SYNTHETIC AND PHYSICAL ORGANIC STUDIES OF CHROMONE DERIVATIVES

THESIS

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ABBREVIATIONS

THF	=	tetrahydrofuran
DMF	=	dimethylformamide
DBU	=	1,8-diazabicyclo[5.4.0]undecene-7
LDA	=	lithium diisopropylamide
NMR	=	nuclear magnetic resonance
IR	=	infra red
Tf_2O	=	triflic anhydride (trifluoromethanesulphonic anhydride)
Lawesson's reagent	=	2,4-*bis*(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide
COSY	=	^1H-^1H correlation spectroscopy
HETCOR	=	^1H-^{13}C heteronuclear correlation spectroscopy
s	=	singlet
br s	=	broad singlet
d	=	doublet
dd	=	doublet of doublets
ddd	=	double doublet of doublets
tt	=	triplet of triplets
m	=	multiplet
Ac	=	acetyl group
Et	=	ethyl group

ABSTRACT

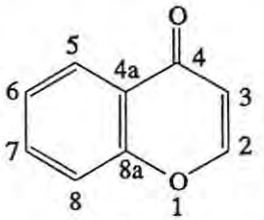
A range of chromone-2-carboxylic acids has been prepared by condensing suitably substituted 2-hydroxyacetophenones with diethyl oxalate. pK_a Studies of these acids revealed that 6- or 7-methoxy substituents decreased acidity while the 6-nitro group enhanced acidity; the strongest acid was the 3-chloro derivative, the increase in acidity being attributed to steric inhibition of acid-weakening delocalisation between the carboxyl group and the chromone system.

Various chromone-2-carboxamides, derived from acid chloride precursors, were converted to polysubstituted acrylamides by nucleophilic ring-opening with selected amine nucleophiles. The main fragmentation patterns exhibited by these acrylamides were elucidated using a combination of low resolution, high resolution and meta-stable peak analysis, while the effect of substituents on the simultaneous internal rotation involving the carboxamide and enamine moieties were studied using dynamic NMR spectroscopy. Rotational barriers of *ca.* 67.1 $kJmol^{-1}$ and *ca.* 102 $kJmol^{-1}$ were found for the enamine and amide rotors, respectively.

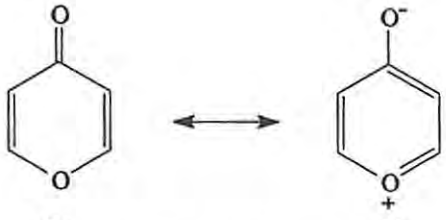
Several synthetic pathways were followed to prepare a series of 2-(*N,N*-dialkylamino)-chromones which were subjected to detailed mass spectral analysis. In addition to substituent-specific fragmentations, the 2-aminochromones appear to fragment *via* 3 major pathways. The effect of substituents on the internal rotation of the amino moeity was investigated by variable temperature ^1H NMR spectroscopy and the resulting DNMR data was used to calculate the rotational barriers. Examination of the data reveals that the electron-releasing 6- and 7- substituents reduce the C-NMe_2 rotational barrier to *ca.* 43.5 $kJmol^{-1}$, while the nitro analogue has the largest rotational barrier (*ca.* 46.1 $kJmol^{-1}$) because of the electron-withdrawing effect of this substituent.

1. INTRODUCTION

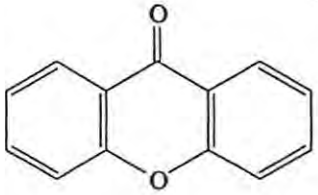
Chromones (**1**) are an important class of benzannulated derivatives of γ-pyrone (**2**) but, chemically, very different to the doubly benzannulated derivative, xanthone (**3**), in which the γ-pyrone ring properties are suppressed.[1] The name "chromone" was first used by Block and Kostanecki[2] to describe several coloured, naturally occurring compounds known to contain the benzopyran-4-one structure. These compounds are important because many of them occur in plants, while others have useful pharmacological properties or exhibit interesting chemical reactions. Modern systematic nomenclature of chromones is based on the pyran analogues (**4**), (**5**) and (**6**). Chromone (**1**) is isomeric with coumarin (**7**), the only structural difference being the location of the carbonyl group.



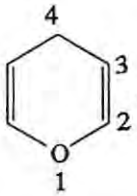
1 chromone (benzo-4*H*-pyran-4-one)
(4-oxo-4*H*-benzopyran)
(4-oxo-4*H*-chromene)



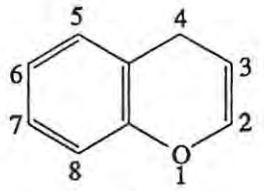
2a **2b**
γ-pyrone (4*H*-pyran-4-one)



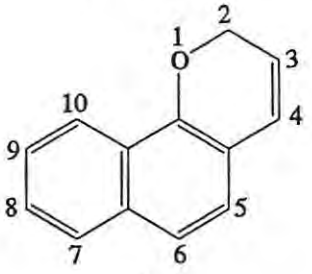
3
xanthone



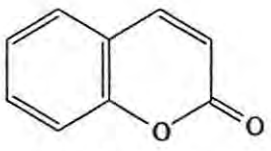
4*H*-pyran
4



5
4*H*-1-benzopyran
(4*H*-chromene)
(γ-chromone)



6
benzo[*h*]chromene
{2*H*-naptho[1,2-*b*]pyran}



7
coumarin
(2*H*-1-benzopyran-2-one)

1.1 Review of chromone chemistry

The synthesis of chromones and flavones has been extensively reviewed,[1-3] and this introduction will mostly cover work done from 1977 to date (1995).

1.1.1 Structure and spectroscopic studies

Most properties of chromones follow the pattern established by γ-pyrone **2**, and can be explained in terms of an aliphatic dienone structure (**2a**) rather than an aromatic pyrylium betaine structure (**2b**). However, some properties of γ-pyrones and chromones, such as lack of normal ketonic properties, may be ascribed to the pyrylium betaine structure (**2b**).[4] The great tendency of γ-pyrone ($pK_a = 0.1$) and chromone ($pK_a = 2.0$) to form salts, has been rationalized in terms of the basicity of the betaine structure.[3]

The observed properties of these systems are, of course, accommodated by a delocalization model, and it was Arndt who first suggested that the ether oxygen in the γ-pyrone could interact electronically with the carbonyl group and so modify the properties of the latter.[4] This was the first explanation of the theory of mesomerism - a fact which gives γ-pyrones an important place in the history of organic chemistry.

The assumption that the γ-pyrone ring has substantial π-electron delocalization is further supported by the failure to obtain a Diels-Alder adduct on treatment of 2,3-dimethylbuta-1,3-diene with the "dienophile" (**2a**) and cogeneric compounds; thiopyran-4-one similarly fails to react. The Diels-Alder reaction has in fact been used to assess aromaticity in pyran-4-one

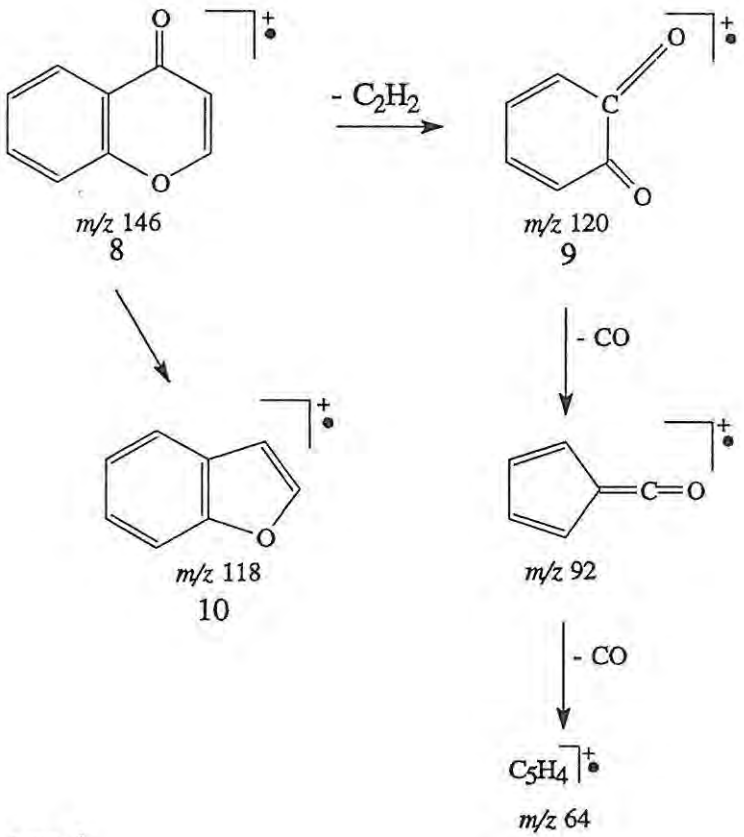
and cogeneric compounds,[3] - a lack of reactivity being indicative of aromaticity.

Studies of the M.O. delocalization energy (DE), dipole moments and ^{1}H and ^{13}C NMR data has shown that pyran-4-one and chromone possess some degree of aromaticity.[3] Nevertheless, certain spectroscopic properties of chromones may often be rationalized in terms of an aliphatic π-system in a heterocyclic ring, as in structure (**2a**), rather than as an "aromatic" pyrylium betaine, as in structure (**2b**). The IR carbonyl stretching frequency for chromone (ν_{max} 1660 cm^{-1}) is higher than that of γ-pyrone (ν_{max} 1650 cm^{-1}) but much lower than for the isomeric coumarin (**7**) (ν_{max} 1710 cm^{-1}). The UV spectra of chromones are characterized by two strong peaks at approximately 225 and 290 nm. Chromone itself has maxima at 245 nm (10 000) and 297 nm (6460).

In a detailed ^{1}H NMR study published by Mathis and Goldstein,[6] chromones and chromanones are characterized by the 5-H signal, which is separated from those of the other benzenoid hydrogens and which is not shown by the isomeric coumarins.[6] In chromone (**1**), the 2-H and 3-H signals are very close to those found for γ-pyrone (**2**), suggesting that the ring current in the heterocyclic ring is not significantly affected by benzannulation.[5,6] In the ^{13}C NMR spectra of chromones, the signal for the carbonyl carbon is always at lowest field and is relatively unaffected by substitution in the system.

When subjected to electron impact mass spectrometry, chromone (**1**) fragments *via* two main pathways, involving either loss of carbon monoxide or ring cleavage by a *retro*-Diels-Alder (RDA) reaction as depicted in **Scheme 1**.[8,9] The base peak (*m/z* 146) is due to the molecular ion (**8**). Loss of acetylene by the RDA pathway gives the radical cation (**9**) (*m/z* 120), which

then decomposes by further loss of carbon monoxide. Decomposition of fragment (**10**) gives ions at *m/z* 90 and 89, corresponding to initial loss of carbon monoxide followed by loss of a hydrogen radical. Substituents may, however, divert the above fragmentation pattern.[8,9]

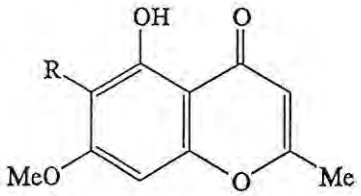


Scheme 1

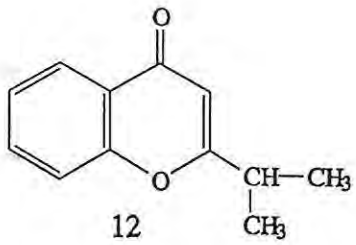
1.1.2 Occurrence and biological activity of chromone derivatives

Most naturally occurring chromones contain hydroxyl (at C-5 and C-7), methyl (at C-2) and/or phenyl groups.[10] Eugenin (**10**) and egenitin (**11**) are constituents of the wild clove *Eugenia caryophyllata L. Thumb*,[11] while 2-isopropylchromone (**12**) has been isolated from *Laphomyrtus bullata* in New Zealand.[12] The first naturally occurring chromone found to be unsubstituted at C-2 (**13**) was isolated from *Leptorusmol miquelina*.[13]

Peucinin (**14**), isolated from the rhizome of the masterwort, *Peucedanum ostruthium Koch*, was the first naturally occurring chromone to be found having a hydroxyl group at C-5 and C-7 and a methyl group at C-2; it has also been isolated from the heartwood of the South African sneezewood tree, *Ptaeroxylon obliquum* Thum. Radik and from the Madagascan tree, *Cedrelopsia grevei*.[2] Gregei-chromenol (**15**) and an isomer of peucinin, heteropeucinin (**16**), were also isolated from the same trees.[2]



10 (R = H)
11 (R = Me)



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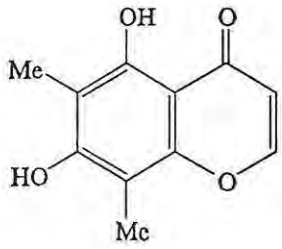

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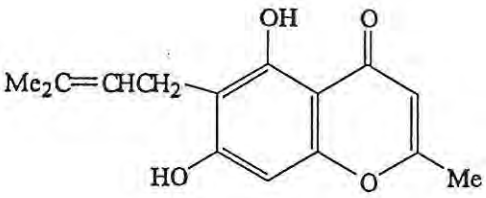
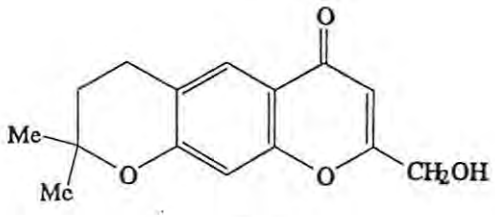


14

Rohitukine (**17**), first isolated from the leaves and stem of *Amoora rohituka* (Meliacea) by Wright and Arn in 1979, has also been isolated from another meliaceous species, *Dysoxylum binectariferum* Hook, and from *Schumanniophyton magnificum* Harms (Rubiaceae). The stem juice of *S. magnificum* Harms has been used for treatment of snakebite in Nigeria. Rohitukine (**17**) has also been shown to have good anti-inflammatory, analgesic and immunomodulatory effects in both *in vivo* and *in vitro* tests.[13]



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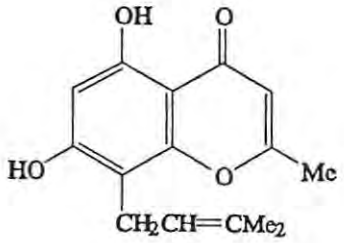

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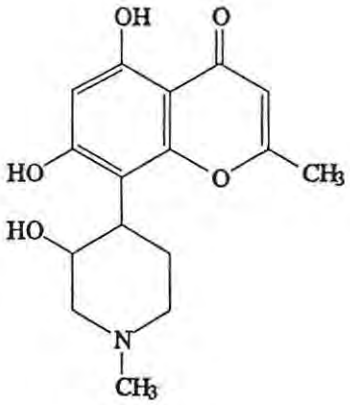
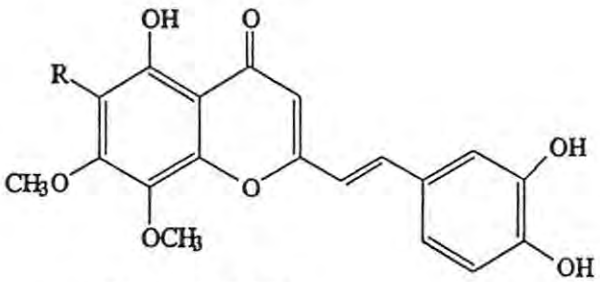


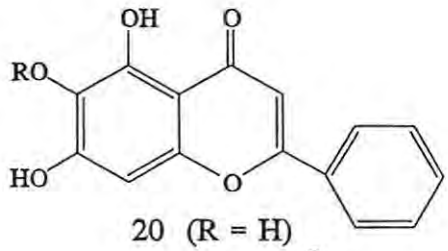
17

Hormothamnione (**18**) and 6-desmethoxyhormothamnione (**19**) were isolated from blue-green algae, *Chrysophaeum taylori* in 1984 off the northern coast of Puerto Rico.[14] The structure of hormothamnione (**18**) was established in 1986 and that of the desmethoxy analogue (**19**) in 1991. Hormothamnione (**18**) has shown cytotoxicity toward P388 Leukaemia and HL-60 human promyelocytic cells *in vitro* by inhibiting RNA synthesis; and it was the first naturally occurring styrylchromone to be isolated. The biological significance of the above-mentioned compound has stimulated interest in the synthesis of analogues of these compounds.[14-17]



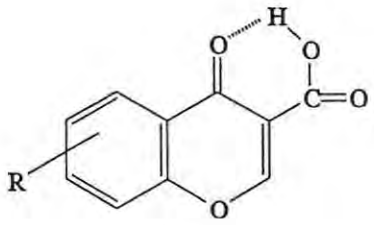
18 (R = OCH_3
19 (R = H)

Baicalein (**20**) is a flavonoid present in the dried radix of *Scutellaria baicalensis* George, which was used in ancient Chinese medicine as a diuretic or antiallergic drug.[18,19] Koda *et al.*[18,19] have shown that baicalein (**20**) and its water-soluble derivative, sodium baicalein-6-phosphate (**21**) have anti-anaphylactic activity. Structure-activity studies on baicalein (**20**) analogues have shown that introduction of an additional carbonyl group at C-3 enhanced activity; the acid, however, was inactive probably due to interference by hydrogen bonding as in compound (**22**).[18,19] Replacement of the acid group at C-3 by the tetrazole group gave positive results.[19] Introduction of an alkyl or alkoxy group at C-6 or C-8 results in greatest enhancement of passive cutaneous anaphylaxis in rats, whereas attachment of an acrylic acid side chain at position 2 of the chromone destroys the biological activity.[18]



20 (R = H)

21 (R = —P(=O)(ONa)—ONa)



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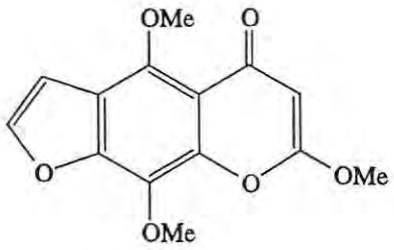


23

Khellin (**23**),[19-21] a natural furochromone, was isolated from the fruits and seeds of *Ammi visnaga*. Khellin (**23**) has been used in the Middle East for asthma therapy, but unpleasant

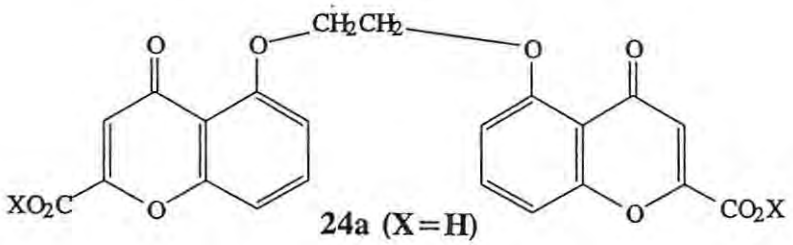
side effects, such as nausea and vomiting, have limited its clinical use. Khellin also reduces the levels of very low density lipoprotein (VLDL) and low density lipoproteins (LDL) and elevates high density lipoprotein (HDL), thus providing a valuable therapy for reducing the risk of cardiovascular disease.

The antispasmodic action of khellin (**23**) was later shown to be exhibited by other chromones more easily synthesized than the furochromone.[23] In the quest for a khellin replacement, further research failed to produce an effective antispasmodic drug but, instead, led to the discovery of an anti-allergic drug, cromoglycic acid (**24a**) which is used clinically as the disodium salt (DSCG) (**24b**).[23] Disodium cromoglycate (**24b**) is used for the treatment and prophylaxis of asthma and other allergic conditions. Unlike antihistamines, bronchodilators and corticosteroids, designed to provide symptomatic relief from the vasoactive and spasmogenic effects of mediators from released mast cells, cromoglycate is believed to act directly on the mast cells.[24]

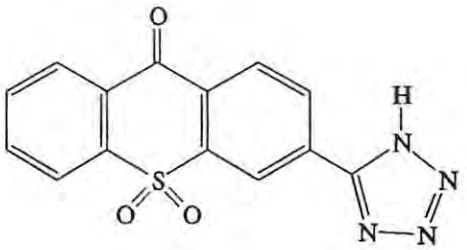
Disodium cromoglycate (**24b**) is, however, not effective for all kinds of allergies, and it is inactive when taken orally. A large number of other anti-allergic drugs have subsequently been developed, including orally active agent doxantrazole (**26**). However, only ketotifen (**27**) has been accepted into clinical use.[25] Ketotifen (**27**) has both anti-anaphylactic and antihistamine properties.[25]

It has been found[26,27] that chromones and flavones having hydroxy substituents can inhibit HIV-1 proteanase, which is an important constituent enzyme of the AIDS virus that is responsible for viral replication. This recently demonstrated inhibition of a crucial

component enzyme of HIV-1 suggests flavones as potential non-peptidic synthons for the development of drugs with enhanced activity and selectivity.



24a (X=H)
25a (X=Na)



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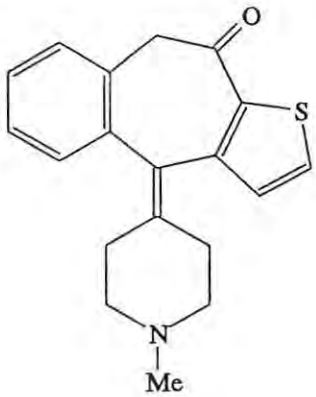

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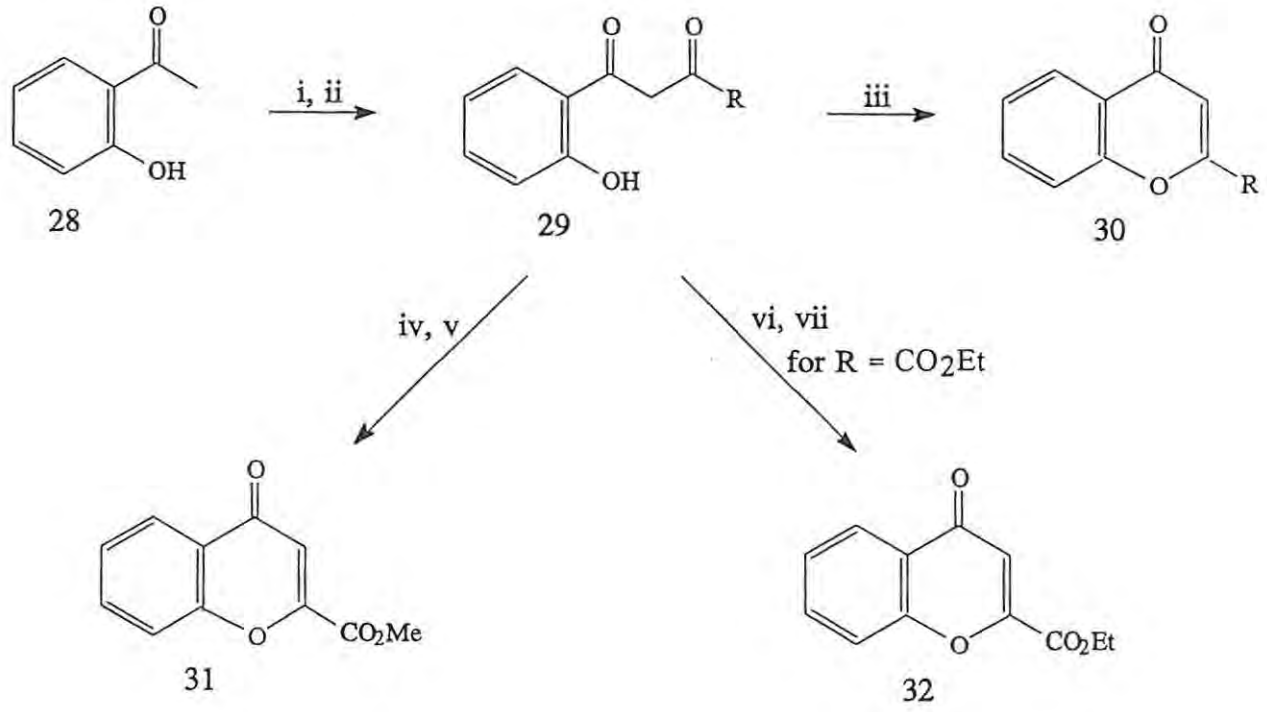
1.1.3 Synthesis of chromones

The synthesis of chromones and flavones has been extensively reviewed;[1-3] and in this introduction, a brief review of the classical synthesis, followed by a survey of more recent methods will be discussed.

2-Hydroxyacetophenones and phenols are the two most common precursors used in chromone syntheses. The general strategy involves building a side-chain on the phenolic substrate

before cyclization to the desired chromone; the intermediate, however, is not always isolated.[2]

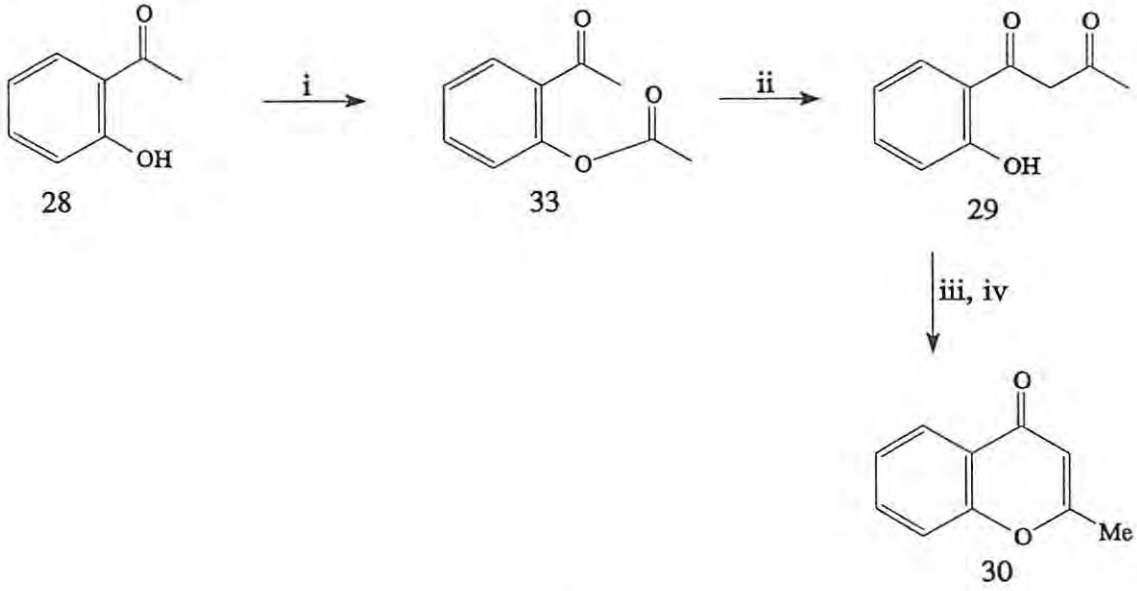
In the Claisen condensation, an *o*-hydroxyaryl alkyl ketone (**28**) is reacted with a carboxylic ester in the presence of a strong base to give a 1,3-diketo ester intermediate (**29**) which is subsequently cyclized in acidic medium to the chromone (**30**) (**Scheme 2**).[28,29] The method was first described by Kostanecki *et al.*[28,29] in their synthesis of 7-ethoxy-4*H*-1-benzopyran-2-carboxylic acid from 4′-ethoxy-2′-hydroxyacetophenone, diethyl oxalate, and metallic sodium. The presence of substituents in the aromatic ring has little effect on the reaction, and either electron-withdrawing or electron-releasing substituents may be present. The use of diethyl oxalate offers an added advantage in that the intermediate 1,3-diketo ester (**29**) (R = CO_2Et) readily undergoes transesterfication, thereby permitting the synthesis of various chromone-2-carboxylic esters, eg. (**31**) and (**32**), from one precursor.



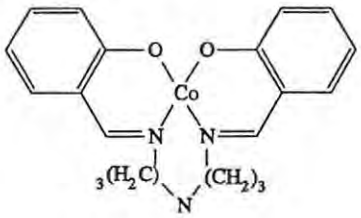
Reagents: i) strong base; ii) RCO_2Et; iii) H^+; iv) MeOH, H_2SO_4, 0°C; v) MeOH, HCl, boil; vi) EtOH; vii) H_2SO_4

Scheme 2

The Baker-Venkataraman rearrangement of 2-acyloxyacetophenones (**33**)[28,29] (**Scheme 3**) involves an intramolecular migration of an acyl group from oxygen to the carbon atom α to the ketone carbonyl group, and provides an alternative route to the 1,3-diketone intermediate (**20**) encountered in the Claisen condensation.[28,29] The migrating acyl group may be aliphatic or aromatic and, hence, this approach is useful for the preparation of flavones as well as chromones (**30**). Catalysts, other than potassium carbonate, recommended for the Baker-Venkataraman rearrangement include sodium sodamide, sodium alkoxides, sodium hydride, and potassium or sodium hydroxide.[28,29]



Reagents: i) MeCOCl, pyridine; ii) KOH, pyridine or K_2CO_3; iii) H^+ or iv)

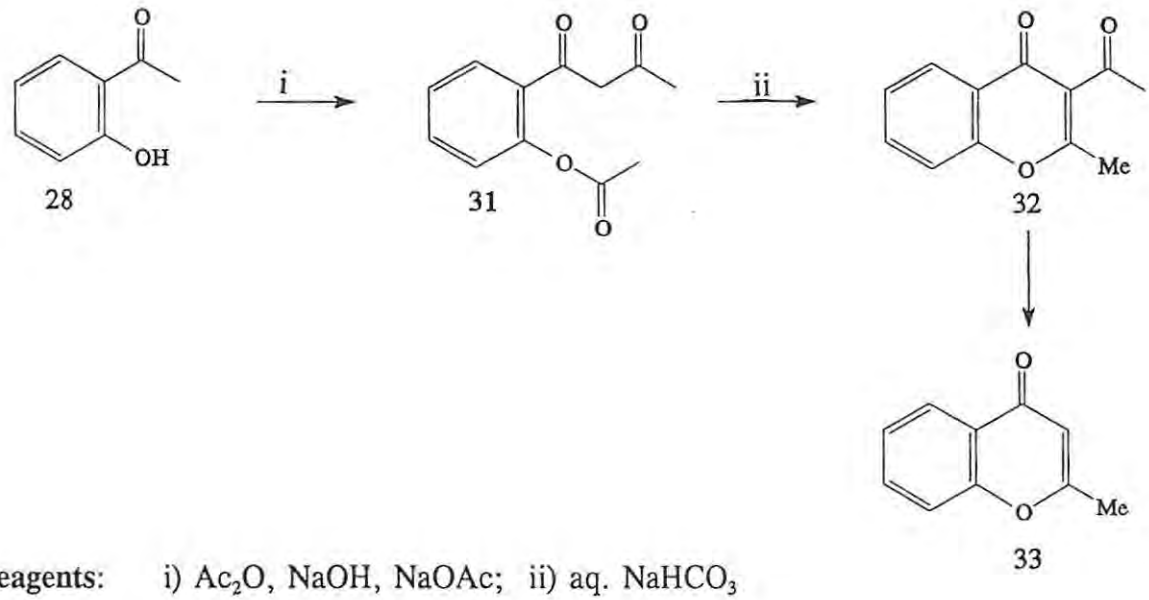


Co(III)(salpr)(OH)

Scheme 3

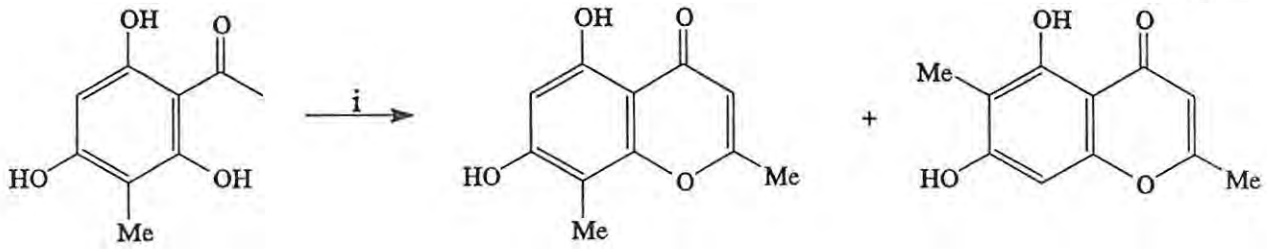
The 1,3-diketo ester intermediate (**29**) formed as a result of a Claisen condensation or Baker-Venkataraman rearrangement has recently been cyclized to the desired chromones (**30**) in high yield, by use of Co(III)(salpr)(OH) (a six-membered co-ordinate Schiff base complex) in 2,2,2-trifluoroethanol.[31]

The Kostanecki-Robinson synthesis,[29] first applied by Nagai and Tahara, involves the reaction of 2-hydroxyacetophenones (**28**) with acetic anhydride, and sodium salt of an aliphatic acid *via* the acylated intermediate (**31**) (**Scheme 4**). Cleavage of the chromone under alkaline conditions occurs readily, as it is part of a 1,3-dicarbonyl system. Substituents that do not react under the experimental conditions may be present on the aromatic ring, and examples include alkyl, acyl, alkoxy, halogeno, nitro and cyano groups. Hydroxy groups, however, may be acylated during the reaction and, sometimes, hydrolysed back during work-up, while an ester group may be hydrolysed or removed and an alkoxy group dealkylated.[28] Where the formation of isomeric chromone can be envisaged (**Scheme 5**), no particular regioselectivity is observed.



Reagents: i) Ac_2O, NaOH, NaOAc; ii) aq. $NaHCO_3$

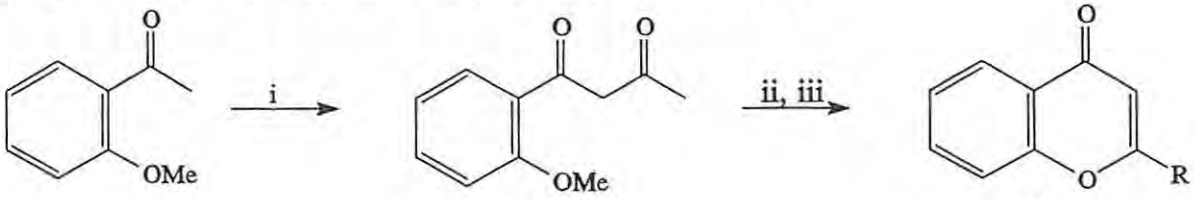
Scheme 4



Reagents: i) Ac_2O, NaOAc

Scheme 5

Methyl ethers have been used instead of the free phenolic substrates in the Kostanecki-Robinson chromone synthesis, cleavage of the ether and cyclization to the chromone (**35**) being achieved in the presence of hydriodic acid (**Scheme 6**).

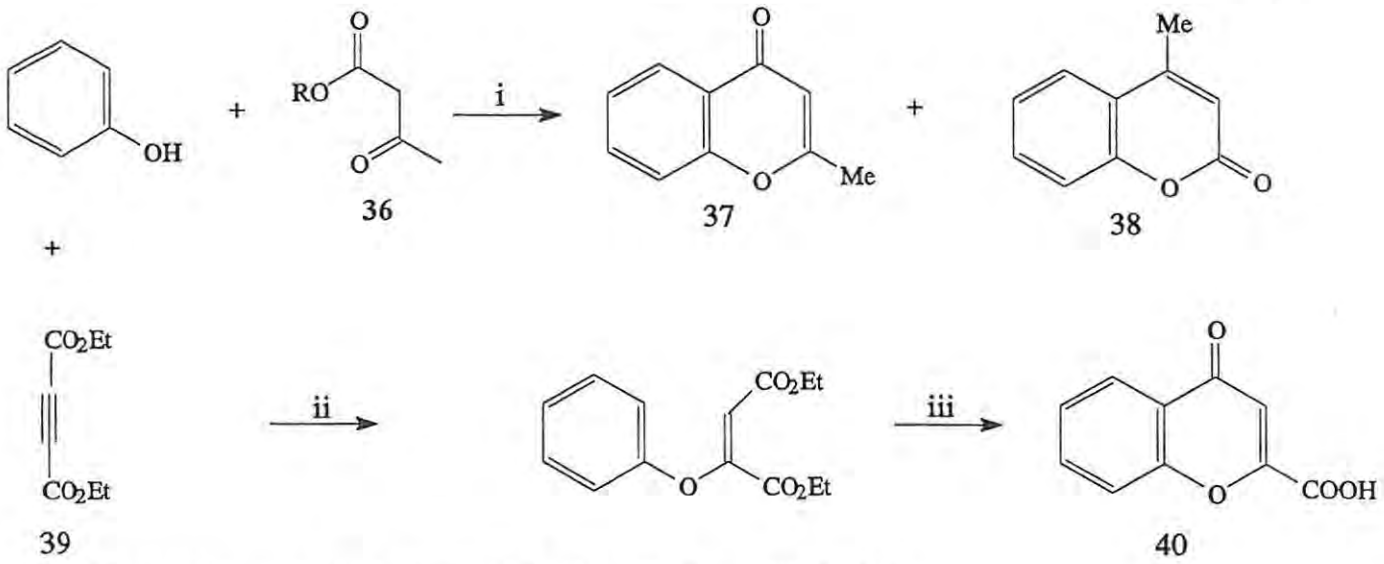


34 35

Reagents: i) NaOEt; ii) $MeCO_2Et$; iii) HI

Scheme 6

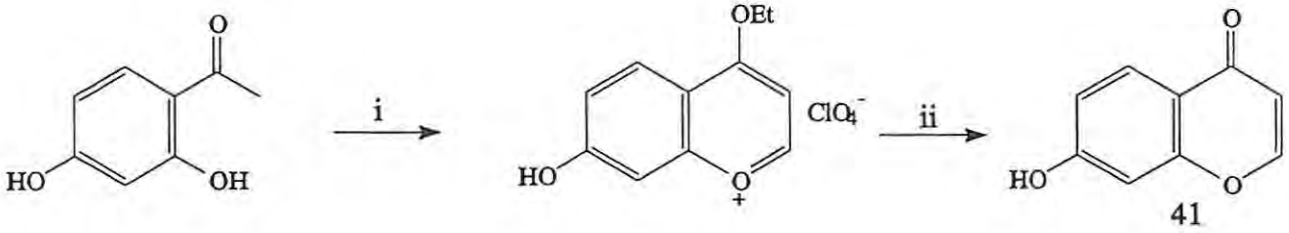
In the Simonis condensation,[28-30] a phenol may react with a ß-ketoester (**36**) to give a chromone (**37**), a coumarin (**38**) or a mixture of both (**Scheme 7**). The reaction which leads to a coumarin is called the Pechmann condensation, and sulphuric acid is a necessary condensing agent. Chromone formation is favoured by the use of phosphorus pentoxide, and when either the phenol contains a deactivating group or when the ß-ketoester is α-substituted. Phenol may also react with diethyl acetylenedicarboxylate (**39**) to give chromone-2-carboxylic acid (**40**) (**Scheme 7**), a widely used synthetic route.



Reagents: i) H^+ (H_2SO_4 or P_2O_5); ii) Base; iii) H_2SO_4

Scheme 7

Treatment of 2-hydroxyacetophenones (that lack electron-withdrawing substituents) with triethyl orthoformate and strong acid, under mild conditions give benzopyrylium salts that are unsubstituted at C-2; the chromone (**41**) is then formed by warming the salt with water (**Scheme 8**).[29] Catalysts used for this reaction include perchloric acid, hydrogen chloride, hydrogen bromide, iron (III) chloride and hydrogen iodide - the catalyst which gave the highest yield.

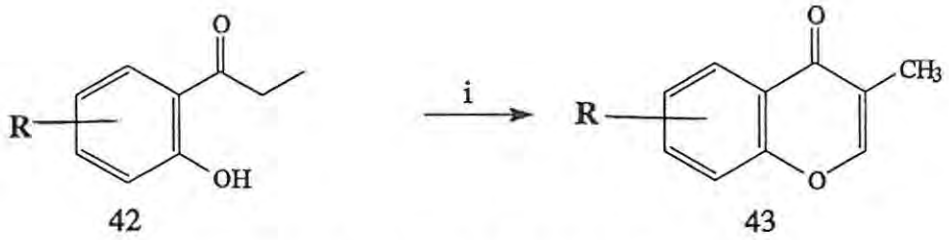


Reagents: i) $HC(OEt)_3$, $HClO_4$, 20°C; ii) H_2O

Scheme 8

3-Methylchromones (**43**) find use as fungicides, cardiovascular agents and in the treatment of allergic conditions or hyperacidity. These compounds have been synthesized by treatment

of 2-hydroxypropiophenone (**42**) with DMF, BF_3-etherate and methanesulphonyl chloride[32] (**Scheme 9**).



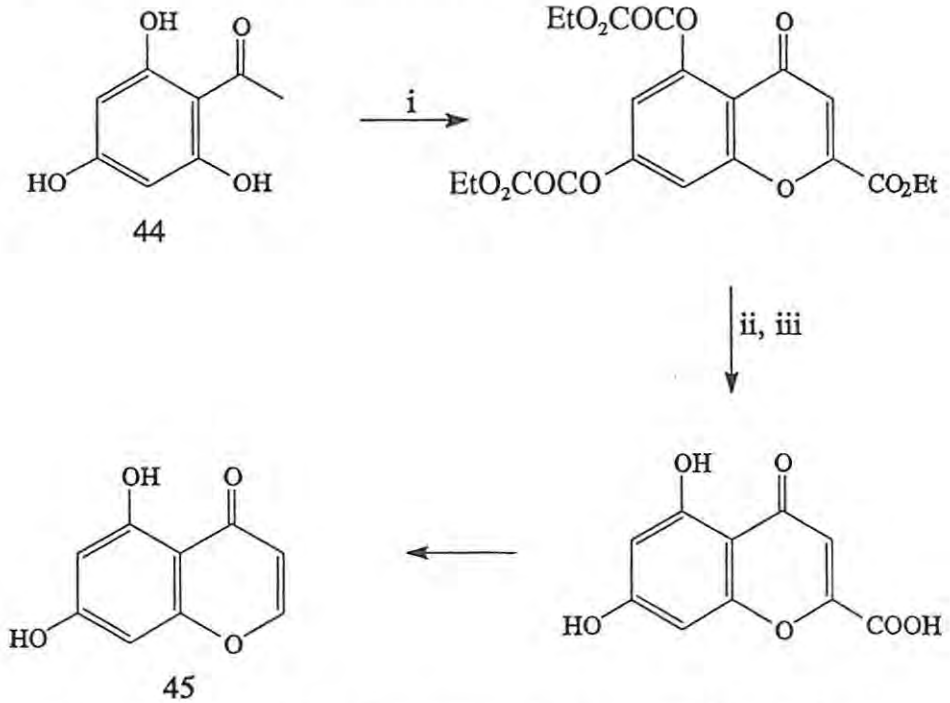
42 43

R = various substituents

Reagents: i) DMF, BF_3-OEt_2, $MeSO_2Cl$

Scheme 9

5,7-Dihydroxychromone (**45**),[33] a flavanoid decomposition product found in some plant extracts, is a germination and growth inhibitor that has been prepared by condensation of 2,4,6-trihydroxyacetophenone monohydrate (**44**) with ethyl oxalyl chloride, followed by acidification and decarboxylation (**Scheme 10**).



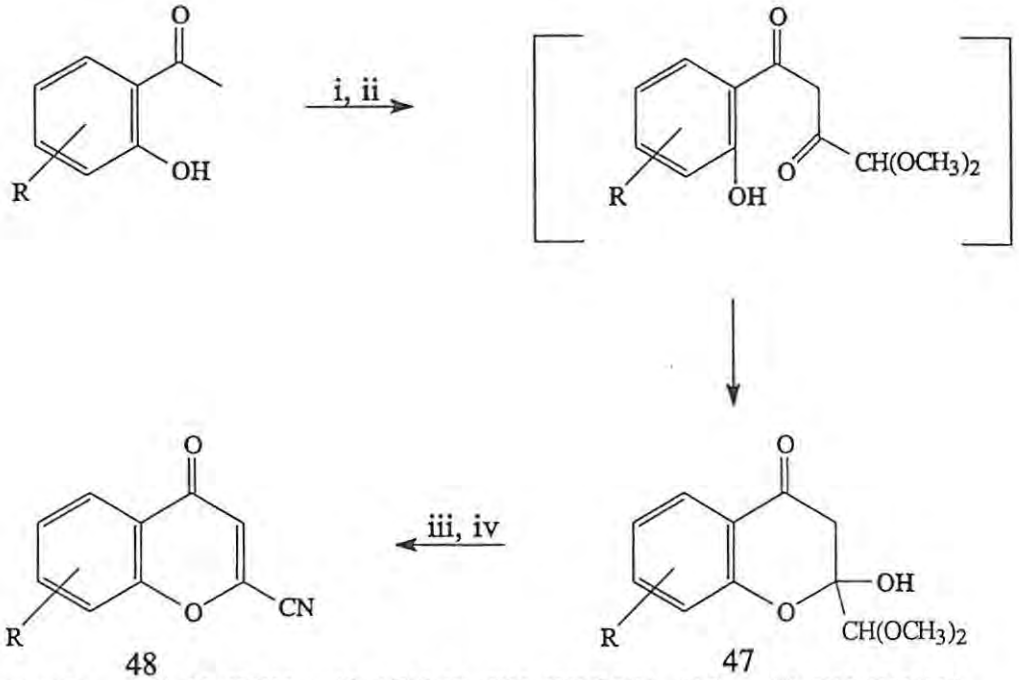
44 45

Reagents: i) EtOOCCOCl, pyridine; ii) OH^-; iii) H^+; iv) heat

Scheme 10

Chromones have also been prepared by dehydrogenation reactions, *eg.* chromanones are dehydrogenated to chromones in high yields, by use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[34] The use of active manganese dioxide in a solvent like benzene, chloroform, or acetone, failed to effect dehydrogenation and, in all cases, the starting chromanone was recovered. Recently,[35] the use of DMSO-I_2-H_2SO_4 or DMSO-I_2 for dehydrogenation of chromanones to the corresponding chromones was reported.[35]

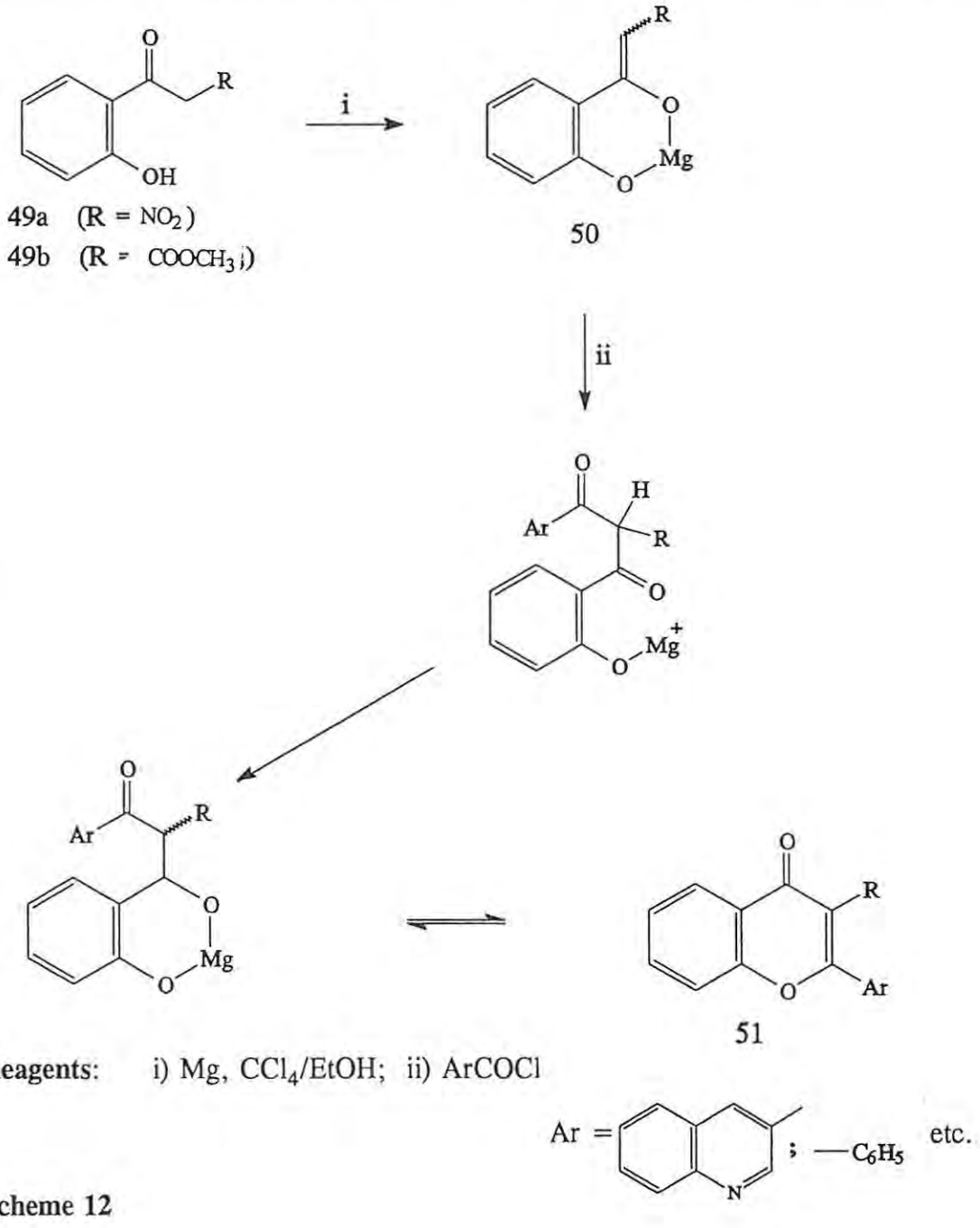
Chromone-2-carbonitriles (**48**), key intermediates in the synthesis of active 2-(tetrazol-5-yl) chromones have been synthesized in high yields (*ca.* 88%) as outlined in **Scheme 11.** Treatment of 2-hydroxyacetophenone with sodium methoxide and methyl dimethoxyacetate (**46**), followed by sequential one-flask reactions with acidic methanol, aqueous hydroxylamine hydrochloride under reflux, and trifluoroacetic anhydride/pyridine at room temperature afforded the 2-cyano products (**48**).[36]



Reagents: i) $NaOCH_3$; ii) $(CH_3O)_2CH\text{-}COOCH_3$ (**46**); iii) CH_3OH/H^+; iv) $NH_2OH.HCl/H_2O$; v) $(CF_3\text{-}CO)_2O$/pyridine

Scheme 11

2-Aryl-3-substituted chromones (**51**) have been prepared from 2-hydroxy-α-nitro-acetophenones (**49a**) and 2-hydroxy-α-(methoxycarbonyl)acetophenones (**49b**) by using magnesium chelates (**Scheme 12**).[37] Treatment of the substrates (**49**) with magnesium ethoxide gave the magnesium chelates (**50**), which were then treated with an acid chloride to effect C-acylation of the magnesium enolates in non-polar solvents.[37] This method avoids preformed flavones as well as the troublesome dehydrogenations of 3-substituted flavanones.



49a (R = NO_2)
49b (R = $COOCH_3$)

50

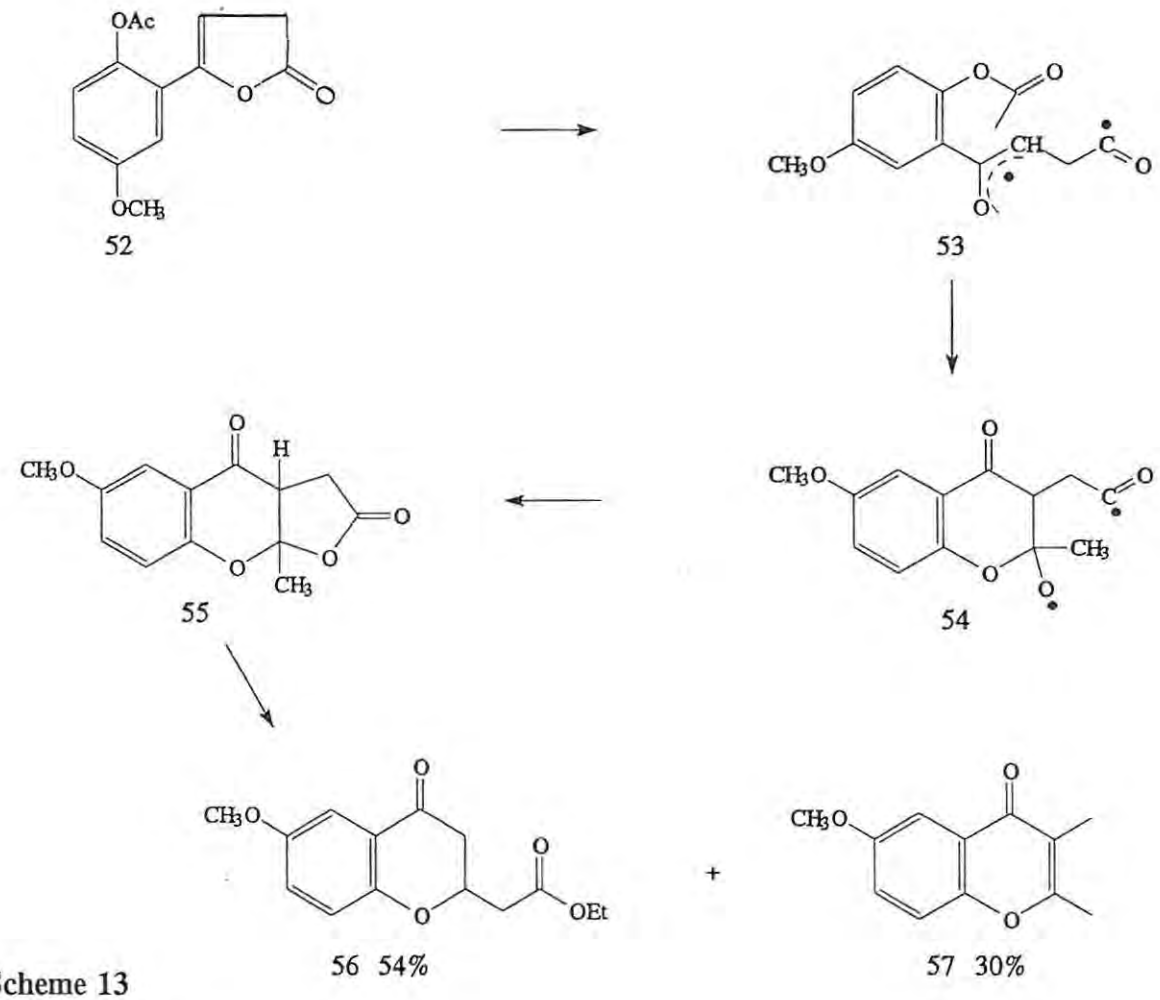
51

Reagents: i) Mg, CCl_4/EtOH; ii) ArCOCl

Ar = ; $-C_6H_5$ etc.

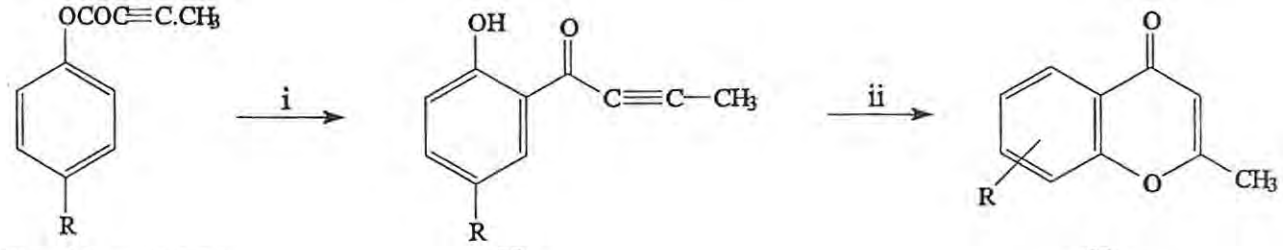
Scheme 12

The chromones (**56**) and (**57**) have been obtained by irradiation of benzene or ethanol solutions of 5-(2-acetoxy-5-methoxyphenyl)-2(3*H*)furanone (**52**) (**Scheme 13**).[38] The formation of the chromone may be explained by assuming the cleavage of the lactonic O-CO bond in the intermediate (**55**) to be also the primary photochemical step in *O*-acetoxyaryl furanones. The presence of the *O*-acetoxy group changes the fate of (**53**); the initially formed diradical being converted into diradical (**54**) rather than being decarboxylated to give an aryl vinyl ketone. The final products (**56**) and (**57**) are connected to the diradical (**54**), *via* the common intermediate (**55**), formed from (**54**). Chromone (**56**) is obtained from chromanone (**55**) by a solvolytic process, followed by elimination. When benzene is used as a solvent, photodecarboxylation and rearrangement occurs to give chromone (**57**).



Scheme 13

Irradiation of the *p*-methoxyphenyl (**58a**) and *p*-methylphenyl esters (**58b**) of 2-butynoic acid, affords the corresponding photo-Fries products (**59a**) and (**59b**), which can be readily cyclized to the chromones (**60**) under basic or acidic conditions (**Scheme 14**).[39]



58a (R = OCH_3)
58b (R = CH_3)

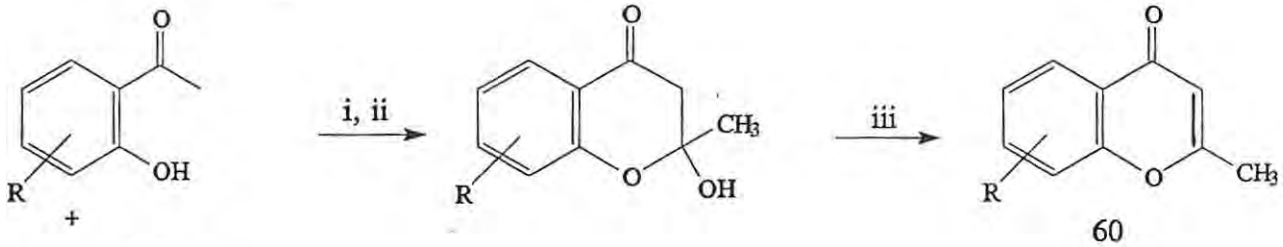
59

60

Reagents: i) hν; ii) PTSA or K_2CO_3

Scheme 14

2-Methylchromones (**60**) [including khellin (**23**)] have been synthesized in high yield by the reaction of *t*-butyl lithioacetate (**61**) with various polysubstituted *o*-hydroxyacetophenones and subsequent acid-catalysed dehydration of the resulting hemiacetals (**Scheme 15**).[40]



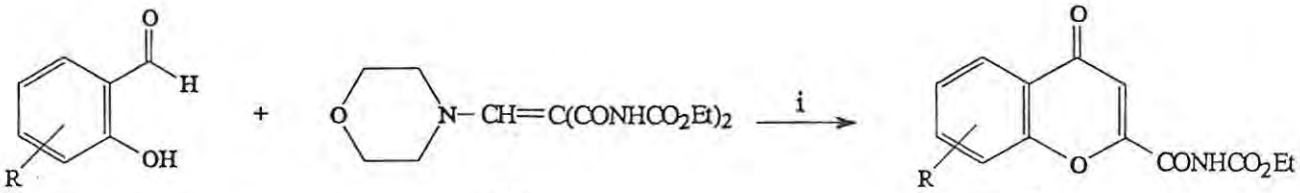
$LiCH_2COO^tBu$
61

60

Reagents: i) Toluene/100°C; ii) sat. aq. NaCl; ii) 20% HCl/MeOH, < 10 min

Scheme 15

Substituted chromones (**64**) are rapidly produced in high yield (> 90%) by reacting salicylaldehyde (**62**) and the enamine (**63**), in ethanol (**Scheme 16**).[41]

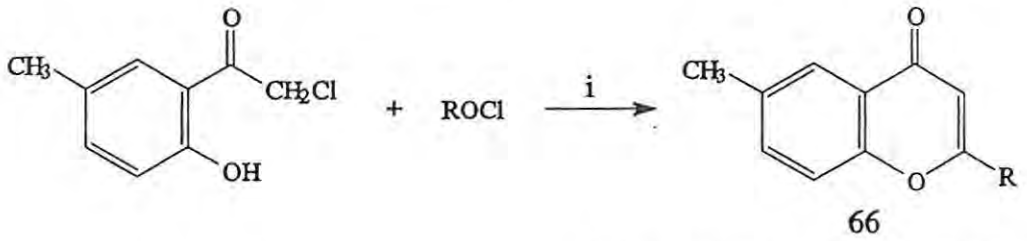


63 64

Reagents: i) morpholine/EtOH

Scheme 16

A base-free intramolecular Wittig reaction provides a convenient one-pot synthesis of chromones (**66**), as shown in **Scheme 17**.[42]



66

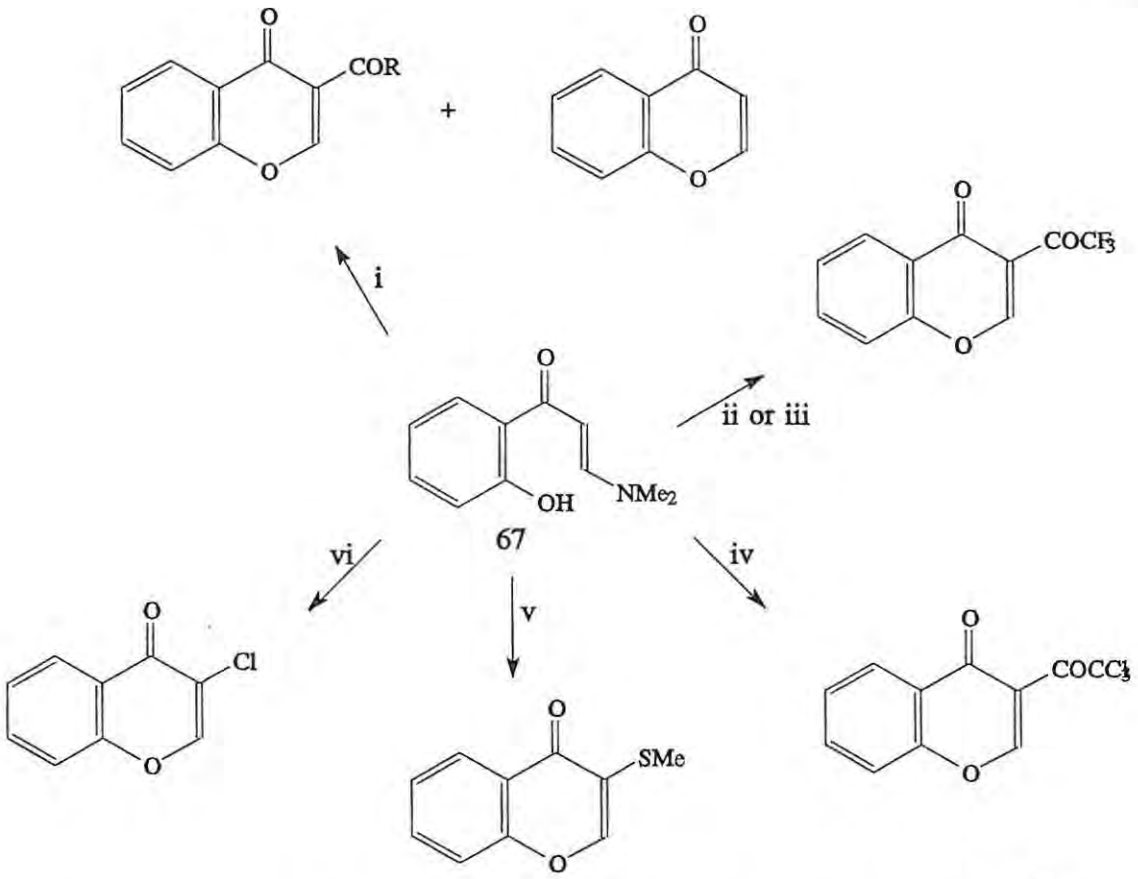
R = Me, CO_2Et, Ph, 4-$MeOC_6H_4$ and cyclopropyl

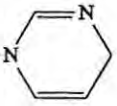
Reagents: i) Ph_3P/toluene, reflux

Scheme 17

3-Substituted chromones are important natural products and some are medicinally useful, and have recently been synthesized from the enaminoketone (**67**), as shown in **Scheme 18**.[43] Thus, the enaminoketone (acrylamide) (**67**) may be used for the synthesis of 3-chloro, 3-acetyl, 3-trifluoroacetyl, 3-trichloroacetyl, and 3-methylthiochromones in high yields (*ca.* 62 - 93%).

