CHEMICAL AND SPECTROSCOPIC STUDIES OF CHROMONE DERIVATIVES

THESIS

Submitted in fulfilment of the

Requirements for

the degree of

MASTER OF SCIENCE

of Rhodes University

by

IPFANI DAVID ISAIAH RAMAITE

January 1993

Department of Chemistry

Rhodes University

Grahamstown

CONTENTS

ACKNOWLEDGEMENTS

I would like to thank Professor P T Kaye for his continuous assistance, guidance and supervision throughout this project.

Thanks are also due to Stephanie Burton and Mr W Mushwana for proof-reading the manuscript; Steve Taylor and Ruth Grue for typing the manuscript and to Dr D N Davidson and Swarna Ravindran for their advice and suggestions.

Finally, I would like to thank DAAD for their generous financial support.

To my parents, for their support and motivation throughout my studies.

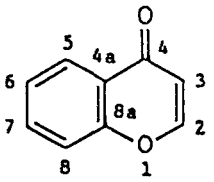
ABSTRACT

A number of biologically active chromones occur in plants (eg. Khellin) and research in this field has eventually led to the discovery of chromoglycic acid, which is widely used as a sodium salt in asthma therapy. Since biological activity may be related to acidity, a range of chromone-2-carboxylic acids have been prepared *via* Claisen acylation of substituted *o*-hydroxyacetophenones and their acid dissociation constants determined potentiometrically to explore substituent effects. From this study it has been found that introduction of certain groups does have a marked effect on acidity.

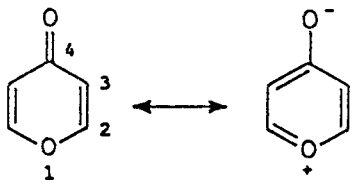
A variety of acrylamide derivatives have been prepared *via* the dimethylamine-mediated ring opening of chromone-2-carboxamides which, in turn, were prepared from the chromone-2-carboxylic acids *via* the corresponding acid chlorides. Variable temperature NMR spectroscopy was employed to examine the effect of substituents on the rotational barriers and it has been found that for the acrylamides examined, ring substituents have little effect on the rotational barriers. A combination of low resolution, high resolution and meta-stable peak analysis has been used to study mass fragmentation patterns for a series of acrylamide derivatives. The proposed fragmentation pathways for selected peaks have been found to be common to all the spectra examined when differences in the atomic masses of substituents were taken into account.

1. INTRODUCTION

Chromones (1) are heterocyclic compounds in which a benzene and pyran-4-one (2) are fused together.



1
Chromone
(Benzo-4*H*-pyran-4-one)
(4-Oxo-4*H*-1-benzopyran)
(4-Oxo-4*H*-chromene)

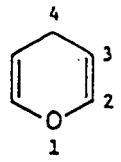


2a
γ-Pyrone
(4*H*-Pyran-4-one)

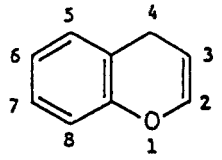
2b

The name "chromone", first used by Bloch and Kostanecki,[1] was chosen because several coloured, naturally occurring compounds were known to contain the benzopyran-4-one structure. Their systemic nomenclature originates from the pyran analogues (3) and (4).

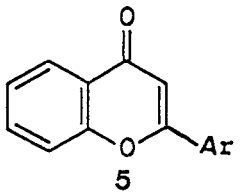
Chromones are important because many of them occur in plants and others are medicinally useful.[1] The occurrence and chemistry of chromones has been extensively reviewed.[1-3] Other, related families of compounds are the flavones and isoflavones, which are derivatives of 2-arylchromone (5) and 3-arylchromone (6),[4] respectively.



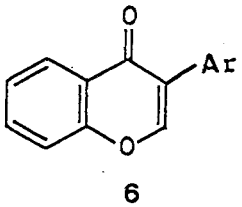
3
4*H*-Pyran



4
4*H*-1-Benzopyran
(4*H*-Chromene)
(γ-Chromone)

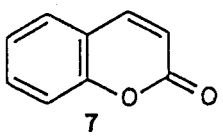


5



6

Ar = ARYL GROUP



7

1.1 Structure and Spectroscopic Properties.

The properties of the γ-pyrone ring, and hence of chromones, can be explained in terms of the aliphatic dienone structure (**2a**). However, some properties of chromones, such as their basicity and the relative lack of normal ketonic properties, are consistent with the aromatic pyrylium betaine structure (**2b**). These apparent anomalies presented an elusive goal for early researchers in the field until, in 1924, Arndt suggested that the ether oxygen in γ-pyrone

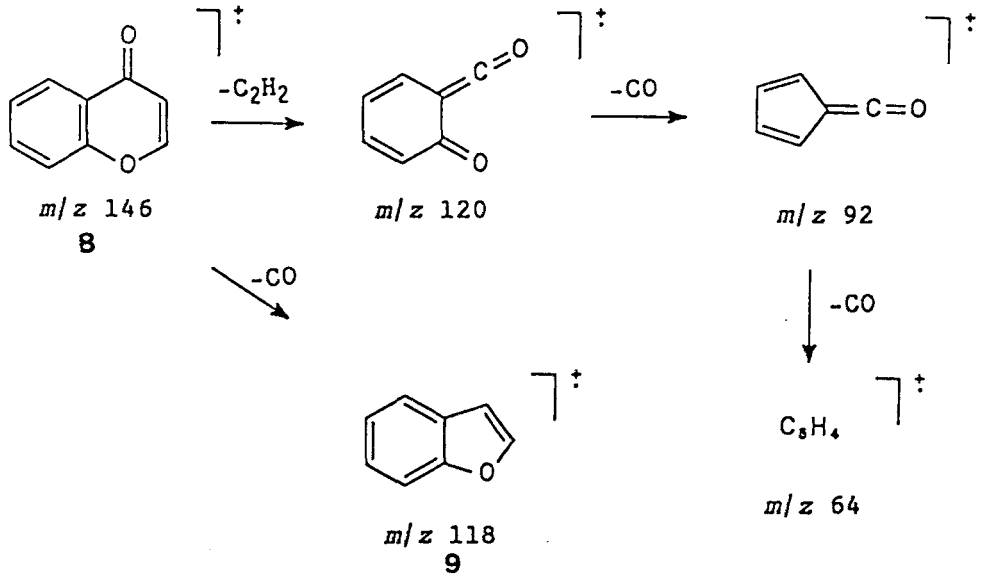
could interact electronically with the carbonyl group and so modify the properties of the latter.[5] The failure to obtain a Diels-Alder adduct on treatment of 2,3-dimethylbuta-1,3-diene with the 'dienophile' (**2a**) and congeneric compounds has further supported the assumption that the γ-pyrone ring has substantial π-electron delocalisation consistent with the "aromatic" structure (**2b**).[6]

Studies of dipole moments and ^{1}H and ^{13}C NMR spectroscopy support the theory that some degree of aromaticity is also evident in chromones. Nevertheless, spectroscopic properties of chromones may often be interpreted in terms of an aliphatic π system in the heterocyclic ring as in structure (**2a**) rather than as an "aromatic" pyrylium betaine as in structure (**2b**). The carbonyl stretching frequency in the IR spectrum occurs at 1660 cm^{-1}, which is higher than that of γ-pyrone (υ_{max} 1650 cm^{-1}) but much lower than that of coumarins (**7**).[7]
The UV spectra of chromones are characterised by two strong peaks at approximately 225 and 290 nm. Chromone itself, for instance, has UV absorption maxima at 245 nm and 297 nm.[7]

A detailed ^{1}H NMR study of chromone has been published by Mathis and Goldstein,[8,9] and the chemical shifts agree well with those predicted from electron density calculations. In the ^{1}H NMR spectrum of chromone, the 2-H and 3-H signals appear very close to those found for γ-pyrone, suggesting that the ring current in the heterocyclic ring is not significantly affected by benzannulation.[7] The separation of the 5-H signal from those of the other benzenoid hydrogens is characteristic of chromones and chromanones but is not shown by the isomeric coumarins.[8]

A number of general features of the ^{13}C NMR spectra of chromones can be recognised.[10] The signal from the carbonyl carbon is always at the lowest field and is essentially unaffected by substitution in the system. The C-3 signal is at higher frequency than all the other methine carbon signals and the ring junction signals are largely unaffected by changes in the substituents in either ring.[10]

The mass spectrum of chromone yields a molecular ion which then fragments by two pathways involving either loss of carbon monoxide or ring cleavage by a retro-Diels-Alder (RDA) reaction (**scheme 1**).[11,12] The base peak is due to the molecular ion (**8**) and appears at *m/z* 146. The presence of substituents may divert the course of fragmentation from that shown in **scheme 1**.[12] Decomposition of fragment (**9**) occurs to give ions at *m/z* 90 and 89, which correspond to loss of CO and then H·. Analogous behaviour has been observed for benzofuran itself.[12]



SCHEME 1

1.2 Natural Distribution and Biological Activity.

The majority of naturally occurring chromones contain hydroxyl (at C-5 and C-7), methyl (at C-2) and/or phenyl groups.[13]

Two of the simplest naturally occurring chromones are euginin (**10**) and eugenitin (**11**), both of which are constituents of the wild clove *Eugenia Caryophyllata L. Thunb.*[14]

Peucinin (**12**),[13] found in the rhizome of *Imperatoria Ostruthium* is an example of a prenylated chromone. It has also been extracted from the heartwood of the South African tree, sneezewood (*Ptaeroxylon Obliquum* Thum. Radik) and from the Madagascan tree, *Cedrelopsia grevei*. An isomer of peucinin, heteropeucinin (**13**)[13] was also isolated from the same trees.

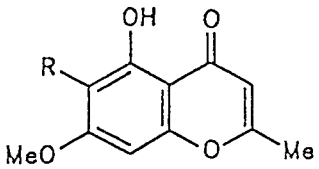
Leptorumol (**14**),[13,14] a constituent of a Japanese plant, *Leptorumohra miqueliana*, was the first natural chromone found to be unsubstituted at C-2. But, since its isolation in 1968, another chromone lacking a 2-methyl substituent has been identified in plants.[13]

Naturally occurring chromones, having long-chain 2-alkyl groups are rare, but Cook and Down[13] isolated 5,7-dihydroxy-6-methyl-2-nonacosylchromone (**15**) from two Australian plants, *Dienella revoluta* and *Stypandra grandis*.

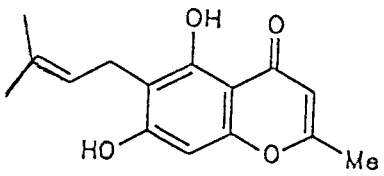
The Styrylchromone, Hormothamnione (**16**),[15] was isolated from the marine cryptophyte *Chrysophaem taylori* in small quantities. Hormothamnione (**16**) is a potent cytotoxin to

several human leukaemia cell lines *in vitro*, and it was the first naturally occurring styrylchromone to be isolated.

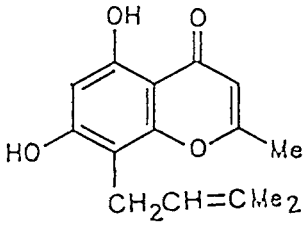
Baicalein (17),[16,17] a constituent of the dried radix of *Sculellaria baicalensis* Georg, was used in ancient medicine as a diuretic and its anti-allergic activity has, in fact, been demonstrated by Koda *et al.*



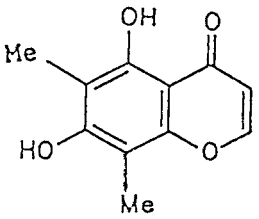
10(R = H)
11(R = Me)



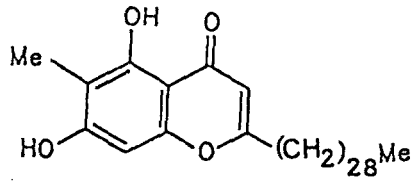
12



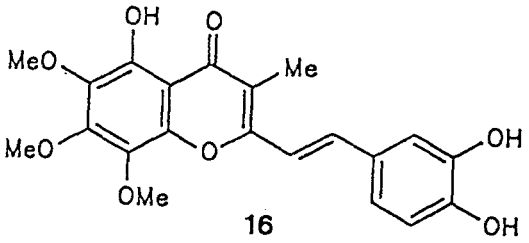
13



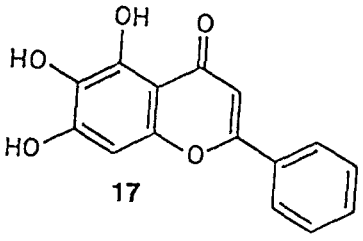
14


OH
O
Me
HO
O
$(CH_2)_{28}Me$

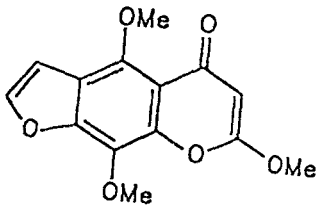
15


OH
O
MeO
Me
MeO
O
OH
OMe
OH

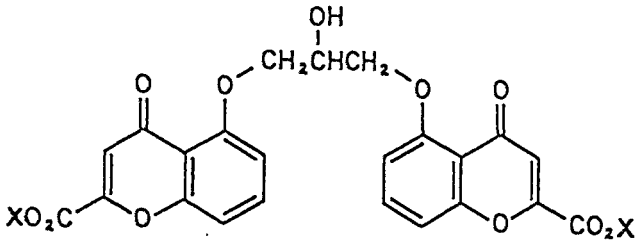
16


OH
O
HO
HO
O

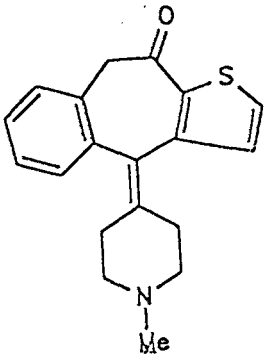
17


OMe
O
O
O
OMe
OMe

18



19a (X=H)
19b (X=Na)



20

Khellin (**18**),[18,19] a furochromone found in the fruits and seeds of *Ammi Visnaga* exhibits lipid-altering, anti-atherosclerotic activity and may thus provide a valuable therapy for reducing the risk of cardiovascular disease. Extracts of this plant have been used in asthma therapy, but unpleasant side effects, such as nausea and vomiting, have limited its clinical use. The anti-spasmodic action of khellin was later shown to be exhibited by other, synthetic chromones,[20] and further research led to the discovery of chromoglycic acid (**19a**), an anti-allergic drug which is used as the disodium salt (DSCG) (**19b**). This drug is, however, not

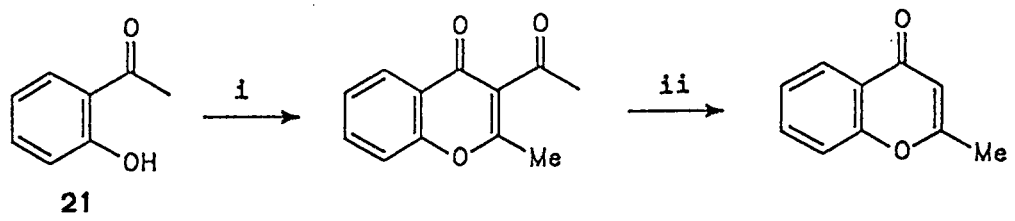
effective for all kinds of allergies, and it is inactive when taken orally. Many other anti-allergic compounds,[21] such as ketotifen (**20**), have subsequently been developed in the search for an orally active successor to cromoglycic acid with an improved clinical profile.

1.3 Synthesis of Chromones.

2-Hydroxyacetophenones and phenols are the two most common precursors of chromones. A side chain is built on the substrate and subsequent cyclization leads to the formation of chromones.[22]

The Kostaneki-Robinson[22] synthesis of chromones involves reaction of a 2-hydroxyacetophenone (**21**) with the anhydride and sodium salt of an aliphatic acid (**scheme 2**). Almost any group may be present in the aromatic ring (provided that it does not react under the experimental conditions) and chromones containing alkyl, acyl, alkoxy, halogeno, nitro and cyano groups, have been synthesized by this route. Methyl ethers (**22**) have been used in place of the free phenol in the chromone synthesis outlined in **scheme 3**.[24] Use of hydriodic acid after formation of the 1,3-diketone (**23**) cleaves the ether link and the chromone forms spontaneously.

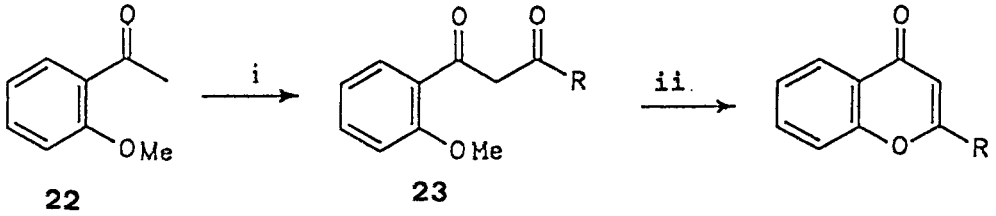
The Claisen condensation of an *o*-hydroxyacetophenone (**21**) with a carboxylic ester, *e.g.* diethyl oxalate, in the presence of a strong base, *e.g.* sodium ethoxide, is the most frequently used method of preparing chromones (**scheme 4**). Cyclization of the 1,3-diketone intermediate (**24**) to the desired chromone (**25**) is achieved by refluxing the intermediate with



21

SCHEME 2

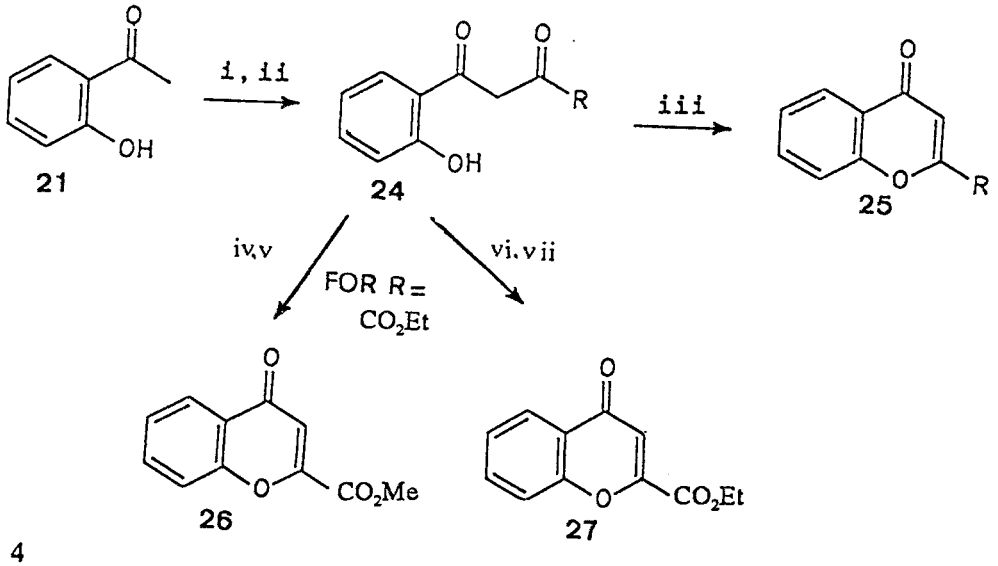
Reagents: i) Ac_2O, NaOH, NaOAc ii) aq. $NaHCO_3$



22 23

SCHEME 3

Reagents: i) NaOEt, $MeCO_2Et$ ii) HI



21 24 25 26 27

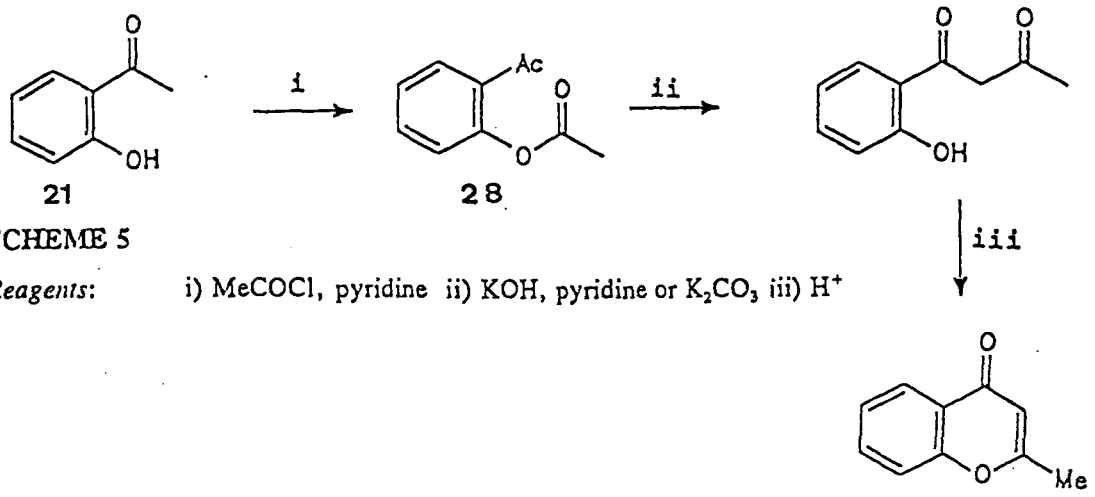
SCHEME 4

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

acid. This method was first described by Kostancki *et al.*[22] in 1901. The presence of substituents in the aromatic ring has minimal effect on the course of the reaction; both electron-releasing and electron-withdrawing substituents may be present. The use of diethyl oxalate offers an added advantage in that the intermediate 1,3-diketone (**24**) ($R=CO_2Et$) readily undergoes transesterification, thereby permitting the synthesis of various chromone-2-carboxylic esters, *e.g.* (**26**) and (**27**), from one starting material (**22**).

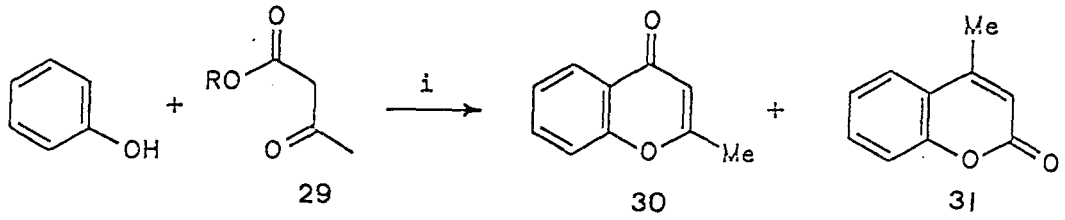
The 1,3-diketone intermediate encountered in the Claisen condensation (**scheme 4**) may also be prepared from the *o*-acyloxyacylbenzene (**28**), generated by *O*-acylation of a 2-hydroxyacetophenone (**21**). Treatment with potassium carbonate initiates an intramolecular rearrangement in which the acyl group migrates from oxygen to the carbon atom α to the carbonyl of the other acyl group by the Baker-Venkataraman rearrangement (**scheme 5**). The migrating group may be aliphatic or aromatic, and hence this approach is useful for the synthesis of flavones as well as chromones.[22]

In the Simonis reaction,[24,26] a ß-ketoester (**29**) is condensed with a phenol to give a chromone (**30**), coumarin (**31**), or a mixture of both (**scheme 6**). The reaction which leads to the coumarin (Pechmann condensation) was first described in 1883[26] and sulphuric acid is necessary as a condensing agent. On the other hand, chromone formation predominates with the use of phosphorous pentoxide, and when either the phenol contains a deactivating group, or when the ß-ketoester is α-substituted.[24] The reaction between a phenol and an unsaturated carboxylate ester, *e.g.* diethyl acetylenedicarboxylate (**32**) has been widely used for the synthesis of chromone-2-carboxylic acids (**33**) (**scheme 7**).[22]



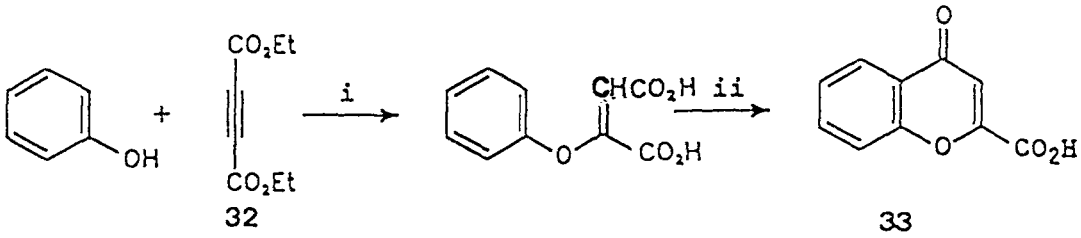
SCHEME 5

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



SCHEME 6

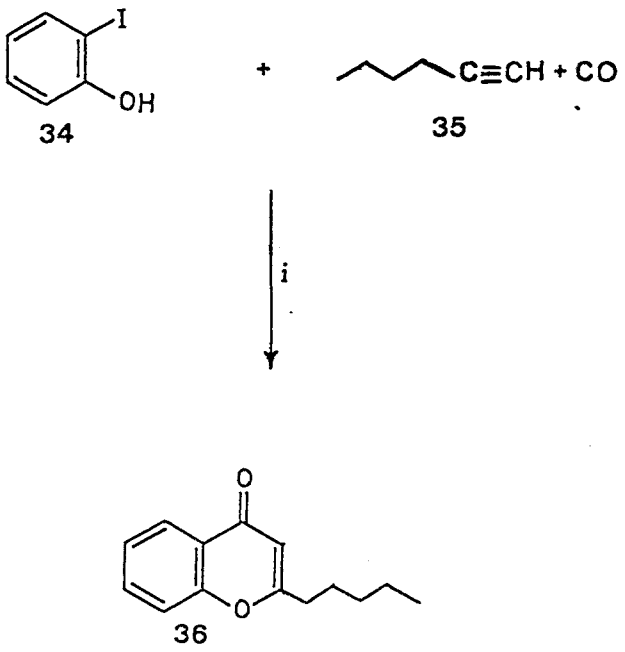
Reagents: i) H^+ (H_2SO_4 or P_2O_5)



SCHEME 7

Reagents: i) base ii) H_2SO_4

2-Substituted chromones (**36**) have recently been synthesized[27] in good yields from the reaction of *o*-iodophenols (**34**) with terminal acetylenes (**35**) under carbon monoxide in the presence of a secondary amine and catalytic amounts of palladium complex (**scheme 8**).



SCHEME 8

Reagents: i) Pd-cat, Et_2NH, 120°C, 2h

Chromones have also been prepared from preformed heterocycles such as furans, chroman-4-ones, chroman-4-ols, benzopyryllium salts and others.[22]

1.4 Reactivity of Chromone Derivatives.

1.4.1 Reactions with Nucleophiles.

Chromones and their derivatives undergo nucleophilic cleavage at the C-2 position with ease. Various kinds of nitrogen, oxygen and carbon nucleophiles have been used for the ring-opening reaction of the pyran-4-one ring. Only a few illustrative examples will be discussed here.

1.4.1.1 Reactions With Nitrogen Nucleophiles.

The pyran-4-one ring in chromone (**37**) is cleaved either by secondary or primary amines to afford enamines (**38**). The starting material may be recovered by treating these enamines with acid. Various amines have been studied, and the products characterized as the enamines which have also been obtained from 3-(2-hydroxyphenyl)-3-oxopropanal (**39**) (**scheme 9**).[28,29]

Treatment of chromone with hydroxylamine hydrochloride in ethanol yields, *via* pyran ring fission, a mixture of two isomeric isoxazoles (**40a**) and (**40b**), compound (**40a**) being the major product. However, under anhydrous conditions, chromone oxime (**41**) is formed (**scheme 10**).[31]

3-Nitrochromone undergoes base-catalysed Michael addition followed by intramolecular condensation to yield pyrrolyl, phenyl, pyridyl, pyrimidyl and pyrazolyl nitroaromatics.[30] These reactions proceed in fairly high yields.

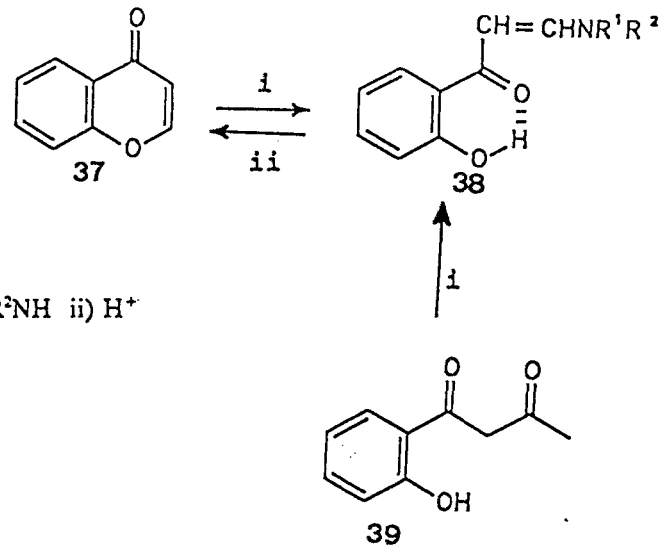
1.4.1.2 Reactions With Oxygen Nucleophiles.

Aqueous alkali causes cleavage of the pyran-4-one ring of chromones to give salts of the ß-diketone (**42**), which may recyclize to the starting reactant (chromone). Hence, the ß-diketone cannot be easily isolated. However, cleavage of the carbon-carbon bond of the ß-diketone takes place under more severe conditions to give mixtures of products, the distribution depending on the reaction conditions (**scheme 11**).[5,28]

Ring opening also occurs when ethyl 5,7-dibromo-6-hydroxychromone-2-carboxylate (**43**) is heated under reflux with aqueous sodium hydroxide to yield 4,6-dibromo-2,5-dihydroxyacetophenone (**44**) (**scheme 12**).[28] Sodium alkoxides also react with chromones; treatment of 2-methylchromone (**45**) with sodium ethoxide cleaves the pyran ring to give a dimeric product (**46**), which may be reversed to compound (**45**) on treatment with acid (**scheme 13**).[28]

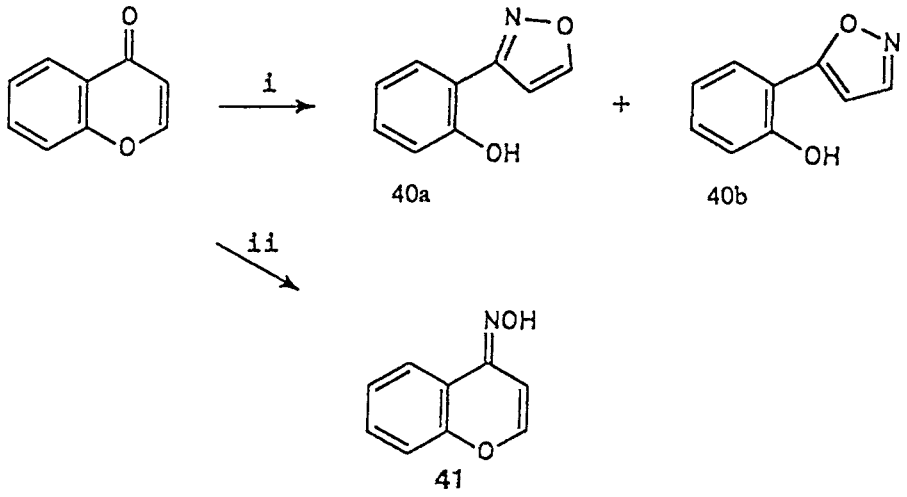
1.4.1.3 Reactions With Carbon Nucleophiles.

Reactions of chromones with carbon nucleophiles may lead to attack at the C-2 or C-4 positions, resulting in cleavage or transformation of the ring.[5] When a chloroform solution of 3-bromochromone (**47**) is reacted with a ß-keto ester or ß-diketone, *e.g.* acetylacetone, in the presence of 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) at room temperature cleavage of the pyran ring occurs to form trisubstituted furan (**48**) (**scheme 14**).[32] Grignard reagents add to the carbonyl group of the chromone, and on acidification, the adducts yield a stable benzopyrylium salt, *e.g.* (**49**) (**scheme 15**). On the



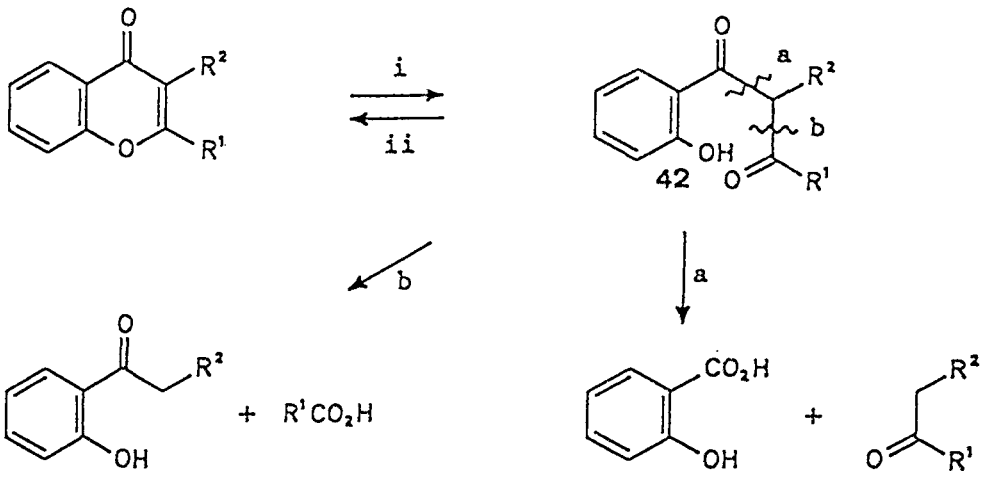
SCHEME 9

Reagents: i) R^1R^2NH ii) H^+



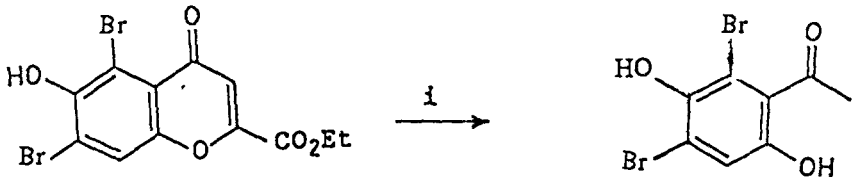
SCHEME 10

Reagents: i) $NH_2OH.HCl$, EtOH ii) anhyd. MeOH, HCl



SCHEME 11

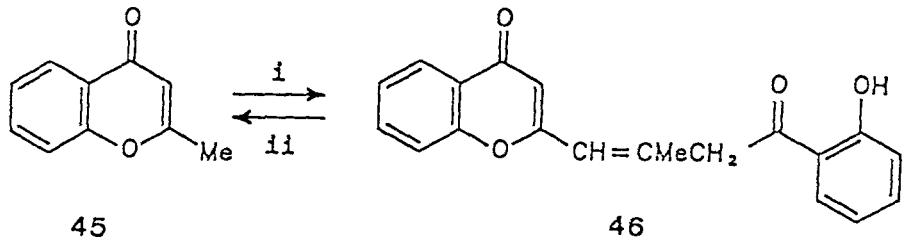
Reagents: i) OH^- ii) H^+



43 44

SCHEME 12

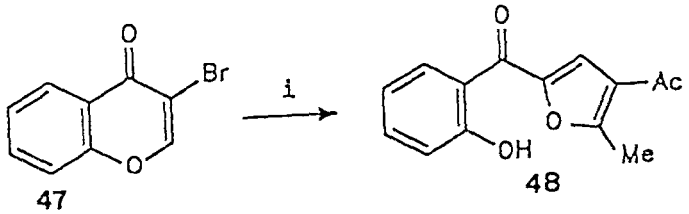
Reagents: i) aq. NaOH



45 46

SCHEME 13

Reagents: i) OEt^-, 18°C ii) H^+



47 48

SCHEME 14

Reagents: i) CH_2Ac_2, DBN, 18°C

other hand, reaction of isoflavone (**50**), with a Grignard reagent in the presence of copper (I) chloride, cleaves the pyran-4-one ring and leaves the carbonyl group unchanged (**scheme 16**).[28]

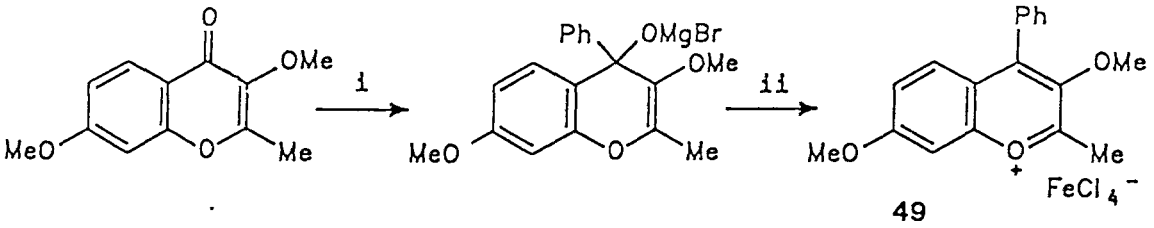
The reaction of 3-nitrochromone (**51**) with diazomethane, under mild conditions, yields cyclopropabenzopyranone (**52**), which reacts with either water or ethanol to give 3,4-dihydro-2-hydroxy-4-nitro-1-benzoxepinone (**54**). The use of 2-diazopropane gives compound (**53**), which reacts slowly with EtOH to give chromanone (**55**) (**scheme 17**).[33]

Lee *et al.*[34] recently reported reactions of 4-[(tert-butyldimethylsilyl)oxy]-1-benzopyrylium triflates (**56**) (prepared from chromones), in which, for example, compound (**56**) reacts with compound (**57**) to afford 4-siloxybenzopyran (**58**), while reaction with compound (**59**) gives the unexpected cyclopentane annulation product (**60**) (**scheme 18**).

