydroxychalcone (103).[108] - The experimental procedure employed for the preparation of 4-fluoro-2'-hydroxychalcone (102) was followed using 60% KOH (55ml), 2-hydroxyacetophenone (5g, 0.037mol), 4-fluorobenzaldehyde (4g, 0.032mol), and EtOH (60ml). Work-up gave 4-fluoro-2'-hydroxychalcone (103) (4,62g, 59%), m.p. 108-110°C (lit.[123] 118-119°C); δ_H (60MHz; $CDCl_3$) 7.0-7.2 (2H, 2 x br s, CH = CH), 7.3-8.0 (8H, m, ArH), and 13.81 (1H, s, OH); υ_{max} 1650cm^{-1} (CO).

Flavanone (9).[108,124] - A solution of 2'-hydroxychalcone (61) (2g, 0.0089mol) and H_3PO_4 (5ml) in EtOH (200ml) was boiled under reflux for 48 hours. The resulting solution was concentrated and the resulting crystals were collected at the pump and recrystallised from EtOAc - hexane (1:3) to give flavanone (9) (1.8g, 90%), m.p. 70-71°C (lit.[125] 75-76°C); δ_H (60MHz; $CDCl_3$) 2.9-3.12 (2H, m, 2 x 3-H),5.37-5.7 (1H, m, 2-H), and 6.95-8.1 (9H, m, ArH); υ_{max} 1690cm^{-1} (CO).

7-Bromoflavanone (105).[108] - A solution of 4'-bromo-2'-hydroxychalcone (97) (2.5g, 0.0082mol) and H_3PO_4 (10ml) in EtOH (375ml) was boiled under reflux for 72 hours. The resulting

solution was concentrated and the resulting crystals were collected at the pump and recrystallised from EtOH to afford 7-bromoflavanone (105) (1.2g, 48%), m.p. 73-75°C (lit.[108] 79-80°C); δ_H (60MHz; $CDCl_3$) 2.92-3.11 (2H, m, 2 x 3-H), 5.35-5.62 (1H, m, 2-H), and 7.1-7.9 (8H, m, ArH); υ_{max} 1685cm^{-1} (CO).

7-Chloroflavanone (106).[108] - The experimental procedure employed for the preparation of 7-bromoflavanone (105) was followed, using 4'-chloro-2'-hydroxychalcone (98) (4g, 0.0155mol), H_3PO_4 (17.3ml), and EtOH (400ml). Work-up gave 7-chloroflavanone (106) (2.1g, 53%), m.p. 51-52°C (lit.[108] 54-55.5°C); δ_H (60MHz; $CDCl_3$) 2.91-3.1 (2H, m, 2 x 3-H), 5.4-5.69 (1H, m, 2-H), and 7.05-8.1 (8H, m, ArH); υ_{max} 1690cm^{-1} (CO).

7-Fluoroflavanone (107).[108] - A solution of 4'-fluoro-2'-hydroxychalcone (99) (1g, 0.0041mol) and H_3PO_4 (4.5ml) in EtOH (150ml) was boiled under reflux for 48 hours. The resulting solution was concentrated and the crystals formed were collected at the pump and recrystallised from EtOH to give 7-fluoroflavanone (107) (0.82g, 82%). δ_H (60MHz; $CDCl_3$) 2.85-3.04 (2H, m, 2 x 3-H), 5.35-5.61 (1H, m, 2-H), and 6.65-8.1 (8H, m, ArH); υ_{max} 1698cm^{-1} (CO).

7-Methoxyflavanone (108).[108] - A solution of 2'-hydroxy-4'-methoxychalcone (100) (4g, 0.016mol) and H_3PO_4 (10ml) in EtOH (300ml) was boiled under reflux for 48 hours. The resulting solution was concentrated and the resulting crystals were collected at the pump and recrystallised from EtOAc-hexane (1:3) to afford 7-methoxy flavanone (108) (1.15g, 29%), m.p. 79-81°C (lit.[126] 91°C); δ_H (60MHz;

$CDCl_3$) 2.85-3.08 (2H, m, 2 x 3-H), 3.88 (3H, s, CH_3), 5.4-5.68 (1H, m, 2-H), and 6.64-8.1 (8H, m, ArH); υ_{max} 1665cm^{-1} (CO).

7-Nitroflavanone (109).[127] - A solution of 4'-nitro-2-hydroxychalcone (101) (0.28g, 0.001mol) in EtOH (104ml), conc. HCl (3.5ml), and water (3.5ml) was refluxed for 24 hours. The resulting solution was concentrated and the resulting crystals were collected at the pump and recrystallised from EtOH to obtain 7-nitroflavanone (109) (0.2g, 71%), m.p. 127°C (lit.[127] 132-4°C); δ_H (60MHz; $CDCl_3$) 3.05-3.25 (2H, m, 2 x 3-H), 5.5-5.58 (1H, m, 2-H), and 7.5-8.3 (8H, m, ArH).

4'-Chloroflavanone (110).[108] - A solution of 4-chloro-2'-hydroxychalcone (102) (7g, 0.027mol) and H_3PO_4 (31.5ml) in EtOH (150ml) was boiled under reflux for 48 hours. The resulting solution was concentrated and the resulting crystals were collected at the pump and recrystallised from EtOH-hexane (1:3) to afford 4'-chloroflavanone (110) (2.5g, 36%), m.p. 72-75°C (lit.[122] 87°C); δ_H (60MHz; $CDCl_3$) 2.85-3.1 (2H, m, 2 x 3-H), 5.45-5.75 (1H, m, 2-H), and 7.1-8.2 (8H, m, ArH); υ_{max} 1700cm^{-1} (CO).

4'-Fluoroflavanone (111).[108] - The experimental procedure employed for one preparation of 4'-chloroflavanone (110) was followed using 4-fluoro-2'-hydroxychalcone (103) (4g, 0.017mol), H_3PO_4 (18ml), and EtOH (600ml). Work-up afforded 4'-fluoroflavanone (111) (1.5g, 38%), m.p. 68-70°C (lit.[123] 59-60°C); δ_H (60MHz; $CDCl_3$) 2.9-3.1 (2H, m, 2 x 3-H), 5.36-5.65 (1H, m, 2-H), and 7.0-8.1 (8H, m, ArH); υ_{max} 1698cm^{-1} (CO).

2-Phenyl-1,5-benzodioxepan-4-one (113).[82,84] - A mixture of flavanone (9) (1g, 5mmol) and MCPBA (85%; 1.73g, 10mmol) in dry CH_2Cl_2 (20ml) was boiled under reflux over a period of 24 hours. The solvent was evaporated and the residue dissolved in EtOAc (50ml). The resulting solution was washed with aq.$NaHCO_3$ (2 x 30ml) (to remove unreacted MCPBA) and then with H_2O (20ml), and dried (anhyd.Na_2SO_4). Evaporation of the solvent left a brown residue which was purified by sublimation and recrystallisation from MeOH to give ***2-phenyl-1,5-benzodioxepan-4-one*** (113) (0.83g, 69%), m.p. 85-86°C; (Found: C, 75.0; H, 5.0. $C_{15}H_{12}O_3$ requires: C, 75.0; H, 5.0%); δ_H (500MHz; $CDCl_3$) 3.11(2H, dd, *J* 8 and 13Hz; 2 x 3H), 5.70 (1H,m,2-H), and 7.01-7.42 (9H, m, ArH); δc (500MHz; $CDCl_3$) 38.45 (t, C-3), 83.41 (d, C-2), 120.37 (d, C-9), 124.19 (d, C-7), 125.62 (d, C-6), 126.10 (d, C-4'), 126.47 (d, C-2' and C-6'), 128.74 (s, C-8), 128.96 (d, C-3' and C-5'), 138.54 (s, C-5a), 145.13 (s, C-1'), 145.59 (s, C-9a), and 167.36 (s, C-4); υ_{max}. 1754cm^{-1} (CO).

8-Chloro-2-phenyl-1,5-benzodioxepan-4-one (114).[82,84] - A mixture of 7-chloroflavanone (98) (1g, 3.9mmol) and MCPBA (85%; 2.1g, 9.7mmol) in dry CH_2Cl_2 (20ml) was boiled under reflux for 16 hours. The solvent was evaporated and the residue dissolved in EtOAc (50ml). The resulting solution was washed with aq.$NaHCO_3$ (3 x 30ml) and then with H_2O (1 x 30ml), and dried (anhyd.Na_2SO_4). Evaporation of the solvent gave a residue which was purified by flash chromatography [elution with EtOAc-hexane (1:3)] to give ***8-chloro-2-phenyl-1,5-benzodioxepan-4-one*** (114) (0.39g, 36%); m.p. 115-117°C; (*m/z* Found: 292.0516, $C_{15}H_{11}O_3Cl$ requires: 292.0502); δ_H (200MHz, $CDCl_3$) 3.03 (2H, dd, 2 x 3-H), 5.36 (1H, m, 2-H), and 6.5-7.4 (8H,

m, ArH); δc (200MHz; $CDCl_3$) 42.20 (t, C-3), 79.16 (d, C-2), 116.43 (d, C-9), 118.45 (d, C-7), 123.60 (d, C-6), 126.36 (d,C-2′ and C-6′), 129.09 (d, C-3′ and C-5′), 138.43 (s, C-5a), 144.63 (s, C-1′), 146.46 (s, C-9a), and 176.5 (s, C-4); υ_{max}. (Thin film) 1765cm^{-1} (CO).

8-Methoxy-2-phenyl-1,5-benzodioxepan-4-one (115).[82,84] - A mixture of 7-methoxyflavanone (9) (1g, 4mmol) and MCPBA (85%; 1.70g, 10mmol) in dry CH_2Cl_2 (15ml) was boiled under reflux for 16 hours. The solvent was evaporated and the residue dissolved in EtOAc (50ml). The reuslting solution was washed with aq.$NaHCO_3$ (3 x 30ml) and then with H_2O (30ml), and dried (anhyd.Na_2SO_4). Evaporation of the solvent gave a residue which was purified by flash chromatography [elution with EtOAc-hexane (1.5:8.5)] and recrystallisation from MeOH to give ***8-methoxy-2-phenyl-1,5-benzodioxepan-4-one*** (115) (0.18g, 17%), m.p.72-74°C; (*m/z* Found: 270.089. $C_{16}H_{14}O_4$ requires: 270.089); δ (200MHz, $CDCl_3$) 3.13 (2H, dd, 2x3-H), 3.74 (3H, s, OCH_3), 5.71 (1H, m, 2-H), and 6.58-7.39 (8H, m, ArH); δc (200MHz, $CDCl_3$) 38.56 (t, C-3), 55.88 (q, CH_3), 83.60 (d, C-2), 109.79 (d, C-9), 110.95 (d,C-7), 121.05 (d, C-6), 126.49 (s, C-4′), 129.18 (d, C-2′ and C-6′), 129.40 (d, C-3′ and C-5′), 139.06 (s, C-5a), 139.49 (s, C-1′), 146.19 (s, C-9a), 158.19 (s, C-8), and 168.45 (s, C-4); υ_{max}. 1765cm^{-1} (CO).