Crown ethers containing the chromone moiety (**69**) have recently been synthesized by condensation of 4′-formylbenzo-15-crown-5 (**68**) with acetophenone in DMF in the presence of KOH, followed by cyclization of the chalcones in the presence of a catalytic amount of I_2 in DMSO (**Scheme 19**).[44]

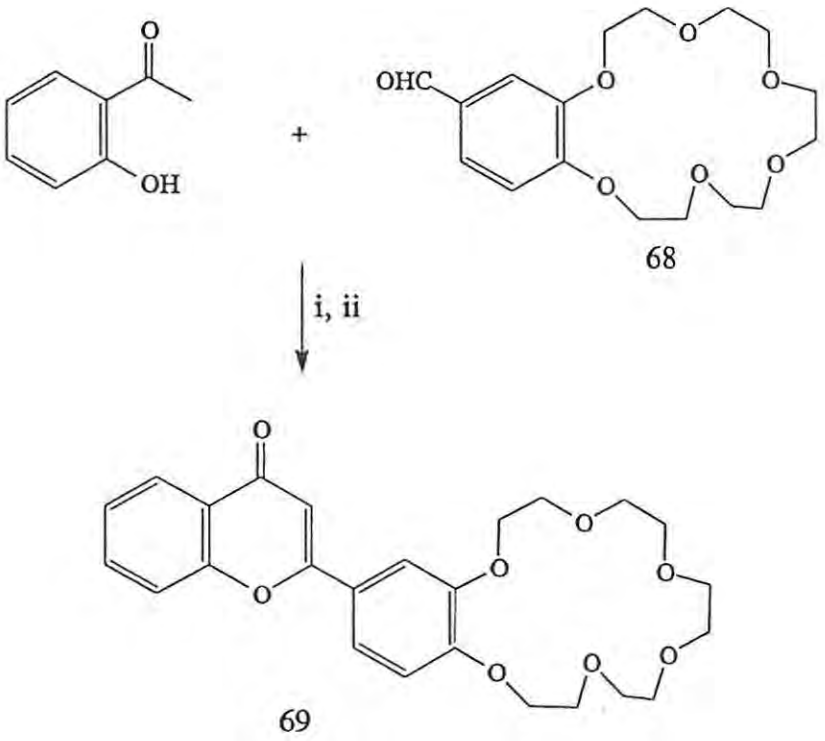


Reagents: i) $(RCO)_2O$; R = Me, Et, *n*-Pr; ii) $(CF_3CO)_2O$; iii) 

iv) $(CCl_3CO)_2O$; v) $Me_2S^+SMe\ BF_4^-$, dry DMF, r.t., 15 min;
vi) Cl-I, dry MeCN, r.t., 30 min

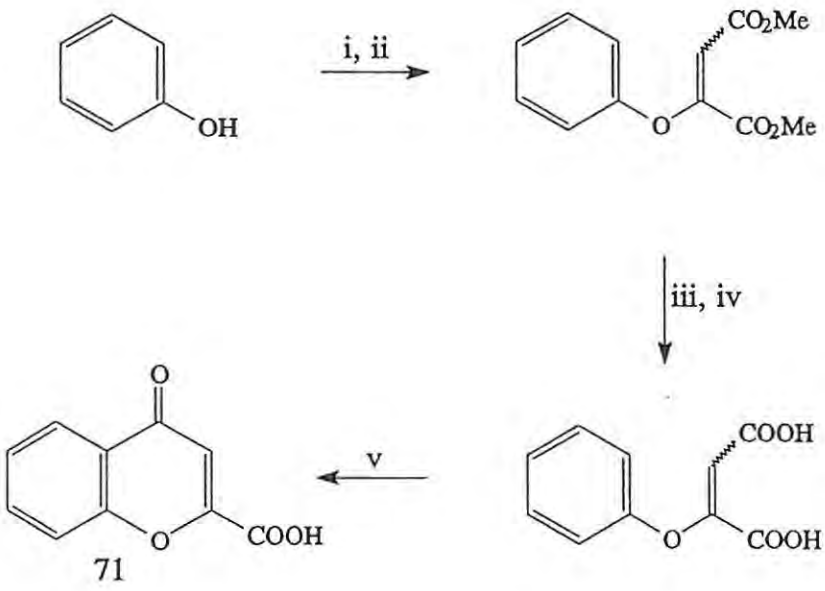
Scheme 18

The addition of substituted phenols to dimethyl acetylenedicarboxylate (**70**) has been recently reported as a versatile high-yield step in a three-step synthesis of chromone-2-carboxylic acids (**71**). Substituted phenols are deprotonated by triethylamine followed by addition to dimethyl acetylenedicarboxylate (**70**) under mild conditions, the reaction tolerating a range of functional groups on the phenol. The reaction is not stereospecific in the sense that both fumarate and maleate amyloxy products can be cyclized to chromones without contamination by isomeric coumarins (**Scheme 20**).[26] This reaction may be useful as a general synthesis of chromones.



Reagents: i) DMF; ii) I_2, DMSO

Scheme 19



Reagents: i) Et_3N/Et_2O; ii) $MeO_2CC{\equiv}CCO_2Me$ (**70**); iii) OH^-/H_2O; iv) H^+/H_2O; v) $AcCl/H_2SO_4$

Scheme 20

1.1.4 Reactivity of chromone derivatives

Chromones may react with nucleophiles, electrophiles, or other reagents to give various derivatives as discussed below with the aid of illustrative examples in each case dealt with separately.

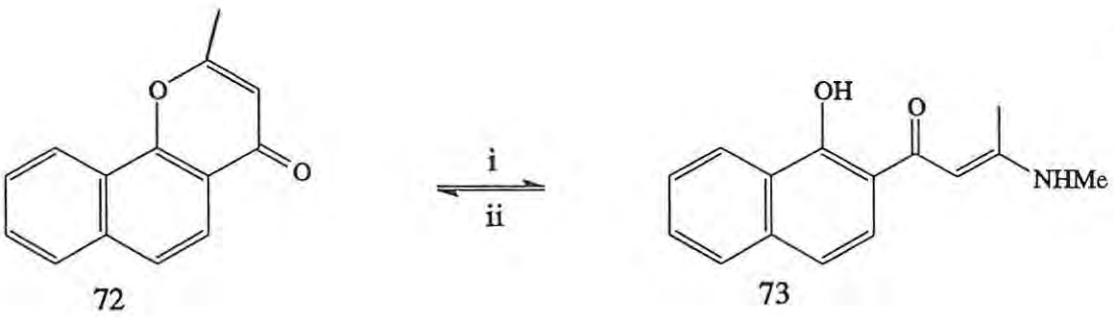
I. Reaction with Nucleophiles

Chromones readily undergo nucleophilic cleavage at the C-2 position. Different kinds of nitrogen, oxygen and carbon nucleophiles have been used for the ring-opening or ring-transformation, as will be shown in various examples below.

a) Reactions with nitrogen nucleophiles

The pyran-4-one ring in chromone (**72**) is cleaved by both primary and secondary amines to yield enamines (**73**), which may be recyclized to the starting material by treatment with acid (**Scheme 21**).[45]

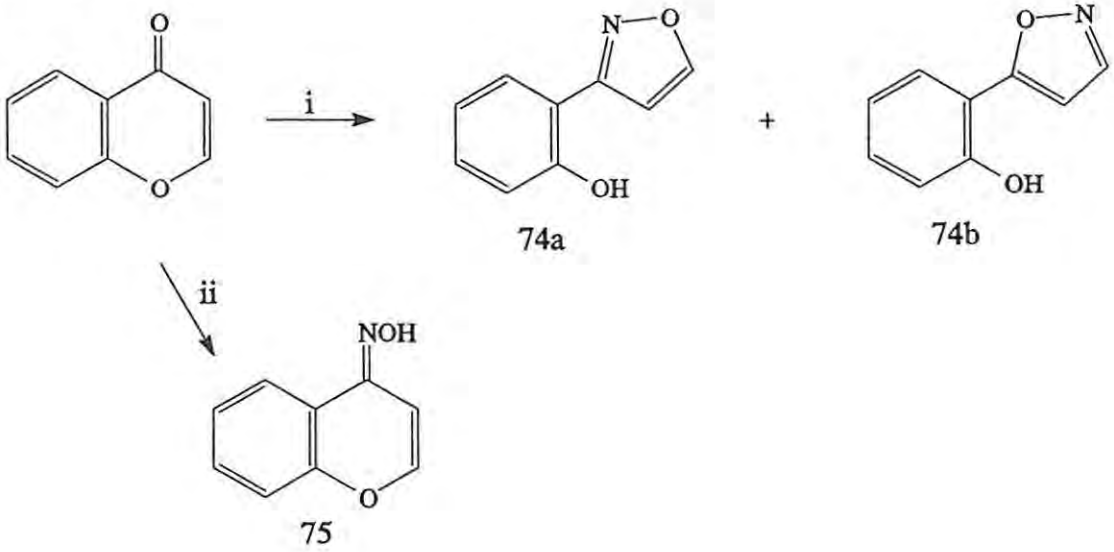
When chromone itself is treated with hydroxylamine hydrochloride in ethanol, a mixture of isomeric isoxazoles (**74a**) and (**74b**) is formed, the latter being the major product. The two isomers may be distinguished by mass spectrometry. However, under anhydrous conditions, chromone oxime (**75**) is formed (**Scheme 22**).[45,46]



72 73

Reagents: i) $MeNH_2$; ii) H^+

Scheme 21

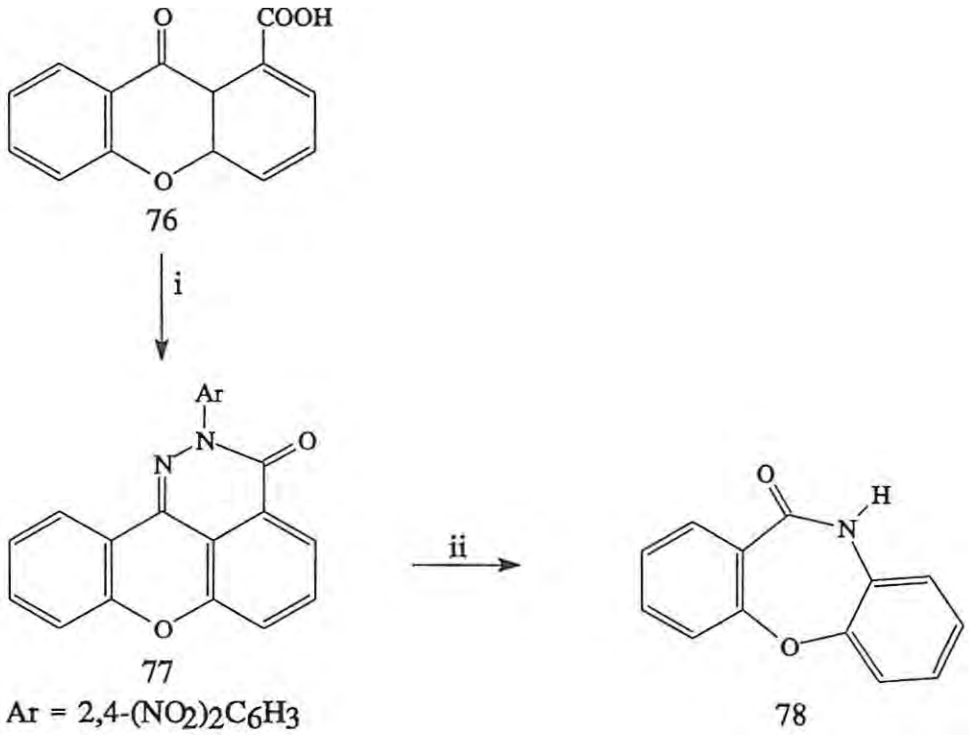


74a 74b 75

Reagents: i) $NH_2OH.HCl$; ii) anhyd. $NH_2OH.HCl$

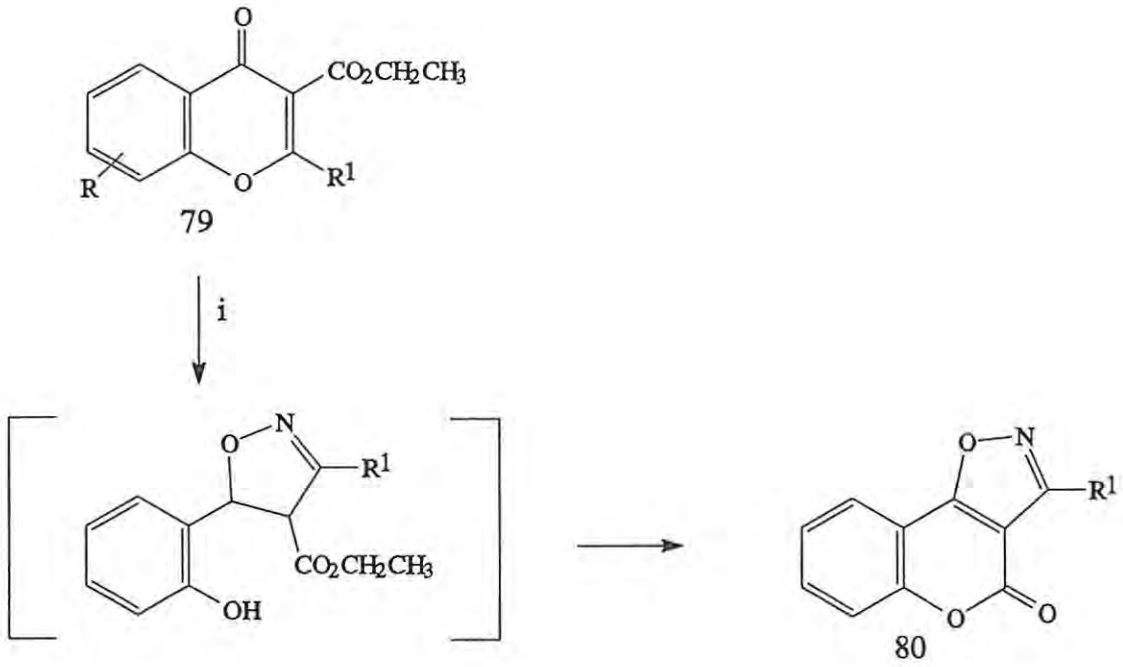
Scheme 22

Treatment of xanthone-1-carboxylic acid (**76**) with 2,4-dinitrophenylhydrazine gives the pyridazinone (**77**), probably *via* the hydrazone which, when reacted with phosphorus pentachloride, undergoes a Beckmann rearrangement to afford the amide (**78**) (**Scheme 23**).[45] Treatment of chromone-3-carboxylic esters (**79**) with hydroxylamine hydrochloride in refluxing acetic acid yields fused isoxazoles (**80**). These compounds (**80**) are formed as a result of nucleophilic attack at the C-2 position of the chromone ring, followed by ring opening, and subsequent cyclisation in acidic medium (**Scheme 24**).[47]



Reagents: i) $ArNHNH_2$, H^+, EtOH; ii) PCl_5

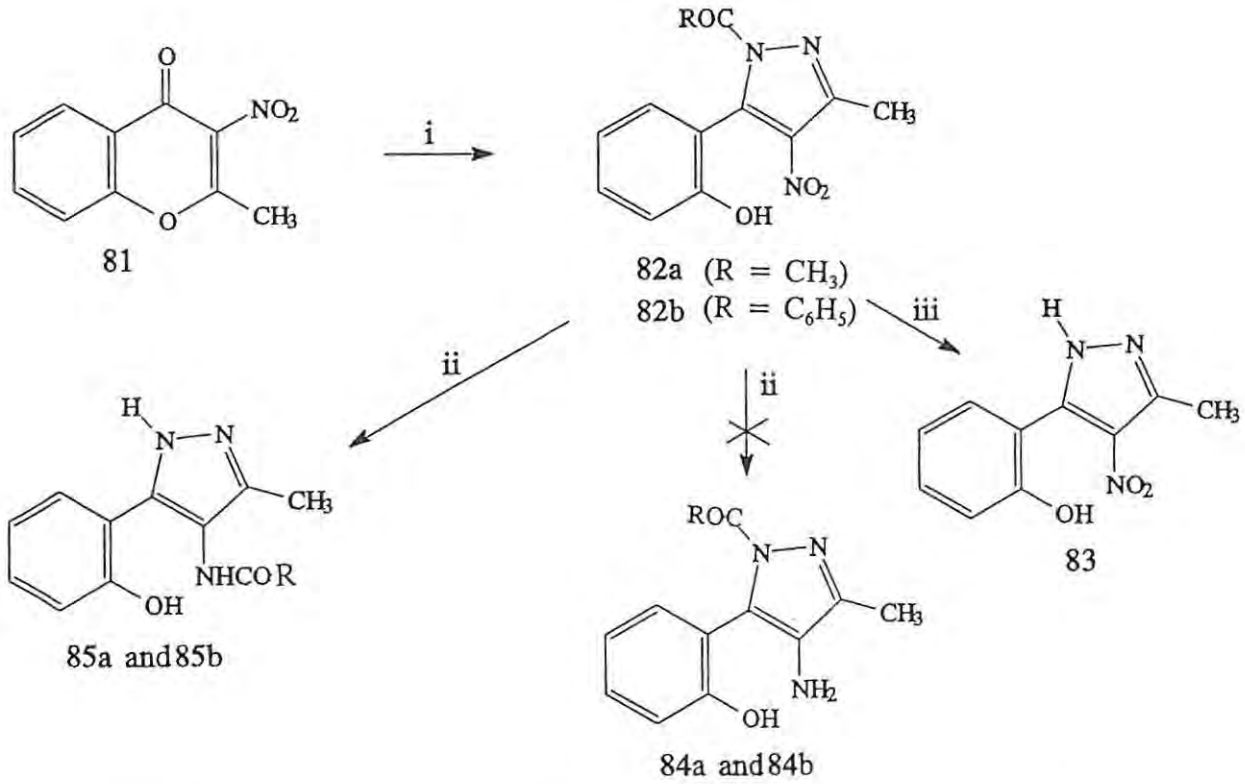
Scheme 23



Reagents: i) $NH_2OH.HCl$, CH_3COOH

Scheme 24

Sometimes, unexpected rearrangements are observed as illustrated by the work of Takagi *et al.*.[48] Treatment of 3-nitro-2-methylchromone (**81**) with acetic acid hydrazide or benzoic acid hydrazide in ethanol at room temperature gives 1-acetyl- or 1-benzyl-5-(2-hydroxyphenyl)-3-methyl-4-nitropyrazole (**82a**) and (**82b**), respectively.[48] Hydrolyses of these products yields 3(5)-(2-hydroxyphenyl)-5(3)-methyl-4-nitropyrazole (**83**). However, catalytic hydrogenation of (**82a**) and (**82b**) does not give the corresponding 1-acyl-4-aminopyrazoles (**84a**) and (**84b**) as expected, but rather the 4-acylamino-3(5)-(2-hydroxyphenyl)-5(3)-methylpyrazoles (**85a**) and (**85b**) which are formed by migration of the acyl group during reduction. (**Scheme 25**).[48]

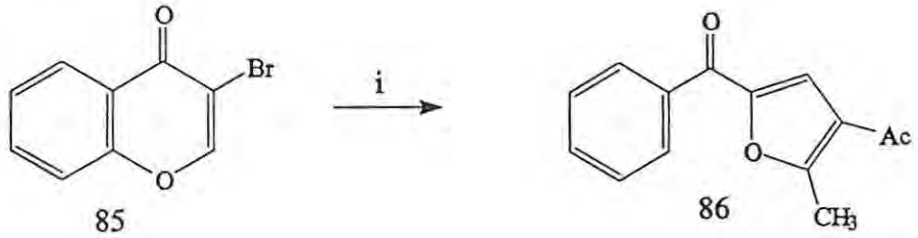


Reagents: i) $RCONHNH_2$ (R = CH_3, C_6H_5); ii) H_2, Pd-C; iii) KOH

Scheme 25

b) Reactions with carbon nucleophiles

Carbon nucleophiles react with chromones at position C-2 or C-4, resulting in cleavage or ring transformation.[45] The pyran-4-one of 3-bromochromone (**85**) is, for example, cleaved by an acidic methylene in the presence of DBN or DBU to form the furan (**86**) (**Scheme 26**).[45,46]

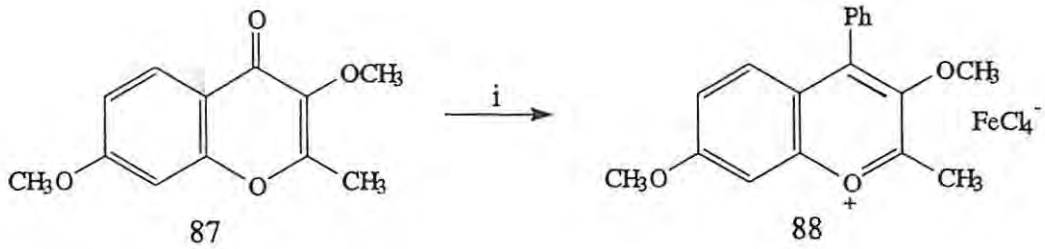


85 86

Reagents: i) CH_2Ac_2, DBN/DBU, 18°C

Scheme 26

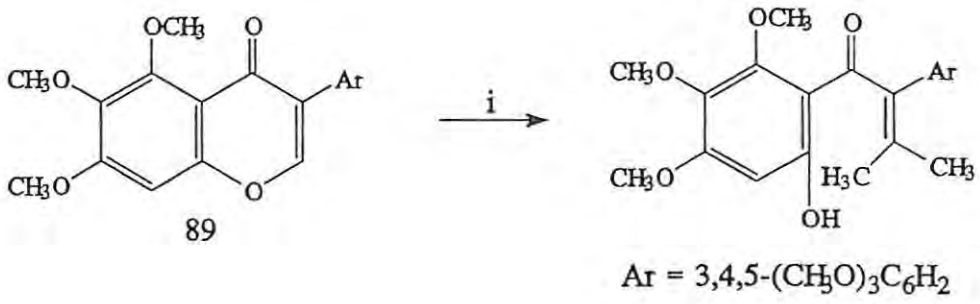
The carbonyl group of chromones is attacked by Grignard reagents to give the benzopyrylium salts (**88**), illustrated for 3,7-dimethoxy-2-methylchromone (**87**) in (**Scheme 27**). The isoflavone (**89**), on the other hand, is cleaved by a Grignard reagent in the presence of copper (II) chloride (**Scheme 28**).[45]



87 88

Reagents: PhMgBr, H^+, $FeCl_3$

Scheme 27



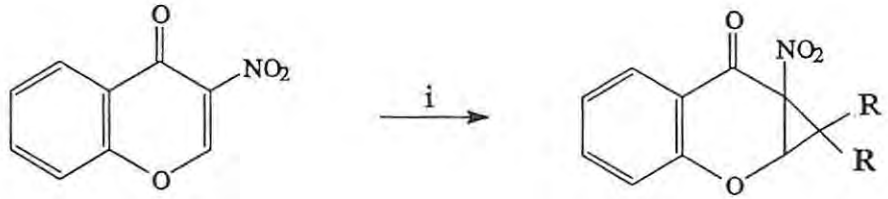
89

Ar = 3,4,5-$(CH_3O)_3C_6H_2$

Reagents: i) MeMgI, $CuCl_2$

Scheme 28

The reaction of diazomethane with 3-nitrochromone (**90**) under mild conditions yields cyclopropabenzopyran (**91**) (**Scheme 29**).[49]

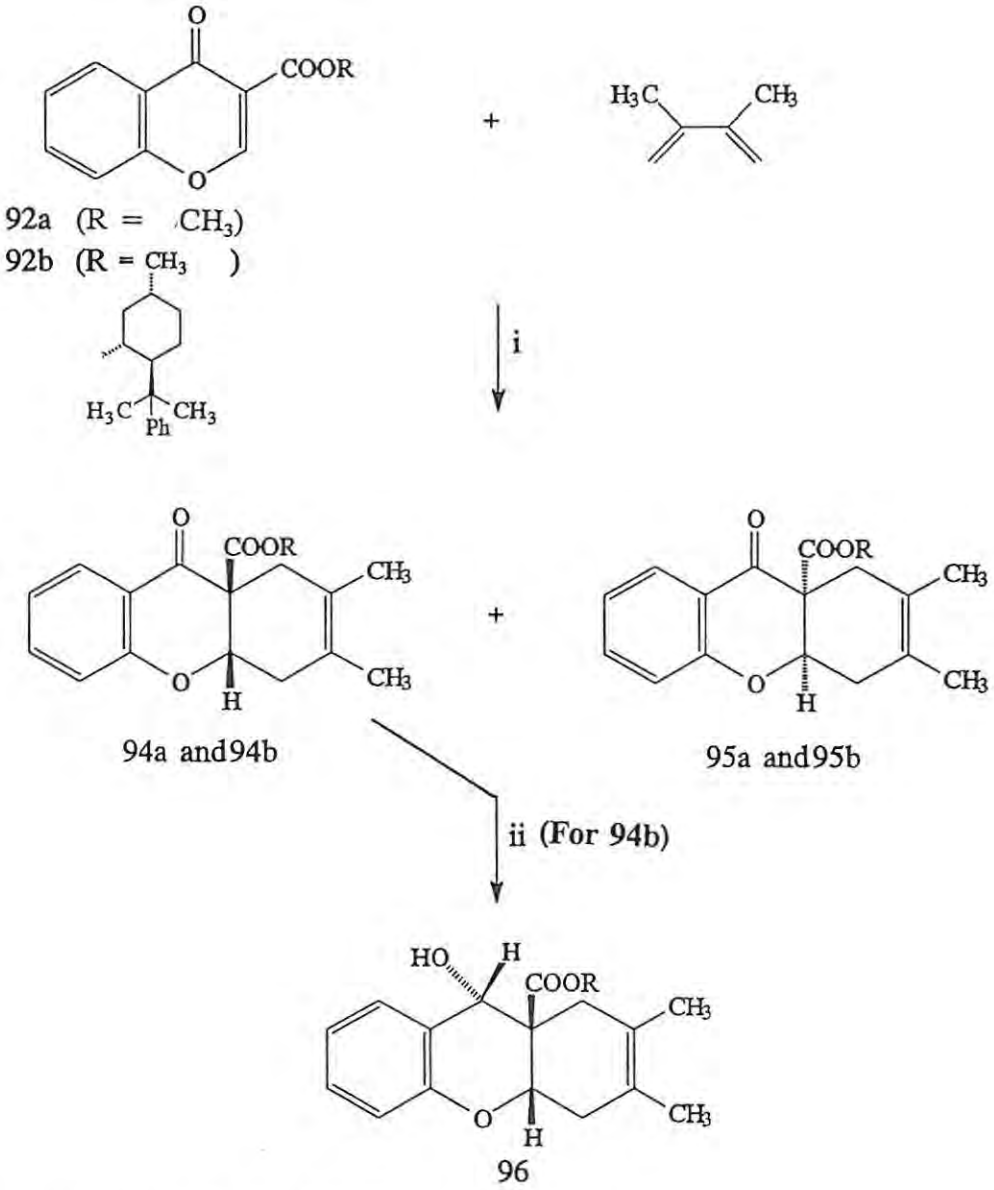


90 91

Reagents: i) R_2CN_2

Scheme 29

Ohkata *et al.*[50] have recently described diastereofacial selectivity in the Diels-Alder reactions of pyran-4-one derivatives. Thus, the reactions of chromones (**92a** - **92b**) with 2,3-dimethyl-1,3-butadiene (**93**) in the presence of $ZnCl_2$ in CH_2Cl_2 afforded the [4 + 2] adducts (**94a** - **94b**) and (**95a** - **95b**) (**Scheme 30**). Reduction of (**94b**) with sodium borohydride gave the hydroxy ester (**96**) stereoselectively in 72% yield. The stereochemistry of the hydroxy group was determined by means of a NOESY NMR experiment.[50]



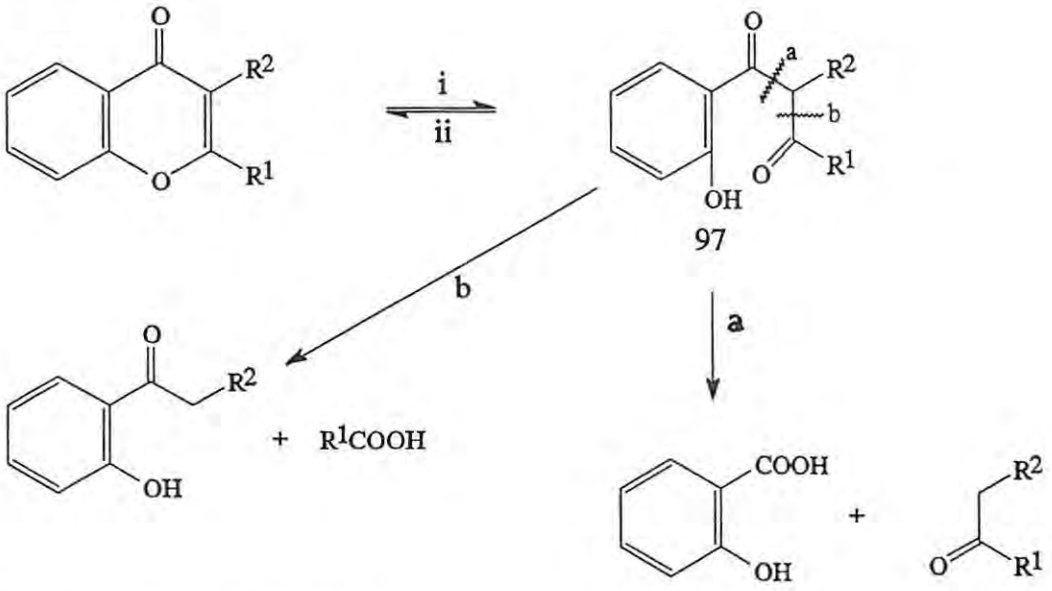
Reagents: i) $ZnCl_2$, CH_2Cl_2/r.t.; ii) $NaBH_4$

Scheme 30

c) Reactions with oxygen nucleophiles

The pyran-4-one ring of chromones is cleaved by aqueous alkali, giving the salt of the ß-diketone (**97**) which may recyclize on acidification (**Scheme 31**).[5,45] However, prolonged rigorous treatment with the alkali may lead to carbon-carbon bond cleavage of the ß-diketone

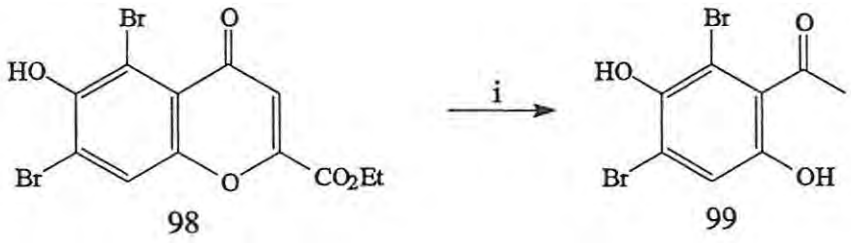
(**97**) to give a mixture of products, the distribution depending on the reaction conditions. This hydrolytic cleavage has been used for structural elucidation in chromones, flavones and isoflavones.



Reagents: i) OH^-; ii) H^+

Scheme 31

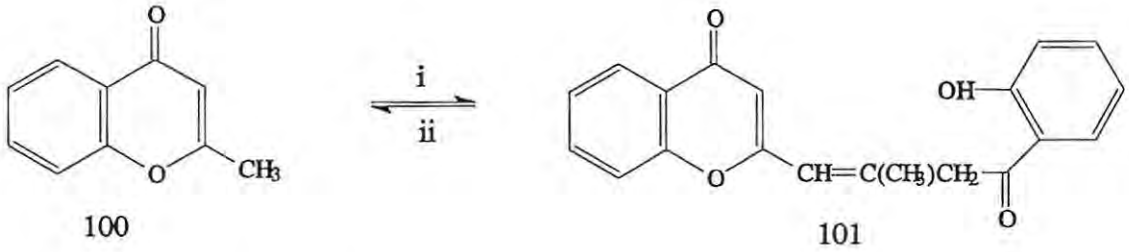
When ethyl 5,7-dibromo-6-hydroxychromone-2-carboxylate (**98**) is heated under reflux with aqueous sodium hydroxide, ring-opening occurs to give 4,6-dibromo-2,5-dihydroxy-acetophenone (**99**) (**Scheme 32**).[45] Sodium alkoxides may also react with chromones; *eg.* treatment of 2-methylchromone (**100**) with sodium ethoxide cleaves the pyran-4-one ring to give a dimeric product (**101**) in 50% yield, which may be reversed to the starting material (**100**) on treatment with acid (**Scheme 33**).[45] Bubbling oxygen through a solution of flavone (**102**) yields aroylsalicylic acid (**103**) under mildly alkaline conditions,[45,51] while alkaline hydrolysis of (**103**) gives 4-hydroxybenzoic acid (**104**) and salicylic acid(**105**) in quantitative yield. The presence of certain functional or leaving groups in a side chain may, however, alter the course of the reaction.



98 99

Reagents: i) aq. NaOH

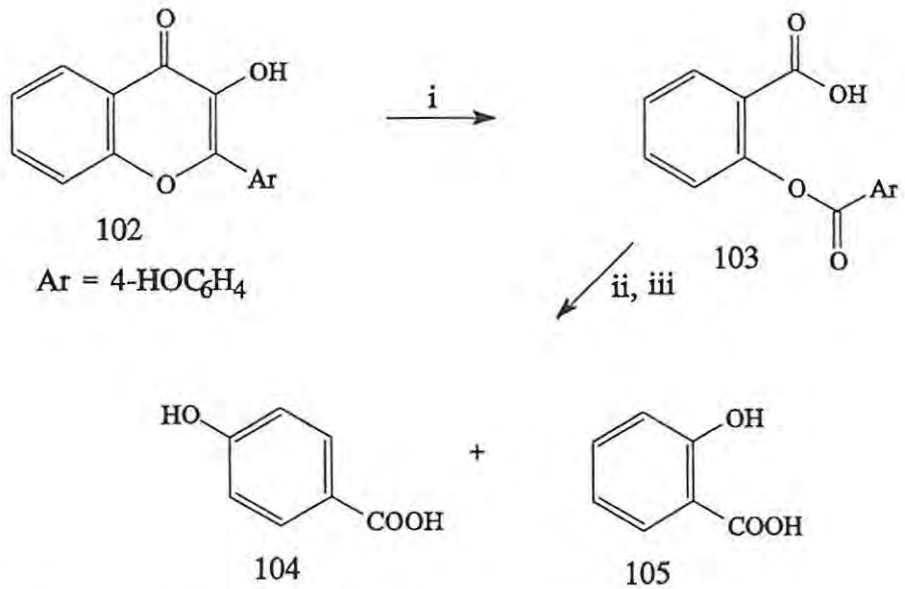
Scheme 32



100 101

Reagents: i) EtO^-, 18°C; ii) H^+

Scheme 33



102 103 104 105

Ar = 4-HOC_6H_4

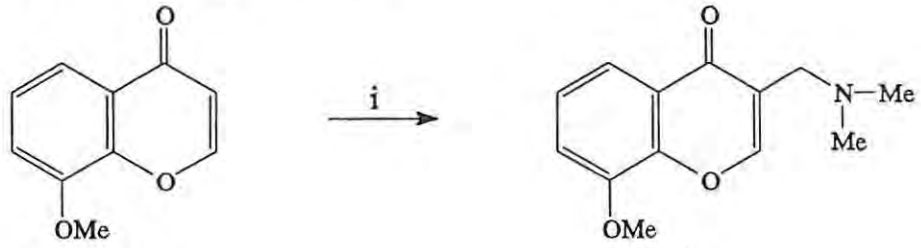
Reagents: i) K-^{t}butoxide /DMF, O_2, r.t.; ii) NaOH; iii) H^+

Scheme 34

II Reactions with Electrophiles

Chromones are relatively resistant to attack by electrophiles, particularly since electrophilic reagents are often strongly acidic (*eg.* nitric-sulphuric acid mixture or sulphuric acid) or produce strong acids during the reaction (*eg.* halogens) and, hence, are likely to protonate the pyran-4-one ring and thus inhibit further attack by the electrophile.[45]

Aminomethylation of 8-methoxychromone (**105**), under Mannich reaction conditions, is usually achieved under less acidic conditions and this may explain the formation of 3-aminomethylchromone (**106**) (**Scheme 35**).[45] This reaction is, however, inhibited by a methyl substituent at position 2.

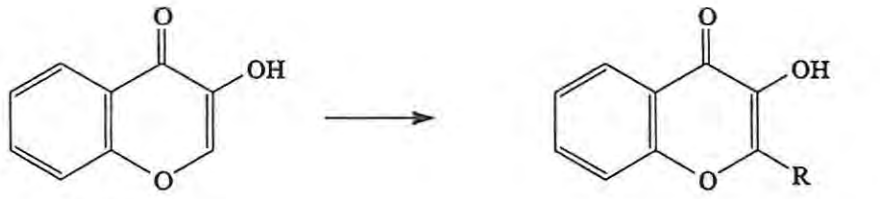


105 106

Reagents: i) HCHO, $HNMe_2$, AcOH

Scheme 35

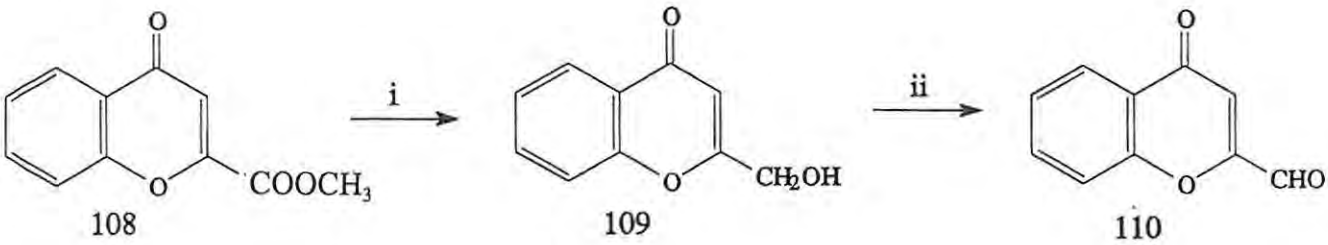
3-Hydroxychromone (**107**) may be brominated, nitrated and aminated at C-2, a position usually depleted of electrons (**Scheme 36**).[45]



Scheme 36

III Other reactions of chromones

2-Formylchromone (**110**) may be conveniently prepared from methyl chromone-2-carboxylate (**108**) by the selective reduction of the ester group with sodium borohydride followed by oxidation of the resultant 2-hydroxymethylchromone (**109**) with manganese dioxide (**Scheme 37**).[52]

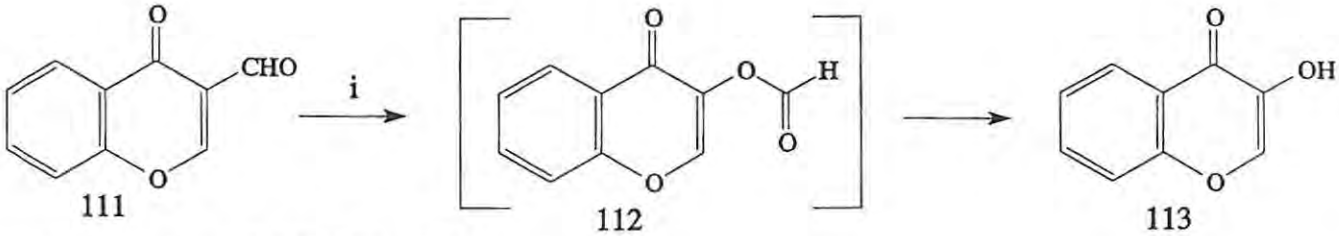


Reagents: i) $NaBH_4/CH_3OH$; ii) $MnO_2/CHCl_3$

Scheme 37

Baeyer-Villiger oxidation of 3-formylchromone (**111**) using *m*-chloroperbenzoic acid (MCPBA) in boiling dichloromethane has been reported to afford 3-hydroxychromones (**113**) in good yield, compared to other existing methods. In these reactions, the intermediate (**112**) could not be isolated (**Scheme 38**). 3-Hydroxychromones (**113**) have also been prepared by

simply oxidizing 2,3-unsubstituted chromones with *m*-chloroperbenzoic acid (MCPBA) in dry benzene.[54]



111 112 113

Reagents: i) MCPBA, CH_2Cl_2

Scheme 38

1.2 Aims of the present study

This research project has been mainly concerned with the synthesis and spectroscopic studies of chromone (4-oxo-4*H*-benzopyran) derivatives, and completion of work initiated in an MSc program. The specific aims of the study are the following:-

1.2.1 The synthesis of selected series of chromone derivatives were required for various physical organic studies; these systems were to include:- chromone-2-carboxylic acids and amides; chromone-derived acrylamides; 2(*N,N*-dialkylamino)chromones; and naphthopyran-4-one analogues.

1.2.2 Investigation of the mass fragmentation patterns exhibited by 2-(*N,N*-dialkylamino)chromones, 2-(*N,N*-dimethylamino)naphthopyran-4-one and chromone-derived acrylamides.

1.2.3 Dynamic nuclear magnetic resonance studies to explore the influence of substituents on rotational barriers in 2-aminochromones and chromone-derived acrylamides.

1.2.4 An investigation of substituent effects on the basicity (pK_b) of 2-aminochromones and the acidity (pK_a) of chromone-2-carboxylic acids.

2. RESULTS AND DISCUSSION

In the research discussed here attention will be given first to the various synthetic approaches followed (Section 2.1) and then to the physical organic investigation, *viz.*, mass spectrometry (Section 2.2.1), dynamic NMR (DNMR) spectroscopy (Section 2.2.2) and pK_a studies (Section 2.3).

2.1 Synthesis of 4*H*-1-benzopyran-4-one derivatives

A number of 4*H*-1-benzopyran-4-one derivatives, both naturally occurring and synthetic, are known for their medicinal use. In this study, a range of 4*H*-1-benzopyran-4-ones and their ring-opened acrylamide derivatives were prepared either directly or indirectly from *o*-hydroxyacetophenone or hydroxyacetonaphthone, methyl salicylates, or ethyl (*N,N*-dialkyl-carbamoyl) ethanoate. These compounds were required for mass spectrometric, DNMR and pK_a studies described in Sections 2.2 and 2.3.

2.1.1 Preparation of *o*-hydroxyacetophenones and 3-hydroxy-2-acetonaphthone

The *o*-hydroxyacetophenones (**125** - **127**) were prepared *via* Fries rearrangement[3] of the corresponding phenyl acetates (**118** - **120**) which, in turn, were obtained by acetylation of the appropriate phenols (**114** - **116**) (**Scheme 39**), as described by Bryan *et al.*.[57] The acetates were heated at high temperatures (*ca.* 175°C) which favour rearrangement to the *o*-hydroxyacetophenones over the *p*-analogues.[58] The Fries rearrangement of 3-nitrophenyl acetate (**121**), using dry nitrobenzene as a solvent at *ca.* 140°C, is known to afford moderate

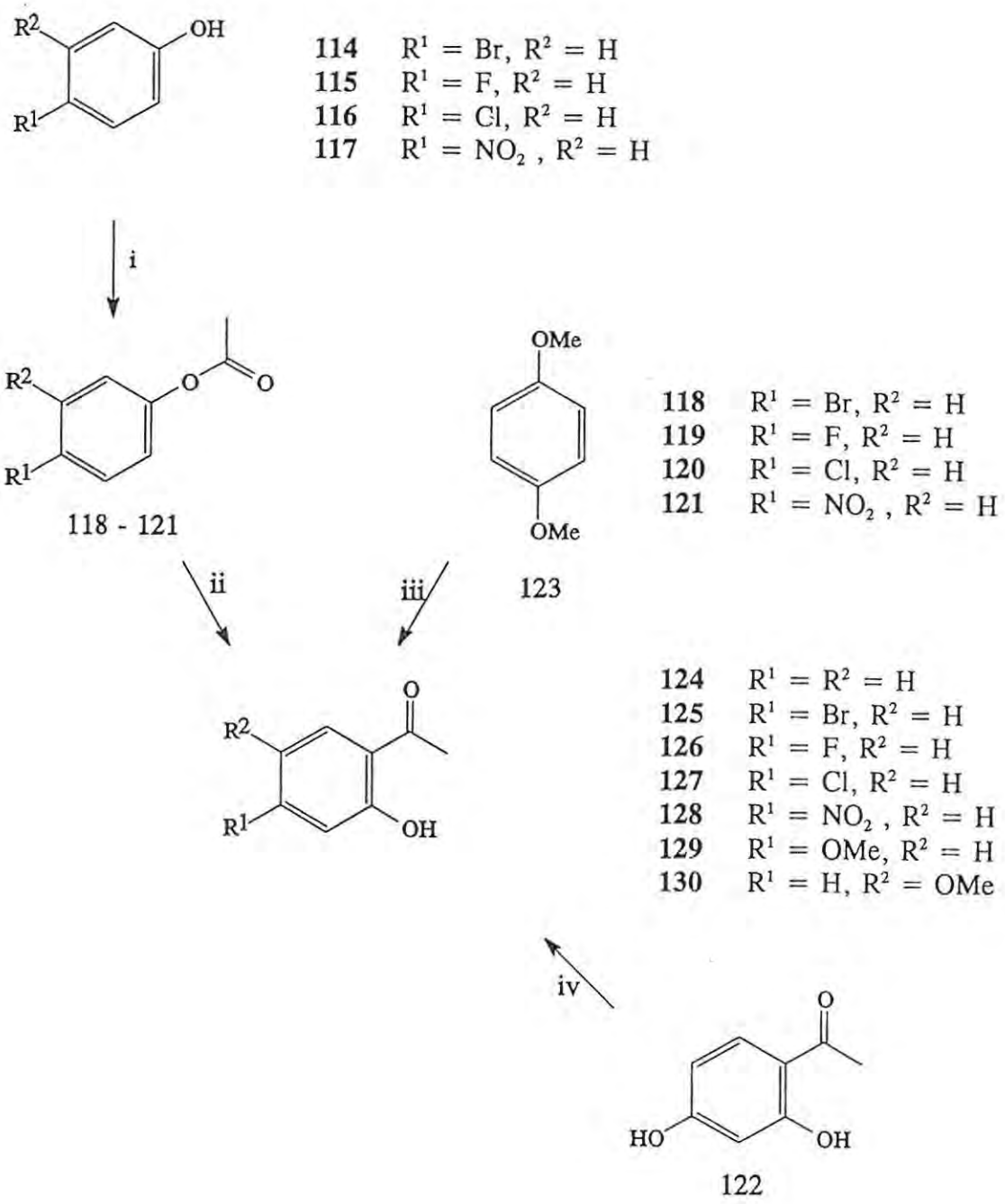
yields of 2-hydroxy-4-nitroacetophenone **128**.[57,59] However, repeated attempts consistently gave 2-hydroxy-4-nitroacetophenone in very low yields (*ca.* 1%).

2-Hydroxy-5-methoxyacetophenone (**130**) was prepared by acylating hydroquinone dimethyl ether (**123**) with acetyl chloride in the presence of anhydrous aluminium trichloride,[69] while 2-hydroxy-4-methoxyacetophenone (**129**) was obtained *via* methylation of resacetophenone (**122**) as shown in **Scheme 39**.[61]

^{1}H NMR and IR spectroscopy were used to distinguish the phenyl acetates from the corresponding hydroxyacetophenones. The acetate methyl singlet resonates at *ca.* 2.25 ppm, while the acetyl methyl signals in the hydroxyacetophenones appear at *ca.* 2.60 ppm. The hydroxyl group may also be used to distinguish the rearrangement products from their precursors, being absent in the starting phenyl acetates but present in the products, as evidenced by both the IR and ^{1}H NMR data.

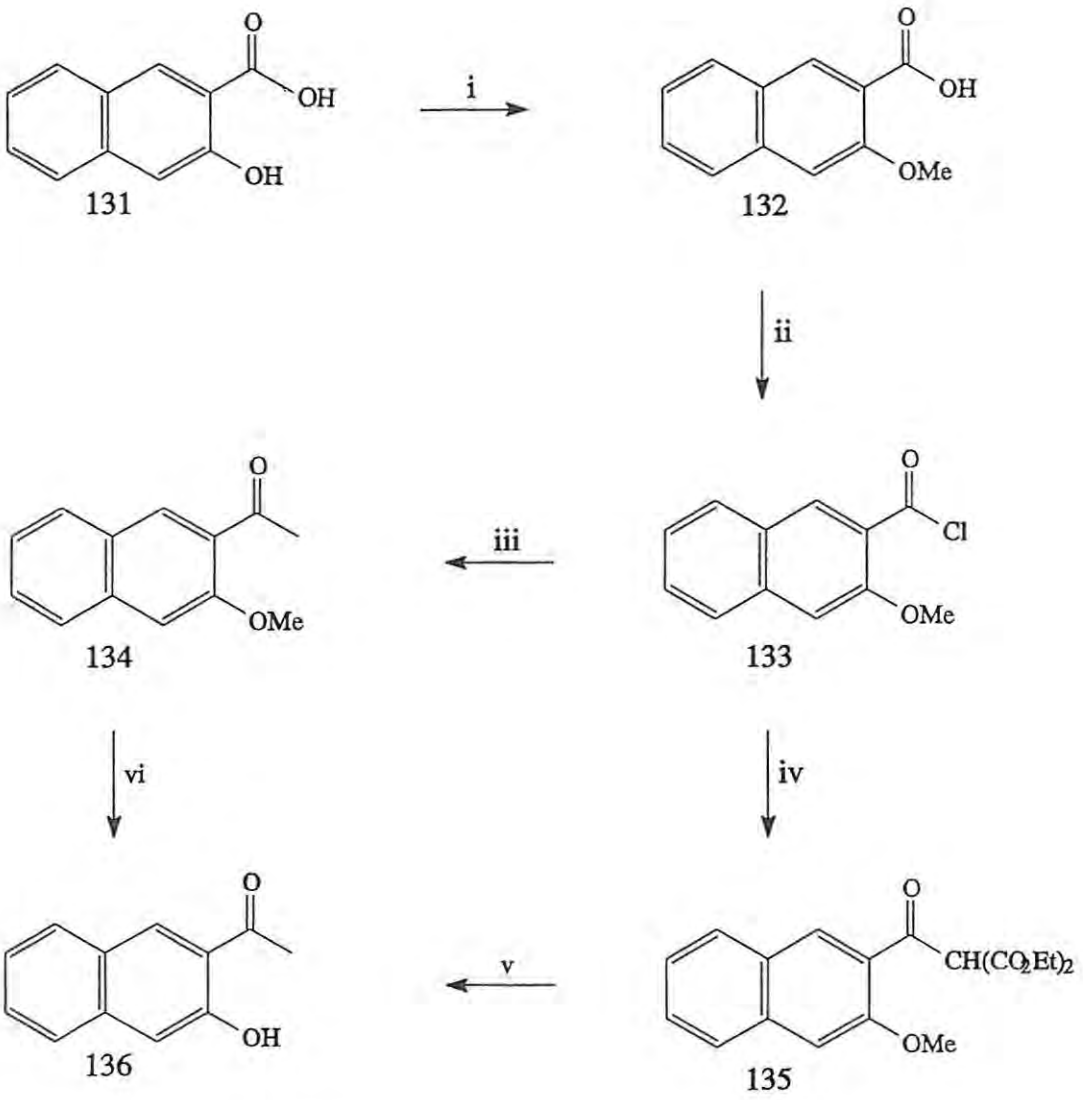
3-Hydroxy-2-acetonaphthone (**136**), which was required as a precursor for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-naphthopyran-4-one (**188**) and ethyl 4-oxo-4*H*-napthopyran-2-carboxylate (**200**), is not commercially available, and consequently was synthesized as indicated in **Scheme 40**. This method involves the initial methylation of the hydroxy group of 3-hydroxy-2-acetonaphthoic acid (**131**) following Schmid and Seiler's procedure[61] prior to treatment with thionyl chloride to afford the acid chloride (**133**). Treatment of this acid chloride with dimethylcadmium[62] [or with ethoxymagnesium malonic ester[63,64], *via* intermediate (**135**)] gave 3-methoxy-2-acetonaphthone (**134**) which, when demethylated with pyridine hydrochloride at high temperature (*ca.* 220°C), afforded 3-hydroxy-2-

acetonaphthone.[62] The conversion of 3-methoxy-2-naphthoic acid (**132**) to 3-hydroxy-2-acetonaphthone (**136**) is evidenced by the disappearance of the methyl singlet at *ca.* 4.15ppm and appearance of the acyl methyl singlet at *ca.* 3.80 ppm (Figure 1).



Reagents: i) aq NaOH-Ac_2O, 0°C; ii) $AlCl_3$, heat; iii) $AlCl_3$, CH_3COCl, heat; iv) Me_2SO_4, dry acetone

Scheme 39

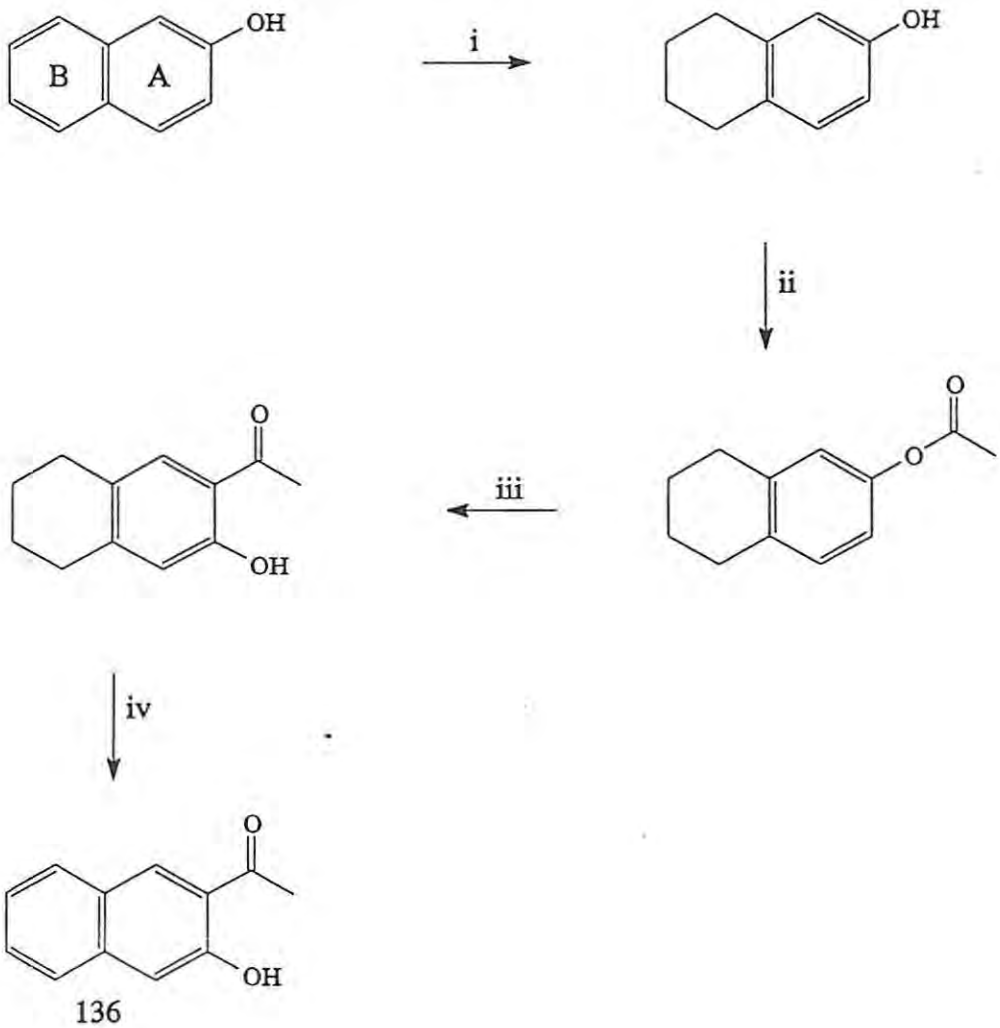


Reagents: i) Me_2SO_4-20% methylated NaOH-acetone-H_2O; ii) $SOCl_2$;
iii) $(CH_3)_2Cd$ or iv) $C_2H_5OMgCH(CO_2C_2H_5)_2$; v) AcOH, H_2SO_4, Δ
vi) pyridine hydrochloride salt, *ca.* 220°C

Scheme 40

An alternative approach to compound (**136**) involves the use of 5,6,7,8-tetrahydro-2-naphthol which, followed by acetylation with acetic anhydride and subsequent Fries rearrangement at 120°C for 13 - 14 hours, favours formation of the *o*-hydroxy product. Finally, dehydrogenation with palladium on carbon in carbon monoxide gives the desired product, as shown in **Scheme 41**. Application of this approach, developed by O'Farrel *et al.*,[65,66]

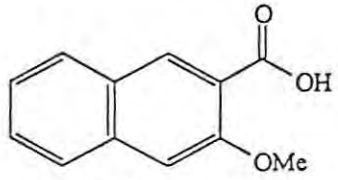
however was not necessary as the required product (**136**) was conveniently obtained as indicated in **Scheme 40.**



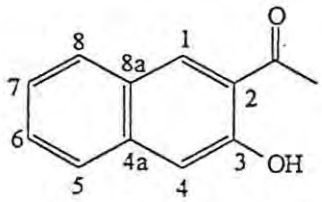
136

Reagents: i) AcOH, Raney nickel catalyst, autoclave 150 - 160°C;
ii) 2% NaOH, Ac_2O; iii) $AlCl_3$, 120°C, 13-14 h;
iv) Pd-C in CO 270 - 300°C

Scheme 41



132



136

Figure 1 400 MHz ^{1}H NMR spectrum of 3-methoxy-2-naphthoic acid (**132**) and 3-hydroxy-2-acetonaphthone (**136**)

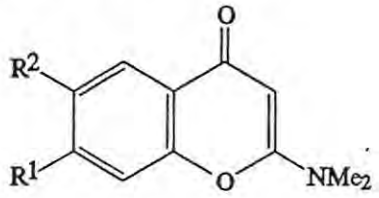
2.1.2 Preparation of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones

Various approaches used in the preparation of 2-(*N,N*-dialkylamino)-4*H*-1-benzoypyran-4-ones in this study are discussed below, *eg.* preparation of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran *via* 4-hydroxy-2*H*-1-benzopyran-2-thiones.

2.1.2.1 Preparation of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one *via* phosphogeniminium salt intermediates

The 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (**148** - **152**) were prepared following the method reported by Morris *et al.*[67] and summarised in **Scheme 42**. Treatment of *o*-hydroxyacetophenones (**124** - **127** and **130**) with boron trifluoride etherate in diethyl ether gave the corresponding 1-(2-hydroxyphenyl)ethanone, boron difluoride complexes (**137** - **141**), which were then reacted with *N,N*-dimethyl dichloromethyleniminium chloride (**142**) to afford the 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complexes (**143** - **147**); subsequent hydrolysis with methanol at *ca.* 50°C finally afforded the required 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones in high yield (83 - 95%) (Table 1). After methanolysis of the intermediates (**143** - **147**) there was no need for any chromatographic purification. The initial protection of the phenol with boron trifluoride etherate is necessary in order to direct the reaction of the phosphogeniminium salt to the methyl ketone, instead of the hydroxyl group as observed by Morris *et al.* in their preliminary experiments.[67]

Table 1 Comparative yields (%) of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (**148** - **152**), prepared as shown in Scheme 42.



Compd	R^1	R^2	Yield (%)[a]
148	H	H	91
149	Br	H	88
150	F	H	83
151	Cl	H	83
152	H	OMe	95

[a]Isolated

Even though the ^{1}H NMR spectra of the crude, intermediate 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complexes appear to be highly contaminated, treatment with methanol gave highly pure products. Hence, only a small amount of the intermediate need be purified for spectral and elemental analysis.

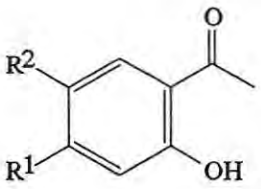
The use of other reagents for cleavage of the boron difluoride complexes (**143** - **147**), such as acetonitrile-water, acetonitrile-aq. $NaHCO_3$, or acetonitrile-aq. NaOH, led to lower yields and mixtures of products which required purification by flash chromatography.

The 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenones, boron difluoride complexes (**143** - **147**) and 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (**148** - **152**) were characterized by spectroscopic (^{1}H, ^{13}C NMR and 2D HETCOR and COSY experiments), and elemental combustion or high resolution MS analysis. Some of the ^{13}C NMR signal

assignments were confirmed by calculation using correlation tables.[73] In some boron trifluoride complexes the ^{13}C NMR spectra could not be recorded, even after a very long run, nor could satisfactory combustion analyses be obtained. Table 2 shows the ^{1}H and ^{13}C NMR shifts of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complexes.

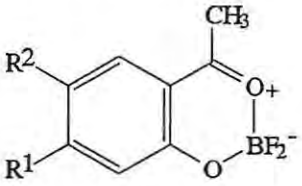
Figure 2 illustrates the ^{1}H NMR spectra of the formation of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones from *o*-hydroxyacetophenone, while Tables 2 and 3 show the effect of substituents on the ^{1}H and ^{13}C chemical shifts in the boron trifluoride complex intermediates and final products. Figure 3 shows the COSY spectrum of compound (**148**) and Figure 4 shows the HETCOR spectrum of compound (**152**).

The ^{1}H NMR spectra of the 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones are characterized by the methine proton (3-H) at δ *ca* 5.36. The dimethylamino ^{13}C peak appears as a singlet at δ *ca.* 37.5, but becomes two singlets at ambient temperature in the carbon-13 spectra in $CDCl_3$. The substituent changes do not appear to alter the ^{13}C chemical shifts significantly, except at position 6, where variation of the substituent results in large chemical shift changes. The methoxy substituent at position 6 in compound (**152**) is responsible for the large upfield shift of the C-5′ nucleus compared to the rest of the compounds examined. For the parent compound (**148**), the C-8a signal is slightly downfield (δ 153.5 ppm) of the C-8a signals for the other compounds in the series (**149** - **152**) (δ *ca.* 163.7). In the IR spectra, the chromone carbonyl absorption band appears at *ca.* 1622 cm^{-1}. Table 3 shows the ^{1}H and ^{13}C NMR chemical shifts for 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (p.50).



