CHEMICAL AND SPECTROSCOPIC STUDIES OF CHROMONE DERIVATIVES

THESIS

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ABSTRACT

Various chromone derivatives have been used in asthma therapy, and their biological activity is apparently related to certain chemical features which include conformation and acidity. In the present study, substituent effects on conformation and acidity have been explored in chromone systems with potential biological activity. A range of variously substituted symmetrical chromone-2-carboxamides (including a series of *N*,*N*-dimethylchromone-2-carboxamides) have been prepared *via* chromone-2-carboxylic acids, which, in turn, were prepared from the corresponding *o*-hydroxyacetophenones. The *N*,*N*-dimethylchromone-2-carboxamides were prepared by reacting the appropriate chromone-2-carbonyl chlorides with dimethylammonium chloride in pyridine, in an approach which resolved various problems encountered in the preparation of these compounds. Substituent effects on the conformation of chromone-2-carboxamides have been explored using dynamic NMR spectroscopy, and the observed splitting of the *N*-alkyl signals has been attributed to slow site-exchange of the *N*-alkyl substituents. Dynamic NMR frequency separations and coalescence temperatures have been used to calculate rotational energy barriers, and substituent effects on these rotational energy barriers have been analysed.

The possible implication of ring-opening of chromones in chromone pharmacology has also been examined. A range of 3-(2-hydroxybenzoyl)-acrylamides has been prepared *via* the dimethylamine-mediated ring-opening of *N*,*N*-dimethylchromone-2-carboxamides and the *E*-double-bond configuration of the ring-opened products has been unambiguously established by single crystal analysis of the parent system. The configuration and conformation of the crystal structure of the parent

system have been shown, using IR and NMR spectroscopic, and molecular graphics techniques, to be maintained in solution and to characterise the whole series. ^{1}H and ^{13}C NMR spectroscopy have also been used to study the dimethylamine-mediated ring-opening of disodium cromoglycate.

The kinetics of the dimethylamine-mediated ring-opening of *N,N*-dimethylchromone-2-carboxamides have been studied using UV spectroscopy. These reactions have been shown to follow third-order kinetics overall and a mechanism accommodating the observed third-order kinetics has been proposed.

Substituent effects have been further investigated by the potentiometric determination of the pK_a values for a series of chromone-2-carboxylic acids. The relationship between acidity and the observed rate constants has been explored and has verified that the observed rate constants are sensitive to the influence of *meta*-substituents on the stability of the phenoxide ion "leaving group" rather than C-2 electrophilicity.

CONTENTS

ACKNOWLEDGEMENTS

Firstly, I would like to thank Prof. P.T. Kaye for his continuous assistance and guidance throughout this investigation. I found the numerous, stimulating discusions invaluable and always a source of encouragement and motivation. The assistance of Prof. D.J. Eve throughout the kinetic and pK_a studies, and Dr. R.B. English for the crystallographic studies was also appreciated. The variable-temperature NMR data were obtained with the assistance of Prof. V. Brandt (University of the Orange Free State).

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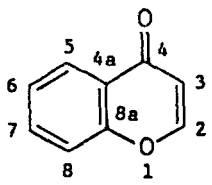
ABBREVIATIONS

t-$BuMe_2OTf$	-	*tert*-butyldimethylsilyl triflate
COSY	-	^1H - ^1H correlated experiment
DBN	-	1,5-diazabicyclo[4,3,0]non-5-ene
DBU	-	1,8-diazabicyclo[5,4,0]undec-7-ene
DMF	-	dimethylformamide
GLC	-	gas-liquid chromatography
HETCOR	-	^1H - ^{13}C correlated experiment
IR	-	infrared spectroscopy
NMR	-	nuclear magnetic resonance spectroscopy
OTf^-	-	triflate
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
UV	-	ultraviolet spectroscopy

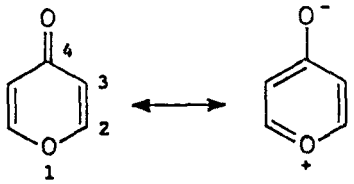
To my Parents, for their encouragement and support throughout my studies.

1. INTRODUCTION

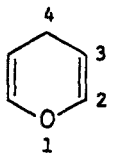
The name "chromone", first used by Bloch and Kostanecki in 1900, was chosen to describe coloured, naturally occurring compounds known to contain the benzo-4*H*-pyran-4-one structure 1.[1] The chemistry of chromones has been extensively reviewed.[1-3] Chromones are benzanulated analogues of γ-pyrone 2a and their systematic nomenclature originates from the pyran analogues 3 and 4.[4] The chromone structure will be denoted simply as chromone rather than 4-oxo-4*H*-chromene. Many chromones occur naturally in plants and exhibit biological activity.[5] Potentially active structural chromone analogues have been synthesised in attempts to improve potency or reduce unwanted side effects. Another related family of compounds are the flavanoids, which are derivatives of the 2- and 3-arylchromones respectively[4] and which are widely distributed in plants.[6]



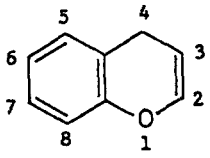
1
Chromone
(Benzo-4*H*-pyran-4-one)
(4-Oxo-4*H*-1-benzopyran)
(4-Oxo-4*H*-chromene)



2a **2b**
γ-Pyrone
(4*H*-Pyran-4-one)



3
4*H*-Pyran



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

1.1 CHROMONE CHEMISTRY

1.1.1 PROPERTIES OF THE CHROMONE NUCLEUS.

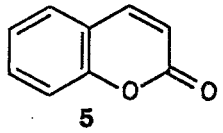
Most properties of γ-pyrones, and hence chromones, are attributable to the aliphatic dienone system **2a**, although some properties, such as the lack of normal ketonic activity and the exceptional reactivity of the carbonyl oxygen, may be attributed to substantial π-electron delocalization consistent with the aromatic pyrylium betaine structure **2b**. The electronic interaction of the ether oxygen with the carbonyl group was first proposed by Arndt in 1924.[4]

1.1.1.1 PHYSICAL AND SPECTRAL PROPERTIES.

The great propensity of γ-pyrone and chromone to form salts with acids results from their observed basicity, which has been rationalised in terms of the betaine structure **2b**.[7] Although the pK_a value of γ-pyrone (0.1) is comparable to nitrogen bases with very low basic strength, *e.g.* urea (pK_a 0.1) and *p*-nitroaniline (pK_a 1.0), it is nevertheless remarkably high compared to other oxygen bases, *e.g.* acetone (pK_a -7.2). The pK_a of chromone (2.0) is significantly higher than γ-pyrone.[7]

Spectroscopic properties are rationalised in terms of an aliphatic dienone system **2a**. The IR carbonyl stretching frequency of chromone occurs at *ca.* 1660 cm^{-1}, the exact value depending on the solvent used.[4,8] This value is lower than the carbonyl stretching frequency of

coumarin 5 (ν_{max} 1710 cm^{-1}) and IR spectroscopy may thus be used to distinguish chromones from coumarins. The UV spectra of chromone[9] and many of its derivatives are characterised by four bands centred at 205, 225, 240 and 300 nm, the last two being major absorption peaks. Solvent studies have shown that the lowest wavelength band is probably a $\pi \rightarrow \sigma^*$ transition involving the heteroatom lone-pair electrons, while the three higher wavelength bands arise from $\pi \rightarrow \pi^*$ transitions. The latter wavelength bands are generally red-shifted by C-2 electron withdrawing groups or blue-shifted by a C-2 methyl group. Introduction



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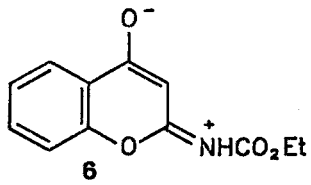
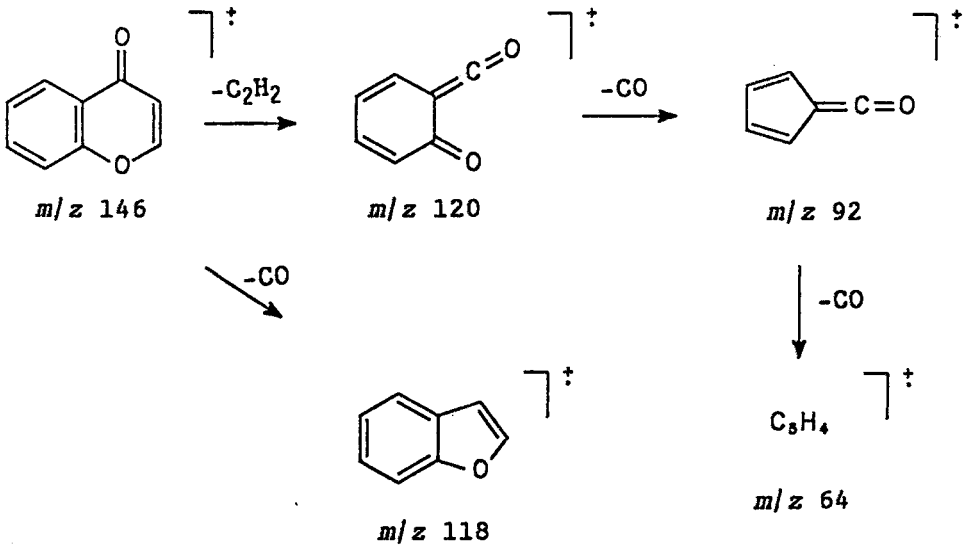


6

of $NHCO_2Et$ at C-2 causes pronounced spectral changes which are associated with the charge transfer species 6. In mass spectrometric analysis,[10] the chromone molecular ion fragments *via* two pathways involving either the loss of carbon monoxide or ring cleavage by a retro-Diels-Alder reaction (Scheme 1).



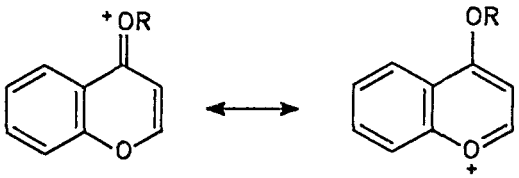
SCHEME 1

A detailed ^{1}H NMR study of chromone has been published by Mathis and Goldstein.[11] The benzenoid proton signals in chromone are shifted downfield, relative to those of the isomeric coumarin, as a result of the close proximity of the carbonyl group to the benzene ring. This effect is greatest at C-5 and the separation of this signal from the other benzenoid signals is characteristic of chromones and is not shown in coumarins. The ^{13}C NMR spectra of chromones[11] are characterised by a number of general features : (i) the carbonyl carbon signal is always at the lowest field and is essentially unaffected by substitution in the system; (ii) the C-3 signal is at a higher frequency than all the other methine carbon signals; and (iii) the ring junction signals are largely unaffected by substitution in either ring.

1.1.1.2 CHEMICAL PROPERTIES.

(i) Salt Formation.

Both γ-pyrone and chromone form oxonium or benzopyrylium salts, *e.g.* chromone forms the hydrochloride **7**, methoxonium **8**, or 4-siloxybenzopyrylium salt **9** when treated with hydrochloric acid, methyl *o*-nitrobenzenesulphonate, or *t*-butyldimethylsilyl triflate respectively.[4,12,13] These reactions all reflect the latent aromaticity of the heterocyclic ring.[4]



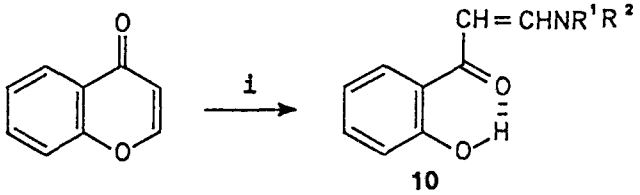
7 (R = H)
8 (R = Me)
9 [R = $Si(Me)_2Bu^t$]

(ii) **Ring-opening Reactions.**

Chromones readily undergo C-2 nucleophilic cleavage of the heterocyclic ring.[4] Consequently, there are few synthetic methods for introducing nucleophiles at this position without ring-opening or ring-transformation.[13] A variety of nitrogen, oxygen and carbon nucleophiles have been used in the ring-opening of chromones, and only selected examples will be discussed.

(a) **Reactions with nitrogen nucleophiles.**

Kostka[14] showed that chromones react with primary and secondary amines to produce β-aminovinylketones **10** having either *E*- or *Z*-double-bond configurations (Scheme 2). Zagorevskii *et al.*[15,16] used ^{1}H NMR spectroscopy to study the detailed structure of the β-aminovinylketone products (Section 2.3) and proposed a feasible reaction mechanism using ^{1}H NMR spectroscopic and deuterium labelling techniques (Section 2.5).

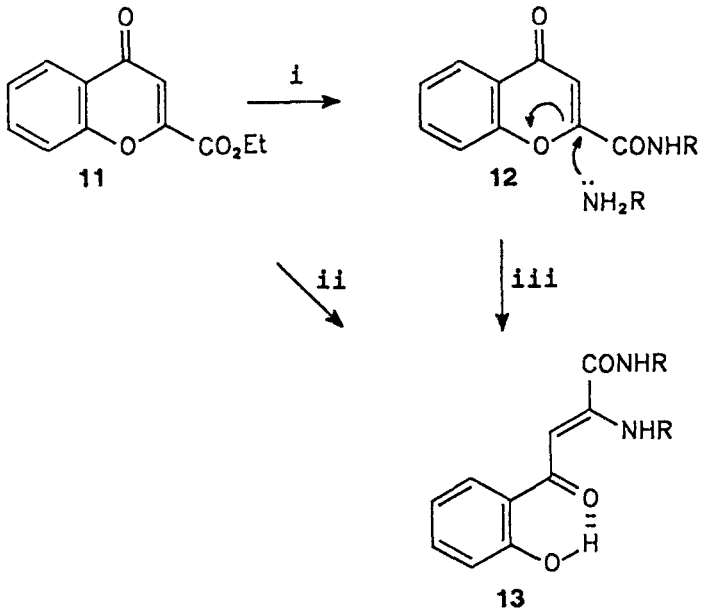


10

SCHEME 2

Reagents : i) R^1R^2NH, 80-85°C, 2h.

Chromone-2-carboxylate esters (*e.g.* 11) react with amine or ammonia to give different products according to the nature and quantity of the amine, and the reaction conditions (Scheme 3); secondary and tertiary carboxamides (*e.g.* 12) are produced under very mild, anhydrous conditions while an excess of amine or prolonged reaction affords coloured acrylamides 13.[15,17-20] The latter reaction is presumed to proceed *via* the carboxamide with a second mole of amine cleaving the ring, since treatment of the preformed carboxamide (12; R=CH_2Ph) with benzylamine afforded the corresponding acrylamide.[21]



SCHEME 3

Reagents : i) RNH_2 (1 Molar eq.);

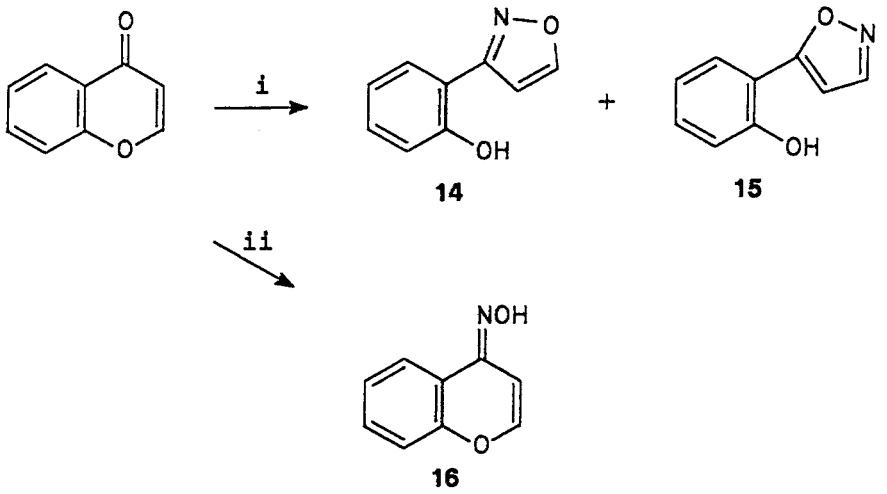
ii) RNH_2 (2 Molar eq.);

iii) RNH_2 (1 Molar eq.).

Reaction of chromones with ambident nucleophiles or those containing an N-C-N group results in ring cleavage and subsequent cyclization to other heterocyclic systems. Reactions with hydroxylamine, for example, afford isomeric isoxazole derivatives **14** and **15**, and the oxime derivative **16** is only obtained under anhydrous conditions (Scheme 4).[22] Base catalysed reaction of 3-nitrochromone **17** with a series of nucleophiles affords heteroaromatic nitro compounds,[23] *e.g.* reaction with glycine ethyl ester hydrochloride or benzamidine affords the pyrrolyl- or pyrimidyl-derivatives **18** and **19** respectively (Scheme 5). Analogous reactions occur with 2-carbonyloxychromones, *e.g.* ethyl chromone-2-carboxylate has been cleaved by hydrazine, diaminoethane and 1,2-diaminobenzene,[24,25] while chromone-2-carboxylic acid reacts with hydrazine to produce pyrazole derivatives.[20]

(b) **Reactions with oxygen nucleophiles.**

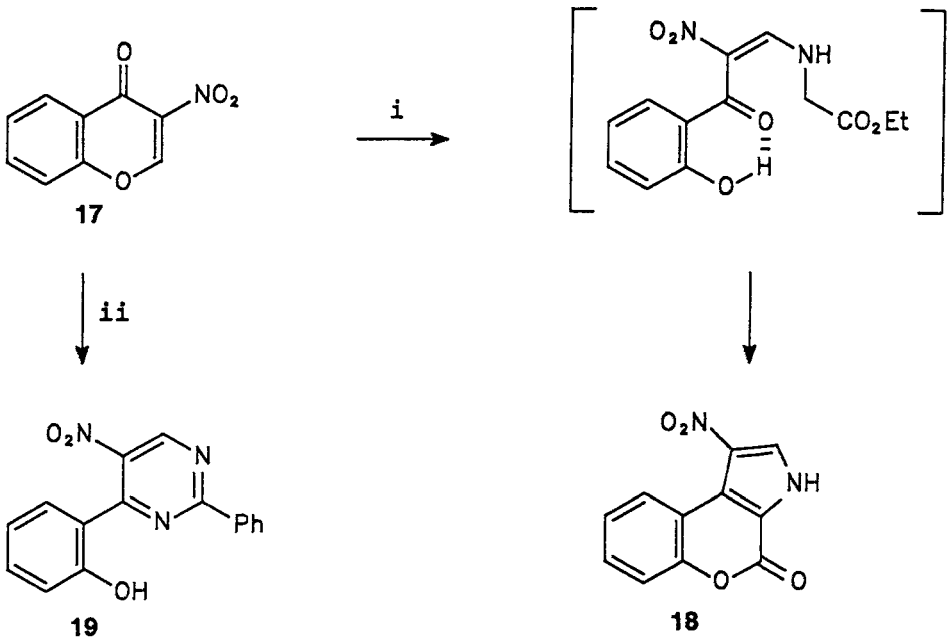
Chromones undergo ring opening when treated with aqueous alkali;[4] cyclization of the resultant salt of the β-diketone **20** to the chromone on acidification often prevents isolation of the free β-diketone **20** (Scheme 6). Hydrolytic carbon-carbon cleavage of the β-diketone **20** occurs under vigorous, prolonged treatment with aqueous alkali to afford a mixture of products and this reaction has been widely used in chromone structural analysis. Szabo *et al.* have studied the kinetics of this reaction of chromones[26] and isoflavanoids[27,28] and have proposed a mechanism in which C-2 nucleophilic attack occurs in the rate-determining step whose rate constant varies with electron density at C-2 (Section 2.5). Treatment of chromones with sodium alkoxide may also result in ring cleavage, *e.g.* 2-methylchromone **21** affords the dimeric product **22** which, on treatment with acid, is reconverted to 2-methylchromone (Scheme 7).[22]



14 15 16

SCHEME 4

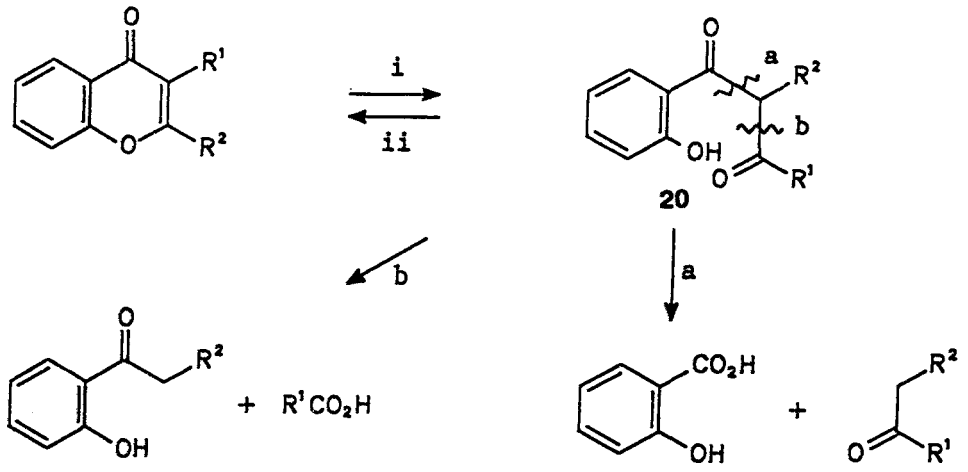
Reagents : i) $NH_2OH.HCl$; ii) anhydrous $NH_2OH.HCl$.



17 19 18

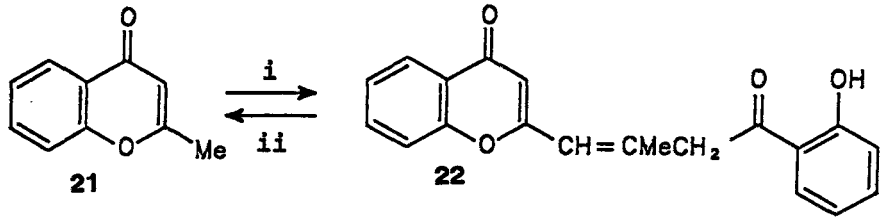
SCHEME 5

Reagents : i) $H_2NCH_2CO_2Et.HCl$, NaOEt; ii) $(H_2N)(Ph)C{=}NH$, NEt_3.



SCHEME 6

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



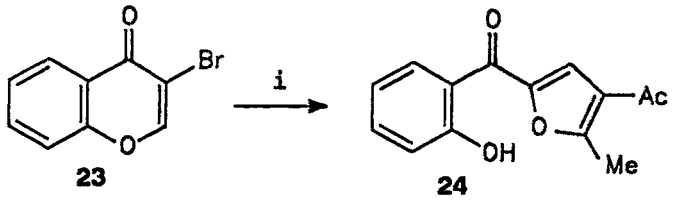
SCHEME 7

Reagents : i) OEt^-, 18°C; ii) H^+.

(c) **Reactions with carbon nucleophiles.**

Carbon nucleophiles attack either the C-2 or C-4 positions of chromones resulting in ring cleavage or ring transformation. Ring-opening reactions of chromones with an active methylene species,[29] in the presence of DBN or DBU, occur at room temperature, *e.g.* reaction of 3-bromochromone **23** affords the furan derivative **24** (Scheme 8). Some heterocyclic quaternary compounds (*e.g.* *N*-ethyl-2-methylbenzothiazolium tosylate **25**) cleave chromones to form compounds (*e.g.* **26**) which are potentially useful as dyes (Scheme 9).[30] Nucleophilic attack on the carbonyl group of chromones by Grignard reagents followed by acidification affords benzopyrylium salts (*e.g.* **27**) (Scheme 10), although the Grignard reaction of isoflavone **28** in the presence of copper (I) chloride, affords the ring-opened product **29**.[29]

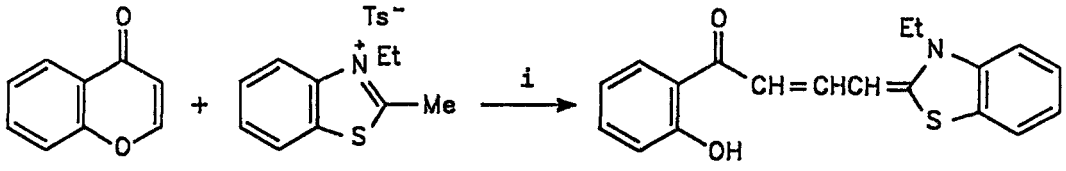
C-2 Nucleophilic attack may not always result in ring cleavage. The reaction of 3-nitrochromone **30** with diazomethane or diazopropane affords a cyclopropabenzopyran **31** or the homologous dimethylcyclopropane **32** respectively (Scheme 11).[29] Akiba *et al.*[13] recently reported reactions of the siloxybenzopyrylium salts **33** (generated from chromone using *t*-butyldimethylsilyl triflate) with silyl enol ethers or alkyl organometallic reagents in the presence of 2,6-lutidine. For example, reaction with the ketene silyl acetyl **34** affords 4-siloxybenzopyran **35**, while reaction with 3-(trimethylsilyl)-1-butene **36** affords the unexpected cyclopentane annulation product **37** (Scheme 12). A second substituent may be introduced at the C-3 position of the 2-substituted 4-siloxybenzopyrans *via* reaction with electrophiles, *e.g.* reaction of compound **35** with the appropriate iminium salt affords the 3-methylenechromone derivative **38**.



23 24

SCHEME 8

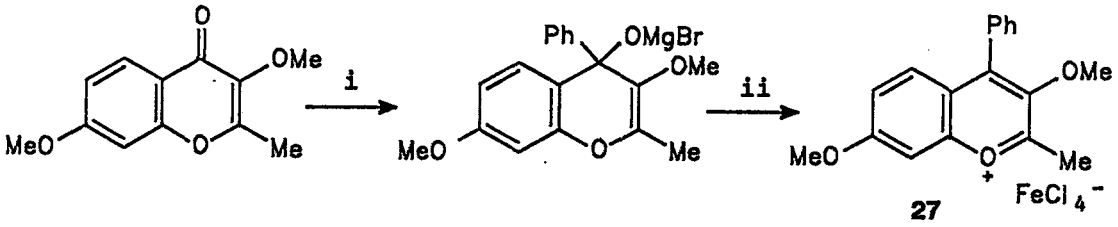
Reagents : i) CH_2Ac_2, DBN, 18°C.



25 26

SCHEME 9

Reagents : i) AcONa, EtOH.



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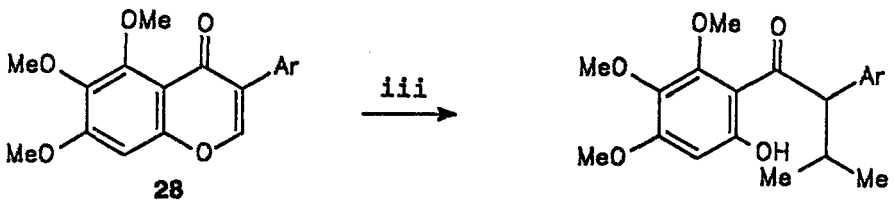
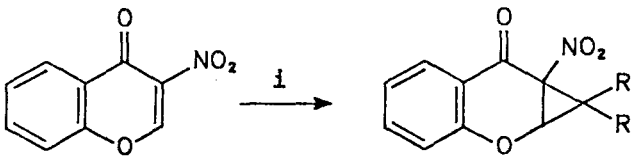


28 29

SCHEME 10

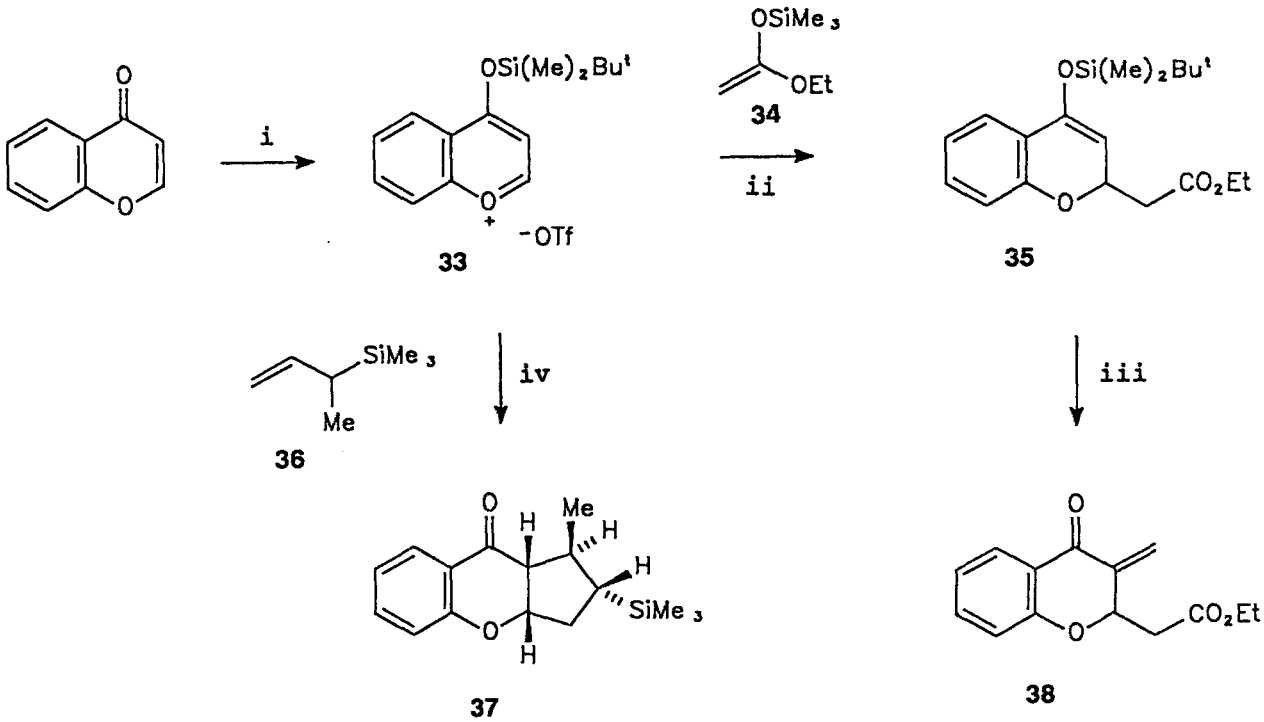
Reagents : i) PhMgBr; ii) HCl, $FeCl_3$; iii) MeMgI, Cu_2Cl_2.



30 **31** (R = H)
32 (R = Me)

SCHEME 11

Reagents : i) R_2CN_2.



33 **34** **35** **36** **37** **38**

SCHEME 12

Reagents : i) $Bu^t(Me)_2SiOTf$, 80°C, 1 h;

ii) 2,6-lutidine, CH_2Cl_2, rt, 1 h;

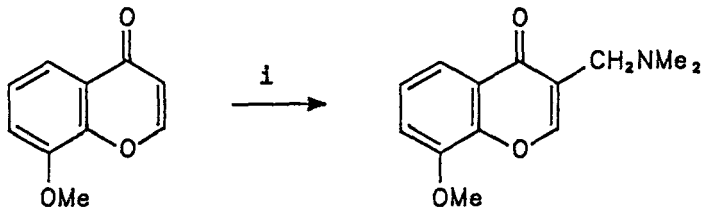
iii) $Et_2N{=}CH_2.HCl$, CH_2Cl_2, rt, 5 h; Na_2CO_3;

iv) 2,6-lutidine, CH_2Cl_2, rt, 4.5 h; Na_2CO_3.

iii) Electrophilic Addition and Substitution Reactions.

Both chromone rings are relatively resistant to electrophilic attack[31] since strongly acidic electrophilic reagents (*e.g.* sulphuric acid or nitric-sulphuric acid mixtures) or strong acids (*i.e.* halogen acids) produced during the reaction, may result in protonation of the pyran ring thus inhibiting further electrophilic attack.[29] Nitration,[31,32] under forcing conditions, is the most readily achieved electrophilic substitution reaction and affords mainly the 6-nitrochromone derivative, while bromination,[29,32] using bromine in carbon disulphide, affords a 2,3-dibromo adduct which on treatment with a secondary amine gives 3-bromochromone. The less acidic conditions of the Mannich reaction afford salts of 3-aminomethylchromone **39** (Scheme 13), the reaction probably proceding *via* electrophilic attack on a β-diketone intermediate produced by heterolytic cleavage of the chromone system.[29,31]

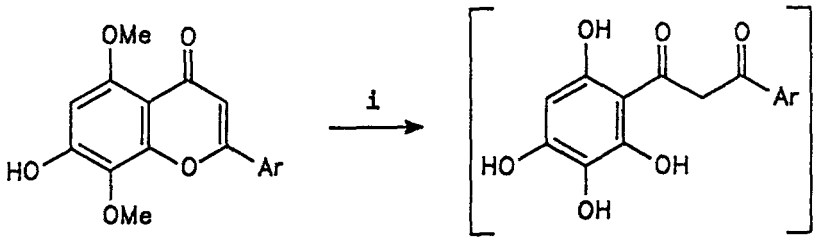
Treatment of hydroxylated or methylated chromones with hydroiodic acid induces an interesting and occasionally useful rearrangement (Scheme 14).[29] Demethylation of the flavone dimethyl ether **40** with hydroiodic acid proceeds *via* the Wessely-Moser rearrangement of the ring-opened diketone **41** which cyclises to the flavone scutellarein **42** which has a different trihydroxy substitution pattern.



39

SCHEME 13

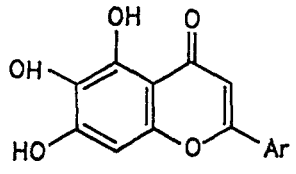
Reagents : i) H_2CO, Me_2NH, AcOH.



40

(Ar = 4-OHC_6H_4)

41



42

SCHEME 14

Reagents : i) HI.