1.4.2 Reactions With Electrophiles.

Chromones are relatively resistant to attack by electrophiles,[5] since electrophilic reagents are strongly acidic or produce strong acids during reaction, and hence, are likely to protonate the pyran-4-one ring and thus inhibit further attack by the electrophile.[28]

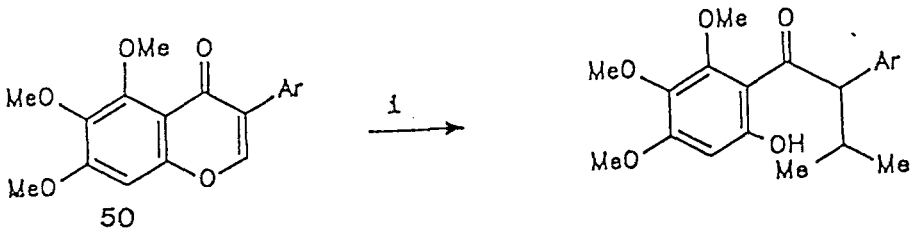
Nitration of chromones to afford 6-nitro derivatives may be achieved under forcing conditions.[28] However, when chromone is warmed with bromine in carbon disulphide, an adduct is obtained which when treated with secondary amine forms 3-bromochromone.[28,35] The presence of an electron-releasing substituent at C-2 or C-3 activates the adjacent empty



49

SCHEME 15

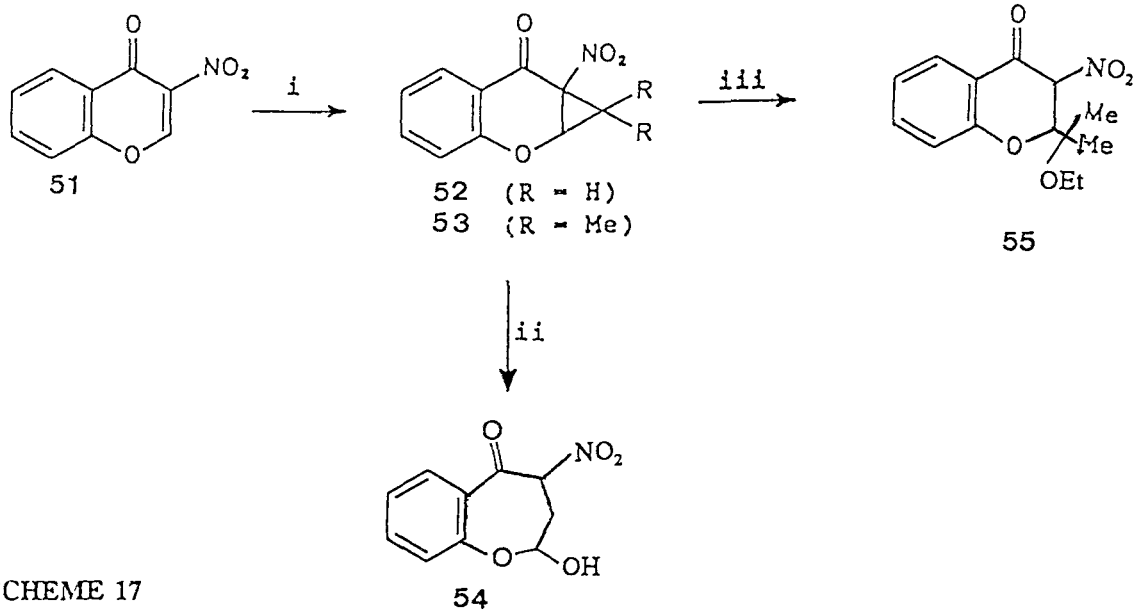
Reagents: i) PhMgBr ii) HCL, $FeCL_3$



50

SCHEME 16

Reagents: i) MeMgI, $CuCl_2$



51

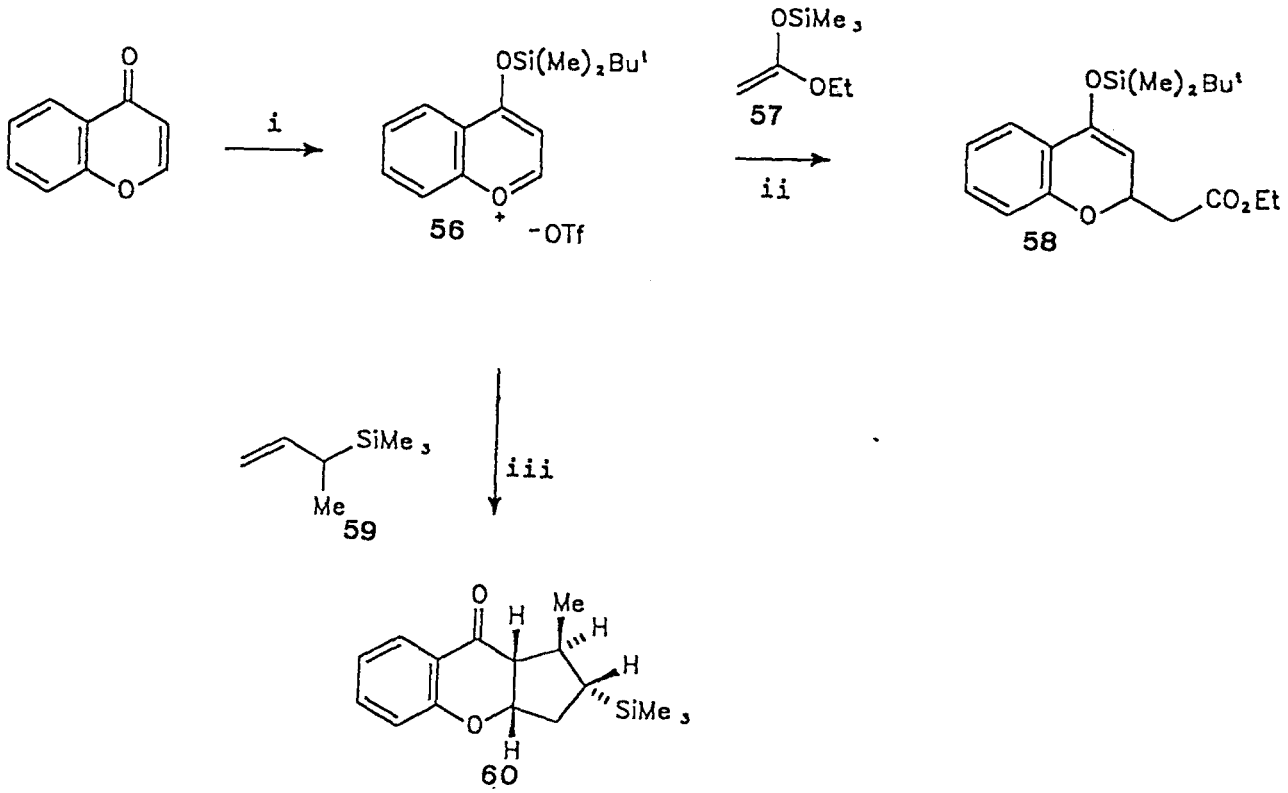
52 (R = H)
53 (R = Me)

55

54

SCHEME 17

Reagents: i) R_2CN_2 ii) H_2O or ROH iii) ROH



SCHEME 18

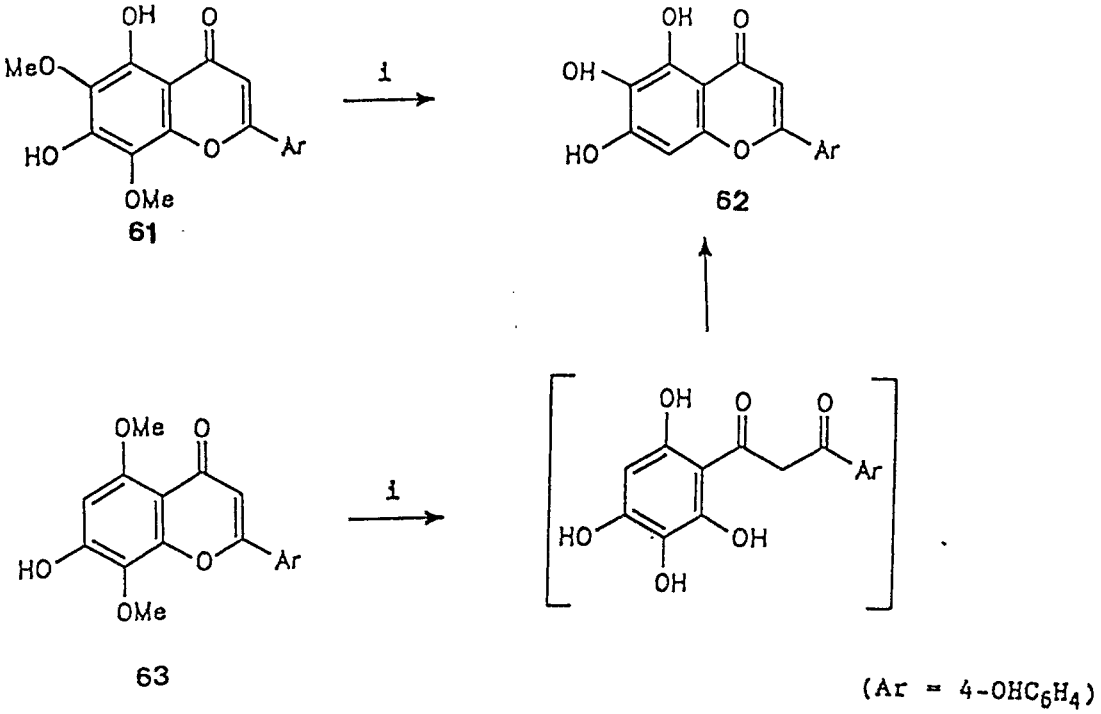
Reagents: i) But(Me)$_2$SiOTf, 80°C, 1h ii) 2,6-lutidine, CH_2Cl_2, RT, 1h
iii) 2,6-lutidine, CH_2Cl_2, RT, 4.5h ; Na_2CO_3

position (*e.g.*, 3-hydroxychromone can be brominated, nitrated and aminated at C-2).[28] Chromones, flavones, isoflavones and xanthones may undergo the Wessely-Mosser rearrangement which occurs when a methoxylated or hydroxylated derivative is heated with hydriodic acid (**scheme 19**). This rearrangement may be useful, *e.g.* the formation of flavone sculellarein (**62**) is not only achieved by simple demethylation of the 6-methyl ether (**61**), but also by demethylation and rearrangement of the dimethyl ether (**63**).[28]

1.4.3 Other Reactions of Chromones.

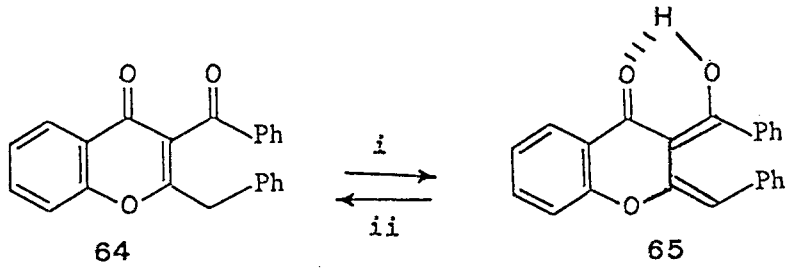
Some substituted chromones undergo a photochromic reaction, *viz.*, the conversion of 3-acyl-2-alkylchromone (**64**) to the bright orange enol (**65**) on irradiation. The colourless chromone may be recovered photochemically or by solvent-mediated proton transfer (**scheme 20**).[5]

Ring opening of the pyran ring may also be achieved by oxidizing chromone with permanganate or dichromate. In such cases, salicylic acid is formed. Catalytic reduction of chromones has been shown to yield several products.[28]



SCHEME 19

Reagents: i) HI



SCHEME 20

Reagents: i) hν ii) 310-410nm

1.5 Aims of the present investigation

This research project was concerned with the synthesis and spectroscopic analysis of chromone derivatives. Specific aims have included:

1. Synthesis of chromone-2-carboxylic acid and analogues.
2. Determination of the dissociation constants (pKa) for chromone-2-carboxylic acids by potentiometric titration.
3. Synthesis and ring-opening of chromone-2-carboxamides to acrylamide derivatives.
4. Mass spectrometric studies of acrylamide derivatives.
5. Dynamic nuclear magnetic resonance studies of rotational isomerism in the acrylamide derivatives.

2. DISCUSSION.

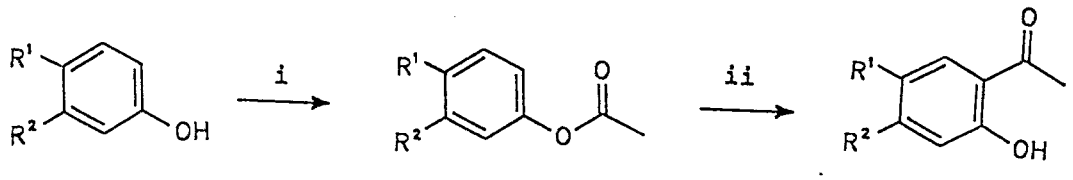
2.1 Synthesis of Chromone Derivatives.

A range of substituted chromone-2-carboxylic acids was prepared using *o*-hydroxyacetophenones, *o*-hydroxypropiophenone and chromone-2-carboxylic acids as precursors. The chromone-2-carboxylic acids were required for studies of substituents effects on acidity and also as intermediates for the preparation of chromone-2-carboxamides. Acrylamide derivatives, required for conformational analysis, were prepared, in turn, from the corresponding chromone-2-carboxamides.

2.1.1 Preparation of *o*-Hydroxyacetophenones.

The approach to the *o*-hydroxyacetophenones is outlined in Schemes 21 and 22. The 4-chloro- and 5-chloro-2-hydroxyacetophenones, (**70**) and (**71**) respectively, were prepared *via* the Fries rearrangement[36] of the corresponding phenyl acetates (**68**) and (**69**) which, in turn, were obtained by acetylation of the appropriate phenols (scheme 21), as described by Bryan *et al.*[37] The acetates were heated at high temperatures (*ca.* 175°C) to direct the course of the reaction to the *o*-hydroxyacetophenones rather than the *p*-analogues.[38] 2-Chlorophenyl acetate (**73**), however, did not undergo Fries rearrangement as described in the literature,[39,40] the *major* product being 3-chloro-4-hydroxyacetophenone (**75**) instead of the desired 3-chloro-2-hydroxyacetophenone (**74**) which could only be isolated as the *minor* product, in 9% yield (scheme 22).

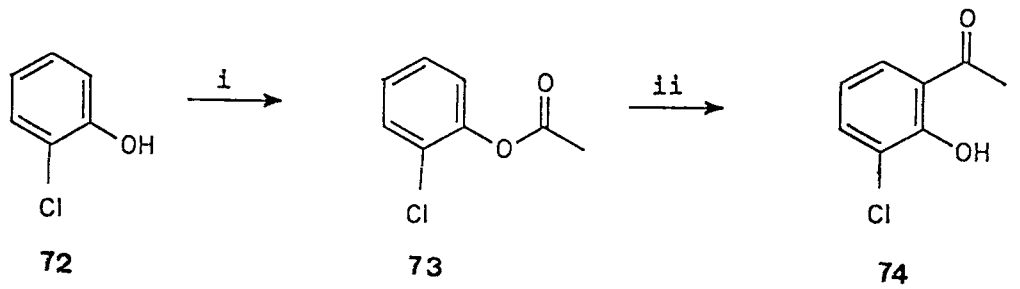
Attempts to separate the mixture of isomers by flash chromatography led to an even greater loss of required product (**74**). No other method could be found in the literature to improve the yield.



R^1	R^2			
H	Cl	**66**	**68**	**70**
Cl	H	**67**	**69**	**71**

SCHEME 21

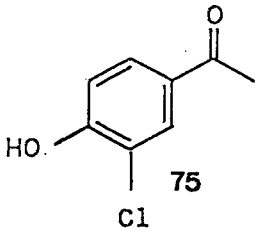
Reagents: i) aq. $NaOH\text{-}Ac_2O$, O°C ii) $AlCl_3$, Δ



72 **73** **74**

SCHEME 22

Reagents: i) aq. $NaOH\text{-}Ac_2O$, O°C ii) $AlCl_3$, Δ



75

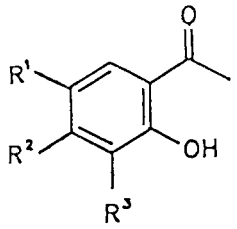
2.1.2 Preparation Of Chromone-2-carboxylic Acids.

Chromone-2-carboxylic acids (**87-91**) were prepared, as indicated in scheme 23. Claisen acylation of the *o*-hydroxyacetophenones (**70**), (**71**), (**74**), (**76**) and (**77**) with diethyl oxalate in the presence of sodium ethoxide, followed by cyclization of the intermediates and subsequent hydrolysis, as described by Fitton and Smalley[41] and Bryan *et al.*[37] afforded the acids (**87-91**). In general, two types of reaction intermediate were detected by the ^{1}H NMR spectroscopy, the diketones (**78**), (**79**), (**81**), (**83**) and (**85**) and the 2-hydroxychromanones (**80**), (**82**), (**84**) and (**86**). The presence of a doublet or doublet of doublets between *ca.* 2.95 and 3.40 ppm can be assigned to the C-2 methylene protons of the 2-hydroxychromanone intermediates, while the methylene protons of the diketone intermediates resonate at lower field at *ca.* 7.0 ppm. In the preparation of chromone-2-carboxylic acid (**87**), only the diketone intermediate (**78**) was isolated. However, for chromone-2-carboxylic acids (**88**)-(**91**), mixtures of the corresponding diketone and hydroxychromanone intermediates were obtained and these mixtures were used directly without further purification for the preparation of the required acids.

The chloro-substituted chromone-2-carboxylic acids (**88-90**) were isolated along with small proportions of their ethyl esters (*ca.* 10-14%) and were purified by extraction. Attempts to optimise the yields of 8-chlorochromone-2-carboxylic acid (**90**) by using a mixture of 3-chloro-2-hydroxyacetophenone (**74**) and 3-chloro-4-hydroxyacetophenone (**75**) as the starting material (crude products of the Fries rearrangement of 2-chlorophenylacetate (**73**)) instead of separating them, gave an extremely complex mixture. In all cases, the yields were calculated on the basis of the *o*-hydroxyacetophenone used as starting material.

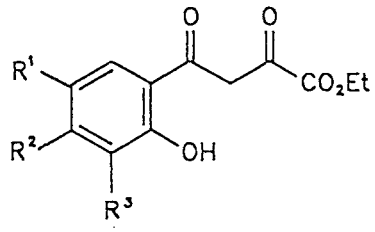
3-Methylchromone-2-carboxylic acid (**94**) was prepared by acid hydrolysis of its ethyl ester (**93**). The ethyl ester (**93**) was, in turn, prepared by treating *o*-hydroxypropiophenone (**92**) and diethyl oxalate with sodium hydride (scheme 24).[42] 6-Nitrochromone-2-carboxylic acid (**95**) was synthesized by nitration of chromone-2-carboxylic acid (**87**) (scheme 25);[43] in this case, chromone-2-carboxylic acid (**87**) was dissolved, with some difficulty, in concentrated nitric acid.

3-Chlorochromone-2-carboxylic acid (**99**) was prepared by acid hydrolysis of its methyl ester (**97**), which in turn, was prepared by treatment of methyl chromone-2-carboxylate (**96**) with sulfuryl chloride and benzoyl chloride using a method described by Bevan and Ellis (Scheme 26).[44] Compound (**96**) was prepared by esterification of chromone-2-carboxylic acid (**87**) with MeOH. In some cases, mixtures of the required mono-chlorochromone (**97**) and the 2,3-dichlorochromanone (**98**) were obtained. Treatment of this mixture with hot pyridine, following a literature procedure, afforded the ester (**97**) and the acid (**99**).[43] The ester (**97**) was converted into its corresponding acid (**99**) by acid hydrolysis.

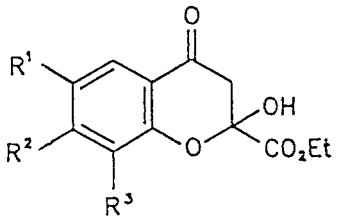


R^1	H	H	Cl	H	OMe
R^2	H	Cl	H	H	H
R^3	H	H	H	Cl	H

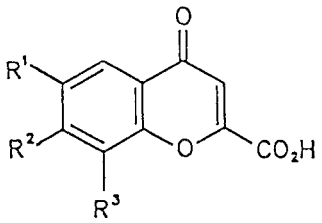
i



+



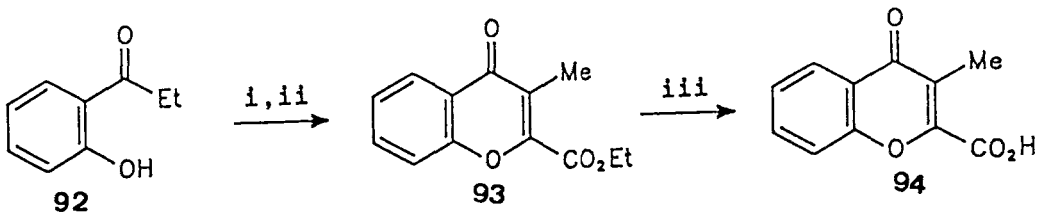
ii



76	70	71	74	77
78	79	81	83	85
-	80	82	84	86
87	88	89	90	91

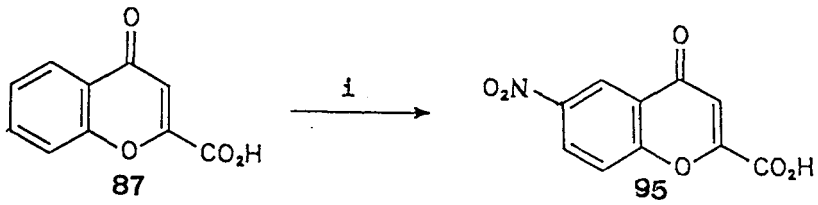
SCHEME 23

Reagents: i) NaOEt-EtOH, $(CO_2Et)_2$ ii) HCl-AcOH (1:1), Δ



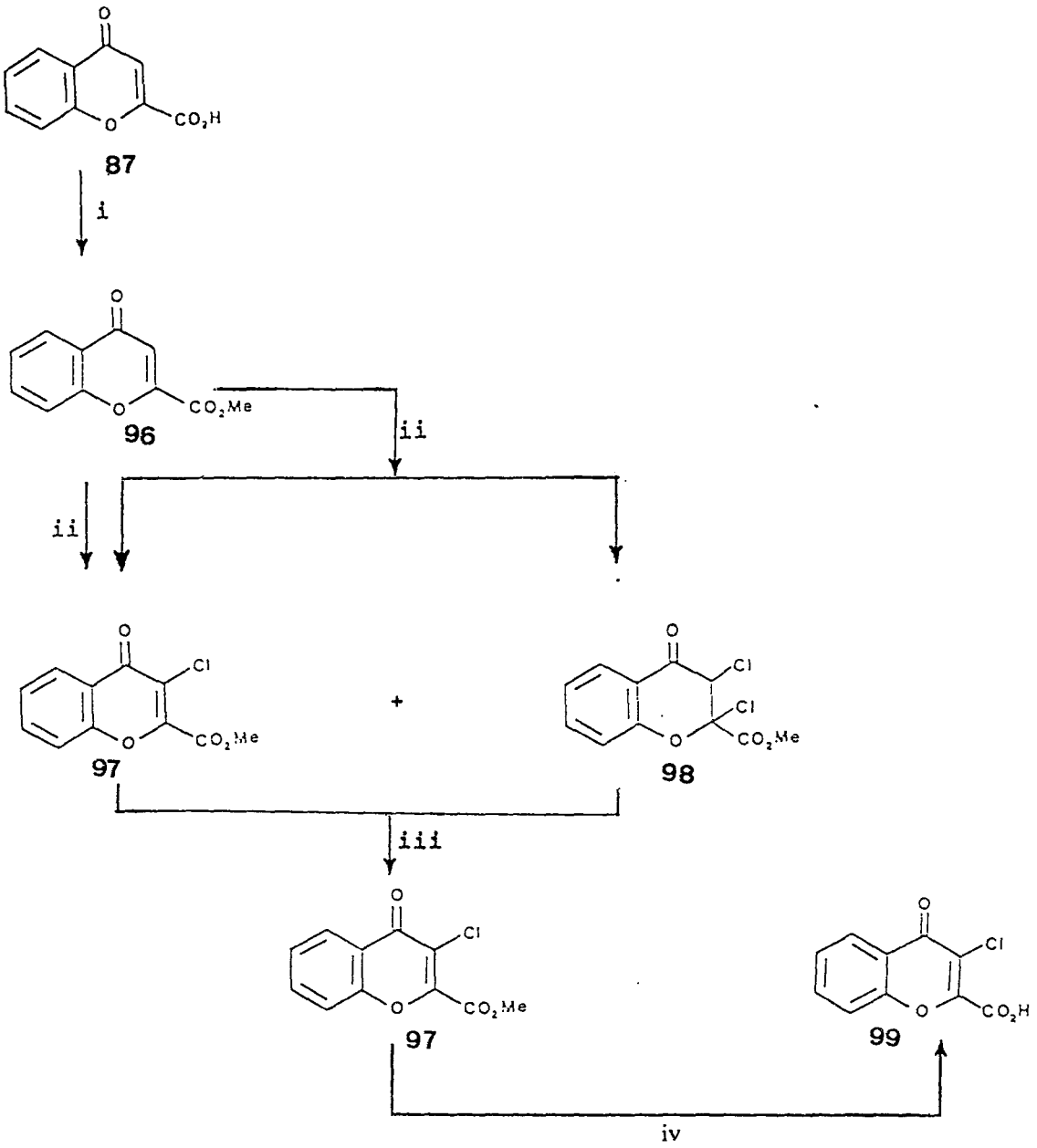
SCHEME 24

Reagents: i) NaH, $(CO_2Et)_2$, Et_2O ii) H^+, Δ iii) H^+, Δ



SCHEME 25

Reagents: i) H_2SO_4, HNO_3, Δ



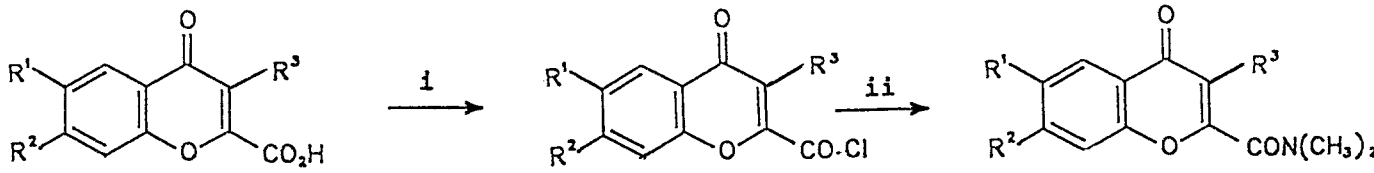
SCHEME 26

Reagents: i) MeOH, H_2SO_4, Δ ii) SO_2Cl_2, $(PhCO_2)_2$ iii) Pyridine, Δ iv) AcOH-HCl, Δ.

2.1.3 Preparation of Chromone-2-carboxamides.

The chromone-2-carboxamides (**108-114**) were prepared from the corresponding chromone-2-carbonyl chlorides (**100-106**), which, in turn, were prepared from their respective chromone-2-carboxylic acids (**87-89**), (**91**), (**94**), (**95**) and (**99**) as outlined in scheme 27. Treatment of the acids with thionyl chloride and *N,N*-dimethylformamide in 1,2-dichloroethane, using a method described by Ellis *et al.*,[46] gave the acid chlorides which were then reacted with dimethylammonium chloride (**107**) in pyridine, at *ca.* 0°C, to afford the corresponding chromone-2-carboxamides (**108-114**) by a method described by Davidson and Kaye.[47]

In all cases, the crude chromone-2-carboxamides were purified by flash chromatography,[48] using ethyl acetate or a mixture of ethyl acetate and ethanol as eluent. The chromatographed products were further purified by recrystallization.



R^1	R^2	R^3			
H	H	H	**87**	**100**	**108**
H	Cl	H	**88**	**101**	**109**
Cl	H	H	**89**	**102**	**110**
OMe	H	H	**91**	**103**	**111**
H	H	Me	**94**	**104**	**112**
NO_2	H	H	**95**	**105**	**113**
H	H	Cl	**99**	**106**	**114**

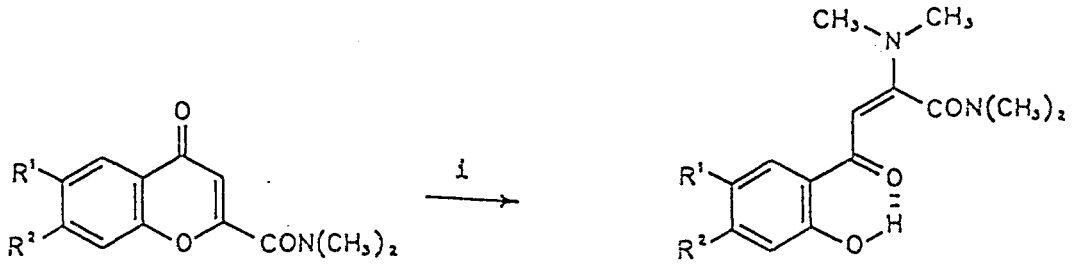
SCHEME 27

Reagents: i) $SOCl_2$-DMF-$ClCH_2CH_2Cl$, Δ ii) Me_2NH_2Cl (**107**)-Pyridine, O°C

2.1.4 Ring-opening of Chromone-2-carboxamides.

The acrylamides (**115-119**), required for a dynamic NMR study of rotational isomerism, were prepared from their respective chromone-2-carboxamides (**108-111**) and (**113**) by treatment with 33% w/w ethanolic dimethylamine (scheme 28).[49]

The crude acrylamides were purified by flash chromatography and subsequent recrystallization. Attempts to prepare the acrylamides of the chromone-2-carboxamides (**112**) and (**114**) resulted in isolation of material which, in each case, was shown, by ^1H nmr spectroscopy, to be the starting compound.



R^1	R^2		
H	H	108	115
H	Cl	109	116
Cl	H	110	117
MeO	H	111	118
NO_2	H	113	119

SCHEME 28

Reagents: i) 33% w/w ethanolic Me_2NH-EtOH

2.2 Acid Dissociation (pK_a) Studies of Chromone-2-carboxylic Acids.

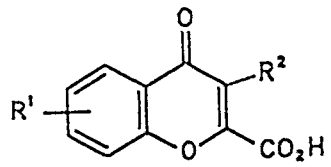
The activity of anti-allergic compounds, such as disodium cromoglycate (**19b**), may be related to acidity, but no satisfactory correlations have been found.[50] The pK_a of chromone-2-carboxylic acid (**87**), as determined by conductimetry at 25°C, has been found to be 2.96[51] but has a reported value of 2.8 when determined potentiometrically in 50% ethanol.[52] In a preliminary study, Davidson[53] has recently determined the pK_a of chromone-2-carboxylic acid (**87**) to be 2.69 by potentiometric titration of 0.01**M** solutions in aqueous ethanol (50% v/v).

In the present study, the pK_a values (Table 1) for the chromone-2-carboxylic acids (**87-91**), (**94**), (**95**) and (**99**) were determined in order to explore substituent effects on acidity. The chloro-substituted chromone-2-carboxylic acids (**88-90**) and (**99**) were chosen to illustrate the effect of changing the substituent position. The 6-substituted chromone-2-carboxylic acids (**89**), (**91**) and (**95**) and the 3-substituted acids (**94**) and (**99**) were chosen to study substituent electronic effects.

The pK_a values for the chromone-2-carboxylic acids listed in Table 1 were obtained by potentiometric titration of 0.01**M** solution in aqueous ethanol (50% v/v). In almost all cases, the 0.01**M**-aqueous ethanolic solutions were titrated with 0.01**M**-aqueous sodium hydroxide, which is recommended in the literature[54] because activity effects at this concentration are usually very small.