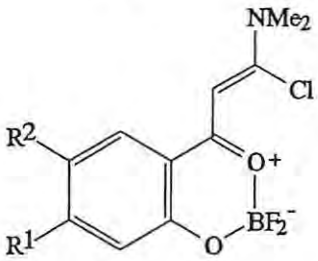
R^1	H	Br	F	Cl	H
R^2	H	H	H	H	OMe
No	124	125	126	127	130

i



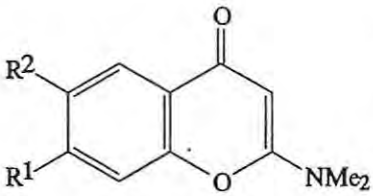
R^1	H	Br	F	Cl	H
R^2	H	H	H	H	OMe
No	137	138	139	140	141

ii



R^1	H	Br	F	Cl	H
R^2	H	H	H	H	OMe
No	143	144	145	146	147

iii



R^1	H	Br	F	Cl	H
R^2	H	H	H	H	OMe
No	148	149	150	151	152

Reagents: i) $BF_3.OEt_2$, Et_2O; ii) $Cl_2C{=}N^+Me_2.Cl^-$ (**142**), $Cl(CH_2)_2Cl$; iii) MeOH, 50°C

Scheme 42

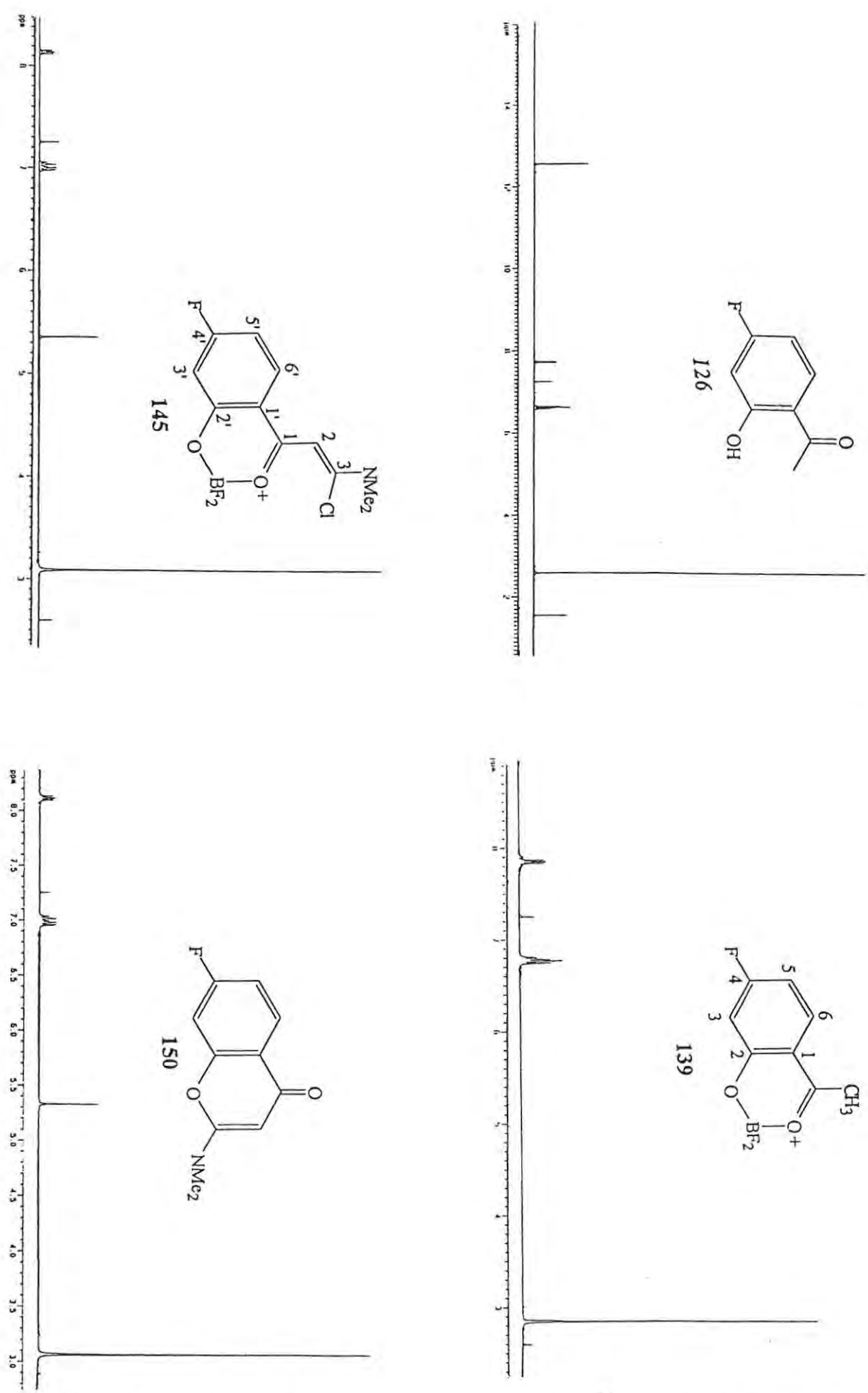
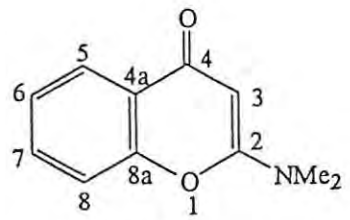


Figure 2 400 MHz ^1H spectrum of compounds (126), (139), (145) and (150)



148

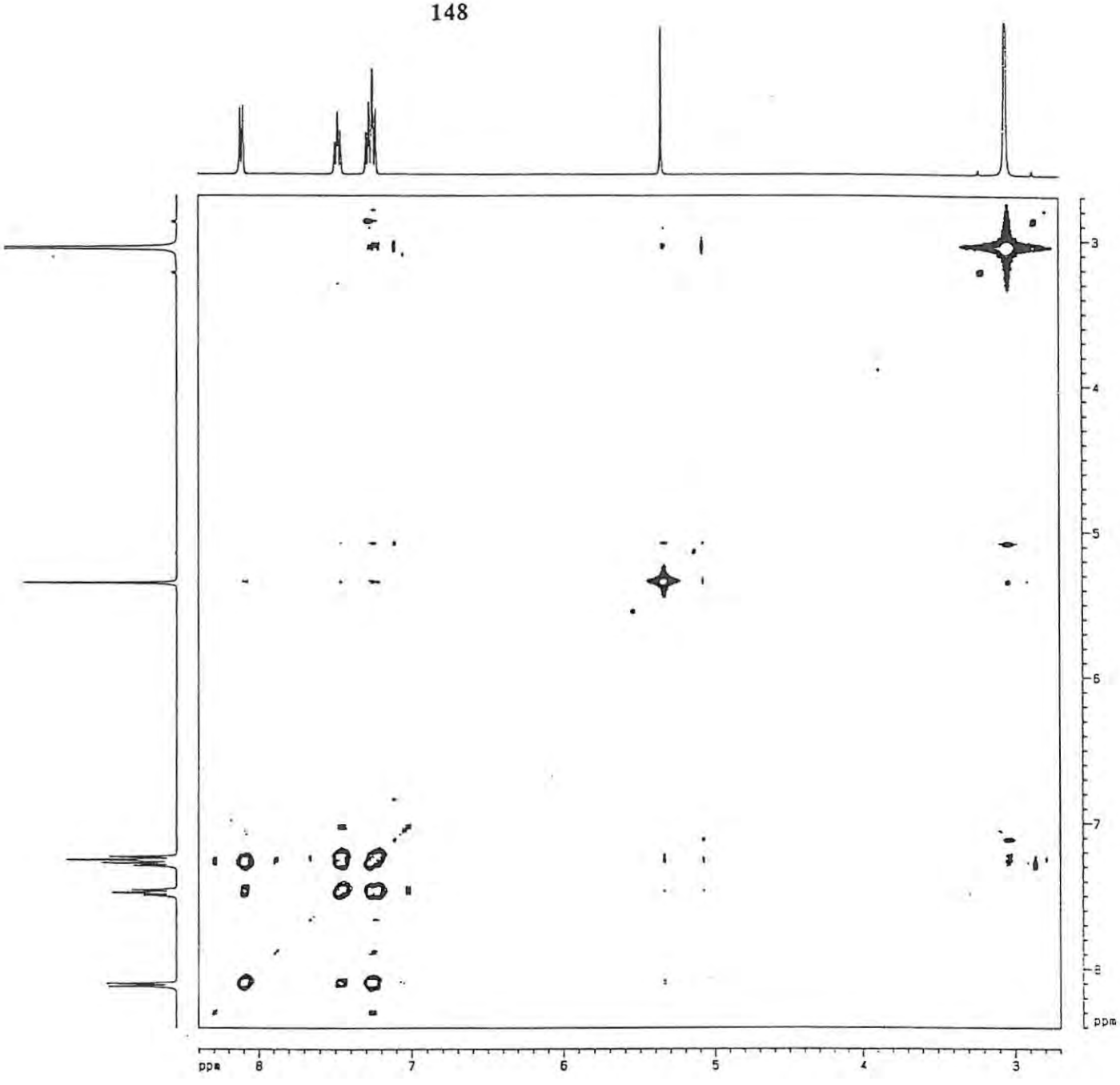
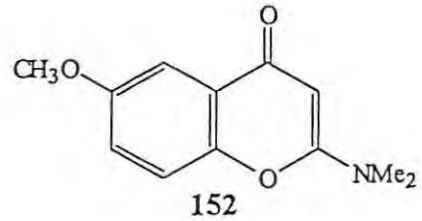


Figure 3 400 MHz COSY spectrum of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**)



152

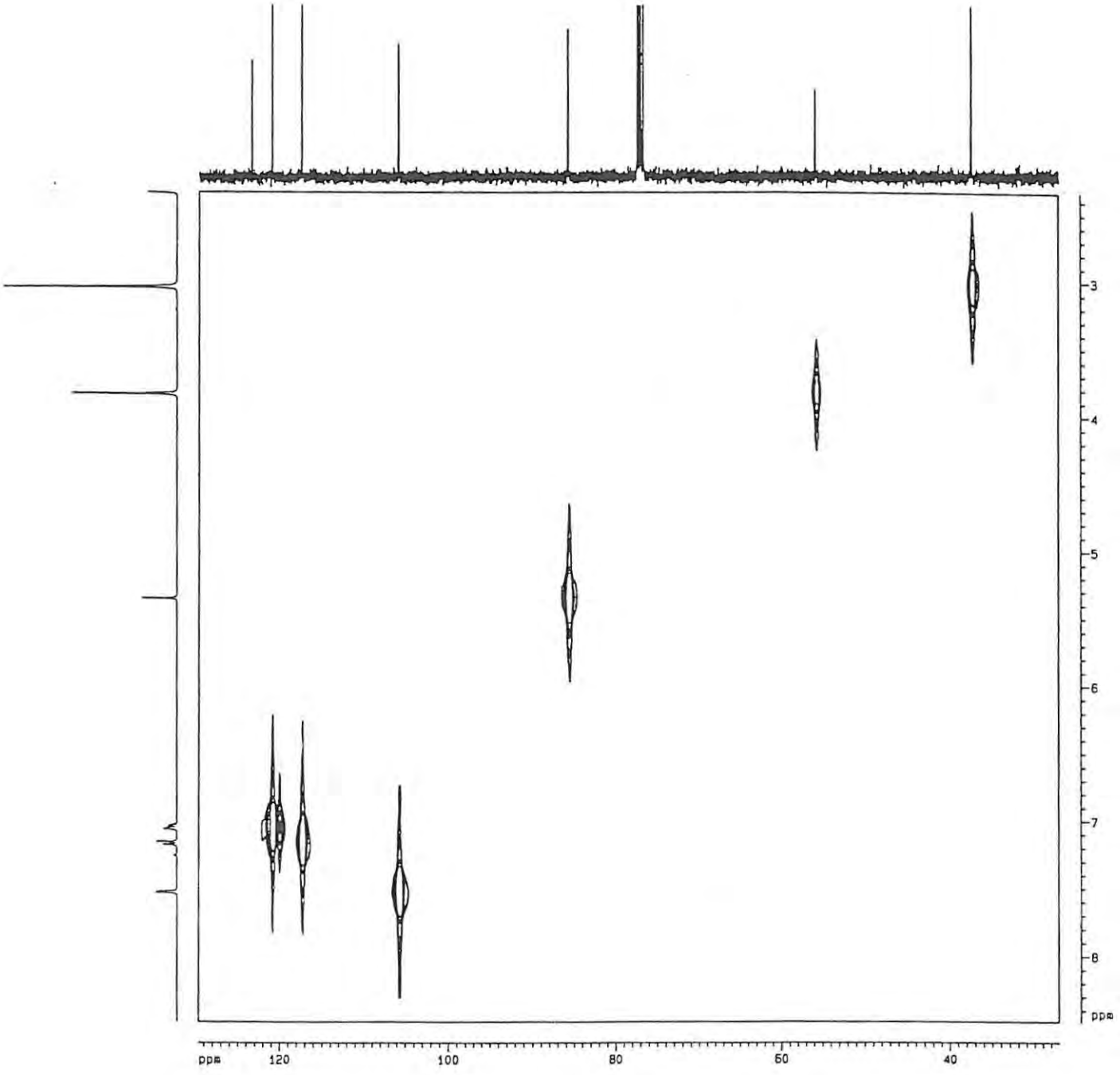
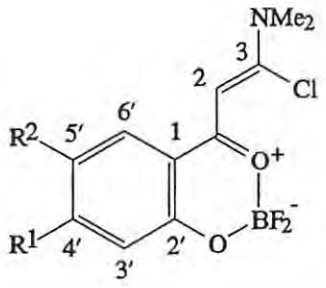


Figure 4 400 MHz HETCOR spectrum of 2-(*N,N*-dimethylamino)-6-methoxy-4*H*-1-benzopyran-4-one (**152**)

Table 2 ^{1}H NMR shifts (δ ppm) (a) of 3-chloro-(3-*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complexes, followed by ^{13}C NMR shifts (ppm) (b) in $CDCl_3$ (7.25 for ^{1}H and 77.0 ppm for ^{13}C NMR).



(a)

Compd	R^1	R^2	NMe_2	2-H	3'-H	4'-H	5'-H	6'-H
143	H	H	3.11	5.41	7.31	7.52	7.31	8.16
144	Br	H	3.10	5.39	7.50	-	7.45	8.01
145	F	H	3.08	5.35	6.98	-	7.03	8.14
146	Cl	H	3.10	5.28	7.33	-	7.29	8.08
147[a]	H	OCH_3	3.21	6.20	7.29	7.18	-	7.52

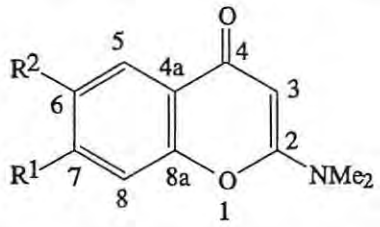
[a]OCH_3 ^{1}H NMR shift at 3.83

(b)

Compd	R^1	R^2	NMe_2	C-1	C-2	C-3	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
143	H	H	37.5	168.7	86.2	153.7	122.9	163.1	116.2 or 124.6	131.9	116.2 or 124.6	125.6
145	F	H	37.5	175.7	85.8	154.4[b]	163.3[c]	165.9	103.4[d]	119.6	112.8[e]	127.7[f]
146	Cl	H	37.6	175.6	86.2	175.6	153.8	163.0	116.5	121.6	125.3	127.0
147[a]	H	OCH_3	38.1	175.9	86.3	148.0	120.9	163.4	117.6	122.3	157.1	105.7
144[g]												

[a]OCH_3 ^{13}C shift value at 56.0; [b] $^{7}J_{CF}$ 13.1 Hz; [c] $^{2}J_{CF}$ 14.1 Hz; [d] $^{2}J_{CF}$ 26.2 Hz; [e] $^{2}J_{CF}$ 23.1 Hz ; [f] $^{3}J_{CF}$ 10.1 Hz; [g]No satisfactory ^{13}C NMR ws obtained.

Table 3 a) ^{1}H- and b) ^{13}C chemical shifts (δ ppm/$CDCl_3$) for 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (*J* values in Hz).



(a)

Compd	R^1	R^2	NMe_2	3-H	5-H	6-H	7-H	8-H
148	H	H	3.08	5.38	8.14 (dd) *J* 1.7 and 7.8	7.29 (m)	7.50 (m)	7.29 (m)
149	Br	H	3.05	5.33	7.97 (d) *J* 8.4	7.40 (dd) *J* 1.7 and 8.4	-	7.44 (d) *J* 1.7
150	F	H	3.09	5.35	8.14 (dd) *J* 6.5 and 8.7	7.02 (m)	-	7.02 (m)
151	Cl	H	3.09	5.36	8.07 (d) *J* 8.4	7.28 (dd) *J* 1.9 and 8.4	-	7.31 (d) *J* 1.9
152[a]	H	OCH_3	3.11	5.37	7.55 (d) *J* 3.1	-	7.07 (dd) *J* 3.2 and 9	7.19 (d) *J* 9

(b)

Compd	R^1	R^2	NMe_2	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
148	H	H	37.3	162.9	85.8	176.3	122.9	125.3	124.4 or 116.1	131.8	116.1 or 124.4	153.5
149	Br	H	37.5	153.7	86.1	175.5	121.9	127.0	128.0	125.5	119.4	162.8
150	F	H	37.6	163.3	85.8	175.7	119.6	127.7	103.4 or 112.7	154.4	103.4 or 112.7	165.9
151	Cl	H	37.5	153.7	86.1	175.5	121.5	126.8	125.2	137.6	116.5	162.9
152[a]	H	OCH_3	37.4	156.0	85.9	176.4	123.5	105.8	148.2	121.0	117.4	163.0

[a] OCH_3 ^{13}C shift value at 55.9

2.1.2.2 Preparation of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones *via* 4-hydroxy-2*H*-1-benzopyran-2-thione

The Bantick and Suschitsky[68] approach to 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones is outlined in **Scheme 43**. These compounds (**148**, **158** - **160**) were prepared by treating 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) with an appropriate amine, *viz.* 33% ethanolic dimethylamine, diethylamine, piperidine or pyrrolidine. In this reaction the sulphinyl moeity acts as the leaving group for nucleophilic displacement by the amine. The key 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) was prepared by treating 2-ethylthio-4*H*-1-benzopyran-4-one (**156**) with *m*-chloroperbenzoic acid in dry 1,2-dichloroethane, which, in turn, was prepared from 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**) as shown in Scheme 43. For the preparation of compound (**158**) the intermediate (**155**) was prepared by condensing of 2-hydroxyacetophenone (**124**) with carbon disulphide in dry benzene in the presence of potassium-*t*-butoxide. Figures 5 and 6 show the ^{1}H NMR spectra of selected intermediates at various stages of the synthesis, summarised in Scheme 43.

4-Hydroxy-2*H*-1-benzopyran-2-thione (**155**) was typically obtained in poor yields, probably because the reaction mixture becomes very thick and difficult to stir. Attempts were made to use a sealed stirrer, but without appreciable improvement of the yield. However, stirring the reaction mixture for up to 4 days improved the yield of the expected product from 22% to 53%. The sulphinyl group is a better leaving group than the sulphide group in the aromatic nucleophilic substitution reaction because the developing negative charge can be more effectively accommodated by the sulphinyl oxygen.

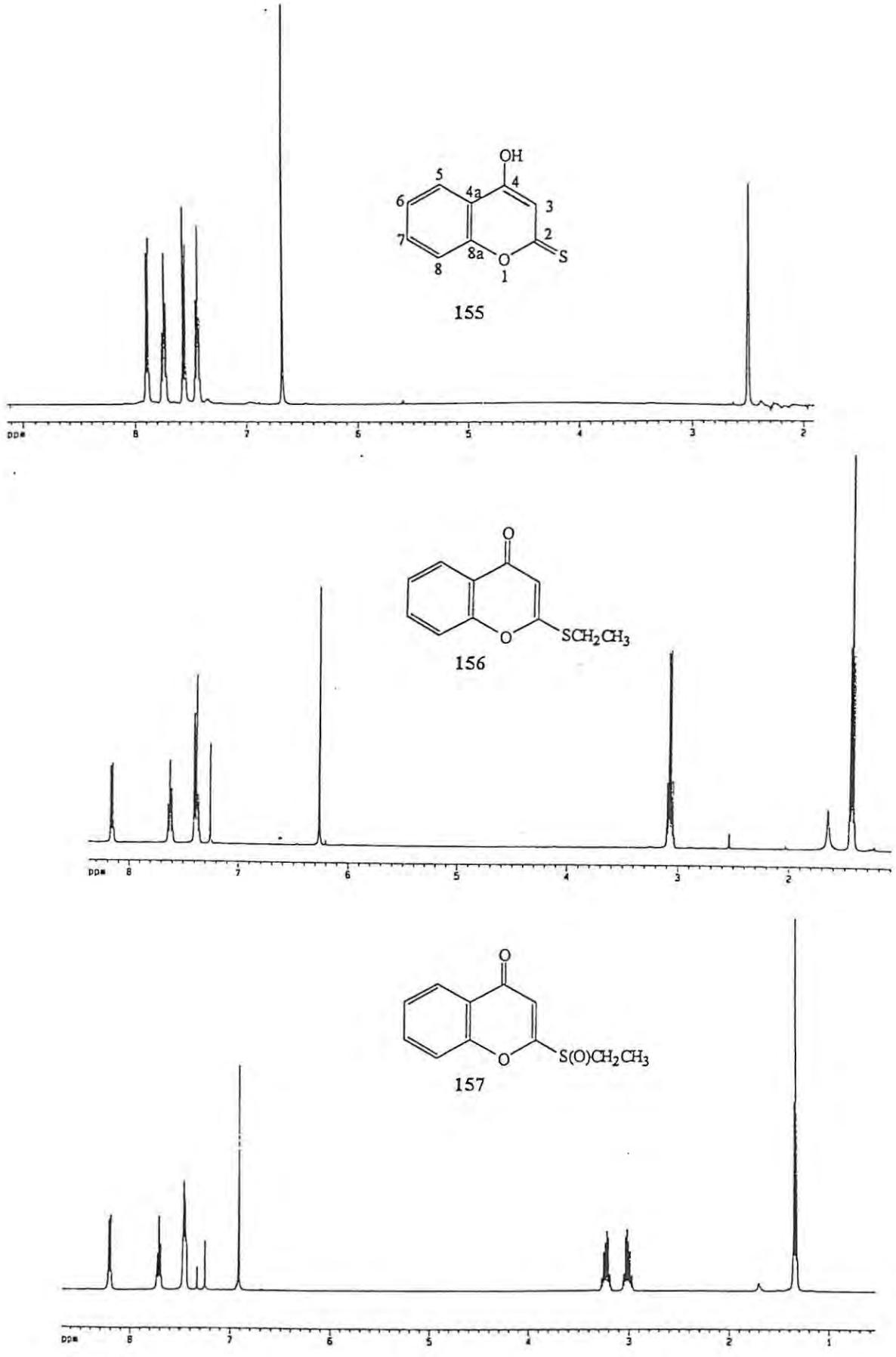


Figure 5 400 MHz ^{1}H NMR spectrum of 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**), 2-ethylthio-4*H*-1-benzopyran-4-one (**156**) and 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**).

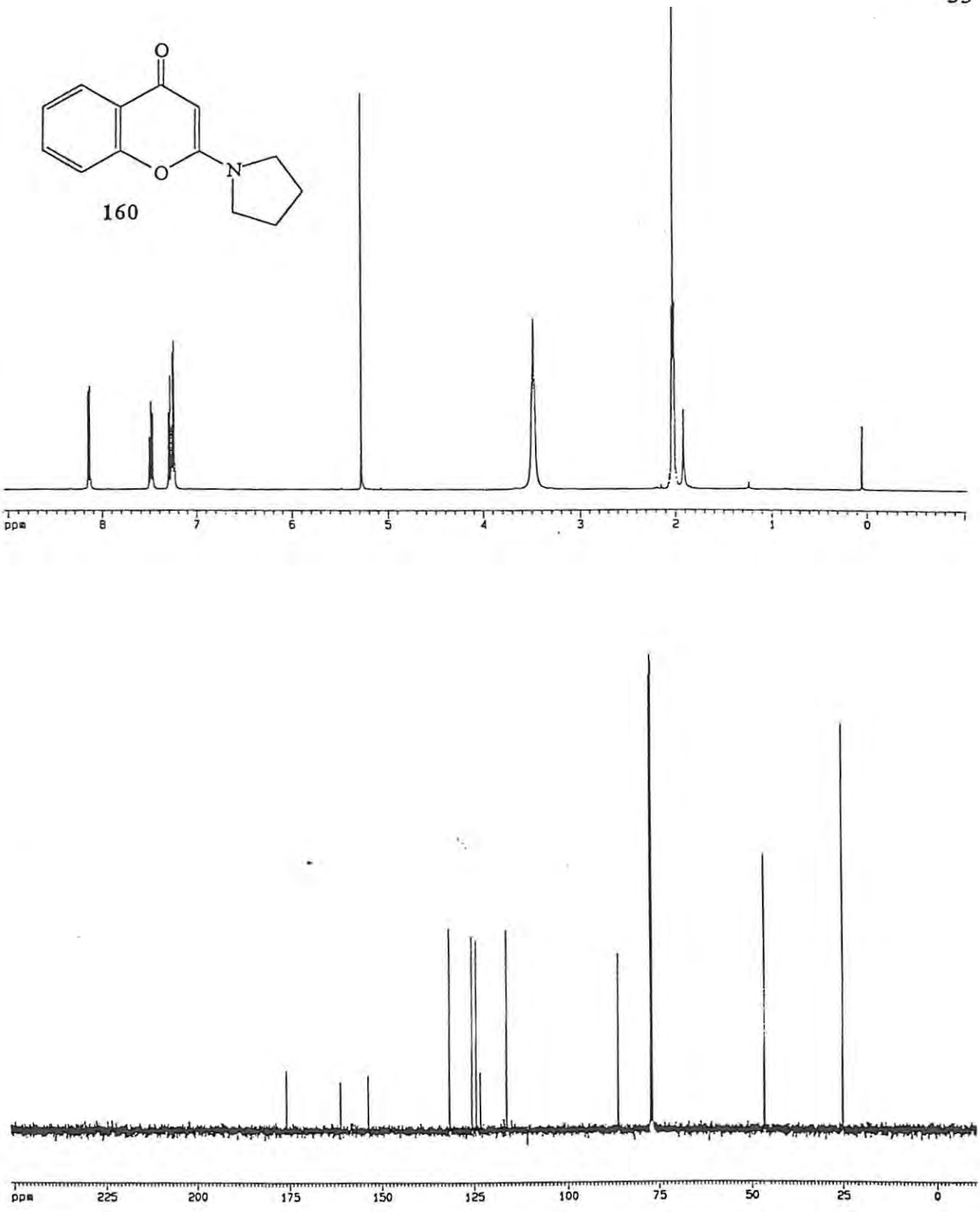
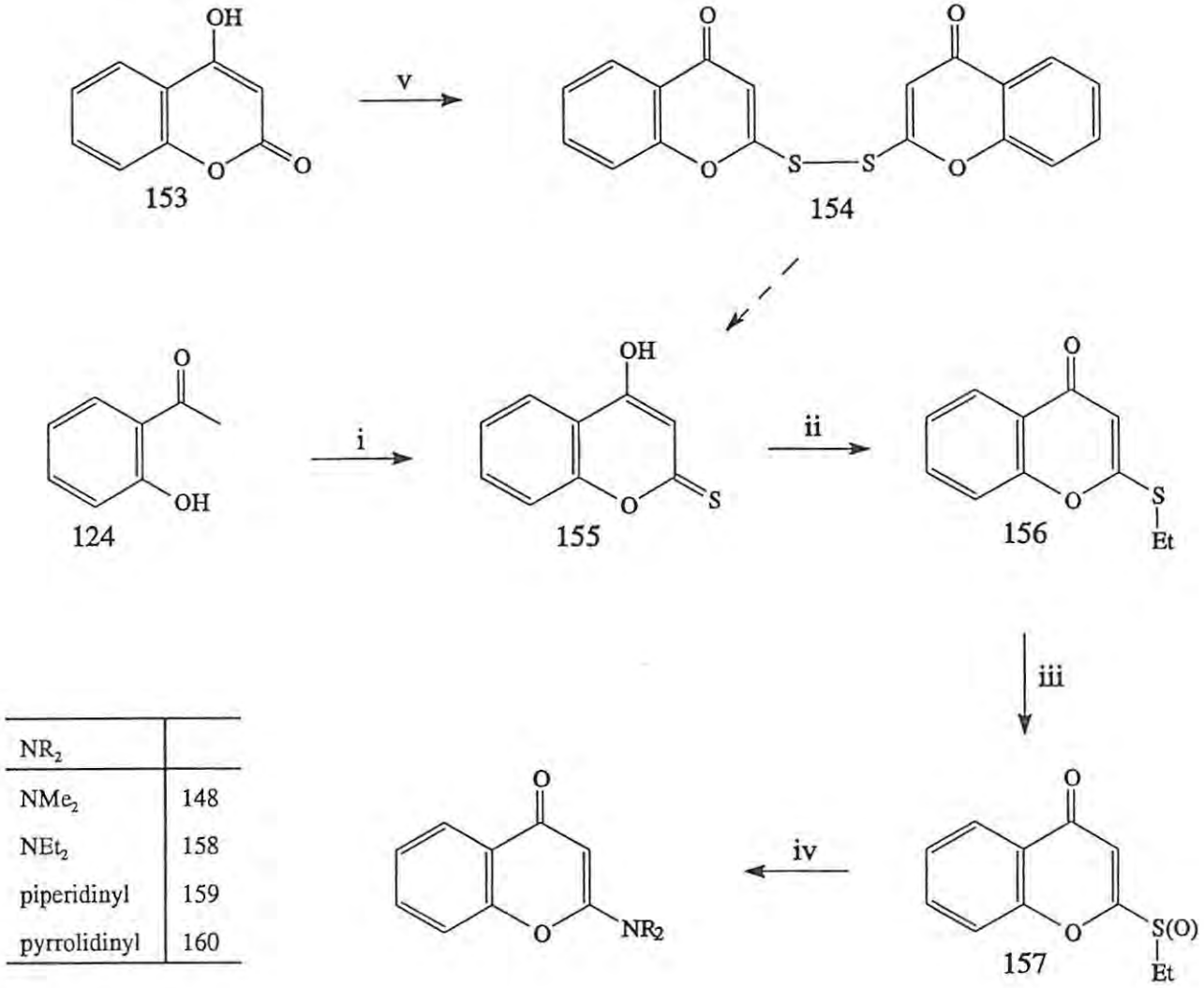


Figure 6 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra of 2-(pyrrolidin-1-yl)-4*H*-1-benzopyran-4-one (**160**)



NR_2	
NMe_2	148
NEt_2	158
piperidinyl	159
pyrrolidinyl	160

Reagents: i) Bu^{t}OK, CS_2, C_6H_6; ii) K_2CO_3, EtI, dry acetone; iii) MCPBA, $ClCH_2CH_2Cl$; iv) R_2NH; v) Lawesson's reagent

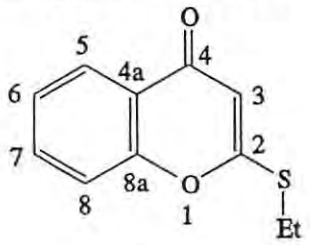
Scheme 43

An alternative method for the preparation of compound (**155**), involving direct thianation of 4-hydroxy-2*H*-1-benzopyran-2-one (**153**) with the Lawesson's reagent, as described by Fahmey *et al.*[69] was explored. Application of this method afforded the disulphide (**154**) reductive cleavage of which was expected to yield the desired compound (**155**). But time did not permit this approach to be developed effectively.

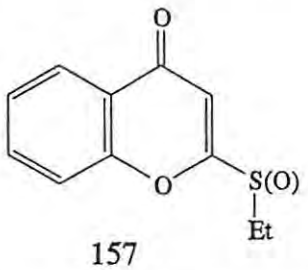
The crude 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-one products (**148**, **158** - **160**), obtained by this method, could be chromatographed to obtain a pure product, or isolated as the hydrochloride salt prior to purification. Attempts to introduce the diisopropylamino group using this method failed, possibly for steric reasons.

In the ^{1}H NMR spectrum of 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**), the 3-H signal appears at δ 6.68 ppm in DMSO-d_6. Not surprisingly, the chemical shift of the vinyl proton signal appears to be influenced by the nature of the group at position 2. Thus, the 3-H nucleus in 2-ethylthio-4*H*-1-benzopyran-4-one (**156**) and in 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) resonates at 6.26 and 6 .91 ppm respectively (in $CDCl_3$). The methylene protons of 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) are diastereotopic and appear as two sextets at δ *ca.* 3.23 and 3.01 ppm, distinguishing them from the methylene protons in compound (**156**), which resonate as a 2-proton quartet at δ 3.07 ppm. From Table 4, it is apparent that the ^{13}C methylene signal of the ethylsulphinyl compound (**157**) appears at relatively low field (δ 45.9 ppm), whereas that of the ethylthio compound (**156**) appears much further upfield (δ 25.5 ppm); the same pattern is observed with the methyl ^{13}C signals of the two compounds. The remaining ^{13}C signals for compound (**156**) appear to be unaffected by introduction of the sulfoxide oxygen.

Table 4 ^{13}C NMR chemical shifts for 2-ethylthio- (**156**) and 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) in $CDCl_3$



156



157

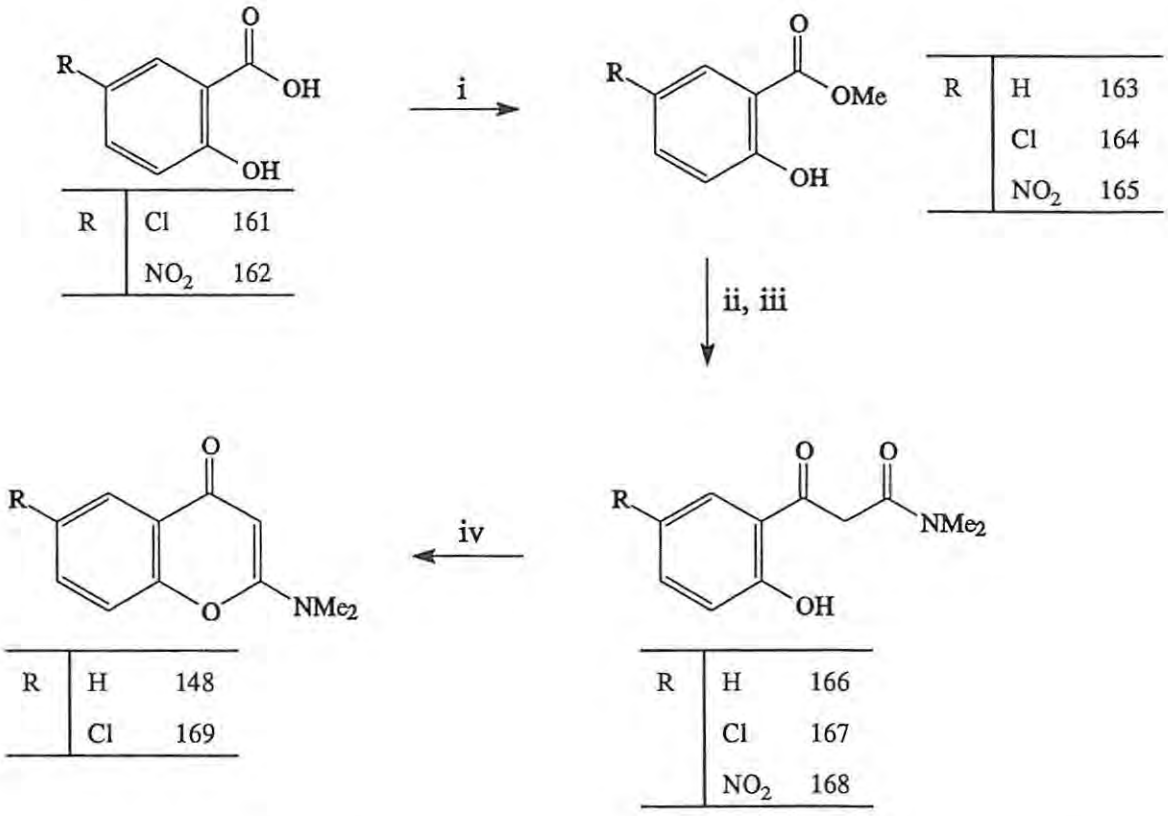
Compd	CH_2	CH_3	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
156	25.5	14.2	156.7	108.7	175.7	123.6	125.8	125.2	133.3	117.2	168.6
157	45.9	5.3	156.2	111.0	175.9	124.3	126.2	126.4	134.5	117.9	169.6

2.1.2.3 Preparation of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones from methyl salicylates

Yet another method used for the synthesis of substituted 2-(*N,N*-dimethylamino)-4*H*-benzopyran-4-ones involved preparation of methyl salicylates (**164**) and (**165**) by direct methylation of the substituted salicylic acids (**161**) and (**162**) with methanol in the presence of concentrated sulphuric acid, or phosphorus oxychloride (**Scheme 44**). Addition of the methyl salicylates to a mixture of lithium diisopropylamide and *N,N*-dimethylacetamide in dry tetrahydrofuran gave the *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamides (**166**) and (**167**), which when treated with trifluoromethanesulphonic anhydride were dehydrated to afford the 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones (**148**) and (**169**) (**Scheme 44**).[70] Comparative ^{1}H NMR spectra for compounds in one synthetic sequence (**164** → **167** → **169**) are illustrated in Figure 7. Figure 8 shows the ^{13}C NMR spectrum of compound (**169**).

When methyl 5-nitrosalicylate (**165**) was used as a precursor, the work-up was complicated by formation of an intractable mass and the required intermediate (*N,N*-dimethyl)-3-(2-hydroxy-5-nitrophenyl)-3-oxopropanamide (**168**) could not be isolated. Hence, 2-(*N,N*-dimethylamino)-6-nitro-4*H*-1-benzopyran-4-one (**170**) was prepared by direct nitration of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (**Scheme 45**).

The neutralization of the *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamides *eg.* (**166**) and (**167**) with 10% hydrochloric acid must be performed cautiously because excess acid leads exclusively to the 4-hydroxy-4*H*-1-benzopyran-2-one (*eg.* **153**). The intermediates (**166**) and (**167**) may also be prepared from compounds (**143** - **147**) (see Scheme 42) by hydrolysis of the appropriate compound with CH_3CN/2 **M** NaOH.[72]



R		
R	Cl	161
	NO_2	162

R		
R	H	163
	Cl	164
	NO_2	165

R		
R	H	166
	Cl	167
	NO_2	168

R		
R	H	148
	Cl	169

Reagents: i) MeOH, H_2SO_4 or $POCl_3$; ii) LDA, dry THF; iii) $MeCONMe_2$; iv) TF_2O, CH_2Cl_2

Scheme 44

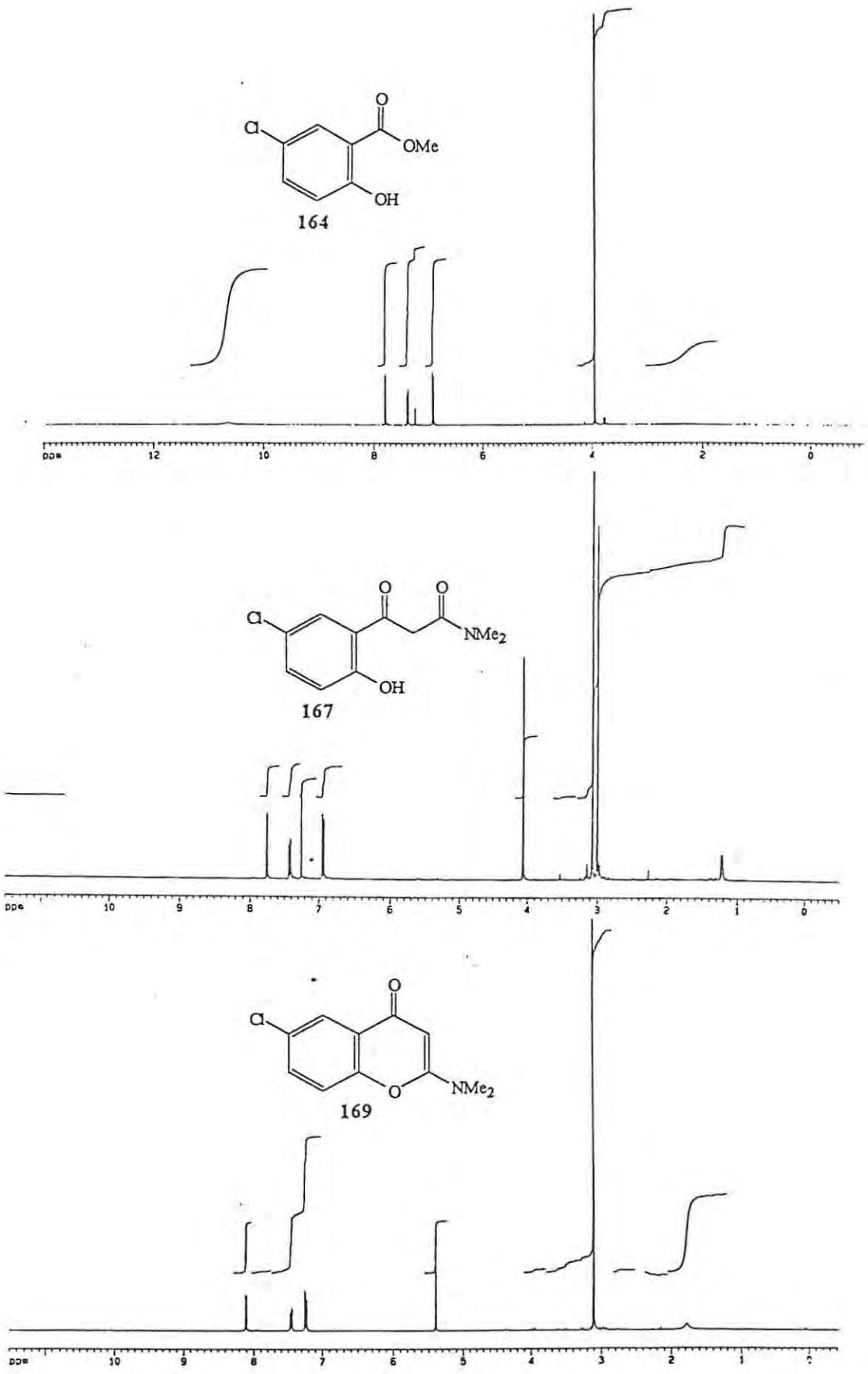


Figure 7 400 MHz ^{1}H NMR spectrum of methyl 5-chlorosalicylate (**164**), *N,N*-dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide (**167**) and 2-(*N,N*-dimethylamino)-6-chloro-4*H*-1-benzopyran-4-one (**169**)

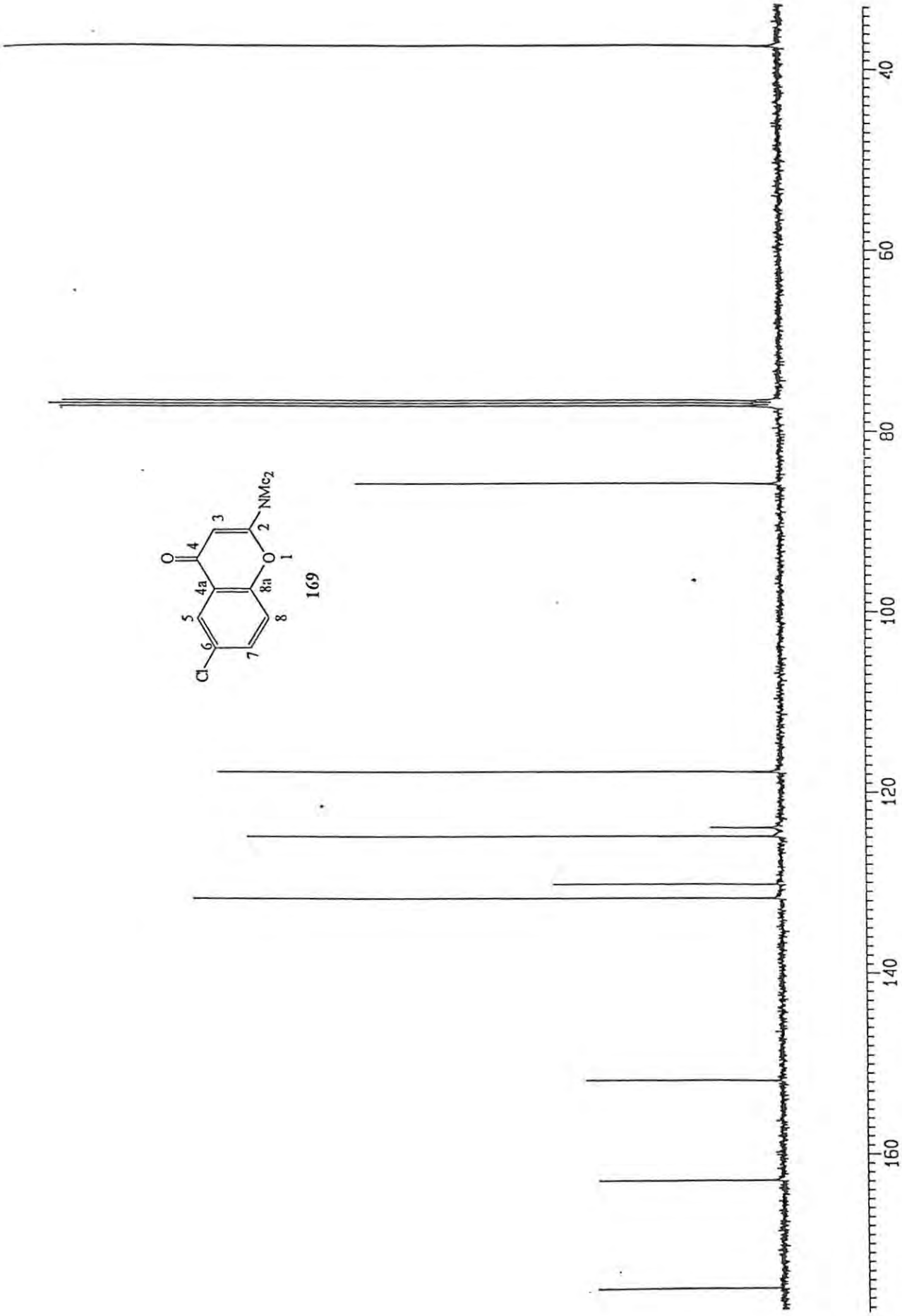


Figure 8 100 MHz ^{13}C NMR spectrum of 2-(*N,N*-dimethylamino)-6-chloro-4*H*-1-benzopyran-4-one (**169**).

148 170

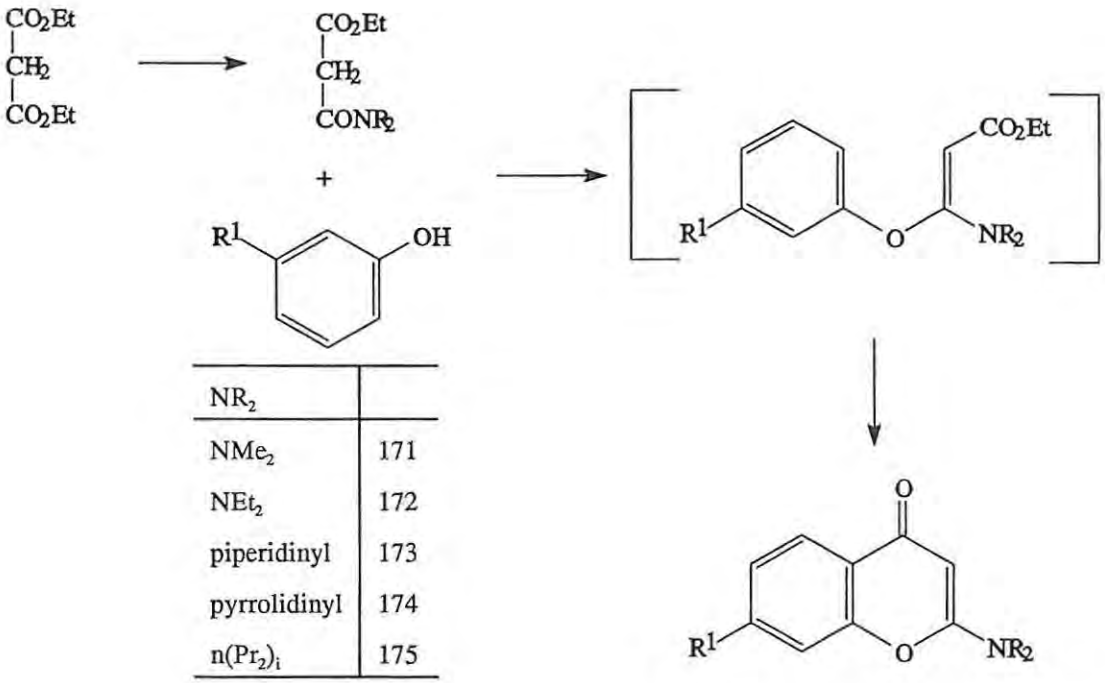
Reagents: i) H_2SO_4-HNO_3, r.t.

Scheme 45

^{1}H NMR spectroscopy is a useful tool in distinguishing the intermediate 3-oxopropanamides (**166**) or (**167**) from the final products (**148**) or (**169**). The dimethylamino signal appears as two singlets in the amide intermediates, but becomes a time-averaged singlet in the product at ambient temperature due to more rapid internal rotation. The methylene protons which resonate at δ *ca.* 4.09 in the intermediate are replaced by the 3-methine signal in the product (δ *ca.* 5.40). Furthermore, the aromatic protons in the intermediate generally resonate upfield of the corresponding protons in the product (see Figure 7).

2.1.2.4 Preparation of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-one from ethyl (*N,N*-dialkylcarbamoyl) ethanoate

The 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones (**148**, **158**, **176** and **177**) were prepared from phenol or 3-methoxyphenol with the appropriate ethyl (*N,N*-dialkylcarbamoyl)ethanoate, prepared in turn, by autoclaving diethyl malonate with the appropriate amine (**Scheme 46**). This method only afforded compounds (**148**), (**158**), (**176**) and (**177**) in low to very low yields (Table 5).

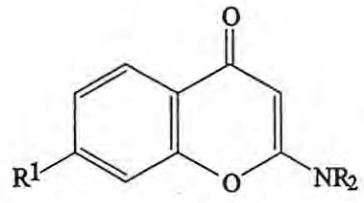


NR_2	
NMe_2	171
NEt_2	172
piperidinyl	173
pyrrolidinyl	174
$n(Pr_2)_i$	175

R^1	NR_2	
H	NMe_2	148
H	NEt_2	158
OMe	NMe_2	176
OMe	NEt_2	177

Scheme 46

Table 5 Comparative yields (%) of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones (**148**), (**158**), (**176**) and (**177**), prepared as shown in **Scheme 46**.



Compd	R^1	NR_2	Yield (%)
148	H	NMe_2	6
158	H	NEt_2	6
176	OCH_3	NMe_2	32
177	OCH_3	NEt_2	20

Compound (**148**) was also synthesized in very high yield (*ca.* 91 %) by the alternative method discussed in Section 2.1.2.1. In this synthesis, outlined in **Scheme 46**, the intermediate enol ethers were not isolated. Figures 9 and 10 show the ^{1}H NMR spectra of ethyl (*N,N*-diethylcarbamoyl)ethanoate (**172**) and the 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-one (**177**) prepared by this method, while Figure 11 shows the HETCOR spectrum of the analogue (**176**).

Attempts to synthesize 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones by using phenol and one of the ethyl (*N,N*-dialkycarbamoyl)ethanoate esters (**173**), (**174**) or (**175**) resulted in mixtures of products which were difficult to separate chromatographically. Attempts to isolate the expected product as the hydrochloride salt also failed, as did attempts to prepare ring-substituted 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones, where R^1 = Cl, F, or Br (**Scheme 46**).

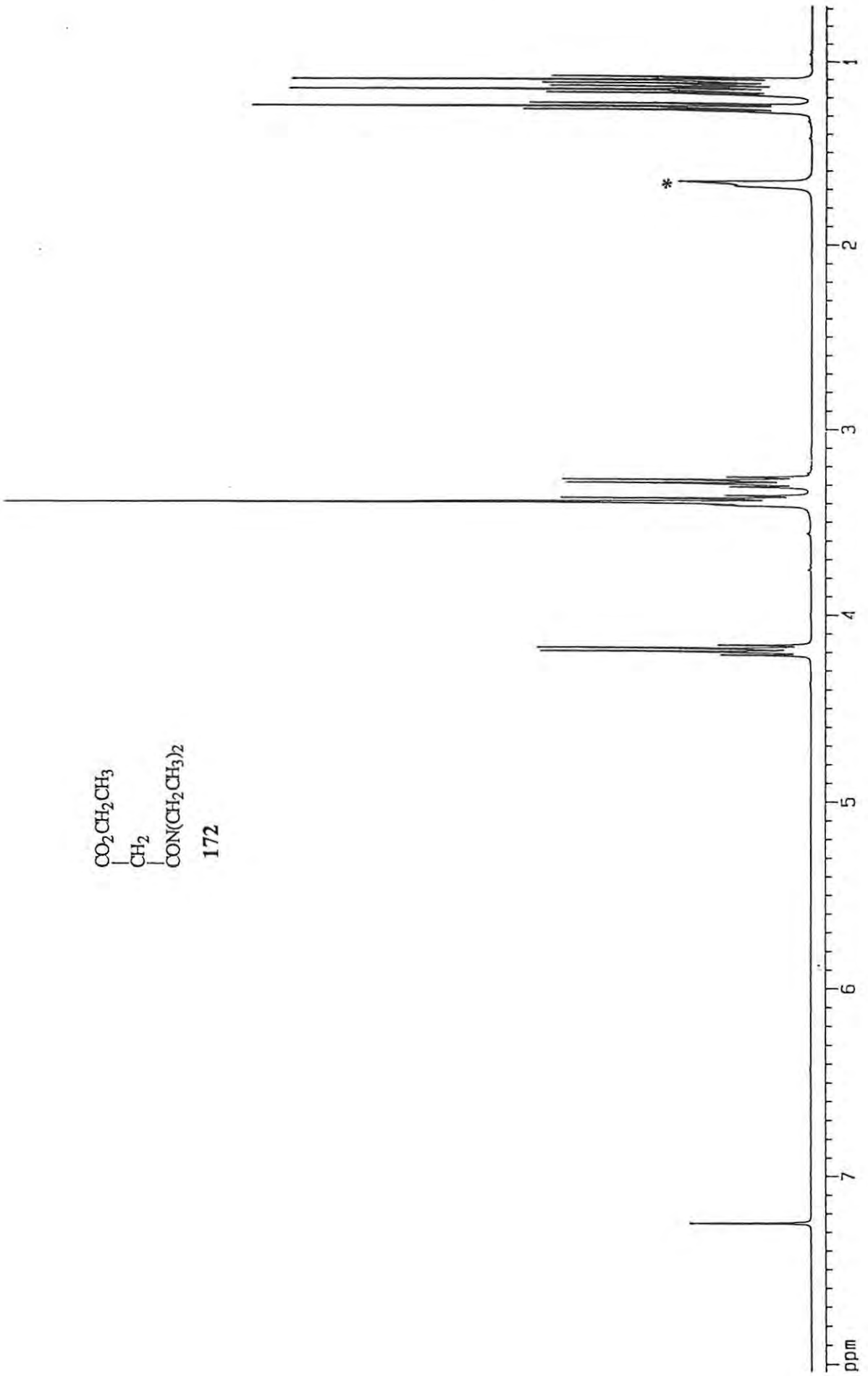
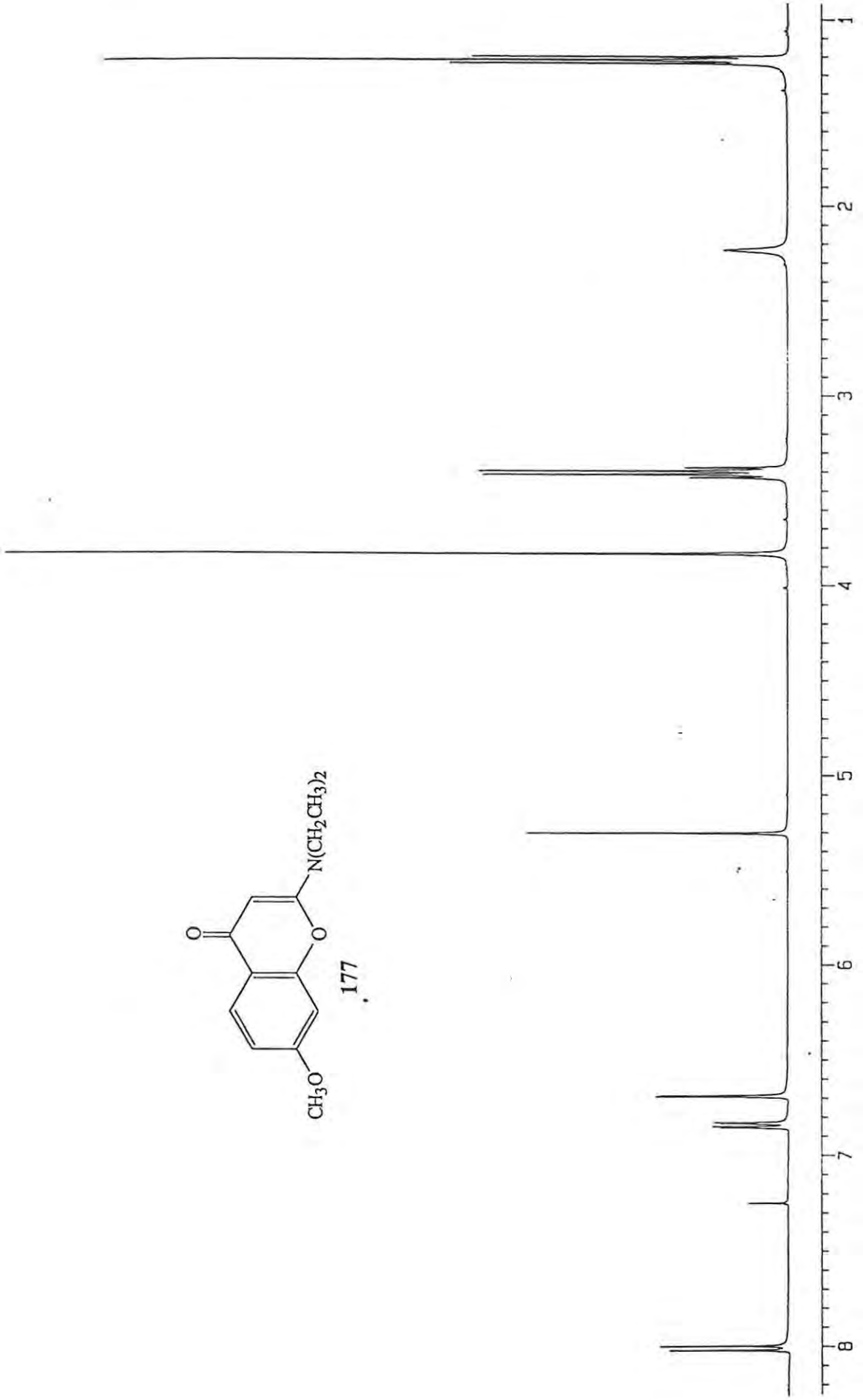
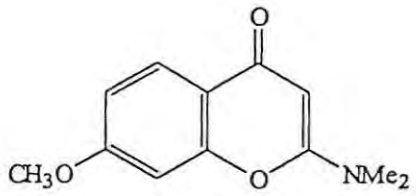


Figure 9 400 MHz ^{1}H NMR spectrum of ethyl-(*N,N*-diethylcarbamoyl)ethanoate (**172**).
*** = solvent impurity**



177

Figure 10 400 MHz ^{1}H NMR spectrum of 2-(*N,N*-diethylamino)-7-methoxy-4*H*-1-benzopyran-4-one (**177**).



176

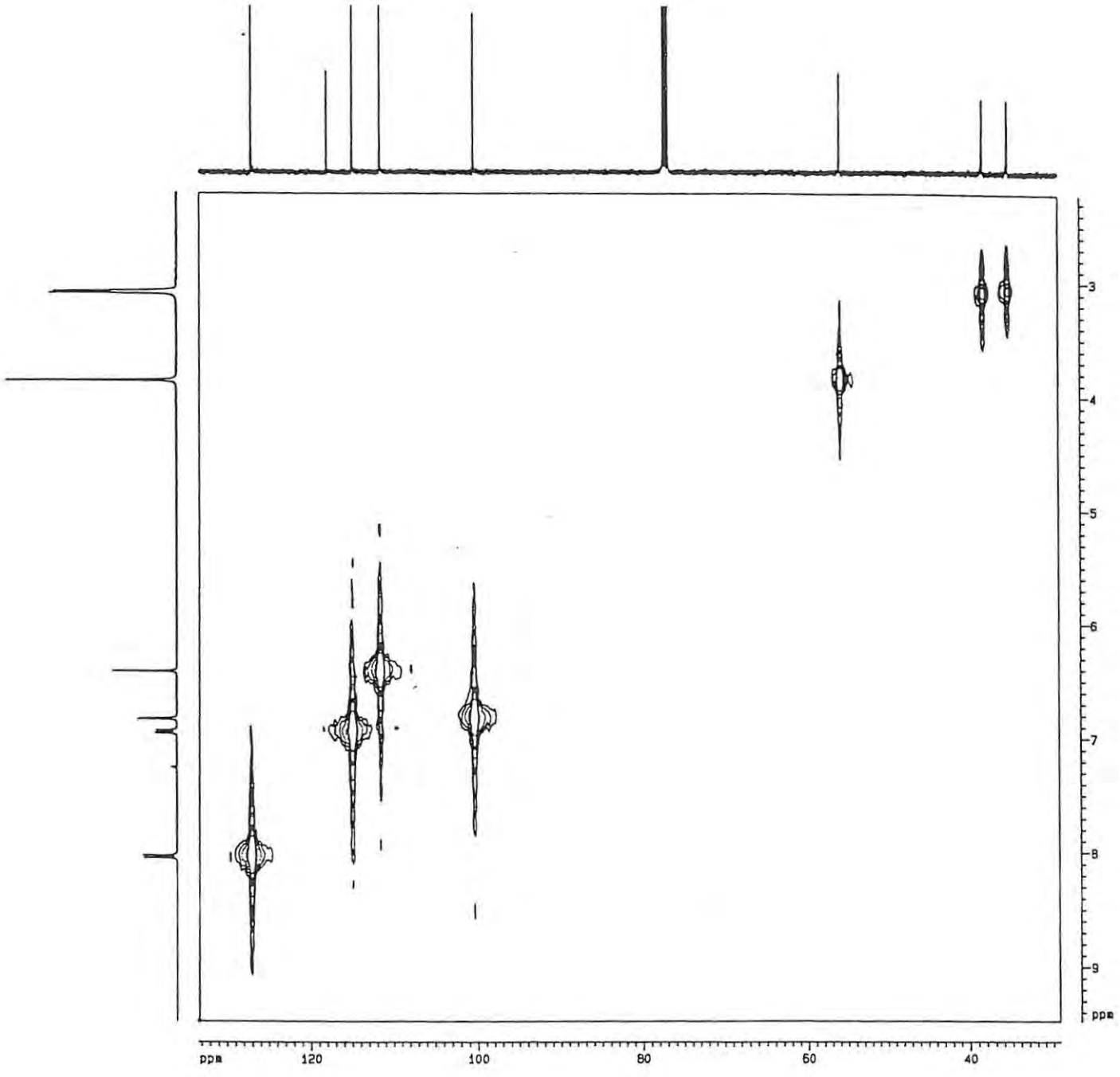
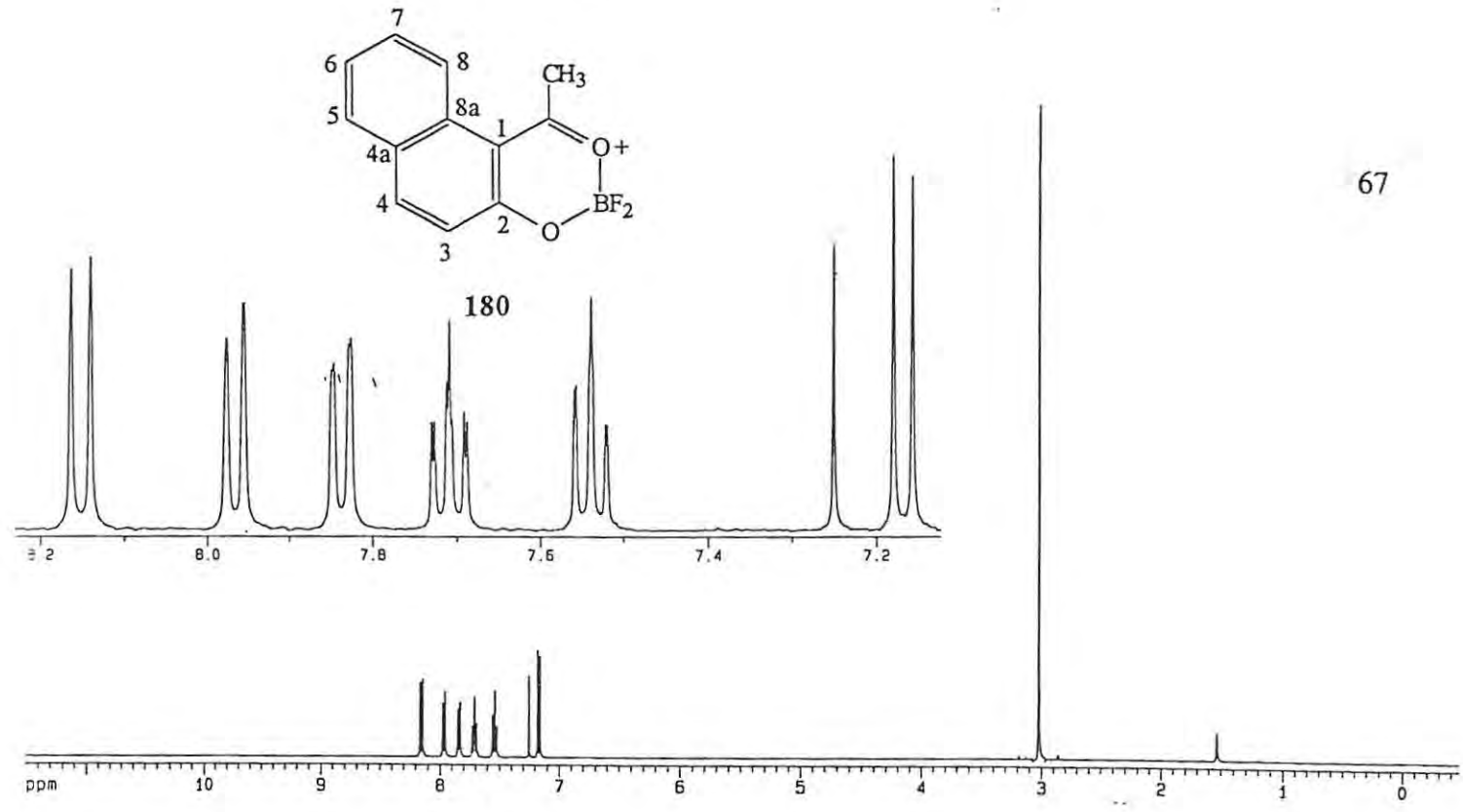


Figure 11 400 MHz HETCOR spectrum of 2-(*N*,*N*-dimethylamino)-7-methoxy-4*H*-1-benzopyran-4-one (**176**).

2.1.2.5 Preparation of 2-(*N,N*-dimethylamino)-4*H*-naphthopyran-4-ones

The approach to the 2-(*N,N*-dimethylamino)-4*H*-naphthopyran-4-ones (**186** - **188**) is depicted in **Scheme 47**, which is almost identical to **Scheme 42** except for the introduction of an extra benzene ring fused at different positions to the 4*H*-1-benzopyran-4-one moeity. The boron difluoride complex (**181**) was also prepared from 1-naphthol, acetic anhydride and $BF_3.OEt_2$ (not shown in **Scheme 47**), while methanolysis of the following intermediate (**184**) required more time and more methanol than the methanolysis of intermediate (**183**). Illustrative ^1H NMR spectra of the intermediates (**180**) and (**183**) and the final product (**186**) are provided in Figures 12 and 13. Figures 14 and 15 show the COSY and ^{13}C NMR spectra of (**186**).

In the ^1H NMR spectra of the boron difluoride complexes (**180** - **182**), the methyl signal resonates at δ *ca.* 3.02 ppm; of course, this signal disappears on formation of the subsequent boron difluoride complexes (**183** - **185**), which can be distinguished from their precursors by the appearance of the dimethylamino signal at δ *ca.* 3.46 ppm and the vinyl proton at δ *ca.* 6.10 ppm. There do not appear to be very significant changes in the chemical shifts of the aromatic protons. In the ^1H spectrum of 2-(*N,N*-dimethylamino)-4*H*-naphthopyran-4-one (**186**), the 3-H proton signal [corresponding to the vinyl proton 2-H in the precursor (**183**)] resonates upfield (δ *ca.* 5.51) compared to its precursor which resonates at chemical shifts of δ *ca.* 6.10; there are slight differences in the chemical shifts of the aromatic proton signals. The ^{13}C NMR spectrum of the 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-naphthyl)propenones, boron difluoride complex (**183**) differs significantly from that of the final product (**186**). No satisfactory ^{13}C NMR was observed in the case of intermediate (**184**) and intermediate (**185**) was not isolated.



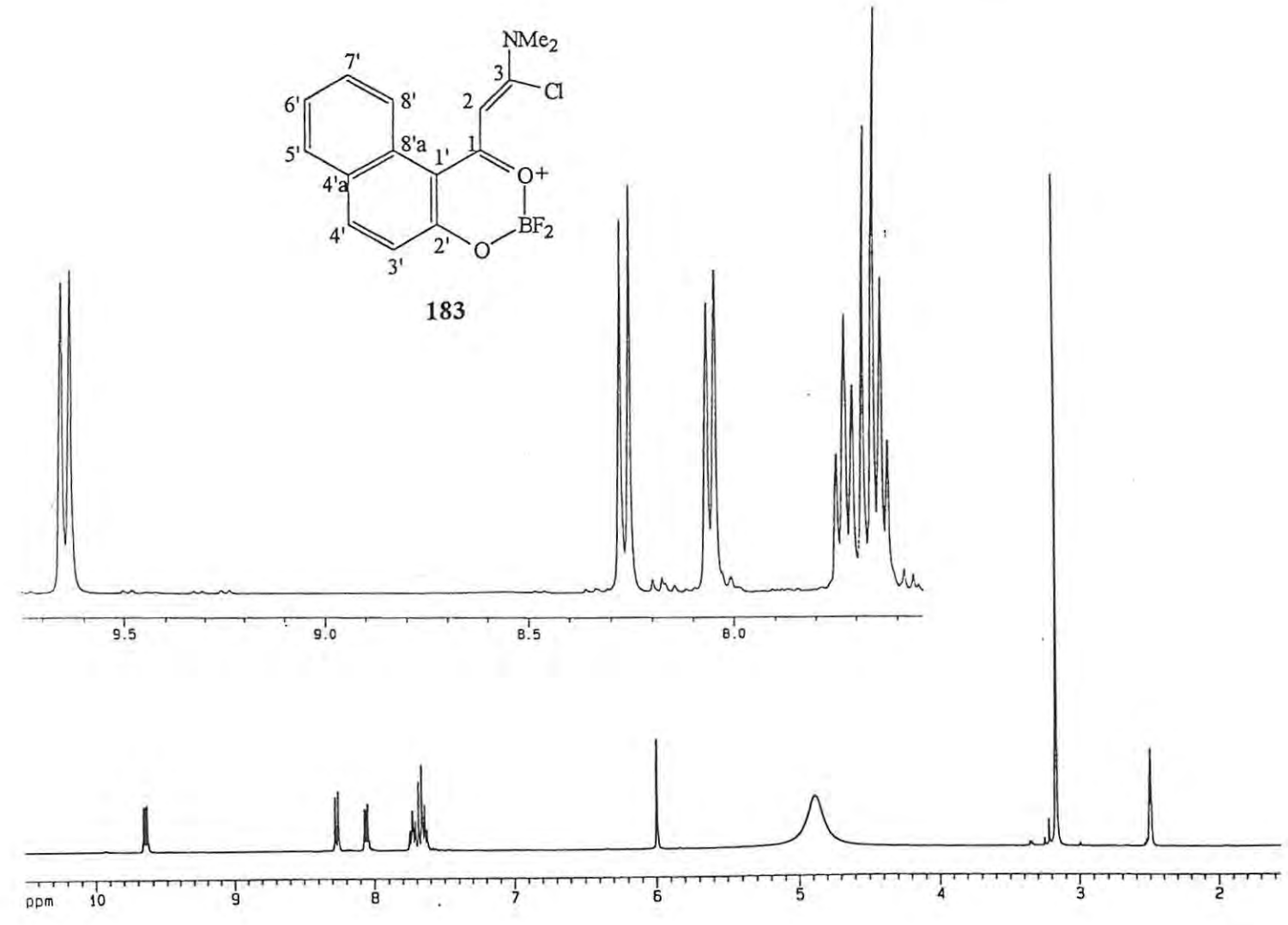


Figure 12 400 MHz ^{1}H NMR spectrum of 1-(2-hydroxynaphthyl)ethanone, boron difluoride complex (**180**) and 3-chloro-3-(*N*,*N*-dimethylamino)-1-(2-hydroxynaphthyl)propenone, boron difluoride complex (**183**).