2-(4-Bromophenyl)-1,5-benzodioxepan-4-one (116).[82,84] - A mixture of 4′-bromoflavanone (105) (0.34g, 1.1mol) and MCPBA (85%; 0.56g, 2.8mol) in dry CH_2Cl_2 (15ml) was boiled under reflux over a period of 48 hours. The solvent was evaporated and the residue dissolved

in EtOAc (30ml). The resulting solution was washed with aq.$NaHCO_3$ (3 x 20ml) and then with H_2O (1 x 20ml), and dried (anhyd.Na_2SO_4). Evaporation of the solvent left a brown residue which was purified by flash chromatography [elution with EtOAc-hexane (1:3)] to give ***2-(4-bromophenyl)-1,5-benzodioxepan-4-one*** (116) (0.17g, 48%), m.p. 115-117°C; (Found: C,55.8; H, 3.5, $C_{15}H_{10}O_3Br$ requires: C, 56.6; H, 3.2%); δ_H (200MHz; $CDCl_3$) 3.10 (2H, dd, *J* 6.8 and 14Hz, 2x3-H), 5.69 (1H, m, 2-H), and 7.0-7.60 (8H, m, ArH); δc (200MHz; $CDCl_3$) 38.39 (t, C-3), 82.75 (d, C-2), 120.46 (d, C-9), 124.04 (d, C-6), 125.92 (d, C-8), 126.63 (d, C-2′ and C-6′), 127.81 (d, C-3′ and C-5′), 131.95 (s, C-4′), 137.52 (s, C-1′), and 169.12 (s, C-4).

2-(4′-Chlorophenyl)-1,5-benzodioxepan-4-one (117).[82,84] - A mixture of 4′-chloroflavanone (106) (0.34g, 1.3mmol) and MCPBA (85%; 0.65g, 3.3mmol) in dry CH_2Cl_2 (15ml) was boiled under reflux for 48 hours. The solvent was evaporated and the residue dissolved in EtOAc (30ml). The resulting solution was washed by aq.$NaHCO_3$ (3 x 20ml) and then dried with anhyd.Na_2SO_4. The solvent was evaporated to give a residue which was recrystallised from MeOH to afford ***2-(4′-chlorophenyl)-1,5-benzodioxepan-4-one*** (117) (0.28g, 78%), m.p. 113-114°C, (Found: C, 66.2; H, 3.8. $C_{15}H_{10}O_3Cl$ requires: C, 65.8; H, 3.7%); δ_H (200MHz; $CDCl_3$) 3.10 (2H, dd, *J* 6.8 and 13Hz, 2x3-H), 5.52 (1H, m, 2-H), and 7.0-7.4 (8H, m, ArH); δ_C (200MHz; $CDCl_3$) 38.43 (t, C-3), 82.71 (d, C-2), 120.46 (d, C-9), 124.05 (d, C-7), 125.91 (d, C-6), 126.62 (d, C-8), 127.53 (d, C-2′ and C-6′), 128.99 (d, C-3′ and C-5′), 134.88 (s, C-4′), 137.04 (s, C-5a), 145.03 (s, C-1′), 145.60 (s, C-9a), and 167.07 (s, C-4); υ_{max}. 1745cm^{-1} (CO).

2-(4'-Fluorophenyl)-1,5-benzodioxepan-4-one (118).[82,84] - A mixture of 4'-fluoroflavanone (107) (1g, 4.1mmol) and MCPBA (85%; 1.42g, 8.3mmol) in dry CH_2Cl_2 (30ml) was boiled under reflux for 16 hours. The solvent was evaporated and the residue dissolved in EtOAc (50ml). The resulting solution was washed by aq.$NaHCO_3$ (3 x 20ml) and then dried with anhyd.Na_2SO_4. The solvent was evaporated to give a residue which recrystallised from MeOH to afford ***2-(4-fluorophenyl)-1,5-benzodioxepan-4-one*** (118) (0.26g. 25%), m.p. 122-124°C; (*m/z* Found: 215.0505. $C_{13}H_8O_2F$ (m^+ - C_2H_3O) requires: 215.0524); δ_H (200MHz; $CDCl_3$) 3.10 (2H, dd, *J* 8 and 16Hz, 2x3H), 5.70 (1H, m, 2-H), and 7.0-7.42 (8H, m, ArH); δ_C (200MHz; $CDCl_3$) 38.5 (t, C-3), 8.31 (d, C-2), 116.10 (d, $^2J_{CF}$ 21.9Hz,C-3' and C-5'), 120.79 (d, C-7), 124.47 (d, C-6), 126.26 (d, C-8), 128.42 (d, $^3J_{CF}$ 8.4Hz,C-2' and C-6'), 134.86 (s, C-5a), 145.47 (d, C-1'), 146.80 (s, C-9a), 163.43 (d, $^1J_{CF}$ 248.8Hz, C-4'), and 167.77 (s, C-4); υ_{max}. 1750cm^{-1} (CO).

2-(4-Methoxyphenyl)-1,5-benzodioxepan-4-one (119).[82,84] - A mixture of 4'-methoxyflavanone (108) (0.6g, 2.4mmol) and MCPBA (85%; 1.02g, 5.9mmol) in dry CH_2Cl_2 (20ml) was boiled under reflux for 23 hours. The solvent was evaporated and the residue dissolved in EtOAc (30ml). The resulting solution was washed with aq.$NaHCO_3$ (3 x 30ml) and then with H_2O (20ml) and dried (anhyd.Na_2SO_4). Evaporation of the solvent gave a residue which was recrystallised from MeOH to give ***2-(4-methoxyphenyl)-1,5-benzodioxepan-4-one*** (119) (0.14g, 22%), m.p. 121-122°C; (*m/z* Found: 270.089. $C_{16}H_{14}O_4$ requires 270.089); δ_H (200MHz; $CDCl_3$) 3.10 (2H, dd, 2 x 3-H), 3.82 (3H, s, OCH_3), 5.69 (1H, m, 2-H), and 6.89 - 7.31 (8H, m, ArH); δ_C (200MHz; $CDCl_3$) 38.49 (t,

C-3), 55.48 (q, OCH_3), 83.51 (d, C-2), 114.41 (d, C-3′ and C-5′), 120.67 (d, C-9), 124.76 (d, C-7), 126.03 (d, C-6), 126.85 (d, C-8), 128.02 (d, C-2′ and C-6′), 130.97 (s, C-5a), 145.42 (s, C-1′), 146.18 (s, C-9a), 160.54 (s, C-4′), and 168.16 (s, C-4); υ_{max}. 1755cm^{-1} (CO).

2-Butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one (130). - n-Buli (15%: 24ml, 36mmol) was added slowly to a solution of ethyl chromone-2-carboxylate (0.5g, 2.3mmol) in dry THF (50ml) at -78°C. The resulting solution was stirred for 1 hour at the same temperature and was then allowed to warm to room temperature. Aq.$NaHCO_3$ (1.22g in 50ml H_2O) was then added to destroy unreacted butyllithium. The mixture was extracted with ethyl acetate (2 x 50ml), dried (anhyd.$MgSO_4$), and the solvent evaporated to abtain a crude product which was shown by TLC to be a mixture of several compounds. Flash chromatography of the crude material gave three fractions. The cleanest fraction was further purified by preparative layer chromatography to obtain ***2-butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one*** (130) (0.06g, 9%); (*m/z* Found: 276.135. $C_{16}O_4H_{20}$ requires: 276.136); δ_H (200MHz; $CDCl_3$) 0.8-1.6 (10H, m), 2.0 (2H, m), 3.0 (2H, dd, *J* 17.6 and 35Hz, 2 x 3-H), 4.1 (2H, m, OCH_2CH_3), and 6.8-7.83 (4H, m, ArH); δ_C (200MHz; $CDCl_3$) 61.85 (s, C-2), 84.18 (t, C-3), 118.18 (d, C-8), 120.62 (d, C-6), 121.66 (s, C-4a), 126.68 (d, C-5), 136.33 (d, C-7), 160.41 (s, C-8a), 171.24 (s, COO), and 190.37 (s, C-4).