In acids, provided they are not too weak, the pK_a is equivalent to the pH at half-equivalence point.[55] In the present study, plots of first and second derivatives (*i.e.* $\Delta pH/\Delta V$ and

Table 1. Dissociation Constants (pK_a) Of Chromone-2-carboxylic Acids.



compd.	R^1	R^2	pK_a[a]
87	H	H	2.65[b] ± 0.005
88	7-Cl	H	2.66 ± 0.005
89	6-Cl	H	2.65 ± 0.008
90	8-Cl	H	2.65 ± 0.022
91	6-MeO	H	2.90[c] ± 0.009
94	H	Me	2.71 ± 0.009
95	6-NO_2	H	2.64 ± 0.009
99	H	Cl	2.48 ± 0.014

[a] Mean of 3 results, obtained by potentiometric titration of 0.01**M** solution in aqueous EtOH (50% v/v), followed by the standard deviation.

[b] Lit.[51-53] 2.96 (by conductimetry at 25 °C); 2.8 (by potentiometry in 50% aqueous EtOH); and 2.69 [by potentiometric titration of 0.01**M** solution in aqueous EtOH (50% v/v)].

[c] Obtained by potentiometric titration of 0.005**M** solution in aqueous EtOH (50% v/v).

$\Delta^2pH/\Delta V^2$, respectively) of the titration curve were used to determine the equivalence point. The pK_a at half-equivalence point was then obtained from a plot of pH versus volume.[56] Figure 3 illustrates the plot obtained for compound (**99**). In all cases, the potentiometric determinations were replicated.

In an earlier study in these laboratories, Davidson[53] determined pK_a values for several 7-

substituted chromone-2-carboxylic acids, *viz.*, the 7-MeO, 7-NO_2, 7-F, 7-Cl and 7-Br derivatives, and found that the pK_a values varied in the order :-

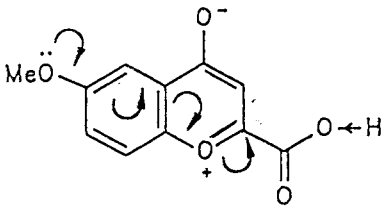
$$7\text{-MeO} > H > 7\text{-Cl, 7-Br, 7-F} > 7\text{-}NO_2$$

This gradation follows the pK_a trend for *para*-substituted benzoic acids.[57] In the present study, the 6-substituted acids (**89**), (**91**) and (**95**) showed a similar trend to that reported for the pK_a of *meta*-substituted benzoic acids[57] *i.e.*

$$MeO > Cl > NO_2,$$

although it should be noted that the pK_a difference for the 6-Cl and 6-NO_2 analogues is comparable to the standard deviation. The higher pK_a value of the 6-methoxy analogue (**91**) [compared to the parent compound (**87**)] may be explained in terms of an electron-releasing resonance effect which increases electron density at the C-2 position (fig. 1a). Similar effects presumably account for the relative enhancement observed[53] for the pKa of the 7-methoxy analogue (fig. 1b).

(a)



(b)

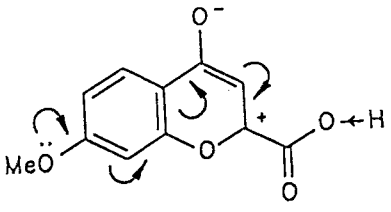
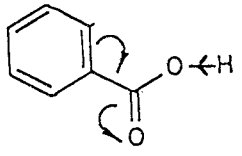


Figure 1:

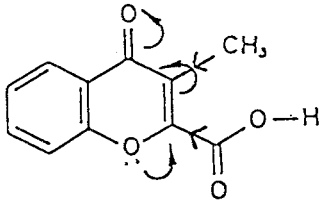
Introduction of a chloro substituent at positions C-6, C-7 or C-8 does not appear to affect the

pK_a significantly. However, introduction of a chloro substituent at the C-3 position results in a marked decrease in the pK_a value. This may be rationalized in terms of the electron-withdrawing effect of chlorine (thus decreasing the electron density at the C-2 position) and also possibly by the steric effect exerted by the bulky chlorine atom forcing the carbonyl group out of the plane of the ring and, hence, inhibiting acid-weakening conjugative interaction with the chromone nucleus.

The 3-methyl analogue (94) has a higher pK_a value (2.71) than the parent compound (87), and this is attributed to the electron releasing effect of the methyl group. The 3-methyl analogue (94) may have been expected to have a lower pK_a value than the parent compound (87) since *o*-toluic acid is a stronger acid than benzoic acid.[57] This may be rationalized in terms of the acid-weakening π-delocalisation in the case of *o*-toluic acid being less effective than in benzoic acid (Fig. 2a) since, in the former case, the carboxyl group is forced out of the aromatic plane. In chromone-2-carboxylic acid π-delocalisation towards the chromone carbonyl group is very effective and delocalisation towards the carboxyl carbonyl (as in fig. 2a) is presumably inhibited. Introduction of the 3-Me group will, undoubtedly, force the carboxyl group out of the aromatic plane but, more importantly, the electron releasing inductive effect (fig 2b) will increase electron density at C-2 and hence reduce acidity. All estimated experimental errors are within the typical scale of 0.006 reported for the potentiometric determinations.[58]



(a)



(b)

Figure 2:

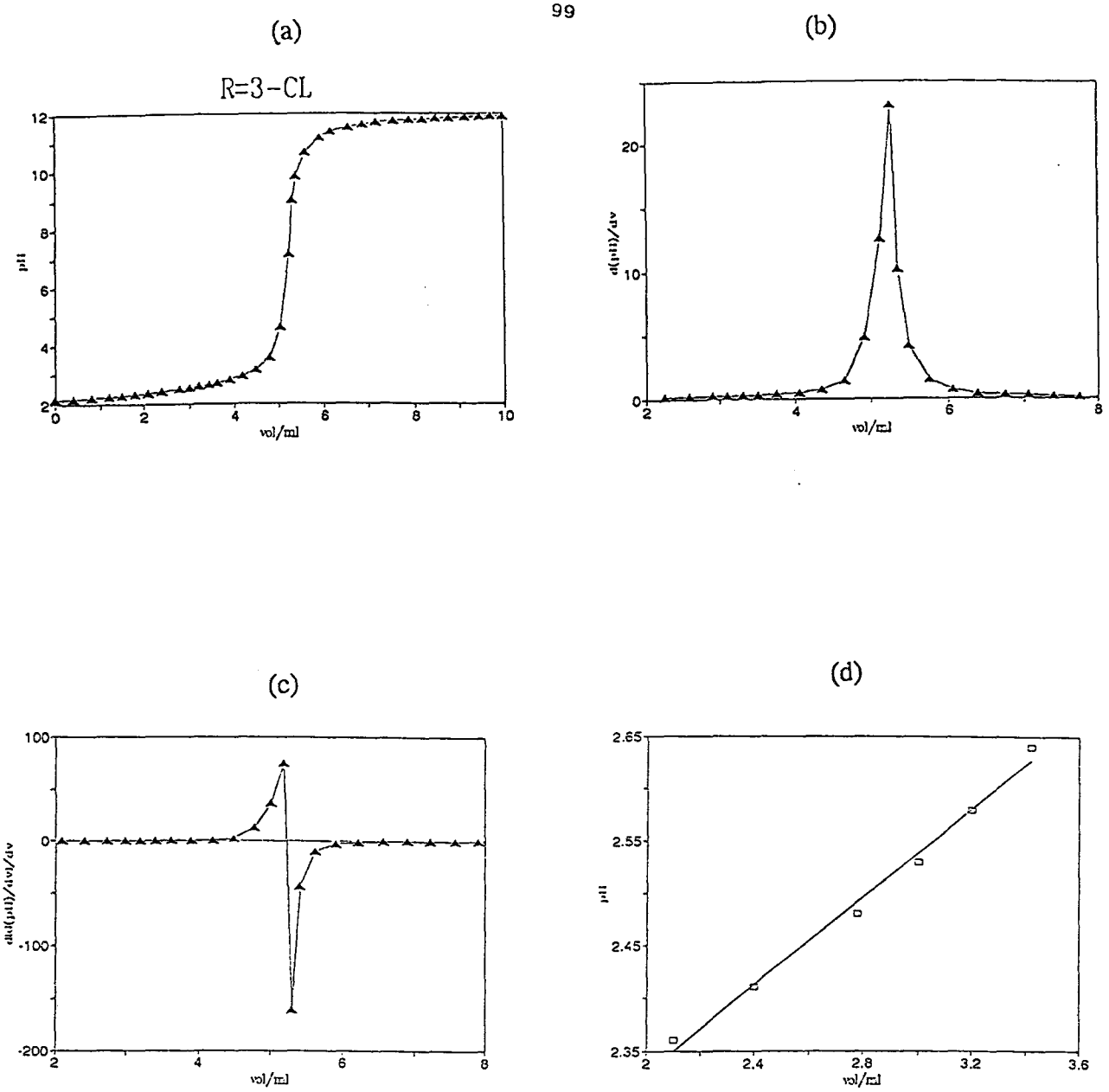


Figure 3: Curves for the titration of 0.01M - 3-chlorochromone-2-carboxylic acid (99) against 0.01M - NaOH

(a) Titration curve;

(b) Plot of the first derivative ($\Delta pH/\Delta V$) vs. volume;

(c) Plot of the second derivative ($\Delta^2 pH/\Delta V^2$) vs. volume;

(d) Plot of pH vs. volume

2.3 Spectroscopic studies of Chromone derivatives

2.3.1 MS fragmentation analysis

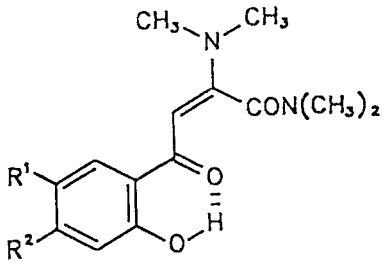
Low resolution mass spectra of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**115**) and analogues (**116-119**) were obtained from solid probe experiments as a further means of confirming their identities. One of the most intense peaks (*m/z* 72) was found to be common to all spectra irrespective of the substituents, whilst many of the peaks were found to be common to all the spectra when the differences in atomic masses of the substituent were taken into account as shown in Table 2 below.

The fragmentation pathways for the parent compound (**115**) shown in Scheme 29 provide a tentative rationalization of the mass spectrometric data. Loss of the dimethylamine radical to form fragment (I) (*m/z* 218), followed by loss of carbon monoxide, may be responsible for the base peak cation (II) (*m/z* 190/100%). On the other hand, cation (II) may also be formed directly by cleavage at (a) from the molecular ion (*m/z* 262). Fragment (I) may also lose a hydrogen radical to form fragment (VII) (*m/z* 217) which then loses carbon monoxide to form fragment (VIII) (*m/z* 189). Cleavage of the enamine radical at (b) from the molecular ion forms the acylium cation (IV) (*m/z* 121) which then loses carbon monoxide to afford fragment (V), $C_6H_5O^+$ (*m/z* 93), which in turn loses a further molecule of carbon monoxide, probably *via* ring contraction, to form a cyclopentadiene cation (VI) (*m/z* 65). Loss of a benzoyl radical is responsible for the $(CH_3)_2N\text{-}C\equiv O^+$ ion (III) (*m/z* 72).

The proposed fragmentations are supported by high resolution analysis of selected fragments and metastable peak analysis as indicated in Scheme 29. In the case of the nitro analogue **119**, the molecular formulae of the peaks at *m/z* 263, 262, 235 and 234 (corresponding to

fragments 218, 217, 190 and 189 in the parent compound **115**) were also confirmed by high resolution analysis, and metastable peak analysis supports the following fragmentations: 307→262, 307→235, 262→234 and 263→235. In the case of the methoxy analogue **118**, the base peak was observed at *m/z* 83 which could correspond to a formula $C_4H_3O_2^+$. Future investigation is expected to confirm this formulation and clarify other aspects of the mass fragmentation pathways of these substituted acrylamides.

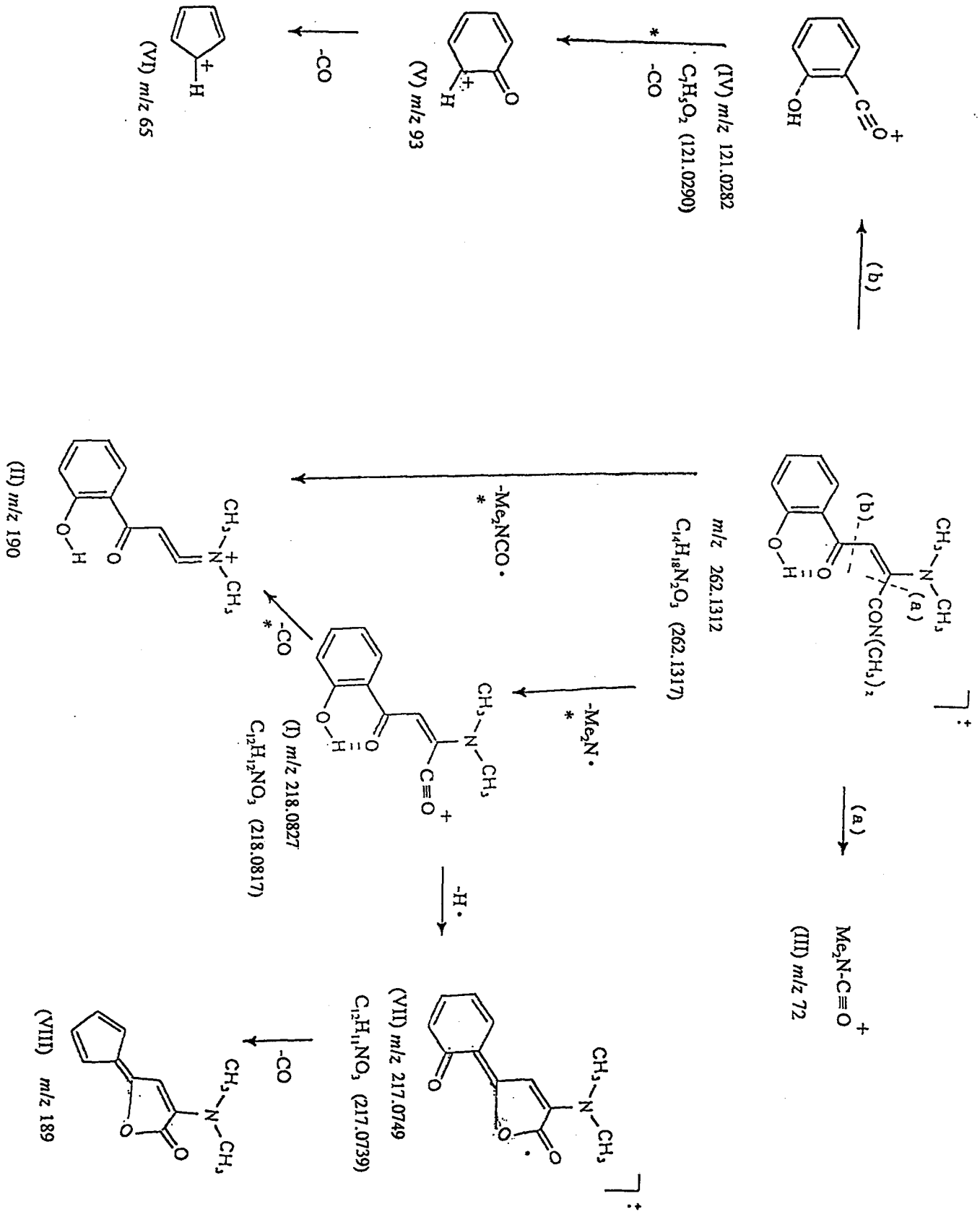
Table 2: **Selected peaks from mass spectra of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (115) and analogues (116-119)**



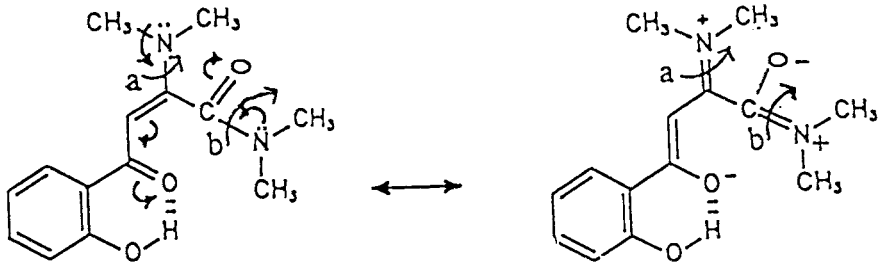
Compound	R^1	R^2	Nominal mass peaks (*m/z*)								
115	H	H	262	218	217	190	189	121	93	72	65
116	H	Cl	296	252	251	224	223	155	127	72	99
117	Cl	H	296	252	251	224	223	155	127	72	99
118	MeO	H	292	248	247	220	219	151	123	72	95
119	NO_2	H	307	263	262	235	234	166	138	72	110

SCHEME 29: MS fragmentation patterns for 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (115). The accurate masses (*m/z*) determined for individual ions are followed, in parentheses, by calculated formula masses.

* = confirmed by metastable peak analysis.



2.3.2 DNMR Analysis of Rotational Isomerism in Substituted Acrylamides



115

Figure 4:

In an earlier work,[49] it has been found from IR and NMR spectroscopic data that the solid state conformation of the parent acrylamide **115** is maintained in chloroform solution. The crystal structure indicates the *E*-geometry of the double bond and intramolecular hydrogen bonding between the phenolic hydroxyl and the *syn*-oriented ketone carbonyl groups. The co-planarity of the entire molecule with the exception of the orthogonal carboxamide moeity, results in significant delocalisation of the dimethylamino nitrogen lone pair (**Fig.4**). The overall is the presence of a partial double bond which restricts rotation "a"; similar restriction of rotation "b" arises from nitrogen lone pair delocalisation in the carboxamide group (**Fig.4**). Hence the ^{1}H NMR spectra (**Fig.5**) show splitting of the *N*-methyl signals. In this project, we examined rotation of these NMe_2 groups in the acrylamides (**115-119**) using Dynamic NMR (DNMR) techniques.

The acrylamides (**115-119**) were prepared from the corresponding chromone-2-carboxamides (**108-111**) and (**113**), as described previously in section 2.1.4. The low field (C-NMe_2) and highfield *N*-methyl (CO-NMe_2) signals were assigned from recently published work.[49] The rotational energy barriers ($\Delta G^{\ddagger}$) for the C-NMe_2 groups of the acrylamides were calculated from the coalescence temperature (T_c) and the frequency separation at coalescence ($\Delta\nu_c$) using

equation 1.[59] The coalescence temperatures (T_c) were obtained from variable temperature spectra (eg. **Fig.5**) and the frequency differences at coalescence ($\Delta\nu_c$) were obtained by extrapolation of linear plots of the frequency separation ($\Delta\nu$) against temperature (T), as described by Lai and Chen.[60]

In the case of the high field signals ($CO\text{-}NMe_2$), no coalescence was observed up to 423K. However, with increasing temperature, the *N*-methyl signals broaden and move closer together. The isomerisation rate constant was calculated by use of equation 2. Equation 3 was then used to calculate ΔG^* at 423K.

$$\Delta G^* = R\,T_c\,(22.96 + \ln\frac{T_c}{\Delta\nu_c}) \quad (1)$$

$$k = \pi\,[\tfrac{1}{2}(\delta_0^2 - \delta_0^2)]^{\frac{1}{2}} \quad (2)$$

$$\Delta G^* = 2.303\,R\,T\,(\log\frac{k_B T}{h} - \log k^1) \quad (3)$$

Where ΔG^* = rotational free energy

R = gas constant

T_c = coalescence temperature (K)

$\Delta\nu_c$ = frequency separation at coalescence (Hz)

k = isomerisation rate constant

δ_0 = maximum separation between split signals

δ_0 = separation at temperature T (Hz)

$logk^1$ = "notional" value at T = 423K

k_B = Boltzman constant

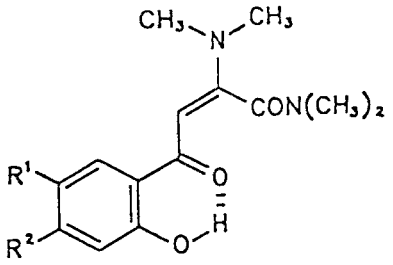
h = Planck's constant

The data from the dynamic NMR study of acrylamides (**115-119**) and rotational energy barriers (ΔG^*) are summarized in Table 3 below.

Within the limits of experimental error, the rotational energy barriers (ΔG^*) are similar for all the acrylamides examined, indicating that the substituents have little effect on the C-NMe_2 rotational barrier. This is perhaps not surprising considering the distance of separation between the substituents and the C-NMe_2 group.

In the case of the CO-NMe_2 rotation, no coalescence was observed up to 423K. The ΔG^* values at 423K are remarkably high. This may be explained in terms of a combination of electronic and steric effects. The electronic effect involves delocalisation of the nitrogen lone pair resulting in a partial double bond (**Fig.4**), which in turn restricts rotation "b". The X-ray crystallographic structure[49] of the parent compound shows that the CO-NMe_2 is hindered by the bulky NMe_2 group and the ketone carbonyl group, thus resulting in further inhibition of rotation. The overall effect is a very high rotational barrier for the CO-NMe_2 group. It should be noted that, within limits of experimental error, the ΔG^* values are also indistinguishable indicating that the remote substituents have little effect on the CO-NMe_2 rotational barriers.

Table 3: Rotational energy barriers ($\Delta G^{\ddagger}$) and dynamic NMR data[a] for C-NMe_2 and CO-NMe_2 rotation in the acrylamides (115-119)



Compound	R^1	R^2	NMe_2 rotation			CO-NMe_2 rotation	
			T_c[b]/K	$\Delta\nu_c$[c]/Hz	$\Delta G^{\ddagger}$[d]/ kJmol^{-1}	logk[1][e]	$\Delta G^{\ddagger}$[f]/ kJmol^{-1}
115	H	H	315	20.18	67.33 ±0.72	1.791	90.34
116	H	Cl	320	22.03	68.20 ±0.70	1.767	90.54
117	Cl	H	325	31.00	68.39 ±0.62	1.710	91.00
118	MeO	H	313	29.28	65.91 ±0.63	1.794	90.31
119	NO_2	H	322	43.60	66.82 ±0.56	1.761	90.58

[a]Variable temperature 400MHz ^{1}H NMR spectra recorded using solutions in DMSO-d_6.
[b]Coalescence temperature (±2K).
[c]Frequency separation at coalescence (±2Hz).
[d]Free energy of activation for C-NMe_2 rotation [$\Delta G^{\ddagger} = RT_c(22.96 + \ln T_c/\Delta\nu_c)$, followed by estimated error].
[e]"Notional" value of isomerisation rate constant for CO-NMe_2 rotation.
[f]Free energy of activation for CO-NMe_2 rotation at 423K [$\Delta G^{\ddagger} = 2.303RT(\log k_B T/h - \log k^1)$; estimated error ±0.45kJmol^{-1}].

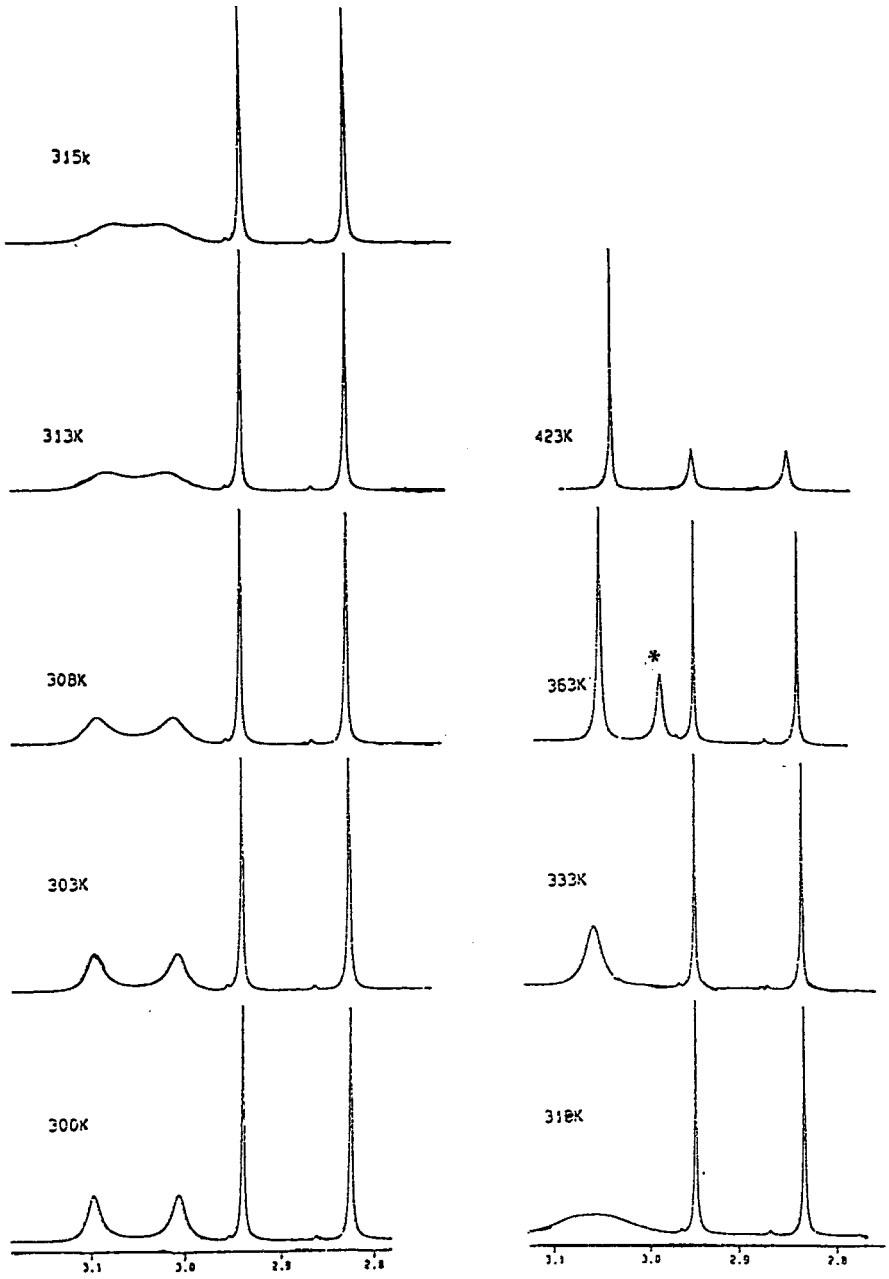
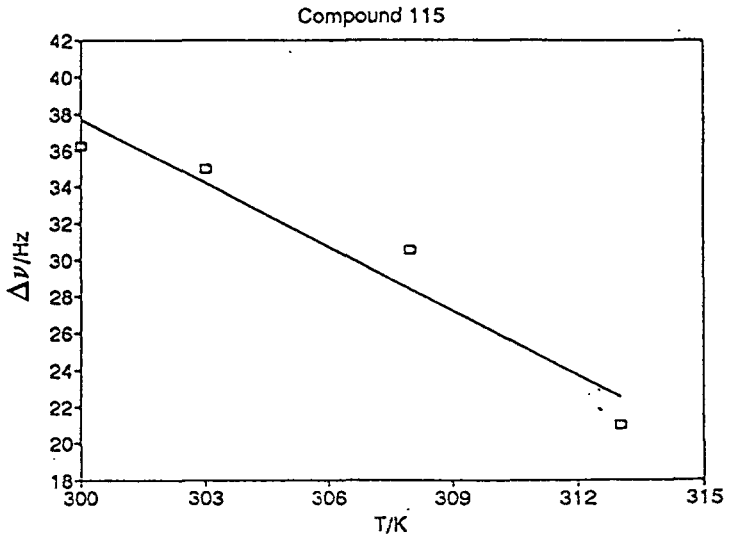
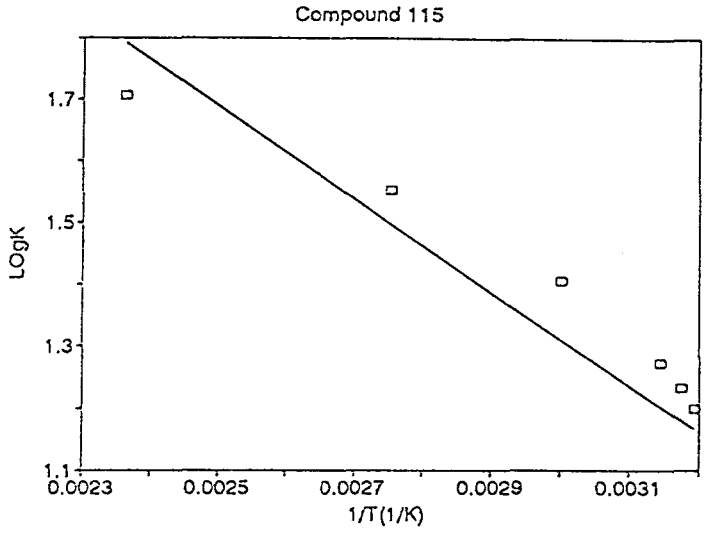


Figure 5: Variable ^1H NMR spectra showing *N*-methyl signals for the acrylamide (115), followed by plot of frequency differences ($\Delta\nu$) vs. Temperature (T) (N-Me_2 groups), and logk vs. 1/T (CO-NMe_2 groups).

* = H_2O peak


Compound 115
42
40
38
36
34
32
30
28
26
24
22
20
18
Δν/Hz
300
303
306
309
312
315
T/K


Compound 115
1.7
1.5
1.3
1.1
LOgK
0.0023
0.0025
0.0027
0.0029
0.0031
1/T(1/K)

2.4 Conclusion

In this project, various chromones and their derivatives have been successfully synthesized. The pKa and spectroscopic studies have also been completed successfully.

In the chromone-2-carboxylic acids studied, it has been found that introduction of certain substituents on the chromone ring does have a marked effect on the acid. However, DNMR analysis of the series of acrylamides examined indicates that the substituents exhibit little effect on the rotational energy barriers. In a preliminary study of the mass spectra of the substituted acrylamides, using a combination of low resolution, high resolution and meta-stable peak analysis, several fragmentation pathways have been established. Future research is expected to involve:-

i) DNMR studies of acrylamide analogues in which the position of substitution is varied;

ii) extension of the mass spectrometric studies to establish molecular formulae of additional fragments; and

iii) synthesis of novel chromone derivatives with biological potential.

3. EXPERIMENTAL

3.1 General

Melting points were recorded on a Kofler hot-stage, Gallenkamp or an automatic Mettler FP1 melting point apparatus (m.p. > 200°C) and are uncorrected.

NMR spectra were recorded on a Bruker 400 AMX spectrometer, whilst routine ^1H NMR spectra were recorded on a Perkin-Elmer R12 60 MHz NMR spectrometer.

IR spectra were recorded on a Perkin-Elmer 180 or Beckman 4260 IR spectrophotometer using KBr discs or liquid films.

Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer.

Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

TLC plates were analysed under UV light.

All solvents were dried prior to use by standard literature procedures[68] and stored over 4A molecular sieves.

HCl gas was generated from HCl-H_2SO_4 using a standard literature procedure.[69]

3.2 Preparation of chromone derivatives

3-*Chlorophenyl acetate* (**68**).[37] - Ac_2O (15.6ml, 0.165mol) was added to a stirred solution of 3-chlorophenol (15g, 0.12mol) and NaOH (6.6g, 0.17mol) in H_2O (80ml) maintained at *ca.* 0°C in an ice-salt bath. The resulting mixture was extracted with Et_2O (3x40ml) and the combined extracts were sequentially washed with 5% aq. $NaHCO_3$ (2x50ml) and saturated NaCl (50ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford a yellow

oil which was distilled to give 3-chlorophenyl acetate (**68**) (17.80g, 89%), b.p. 68-70°C/0.45mmHg (lit.,[37] 105-107°C/13mmHg); δ_H (60MHz; CCl_4) 2.30 (3H,s,CH_3) and 7.10-7.50 (4H,m,ArH); υ_{max} (liquid film)/cm^{-1} 1760 (CO).

4-*Chlorophenyl acetate* (**69**).[37] - The experimental procedure employed for the synthesis of 3-chlorophenyl acetate (**68**) was followed, using Ac_2O (10.4ml, 110mmol), 4-chlorophenol (10g, 78mmol), and NaOH (4.4g, 0.11mol) in H_2O (*ca.* 75ml). Work-up afforded an oil which was distilled to give 4-chlorophenyl acetate (**69**) (9.62g, 72%), b.p. 48°C/0.7mmHg (lit.,[61] 109°C/13mmHg); δ_H (60MHz; $CDCl_3$) 2.25 (3H,s,CH_3) and 6.90-7.50 (4H,m,ArH); υ_{max} (liquid film)/cm^{-1} 1760 (CO).

4-*Chloro-2-hydroxyacetophenone* (**70**).[38] - A stirred mixture of 3-chlorophenyl acetate (**68**) (15.0g, 88mmol) and $AlCl_3$ (28g, 0.21mol) was heated in an oil bath at 175-180°C for 1.5h. The cooled mixture was treated with 2**M**-HCl (150ml) and then steam distilled until no more milky product was collected. The distillate was extracted with $CHCl_3$ (3x70ml). The chloroform solution was extracted with 0.5 **M**-KOH (3x60ml) and the combined aqueous, alkali solutions were washed with $CHCl_3$ (3x70ml), acidified and then re-extracted into $CHCl_3$ (3x70ml). The combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford an oil which was distilled to give 4-chloro-2-hydroxyacetophenone (**70**) (7.0g, 47%), b.p. 90-92°C/2mmHg (lit.,[38] 121-124°C/15mmHg); δ_H (60MHz; CCl_4) 2.60 (3H,s,CH_3), 6.80-7.20 (2H,m,3-H and 5-H), 7.23 (1H,d,*J* 9Hz,6-H) and 12.20 (1H,br s,OH); υ_{max} (liquid film)/cm^{-1} 3500-2500 (OH) and 1640 (CO).

5-Chloro-2-hydroxyacetophenone (**71**).[38] - The experimental procedure employed for the synthesis of 4-chloro-2-hydroxyacetophenone (**70**) was followed; using 4-chlorophenyl acetate (**69**) (9g, 0.05mol). Work-up afforded an oil which crystallised to give crude 5-chloro-2-hydroxyacetophenone (**71**) [(5.94g, 66%), m.p. 50°C (lit.,[62] 52.5°C); δ_H (60MHz; $CDCl_3$) 2.60 (3H,s,$COCH_3$), 6.90-8.75 (3H,m,ArH) and 12.15 (1H,s,OH); υ_{max} (nujol mull)/cm^{-1} 3400-2500 (OH) and 1650 (CO)], which was used without further purification.

2-Chlorophenyl acetate (**73**).[61] - The experimental procedure employed for the synthesis of 3-chlorophenyl acetate (**68**) was followed, using Ac_2O (15.6ml, 165mmol), 2-chlorophenol (**72**) (15g, 0.12mol), and NaOH (6.6g 0.16mol) in H_2O (*ca.* 113ml). Work-up afforded an oil which was distilled to give 2-chlorophenyl acetate (**73**) (18.5g, 93%), b.p. 66-69°C/0.8mmHg (lit.,[61] 100°C/9mmHg); δ_H (60MHz; CCl_4) 2.28 (3H,s,CH_3) and 7.00-7.60 (4H,m,ArH); υ_{max} (liquid film)/cm^{-1} 1770 (CO).