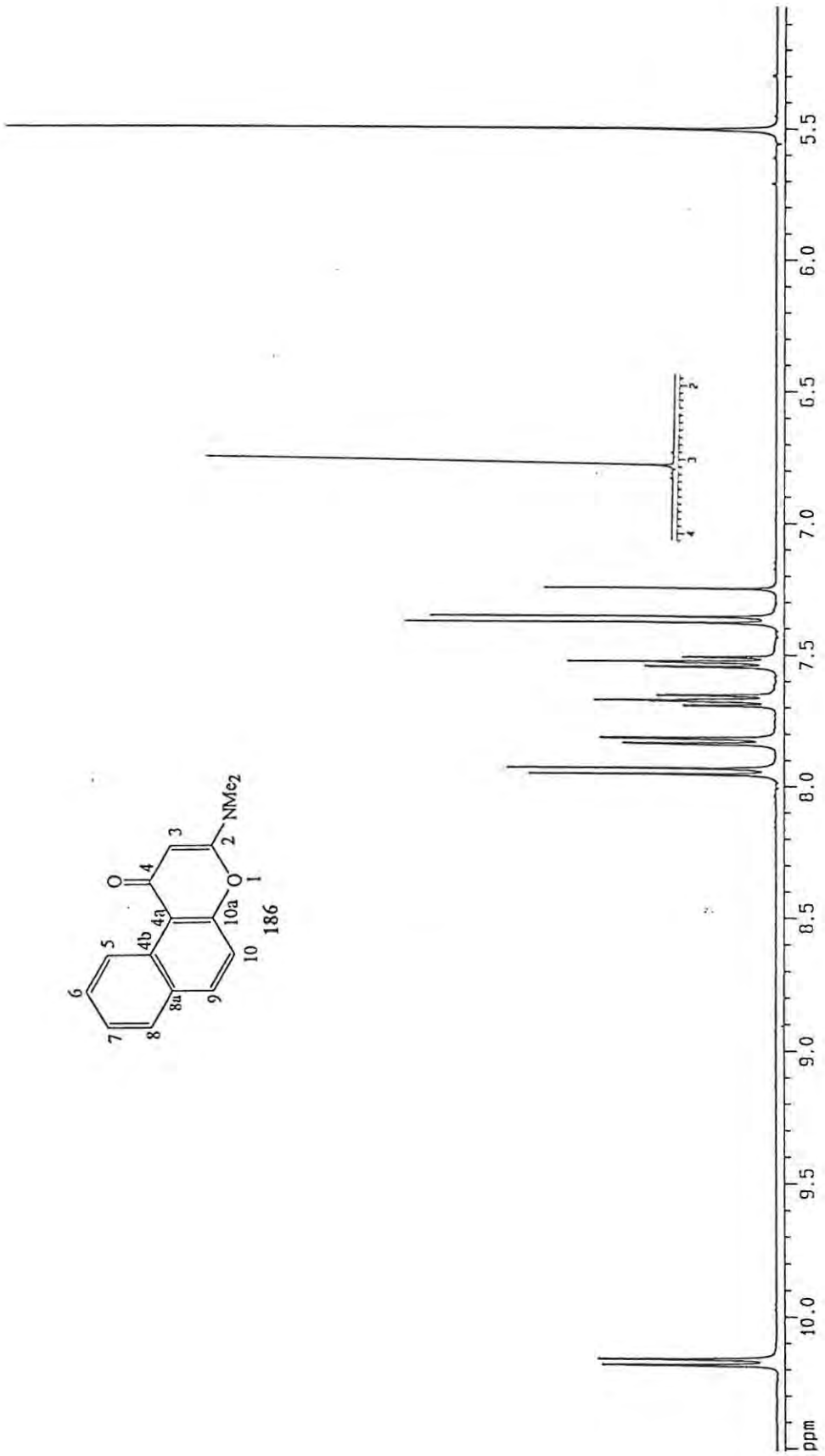
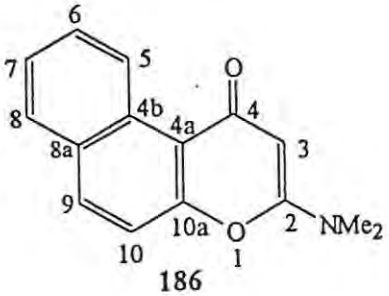


Figure 13 400 MHz ^{1}H NMR spectrum of 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-*e*]pyran-4-one (**186**).



186

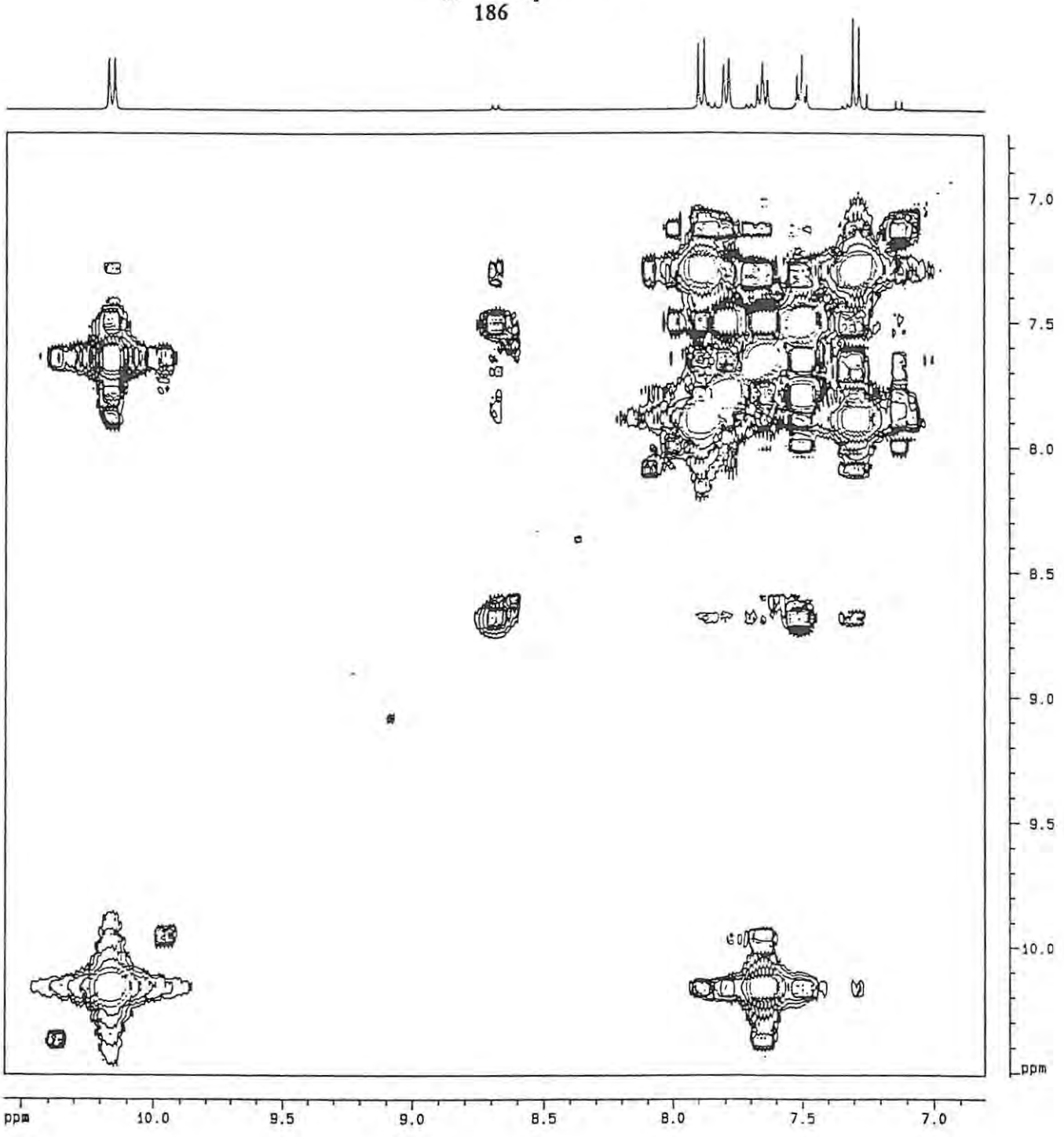


Figure 14 Partial 400 MHz COSY spectrum of 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-*e*]pyran-4-one (**186**)

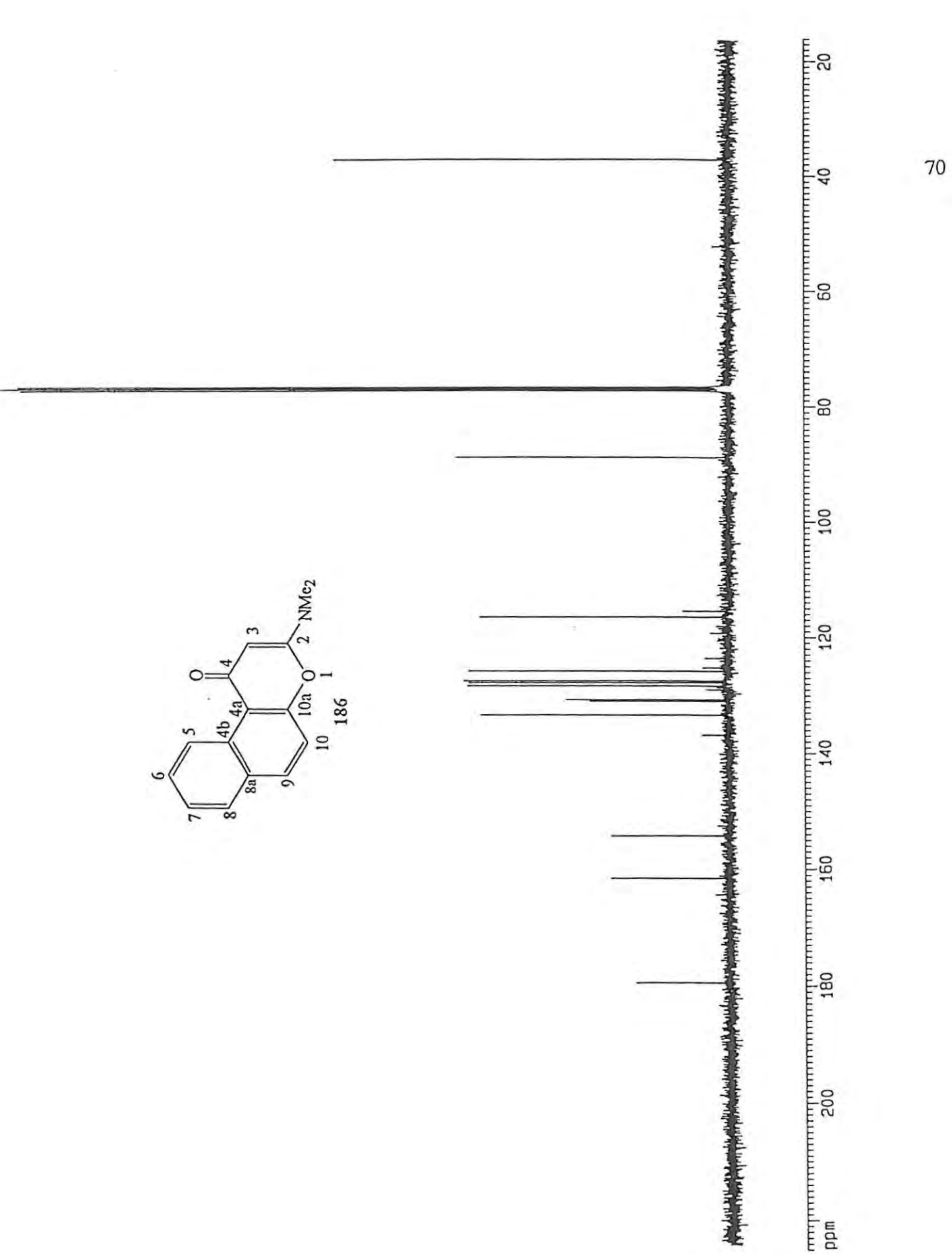
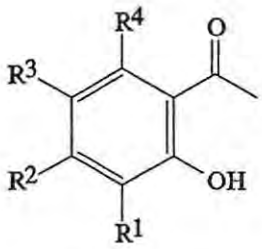
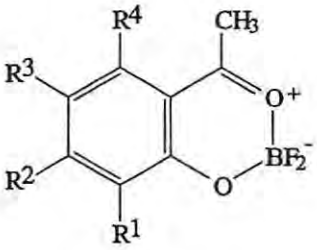


Figure 15 100 MHz ^{13}C NMR spectrum of 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-*e*]pyran-4-one (**186**)



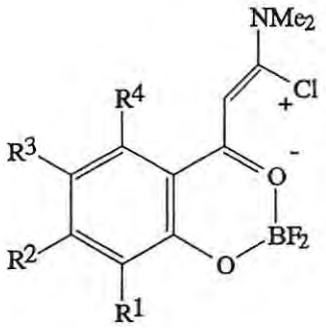
178 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
179 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$
136 $R^1 = H$; R^2 & $R^3 = C_6H_4$; $R^4 = H$

i



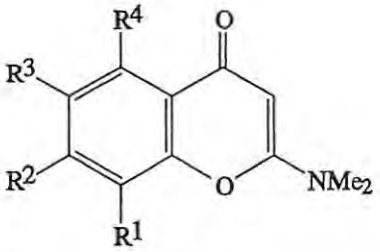
180 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
181 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$
182 $R^1 = H$; R^2 & $R^3 = C_6H_4$; $R^4 = H$

ii



183 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
184 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$
185 $R^1 = H$; R^2 & $R^3 = C_6H_4$; $R^4 = H$

iii



186 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
187 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$
188 $R^1 = H$; R^2 & $R^3 = C_6H_4$; $R^4 = H$

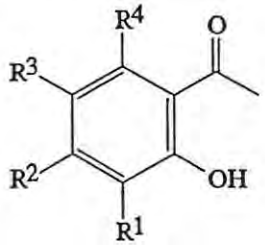
Reagents: i) $BF_3.OEt_2$, dry Et_2O; ii) $Cl_2C{=}N^+Me_2Cl^-$ (**142**), $Cl(CH_2)_2Cl$; iii) MeOH, *ca.* 50°C

Scheme 47

2.1.3 Preparation of ethyl 4-oxo-4*H*-naphthopyran-2-carboxylates

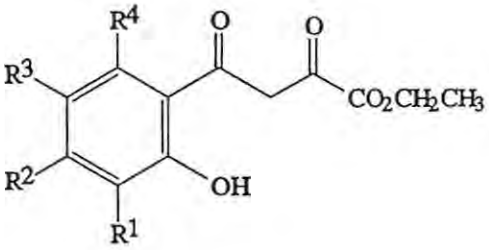
The ethyl 4-oxo-4*H*-naphthopyran-2-carboxylates (**196**) and (**197**) were generally prepared by acylation of the *o*-hydroxyacetonaphthone (**178**) and (**179**) with diethyl oxalate, followed by cyclization of the diketo ester and subsequent dehydration by a method described by Fitton *et al.*[75] (**Scheme 48**).

Two types of intermediate are generally isolated as mixtures, *viz.*, the diketones (**189**) and (**190**) and the hydroxychromanones (**192**) and (**193**) . The diketone is readily distinguished from the hydroxychromanone by ^{1}H NMR spectroscopy. The presence of doublets at δ *ca.* 3.04 and 3.51 can only be assigned to the hydroxychromanone. The corresponding protons in the isomeric diketone resonate as a singlet at δ 2.16. No attempt was made to separate the two isomers, and, in each case, the mixture was used directly without any further purification. The ^{1}H NMR signals of the product are generally at a higher field than those corresponding signals of the precursor diketone or hydroxychromanone. Use of COSY and HETCOR experiments simplified the interpretation of both the ^{1}H and ^{13}C NMR spectra. Figures 16 illustrate the ^{1}H NMR spectra of the intermediates (**189**) and (**192**), while Figures 17 and 18 show the ^{1}H and ^{13}C NMR spectra of the final product (**196**).



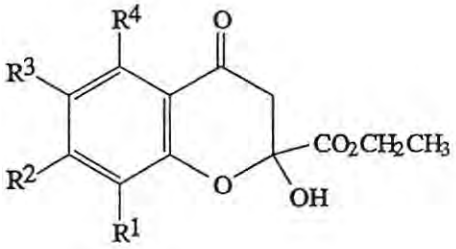
178 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
179 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

i



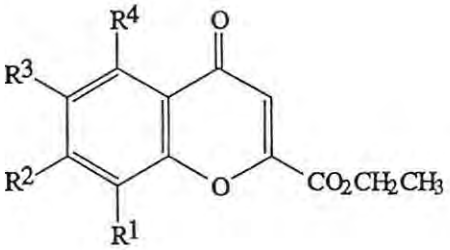
189 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
190 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

+



192 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
193 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

ii



196 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
197 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

Reagents: i) NaOEt-EtOH, $(CO_2Et)_2$; ii) AcOH, HCl (trace)

Scheme 48

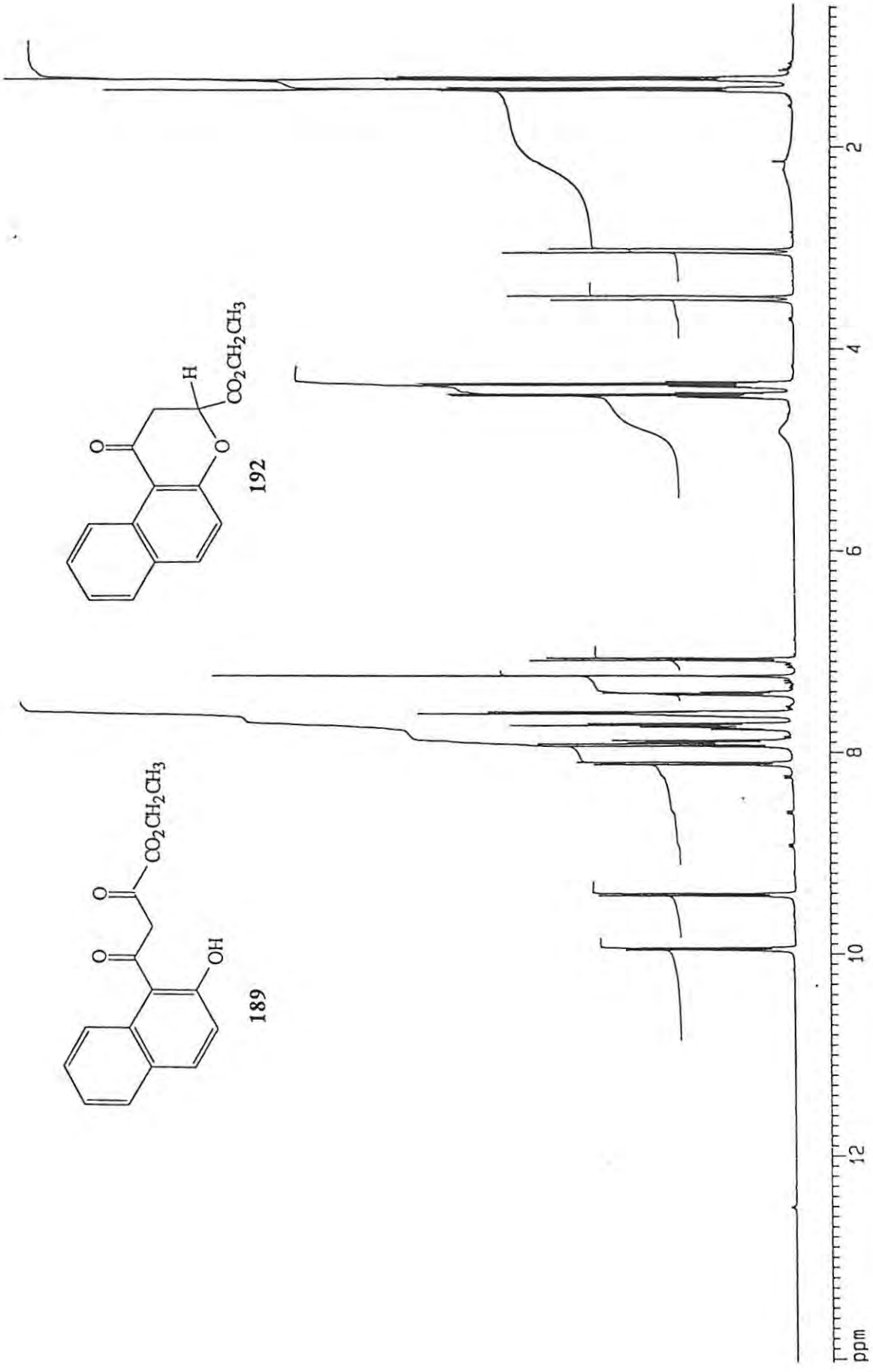


Figure 16 400 MHz ^{1}H NMR spectrum of ethyl 4(-2-hydroxynaphthyl)-2,4-dioxobutanoate (**189**) and ethyl 2-hydroxy-3-hydro-2,3-dihydro-4-oxo-4*H*-naphtho[1,2*e*]pyran-2-carboxylate (**192**).

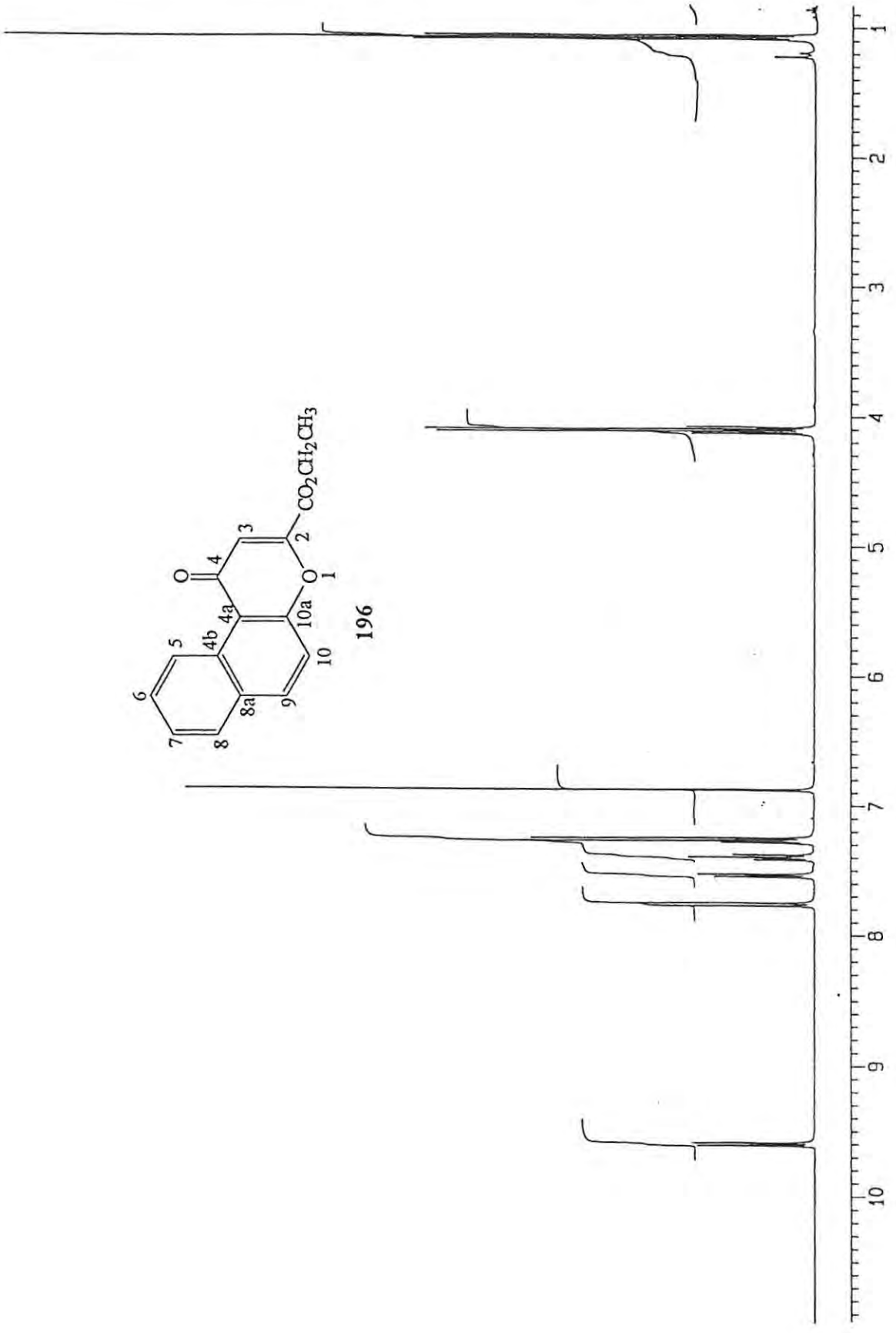


Figure 17 400 MHz ^{1}H NMR spectrum of ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**196**).

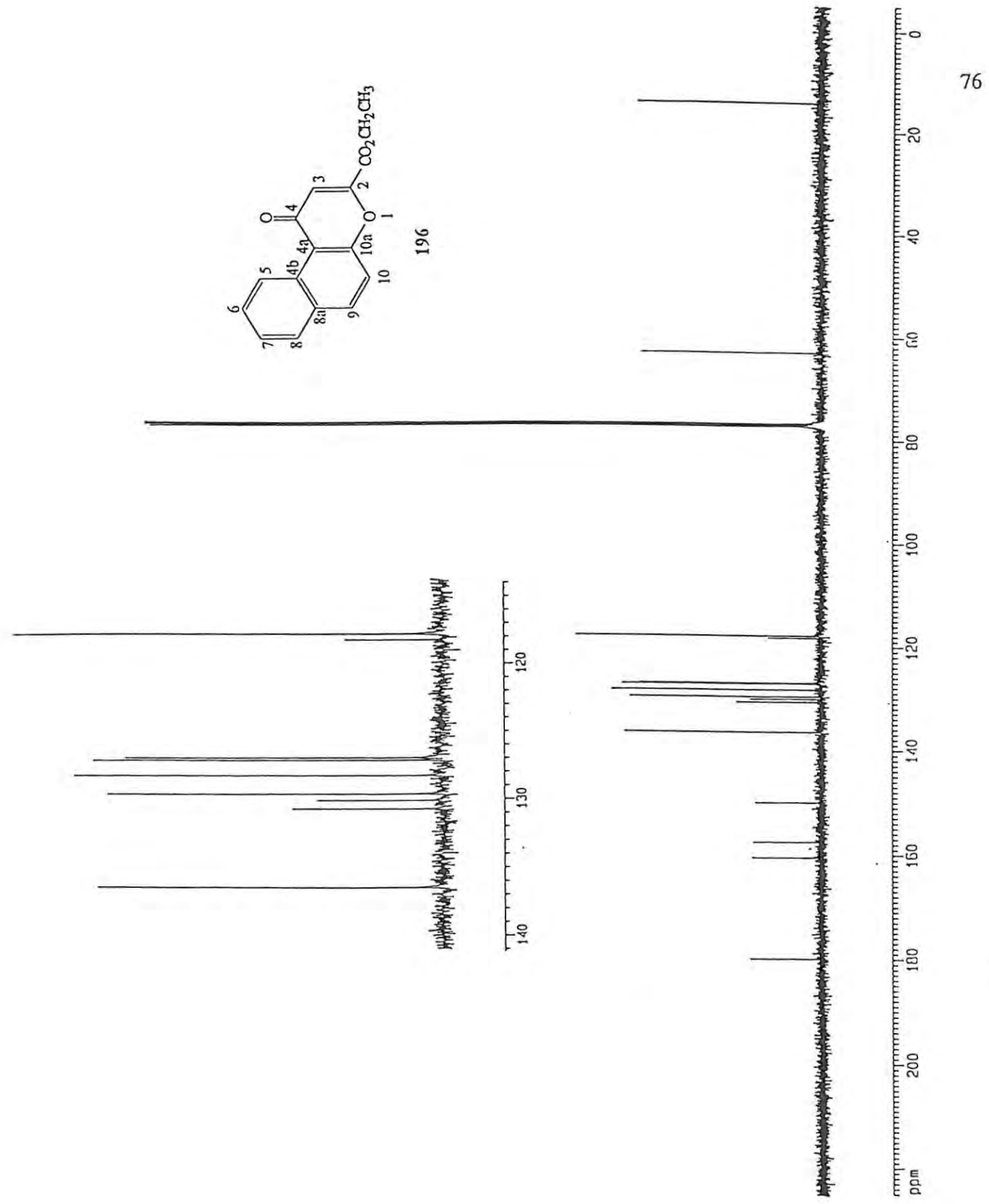


Figure 18 100 MHz ^{13}C NMR spectrum of ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**196**).

2.1.4 Preparation and ring-opening of *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamides

The acrylamides (**215** - **217** and **219**), required for the completion of MS, DNMR[56] and other studies on these derivatives, were prepared by ring-opening reactions of the corresponding *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamides.

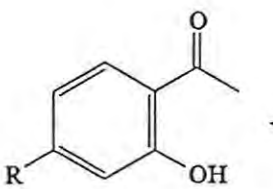
2.1.4.1 Preparation of *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamides

N,N-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamides (**212** - **214**)[76] were prepared from their corresponding 4-oxo-4*H*-1-benzopyran-2-carbonyl chlorides (**209** - **211**) obtained, in turn, from their respective 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (**206** - **208**) (**Scheme 49**) by treatment with thionyl chloride and *N,N*-dimethylformamide in 1,2-dichloroethane, as described by Ellis *et al.*.[77] 1-Pyrrolidine-4-oxo-4*H*-1-benzopyran-2-carboxamide (**218**) was prepared by treatment of 4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**209**) with pyrrolidine in the presence of sodium hydrogen carbonate. The 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (**206** - **208**), required as intermediates in this synthesis, were obtained by Claisen acylation of the corresponding *o*-hydroxyacetophenones (**124**, **127** and **129**) with diethyl oxalate in the presence of sodium ethoxide, followed by cyclization of the intermediate and subsequent dehydration, as described in the literature[75,78] and outlined in **Scheme 49**.

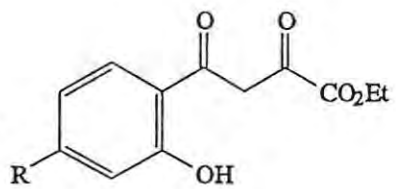
The acrylamides (**215**) and (**219**) were then obtained from their respective 4-oxo-4*H*-1-benzopyran-2-carboxamides by treatment with 33% w/w ethanolic dimethylamine, whilst acrylamides (**216**) and (**217**) were obtained by treatment of the amide precursors with

ethanolic glycine ethyl ester. Figure 19 shows the ^{1}H NMR spectra of the intermediate carboxamide (**214**), and Figures 20 - 22 show the ^{1}H NMR, COSY and ^{13}C NMR spectra of the final product (**216**).

The yields of compounds (**216**) and (**217**) were generally low in spite of longer reaction times. The pyrrolidine carboxamide (**218**) was synthesized in order to differentiate NMe_2 and $CONMe_2$ signals in the ^{1}H NMR spectra of the acrylamides.

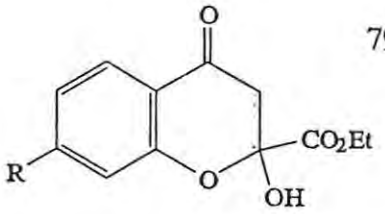


R		
	H	124
	Cl	127
	OMe	129



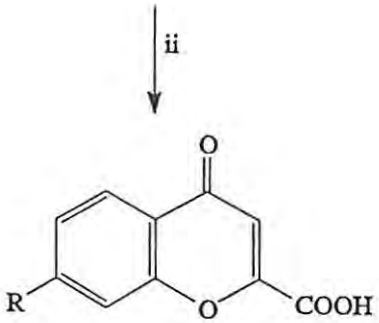
R		
	H	201
	Cl	202
	OMe	204

+

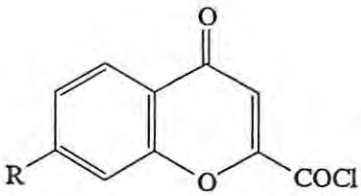


R		
	Cl	203
	OMe	205

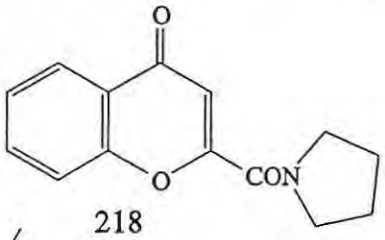
Reagents:
i) NaOEt-EtOH, $(CO_2Et)_2$
ii) AcOH-HCl (1:1)
iii) $SOCl_2$-DMF-$Cl(CH_2)_2Cl$, Δ
iv) Me_2NH_2Cl (**199**)-pyridine, 0°C
v) pyrrolidine- aq. $NaHCO_3$
vi) 33% w/w ethanolic Me_2NH for **215**
vii) $EtO_2CCH_2NH_3^+Cl^-$ (**200**) for **216** and **217**



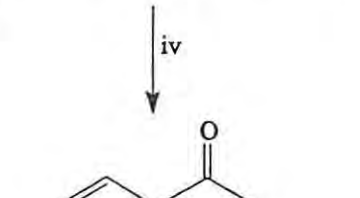
R			
	H	Cl	OMe
	206	207	208

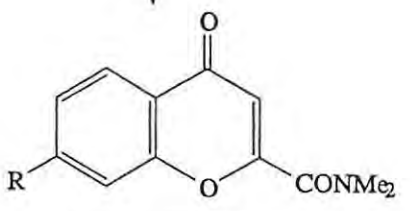


R			
	H	Cl	OMe
	209	210	211

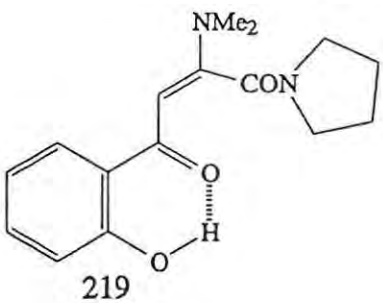


218



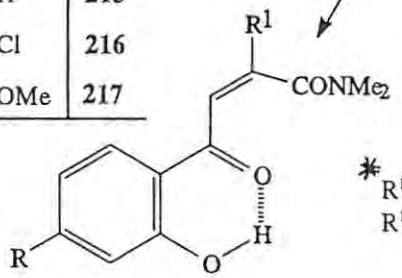


R			
	H	Cl	OMe
	212	213	214



219

R*	
H	**215**
Cl	**216**
OMe	**217**



* $R^1 = NMe_2$ (**215**)
$R^1 = NHCH_2CO_2CH_2CH_3$ (**216** & **217**)

Scheme 49

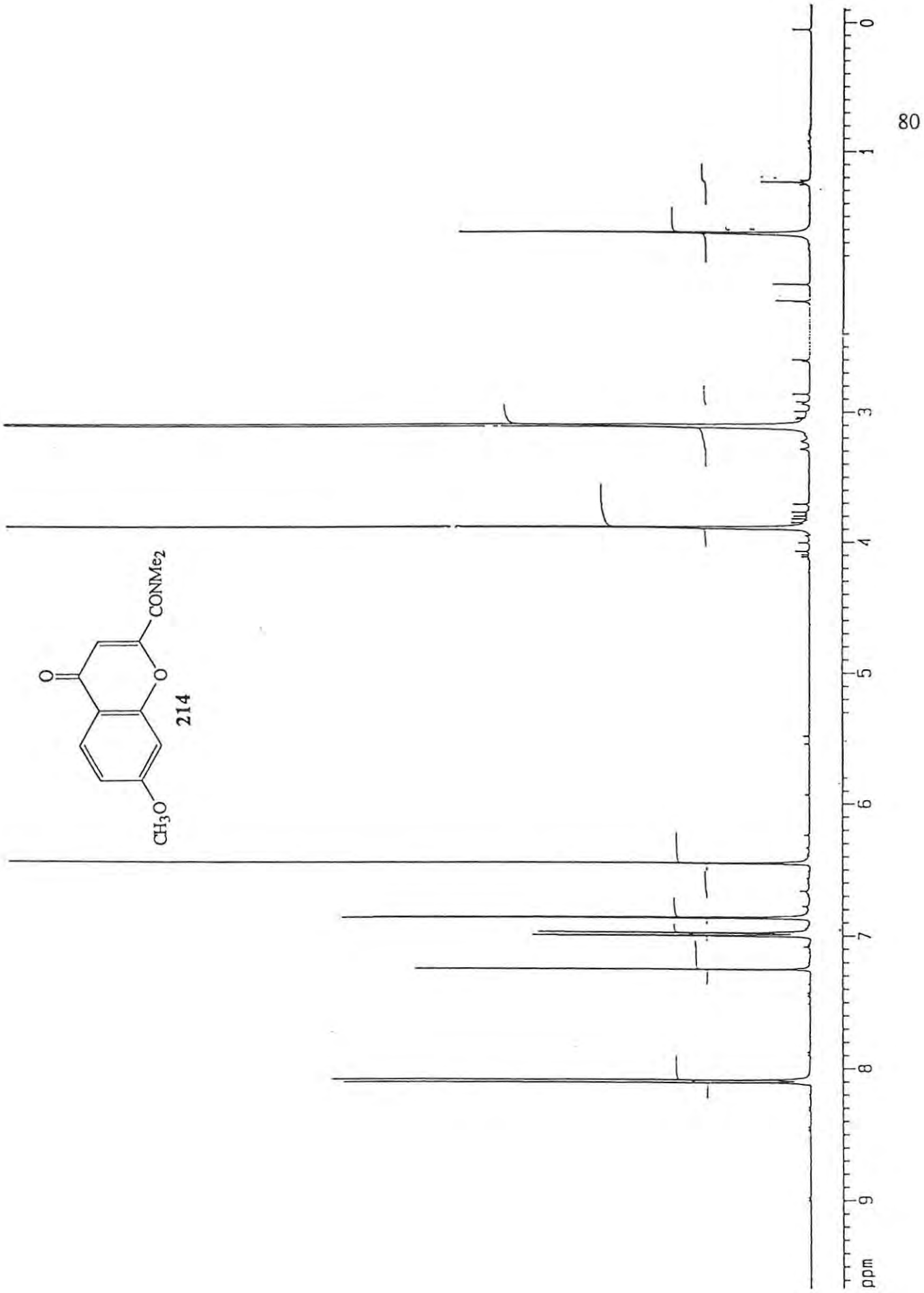


Figure 19 400 MHz ^{1}H NMR spectrum of 7-methoxy-*N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**214**).

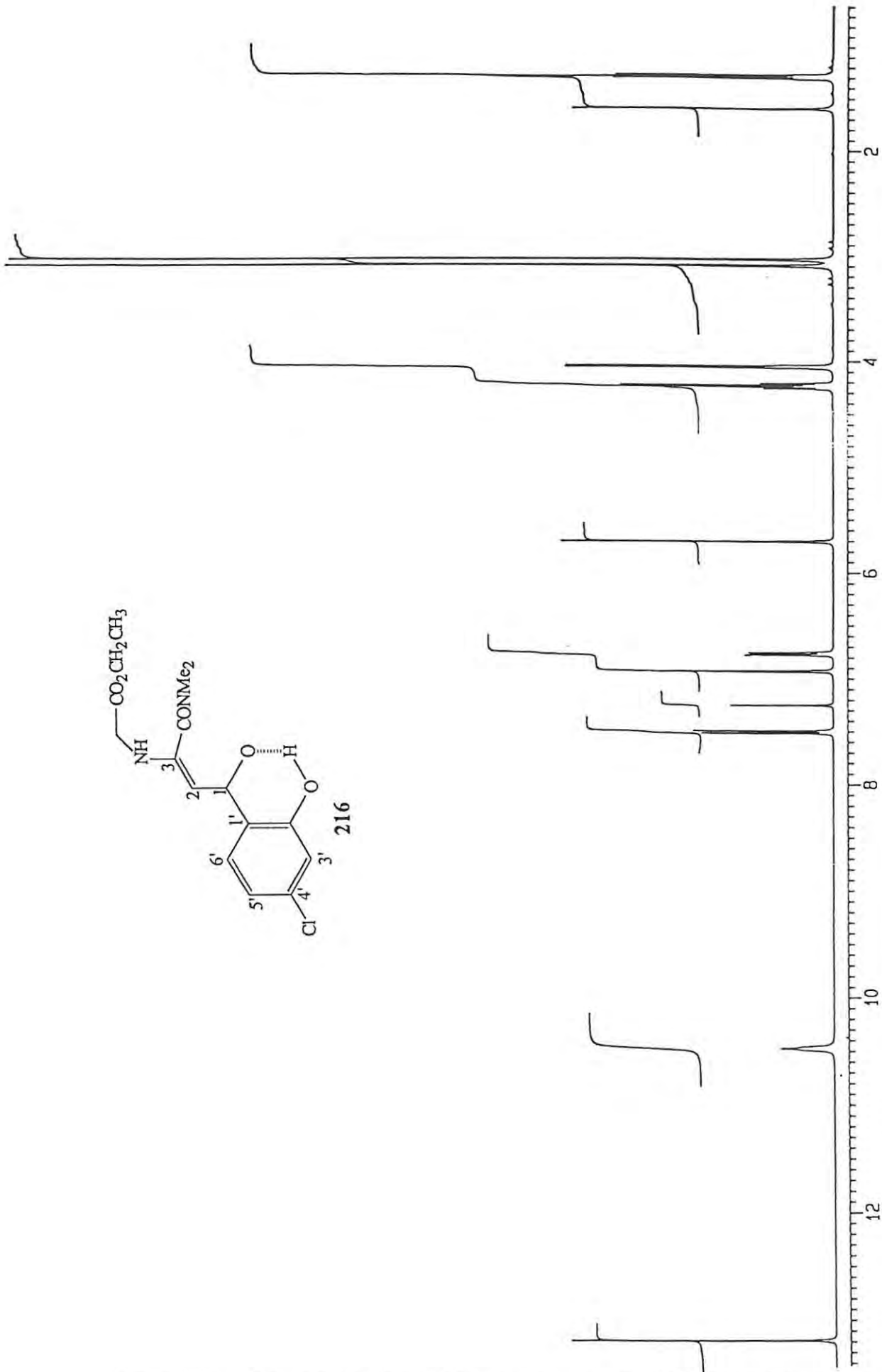


Figure 20 400 MHz ^{1}H NMR spectrum of 3-(4-chloro-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-*N,N*-dimethylacrylamide (**216**).

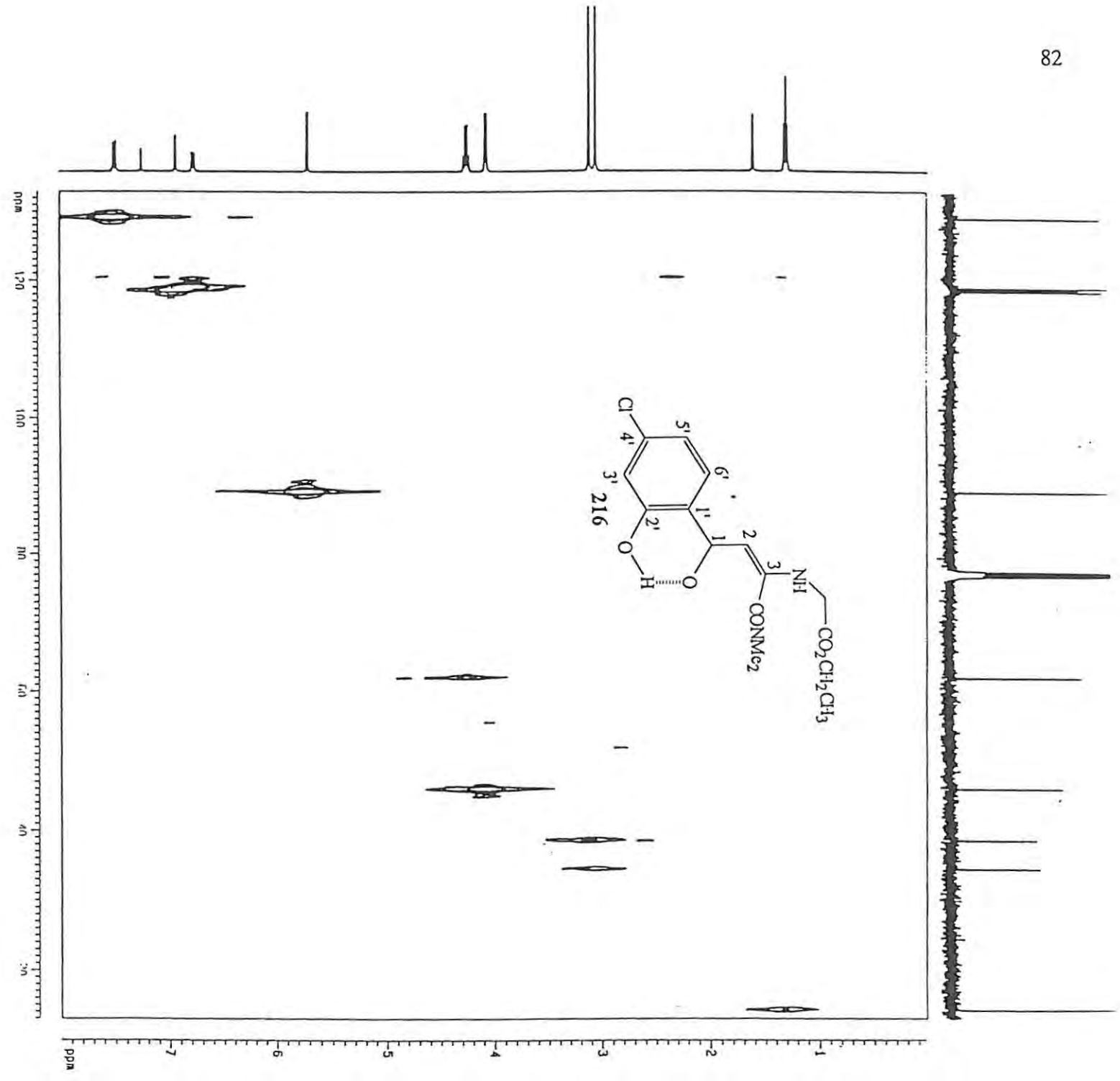


Figure 21 400 MHz HETCOR spectrum of 3-(4-chloro-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-*N*,*N*-dimethylacrylamide (**216**).

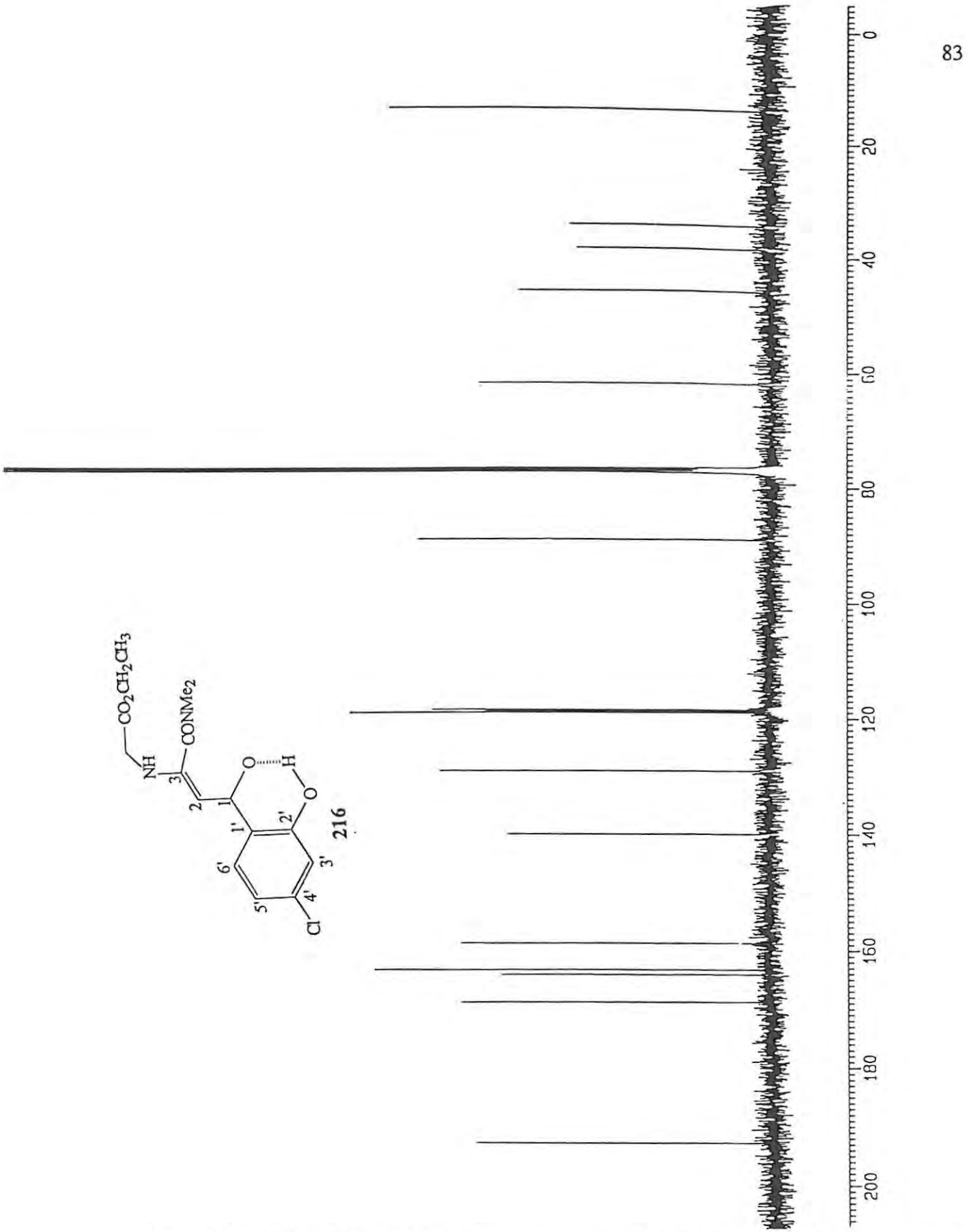


Figure 22 100 MHz ^{13}C NMR spectrum of 3-(4-chloro-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-*N,N*-dimethylacrylamide (**216**).

2.1.4.2 Ring-opening of ethyl 4-oxo-4*H*-naphthopyran-2-carboxylates

It was considered that ring-opened 4-oxo-4*H*-naphthopyran-2-carboxylates might be useful in DNA intercalation studies as it is anticipated that such intercalation could be facilitated by their extensive planar structure. Consequently, some attention was given to exploring synthetic pathways to these systems.

In the treatment of a mixture of 4-oxo-4*H*-naphthopyran-2-carboxylates (**196** and **197**) with 33% w/w ethanolic dimethylamine we expected to isolate compounds (**223** and **224**). However, compounds (**220** - **222**) were obtained.

Thus, treatment of ethyl 4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxylate (**198**) with excess 33% w/w ethanolic dimethylamine afforded the starting material, together with *N,N*-dimethyl-4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxamide (**220**)[20%] and 2-(dimethylamino)-3-(2-hydroxy-naphthoyl)-*N,N*-dimethylacrylamide (**221**)[9%]. However, treatment of ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**197**) with excess 33% w/w ethanolic solution of dimethylamine afforded 2-(dimethylamino)-3-(1-hydroxy-2-naphthoyl)-*N,N*-dimethyl-acrylamide (**222**), as the only product, in 70% yield. Figures 17 and 23 show the ^{1}H NMR spectra of the intermediate (**196**) and final products (**220**) and (**221**), respectively. Figure 24 shows HETCOR spectra of the final products (**220**) and (**221**), while Figure 25 is the ^{13}C NMR spectrum of compound (**220**).

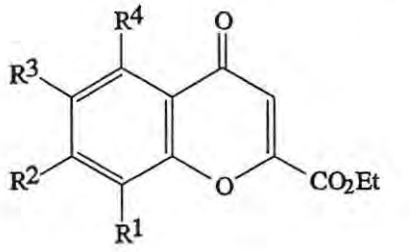
The above observed reaction is perhaps not surprising because in a related study,[79] it has been reported that ammonolysis of ethyl 4-oxo-4*H*-1-benzopyrancarboxylate with 1 equivalent of amine afforded the carboxamide, whilst the use of two equivalents of the amine gave the

acrylamide. Figure 26 shows the ^{1}H NMR spectrum of the starting material (**197**) and the final product (**222**), while Figure 27 is the COSY spectrum of the product (**222**).

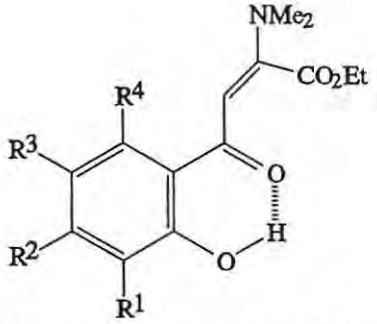
In the case of ethyl 4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxylate (**196**), the reaction mixture had to be warmed to *ca.* 55°C to effect dissolution, and for ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate the mixture was warmed to *ca.* 50°C. In both cases, after dissolution, the reaction proceeded and was monitored by TLC. ^{1}H and ^{13}C NMR spectra were also interpreted with the aid of complete COSY and HETCOR data. In *N,N*-dimethyl-4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxamide (**220**) the vinyl 3-H proton resonates at δ 6.70 ppm, while in the ring-opened derivative (**221**) the corresponding proton appears much further upfield at δ 5.79 ppm. The appearance of the hydrogen-bonded hydroxyl signal at 12.37 ppm in the ring-opened compound (**221**) [absent in compound (**220**)] clearly distinguishes it from its carboxamide precursor (**220**). The dimethylamino and carboxamide signals of the ring-opened product (**221**) appear as two singlets at high field, while the aromatic protons of the carboxamide (**220**) generally appear downfield of the corresponding signals of the ring-opened acrylamide derivative (**221**). In the ^{13}C NMR spectra of the carboxamide (**220**), the C-4 (carbonyl) signal appears at δ *ca.* 179 ppm, while in the ring-opened acrylamide (**221**) it is shifted slightly downfield to δ *ca.* 190 ppm. The vinyl carbon (C-3) of the carboxamide (**220**) resonates at δ *ca.* 115 ppm while in the ring-opened product (**221**) the signal appears upfield at δ *ca.* 97 ppm.

In the event, time did not permit the evaluation of these compounds in DNA intercalation.

196 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
197 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

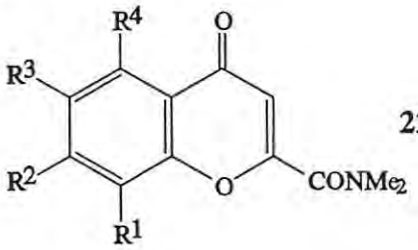


i



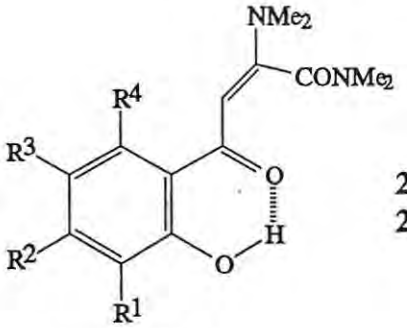
223 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
224 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

i



220 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$

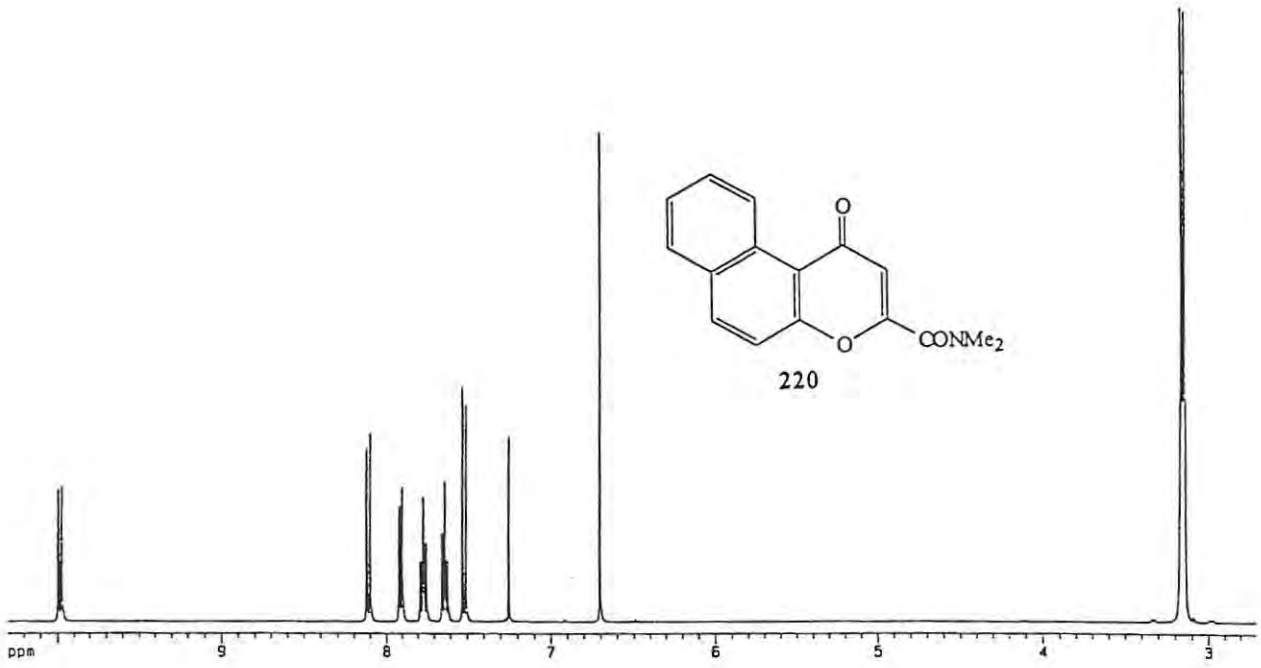
+



221 $R^1 = R^2 = H$; R^3 & $R^4 = C_6H_4$
222 R^1 & $R^2 = C_6H_4$; $R^3 = R^4 = H$

Reagents: i) 33% w/w ethanolic Me_2NH

Scheme 50



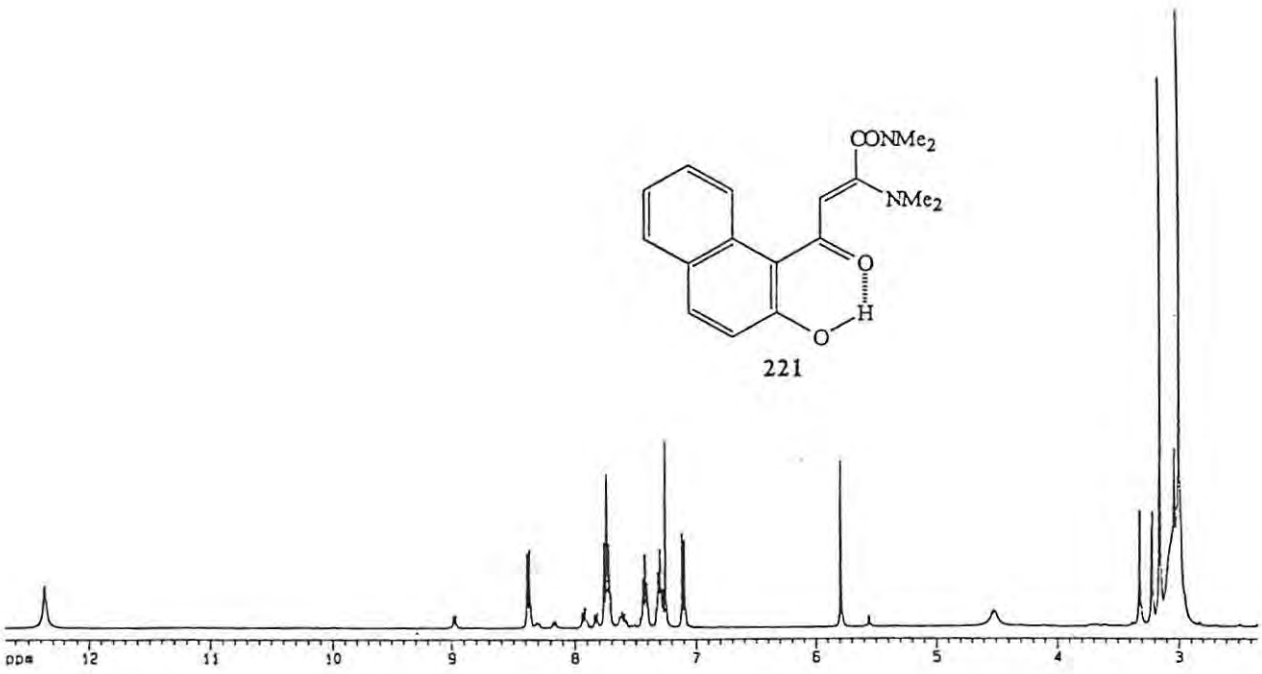


Figure 23 400 MHz ^{1}H NMR spectrum of *N,N*-dimethyl-4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxamide (**220**) and 2-(dimethylamino)-3-(2-hydroxynaphthyl)-*N,N*-dimethylacrylamide (**221**).

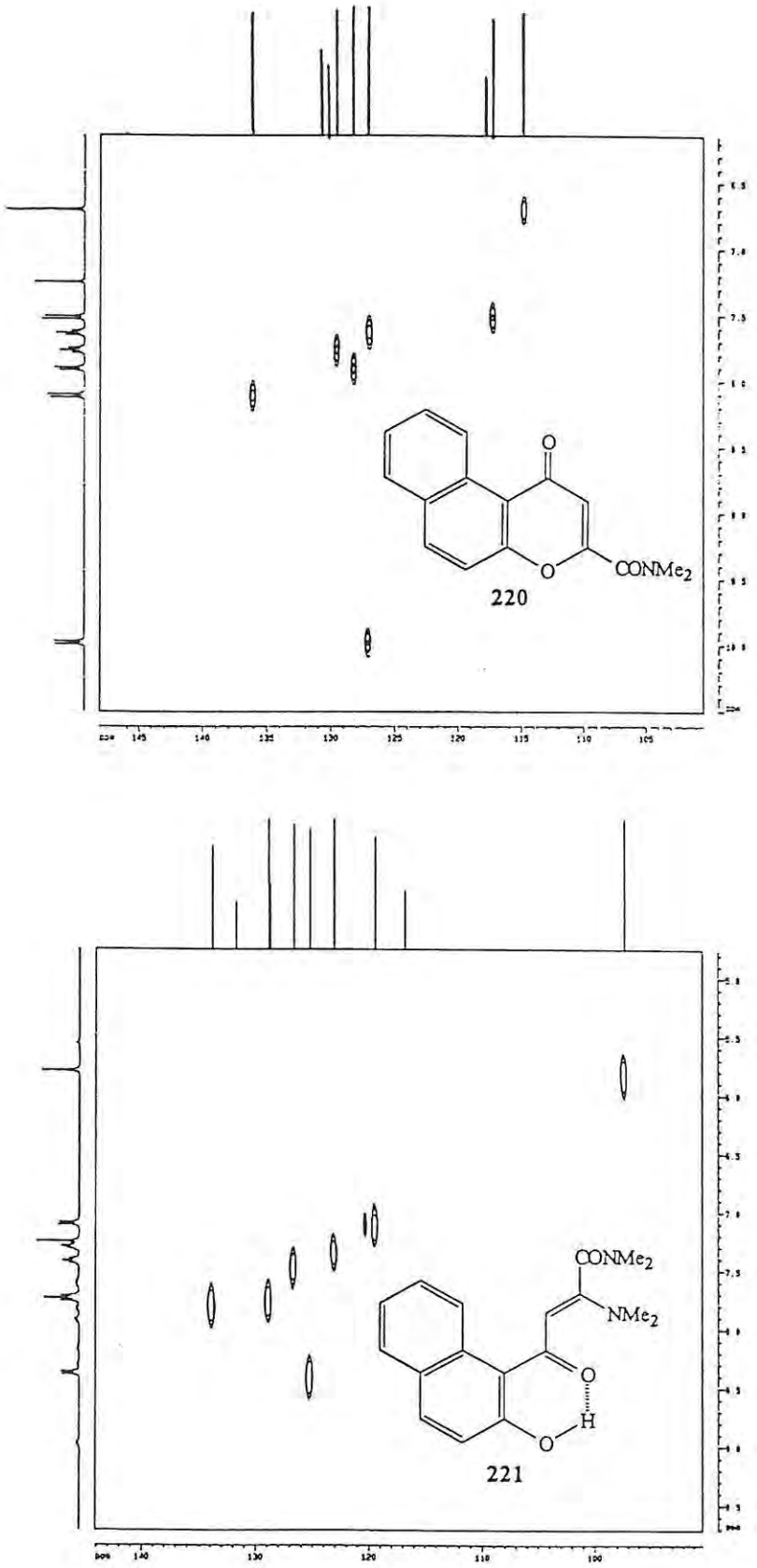


Figure 24 400 MHz HETCOR spectrum of *N,N*-dimethyl-4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxamide (**220**) and 2-(dimethylamino)-3-(2-hydroxynaphthyl)-*N,n*-dimethylacrylamide (**221**).

Figure 25 100 MHz ^{13}C NMR spectrum of *N,N*-dimethyl-4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxamide (**220**).