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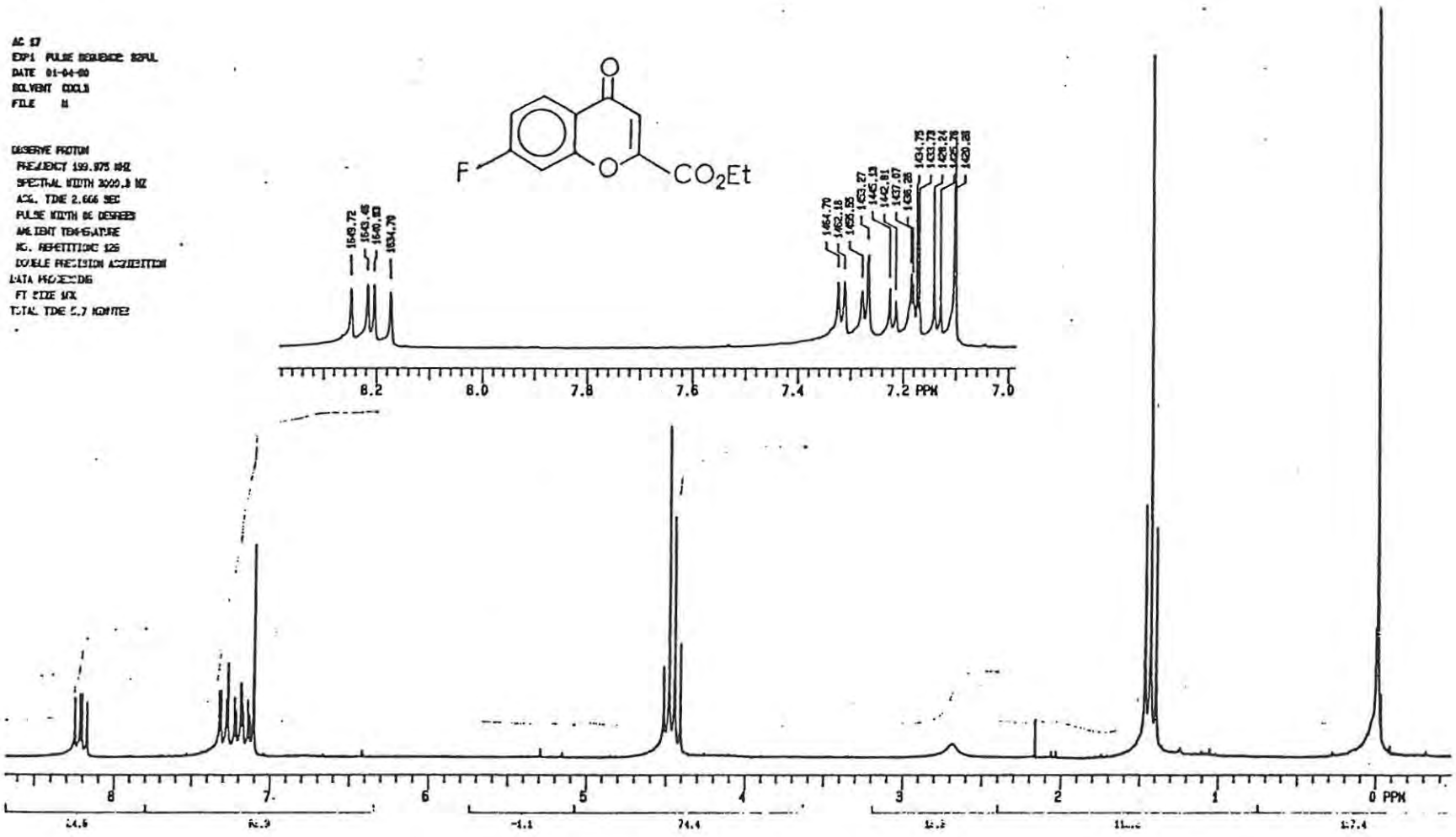
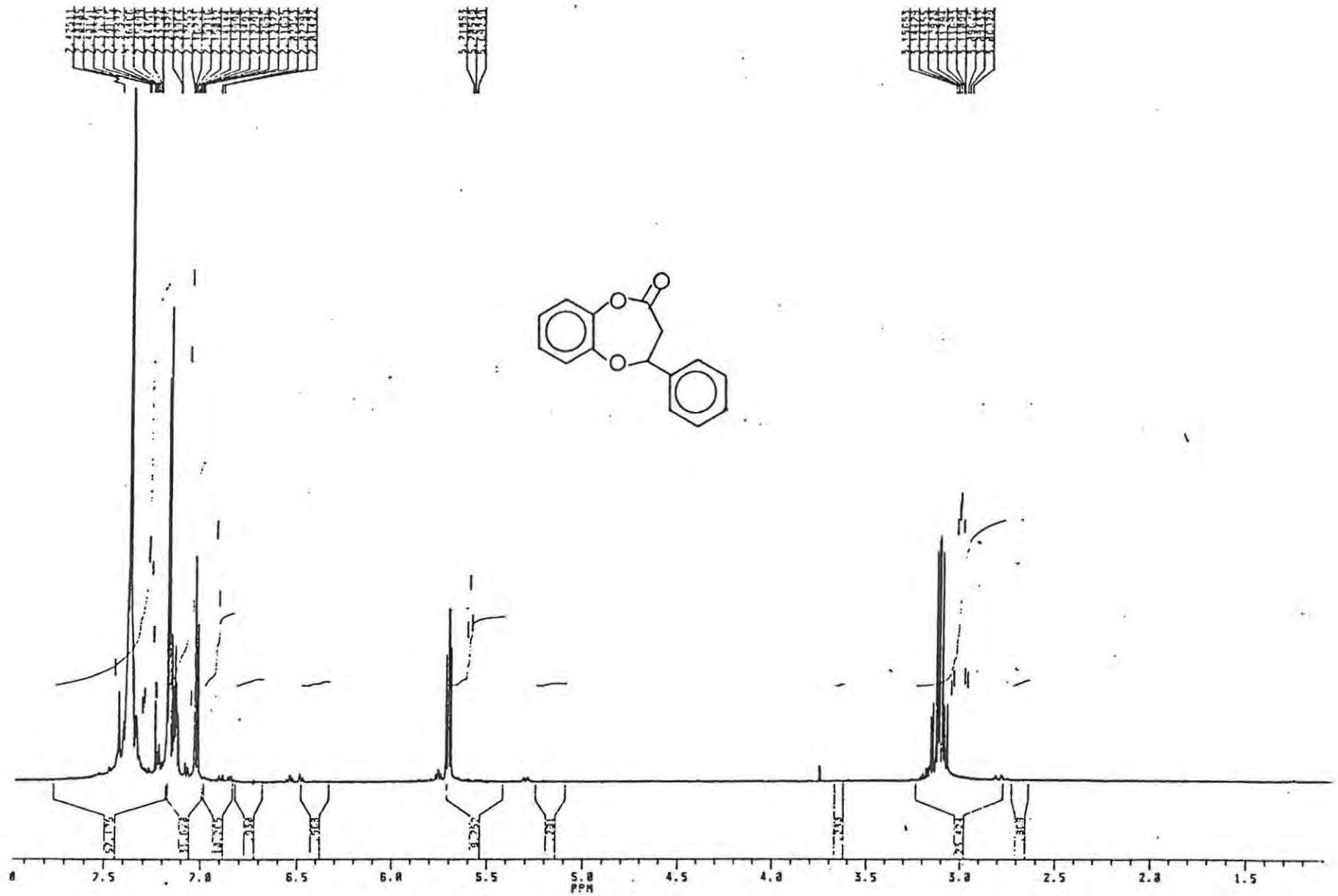
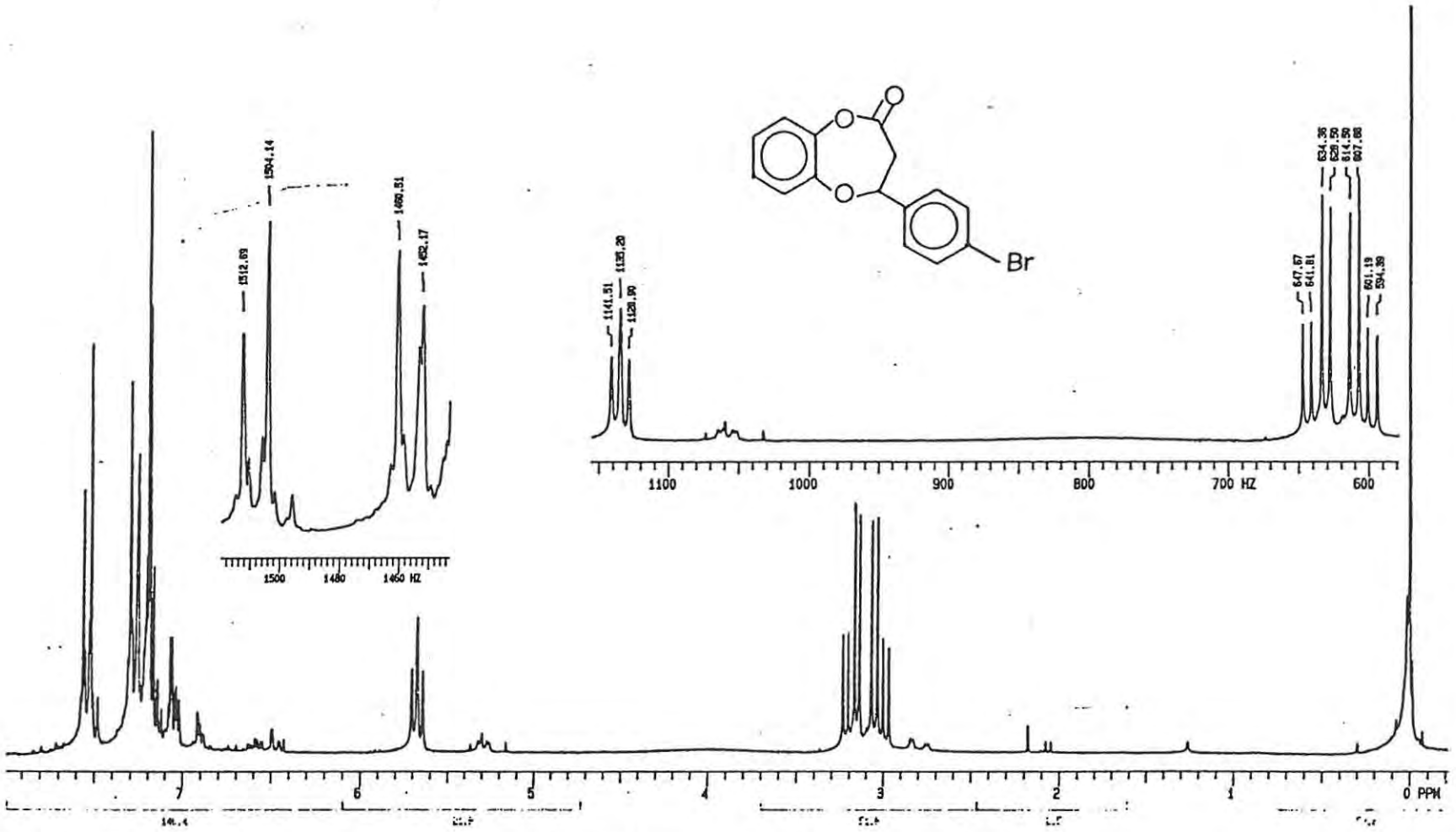
5. APPENDICES