(iv) **Other Reactions of Chromones.**

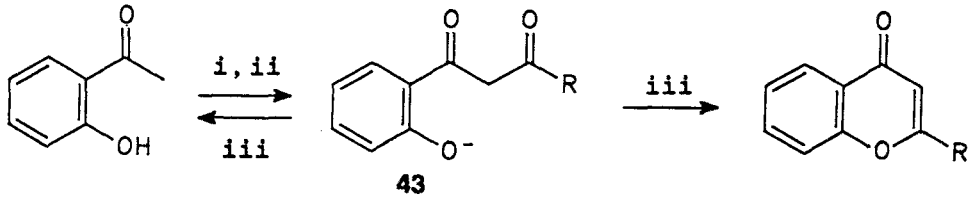
The oxidation of chromones using permanganate or dichromate results in ring-opening and the formation of salicylic acid.[29] Catalytic reduction of chromones, on the other hand, may produce several products. Thus conditions favourable for the production of a specific product from a particular substrate may be selected. For example, hydrogenation of 6-chlorochromone-2-carboxylic acid with palladium-charcoal in acetic acid at 70°C at low pressure results in the loss of the 2,3-double bond, ketone carbonyl and chlorine functions, while the use of Raney nickel at low pressure, or at high pressure and temperature over copper chromate, failed to effect reduction.[22] Chromones also react with free radicals, and undergo thermal and photochemical reactions.[22,31]

1.1.2. SYNTHESIS OF CHROMONES.

Preparative methods for chromones have been extensively reviewed.[1-3] Although chromones may be synthesised from a variety of substrates, the two most common precursors are *o*-hydroxyacetophenones and phenols. In both instances, a side-chain is linked to the substrate, followed by cyclisation. The source of the side-chain differentiates each synthetic route[33] and aromatic substituents may be introduced without any substantial changes in synthetic methodology.[34]

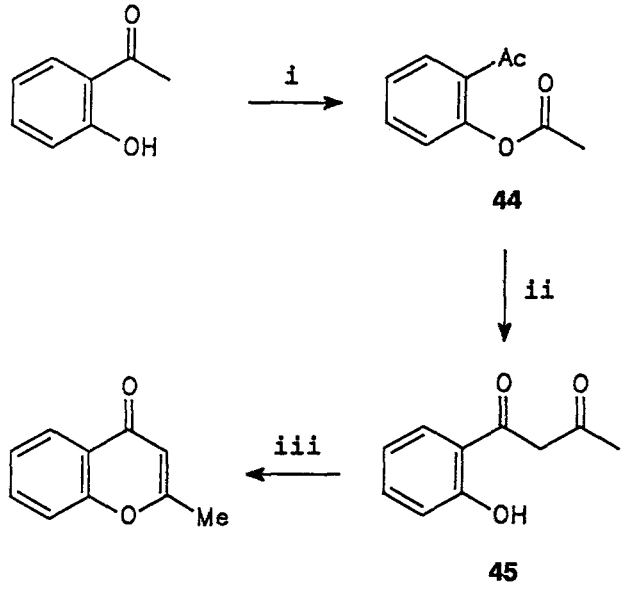
The Claisen condensation[34] of an *o*-hydroxyacetophenone with an ester (Scheme 15) is one of most frequently used synthetic methods, and was first described by Kostanecki *et al.* in 1901. Condensation with an ester, *e.g.* diethyl oxalate ($R=CO_2Et$), in the presence of strong base, usually sodium ethoxide, affords a 1,3-diketone **43** which readily cyclises in acidic solution.

An alternative route to the 1,3-diketones involves the *O*-acylation of an *o*-hydroxyacetophenone to afford an acyloxybenzene **44** which, on treatment with potassium carbonate, undergoes an intramolecular Baker-Venkataraman rearrangement to the 1,3-diketone **45** (Scheme 16).[33] In the Kostanecki-Robinson[35] synthesis of chromones an *o*-hydroxyacetophenone is reacted with an aliphatic anhydride and the sodium salt of the corresponding acid (Scheme 17). This reaction may produce a mixture of products and alkaline cleavage of the 3-acyl group may occur during isolation of the product.



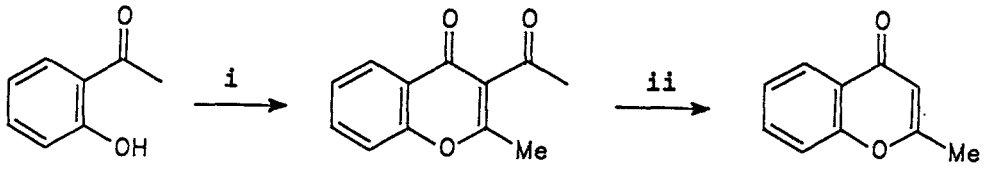
SCHEME 15

Reagents : i) base (NaOEt); ii) RCO_2Et; iii) H^+.



SCHEME 16

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



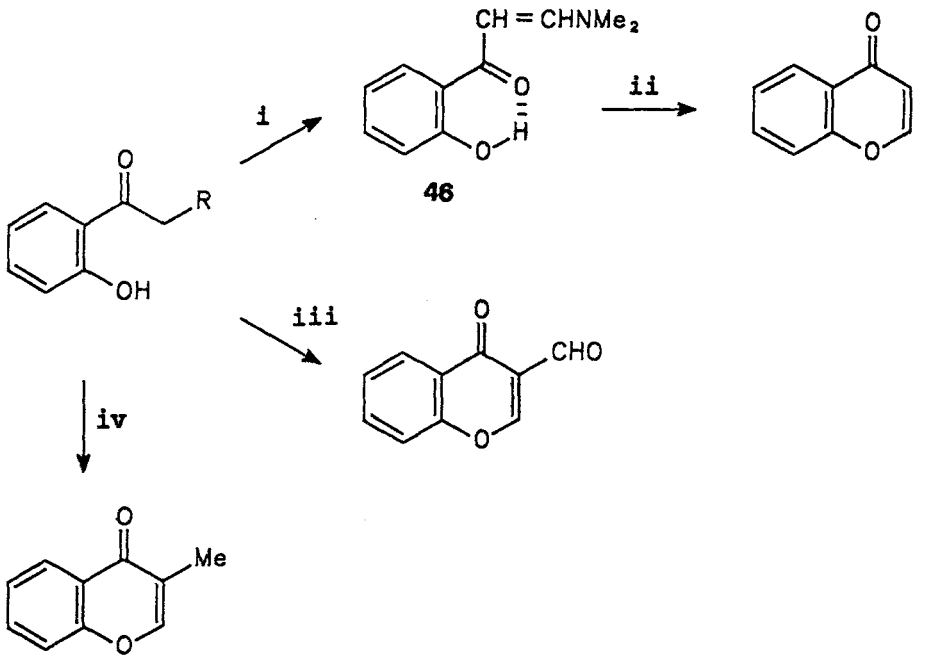
SCHEME 17

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

The reaction of an *o*-hydroxyacetophenone with dimethylformamide (DMF) under Vilsmeier conditions is used for the synthesis of 2-unsubstituted chromones (Scheme 18).[36,37] Reactions with DMF or its dimethyl acetal in the absence of phosphorous oxychloride afford chromone itself *via* cyclization of the β-aminovinylketone **46**.

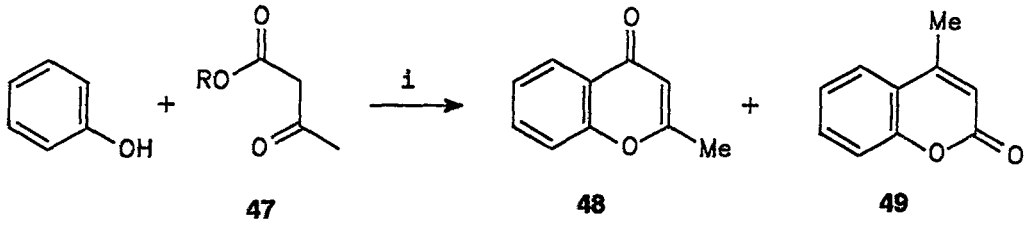
The Simonis reaction[31,38] is also widely used and involves the condensation of a phenol with a β-keto ester **47** (Scheme 19). The reaction may produce a chromone **48**, or a coumarin **49** (the Pechmann reaction), or a mixture of both. Chromone formation predominates with the use of phosphorous pentoxide while sulphuric acid effects cyclisation to the coumarin; complete selectivity is, however, not always observed.

The reaction of a phenol with an unsaturated ester, *e.g.* diethyl acetylene dicarboxylate **50** or diethyl chlorofumarate[38] is widely used in the synthesis of chromone-2-carboxylic acids **53** (Scheme 20) and was developed by Ruhemann *et al.* between 1900 and 1921.[39] Readily available substituted phenols may be used, and yields are reasonable, *e.g.* *o*-iodophenol is converted into 8-iodochromone-2-carboxylic acid in about 33% yield.[40] Cyclization of the aryloxyalkenoic acid **51** or ester **52** intermediates is effected by treatment with a mineral acid or acetyl chloride.



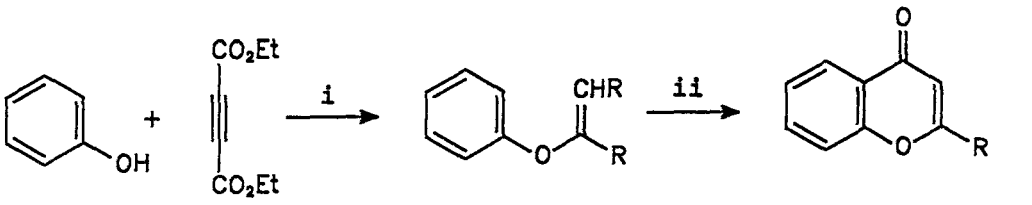
SCHEME 18

Reagents : i) R=H, $Me_2NCH(OMe)_2$; ii) H_2SO_4, 100°C;
iii) R=H, DMF, $POCl_3$; iv) R=Me, DMF, $POCl_3$.



SCHEME 19

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

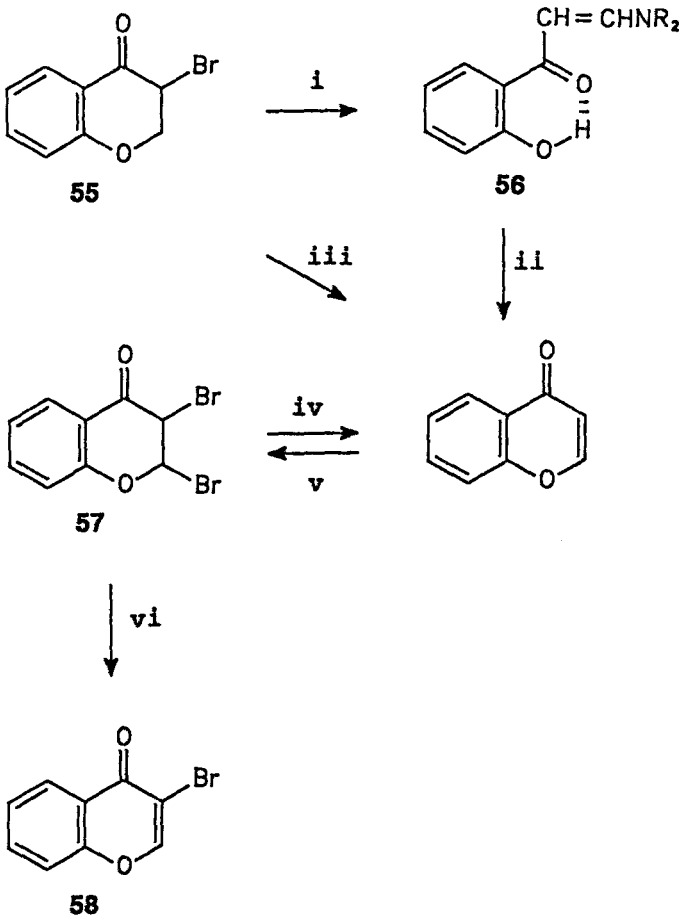


SCHEME 20

Reagents : i) base; ii) R=CO_2Et, MeCOCl, or R=CO_2H, H_2SO_4.

Chroman-4-ones are also used in chromone synthesis although their poor availability and low yields reduce their preparative value.[41] Conversion to chromones is effected by dehydrogenation or oxidation using selenium dioxide or palladium on charcoal. A more reliable conversion is the dehydrobromination of 3-bromochroman-4-one **55** using an amine (Scheme 21). The β-aminovinylketone **56**, isolated in some instances, is subsequently cyclized on acidification to chromone. The 2,3-dibromochroman-4-one **57** affords chromone on treatment with zinc dust and is dehydrobrominated to 3-bromochromone **58** in pyridine.[38]

Chromones are also synthesised from salicylic acid derivatives,[36] enamines,[42] coumarins, benzopyrylium salts, chroman-4-ols, furans, and benzofurans.[38]



SCHEME 21

Reagents : i) R_2NH, 20°C; ii) H^+; iii) Me_2NPh;
iv) Zn; v) Br_2; vi) pyridine.

1.2 CONFORMATIONAL ANALYSIS

The energetics and origins of conformational preferences may be studied using various techniques[43] including (i) IR, NMR, Raman, and microwave spectroscopy; (ii) dipole moment measurements; and (iii) electron diffraction and x-ray diffraction studies. Isomeric, stable conformers in dynamic equilibrium may be separately observed provided the time-scale of the spectroscopic detection method is sufficiently fast relative to the interconversion rate of the isomers, *i.e.* the average lifetime of the species must be greater than the (inverse) frequency of the absorbed radiation.[44] Each isomer must also possess different absorption characteristics and be present within the concentration detection limits.

1.2.1 NMR SPECTROSCOPIC STUDIES OF AMIDES.

Rotational isomerism of amides has largely been studied using variable-temperature dynamic NMR spectroscopy.[44,45] The partial double-bond character of the amide N-CO bond arising from nitrogen lone-pair delocalization (Figure 1) has the following consequences :

(i) a large rotational barrier about the amide N-CO bond ranging between 50-100 kJ mol^{-1};[44]

(ii) a rigid planar amide framework;

(iii) the non-equivalence of the nitrogen substituents, even when $R^1 = R^2$; and

(iv) the possibility of long-range spin-coupling from R to R^1 and R^2.

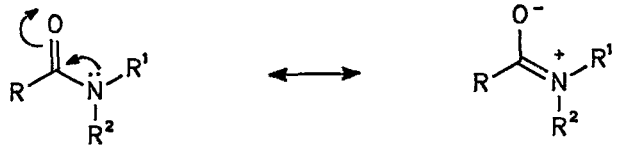


FIGURE 1.

Since the rotational barriers of amides are large, *N*,*N*-dialkyl amides often show splitting of the ^1H *N*-alkyl signals at ambient temperature. The separate chemical shifts for identical *N*-alkyl protons of *N*,*N*-dialkyl amides (under conditions of slow site-exchange relative to the NMR time-scale) have been attributed to the anisotropy of the diamagnetic susceptibility of the amide carbonyl group.[45]

The heights of rotational barriers are measured using various methods,[44,45] which include lineshape analysis, approximate methods, and the spin-echo method. For example, using approximate methods, the site-exchange rate constant (k; Equation 1) for equivalent populations at coalescence temperature (T_c) may be calculated from the chemical shift difference at infinitely slow site-exchange ($\delta\nu_\infty$).[44,45] Alternatively, the energy of activation (ΔG^*; Equation 2) and hence the first-order rate constant (k; Equation 3) may be calculated from the coalescence temperature (T_c) and the chemical shift difference at coalescence ($\Delta\nu_c$).[46]

$$k = \pi\delta\nu_\infty / \sqrt{2} \qquad (1)$$

$$\Delta G^* = RT_c\ (22.96 + \ln\ T_c/\Delta\nu_c) \qquad (2)$$

$$\ln\ k = \ln\ (k_bT/h) - \Delta G^*/RT \qquad (3)$$

where R = Gas constant

k_b = Boltzmann constant

h = Planck constant

T = 298 K

Interpretation of variable-temperature spectra may be complicated by factors such as the non-equivalence of conformers which may require application of the Winstein-Holness principle.[44] Simultaneous rotation may also occur about two separate bonds, and individual rotational

barriers may be determined provided that both site-exchange processes are sufficiently slow, as shown in two recent dynamic NMR studies.[46,47] In heterocyclic amides, nitrogen inversion and ring reversal conformational changes may also establish additional rotational equilibria, although these processes are considered to be faster than N-CO rotation.[48] For example,[48] rotational barriers about the N-CO bond of *N*-substituted benzamides are generally larger than 60 kJ mol^{-1}. Ring-reversal rotational barriers of piperidines are smaller (40-44 kJ mol^{-1}) and those of pyrrolidines are expected to be even lower. Rotational barriers due to nitrogen inversion in heterocyclic amides are generally too small to be detected by NMR spectroscopy.

The energy minima of amides correspond to conformations which favour a planar amide function.[44] In symmetrically substituted *N,N*-dialkylbenzamides, steric interactions between the *o*-hydrogen and the *N*-alkyl substituents apparently disrupt the co-planarity of the *N*-alkyl substituents in the near planar amide group, and may increase the torsion angle between the planar amide and aromatic functions.[49] (In the crystal structure of *p*-bromo-*N,N*-dimethylbenzamide, the *N*-methyl substituents are twisted out of plane by 9° and the torsion angle between the amide and aromatic planes is 45°.) Site-exchange of the *N*-alkyl substituents apparently involves a rotational equilibrium between two quasi-planar conformers.[49] Rotational barriers of *N,N*-dialkylbenzamides are reduced relative to *N,N*-dialkylacetamides, for example, since competitive delocalization stabilises the activated state (Figure 2), thus reducing the rotational barriers.[45] The lower

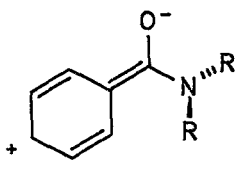


FIGURE 2.

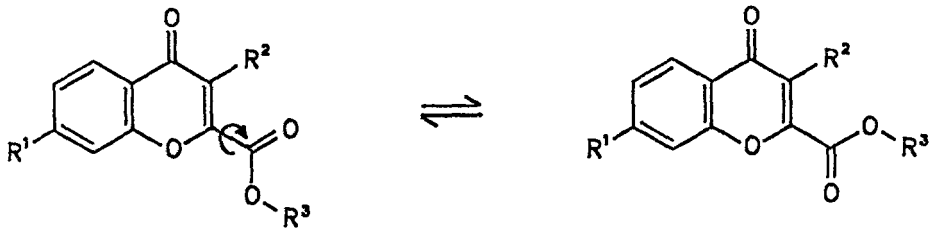
rotational barriers obtained in piperidides[50] relative to *N*,*N*-dimethylamides[50] have been attributed to repulsions, between the *N*-acyl group and the vicinal equatorial hydrogens, which impart more sp^3 character to the nitrogen in piperidines than in acyclic analogues. In simple piperidine and pyrrolidine amides,[45] rotational barriers for the five-membered ring systems have been shown to be consistently larger (8-12 kJ mol^{-1}) than those of the six-membered ring systems. In general, larger *N*-alkyl groups tend to result in smaller rotational energy barriers.[45] However, reasons for this trend are not clearly understood and there are exceptions to the trend.

The rigidity of the planar (or near planar) amide framework may also result in additional slow rotations about bonds other than the N-CO amide bond.[45] For example, in *o*-substituted benzamides, rotation about the C(1)-CO bond involves site-exchange between conformers in which the aromatic group is rotated out-of-plane relative to the planar amide group. Such rotational barriers range between 32-56 kJ mol^{-1}.[45]

1.2.2 IR SPECTROSCOPIC STUDIES OF CHROMONE-2-CARBOXYLATE ESTERS.

Rapid internal rotations involving carbonyl systems may be studied using IR spectroscopy since IR carbonyl absorption bands are sensitive to conformational change and this detection method has a much shorter time-scale than that required for NMR spectroscopic detection. In an IR study of solvent, substituent and temperature effects on rotational

isomerism in a series of chromone-2-carboxylate esters, Drews and Kaye[51] rationalised the observed doubling of the carboxylate carbonyl absorption bands in terms of a rotational equilibrium between *syn-s-trans* II and *anti-s-trans* I conformers (Scheme 22). The absence of splitting of the carboxylate carbonyl bands for the 3-methyl-, 3-chloro-, and 3-bromochromone-2-carboxylate esters was rationalised in terms of unfavourable steric and dipolar interactions which disrupted the co-planarity of the chromone and carboxylate functions.



anti-s-trans (I) *syn-s-trans* (II)

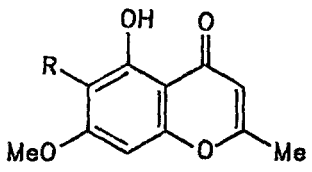
SCHEME 22

1.3 BIOLOGICALLY ACTIVE CHROMONES

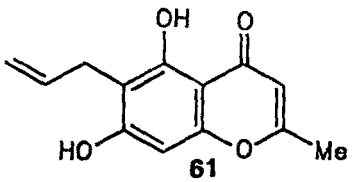
1.3.1 NATURALLY OCCURRING CHROMONES

By 1975, the number of isolated naturally occurring chromones exceeded fifty five.[52] The present discussion, however, will be confined to a limited number of examples which illustrate their diversity of location, structure, and biological or pharmacological activity.

Many natural chromones contain hydroxy, methyl and/or prenyl substituents.[53] Thus, eugenin 59, one of the simplest chromones, and eugenitin 60 are both constituents of the Javan wild clove *Eugenia caryophyllata* L. Thunbg., while peucenin 61 is found in the rhizome of the masterwort *Imperatoria ostruthium* and the South African sneezewood tree.[54] The halogenated hydroxychromone rupicolon 62 has been isolated from extracts of lichens, while siphulin 63, the only natural chromone carboxylic acid, occurs in a Scandinavian lichen, *Siphula ceretites*. A



59 (R = H)
60 (R = Me)



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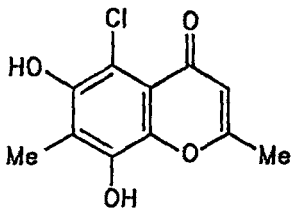

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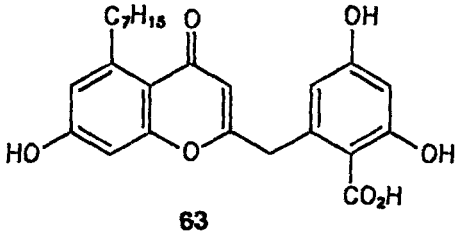

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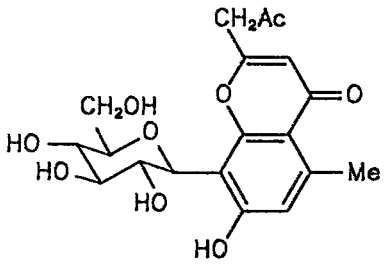
rare *C*-glycosylchromone, aloesin 64, has been identified in several species of bitter aloes.[55] Natural 3-methylchromones are also rare and hormothamnione 65, isolated by Gerwick *et.al*[56,57] in small quantities from the marine cyanophyte *Hormothamnion enteromorphoides* or from the marine cryptophyte *Chrysophaeum taylori*, was the first reported styrylchromone. Hormothamnione is a potent cytotoxin to cancer cells *in vitro* and, although the mechanism for its cytotoxic activity has not been completely established, it appears to selectively inhibit RNA synthesis.[56]



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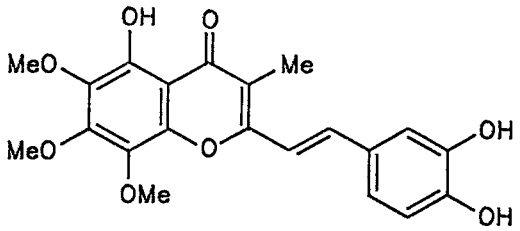

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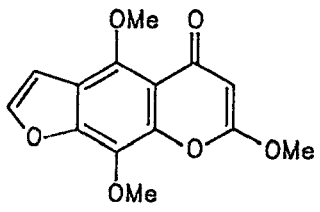
The natural furochromone, khellin 66,[58,59] was isolated by Mustapha in 1897 from the seeds and fruit of a Middle Eastern plant *Ammi Visnaga*. Khellin induces relaxation of the bronchial musculature (anti-spasmodic activity) thereby alleviating the symptoms of bronchial asthma; a direct action on heart muscle causes vasodilation thus offering relief for angina pains. Khellin also exhibits lipid-altering, anti-atherosclerotic activity[60] and may thus provide a valuable therapy for reducing the risk of cardiovascular disease. Extracts of this plant have been used since ancient times for the treatment of colics, and more recently, in asthma therapy but unpleasant side effects, such as nausea and vomiting, have limited its clinical use.

The flavanoid, baicalein **67**,[61,59] a constituent of the dried radix of *Scutellaria baicalensis* Georg which was used in ancient Chinese medicine as a diuretic and anti-allergic drug, has been shown by Koda *et al.* to exhibit anti-allergic activity.



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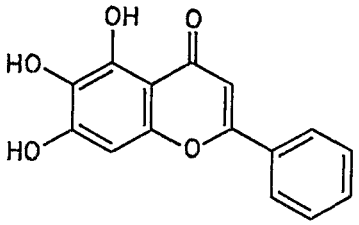

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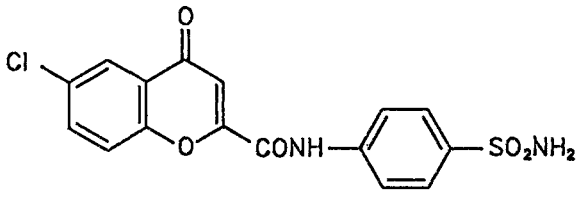
1.3.2 SYNTHETIC CHROMONE DERIVATIVES

Some chromonecarboxamides have an effect on the central nervous system[62] (*e.g.* *N*,*N*-diethylchromone-2-carboxamide exhibits sedative and hypnotic activity) while analgesic properties are exhibited by several *N*-arylamides of which the sulphonamide **68** was found to be the most potent. The amide **69** exibits anti-histaminic activity and *N*-arylchromone-3-carboxamides **70** show anti-bacterial activity.[62] Anti-inflammatory



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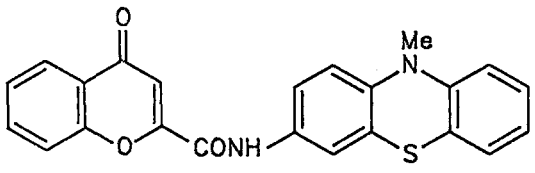

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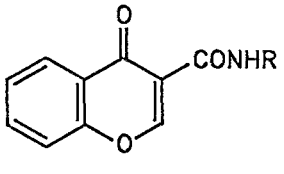

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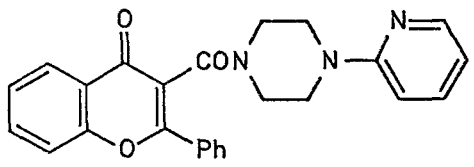
activity is exhibited by the substituted chromone-2- or 3-carboxamides of which the flavone 71 was found to be the most potent.[63] Several chromonecarboxamides[64] [*e.g.* substituted *N*-(tetrazol-5-yl)chromone-2-carboxamides 72] also exhibit anti-allergic activity and will be discussed in Section 1.3.3 (i).



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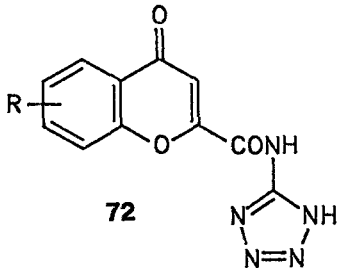

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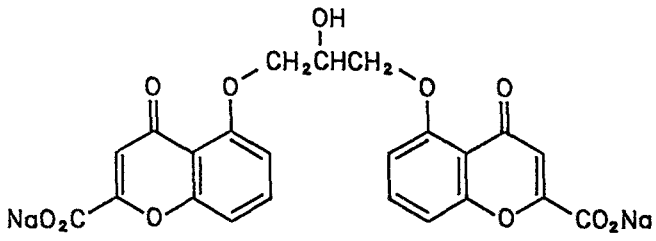
The biological properties of various chromone-2-carboxylic acids[58] have been explored in the search for a khellin (66) replacement which is more soluble and which has improved muscle relaxing properties, but none of the unwanted side-effects of khellin. The search for a more specific treatment for bronchial asthma began in 1956 with the synthesis of the hydrophylic 2-carboxychromones by Cox *et al.*[58] They established that these compounds exhibit anti-allergic activity rather than the anti-spasmodic activity of khellin. However, since the duration of their prophylactic action was short, it was concluded that mono-chromone-2-carboxylic acids were unlikely to be of any clinical use. Consequently, research was directed towards the synthesis of novel bischromones.

The discovery of disodium cromoglycate (DSCG) 73[58] in 1965 undoubtedly provided a major advance in the treatment and prophylaxis of bronchial asthma and other allergic diseases.[65] DSCG is widely used in asthma therapy[66] under commercial names of Intal or Lomudal.[40] In 1967, Altouyan[58] showed that DSCG exhibits anti-allergic activity. This

protective effect lasts several hours and long-term use of the drug can reduce the number and frequency of exacerbations in the clinical course of asthma.[66] Partly due to its size and the acidity of the two carboxylic acid groups, DSCG is poorly absorbed and is thus administered by inhalation as a fine powder or as an aqueous aerosol.[59] Many other anti-allergic compounds,[67] such as ketotifen 74 and doxantrazole 75, have subsequently been developed in the search for an orally active successor to DSCG with an improved clinical profile.[59] By 1985, little success had been achieved and tranilast (N-5') 76, an orally active oxanilic acid derivative, was the only such drug to have been marketed.[59]



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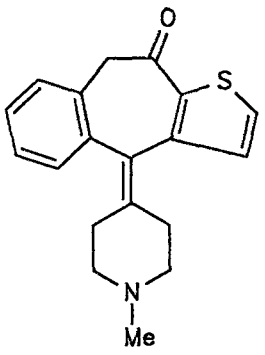

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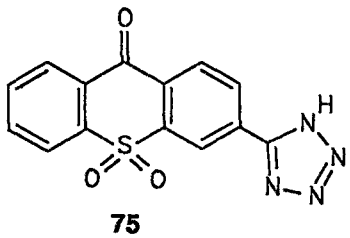

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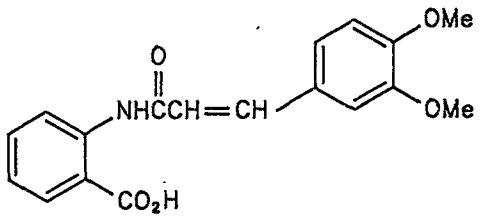

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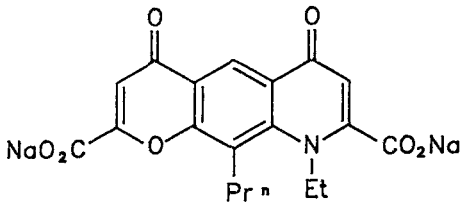
A novel pyranoquinoline dicarboxylic acid, nedocromil sodium (Tilade ®) 77, has recently been used as an anti-inflammatory, effective in the treatment of mild asthma.[68,69] It is also interesting to note that cromakalim BRL 34915, 78 is an effective bronchodilator.[70,71] The mechanism of this action involves the opening and activation of potassium channels in the cytosol of the smooth muscle cells. The potential of such potassium channel activators in asthma therapy is currently being investigated.



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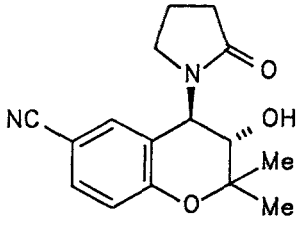

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1.3.3 THE MODE OF ACTION OF ANTI-ALLERGIC CHROMONES

(i) Structure-activity Relationships of Anti-allergic Chromones.

The chemical structure of a drug determines its affinity for a specific receptor and hence the intrinsic activity of the drug. The correlation of the action of drugs with their chemical structure is an integral link in the analysis of drug action, and an exploitation of these relationships has often resulted in the development of better drugs.[72]

Common structural features of anti-allergic compounds include (Figure 3.)[73] :

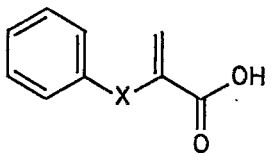
(i) a planar system with extended π-bonding;

(ii) a benzene ring;

(iii) an attached oxygen or nitrogen atom; and

(iv) an sp^2-hybridised carbon atom (designated by the incomplete double bond) separating the heteroatom and the carboxylic acid, or its equivalent.

Charge delocalisation and acidity may thus be important contributing features for significant activity.



X = O or NH

FIGURE 3. Structural requirements for anti-allergic activity.

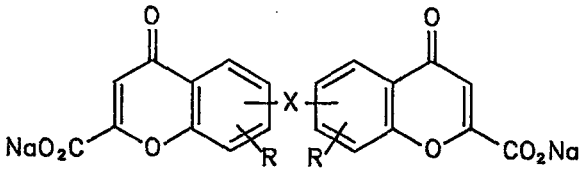
Structure-activity studies[40] of a number of bischromone DSCG analogues **79** suggest that co-planarity of the two chromone rings is an important property as shown :

(i) by the higher activity of the planar compound **80** and

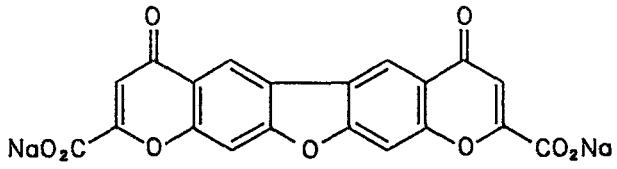
(ii) by the reduced potency of compounds (**79**; R = H) with a bridging alkylenedioxy chain [**79**; X = 5,5'-$O(CH_2)_nO$] comprising more than six atoms or a single methylene bridging group (**79**; X = 6,6'-CH_2) which, in either case, reduces co-planarity of the two nuclei.

The presence of terminal oxygen atoms in the bridging chain is not essential for activity, and the position of attachment of the chromone rings to the bridging chain [**79**; X = $OCH_2CHOHCH_2O$ or $O(CH_2)_5O$] is unimportant, with the exception of the 8,8' positions which produce compounds with little or no activity. Introduction of alkoxy groups

generally maintains or enhances activity, although the disubstituted methoxy analogue (79; R = 7,7′ di-OMe, X=$OCH_2CHOHCH_2O$) is less active than DSCG.

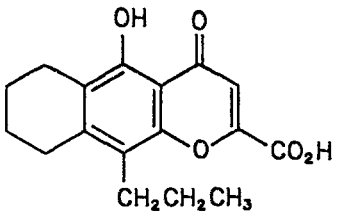


79 [X = $OCH_2CHOHCH_2O$; or
X = 5,5′ $O(CH_2)_nO$ n = 2-6,8-10; or
X = 6,6′ $(CH_2)_n$ n = 1,3,5,6; or
X = 6,6′ O, C=O, NH.]