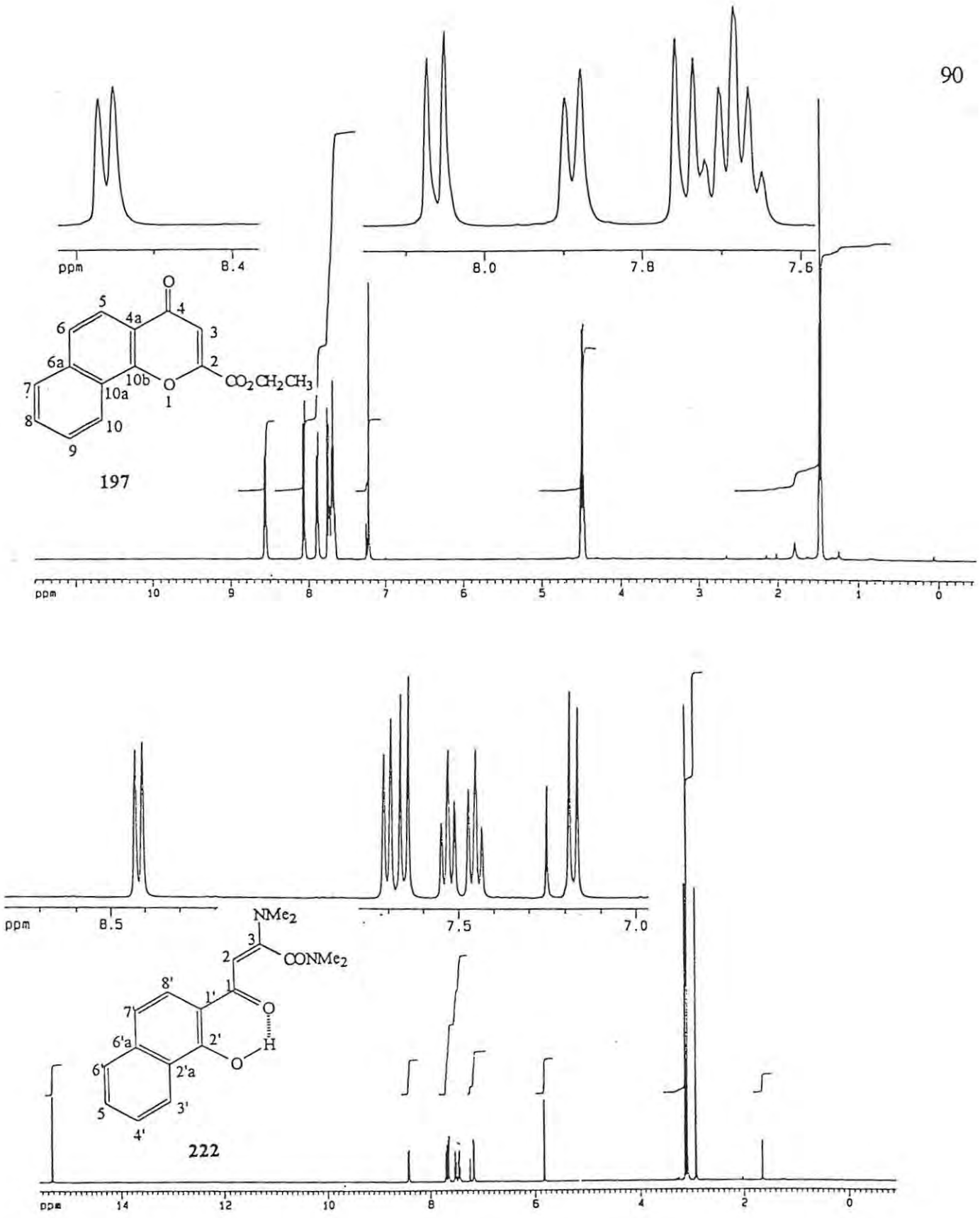


Figure 26 400 MHz ^{1}H NMR spectrum of ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**197**) and *N,N*-dimethyl-2-(dimethylamino)-3-(1-hydroxy-2-naphthoyl)-acrylamide (**222**)

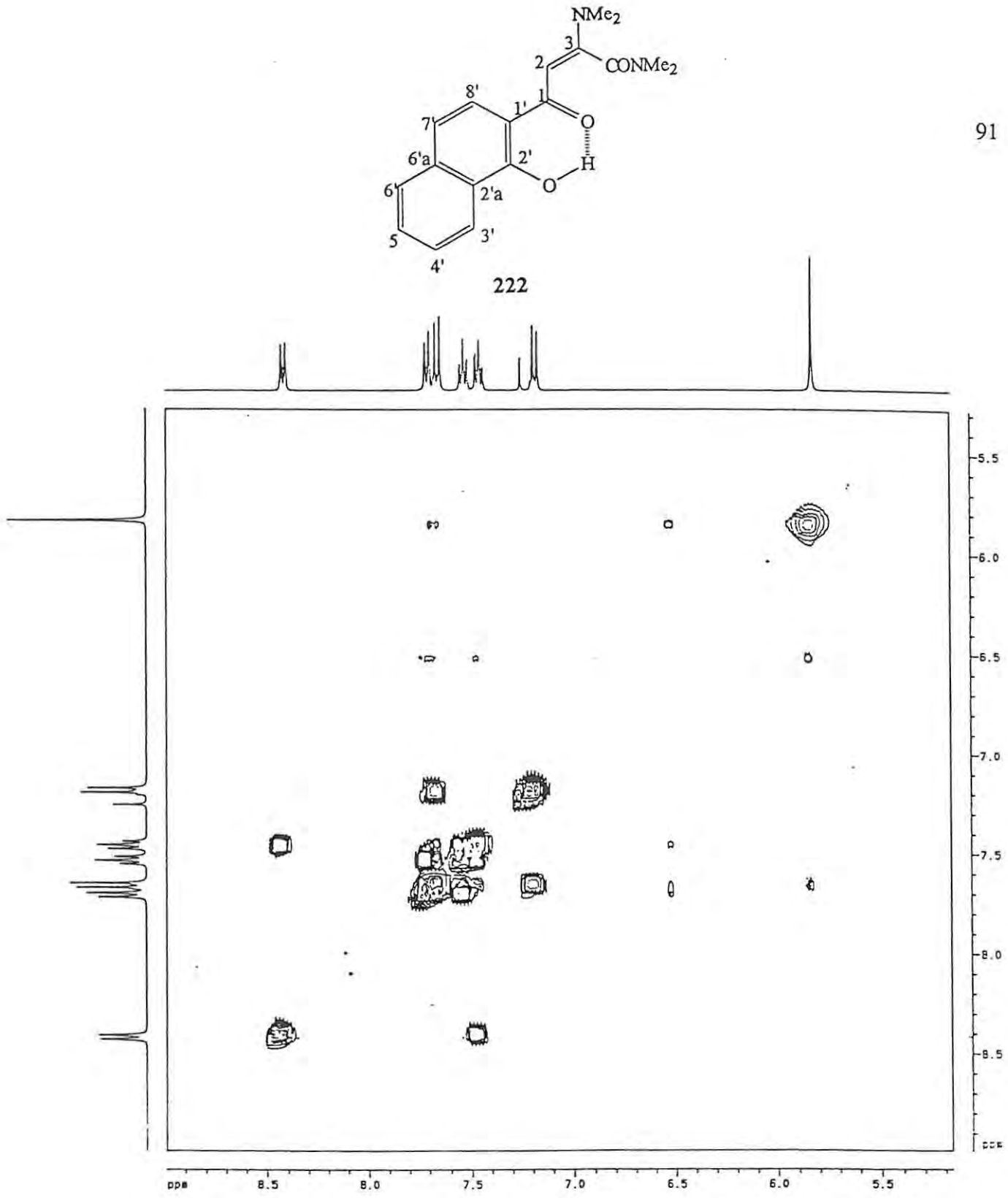


Figure 27 400 MHz COSY spectrum of 2-(dimethylamino)-3-(1-hydroxy-2-naphthoyl)-*N,N*-dimethylacrylamide (**222**)

2.2 Spectroscopic studies of 4*H*-1-benzopyran-4-one derivatives

Previous 4-*H*-benzopyran-4-one studies in our research group have included:- an IR study of rotational isomerism in 4-oxo-4*H*-1-benzopyran-2-carboxylate esters,[81] a Dynamic NMR (DNMR) study of rotational isomerism in 4-oxo-4*H*-1-benzopyran-2-carboxamides,[82] the configurational and conformational preferences of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-acrylamides,[83] and the kinetics of their formation *via* dimethylamine-mediated ring-opening of 4-oxo-4*H*-1-benzopyran-2-carboxamides.[84]

In the discussion which follows, we report the completion of mass spectrometric[85] and rotational isomerism studies[86] initiated previously[56] (Sections 2.2.1 and 2.2.3) and the results of new studies on the mass fragmentation and internal rotation of 2-dialkylamino-4*H*-1-benzopyran-4-one derivatives (Sections 2.2.2 and 2.2.4).

2.2.1 Mass spectrometric studies of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-acrylamides.[56,85]

The synthesis and characterization of the 2-(dimethylamino)-3-(2-hydroxybenzoyl)acrylamides (**215, A - D**) have been reported previously,[56] whilst compound **219** is described in the discussion section 2.1.8.. These compounds were required for the completion of mass spectrometric studies, commenced as part of an MSc programme.[56] The major fragmentation patterns shown by these acrylamides is illustrated for compound **215** in Fig. 28, while comparative low-resolution data for the series of compounds examined is summarised in Table 6.

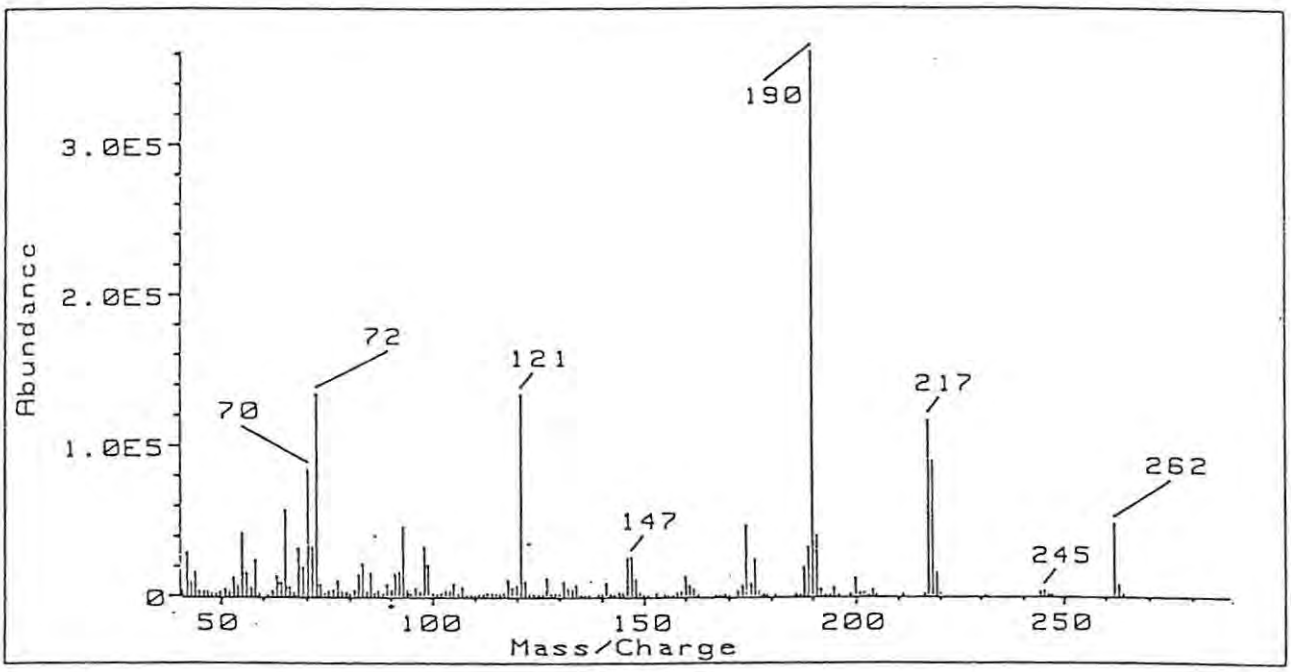


Figure 28 E.I. Mass spectrum of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**)

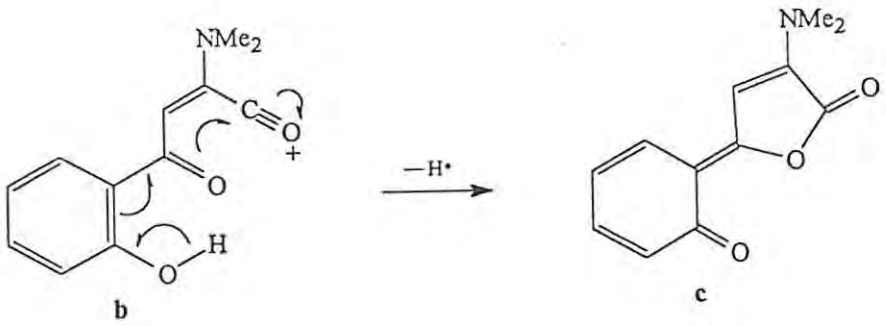
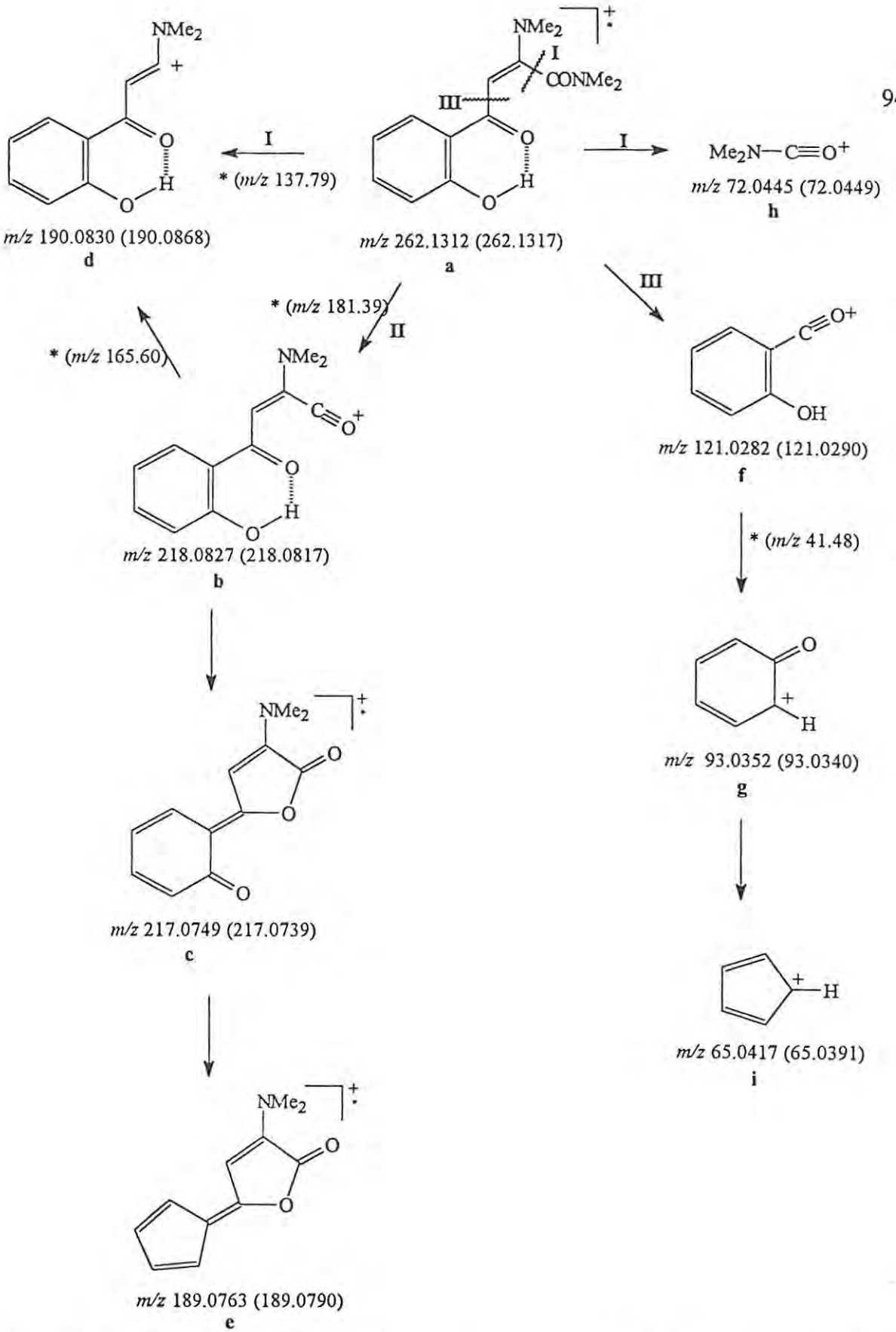
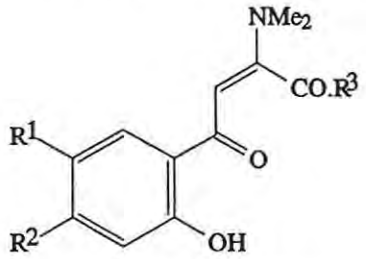


Figure 29 Proposed rearrangement of fragment **b**



Scheme 51 E.I. Mass fragmentation pathways for 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**). Accurate masses (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by the metastable peak given in parentheses.

Table 6 Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from E.I. mass spectra of the 2-(dimethylamino)-3-(2-hydroxybenzoylacrylamides (**215**), (**A** - **D**) and (**219**), classified according to ion types **a** - **i** (**Scheme 51**).



				Ion type								
Compd	R^1	R^2	R^3	a	b	c	d	e	f	g	h	i
215	H	H	NMe_2	262[a]	218[a]	217[a]	190[a]	189[a]	121[a]	93[a]	72[a]	65[a]
				(13)	(25)	(32)	(100)	(9)	(37)	(13)	(37)	(16)
A	H	Cl	NMe_2	296[b]	252[b]	251[b]	224[b]	223[b]	155[b]	127[b]	72	99[b]
				(18)	(26)	(80)	(100)	(15)	(33)	(18)	(71)	(30)
B	Cl	H	NMe_2	296[b]	252[b]	251[b]	224[b]	223[b]	155[b]	127[b]	72	99[b]
				(12)	(17)	(48)	(59)	(9)	(22)	(12)	(36)	(25)
C	OMe	H	NMe_2	292	248	247	220	219	151	123	72	95
				(16)	(25)	(99)	(100)	(6)	(23)	(10)	(74)	(20)
D	NO_2	H	NMe_2	307	263[a]	262[a]	235[a]	234[a]	166	138	72	110
				(16)	(32)	(35)	(38)	(7)	(11)	(4)	(49)	(8)
219	H	H	$N(CH_2)_3CH_2$	288	218	217	190	189	121	93	98	65
				(6)	(31)	(51)	(100)	(19)	(72(	(27)	(15)	(25)

[a]Atomic composition confirmed by high resolution MS analysis
[b]*M/z* value corresponds to ^{35}Cl

A combination of high resolution, comparative low-resolution mass spectrometric analysis and metastable-peak data has allowed the elucidation of the major mass fragmentation patterns shown by the polyfunctional acrylamide derivatives (**215**, **A** - **D** and **219**).

From the pathways proposed in **Scheme 51**, it is clear that fragmentation of the molecular ion **a** follows three general pathways (I, II and III). In pathway I, cleavage of the carboxamide group leads to the resonance-stabilized cations **d** and **h**, fragment **d** being responsible for the base peak in most compounds studied.

The non-hydrogen atoms in fragment **b** (pathway II) are coplanar, allowing the extension of p-π delocalization to include, and thereby stabilize the acylium moiety, a situation prevented in the molecular ion **a** by the sterically determined orthogonal arrangement of the carboxamide function. The formation of the even-electron species **d** *via* decarboxylation of fragments of type **b** (i.e. **a** → **b** → **d**) is supported by metastable-peak data. Loss of a hydrogen radical from the cationic species **b** is proposed to involve intramolecular rearrangement to the γ-lactone radical cation **c** (Fig. 29), which when decarbonylated affords the odd-electron species **e**.

In pathway III, classic α-fission of the aryl ketone system is responsible for the conjugated acylium cation **f**. Successive decarbonylation then leads *via* the cyclohexadienone species **g** to the cyclopentadienyl cation **i**; the fragmentation **f** → **g** is supported by a metastable peak at *m/z* 71.48. Metastable-peak data for the 5-chloro- (**B**) and 5-nitro- (**D**) analogues also confirm the pathways summarized in **Scheme 51**.[87] These steps parallel the fragmentation exhibited by phenol to give odd-electron fragments, which contain, in each case, an additional hydrogen atom.[88] Thus, for compound **B** the following fragments have been supported by metastable peak analysis; [**a** → **c** (*m/z* 212.84); **a** → **d** (*m/z* 169.51); **b** → **d** (*m/z* 198.32); and **d** → **g** (*m/z* 72.00)] and for compound **D** [**a** → **c** (*m/z* 223.6); **a** → **d** (*m/z* 179.88); **b** → **d** (*m/z* 209.3); **c** → **d** (*m/z* 210.78) and **c** → **e** (*m/z* 208.99)].

2.2.2 MS Fragmentation analysis of 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones and 4*H*-naphthopyran-4-one analogues

Examination of the high-resolution and low-resolution mass spectrometric data (Table 7) as well as the metastable-peak data has permitted elucidation of the significant peaks in the mass spectra of the 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones (**148** - **152**, **158** - **160**, **169**, **170**, **176** and **177**) and the 2-(*N,N*-dimethylamino)-4*H*-naphtho-4-ones (**186** - **187**).

The major fragmentation patterns shown by the parent systems (2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**), are illustrated in Figure 30 and the proposed fragmentation pathways are shown in **Scheme 52**. In the mass spectra of the parent compound **148**, the base peak is due to the molecular ion **a** (*m/z* 189), which generally follows three major modes of fragmentation (I, II and III).

In mode I, loss of C_2NMe_2 from the molecular ion **a** gives the conjugated acylium cation **h**, which then loses a hydrogen radical to give fragment **i**. Successive decarbonylation *via* species **n** then leads to fragment **q**. Loss of $MeN{=}CH_2$ (mode II) from the molecular ion **a** gives fragment **g**, which then loses C_2HO to yield the resonance stabilized cation **k**, which may either lose a hydrogen radical to give fragment **l**; $C_7H_4^{+\bullet}$ (*m/z* 104) or lose H_2 to give **m**, $C_8H_7^+$ (*m/z* 103). Fragment **g** may also be decarbonylated to afford **j** (*m/z* 118) [also formed *via* mode III). Fragment **e** (*m/z* 148) may arise from loss of an aziridine species, whilst the cation **f** could result from loss of an $Me_2NC{\equiv}C^{\bullet}$ radical from the molecular ion.

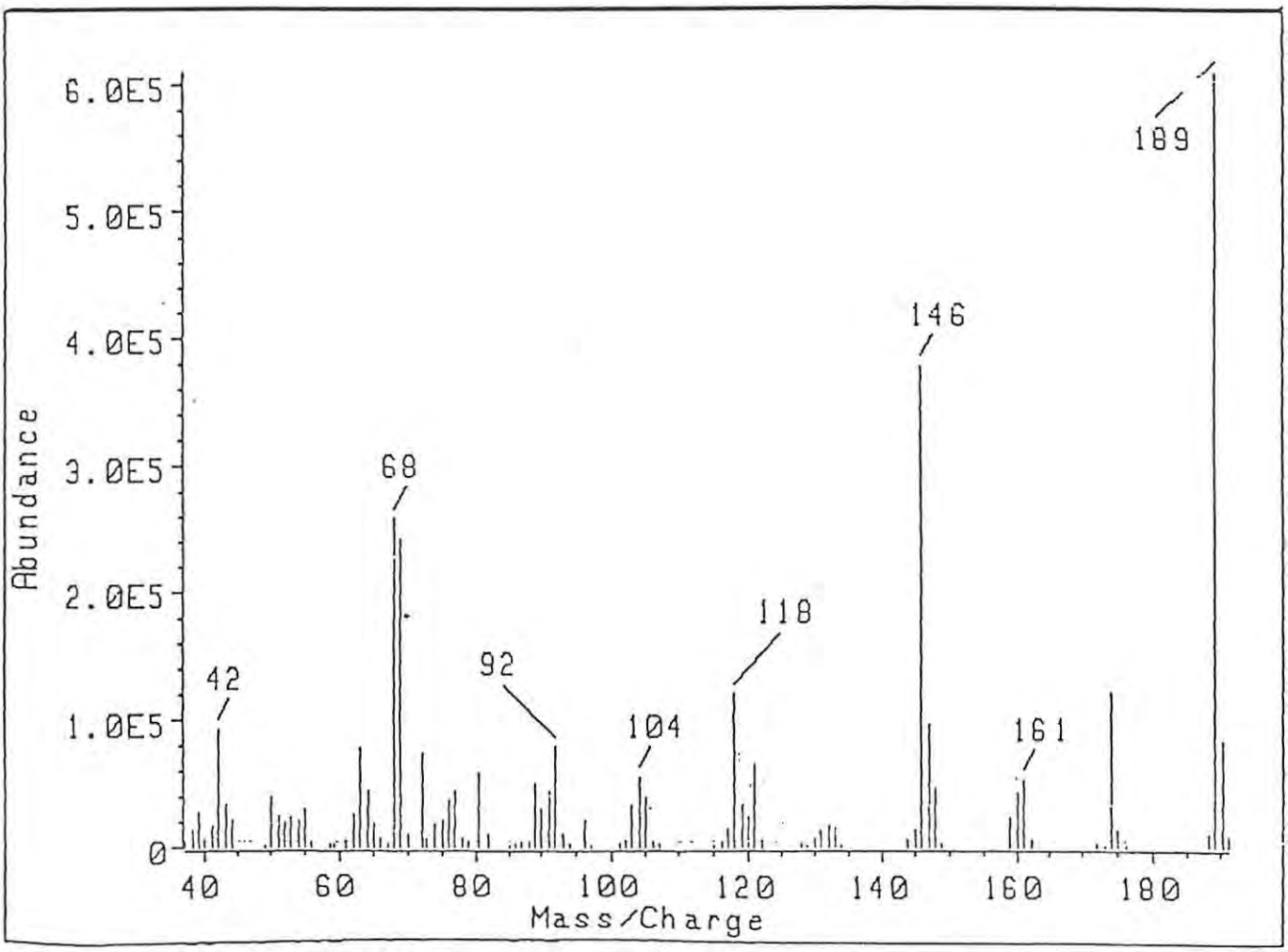
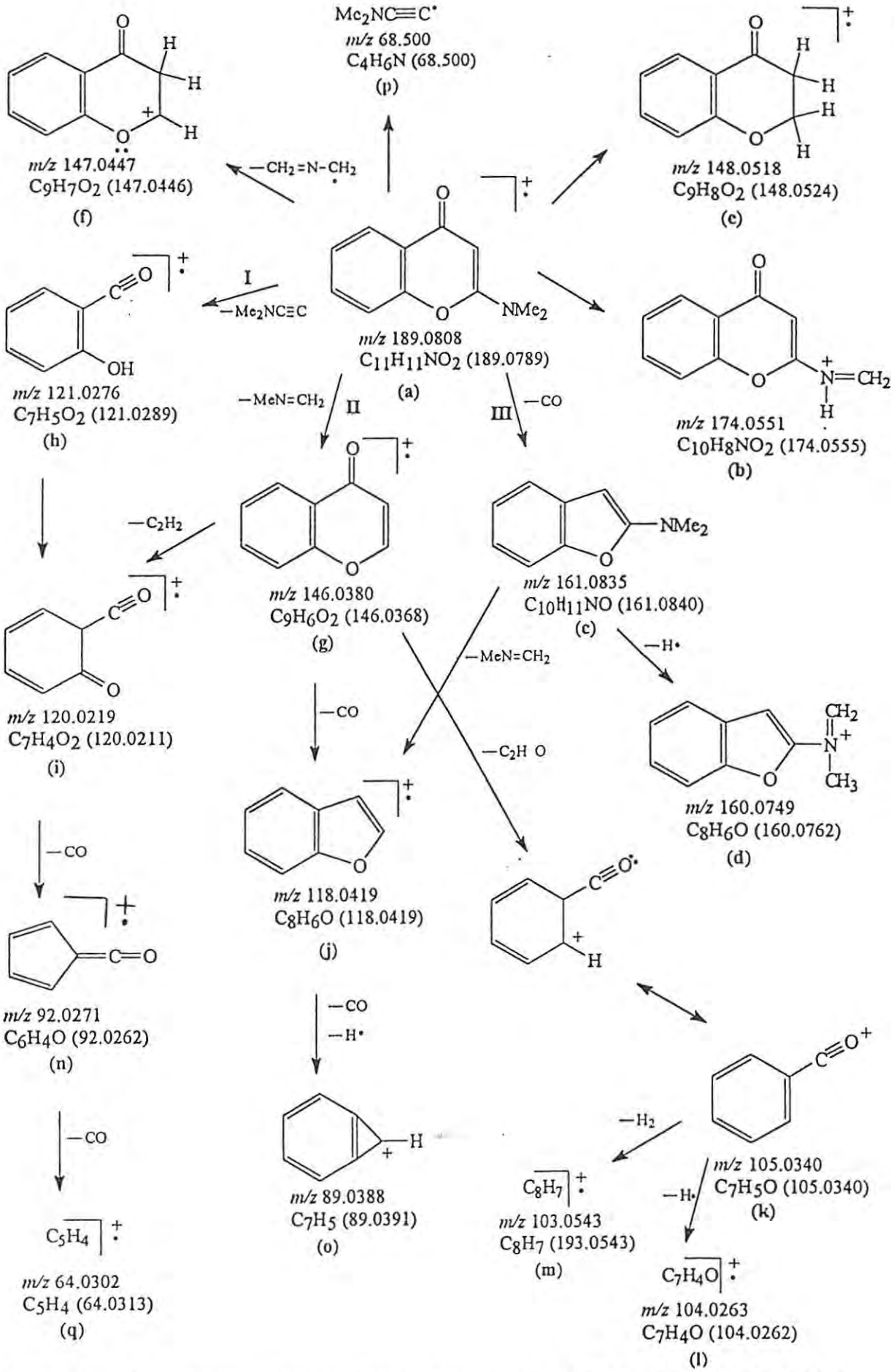


Figure 30 E.I. mass spectrum of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**).



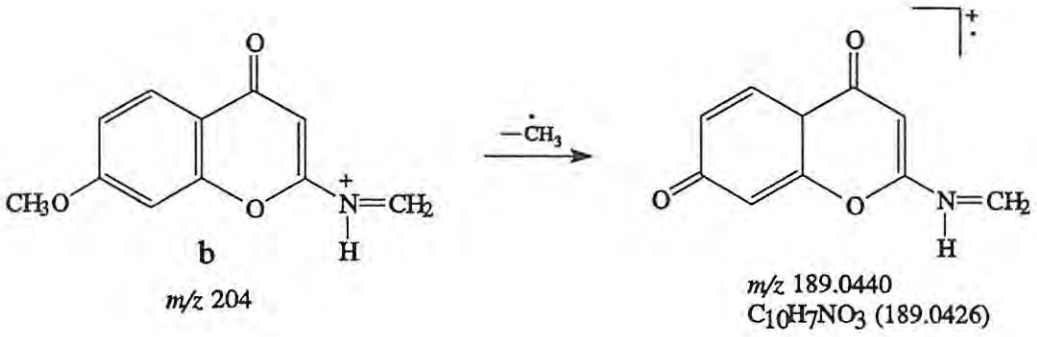
Scheme 52 E.I. mass fragmentation pathways for 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**). Accurate masses (*m/z*) are followed in parentheses by calculated formula masses.

Loss of carbon monoxide (mode III) from the molecular ion **a**, followed by loss of $MeN{=}CH_2$ (*m/z* 43), subsequent decarbonylation and loss of a hydrogen radical are responsible for fragments **c**, **j** and **o**, respectively. Fragment **c** may lose a hydrogen radical to give cation **d**. Fragment **b** is attributed to loss of a methyl radical from the molecular ion.

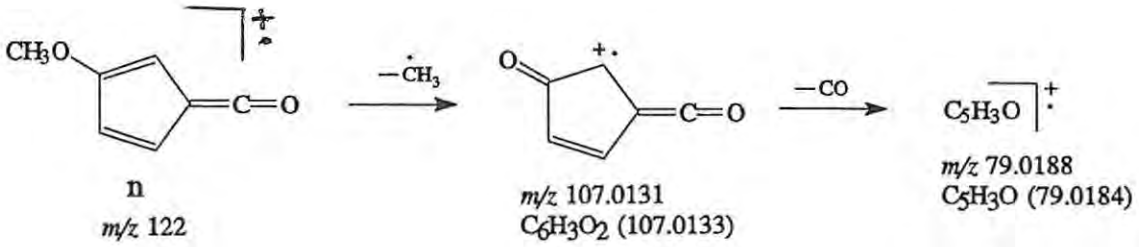
The atomic composition of all fragments (**a** - **q**), for the parent compound (**148**), were established by high-resolution mass analysis as indicated by **Scheme 52**; and the following fragmentations are supported by meta-stable peak analysis: **a** → **b** (*m/z* 160.19); **a** → **g** (*m/z* 112.78); **g** → **j** (*m/z* 95.37) and **g** → **l** (*m/z* 74.08).

All other analogues studied (**149** - **152**, **158** - **160**, **169**, **170**, **176** and **177**) follow the fragmentation patterns shown in **Scheme 52**. Meta-stable peak analysis has also supported most fragmentations in compounds (**152**, **159**, **170**, **177**, **186** and **187**).

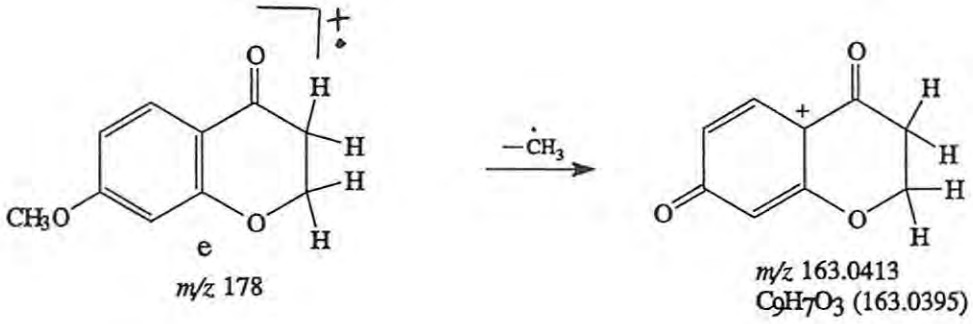
In the methoxy analogues (**152**, **176** and **177**) studied, additional fragments have also been observed and these are illustrated in **Schemes 53 - 55** below. In the methoxy analogue (**176**) loss of a methyl radical from ion type **b** (*m/z* 204) affords a fragment at *m/z* 189, the atomic composition being confirmed by high resolution analysis (**Scheme 53**). The methoxy analogue (**152**) undergoes loss of a methyl radical from ion type **n** (*m/z* 122), followed by decarbonylation, giving rise to peaks at *m/z* 107 and 79, respectively, the atomic composition again being confirmed by high resolution analysis, as indicated in **Scheme 54**. Finally, in the methoxy analogue (**177**), loss of a methyl radical from an ion of type **e** (corresponding to *m/z* 178) gives rise to a fragment with *m/z* 163 as shown in **Scheme 55**.



Scheme 53 Fragmentation of ion type **b** from compound (**176**)

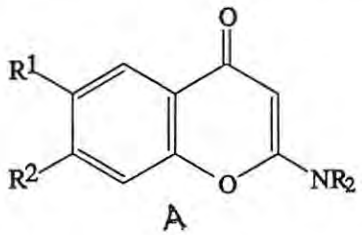


Scheme 54 Fragmentation of ion type **n** from compound (**152**)

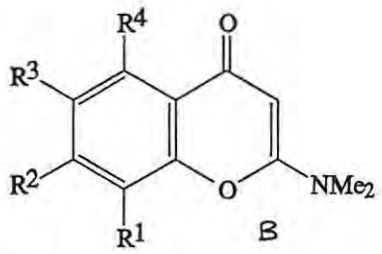


Scheme 55 Fragmentation of ion type **e** from compound (**177**)

Table 7 Selected peaks (*m/z*, followed, in parentheses, by % relative abundance from E.I. mass spectra of the 4*H*-1-benzopyran-4-ones, classified according to ion type **a** - **q** (**Scheme 52**)



A



B

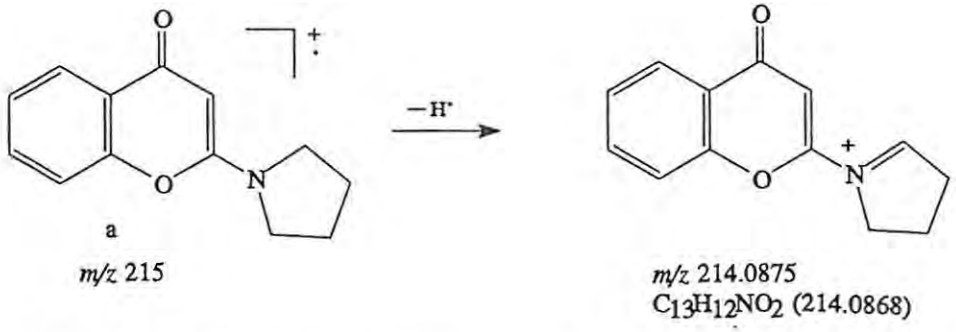
A				Ion type																
Compd	R^1	R^2	NR_2	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
148	H	H	NMe_2	189[a]	174[a]	161[a]	160[a]	148[a]	147[a]	146[a]	121[a]	120[a]	118[a]	105[a]	104[a]	103[a]	92[a]	89[a]	68[a]	64[a]
				(100)	(20)	(9)	(7)	(8)	(16)	(62)	(11)	(4)	(20)	(7)	(9)	(6)	(13)	(8)	(43)	(70)
149	H	Br	NMe_2	269[b]	254[b]	241[b]	240[b]	228[b]	227[b]	226[b]	201[b]	200[b]	198[b]	185[b]	184[b]	183[b]	172[b]	169[b]	68	144[b]
				(60)	(10)	(5)	(3)	(4)	(10)	(37)	(4)	(1)	(11)	(3)	(5)	(5)	(5)	(4)	(83)	(3)
150	H	F	NMe_2	207[b]	192	179	178	166	165	164	139	138	136	123	122	121	110	107	68	82
				(100)	(18)	(6)	(5)	(9)	(17)	(47)	(10)	(3)	(17)	(8)	(11)	(4)	(10)	(13)	(78)	(16)
151	H	Cl	NMe_2	223[a,c]	208[c]	195[c]	194[c]	182[c]	181[c]	180[c]	155[c]	154[c]	152[c]	139[c]	138[c]	137[c]	126[c]	123[c]	68	98[c]
				(100)	(20)	(11)	(5)	(30)	(17)	(52)	(9)	(7)	(18)	(7)	(10)	(3)	(10)	(7)	(73)	(14)
152	OMe	H	NMe_2	219[a]	204[a]	191	190	178	177	176	151	150	148	135[a]	134	133	122	119	68	94
				(100)	(23)	(4)	(7)	(26)	(7)	(26)	(7)	(25)	(17)	(21)	(9)	(9)	(22)	(6)	(83)	(12)
158	H	H	NEt_2	217[a]	202	189	188	148	147	146	121	120	146	133	132	131	92	89	96	64
				(90)	(49)	(5)	(38)	(1)	(4)	(7)	(100)	(9)	(7)	(8)	(11)	(2)	(24)	(12)	(5)	(14)
159	H	H	piperidine	229[a]	214	201	200	148	147	146	121	120	118	145	144	143	92	89	83[a]	64
				(69)	(19)	(2)	(7)	(1)	(7)	(20)	(34)	(10)	(4)	(6)	(3)	(1)	(22)	(12)	(100)	(12)

A				Ion type																
Compd	R^1	R^2	NR_2	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
160	H	H	pyrrolidine	215[a]	-	187	186	148	147	146	121	120	118	131	130	129	92	89	69	64
				(100)		(14)	(22)	(1)	(9)	(73)	(12)	(12)	(6)	(10)	(3)	(1)	(18)	(13)	(16)	(7)
169	Cl	H	NMe_2	223[a,c]	208[c]	195[c]	194[c]	182[c]	181[c]	180[c]	155[c]	154[c]	152[c]	139[c]	138[c]	137[c]	126[c]	123[c]	68	98[c]
				(100)	(23)	(7)	(5)	(18)	(10)	(54)	(6)	(9)	(12)	(5)	(4)	(3)	(9)	(5)	(44)	(10)
170	NO_2	H	NMe_2	234[a]	219	206	205	193	192	191	166	165	163	150	149	148	-	134	68	-
				(100)	(9)	(2)	(1)	(1)	(3)	(5)	(1)	(0.6)	(2)	(2)	(1)	(1)		(1)	(24)	
176	H	OMe	NMe_2	219[a]	204	191	190	178	177	176	151	150	148	135[a]	134	133	122	119	68	94
				(84)	(24)	(2)	(4)	(4)	(18)	(100)	(18)	(3)	(14)	(6)	(12)	(6)	(8)	(6)	(44)	(3)
177	H	OMe	NEt_2	247[a]	232	219	218	178	177	176	151	150	148	135[a]	134	133	122	119	86	94
				(100)	(45)	(7)	(49)	(2)	(8)	(21)	(93)	(6)	(4)	(8)	(6)	(3)	(8)	(9)	(4)	(3)

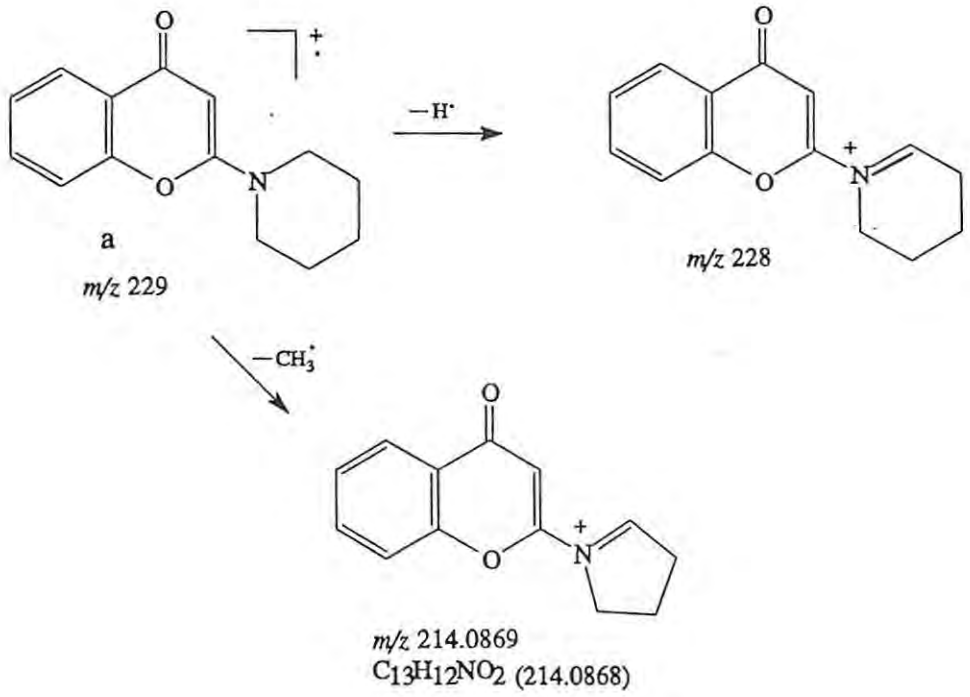
B					Ion type																
Compd	R^1	R^2	R^3	R^4	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
186	H	H	C_6H_4	C_6H_4	239[a]	224	211	210	198	197	196	171	170	168	155	154	153	142	139	68	114
					(100)	(20)	(23)	(6)	(10)	(14)	(52)	(6)	(12)	(11)	(5)	(2)	(7)	(11)	(12)	(49)	(33)
187	C_6H_4	C_6H_4	H	H	239[a]	224	211	210	198	197	196	171	170	168	155	154	153	142	139	68	114
					(100)	(30)	(6)	(9)	(13)	(14)	(38)	(9)	(41)	(8)	(4)	(3)	(6)	(9)	(9)	(44)	(62)

[a]Atomic composition confirmed by high-resolution ms analysis.
[b]*m/z* value corresponds to ^{81}Br
[c]*m/z* value corresponds to ^{35}Cl

The pyrrolidinyl and piperidinyl analogues (**159** and **160**) also exhibit substituent-specific fragments due to loss of a hydrogen radical from the molecular ions, affording the corresponding iminium cations at *m/z* 214 and *m/z* 228 respectively, as shown in **Schemes 56** and **57**. Loss of a methyl radical from the piperidinyl analogue (**159**) was also observed, presumably affording the ring-contracted iminium cation at *m/z* 214.

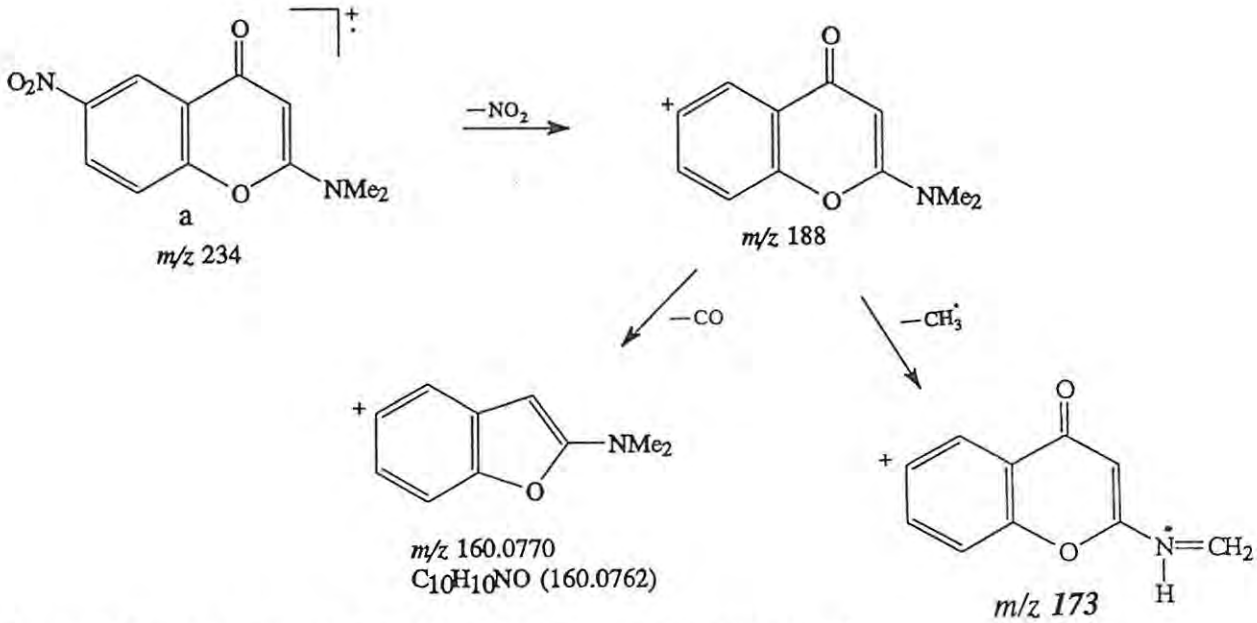


Scheme 56 Fragmentation of ion type **b** from compound (**160**)



Scheme 57 Fragmentation of ion type **a** from compound (**159**)

Additional fragments were also observed in the mass spectrum of the nitro analogue (**170**) and these are illustrated in **Scheme 58**. Loss of the nitro radical (*m/z* 46) from the molecular ion **a** (*m/z* 234), followed by carbon monoxide or a methyl radical is responsible for the fragments observed at *m/z* 188 and 173, respectively. Decarbonylation from the cation (*m/z* 188) gives a fragment with *m/z* 160. Fragments corresponding to **n** and **q** in the parent compound (**148**), however, were not observed.



Scheme 58 Fragmentation of ion type **a** from compound (**170**)

2.2.3 Dynamic NMR analysis of Rotational Isomerism in 4*H*-1-benzo-pyran-4-one-derived polyfunctional acrylamides

It has been previously suggested[83,84] that the pharmacological action of anti-allergic 4*H*-1-benzopyran-4-ones might involve opening of the heterocyclic ring by biogenetic nucleophiles. From X-ray crystallographic and spectroscopic analysis,[84] it was found that the acrylamides **215**, **A** - **D** and **219**, adopt a remarkably planar conformation, apart from the carboxamide moiety which is orthogonal to the molecular plane (Fig. 31).

The ^{1}H and ^{13}C NMR spectra of these acrylamides show splitting of the N-methyl signals of the *N,N*-dimethylamino and *N,N*-dimethylcarboxamide groups, which is indicative of hindered rotation about the Me_2N-C and Me_2N-CO bonds. Dynamic NMR analysis (illustrated for compound **215** in Fig. 32) has allowed the simultaneous investigation of both internal rotors. The dimethylamino group was assigned the lower field *N*-methyl signals after comparison with the ^{1}H NMR data for the pyrrolidinyl derivative **219**; for acrylamides (**215**), (**A** - **D**), coalescence for these N-methyl signals occurs in the temperature range 314 - 328 K (Table 8). Finalisation of this study, which had been initiated earlier[56] required further synthesis and recalculation of all data, following application of an extrapolation method[92] for determining frequency separations at coalescence.

The preparation of 2-(dimethylamino)-3-(2-hydroxybenzoyl)acrylamides (**215**, **A** - **D** and **219**) has already been described.[56] Variable-temperature NMR spectra were recorded for solutions of the acrylamides (**215**, **A** - **D**) in deuterated dimethylsulfoxide [$(CD_3)_2SO$] on a Bruker AMX 400 MHz NMR spectrometer equipped with a variable temperature unit. Frequency

separation

at coalescence ($\Delta\nu_c$) was determined, in each case, by extrapolation using the method described by Lai and Chen.[92]

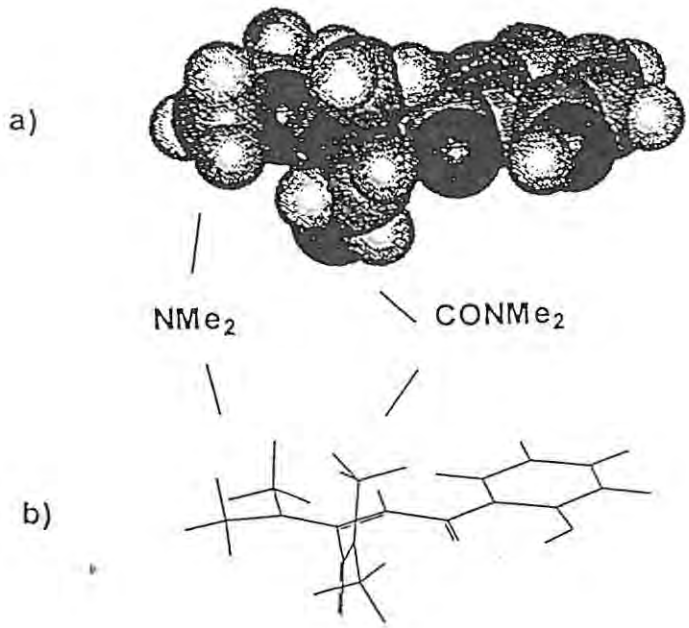


Figure 31 Computer-modelled conformation of the acrylamide derivative (**215**): a) spacefilling and b) "wire-frame" representations.

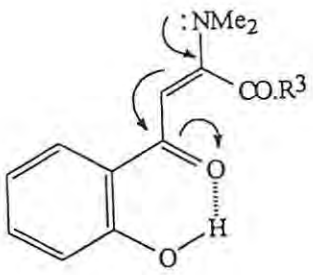


Figure 33 Delocalization in the acrylamides

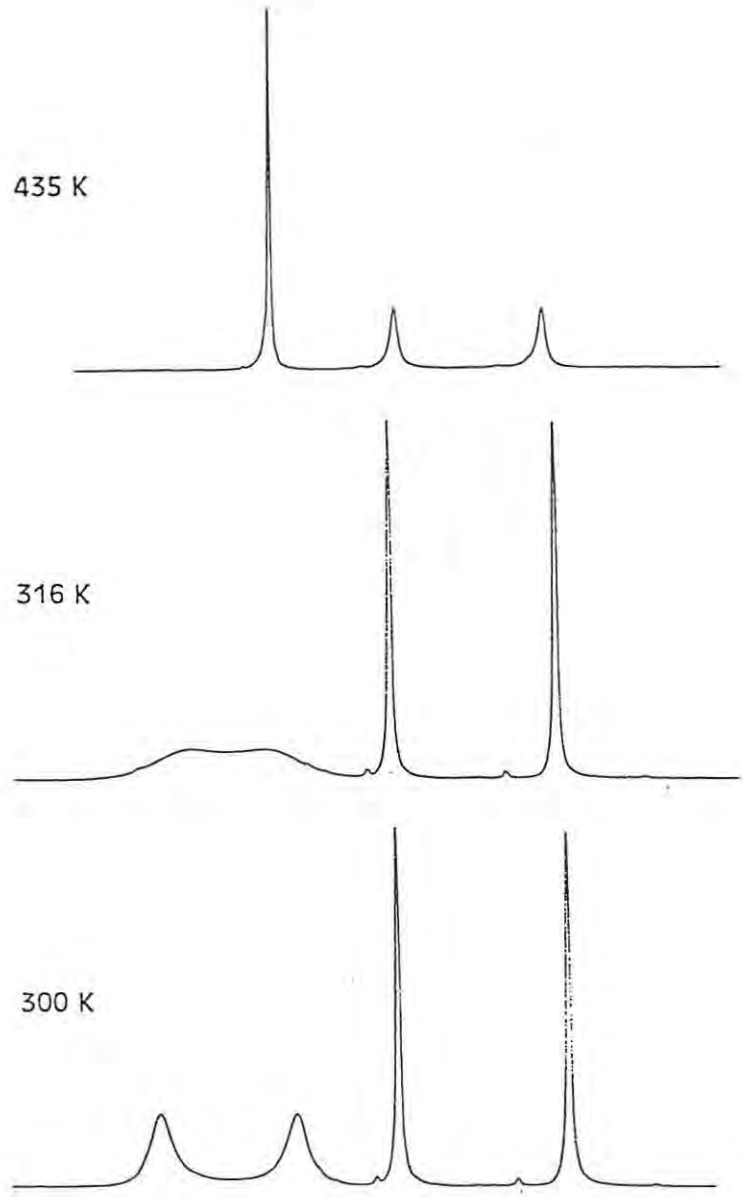


Figure 32 Partial ^1H NMR spectra of compound (**215**) at different temperatures, showing NMe_2 (downfield) and $CONMe_2$ (upfield) signals.

The rotational energy barriers for these acrylamides (**215, A - D**) (*ca* 67 $kJmol^{-1}$) were calculated from the coalescence data, and are high for enamine rotors. Rotational barriers (ΔG^*), for C-N rotation, have been determined for 1-(dimethylamino)cyclohexene (24.9 $kJmol^{-1}$)[89] and for the conjugated enamine, 4-(dimethylamino)but-3-en-2-one (55.8 $kJmol^{-1}$).[90] The high enamine rotational barriers in the acrylamides examined here clearly reflect the extensive delocalisation anticipated in these systems (Figure 33).

The substituents (R^1 and R^2) are expected to influence the acidity of the phenolic group and, hence, its intramolecular hydrogen bonding to the ketone carbonyl oxygen. The observed rotational barriers (ΔG^*) lie within a very small range (*ca.* 67.1 $\pm$ 1.1 kJ mol^{-1}), and it is apparent that these substituents have little effect on the internal rotation of the dimethylamino group.

For the higher-field *N,N*-dimethylcarboxamido signals, no coalescence could be achieved even at temperatures as high as 435 K. However, at higher temperatures, the *N*-methyl signals broaden and move closer together (see Fig. 32).

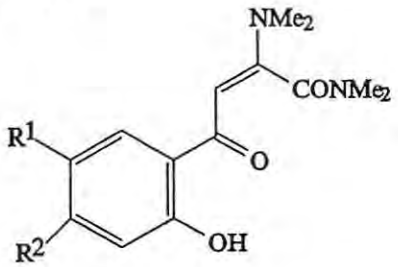
The computer-modelled structure of the acrylamide derivative (**215**) (Figure 31) has shown that rotation about the CO-NMe_2 bond is severely obstructed by the flanking, coplanar dimethylamino and carbonyl moeities. The rate constants (k) for CO-NMe_2 rotation at 435 K were calculated from data at 435 K using the equation :-

$$\Delta G^* = 2.303\ R\ T\ (\log\frac{k_{bT}}{h} - \log k)$$

where K_b is the Boltzmann constant and h is Planck's constant.[91] Rotational barriers (ΔG^*) in the range 64 - 72 $kJmol^{-1}$ have been measured for 2-carboxamidochromones.[83] Thus, the rate constants (K) for CO-NMe_2 rotation at 435 K correspond to remarkably high rotational

rate constants (K) for CO-NMe_2 rotation at 435 K correspond to remarkably high rotational barriers (ΔG^* *ca.* 102 $kJmol^{-1}$). These high energy barriers presumably show sustained coplanarity of the conjugated skeleton at high temperatures (see Figure 33).

Table 8 Dynamic NMR data for C-NMe_2 and CO-NMe_2 rotation in the acrylamide derivatives **(215, A-D)**



			C-NMe_2 rotation			CO-NMe_2 rotation
Compd	R^1	R^2	T_c[a]/K	$\Delta\nu_c$[b]/Hz	ΔG^*[c]/$kJmol^{-1}$	k[d]/s^{-1}
215	H	H	316	28.1	66.7	6.2
A	H	Cl	321	32.2	67.4	4.9
B	Cl	H	328	41.8	68.2	4.9
C	MeO	H	314	31.2	66.0	5.9
D	NO_2	H	324	46.2	67.1	4.2

[a]Coalescence temperature ($\pm$ 2 K) in DMSO-d_6
[b]Frequency separation of bands at coalescence; estimated errors $\leq \pm$ 2.0 Hz.

[c]Free energy of activation, $\Delta G^* = R\,T_c\,(22.96 + \frac{lnT_c}{\Delta\nu_c})$;
(See Ref. 95);
estimated errors $\pm$ 0.5 $kJmol^{-1}$
[d]Rate constant for internal rotation at 435 K, $k = \pi\,(\omega - \omega_0)s^{-1}$

where ω and ω_0 are the mean half-height linewidths of the CO-NMe_2 ^1H NMR signals at 435K and 303K respectively (see Ref. 91); estimated errors $\leq \pm 0.3s^{-1}$

2.2.4 Dynamic NMR Analysis of Rotational Isomerism in 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-one derivatives

In previous studies, our research group has explored substituent effects on:- the acidity of 4-oxo-4*H*-1-benzopyran-2-carboxylic acids;[93] the nucleophilic ring opening of 4-oxo-4*H*-1-benzopyran-2-carboxamides;[94] and internal rotation of the amide moeity in the latter compounds.[83] The results of these studies indicated that the effects of remote substituents on these properties are relatively small. In the present study the influence of substituents on electron density at C(1) was explored by DNMR analysis of internal rotation about the C(1)-N bond in 2-(*N,N*-dialkylamino)-4*H*-benzopyran-4-ones.

The synthetic approaches to the 2-(*N,N*-dialkylamino-4*H*-1-benzopyran-4-ones (**148** - **152**, **158** - **160**, **169**, **170**, **176** and **177**), required for the DNMR analysis, were as discussed in Section 2.1.1 - 2.1.6.

In these compounds, internal rotation about the C(1)-N bond results in site exchange of the *N*-substituents (Figure 34). The amino groups chosen for these studies are symmetrically substituted in order to simplify analysis of dynamic NMR data, hence rotamers I and II are equivalent (See Figure 34). The delocalization of the nitrogen lone pair (Figure 35) is responsible for stabilization of the planar rotamers and hence for the rotational barrier and the *N*-alkyl and ring substituents were chosen to elucidate electronic and steric effects on the rotameric equilibria.

The rotational energy barriers (ΔG^*; Table 9) for the C-NR_2 groups of the 2-aminochromones were determined from the coalescence temperature (T_c) and the frequency separation at coalescence ($\Delta\nu_c$) using equation 1. The coalescence temperatures (T_c) were obtained from variable temperature spectra (*eg.* Figure 36) and the frequency differences at coalescence ($\Delta\nu_c$) were obtained by extrapolation of linear plots of the frequency separation ($\Delta\nu$) against (T) as described by Lai and Chen.[92] The first-order rate constants (k at 298, Table 9) were also determined from the coalescence data using equation 2.

equation 1:

$$\Delta G = R\ T_c\ (22.96 + \frac{lnT_c}{\Delta\nu_c})$$

equation 2:

$$\ln k = \ln(\frac{k_b T}{h}) - \frac{\Delta G^*}{RT}$$

where

R	=	gas constant
K_b	=	Boltzmann constant
h	=	Planck's constant
T	=	298 k
T_c	=	coalescence temperature/K
$\Delta\nu_c$	=	frequency separation at coalescence/Hz

The effects of delocalization of the A-ring substituents (R^1 and R^2) and inductive effects, involving the N-substituents, were expected to influence the rotational barriers ΔG^* significantly. Examination of the data (Table 9) shows that variations in the magnitude of ΔG^* are, in fact, relatively small (44.5 ± 1.6 $kJmol^{-1}$) in dimethylamino analogues. This may indicate that substituent effects are marginal compared to the strong conjugative influence of the 4*H*-1-benzopyran-4-one α, β-unsaturated moiety.

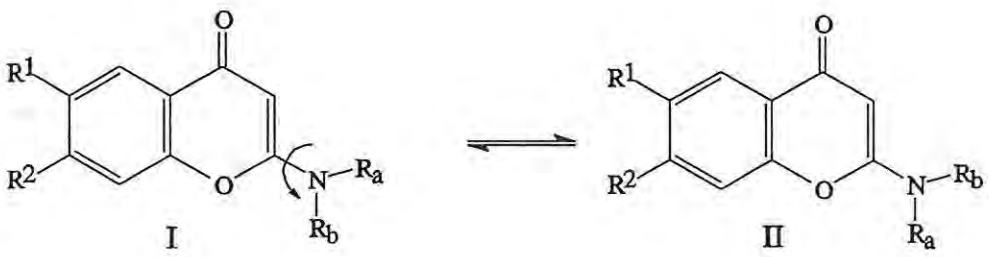


Figure 34 Internal rotation about C(1) bond

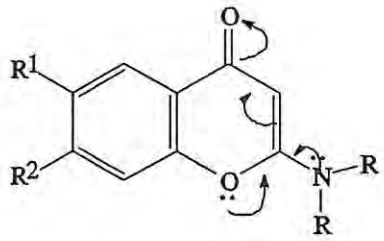
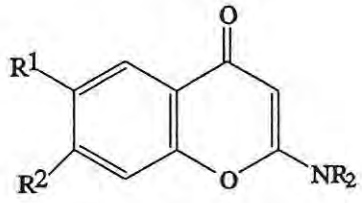


Figure 35

Table 9 Dynamic ^1H NMR for 2-aminochromones



Compd.	R^1	R^2	NR_2	T_c[a]/ K	$\Delta\nu_c$[b]/ Hz	ΔG^{*}[c]/ $kJmol^{-1}$	lnk_{298}[d]/ s^{-1}
148	H	H	NMe_2	222	81.8	44.2	11.6
158	H	H	NEt_2	226	78.3	45.1	11.3
152	OMe	H	NMe_2	219	65.6	44.0	11.7
176	H	OMe	NMe_2	213	43.2	43.5	11.9
177	H	OMe	NEt_2	219	72.0	43.8	11.8
151	H	Cl	NMe_2	223	72.4	44.7	11.4
150	H	F	NMe_2	221	73.5	44.2	11.6
149	H	Br	NMe_2	222	77.7	44.3	11.6
170	NO_2	H	NMe_2	233	95.0	46.1	10.9
169	Cl	H	NMe_2	225	83.0	44.8	11.4
160	H	H	pyrrolidine	267	142.4	52.4	8.3
160	H	H	pyrrolidine	264	115.9	52.2	8.4[e]
159	H	H	piperidine	194	120.3	37.8	14.2[e]

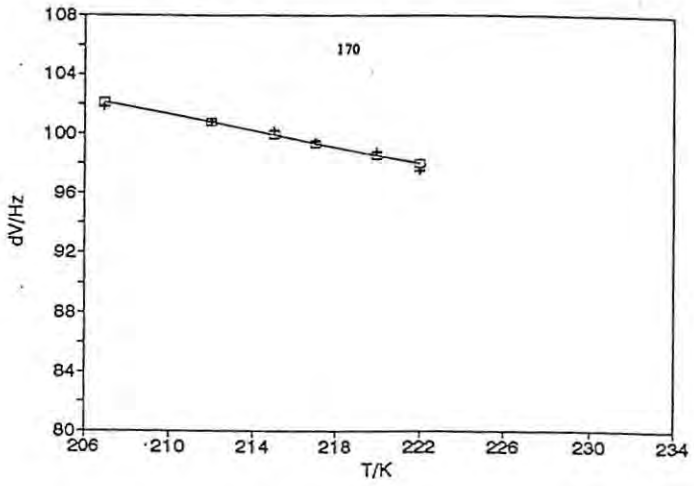
[a]Coalescence temperature (± 2K) in $CDCl_3$.
[b]Frequency separation of bands at coalescence.
[c]Free energy of activation for internal rotation.
[d]Log of first-order rate constant at 298K.
[e]Variable temperature spectra recorded in CD_2Cl_2.

In the methoxy analogues (R^1, R^2 = MeO), the electron-releasing methoxy substituents oppose nitrogen lone pair delocalization into the ring, reduce the double-bond character of the C(1)-N bond and, hence, reduce ΔG^{*}. However, in the nitro analogue (**170**), the electron-withdrawing nitro group has the opposite effect, and hence, compound (**170**) has a larger ΔG^{*} value than the parent compound (**148**).

Changing the amino substituent (Me → Et) results in an increase in ΔG^* and this may be explained in terms of the increase in electron-releasing inductive effect. The influence of electron-releasing inductive effects on nitrogen lone-pair delocalization (Figure 35) also appears to be illustrated by the higher rotational barrier of the pyrrolidine derivative (**160**) [relative to the parent compound (**148**)] and, to a lesser extent, for the piperidine analogue (**159**). The difference in ΔG^* for the amino compounds (**160**) and (**159**) is consistent with the greater ease with which a pyrrolidine nitrogen is expected to adopt the planar sp^2 arrangement necessary for effective lone-pair delocalization.

It should be noted that in the case of the piperidine compound (**159**), no coalescence was observed even at temperatures as low as 213 K. Hence, CD_2Cl_2 (freezing point 176 K) was used instead of $CDCl_3$. The pyrrolidine analogue **160** was also re-examined in CD_2Cl_2 in order to compare the effect of the solvent on ΔG^*. In fact, no significant solvent effect was observed.