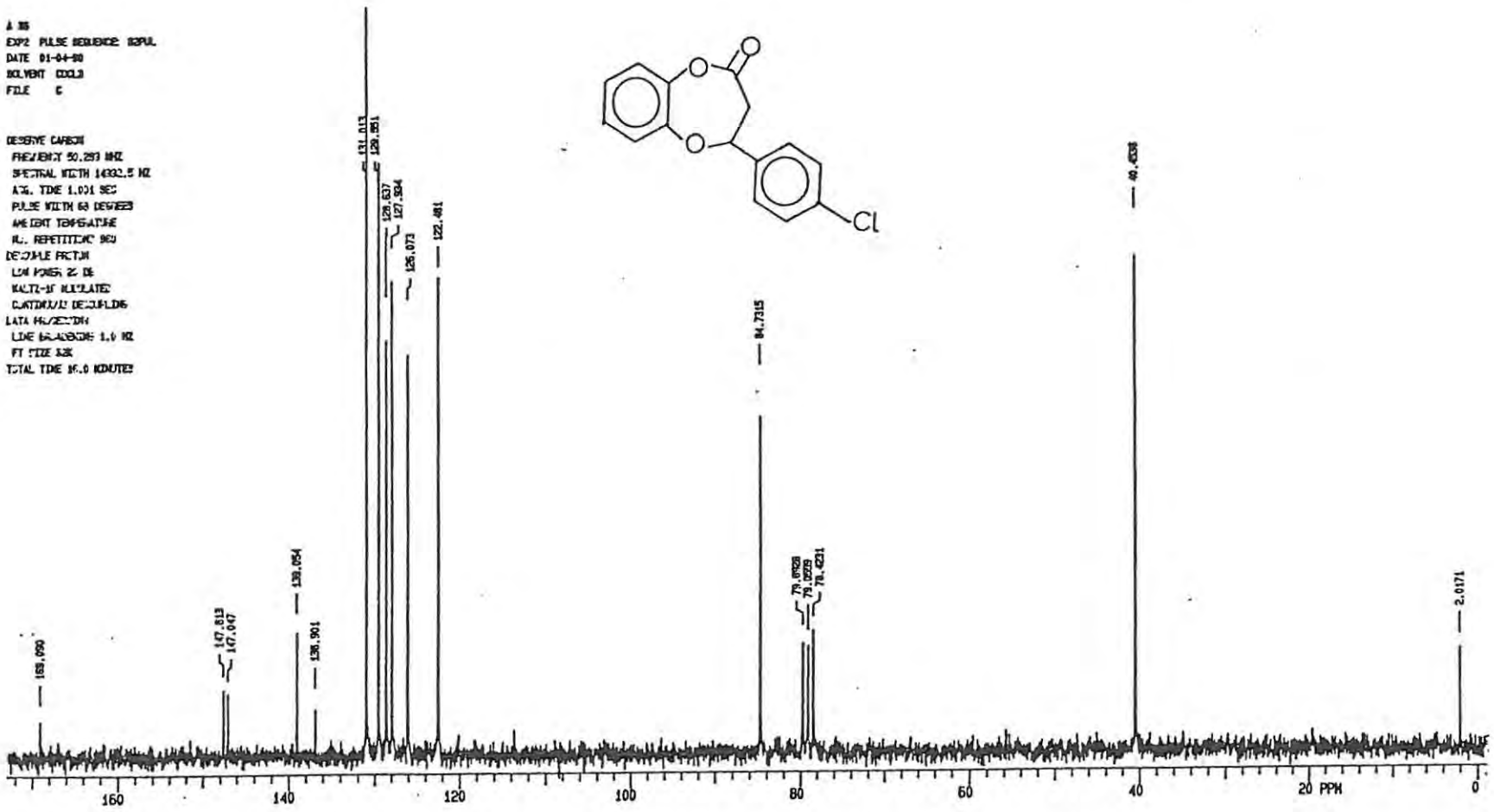
SPECTRUM 1 : ^{1}H n.m.r. spectrum of ethyl 7-fluorochromone-2-carboxylate.



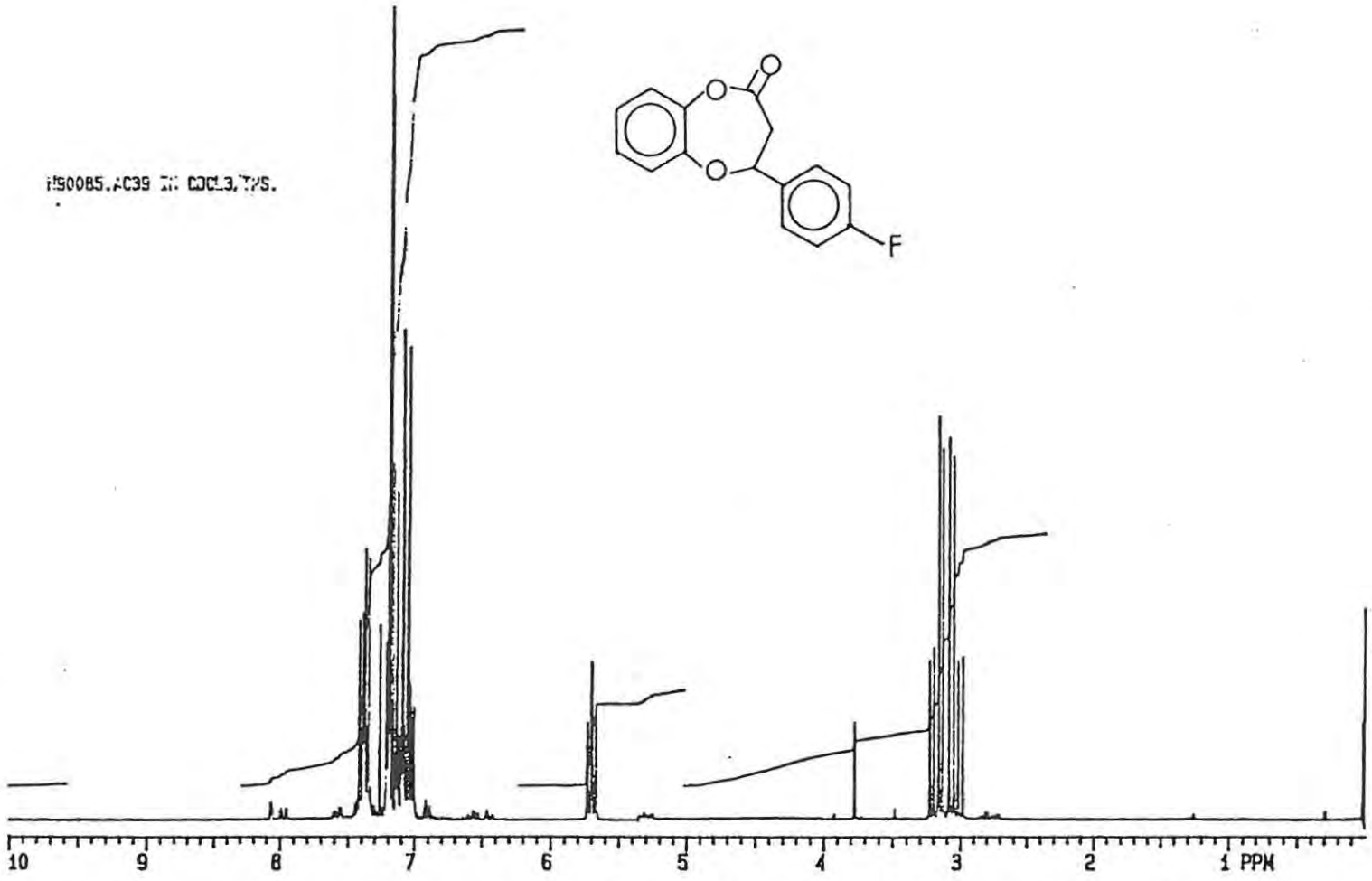
SPECTRUM 2 : ^{1}H n.m.r. spectrum of 2-phenyl-1,5-benzodioxepan-4-one.



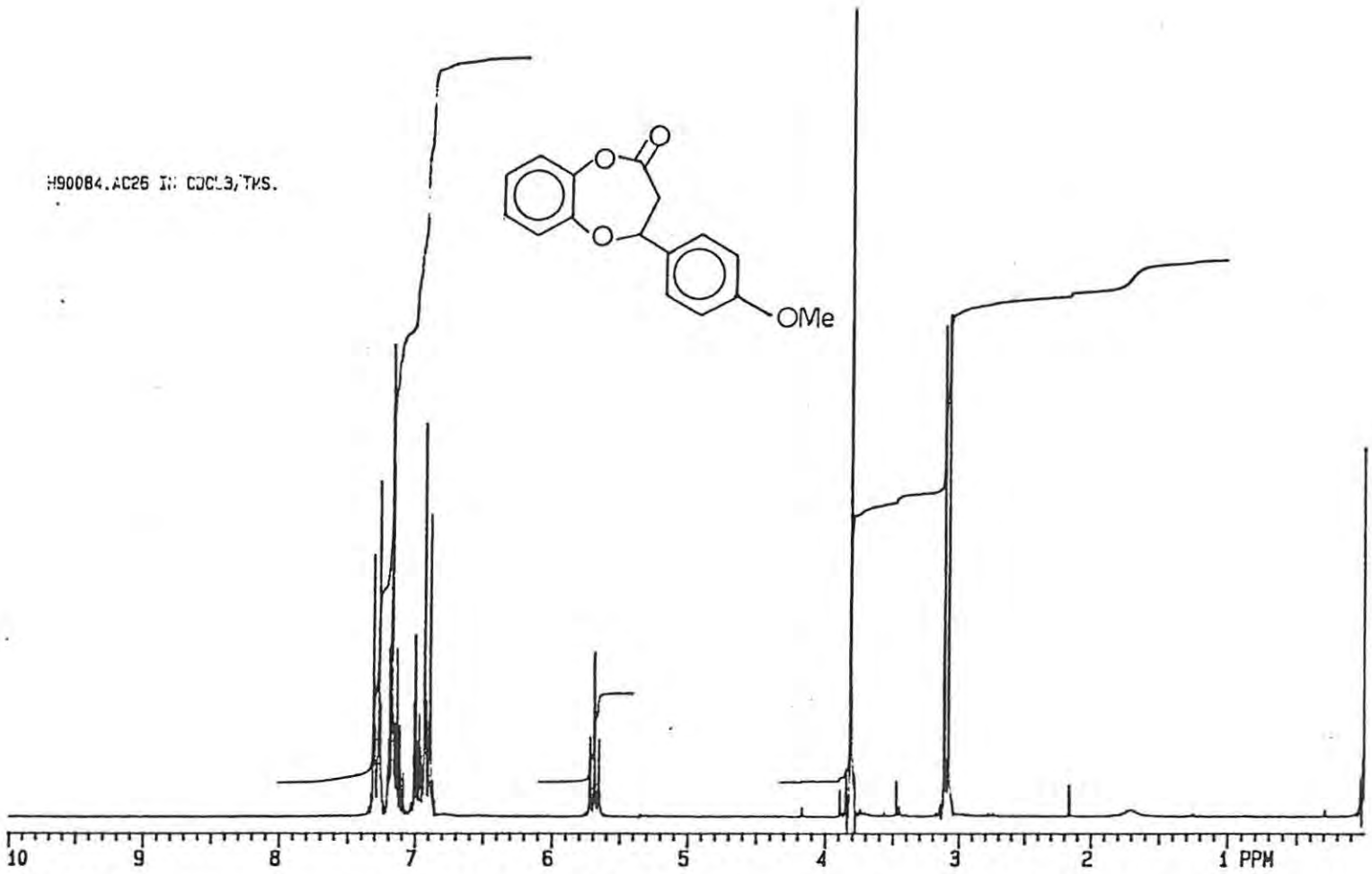
SPECTRUM 3 : ^{1}H n.m.r. spectrum of 2-(4-bromophenyl)-1,5-benzodioxepan-4-one.