3-Chloro-2-hydroxyacetophenone (**74**) and *3-chloro-4-hydroxyacetophenone* (**75**).[35] - A mixture of 2-chlorophenyl acetate (**73**) (15g, 88mmol) and anhydrous $AlCl_3$ (38g, 0.29mol), in a flask fitted with a $CaCl_2$ drying tube, was heated in an oil bath to 150°C and this temperature was maintained for 2h. The cooled mixture was decomposed with conc. HCl (5ml) and then steam distilled until no more milky product was collected. After cooling the distillate to room temperature, the resulting needles were collected, chromatographed [flash chromatography on silica gel; elution with hexane:EtOAc (1:1)] and recrystallized from light petroleum (40-60°C) to afford 3-chloro-2-hydroxyacetophenone (**74**) [(1.14g, 8%), m.p. 46°C (lit., 55°C[39] and 49.5-50°C[40]); δ_H (400MHz; $CDCl_3$) 2.65 (3H,s,CH_3), 6.86 (1H,t,*J* 7.9Hz,5-H), 7.56 (1H,d,*J* 7.8Hz,4-H), 7.67 (1H,d,*J* 8Hz,6-H) and 12.83 (1H,s,OH); υ_{max}

(KBr)/cm^{-1} 3700-2600 (OH) and 1650 (CO)] and 3-chloro-4-hydroxyacetophenone (**75**) [(2.99, 20%),[a] m.p. 90-92°C (lit.,[40] 96°C); δ_H (60MHz; DMSO-d_6/CCl_4) 2.55 (3H,s,CH_3), 7.10-7.25 and 7.80-8.05 (3H,m,ArH); υ_{max} (KBr)/cm^{-1} 3500-2500 (OH) and 1650 (CO)].

Ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**78**).[41] - A mixture of diethyl oxalate (15ml, 0.11mol) and *o*-hydroxyacetophenone (**76**) (12ml, 0.10mol) was added dropwise under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding sodium metal (6.9g, 0.3mol) to dry EtOH (200ml)]. The resulting yellow mixture was boiled gently under reflux for 0.5h, during which time a thick yellow slurry was formed. After cooling, the yellow reaction mixture was poured into Et_2O (300ml). After standing for 0.5h, the yellow sodium salt was filtered off, washed (Et_2O), and dissolved in 2-HCl (200ml) and extracted with Et_2O (3x50ml). The ethereal solutions were combined, dried (anhyd. $MgSO_4$). filtered and evaporated to afford the diketone, ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**78**) [δ_H (60MHz; DMSO-d_6) 1.25 (3H,t,CH_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 (**78**) was shown by ^1H NMR spectroscopy to be partially enolised and was used without further purification.

Ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**80**).[37] - A warm solution of 4-chloro-2-hydroxyacetophenone (**70**) (6.0g, 35mmol) and diethyl oxalate (26.10ml, 194mmol) was added dropwise under N_2 to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (3.20g, 139mmol) to dry EtOH (60ml)]. The stirred mixture was gently boiled under reflux for 40min. becoming a thick, yellow slurry. The reaction mixture was

[a] This yield does not include material which did not distill over.

allowed to cool, and poured into Et_2O (146ml). The resulting yellow solid was filtered off, washed (Et_2O), and acidified with 2M-HCl (200ml). The resulting semi-solid was extracted with Et_2O (3x50ml) and the combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford crude ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**80**)[a] δ_H (60MHz; DMSO-d_6) 1.30 (3H,t,CH_3), 2.87 and 3.33 (2H,dd,*J* 17Hz,$COCH_2$), 4.34 (2H,q,CH_2CH_3), 7.10-7.40 (2H,m,6-H and 8-H) and 7.93 (1H,d,*J* 9Hz,5-H).

Ethyl 4-(2-hydroxy-5-methoxyphenyl)-2,4-dioxobutanoate (**85**). - The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**80**) was followed, using 2-hydroxy-5-methoxyacetophenone (**77**) (2.5g, 15mmol), diethyl oxalate (11.2ml, 83mmol), Na metal (1.39g, 61mmol) and dry EtOH (25.8ml). Work-up afforded crude ethyl 4-(2-hydroxy-5-methoxyphenyl)-2,4-dioxobutanoate (**85**) [(3.62g, 91%);[b] δ_H (60MHz; $CDCl_3$) 1.40 (3H,t,CH_3), 3.95 (3H,t,OMe), 7.20-7.80 (3H,m,ArH) and 9.10 (1H,br s,OH)], which was used without further purification.

Chromone-2-carboxylic acid (**87**).[41] - A mixture of ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**78**), conc. HCl (40ml) and AcOH (40ml) was boiled under reflux for 1h. After cooling, the precipitated solid was filtered off, washed with AcOH and recrystallised from AcOH to afford chromone-2-carboxylic acid (**87**) (11.40g, 60%), m.p. 250.1°C (decomp.) (lit.,[41] 250-251°C); δ_H (60MHz; DMSO-d_6) 7.00 (1H,s,3-H) and 7.50-8.30

---

[a] ^{1}H NMR spectroscopy indicated the presence of a small proportion of the ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**79**).

[b] ^{1}H NMR spectroscopy showed a small proportion of the ethyl 6-methoxychromanone-2-carboxylate (**86**).

(4H,m,ArH); υ_{max} (KBr)/cm^{-1} 3300-2000 (CO_2H), 1740 (CO_2H) and 1630 (CO).

7-Chlorochromone-2-carboxylic acid (**88**).[37] - A mixture of crude ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**80**), AcOH (30ml) and conc. HCl (15ml) was boiled gently under reflux for 1.5h. After cooling, H_2O (50ml) was added and the precipitated solid was filtered off and recrystallised from EtOH to afford the required product contaminated with its ethyl ester (14%). The contaminated product was dissolved in EtOAc (50ml) and washed with 5% aq. $NaHCO_3$ (2x50ml). The combined aqueous solutions were acidified and then extracted into EtOAc (3x50ml). The extract was dried (anhyd. $MgSO_4$) and evaporated to afford 7-chlorochromone-2-carboxylic acid (**88**) (3.23g, 41%),[a] m.p. 248°C (decomp.) (lit.,[37] 248-250°C); δ_H (60MHz; DMSO-d_6) 7.10 (1H,s,3-H) and 7.60-8.30 (3H,m,ArH); υ_{max} (KBr)/cm^{-1} 3200-2300 (CO_2H), 1710 (CO_2H) and 1650 (CO).

6-Chlorochromone-2-carboxylic acid (**89**). - The experimental procedure employed for the synthesis of ethyl 7-chlorochromanone-2-carboxylate (**80**) was followed, using 5-chloro-2-hydroxyacetophenone (**71**) (4.65g, 27mmol), diethyl oxalate (21.75g, 0.15mol), Na metal (2.51g, 0.11mol) and dry EtOH (70ml). Work-up afforded a solid, which was shown by ^{1}H nmr spectroscopy to be a mixture of ethyl 6-chlorochromanone-2-carboxylate (**82**) and ethyl 4-(5-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**81**) and which was used directly. The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**88**) was then followed using the crude solid, AcOH (22.5ml) and conc. HCl (11.3ml). Work-up afforded a solid which was recrystallised from EtOH to afford 6-chlorochromone-2-

[a] Yield calculated on the basis of 4-chloro-2-hydroxyacetophenone (**70**).

carboxylic acid (**89**) (3.48g, 57%),[a,b] m.p. 265°C (decomp.) (lit., various values quoted, *viz.*, 262°C,[62] 267-269°C[68] and 275°C[68]); δ_H (400MHz; DMSO-d_6) 3.83 (1H,br s,OH), 6.98 (1H,s,3-H), 7.71 (1H,d,*J* 9Hz,8-H), 7.80 (1H,dd,*J* 2.6Hz and 9Hz,7-H) and 8.02 (1H,d,*J* 2.4Hz,5-H); υ_{max} (KBr)/cm^{-1} 1740 (CO.O), 1630 (CO).

8-Chlorochromone-2-carboxylic acid (**90**). - The experimental procedure for the synthesis of ethyl 7-chlorochromanone-2-carboxylate (**80**) was followed, using 3-chloro-2-hydroxyacetophenone (**74**) (1.0g, 6mmol), diethyl oxalate (4.4ml, 32mmol), Na metal (0.54g, 24mmol) and dry EtOH (10ml). Work-up afforded a solid, which was shown by ^{1}H nmr spectroscopy to be a mixture of ethyl 4-(3-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**83**) and 8-chlorochromanone-2-carboxylate (**84**) and which was used directly. The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**88**) was then followed using the crude solid, AcOH (5ml) and conc. HCl (2.5ml). Work-up afforded a solid which was recrystallized from EtOH to afford *8-chlorochromone-2-carboxylic acid* (**90**) (0.54g, 42%),[c,d] m.p. 261.2°C (from EtOH) (Found: C, 53.2; H, 2.5. $C_{10}H_5ClO_4$ requires: C, 53.5; H, 2.2%); δ_H (400MHz; DMSO-d_6) 3.33 (1H,br s,OH), 6.96 (1H,s,3-H), 7.53 (iH,t,*J* 7.9Hz,6-H), 8.00 (1H,dd,*J* 1.6 and 8Hz,7-H) and 8.05 (1H,dd,*J* 1.5 and 7.7Hz,5-H); δ_C (100MHz; DMSO-d_6) 113.93 (C-3), 122.75 (C-4a), 124.12 (C-8), 125.42 (C-6), 126.48 (C-5), 135.24 (C-2 and C-7), 151.29 (C-8a), 161.20 (CO.O) and

---

[a] Yield calculated on the basis of 5-chloro-2-hydroxyacetophenone (**71**).

[b] The acid was isolated with its ethyl ester (10%) and was separated by extraction as for compound (**88**).

[c] Yield calculated on the basis of 3-chloro-2-hydroxyacetophenone (**74**).

[d] The acid was isolated with its ethyl ester and was separated by extraction as for compound (**88**).

177.33 (C-4); υ_{max} (KBr)/cm^{-1} 3300-2000 (OH), 1750 (CO_2H) and 1650 (CO).

6-Methoxychromone-2-carboxylic acid (**91**). - The experimental procedure for the synthesis of 7-chlorochromone-2-carboxylic acid (**88**) was followed, using crude ethyl 4-(2-hydroxy-5-methoxyphenyl)-2,4-dioxobutanoate (**85**), conc. HCl (6.5ml) and AcOH (13ml). Work-up afforded a solid which was recrystallized from EtOH to afford 6-methoxychromone-2-carboxylic acid (**91**) (2.50g, 76%),[a] m.p. 268°C (decomp) (lit.,[64] 268°C); δ_H (400MHz; DMSO-d_6) 3.87 (3H,s,OCH_3), 6.88 (1H,s,3-H), 7.40 (1H,d,*J* 3.2Hz,6-H), 7.45 (1H,dd,*J* 3.1 and 9.2Hz,7-H) and 7.69 (1H,d,*J* 7.69Hz,5-H); υ_{max} (KBr)/cm^{-1} 3300-2400 (OH), 1720 (CO_2H) and 1620 (CO).

Ethyl 3-methylchromone-2-carboxylate (**93**).[42] - A mixture of *o*-hydroxypropiophenone (**92**) (10.0g, 67mmol) and diethyl oxalate (27ml, 0.20mol) was cooled in an ice bath. NaH (80% dispersion in oil; 6g, 0.20mol) was then added portion-wise to the vigorously stirred mixture. The ice bath was removed occasionally to allow the reaction to proceed and additional dry Et_2O (100ml) was added to disperse the solid NaH within the slurry. After addition of NaH, the cold mixture was stirred for a further 0.5h and then for 48h at room temperature. The resulting solid was filtered off, and added to a stirred mixture of AcOH (16ml), H_2O (50ml) and ice (40g). After stirring for 2h, this mixture was extracted with Et_2O (3x50ml). The ethereal extracts were combined, washed with H_2O (2x20ml), dried (anhyd. $MgSO_4$), and evaporated. The residue was dissolved in AcOH (20ml) and conc. HCl (2ml), and the resulting solution boiled under reflux for 0.5h. After cooling, H_2O (20ml) was added; the solid material was filtered off and dissolved in Et_2O (100ml). The ethereal extract was

[a] Yield calculated on the basis of 2-hydroxy-5-methoxyacetophenone (**77**).

washed sequentially with 5% aq. $NaHCO_3$ (2x50ml) and H_2O (50ml) and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford ethyl 3-methylchromone-2-carboxylate (**93**) (5.18g, 34%), m.p. 88°C (from ethanol) (lit.,[42] 89-90°C); δ_H (60MHz; $CDCl_3$) 1.45 (3H,t,CH_2CH_3), 2.35 (3H,s,3-Me), 4.50 (2H,q,CH_2CH_3) and 7.30-8.35 (4H,ArH); υ_{max} (KBr)/cm^{-1} 1730 (CO.O) and 1645 (CO).

3-Methylchromone-2-carboxylic acid (**94**).[42] - A solution of ethyl 3-methylchromone-2-carboxylate (**93**) (4.50g, 19mmol), AcOH (18ml) and 8M-H_2SO_4 (9ml) was boiled under reflux for 12h. The resulting mixture was allowed to cool and H_2O (36ml) was added. The precipitated solid was filtered off, dried and recrystallised from EtOH to afford 3-methylchromone-2-carboxylic acid (**94**) (3.04g, 77%), m.p. 230°C (lit.,[42] 233-234°C); δ_H (60MHz; DMSO-d_6) 2.30 (3H,s,3-Me) and 7.40-8.30 (4H,m,ArH); υ_{max} (KBr)/cm^{-1} 3400-2200 (CO_2H), 1800 (CO_2H) and 1625 (CO).

6-Nitrochromone-2-carboxylic acid (**95**).[43] - Conc. HNO_3 (0.9ml) was added to a stirred solution of chromone-2-carboxylic acid (**87**) (1.5g, 7.9mmol) and conc. H_2SO_4 (7.5ml) at 30°C. The resulting solution was stirred at 70°C for 1h. After cooling, the solution was poured into ice and the precipitated solid was filtered off to give 6-nitrochromone-2-carboxylic acid (**95**) (1.80g, 97%), m.p. 268°C (decomp.) (from ethanol) (lit.,[43] 267-268°C); δ_H (400MHz; DMSO-d_6) 3.75 (1H,br s,OH), 7.02 (1H,s,3-H), 7.99 (1H,d,*J* 9.3Hz,8-H), 8.61 (1H,dd,*J* 2.8 and 9.2Hz,7-H) and 8.72 (1H,d,*J* 2.8Hz,5-H); υ_{max} (KBr).cm^{-1} 3200-2000 (CO_2H), 1740 (CO_2H) and 1620 (CO).

Methyl chromone-2-carboxylate (**96**).[42] - A solution of chromone-2-carboxylic acid (**87**) (2.50g, 132mmol), MeOH (125ml) and conc. H_2SO_4 (0.5ml) was boiled under reflux for 2.5h. After cooling, the solution was poured into ice-water (40ml), basified with 5% aq. $NaHCO_3$ and extracted with EtOAc (3x35ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and evaporated to afford crude methyl chromone-2-carboxylate (**96**) (2.39g, 89%), m.p. 118-120°C (from MeOH) (lit.,[42] 122-123°C); δ_H (60MHz; DMSO-d_6/CCl_4) 3.90 (3H,s,OCH_3), 6.88 (1H,s,3-H) and 7.30-8.10 (4H,m,ArH); υ_{max} (KBr)/cm^{-1} 1730 (CO.O) and 1655 (CO).

Methyl 3-chlorochromone-2-carboxylate (**97**).[44] - A solution of methyl chromone-2-carboxylate (**96**) (4.0g, 196mmol), benzoyl peroxide (9.05mg) and SO_2Cl_2 (25.10ml, 314mmol) was boiled gently under reflux for 10h. The solvent was evaporated and MeOH (30ml) was added to the residual oil. The resulting solution was concentrated *in vacuo* to *ca.* 7ml and cooled to precipitate the product. Filtration afforded crude methyl 3-chlorochromone-2-carboxylate (**97**) (3.74g, 80%), m.p. 122-123°C (lit.,[44] 126°C); δ_H (60MHz; DMSO-d_6/CCl_4) 4.10 (OCH_3) and 7.60-8.40 (4H,m,ArH); υ_{max} (KBr)/cm^{-1} 3090 and 2980 (C-H), 1730 (CO.O) and 1650 (C=O).

Note: Application of this procedure[44] occasionally resulted in a mixture of the required mono-chloro ester (**97**) and the 2,3-dichlorochromanone (**98**). Treatment of this mixture, as described below,[45] gave methyl 3-chloro-chromone-2-carboxylate (**97**) and 3-chlorochromone-2-carboxylic acid (**99**).

The mixture of the two compounds (1.30g) was added to dry pyridine (6ml) and warmed on a steam-bath for 1h. After cooling, the solution was acidified

with 2M-HCl and extracted with EtOAc (3x30ml). The combined organic extracts were then washed with 5% aq. $NaHCO_3$ (3x30ml) and then H_2O (2x20ml), dried (anhyd. $MgSO_4$) and evaporated to afford methyl 3-chlorochromone-2-carboxylate (**97**) (0.26g). The aqueous washings were acidified and extracted with EtOAc (3x30ml) and the combined organic extracts were dried (anhyd. $MgSO_4$) and evaporated to afford 3-chlorochromone-2-carboxylic acid (**99**) (0.49g).

3-Chlorochromone-2-carboxylic acid (**99**). - A mixture of methyl 3-chlorochromone-2-carboxylate (**97**) (3.30g, 138mmol), AcOH (15ml) and conc. HCl (22.5ml) was boiled gently under reflux for 3h. After cooling, H_2O (30ml) was added and the semi-solid mixture set aside for several hours. The solid was filtered off and recrystallised from AcOH to afford 3-chlorochromone-2-carboxylic acid (**99**) (2.48g, 80%), m.p. 207°C (lit.,[65] 206°C); δ_H (60MHz; DMSO-d_6/CCl_4) 7.50-8.50 (4H,m,ArH) and 10.65 (1H,br s,OH); υ_{max} (KBr)/cm^{-1} 3300-2300 (CO_2H), 1710 (CO_2H) and 1650 (C=O).

Chromone-2-carbonyl chloride (**100**).[46] - Thionyl chloride (0.88ml, 12mmol) was added to a suspension of chromone-2-carboxylic acid (**87**) (1.75g, 9.2mmol) in dry 1,2-dichloroethane (10.5ml) and dry *N*,*N*-dimethylformamide (0.36ml, 4.6mmol). The resulting mixture was boiled under reflux for 1h. After cooling, the solvent was removed by vacuum distillation. Additional dry 1,2-dichloroethane (10.5ml) was added and then removed under vacuum to afford the crude, yellow chromone-2-carbonyl chloride (**100**) [(1.77g, 89%), m.p. 94°C (lit., 104-108°C); δ_H (60MHz; $CDCl_3$) 7.30 (1H,s,3-H) and 7.45-8.40 (4H,m,ArH); υ_{max} (KBr)/cm^{-1} 1730 (CO.Cl) and 1625 (CO)], which was used without further purification.

7-Chlorochromone-2-carbonyl chloride (**101**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed, using 7-chlorochromone-2-carboxylic acid (**88**) (2.50g, 11.13mmol), dry 1,2-dichloroethane (13ml), dry *N,N*-dimethylformamide (0.21ml, 2.78mmol) and $SOCl_2$ (1.06ml, 14.55mmol). In this case, the reaction time was 1.5h. Work-up afforded crude, brick red, crystalline 7-chlorochromone-2-carbonyl chloride (**101**) [m.p. 176-177°C (sublimed) (lit.,[53] 179-182°C); δ_H (60MHz; $CDCl_3$) 7.35 (1H,s,3-H), 7.55 (1H,dd,*J* 2 and 9Hz,6-H), 7.70 (1H,d,*J* 2Hz,8-H) and 8.22 (1H,d,*J* 9Hz,5-H); υ_{max} (KBr)/cm^{-1} 1765 (CO.Cl) and 1650 (CO)], which was used without further purification.

6-Chlorochromone-2-carbonyl chloride (**102**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed using 6-chlorochromone-2-carboxylic acid (**89**) (2.00g, 8.90mmol), dry 1,2-dichloroethane (10ml), dry *N,N*-dimethylformamide (0.17ml, 2.2mmol) and $SOCl_2$ (0.85ml, 12mmol). In this case, the reaction time was 3h. Work-up afforded crude, brown, crystalline *6-chlorochromone-2-carbonyl chloride* (**102**) [(2.04g, 94%); δ_H (400MHz; $CDCl_3$) 6.77 (1H,s,3-H), 7.86 (1H,dd,7-H), 7.96 (1H,d,8-H) and 8.27 (1H,d,5-H); υ_{max} (KBr)/cm^{-1} 1735 (CO.Cl) and 1665 (CO)], which was used without further purification.

6-Methoxychromone-2-carbonyl chloride (**103**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed, using 6-methoxychromone-2-carboxylic acid (**91**) (2.0g, 9.1mmol), dry 1,2-dichloroethane (13.6ml), dry *N,N*-dimethylformamide (0.18ml) and $SOCl_2$ (0.87ml, 12mmol). In this case, the reaction time was 2.5h. Work-up afforded crude *6-methoxychromone-2-carbonyl chloride* (**103**) [(2.0g, 96%); δ_H (60MHz; CCl_4) 3.92 (3H,s,OMe), 6.51 (1H,s,3-H) and 7.04-7.70 (3H,m,ArH); υ_{max} (KBr)/cm^{-1} 1730 (CO.Cl) and 1650 (CO)], which was used without further purification.

3-Methylchromone-2-carbonyl chloride (**104**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed, using 3-methylchromone-2-carboxylic acid (**94**) (2.75g, 13.47mmol), dry 1,2-dichloroethane (15ml), dry *N,N*-dimethylformamide (0.25ml, 3.44mmol)) and $SOCl_2$ (1.30ml, 17.50mmol). In this case, the reaction time was 2.75h. Work-up afforded crude, crystalline 3-methylchromone-2-carbonyl chloride (**104**) [δ_H (400MHz; DMSO-d_6) 2.22 (3H,s,3-Me), and 7.26-8.05 (4H,m,ArH); υ_{max} (KBr)/cm^{-1} 1760 (CO.Cl) and 1640 (CO)], which was used without further purification.

6-Nitrochromone-2-carbonyl chloride (**105**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed, using 6-nitrochromone-2-carboxylic acid (**95**) (1.35g, 5.74mmol), dry 1,2-dichloroethane (6.6ml), dry *N,N*-dimethylformamide (0.11ml, 1.4mmol)) and $SOCl_2$ (0.70ml, 9.63mmol). In this case, the reaction time was 3h at 120°C. Work-up afforded crude *6-nitrochromone-2-carbonyl chloride* (**105**) [(1.52g, 99%); δ_H (60MHz; $CDCl_3$) 7.35 (1H,s,3-H), 7.80 (1H,d,8-H) , 8.65 (1H,dd,7-H) and 9.05 (1H,d,5-H); υ_{max} (KBr)/cm^{-1} 1780 (CO.Cl) and 1670 (CO)], which was

used without further purification.

3-Chlorochromone-2-carbonyl chloride (**106**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**100**) was followed, using 3-chlorochromone-2-carboxylic acid (**99**) (2.20g, 9.80mmol), dry 1,2-dichloroethane (12ml), dry *N,N*-dimethylformamide (0.19ml, 2.45mmol)) and $SOCl_2$ (0.94ml, 12.8mmol). In this case, the reaction time was 3h. Work-up afforded crude, pink, crystalline *3-chlorochromone-2-carbonyl chloride* (**106**) [(2.37g, 100%), m.p. 198°C; δ_H (400MHz; DMSO-d_6/CCl_4) 7.58 (1H,t,*J* 8Hz,6-H), 7.44 (1H,d,*J* 8.5Hz,8-H), 7.88-7.93 (1H,m,7-H) and 8.10 (1H,dd,*J* 1.5 and 8Hz,5-H); υ_{max} (KBr)/cm^{-1} 1760 (CO.Cl) and 1650 (CO)], which was used without further purification.

Dimethylammonium chloride (**107**).[53] - HCl gas was bubbled through a stirred solution of dimethylamine (33% w/w solution in EtOH; 36ml, 0.20mol) and dry EtOH (80ml) for 2h at *ca.* 0°C. The solvent was evaporated and the white, crystalline slurry was dried under vacuum for 1h. Dry Et_2O (50ml) was added and the mixture cooled to *ca.* 0°C. The solvent was decanted off and the crystals dried under vacuum for 1h. The crystals were then washed with Et_2O (6x10ml) by filtration under N_2 and vacuum dried for 2h to afford crude dimethylammonium chloride (**107**) (14.12g, 86%), m.p. 170°C (lit.,[66] 171°C); δ_H (60MHz; $CDCl_3$) 2.80 (6H,t,Me) and 9.45 (1H,br s,NH).

N,N-*dimethylchromone-2-carboxamide* (**108**).[47] - A stirred suspension of the crude chromone-2-carbonyl chloride (**100**) (2.00g, 9.20mmol) in dry pyridine (15ml) was cooled in ice for 0.25h. and a slurry of dimethylammonium chloride (**107**) (0.78g, 9.6mmol) in dry

pyridine (5ml) was then added dropwise to the suspension. After stirring for 3h. in an ice bath and 20h. at room temperature, the reaction mixture was poured into 2**M**-HCl (200ml). The resulting mixture was cooled in ice for 0.5h., and then extracted with EtOAc (4x70ml). The combined extracts were washed sequentially with 5% aq. $NaHCO_3$ (2x50ml) and saturated aq. NaCl (50ml) and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford a solid product (1.36g), which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *N,N*-dimethylchromone-2-carboxamide (**108**) (1.17g, 59%),[a] m.p. 114°C (from EtOAc) (lit.,[27] 115-116°C); δ_H (400MHz; $CDCl_3$) 3.11 (6H,s,NMe_2), 6.51 (1H,s,3-H), 7.40-7.48 (2H,m,6-H and 8-H), 7.69 (1H,m,7-H) and 8.19 (1H,dd,*J* 1.6 and 8Hz,5-H); δ_C (100MHz; $CDCl_3$) 35.47 and 38.32 (NMe_2), 111.67 (C-3), 118.17 (C-8), 124.27 (C-4a), 125.79 and 125.81 (C-5 and C-6), 134.25 (C-7), 155.72 (C-8a), 158.20 (C-2), 162.34 (CO.N) and 177.48 (C-4); υ_{max} (KBr)/cm^{-1} 3060 (CH), 1650 (CO) and 1635.

7-Chloro-N,N-*dimethylchromone-2-carboxamide* (**109**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 7-chlorochromone-2-carbonyl chloride (**101**) (2.71g, 11.1mmol), dimethylammonium chloride (**107**) (0.95g, 12mmol) and dry pyridine (18ml). In this case, the reaction time was 3h. at 0°C and 16h. at room temperature. Work-up afforded crude, brown product (1.85g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford 7-chloro-*N,N*-dimethylchromone-2-carboxamide (**109**) (1.56g, 56%),[b] m.p. 147°C (from EtOH) (lit.,[47] 146-147°C); δ_H (400MHz; $CDCl_3$) 3.12 (6H,s,NMe_2) 6.52 (1H,s,3-H),

---

[a] Yield calculated on the basis of chromone-2-carboxylic acid (**87**).

[b] Yield calculated on the basis of 7-chlorochromone-2-carboxylic acid (**88**).

7.40 (1H,dd,*J* 2 and 9Hz,6-H), 7.50 (1H,d,*J* 2Hz,8-H) and 8.14 (1H,d,*J* 9Hz,5-H); δ_C (100MHz; $CDCl_3$) 35.55 and 38.35 (NMe_2), 112.00 (C-3), 118.27 (C-8), 122.81 (C-4a), 126.73 and 127.25 (C-5 and C-6), 140.47 (C-7), 155.81 (C-8a), 158.28 (C-2), 161.98 (C-1) and 176.62 (C-4); υ_{max} (KBr)/cm^{-1} 1660 and 1650 (CO).

6-Chloro-N,N-*dimethylchromone-2-carboxamide* (**110**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 6-chlorochromone-2-carbonyl chloride (**102**) (2.2g, 9.0mmol), dimethylammonium chloride (**107**) (0.76g, 9.3mmol) and dry pyridine (15ml). In this case, the reaction time was 3h. at 0°C. Work-up afforded crude, brown product (2.04g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *6-chloro*-N,N-*dimethylchromone-2-carboxamide* (**110**) (1.48g, 66%),[a] m.p. 130-131°C (from EtOH) (Found: C, 57.05; H, 4.2; N, 5.3. $C_{12}H_{10}ClNO_3$ requires C, 57.3; H, 4.0; N, 5.6%); δ_H (400MHz; $CDCl_3$) 3.06 (6H,s,NMe_2), 6.47 (1H,s,3-H), 7.39 (1H,d,*J* 9Hz,5-H), 7.59 (1H,dd,*J* 2.6 and 9Hz,7-H) and 8.11 (1H,d,*J* 2.5Hz,8-H); δ_C (100MHz; $CDCl_3$) 35.52 and 38.37 (NMe_2), 111.60 (C-3), 119.93 (C-8), 125.21 and 125.32 (C-5 and C-6), 131.94 (C-4a), 134.55 (C-7), 154.08 (C-8a), 158.35 (C-2), 162.05 (CO.N) and 176.30 (C-4); υ_{max} (KBr)/cm^{-1} 1650 and 1660 (CO); *m/z* 251 (m^+, 52%) and 72 (100).

6-Methoxy-N,N-*dimethylchromone-2-carboxamide* (**111**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 6-methoxychromone-2-carbonyl chloride (**103**) (2.17g, 9.08mmol), dimethylammonium chloride (**107**) (1.48g, 18.2mmol) and dry pyridine (23ml). In this case, the reaction time

---

[a] Yield calculated on the basis of 6-chlorochromone-2-carboxylic acid (**89**).

was 3h. Work-up afforded crude, brown product (1.57g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *6-methoxy*-N,N-*dimethylchromone-2-carboxamide* (**111**) (0.98g, 44%), m.p. 151-152°C (from EtOAc) (Found: C, 63.0; H, 5.7; N, 6.05. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.3; N, 5.7%); δ_H (400MHz; $CDCl_3$) 3.12 (6H,br s,$CONMe_2$), 3.90 (3H,s,OMe), 6.52 (1H,s,3-H), 7.29 (1H,dd,*J* 3 and 9Hz,7-H), 7.42 (1H,d,*J* 9Hz,8-H) and 7.56 (1H,d,*J* 3Hz,5-H); δ_C (100MHz; $CDCl_3$) 35.52 and 38.36 (NMe_2), 55.97 (OMe), 85.87 (C-3), 150.53 (C-2), 157.44 (C-7), 157.95 (C-8), 161.92 (CO.N), 177.42 (C-4) and 104.94, 110.92, 119,62 and 124.39 (4xArC); υ_{max} (KBr)/cm^{-1} 3075 (C-H) and 1640 (CO); *m/z* 347 (M^+, 100%).

N,N-*3-trimethylchromone-2-carboxamide* (**112**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 3-methylchromone-2-carbonyl chloride (**104**) (2.86g, 12.9mmol), dimethylammonium chloride (**107**) (2.09g, 23.6mmol) and dry pyridine (15ml). In this case, the reaction time was 3h at room temperature. Work-up afforded crude product (2.20g), which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *N,N*,3-trimethylchromone-2-carboxamide (**112**) (1.50g, 51%),[a] m.p. 77-79°C (from EtOAc) (lit.,[47] 74-76°C); δ_H (60MHz; $CDCl_3$) 2.04 (3H,s,3-Me) 3.05 and 3.15 (6H,2xs,NMe_2), 7.20-7.80 (3H,m,6-H,7-H and 8-H) and 8.30 (1H,dd,5-H); υ_{max} (KBr)/cm^{-1} 1650 (CO).

N,N-*Dimethyl-6-dinitrochromone-2-carboxamide* (**113**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 6-nitrochromone-2-carbonyl chloride (**105**) (1.46g, 5.74mmol), dimethylammonium

[a] Yield calculated on the basis of 3-methylchromone-2-carboxylic acid (**94**).

chloride (**107**) (0.93g, 11.4mmol) and dry pyridine (9.3ml). In this case, the reaction time was 20h at room temperature. Work-up afforded the crude product (0.97g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford N,N-*dimethyl-6-nitrochromone-2-carboxamide* (**113**) (0.70g, 47%),[a] m.p. 171-172°C (from EtOAc) (Found: C, 55.0; H, 3.8; N, 10.7. $C_{12}H_{10}N_2O_5$ requires C, 55.0; H, 4.05; N, 11.0%); δ_H (400MHz; $CDCl_3$) 3.15 (6H,s,$CONMe_2$), 6.58 (1H,s,3-H), 7.65 (1H,d,*J* 9.3Hz,8-H), 8.53 (1H,dd,*J* 2.8 and 9.2Hz,7-H) and 9.07 (1H,d,*J* 2.7Hz,5-H); δ_C (100MHz; $CDCl_3$) 35.56 and 38.40 (NMe_2), 112.04 (C-3), 145.20 (C-8a), 158.57 (C-2), 161.47 (CO.N), 175.83 (C-4) and 120, 122.54, 124.37 and 128.12 (4xArC); υ_{max} (KBr)/cm^{-1} 3020 (C-H) and 1650 (CO); *m/z* 262 (m^+, 28%) and 72 (100).

3-Chloro-N,N-*dimethylchromone-2-carboxamide* (**114**). - The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**108**) was followed, using 3-chlorochromone-2-carbonyl chloride (**106**) (2.37g, 9.80mmol), dimethylammonium chloride (**107**) (0.84g, 10.24mmol) and dry pyridine (16ml). Work-up afforded the crude product (1.92g), which was chromatographed [flash chromatography on silica gel; elution with EtOAc:hexane (5:2)] to afford *3-chloro*-N,N-*dimethylchromone-2-carboxamide* (**114**) (1.77g, 72%),[b] m.p. 143-144°C (from EtOAc) (Found: C, 57.5; H, 4.5; N, 5.7. $C_{12}H_{10}ClNO_3$ requires C, 57.3; H, 4.0; N, 5.6%); δ_H (400MHz; $CDCl_3$) 3.08 and 3.18 (6H,2xs,$CONMe_2$), 7.47-7.52 (2H,m,6-H and 8-H), 7.75 (1H,m,7-H) and 8.28 (1H,dd,*J* 1.5 and 8Hz,5-H); υ_{max} (KBr)/cm^{-1} 1650 (CO) and 1620 ($COMe_2$); *m/z* 252 (m^+, 48%) and 72 (100).

---

[a] Yield calculated on the basis of 6-nitrochromone-2-carboxylic acid (**95**).