The rotational energy barriers (ΔG^*) determined for the above studied compounds are considerably smaller than those observed for enamine C-NMe_2 rotation in chromone-derived 2-(dimethylamino)-acrylamides (ΔG^* *ca.* 67 $kJmol^{-1}$);[86] this may reflect competitive electron donation by the chromone ether oxygen with a consequent reduction in the nitrogen lone pair delocalization.



170

No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	101.8	102.1
2.0	212.0	100.8	100.7
3.0	215.0	100.2	99.9
4.0	217.0	99.5	99.4
5.0	220.0	98.8	98.5
6.0	222.0	97.5	98.0
7.0	230.0	80.3	95.8
	233.0		95.0

Regression Output:

Constant	158.2904
Std Err of Y Est	0.3562
R Squared	0.955996
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	-0.27157
Std Err of Coef.	0.029132

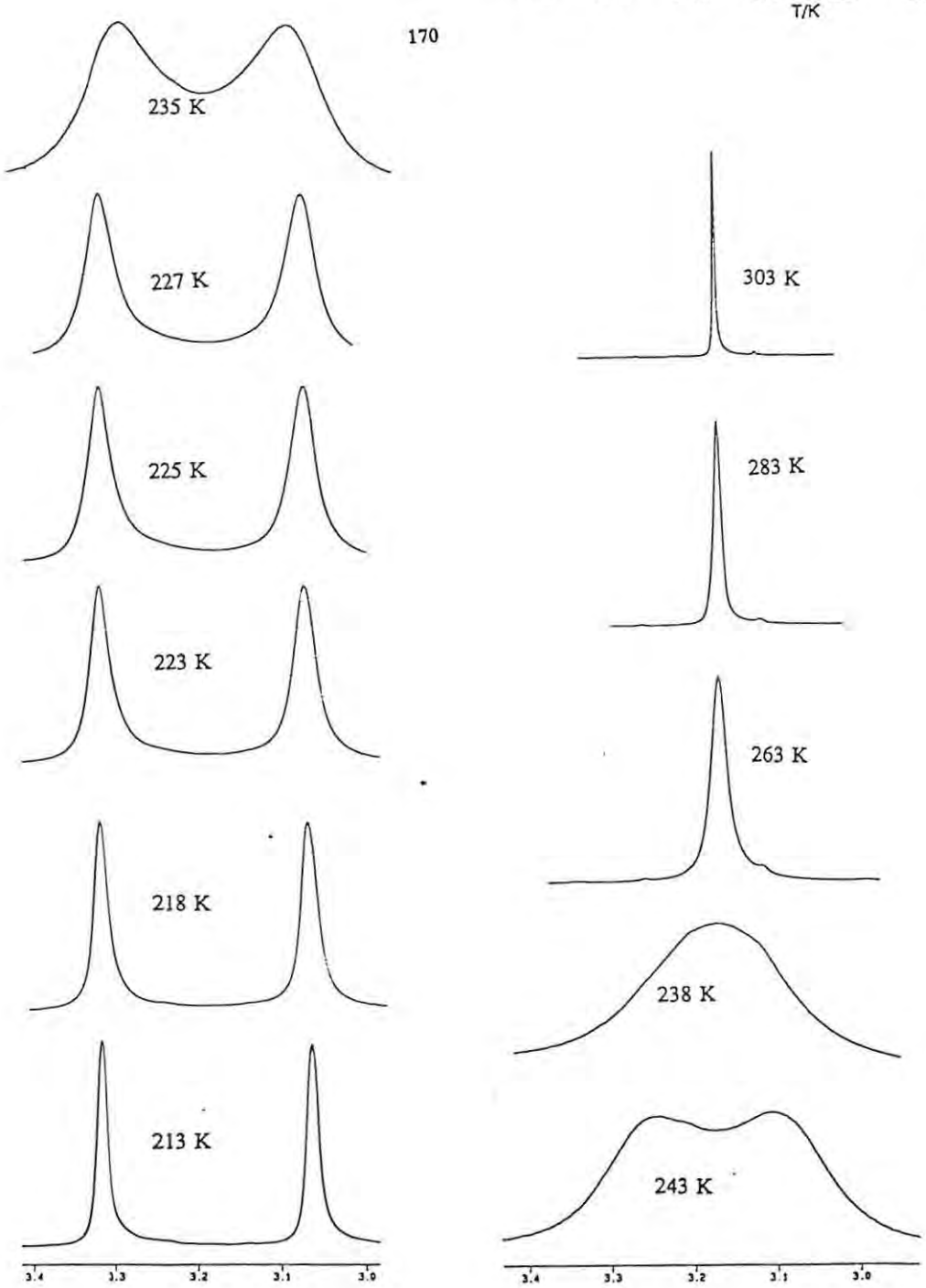
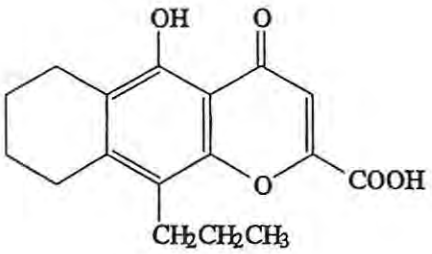


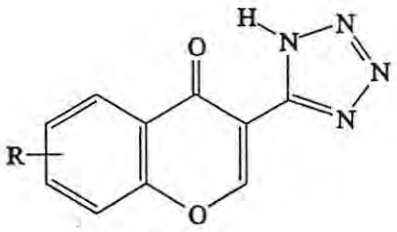
Figure 36 Variable ^{1}H NMR spectra of compound (**173**), followed by a plot of frequency differences ($\Delta\nu$) vs temperature (T).

2.3 pK_a studies of 4-oxo-4*H*-1-benzopyran-2-carboxylic acids: Influence of substituents on the acidity of 4-oxo-4*H*-1-benzopyran-2-carboxylic acids.[93]

Anti-allergic chromone derivatives usually contain one or two acid groups. For example, cromoglycic acid (a *bis*-chromone) is a dicarboxylic acid and is widely used as the disodium salt (DSCG),[70] while proxicromil (**232**), a mono-chromone carboxylic acid, has significant oral activity although its toxicity has precluded clinical application.[19] Intramolecular hydrogen bonding reduces the acidity of 3-carboxychromone, hence making it inactive. However, replacement of the 3-carboxy group by a 1*H*-tetrazolo group [which has comparable acidity (pK_a *ca.* 3)[23]], has led to compounds, such as the 3-(1*H*-tetrazol-5-yl)chromone (**233**), which shows an even greater activity than DSCG.[96] It is therefore clear that acidity may influence anti-allergic activity in chromone derivatives and, as part of an on-going investigation of these systems, we decided to study the substituent effects on the acidity of a range of 2-carboxychromones. The discussion which follows incorporates the results of previous studies,[56,93] their extension and completion. The synthesis and characterization of the acids required (**A** - **I**) for the study has been discussed earlier.[56]



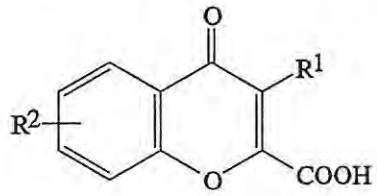
232



233

(R = 6-Et, 6-Cl, 6-Ph, 6-NO_2 and 6,8-Di-Me)

Table 10 Acid dissociation data for chromone-2-carboxylic acids at 25°C



Compound	R^1	R^2	pK_a[a]
206	H	H	2.69 ± 0.05[b] 2.65 ± 0.01
A	H	7-Br	2.64 ± 0.02[C]
B	H	6-Cl	2.62 ± 0.02[b] 2.65± 0.01
207	H	7-Cl	2.64 ± 0.04[b] 2.66 ± 0.01
C	H	8-Cl	2.65 ± 0.03
D	Cl	H	2.48 ± 0.02
E	H	7-F	2.63 ± 0.01[C]
F	Me	H	2.71 ± 0.01
G	H	6-MeO	2.90 ± 0.01[d]
208	H	7-MeO	2.96 ± 0.02[c,d]
H	H	6-NO_2	2.64 ± 0.01
I	H	7-NO_2	2.60 ± 0.03[c]

[a]Mean of replicate results [obtained by potentiometric titration of 0.01 **M** solutions in aqueous EtOH (50% v/v)]; [b]Results obtained in two independent determinations; see refs. 56 and 100; [c]Data from cognate study by D.N. Davidson[80]; [d]Potentiometric titration of 0.005 **M** solutions in aqueous EtOH (50% v/v).

The acid dissociation (pK_a) data for the 2-carboxychromones (**206** - **208**, **A** - **I**) are shown in Table 10, and were obtained by potentiometric titration of dilute aqeous-ethanolic solutions using sodium hydroxide as a standard base. The solvent was chosen so as to correspond to that used in an earlier determination of the parent compound **A**,[97] and in order to minimize activity effects, low concentrations (0.005 - 0.01 $mol.dm^{-3}$) were used.[98] The pK_a of the

parent compound **206** has been reported as 2.96[19] when determined by conductimetry at 25°C and 2.8[97] when determined potentiometrically in 50% aqueous ethanol. To our knowledge, pK_a data for the remaining compounds (**206** - **208**, **A** - **I**) detailed in Table 10 had not been determined prior to our study.

Significant delocalization towards the carbonyl oxygen of the pyran-4-one ring (Fig. 37) may:-

i) inhibit competitive delocalization towards the carboxy function, thus resulting in an increased acidity of 2-carboxychromones relative to their benzoic acid counterparts, and

ii) reduce the mesomeric effect of the remote substituents.

As a result, the pK_a values determined for compounds **206** - **208**, **A** - **I** (Table 10) lie within a narrow range (2.48 - 2.96).[a] For the methoxy analogues **G** and **208**, the higher pK_a values are attributed to the stronger p-π electron-donating capacity of the methoxy group, as well as the potential for conjugative interaction from *either* position 6 or 7 (Figure 38) and enhances the acid weakening delocalisation effects of the ring system. Even though the variations are small, the general pK_a trend typical of *p*-substituted benzoic acids is shown by the 7-substituted 2-carboxychromones, *viz.*, MeO > H > Br, Cl, F > NO_2.

2-Carboxy-3-methylchromone (**F**) was expected to be more acidic than the parent compound **A**, since *o*-toluic acid is a stronger acid than benzoic acid.[97] An ortho substituent will tend to force an adjacent carboxy group out of the plain with concomitant reduction in the *acid-weakening* delocalization effects illustrated in Figure 39. However, in 2-carboxychromones,

---

[a]The estimated errors are typically small (± 0.01 - 0.02) and, in all cases, within accepted limits (± 0.06) for potentiometric determinations, see ref. 98, p. 12.

such *acid-weakening* delocalization is less likely to be important because of the competing delocalization towards the pyran-4-one carbonyl as discussed above (illustrated in Figure 37) and the *reduced* acidity of the 3-methyl analogue (**F**) may be explained in terms of the electron-releasing inductive effect of the methyl group. In the case of the chloro analogue **D** the electron-*withdrawing* inductive effect of the bulky chloro substituent will *reinforce* any acid-*strengthening* steric inhibition of resonance and hence, the 3-chloro- analogue **D** (pK_a 2.48) is the strongest of the acids investigated.

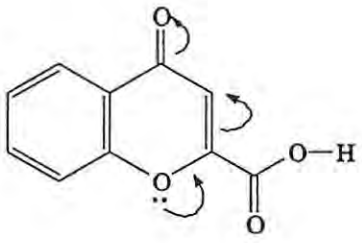


Figure 37 Delocalization effects in chromone-2-carboxylic acids

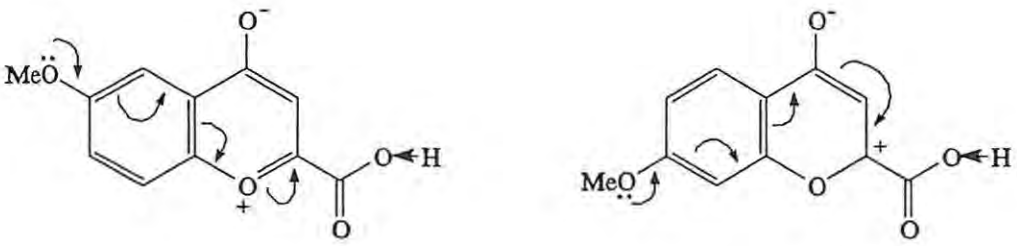


Figure 38 Conjugative interaction of 6- and 7-methoxy substituents with the chromone system

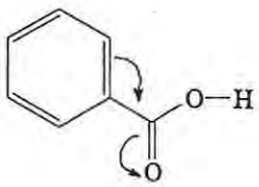


Figure 39 Acid-weaking delocalization

2.4. Conclusion

In this study, a variety of 2-aminochromones, chromone-2-carboxylic acids and their derived acrylamides, and naphthopyran-4-one analogues have been successfully prepared. 1D and 2D spectroscopic techniques have been used to establish the structures of these compounds, a number of which are new.

Extensive use of low resolution, high resolution and meta-stable peak analysis has permitted the elucidation of the major fragmentation patterns exhibited by 2-(*N,N*-dialkylamino)-chromones, 2-(*N,N*-dimethylamino)-naphthopyran-4-one and chromone-derived polyfunctional acrylamides.

In the dynamic nuclear magnetic resonance studies of rotational isomerism in substituted 2-aminochromones, it has been found that the methoxy-substituted analogues exhibited reduced C-NMe_2 rotational barriers (ΔG^* *ca.* 44 kJ mol^{-1}), reflecting the electron-releasing properties of the methoxy substituent, while the nitro analogue has the largest rotational energy barrier (ΔG^* 46.1 $kJmol^{-1}$) because of the opposite, electron-withdrawing effect of the nitro substituent. Studies of chromone-derived acrylamides revealed rotational energy barriers (ΔG^*) for enamine *N*-Me_2 rotation which lay within a narrow range (ΔG^* 67.1 $\pm$ 1.1 $kJmol^{-1}$), and it is apparent that the substituents have little effect on the rotational barrier of the dimethylamino group in the lower field dimethyl signals. In the case of the higher-field signals, no coalescence was observed even at higher temperatures when the carboxamido *N*-methyl signals broaden and become closer together.

In the acidity (pK_a) study of chromone-2-carboxylic acids it was found that the methoxy analogues have the highest pK_a value (weakest acid), an observation attributed to the stronger p-π electron-releasing ability of the methoxy group, while the 3-chloro analogue has the lowest pK_a value (strongest acid). This latter observation is attributed to the acid-strengthening steric inhibition of resonance by the bulky chlorine atom.

The results obtained in the pK_a study of chromone-2-carboxylic acids, and the MS and DNMR studies of the chromone-derived acrylamides have already been published.[85,86,93] Future research in this field is expected to involve the following:-

1) the determination of basicity constants for 2-aminochromones;

2) synthesis and/or ring-opening of substituted ethyl 4-oxo-4*H*-naphthopyran-2-carboxylates for DNA intercalation studies; and

3) DNMR studies of substituted 2-(*N,N*-dimethylamino)-4*H*-naphthopyran-4-ones.

3. EXPERIMENTAL

3.1 General Methods

All melting points were recorded on a Kofler hot-stage, Gallenkamp or automatic Mettler FP1 melting point apparatus (m.p. > 200°C) and are uncorrected. Most of the NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer, whilst routine ^{1}H NMR spectra were recorded on a Perkin-Elmer R12 spectrometer, from $CDCl_3$ or DMSO-*d*-$_6$ solutions using TMS or chloroform peak as internal standard.

IR spectra were recorded on a Perkin-Elmer 180 spectrometer, using KBr discs or liquid films.

Low resolution mass spectra were obtained using a Hewlett-Packard 5988A mass spectrometer, and high resolution mass spectra using a Varian Mat 212 or Kratos MS 80RF mass spectrometer.

Flash chromatography[102] was performed on Merck silica gel 60 [particle size 0.040 - 0.063 (230 - 400 mesh)]. Preparative layer chromatography was achieved on Merck silica gel 60 F_{254} precoated plates. TLC plates were analysed by inspection under UV light or by visualization with iodine.

Solvents were dried (and stored over 4A molecular sieves) using procedures described by Perrin and Armarego[101]:-

1) Benzene, ether and THF were dried over Na wire, and distilled from Na wire under N_2 with benzophenone as an indicator.
2) 1,2-Dichloroethane and dichloromethane were initially dried over $CaCl_2$ and then distilled from P_2O_5.
3) DMF was dried over 4A molecular sieves.
4) Ethanol was distilled under N_2 from magnesium ethoxide.
5) Pyridine was dried over KOH overnight and distilled from fresh KOH.

HCl gas was generated from HCl-H_2SO_4 using a standard literature procedure.[128]

INDEX OF COMPOUNDS PREPARED

3.2 Syntheses

*3-Bromophenyl acetate (**118**)*[58]

Ac_2O (8.70 ml, 93 mmol) was added to a stirred solution of 3-bromophenol (**114**) (10.0 g, 58 mmol) and NaOH (3.70 g, 93 mmol) in H_2O (*ca.* 70 ml) and maintained at *ca.* 0° C in an ice-salt bath. After stirring for 1 h., the resulting mixture was extracted with EtOAc (3 x 50 ml) and the combined extracts were sequentially washed with 5% *aq.* $NaHCO_3$ (2 x 50 ml) and saturated NaCl (50 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford a yellow oil which was distilled to give 3-bromophenyl acetate (**118**) (11.79 g, 95%), b.p. 70 - 75°C/2 mmHg (lit.,[103] 149°C/40 mmHg); δ_H (400 MHz; $CDCl_3$) 2.24 (3H, s, CH_3), 7.04 (1H, ddd, 6-H), 7.23 (1H, t, *J* 8.2 Hz, 5-H), 7.29 (1H, t, *J* 2.1 Hz, 2-H) and 7.36 (1H, ddd, 4-H); δ_C (100 MHz; $CDCl_3$) 120.4 (C-6), 122.3 (C-3), 125.0 (C-2), 128.0 (C-4), 130.4 (C-5), 151.1 (C-1) and 168.9 (C=O); ν_{max} (liquid film)/cm^{-1} 1760 (CO).

*3-Fluorophenyl acetate (**119**)*[58]

The experimental procedure employed for the synthesis of 3-bromophenyl acetate (**118**) was followed, using Ac_2O (14.80 ml, 156 mmol), 3-fluorophenol (**115**) (10.0 g, 110 mmol), and NaOH (6.20 g, 158 mmol) in H_2O (*ca.* 100 ml). Work-up afforded an oil which was distilled to give 3-fluorophenyl acetate (**119**) (10.75 g, 78%), 60 - 65°C/1 mmHg (lit.,[104] 77°C/16 mmHg); δ_H (400 MHz; $CDCl_3$) 2.23 (3H, s, CH_3), 6.86 (3H, m, 2-H, 4-H and 6-H) and 7.29 (1H, m, 5-H); δ_C (100 MHz; $CDCl_3$) 20.7 (CH_3), 109.5 (C-2), 112.6 (C-4), 117.3 (C-6), 130.0 (C-5), 151.5 (C-1), 162.7 (C-3) and 168.7 (C=O); ν_{max} (liquid film)/cm^{-1} 1760 (CO).

*3-Chlorophenyl acetate (**120**)*[58]

The experimental procedure employed for the synthesis of 3-bromophenyl acetate (**118**) was followed, using Ac_2O (10.40 ml, 110 mmol), 3-chlorophenol (**116**) (10.0 g, 78 mmol), and NaOH (44 g, 110 mmol) in H_2O (*ca.* 75 ml). Work-up afforded an oil which was distilled to give 3-chlorophenyl acetate (**120**) (10.49 g, 79%), b.p. 84 - 86°C/0.45 mmHg (lit.[105] 109°C/13 mmHg); δ_H (400 MHz; $CDCl_3$) 2.24 (3H, s, CH_3), 6.99 (1H, ddd, 6-H), 7.14 (1H, t, *J* 2.1 Hz, 2-H), 7.19 (1H, ddd, 4-H) and 7.26 (1H, t, *J* 8.1 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.6 (CH_3), 119.8 (C-6), 122.0 (C-2), 125.8 (C-4), 129.0 (C-5), 134.4 (C-3), 151.0 (C-1) and 168.6 (C=O); ν_{max} (liquid film)/cm^{-1} 1760 (CO).

*3-Nitrophenyl acetate (**121**)*[58]

The experimental procedure employed for the synthesis of 3-bromophenyl acetate (**118**) was followed, using Ac_2O (21.80 ml, 236 mmol), 3-nitrophenol (**117**) (20 g, 144 mmol), and NaOH in H_2O (200 ml). Work-up afforded crude 3-nitrophenyl acetate (**121**) (24.47 g, 94%), m.p. 54 - 55°C (lit.,[106] 55 - 56°C); δ_H (400 MHz; $CDCl_3$) 2.34 (3H, s, CH_3), 7.44 (1H, ddd, 6-H), 7.55 (1H, t, *J* 8.2 Hz, 5-H), 7.99 (1H, t, *J* 2.1 Hz, 2-H), and 8.10 (1H, dd, *J* 1.1 and 8.2 Hz); ν_{max} (KBr)/cm^{-1} 1755 (CO).

*4-Bromo-2-hydroxyacetophenone (**125**)*[58]

A stirred mixture of 3-bromophenyl acetate (**118**) (10.0 g, 42 mmol) and anhyd. $AlCl_3$ (20.3 g, 152 mmol) was heated in an oil bath at *ca.* 175°C for 3 h. The cooled reaction mixture was treated with 2 **M** HCl (110 ml) and steam distilled until no more milky product was collected. The distillate was extracted with $CHCl_3$ (3 x 55 ml). The chloroform solution was extracted with 0.5 **M** KOH (3 x 50 ml), washed with $CHCl_3$ (3 x

50 ml), acidified and then re-extracted into $CHCl_3$ (3 x 50 ml). The combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford an oil which was distilled to give 4-bromo-2-hydroxyacetophenone (**125**) (4.6 g, 46%), m.p. 40 - 41°C (lit.[58] 42 - 43°C); δ_H (400 MHz; $CDCl_3$) 2.59 (3H, s, $COCH_3$), 7.22 (1H, dd, *J* 1.9 and 8.5 Hz, 5-H), 7.15 (1H, d, *J* 1.9 Hz, 3-H), 7.55 (1H, d, *J* 8.6 Hz, 6-H) and 12.37 (1H, s, OH); ν_{max} (nujol mull)/cm^{-1} 3500 - 3600 (OH) and 1640 (CO).

4-Fluoro-2-hydroxyacetophenone (126)[58]

The experimental procedure employed for the synthesis of 4-bromo-2-hydroxy-acetophenone (**125**) was followed, using 3-fluorophenyl acetate (**115**) (9.0 g, 139 mmol) and $AlCl_3$ (18.6 g, 139 mmol). Work-up afforded an oil which crystallized to give 4-fluoro-2-hydroxyacetophenone (**126**) (6.2 g, 69%), m.p. 29 - 31°C (from hexane) (lit.[107] 24°C); δ_H (400 MHz; $CDCl_3$) 2.59 (3H, s, $COCH_3$), 6.57 - 6.65 (2H, m, 3-H and 5-H), 7.73 (1H, dd, *J* 6.4 and 8.9 Hz, 6-H) and 12.66 (1H, s, OH); ν_{max})KBr)/cm^{-1} 3500 - 2650 (OH) and 1645 (CO).

4-chloro-2-hydroxyacetophenone (127)[58]

The experimental procedure employed for the synthesis of 4-bromo-2-hydroxy-acetophenone (**125**) was followed; using 3-chlorophenyl acetate (**116**) (10.0 g, 59 mmol) and anhyd. $AlCl_3$ (18.6 g, 140 mmol). Work-up afforded an oil which was distilled to give 4-chloro-2-hydroxyacetophenone (**127**) (6.90 g, 69%), b.p. 81 - 84°C/0.6 mmHg (lit.,[58] 121 - 124°C/15 mmHg); δ_H (400 MHz; $CDCl_3$) 2.60 (3H, s, $COCH_3$), 6.86 (1H, dd, *J* 2.1 and 8.6 Hz, 5-H), 6.98 (1H, d, *J* 2.1 Hz, 3-H), 7.64 (1H, d, *J* 8.6 Hz, 6-H) and 12.31 (1H, s, OH); ν_{max} (liquid film)/cm^{-1} 3500 - 2000 (OH) and 1760 (CO).

2-Hydroxy-4-nitroacetophenone (128)[108]

A mixture of 3-nitrophenyl acetate (**121**) (20 g, 110 mmol), $AlCl_3$ (28.0 g, 210 mmol) and dry, distilled nitrobenzene (100 ml) was heated at 140°C for 8 h. After cooling overnight, a mixture of ice (80 g) and conc. HCl (32 ml) was added and the resulting mixture steam distilled. The distillate was extracted with EtOAc (3 x 100 ml) and the combined EtOAc solutions were extracted with 0.50 M NaOH. The combined aqueous solutions were acidified and extracted with EtOAc (3 x 80 ml). The EtOAc extracts were dried (anhyd. $MgSO_4$) and evaporated to give the crude 2-hydroxy-4-nitroacetophenone (**128**) (0.26 g, 1%) m.p. 65°C (lit.,[108] 67 - 68°C); δ_H (400 MHz; $CDCl_3$) 2.71 (3H, s, $COCH_3$), 7.71 (1H, dd, *J* 2.3 and 8.7 Hz, 5-H), 7.80 (1H, d, *J* 2.2 Hz, 3-H), 7.91 (1H, d, *J* 8.7 Hz, 6-H) and 12.31 (1H, s, OH); ν_{max} (liquid film)/cm^{-1} 3650 - 3350 (OH) and 1650 (CO).

2-Hydroxy-5-methoxyacetophenone (130)[109]

Anhyd. $AlCl_3$ (18.7 g, 0.14 mol) and acetyl chloride (8.9 ml, 0.12 mol) were added to a cold solution of hydroxyquinone dimethyl ether (**123**) (18.7 g, 0.135 mol) in dry CS_2 (50 ml), and stirred for 24 h. The CS_2 was distilled off and dry Et_2O (300 ml) and anhyd. $AlCl_3$ (66.7 g, 2 mol) were added to the residue, and the resulting mixture boiled under reflux for 12 h. After cooling, the reaction mixture was cautiously poured onto ice and stirred. The ether layer was separated, the aqueous layer shaken with more ether, and the combined ethereal solutions shaken with aq. NaOH. The aqueous layers were combined, acidified and extracted with Et_2O (3 x 100 ml). The Et_2O extracts were combined, dried (anhyd. $MgSO_4$) and evaporated to yield an oil which crystallized to give crude 2-hydroxy-5-methoxyacetophenone (**130**) 12.8 g, 57%), m.p. 46 - 48°C (from hexane)

(lit.,[109] 47 - 48°C); δ_H (400 MHz; $CDCl_3$) 2.61 (3H, s, $COCH_3$), 3.79 (3H, s, OCH_3), 6.91 (1H, d, *J* 9 Hz, 3-H), 7.10 (1H, dd, *J* 3 and 9 Hz, 4-H), 7.16 (1H, d, *J* 3 Hz, 6-H), and 11.83 (1H, s, OH); ν_{max} (KBr)/cm^{-1} 3700 - 3100 (OH) and 1610 (CO).

*2-Hydroxy-4-methoxyacetophenone (**129**)*[110]

A mixture of resacetophenone (**122**) (10.0 g, 66 mmol), dry acetone (100 ml) and Me_2SO_4 (4.8 ml, 50 mmol) was boiled under reflux over K_2CO_3 (10.2 g, 64 mmol) for 6 h. The resulting solution was allowed to cool and the acetone removed under reduced pressure. The excess Me_2SO_4 was destroyed with a 25% ammonia-ice mixture (50 ml). The resulting solution was then extracted with EtOAC (3 x 60 ml) and the combined organic solutions dried (anhyd. $MgSO_4$), evaporated *in vacuo*, and distilled to afford 2-hydroxy-4-methoxyacetophenone (**129**) (8.9 g, 82%), b.p. 130°C/8.5 mmHg (lit.,[110] m.p. 48°C); δ_H (400 MHz; $CDCl_3$) 2.45 (3H, s, $COCH_3$), 3.74 (3H, s, OCH_3), 6.33 (1H, dd, *J* 2.5 and 8.2 Hz, 5-H), 6.36 (1H, d, *J* 2.5 Hz, 3-H) and 7.52 (1H, d, *J* 8.9 Hz, 6-H); ν_{max} (KBr)/cm^{-1} 3500 - 2500 (OH) and 1625 (CO).

*3-Methoxy-2-naphthoic acid (**132**)*[61]

A solution of 3-hydroxy-2-naphthoic acid (**131**) (25 g, 0.13 mmol) in acetone (125 ml), H_2O (125 ml), Me_2SO_4 (121 ml, 1.27 mol) and 20% methylated NaOH (1 l) was heated under reflux at *ca.* 90 - 110°C for 2 h. After cooling, the reaction solution was acidified with conc. HCl and extracted with CH_2Cl_2 (3 x 300 ml). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated to afford 3- methoxy-2-naphthoic acid (**132**) (20.7 g, 77%), m.p. 134°C (from EtOH) (lit.,[61] 132 - 133°C); δ_H (400 MHz; $CDCl_3$) 4.13 (3H, s, OCH_3), 7.25 (1H, s, 4-H), 7.42 and 7.56 (2H, 2 x t, 6-H and 7-H), 7.75 and

7.86 (2H, 2 x d, 5-H and 8-H), 8.73 (1H, s, 1-H) and 10.43 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 56.6 (OCH_3), 107.1 (C-4), 117.9, 128.3 and 136.5 (C-2, C-4a and C-8a), 125.3, 126.5 and 129.3 (C-5, C-6, C-7 and C-8), 154.3 (C-3) and 165.7 (C=O); ν_{max} (KBr)/cm^{-1} 2500 - 2000 (OH) and 1690 (CO.O).

*3-Methoxy-2-naphthoyl chloride (**133**)*[61]

A mixture of 3-methoxy-2-naphthoic acid (**132**) (8.0 g, 40 mmol) and $SOCl_2$ (36 ml, 50 mmol) was heated under reflux for 3 h. The reaction solution was allowed to cool, and the excess $SOCl_2$ distilled off by vacuum distillation to afford crude 3-methoxy-2-naphthoyl chloride (**133**) [(8.4 g, 96%) (lit. b.p.,[61] 131 - 132°C/0.01 mm Hg); δ_H (400 MHz; $CDCl_3$) 3.99 (3H, s, OCH_3), 7.17 (1H, s, 4-H), 7.41 and 7.58 (2H, 2 x t, 6-H and 7-H), 7.73 and 7.85 (2H, 2 x d, 5-H and 8-H) and 8.61 (1H, s, 1-H); δ_C (100 MHz; $CDCl_3$) 56.0 (OCH_3), 107.1 (C-4), 123.9, 127.1 and 137.2 (C-2, C-4a and C-8a), 125.0, 126.4, 129.4 and 130.0 (C-5, C-6, C-7 and C-8), 137.0 (C-1), 155.2 (C-3) and 164.0 (C=O); ν_{max} (KBr)/cm^{-1} 1770 (CO.Cl)], which was used without further purification.

*Diethyl (3-methoxy-2-naphthoyl)malonate (**135**)*[63]

A solution of 3-methoxy-2-naphthoyl chloride (4 g, 18 mmol) in dry Et_2O (15 ml) was added dropwise to a solution of ethoxymagnesium malonic ester [prepared *in situ* from freshly distilled diethylmalonate (3.20 g, 20 mmol), Mg turnings (0.50 g, 21 mmol), dry absolute ethanol (0.5 ml) and CCl_4 (0.6 ml)][64] and the mixture was stirred overnight at r.t., 2 M-H_2SO_4 (15 ml) was then added and the reaction mixture was extracted with Et_2O (3 x 25 ml), dried (anhyd. $MgSO_4$) and evaporated *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford

an oil from which crystallized diethyl (3-methoxy-2-naphthoyl)malonate (**135**) (4.33 g, 81%), m.p. 80°C(lit.,[63] 94 - 95°C); δ_H (400 MHz; $CDCl_3$) 1.26 (6H, m, 2 x CH_3CH_2), 3.95 (3H, s, OCH_3), 4.19 and 4.25 (4H, 2 x q, 2 x CH_2CH_3), 5.36 (1H, s, COCH-), 7.16 (1H, s, 4-H), 7.37 and 7.52 (2H, 2 x t, 6-H and 7-H), 7.71 and 7.86 (2H, 2 x d, 5-H and 8-H) and 8.49 (1H, s, 1-H); ν_{max} (KBr)/cm^{-1} 1750 (CO.O) and 1630 (CO).

3-Methoxy-2-acetonaphthone (134)

Method 1[62,111,112]

MeI (1.58 ml, 25 mmol) in dry Et_2O (15 ml) was added dropwise over 15 min. to a stirred suspension of dry Mg turnings (0.62 g, 25 mmol) in dry Et_2O (5 ml) to which had been added a few iodine crystals, and the resulting mixture stirred at r.t. for 2 h. Anhydrous $CdCl_2$ (2.50 g, 14 mmol) in dry Et_2O (5 ml) was added during 5 min. to the ice-cold solution of CH_3MgI, and the resulting mixture was stirred at r.t. for 20 min. The Et_2O was removed *in vacuo*, dry benzene (20 ml) was added and the reaction mixture gently refluxed for 2 h. After cooling, the solvent was removed by distillation and fresh dry benzene (20 ml) was added. 3-Methoxy-2-naphthoyl chloride (**133**) (5.57 g, 23 mmol) in dry benzene (15 ml) was then added slowly over 20 min. with constant stirring. After stirring for a further 1 h., the mixture was allowed to warm to 30°C, then gently heated under reflux for 2 h. The reaction mixture was allowed to cool to r.t., and carefully decomposed with ice and water. Dil. H_2SO_4 was added to dissolve the white precipitate. The benzene layer was separated and the aqueous layer extracted with benzene (2 x 25 ml). The combined benzene extract was successively washed with H_2O, aq. $NaHCO_3$ (dil.), and water, dried (anhyd. $MgSO_4$) and evaporated to give and oil which was chromatogaphed [flash chromatography on silica gel; elution with EtOAc] to

afford 3-methoxy-2-acetonaphthone (**134**) (3.96 g, 78%); m.p. 40°C (lit.,[63] 42 - 43°C); δ_H (400 MHz; $CDCl_3$) 2.67 (3H, s, $COCH_3$), 3.98 (3H, s, OCH_3), 7.16 (1H, s, 4-H), 7.35 and 7.49 (2H, 2 x t, 6-H and 7-H), 7.71 and 7.82 (2H, 2 x d, 5-H and 8-H) and 8.16 (1H, s, 1-H); ν_{max} (KBr)/cm^{-1} 1630 (CO).

Method 2[64]

A mixture of diethyl (3-methoxy-2-naphthoyl)malonate (**135**) (4.0 g, 14 mmol), AcOH (7.5 ml), conc. H_2SO_4 (0.61 ml) and H_2O (5 ml) was boiled under reflux for 6 h. After cooling the mixture was made alkaline with 20% *aq.* NaOH and the organic layer was extracted with Et_2O, washed with water, dried (anhyd. $MgSO_4$) and evaporated *in vacuo* to give an oil which was chromatographed (flash column chromatography on silica gel; elution with EtOAc) to afford 3-methoxy-2-acetonaphthone (**134**) (1.84 g, 68%), m.p. 41°C (lit.,[63] 42 - 43°C).

3-Hydroxy-2-acetonaphthone (136)[62]

3-Methoxy-2-acetonaphthone (**134**) (1.80 g, 9 mmol) and pyridine hydrochloride (3.64 g, 31.5 mmol) [prepared[34A] by bubbling dry HCl gas through dry pyridine for 2 h., and filtering the resulting salt] were heated under reflux at *ca.* 220°C for 1.5 h. The mixture was acidulated while hot, then poured into ice-cold water. The precipitated material was filtered off and washed to afford a solid which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford 3-hydroxy-2-acetonaphthone (**136**) (0.98 g, 59%), m.p. 115°C (from light petroleum ether, b.p. 80 - 100°C) (lit.,[62] 113.5 - 114.6°C); δ_H (400 MHz; $CDCl_3$) 2.78 (3H, s, $COCH_3$), 7.27 (1H, s, 4-H), 7.32 and 7.50 (2H, 2 x t, 6-H and 7-H), 7.67 and 7.80 (2H, 2 x d, 5-H and 8-H), 8.34 (1H,

s, 1-H) and 11.54 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 26.9 (CH_3), 112.3 (C-4), 121.4 and 126.9 (C-4a and C-8a), 124.0 and 129.7 (C-6 and C-7), 126.3 and 129.3 (C-5 and C-8), 133.5 (C-1), 138.2 (C-2), 158.1 (C-3) and 204.7 (CO); ν_{max} (KBr)/cm^{-1} 3500 - 2500 (OH) and 1630 (CO).

1-(2-Hydroxyphenyl)ethanone, boron difluoride complex (137)[70]

$BF_3.OEt_2$ (7.86 ml, 60 mmol) was added to a solution of 2-hydroxyacetophenone (**124**) (7.22 ml, 60 mmol) in dry Et_2O (60 ml) and the mixture stirred at room temperature for 1 h. The resulting mixture was filtered and the solid product washed well with Et_2O (*ca.* 45 ml) to give 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) (7.52 g, 68%), m.p. 144 - 145°C (lit., 143 - 145.5°C[70] and 146 - 147°C[113]); (Found: $\mathbf{M}^+$, 184.0517; $C_8H_7BF_2O_2$ requires **M**, 184.0506); δ_H (400 MHz; $CDCl_3$) 2.87 (3H, s, $COCH_3$), 7.03 (1H, tt, *J* 8.1 Hz, 4-H or 5-H), 7.10 (1H, dd, *J* 0.8 and 9.0 Hz, 3-H), and 7.76 - 7.80 (2H, m, 6-H and 4-H or 5-H); ν_{max} (KBr)/cm^{-1} 1630 (CO).

1-(4-Bromo-2-hydroxyphenyl)ethanone, boron difluoride complex (138)[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 4-bromo-2-hydroxyacetophenone (**125**) (4.0 g, 18.6 mmol), dry Et_2O (20 ml) and $BF_3.OEt_2$ (2.44 ml, 18.6 mmol). In this case the reaction time was 3 h. Work-up afforded 1-(4-bromo-2-hydroxyphenyl)-ethanone, boron difluoride complex (**138**) [(3.1 g, 63%); δ_H (400 MHz; $CDCl_3$) 2.84 (3H, s, $COCH_3$), 7.17 (1H, dd, *J* 1.8 and 8.7 Hz, 5-H), 7.33 (1H, d, *J* 1.7 Hz, 3-H), and 7.63 (1H, d, 6-H)], which was used without further purification.

1-(4-Fluoro-2-hydroxyphenyl)ethanone, boron difluoride complex (139)[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 2-hydroxy-4-fluoroacetophenone (**126**) (4.6 g, 30 mmol), dry Et_2O (30 ml) and $BF_3.OEt_2$ (3.9 ml, 30 mmol). In this case the reaction time was 3.5 h. Work-up afforded 1-(4-fluoro-2-hydroxyphenyl)ethanone, boron difluoride complex (**139**) (3.9 g, 64%) m.p. 128 - 130°C; δ_H (400 MHz; $CDCl_3$) 2.84 (3H, s, $COCH_3$), 6.77 (2H, m, 3-H and 5-H) and 7.85 (1H, m, 6-H); ν_{max} (KBr)/cm^{-1} 1625 (CO).

1-(4-Chloro-2-hydroxyphenyl)ethanone, boron difluoride complex (140)[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 4-chloro-2-hydroxyacetophenone (**127**) (5.1 g, 30 mmol), dry Et_2O (30 ml) and $BF_3.OEt_2$ (3.9 ml, 30 mmol). In this case, the reaction mixture was stirred overnight. Work-up afforded 1-(4-chloro-2-hydroxyphenyl)ethanone, boron difluoride complex (**140**) [(2.2 g, 33%); δ_H (400 MHz; $CDCl_3$) 2.86 (3H, s, $COCH_3$), 7.01 (1H, dd, *J* 1.9 and 8.8 Hz, 5-H), 7.15 (1H, d, *J* 1.9 Hz, 3-H), and 7.71 (1H, d, 8.8 Hz, 6-H)] which was used without further purification.

1-(2-Hydroxy-5-methoxyphenyl)ethanone, boron difluoride complex (141)[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 2-hydroxy-5-methoxyacetophenone (**130**) (5.0 g, 30 mmol), dry Et_2O (30 ml), and $BF_3.OEt_2$ (3.9 ml, 30 mmol). In this case, the reaction time was 2.75 h. Work-up afforded *1-(2-hydroxy-5-methoxyphenyl)-ethanone, boron difluoride complex* (**141**) (5.0 g, 78%), m.p. 144 - 146°C (**Found**: M^+,

214.0602; $C_9H_9BF_2O_3$ requires **M**, 214.0612); δ_H (400 MHz; $CDCl_3$) 2.83 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 6.96 (1H, d, *J* 3.1 Hz, 6-H), 7.06 (1H, d, *J* 9.3 Hz, 3-H), and 7.45 (1H, dd, *J* 3.1 and 9.3 Hz, 4-H); ν_{max} (KBr)/cm^{-1} 1620 (CO).

*3-Chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**)*[70]

A suspension of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) (5.66 g, 31 mmol) and *N,N*-dimethyldichloromethyleniminium chloride (95%, 5.26 g, 31 mmol) in dry 2-dichloroethane (100 ml) was heated at 80°C for 2 h. The mixture was cooled to 0°C, and the resulting solid was filtered off and washed with cold 1,2-dichloroethane (45 ml) and Et_2O (50 ml) to afford crude 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenylpropenone, boron difluoride complex (**143**) (7.9 g, 94%)[a] m.p. 170 - 173°C (lit.,[70] 180 - 182°C); δ_H (400 MHz; $CDCl_3$) 3.11 (6H, s, NMe_2), 5.41 (1H, s, 2-H), 7.31 (2H, m, 3′-H and 5′-H), 7.52 (1H, t, *J* 7.7 Hz, 4′-H) and 8.16 (1H, d, *J* 8.16 Hz, 6′-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 86.2 (C-2), 116.2 and 124.6 (C-3′ and C-5′), 122.9 (C-1′), 125.6 (C-6′), 131.9 (C-4′), 153.7 (C-3), 163.1 (C-2′) and 168.7 (C-1); ν_{max} (KBr)/cm^{-1} 1630 (CO).

*3-Chloro-3-(*N,N*-dimethylamino)-1-(4-bromo-2-hydroxyphenyl)propenone, boron difluoride complex (**144**)*[70]

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) was

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[a]Chromatographed [flash chromatography on silica gel; elution with EtOAc] and further purified by preparative thin layer chromatography (10% MeOH/CH_2Cl_2 as solvent).

followed, using 1-(4-bromo-2-hydroxyphenyl)ethanone, boron difluoride complex (**138**) (2.8 g, 11.5 mmol), dry 1,2-dichloroethane (50 ml) and *N,N*-dimethyldichloro-ethyleniminium chloride (**143**) (95%, 1.8 g, 10.50 mmol). Work-up afforded *3-chloro-3-(*N,N-*dimethylamino)-1-(4-bromo-2-hydroxyphenyl)propenone, boron difluoride complex* (**144**) (3.3 g, 88%); (**Found**: C, 37.6; H, 2.9; N, 3.9; $\mathbf{M}^+$, 350.9850; $C_{11}H_{10}BBrClF_2NO_2$ requires: C, 37.5; H, 2.9; N, 4.0%; **M**, 350.9836); δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_3), 5.39 (1H, s, 2-H), 7.45 (1H, dd, *J* 1.6 and 8.4 Hz, 5′-H), 7.50 (1H, d, *J* 1.5 Hz, 3′-H), and 8.01 (1H, d, *J* 8.4 Hz, 6′-H); ν_{max} (KBr)/cm^{-1} 1640 (CO).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone, boron difluoride complex (**145**)*[70]

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) was followed, using 1-(4-fluoro-2-hydroxyphenyl)ethanone, boron difluoride complex (**139**) (2.75 g, 13.6 mmol), dry 1,2-dichloroethane (45 ml) and *N,N*-dimethyldichloro-methyleniminium chloride (**142**) (95%, 2.3 g, 13.6 mmol). Work-up afforded *3-chloro-3-(*N,N-*dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone, boron difluoride complex* (**145**) (3.8 g, 69%), m.p. 118 - 120°C; δ_H (400 MHz; $CDCl_3$) 3.08 (6H, s, NMe_2), 5.35 (1H, s, 2-H), 6.98 (1H, dd, *J* 2.3 and 9 Hz, 3′-H), 7.03 (1H, tt, *J* 8.5 Hz, 5′-H), and 8.14 (1H, dd, *J* 6.4 and 8.7 Hz, 6′-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 85.8 (C-2), 103.4 (C-3′) 112.8 (C-5′), 119.6 (C-4′), 127.7 (C-6′), 175.7 (C-1), 154.4, (C-3′), 163.3 (C-1′), 165.9 (C-2′) and 175.7 (C-1); ν_{max} (KBr)/cm^{-1} 1620 (CO).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(4-chloro-2-hydroxyphenyl)propenone, boron difluoride complex (**146**)*[70]

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenylpropenone, boron difluoride complex (**143**) was followed, using 1-(4-chloro-2-hydroxyphenyl)ethanone, boron difluoride complex (**140**) (2.0 g, 9.2 mmol), dry 1,2-dichloroethane (30 ml) and *N,N*-dimethyldichloro-methyleniminium chloride (**142**) (95%, 1.6 g, 9.2 mmol). Work-up afforded *3-chloro-3-(*N,N-*dimethylamino)-1-(4-chloro-2-hydroxyphenyl)propenone, boron difluoride complex* (**146**) (2.5 g, 89%), m.p. 172 - 174°C; δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_2), 5.28 (1H, s, 2-H), 7.29 (1H, dd, *J* 1.8 and 8.4 Hz, 5′-H), 7.33 (1H, d, *J* 1.7 Hz, 3′-H) and 8.08 (1H, d, *J* 8.4 Hz, 6′-H); δ_C (100 MHz; $CDCl_3$) 37.6 (NMe_2), 86.2 (C-2), 116.6 (C-3′), 121.6 (C-4′), 125.3 (C-5′), 127.0 (C-6′), 153.8 (C-1′) and 163.0 (C-2′), and 175.6 (C-1); ν_{max} (KBr)/cm^{-1} 1630 (CO).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone, boron difluoride complex (**147**)*[70]

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) was followed, using 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (3.95 g, 18.5 mmol), dry 1,2-dichloroethane (60 ml) and *N,N*-dimethyldichloromethyleniminium chloride (**142**) (95%, 3.2 g, 18.5 mmol). Work-up afforded *3-chloro-(3-*N,N-*dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone, boron difluoride complex* (**147**) (5.4 g, 95%), m.p. 207 - 209°C; δ_H (400 MHz; $CDCl_3$) 3.21 (6H, s, NMe_2), 3.83 (3H, s, OCH_3), 6.20 (1H, s, 2-H), 7.18 (1H, dd, *J* 3 and 9.1 Hz, 4′-H), 7.29 (1H, d, *J* 9.1

Hz, 3′-H) and 7.52 (1H, d, *J* 7.52, 6′-H); δ_C (100 MHz; $CDCl_3$) 38.1 (NMe_2), 56.0 (OCH_3), 86.8 (C-2), 105.7 (C-6′), 117.6 (C-3′), 120.9 (C-1′), 122.3 (C-4′), 148.0 (C-3), 157.1 (C-5′), 163.4 (C-2′) and 175.9 (C-1); ν_{max} (KBr)/cm^{-1} 1630 (CO).

*4-Hydroxy-2-*H*-1-benzopyran-2-thione (**155**)*[68,114]

Method 1

A solution of 2-hydroxyacetophenone (**124**) (8.11 g, 7.18 ml, 59.6 mmol) and dry CS_2 (3.55 ml, 59.6 mmol) in dry benzene (100 ml) was added to a suspension of potassium *t*-butoxide (20 g, 0.18 mmol) in dry benzene (150 ml) at 15°C under N_2 maintaining the temperature between 15 and 22°C. The resulting yellow viscous mixture was stirred for 4 d. at r.t., and then poured into H_2O (*ca.* 1000 ml). The aqueous phase was washed with ether and cooled to < 5°C, acidified with 10% ice-cold H_2SO_4 and stirred overnight. The resulting precipitate was filtered off and washed well with hot petroleum ether (b.p. 60 - 80°C) to afford 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**) (5.61 g, 53%), m.p. 214°C (lit.,[69] 180°C); (Found: M^+, 178.0076; $C_9H_6O_2S$ Calc for: **M**, 178.0088); δ_H (400 MHz; DMSO-d_6) 6.68 (1H, s, 3-H), 7.45 (1H, t, 6-H), 7.74 (1H, t, 7-H), 7.56 (1H, d, 8-H) and 7.90 (1H, d, 5-H); δ_C (100 MHz; DMSO-d_6) 107.9 (C-3), 116.4 (C-8), 116.7 (C-4), 123.2 (C-5), 125.2 (C-6), 133.4 (C-7), 156.9 (C-8a), 161.7 (C-4), 196.9 (C-2); *m/z* 178 (M^+, 100).

*2-Ethylthio-4*H*-1-benzopyran-4-one (**156**)*[68]

A mixture of 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**) (3.50 g, 19.6 mmol), K_2CO_3 (2.99 g, 21.60 mmol) and iodoethane (4.0 ml, 50 mmol) in dry acetone (40 ml) was heated under reflux for 3 h. The resulting mixture was filtered hot, and the filtrate was

concentrated *in vacuo*. The residue was partitioned between water and chloroform. The chloroform layer was dried (anhyd. $MgSO_4$) and the solvent evaporated to afford a solid (3.18 g), which was chromatographed [flash chromatography on silica gel; elution with EtOAc:Hexane (3:2)] to afford *2-ethylthio-4*H*-1-benzopyran-4-one* (**156**) (1.90 g, 47%), m.p. 84 - 86°C (from hexane) (**Found**: C, 64.2; H, 4.8; $\mathbf{M}^+$, 206.0408. $C_{11}H_{10}O_2S$ requires: C, 64.1; H, 4.85%; **M**, 206.0401); δ_H (400 MHz; $CDCl_3$) 1.44 (3H, t, CH_2CH_3), 3.07 (2H, q, CH_2CH_3), 6.26 (1H, s, 3-H), 7.38 (2H, m, 6-H and 8-H), 7.62 (1H, m, 7-H) and 8.16 (1H, dd, *J* 1.3 and 7.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 14.2 (CH_3), 25.5 (CH_2), 108.7 (C-3), 117.2 and 125.2 (C-6 and C-8), 123.6 (C-4a), 125.8 (C-5), 133.3 (C-7), 156.9 (C-2), 168.6 (C-8a) and 175.7 (C-4); *m/z* 206 (M^+, 18%) and 121 (100); ν_{max} (KBr)/cm^{-1} 1660 (CO).

*2-Ethylsulphinyl-4*H*-benzopyran-4-one (157)*[68]

A suspension of *m*-1-chloroperbenzoic acid (MCPBA) (55%; 2.06 g, 6.57 mmol) in dry 1,2-dichloroethane (15 ml) was added to a cooled (*ca.* 0°C), stirred solution of 2-ethylthio-4*H*-1-benzopyran-4-one (**156**) (1.30 g, 6.30 mmol) in dry 1,2-dichloroethane (30 ml). The resulting mixture was stirred for 2 h. and then filtered. The filtrate was washed with cold 5% aq. Na_2CO_3, saturated aq. sodium bisulphite and H_2O. The 1,2-dichloroethane layer was dried (anhyd. $MgSO_4$) and the solvent evaporated to afford *2-ethylsulphinyl-4*H*-benzopyran-4-one* (**157**) (1.04 g, 74%), m.p. 120 - 122°C (dry benzene) (**Found**: C, 59.3; H, 4.5; $\mathbf{M}^+$ 222.0338. $C_{11}H_{10}O_3S$ requires: C, 59.5; H, 4.5%; **M**, 222.0350); δ_H (400 MHz; $CDCl_3$) 1.34 (3H, t, CH_2CH_3), 3.01 and 3.23 (2H, 2 x sextet, CH_2CH_3), 6.91 (3-H), 7.45 (2H, m, 6-H and 8-H), 7.71 (1H, m, 7-H) and 8.21 (1H, dd, *J* 1.6 and 8.2 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 5.3 (CH_3), 45.9 (CH_2),

111.0 (C-3), 117.9 (C-8), 124.3 (C-4a), 126.2 and 126.4 (C-5 and C-6), 134.5 (C-7), 156.2 (C-2), 169.6 (C-8a) and 175.9 (C-4); ν_{max} (KBr)/cm^{-1} 1640 (CO); *m/z* 222 (M^+, 60%) and 146 (100).

*Methyl 5-chlorosalicylate (**164**)*[116]

5-Chlorosalicylic acid (**161**) (10 g, 58 mmol), methanol (50 ml) and $POCl_3$ (5 ml) were heated under reflux for 5 h. The solution was allowed to cool, and the precipitated solid was filtered off to afford methyl 5-chlorosalicylate (**164**) (9.18 g, 85%), m.p. 44 - 46°C (from EtOH-H_2O) (lit.,[116] 43 - 50°C); δ_H (400 MHz; $CDCl_3$) 3.95 (3H, s, OCH_3), 6.91 (1H, d, *J* 8.9 Hz, 3-H), 7.38 (1H, dd, *J* 2.7 and 8.9 Hz, 4-H), 7.79 (1H, d, *J* 2.7 Hz) and 10.64 (1H, br s, OH); ν_{max} (KBr)/cm^{-1} 3700 - 3000 (OH) and 1620 (CO).

*Methyl 5-nitrosalicylate (**165**)*[117]

5-Nitrosalicylic acid (**162**) (10.0 g, 55 mol), methanol (100 ml) and conc. H_2SO_4 (9 ml) were heated under reflux for 20 h. After cooling, the resulting precipitate was filtered off and dried to afford methyl 5-nitrosalicylate (**165**) (7.60 g, 71%), m.p. 98 - 100°C (from petroleum ether or ethanol) (lit.,[118] 96°C); δ_H (400 MHz; $CDCl_3$) 4.05 (3H, s, OCH_3), 7.07 (1H, d, *J* 9.2 Hz, 3-H), 8.32 (1H, dd, *J* 2.8 and 9.2 Hz, 4-H), 8.77 (1H, d, *J* 2.8 Hz, 6-H) and 11.40 (1H, s, OH); ν_{max} (KBr)/cm^{-1} 3500 - 2500 (OH) and 1625 (CO).

N,N-*dimethyl-3-(2-hydroxyphenyl)-3-oxo-propanamide (**166**)*[119]

Butyllithium (1.5 **M** solution in hexane; 83.0 ml, 124 mmol) was added dropwise to a cold solution (*ca.* 0°C) of dry, distilled diisopropylamine (17.55 ml, 124 mmol) in dry THF (100 ml) under dry N_2. After stirring for 40 min., *N,N*-dimethylacetamide (5.74

ml, 62.12 mmol) was added and the solution stirred for 30 min., before adding methyl salicylate (**163**) (5.0 ml, 39 mmol) in THF (5 ml) at 0°C. The resulting solution was heated under reflux for 2 h. (or overnight at r.t.), cooled, neutralized with 10% HCl, and then extracted with CH_2Cl_2 (3 x 75 ml). The combined organic layers were dried (anhyd. $MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was triturated with Et_2O and filtered to afford *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxo-propanamide (**166**) (5.44 g, 68%), m.p. 70°C (lit.,[119] 71 - 73°C); (Found: $\mathbf{M}^+$, 207.0828. $C_{11}H_{13}NO_3$ calculated: **M**, 207.0816); δ_H (400 MHz; $CDCl_3$) 2.98 and 3.05 (6H, 2 x s, NMe_2), 4.09 (2H, s, CH_2), 6.90 (1H, t, *J* 8 Hz, 5′-H), 6.96 (1H, d, *J* 8.4 Hz, 3′-H), 7.46 (1H, m, 4′-H), 7.80 (1H, dd, *J* 1.5 and 8.1 Hz, 6′-H) and *ca.* 11.80 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 35.2 (NMe_2), 88.1 (C-2), 116.3 and 123.0 (C-3′ and C-5′), 121.8 (C-1′), 124.3 (C-6′), 131.1 (C-4′), 154.2 (C-2′), 168.3 (C-1) and 177.2 (C-3); *m/z* 207 (M^+, 2%) and 120 (100).

N,N-*dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide (167)*[119]

The experimental procedure employed for the synthesis of *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxo-propanamide (**166**) was followed using butyllithium (41.5 ml, 62 mmol), dry, distilled diisopropylamine (8.75 ml, 62 mmol) in dry THF (50 ml), *N,N*-dimethylacetamide (2.87 ml, 31.0 mmol) and methyl 5-chlorosalicylate (**164**) (3.62 g, 19.4 mmol). Work-up afforded N,N-*dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide* (**167**) (3.44 g, 73%), m.p. 106 - 108°C; (**Found**: $\mathbf{M}^+$, 241.0515. $C_{11}H_{12}ClNO_2$ requires **M**, 241.0504); δ_H (400 MHz; $CDCl_3$) 3.01 and 3.08 (6H, 2 x s, NMe_2), 4.06 (2H, s, CH_2), 6.94 (1H, d, *J* 9 Hz, 3′-H), 7.42 (1H, dd, *J* 2.5 and 8.9 Hz, 4′-H), and 7.76 (1H, d, *J* 2.6 Hz, 6′-H); δ_C (100 MHz; $CDCl_3$) 35.1 (NMe_2), 88.1

(C-2), 117.7, 128.4, 123.8, 130.8 and 136.6 (5 x ArC), 152.4 (C-2′), 168.0 (C-1) and 175.9 (C-3); *m/z* 241 (M^+, 30%) and 45 (100).

*Ethyl (*N,N-*dimethylcarbamoyl)ethanoate (**171**)*[115]

Diethyl malonate (18.96 ml, 125 mmol) and dimethylamine (33 % ethanolic solution; 22.47 ml, 125 mmol) were heated in a sealed stainless steel autoclave at 140°C for 40 h. The resulting mixture was distilled[a] to afford ethyl (N,N-dimethylcarbamoyl)ethanoate (**171**) (8.0 g, 40%), b.p. 143 - 145°C/0.9 mm Hg (lit.,[115] 110 - 112°C/3.0 mm Hg); δ_H (400 MHz; $CDCl_3$) 1.17 (3H, t, CH_2CH_3), 2.86 and 2.92 (6H, 2 x s, $CONMe_2$), 3.34 (2H, s, $-CH_2-$) and 4.09 (2H, q, CH_2CH_3); ν_{max} (liquid film)/cm^{-1} 1740 (CO.O) and 1650 (CO).

*Ethyl (*N,N-*diethylcarbamoyl)ethanoate (**172**)*[115]

The experimental procedure employed for the synthesis of ethyl (*N,N*-dimethyl-carbamoyl)ethanoate (**171**) was followed, using diethyl malonate (18.9 ml, 125 mmol) and diethylamine (13.0 ml, 125 mmol). In this case, the reaction temperature was 150°C and reaction time 37 h. Work-up afforded ethyl (*N,N*-diethylcarbamoyl)ethanoate (**172**) (12.66 g, 53%), b.p. 90°C/0.1 mm Hg (lit.,[115] 86 - 88°C/0.6 mmHg; 151°C/12 mmHg); δ_H (400 MHz; $CDCl_3$) 1.10 and 1.15 (6H, 2 x t, 2x CH_3), 1.24 (3H, t, CH_2CH_3), 3.26 and 3.36 (4H, 2 x q, 2 x N-CH_2), 3.37 (2H, s, CH_2CH_3) and 4.16 (2H, q, $COCH_2$); ν_{max} (liquid film)/cm^{-1} 1735 (CO.O) and 1640 (CO).

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[a]In certain cases, the crude product was chromatographed [flash chromatography on silica gel, elution with EtOAc] and then further purified by vacuum distillation.

*Ethyl[(pyrrolidin-1-yl)carbamoyl]ethanoate (**174**)*[115]

The experimental procedure employed for the synthesis of ethyl-(*N,N*-dimethylcarbamoyl)-ethanoate (**171**) was followed, using diethyl malonate (18.9 ml, 125 mmol) and pyrrolidine (10.3 g, 125 mmol). In this case, the reaction temperature was 150°C and reaction time 37 h. Work-up afforded ethyl [(pyrrolidin-1-yl)carbamoyl]-ethanoate (**174**) (6.35 g, 28%), b.p. 106 - 108°C/0.1 mmHg (lit.,[120] 105.6°C/0.08 mmHg); δ_H (400 MHz; $CDCl_3$) 1.25 (3H, t, CH_2CH_3), 1.85 and 1.94 [4H, 2 x t, $(CH_2)_2$), 3.35 (2H, s, $-CH_2-$), 3.41 and 3.47 (4H, 2 x t, 2 x NCH_2) and 4.17 (3H, q, CH_2CH_3); ν_{max} (liquid film)/cm^{-1} 1730 (CO.O) and 1640 (CO).

*Ethyl [(piperidin-1-yl)carbamoyl]ethanoate (**173**)*[115]

The experimental procedure employed for the synthesis of ethyl (*N,N*-dimethylcarbamoyl)-ethanoate (**171**) was followed, using diethyl malonate (18.9 ml, 125 mmol) and piperidine (12.34 g, 125 mmol). In this case, the reaction temperature was 150°C and reaction time 38 h. Work-up afforded ethyl [(piperidin-1-yl)carbamoyl]-ethanoate (**173**) (12.20 g, 49%), b.p. 118 - 120°C/0.6 mmHg (lit.,[120] 101 - 102/0.06 mmHg); δ_H (400 MHz; $CDCl_3$) 1.18 (3H, t, CH_3CH_3), 1.50 (6H, m, $-(CH_2)_3-$), 3.26 and 3.47 (4H, 2 x t, NCH_2), 3.35 (2H, s, CH_2) and 4.10 (2H, q, CH_2CH_3); ν_{max} (liquid film)/cm^{-1} 3000 and 2920 (CH), 1730 (CO.O) and 1650 (CO).

Ethyl (N,N-*diisopropylcarbamoyl)ethanoate (**175**)*[115]

The experimental procedure employed for the synthesis of ethyl (*N,N*-dimethyl-carbamoyl)ethanoate (**171**) was followed, using diethyl malonate (18.9 ml, 125 mmol) and diisopropylamine (17.64 ml, 125 mmol). Work-up afforded ethyl (*N,N*-diisopropyl-

carbamoyl)ethanoate (**175**) (3.71 g, 14%); b.p. 96 - 102°C/0.5 mmHg (lit.,[121] 74 - 75°C/0.08mm Hg); δ_H (400 MHz; $CDCl_3$) 1.13 and 1.15 [6H, 2 x s, $CH(CH_3)_2$], 1.21 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.32 and 1.33 [6H, 2 x s, $CH(CH_3)_2$], 3.34 (2H, s, $-CH_2-$), 3.41 and 3.77 (2H, 2 x quintet, 2 x NCH), and 4.13 (2H, q, *J* 9.8 and 17 Hz, CH_2CH_3); ν_{max} (liquid film)/cm^{-1} 1725 (CO.O) and 1630 (CO.N).

*2-(*N,N-*dimethylamino)-4*H-*1-benzopyran-4-one (148)*

Method 1[70]

A solution of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) (6.0 g, 22 mmol) in MeOH (200 ml) was stirred at 50°C for 45 min.[a] The solvent was evaporated and the residue was dissolved in saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 75 ml) and the combined extracts were washed with brine (1 x 75 ml), dried (anhyd. $MgSO_4$) and evaporated to give 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (3.8 g, 91%), m.p. 122 - 124°C (from EtOAc) (lit.,[70] 122 - 123°C); (Found: C, 69.8; H, 5.9; N, 7.4; M^+, 189.0779. $C_{11}H_{11}NO_2$ requires: C, 69.9; H, 5.8; N, 7.4%; **M**, 189.0790); δ_H (400 MHz; $CDCl_3$) 3.08 (6H, s, NMe_2), 5.38 (1H, s, 3-H), 7.29 (2H, m, 6-H and 8-H), 7.50 (1H, m, 7-H) and 8.14 (1H, dd, *J* 1.7 and 7.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.3 (NMe_2), 85.8 (C-3), 116.1 (C-6 or C-8), 124.4 (C-8 or C-6), 122.9 (C-4a), 125.3 (C-5), 131.8 (C-7), 153.5 (C-8a), 162.9 (C-2) and 176.3 (C-4); ν_{max} (KBr)/cm^{-1} 1630 (CO); *m/z* 189 (M^+, 100%).

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[a]or until the bright colour disappears and the solution becomes almost clear.

2-(N,N-*dimethylamino)-4*H-*1-benzopyran-4-one (148)*[119]

Method 2[119]

Triflic anhydride (7.30 ml, 43.4 mmol) was added to a solution of *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxo-propanamide (**166**) (2.50 g, 13.2 mmol) in dry CH_2Cl_2 (60 ml). After stirring overnight at r.t., the solvent was evaporated, the residue dissolved in methanol and the resulting solution stirred for 4 h. The methanol was evaporated and the residue diluted with half saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 70 ml). The combined organic extracts were washed with saturated NaCl (1 x 70 ml), dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford an oil (4.18 g) which was chromatographed [flash chromatography on silica gel; elution with 5% MeOH-CH_2Cl_2] to afford 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran4-one (**148**) (1.21 g, 53%), m.p. 120 - 121°C (from EtOAc) (lit.,[119] 123.5 - 124.5°C).

2-(N,N-*dimethylamino)-4*H-*1-benzopyran-4-one (148)*

Method 3[68]

Dimethylamine (33% w/w solution in EtOH; 9.71 ml, 54.0 mmol) was added to a warm, stirred solution of 2-ethylsulphinyl-4*H*-benzopyran-4-one (**156**) (2.00 g, 9.0 mmol). After stirring for 2 d. at r.t., the solvent was evaporated to afford an oil which was chromatographed [flash chromatography on silica gel, elution with EtOAc] to afford 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**)] (0.96 g, 56%), m.p. 119 - 121°C (from EtOAc) (lit.,[119] 123.5 - 124.5°C).