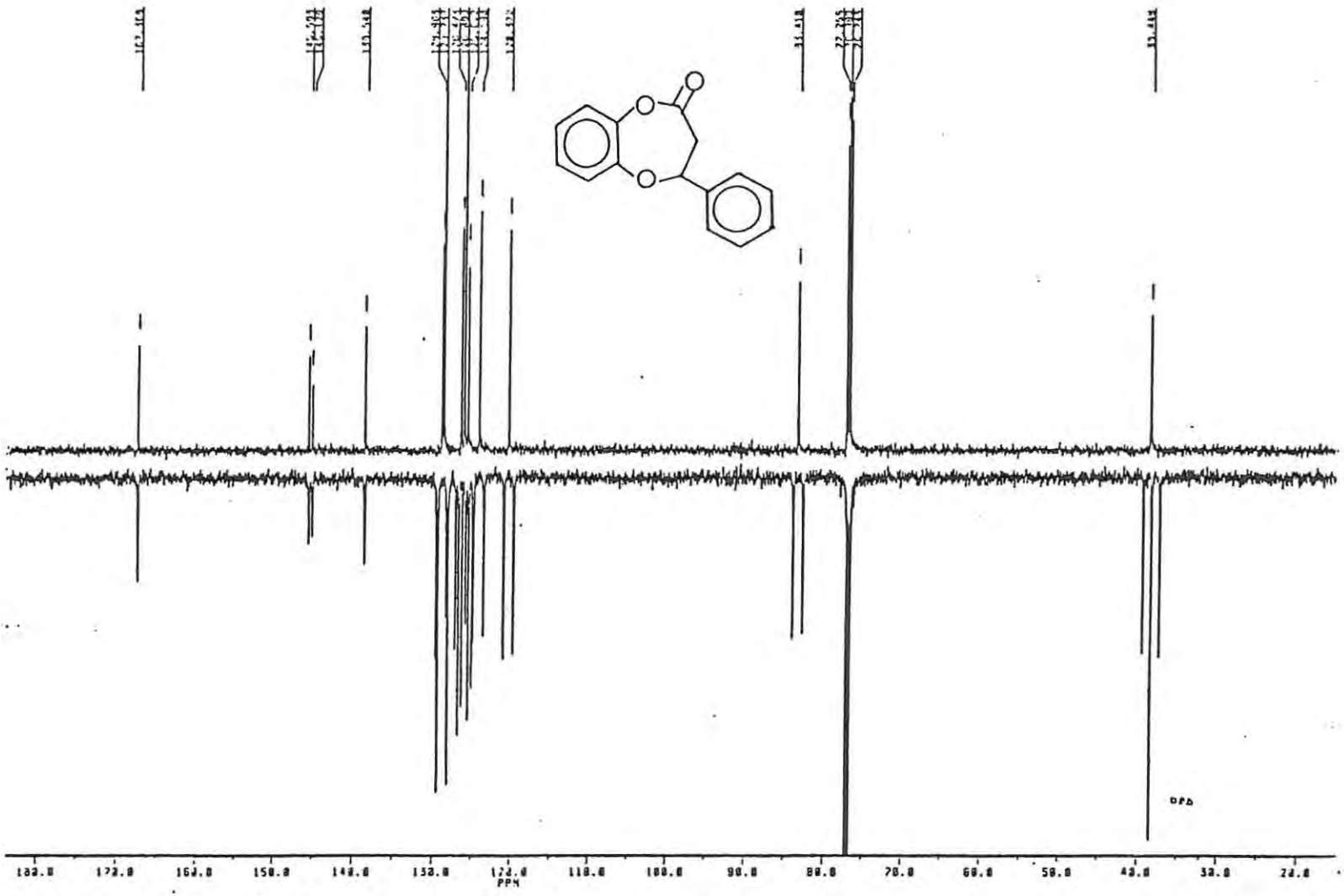
SPECTRUM 4 : ^{1}H n.m.r. spectrum of 2-(4-chlorophenyl)-1,5-benzodioxepan-4-one.



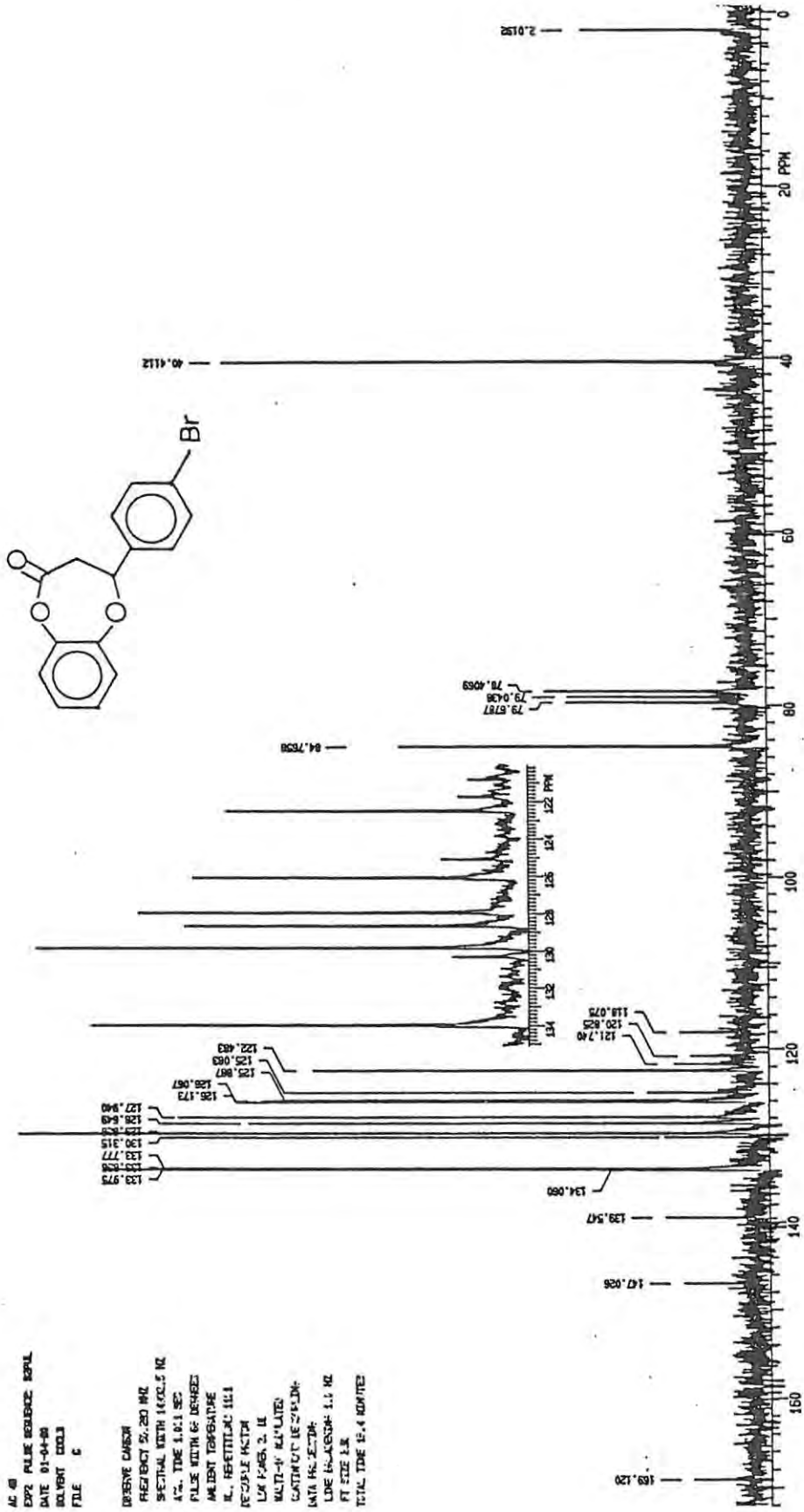
SPECTRUM 5 : ^{1}H n.m.r. spectrum of 2-(4-fluorophenyl)-1,5-benzodioxepan-4-one.