[b] Yield calculated on the basis of 3-chlorochromone-2-carboxylic acid (**99**).

2-(Dimethylamino)-3-(2-hydroxybenzoyl)-N,N-*dimethylacrylamide* (**115**).[49] - Dimethylamine (33% w/w solution in EtOH; 2.39ml, 132mmol) was added to a solution of *N,N*-dimethylchromone-2-carboxamide (**108**) (0.50g, 2.3mmol) in dry EtOH (17ml). The reaction mixture was stirred at room temperature for 20h. The solvent was 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 (**115**) (0.35g 58%), m.p. 166-167°C (from EtOH) (lit.,[49] 166-167°C); δ_H (400MHz; $CDCl_3$) 2.91 and 3.11 (6H,2xs,$CONMe_2$), 3.08 (6H,s,NMe_2), 5.77 (1H,s,3-H), 6.77-6.81 and 7.31-7.35 (2H,2xm,4′-H and 5′-H), 6.90 (1H,dd,*J* 1 and 9.4Hz,3′-H), 7.68 (1H,dd,*J* 1.6 and 9.7Hz,6′-H); δ_C (100MHz; $CDCl_3$) 34.43 ($CONMe_2$), 37.17 (NMe_2), 89.30 (C-3), 117.96 and 118.36 (C-3′ and C-5′), 120.44 (C-1′), 128.23 (C-6′), 134.09 (C-4′), 158.85 (C-2), 162.88 (C-2′), 166.79 (C-1) and 190.15 (C-4); υ_{max} (KBr)/cm^{-1} 3200-2500 (OH), 2920 (CH) and 1650 (CO).

3-(4-Chloro-2-hydroxybenzoyl)-2-(dimethylamino)-N,N-*dimethylacrylamide* (**116**). - The experimental procedure employed for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using 7-chloro-*N,N*-dimethylchromone-2-carboxamide (**109**) (1.00g, 3.97mmol), dry EtOH (25ml) and dimethylamine (33% w/w solution in EtOH; 3.53ml, 19.5mmol). In this case, the reaction time at room temperature was 20h. Work-up afforded a crude product which was chromatographed [flash chromatography on silica gel; elution with EtOAc : EtOH (5:2)] to give 3-(4-chloro-2-hydroxybenzoyl)-2-(dimethylamino)-*N.N*-dimethylacrylamide (**116**) (0.95g, 81%), m.p. 124°C (from EtOAc) (lit.,[49] 124-125°C); δ_H (400MHz;$CDCl_3$) 2.91 and 3.10 (6H,2xs,$CONMe_2$), 3.08 (6H,s,NMe_2), 5.67 (1H,s,3-H), 6.76 (1H,dd,*J* 2 and 8.5Hz,5′-H),

6.91 (1H,d,*J* 2Hz,3′-H), 7.59 (1H,d,*J* 8.6Hz,6′-H) and 13.71 (1H,s,OH); δ_C (100MHz;$CDCl_3$) 34.44 and 37.15 ($CONMe_2$), 40.58 (NMe_2), 88.94 (C-3), 118.34, 118.45 and 118.95 (C-3′,C-5′ and C-1′), 129.17 (C-6′), 139.44 (C-4′), 159.26 (C-2), 163.68 (C-2′), 166.55 (C-1) and 189.20 (C-4); υ_{max} (KBr)/cm^{-1} 3200-2400 (OH), 1660 (CO) and 1530 ($CONMe_2$).

3-(5-Chloro-2-hydroxybenzoyl)-2-(dimethylamino)-N,N-*dimethylacrylamide* (**117**). - The experimental procedure employed for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using 6-chloro-*N,N*-dimethylchromone-2-carboxamide (**110**) (0.55g, 2.2mmol), dry EtOH (14ml), and dimethylamine (33% w/w solution in EtOH; 1.94ml, 10.7mmol). In this case, the reaction time was 24h at room temperature. Work-up afforded a crude, yellow solid (0.63g) which was recrystallized from EtOAc to give *3-(5-Chloro-2-hydroxybenzoyl)-2-(dimethylamino)*-N,N-*dimethylacrylamide* (**117**) (0.40g, 64%), m.p. 184-186°C; (found: C, 56.3; H, 5.75; N, 9.3. $C_{14}H_{15}ClN_2O_3$ requires C, 56.7; H, 5.8; N. 9.4%); δ_H (400MHz; $CDCl_3$) 2.90 and 3.10 (6H,2xs,$CONMe_2$), 3.096 (6H,s,NMe_2), 5.65 (1H,s,3-H), 6.85 (1H,d,*J* 9Hz,5-H), 7.26 (1H,dd,*J* 2.5 and 8Hz,7-H), 7.61 (1H,d,*J* 2.5Hz,8-H) and 13.40 (1H,s,OH); δ_C (100MHz; $CDCl_3$) 34.39 and 37.09 ($CON\mathit{Me}_2$), 39.09 and 39.76 (NMe_2), 88.72 (C-3), 119.83 (C-3′), 121.13 (C-5′), 122.47 (C-1′), 127.53 (C-6′), 133.76 (C-4′), 159.54 (C-2), 161.36 (C-2′), 165.03 (C-1) and 188.72 (C-4); υ_{max} (KBr)/cm^{-1} 3300-2800 (OH) and 1660 (CO); *m/z* 296 (M^+, 12%) and 149 (100).

2-(Dimethylamino)-3-(2-hydroxy-5-methoxybenzoyl)-N,N-*dimethylacrylamide* (**118**). - The experimental procedure employed for the synthesis of 2-(dimethylamine)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using 6-methoxy-*N,N*-dimethylchromone-2-carboxamide (**111**) (0.60g, 2.43mmol), dry EtOH (13ml) and dimethylamine (33% w/w solution in EtOH; 2.6ml, 15mmol). In this case, the reaction time was 60h. at room temperature. Work-up afforded a crude product (0.60g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc:EtOH (2:1)] to give *2-(dimethylamino)-3-(2-hydroxy-5-methoxybenzoyl)*-N,N-*dimethylacrylamide* (**118**) (0.48g, 68%), m.p. 196-197°C (from EtOH) (Found: C, 61.5; H, 7.25; N, 9.95. $C_{15}H_{20}N_2O_4$ requires C, 61.6; H, 6.9; N, 9.6%); δ_H (400MHz; $CDCl_3$) 2.91 and 3.11 (6-H, 2xs, $CONMe_2$), 3.07 (6-H, s, NMe_2), 3.78 (3-H, s, OMe), 5.70 (1H, s, 3-H), 6.85 (1H, d, J 9Hz,3′-H), 6.98 (1H, dd,J 3 and 9Hz,4′-H) and 7.19 (1H,d.J 3Hz,6′-H); δ_C (100MHz; $CDCl_3$) 34.44 and 34.61 ($CONMe_2$), 37.17 (NMe_2), 56.19 (OMe), 89.35 (C-3), 151.18 (C-2), 157.02 (C-4′), 158.98 (C-2′), 166.75 (C-1), 189.76 (C-4) and 113.13, 118.79, 120.36 and 120.59 (4xArC); υ_{max} (KBr)/cm^{-1} 3200-2200 (OH), 1660 (CO) and 1540 (CO.N); *m/z* 292 (m^+, 14%) and 83(100).

2-(Dimethylamino)-3-(2-hydroxy-5-nitrobenzoyl)-N,N-*dimethylacrylamide* (**119**). - The experimental procedure employed for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using *N,N*-dimethyl-6-nitrochromone-2-carboxamide (**113**) (0.50g, 1.9mmol), dry EtOH (14ml) and dimethylamine (33% w/w solution in EtOH; 1.98ml, 11.0mmol). Work-up afforded a crude product which was chromatographed [flash chromatography on silica gel; elution with EtOAc : EtOH (2:1)] to give *2-(dimethylamino)-3-(2-hydroxy-5-nitrobenzoyl)*-N,N-*dimethylacrylamide* (**119**)

(0.54g, 92%), m.p. 192-193°C (from EtOAc); (Found: C, 54.4; H, 5.9; N, 14.0. $C_{14}H_{17}N_3O_5$ requires C, 54.7; H, 5.6; N, 13.7%); δ_H (400MHz;$CDCl_3$) 2.91 and 3.10 (6H,2xs,$CONMe_2$), 3.14 and 3.16 (6H,2xs,NMe_2), 5.75 (1H,s,3-H), 6.94 (1H,d,*J* 9.2Hz,3′-H), 8.19 (1H,dd,*J* 2.7 and 9.2Hz,4′-H), 8.61 (1H,d,*J* 2.7Hz,6′-H) and 13.49 (1H,s,OH); δ_C (100MHz;$CDCl_3$) 34.40 and 34.58 ($CONMe_2$), 40.00 and 40.86 (NMe_2), 87.99 (C-3), 119.12 and 119.26 (C-3′and C-5′), 124.63 (C-1′), 128.92 (C-6′), 138.84 (C-4′), 160.61 (C-2′), 165.92 (C-2), 168.55 (C-1) and 180.09 (C-4); υ_{max} (KBr)/cm^{-1} 3000-2200 (OH) and 1620 (CO); *m/z* 307 (m^+, 16%) and 149 (100).

Attempted preparation of *2-(dimethylamino)-3-(2-hydroxybenzoyl)-3-chloro*-N,N-*dimethylacrylamide*. - The experimental procedure for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using 3-chloro-*N,N*-dimethylchromone-2-carboxamide (**114**) (1.0g, 3.97mmol), dry EtOH (25ml) and dimethylamine (33% w/w solution in EtOH; 3.50ml, 19.24mmol). The reaction mixture was stirred at room temperature for 3d. and monitored by TLC. After work-up, a solid was obtained, which was shown by ^1H nmr spectroscopy to be the starting material.

Attempted preparation of *2-(dimethylamino)-3-(2′-hydroxybenzoyl)*-N,N,*3-trimethylacrylamide*. -

Method 1.

The experimental procedure for the synthesis of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**115**) was followed, using *N,N*,3-trimethylchromone-2-carboxamide (**112**) (0.56g, 2.42mmol), dry EtOH (18ml) and dimethylamine (33% w/w solution in EtOH; 2.50ml, 13.9mmol). The reaction mixture was stirred at room temperature for 3d. After

work-up, a solid product was obtained, which was shown by ^{1}H nmr spectroscopy to be the starting material.

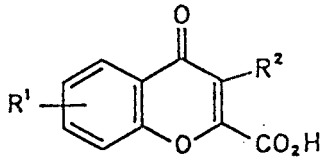
Method 2.

Method 1 was repeated at 35°C. After 5d additional dimethylamine (33% w/w solution in EtOH; 2.50ml, 13.86mmol) was added to speed up the reaction. The reaction mixture was stirred for a further 2d. After work-up, a solid product was obtained, which was shown by ^{1}H NMR spectroscopy to be the starting material.

3.3 Potentiometric Determination Of Acid Dissociation Constants (pK$_a$'s) of Chromone-2-carboxylic acids.

Standard 0.01**M** solutions of the chromone-2-carboxylic acids in aqueous ethanol (50% v/v) were prepared by dissloving the accurately weighed acids (Table 4) in 95% EtOH, by warming in a waterbath and stirring. After cooling, the ethanolic solutions were diluted to the required volume with distilled water and then stirred overnight. Standard 0.01**M**-NaOH solutions were obtained by diluting standard 0.1**M**-NaOH with distilled water. However, for the 6-methoxychromone-2-carboxylic acid (**91**), 0.005**M** standard solutions of the acid and the base were used. Buffers of pH 2.0, 4.0 and 7.0 were used to calibrate the pH meter and were prepared from commercial vials or tablets diluted to the required volumes.

Table 4. Masses of chromone-2-carboxylic acids and volumes of aqueous ethanol (50% v/v) used to prepare standard solutions.

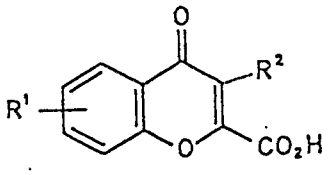


Compd.	R^1	R^2	Mass (g)	Vol (ml)	Molarity (M)
87	H	H	0.03803	20	0.01
88	7-Cl	H	0.05615	25	0.01
89	6-Cl	H	0.05615	25	0.01
90	8-Cl	H	0.05615	25	0.01
91	6-MeO	H	0.02202	20	0.005
94	H	Me	0.04084	20	0.01
95	6-NO_2	H	0.04703	20	0.01
99	H	Cl	0.04492	20	0.01

The pH measurements were made on a Knick model 646 digital pH-meter with an Ingold electrode, calibrated using the standard method.[56] The standard 0.01**M**-chromone-2-carboxylic acid solutions (5ml) were titrated with *ca.* 10ml of 0.01**M**-NaOH maintaining the temperature at 25°C in a waterbath and stirring throughout (except when taking pH readings).

In all cases, the potentiometric determinations were replicated and the derived pK_a values are summarized in Table 5. The reported pK_a value, in each case, is the mean of three pKa values determined for each acid. Sample titration curves for each of the acids are reproduced below (pp.73-80).

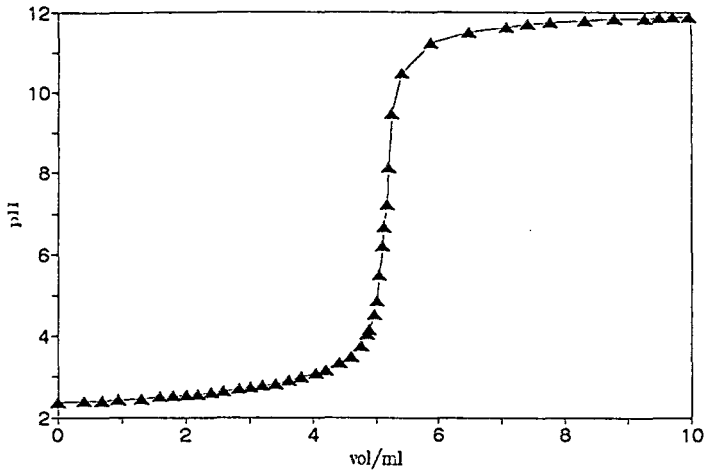
Table 5 **Acid Dissociation Constants (pK_a) of Chromone-2-carboxylic Acids At 25°C.**

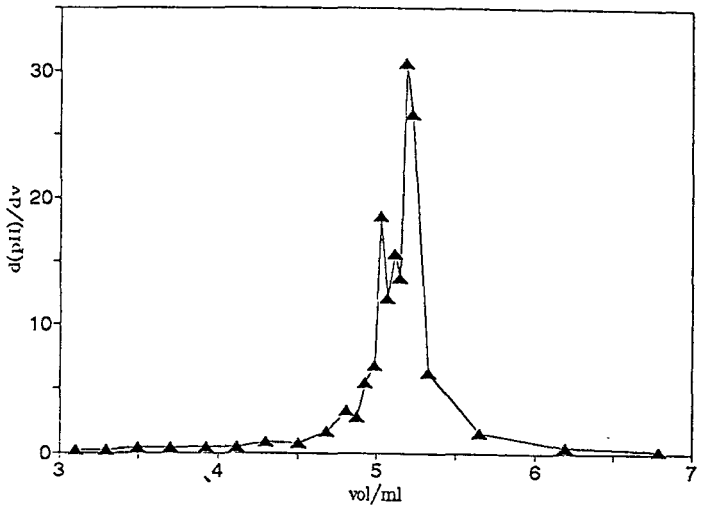


			pK_a[a]			
Compound	R^1	R^2	Detn. 1	Detn. 2	Detn. 3	Mean Value[c]
87	H	H	2.65	2.66	2.65	2.65±0.005
88	7-Cl	H	2.66	2.67	2.66	2.66±0.005
89	6-Cl	H	2.65	2.66	2.64	2.65±0.008
90	8-Cl	H	2.67	2.62	2.66	2.65±0.022
91	6-MeO	H	2.91[b]	2.91[b]	2.89[b]	2.90[b]±0.009
94	H	Me	2.71	2.69	2.71	2.71±0.009
95	6-NO_2	H	2.65	2.64	2.63	2.64±0.009
99	H	Cl	2.46	2.49	2.49	2.48±0.014

[a] Obtained by potentiometric titration of 0.01**M**-aqueous ethanonic solutions (50% v/v).
[b] Obtained by titration of 0.005**M**-aqueous ethanonic titration of 0.005**M**-aqueous ethanolic solutions (50% v/v).
[c] Followed by the standard deviation.

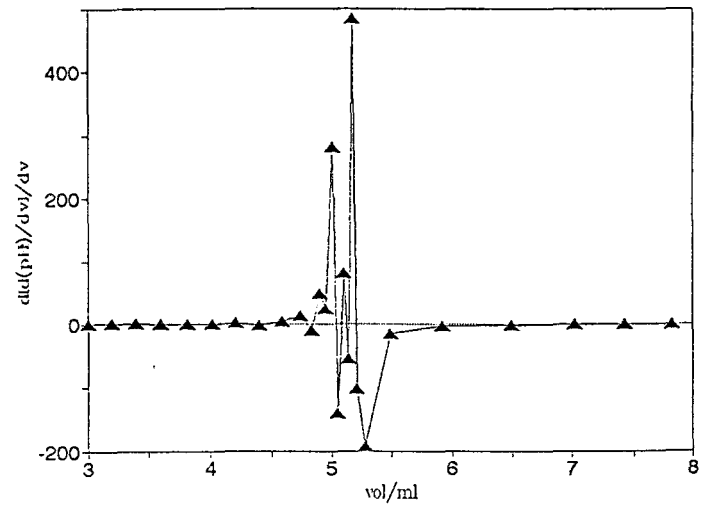
R=H





R=H

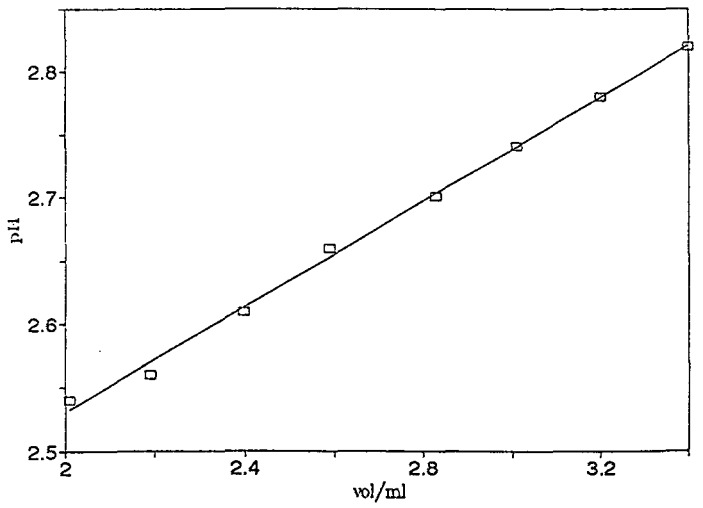
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.000	2.37					
2	0.420	2.39	0.210	0.048			
3	0.690	2.40	0.555	0.037	0.383	-0.031	
4	0.941	2.42	0.816	0.080	0.685	0.164	
5	1.300	2.45	1.121	0.084	0.968	0.013	
6	1.600	2.50	1.450	0.167	1.285	0.252	
7	1.800	2.52	1.700	0.100	1.575	-0.267	
8	2.010	2.54	1.905	0.095	1.803	-0.023	2.532547
9	2.190	2.56	2.100	0.111	2.002	0.081	2.569832
10	2.400	2.61	2.295	0.238	2.198	0.651	2.613331
11	2.590	2.66	2.495	0.263	2.395	0.125	2.652688
12	2.830	2.70	2.710	0.167	2.603	-0.449	2.702401
13	3.010	2.74	2.920	0.222	2.815	0.265	2.739687
14	3.200	2.78	3.105	0.211	3.013	-0.063	2.779043
15	3.400	2.82	3.300	0.200	3.203	-0.054	2.820471
16	3.600	2.90	3.500	0.400	3.400	1.000	
17	3.810	2.98	3.705	0.381	3.603	-0.093	
18	4.040	3.08	3.925	0.435	3.815	0.245	
19	4.200	3.15	4.120	0.437	4.023	0.014	
20	4.410	3.33	4.305	0.857	4.213	2.268	
21	4.600	3.47	4.505	0.737	4.405	-0.602	
22	4.760	3.74	4.680	1.687	4.593	5.432	
23	4.850	4.04	4.805	3.333	4.743	13.167	
24	4.890	4.15	4.870	2.750	4.838	-8.974	
25	4.960	4.53	4.925	5.429	4.897	48.701	
26	5.008	4.86	4.984	6.875	4.955	24.516	
27	5.043	5.51	5.026	18.571	5.005	281.842	
28	5.100	6.20	5.072	12.105	5.049	-140.569	
29	5.130	6.67	5.115	15.667	5.093	81.871	
30	5.170	7.22	5.150	13.750	5.133	-54.762	
31	5.200	8.14	5.185	30.667	5.168	483.333	
32	5.250	9.47	5.225	26.600	5.205	-101.667	
33	5.410	10.48	5.330	6.312	5.278	-193.214	
34	5.890	11.22	5.650	1.542	5.490	-14.909	
35	6.500	11.50	6.195	0.459	5.923	-1.987	
36	7.080	11.63	6.790	0.224	6.493	-0.395	
37	7.430	11.70	7.255	0.200	7.023	-0.052	
38	7.780	11.75	7.605	0.143	7.430	-0.163	
39	8.320	11.79	8.050	0.074	7.828	-0.155	
40	8.800	11.83	8.560	11.810	8.305	5.942	
41	9.260	11.84	9.030	11.835	8.795	11.823	
42	9.500	11.86	9.380	11.850	9.205	11.843	
43	9.710	11.87	9.605	11.865	9.493	11.857	
44	9.980	11.88	9.845	11.875	9.725	11.870	

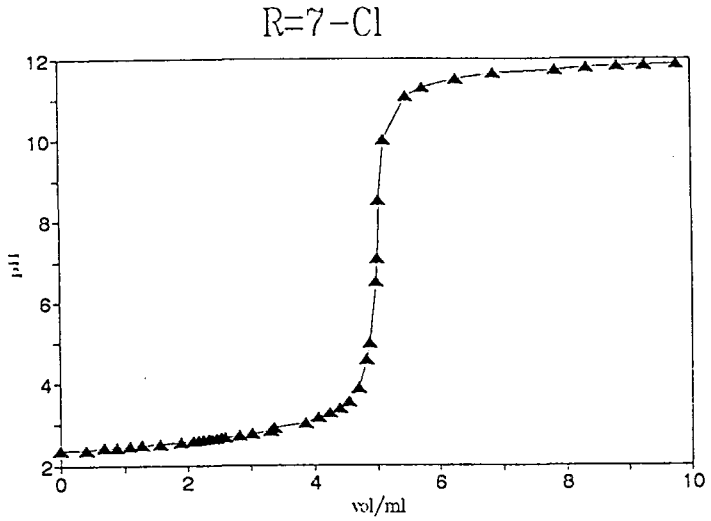


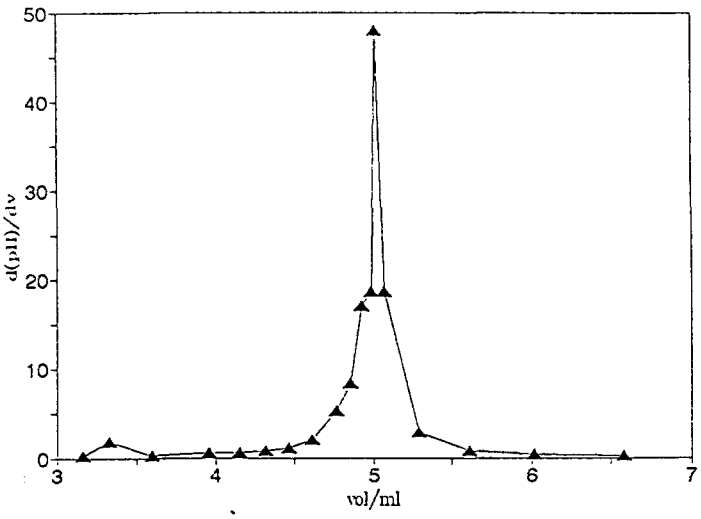
Regression Output:

Constant	2.116195
Std Err of Y Est	0.006107
R Squared	0.996926
No. of Observations	8
Degrees of Freedom	6

X Coefficient(s) 0.20714
Std Err of Coef. 0.004696





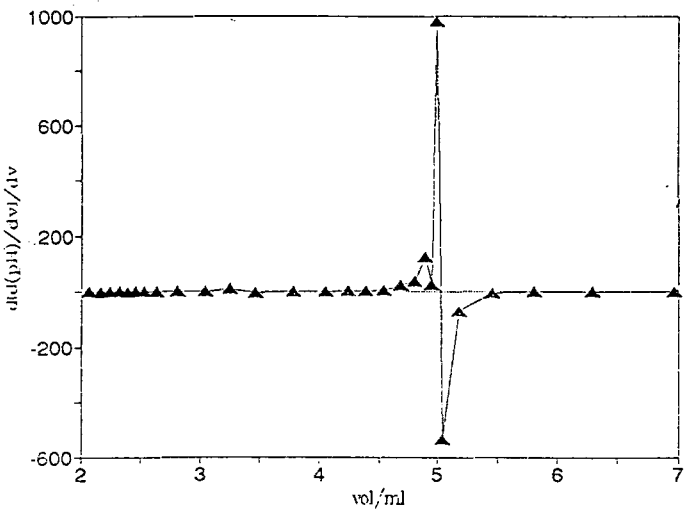


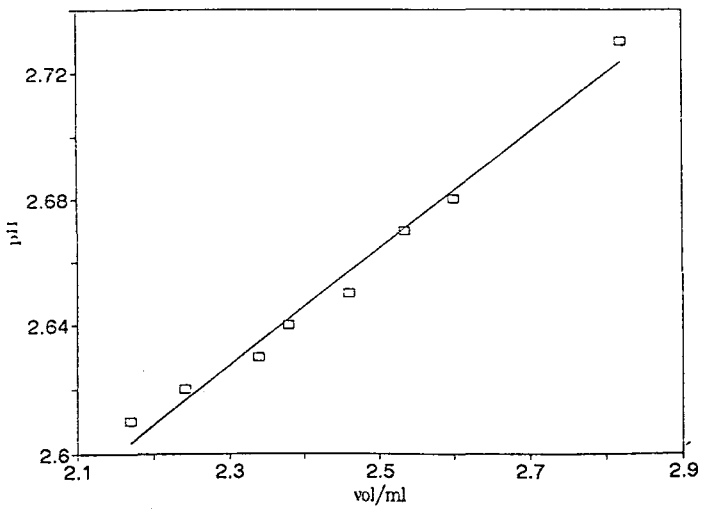
R=7-Cl

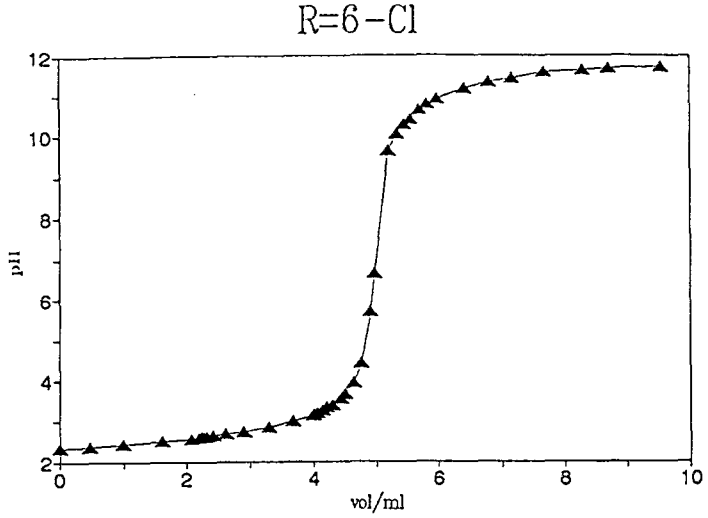
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.000	2.37					
2	0.400	2.38	0.200	0.025			
3	0.680	2.42	0.540	0.143	0.370	0.347	
4	0.880	2.43	0.780	0.050	0.660	-0.387	
5	1.090	2.46	0.985	0.143	0.883	0.453	
6	1.280	2.48	1.185	0.105	1.085	-0.188	
7	1.560	2.51	1.420	0.107	1.303	0.008	
8	1.898	2.56	1.729	0.148	1.575	0.132	
9	2.100	2.59	1.999	0.149	1.864	0.002	
10	2.170	2.61	2.135	0.286	2.067	1.009	2.603259
11	2.242	2.62	2.206	0.139	2.171	-2.068	2.616557
12	2.340	2.63	2.291	0.102	2.249	-0.434	2.634657
13	2.380	2.64	2.360	0.250	2.326	2.144	2.642045
14	2.460	2.65	2.420	0.125	2.390	-2.083	2.656821
15	2.535	2.67	2.498	0.267	2.459	1.828	2.670673
16	2.600	2.68	2.568	0.154	2.533	-1.612	2.682678
17	2.820	2.73	2.710	0.227	2.639	0.515	2.72331
18	3.020	2.77	2.920	0.200	2.815	-0.130	
19	3.310	2.83	3.165	0.207	3.043	0.028	
20	3.355	2.91	3.333	1.778	3.249	9.378	
21	3.850	3.03	3.603	0.242	3.468	-5.686	
22	4.070	3.16	3.960	0.591	3.781	0.975	
23	4.240	3.26	4.155	0.588	4.058	-0.014	
24	4.400	3.39	4.320	0.813	4.238	1.359	
25	4.535	3.54	4.468	1.111	4.394	2.024	
26	4.700	3.88	4.618	2.061	4.543	6.330	
27	4.830	4.56	4.765	5.231	4.691	21.493	
28	4.880	4.98	4.855	8.400	4.810	35.214	
29	4.970	6.52	4.925	17.111	4.890	124.444	
30	5.000	7.08	4.985	18.667	4.955	25.926	
31	5.030	8.52	5.015	48.000	5.000	977.778	
32	5.110	10.01	5.070	18.625	5.043	-534.091	
33	5.470	11.07	5.290	2.944	5.180	-71.275	
34	5.750	11.29	5.610	0.786	5.450	-6.746	
35	6.280	11.50	6.015	0.396	5.813	-0.962	
36	6.880	11.64	6.580	0.233	6.298	-0.288	
37	7.840	11.72	7.360	0.083	6.970	-0.192	
38	8.340	11.78	8.090	0.120	7.725	0.050	
39	8.840	11.81	8.590	0.060	8.340	-0.120	
40	9.260	11.83	9.050	0.048	8.820	-0.027	
41	9.780	11.85	9.520	0.038	9.265	-0.019	

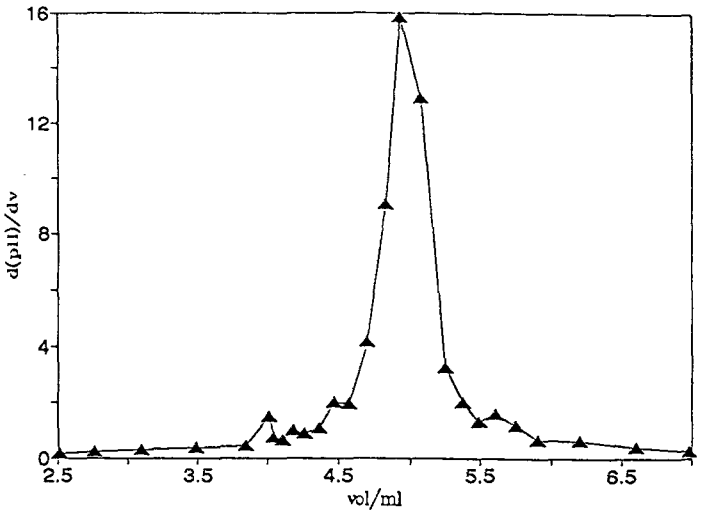
Regression Output:

Constant	2.202473
Std Err of Y Est	0.005508
R Squared	0.982805
No. of Observations	8
Degrees of Freedom	6
X Coefficient(s)	0.184694
Std Err of Coef.	0.009974