*2-(*N,N-*dimethylamino)-4*H-*1-benzopyran-4-one (148)*

Method 4[71,74]

Phosphorus oxychloride (1.72 ml, 18.8 mmol) was added to cooled ethyl (*N,N*-dimethylcarbamoyl)ethanoate (**171**) (2.19 g, 13.8 mmol) and the mixture stirred at r.t. for 30 min. Phenol (1.17 g, 12.5 mmol) in dry chlorobenzene (10 ml) was heated under reflux for 6 h. After cooling, a solution of CH_3COONa (17 g) in H_2O (50 ml) was added and the resulting mixture was stirred vigorously at 90 - 95°C for 1.5 h. The mixture was allowed to cool, and the organic layer removed. The aqueous layer was extracted with $CHCl_3$ (3 x 50 ml) and the combined organic layers were washed with H_2O, dried (anhyd. $MgSO_4$) and concentrated *in vacuo* to afford a viscous reddish oil[a] (0.82 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc:EtOH (3:1)] to afford 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (0.13 g, 6%).

*2-(*N,N-*Dimethylamino)-7-bromo-4*H-*1-benzopyran-4-one (149)*[70]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using *3-chloro-3-(*N,N-*dimethylamino)-1-(4-bromo-2-hydroxyphenyl)propenone, boron difluoride complex* (**144**) (2.15 g, 10.5 mmol) and MeOH (90 ml). Work-up afforded 2-(*N,N*-dimethylamino)-7-bromo-4*H*-1-benzopyran-4-one (**149**) (1.80 g, 88%), m.p. 203°C (from 10% MeOH/CH_2Cl_2) (**Found**: M^+, 266.9884. $C_{11}H_{10}BrNO_2$ requires: **M**, 266.9895); δ_H (400 MHz; $CDCl_3$) 3.05 (6H, s, NMe_2), 5.33 (1H, s, 3-H), 7.40 (1H, dd, *J* 1.7 and 8.4 Hz, 6-H), 7.44 (1H, d, *J* 1.7 Hz, 8-H) and 7.97 (1H, d, *J* 8.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 86.1 (C-3), 119.4 (C-8), 121.9 (C-4a), 125.5 (C-7), 127.0 (C-5), 128.0 (C-6), 153.7 (C-2), 162.8

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[a]The oil may be treated as for compound (**159**) to afford the expected product.

(C-8a) and 175.5 (C-4); ν_{max} (KBr)/cm^{-1} 1610 (CO); *m/z* 269 (M^+, 60%) and 69 (100).

*2-(*N,N-*Dimethylamino)-7-fluoro-4*H-*1-benzopyran-4-one (150)*[70]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone, boron difluoride complex (**145**) (2.75 g, 13.6 mmol) and MeOH (90 ml). Work-up afforded *2-(*N,N-*dimethylamino)-7-fluoro-4*H-*1-benzopyran-4-one* (**150**) (1.76 g, 83%), m.p. 138 - 140°C (from EtOAc); (**Found**: **M**$^+$, 207.0679. $C_{11}H_{10}FNO_2$ requires: **M**, 207.0695); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.35 (1H, s, 3-H), 7.02 (2H, m, 6-H and 8-H) and 8.14 (1H, dd, *J* 6.5 and 8.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.6 (NMe_2), 85.8 (C-3), 103.4 and 112.7 (C-6 and C-8), 119.6 (C-4a), 127.7 (C-5), 154.4 (C-7), 163.3 (C-2), 165.9 (C-8a), and 175.7 (C-4); ν_{max} (KBr)/cm^{-1} 1620 (CO); *m/z* 207 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-7-chloro-4*H-*benzopyran-4-one (151)*[70]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(4-chloro-2-hydroxyphenyl)propenone, boron difluoride complex (**146**) (2.00 g, 9.2 mmol) and MeOH (55 ml). Work-up afforded *2-(*N,N-*dimethylamino)-7-chloro-4*H-*benzopyran-4-one* (**151**) (1.21 g, 83%), m.p. 185°C; (**Found**: C, 58.5; H, 4.5; N, 6.1; **M**$^+$, 223.0408. $C_{11}H_{10}ClNO_2$ requires: C, 59.2; H, 4.5; N, 6.3%; **M**, 223.0399); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.36 (1H, s, 3-H), 7.28 (1H, dd, *J* 1.9 and 8.4 Hz, 6-H), 7.31 (1H, d, *J* 1.9 Hz, 8-H) and 8.07 (1H, d, *J* 8.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 86.1 (C-3), 116.5 (C-8), 121.5 (C-4a), 125.2 (C-6), 126.8 (C-5), 137.6 (C-7), 153.7 (C-

2), 162.9 (C-8a) and 175.5 (C-4); ν_{max} (KBr)/cm^{-1} 1620 (CO); *m/z* 223 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-6-methoxy-4*H-*1-benzopyran-4-one (152)*[70]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone, boron difluoride complex (**147**) (4.80 g, 15.8 mmol) and MeOH (144 ml). Work-up afforded *2-(*N,N-*dimethylamino)-6-methoxy-4*H-*1-benzopyran-4-one* (**152**) (3.28 g, 95%), m.p. 150 - 152°C (from EtOAc); (**Found**: C, 65.2; H, 6.05; N, 6.3; **M**$^+$, 219.0886. $C_{12}H_{13}NO_3$ requires: C, 65.7; H, 5.9; N, 6.4%; **M**, 219.0895); δ_H (400 MHz; $CDCl_3$) 3.11 (6H, s, NMe_2), 3.90 (3H, s, OCH_3), 5.37 (3-H), 7.07 (1H, dd, *J* 3.2 and 9 Hz, 7-H), 7.19 (1H, d, *J* 9Hz, 8-H) and 7.55 (1H, d, *J* 3.1 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 55.9 (OCH_3), 85.9 (C-3), 105.8 (C-5), 117.4 (C-8), 121.0 (C-7), 123.5 (C-4a), 148.2 (C-6), 156.0 (C-2), 163.0 (C-8a), 176,3 (C-4); ν_{max} (KBr)/cm^{-1} 1620 (CO); *m/z* 219 (M^+, 100%).

*2-(*N,N-*diethylamino)-4*H-*1-benzopyran-4-one (158)*

Method 1[68]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 2-ethylsulphinyl-4*H*-benzopyran-4-one (**156**) (1.00 g, 4.50 mmol), acetonitrile (40 ml) and diethylamine (2.8 ml, 27 mmol). Work-up afforded a crude oil (1.18 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc:EtOH (5:1)] to afford 2-(*N,N*-diethylamino)-4*H*-1-benzopyran-4-one (**158**) (0.90 g, 92%), m.p. 93 - 94°C (from ligroin) (lit.,[74] 96 - 97°C); (**Found**: C, 71.9; H, 7.05; N, 6.2; **M**$^+$, 217.1108. $C_{13}H_{15}NO_2$ requires: C, 71.9; H, 6.9; N, 6.45%;

M, 217.1103); δ_H (400 MHz; $CDCl_3$) 1.25 (6H, t, 2 x CH_2CH_3), 3.34 (4H, q, 2 x CH_2CH_3), 5.40 (1H, s, 3-H), 7.27 (2H, m, 6-H and 8-H), 7.49 (1H, m, 7-H) and 8.13 (1H, dd, *J* 1.6 and 7.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 13.1 (CH_3), 43.2 (CH_2), 85.8 (C-3), 116.1 (C-8), 123.1 (C-4a), 124.5 and 125.5 (C-5 and C-6), 131.7 (C-7), 153.8 (C-2), 162.0 (C-8a) and 176.4 (C-4); ν_{max} (KBr)/cm^{-1} 2990 (OH) and 1600 (CO); *m/z* 217 (M^+, 90%) and 121 (100).

*2-(*N,N-*diethylamino)-4*H-*1-benzopyran-4-one (158)*

Method 2[74]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (Method 4) was followed, using ethyl (*N,N*-diethylcarbamoyl)-ethanoate (**172**) (3.0 g, 16.0 mmol), phosphorus oxychloride (2.35 ml, 21.0 mmol) and phenol (1.01 g, 10.7 mmol) in dry chlorobenzene (6.5 ml). In this case the reaction solution was heated under reflux for 7 h. Work-up afford 2-(*N,N*-diethylamino)-4*H*-1-benzopyran-4-one (**158**) (0.14 g, 6%).

*2-(Piperidin-1-yl)-4*H-*1-benzopyran-4-one (159)*[68]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) (0.50 g, 2.3 mmol), acetonitrile (20 ml) and piperidine (0.30 ml, 3.0 mmol). Work-up afforded a crude solid (0.62 g) which was dissolved in a minimum amount of dry $CHCl_3$ (10 ml) and then treated with an excess of ethereal HCl. After cooling, the hydrochloride salt of the amine was filtered off, treated with aqueous sodium hydrogen carbonate, and the resulting mixture extracted with $CHCl_3$ (3 x 30 ml). The combined

extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated to afford 2-(piperidin-1-yl)-4*H*-1-benzopyran-4-one (**159**) (0.39 g, 75%), m.p. 118 - 119°C (from ligroin) (lit.,[74] 118 - 119°C); (**Found**: C, 73.7; H, 6.7; N, 6.2; M^+, 229.1117. $C_{14}H_{15}NO_2$ requires: C, 73.6; H, 6.55; N, 6.1%; M, 229.1103); δ_H (400 MHz; $CDCl_3$) 1.67 (6H, s, $-(CH_2)_3-$), 3.48 and 3.49 (4H, 2 x s, 2 x N-CH_2), 7.26 (2H, m, 6-H and 7-H), 7.49 (1H, m, 8-H) and 8.11 (1H, dd, *J* 1.7 and 7.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 24.1 and 25.2 [$(CH_3)_2$], 45.9 (2 x NCH_2), 86.8 (C-3), 116.2 (C-8), 123.0 (C-4a), 124.5 (C-6), 125.4 (C-5), 131.9 (C-7), 153.7 (C-8a), 162.4 (C-2) and 177.0 (C-4); ν_{max} (KBr)/cm^{-1} 1630 (CO); *m/z* 229 (M^+, 69%) and 83 (100).

*2-(Pyrrolidin-1-yl)-4*H*-1-benzopyran-4-one (**160**)*[68]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) (0.75 g, 3.4 mmol), acetonitrile (25 ml) and pyrrolidine (0.33 ml, 4 mmol). Work-up afforded *2-(pyrrolidin-1-yl)-4*H*-1-benzopyran-4-one* (**160**) (0.60 g, 82%), m.p. 148 - 150°C (from ligroin) (**Found**: C, 72.6; H, 6.2; N, 6.3%; $C_{13}H_{13}NO_2$ requires C, 72.6; H, 6.05; N, 6.5%); δ_H (400 MHz; $CDCl_3$) 2.03 (4H, m, $-(CH_2)-$), 3.49 (4H, br s, 2 x NCH_2), 5.28 (1H, s, 3-H), 7.28 (2H, m, 6-H and 8-H), 7.49 (1H, m, 7-H) and 8.14 (1H, dd, *J* 1.7 and 7.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 25.1 [$-(CH_2)-$], 46.6 (NCH_2), 86.3 (C-3), 116.2 and 124.4 (C-6 and C-8), 123.3 (C-4a), 125.6 (C-5), 131.7 (C-7), 153.8 (C-2), 161.3 (C-8a) and 176.0 (C-4); ν_{max} (KBr)/cm^{-1} 1606 (CO); *m/z* 215 (M^+, 100%).

*2-(*N,N*-dimethylamino)-6-chloro-4*H*-1-benzopyran-4-one* ***(169)***[119]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (Method 2) was followed, using 5-chloro-*N,N*-dimethylsalicylyl-acetamide (**167**) (2.00 g, 8.28 mmol), triflic anhydride (5.03 ml, 29.8 mmol) and dry CH_2Cl_2 (40 ml). Work-up afforded *2-(*N,N*-dimethylamino)-6-chloro-4*H*-1-benzopyran-4-one* (**169**) (1.18 g, 64%), m.p.† 158 - 160 °C (from EtOAc) (**Found**: C, 58.6; H, 4.5; N, 6.05%; $\mathbf{M}^+$, 223.0398. $C_{11}H_{10}NO_2Cl$ requires: C, 59.1; H, 4.5; N, 6.3%; **M**, 223.0399); δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_2), 5.39 (1H, s, 3-H), 7.23 (1H, d, *J* 8.8 Hz, 8-H), 7.45 (1H, dd, *J* 2.7 and 8.8 Hz, 6-H) and 8.10 (1H, d, *J* 2.6 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 85.9 (C-3), 117.8 (C-8), 124.0 (C-6), 124.9 (C-5), 130.2 (C-4a), 131.7 (C-7), 151.8 (C-2), 162.9 (C-8a) and 174.8 (C-4); ν_{max} (KBr)/cm^{-1} 1610 (CO).

*2-(*N,N*-dimethylamino)-6-nitro-4*H*-1-benzopyran-4-one* ***(170)***[122]

Conc. HNO_3 (0.23 ml) and cold conc. H_2SO_4 (1.55 ml) was added to a stirred solution of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (1.14 g, 6 mmol). The resulting solution was poured onto ice, basified with aq. Na_2CO_3, and the precipitated solid was filtered off to give *2-(*N,N*-dimethylamino)-6-nitro-4*H*-1-benzopyran-4-one* (**170**) (0.84 g, 60%), m.p. 216 - 218°C (from EtOH); (**Found:** $\mathbf{M}^+$, 234.0632. $C_{11}H_{10}N_2O_4$ requires: **M**, 234.0640); δ_H (400 MHz; $CDCl_3$) 3.13 (6H, s, NMe_2), 5.41 (1H, s, 3-H), 7.40 (1H, d, *J* 9.1 Hz, 8-H), 8.33 (1H, dd, *J* 2.8 and 9.0 Hz, 7-H) and 8.95 (1H, d, *J* 2.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.7 (NMe_2), 86.2 (C-3), 117.7 (C-8), 122.0 (C-5), 123.4 (C-4a), 126.5 (C-7), 144.6 (C-6), 156.5 (C-2), 162.8 (C-8a) and 174.1 (C-4); ν_{max} (KBr)/cm^{-1} 1615 (CO); *m/z* 234 (M^+, 100%).

*2-(*N,N-*dimethylamino)-7-methoxy-4*H-*1-benzopyran-4-one (176)*

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (Method 4) was followed, using ethyl (*N,N*-diethylcarbamoyl)-ethanoate (**171**) (2.19 g, 13.8 mmol), phosphorus oxychloride (1.72 ml, 18.8 mmol) and *m*-methoxyphenol (1.37 ml, 12.5 mmol) in dry 1,2-dichloroethane (10 ml). In this case, the reaction time was 5 h. After cooling, $CHCl_3$ (12.5 ml) and a solution of CH_3COONa (17 g) in H_2O (75 ml) was added and the resulting mixture was heated under reflux for 90 min. The solution was allowed to cool, and the organic layer was removed. The aqueous layer was extracted with $CHCl_3$ (3 x 40 ml) and the combined organic layers were washed with H_2O, dried (anhyd. $MgSO_4$) and the solvent was evaporated to yield a dark red oil which was stirred together with 2 **M**-NaOH (50 ml) and light petroleum ether (12.5 ml) for 2 h. The resulting solid was filtered off and washed with water to afford 2-*N,N*-dimethylamino-7-methoxy-4*H*-1-benzopyran-4-one (**176**) (0.87 g, 32%), m.p. 174.2°C (lit.,[123] 178 - 179°C); δ_H (400 MHz; $CDCl_3$) 3.06 (6H, s, NMe_2), 3.85 (3H, s, OCH_3), 5.29 (1H, s, 3-H), 6.71 (d, *J* 2Hz, 8-H), 6.86 (1H, dd, *J* 2.2 and 8.8 Hz, 6-H), 8.03 (1H, d, *J* 8.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 55.7 (OCH_3), 85.5 (C-3), 100.0 and 112.4 (C-6 and C-8), 116.5 (C-4), 163.1 (C-8a) and 176.5 (C-4); ν_{max} (KBr)/cm^{-1} 1610 (CO); *m/z* 219 (M^+, 84%) and 176 (100).

*2-(*N,N-*diethylamino)-7-methoxy-4*H-*1-benzopyran-4-one (177)*

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-7-methoxy-4*H*-1-benzopyran-4-one (**176**) was followed, using ethyl(*N,N*-diethylcarbamoyl)-ethanoate (**172**) (2.57 g, 13.8 mmol), phosphorus oxychloride (1.72 ml, 18.8 mmol) and *m*-methoxyphenol (1.37 ml, 12.5 mmol) in dry 1,2-dichloroethane (20 ml). Work-up

afforded 2-(*N,N*-diethylamino)-7-methoxy-4*H*-1-benzopyran-4-one (**177**) (0.63g, 20%), m.p.† 76 - 78°C (from ligroin) (lit.,[123] 86 - 87°C); δ_H (400 MHz; $CDCl_3$) 1.22 (6H, t, 2 x CH_2CH_3), 3.41 (4H, q, 2 x CH_2CH_3), 3.83 (3H, s, OCH_3), 5.31 (1H, s, 3-H), 6.69 (1H, d, *J* 2.3 and 8.7 Hz, 8-H), 6.84 (1H, dd, *J* 2.3 and 8.7 Hz, 6-H), 8.01 (1H, d, *J* 8.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 13.0 (CH_3), 43.1 (CH_2), 55.6 (OCH_3), 85.1 (C-3), 99.4 and 112.3 (C-6 and C-8), 116.5 (C-4a), 126.7 (C-5), 155.1 (C-7), 162.0 (C-2), 162.7 (C-8a) and 176.4 (C-4); ν_{max} (KBr)/cm^{-1} 1600 (CO); *m/z* 247 (M^+ 100%).

*1-(2-Hydroxynaphthyl)ethanone, boron difluoride complex (**180**)*[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 2-hydroxy-1-acetonaphthone (**178**) (2.79 g, 15 mmol), dry Et_2O (20 ml) and $BF_3.OEt_2$ (1.97 ml, 15 mmol). In this case the reaction time was 2 h. Work-up afforded 1-(2-hydroxynaphthyl)ethanone, boron difluoride complex (**189**) (3.2 g, 93%), m.p. 182 - 184°C (lit.,[124] 180 - 181°C); δ_H (400 MHz; $CDCl_3$) 3.02 (CH_3), 7.17 (1H, d, *J* 9.1 Hz, 3-H), 7.54 (1H, m, 6-H), 7.71 (1H, m, 7-H), 7.84 (1H, dd, *J* 1.1 and 8 Hz, 5-H), 7.97 (1H, d, *J* 8.4 Hz, 4-H) and 8.15 (1H, d, *J* 9.2 Hz, 8-H); δ_C (100 MHz; DMSO-d_6) 32.3 (CH_3), 118.2 (C-3), 123.1 and 123.2 (C-5 and C-6), 127.2 (C-7), 128.1 (C-4), 121.1, 127.6 and 130.4 (C-1, C-4a and C-8a), 131.5 (C-8), 153.2 (C-2) and 204.0 (C=O); ν_{max} (KBr)/cm^{-1} 1630 (CO).

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† Compound (**177**) was recrystallized from ligroin and was essentially pure by ^1H NMR spectroscopy.

1-(1-hydroxynaphthyl)ethanone, boron difluoride complex (181)

Method 1[70]

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 1-hydroxy-2-acetonaphthone (**179**) (4.1 g, 22.5 mmol), dry Et_2O (80 ml) and $BF_3.OEt_2$ (5.91 ml, 45 mmol). In this case, the reaction mixture was stirred overnight. Work-up afforded 1-(1-hydroxynaphthyl)-ethanone, boron difluoride complex (**181**) (4.56 g, 87%), m.p. 243 - 245°C (from CH_3CN) (lit.,[124] 247 - 248°C); δ_H (400 MHz; DMSO-d_6) 2.72 (3H, s, CH_3), 7.41 (1H, d, *J* 8.8 Hz, 4-H), 7.58 (1H, t, 7-H), 7.85 (1H, d, *J* 8.8 Hz, 3-H), 7.90 (1H, d, *J* 8.2 Hz, 5-H) and 8.32 (1H, d, *J* 8.8 Hz, 8-H); δ_C (100 MHz; DMSO-d_6) 26.9 (CH_3), 113.1 (C-4a), 118.2 (C-4), 123.5 (C-8), 124.1 (C-8a), 125.7 (C-3), 126.1 (C-7), 127.5 (C-5), 130.1 (C-6), 136.9 (C-2), 160.9 (C-1) and 205.3 (C=O).

Method 2[124]

A mixture of 1-naphthol (5.0 g, 35 mmol), Ac_2O (12.5 ml, 132 mmol) and $BF_3.OEt_2$ (7.5 ml, 60 mmol) was heated on the steam bath for 1 h. After cooling, the resulting solid was filtered off and dried to afford crude 1-(1-hydroxynaphthyl)ethanone, boron difluoride complex (**181**) (3.54 g, 44%).

1-(3-Hydroxynaphthyl)ethanone, boron difluoride complex (182)

The experimental procedure employed for the synthesis of 1-(2-hydroxyphenyl)ethanone, boron difluoride complex (**137**) was followed, using 3-hydroxy-2-acetonaphthone (**136**) (0.30 g, 1.61 mmol), $BF_3.OEt_2$ (0.23 ml, 1.77 mmol) and dry ether. The reaction mixture was stirred for 7 h. and filtered to afford a solid product, which was shown by

^{1}H NMR spectroscopy to comprise a mixture of the starting material (53%) and 1-(3-hydroxynaphthyl)ethanone, boron difluoride complex (**185**) (47%) [δ_H (400 MHz; $CDCl_3$) 3.05 (3H, s, CH_3), 7.41 (1H, s, 4-H), 7.51 - 7.82 (4H, m, 5-H to 8-H) and 8.50 (1H, s, 1-H)] which was used without further purification.

*3-Chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxynaphthyl)propenone, boron difluoride complex (183)*[70]

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) was followed, using 1-(2-hydroxynaphthyl)ethanone, boron difluoride complex (**180**) (2.50 g, 10.7 mmol), dry 1,2-dichloroethane (45 ml) and *N,N*-dimethyldichloromethyleniminium chloride (**142**) (1.95 g, 12 mmol). In this case, the reaction time was 3 h. Work-up afforded *3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxynaphthyl)propenone boron difluoride complex* (**183**) (1.37 g, 40%), m.p. 124 - 126°C; (**Found**: M^+, 323.0698. $C_{15}H_{13}BClF_2NO_2$ requires: **M**, 323.0695); δ_H (400 MHz; DMSO-d_6) 3.17 (6H, s, NMe_2), 6.00 (1H, s, 2-H), 7.66 (2H, m, 3′-H and 6′-H), 7.45 (1H, t, 7′-H), 8.06 (1H, d, *J* 8Hz, 5′-H), 8.27 (1H, d, *J* 9Hz, 4′-H) and 9.65 (1H, d, *J* 8.6 Hz, 8′-H); δ_C (100 MHz; DMSO-d_6) 37.4 (NMe_2), 87.5 (C-2), 111.7 (C-4′a), 116.7 (C-7′), 126.3 and 128.7 (C-3′, C-5′ and C-6′), 153.9 (C-1′), 161.5 (C-2′) and 174.4 (C-1); ν_{max} (KBr)/cm^{-1} 1630 (CO).

*3-Chloro-3-(*N,N*-dimethylamino)-1-(1-hydroxynaphthyl)propenone, boron difluoride complex (184)*[70]

The experimental procedure employed for the synthesis of 3-chloro-(*N,N*-dimethylamino)-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**), was followed, using 1-(1-

hydroxynaphthyl)ethanone, boron difluoride complex (**181**) (2.36 g, 10.1 mmol), dry 1,2-dichloroethane (50 ml) and *N,N*-dimethyldichloromethyleniminium chloride (**142**) (1.78 g, 10.9 mmol). Work-up afforded 3-chloro-3-(*N,N*-dimethylamino)-1-(1-hydroxynaphthyl)-propenone, boron difluoride complex (**184**) [(2.71 g, 83%); (**Found**: M^+, 323.0688. $C_{15}H_{13}BClF_2NO_2$ requires: **M**, 323.0695); δ_H (400 MHz; $CDCl_3$) 5.97 (6H, s, NMe_2), 6.99 (1H, s, 2-H), 7.44 (1H, d, *J* 8.7 Hz, 4-H), 7.53 and 7.62 (2H, 2 x t, 6-H and 7-H), 7.71 (1H, d, *J* 7.6 Hz, 3-H) and 8.58 (1H, d, *J* 7.7 Hz, 8-H)] which was used without further purification.

*2-(*N,N-*Dimethylamino)-4*H-*naphtho[1,2-*e*]pyran-4-one (186)*[70]

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxynaphthyl)propenone, boron difluoride complex (**183**) (0.50 g, 1.6 mmol) and MeOH (20 ml). Work-up afforded 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-*e*]pyran-4-one (**186**) (0.25 g, 68%), m.p. 190°C (lit.,[120] 190 - 191°C); (**Found**: C, 74.5; H, 5.5; N, 5.4. $C_{15}H_{13}NO_2$ requires: C, 75.3; H, 5.4; N, 5.9%); δ_H (400 MHz; $CDCl_3$) 3.08 (6H, s, NMe_2), 5.51 (1H, s, 3-H), 7.37 (1H, d, *J* 8.9 Hz, 10-H), 7.53 (1H, m, 7-H), 7.68 (1H, m, 6-H), 7.83 (1H, d, *J* 8 Hz, 8-H), 7.95 (1H, d, *J* 9 Hz, 9-H) and 10.17 (1H, d, *J* 8.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.2 (NMe_2), 88.8 (C-3), 115.4 (C-8a), 116.4 (C-10), 125.8 (C-7), 127.4 and 127.8 (C-6 and C-8), 128.3 (C-5), 130.7 (C-4b), 131.0 (C-4a), 133.3 (C-9), 154.1 (C-2), 161.4 (C-10a) and 179.3 (C-4); ν_{max} (KBr)/cm^{-1} 1625 (CO); *m/z* 239 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-4*H-*naphtho[2,1-*e*]pyran-4-one (187)*

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-(1-hydroxy-naphthylpropenone, boron difluoride complex (**184**) (1.50 g, 4.65 mmol) and MeOH (100 ml). Work-up afforded *2-(*N,N-*dimethylamino)-4*H-*naphtho[2,1-*e*]pyran-4-one* (**187**) (0.68 g, 61%), m.p. 199 - 200°C (from EtOH) (**Found**: C, 75.0; H, 5.5; N, 5.4%; $\mathbf{M}^+$, 239.0932. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.85%; **M**, 239.0946); δ_H (400 MHz; $CDCl_3$) 3.20 (6H, s, NMe_2), 5.66 (1H, s, 3-H), 7.61 (2H, m, 8-H and 9-H), 7.72 (1H, d, *J* 8.6 Hz, 6-H), 7.80 (1H, dd, *J* 3.8 and 9.5 Hz, 10-H), 8.15 (1H, d, *J* 8.7 Jz, 5-H) and 8.26 (1H, dd, *J* 2.9 and 6.3 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 37.6 (NMe_2), 86.9 (C-3), 118.7 and 123.2 (C-4a and C-10a), 121.2 and 131.3 (C-5 and C-7), 124.3 (C-6), 126.6 (C-8 and C-9/C-10), 128.1 (C-9/C-10), 135.3 (C-6a), 150.2 (C-10b), 162.7 (C-2) and 176.7 (C-4); ν_{max} (KBr)/cm^{-1} 1640 (CO); *m/z* 239 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-4*H-*naphtho[5,6-*b*]pyran-4-one (188)*

The experimental procedure employed for the synthesis of 3-chloro-(*N,N*-dimethylamino)-(2-hydroxyphenyl)propenone, boron difluoride complex (**143**) was followed, using 1-(3-hydroxynaphthyl)ethanone, boron difluoride complex (**185**) (0.22 g, 1.0 mmol), *N,N*-dimethyldichloromethylenimium chloride (**142**) and dry 1,2-dichloroethane (7.50 ml). Work-up afforded crude 3-chloro-3-(*N,N*-dimethylamino)-1-(3-hydroxynaphthyl)-propenone, boron difluoride complex (**185**), which was refluxed with MeOH (15 ml) for 1.5 g. After cooling to r.t., the solvent was removed and the residue dissolved in aq. $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 ml) and the combined extracts were washed with brine (1 x 20 ml), dried (anhyd. $MgSO_4$) and

evaporated to give *2-(N,N-dimethylamino)-4H-naphtho[5,6-b] pyran-4-one* (**188**) (60 mg, 38%), m.p. 175 - 176°C; δ_H (400 MHz; $CDCl_3$) 3.17 (6H, s, NMe_2), 5.45 (1H, s, 3-H), 7.47 and 7.55 (2H, 2 x t, 7-H and 8-H), 7.73 (1H, s, 10-H), 7.85 and 8.01 (2H, 2 x d, 6-H and 9-H) and 8.72 (1H, s, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 84.1 (C-3), 112.2 (C-10), 125.4 and 127.9 (C-7 and C-8), 126.1 (C-5), 126.9 and 129.3 (C-6 and C-9), 122.1, 130.3 and 134.9 (C-4a, C-5a and C-9a), 150.5 (C-2), 163.3 (C-10a) and 176.5 (C-4); ν_{max} (KBr)/cm^{-1} 1645 (CO).

*Ethyl 4-(2-hydroxynaphthyl)-2,4-dioxobutanoate (**189**)*[75] and *2-hydroxy-3-hydro-2,3-dihydro-4-oxo-4H-naphtho[1,2-e]pyran-4-one (**192**)*[75]

A mixture of diethyl oxalate (2.69 ml, 19.7 mmol) and 2-hydroxy-1-acetonaphthone (**178**) (2.50 g, 13.4 mmol) was added dropwise under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding sodium metal (0.92 g, 40 mmol) to dry EtOH (30 ml)]. The resulting reddish brown mixture was boiled gently under reflux for 2 h., during which time a thick brick red slurry was formed. After cooling, the brick red sodium salt was filtered off, washed (Et_2O), and dissolved in 2 M-HCl (45 ml) and the resulting solution was extracted with Et_2O (3 x 45 ml). The ethereal solutions were combined, dried (anhyd. $MgSO_4$), filtered and evaporated *in vacuo* to afford a solid (3.29 g, 86%) shown by ^1H NMR spectroscopy to comprise a mixture of ethyl 4-(2-hydroxynaphthyl)-2,4-dioxobutanoate (**189**) (78%) [δ_H (400 MHz; $CDCl_3$) 1.34 (3H, t, CH_2CH_3), 2.16 (2H, s, $COCH_2$), 4.39 (2H, q, CH_2CH_3), 7.10 (1H, d, *J* 9 Hz, 3′-H), 7.64 (1H, m, 7′-H), 7.75 (1H, d, *J* 7.8 Hz, 5′-H) 7.78 (1H, dd, *J* 1.2 and 8.4 Hz, 6′-H), 7.96 (1H, d, *J* 9 Hz, 4′-H), 7.96 (1H, d, *J* 9 Hz, 4′-H) and 9.43 (1H, d, *J* 8.7 Hz)] and 2-hydroxy-3-hydro-2,3-dihydro-4-oxo-4*H*-naphtho[1,2-*e*]pyran-4-one (**192**) (22%) [δ_H

(400 MHz; $CDCl_3$) 1.43 (3H, t, CH_2CH_3), 3.03 and 3.52 (2H, dd, *J* 16.2 Hz, $COCH_2$), 4.48 (2H, q, CH_2CH_3), 7.27 (1H, s, 10-H), 7.44 (1H, t, 7-H), 7.64 (1H, m, 6-H), 1.92 (1H, d, *J* 8 Hz, 8-H), 8.14 (1H, d, *J* 9.1 Hz, 9-H) and 9.98 (1H, d, *J* 8.6 Hz, 5-H)]. The mixture was used without further purification.

Ethyl 4-(1-hydroxynaphthyl)-2,4-dioxobutanoate ***(190)***[75] and *ethyl 2-hydroxy-3-hydro-2,3-dihydro-4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate* ***(193)***[75]

Method 1

A warm solution of 1-hydroxy-2-acetonaphthone (5.0 g, 27 mmol) in dry EtOH (10 ml) and diethyl oxalate (5.38 ml, 39.4 mmol) was added dropwise under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (1.84 g, 80.6 mmol) to dry EtOH (60 ml)]. The stirred mixture was gently boiled under reflux for 2 h., becoming a thick, yellow slurry. The reaction mixture was allowed to cool, and the solid was filtered off, washed (Et_2O), acidified with 2 M-HCl (100 ml), and the resulting mixture extracted with Et_2O (3 x 75 ml). The ethereal solutions were combined, dried (anhyd. $MgSO_4$), filtered and evaporated *in vacuo* to afford a product which was shown by ^1H NMR spectroscopy to be a mixture of ethyl 4-(1-hydroxynaphthyl)-2,4-dioxobutanoate (**190**), ethyl 2-hydroxy-3-hydro-4-oxo-2,3-dihydro-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**193**) and ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**197**)]; the mixture was used without further purification.

Method 2

A mixture of 1-hydroxy-2-acetonaphthone (4.0 g, 22 mmol) and diethyl oxalate (16.80 ml, 123 mmol) in dry toluene (50 ml) was cooled to 0°C in an ice-salt bath. NaH (50%

dispersion in oil; 6.0 g, 0.25 mol) was then added portion-wise to the stirred mixture. After addition of NaH, the cold mixture was stirred overnight at room temperature and then added to ice (200 g) and AcOH (9 ml). The resulting mixture was extracted with Et_2O (3 x 100 ml), and the combined ethereal extracts dried (anhyd. $MgSO_4$), and evaporated *in vacuo* to give a crude product which was shown by ^1H NMR spectroscopy to be a mixture of 4-(1-hydroxynaphthyl)-2,4-dioxobutanoate (**190**) and ethyl 2-hydroxy-3-hydro-2,3-dihydro-4-oxo-4*H*-naphtho[2,1-*e*]-pyran-2-carboxylate (**193**). The mixture was used without further purification.

*Ethyl 4-oxo-4*H*-naphtho[2,1-e]pyran-2-carboxylate (**196**)*[75]

A mixture of crude ethyl 4-(2-hydroxynaphthyl)-2,4-dioxobutanoate (**189**) and 2-carboethoxy-2-hydroxy-3-hydro-4*H*-naphtho[1,2-*e*]pyran-4-one (**192**) (2.75 g, 9.6 mmol), AcOH (10 ml) and conc. HCl (0.20 ml) was boiled under reflux for 1 h. After cooling, a mixture of ice and water (40 ml) was added and the resulting precipitate filtered off and then dissolved in EtOAc (50 ml). The solution was then washed with 5% aq. $NaHCO_3$ (3 x 50 ml), dried (anhyd. $MgSO_4$) and evaporated *in vacuo* to afford ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**196**) (1.62 g, 63%), m.p.† 140 - 141°C (from EtOH) (lit.,[63] 146 - 147°C); (**Found**: C, 71.55; H, 4.5; $\mathbf{M}^+$, 268.0736. $C_6H_{12}O_4$ Calc for: C, 71.6; H, 4.5%; **M**, 268.0734); δ_H (400 MHz; $CDCl_3$) 1.08 (3H, t, CH_2CH_3), 4.11 (2H, q, CH_2CH_3, 6.88 (1H, s, 3-H), 7.27 (1H, s, 10-H), 7.28 (1H, m, 7-H), 7.40 (1H, m, 6-H), 7.54 (1H, d, *J* 8 Hz, 8-H), 7.76 (1H, d, *J* 9.1 Hz, 9-H) and 9.39 (1H, d, *J* 8.6 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 62.9 (CH_2), 117.8 (C-3), 117.8 (C-10),

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† Compound (**196**) was essentially pure by ^1H NMR spectroscopy.

118.2 (C-8a), 127.0 (C-7), 127.2 and 128.3 (C-6 and C-8), 129.6 (C-5), 130.1 and 130.7 (C-4a and C-4b), 136.5 (C-9), 150.0 (C-2), 157.5 (C-10a), 160.5 and 179.9 (C-4); ν_{max} (KBr)/cm^{-1} 1735 (CO.O) and 1650 (CO).

*Ethyl 4-oxo-4*H*-naphtho[2,1-e]pyran-2-carboxylate (**197**)*[75]

The experimental procedure employed for the synthesis of ethyl 4-oxo-4*H*-naphtho[1,2-*e*]pyran-2-carboxylate (**196**) was followed, using ethyl 4-(1-hydroxynaphthyl)-2,4-dioxobutanoate (**190**) (6.16 g, 21.5 mmol), AcOH (40 ml) and conc. HCl (1 ml). Work-up afforded crude *ethyl 4-oxo-4*H*-naphtho[2,1-e]pyran-2-carboxylate* (**197**) (4.17 g, 72%), m.p. 143 - 145°C (from EtOH); (Found: $\mathbf{M}^+$, 268.0739. $C_{16}H_{12}O_4$ requires **M**, 268.0734); δ_H (400 MHz; $CDCl_3$) 1.48 (3H, t, CH_2CH_3), 4.51 (2H, q, CH_2CH_3), 7.25 (1H, s, 3-H), 7.71 (2H, m, 8-H and 9-H/10-H), 7.78 (1H, d, *J* 8.8 Hz, 6-H), 7.89 (1H, d, *J* 12.5 Hz, 9H/10H), 8.10 (1H, d, *J* 8.7 Hz, 5-H) and 8.61 (1h, d, *J* 7.5 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 62.9 (CH_2), 116.0 (C-2), 120.3 (C-5), 121.0 and 124.0 (C-6a and C-10), 122.8 (C-7), 126.1 (C-6), 127.4 and 129.8 (C-8 and C-9), 128.0 (C-10), 136.2 (C-10b), 151.6 (C-2), 153.5 (C-4a), 160.4 (CO_2) and 178.0 (C-4); ν_{max} (KBr)/cm^{-1} 3000 (CH), 1740 (CO.O) and 1640 (CO); *m/z* 268 (M^+, 100%).

*Ethyl 3-(2-hydroxyphenyl)-2,4-dioxobutanoate (**201**)*[57]

A mixture of diethyl oxalate (15 ml, 0.11 mol) and *o*-hydroxyacetophenone (**124**) (12 ml, 0.10 mol) was added under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (6.9 g, 0.3 mol) to dry EtOH (200 ml)]. The resulting yellow mixture was boiled gently under reflux for 0.5 h., during which time a thick yellow

slurry was formed. After cooling, the yellow reaction mixture was poured in Et_2O (300 ml). After standing for 0.5 h., the yellow sodium salt was filtered off, washed with Et_2O, acidified with 2 **M**-HCl (200 ml) and the resulting mixture extracted with Et_2O (3 x 50 ml). The ethereal solutions were combined, dried (anhyd. $MgSO_4$), filtered and evaporated *in vacuo* to give ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**210**); δ_H (60 MHz; DMSO-d_6) 1.25 (3H, t, CH_2CH_3), 4.30 (2H, q, CH_2CH_3), 6.85 (2H, s, $COCH_2$), 7.45 - 8.05 (4H, m, ArH) and 8.75 (1H, br s, OH). This product was shown by ^1H NMR spectroscopy to be partially enolised and was used without further purification.

*Ethyl 7-chloro-2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (203)*[57]

A warm solution of 4-chloro-2-hydroxyacetophenone (**127**) (6.0 g, 35 mmol) and diethyl oxalate (26.10 ml, 194 mmol) was added dropwise under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (3.20 g, 139 mmol) to dry EtOH (60 ml)]. The stirred mixture was gently boiled under reflux for 40 min., becoming a thick yellow slurry. After cooling, the reaction mixture was poured into Et_2O (146 ml) and the resulting yellow solid was filtered off, washed (Et_2O) and acidified with 2**M**-HCl (200 ml). The resulting semi-solid was extracted with Et_2O (3 x 50 ml) and the combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated *in vacuo* to afford crude ethyl 7-chloro-2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**127**)[a]; [δ_H (60 MHz; DMSO-d_6) 1.30 (3H, t, CH_3), 2.88 and 2.33 (2H, dd, *J* 17 Hz, $COCH_2$), 4.34 (2H, q, CH_2CH_3), 7.10 - 7.40 (2H, m, 6-H and 8-H) and 7.93 (1H, d, *J* 9 Hz, 5-H)] which was used without further purification.

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[a] ^1H NMR spectroscopy indicated the presence of a small proportion of the ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**202**).

*Ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (**204**) and ethyl 2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**205**)*

The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**203**) was followed, using 2-hydroxy-4-methoxyacetophenone (**127**) (6.0 g, 36 mmol), diethyl oxalate (7.3 ml, 54 mmol), Na metal (1.3 g, 54 mmol) and dry EtOH (60 ml). In this case the reaction time was 70 min. Work-up afforded a solid shown by ^{1}H NMR spectroscopy to comprise a mixture of ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (**204**) (70%) [δ_H (400 MHz; $CDCl_3$) 1.34 (3H, t, CH_3), 3.82 (3H, s, OCH_3), 4.36 (2H, q, CH_2CH_3), 6.42 (1H, d, *J* 2.3 Hz, 5-H), 6.99 (1H, *J* 1.9 Hz, 3-H) and 7.84 (1H, d, *J* 8.7 Hz, 6-H)] and ethyl 2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**205**) (30%) [δ_H (400 MHz; $CDCl_3$) 1.42 (3H, t, CH_3), 2.88 and 3.32 (2H, dd, *J* 16.6 Hz, $COCH_2$), 3.91 (3H, s, OCH_3), 4.45 (2H, q, CH_2CH_3), 6.62 (1H, dd, *J* 2.4 and 8.8 Hz, 6-H), 7.01 (!H, d, *J* 2.4 Hz, 8-H) and 8.09 (1H, dd, *J* 2.1 and 7.3 Hz, 5-H)], which was used without further purification.

*4-Oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**)*[75]

A mixture of ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**201**), conc. HCl (20 ml) and AcOH (20 ml) was boiled under reflux for 1 h. After cooling, the precipitated solid was filtered off, washed with AcOH and recrystallized from AcOH to afford 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**) (5.6 g, 60%), m.p. 250°C (decomp.) (lit.,[75] 250 - 251°C; δ_H (60 MHz; DMSO-d_6) 7.00 (1H, s, 3-H) and 7.50 - 8.30 (4H, m, ArH); ν_{max} (KBr)/cm^{-1} 3300 - 2000 (CO_2H), 1740 (CO_2H) and 1630 (CO).

*7-Chloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (207)*[75]

The mixture of crude ethyl 7-chloro-2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**203**), AcOH (30 ml) and conc. HCl (15 ml) was boiled under reflux for 1.5 h. The reaction mixture was allowed to cool, H_2O (50 ml) was added and the precipitated solid was filtered off and recrystallized from EtOH to afford 7-chloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**207**) (3.2 g, 41%),[a] m.p. 248°C (decomp.) (lit.,[75] 248 - 250°C); δ_H (400 MHz; DMSO-d_6) 7.10 (1H, s, 3-H), 7.60 (1H, dd, *J* 8.1 and 2.0 Hz, 6-H), 7.88 (1H, d, *J* 2 Hz, 8-H) and 8.12 (1H, d, *J* 8.2 Hz, 5-H); ν_{max} (KBr)/cm^{-1} 3200 - 2500 (CO_2H), 1715 (CO_2H) and 1650 (CO).

*7-Methoxy-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (208)*

The experimental procedure employed for the synthesis of 7-chloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**207**) was followed, using the crude ethyl 4-(4-methoxy-2-hydroxyphenyl)-2,4-dioxobutanoate (**204**), AcOH (30 ml) and conc. HCl (15 ml). Work-up afforded crude 7-methoxy-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**208**) (3.12 g, 39%),[b] m.p. 268°C (decomp.) (from EtOH) [lit.,[125] 270°C (decomp.)]; δ_H (400 MHz; DMSO-d_6) 3.91 (3H, s, OCH_3), 6.84 (1H, s, 3-H), 7.10 (1H, dd, *J* 2.4 and 8.9 Hz, 6-H), 7.20 (1H, d, *J* 2.3 Hz, 8-H) and 7.95 (1H, d, *J* 8.9 Hz, 5-H); ν_{max} (KBr)/cm^{-1} 3200 - 2100 (CO_2H), 3040 (OH), 1720 (CO_2H) and 1618 (CO).

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[a]Yield calculated on the basis of ethyl 7-chloro-2-hydroxy-2,3-dihydro-4-oxo-4*H*-1-benzopyran-2-carboxylate (**203**).

[b]Yield calculated on the basis of ethyl 4-(4-methoxy-2-hydroxyphenyl)-2,4-dioxobutanoate (**204**).

*4-Oxo-4*H*-1-benzopyran-2-carbonyl chloride (209)*[77]

Thionyl chloride was added to a suspension of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**) (1.75 g, 9.25 mmol) in dry 1,2-dichloroethane (10.50 ml) and dry *N,N*-dimethylformamide (0.36 ml, 4.65 mmol). The resulting mixture was boiled under reflux for 1 h. After cooling, the solvent was removed *in vacuo* to afford crude, yellow 4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**209**) [(1.77 g, 89%), m.p. 94°C (lit.,[77] 104 - 108°C); δ_H (60 MHz; $CDCl_3$) 7.30 (1H, s, 3-H) and 7.45 - 8.40 (4H, m, ArH); ν_{max} (KBr)/cm^{-1} 1730 (CO.Cl) and 1625 (CO)], which was used without further purification.

*7-Chloro-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (210)*

The experimental procedure employed for the synthesis of 4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**209**) was followed, using 7-chloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**207**) (2.00 g, 8.90 mmol), dry 1,2-dichloroethane (10 ml), dry *N,N*-dimethylformamide (0.17 ml, 2.2 mmol) and $SOCl_2$ (0.85 ml, 12 mmol). In this case, the reaction time was 3 h. Work-up afforded crystalline 7-chloro-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**210**) [(2.04 g,94%), m.p. 176 - 177°C (sublimed) (lit.,[76] 179 - 181°C); δ_H (60 MHz; $CDCl_3$) 7.35 (1H, s, 3-H), 7.55 (1H, dd, *J* 2 and 9 Hz, 6-H), 7.72 (1H, d, *J* 2 Hz, 8-H) and 8.22 (1H, d, *J* 9 Hz, 5-H); ν_{max} (KBr)/cm^{-1} 1760 (CO.Cl) and 1650 (CO)] which was used without further purification.

*7-Methoxy-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (211)*

The experimental procedure employed for the synthesis of 4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**209**) was followed, using 7-methoxy-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**208**) (1.50 g, 6.83 mmol), dry 1,2-dichloroethane (10 ml), dry *N,N*-

dimethylformamide (**78**) (0.14 ml) and $SOCl_2$ (0.65 ml, 9 mmol). Work-up afforded crude 7-methoxy-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**211**) [(1.58 g,97%); δ_H (60 MHz; DMSO-d_6/$CDCl_3$) 3.96 (3H, s, OCH_3), 6.97 (1H, s, 3-H), 7.05 - 7.32 (2H, m, 6-H and 8-H) and 8.08 (1H, d, *J* 8.1 Hz, 5-H)], which was used without further purification.

Dimethylammonium chloride (199)[80]

HCl gas was bubbled through a stirred solution of dimethylamine (33% w/w solution in EtOH; 36 ml, 0.20 mol) and dry EtOH (80 ml) for 2 h. at *ca.* 0°C. The solvent was evaporated and the white, crystalline slurry was dried *in vacuo* for 1 h. Dry Et_2O (50 ml) was added and the mixture cooled to *ca.* 0°C. The solvent was decanted off and the crystals dried *in vacuo* for 1 h. The crystals were then washed with Et_2O (6 x 10 ml) on a filter funnel under N_2 and vacuum dried for 2 h. to afford crude dimethylammonium chloride (**199**) (14.12 g, 86%), m.p. 170°C (lit.,[126] 171°C); δ_H (60 MHz; $CDCl_3$) 2.80 (6H, t, Me) and 9.45 (1H, br s, NH).

N,N-*Dimethyl-4-oxo-4*H-*1-benzopyran-2-carboxamide (212)*[76]

A stirred suspension of the crude 4-oxo-4*H*-benzopyran-2-carbonyl chloride (**209**) (2.00 g, 9.20 mmol) in dry pyridine (15 ml) was cooled in ice for 0.25 h. and a slurry of dimethylammonium chloride (**199**) (0.78 g, 9.6 mmol) in dry pyridine (5 ml) was added dropwise to the suspension. After stirring at room temperature, the reaction mixture was poured into 2 M-HCl (200 ml). The resulting mixture was cooled in ice for 0.5 h., and then extracted with EtOAc (4 x 70 ml). The combined extracts were washed sequentially with 5% aq. $NaHCO_3$ (2 x 50 ml) and saturated aq. NaCl (50 ml) and then dried (anhyd.

$MgSO_4$). The solvent was evaporated *in vacuo* to afford a solid product (1.36 g) which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**212**) (1.17 g, 59%),[a] m.p. 114°C (from EtOAc) (lit.,[76] 115 -116°C); δ_H (400 MHz; $CDCl_3$) 3.11 (6H, s, NMe_2), 6.51 (1H, s, 3-H), 7.44 (2H, m, 6-H and 8-H), 7.69 (1H, m, 7-H) and 8.19 (1H, dd, *J* 1.6 and 8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 35.5 and 38.3 (NMe_2), 111.7 (C-3), 118.2 (C-8), 124.3 (C-4a), 125.8 and 125.8 (C-5 and C-6), 123.3 (C-7), 155.7 (C-8a), 158.2 (C-2), 162.3 (CO.N) and 177.5 (C-4); ν_{max} (KBr)/cm^{-1} 3060 (CH), 1650 and 1635 (CO).

N,N-*dimethyl-7-chloro-4-oxo-4*H-*1-benzopyran-2-carboxamide (213)*

The experimental procedure employed for the synthesis of *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**212**) was followed, using 7-chloro-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**210**) (2.71 g, 11 mmol), dimethylammonium chloride (**199**) (0.95 g, 12 mmol) and dry pyridine (18 ml). In this case, the reaction time was 3 h. at 0°C and 20 h at room temperature. Work-up afforded crude solid (1.85 g) which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford *N,N*-dimethyl-7-chloro-4-oxo-4*H*-1-benzopyran-2-carboxamide (**213**) (1.56 g, 56%),[b] m.p. 147°C (from EtOH) (lit.,[76] 146 - 147°C); δ_H (400 MHz; $CDCl_3$) 3.12 (6H, s, NMe_2), 6.52 (1H, s, 3-H), 7.41 (1H, dd, *J* 2 and 9 Hz, 6-H), 7.50 (1H, d, *J* 2 Hz, 8-H) and 8.14 (1H, d, *J* 9 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 35.6 and 38.4 (NMe_2), 112.0 (C-3), 118.3 (C-8), 122.8 (C-4a), 126.7 and 127.3 (C-5 and C-6), 140.5 (C-7), 155.8 (C-8a), 158.3 (C-2), 162.0 (C-1) and 176.6 (C-4); ν_{max} (KBr)/cm^{-1} 1660 and 1650 (CO).

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[a]Yield calculated on the basis of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**).

[b]Yield calculated on the basis of 7-chloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**207**).

N,N-*dimethyl-7-Methoxy-4-oxo-4*H-*1-benzopyran-2-carboxamide (214)*

The experimental procedure employed for the synthesis of *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**212**) was followed, using 7-methoxy-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**211**) (1.63 g, 6.83 mmol), dimethylammonium chloride (**199**) (0.84 g, 10.25 mmol) and dry pyridine (155 ml). Work-up afforded crude solid (1.58 g) which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford *N,N*-dimethyl-7-methoxy-4-oxo-4*H*-1-benzopyran-2-carboxamide (**214**) (1.15 g, 68%),[a] m.p. 118 - 120°C (lit.,[76] 120 - 122°C); δ_H (400 MHz; $CDCl_3$) 3.12 (6H, s, $CONMe_2$), 3.89 (3H, s, OCH_3), 6.45 (1H, s, 3-H), 6.87 (1H, d, *J* 2.3 Hz, 8-H), 6.99 (1H, dd, *J* 2.4 and 8.9 Hz, 6-H) and 8.10 (1H, d, *J* 8.9 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 35.4 and 38.3 (NMe_2), 55.8 (OCH_3), 100.4 (C-8), 111.6 (C-6), 118.0 (C-4a), 127.0 (C-5) 157.4 (C-8a), 157.6 (C-2), 162.3 (CO.N), 164.5 (C-7) and 176.7 (C-4); ν_{max} (KBr)/cm^{-1} 1660 and 1650 (CO).

*1-[(4-Oxo-4*H*-1-benzopyran-2-yl)carbonyl]-pyrrolidine (218)*

4-Oxo-4*H*-1-benzopyran-2-carbonyl chloride (**209**) (1.88 g, 8.4 mmol) was cautiously added to a precooled (0°C), stirred solution of pyrrolidine (0.82 ml, 10 mmol) and $NaHCO_3$ (1.2 g, 14 mmol) in ice-cold H_2O. The reaction mixture was stirred for *ca.* 3 h. and the resulting precipitate was filtered and washed (5% aq. $NaHCO_3$). The crude solid was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford 1-[(4-oxo-4*H*-1-benzopyran-2-yl)carbonyl]-pyrrolidine (**218**) (0.16 g, 7%),[b] m.p.

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[a]Yield calculated on the basis of 7-methoxy-4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**211**).

[b]Yield calculated on the basis of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**).

102°C (lit.,[84] 103 - 105°C); δ_H (400 MHz; $CDCl_3$) 1.96 [4H, m, $CH_2(CH_2)_2CH_2$], 3.64 and 3.72 (4H, 2 x t, 2 x NCH_2), 6.75 (1H, s, 3-H), 7.43 and 7.47 (2H, m, 6- and 7-H), 7.00 (1H, m, 8-H) and 8.20 (1H, dd, *J* 1.5 and 8.0 Hz, 5-H); ν_{max} (KBr)/cm^{-1} 1640 and 1635 (CO).

2-(Dimethylamino)-3-(2-hydroxybenzoyl)-N,N-*dimethylacrylamide (215)*[84]

Dimethylamine (33% w/w solution in EtOH; 2.39 ml, 132 mmol) was added to a solution of *N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**212**) (0.50 g, 2.3 mmol) in dry EtOH (17 ml). The reaction mixture was stirred at room temperature for 20 h., and the solvent evaporated under reduced pressure to afford crude product which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (0.35 g, 58%), m.p. 166 - 167°C (from EtOH) (lit.,[84] 166 - 167°C); δ_H (400 MHz; $CDCl_3$) 2.91 and 3.11 (6H, 2 x s, $CONMe_2$), 3.08 (6H, s, NMe_2), 5.77 (1H, s, 3-H), 6.79 and 7.33 (2H, 2 x m, 4′-H and 5′-H), 6.90 (1H, dd, *J* 1 and 9.4 Hz, 3′-H), 7.68 (1H, dd, *J* 1.6 and 9.7 Hz, 6′-H); δ_C (100 MHz; $CDCl_3$) 34.4 ($CONMe_2$), 37.2 (NMe_2), 89.3 (C-3), 118.0 and 118.4 (C-3′ and C-5′), 120.4 (C-1′), 128.2 (C-6′), 134.1 (C-4′), 158.9 (C-2), 162.9 (C-2′), 166.8 (C-1) and 190.2 (C-4); ν_{max} (KBr)/cm^{-1} 3200 - 2500 (OH), 2920 (CH) and 1650 (CO).

Glycine ethyl ester hydrochloride (200)[127]

Dry HCl gas was bubbled through a solution of glycine (7.50 g, 10 mmol) in dry EtOH (40 ml) on a boiling water bath until a clear solution was formed (*ca.* 1 h.). Once the glycine had dissolved, bubbling of dry HCl was continued for a further 10 min. The

resulting solution was cooled in an ice bath, and the resulting white crystals (needles) were filtered and washed with cold ethanol (10 ml). The product was recrystallized from a minimum of hot ethanol to afford glycine ethyl ester hydrochloride (**200**) (11.70 g, 89%), m.p. 142 - 144°C (lit.,[127] 144°C); δ_H (400 MHz; DMSO-d_6) 1.23 (3H, t, CH_2CH_3), 3.76 (2H, s, $CH_2NH_3^+Cl^-$), 4.20 (2H, q, CH_2CH_3) and 8.45 (3H, s, NH_3^+); ν_{max} (KBr)/cm^{-1} 1740 (CO).

3-(4-Chloro-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-N,N-*dimethylacrylamide (216)* Ethanolic glycine ethyl ester [generated by adding a solution of KOH (0.84 g, 15 mmol) in dry EtOH (10 ml) dropwise to a solution of glycine ester hydrochloride (**200**) (2.1 g, 15 mmol) in dry EtOH (30 ml)] was added dropwise to a solution of 7-chloro-*N,N*-dimethyl-4-oxo-4*H*-1-benzopyran-2-carboxamide (**213**) (0.20 g, 2 mmol) in dry EtOH (10 ml). The resulting mixture was heated under reflux for 5 d. The reaction solution was allowed to cool, and the solvent evaporated to give a very dark oil which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford *3-(4-chloro-2-hydroxybenzoyl)-2-(carboxyethyl)amino*-N,N-*dimethylacrylamide* (**216**) (0.22 g, 31%), m.p. 131 - 133°C (from EtOAc); δ_H (400 MHz; $CDCl_3$) 1.19 (3H, t, CH_2CH_3), 3.04 and 3.10 (6H, 2 x s, $CONMe_2$), 4.06 (2H, d, *J* 6Hz, CH_2NH), 4.24 (2H, q, CH_2CH_3), 5.70 (1H, s, 3-H), 6.76 (1H, dd, *J* 1.8 and 8.6 Hz, 5′-H), 6.92 (1H, d, *J* 1.8 Hz, 3′-H), 7.50 (1H, d, *J* 8.6 Hz, 6′-H), 10.47 (1H, br s, NH) and 13.19 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_2CH_3), 34.4 and 39.5 ($CONMe_2$), 45.9 (CH_2NH), 61.9 (CH_2CH_3), 89.0 (C-3), 118.4 (C-3), 118.7 (c-1′), 118.9 (C-5′), 129.0 (C-6′), 139.9 (C-4′), 158.6 (C-2), 163.1 (C-2′), 164.0 (CO.N), 168.7, 168.0 and 192.6 (CO); ν_{max} (KBr)/cm^{-1} 1750 (CO.O), 1640 and 1570 (CO).

3-(4-Methoxy-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-N,N-*dimethylacrylamide (217)*

The experimental procedure for the synthesis of 3-(4-chloro-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino-*N,N*-dimethylacrylamide(**216**) was followed, using 7-methoxy-4-oxo-4*H*-1-benzopyran-2-*N,N*-dimethylcarboxamide (**214**) (0.25 g, 1 mmol), glycine ethyl ester hydrochloride (**200**) (1.48 g, 10 mmol) in dry EtOH (20 ml) and KOH (0.56 g, 10 mmol). After stirring under reflux for 13 d., the reaction mixture was allowed to stand at room temperature for 3 d. Work-up afforded *3-(4-methoxy-2-hydroxybenzoyl)-2-(carboethoxymethyl)amino*-N,N-*dimethylacrylamide* (**217**) (0.09 g, 26%); m.p. 118 - 120°C; δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, CH_2CH_3), 3.01 and 3.08 (6H, 2 x s, $CONMe_2$), 3.77 (3H, s, OCH_3), 4.01 (2H, d, *J* 6Hz, CH_2NH), 4.20 (2H, q, CH_2CH_3), 5.65)1H, s, 3-H), 6.33 (1H, dd, *J* 2.5 and 8.8 Hz, 5′-H), 6.37 (1H, d, *J* 2.4, 3′-H), 7.48 (1H, d, *J* 8.9, 6′-H), 10.28 (1H, br s, NH) and 10.67 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_2CH_3), 34.3 and 38.5 ($CONMe_2$), 45.8 (CH_2NH), 55.3 (OCH_3), 61.8 (CH_2CH_3), 89.0 (C-3), 101.2 (C-3), 106.8 (C-1′), 113.8 (C-5′), 129.6 (C-6′), 157.3 (C-2), 164.4 (C-4′), 164.7 (C-2′), 165.0 (CO.N), 169.0 (CO.O) and 192.7 (CO).

N-[2-Dimethylamino-3-(2-hydroxybenzoyl)acryloyl]pyrrolidine (219)

The experimental procedure employed for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) was followed, using 1-[(4-oxo-4*H*-1-benzopyran-2-yl-carbonyl]pyrrolidine (**218**) (0.15 g, 0.62 mmol), dry EtOH (10 ml) and dimethylamine (33% w/w solution in EtOH; 0.62 ml, 3.4 mmol). In this case the reaction time was 45 h. Work-up afforded a crude product which was chromatographed [flash column chromatography; elution with EtOAc:EtOH (4:1)] to give *N-[2-*

dimethylamino)-3-(2-hydroxybenzoyl)acryloyl]pyrrolidine (**219**) (0.15 g, 83%), m.p. 186 - 190°C (from EtOH) (**Found**: M^+, 288.1472; $C_{16}H_{20}N_2O_3$ requires: **M**, 288.1474); δ_H (400 MHz; $CDCl_3$) 1.91 (4H, m, NCH_2CH_2), 3.05 (6H, s, NMe_2), 3.18, 3.36, 3.53 and 3.81 (4H, 4 x m, NCH_2), 5.70 (1H, s, 3-H), 6.77 and 7.29 (2H, 2 x m, 4′-H and 5′-H), 6.87 (1H, dd, *J* 8.3 and 1 Hz, 3′-H), 7.67 (1H, d, *J* 8 Hz, 6′-H) and 13.49 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 24.3 and 25.7 (2 x CH_2), 39.6 and 40.4 (NMe_2), 45.3 and 47.1 [$N(CH_2)_2$], 88.5 (C-3), 117.9, 118.2, 120.4, 128.2, 133.9 and 162.8 (ArC), 159.5 (C-2), 164.9 (C-1) and 190.0 (C-4); ν_{max} (KBr)/cm^{-1} 3000 - 2500 (OH), 1650 and 1610 (CO); *m/z* 288 (M^+, 6%) and 190 (100).

N,N-*Dimethyl-4-oxo-4*H-*naphtho-[1,2-*e*]pyran-2-carboxamide (220)*[84] and *2-(dimethylamino)-3-(2-hydroxynapthyl)*-N,N-*dimethylacrylamide (221)*[84]

Dimethylamine (33% w/w solution in EtOH; 2.91 ml, 16.1 mmol) was added to a solution of 2-(carboethoxy)-4*H*-naphtho[1,2-*e*]pyran-4-one (**196**) (0.75 g, 2.8 mmol) in dry EtOH (20 ml) at 55°C. The reaction mixture was stirred for 2 d. at room temperature. The solvent was evaporated under reduced pressure to afford a crude product (0.73 g) which was chromatographed (flash chromatography on silica gel; elution with EtOAc) to give starting material (**196**) (0.39 g), N,N-*dimethyl-4-oxo-4*H-*naphtho-[1,2-*e*]pyran-2-carboxamide* (**220**) (0.15 g, 20%), m.p. 154 - 156°C (from EtOAc); (**Found**: C, 71.65; H, 5.2; N, 5.15; M^+, 267.0895. $C_{16}H_{13}NO_3$ requires: C, 71.9; H, 4.9; N, 5.2%; **M**, 267.0895); δ_H (400 MHz; $CDCl_3$) 3.15 and 3.17 (6H, 2 x s, $CONMe_2$), 6.70 (1H, s, 3-H), 7.52 (1H, d, *J* 9 Hz, 10-H), 7.63 (1H, m, 7-H), 7.76 (1H, m, 6-H), 7.90 (1H, d, *J* 8 Hz, 8-H), 8.11 (1H, d, *J* 9 Hz, 9-H) and 9.98 (1H, d, *J* 8.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 35.6 and 38.5 ($CONMe_2$), 114.9 (C-3), 117.4 (C-10),

117.9 (C-4b), 127.1 (C-5), 128.3 (C-6), 129.6 (C-8), 130.3 (C-4a), 130.8 (C-10a), 136.1 (C-9), 155.5 (C-2), 157.1 (C-8a), 162.3 (CO.N) and 179.3 (C-4); ν_{max} (KBr)/cm^{-1} 3030 (OH) and 1630 (CO). The crude product was further chromatographed [flash chromatography on silica gel; followed by preparative TLC; elution with EtOAc:EtOH (5:2)] to give *2-(dimethylamino)-3-(2-hydroxynaphthoyl)*-N,N-*dimethylacrylamide* (**221**) (0.08 g, 9%), m.p. 172 - 174°C; (**Found**: **M**$^+$, 267.0895. $C_{18}H_{20}N_2O_3$ requires: **M**, 267.0895); δ_H (400 MHz; $CDCl_3$) 3.00 and 3.15 (6H, 2 x s, $CONMe_2$), 3.21 and 3.32 (6H, 2 x s, NMe_3), 5.79 (1H, s, 3-H), 7.10)1H, d, *J* 8.9 Hz, 3′-H), 7.30 (1H, m, 6′-H), 7.42 (1H, t, 7′-H), 7.74 (2H, t, 4′- and 5′-H), 8.37 (1H, d, *J* 8.6, 8′-H) and 12.37 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 34.5 ($CONMe_2$), 37.4 (NMe_2), 97.3 (C-3), 116.8, 128.7 and 131.7 (C-4′a, C-8′a and C-1′), 119.4 (C-3′), 123.0 (C-6′), 125.2 (C-8′), 126.6 (C-7′), 128.8 and 133.8 (C-4′ and C-5′), 158.1 (C-2′), 160.0, 166.8 (CO.N) and 190.3 (C-4); ν_{max} (KBr)/cm^{-1} 1645 (CO).

2-(Dimethylamino)-3-(1-hydroxy-2-naphthoyl)-N,N-*dimethylacrylamide (222)*[84]

The experimental procedure employed for the synthesis of *N,N*-dimethyl-4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxamide (**196**) was followed, using ethyl 4-oxo-4*H*-naphtho[2,1-*e*]pyran-2-carboxylate (**197**) (1.50 g, 5.6 mmol) in dry EtOH (45 ml) and dimethylamine(33% w/w solution in EtOH; 5.82 ml, 5.6 mmol). Work-up afforded a crude product which was chromatographed [flash chromatography on silica gel; elution with EtOAc:EtOH (4:1)] to give *2-(dimethylamino)-3-(1-hydroxy-2-naphthoyl)*-N,N-*dimethylacrylamide* (**222**) (1.04 g, 70%), m.p. 188 - 190°C (from EtOAc); δ_H (400 MHz; $CDCl_3$) 2.92 and 3.12 (6H, 2 x s, $CONMe_2$), 3.08 (6H, s, NMe_2), 5.82 (1H, s, 3-H), 7.18 (1H, d, *J* 8.8 Hz, 4′-H), 7.45 (1H, t, *J* 7.6 Hz, 7′-H), 7.53 (1H, t, *J* 7.5 Hz,

6′-H), 7.65 (1H, d, *J* 8.8 Hz, 3′-H), 7.70 (1H, d, *J* 8 Hz, 5′-H), 8.42 (1H, d, *J* 8.3 Hz, 8′-H) and 15.32 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 34.4 and 37.2 (CON*Me*$_2$), 40.0 (NMe_2), 89.6 (C-3), 113.4 (C-4′a), 117.1 (C-4′), 123.9 (C-3′), 124.1 (C-8′), 125.2 (C-7′)), 125.9 (C-8′a), 127.1 (C-5′), 128.8 (C-6′), 136.5 (C-2), 158.6 (C-2′), 162.5 (C-1′), 166.9 (CO.N) and 190.0 (CO); ν_{max} (KBr)/cm^{-1} 1655 (CO).