80

Many mono-chromones have proven to be orally active, a result partly due to increased lipophilicity and decreased polarity.[59] Proxicromil 81 (FPL-57787)[59] was, perhaps, the most promising orally active chromone in clinical trials but toxicity prevented further development. Chromone-3-carboxylic acid 82 is inactive, perhaps due to the loss of acidity resulting from intra-molecular hydrogen bonding. Structure-activity



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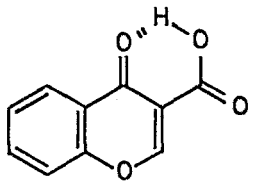


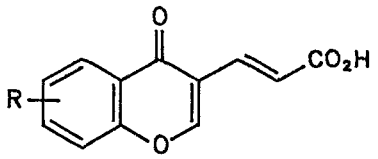
82

studies of chromone-3-acrylic acids 83,[61] in which intra-molecular hydrogen bonding between the carboxylic acid and the carbonyl oxygen is sterically impossible, have established that :

(i) only the *trans* isomers are active;

(ii) introduction of an alkyl or alkoxy group at C-6 or C-8 leads to the greatest enhancement of activity; and

(iii) activity is destroyed by moving the acrylic group to C-2, or by modifying it by introducing an α-substituent or saturating the double bond.

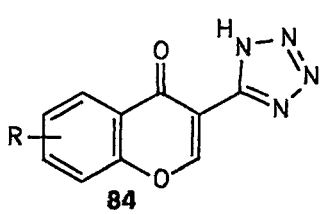


83

The carboxylic acid group of biologically active chromones has often been replaced by the 1H-tetrazole moiety, which exhibits comparable acidity[74] (pK_a *ca.* 3).[75] Such replacement has often resulted in compounds with increased activity.[64] Structure-activity studies[74] of 3-(1H-tetrazol-5-yl)chromone AA-344 (84; R = 6-Et), modelled on the anti-allergic flavanoid baicalein (67),[59] have established that :

(i) the analogues (84; R = 6-Et, 6-Cl, 6,8-di-Me, 6-NO_2, and 6-OH) are all *ca.* 4-10 times more active then DSCG; and

(ii) the parent compound is at least 2.5 times as active as the isomeric 2-(1H-tetrazol-5-yl)chromone.



84

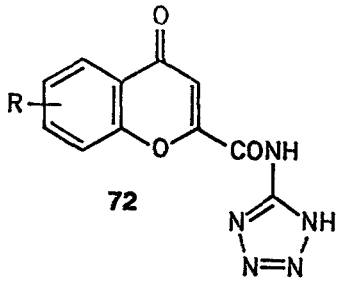
The *N*-(tetrazol-5-yl)chromone-2-carboxamides 72 are *ca.* 80 times more active than DSCG with a longer duration of action[75] and structure-activity studies[64] have established that :

(i) a source of acidity near the pyran ring is desirable;

(ii) the analogues (72; R = 7-OMe or 6-Me) are more potent than the parent compound;

(iii) introduction of a C-3 chloro or methyl group lowers the activity, although a basic C-3 side chain [*e.g.* 3-NH$(CH_2)_2$OH or 3-NHMe] retained high activity; and

(iv) replacement of either hydrogen of the *N*-tetrazolylcarboxamido group by a methyl group resulted in loss of activity.



72

(ii) **Mechanisms of Anti-asthmatic Drugs.**

The word asthma was derived from a Greek word which means "to pant."[76] In 1984, Scanlon[77] described bronchial asthma as "a generalised condition of the lung characterised by bronchospasm, mucosal edema" (an abnormal accummulation of fluid in the tissues causing puffiness), "and thick mucus that can lead to ventilatory insufficiency." A cyclic nucleotide imbalance in airway smooth muscle appears to modulate bronchospasm. Factors causing this imbalance include nervous system imbalances, diminished response(s) of beta-receptors located in the lung, or the effects of histamine. Involvement of the nervous system, including beta receptor malfunction, is referred to as the "intrinsic defect", while external influence, especially allergy, is referred to as the "extrinsic component" of bronchial asthma.

When considering the mechanisms of asthma Salter[78] wrote in 1868, "... it is clear that the vice of asthma is not in the production of any special irritant, but in the irritability of the part irritated." Persson[80] relates this to the present "difficulty in finding a mediator that is peculiar to asthma or a type of cell of the airway in asthma that is abnormally prone to release mediators." There is a resurging interest in the inflammation aspects of asthma[68,80] with a major emphasis on :

(i) plasma exudation;

(ii) the nerve axon mechanism (a neural locus);

(iii) primary effector cells (*e.g.* epithelial cells, mast cells, macrophages, eosinophils, neutrophils, and platelets); or

(iv) mediators from these sources.

Most asthmatic patients suffer with allergy; the allergen may vary but common ones include pollen, feathers and house dust mites (Figure 4).[81] The allergic reaction, or so-called anaphylactic reaction, is mediated by the binding of IgE-antibodies[a] to receptors on the surface of mast cells.[82] Mast cells are located within the muscular wall of the lower airways or bronchioles, among other places, and they contain granules which store a number of potent mediators, including histamine.[81] Mast cell activation is initiated by the bridging of two IgE-molecules by the inhaled allergen or antigen.[83] Activation of mast cells causes degranulation and the release of mediators into the surrounding smooth

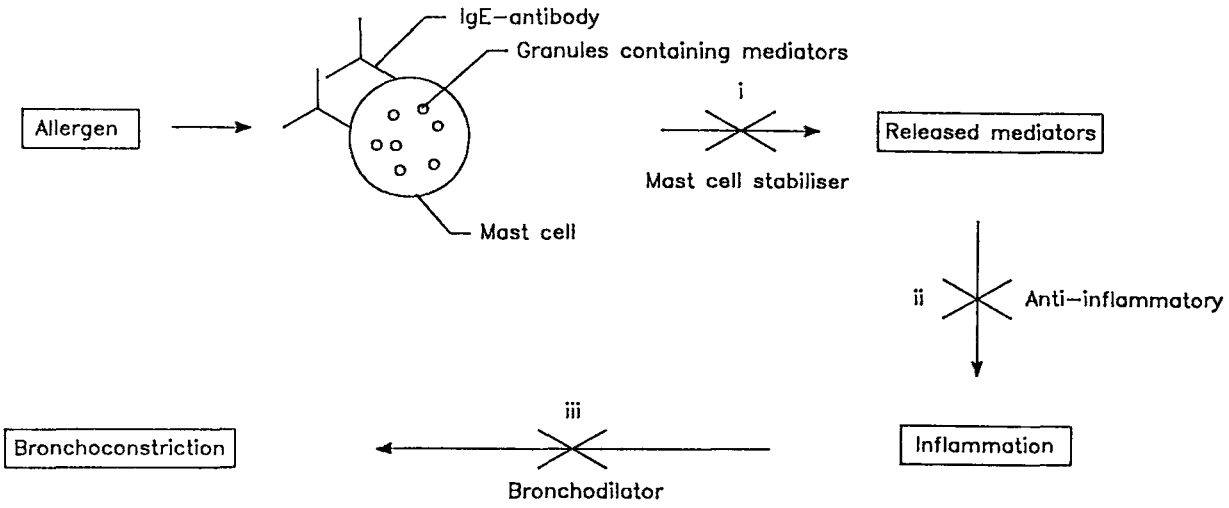


FIGURE 4. A schematic representation of the 'asthmatic response' in humans.[81]

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[a] Anti-bodies are termed immunoglobins (abbrev. Ig) since they are globular proteins with an immune function. IgE-antibodies, one of the five classes of immunoglobins, are responsible for allergic reactions.[82]

muscle. This initiates an inflammatory response[a] which causes bronchial smooth muscle contraction, thereby inducing an asthmatic attack.[84]

Consideration of these events suggests three possible mechanisms for an anti-asthmatic drug (Figure 4).[81] (i) The drug should stabilise mast cells and prevent mediator release after allergen challenge. (ii) The drug should block the action of the released mediators thereby functioning as antagonists, or alternatively, it should act as an anti-inflammatory. [Anti-inflammatory steroids introduced directly into the lung using inhalers are an accepted first-line treatment.] (iii) The drug should relax the contracted airway's smooth muscle thus functioning as a bronchodilator.

Disodium cromolycate (DSCG 73) is generally believed to act on pulmonary mast cells to suppress the secretory response, thus stabilising the membrane.[77] It is used prophylactically as a preventative drug which over time preserves mast cell membrane integrity.[77] DSCG has also been shown to block the late asthmatic response which occurs 3-4 hours after mast cell degranulation and lasts for 10 hours. This response may be caused by mast cell degranulation and increased inflammation, and subsequent non-allergic bronchial hyper-responsiveness lasting up to 10 days can also occur. (This action explains the use of DSCG by seasonal asthmatics). Two additional actions include the ability to modulate

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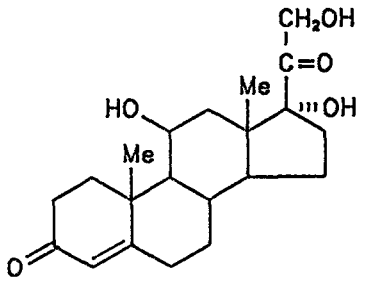
[a] Inflammation[85] is a defensive reaction of the tissues to injury or infection; the blood vessels in the effected area swell and allow their contents to ooze out. Many protective substances, including white blood cells, are released which destroy the foreign particles and bacteria. This process is often referred to as plasma exudation or edema.

bronchoconstrictor response to cooling and the inhibition of irritant receptors; DSCG is thus effective in exercise-induced asthma and in periods of high air pollution.[77] DSCG does not, however, relax bronchial smooth muscle or antagonise any of the known mediators, *e.g.* histamine.[65,72] Since the mode of action of DSCG appears to be limited to mast cell stabilisation and anti-inflammation, only these two aspects will be discussed shortly in detail.

The prophylactic action of DSCG and consideration of the events outlined in Figure 4, both suggest the use of a combination of anti-asthmatic drugs, either including or excluding DSCG. Alternative asthma therapy involves the use of effective bronchodilators *e.g.* glucocorticoids, sympathomimetic drugs, and xanthines.[77] Glucocorticoids (*e.g.* cortisol 85) often reverse a difficult asthmatic condition when other medications fail and are thus, in a sense, the ultimate drug for bronchial asthma. Peak action only occurs 4-6 hours after administration and adverse side effects have limited their use to the difficult-to-control patients with chronic asthma. Glucocorticoids also function as anti-inflammatories. The fundamental structure of sympathomimetic drugs is derived from adrenaline, the body's natural bronchodilator, and salbutamol 86 is the most widely used bronchodilator in the world.[81] Theophylline 87, a xanthene, is generally considered to be the first line of defence in the United States.[77]



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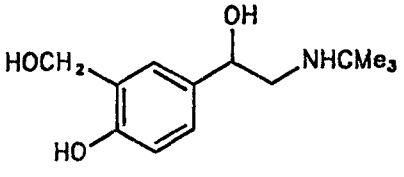

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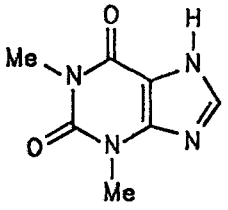

87

(iii) Mast Cell Activation and Histamine Secretion.

The biochemical changes accompanying mast cell activation and the subsquent secretion of histamine were reviewed by Siraganian[83] in 1983. These changes include : (i) receptor cross-linking; (ii) proteolytic enzyme activation; (iii) increased phospholipid methylation; (iv) increased intracellular cAMP[a] levels; (v) increased phosphorylation of membrane lipids; (vi) Ca^{2+} influx; (vii) phospholipase activation and release of arachidonic acid; (viii) protein phosphorylation; and finally, (ix) secretion of histamine. However, molecular events that terminate the secretory response are not well defined and an understanding of the mode of action of DSCG may provide some of the answers.[86] In the following survey attention will be drawn to those molecular events implicated in the mode of action of DSCG, *viz.*, the increased intracellular cAMP levels, protein phosophorylation, and calcium influx. The role of the mediators of mast cell secretion will then be discussed.

Mast cell activation results in changes in intracellular cAMP levels.[83] The generation of cAMP in localised intracellular compartments[67] by the activation of specific adenylate cyclase complexes or the inhibition of particular phosphodiesterases (enzymes converting cAMP to AMP) may lead

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[a] Cyclic adenosine monophosphate (cAMP)[87,88] is a nucleotide which, in the presence of a hormone at the cell membrane, breaks down adenosine triphosphate (ATP) to cAMP, which then acts in the cell to bring about a functional change. Additional functions include an involvement in controlling gene expression, in immune responses, and in nerve transmission.

to preferential activation of protein kinases and subsequent phosphorylation of proteins involved in either the activation or inhibition of the release mechanism. The former kinases may facilitate calcium influx and/or the mobilization of intracellular stores of calcium, the latter activating the calcium pumps leading to the extrusion of calcium from the cytosol. Selective phosphorylation of three proteins[83] with molecular weights of 42 000, 59 000, and 68 000 occurs rapidly after mast cell activation with Ca^{2+} ionophore. DSCG apparently enhances the selective phosphorylation of a molecular weight 78 000 protein, thus terminating or inhibiting secretion.

The role of Ca^{2+} in the secretory process was reviewed by Pearce[89] in 1982. Although the precise role of Ca^{2+} in histamine secretion is still unclear, several possibilities have been proposed. Mast cell secretion is triggered by an increase in the level of Ca^{2+} ions in the cytosol and this event links the activation to the secretion process. Ca^{2+} ions are obtained from the external environment or by the mobilization of intracellular or membranous stores. The former route may involve the binding of calcium ions to superficial membrane receptors. The polypeptide, calmodulin, has been proposed as a universal receptor for calcium and the major physiological effector for a wide range of cellular responses evoked by the cation. The disodium cromoglycate binding protein [discussed later in Section 1.3.3 (iv)] is a possible site of action for calcium channel antagonists.[90] Several receptor-mediated changes in membrane metabolism have been implicated in the regulation of Ca^{2+} channels and Ca^{2+} mobilization, although their specific roles have not yet been determined.

Calcium influx into the mast cell also activates phospholipase A_2, an enzyme which cleaves phosphatidylcholine to produce arachidonic acid.[83] Released arachidonic acid is metabolised by either the cyclo-oxygenase or the lipoxygenase pathways. The former pathway results in the production of prostaglandins and thromboxanes, while leucotrienes, commonly referred to as the slow reacting substance of anaphylaxis (SRS-A), are produced *via* the latter pathway.

The final steps of secretion are regulated by the influx of calcium and changes in cAMP and cGMP,[a] while phosphorylation of proteins may be important at this stage. Aggregation of microtubules then occurs, allowing granules to open to the extracellular space, resulting in mediator release.[83] Important biogenetic substances or mediators released[77] include vasoactive amines (*e.g.* leukotrienes and histamine), prostaglandins and thromboxanes. The leukotrienes, thromboxanes and some of the prostaglandins (PGF_2 and PGD_2) are potent bronchoconstrictors. However, some of the prostaglandins (PGE_2 and PGI_2) are bronchodilators. Other important mediators released include heparin, platelet activating factor (PAF), enzymes and chemotactic factors.[91] Triptic enzymes activate the kinogenase responsible for the release of bradykinin, an extremely potent vasoactive mediator. Chemotactic factors attract eosinophils which modulate the reactions consequent to mast cell activation by neutralising the effects of the released mediators.

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[a] Cyclic guanosine monophosphate (cGMP), a nucleotide with regulatory functions.

(iv) A Molecular Basis for the Mode of Action of Disodium Cromoglycate.

An understanding of the mode of action of DSCG at a molecular level would not only facilitate the rational development of new and more potent anti-allergic drugs,[92] but would also provide some of the answers to the molecular events that terminate the secretory response.[86] The pharmacological implications of DSCG action have, in fact, prompted extensive research, but still remain the subject of debate and controversy.[66,68,93,94]

An initially proposed, clearly defined and novel mode of action for DSCG involves direct action on mast cells, thereby supressing the secretion process. This mechanism has received the most attention but is not directly involved in many aspects of asthma, *e.g.* exercise induced asthma or that induced by pollution. The drug exhibits additional anti-inflammatory action, involving multiple sites of action[65,93] and other additional cells.[94] In the following survey attention will be drawn to (a) mast cell stabilization and (b) the alternative modes of action of DSCG.

(a) Mast cell stabilization.

DSCG does not inhibit the binding of the IgE molecules or their interaction and crosslinking with specific antigens; it rather supresses the response to this reaction, although how it does so is uncertain.[72] It has become evident that there are either two receptors for DSCG, or the receptor is multifunctional.[94] Three major explanations include :

(i) phosphodiesterase inhibition which affects cyclic nucleotide levels;

(ii) the blocking of calcium channels; and

(iii) the promotion of the phosphorylation of a single mast cell protein.

Initial studies indicated that DSCG inhibited cAMP phosphodiesterase[67] and, considering the importance of this nucleotide (cAMP) in the modulation of histamine secretion, seemed to thus provide an explanation for the drug's activity. Studies discrediting this activity established that, among other things, DSCG concentrations required to inhibit mast cell phosphodiesterase were considerably greater than those required to prevent secretion, and there was no correllation between secretion supression and phosphodiesterase inhibition in a variety of other anti-allergic drugs.

Foreman *et al.*[93] showed that the uptake of radioactive Ca^{2+} by, and histamine secretion of mast cells were both inhibited by DSCG in those cells activated by antigen or similar agonists; neither parameter was affected when the cells were activated by calcium ionophore A23187. It was thus argued that DSCG inhibited the opening of calcium channels since this was the only difference between the two processes. (Ca^{2+} ionophores[89] are organic compounds which activate mast cells by complexing with Ca^{2+} and transfering the cation across the cell membrane, hence bypassing the receptor gating mechanism). Studies[93] contradicting this hypothesis have shown that (i) secretion is inhibited by DSCG in the absence of calcium and that DSCG is at least equipotent and generally more active under conditions of calcium deprivation. (ii) The drug also blocks the mobilization of internal stores and inhibits the secretion induced by a diversity of other ionophores. (iii) The uptake of radioactive Ca^{2+} may also be a consequence and not a cause of the release process since the isotope may possibly bind to new membrane sites which are revealed during the degranulation process.

Despite these problems, Pecht *et al.*[95] have shown, using fluorescence microscopy, that the chromone binds to a specific binding protein, located on the mast cell membrane, which constitutes the Ca^{2+} channel and that it acts by blocking simulated Ca^{2+} fluxes. The drug was coupled or covalently conjugated to an insoluble support of fluorescent polyacrylamide and glutaraldehyde beads, which prevented the penetration of the drug into the cell without reducing its ability to inhibit secretion. This specific DSCG-binding protein was then isolated from rat basophil leukaemic cells using affinity chromatography.[96] IgE mediated challenge of varients of this cell-line lacking in the binding-protein did not result in Ca^{2+} influx or degranulation; however, the action of Ca^{2+} ionophore A 23187 lead to histamine secretion, which indicated that the secretory process distal to Ca^{2+} influx was uneffected. These two findings suggested the involvement of the DSCG-binding protein in transmembrane calcium influx. The responsitivity to immunologic challenge was restored with the implantation of binding proteins into the cells. Moreover, exogenous DSCG blocked the Ca^{2+} influx induced by monoclonal antibodies to the binding protein in synthetic planar lipid bilayers.

The relevance of this work to the mode of action of DSCG[93] has been questioned since interaction of the drug and binding protein is absolutely Ca^{2+} dependent and contradicts the enhanced inhibitory effect of the drug in the absence of Ca^{2+}. In addition, rat basophil leukaemic cells are considered to be resistant to the inhibitory effects of DCSG. It was concluded that the work needed to be confirmed and extended to cells fully active to the drug, since this would prevent the isolation of the binding protein under conditions different from those required to demonstrate the drugs functional activity. Other agents, *e.g.* doxantrazole, claimed to function by inhibition of Ca^{2+} gating,

presumably could not interact with the binding protein, unless it showed remarkable specificity.

The phosphorylation of a specific protein (mol. wt. 78 000) occurs in the final stages of secretion and has been associated with the natural termination of the process.[93] DSCG induces the phosphorylation of this protein and may thus have the unique action of stimulating an endogenous control mechanism. The detailed basis for this effect remains obscure but could involve an interaction with protein kinase C, as suggested by Sagi-Eisenberg.[94] This interaction was proposed since protein kinase C requires Ca^{2+} and phosphatidylserine for optimum activity, and DSCG binding is associated with Ca^{2+}, phosphatidylserine and a membrane protein. The mechanism whereby phosphorylation modulates secretion remains open and could involve an effect on Ca^{2+} gating, *i.e.* they may be regulated by the degree of their phosphorylation, which is controlled by protein kinase C. However, Foreman *et al.*[93] demonstrated that the Ca^{2+} gates remain open for a considerable period after the termination of secretion.

Sagi-Eisenberg[94] also demonstrated that this protein kinase C has an additional role in the activation of secretion and involves the mechanism of secretion distal to Ca^{2+} influx. Additional interaction of DSCG with this protein kinase C would then account for its dual inhibition action, although this hypothesis requires verification. They thus proposed the existence of two forms of protein kinase C, one responsible for Ca^{2+} regulation, the other involved in the activation of secretion. Activation of protein kinase C by itself was insufficient to cause secretion, and they concluded that "receptor aggregation elicits an aditional, as yet unknown, signal, which together with kinase C activation, yields a cellular response." Inhibition activity of DSCG

thus requires the interaction with kinase C which (i) promotes phosphorylation in Ca^{2+} gating, and (ii) inhibits the phosphorylation that stimulates secretion.

(b) **Alternative modes of action of DSCG.**

In 1985, Pearce[93] concluded, however, that the mode of action of DSCG was still an enigma since not all the effects of DSCG can be explained by its mast cell stabilizing activity[65] and premedication with the drug inhibits bronchospasm produced by a diversity of stimuli, including histamine, cold air, aspirin, fog, and exercise, thus implicating at least two different receptors in the lung for the drug. Pretreatment with the drug, in a variety of models of mediator release, has been shown to abolish the inhibitory effect of subsequent doses *i.e.* DSCG exhibits tachyphylaxis[92] which completely contrasts with its regular and prophylactic clinical use in asthma therapy. The drug also shows a high degree of tissue and species selectivity in its action.[65] Many other novel anti-allergic drugs are far more potent than DSCG in mast cell-mediated animal models but have demonstrated little or no efficacy when clinically tested.[97] A more detailed mode of action is thus required.[65]

In 1987 Persson[98] reviewed three alternative modes of action for DSCG which include :

(i) an anti-plasma leakage effect;

(ii) inhibition of an axon reflex mechanism (a neural locus effect); and

(iii) PAF-acether[a] inhibition.

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[a] Platelet activating factor, an ether-linked phospholipid (abbrev. PAF-acether).[84]

DSCG is now also thought to affect a variety of inflammatory cells, such as platelets and macrophages.

In inflamed airways, plasma molecules may readily pass through a microvascular or epithelial barrier.[80,98] Plasma exudation in the lumen and airway wall from tracheobronchial microvessels is regulated by the venular endothelium. This process is induced by many cellular and humoral mediators including bronchoconstrictory mediators (amines, peptides, lipid products, *e.g.* PAF-acether, *etc.*). Exudation in the airway wall contributes to bronchial hyper-responsiveness and damage of airway epithelium, while activation of potent mediators and chemoattractants for effector cells may amplify the inflammatory process. DSCG has a potent ability to reduce and normalise mediator-induced plasma leakage or exudation. It is also "effective against agents such as histamine that increase endothelial-epithelial permeability to macromolecules by direct action without the involvement of neurogenic or mast cell mechanisms."

Asthma provoked by non pharmacological stimulus such as exercise (inhaling dry air) may be associated with plasma exudation in asthmatic airways, the characteristic feature of which, may be vascular leakiness.[98] In inflamed airways it is vessel fluid that humidifies incoming air whereas other sources are used under normal conditions. Thus the effectiveness of DSCG in exercise-induced asthma could be attributed to its anti-plasma-leakage effect.

Damage of the airway epithelium exposes C-fibre afferent nerve endings,[79] and the stimulation of these superficial nerve endings by inflammatory mediators (*e.g.* bradykinin) may result in an axon (local) reflex and the release of sensory neuropeptides which induce

bronchoconstriction, edema, plasma exudation, mucus hypersecretion, and possible inflammatory cell infiltration and secretion. DSCG inhibits bronchial C-fibre reflex activity[98] and preliminary studies show that it reduces bradykinin-induced bronchoconstriction. However this has only been shown in animal models and requires further elucidation. Several factors opposing a neural locus for the drug's effect have also been presented.

The ether-linked phospholipid, PAF-acether,[84] is released from a number of inflammatory cells in the lung (*e.g.* alveolar macrophages) and induces plasma exudation and the activation of platelets. Both the production and action of PAF-acether could be inhibited by DSCG since it also inhibits the late response to PAF-acether in human skin and the IgE activation of human macrophages.[99] Recent work, however, has not provided confirmation of these findings.[98]

The involvement of platlets in inflammation and allergen-induced asthma was reviewed by Page[84] in 1988. Platelets are the smallest blood element and, despite being devoid of a nucleus, they still possess many features of classical inflammatory cells. Their biological activities include chemotaxis, *i.e.* the release of a variety of mediators which augment inflammatory cell recruitment. Furthermore, they possess IgE receptors and their activation, by PAF-acether, results in the generation of free radical species. Platelet aggregation and platelet activation have different pharmacological profiles and this distinction is important in the search for new anti-allergic drugs, *e.g.* DSCG can inhibit IgE dependent release of free radicals, but has no effect on platelet aggregation.

1.4 AIMS OF THE INVESTIGATION

The preceding introduction illustrates the various properties of the chromone nucleus, preparative methods used in chromone synthesis, and the susceptibility of chromones to C-2 nucleophilic attack, with consequent ring opening, by nitrogen and oxygen nucleophiles (Section 1.1). The conformational analysis of amides and chromone-2-carboxylate esters, using variable temperature dynamic NMR and IR spectroscopic techniques respectively, were also presented (Section 1.2). Furthermore, the well established potential of chromone systems in asthma therapy has been discussed, with particular emphasis on two chromone derivatives, *viz.*, the naturally occuring furochromone, khellin **66** (Section 1.3.1), and the widely used anti-allergic drug disodium cromoglycate (DSCG) **73** (Section 1.3.2). While chromonecarboxamides exhibit a wide diversity of biological activities, their anti-allergic activity [*e.g* exhibited by *N*-(tetrazol-5-yl)chromone-2-carboxamides **72**] is of particular interest (Section 1.3.2). The essential structural features apparently required for anti-allergic activity include a planar conformation with extended π-bonding and a source of acidity near the heteroatom attached to the benzene ring. Thus, biological activity is enhanced in rigid planar structures and inhibited by a loss of acidity, while electronic effects of ring substituents and the effect of their positions appear to vary according to the nature of the parent structure [Section 1.3.3 (i)]. In asthma therapy, DSCG stabilises mast cells in the bronchial mucosa, thereby preventing the secretion of histamine and other inflammatory mediators. Furthermore, this action may be associated with the binding of DSCG to a specific protein located on the mast cell membrane [Section 1.3.3 (iv)].

In anti-allergic chromones, biological activity is thus influenced by conformation, acidity, steric effects, and substituent effects. Consequently, similar electronic and steric effects on the conformation and acidity in chromone systems with medicinal potential were investigated. The mode of action of DSCG may involve an *in vivo* interaction with various biological amines or proteins. Furthermore, since ring-opening reactions of chomones may well be implicated in molecular-level chromone pharmacology, the ring-opening of variously substituted chromone-2-carboxamides with dimethylamine was also investigated, and extended to include DSCG. The investigation thus involved the following :

(i) The synthesis of conformationally-mobile, substituted, symmetrical chromone-2-carboxamides with potential anti-allergic activity.

(ii) The conformational analysis of these chromone-2-carboxamides using ^{1}H dynamic NMR spectroscopic and molecular graphics techniques.

(iii) A structural analysis of the ring-opened products of reactions of *N,N*-dimethylchromone-2-carboxamides with dimethylamine.

(iv) An extension of these studies to DSCG.

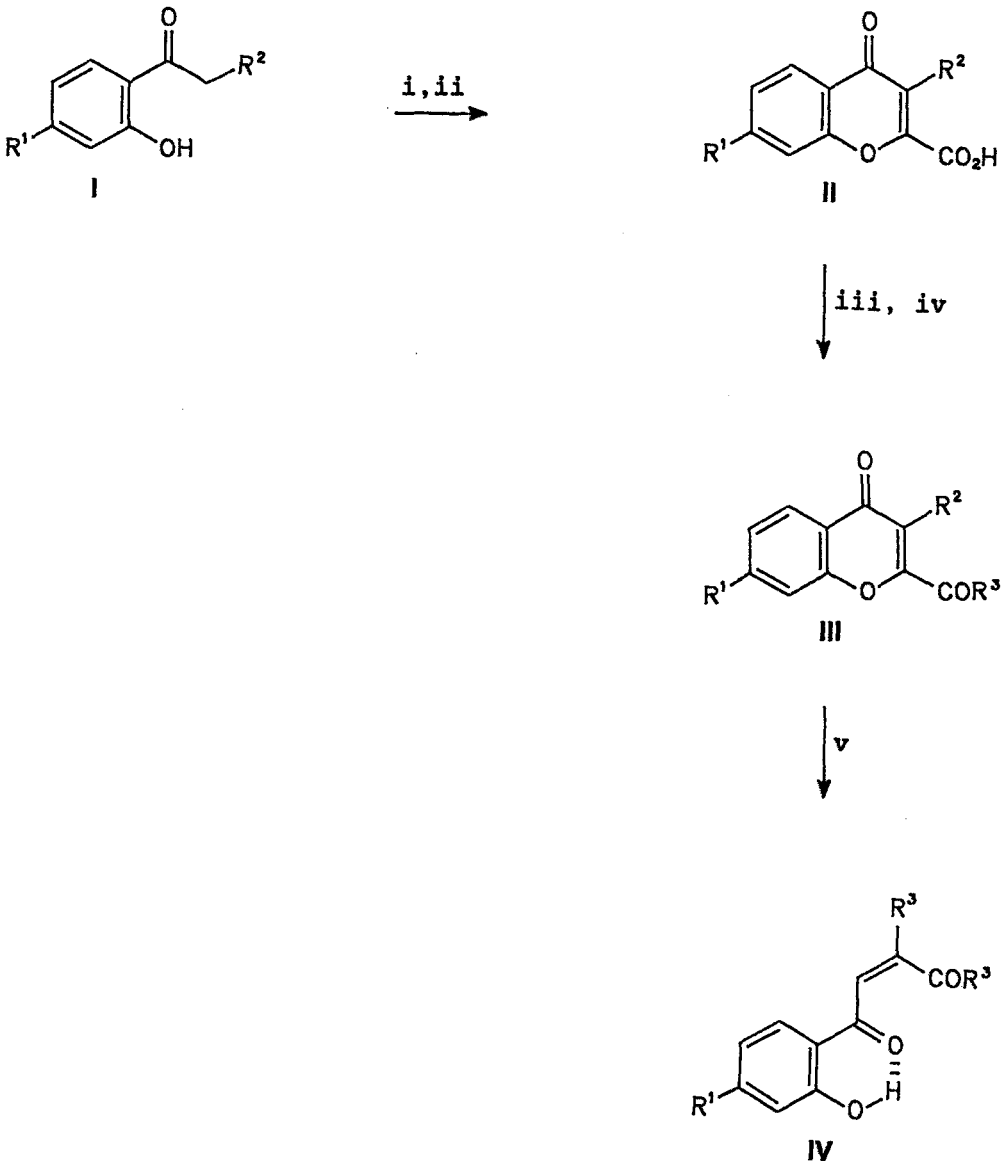
(v) A kinetic study of substituent effects on the ring-opening reactions and a determination of the mechanism.

(vi) A potentiometric study of substituent effects on the dissociation constants of substituted chromone-2-carboxylic acids.

2. DISCUSSION

2.1 PREPARATION OF CHROMONE DERIVATIVES

An investigation of conformation in chromone-2-carboxamides **III** required the preparation of two major intermediates, *viz.*, the substituted *o*-hydroxyacetophenones **I** and chromone-2-carboxylic acids **II**, while structural and kinetic studies required the preparation of acrylamides **IV** from the respective chromone-2-carboxamides **III** (Scheme 23 p.53). Thus, the *o*-hydroxyacetophenones **93-98**, required for the synthesis of the chromone-2-carboxylic acids **112-118**, were prepared from the corresponding phenyl acetates **88-92**, which, in turn, were prepared from *m*-phenols or *p*-chlorophenol; or in the case of the methoxy analogue **93**, *via* methylation of resacetophenone (Schemes 24 and 25 p.54 and p.55). The chromone-2-carboxylic acids **112-118** were prepared from the respective *o*-hydroxyacetophenones **93-98** *via*, in some cases, chromone-2-carboxylate esters **110** and **111** (Schemes 26 and 27 p.56). 3-Methylchromone-2-carboxylic acid **120** was similarly prepared from *o*-hydroxypropiophenone *via* the ethyl carboxylate ester **119** (Scheme 28 p.57). The chromone-2-carboxamides **129-139** were prepared from the corresponding chromone-2-carboxylic acids **112-117** and **120** *via* the chromone-2-carbonyl chloride intermediates **121-127** (Scheme 29 p.61). The acrylamides **140,142-151**, and **153** were prepared *via* amine-mediated ring-opening of the chromone-2-carboxamides **129-134** (Schemes 30-33 p.69 and p.73) or, in some cases (**140** and **141**), of chromone-2-carbonyl chloride **121** (Scheme 29 p.61).



SCHEME 23

Reagents : i) NaOEt - EtOH, $(CO_2Et)_2$, Δ,

ii) HCl - AcOH (1:1), Δ;

iii) $SOCl_2$ - DMF - $ClCH_2CH_2Cl$, Δ;

iv) Me_2NH_2Cl - pyridine, 0°C or

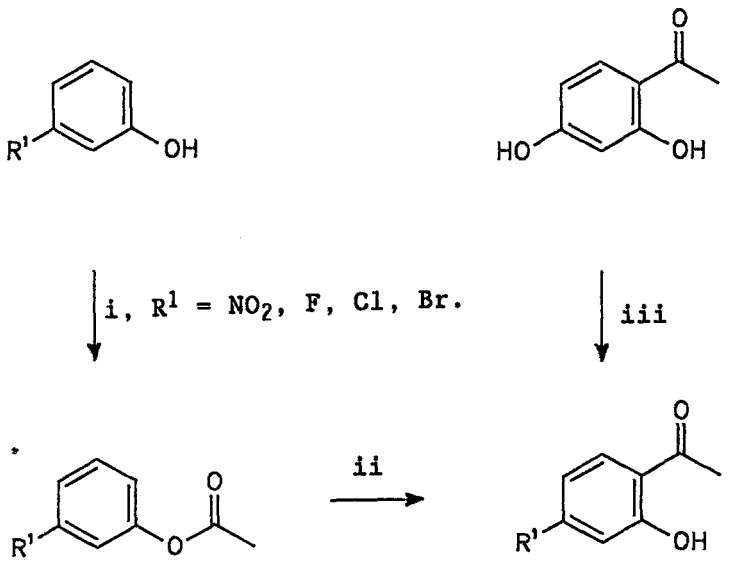
R^3H - aq.$NaHCO_3$ or

R^3H - pyridine;

v) Ethanolic Me_2NH - EtOH, 35°C.