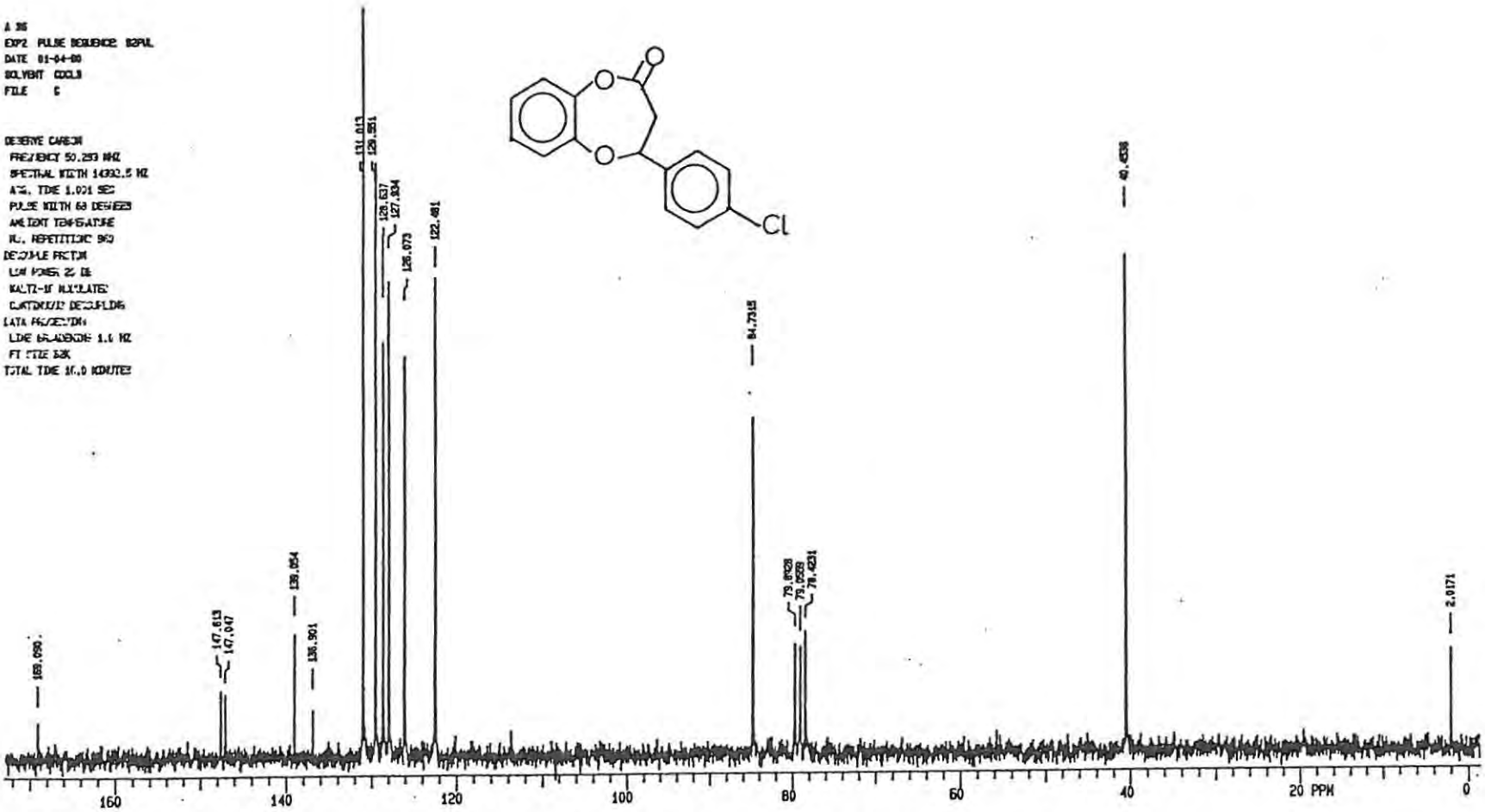
SPECTRUM 6 : ^{1}H n.m.r. spectrum of 2-(4-methoxyphenyl)-1,5-benzodioxepan-4-one.



SPECTRUM 7 : ^{13}C PND and ORD n.m.r. spectra of 2-phenyl-1,5-benzodioxepan-4-one.



SPECTRUM 8 : ^{13}C PND n.m.r. spectrum of 2-(bromophenyl)-1,5-benzodioxepan-4-one.



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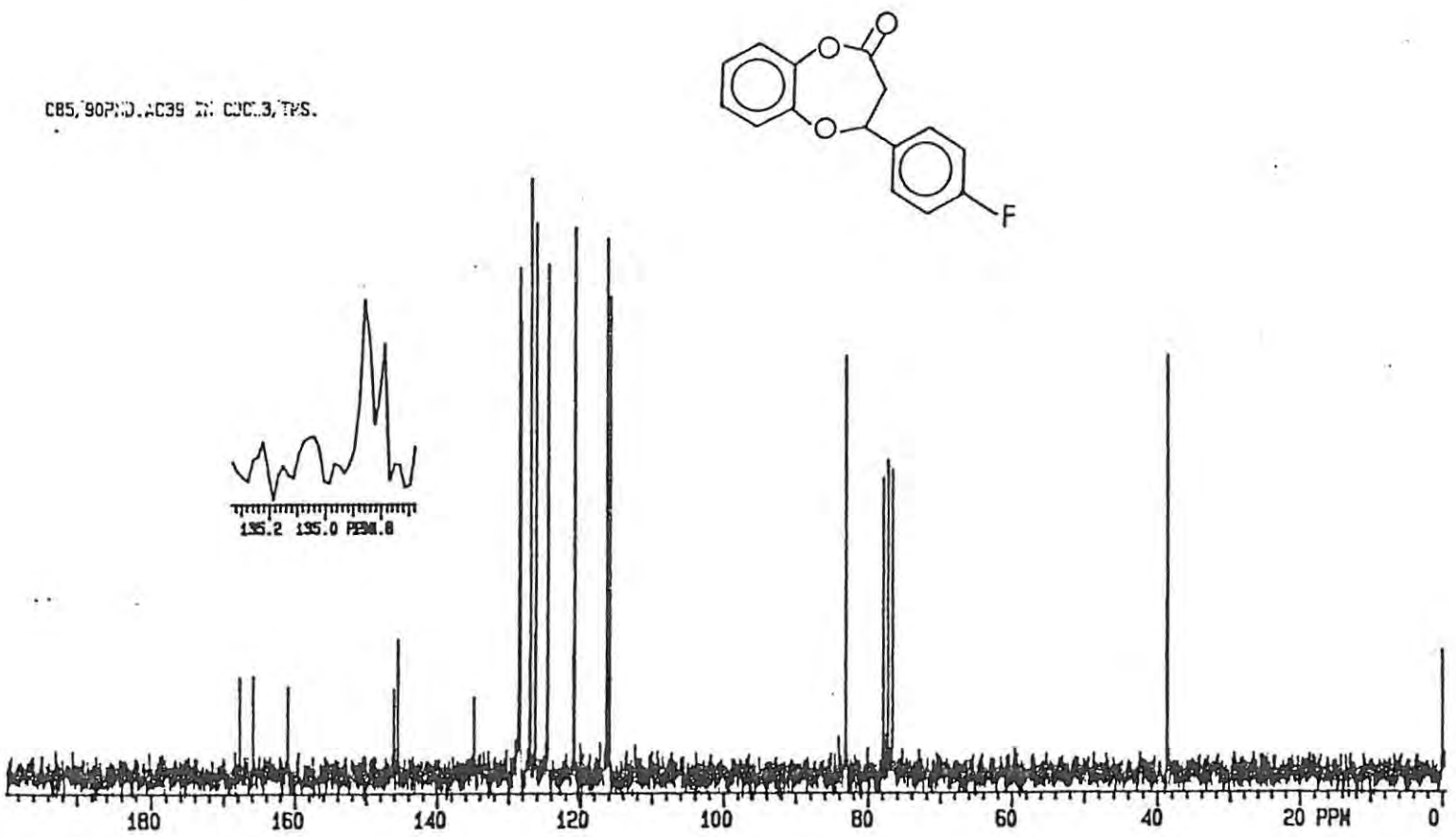