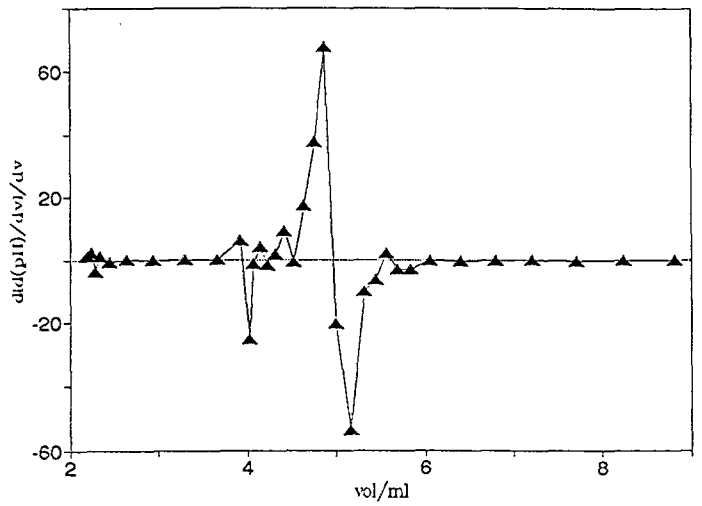


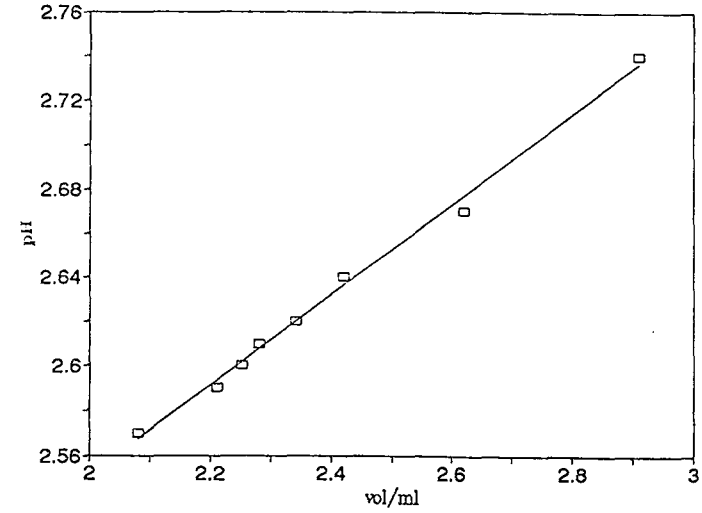
R=6-Cl

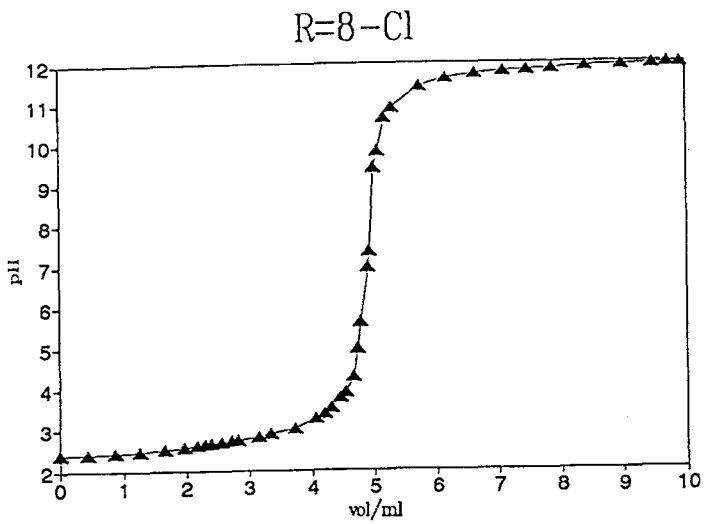
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.000	2.34					
2	0.485	2.38	0.243	0.082			
3	0.990	2.43	0.738	0.099	0.490	0.033	
4	1.610	2.50	1.300	0.113	1.019	0.025	
5	2.080	2.57	1.845	0.149	1.573	0.066	2.566967
6	2.210	2.59	2.145	0.154	1.995	0.016	2.593507
7	2.250	2.60	2.230	0.250	2.188	1.131	2.601674
8	2.280	2.61	2.265	0.333	2.248	2.381	2.607798
9	2.340	2.62	2.310	0.167	2.288	-3.704	2.620047
10	2.420	2.64	2.380	0.250	2.345	1.190	2.63638
11	2.620	2.67	2.520	0.150	2.450	-0.714	2.677211
12	2.910	2.74	2.765	0.241	2.643	0.373	2.736415
13	3.300	2.85	3.105	0.282	2.935	0.120	
14	3.680	2.99	3.490	0.368	3.298	0.224	
15	4.000	3.13	3.840	0.437	3.665	0.197	
16	4.020	3.16	4.010	1.500	3.925	6.250	
17	4.060	3.19	4.040	0.750	4.025	-25.000	
18	4.150	3.25	4.105	0.667	4.073	-1.282	
19	4.220	3.32	4.185	1.000	4.145	4.167	
20	4.300	3.39	4.260	0.875	4.223	-1.667	
21	4.440	3.54	4.370	1.071	4.315	1.786	
22	4.500	3.66	4.470	2.000	4.420	9.286	
23	4.640	3.93	4.570	1.929	4.520	-0.714	
24	4.760	4.43	4.700	4.167	4.635	17.216	
25	4.900	5.70	4.830	9.071	4.765	37.729	
26	4.960	6.65	4.930	15.833	4.880	67.619	
27	5.190	9.62	5.075	12.913	5.003	-20.140	
28	5.320	10.04	5.255	3.231	5.165	-53.790	
29	5.440	10.28	5.380	2.000	5.318	-9.846	
30	5.540	10.41	5.490	1.300	5.435	-6.364	
31	5.680	10.63	5.610	1.571	5.550	2.262	
32	5.820	10.79	5.750	1.143	5.680	-3.061	
33	5.985	10.90	5.903	0.667	5.826	-3.123	
34	6.415	11.17	6.200	0.628	6.051	-0.130	
35	6.800	11.32	6.608	0.390	6.404	-0.585	
36	7.170	11.42	6.985	0.270	6.796	-0.316	
37	7.677	11.57	7.424	0.296	7.204	0.058	
38	8.300	11.62	7.989	0.080	7.706	-0.382	
39	8.705	11.66	8.503	0.099	8.246	0.036	
40	9.550	11.71	9.128	0.059	8.815	-0.063	

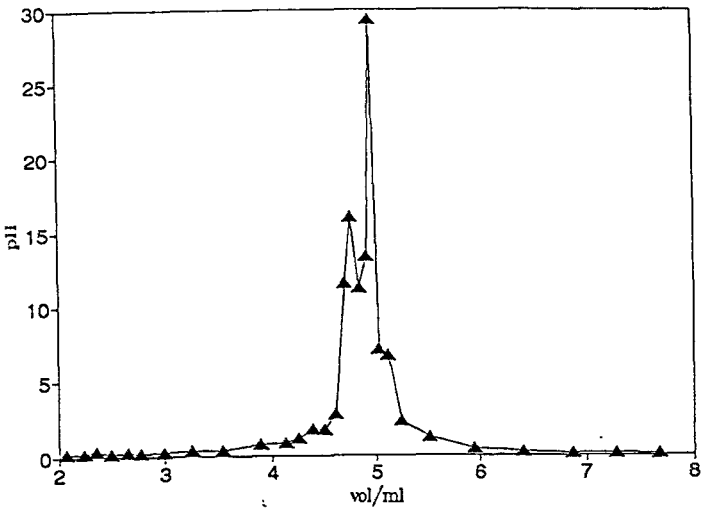
Regression Output:

Constant	2.142327
Std Err of Y Est	0.004225
R Squared	0.99475
No. of Observations	8
Degrees of Freedom	6
X Coefficient(s)	0.204154
Std Err of Coef.	0.006055







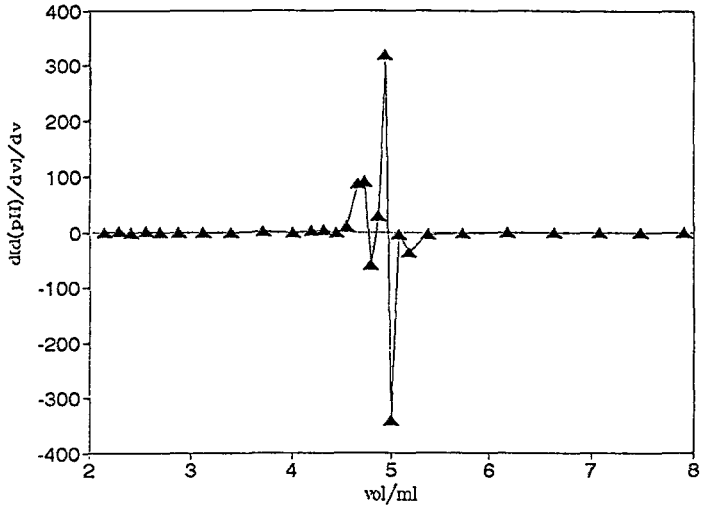


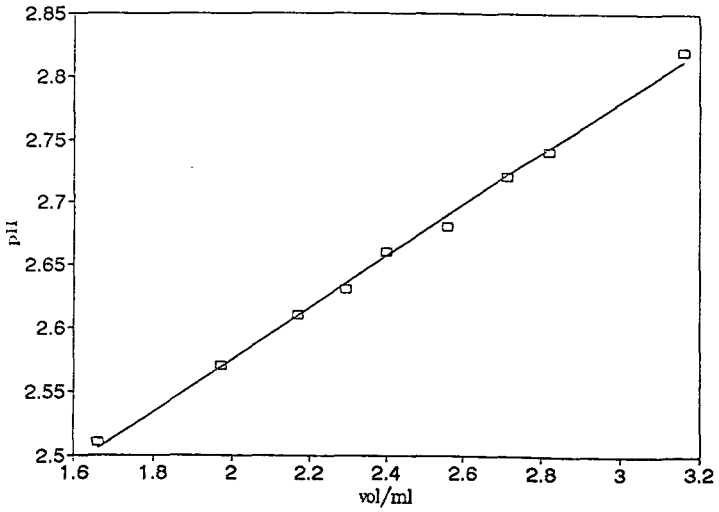
R=8-Cl

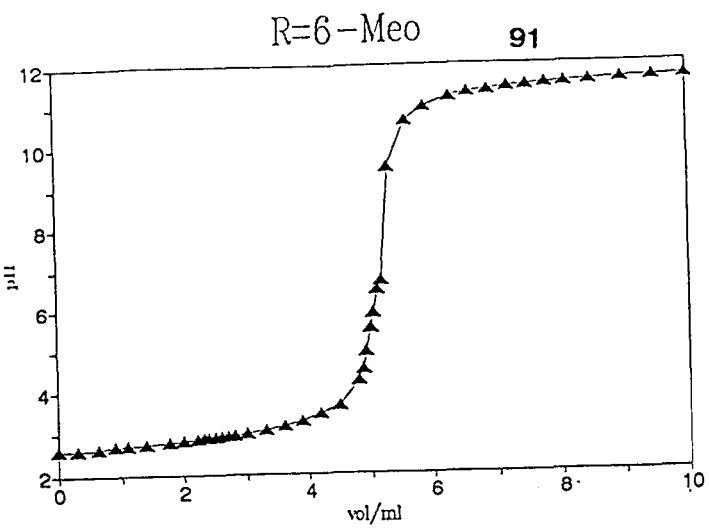
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.000	2.39					
2	0.440	2.40	0.220	0.023			
3	0.860	2.43	0.650	0.071	0.435	0.113	
4	1.250	2.47	1.055	0.103	0.853	0.077	
5	1.660	2.51	1.455	0.098	1.255	-0.013	2.505379
6	1.972	2.57	1.816	0.192	1.636	0.262	2.569107
7	2.170	2.61	2.071	0.202	1.944	0.038	2.609549
8	2.294	2.63	2.232	0.161	2.152	-0.253	2.634877
9	2.400	2.66	2.347	0.283	2.290	1.059	2.656528
10	2.560	2.68	2.480	0.125	2.414	-1.188	2.689208
11	2.716	2.72	2.638	0.256	2.559	0.832	2.721072
12	2.821	2.74	2.769	0.190	2.703	-0.505	2.742519
13	3.160	2.82	2.991	0.236	2.880	0.205	2.811761
14	3.340	2.88	3.250	0.333	3.120	0.375	
15	3.730	3.02	3.535	0.359	3.393	0.090	
16	4.060	3.27	3.895	0.758	3.715	1.107	
17	4.210	3.39	4.135	0.800	4.015	0.177	
18	4.315	3.51	4.263	1.143	4.199	2.689	
19	4.470	3.78	4.393	1.742	4.328	4.608	
20	4.540	3.90	4.505	1.714	4.449	-0.246	
21	4.680	4.28	4.610	2.714	4.558	9.524	
22	4.740	4.97	4.710	11.500	4.660	87.857	
23	4.780	5.61	4.760	16.000	4.735	90.000	
24	4.900	6.95	4.840	11.167	4.800	-60.417	
25	4.930	7.35	4.915	13.333	4.878	28.889	
26	5.000	9.40	4.965	29.286	4.940	319.048	
27	5.060	9.82	5.030	7.000	4.998	-342.857	
28	5.180	10.62	5.120	6.667	5.075	-3.704	
29	5.300	10.89	5.240	2.250	5.180	-36.806	
30	5.730	11.40	5.515	1.186	5.378	-3.869	
31	6.170	11.60	5.950	0.455	5.733	-1.682	
32	6.650	11.71	6.410	0.229	6.180	-0.490	
33	7.100	11.76	6.875	0.111	6.643	-0.254	
34	7.480	11.80	7.290	0.105	7.083	-0.014	
35	7.880	11.83	7.680	0.075	7.485	-0.078	
36	8.410	11.88	8.145	0.094	7.913	0.042	
37	9.000	11.91	8.705	0.051	8.425	-0.078	
38	9.490	11.94	9.245	0.061	8.975	0.019	
39	9.730	11.96	9.610	0.083	9.428	0.061	
40	9.935	11.96	9.833	0.000	9.721	-0.375	

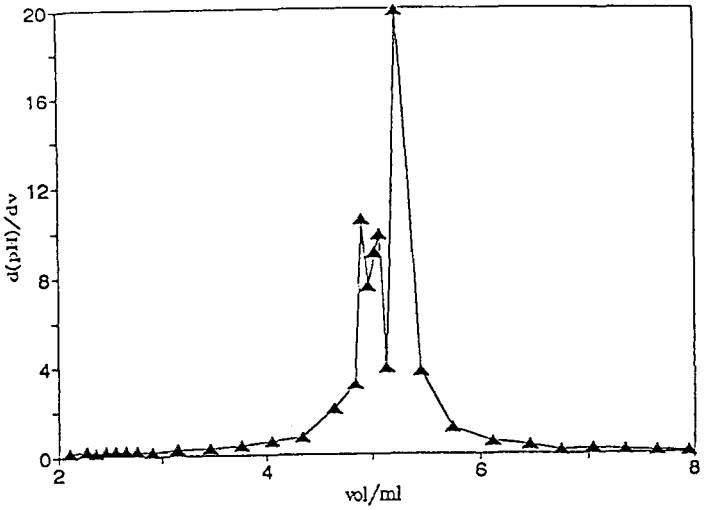
Regression Output:

Constant	2.166316
Std Err of Y Est	0.005585
R Squared	0.996881
No. of Observations	9
Degrees of Freedom	7
X Coefficient(s)	0.204255
Std Err of Coef.	0.004319







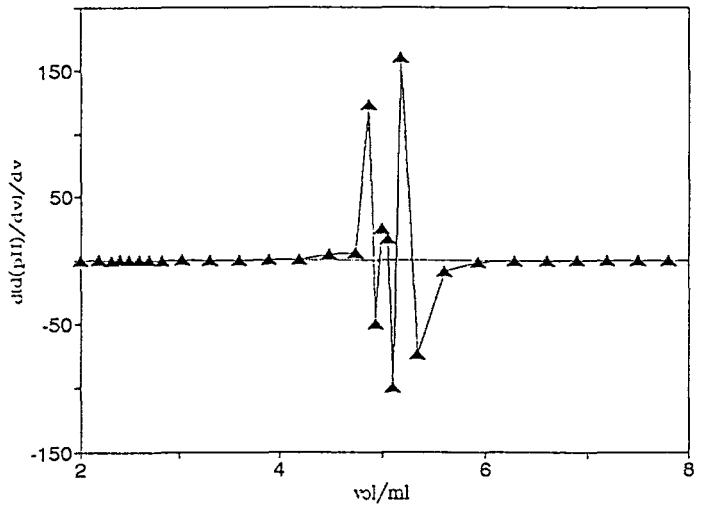


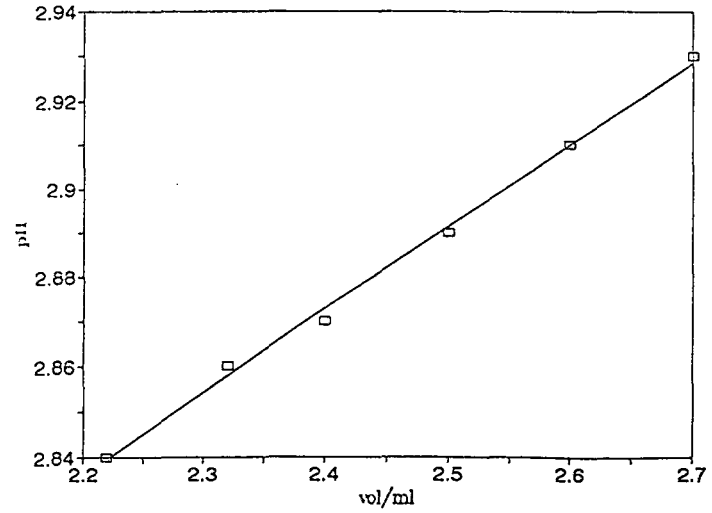
R=6-Meo

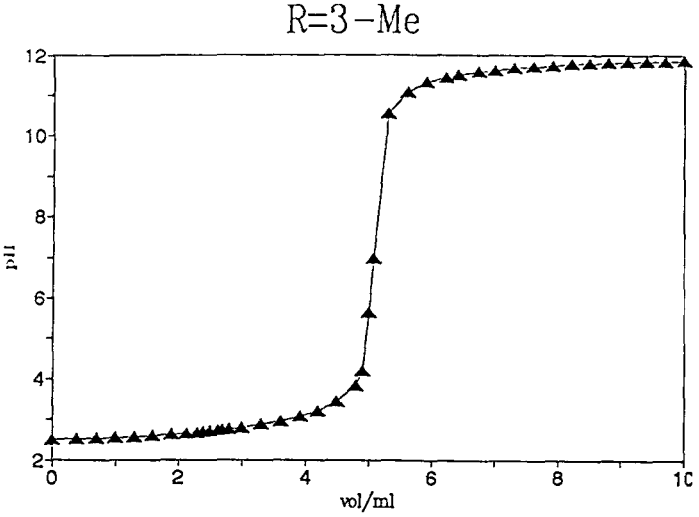
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.00	2.60					
2	0.30	2.61	0.150	0.033			
3	0.64	2.64	0.470	0.088	0.310	0.172	
4	0.90	2.68	0.770	0.154	0.620	0.219	
5	1.10	2.70	1.000	0.100	0.885	-0.234	
6	1.40	2.73	1.250	0.100	1.125	-0.000	
7	1.78	2.77	1.590	0.105	1.420	0.015	
8	2.00	2.81	1.890	0.182	1.740	0.255	
9	2.22	2.84	2.110	0.136	2.000	-0.207	2.839323
10	2.32	2.86	2.270	0.200	2.190	0.398	2.857919
11	2.40	2.87	2.360	0.125	2.315	-0.833	2.872796
12	2.50	2.89	2.450	0.200	2.405	0.833	2.891392
13	2.60	2.91	2.550	0.200	2.500	0.000	2.909987
14	2.70	2.93	2.650	0.200	2.600	0.000	2.928583
15	2.80	2.95	2.750	0.200	2.700	0.000	
16	3.00	2.98	2.900	0.150	2.825	-0.333	
17	3.30	3.06	3.150	0.267	3.025	0.467	
18	3.60	3.15	3.450	0.300	3.300	0.111	
19	3.90	3.27	3.750	0.400	3.600	0.333	
20	4.20	3.44	4.050	0.567	3.900	0.556	
21	4.50	3.66	4.350	0.733	4.200	0.556	
22	4.80	4.27	4.650	2.033	4.500	4.333	
23	4.88	4.52	4.840	3.125	4.745	5.746	
24	4.92	4.94	4.900	10.500	4.870	122.917	
25	5.00	5.54	4.960	7.500	4.930	-50.000	
26	5.04	5.90	5.020	9.000	4.990	25.000	
27	5.10	6.49	5.070	9.833	5.045	16.667	
28	5.16	6.72	5.130	3.833	5.100	-100.000	
29	5.30	9.50	5.230	19.857	5.180	160.238	
30	5.60	10.61	5.450	3.700	5.340	-73.442	
31	5.90	10.96	5.750	1.167	5.600	-8.444	
32	6.32	11.19	6.110	0.548	5.930	-1.720	
33	6.60	11.29	6.460	0.357	6.285	-0.544	
34	6.90	11.34	6.750	0.167	6.605	-0.657	
35	7.20	11.41	7.050	0.233	6.900	0.222	
36	7.50	11.46	7.350	0.167	7.200	-0.222	
37	7.80	11.49	7.650	0.100	7.500	-0.222	
38	8.10	11.51	7.950	0.067	7.800	-0.111	
39	8.50	11.55	8.300	0.100	8.125	0.095	
40	9.00	11.59	8.750	0.080	8.525	-0.044	
41	9.50	11.62	9.250	0.060	9.000	-0.040	
42	10.00	11.65	9.750	0.060	9.500	0.000	

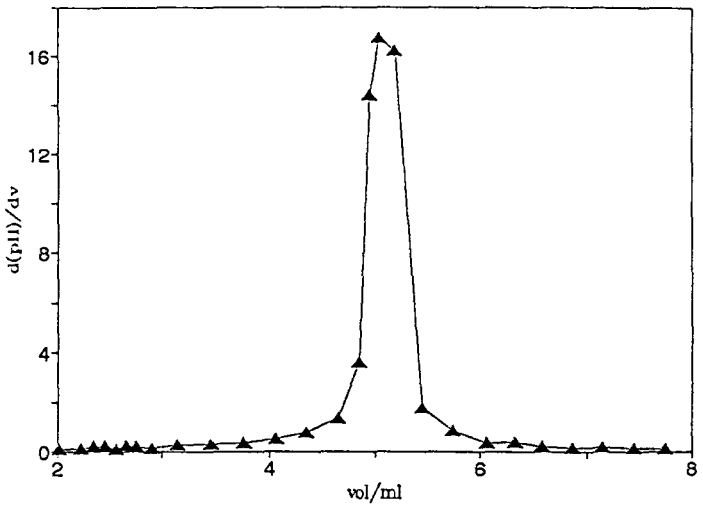
Regression Output:

Constant	2.426494
Std Err of Y Est	0.002034
R Squared	0.997009
No. of Observations	6
Degrees of Freedom	4
Std Err of Coef.	0.005092
X Coefficient(s)	0.185959
Std Err of Coef.	0.005092







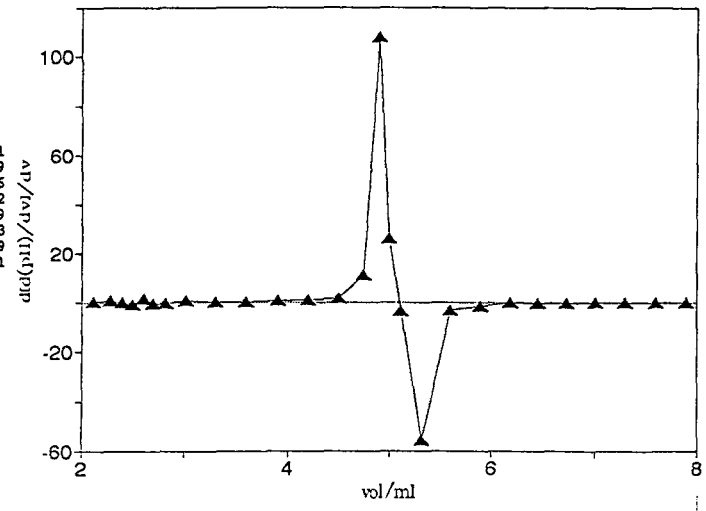


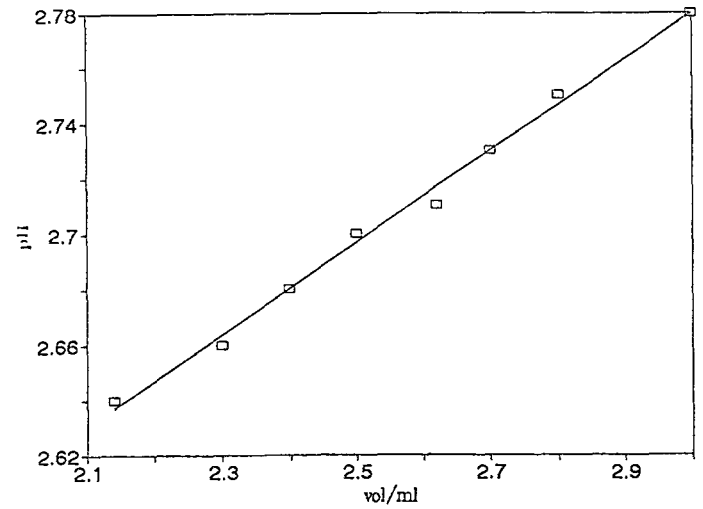
R=3-Me

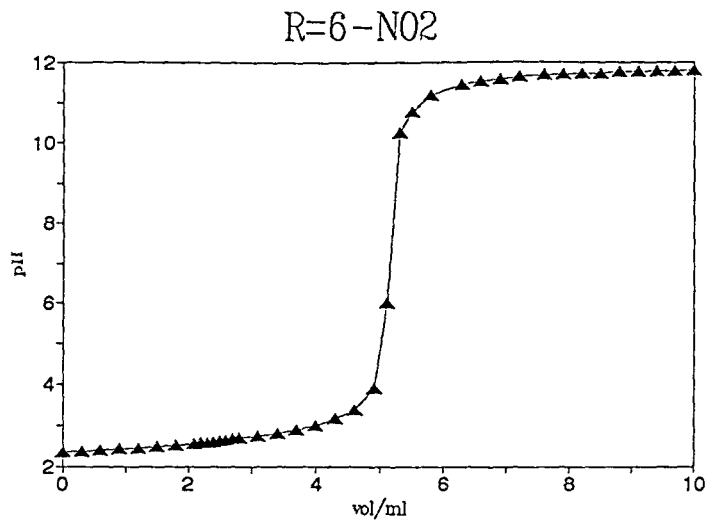
No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.00	2.49					
2	0.40	2.51	0.200	0.050			
3	0.72	2.53	0.560	0.063	0.380	0.035	
4	1.00	2.54	0.860	0.036	0.710	-0.089	
5	1.30	2.57	1.150	0.100	1.005	0.222	
6	1.60	2.59	1.450	0.067	1.300	-0.111	
7	1.90	2.62	1.750	0.100	1.600	0.111	
8	2.14	2.64	2.020	0.083	1.885	-0.062	2.636921
9	2.30	2.66	2.220	0.125	2.120	0.208	2.66349
10	2.40	2.68	2.350	0.200	2.285	0.577	2.680096
11	2.50	2.70	2.450	0.200	2.400	0.000	2.696702
12	2.62	2.71	2.560	0.083	2.505	-1.061	2.716629
13	2.70	2.73	2.660	0.250	2.610	1.667	2.729913
14	2.80	2.75	2.750	0.200	2.705	-0.556	2.746519
15	3.00	2.78	2.900	0.150	2.825	-0.333	2.779731
16	3.30	2.86	3.150	0.267	3.025	0.467	
17	3.60	2.95	3.450	0.300	3.300	0.111	
18	3.92	3.06	3.760	0.344	3.605	0.141	
19	4.20	3.20	4.060	0.500	3.910	0.521	
20	4.50	3.43	4.350	0.767	4.205	0.920	
21	4.80	3.83	4.650	1.333	4.500	1.889	
22	4.90	4.19	4.850	3.600	4.750	11.333	
23	5.00	5.63	4.950	14.400	4.900	108.000	
24	5.08	6.97	5.040	16.750	4.995	26.111	
25	5.30	10.54	5.190	16.227	5.115	-3.485	
26	5.60	11.07	5.450	1.767	5.320	-55.618	
27	5.90	11.32	5.750	0.833	5.600	-3.111	
28	6.22	11.43	6.060	0.344	5.905	-1.579	
29	6.42	11.50	6.320	0.350	6.190	0.024	
30	6.74	11.57	6.580	0.219	6.450	-0.505	
31	7.00	11.61	6.870	0.154	6.725	-0.224	
32	7.30	11.66	7.150	0.167	7.010	0.046	
33	7.60	11.70	7.450	0.133	7.300	-0.111	
34	7.90	11.73	7.750	0.100	7.600	-0.111	
35	8.20	11.76	8.050	0.100	7.900	-0.000	
36	8.50	11.78	8.350	0.067	8.200	-0.111	
37	8.80	11.80	8.650	0.067	8.500	0.000	
38	9.10	11.82	8.950	0.067	8.800	-0.000	
39	9.40	11.83	9.250	0.033	9.100	-0.111	
40	9.70	11.84	9.550	0.033	9.400	0.000	
41	10.00	11.85	9.850	0.033	9.700	-0.000	

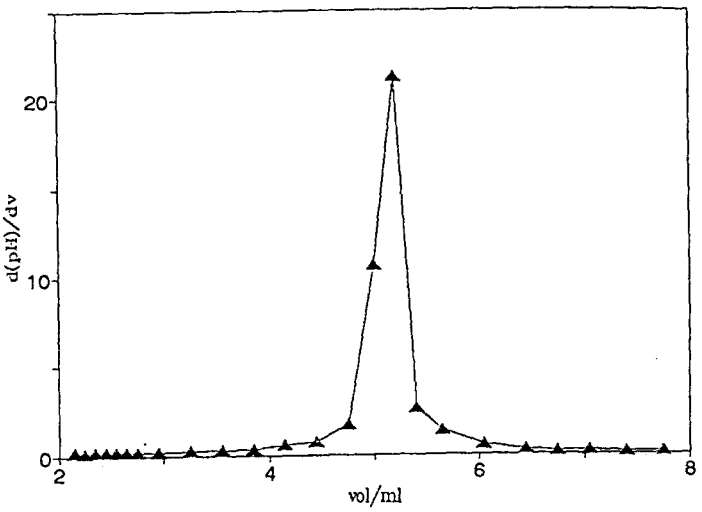
Regression Output:

Constant	2.281557
Std Err of Y Est	0.003845
R Squared	0.994161
No. of Observations	8
Degrees of Freedom	6
X Coefficient(s)	0.166058
Std Err of Coef.	0.005196







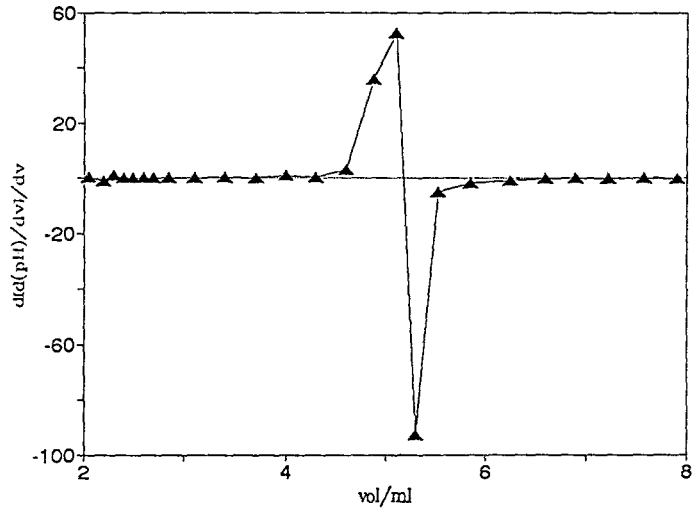


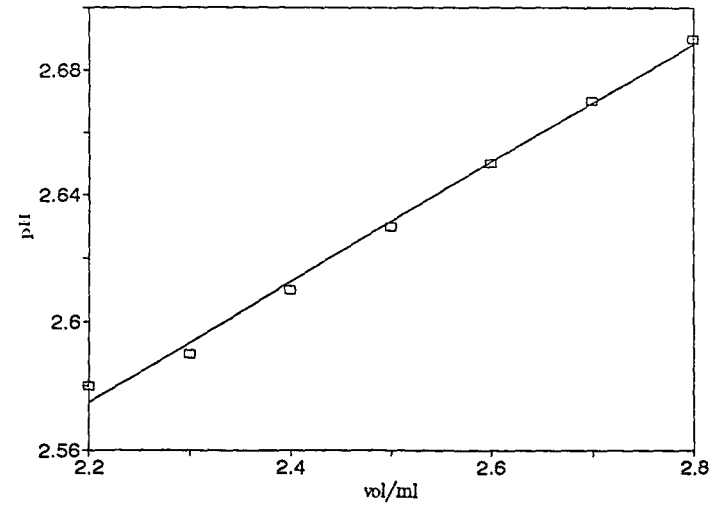
R=6-NO2

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.00	2.35					
2	0.30	2.37	0.150	0.067			
3	0.60	2.39	0.450	0.067	0.300	0.000	
4	0.90	2.42	0.750	0.100	0.600	0.111	
5	1.20	2.45	1.050	0.100	0.900	0.000	
6	1.50	2.48	1.350	0.100	1.200	-0.000	
7	1.80	2.52	1.650	0.133	1.500	0.111	
8	2.10	2.56	1.950	0.133	1.800	0.000	
9	2.20	2.58	2.150	0.200	2.050	0.333	2.574643
10	2.30	2.59	2.250	0.100	2.200	-1.000	2.593571
11	2.40	2.61	2.350	0.200	2.300	1.000	2.6125
12	2.50	2.63	2.450	0.200	2.400	0.000	2.631429
13	2.60	2.65	2.550	0.200	2.500	0.000	2.650357
14	2.70	2.67	2.650	0.200	2.600	0.000	2.669286
15	2.80	2.69	2.750	0.200	2.700	0.000	2.688214
16	3.10	2.75	2.950	0.200	2.850	-0.000	
17	3.40	2.82	3.250	0.233	3.100	0.111	
18	3.70	2.91	3.550	0.300	3.400	0.222	
19	4.00	3.01	3.850	0.333	3.700	0.111	
20	4.30	3.18	4.150	0.567	4.000	0.778	
21	4.60	3.39	4.450	0.700	4.300	0.444	
22	4.90	3.89	4.750	1.667	4.600	3.222	
23	5.10	6.02	5.000	10.650	4.875	35.933	
24	5.30	10.26	5.200	21.200	5.100	52.750	
25	5.50	10.78	5.400	2.600	5.300	-93.000	
26	5.80	11.18	5.650	1.333	5.525	-5.067	
27	6.30	11.46	6.050	0.560	5.850	-1.933	
28	6.60	11.53	6.450	0.233	6.250	-0.817	
29	6.90	11.58	6.750	0.167	6.600	-0.222	
30	7.20	11.64	7.050	0.200	6.900	0.111	
31	7.60	11.68	7.400	0.100	7.225	-0.286	
32	7.90	11.71	7.750	0.100	7.575	0.000	
33	8.20	11.72	8.050	0.033	7.900	-0.222	
34	8.50	11.73	8.350	0.033	8.200	-0.000	
35	8.80	11.76	8.650	0.100	8.500	0.222	
36	9.10	11.77	8.950	0.033	8.800	-0.222	
37	9.40	11.78	9.250	0.033	9.100	-0.000	
38	9.70	11.79	9.550	0.033	9.400	0.000	
39	10.00	11.80	9.850	0.033	9.700	0.000	

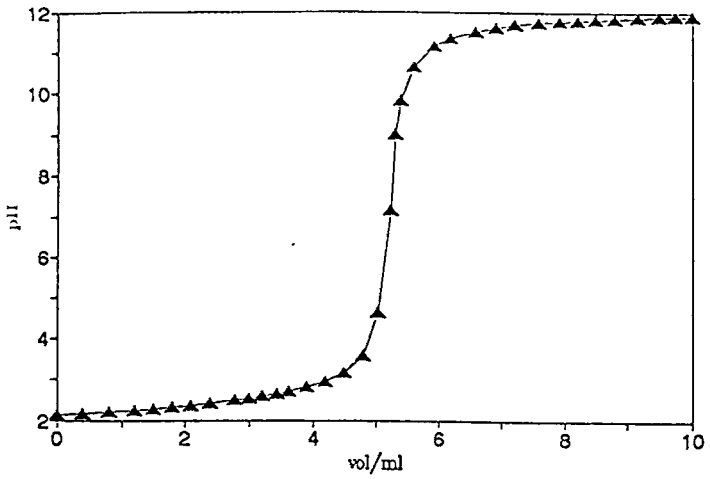
Regression Output:

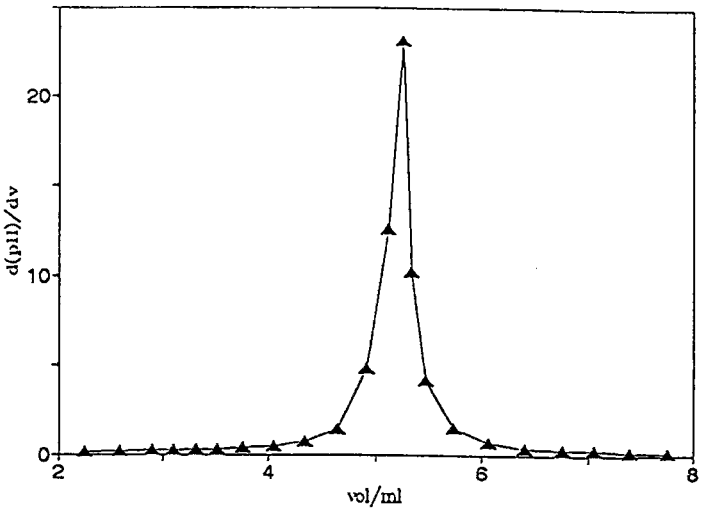
Constant	2.158214
Std Err of Y Est	0.003273
R Squared	0.994688
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	0.189286
Std Err of Coef.	0.006186





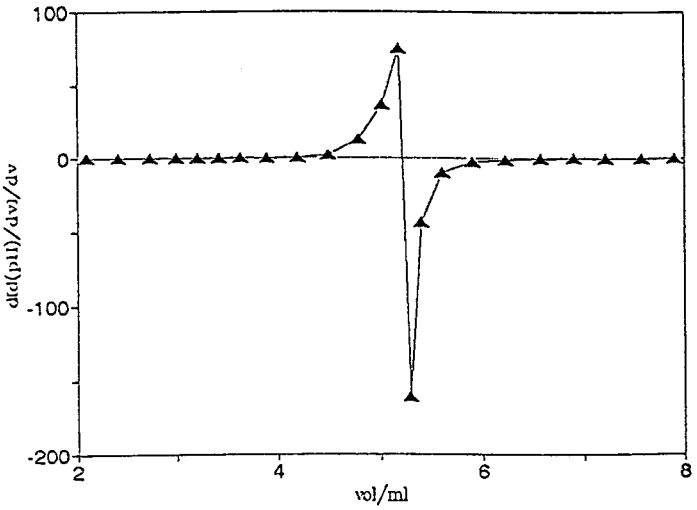
R=3-CL





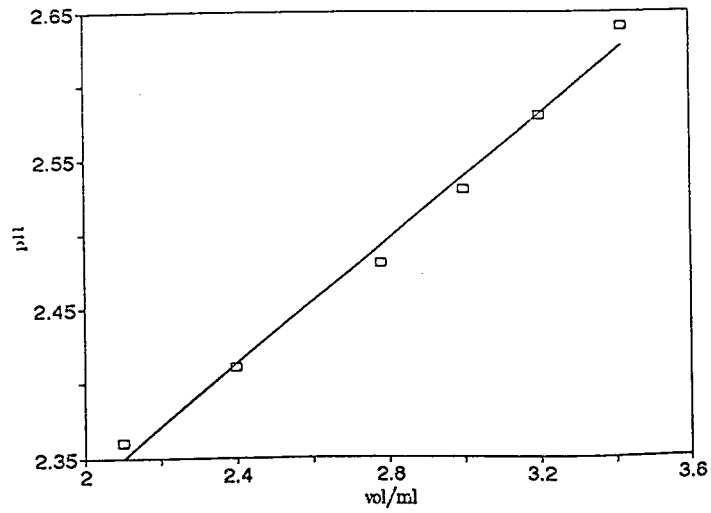
R=3-Cl

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V	
1	0.00	2.14					
2	0.40	2.16	0.200	0.050			
3	0.80	2.20	0.600	0.100	0.400	0.125	
4	1.20	2.23	1.000	0.075	0.800	-0.063	
5	1.50	2.27	1.350	0.133	1.175	0.167	
6	1.80	2.31	1.650	0.133	1.500	0.000	
7	2.10	2.36	1.950	0.167	1.800	0.111	2.349359
8	2.40	2.41	2.250	0.167	2.100	0.000	2.412418
9	2.78	2.48	2.590	0.184	2.420	0.052	2.492293
10	3.00	2.53	2.890	0.227	2.740	0.144	2.538536
11	3.20	2.58	3.100	0.250	2.995	0.108	2.580575
12	3.42	2.64	3.310	0.273	3.205	0.108	2.626818
13	3.60	2.69	3.510	0.278	3.410	0.025	
14	3.90	2.81	3.750	0.400	3.630	0.509	
15	4.20	2.95	4.050	0.467	3.900	0.222	
16	4.50	3.16	4.350	0.700	4.200	0.778	
17	4.80	3.58	4.650	1.400	4.500	2.333	
18	5.02	4.64	4.910	4.818	4.780	13.147	
19	5.22	7.16	5.120	12.600	5.015	37.056	
20	5.30	9.01	5.260	23.125	5.190	75.179	
21	5.38	9.83	5.340	10.250	5.300	-160.937	
22	5.58	10.66	5.480	4.150	5.410	-43.571	
23	5.92	11.17	5.750	1.500	5.615	-9.815	
24	6.20	11.36	6.060	0.679	5.905	-2.650	
25	6.60	11.51	6.400	0.375	6.230	-0.893	
26	6.92	11.60	6.760	0.281	6.580	-0.260	
27	7.20	11.68	7.060	0.286	6.910	0.015	
28	7.58	11.74	7.390	0.158	7.225	-0.387	
29	7.92	11.77	7.750	0.088	7.570	-0.193	
30	8.20	11.79	8.060	0.071	7.905	-0.054	
31	8.50	11.82	8.350	0.100	8.205	0.099	
32	8.80	11.84	8.650	0.067	8.500	-0.111	
33	9.16	11.86	8.980	0.056	8.815	-0.034	
34	9.50	11.88	9.330	0.059	9.155	0.009	
35	9.74	11.89	9.620	0.042	9.475	-0.059	
36	10.00	11.90	9.870	0.038	9.745	-0.013	



Regression Output:

Constant	1.907947
Std Err of Y Est	0.01137
R Squared	0.990598
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.210196
Std Err of Coef.	0.010239



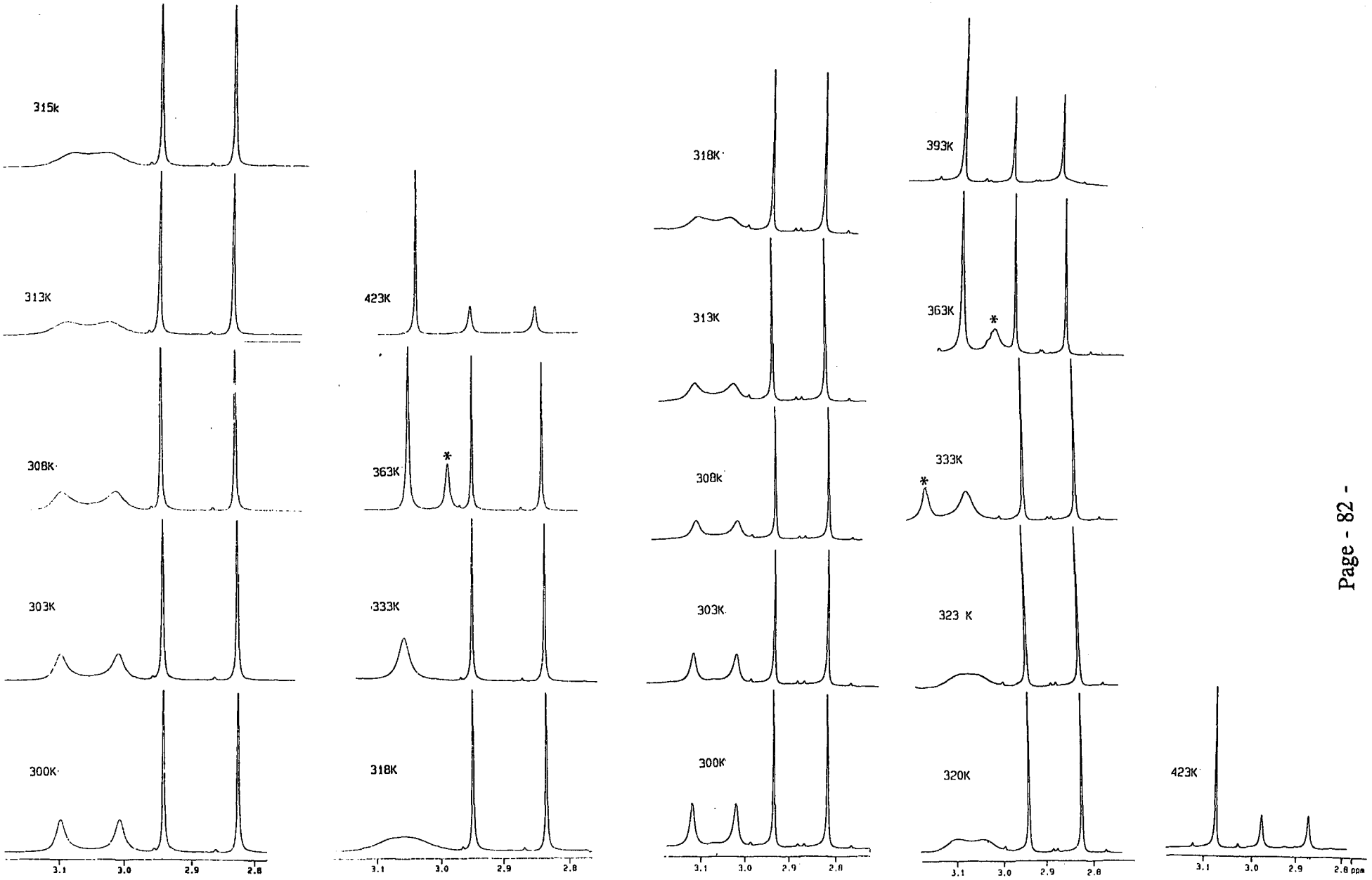
3.4 DNMR Studies of rotational isomerism in acrylamide derivatives

Variable-temperature ^1H NMR spectra were recorded on a Bruker 400 AMX spectrometer, from DMSO-d_6 solutions of the acrylamides (**115-119**).

The coalescence temperatures (T_c) for C-NMe_2 rotation were obtained from the variable-temperature spectra. The frequency differences at coalescence ($\Delta\nu_c$) were obtained from variable-temperature data by extrapolation of linear plots of the frequency ($\Delta\nu$) against temperature (T). The rotational energy barriers (ΔG^*) were calculated from the coalescence temperature (T_c) and frequency separation at coalescence ($\Delta\nu_c$) using equation 1 (p42). The estimated errors in ΔG^* were calculated assuming maximum errors of 2K in T_c and 2Hz in $\Delta\nu_c$.

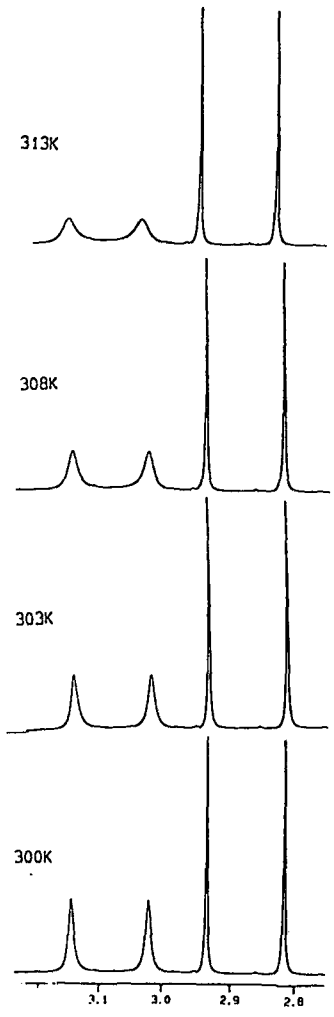
For the carboxamide (CO-NMe_2) rotation, the isomerisation rate constants were calculated using equation 2(p42). The "notional" value ($logk^1$) was obtained from plots of logk against 1/T and was consequently used to estimate the rotational energy barriers (ΔG^*) at 423K using equation 3 (p42).

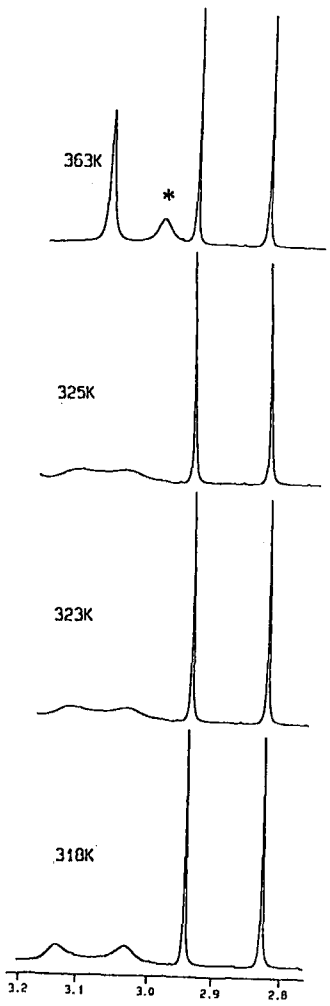
The rotational energy barriers (ΔG^*) for the C-NMe_2 and CO-NMe_2 rotation in the parent acrylamide **115** and its analogues (**116-119**) are summarised in Table 3 (p44). The variable-temperature spectra and plots of the frequency separation ($\Delta\nu$) against temperature (T), followed by plots of logk against 1/T are shown below.



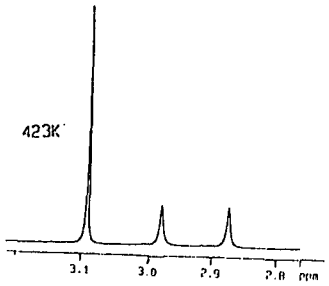
115 **116**

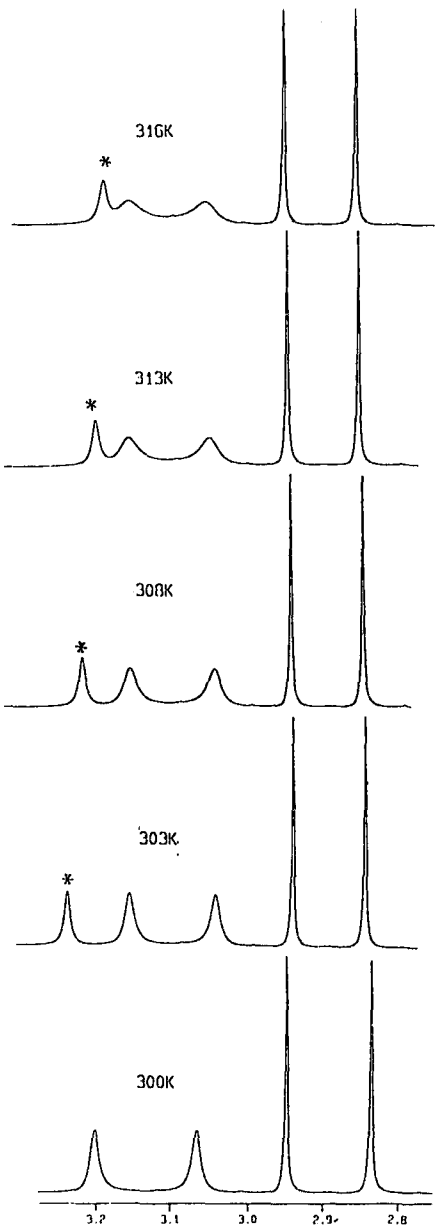
* = H_2O peak

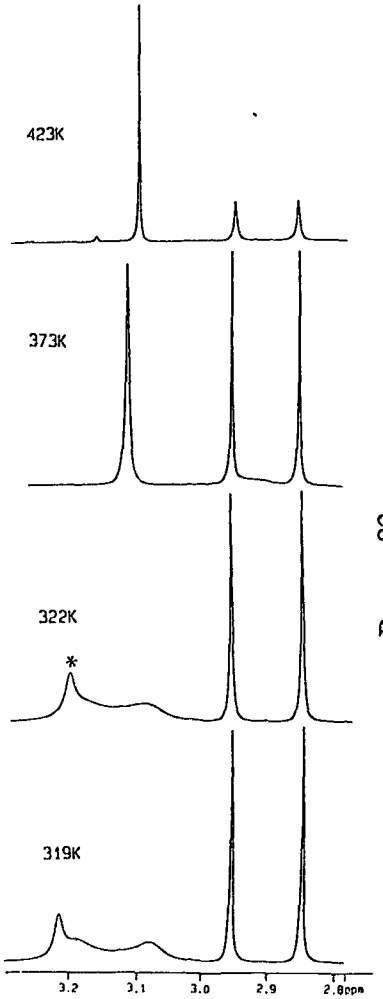

313K
308K
303K
300K
3.1
3.0
2.9
2.8


363K
325K
323K
318K
3.2
3.1
3.0
2.9
2.8

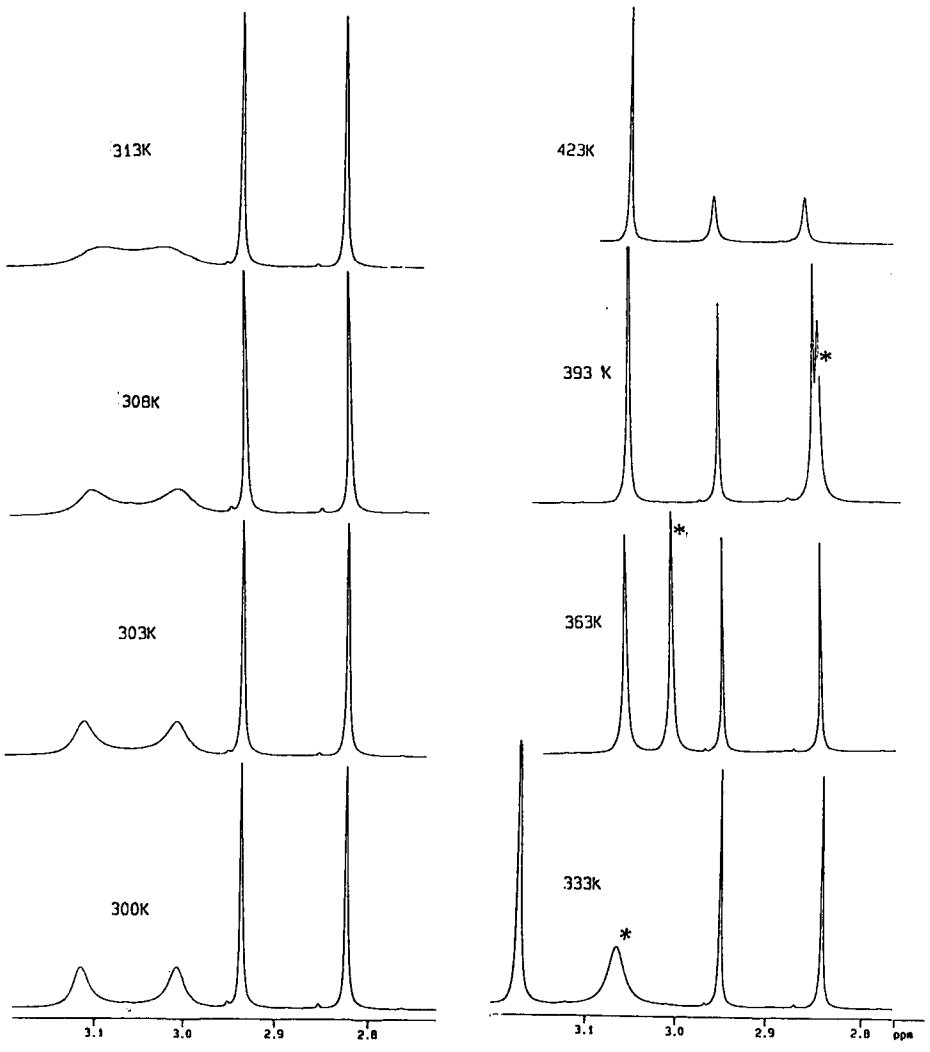
117


423K
3.1
3.0
2.9
2.8 ppm

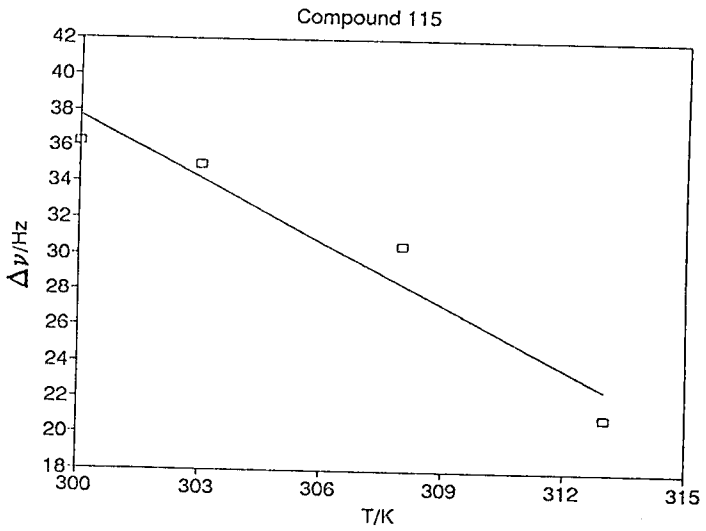

316K
313K
308K
303K
300K
3.2
3.1
3.0
2.9
2.8


423K
373K
322K
319K
3.2
3.1
3.0
2.9
2.8ppm

119



118



Compound 115

No.	T/K	Δν/Hz	Y(CALC.)
1	300	36.26	37.71
2	303	35.01	34.22
3	308	30.58	28.39
4	313	21.03	22.56

Regression Output:

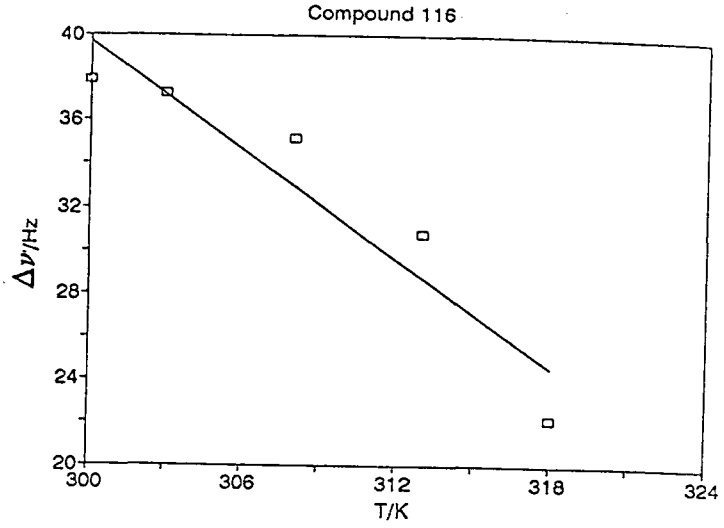
Constant	387.3661
Std Err of Y Est	2.223379
R Squared	0.930867
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-1.16551
Std Err of Coef.	0.224595

Compound 116

No.	T/K	$\Delta\nu$/Hz	Y(CALC.)
1	300	37.89	39.70
2	303	37.22	37.18
3	308	35.18	32.98
4	313	30.78	28.78
5	318	22.16	24.59

Regression Output:

Constant	291.5921
Std Err of Y Est	2.447724
R Squared	0.89319
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.83964
Std Err of Coef.	0.167637

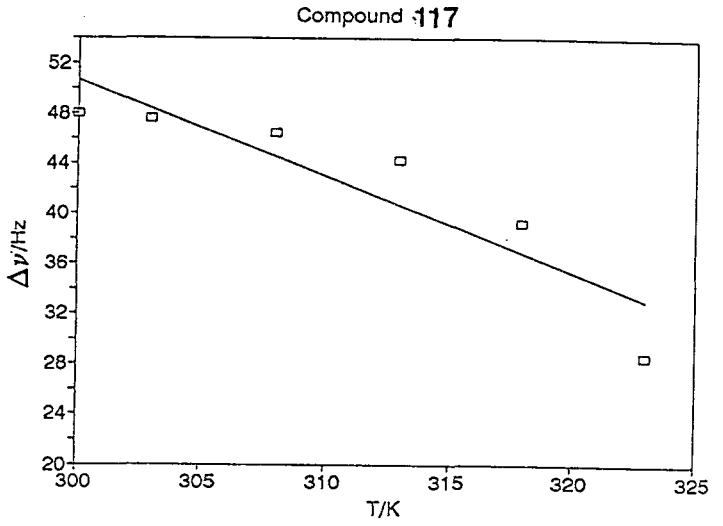


Compound 117

No.	T/K	$\Delta\nu$/Hz	Y(CALC.)
1	300	48.03	50.67
2	303	47.59	48.37
3	308	46.46	44.54
4	313	44.26	40.70
5	318	39.23	36.87
6	323	28.61	33.04

Regression Output:

Constant	280.6512
Std Err of Y Est	3.503286
R Squared	0.823905
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	-0.76661
Std Err of Coef.	0.177207

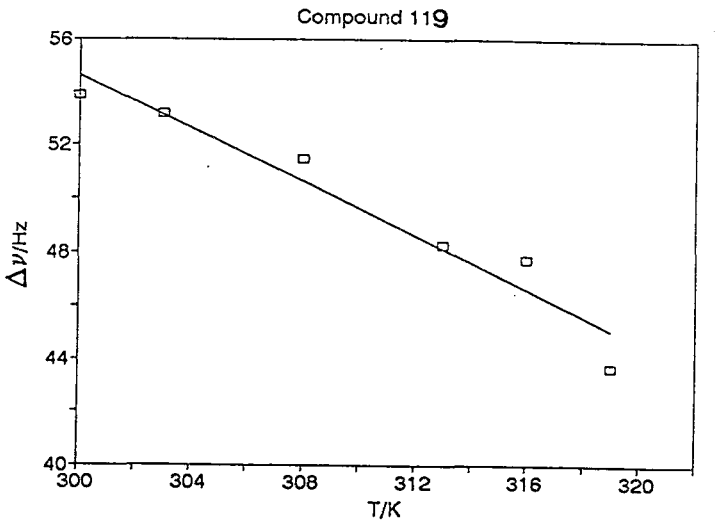


Compound 119

No.	T/K	$\Delta\nu$/Hz	Y(CALC.)
1	300	53.88	54.63
2	303	53.17	53.12
3	308	51.46	50.62
4	313	48.27	48.12
5	316	47.73	46.62
6	319	43.72	45.12

Regression Output:

Constant	204.7532
Std Err of Y Est	1.057146
R Squared	0.939833
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	-0.50042
Std Err of Coef.	0.063309



Compd. 118

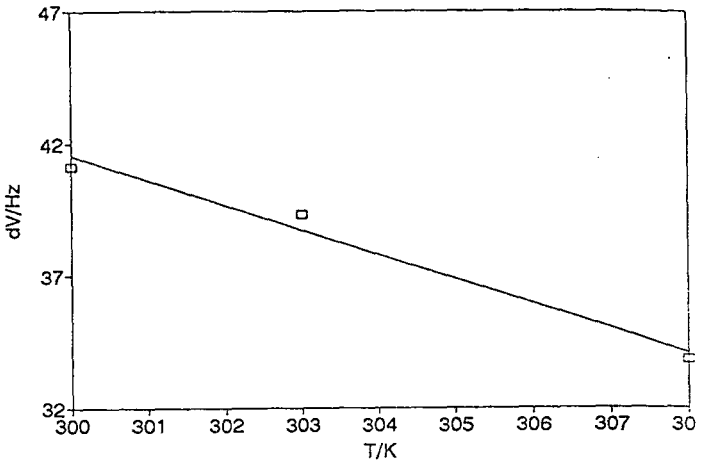
No.	T/K	dV/Hz	Y(CALC.)
1	300	41.17	41.55
2	303	39.36	38.74
3	308	33.83	34.06

Regression Output:

Constant	322.5751
Std Err of Y Est	0.761655
R Squared	0.980163
No. of Observations	3
Degrees of Freedom	1

X Coefficient(s) -0.93673
Std Err of Coef. 0.133262

Compound 118



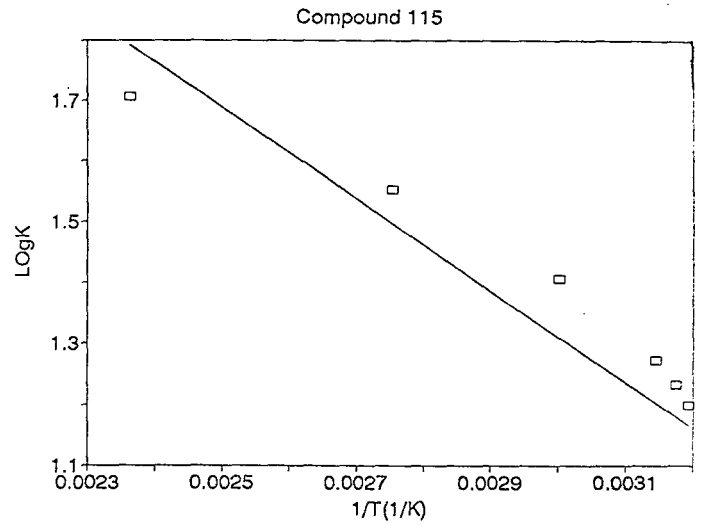
Compound 115

No.	T/K	1/T	δ_0	δ	X	LogK	Y(CALC.)
1	300	0.00333	46.48				
2	303	0.00330	46.48	46.35	7.72	0.888	1.085
3	308	0.00325	46.48	46.14	12.47	1.096	1.125
4	313	0.00319	46.48	45.93	15.84	1.200	1.165
5	315	0.00317	46.48	45.84	17.08	1.233	1.180
6	318	0.00314	46.48	45.71	18.72	1.272	1.202
7	333	0.00300	46.48	45.04	25.51	1.407	1.309
8	363	0.00275	46.48	43.61	35.73	1.553	1.497
9	423	0.00236	46.48	40.45	50.88	1.707	1.791

Regression Output:

Constant	3.574963
Std Err of Y Est	0.106946
R Squared	0.853219
No. of Observations	8
Degrees of Freedom	6

X Coefficient(s) -754.451
Std Err of Coef. 127.75



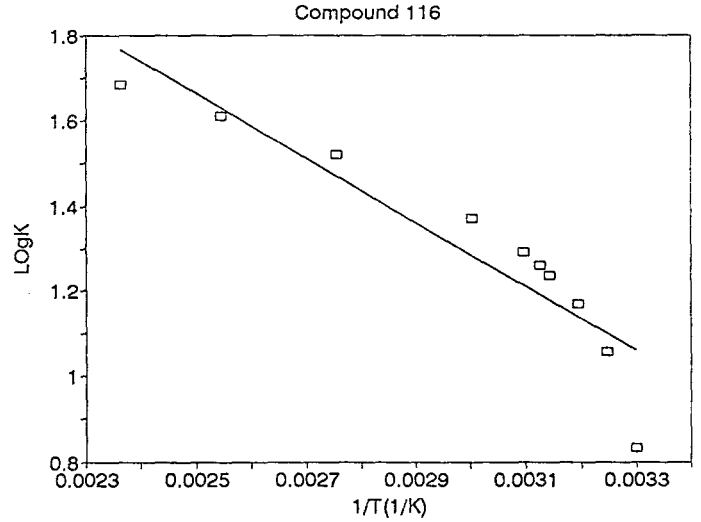
Compound 116

No.	T/K	1/T	δ_0	δ	X	LogK	Y(CALC.)
1	300	0.00333	46.81				
2	303	0.00330	46.81	46.71	6.80	0.832	1.060
3	308	0.00325	46.81	46.53	11.36	1.055	1.100
4	313	0.00319	46.81	46.34	14.70	1.167	1.139
5	318	0.00314	46.81	46.16	17.28	1.237	1.177
6	320	0.00313	46.81	46.09	18.18	1.259	1.192
7	323	0.00310	46.81	45.97	19.62	1.293	1.214
8	333	0.00300	46.81	45.59	23.60	1.373	1.284
9	363	0.00275	46.81	44.35	33.28	1.522	1.472
10	393	0.00254	46.81	43.04	40.90	1.612	1.630
11	423	0.00236	46.81	41.46	48.29	1.684	1.767

Regression Output:

Constant	3.552336
Std Err of Y Est	0.103973
R Squared	0.85607
No. of Observations	10
Degrees of Freedom	8

X Coefficient(s) -755.289



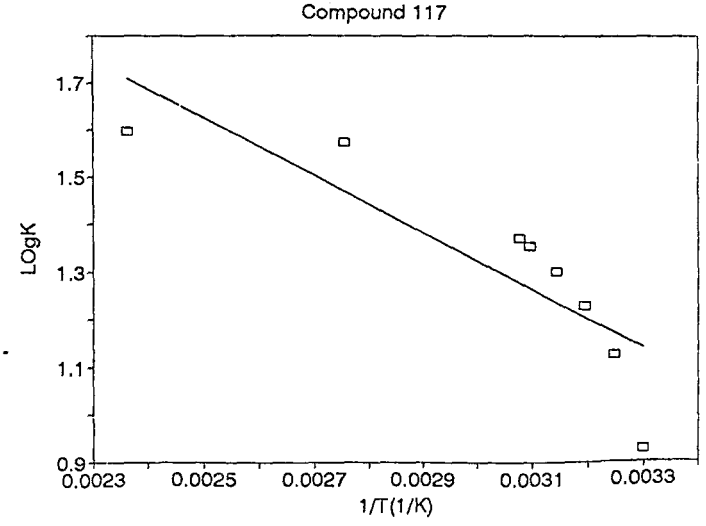
Compound 117

No.	T/K	1/T	δ_0	δ	X	LogK	Y(CALC.)
1	300	0.00333	47.78				
2	303	0.00330	47.78	47.63	8.41	0.925	1.140
3	308	0.00325	47.78	47.40	13.37	1.126	1.173
4	313	0.00319	47.78	47.17	16.91	1.228	1.204
5	318	0.00314	47.78	46.93	19.94	1.300	1.235
6	323	0.00310	47.78	46.69	22.55	1.353	1.264
7	325	0.00308	47.78	46.60	23.45	1.370	1.276
8	363	0.00275	47.78	44.69	37.57	1.575	1.472
9	423	0.00236	47.78	44.33	39.62	1.598	1.710

Regression Output:

Constant	3.150301
Std Err of Y Est	0.124639
R Squared	0.731865
No. of Observations	8
Degrees of Freedom	6

X Coefficient(s) -609.131
Std Err of Coef. 150.5209

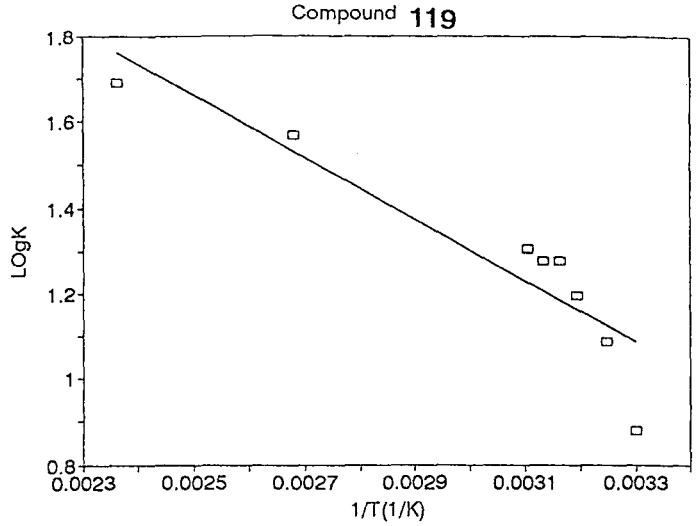


Compound **119**

No.	T/K	1/T	δ_0	δ	K	LogK	Y(CALC.)
1	300	0.00333	44.54				
2	303	0.00330	44.54	44.41	7.56	0.878	1.086
3	308	0.00325	44.54	44.20	12.21	1.087	1.124
4	313	0.00319	44.54	43.98	15.65	1.194	1.162
5	316	0.00316	44.54	43.72	18.91	1.277	1.184
6	319	0.00313	44.54	43.72	18.91	1.277	1.205
7	322	0.00311	44.54	43.60	20.23	1.306	1.226
8	373	0.00268	44.54	41.28	37.17	1.570	1.532
9	423	0.00236	44.54	38.67	49.12	1.691	1.761

Regression Output:

Constant	3.464195
Std Err of Y Est	0.109472
R Squared	0.843639
No. of Observations	8
Degrees of Freedom	6
X Coefficient(s)	-720.636
Std Err of Coef.	126.6563

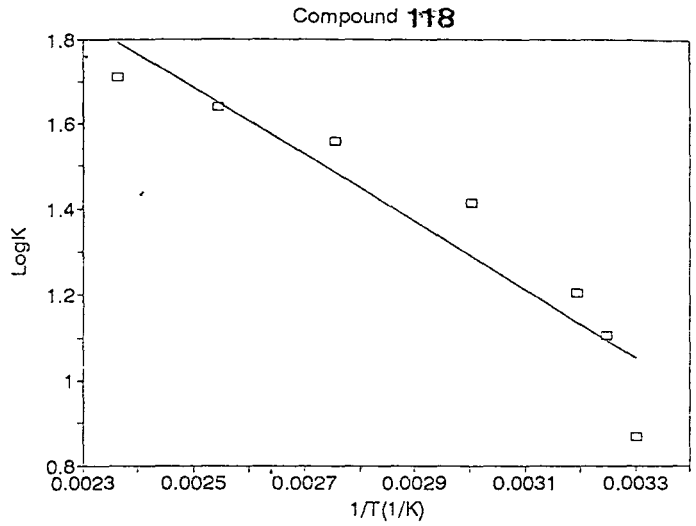


Compound **118**

No.	T/K	1/T	δ_0	δ	K	LogK	Y(CALC.)
1	300	0.00333	46.02				
2	303	0.00330	46.02	45.90	7.38	0.868	1.053
3	308	0.00325	46.02	45.66	12.77	1.106	1.096
4	313	0.00319	46.02	45.45	16.05	1.205	1.137
5	333	0.00300	46.02	44.51	25.98	1.415	1.289
6	363	0.00275	46.02	43.05	36.15	1.558	1.485
7	393	0.00254	46.02	41.60	43.73	1.641	1.651
8	423	0.00236	46.02	39.78	51.42	1.711	1.794

Regression Output:

Constant	3.663558
Std Err of Y Est	0.116078
R Squared	0.882769
No. of Observations	7
Degrees of Freedom	5
X Coefficient(s)	-790.881
Std Err of Coef.	128.8913



4. REFERENCES

1. G.P. Ellis, in *Chromenes, Chromanones and Chromones*, Wiley, New York, 1977. p. 1ff.
2. J. Staunton, *Comprehensive Organic Chemistry*, (D. Barton and W.D. Ollis, eds.) Pergamon, Oxford, 1979, **4**, p. 659ff.
3. P.J. Brogden, G.P. Ellis, C.D. Gabbutt and J.D. Hepworth, *Comprehensive Heterocyclic Chemistry*, (A.R. Katritzky and C.W. Rees, eds.) Pergamon, Oxford, 1984, **3**, p. 573ff.
4. Ref. 2, pp. 659 and 660.
5. Ref. 2, pp. 660-674.
6. Ref. 3, p. 637.
7. Ref. 2, p. 672.
8. Ref. 1, p. 563.
9. Ref. 3, p. 583.
10. Ref. 3, p. 590.
11. Ref. 1, p. 564.
12. Ref. 3, p. 613.
13. Ref. 1, pp. 456-463.
14. S.K. Mukerjee, S. Raychandhuri and T.R. Sethadri, *Chem. Abstracts*, 1970, **72**, 31542u.
15. L.W. McGarry and M.R. Detty, *J. Org. Chem.*, 1990, **55**, 4349.
16. A. Nohara, H. Kuriki, T. Saijo, K. Ukawa, T. Murata, M. Kanno and Y. Sanno, *J. Med. Chem.*, 1975, **18**, 34.