2.1 (i). Preparation of *o*-hydroxyacetophenones.

2-Hydroxy-4-methoxyacetophenone **93** was prepared *via* methylation of resacetophenone (Scheme 24).[100] The series of *o*-hydroxyacetophenones **94-97** were prepared using standard literature procedures[101] involving Fries rearrangement[102] of the corresponding phenyl acetates **88-91**, generated, in turn, by acetylation of the respective *m*-phenols (Scheme 24), as described by Bryan *et al.*[103] The acetates were heated with aluminium trichloride at high temperatures (*ca.* 175°C) which favour *o*-substitution.[101,102] The Fries rearrangement of 3-nitrophenylacetate **88**, using nitrobenzene as a solvent,[101,104] afforded moderate yields (*ca.* 40%) of 2-hydroxy-4-nitroacetophenone **94**. Extended steam distillation was necessary, since the initial fractions were predominantly solvent.

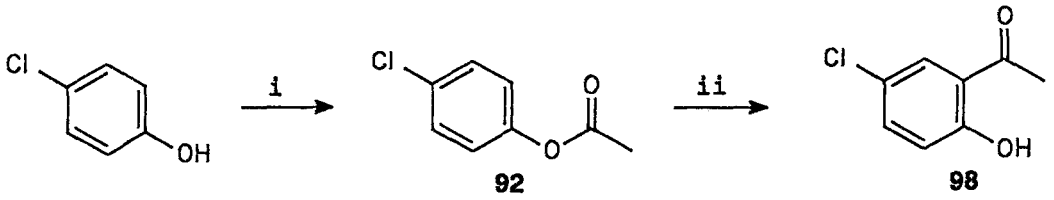


	R^1	
-	OMe	**93**
88	NO_2	**94**
89	F	**95**
90	Cl	**96**
91	Br	**97**

SCHEME 24

Reagents : i) Aq.NaOH - Ac_2O, 0°C; ii) $AlCl_3$, Δ;
iii) Me_2SO_4 - Acetone - K_2CO_3, Δ.

5-Chloro-2-hydroxyacetophenone **98** was similarly prepared from 4-chlorophenyl acetate **92** which, in turn, was prepared from 4-chlorophenol (Scheme 25).

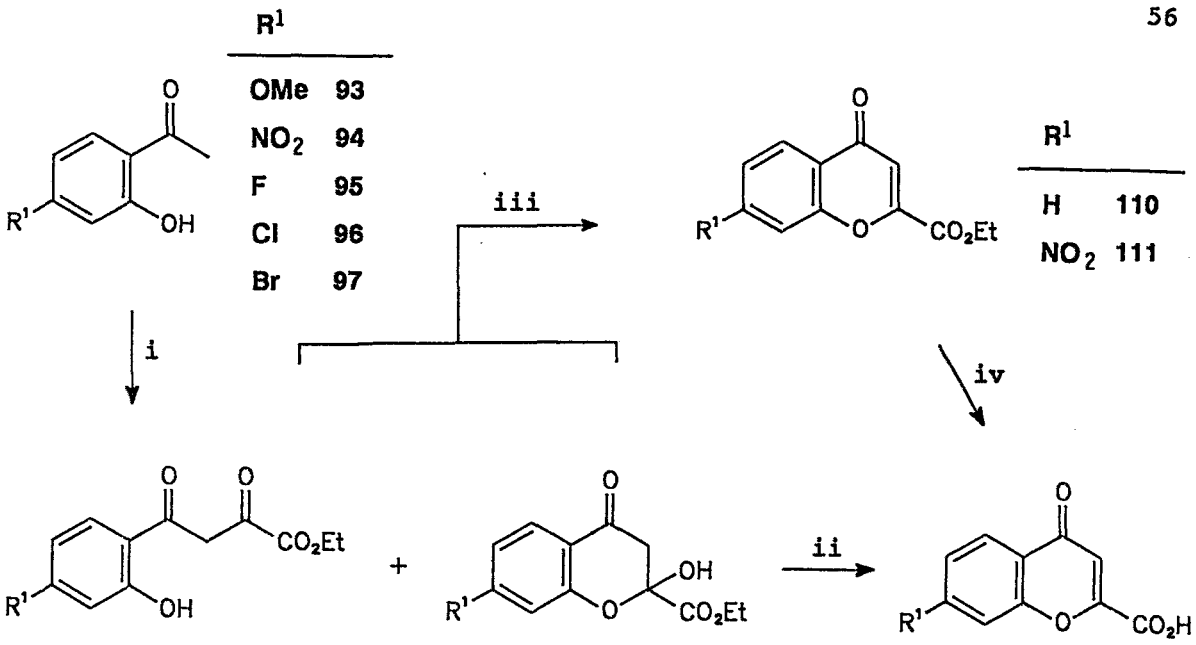


SCHEME 25

Reagents : i) Aq.NaOH - Ac_2O, 0°C; ii) $AlCl_3$, Δ.

2.2 (ii). Preparation of chromone-2-carboxylate esters and chromone-2-carboxylic acids.

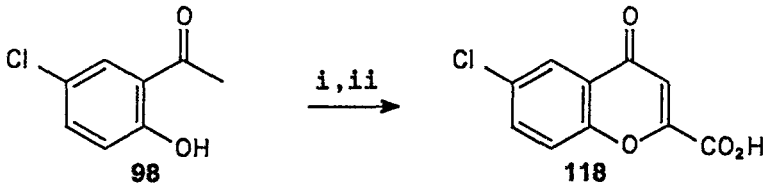
The chromone-2-carboxylic acids **112-117** and **120** (Schemes 26 and 28) were required for the preparation of the chromone-2-carboxamides **129-139**, while, in an investigation of the acidity in the chromone-2-carboxylic acids **112-118** (Schemes 26 and 27), the C-7 and 6-chloro ring substituents (R^1) were chosen to illustrate substituent effects on acidity. The chromone-2-carboxylate esters **110** and **111** and chromone-2-carboxylic acids **112-117** were prepared *via* Claisen acylation of the *o*-hydroxyacetophenones **93-97** with diethyl oxalate in the presence of sodium ethoxide, as described by Fitton and Smalley,[105] and Bryan *et al.*[103] (Scheme 26). Cyclization of the resultant diketo esters using traces of hydrochloric acid in acetic acid afforded the chromone-2-carboxylate esters **110** and **111**,[106,107] while chromone-2-carboxylic acids **112-117** were obtained by using a mixture (1:1) of hydrochloric acid and acetic acid. In both approaches, two reaction intermediates were generally detected by ^1H NMR spectroscopy, *viz.*, a diketone and a 2-hydroxychromanone. The chemical shifts of the methylene protons of the diketone occur at low field



R^1			
H	99 (100%)[a]	-	112
OMe	100 (68%)[a]	105 (32%)[a]	113
NO_2	101 (78%)[a]	106 (22%)[a]	114
F	102 (62%)[a]	107 (38%)[a]	115
Cl	103 (37%)[a]	108 (63%)[a]	116
Br	104 (45%)[a]	109 (55%)[a]	117

SCHEME 26

Reagents : i) NaOEt - EtOH, $(CO_2Et)_2$; ii) HCl - AcOH (1:1), Δ;
iii) HCl(trace) - AcOH, Δ (R^1 = H, NO_2);
iv) H_2SO_4 - AcOH, Δ or HBr - AcOH (45%), Δ (R^1 = H, NO_2).



98 118

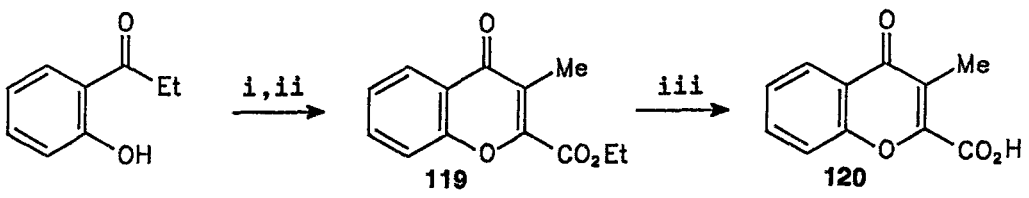
SCHEME 27

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

[a] Calculated from ^1H spectrum of crude intermediate mixtures.

(*ca.* 7.1 ppm), while the diastereotopic (C-3) methylene protons of the 2-hydroxychromanone appear as a doublet of doublets at higher field (*ca.* 2.9 and 3.3 ppm). In the synthesis of chromone-2-carboxylic acid 112, only the diketone intermediate 99 was formed, while in the synthesis of the substituted chromones 111, 113 and 115-117, mixtures of the corresponding intermediates were obtained. In some cases the diketone intermediates 100-102 predominated, while in others, the 2-hydroxychromanones 108-109 were the major isomers (Scheme 26). In all cases the crude intermediate mixtures were used without further purification.

Chromone-2-carboxylic acid 112 was alternately prepared by acid hydrolysis of the ethyl carboxylate ester 110.[107] 7-Nitrochromone-2-carboxylic acid 114 was similarly prepared from the carboxylate ester 111 (Scheme 26) using sulphuric acid and acetic acid,[107] since the use of 45% hydrobromic acid in acetic acid following the literature procedure[106] gave the acid in low yield (*ca.* 33%). 6-Chlorochromone-2-carboxylic acid 118 was prepared *via* Claisen acylation of 5-chloro-2-hydroxyacetophenone 98 (Scheme 27 p.56).[103] 3-Methylchromone-2-carboxylic acid 120 was prepared by acid hydrolysis of the carboxylate ester 119, which in turn, was prepared by Claisen acylation of *o*-hydroxypropiophenone and diethyl oxalate with sodium hydride (Scheme 28).[107]



SCHEME 28

Reagents : i) NaH, $(CO_2Et)_2$, EtO_2; ii) H^+, Δ; iii) H^+, Δ.

Repeated recrystallisation of the acids did not improve the melting points which, in some cases, were well below the literature values. Other methods, such as sublimation and extraction with ethyl acetate, were used in attempts to obtain analytically pure samples.

The ^{1}H chemical shifts of the chromone-2-carboxylic acids and carboxylate esters were assigned using reported values,[51,108] while ^{1}H and ^{13}C signals of the fluoro analogue **115** were assigned using ^{1}H-F and ^{13}C-F coupling constants[109] (Figure 5). The ^{1}H NMR spectra of the chromone-2-carboxylic acids and carboxylate esters are characterised by the vinyl proton (3-H) singlet at *ca.* 7.00 ppm or 7.15 ppm respectively (Table 1). C-7 substituents produce small variations in the (3-H) chemical shift, while changing the chloro substituent position did not affect the (3-H) chemical shift, as illustrated in Table 1. The IR carbonyl absorption bands (*ca.* 1740 cm^{-1}) of the chromone-2-carboxylic acids and carboxylate esters are well separated from the ketone carbonyl absorption bands occuring at *ca.* 1650 cm^{-1}.

Table 1. Selected spectral data for chromone-2-carboxylic acids and chromone-2-carboxylate esters.

Compound Acid	3-H (ppm)	CO.OH (cm^{-1})	CO (cm^{-1})	Compound Ester	3-H (ppm)	CO.OR (cm^{-1})	CO (cm^{-1})
112	7.00	1740	1630	**23**	7.15	1740	1650
113	6.90	1735	1625	-	-	-	-
114	7.20	1730	1640	**24**	7.25	1745	1660
115	6.84	1740	1630	-	-	-	-
116	7.00	1710	1650	-	7.09	1740	1655
117	7.00	1720	1630	-	-	-	-
118	7.00	1735	1630	-	-	-	-
120	2.30[a]	1730	1615	**31**	2.35[a]	1730	1645

[a] (3-Me) ^{1}H chemical shift.

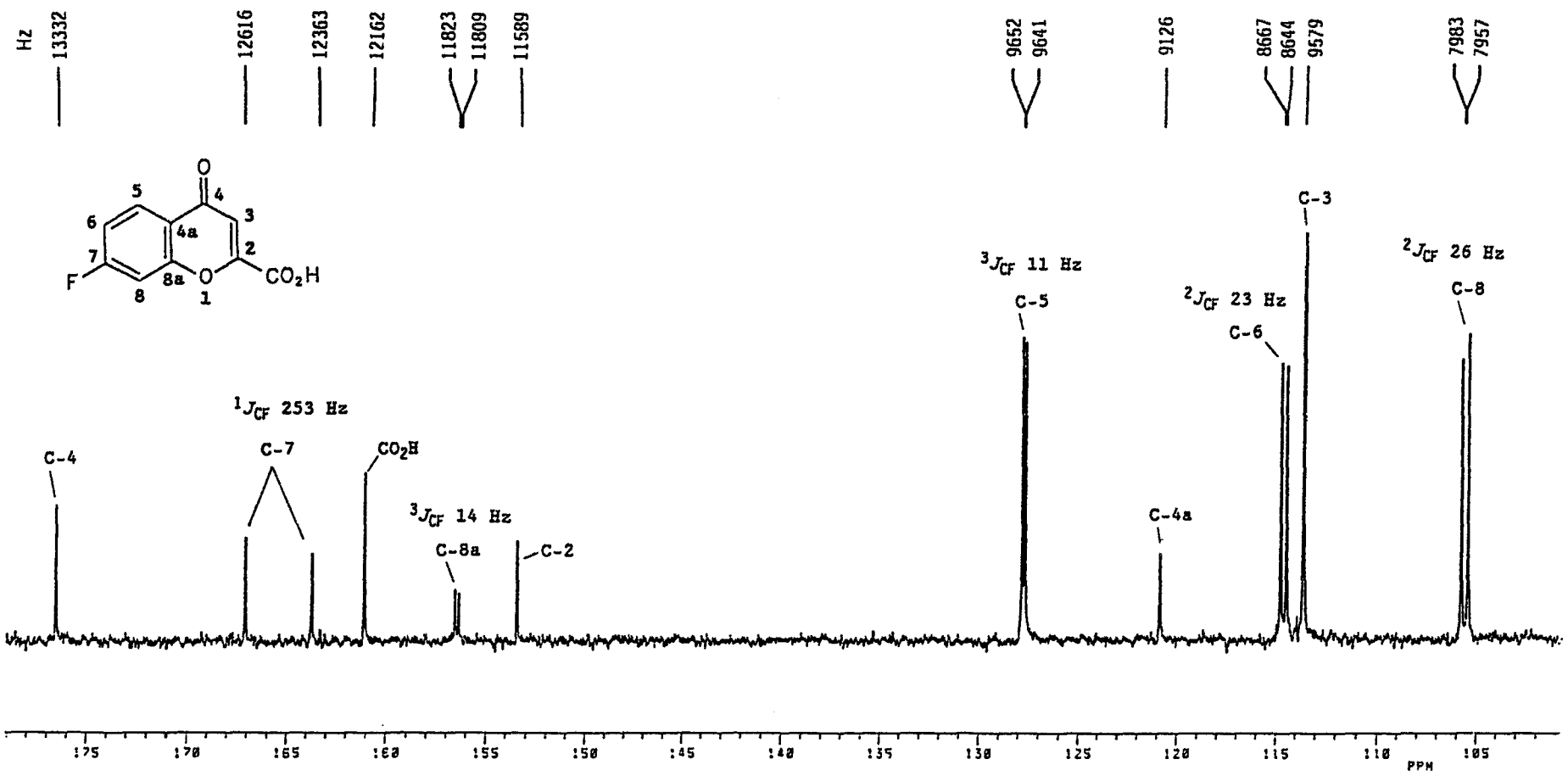
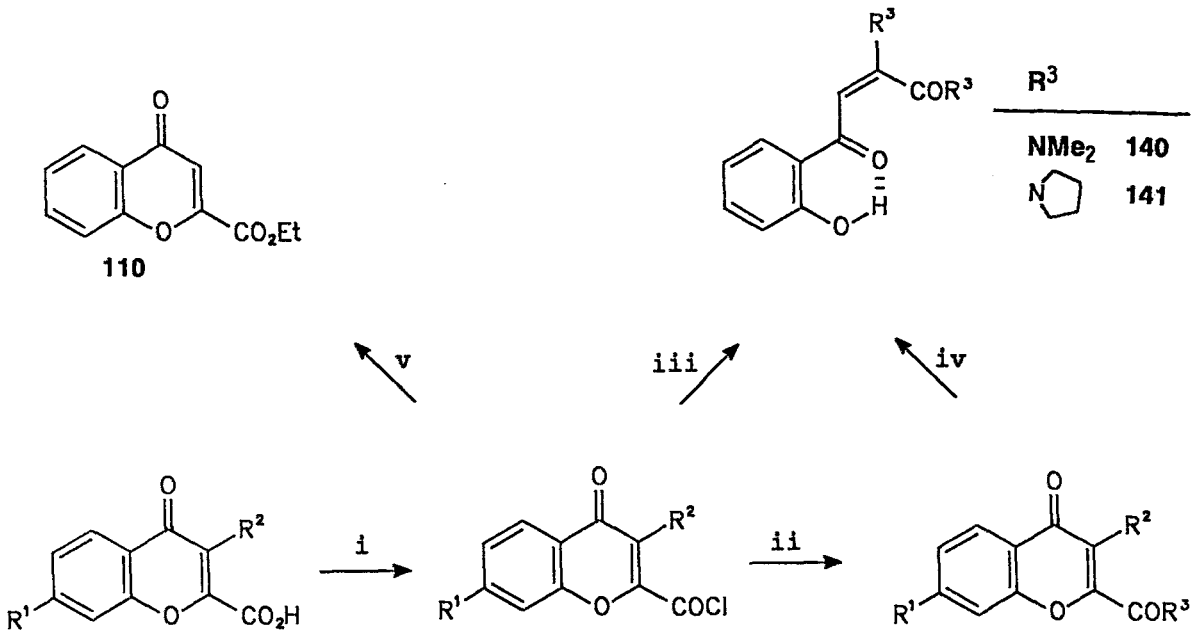


FIGURE 5. 75 MHz ^{13}C spectrum of 7-fluorochromone-2-carboxylic acid 115.

2.1 (iii). **Preparation of chromone-2-carboxamides.**

An NMR study of rotational isomerism in the chromone-2-carboxamides **129-138** (Scheme 29) required the synthesis of a range of substituted *N,N*-dialkyl amides; the ring and *N*-alkyl substituents were chosen to illustrate the influence of electronic and steric effects on rotational barriers. Symmetrically substituted amides were chosen to simplify interpretation of the dynamic NMR spectra. The chromone-2-carboxamides **129-139** were prepared from the corresponding chromone-2-carbonyl chlorides **121-127** generated, in turn, from the respective chromone-2-carboxylic acids **112-117** and **120** using thionyl chloride (Scheme 29).[64] In all cases, yields of the carboxamides were calculated from the corresponding carboxylic acids (Table 2). The crude chromone-2-carbonyl chlorides were reacted, following a literature procedure,[64] with one molar equivalent of primary or secondary amine in aqueous sodium bicarbonate, or in pyridine. An equimolar quantity of amine was used, since C-2 nucleophilic attack by excess amine with consequent ring-opening afforded acrylamides, *e.g.* reaction of chromone-2-carbonyl chloride **121** with excess aqueous dimethylamine afforded the acrylamide **140**. It is interesting to note that in related studies, Jerzmanowska and Kostka[17] have reported the ammonolysis of chromone-2-carboxylate esters using one molar equivalent of amine; while ring-opening of chromone-2-carboxylate esters with two molar equivalents of amine, and subsequent cyclisation of the resulting acrylamides (*e.g.* **140**), afforded chromone-2-carboxamides (*e.g.* **129**). The analogous preparation of *N,N*-dimethylchromone-2-carboxamide **129** *via* ammonolysis of the ethyl carboxylate ester **110** with one molar equivalent of ethanolic dimethylamine in ethanol was unsuccessful.



	R^1	R^2	
112	H	H	121
113	OMe	H	122
114	NO_2	H	123
115	F	H	124
116	Cl	H	125
117	Br	H	126
120	H	Me	127

R^1	R^2	R^3	
H	H	NMe_2	129
OMe	H	NMe_2	130
NO_2	H	NMe_2	131
F	H	NMe_2	132
Cl	H	NMe_2	133
Br	H	NMe_2	134
H	Me	NMe_2	135
H	H	NPr^i_2	136
H	H		137
H	H		138
H	H	NH_2	139

SCHEME 29

Reagents : i) $SOCl_2$ - DMF - $ClCH_2CH_2Cl$, Δ;

ii) Me_2NH_2Cl (128) - pyridine, 0°C, or

R^3H - aq.$NaHCO_3$, or

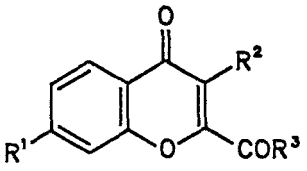
R^3H - pyridine;

iii) R^3H (2 Molar eq.) - H_2O ($R^1 = R^2 = H$);

iv) Ethanolic Me_2NH - EtOH ($R^1 = R^2 = H$);

v) Ethanolic Me_2NH - pyridine ($R^1 = R^2 = H$).

TABLE 2. Preparation of chromone-2-carboxamides 129-138.



Compound	R^1	R^2	R^3	Anhydrous reactions Crude Yield[a] (%)	Anhydrous reactions Chrom. Yield[b] (%)	Aqueous Reactions Crude Yield[a] (%)	Aqueous Reactions Chrom. Yield[b] (%)	Melting Point (°C)
129	H	H	NMe_2	76	62	10[g]	5[h]	115-116[d]
130	OMe	H	NMe_2	92	83	-	-	120-122[c]
131	NO_2	H	NMe_2	68	66	-	-	152-153[c]
132	F	H	NMe_2	76	64	54	43	144-146[c]
133	Cl	H	NMe_2	80	72	61	41	146-147[c]
134	Br	H	NMe_2	96	77	32	21	143-145[c]
135	H	Me	NMe_2	84	71	52	24	74-76[c]
136	H	H	NPr^i_2	-[f]	40	6	-	95-96[c]
137	H	H		-	-	-[i]	22	103-105[c]
138	H	H		-[f]	75	-	-	66-67[e]

[a] Overall yield from the corresponding acid, material essentially clean by ^1H NMR spectroscopy. [b] Overall yield from corresponding acid after flash chromatography. [c] New compound with satisfactory spectroscopic analyses. [d] Lit.[17] 115-116°C. [e] Lit.[17] 90.5-92°C. [f] Crude oil. [g] Recrystallised yield. [h] Flash chromatography of crude motherliquors. [i] Crude mixture of acid and amide.

The *N,N*-dimethylchromone-2-carboxamides **129** and **132-135** were initially prepared in variable yields (15-61%; Table 2 p.62) from the chromone-2-carbonyl chlorides **121** and **124-127** using equimolar quantities of aqueous dimethylamine (40% w/w), and applying the procedure reported by Ellis *et al.*[64] [Low yields were also obtained in the preparation of chromone-2-carboxamides **136** and **137** in aqeuous media (Table 2).] Such low yields may be attributed to factors such as the insolubility of both starting materials and products in aqueous media and the possible hydrolysis of the chromone-2-carbonyl chloride intermediates. The synthesis of chromone-2-carboxamide **138** in higher yield (75%) using dry pyridine as solvent illustrated the advantages of using anhydrous conditions, and this approach was consequently explored for the synthesis of the *N,N*-dimethylchromone-2-carboxamides **129-135**.[110] However, the use of ethanolic dimethylamine (33% w/w) afforded a mixture (1:2) of the carboxamide **129**, in low yield (*ca.* 28%), and the corresponding ethyl carboxylate ester **110**. The use of pure dimethylamine was not considered a viable proposition in view of its volatility (b.p. 7°C), which complicates both handling and measuring of the compressed liquid at room temperature. [An alternative procedure which does not require the "use of the somewhat objectionable dimethylamine", has been reported by Coppinger.[111] This procedure involves the reaction of an acid chloride or anhydride in *N,N*-dimethylformamide at high temperatures (150°C) to afford *N,N*-dimethylcarboxamides.]

The use of dimethylammonium chloride **128** in anhydrous pyridine at 0°C, eliminated the problems associated with the use of aqueous/ethanolic or neat dimethylamine, and afforded the required *N,N*-dimethylchromone-2-carboxamides **129-135** in high yield (68-98%; Table 2).[110] Various quantities of amine hydrochloride were used in the preparation of the unsubstituted analogue **129**, and optimum yields were obtained using two

molar equivalents of the amine hydrochloride. Free dimethylamine is thus generated *in situ via* neutralisation with pyridine, the reaction solvent. Furthermore, acyl substitution[112] is enhanced by the formation of an acylammonium salt,[113] *via* nucleophilic attack of pyridine on the carbonyl chloride intermediate, and the hydrochloric acid produced is neutralised by pyridine. [Ammonium salts have previously been used in the reported acid catalysed ammonolysis of ethyl benzoate;[114] the acylation of amines by carboxamides;[115] and the Schotten-Baumann acylation[116] of 1,3,5-tris(aminomethyl)benzene trihydrochloride.[117]]

Chromone-2-carboxamide **139** was prepared from the carbonyl chloride **121** using a large excess of aqueous ammonia, or two molar equivalents of ammonium chloride in pyridine; the latter preparation represents an extension of the use of ammonium salts in the synthesis of chromone-2-carboxamides. However, in both preparations, impurities were detected in the ^{1}H and ^{13}C NMR spectra.

The ^{1}H NMR chemical shifts of the chromone-2-carboxamides **129-139** were assigned using the literature values for chromone,[11] and correlation data from COSY experiments. Non-quaternary ^{13}C chemical shifts were assigned from HETCOR experiments (Figure 6), while the benzenoid signals were also confirmed by calculation using correlation tables[109] and, in the case of the fluoro-analogue **132**, using ^{13}C-F coupling constants[109] (Figure 7). In general, the C-5 and C-6 ^{13}C chemical shifts are too similar to assign by calculation (in the case of the *N,N*-dimethylchromone-2-carboxamide **129** these signals actually coincide). The quaternary carbons, C-4a and C-8a, and the ketone carbonyl carbon (C-4) signals correlate with reported values for chromone,[11] while C-2 chemical shifts were assigned by comparison with reported values of the corresponding chromone-2-carboxylic acids and carboxylate esters.[51,108]

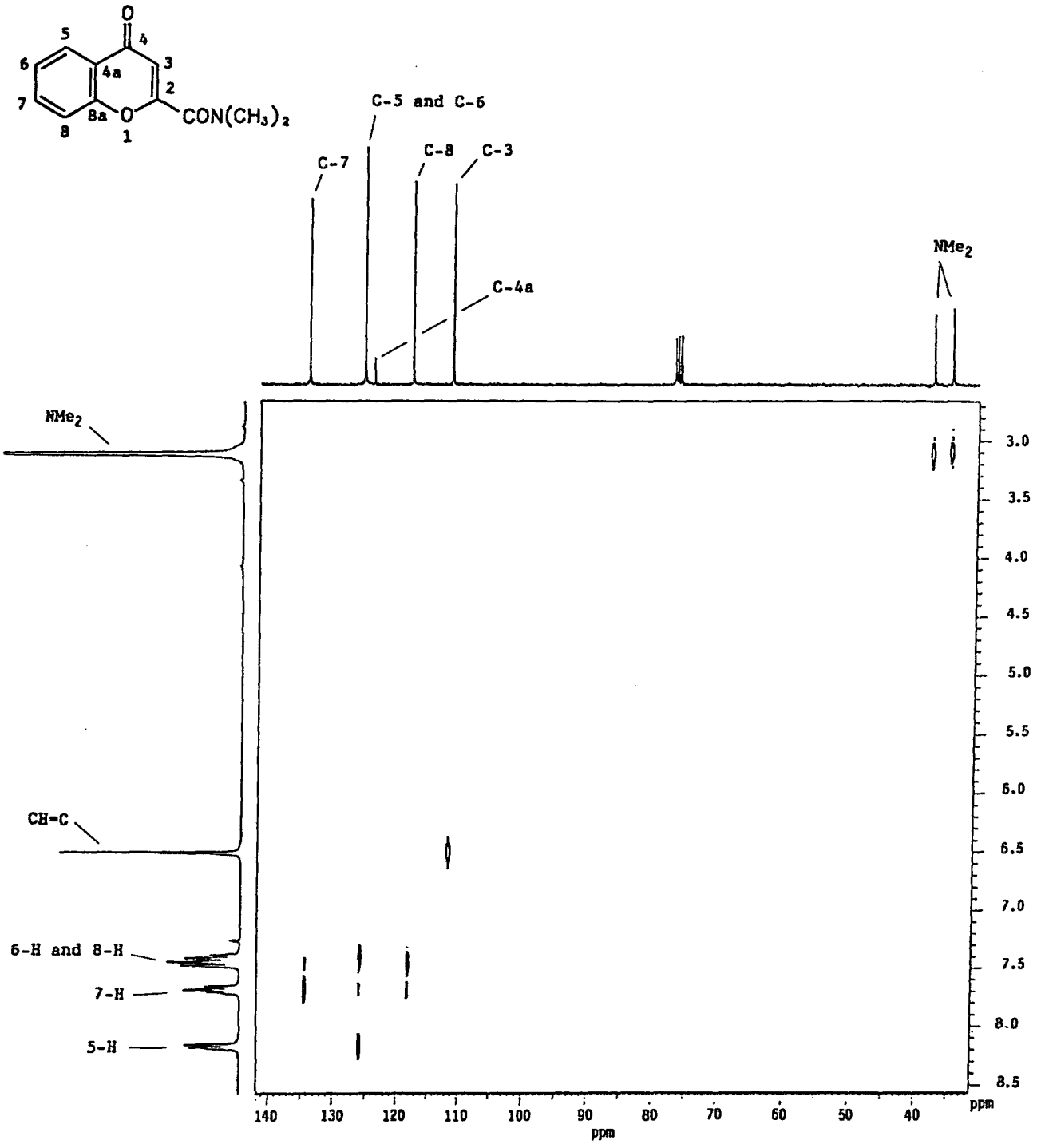


FIGURE 6. 400 MHz HETCOR spectum of *N*,*N*-dimethylchromone-2-carboxamide **129**.

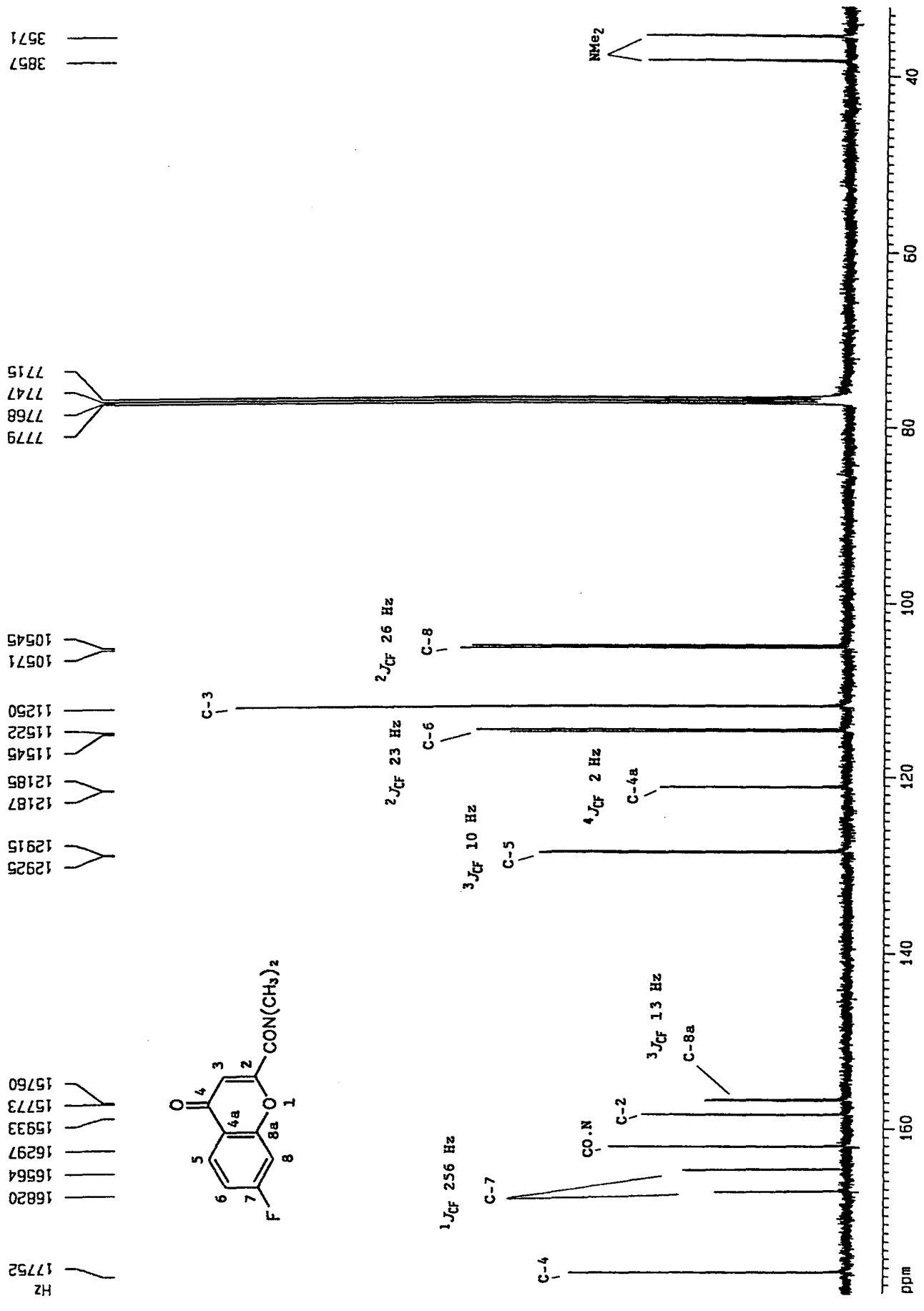


FIGURE 7. 100 MHz ^{13}C spectrum of 7-fluoro-*N*,*N*-dimethyl-chromone-2-carboxamide **132**.