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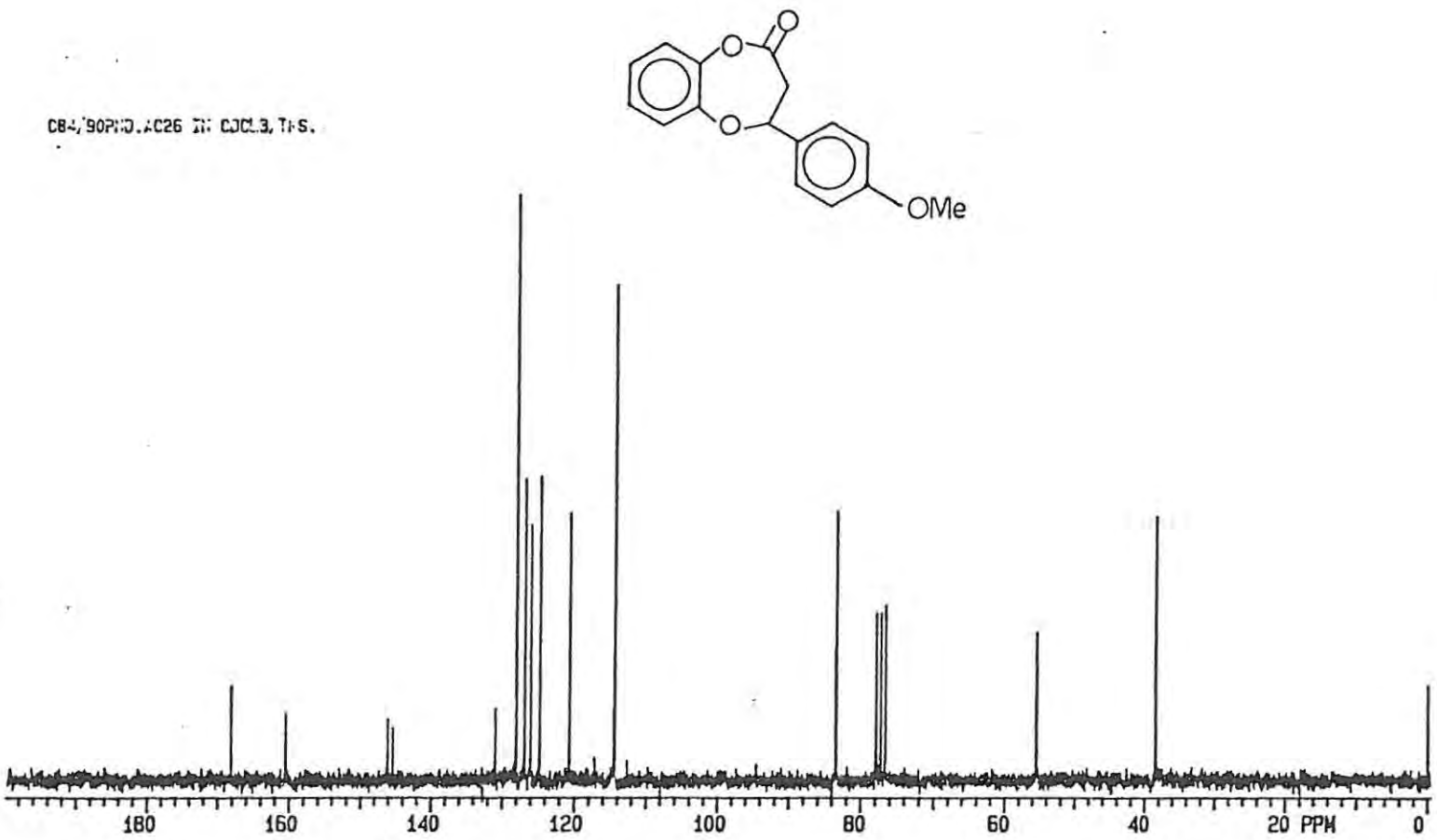
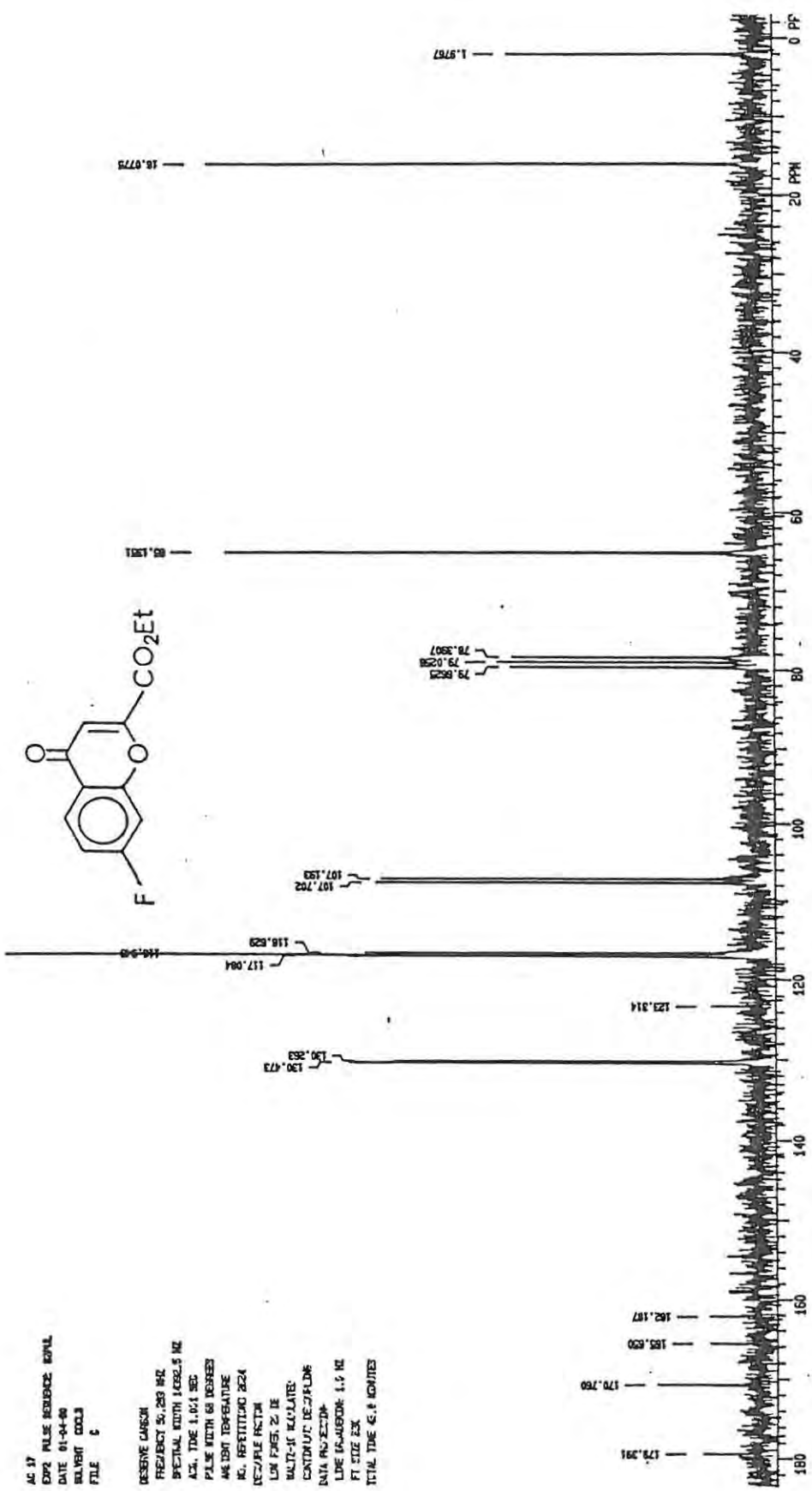
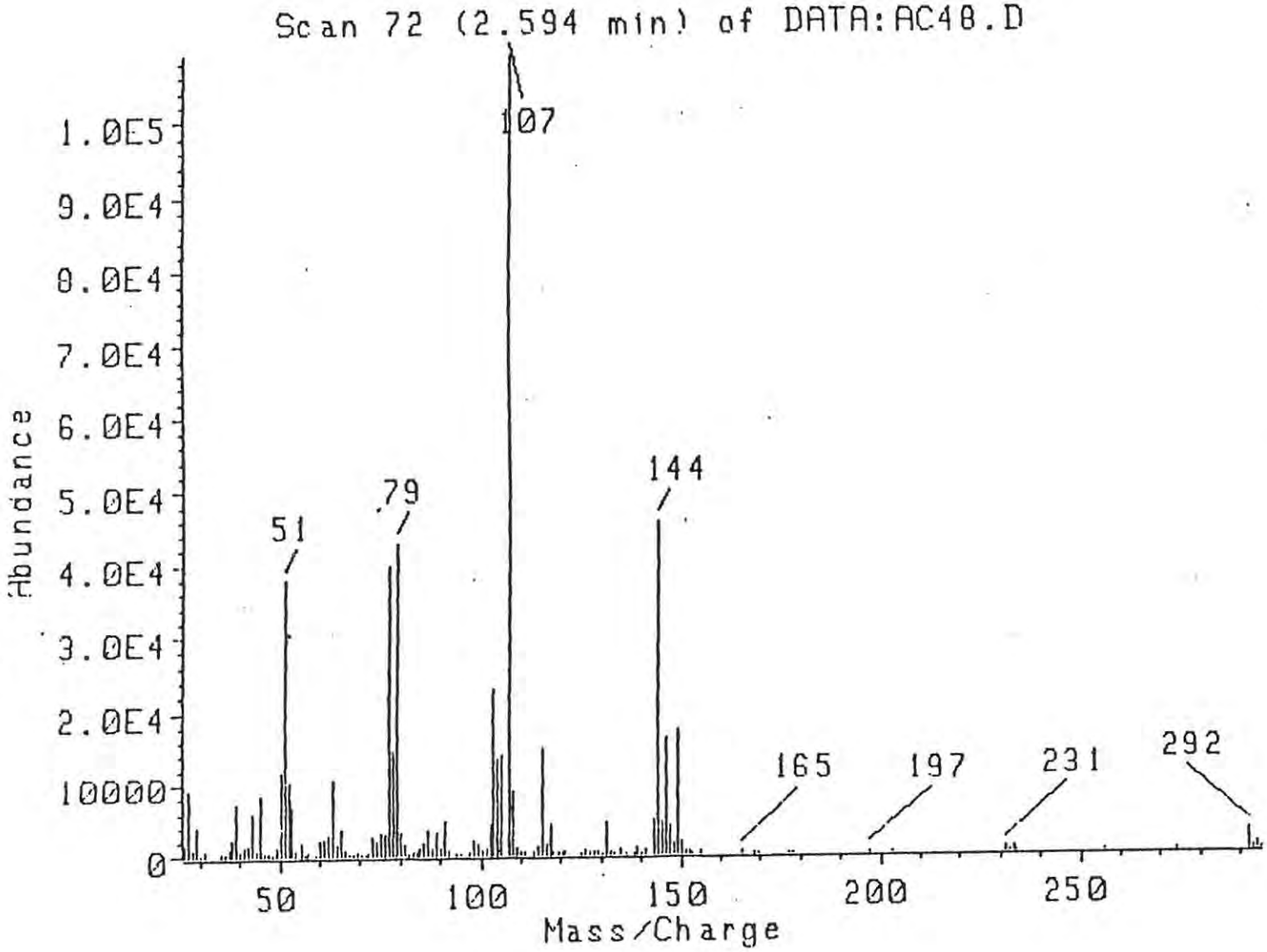