3.3 Attempted preparations

*4-Hydroxy-2-*H*-1-benzopyran-2-thione (**155**)*[68,114]

A mixture of 4-hydroxycoumarin (5.0 g, 31 mmol) and Lawesson's reagent (12.46 g, 30.81 mmol) in dry toluene (30 ml) was heated under reflux at 110°C for 2 h. After cooling, the resulting red solid was filtered off and washed to afford the disulphide of 4-hydroxy-2*H*-1-benzopyran-2-thione (**155**) (4.52 g, 41%), m.p. 226 - 227°C; δ_H (400 MHz; $CDCl_3$) 6.93 (1H, s, 3-H), 7.36 and 7.65 (2H, 6-H and 7-H), 7.51 (1H, dd, *J* 0.9 and 8.4 Hz, 8-H) and 7.78 (1H, dd, *J* 1.4 and 1.9 Hz, 5-H); *m/z* 354 (M^+, 74%) and 321 (100).

*2-(Dimethylamino)-3-(2-methoxybenzoyl)-*N,N*-dimethylacrylamide*

Method 1

2-(Dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (0.50 g, 1.9 mmol) in dry THF (10 ml) was added to NaH (60% dispersion in oil; 8.0 mg, 1.9 mmol) in dry THF (15 ml), and stirred for 1 h. at room temperature. MeI (0.13 ml, 2.1

mmol) in dry THF (5 ml) was added dropwise (with occasional cooling when the reaction temperature rose). The reaction solution was stirred for 1.5 h. (stirring for a longer time, *eg.* 3 d., does not appear to help) and poured into 5% aq. $NaHCO_3$ (15 ml). The resultant solution was extracted with Et_2O (2 x 20 ml), and the combined dried (anhyd. $MgSO_4$) extracts were evaporated under reduced pressure. The ^1H NMR spectrum of the residue showed the presence of the starting material accompanied by a trace of the expected product.

Method 2[128,129]

A suspension of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (0.50 g, 1.9 mmol) in dry chloroform (25 ml), Ag_2O (0.67 g, 2.9 mmol) and CH_3I (0.40 ml, 7.6 mmol) was stirred vigorously for 1 h., follwed by two further additions of Ag_2O (0.34 g, 1.4 mmol) and CH_3I (0.20 ml, 3.82 mmol) at 1 h. intervals. After stirring for 2 d. at room temperature, the reaction mixture was filtered and the residue extracted with warm chloroform (2 x 20 ml). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with EtOAc: EtOH: (3:1)] to give a yellow oil (0.20 g).

A ^1H NMR spectrum showed the oil to be mainly starting material

Method 3

Diisopropylamine (0.27 ml, 1.9 mmol) in dry THF (20 ml) was cooled to < 0°C, and BuLi (1.27 ml, 1.9 mmol) was added dropwise and the resulting mixture stirred for 45 min. before being cooled to -78°C. 2-(Dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (0.50 g, 1.9 mmol) in dry THF (20 ml) was added dropwise

and stirred for a further 45 min at -78°C. MeI (0.13 ml, 21.0 mmol) in dry THF (5 ml) was added and to the reaction solution and stirred for 45 min. at -78°C. The reaction mixture was then allowed to warm to room temperature, and aq. $NaHCO_3$ was cautiously added. The resulting solution was extracted with Et_2O (3 x 40 ml), and the combined extracts were dried (anhyd. $MgSO_4$) and evaporated under reduced pressure to give a solid product (0.46 g) which was shown by ^1H NMR spectroscopy to be the starting material.

Method 4

Et_3N (0.13 ml, 95 mmol) was added to a solution of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (250 mg, 953 mmol) in dry THF (15 ml) under N_2 gas at 0°C, followed by Me_3SiCl (0.13 ml, 1.1 mmol) in dry THF (5 ml). The reaction mixture was allowed to warm to r.t., stirred overnight, and then poured into saturated aq. $NaHCO_3$ (20 ml), and extracted with Et_2O (3 x 30 ml). The combined extracts were dried (anhyd. $MgSO_4$) and evaporated to yield a solid product which was shown by ^1H and ^{13}C NMR spectroscopy to be the starting material (**215**).

Acetylation of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-N,N-*dimethylacrylamide (215)*[130]

A mixture of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**215**) (0.50 g, 1.9 mmol), benzene (15 ml), toluene-*p*-sulphonic acid (14.1 mg, 0.07 mmol) and ethylene glycol (237 mg, 3.82 mmol) were heated under reflux using a Dean-Stark head for 24 h. After cooling, the solution was washed with dil. NaOH and H_2O, acidified with HCl, and extracted with Et_2O (3 x 40 ml). The combined ethereal solutions were dried (anhyd. Na_2SO_4) and evaporated to give a product which was shown by ^1H NMR

spectroscopy to be the starting material (**215**).

*2-(*N,N-*Dimethylamino)-7-fluoro-4*H-*1-benzopyran-4-one* (**150**)

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (Method 4) was followed, using ethyl (*N,N*-dimethylcarbamoyl)-ethanoate (**171**) (2.19 g, 13.8 mmol), $POCl_3$ (1.72 ml, 18.8 mmol) and 3-fluorophenol (1.13 ml, 12.5 mmol). Work-up afforded a viscous reddish oil (1.72 g) which was chromatographed (flash column chromatography on silica gel; elution with EtOAc) to give an oil which was shown by TLC and ^{1}H NMR spectroscopy to comprise a complex mixture, probably including the expected product.

The above method was also attempted with ethyl [(piperidin-1-yl)carbamoyl]ethanoate (**173**), ethyl [(pyrrolidin-1-yl)carbamoyl]ethanoate (**174**) and ethyl-(*N,N*-diisopropylcarbamoyl)-ethanoate (**175**) with either phenol or substituted phenols in dry benzene/chlorobenzne without success.

*2-(*N,N-*Diisopropylamino)-4*H-*1-benzopyran-4-one*

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**148**) (Method 3) was followed, using 2-ethylsulphinyl-4*H*-1-benzopyran-4-one (**157**) (1.00 g, 4.50 mmol), CH_3CN (30 ml) and diisopropylamine (3.81 ml, 27 mmol). In this case, the reaction mixture was stirred under reflux for 5 d. Work-up afforded a product, which was shown by ^{1}H NMR spectroscopy to be the starting material.

*Reaction of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**) with* m*-chloroperbenzoic acid*

A suspension of *m*-chloroperbenzoic acid (55%; 0.47 g, 1.5 mmol), sodium 4-oxo-4*H*-1-benzopyran-2-carboxylate [prepared by adding $NaHCO_3$ (0.11 g, 1.3 mmol) in H_2O (*ca.* 2 ml) to 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**) (0.25 g, 1.3 mmol) and evaporating under reduced pressure], and 18-crown-6 (0.07 g) in dry CH_2Cl_2 (20 ml). After stirring for 5 h., dil. HCl (20 ml) was added to the reaction mixture and the precipitate was filtered off. The aqueous layer was extracted with CH_2Cl_2 (3 x 40 ml), the combined extracts dried (anhyd. $MgSO_4$) and evaporated to give a white solid which was shown by ^1H and ^{13}C NMR spectroscopy to be 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**206**).

N,N-*Dimethyl-3-(5-nitro-2-hydroxyphenyl)-3-oxo-propanamide (**168**)*

The experimental procedure employed for the synthesis of (*N,N*-dimethyl)-3-(2-hydroxyphenyl)-3-oxo-propanamide (**166**) was followed, using butyllithium (41.50 ml, 625 mmol), diisopropylamine (8.75 ml, 62 mmol) in dry THF (*ca.* 50 ml), *N,N*-dimethyl-acetamide (2.87 ml, 31.0 mmol) and methyl 5-nitrosalicylate (**164**) (3.82 g, 19.4 mmol) in dry THF (5 ml). Work-up gave a very viscous dark oil which resisted attempts to achieve chromatographic separation (flash chromatography on silica gel; elution with EtOAc).

*Ring-opening of 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-*e*]pyran-4-one (**186**)*

Dimethylamine (33% w/w ethanolic solution; 3.78 ml, 10.2 mmol) was added to a

stirred solution of 2-(*N,N*-dimethylamino)-4*H*-naphtho[1,2-e]pyran-4-one (**186**)[a] (0.36 g, 1.5 mmol) in dry ethanol (15 ml) for 3 d. at room temperature. The resulting mixture was evaporated under reduced pressure to afford a crude product, which was shown by ^{1}H NMR spectroscopy to be the starting material (**186**).

3.4 DNMR studies of rotational isomerism in 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones

Variable temperature NMR spectra were recorded for solutions of the 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones (**148** - **152**), (**158** - **160**), (**169**), (**170**), (**176**) and (**177**) in $CDCl_3$ (or $CDCl_2$, where stated) on a Bruker AMX400 NMR spectrometer equipped with a variable temperature unit, which has been calibrated using 30% ethylene glycol in DMSO-d_6.

The coalescence temperatures (T_c) for C-NR_2 rotation were obtained from the variable-temperature spectra, whilst the frequency differences at coalescence ($\Delta\nu_c$) were determined by extrapolation, as described by Lai and Chen.[92] Temperature stability is judged to be $\pm$ 0.1 K and the overall error in coalescence ($\Delta\nu_c$) temperatures (T_c) estimated to be $\pm$ 2 K.

The rotational energy barriers ($\Delta G^{\ddagger}$) for the C-NR_2 rotation of compounds studied are summarized in Table 9 (p. 114). The variable-temperature spectra for compounds (**149-**

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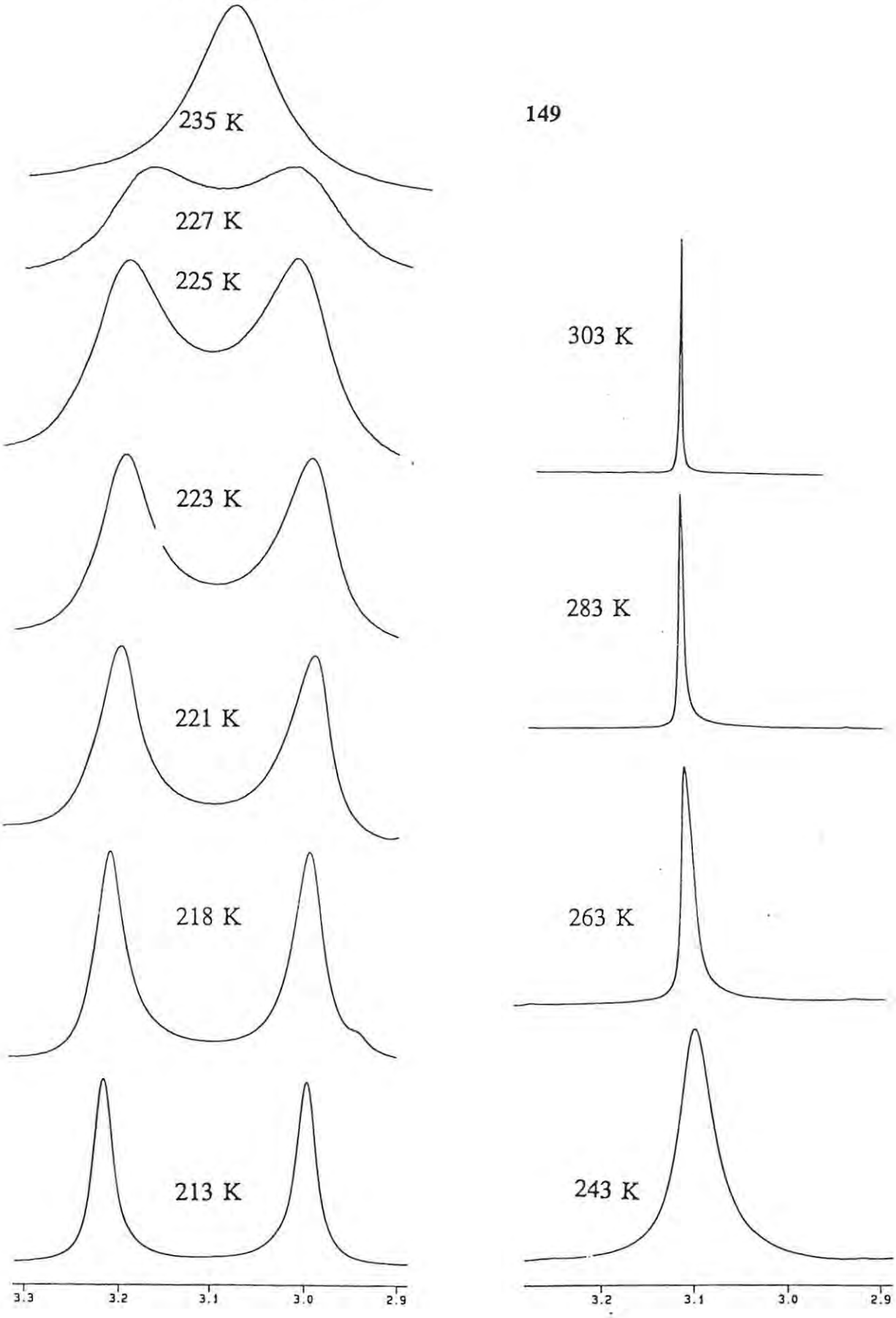
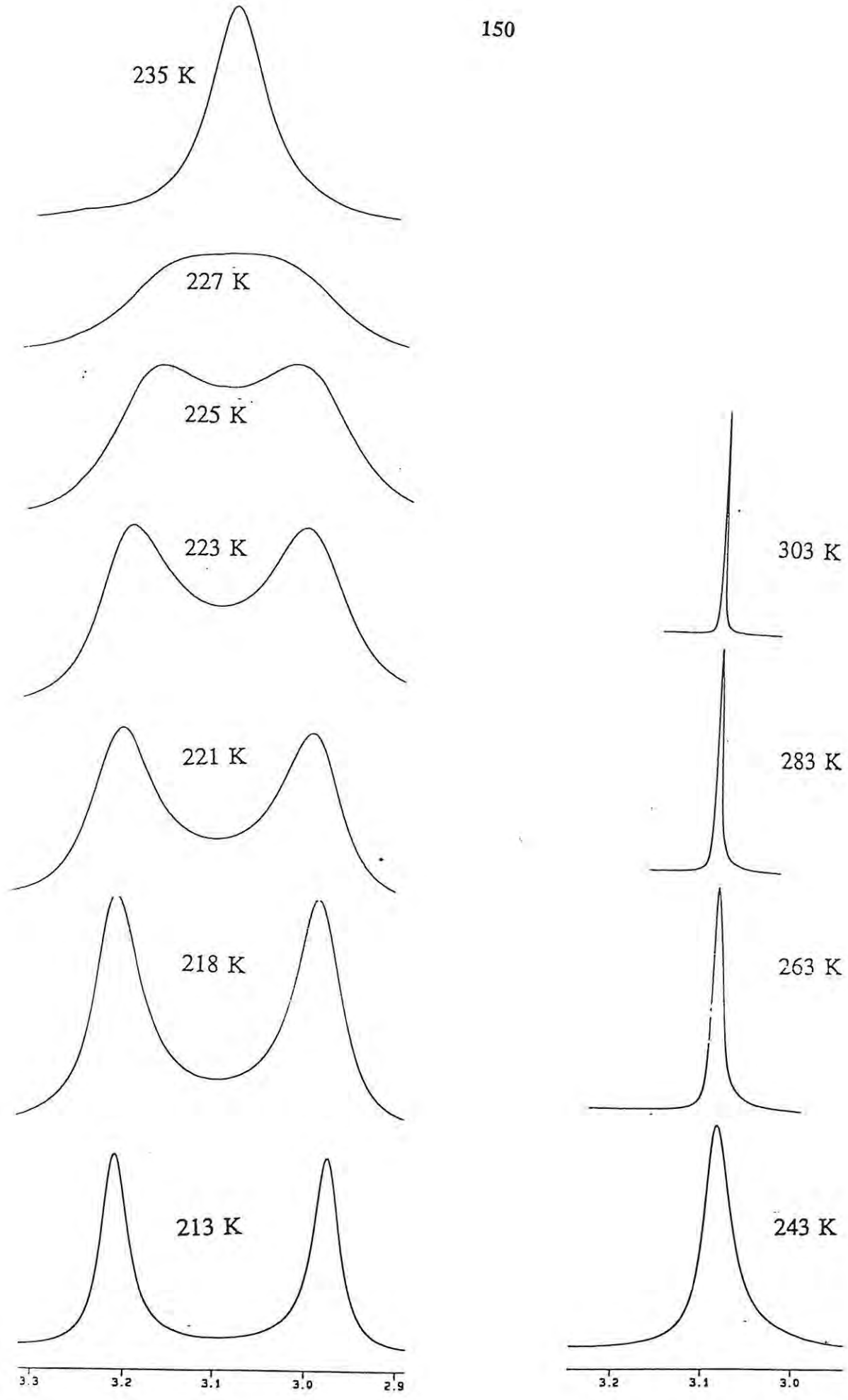
[a]Use of 2-(*N,N*-dimethylamino)-4*H*-naphtho[2,1-*e*]pyran-4-one (**187**) instead of compound (**186**) also gave the starting material.

152),(158-160),(169),(170),(176),(177) (pp.181-190) and **(148)** (p.195) and corresponding plots of the frequency separation ($\Delta\nu$) against temperature (T) (pp. 191-194) are shown below.

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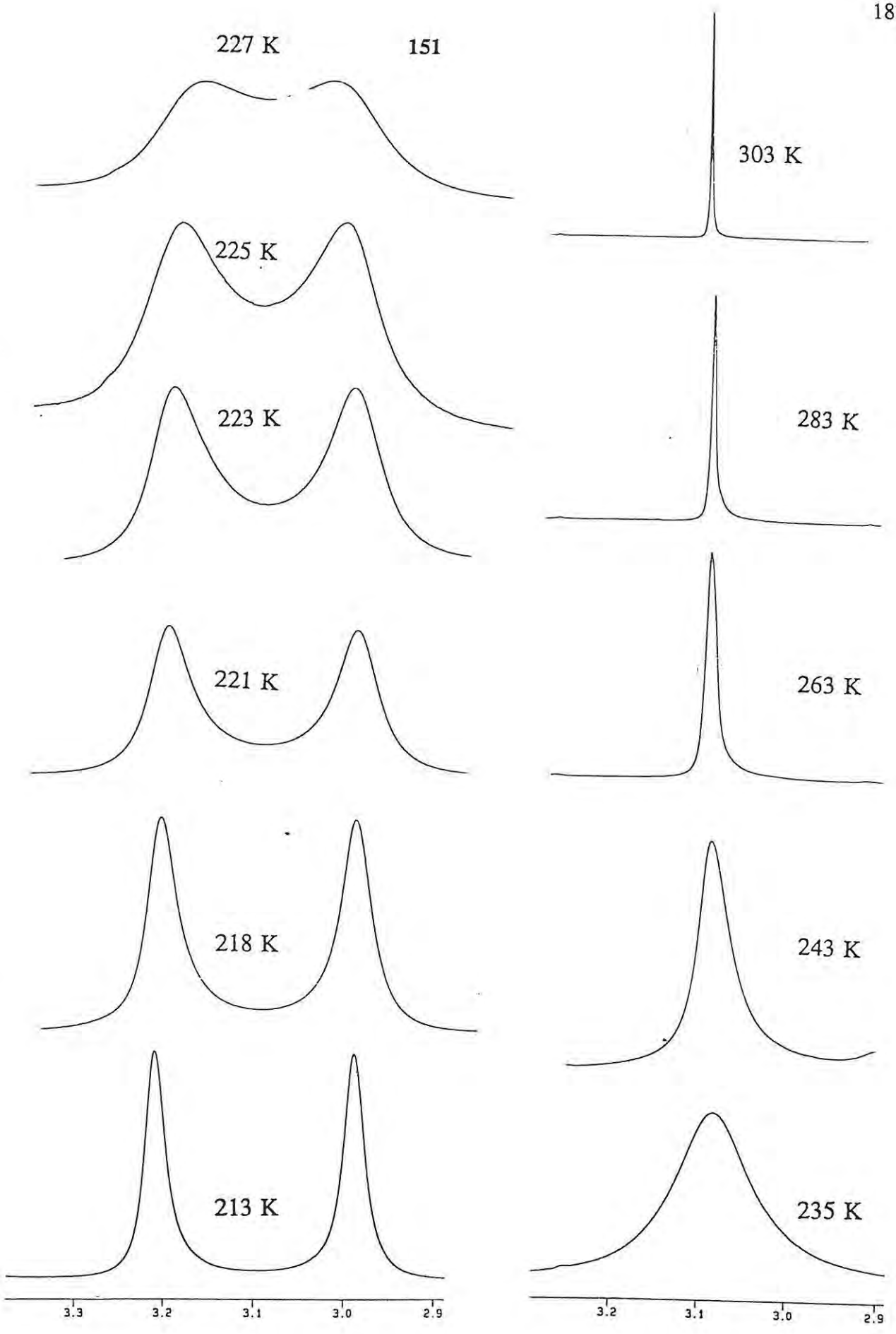
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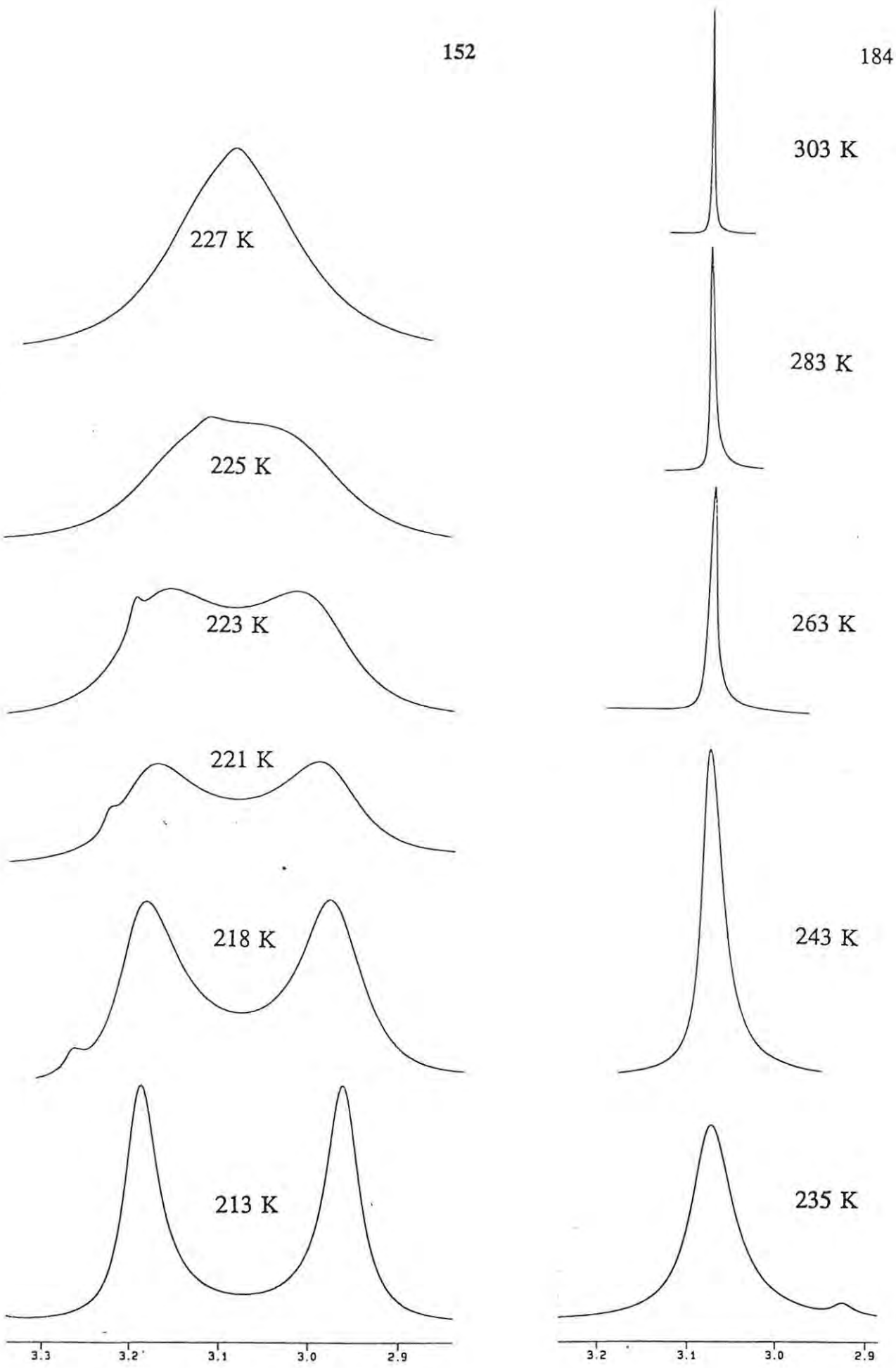
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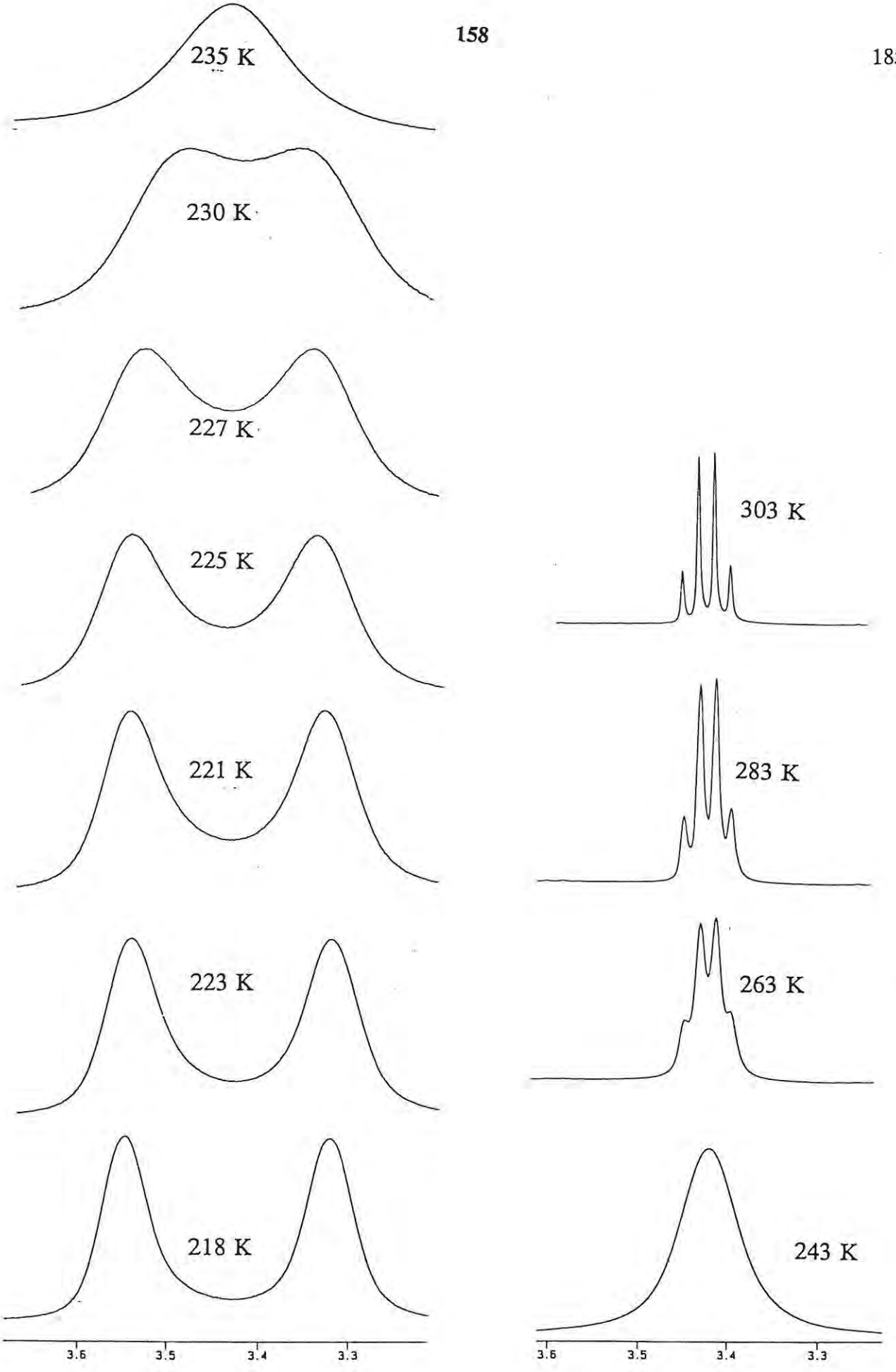
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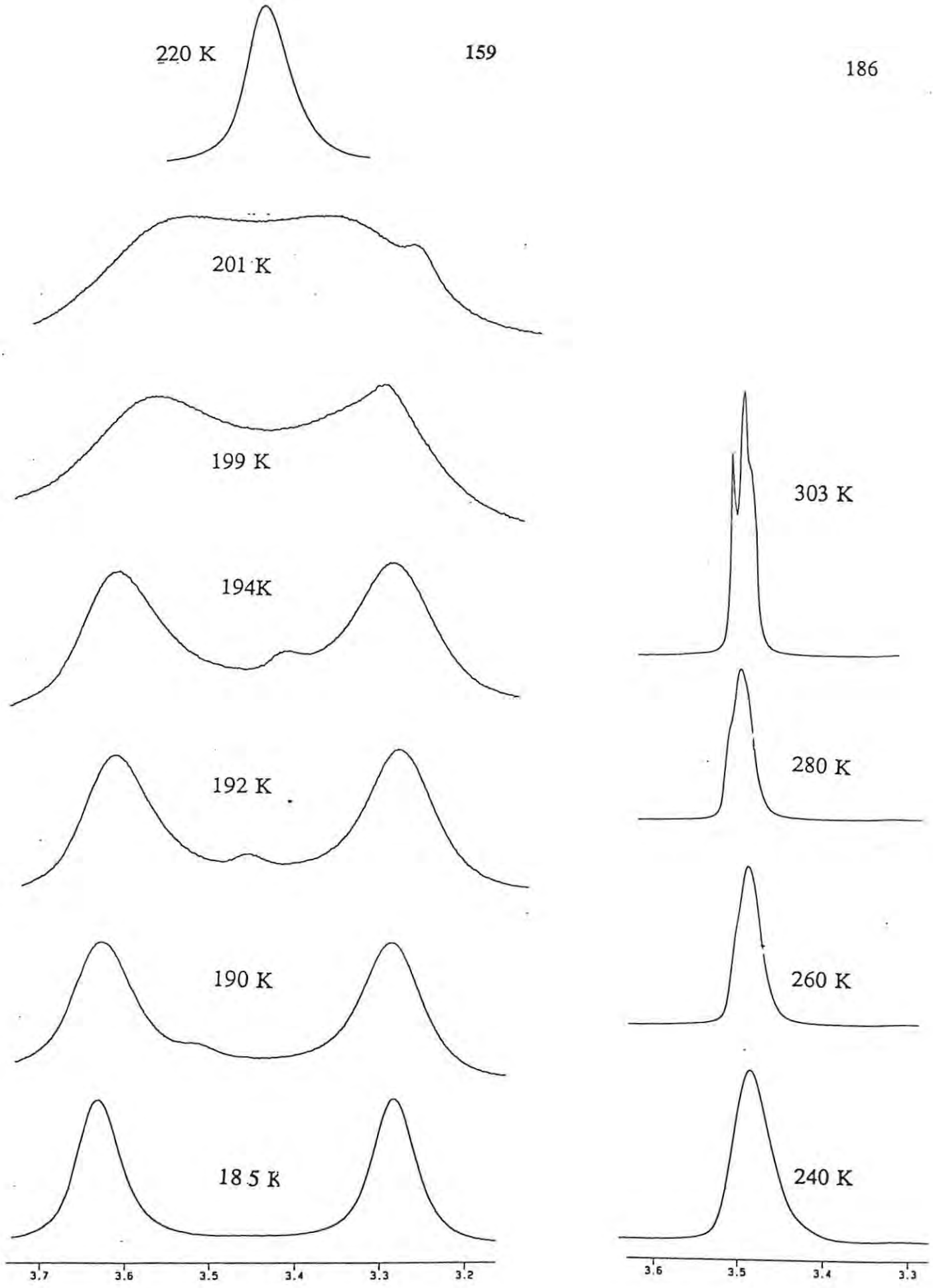
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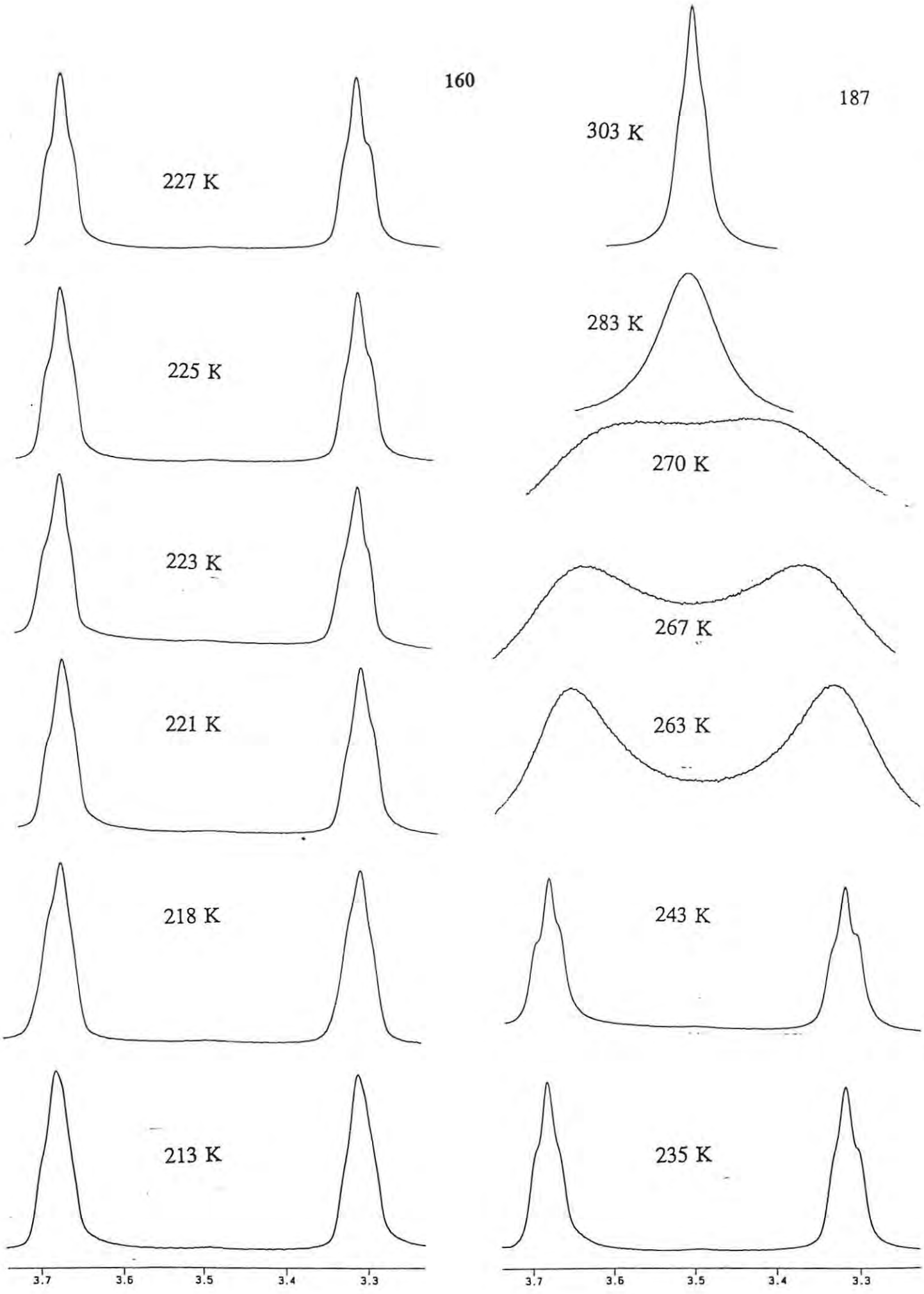
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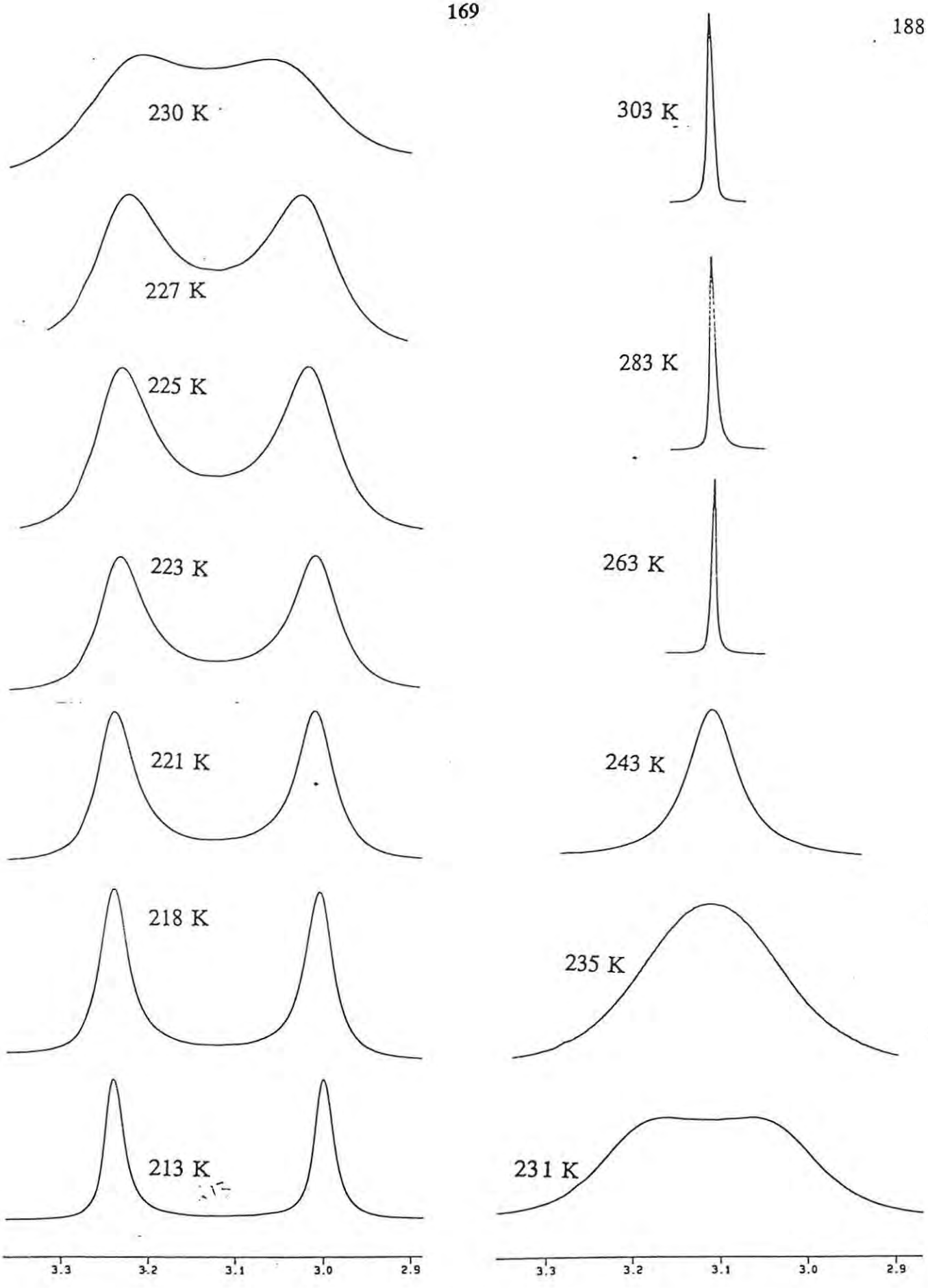
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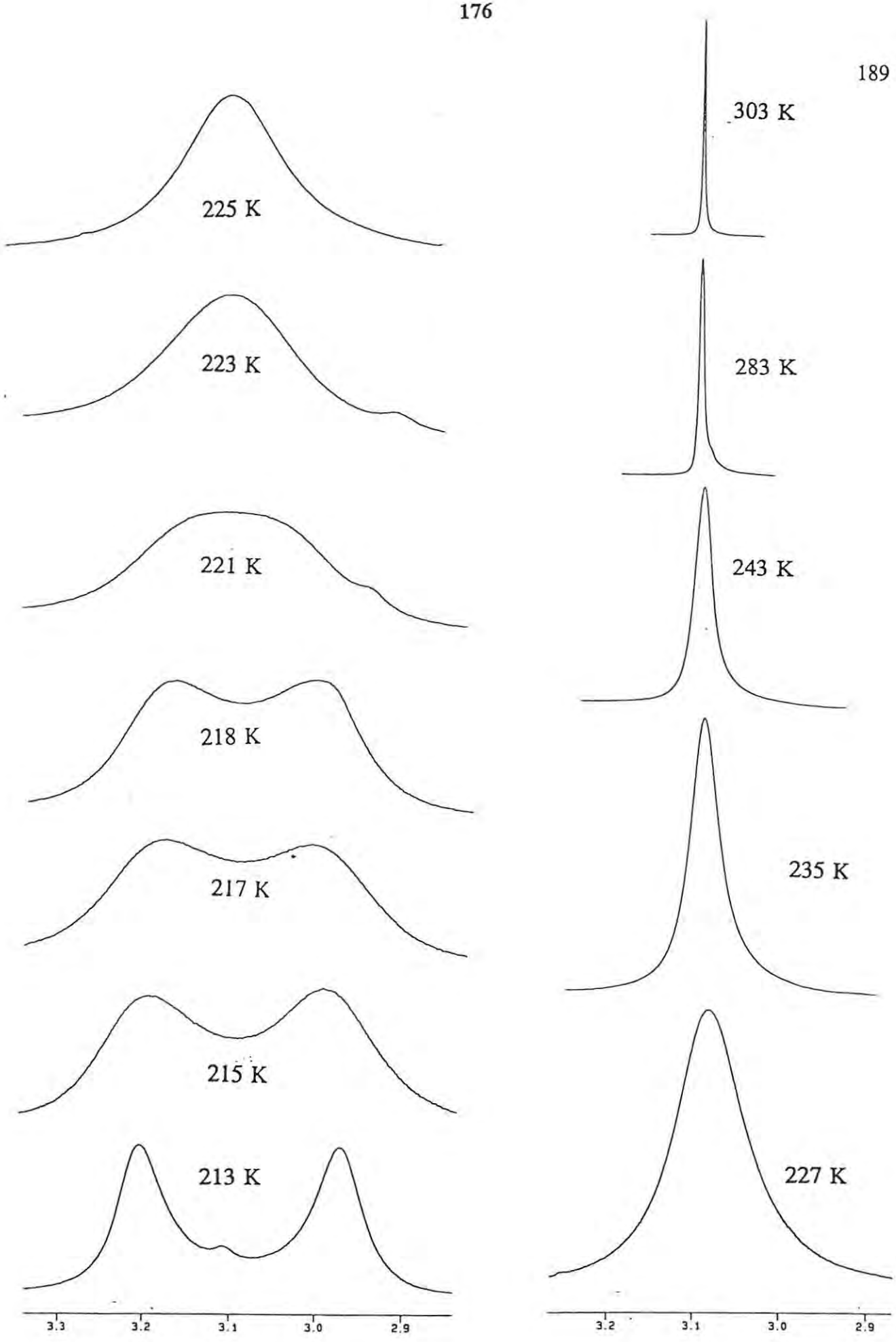
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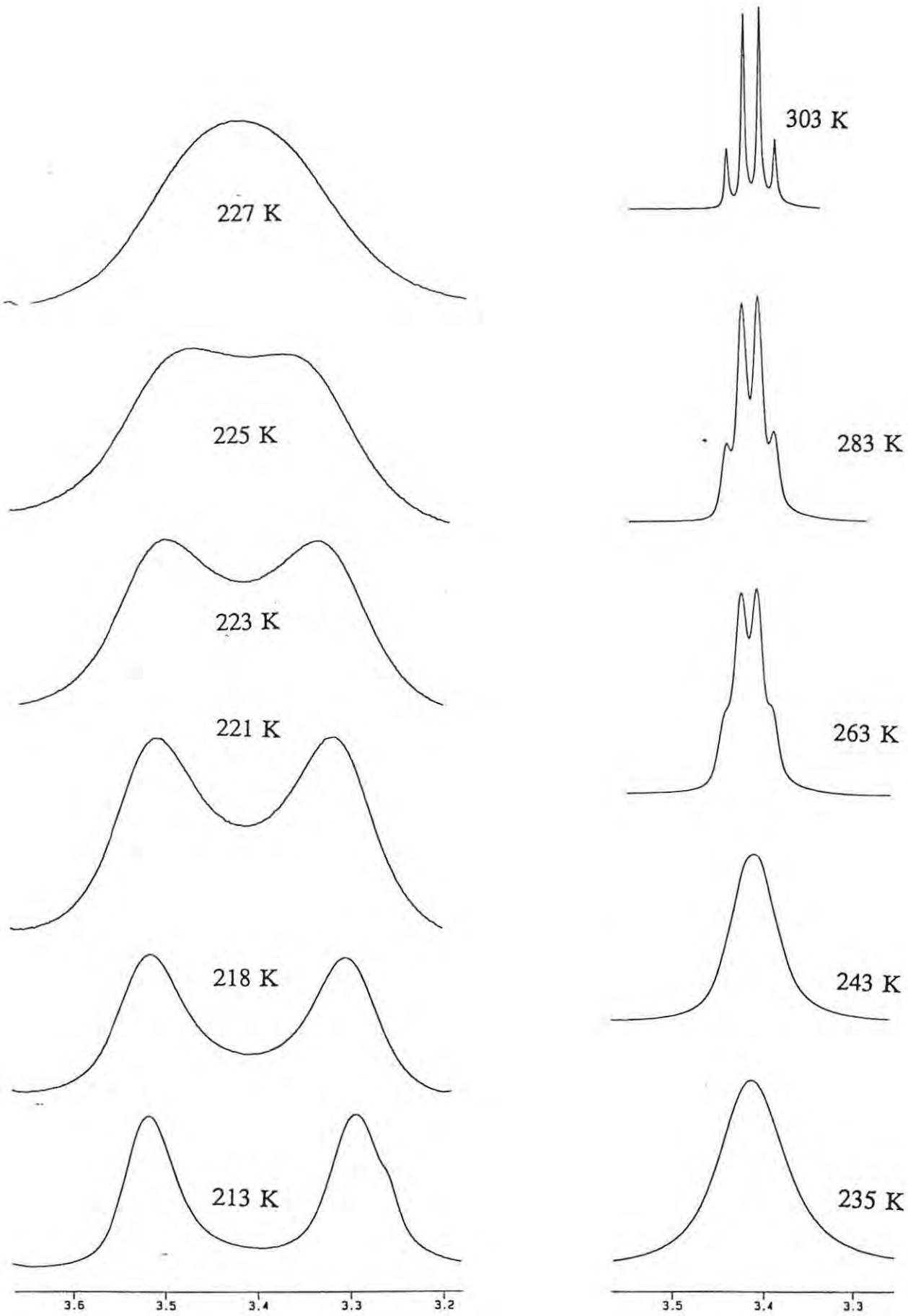
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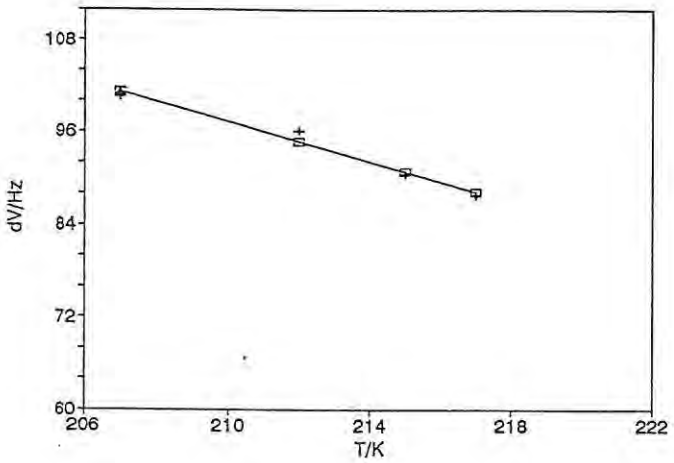
148

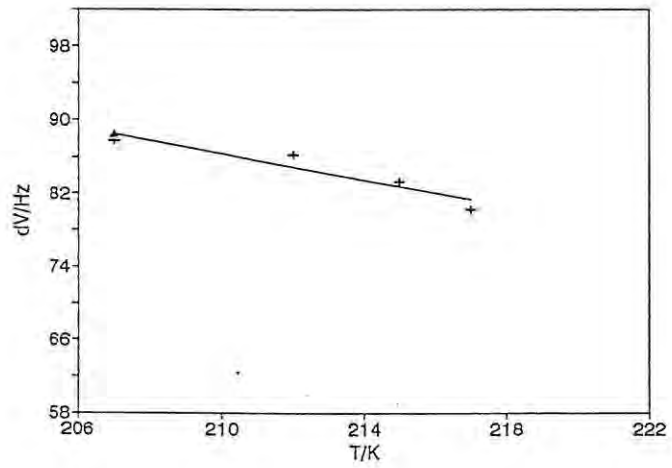


No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	100.5	101.1
2.0	212.0	96.1	94.7
3.0	215.0	90.5	90.8
4.0	217.0	87.8	88.2
	222.0		81.8

Regression Output:

Constant	368.0507
Std Err of Y Est	1.160529
R Squared	0.972244
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-1.28943
Std Err of Coef.	0.154054

149

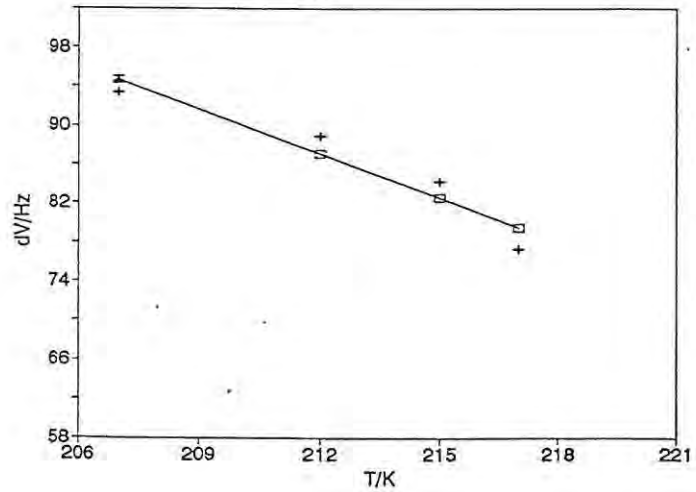


No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	87.7	88.5
2.0	212.0	86.2	84.9
3.0	215.0	83.3	82.7
4.0	217.0	80.2	81.3
	222.0		77.7

Regression Output:

Constant	236.7427
Std Err of Y Est	1.38788
R Squared	0.883154
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-0.7163
Std Err of Coef.	0.184234

150

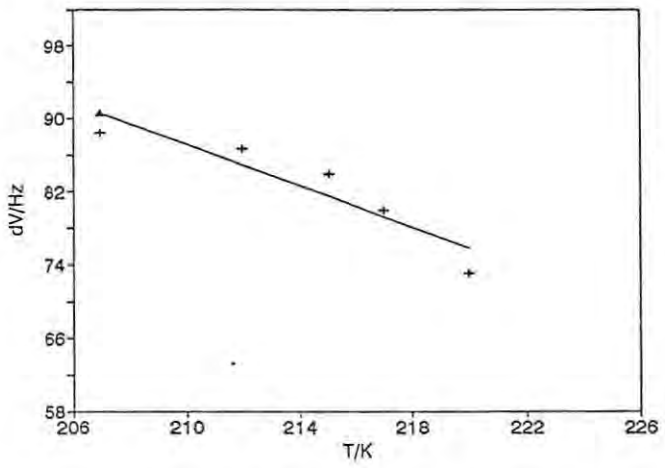


No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	93.4	94.6
2.0	212.0	88.9	87.1
3.0	215.0	84.2	82.6
4.0	217.0	77.3	79.5
	221.0		73.5

Regression Output:

Constant	407.4181
Std Err of Y Est	2.502061
R Squared	0.911882
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-1.51101
Std Err of Coef.	0.332135

151

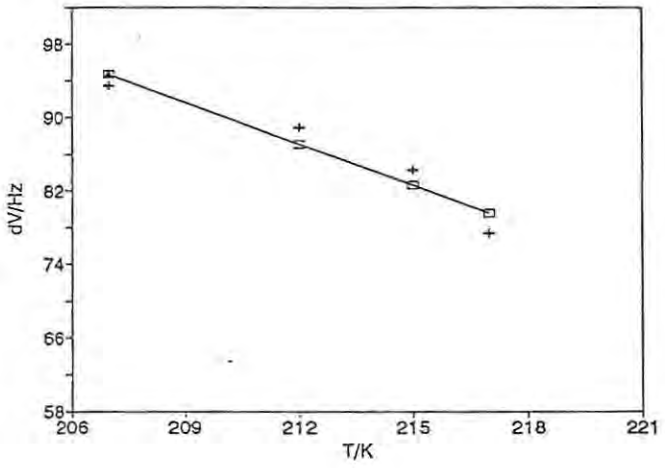


No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	88.4	90.6
2.0	212.0	86.6	84.9
3.0	215.0	83.9	81.5
4.0	217.0	79.9	79.2
5.0	220.0	73.1	75.8
	223.0		72.4

Regression Output:

Constant	325.5881
Std Err of Y Est	2.66183
R Squared	0.856985
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-1.13543
Std Err of Coef.	0.267795

152

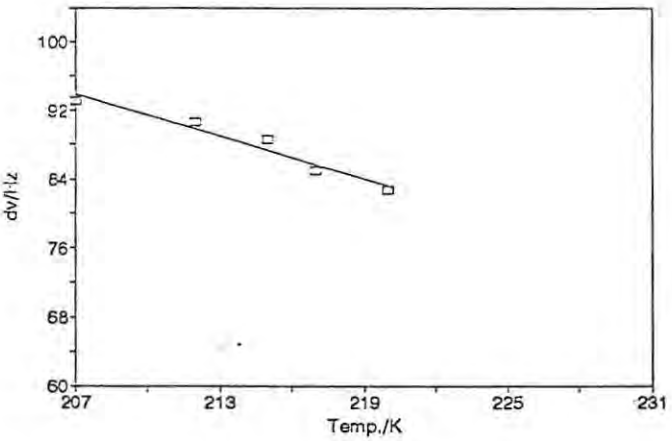


No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	90.1	93.1
2.0	212.0	81.7	77.6
3.0	215.0	73.0	68.3
4.0	217.0	56.2	62.1

Regression Output:

Constant	736.0
Std Err of Y Est	6.4
R Squared	0.9
No. of Observations	4.0
Degrees of Freedom	2.0
X Coefficient(s)	-3.1
Std Err of Coef.	0.9

158



	True Temp	dv/HzCalc	dv/Hz
No.1	207	93.1	93.9
2	212	90.6	89.8
3	215	88.5	87.3
4	217	85.0	85.7
5	220	82.7	83.2
	226		78.3

Regression Output:

Constant	263.9796
Std Err of Y Est	1.065465
R Squared	0.951423
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.82166
Std Err of Coef.	0.107192

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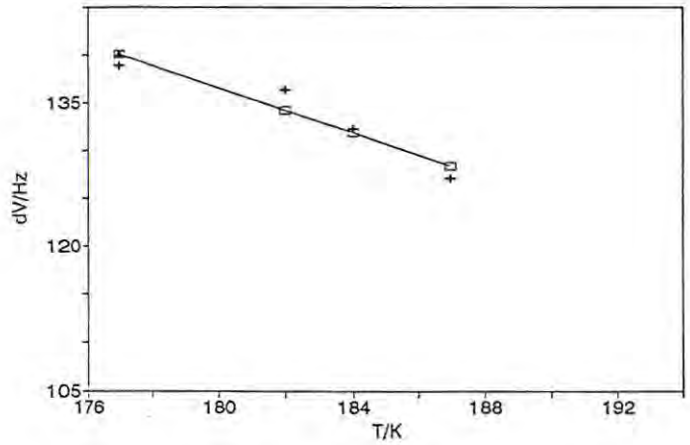
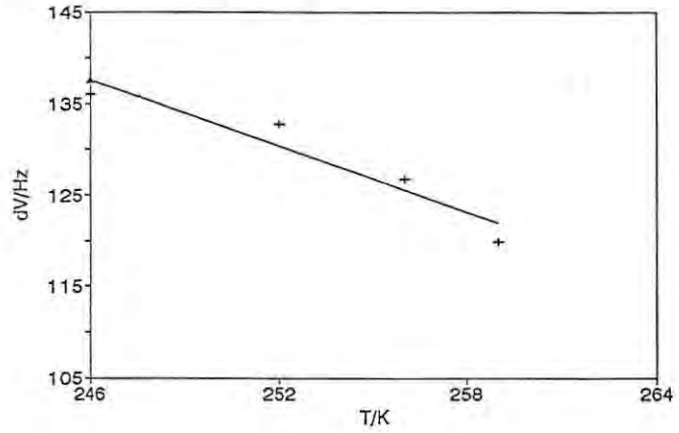


No.	T/K	dV/Hz	Y(CALC.)
1.0	177.0	138.9	140.1
2.0	182.0	136.3	134.2
3.0	184.0	132.3	131.9
4.0	187.0	127.1	128.4
	194.0		120.3

Regression Output:

Constant	346.1075
Std Err of Y Est	1.934152
R Squared	0.905663

160



No.	T/K	dV/Hz	Y(CALC.)
1.0	246.0	136.1	137.7
2.0	252.0	132.8	130.4
3.0	256.0	126.8	125.6
4.0	259.0	119.9	121.9
	264.0		115.9

Regression Output:

Constant	435.2055
Std Err of Y Est	2.631677
R Squared	0.909147
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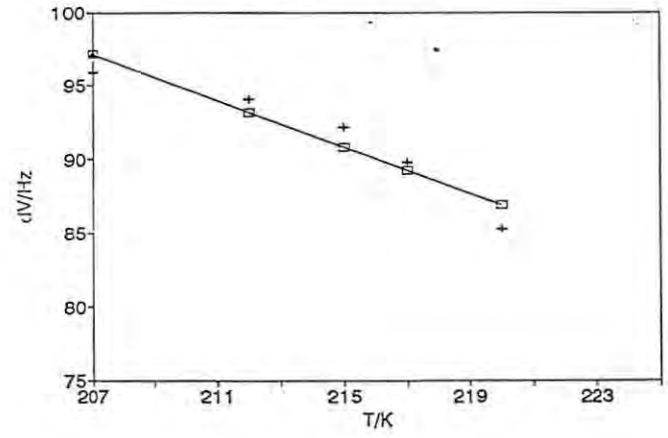
Degrees of Freedom	2
X Coefficient(s)	-1.2095
Std Err of Coef.	0.27036

169



No.	T/K	dV/Hz	Y(CALC.)
1.0	207.0	95.9	97.1
2.0	212.0	94.1	93.2
3.0	215.0	92.2	90.8
4.0	217.0	89.8	89.3
5.0	220.0	85.3	86.9
	225.0		83.0

Regression Output:

Constant	259.6113
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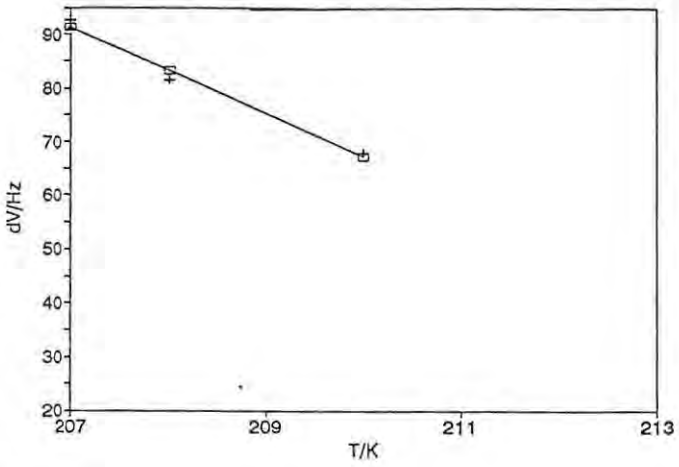
R Squared	0.896281

176



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2.0	208.0	81.5	83.3
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	213.0		43.2

Regression Output:

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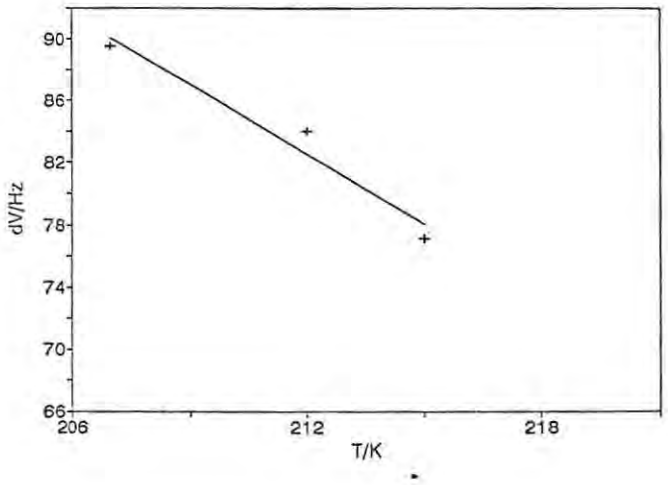
R Squared	0.982741
No. of Observations	3
Degrees of Freedom	1

177



No.	T/K	dV/Hz	Y(CALC.)
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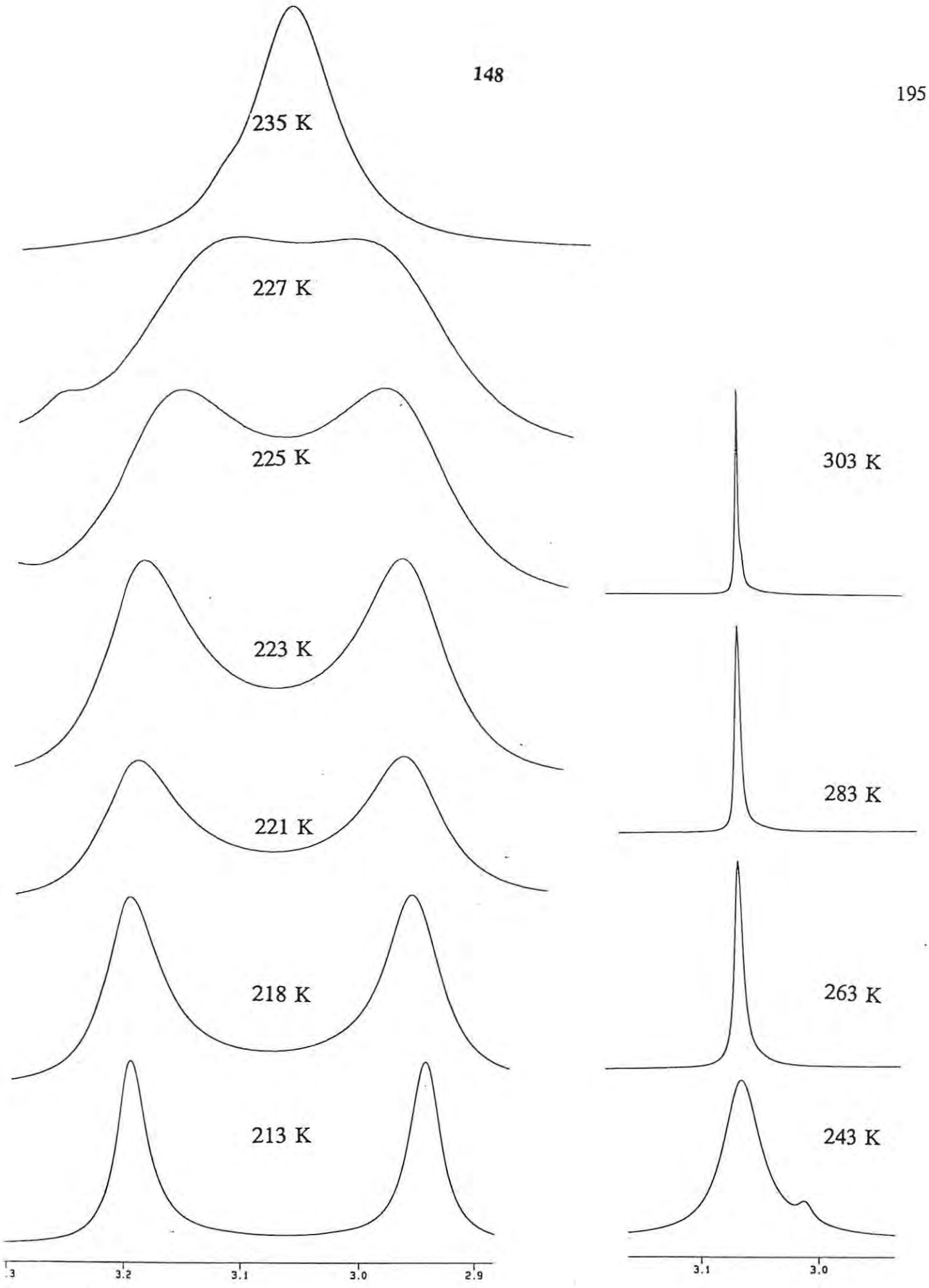
2.0	212.0	84.0	82.5
3.0	215.0	77.1	78.0
	219.0		72.0

Regression Output:

Constant	401.3959
Std Err of Y Est	1.818275
R Squared	0.957178
No. of Observations	3
Degrees of Freedom	1
X Coefficient(s)	-1.50408
Std Err of Coef.	0.318132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