The ^{1}H NMR spectra of chromone-2-carboxamides **129-139** are characterised by the vinyl proton (3-H) singlet at *ca.* 6.45 ppm. The observed splitting of the *N*-alkyl signals at ambient temperature in all the ^{13}C NMR spectra and, with the exception of the *N,N*-dimethylchromone-2-carboxamides **129,132** and **133** in all the ambient ^{1}H NMR spectra, reflects slow site-exchange of the *N*-alkyl substituents. The C-7 substituents produce wide variations in the C-7 ^{13}C chemical shifts relative to the parent system **129**, as illustrated in Table 3. This effect gradually decreases with distance from C-7, and produces small chemical shift variations of the γ-pyrone carbons, particularly the remote C-2. The largest variations were generally due to 7-methoxy-, 7-nitro-, and 7-fluoro- substituents. Variation of the 7-substituent also effected small variations in the vinyl (3-H) ^{1}H chemical shifts. In the IR spectra of the chromone-2-carboxamides **129-139**, the ketone carbonyl absorption band occurs in the typical chromone carbonyl region (*ca.* 1650 cm^{-1}), and the overlapping of the amide carbonyl absorption band in this region is attributable to delocalisation of the nitrogen lone-pair, which increases the single-bond character of the amide carbonyl.

Table 3. Comparative ^{1}H and ^{13}C NMR data for the N,N-dimethylchromone-2-carboxamides **129-134**.

^{13}C Nucleus	δ **129** (ppm)	Δδ[a] (ppm)
CON	162.27	0.94
C-2	158.20	1.08
C-3	111.58	0.83
C-4	177.42	1.61
C-4a	124.20	6.15
C-5	125.73	3.66
C-6	125.73	11.33
C-7	134.25	31.41
C-8	118.13	17.74
C-8a	155.66	1.77
3-H[b]	6.45	0.16

[a] Maximum variation from compound **129**.

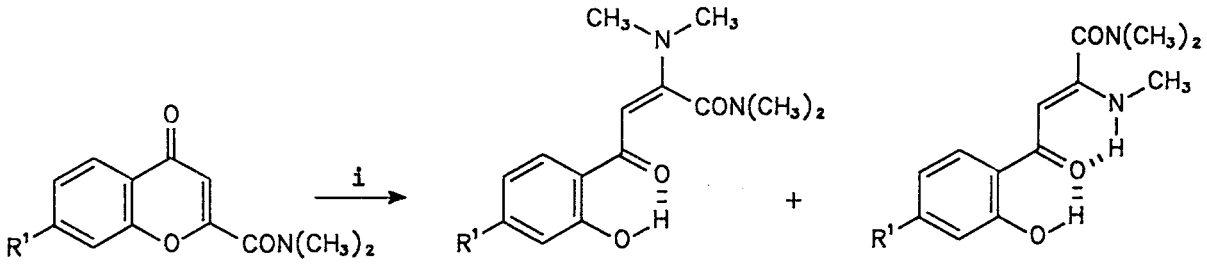
[b] ^{1}H nucleus.

2.1 (iv). **Preparation of 2-amino-3-(2-hydroxybenzoyl)acrylamides.**

A prerequisite for the proposed kinetic study of the dimethylamine-mediated ring-opening of the chromone-2-carboxamides **129-133** was the unambiguous structural analysis of the *N,N*-dimethylaminoacrylamide products **140** and **142-146**. The synthesis of these compounds is illustrated in Scheme 30 (p.69). Ring substituents (R^1) were chosen to illustrate electronic effects on the reaction rates, which, in turn, were used to determine the reaction mechanism. The *N,N*-dimethyl-2-pyrrolidinoacrylamide **151** (Scheme 32 p.72) was prepared to facilitate assignment of the *N*-methyl NMR signals of the substituted *N,N*-dimethylacrylamides **140,142-150**, and **153**. The acrylamide **153** was prepared in order to show the interaction of *N,N*-dimethylchromone-2-carboxamide **129** with glycine (Scheme 33 p.72). The acrylamides **140**, **142-151** and **153** were generally prepared *via* amine-mediated ring-opening of the

corresponding chromone-2-carboxamides (129-134) in ethanol at 35°C, or, in some cases, at ambient temperature (Schemes 30-33). The acrylamides 140 and 141 were obtained by reacting the chromone-2-carbonyl chloride 121 with two molar equivalents of secondary amine in water (Scheme 29 p.61).

Isolation of the substituted *N*-methylaminoacrylamides (147-150; Scheme 30), as minor products in the preparation of the substituted *N,N*-dimethylaminoacrylamides 143-146, is attributed to contamination of the ethanolic dimethylamine (25% w/w) with traces of methylamine. [GLC analysis of ethanolic dimethylamine (25% w/w) showed an additional peak with a retention time corresponding to ethanolic methylamine (5% w/w).]



R^1			
H	129	140	-
OMe	130	142	-
NO_2	131	143	147
F	132	144	148
Cl	133	145	149
Br	134	146	150

SCHEME 30

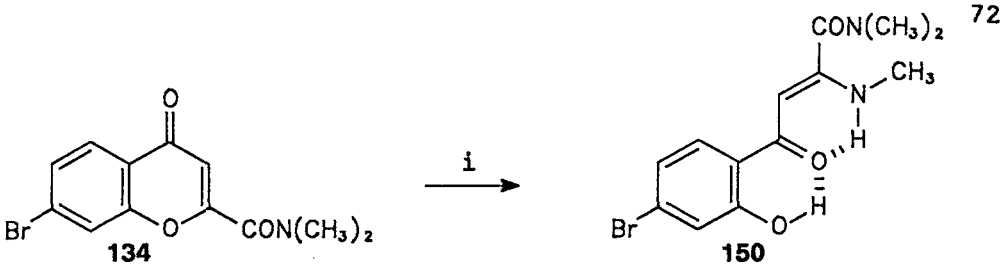
Reagents : i) Ethanolic Me_2NH - EtOH, 35°C (130-134), or rt (129).

The bromo-analogue **150** was also prepared using ethanolic methylamine (Scheme 31 p.72), thus providing an alternative preparation and evidence for the characterisation of the *N*-methylaminoacrylamides **147-150**. The acrylamide **153** was prepared using glycine ethyl ester, generated *in situ* by neutralising the hydrochloride salt **152** with an equimolar quantity of potassium hydroxide using ethanol as solvent (Scheme 33 p.72). [Excess base may catalyse cyclisation of the acrylamide **153** to afford a pyrrolyl derivative[23] (*e.g.* **18**; Scheme 5 p.8), as described previously in Section 1.1.1.2 (ii)].

The ^{1}H and ^{13}C *N*-methyl signals of the *N,N*-dimethylacrylamides **140**, **142-150** and **153** were assigned by comparison with the NMR spectra of *N,N*-dimethyl-2-pyrrolidinoacrylamide **151**, and correlation data from HETCOR experiments on the acrylamide **153** (Figure 8 p.73). The benzenoid ^{13}C chemical shifts were assigned by calculation using correlation tables[109] and, in the case of the fluoro analogue **144**, by ^{13}C-F coupling constants[109] (Figure 10 p.75), while correlation data from HETCOR and COSY experiments were used to establish the ^{1}H chemical shifts (Figures 8 and 9 p.73 and p.74).

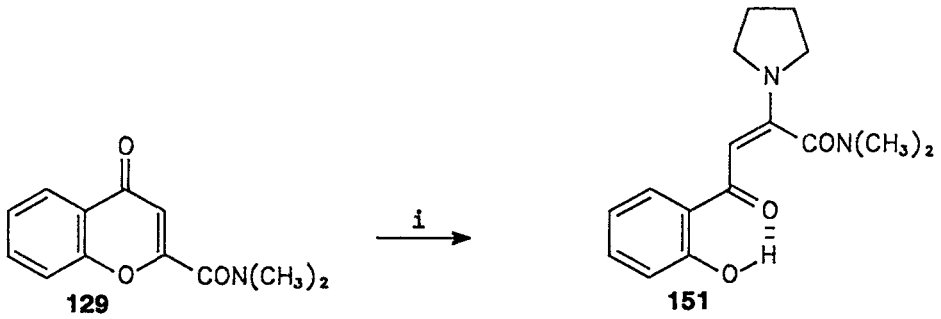
The acrylamides **140-151** and **153** (Schemes 29-33) are differentiated from the chromone-2-carboxamides **129-134** and **137** by the vinyl proton (3-H) singlet which occurs at 5.63 - 5.80 ppm in the acrylamides (Tables 4 and 5), and at lower field, *viz.*, 6.45 - 6.62 ppm in chromone-2-carboxamides. The acrylamides are also characterised by the phenolic proton singlet which occurs at low field, *ca.* 13 - 14 ppm due to intramolecular hydrogen bonding between the phenolic proton and ketone carbonyl group.[15] Determination of the *E*-double bond configurational and the conformational preferences of the *N,N*-dimethylacrylamides **140,142-146** and **151** will be discussed in Section 2.3. Although, the vinyl

proton (3-H) chemical shifts of the *N*-methylaminoacrylamides **147-150** are almost identical to those of the corresponding *(E)*-*N*,*N*-dimethylaminoacrylamides **143-146** (Tables 4 and 5 p.76), the *Z*-double-bond configuration is presumably favoured in the *N*-methylaminoacrylamides **147-150** and the acrylamide **153** due to additional intra-molecular hydrogen bonding between the amino proton and the ketone carbonyl group (Schemes 30 and 33).[15] The *N*-alkylamino acrylamides (**147-150** and **153**; Schemes 30 and 33) are characterised by amino and phenolic proton chemical shift singlets at *ca.* 10 and 13 ppm respectively, and the IR N-H absorption band of the amino group at *ca.* 3200 cm^{-1} (Table 5 and Figure 11 p. 76 and p.77). These values correlate with data reported by Zagorevskii *et al.*[15] in related studies. In the *N*,*N*-dimethylaminoacrylamides (**140**, **142-146**, and **151**) the IR hydroxyl stretching band is shifted below 3000 cm^{-1} due to intramolecular hydrogen bonding, and similar effects are presumed to obtain in the *N*-methylaminoacrylamides (**147-150** and **153**; Figure 11).



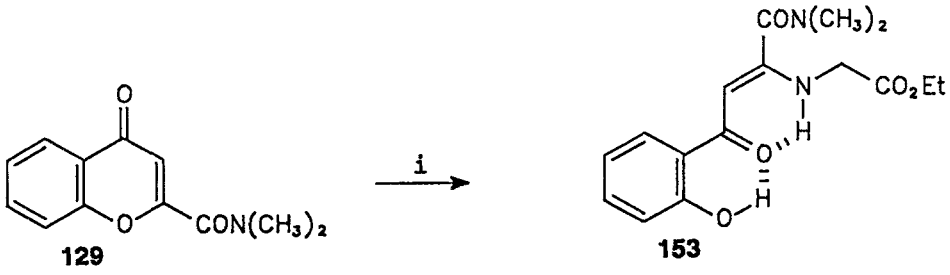
SCHEME 31

Reagents : i) Ethanolic Me_2NH - EtOH, 35°C.



SCHEME 32

Reagents : i) Pyrrolidine - EtOH, 35°C.



SCHEME 33. i) $EtO_2CCH_2NH_2.HCl$ (152), KOH - EtOH; ii) 35°C.

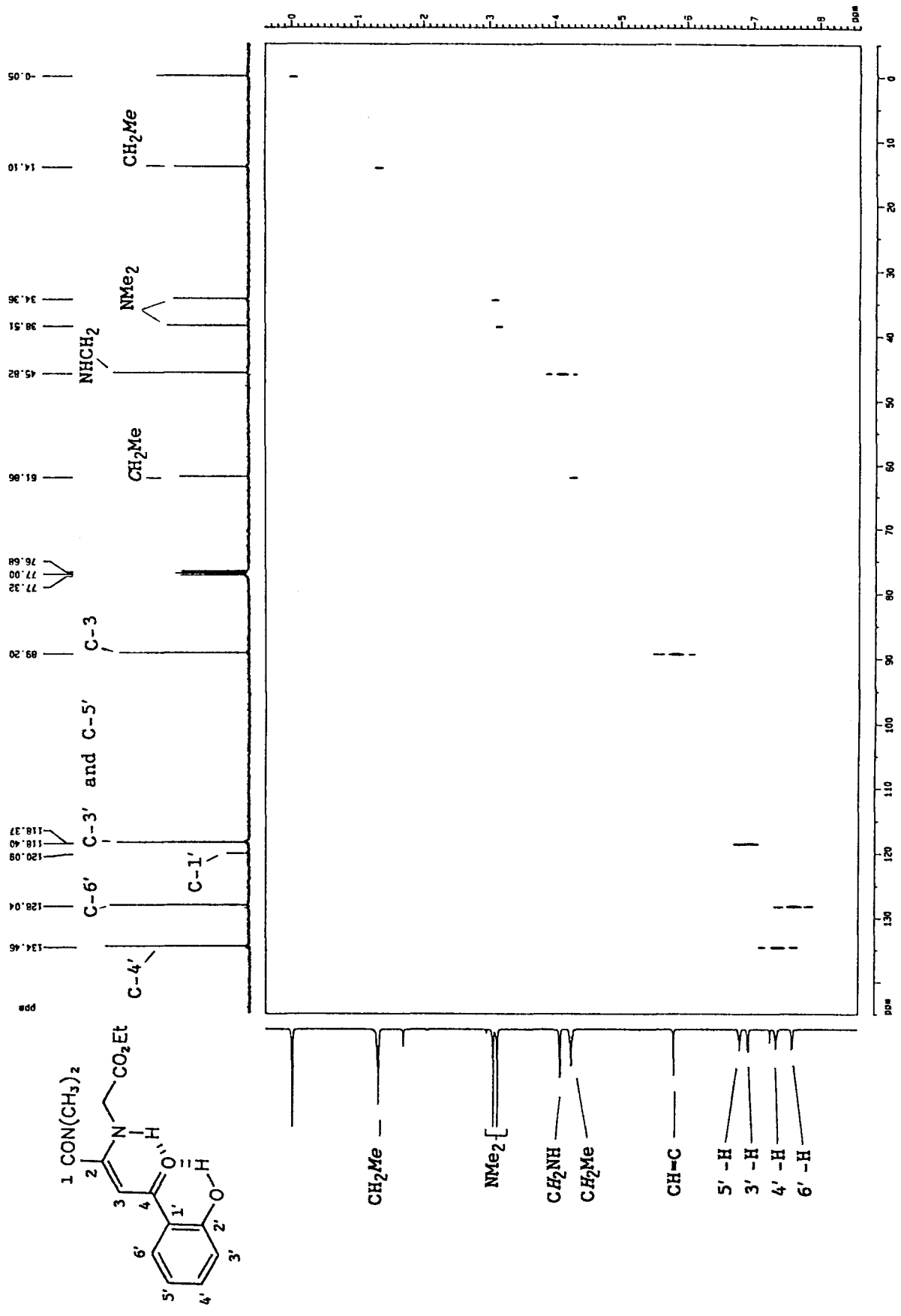


FIGURE 8. 400 MHz HETCOR spectrum of 2-(*N*-carbethoxymethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 153.

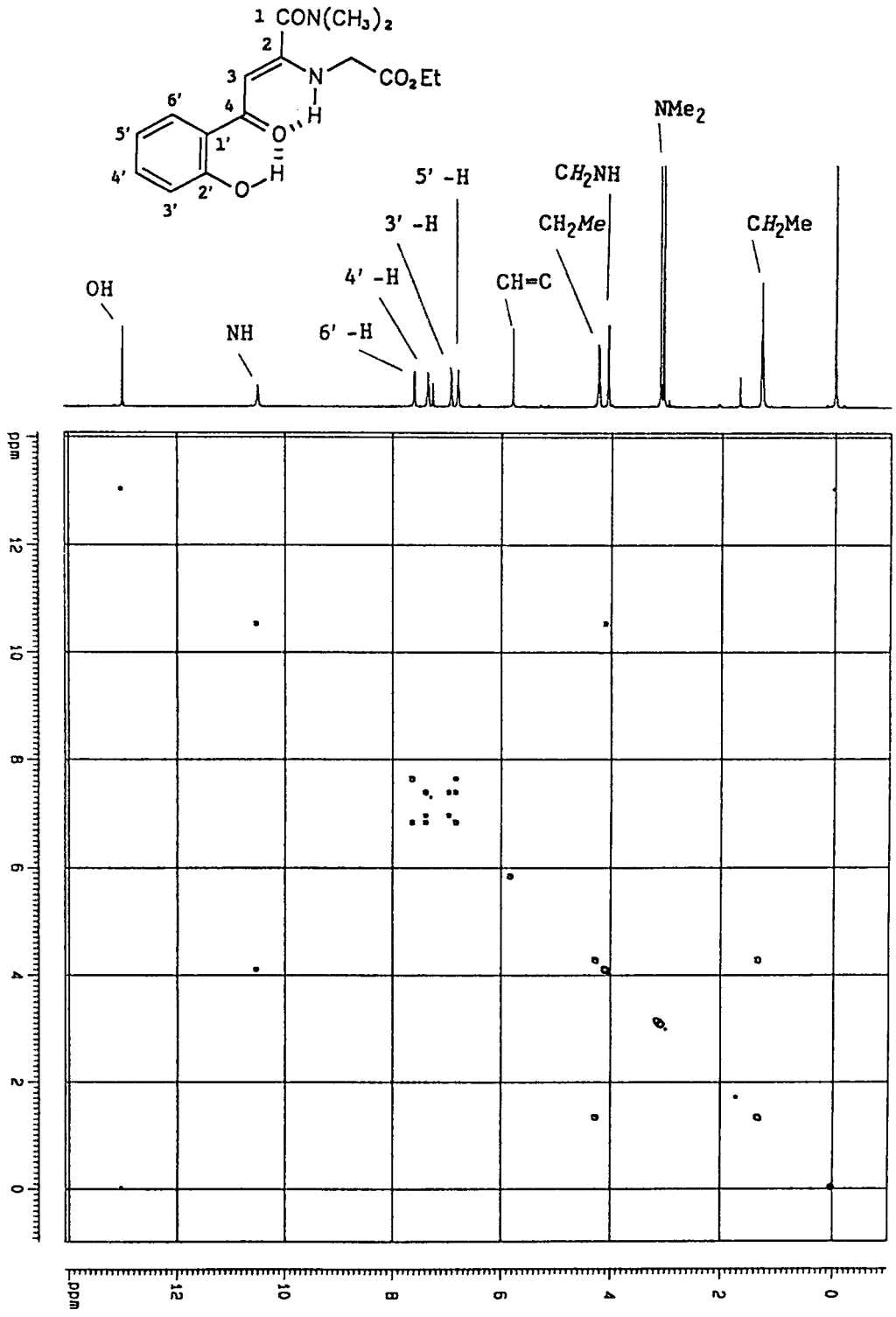


FIGURE 9. 400 MHz COSY spectrum of 2-(*N*-carbethoxymethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 153.

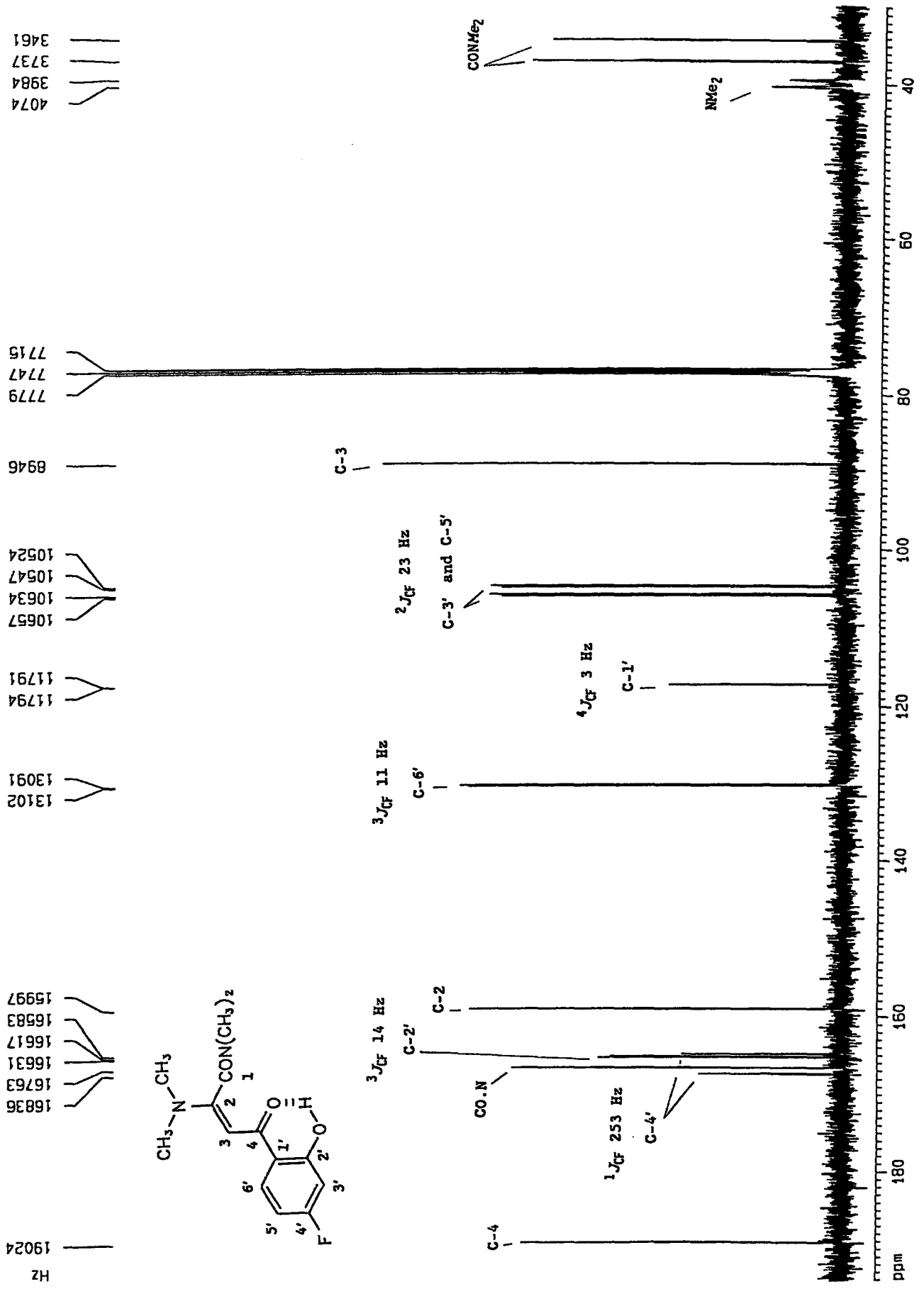


FIGURE 10. 100 MHz ^{13}C spectrum of (*E*)-2-(dimethylamino)-3-(4-flouro-2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 144.

Table 4. Characteristic spectroscopic data for the *N,N*-dialkylamino acrylamides **140-146** and **151**.

Compound	3-H/ppm	OH/ppm
140	5.75	13.60
141	5.57	13.61
142	5.65	14.10
143	5.71	13.85
144	5.63	14.00
145	5.66	13.85
146	5.65	13.70
151	5.72	13.70

Table 5. Characteristic spectroscopic data for the *N*-alkylamino acrylamides **147-150** and **153**.

Compound	3-H/ppm	NH/ppm	OH/ppm	NH[a]/cm^{-1}
147	5.76	10.56	13.52	3235
148	5.62	10.10	13.57	3230
149	5.65	10.30	13.41	3200
150	5.65	10.30	13.36	3200
153	5.80	10.50	13.01	3230

[a] Assigned by comparison with OH absorption bands of *N,N*-dialkylamino acrylamides and reported values for *N*-monosubstituted-β-aminovinylketones (*e.g.* 3310cm^{-1}).[15]

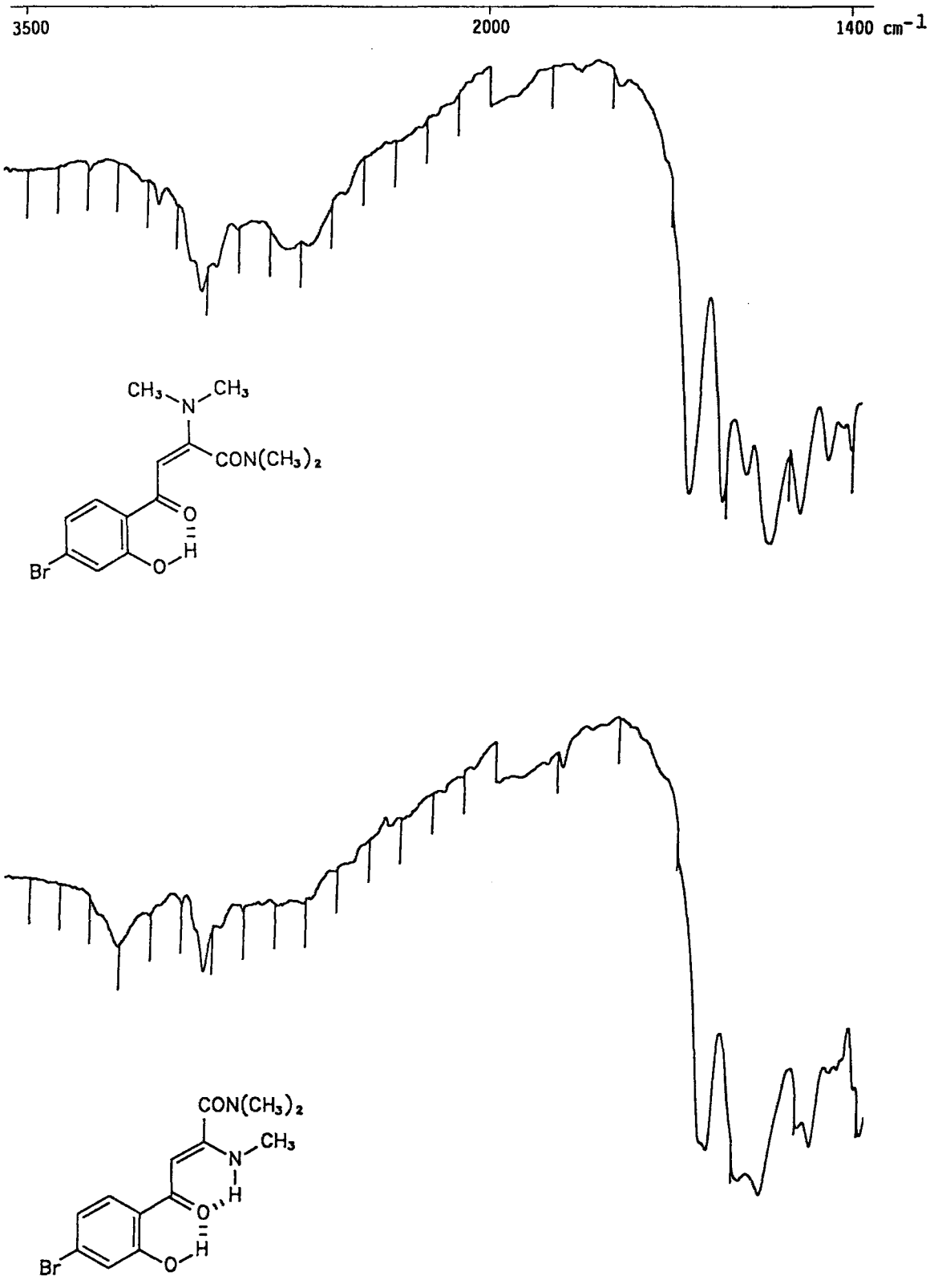
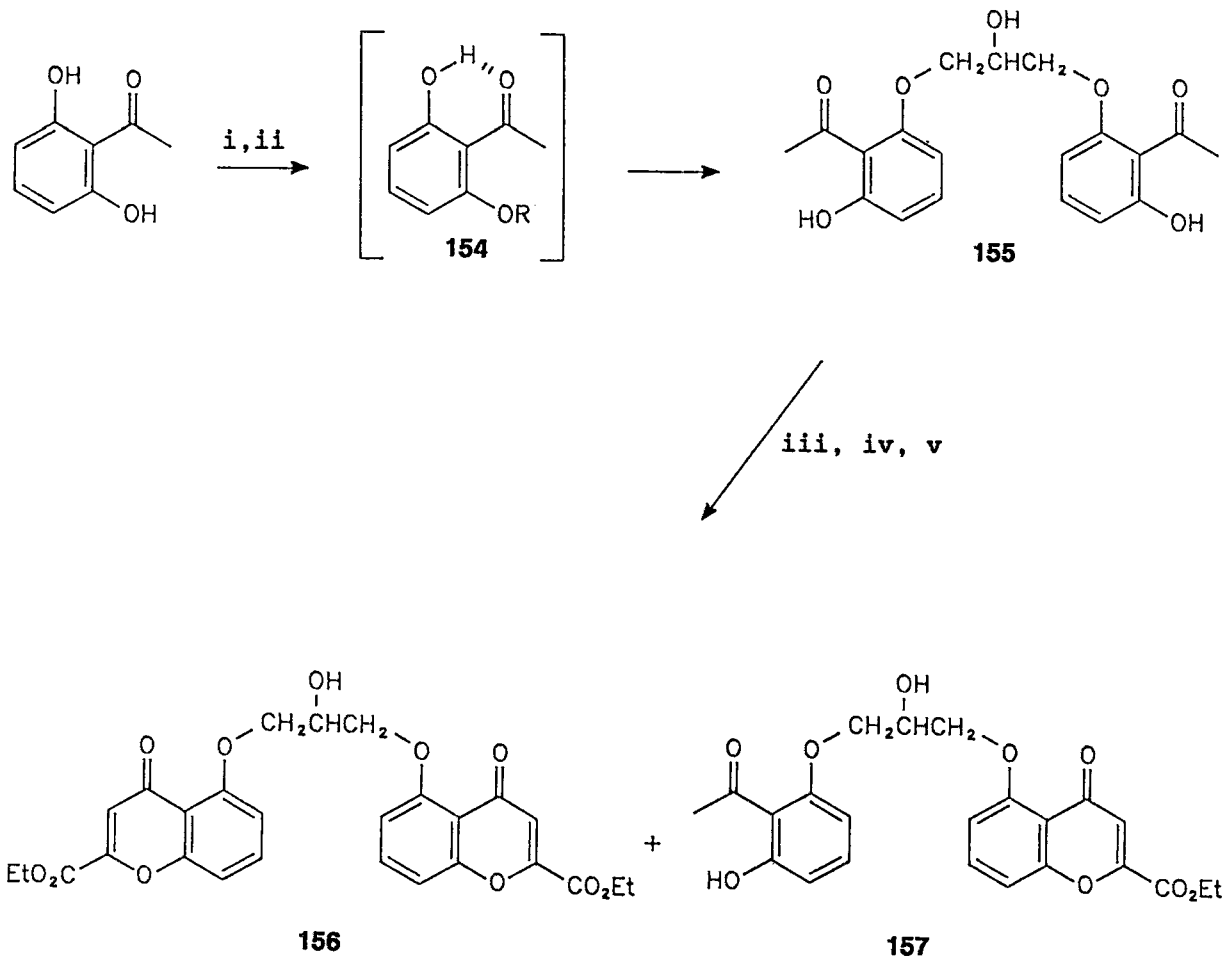


FIGURE 11. Solid-state IR spectra of compounds 146 and 150.

2.1 (v). Preparation of disodium cromoglycate.

As part of an investigation of the significance of ring-opening reactions in molecular-level chromone pharmacology, the dimethylamine-mediated ring-opening reactions were extended to include DSCG **158**. DSCG **158** was prepared following the procedures reported by King *et al.*[40] (Schemes 34 and 35). Thus, the bis(*o*-hydroxyacetophenone) **155** was prepared by condensation of two molar equivalents of 2,6-dihydroxyacetophenone with single molar equivalents of epichlorohydrin and potassium hydroxide (Scheme 34). King *et al.*[40] found that alkylation of the second phenolic group of the monoalkylated intermediate species **154** was prevented by strong intra-molecular hydrogen bonding between the phenolic proton and ketone carbonyl group. Diethyl cromoglycate **156** was prepared *via* Claisen acylation of the bis(*o*-hydroxyacetophenone) **155** with excess diethyl oxalate and sodium ethoxide. Three products, *viz.*, the required diethyl carboxylate ester **156**, starting material **155**, and the major component, 3-(2-acetyl-3-hydroxyphenoxy)-1-(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane **157**, were isolated in yields well below the reported values. Disodium cromoglycate **158** was prepared by hydrolysis of the diethyl carboxylate ester **156**. The quantity of sodium hydroxide used was limited to 2 molar equivalents in order to control contamination by the ring-opened product.[118] The dimethylamine-mediated ring-opening of DSCG **158** (Scheme 35) was performed in an NMR tube, and the reaction was followed by NMR spectroscopy, as described in Section 2.4.



SCHEME 34

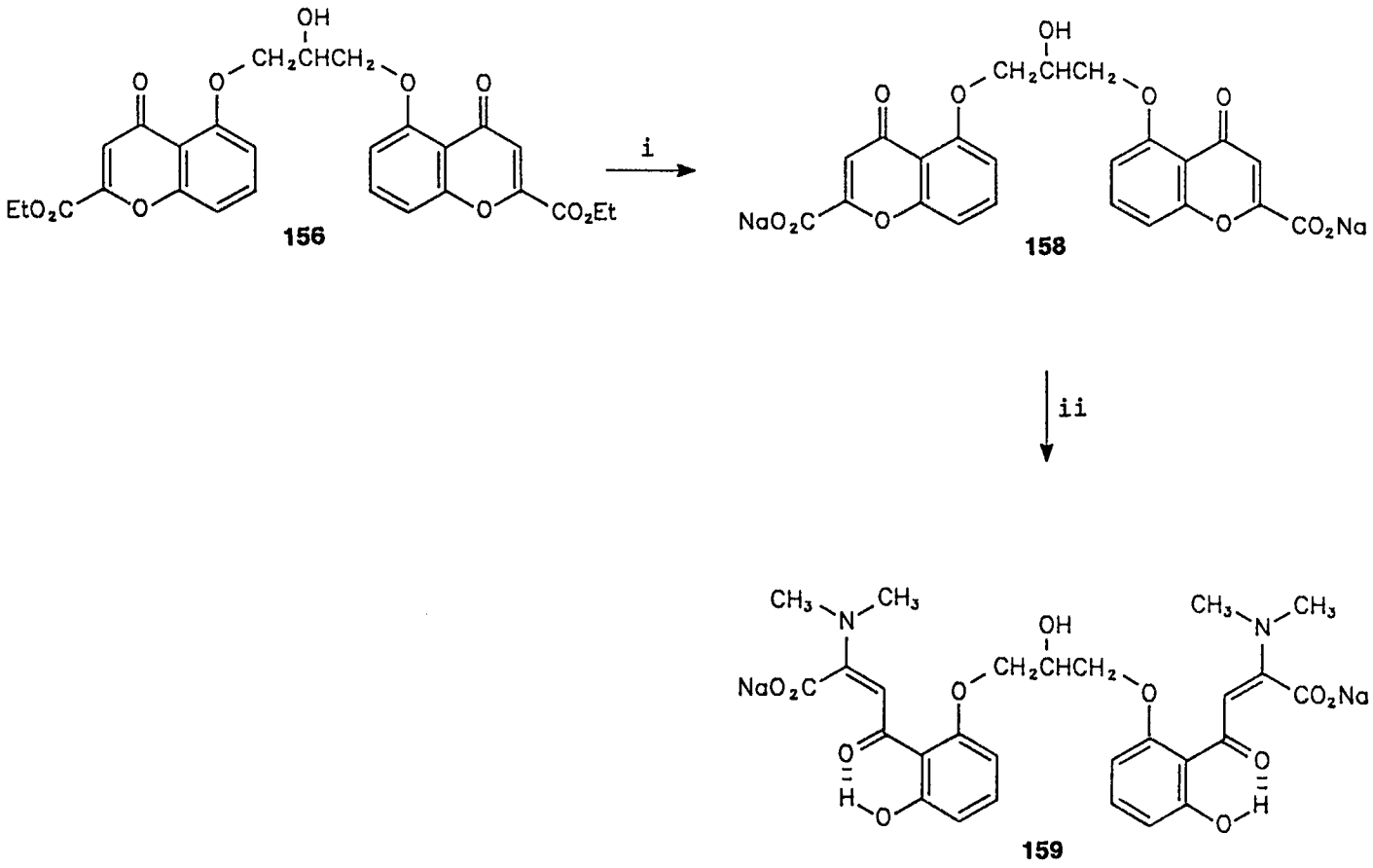
Reagents : i) Epichlorohydrin, *i*-PrOH;

ii) KOH, *i*-PrOH, H_2O, Δ;

iii) NaOEt - EtOH, Et_2O, Δ;

iv) $(CO_2Et)_2$ - EtOH - C_6H_6, Δ;

v) H^+/H_2O; EtOH - C_6H_6, Δ.