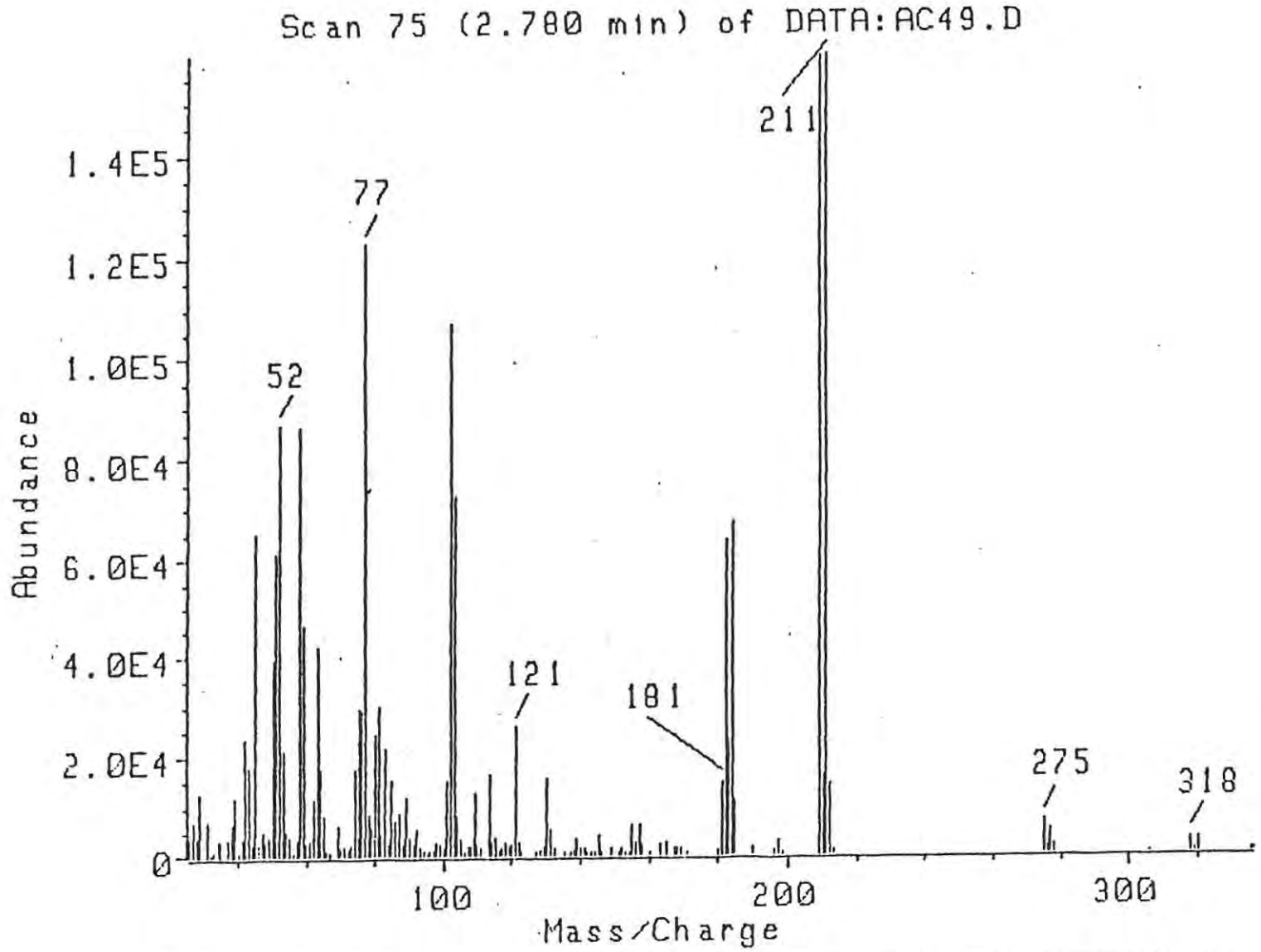
SPECTRUM 11 : ^{13}C PND n.m.r. spectrum of 2-(4-methoxyphenyl)-1,5-benzodioxepan-4-one.



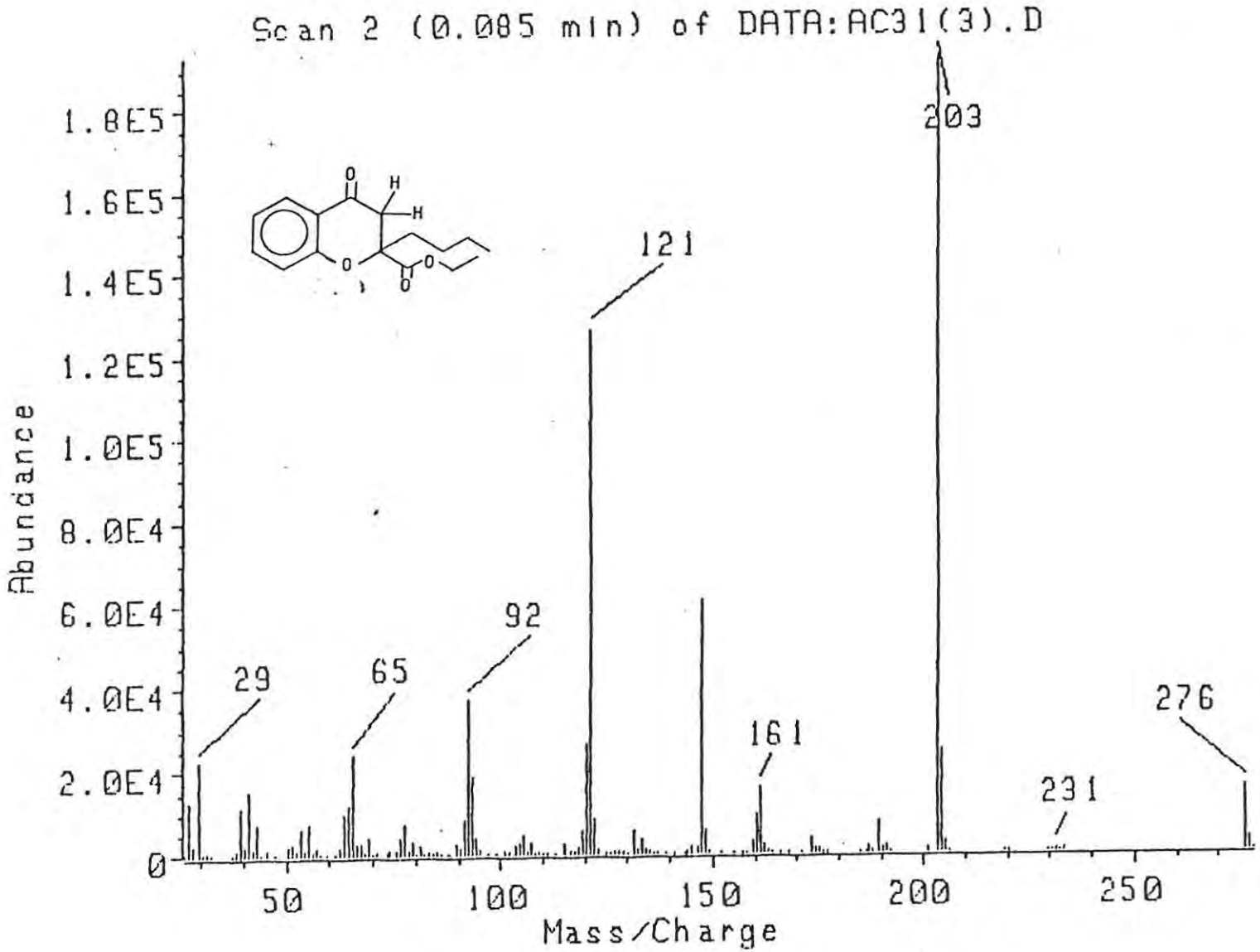
SPECTRUM 12 : ^{13}C PND n.m.r. spectrum of ethyl 7-fluorochrome-2-carboxylate.



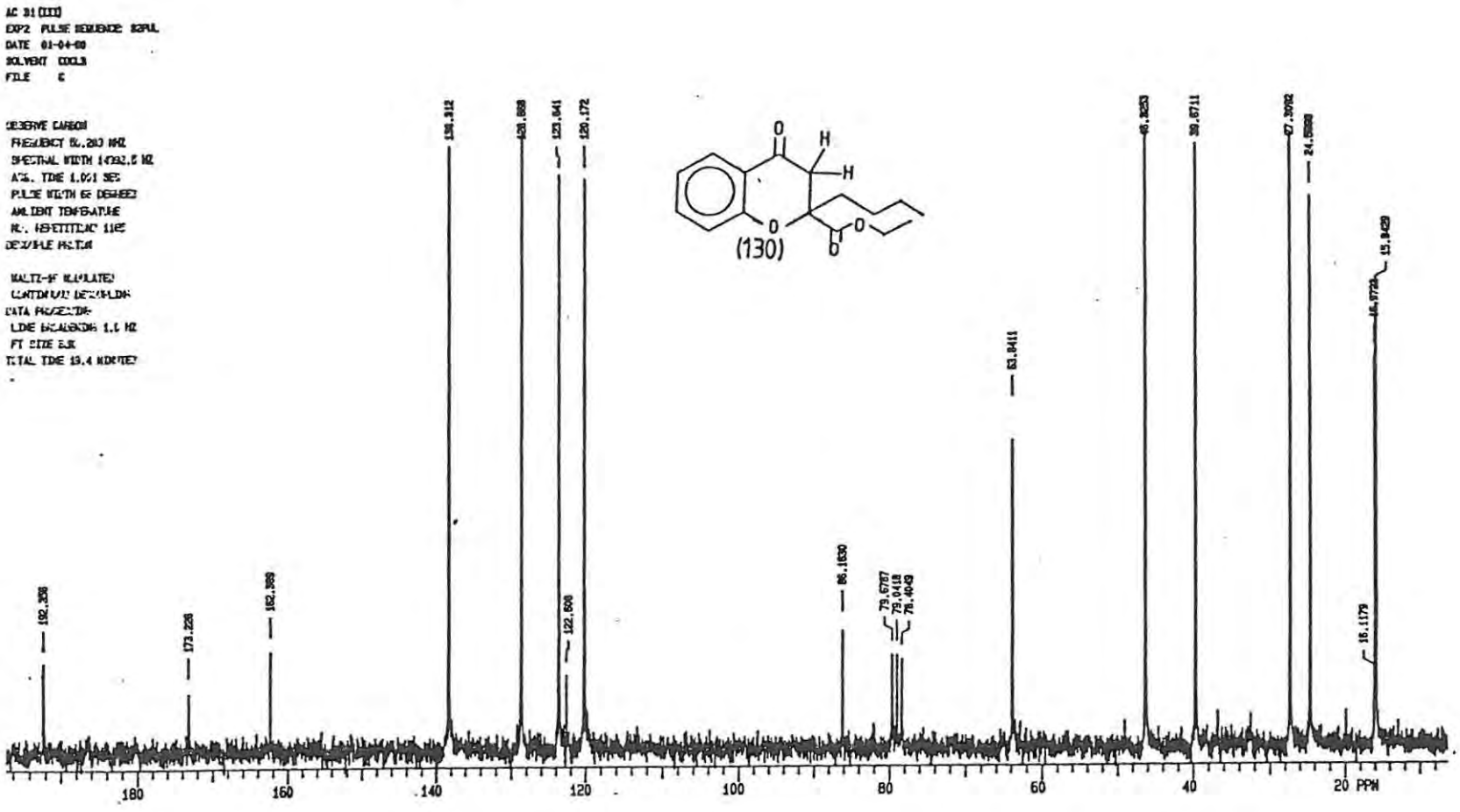
SPECTRUM 13 : Low resolution mass spectrum of 8-chloro-1,5-benzodioxepan-4-one.



SPECTRUM 14 : Low resolution mass spectrum of 2-(4-bromophenyl)-1,5-benzodioxepan-4-one.



SPECTRUM 15 : Low resolution mass spectrum of 2-butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one.



SPECTRUM 16 : ^{13}C PND spectrum of 2-butyl-2-ethoxycarbonyl-2,3-dihydrobenzopyran-4-one.