17. J.P. Devlin and M. Hargrave, *Pulmonary and Antiallergic Drugs*, Wiley, New York, 1985, Chapter 4, Section 2.7.

18. Ref. 2, p. 680.

19. R.B. Gamill, C.E. Day and P.E. Schurr, *J. Med. Chem.*, 1983, **26**, 1672.

20. G.P. Ellis, *Stud. in Org. Chem.*, 1981, **11**, 1 and 2.

21. F.L. Pearse, *Prog. Med. Chem.*, 1982, **19**, 59-109.

22. Ref. 3, pp. 816-830.

23. Ref. 1, p. 496.

24. Ref. 2, pp. 677-679.

25. Ref. 1, p. 502.

26. Ref. 1, p. 526.

27. V.N. Kalimin, M.V. Shostakovsky and A.B. Ponomaryov, *Tetrahedron*, 1990, **31**, 4073-4076, *Chem. Abstracts*, 1990, **113**, 171726x.

28. Ref. 3, pp. 695-706.

29. Ref. 1, p. 573.

30. G. Haas, J.L. Stanton and T. Winkler, *J. Heterocycl. Chem.*, 1981, **18**, 3, 619; *Chem. Abstracts*, 1981, **95**, 97721h.

31. R. Beugelmans and C. Morin, *J. Org. Chem.*, 1977, **42**, 1356.

32. R.B. Gammill, *J. Org. Chem.*, 1979, **44**, 3988.

33. F.M. Dean and R.S. Johnson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2049.

34. Y.G. Lee, K. Ishimaru, H. Iwasaki, K. Ohakata and K. Akiba, *J. Org. Chem.*, 1991, **56**, 2058.

35. Ref. 1, p. 567.

36. P.J. Brogden, G.P. Ellis, C.D. Gabbutt and J.D. Hepworth, *Comprehensive Heterocyclic Chemistry*, (A.R. Katritzky and C.W. Rees, eds.), Pergamon, Oxford, 1984, **1**, p. 1170.

37. J.D. Bryan, A.A. Goldberg and A.W. Wragg, *J. Chem. Soc.*, 1960, 1279.

38. F.C. Chen and C.T. Chang, *J. Chem. Soc.*, 1958, 146.

39. N.M. Shah and S.R. Parikh, *J. Indian Chem. Soc.*, 1959, **36**, 784.

40. J.A. Donnelly and J.J. Murphy, *J. Chem. Soc. (C)*, 1970, **18**, 2596.

41. A.O. Fitton and R.K. Smalley, in *Practical Heterocyclic Chemistry*, Academic Press, London, 1968, p. 95.

42. J. Schmutz, H. Lauener, R. Hirt and M. Sanz, *Helv. Chem. Acta*, 1951, **34**, 767.

43. G. Barker and G.P. Ellis, *J. Chem. Soc.*, 1970, 2230.

44. P.S. Bevan and G.P. Ellis, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1705.

45. G.P. Ellis and I.L. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2570.

46. G.P. Ellis, G.J.P. Becket, D. Shaw, H.K. Wilson, C.J. Vardley and I.F. Skidmore, *J. Med. Chem.*, 1978, **21**, 1120.

47. D.N. Davidson and P.T. Kaye, *Synth. Comm.*, 1990, **20**, 727.

48. W.C. Still, M.Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

49. D.N. Davidson, R.B. English and P.T. Kaye, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1181.

50. H. Cairns, C. Fitzmaurice, D. Hunter, P.B. Johnson, J. King, T.B. Lee, G.H. Lord, R. Minshull and J.S.G. Cox, *J. Med. Chem.*, 1972, **15**, 583.

51. J. Dauphine, D. Chatonier, J. Couguelet, M. Payard and M. Picard, *Labo-Pharma-Probl. Tech.*, 1770, **18**, 58.

52. G.P. Ellis and G. Parker, *Prog. Med. Chem.*, 1973, **9**, 65.

53. D.N. Davidson, PhD Thesis, Rhodes University, 1992.

54. A. Albert and E.P. Serjent, in *Ionization Constants of Acids and Bases*, Methuen, London, 1962, p. 27.

55. Ref. 54, p. 7.

56. A.I. Vogel, in *Textbook of Quantitative Inorganic Analysis*, 4th edition, Longman Group Limited, New York, 1978, pp. 584 and 594.

57. Ref. 54, p. 123-127.

58. Ref. 54, p. 12.

59. R.J. Smith, D.H. Williams and K. James, *J. Chem. Soc., Chem. Commun.*, 1989, 682.

60. Y.H. Lai and P. Chen, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1665.

61. T. Nishioka, T. Fujita, K. Kitamura and M. Nakajima, *J. Org. Chem.*, 1975, **40(17)**, 2520.

62. P. Nieviere, P. Tronche and J. Couquelet, *Chem. Abstracts*, 1966, **64**, 9671g.

63. P.F. Wiley, *J. Am. Chem. Soc.*, 1952, **74**, 4326.

64. V.A. Zagarevskii, I.D. Tsvetkova and E.K. Orlova, *Chem. Abstracts*, 1968, **69**, 2796n.

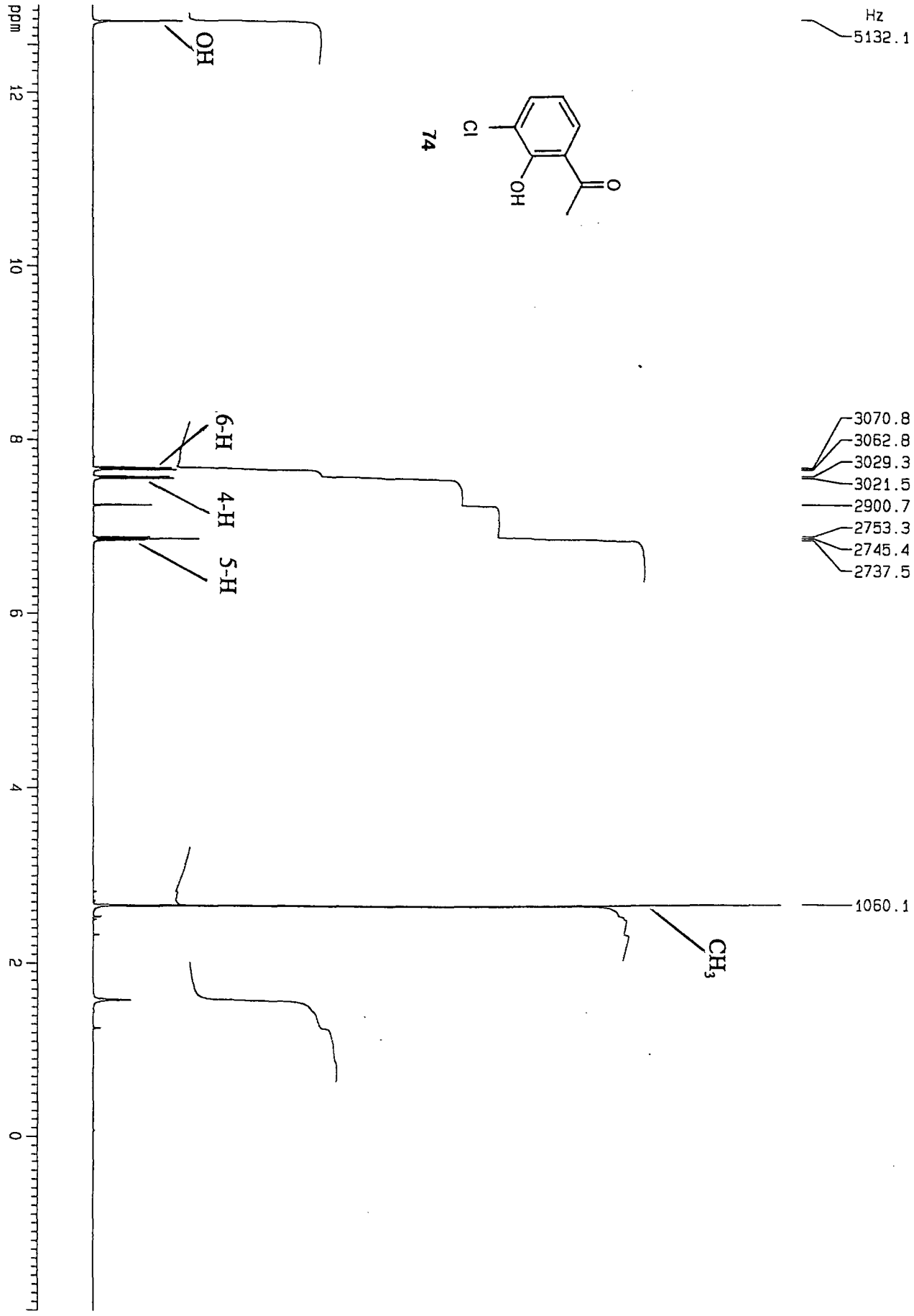
65. *The Merck Index*, (M. Windholz, ed.), 10th edn., Merck and Co., Inc., Rathaway, New Jersy, 1983, p.3215.

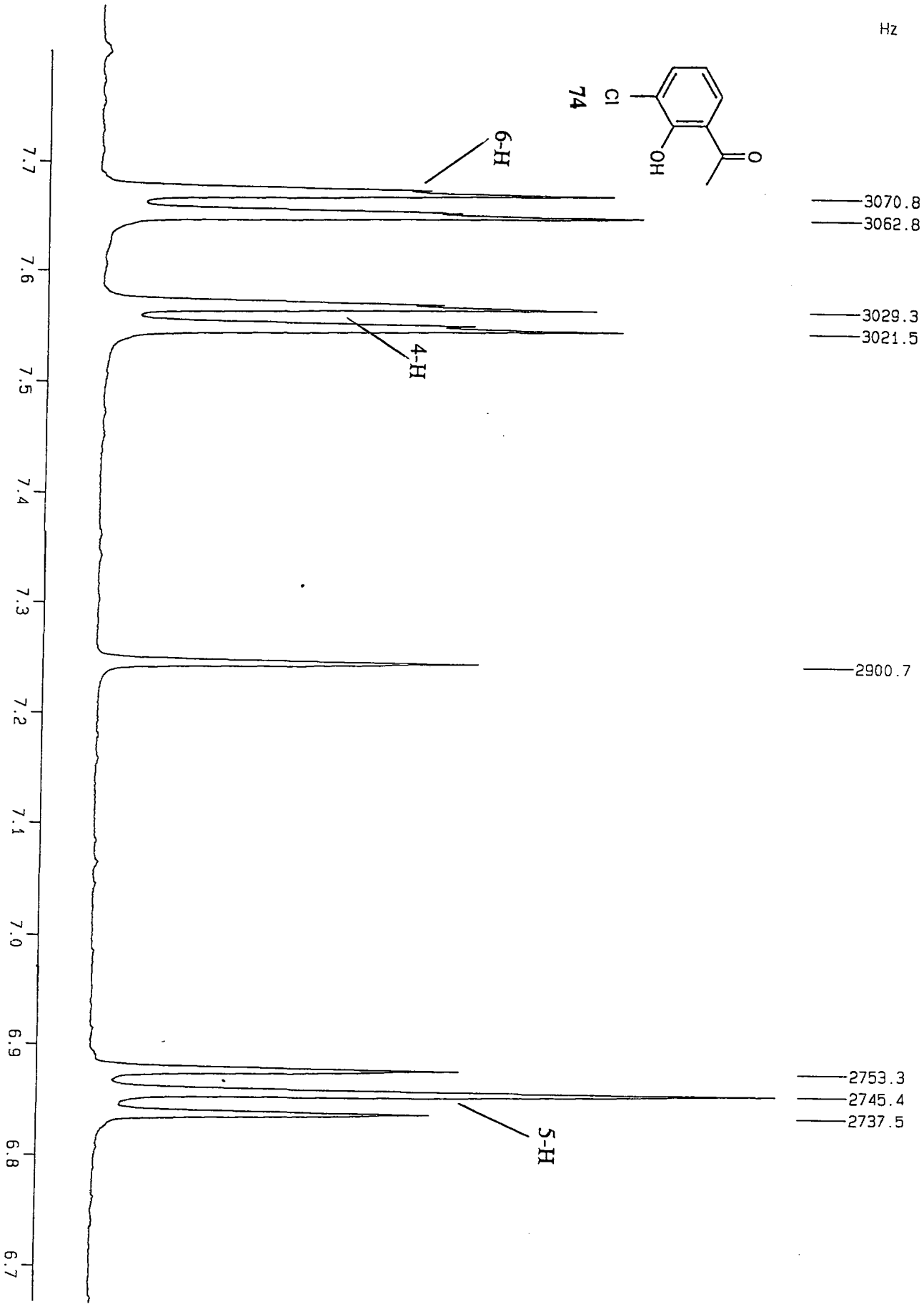
66. Z. Jerzmanowska and K. Kostka, *Roczniki Chem.*, 1963, **37**, 413; *Chem. Abstracts*, 1963, **59**, 12748b.

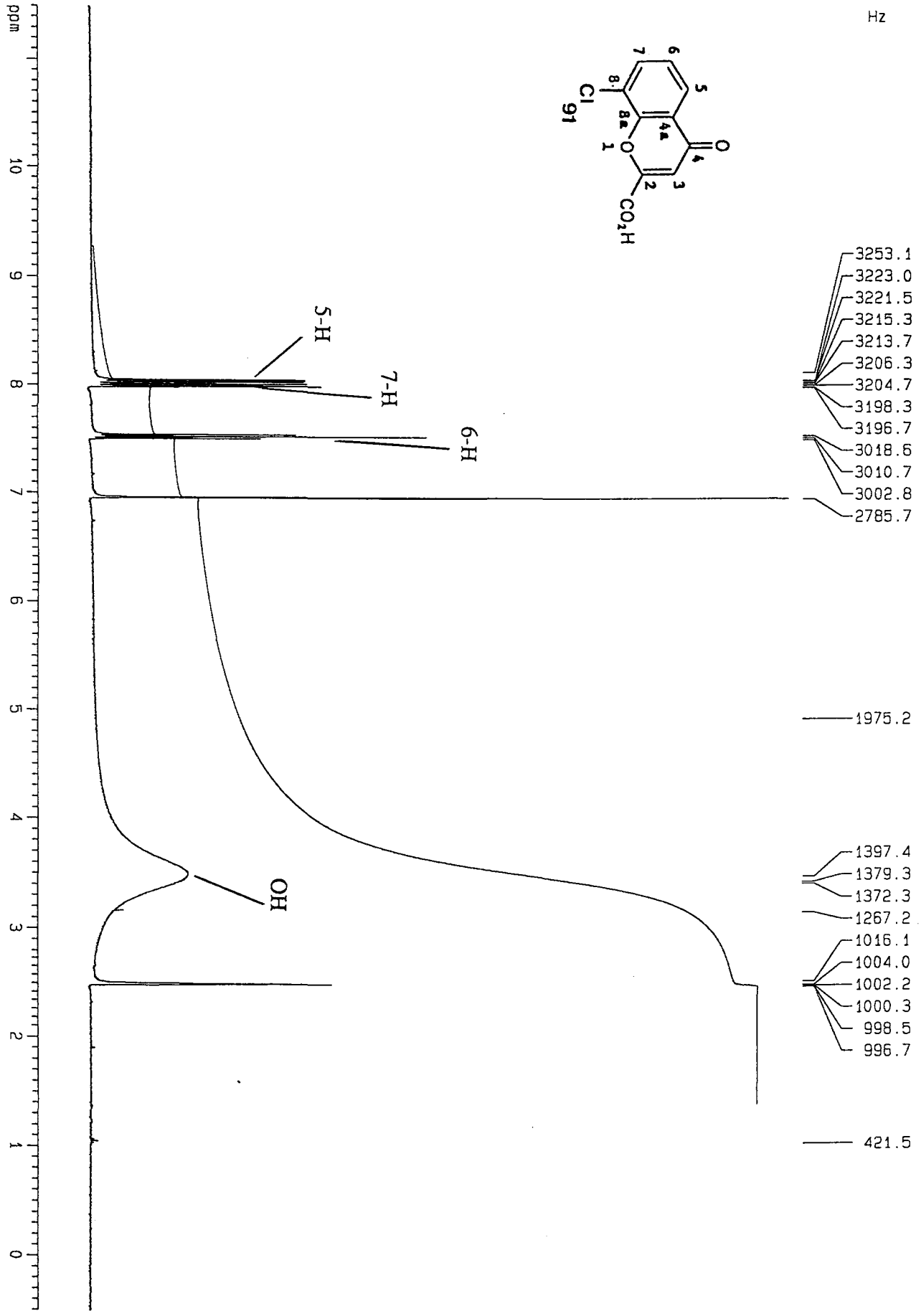
67. Ref. 1, p. 993.

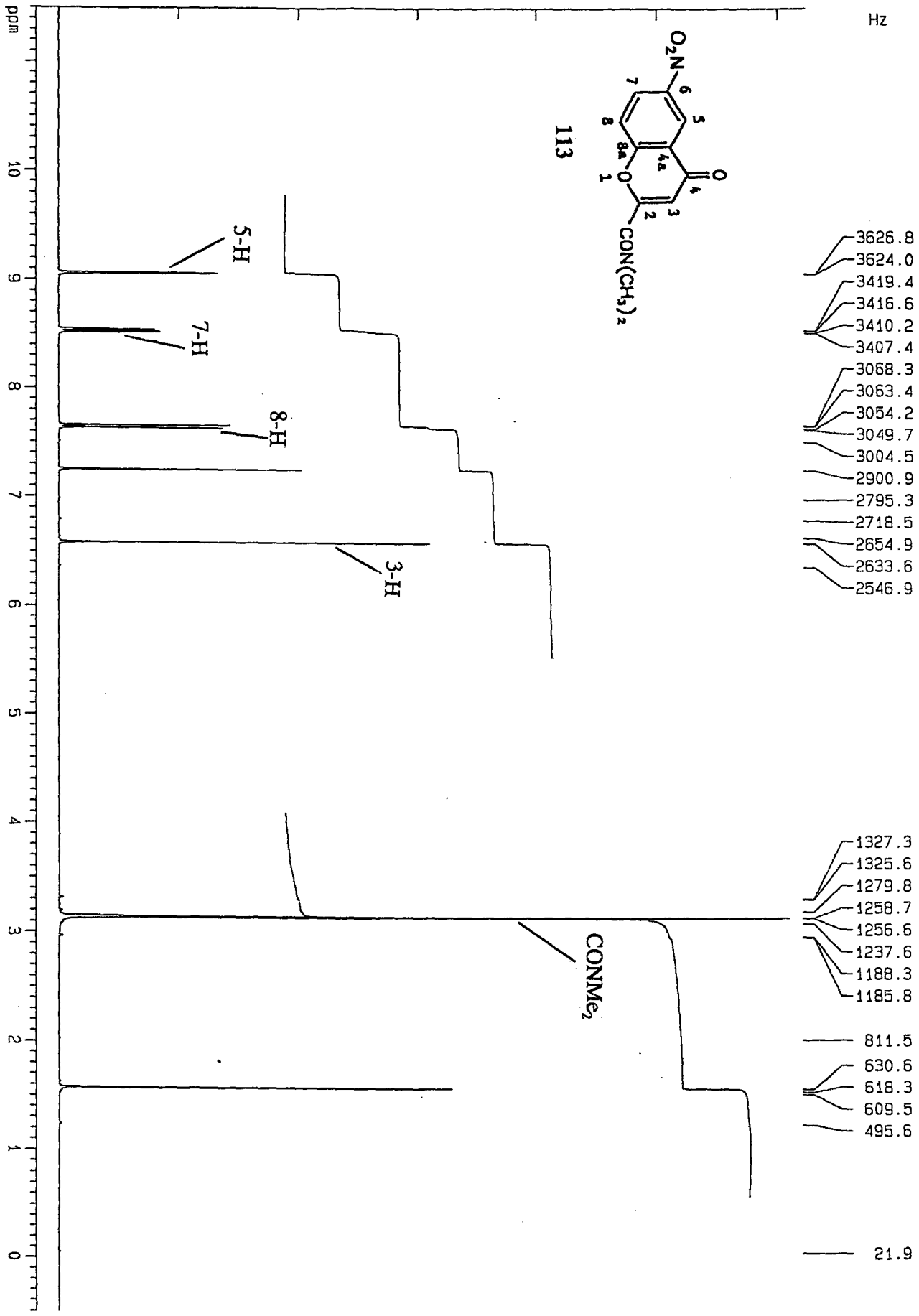
68. D.D. Perrin and W.L.F. Amarego, in *Purification of laboratory Chemicals*, 3rd edn, Pergamon, Oxford, 1988.

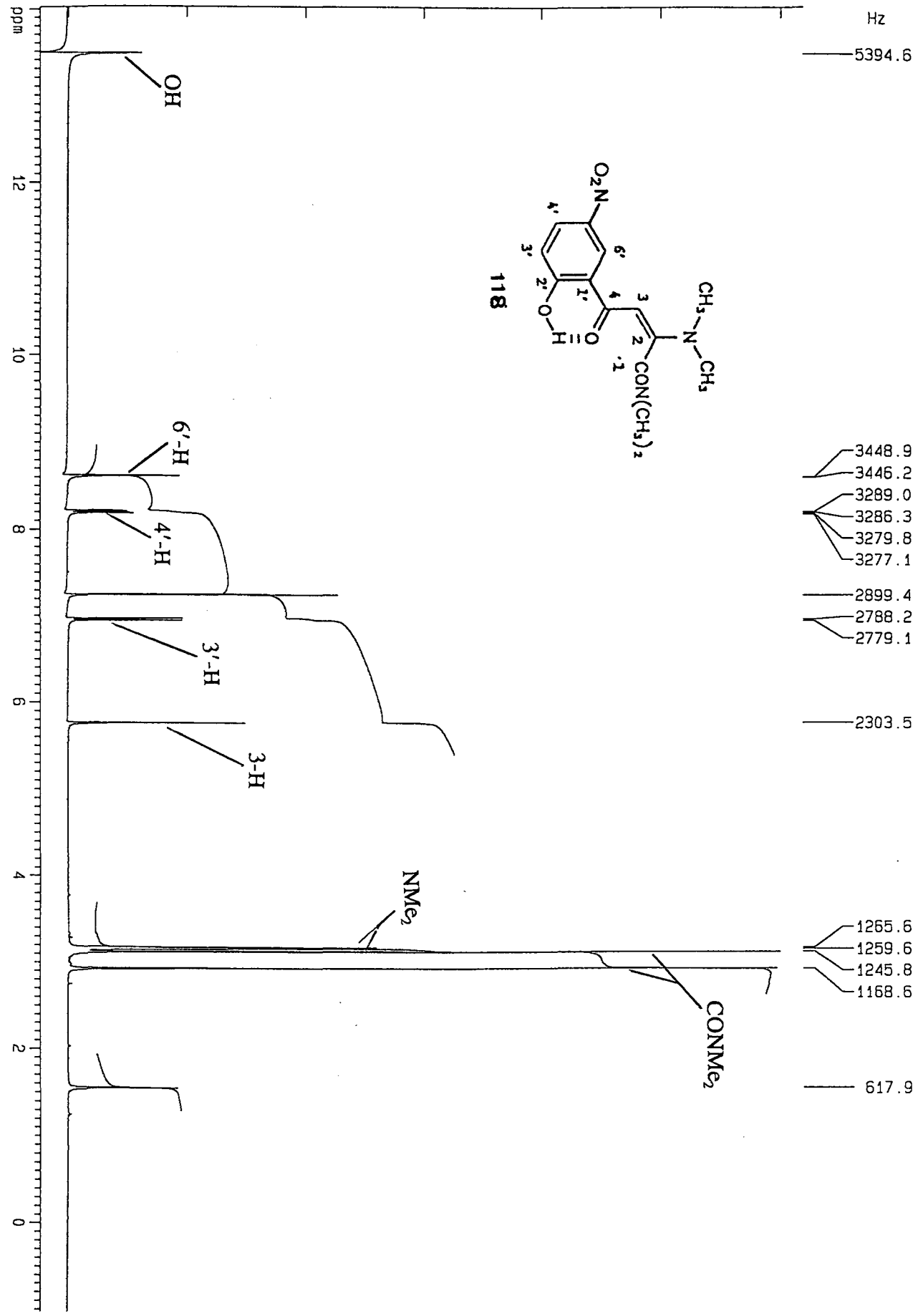
69. A.I. Vogel, in *Vogel's Textbook of Practical Organic Chemistry*, (B.S. Furniss, A.J. Hannaford, P.W.G. Smith and A.R. Tatchell, eds.), 4th edn., Longman Scientific and Technical, London, 1978, p. 297.

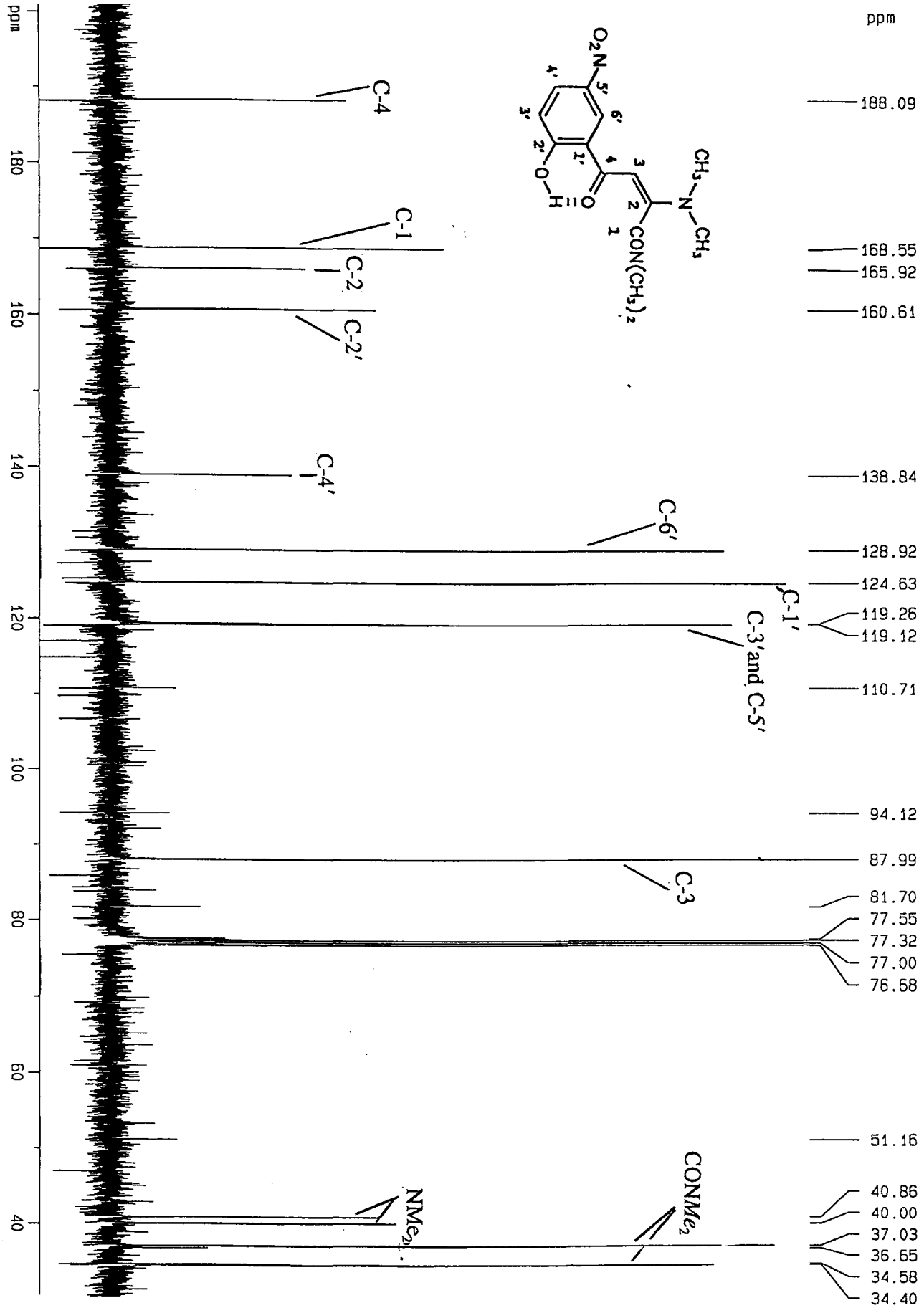

ppm
12
10
8
6
4
2
0
OH
6-H
4-H
5-H
CH3
Cl
OH
O
74
Hz
5132.1
3070.8
3062.8
3029.3
3021.5
2900.7
2753.3
2745.4
2737.5
1060.1


Hz
74
Cl
HO
O
6-H
4-H
5-H
3070.8
3062.8
3029.3
3021.5
2900.7
2753.3
2745.4
2737.5
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7


ppm
Hz
5-H
7-H
6-H
OH
Cl
91
O
O
CO2H
3253.1
3223.0
3221.5
3215.3
3213.7
3206.3
3204.7
3198.3
3196.7
3018.6
3010.7
3002.8
2785.7
1975.2
1397.4
1379.3
1372.3
1267.2
1016.1
1004.0
1002.2
1000.3
998.5
996.7
421.5


ppm
Hz
113
5-H
7-H
8-H
3-H
CONMe2
3626.8
3624.0
3419.4
3416.6
3410.2
3407.4
3068.3
3063.4
3054.2
3049.7
3004.5
2900.9
2795.3
2718.5
2654.9
2633.6
2546.9
1327.3
1325.6
1279.8
1258.7
1256.6
1237.6
1188.3
1185.8
811.5
630.6
618.3
609.5
495.6
21.9


ppm
Hz
5394.6
OH
118
6'-H
4'-H
3'-H
3-H
NMe2
CONMe2
3448.9
3446.2
3289.0
3286.3
3279.8
3277.1
2899.4
2788.2
2779.1
2303.5
1265.6
1259.6
1245.8
1168.6
617.9


ppm
180
160
140
120
100
80
60
40
C-4
C-1
C-2
C-2′
C-4′
C-6′
C-1′
C-3′and C-5′
C-3
NMe2
CONMe2
188.09
168.55
165.92
160.61
138.84
128.92
124.63
119.26
119.12
110.71
94.12
87.99
81.70
77.55
77.32
77.00
76.68
51.16
40.86
40.00
37.03
36.65
34.58
34.40