SCHEME 35

Reagents : i) NaOH - EtOH, H_2O (trace), Δ ; ii) aq. Me_2NH - D_2O.

The ^{1}H and ^{13}C NMR chemical shifts of the 2-hydroxypropane analogues **155-159** were assigned using correlation data from COSY and HETCOR experiments on compound **157** (Figures 12 and 13); the ^{13}C benzenoid signals were assigned by calculation using correlation tables.[109] In diethyl cromoglycate **156**, the aromatic and 2-hydroxypropane proton chemical shifts correlate with the literature values for dimethyl cromoglycate,[119] and the C-2 signal was assigned using the value for ethyl chromone-2-carboxylate **110**.[108]

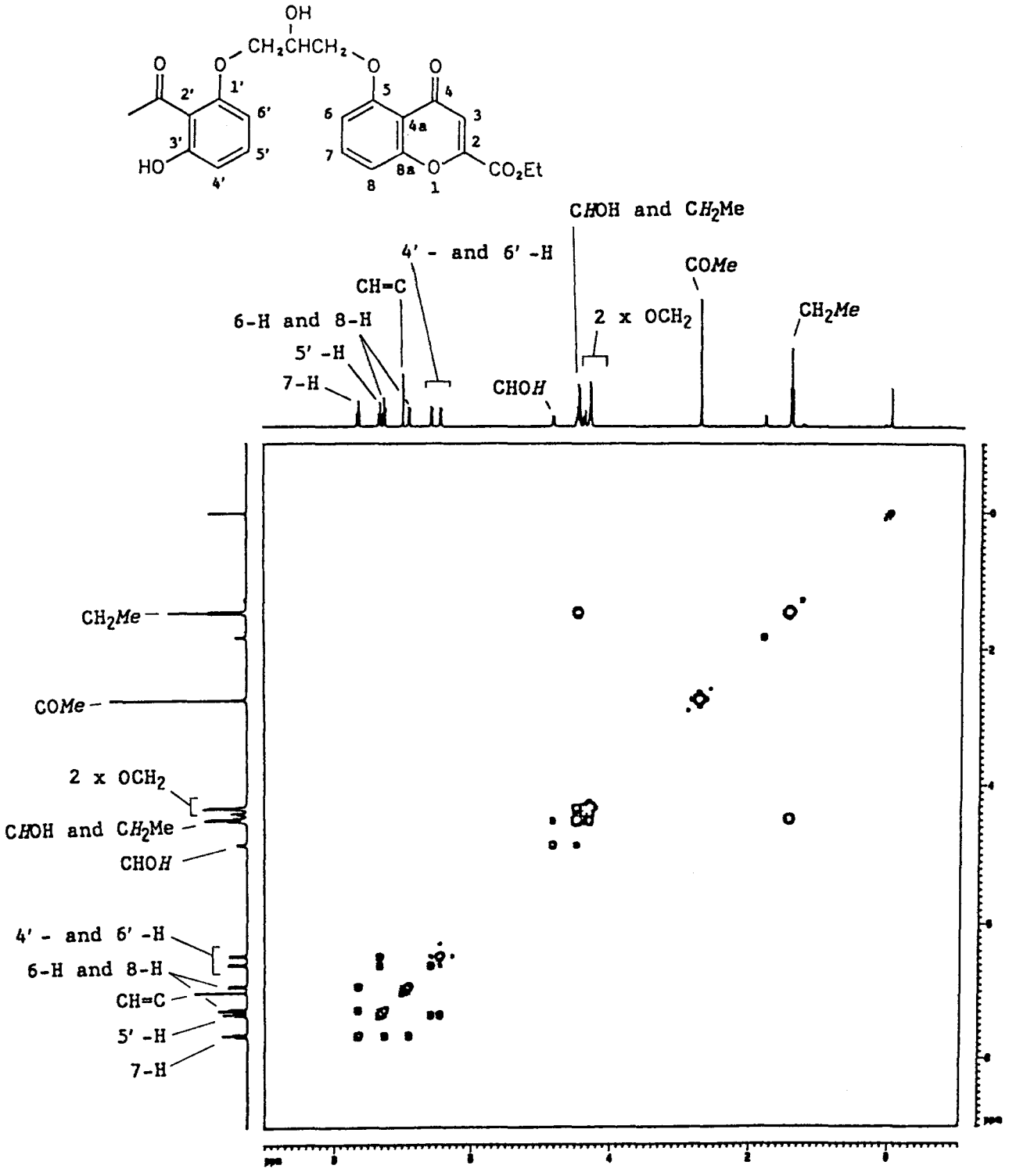


FIGURE 12. 400 MHz COSY spectrum of compound 157.

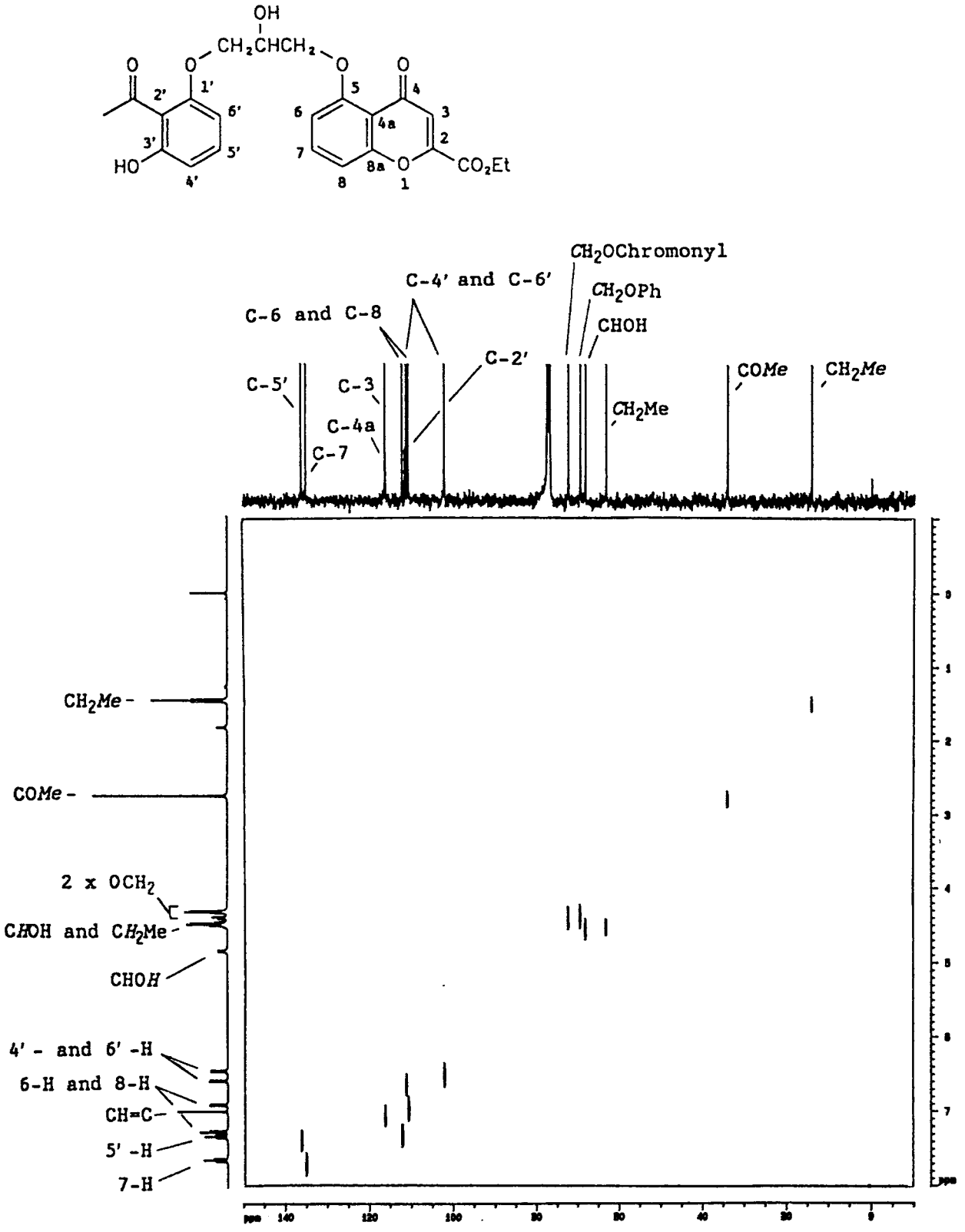


FIGURE 13. 400 MHz HETCOR spectrum of compound 157.

2.2 NMR ANALYSIS OF ROTATIONAL ISOMERISM IN CHROMONE-2-CARBOXAMIDES[120]

The chromone-2-carboxamides (129-138; Table 6 p.85) were prepared from the corresponding acids *via* an acid chloride intermediate, as described previously in Section 2.1 (iii). The ring and *N*-alkyl substituents were chosen to determine electronic and steric effects on the rotational equilibria. Symmetrically substituted *N*,*N*-dialkyl amides were chosen to simplify interpretation of the variable-temperature ^{1}H NMR spectra. The rotational energy barriers (ΔG^*; Table 6) of the chromone-2-carboxamides were determined from variable-temperature ^{1}H spectra (*e.g.* Figure 14), in which the observed splitting of the *N*-alkyl signals was attributed to slow site-exchange of the *N*-alkyl substituents.

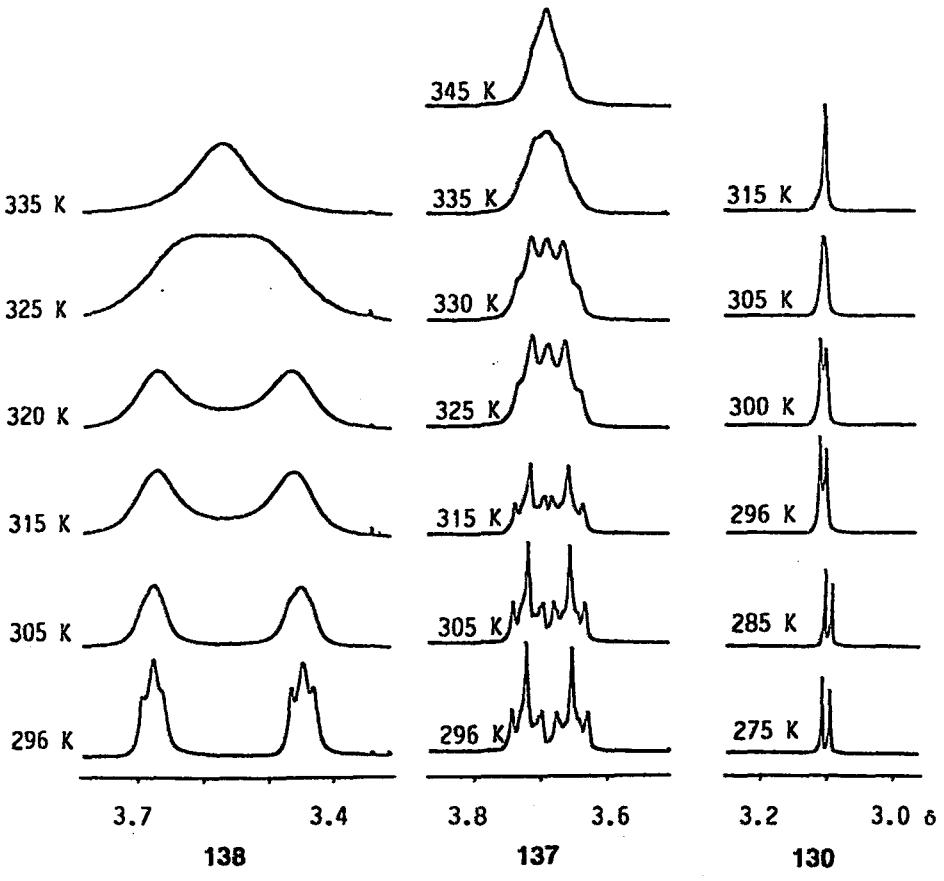
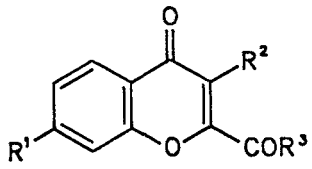


FIGURE 14. Variable temperature ^{1}H NMR spectra showing *N*-alkyl signals for selected chromone-2-carboxamides (129-138).

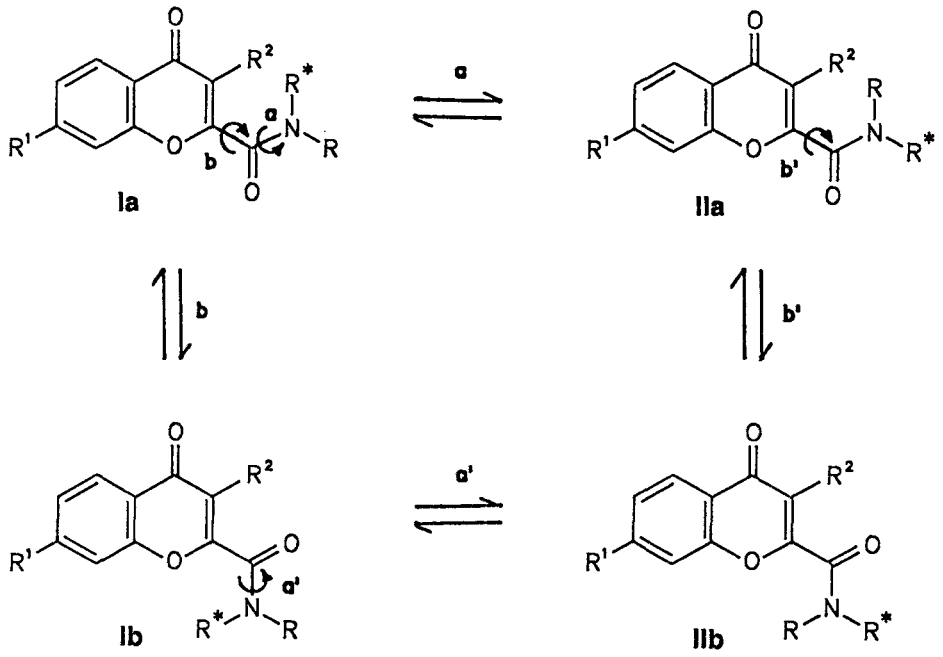
TABLE 6. Data from dynamic NMR study of chromone-2-carboxamides 129-138.[a]



Compound	R^1	R^2	R^3	T_c[b]/K	$\Delta\nu_c$[c]/Hz	ΔG^*[d]/kJmol^{-1}	K_{298}[e]/s^{-1}
130	OMe	H	NMe_2	302	2.5 ± 0.7	69.7 ± 1.5	4
131	NO_2	H	NMe_2	305	1.8 ± 0.6	71.2 ± 1.9	2
132	F	H	NMe_2	270	1.0 ± 0.5	64.1 ± 2.3	36
133	Cl	H	NMe_2	< 255[f]	-	-	-
134	Br	H	NMe_2	290	1.0 ± 0.3	69.0 ± 1.6	5
135	H	Me	NMe_2	> 345[g]	-	> 72.3 ± 0.2	< 1
129	H	H	NMe_2	270	0.8 ± 0.3	64.6 ± 1.9	29
136	H	H	NPr^i_2	315	87.2 ± 2.2	63.5 ± 0.7	46
137	H	H		332	13.6 ± 1.1	72.2 ± 0.9	1
138	H	H		325	61.6 ± 1.6	66.5 ± 0.9	14

[a]Variable temperature 300 MHz ^{1}H NMR spectra recorded using solutions in $CDCl_3$.
[b]Coalescence temperature (± 3 K). [c]Frequency separation at coalescence.
[d]Free energy of activation for N-CO rotation; $\Delta G^* = RT_c\,(22.96 + \ln T_c/\Delta\nu_c)$.
[e]First-order rate constant at 298 K for N-CO rotation; $\ln k = \ln (k_bT/h) - \Delta G^*/RT$.
[f]No splitting of NMe_2 signal observed. [g]No coalescence of the NMe signals observed; $\Delta\nu$ at 345K = 36.5 ± 0.5 Hz.

In chromone-2-carboxamides (Scheme 36 p.87; where $R^* = R$) simultaneous rotation about two bonds, *viz.*, the N-CO and C(2)-CO bonds implies a rotational equilibrium between two equivalent pairs of quasi-planar, resonance-stabilised conformers [(**Ia** ≡ **IIa**) and (**Ib** ≡ **IIb**)]. [In analogous benzamides the amide and aromatic planes are apparently twisted slighly out of plane relative to each other due to steric interactions and the rotational equilibrium apparently comprises two quasi-planar conformers,[49] as discussed in Section 1.2.1.] Site-exchange about the C(2)-CO bond at ambient temperature is expected to be too rapid for dynamic NMR spectroscopic analysis. This expectation may be rationalised by analogous rotational barriers about the C(1)-CO bond in sterically hindered *ortho*-substituted benzamides which have been reported to be less than 60 kJ mol^{-1}.[45] Since IR spectroscopy has a very much shorter time-scale, the rapid C(2)-CO rotation may have been analysed using this alternative detection method. Successful analysis of rapid C(2)-CO rotations have been shown by the IR study of rotational isomerism in chromone-2-carboxylate esters,[51] previously discussed in Section 1.2.2. In chromone-2-carboxamides, however, the infrared ketone and amide carbonyl absorption bands partially coincide at *ca.* 1650 cm^{-1}, which prevented IR analysis of the C(2)-CO rotational barrier. However, rotation about the N-CO bond is expected to be hindered by delocalization of the nitrogen lone-pair (Figure 15 p. 87), and in the rotational equilibria, k_a, $k_{a'} \ll k_b$, $k_{b'}$ (Scheme 36). Consequently, site-exchange of the *N*-alkyl substituents is likely to be sufficiently slow for NMR analysis. Since the rotational equilibria comprise two non-equivalent rotamer types (a) and (b), the measured rate constants



SCHEME 36

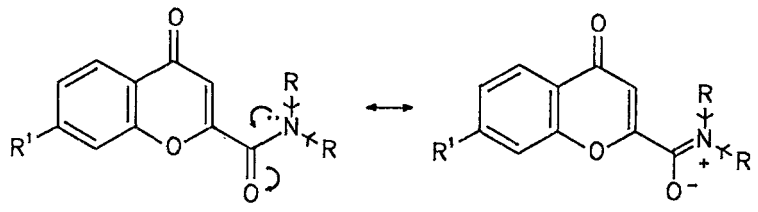


FIGURE 15.

for site-exchange are weighted combinations of the individual rate constants. Use of the Winstein-Holness principle[44] then affords equation 4.

$$k_{obs} = k_a\ [\mathbf{Ia}] + k_{a'}\ [\mathbf{Ib}] \qquad (4)$$

In the series **129-138**, the ^{1}H NMR frequency separations measured at slow site-exchange ($\Delta\nu_0$) range between 1-99 Hz, and are smallest for the *N,N*-dimethylcarboxamides (**129-132** and **134**). Such frequency separations ($\Delta\nu_0$) reflect the difference in the average magnetic environment of each *N*-alkyl substituent in each compound, and more specifically, their average position relative to the magnetically anisotropic chromone and amide[45] functions. The positions of the relevant nuclei relative to the amide function are determined by : dipole-dipole and steric[49] interactions; "gear-meshing"[121] of the isopropyl groups in compound **136**; and ring-conformational constraints in the heterocyclic analogues **137** and **138**. Similar deshielding of the *N*-methyl groups in the *N,N*-dimethylcarboxamides (**129-132** and **134**) may thus account for the small $\Delta\nu_0$ values. In the 7-chloro analogue **133**, the ^{1}H NMR *N*-methyl signal did not split, the material precipitating below 255K. This observation is probably due to identical deshielding of the *N*-methyl groups at slow site-exchange, rather than an unusually low rotational barrier. This argument is also substantiated by the observed splitting of *N*-alkyl ^{13}C signals at ambient temperature for all the chromone-2-carboxamides **129-138**, including the 7-chloro compound **133**.

Rotational energy barriers (ΔG^*; Table 6 p.85), were determined for the chromone-2-carboxamides (129-132,134,136-138) from the coalescence temperatures (T_c) and the frequency separations at coalescence ($\Delta\nu_c$), using equation 2.[46] The latter $\Delta\nu_c$ values were determined by linear extrapolation (Section 3.3), as described by Lai and Chen.[122] Site-exchange rate constants (k) were then determined from the ΔG^* values using equation 3.

$$\Delta G^* = RT_c\ (22.96 + \ln\ T_c/\Delta\nu_c) \qquad (2)$$

$$\ln\ k = \ln\ (k_bT/h) - \Delta G^*/RT \qquad (3)$$

The rotational energy barriers (ΔG^*) range between 64-72 kJ mol^{-1} correlating with typical amide rotational barriers (50-100 kJ mol^{-1}) and, more importantly, with reported ΔG^* data for comparable *N,N*-dialkylbenzamides.[123,124] The slightly higher rotational barriers determined for the chromone analogues, relative to the *N,N*-dialkylbenzamides, may reflect a reduction in competitive delocalisation[45] due to the electron-withdrawing chromone system (Figure 16 p.92). This electron-withdrawing effect consequently increases the double-bond character of the N-CO bond, which effectively increases the magnitude of the chromone-2-carboxamide rotational barriers. In the substituted *N,N*-dimethylcarboxamides, the increasing net electron-withdrawing effects of the substituent R^1 result in decreasing competitive delocalization, and such effects may account for the gradual increase in ΔG^* values in the series R^1 = F (132) < Br (134) < NO_2 (131). This trend also correlates with reported ΔG^* data for the corresponding *para*-substituted *N,N*-dimethylbenzamides.[123] Changing conformer populations may influence the overall rate of rotation and could explain the apparently anomalous result for the 7-methoxy analogue 130.

The rotational barriers for the pyrrolidine derivative **137**, and to a lesser extent, for the piperidine analogue **138** are both higher than that of the *N,N*-dimethyl compound **129**. This may illustrate the influence of electron-releasing inductive effects on nitrogen lone-pair delocalisation (Figure 15 p.87). Ring conformational contraints are expected to allow the pyrrolidine nitrogen to adopt the planar sp^2 arrangement more easily than the piperidine nitrogen. The pyrrolidine nitrogen thus has more sp^2 character and hence more effective nitrogen lone-pair delocalization. This effect may account for higher rotational barrier for the pyrrolidine derivative **137** than for the piperidine analogue **138**. This trend correlates with reported ΔG^* data for simple piperidine and pyrrolidine compounds,[45] as discussed in Section 1.2.1. The electron-releasing inductive effect may be opposed by steric destabilisation of the carboxamide ground-state[125] which inhibits delocalisation, and this effect presumably occurs in the *N,N*-diisopropylchromone-2-carboxamide **136**. An analogous trend occurs in the reported ΔG^* data for benzamide analogues, *viz.*, *N,N*-diisopropylbenzamide $\leq$ *N,N*-dimethylbenzamide[124] $\approx$ 1-benzoyl-piperidine.[50]

As discussed previously in Section 1.2.2, an IR study of rotational isomerism in chromone-2-carboxylate esters has shown that bulky 3-substituents appear to prevent co-planarity of the ester and chromone planes.[51] Similar steric effects were thus expected to occur in 3-methylchromone-2-carboxamide **135** and this expectation is supported both by computer modelling and by earlier studies of benzamide analogues.[49] Steric effects of the bulky 3-methyl substituent are expected to inhibit rotation about both the C(2)-CO and N-CO bonds. This expectation was confirmed by the well separated ^1H NMR *N*-methyl signals (37 Hz) which did not coalescence even at 345 K. The proposed

conformation illustrated in Figure 17 (p.92) rationalises both the failure to achieve coalescence of the ^1H *N*-methyl signals and the expected steric constraints. In the proposed conformation, the essentially planar *N,N*-dimethylcarboxamide group lies perpendicular or nearly perpendicular to the chromone plane, the *N*-methyl groups are diastereotopic, and rotation about both the C(2)-CO and N-CO bonds is significantly hindered due to steric effects of the 3-methyl substituent. These steric interactions were further investigated using nuclear Overhauser enhancement (n.O.e.) experiments, involving the separate irradiation of the 3-methyl group and each of the *N*-methyl groups (Figure 18 p.93). In each case, small enhancements of both non-irradiated methyl groups occur in the n.O.e difference spectra (Figure 19 p.92). [Calculation of the n.O.e. enhancements is described in Section 3.3] These findings suggest that all three methyl groups are closely situated to each other, thus substantiating the proposed conformation (Figure 17). However, in view the small magnitude of the intensity enhancements and the complexity of the internal rotations, arguments based on the n.O.e data cannot be considered conclusive.

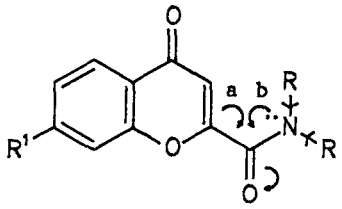


FIGURE 16. a) competitive delocalization;
b) nitrogen lone-pair delocalization.

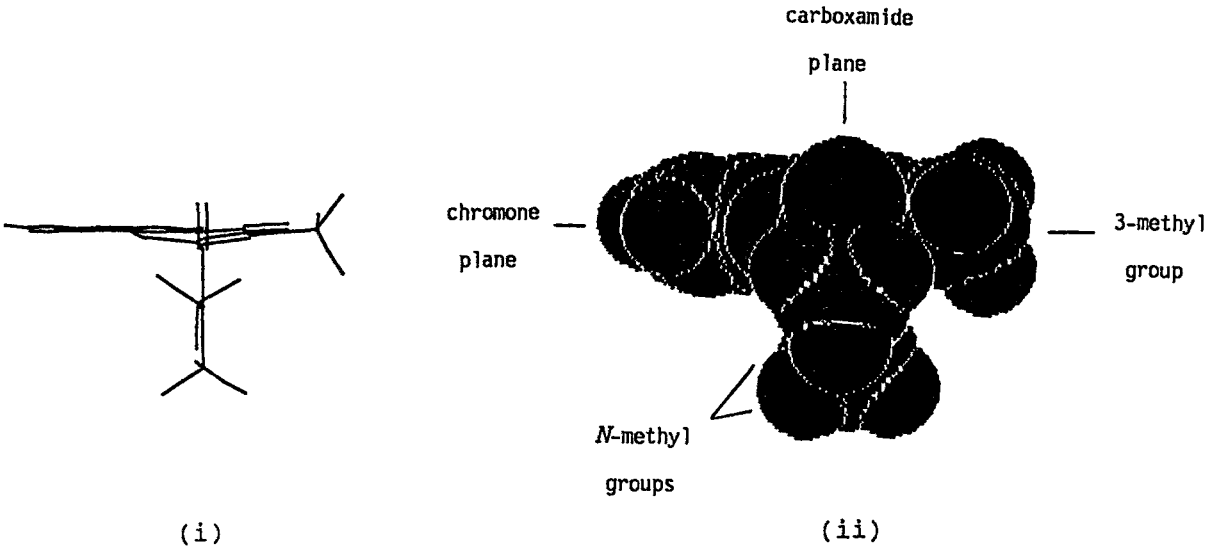


FIGURE 17. Proposed conformation of compound 135 based on computer-modelled structure; (i) "wire-frame" and (ii) "spacefill" representations.

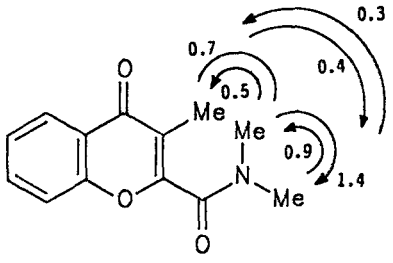


FIGURE 19. Percentage n.O.e. enhancements of compound 135.

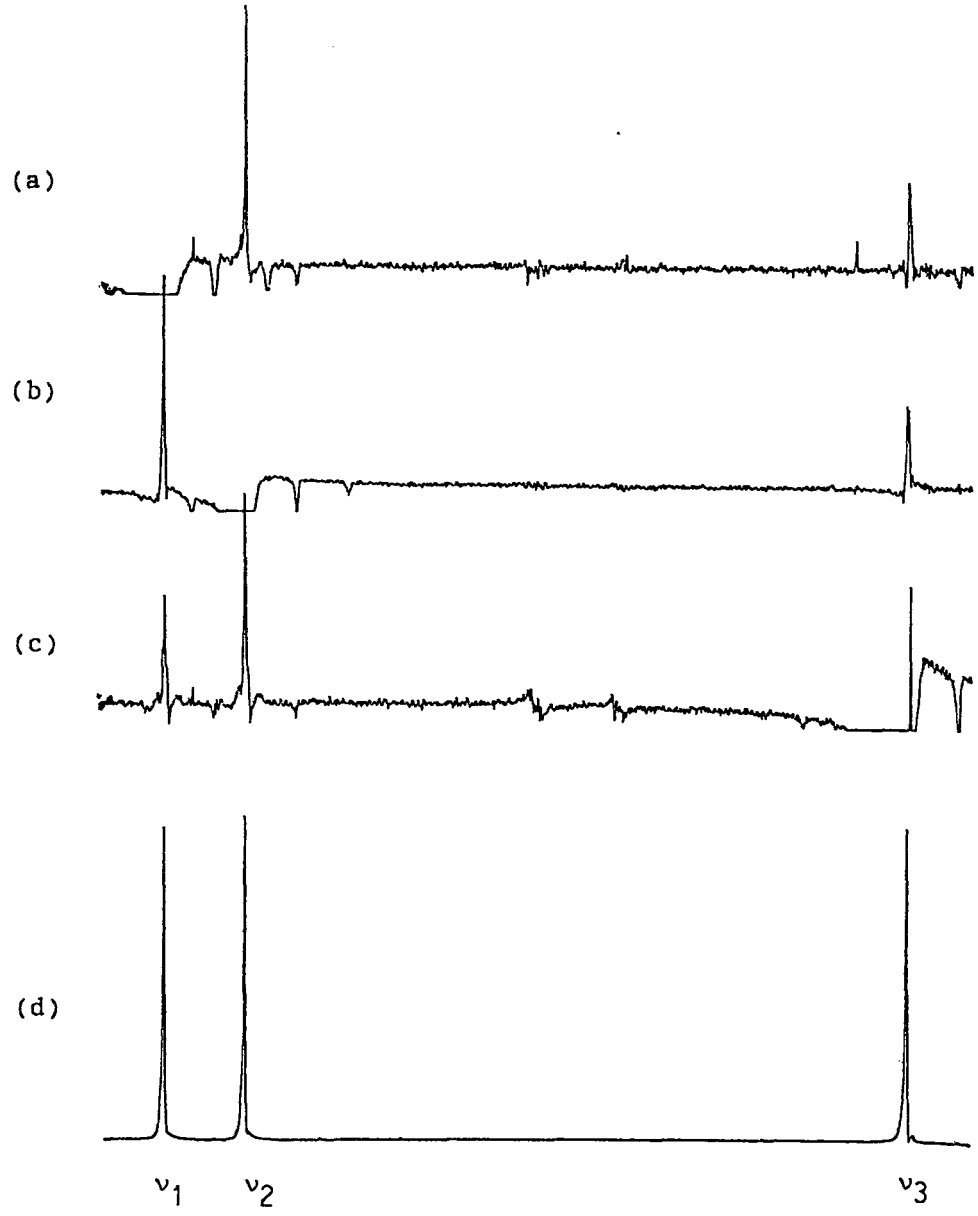


FIGURE 18. ^1H N.m.r. spectra of methyl signals from n.O.e. experiments on chromone-2-carboxamide **135** :- a) irradiation at frequency, ν_1; b) irradiation at frequency ν_2; c) irradiation at frequency, ν_3; and d) reference spectrum.

2.3 STRUCTURAL ANALYSIS OF CHROMONE-DERIVED 2-AMINO-3-(2-HYDROXYBENZOYL)ACRYLAMIDES[126]

As previously discussed in Section 1.3.3 (iv), many different modes of action for DSCG in asthma therapy have been proposed. The mast cell stabilising action[72,93] of DSCG has received the most attention, although, the molecular basis for this action (and all the other proposed modes of action) has not been elucidated.[66,72,93,98] Chromones are susceptible to C-2 nucleophilic attack and are consequently ring-opened by various nitrogen[21] and oxygen nucleophiles.[26] The implications of such reactions in molecular-level chromone pharmacology have thus been explored in the present study. DSCG may interact with biogenetic nucleophiles *via* the ring-opening reaction. Such reactions thus provide a mechanism for the C-2 covalent binding of the drug to mast cell receptor sites such as the DSCG-binding protein (Figure 20).[94,95] The drug may similarly block or antagonise the effects of anti-inflammatory mediators such as histamine. The reactions of the chromone-2-carboxamides with amines as models for *in vivo* nucleophiles were thus investigated (Scheme 37 p.95). The configurational and conformational preferences of the ring-opened 2-amino-3-(2-hydroxybenzoyl)acrylamides **140**, **142-146**, and **151** were determined using a combination of x-ray crystallographic, ^{1}H, ^{13}C NMR and IR spectroscopic, and computer modelling techniques.[126]

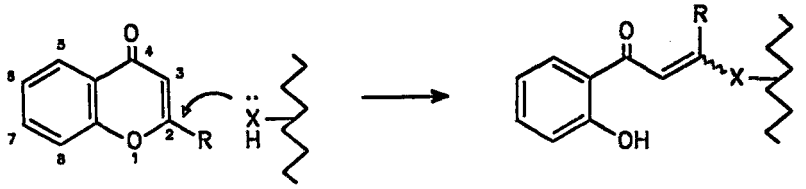
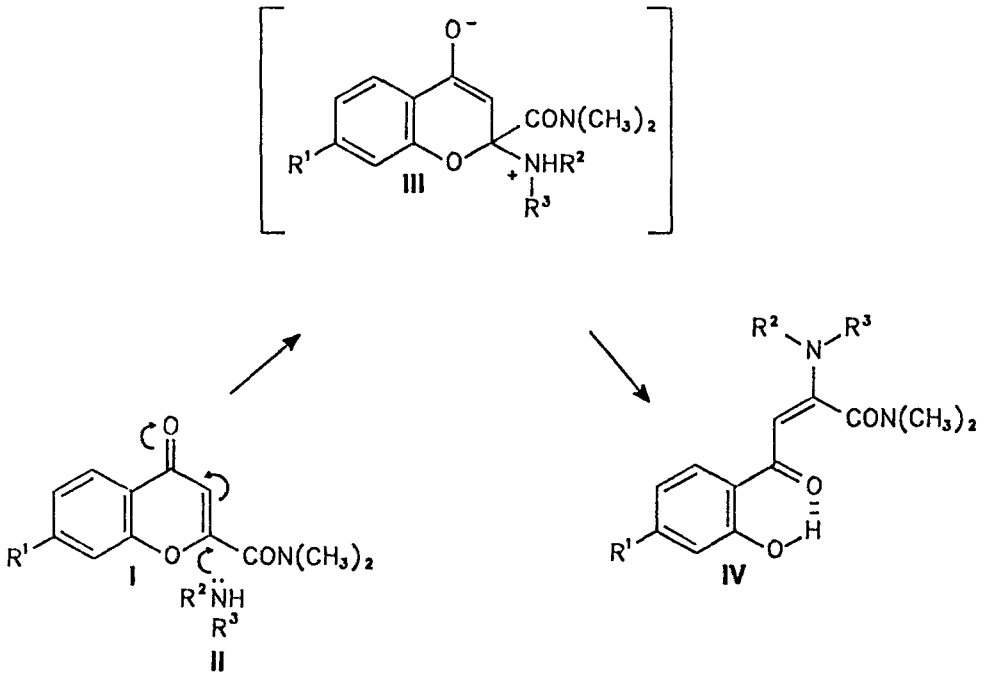


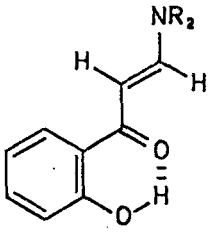
FIGURE 20. Putative interaction of biogenetic nucleophiles (*e.g.* X = N,O,S) with chromone systems.



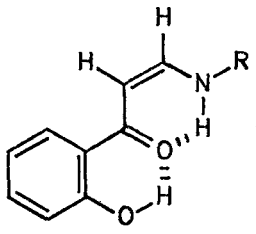
	R^1	R^2	R^3	
129	H	Me	Me	140
130	OMe	Me	Me	142
131	NO_2	Me	Me	143
132	F	Me	Me	144
133	Cl	Me	Me	145
134	Br	Me	Me	146
129	H	$-(CH_2)_4-$		151

SCHEME 37

Chromones are ring-opened to produce products with either *E*- or *Z*-double-bond configurations. Zagorevskii *et al.*[15] have investigated β-aminovinylketone systems using ^1H $J_{1,3}$ vinyl coupling constants to determine the *E*-configuration of *N,N*-disubstituted β-aminovinylketones 160 and the *Z*-configuration of *N-mono*substituted analogues 161. However, they failed to determine the double-bond configuration in the products of reactions of 2-substituted chromones with secondary amines. NMR and IR spectroscopy have also been used[15] to determine the significance of intra-molecular hydrogen-bonding in both series.



160



161

The *E*-double-bond configuration of the parent system 140 was unambiguously determined by single crystal x-ray diffraction analysis. The crystal structure and packing diagrams of this compound (140) are shown in Figures 21 and 22 (p.97 and 98). The crystal stucture also indicates intra-molecular hydrogen-bonding between the phenolic proton and the *syn*-orientated ketone carbonyl group. The amide group is planar with a maximum deviation from the least-square plane of 0.0820 Å, and lies perpendicular (*ca.* 85°) to the rest of the molecule. The remaining crystallographically determined atoms are co-planar, with a maximum deviation from the least-square plane of 0.0796 Å. The planarity of the β-amino-vinyl ketone system implies significant delocalisation of the dimethylamino nitrogen lone pair into the extended conjugated system (Figure 23 p.99). This delocalisation effect is also enhanced by intra-molecular hydrogen-bonding chelation which also encourages the co-planarity of the aryl and β-amino-vinylketone systems.

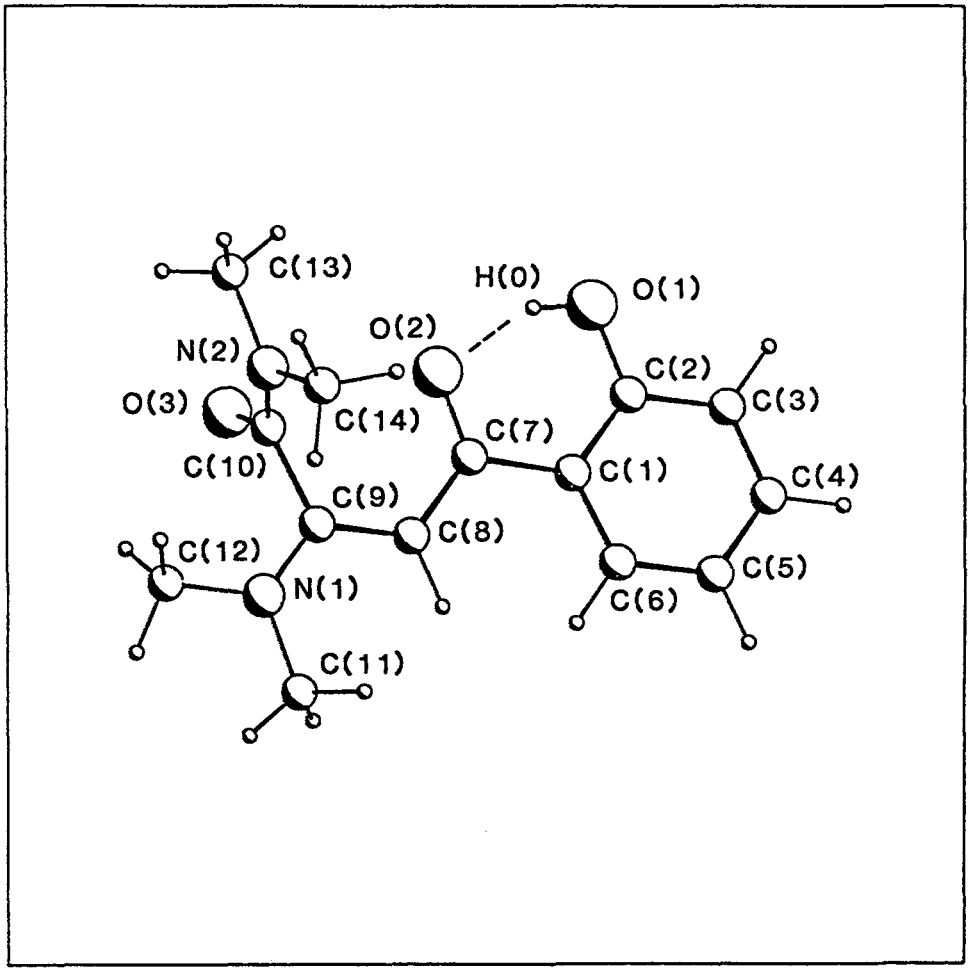


FIGURE 21. X-Ray crystal structure of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide **140**, showing the crystallographic numbering.

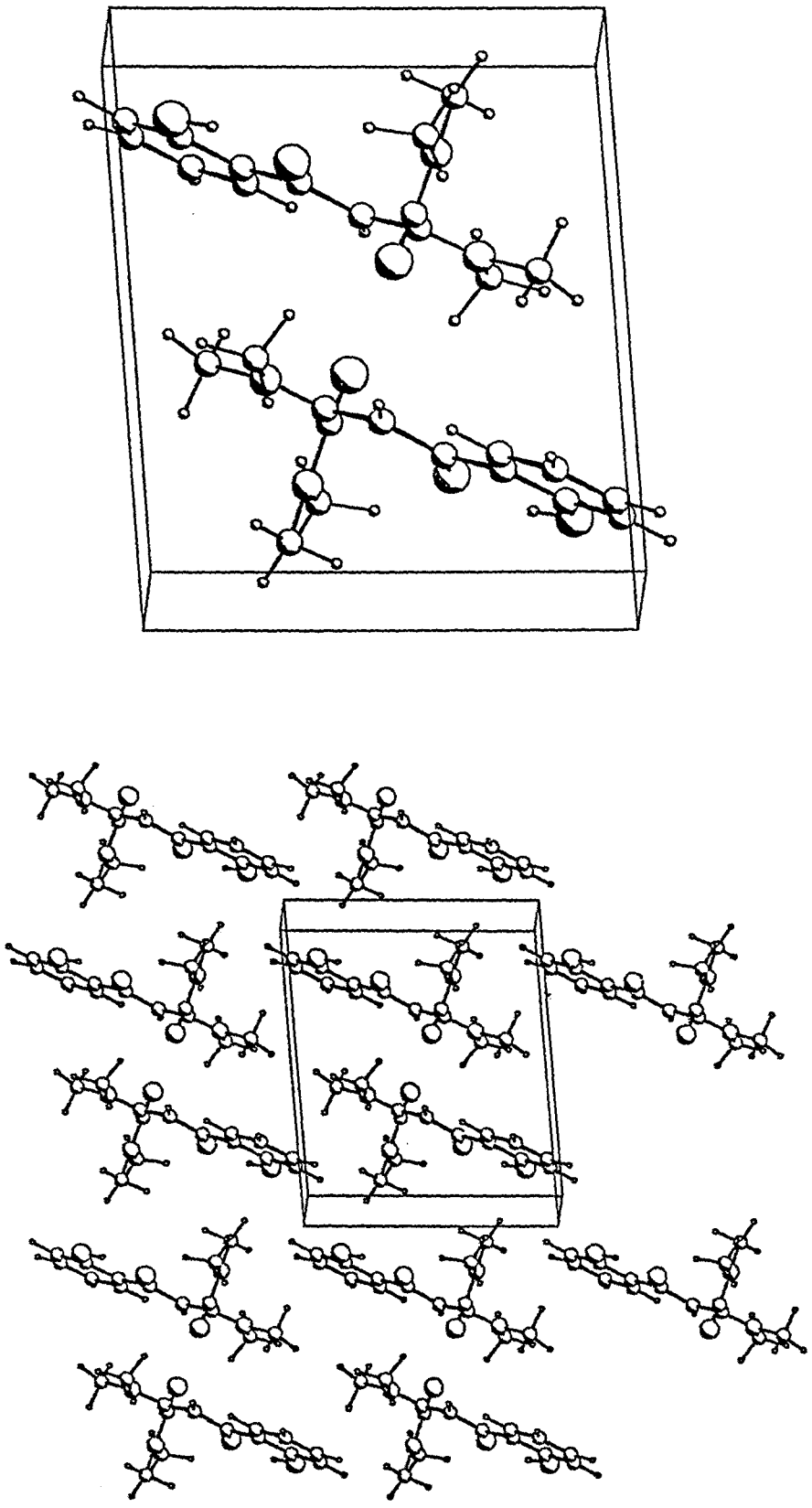


FIGURE 22. Packing diagram of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 140.

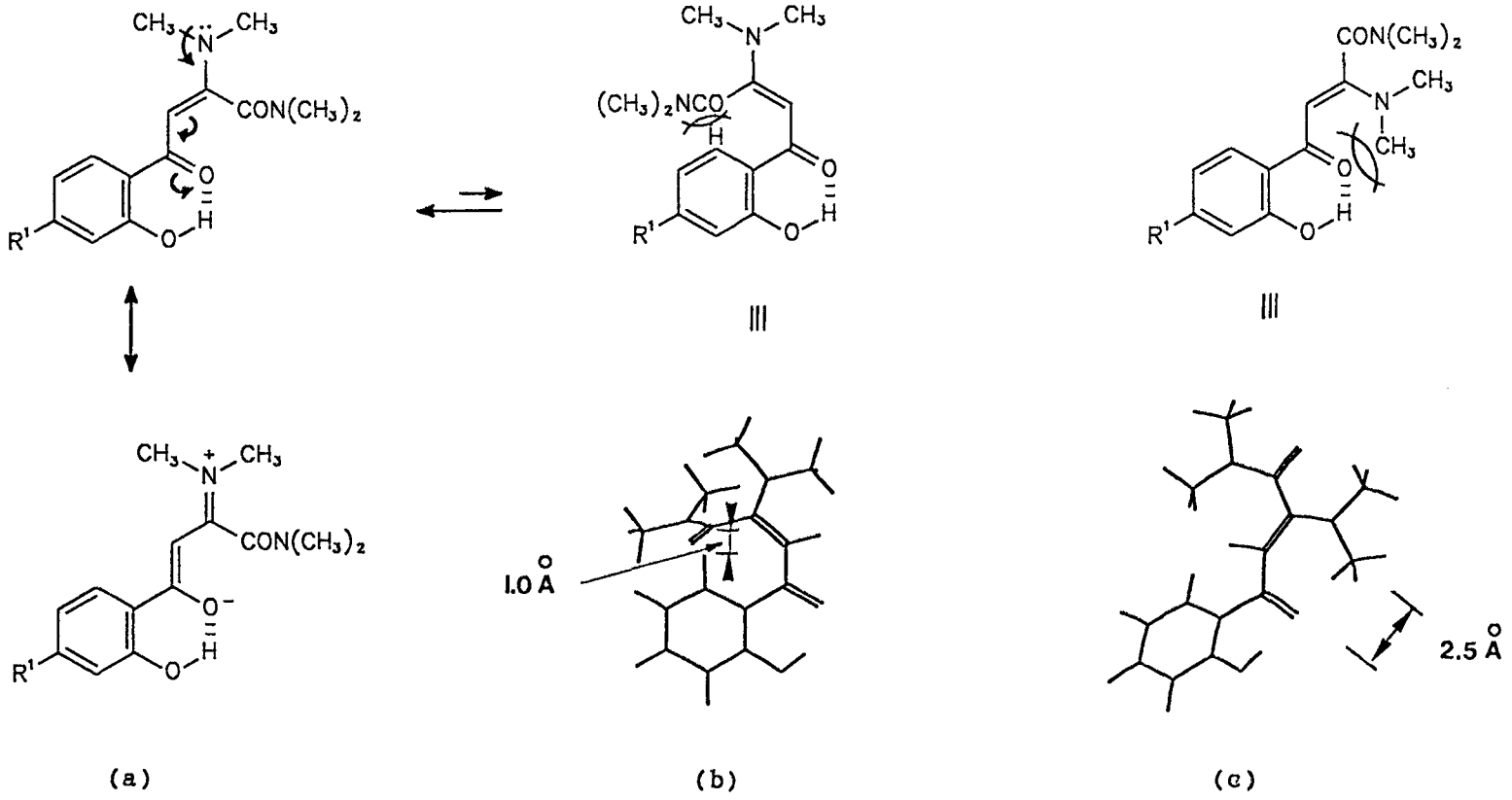


FIGURE 23. (a) Favoured *E*-configuration of compounds **140**,**142-146** and **151** illustrating delocalisation and hydrogen-bonded chelation. (b) Unfavourable steric interaction in the alternative conformer of the *E*-diastereomer. (c) Unfavourable steric interaction in a planar conformation of the *Z*-diastereomer.

NMR and IR data may be used to argue that the solid state (crystal) conformation of the parent system is essentially maintained in solution *i.e.* in chloroform; and the same configurational and conformational preferences are present in all of the 2-amino-3-(2-hydroxybenzoyl)-acrylamides **140**, **142-146**, and **151**. The *E*-double-bond configuration in each of the 2-amino-3-(2-hydroxybenzoyl)acrylamides is substantiated by the following NMR data, obtained for $CDCl_3$ solutions. In the series (Table 7; Figure 24 p.101), the chemical shifts for the vinyl (3-H) protons and the non-aromatic carbons show only small differences and the vinyl 3-H proton chemical shifts correlate more closely to the calculated value for the *E*-isomer (5.51 ppm) than for the *Z*-isomer (6.08 ppm). These calculated values were determined using the method of additive increments described by Matter *et al.*[127] Furthermore, in each of the compounds, the ^{13}C *N*-methylamino and *N*-methylcarboxamido signals are both split at ambient temperature. The corresponding ^{1}H *N*-methylcarboxamido signals are clearly split, while the ^{1}H *N*-methylamino signals form broad, post-coalescence singlets at ambient temperature (Figure 24). *N,N*-disubstituted amides usually exhibit slow site-exchange of *N*-alkyl groups at ambient temperature. However, the analogous splitting of the ^{13}C *N,N*-dimethylamino signals is significant and implies a rotational equilibrium between resonance-stabilised planar conformers due to slow site-exchange of diastereotopic *N*-methyl groups. These conformational options are only possible in the *E*-double-bond configuration of the acrylamide illustrated in Figure 23a (p.99), since molecular modelling studies show that in the *Z*-diastereomer (Figure 23c), unfavourable steric interactions prevent co-planarity of the dimethylamino- and vinyl ketone moieties. The alternative planar conformer (Figure 23b) is destabilised by unfavourable steric interactions even when the planar amide moiety is perpendicular to the rest of the molecule. [The planar arrangements illustrated in Figure 23

Table 7. Comparative ^{1}H and ^{13}C NMR chemical shifts for dimethylamino-*N*,*N*-acrylamides 140,142-146, and 151.

^{13}C Nucleus	δ 140 (ppm)	Δδ[a] (ppm)
CO.NMe_2	34.06	0.44
	36.84	0.46
NMe_2	39.38	0.52
	40.11	0.82
C-1	166.44	1.52
C-2	158.76	1.54
C-3	88.81	0.31
C-4	189.74	1.72
3-H[b]	5.75	0.12

[a] Maximum deviation from compound 140.

[b] ^{1}H nucleus.

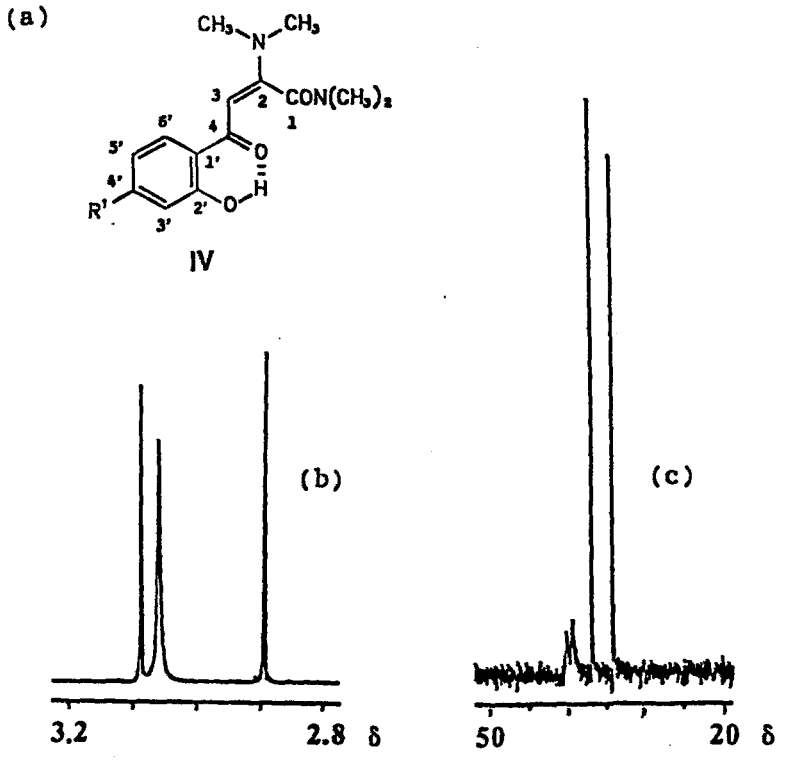


FIGURE 24. (a) Compounds IV with numbering (see Table 7 for NMR data).
(b) Partial ^{1}H NMR spectrum for compound (144; R^1 = F).
(c) Partial ^{13}C NMR spectrum for compound (144; R^1 = F).

were obtained by changing the relevant torsion angles of energy minimised structures.] The perpendicular arrangement of the amide group illustrated in the crystal structure of the parent system is likely to be maintained in solution, and eliminates unfavourable steric interaction with the vinyl ketone oxygen, while still allowing uninhibited delocalisation of the nitrogen lone-pair in the independently planar amide group.

In the IR spectra of the compounds obtained using KBr discs and chloroform solutions, the carbonyl absorption bands differ only by *ca.* ± 10 cm^{-1}. This observation is significant since IR carbonyl band frequencies are sensitive to structural change. Furthermore, in the systems examined, both ketone and amide carbonyl absorption bands are generally superimposed at low frequencies, *viz.*, *ca.* 1650 cm^{-1} [Figure 11 p. 77, Section 2.1 (iv)]. This observation reflects a reduction in the double-bond character of both carbonyl groups due to effective delocalisation. While such frequency shifts are characteristic of planar amide systems, they also independently substantiate the essential co-planarity of the dimethylamino and aryl vinyl ketone systems. The hydroxyl stretching band is shifted below 3000 cm^{-1} in both the solid state and solution IR spectra of each compound, while the phenolic proton chemical shifts occur at low field (*ca.* 14 ppm) in the 60 MHz ^1H NMR spectrum of each compound. Both these observations substantiate[48] the strongly hydrogen-bonded chelate conformation illustrated in Figure 23a (p.99).

C-2 nucleophilic attack may occur at either face of the planar chromone-2-carboxamide (I, Scheme 37 p.95) and ring-opening proceeds *via racemic*, dipolar intermediates III (see mechanistic study in Section 2.5.) Product development control may be responsible for the preferential

formation of the corresponding (*E*)-dimethylaminoacrylamides IV. Alternatively, the predominance of the more stable isomer may result from equilibration to the *E*-product, as a result of the configurational lability of the dimethylaminoacrylamides IV. Analogous configurational labilty has been reported by Shvo and Shanan-Aridi[128] in related systems, and has been rationalised by amino nitrogen lone-pair delocalisation which effectively increases the single-bond character of the double-bond. The essentially planar, conjugated *E*-products IV are the more stable isomers due to effective delocalisation of the dimethylamino nitrogen lone-pair, an effect which is not possible in the *Z*-diastereomers due to steric inhibition of resonance. In the mono-substituted amino analogues 161 (p.96) examined by Zagorevskii *et al.*,[15] however, co-planarity of the *syn*-orientated amino- and vinyl ketone groups may be achieved in the *Z*-isomer without steric strain. The *Z*-double-bond configuration in these compounds is apparently favoured due to stabilisation by additional intra-molecular hydrogen bonding between the amino hydrogen and the ketone carbonyl group.

2.4 NMR ANALYSIS OF THE REACTION OF DISODIUM CROMOGLYCATE WITH DIMETHYLAMINE

The dimethylamine-mediated ring-opening of DSCG **158** (Scheme 35 p.80) was performed in an NMR tube, and the reaction was followed by NMR spectroscopy. ^{1}H and ^{13}C spectra of the starting material, and the reaction mixture after 0.5 h are shown in Figures 25 and 26. The ^{1}H NMR spectrum of the reaction mixture taken after 0.5 h shows the complete disappearance of the vinyl (3-H) proton singlet and the shifting of the benzenoid protons to higher field with chemical shifts comparable to those observed for bis(*o*-hydroxyacetophenone) **155**; the benzenoid proton triplet and doublets are also shifted further apart. In the ^{13}C NMR spectrum, taken after 0.5 h, the vinyl ketone (C-4) chemical shift occurs at lower field (*ca.* 193 ppm) and the benzenoid chemical shifts are comparable to those observed for bis(*o*-hydroxyacetophenone) **155**. The *N*-methylamino ^{13}C signals presumably coincide with those of dimethylamine. The spectra of the reaction mixture after 0.5 h thus show significant differences from the starting material and differences are consistent with formation of the ring-opened product **159**. Isolation of the ring-opened product **159** was then attempted. Surprisingly, however, the ^{1}H and ^{13}C spectra of the crude isolated product (obtained in quantitative yield) correlate with DSCG **158** rather than the ring-opened product **159** [as illustrated in the DEPT spectra (Figure 27)]. While there is clear evidence that ring-opening of DSCG occurs in the reaction solution, the reaction appears to be reversible since the starting material was isolated. This interesting reaction still requires further investigation.

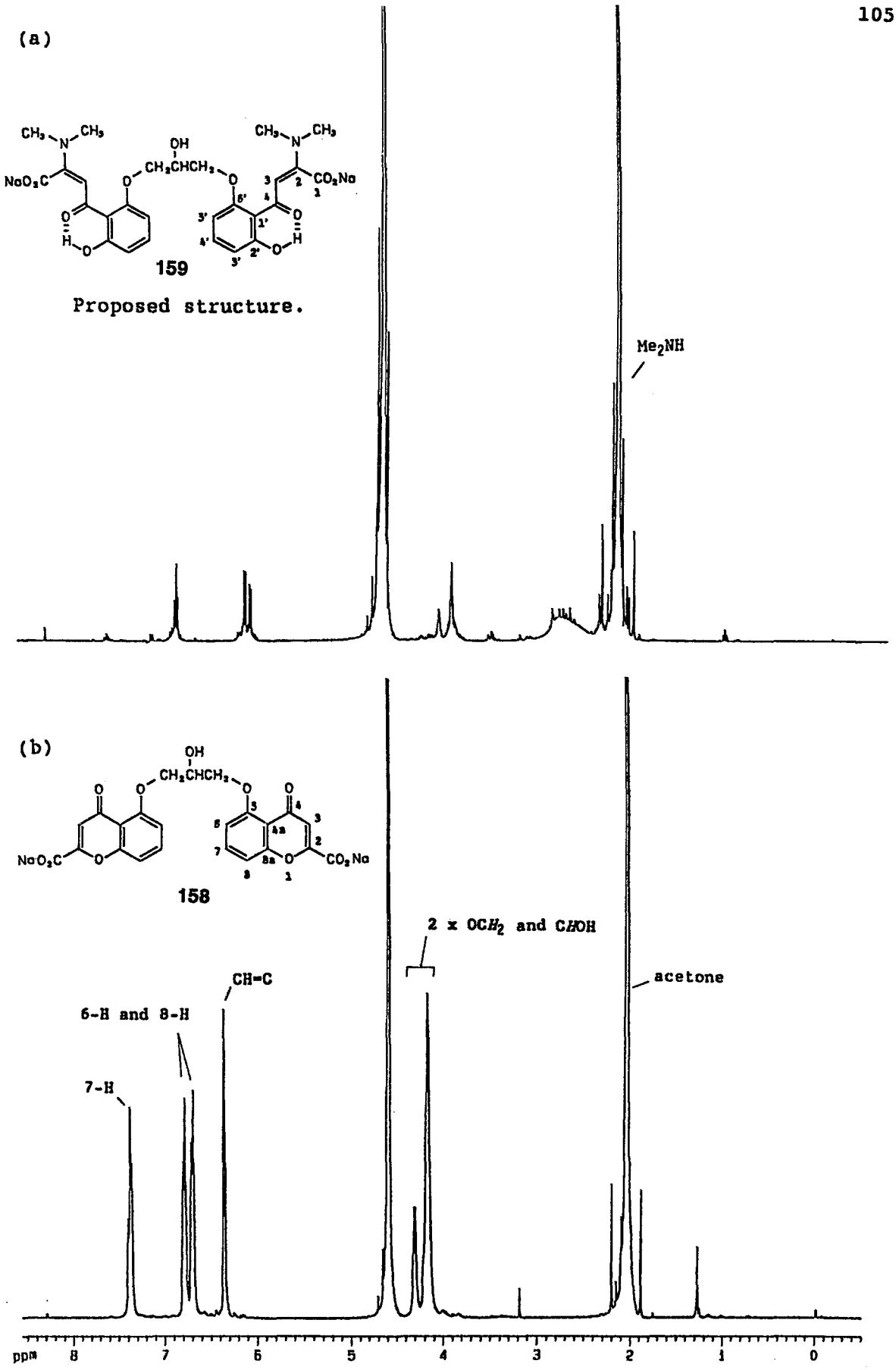
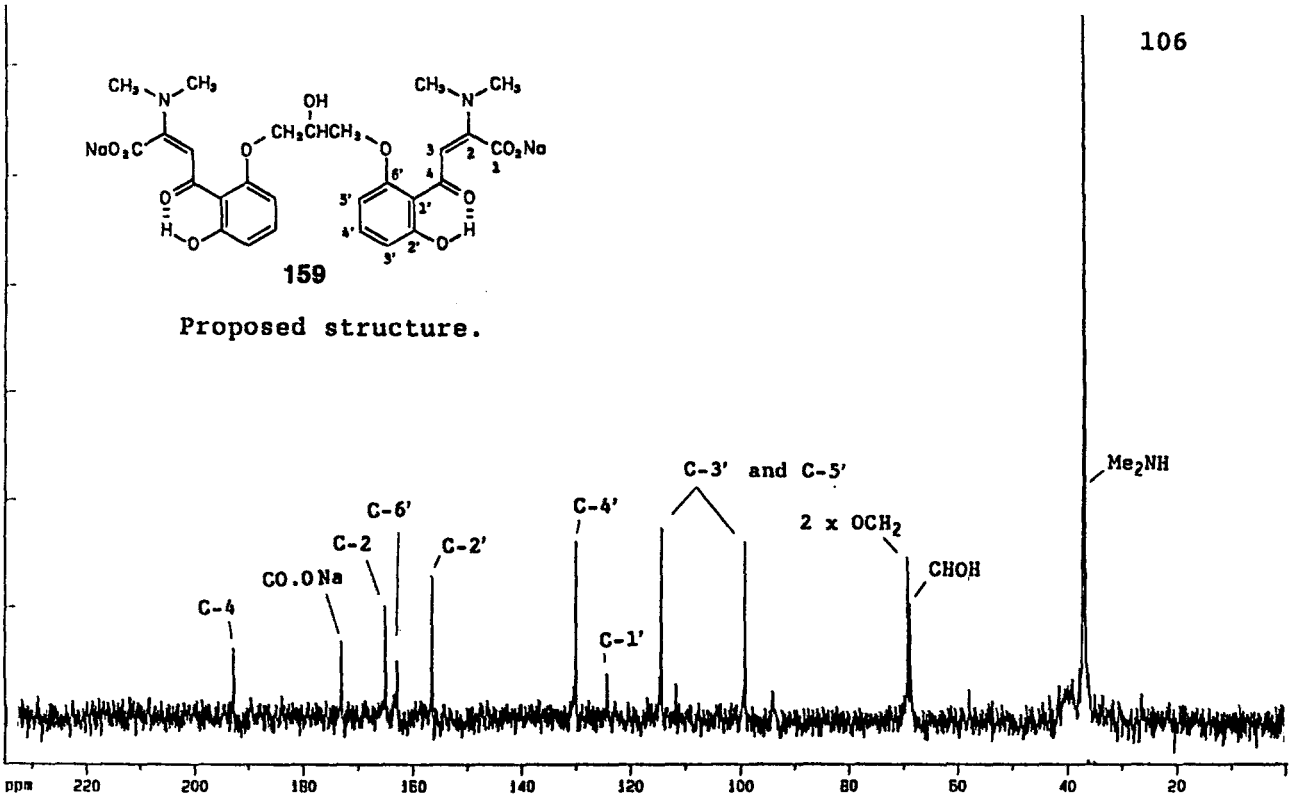


FIGURE 25. 400 MHz ^1H spectra of
a) reaction mixture after 0.5 h.
b) DSCG 158 (starting material).



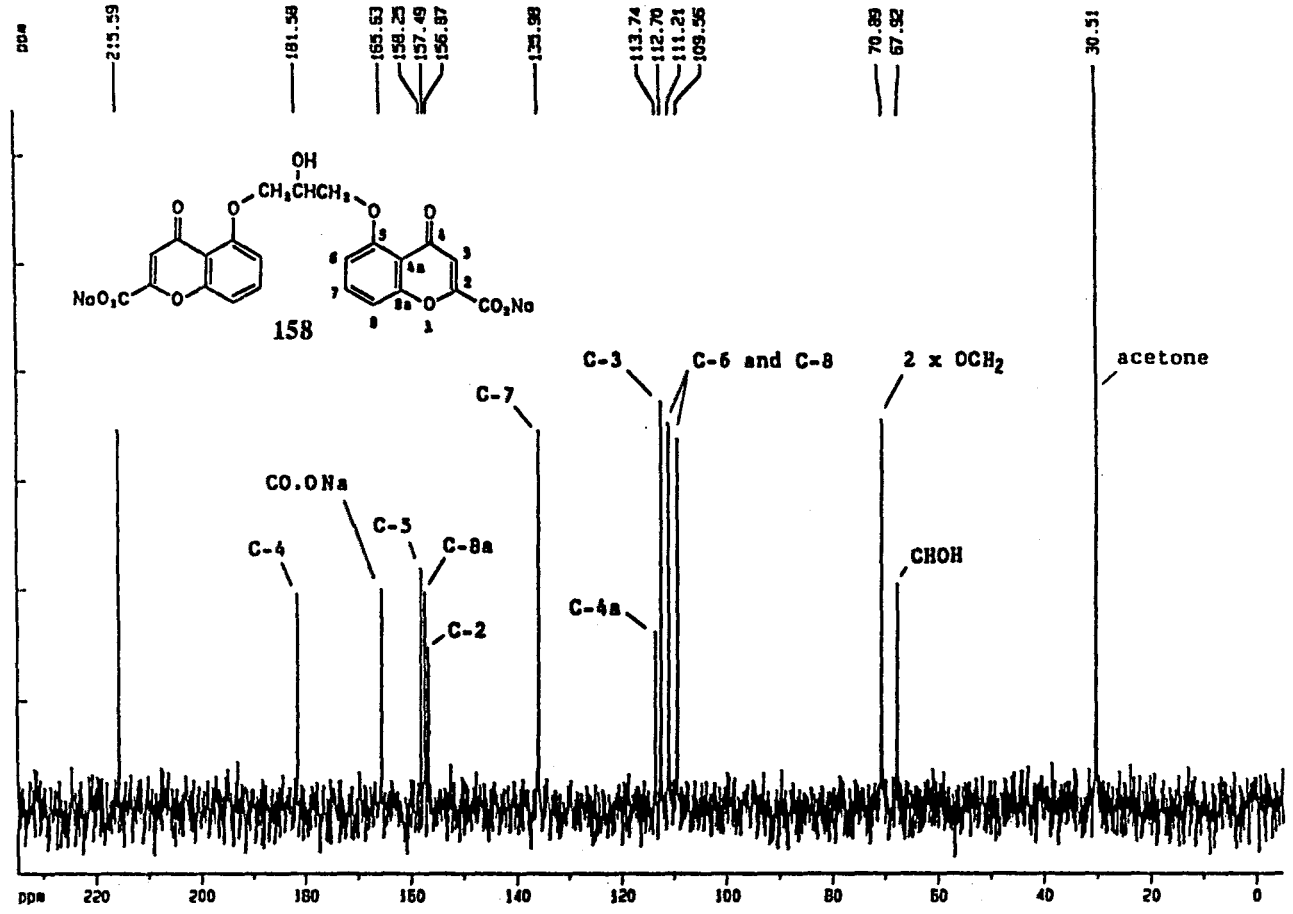


FIGURE 26. 100 MHz ^{13}C spectra of

a) reaction mixture after 0.5 h.

b) DSCG 158 (starting material).

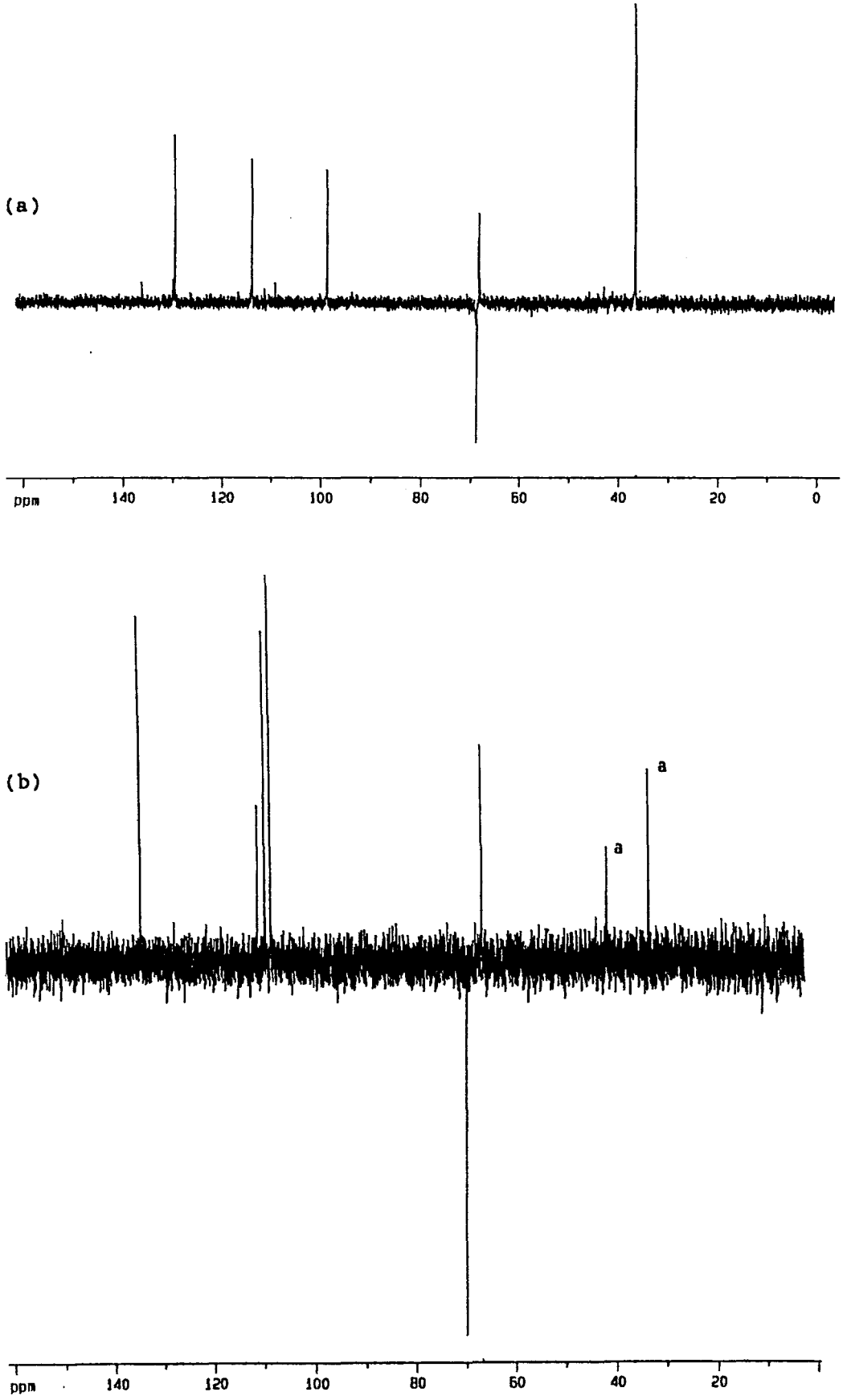


FIGURE 27. 100 MHz DEPT spectra of
a) reaction mixture after 24 h.
b) DSCG 158 (isolated product).

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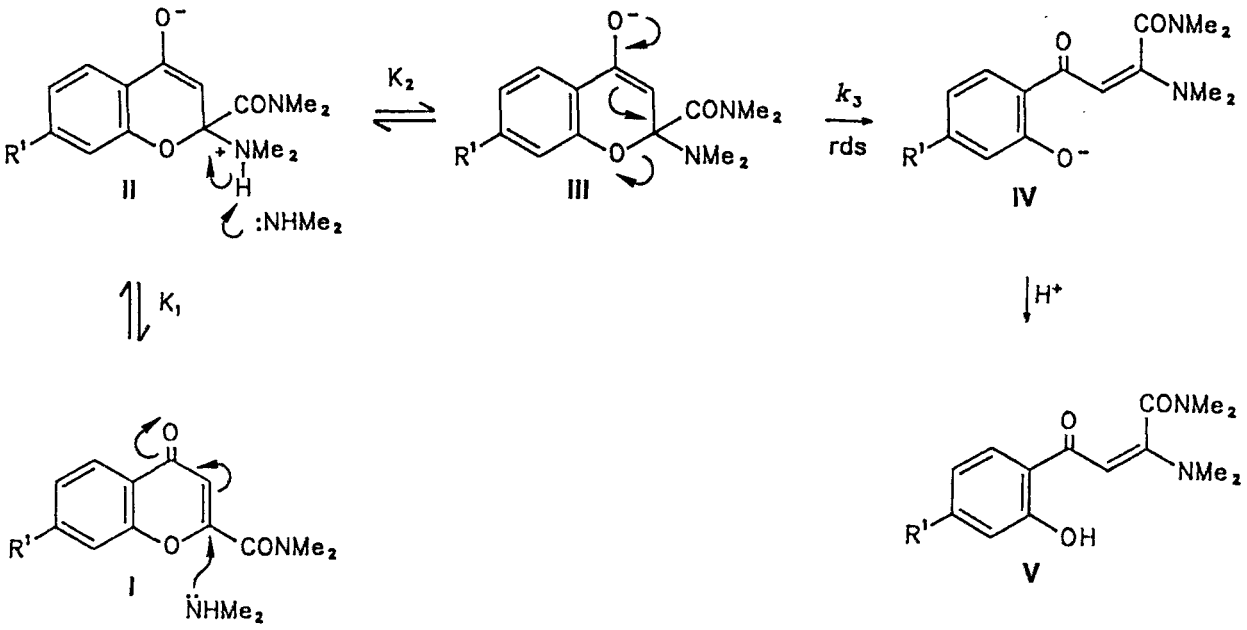
[a] Impurities

2.5 KINETICS AND MECHANISM OF THE REACTION OF CHROMONE-2-CARBOXAMIDES WITH DIMETHYLAMINE[129]

Further investigation of the implications of the ring-opening reactions of chromones in molecular-level chromone pharmacology involved a kinetic study of the dimethylamine-mediated ring-opening of the *N*,*N*-dimethylchromone-2-carboxamides **129**-**133** to the corresponding (*E*)-2-(*N*,*N*-dimethylamino)-3-(2-hydroxybenzoyl)acrylamides **140** and **142**-**145** (Scheme 38).



	R[1]	
129	**H**	**140**
130	**OMe**	**142**
131	**NO_2**	**143**
132	**F**	**144**
133	**Cl**	**145**

SCHEME 38

The ring-opening reactions were followed by ultraviolet spectroscopy. The absorption maxima of the reactants and products were well separated (*e.g.* Figure 28 p.110), in all cases, and the reactions were followed by monitoring the rate of formation of the acrylamides. In each case, the absorbance changes were measured at the wavelength corresponding to the absorption maximum of the particular acrylamide (*e.g.* Figures 29 and 30 p.110 and p.111). The cuvette chamber, reaction flask, and reagent solutions were maintained at 30 (± 0.2)°C. Other reaction parameters such as the wave-length, initial chromone-2-carboxamide- and dimethylamine concentrations, and the duration of each reaction are summarised in Table 8. Initial chromone-2-carboxamide concentrations were chosen to produce maximum acrylamide absorbances of *ca.* 1.0 - 1.2 absorbance units, and dimethylamine concentrations were chosen to ensure *ca.* 80% completion of the reactions within 1-1.5 h. The final absorbance readings ($\lim_{t\to\infty} A_t$) were taken after 15-24 h. All determinations were duplicated. The linear (Beer's Law) relationship between acrylamide concentration and absorbance (*e.g.* Figure 31 p.111) was confirmed over the corresponding ranges used for each system.

TABLE 8. Reaction parameters.

R^1	λ (nm)	[Amide] (mol.dm^{-3} x 10^5)	[Me_2NH] (mol.dm^{-3})	Completion (%)	Reaction time (min)
H	357	3.5	1.0 - 1.8	80 - 85	40 - 120
OMe	361	3.0	1.8 - 2.6	65 - 76	32 - 80
NO_2	388	5.5	0.059 - 0.099	80 - 82	35 - 70
F	353	3.5	0.4 - 0.8	74 - 85	19 - 70
Cl	358	3.5	0.2 - 0.6	80 - 87	17.5 - 130

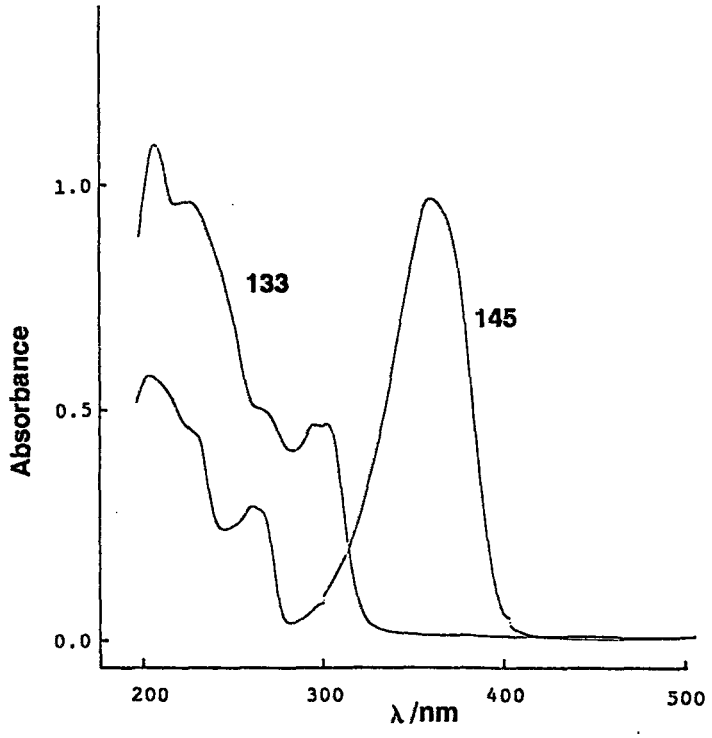


FIGURE 28. UV Spectra of ethanolic solutions of 7-chloro-*N*,*N*-dimethylchromone-2-carboxamide 133 and the corresponding acrylamide 145.

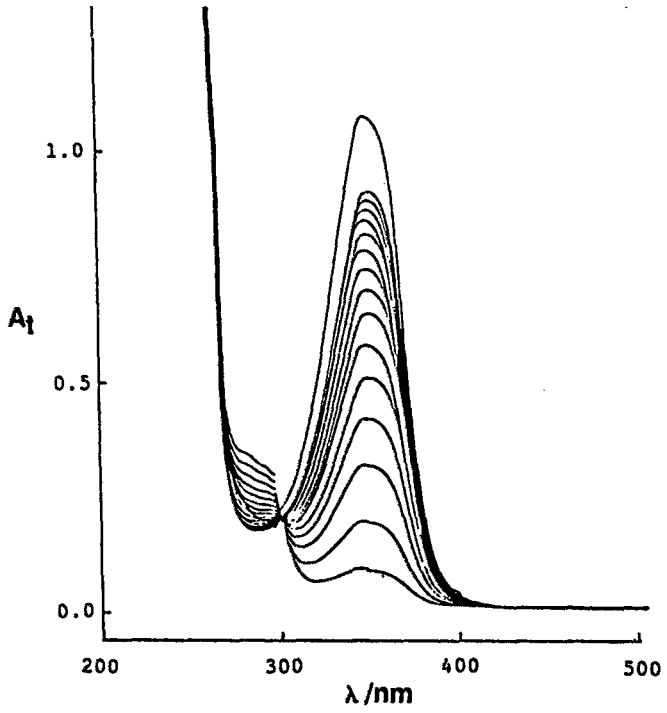


FIGURE 29. UV Spectra showing absorbance changes during the reaction of 7-fluoro-*N*,*N*-dimethylchromone-2-carboxamide 132 with 0.5 M-dimethylamine at 30°C.

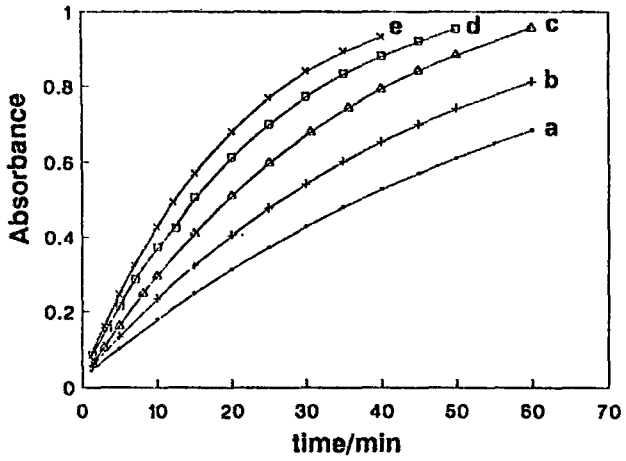


FIGURE 30. Plots of absorbance *vs.* time for reactions at 30°C of *N*,*N*-dimethylchromone-2-carboxamide 129 with (a) 1.0M-Me_2NH; (b) 1.2M-Me_2NH; (c) 1.4M-Me_2NH; (d) 1.6M-Me_2NH; and (e) 1.8M-Me_2NH.

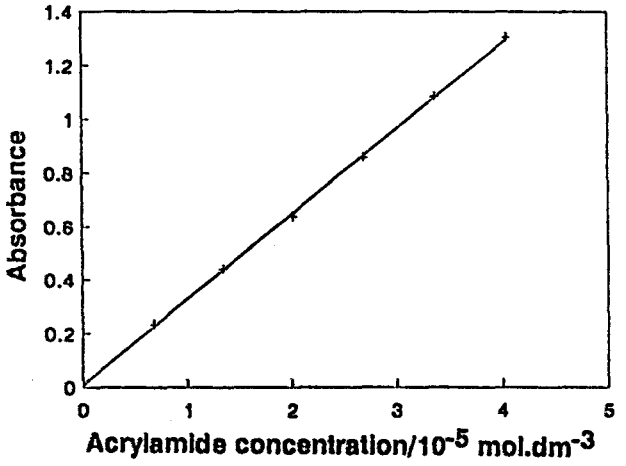


FIGURE 31. Beer's Law plot of absorbance *vs.* concentration of the acrylamide 140.

Large excesses of dimethylamine { > 10^3x[chromone-2-carboxamide I]} were used to produce pseudo first-order reaction conditions (Equation 7). The pseudo first-order rate constants (k_a) at different dimethylamine concentrations were determined from linear plots (*e.g.* Figure 32 p.113) of ln ($A-A_t$) against time using equation 5. The ring-opening reactions were shown to be third-order overall, consistent with equation 6. The rate constants (k_{obs}) were determined from plots of pseudo first-order rate constants (k_a) against the square of the dimethylamine concentration {$[Me_2NH]^2$} (*e.g.* Figure 33 p.113). The relevant data are summarised in Tables 9 and 10 (p.114 and 117). Linear regression analysis of the experimental data afforded best straight line fits (Section 3.5).

$$\ln (A - A_t) = -k_a t + \ln (A - A_o) \qquad (5)$$

where A_o = initial absorbance

A_t = absorbance at time, t

$A = \lim_{t \to \infty} A_t$

$$\text{Rate} = k_{obs}[\text{chromone-2-carboxamide I}]\,[Me_2NH]^2 \qquad (6)$$

$$= k_a\,[\text{chromone-2-carboxamide I}] \qquad (7)$$

where $k_a = k_{obs}[Me_2NH]^2$

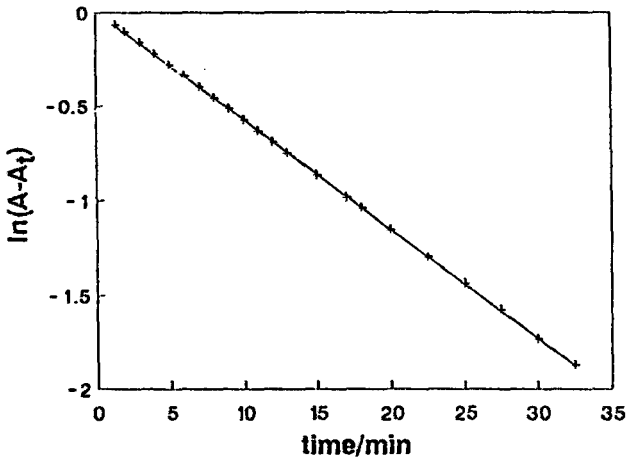


FIGURE 32. Pseudo first-order kinetic plot for the reaction of 7-fluoro-*N*,*N*-dimethylchromone-2-carboxamide 132 with 0.7M-dimethylamine at 30°C.

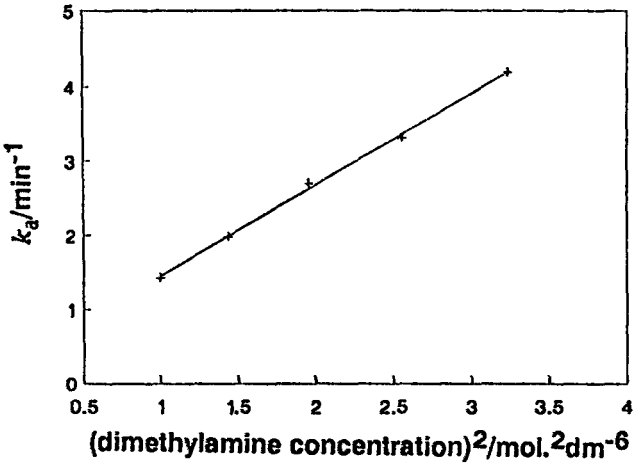


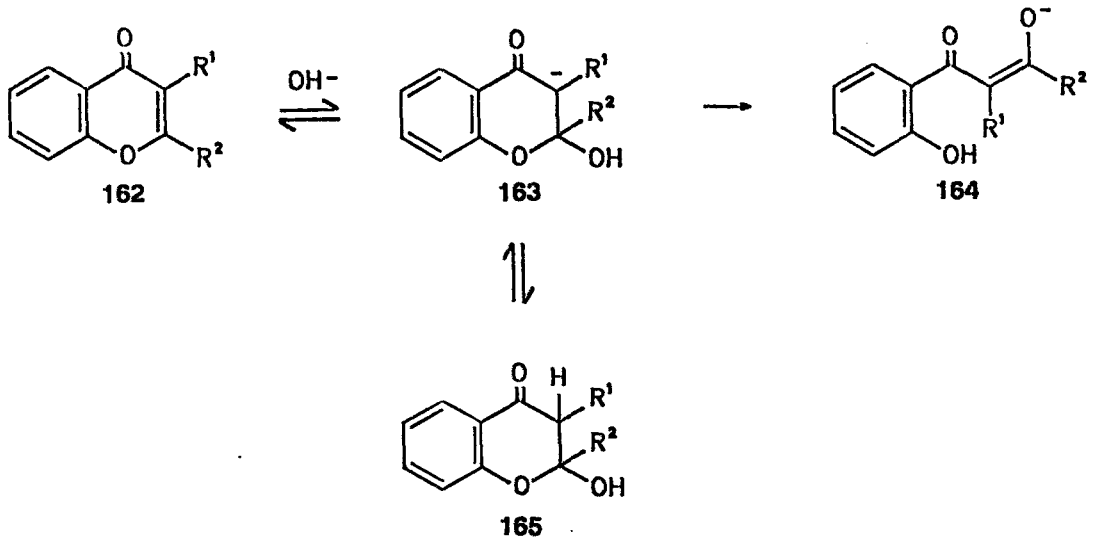
FIGURE 33. Plot of pseudo first-order rate constants (k_a) *vs.* $[Me_2NH]^2$ for the reaction of *N*,*N*-dimethylchromone-2-carboxamide 129 with dimethylamine at 30°C.

TABLE 9. Pseudo first-order rate constants (k_a) for the ring-opening of *N,N*-dimethylchromone-2-carboxamides **129-133** by dimethylamine at 30°C.

R[1]	[Amide] (mol.dm^{-3} x 10^5)	[Me_2NH] (mol.dm^{-3})	k_a[a] (s^{-1} x 10^4)
H	3.5	1.00	2.40 ± 0.02
		1.20	3.45 ± 0.15
		1.40	4.53 ± 0.03
		1.60	5.90 ± 0.38
		1.80	7.10 ± 0.12
OMe	3.0	1.80	3.97 ± 0.05
		2.00	4.98 ± 0.22
		2.10	5.73 ± 0.18
		2.40	6.87 ± 0.25
		2.60	7.97 ± 0.15
NO_2	5.5	0.059	2.53 ± 0.12
		0.069	3.35 ± 0.05
		0.079	4.33 ± 0.10
		0.089	5.67 ± 0.18
		0.099	6.50 ± 0.02
F	3.5	0.40	3.33 ± 0.05
		0.50	4.70 ± 0.20
		0.60	7.23 ± 0.72
		0.70	9.18 ± 0.48
		0.80	12.22 ± 0.65
Cl	3.5	0.20	2.22 ± 0.02
		0.30	4.75 ± 0.03
		0.40	7.05 ± 0.42
		0.50	10.72 ± 0.40
		0.60	15.53 ± 0.65

[a] Mean value from duplicate runs.

Szabo *et al.* have studied the kinetics of hydroxide ion induced ring-opening reactions of chromone-[26] and isoflavonoid derivatives.[27,28] They established that the reactions follow second-order kinetics, in which the rate is directly proportional to the product of the substrate and hydroxide ion concentrations. In their proposed mechanism (Scheme 39), the rate-determining step is considered to be the first step (**162** → **163**) involving C-2 nucleophilic attack by the hydroxide ion. They suggested[26] that the measured rate constants could be used to quantify the electron density at C-2 and, hence, the susceptibility of chromone derivatives to C-2 nucleophilic attack.



162 **163** **164**

165

SCHEME 39

Consequently, the reactions of the *N*,*N*-dimethylchromone-2-carboxamides with dimethylamine were expected to follow second-order kinetics with the rate-determining step involving C-2 nucleophilic attack by dimethylamine. However, the kinetic data show that ring-opening of chromone-2-carboxamides follow third-order (rather than second-order) kinetics overall corresponding to the rate equation 6 (p.112). The proposed mechanism is detailed in Scheme 38 (p.108). The rate

expression (Equation 8) is consistent with the proposed mechanism, and is equivalent to the experimentally determined relationship (Equation 6 p.112) when $k_3K_1K_2 = k_{obs}$.

$$\text{Rate} = k_3K_1K_2[\text{chromone-2-carboxamide I}]\ [Me_2NH]^2 \qquad (8)$$

In the proposed mechanism, two consecutive equilibria are followed by a rate-determining ring-opening step. The first equilibrium involves readily reversible nucleophilic attack by the amine at C-2 of the chromone-2-carboxamide I. The resultant dipolar species II then eliminates the neutral amine (II → I; Figure 34 p.119) more readily than it undergoes ring-cleavage (II → IV). In the second acid-base equilibrium, a second molecule of amine abstracts a proton from the dipolar species II thus acting as a base, rather than a nucleophile. [It is presumably this additional step which is responsible for the overall third-order kinetics, since in the hydroxide mediated reactions, (which follow second-order kinetics), the hydroxide ion does not require deprotonation (Scheme 39 p.115), and is not as easily eliminated as the Me_2NH.] The resulting enolate species III then undergoes ring cleavage in the rate-limiting step (III → IV) which involves the elimination of the resonance stabilised phenoxide ion in preference to Me_2N^- (Figure 34 p.119). The formation of an intermediate addition product analogous to compound **165** (Scheme 39 p.115) has not been included in the proposed mechanism, since Zagorevskii *et al.*[16] have reported an NMR study, in which they have demonstrated the absence of isotope exchange in the reactions of chromone with 1-D-piperidine and of 3-D-chromone with piperidine. Consequently, in their proposed mechanism (Scheme 40 p.119), amine-mediated ring-opening of chromones apparently proceeds *via* the dipolar species **166** without the formation of the addition product **167**.

Two substituent effects are expected to influence the experimentally determined rate constant (k_{obs}). The remote C-7 substituents may influence the electron density at C-2 and hence the equilibrium constant (K_1; Equation 8 p.116). However, as *meta*-substituents, they are also expected to significantly affect the relative stability of the phenoxide "leaving group" in the rate-determining step. Thus, electron-withdrawing substituents should accelerate ring-opening. The experimentally determined rate constants (k_{obs}; Table 10) decrease in the following order *viz.*, $k_{NO_2} > k_{Cl} > k_F > k_H$ and, with the exception of the 7-methoxy analogue **130**, this trend correlates with the reported order of the dissociation constants for *meta*-substituted phenols and benzoic acids,[130] and 4-substituted 2-hydroxyacetophenones.[131] The methoxy analogue **130** was expected to produce a larger rate constant (k_{obs}; Table 10) than the parent system **129**, since the methoxy substituent constant is positive ($\sigma_{m\text{-MeO}} = +0.10$).[132] This apparently anomalous smaller rate constant for the methoxy analogue **130** may be

TABLE 10. Rate constants (k_{obs}) for the ring-opening of *N,N*-dimethylchromone-2-carboxamides **129-133** by dimethylamine at 30°C.

R^1	k_{obs}[a] ($dm^6.mol^{-2}.s^{-1} \times 10^4$)
H	2.12 ± 0.08
OMe	1.13 ± 0.05
NO_2	648 ± 7
F	18.5 ± 1.2
Cl	40.8 ± 1.3

[a] Mean value from duplicate runs.

rationalised by electron-releasing resonance effects, which either reduce electron density at C-2 (Figure 35a p.119) and/or reduce the stability of the phenoxide ion. The phenoxide ion is stabilised by conjugation with the *o*-acyl function, and this effect may be opposed by competitive delocalization involving the electron-releasing *m*-methoxy substituent (Figure 35b p.119).

The reaction constant (ρ; Equation 10) was determined from a linear plot (Figure 36) of log ($k_{obs\text{-}x}/k_{obs\text{-}H}$) against the corresponding *meta*-substituent constants ($\sigma_{m\text{-}x}$),[132] applying the Hammett equation (9).[133] [The x denotes the substituent R^1.] The positive experimentally determined reaction constant (ρ = 4.48 ± 0.45) shows the development of a negative charge at the reaction centre for the rate-determining step,[133] consistent with the deprotonated intermediate species **III** in the proposed mechanism (Scheme 38 p.108).

$$\log (k_x/k_H) = \rho\sigma_x \qquad (9)$$

$$\log (k_{obs\text{-}x}/k_{obs\text{-}H}) = \rho\sigma_{m\text{-}x} \qquad (10)$$

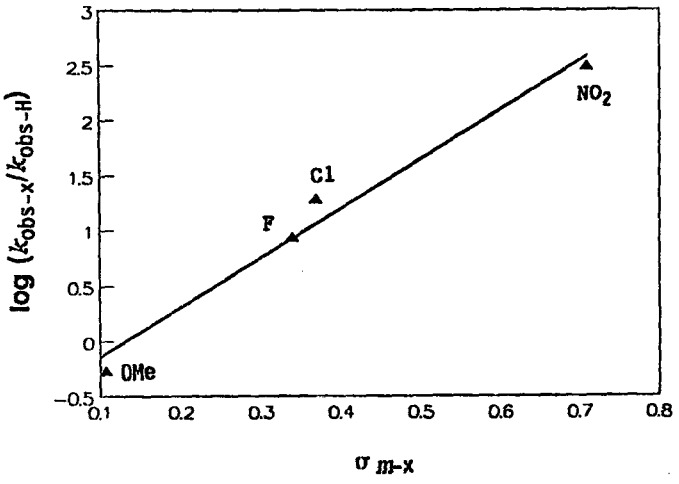
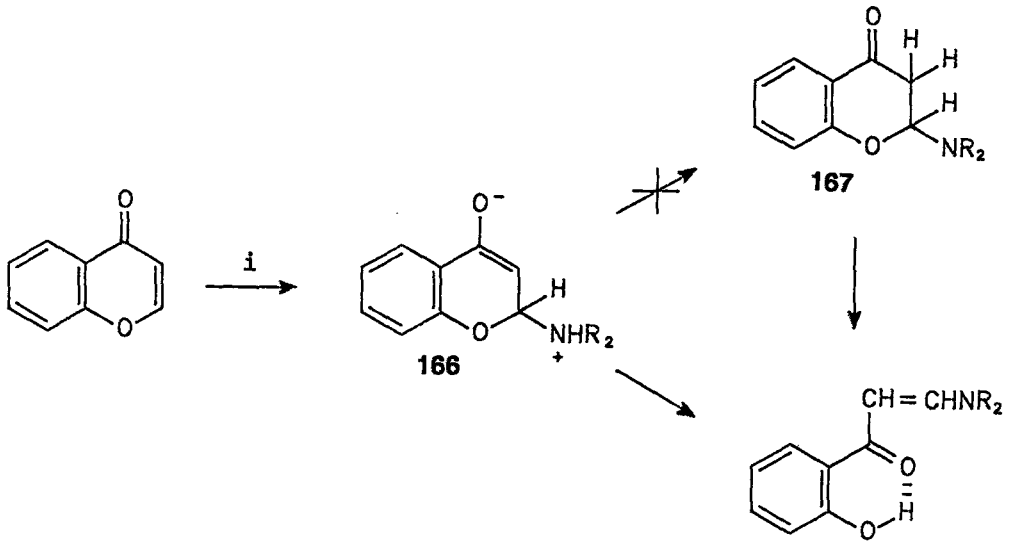


FIGURE 36. Plot of log ($k_{obs\text{-}x}/k_{obs\text{-}H}$) *vs.* ($\sigma_{m\text{-}x}$) for the reaction of the *N*,*N*-dimethylchromone-2-carboxamides **129-133** with dimethylamine at 30°C.



SCHEME 40

Reagents : i) R_2NH

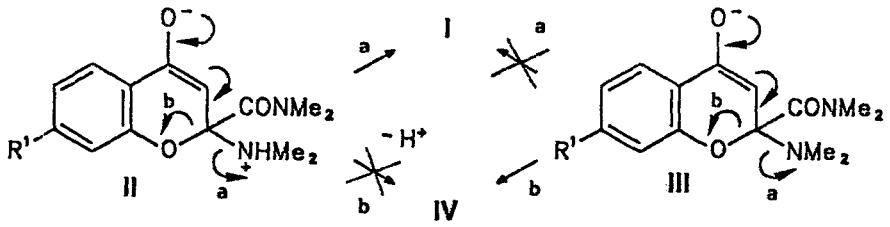


FIGURE 34.

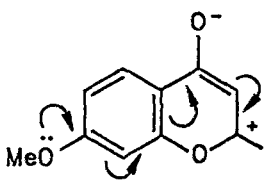


FIGURE 35a.

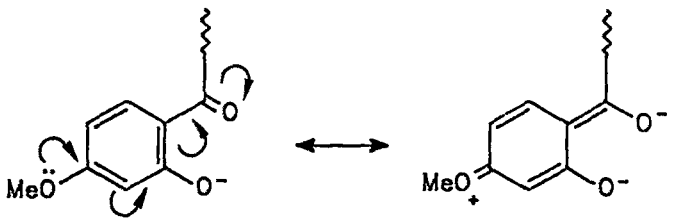


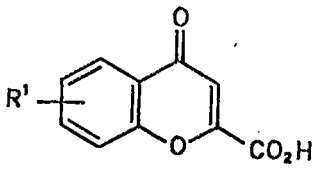
FIGURE 35b.

2.6 POTENTIOMETRIC DETERMINATION OF DISSOCIATION CONSTANTS OF CHROMONE-2-CARBOXYLIC ACIDS

While the acidity of anti-allergic compounds may be an important contributing feature for significant activity [Section 1.3.3 (i)], no satisfactory correlations have been established.[40] The poor solubility of cromoglycic acid in aqueous solutions has been reported to have prevented the determination of its pK_a.[119] The bischromone acids corresponding to the DSCG analogues (79) [discussed in Section 1.3.3 (i)], however, have been reported to exhibit high acidity due to the delocalisation effects of the carbonyl ketone group and the oxygen of the pyran ring, with pK_a values in the range of 1.3 to 2.0.[40] Chromone-2-carboxylic acid (129) has reported pK_a values of 2.96 (determined by conductimetry at 25°C)[134] and 2.8 (determined potentiometrically in 50% ethanol).[135] In chromone-2-carboxylic acids, substitution at C-5 by an alkoxy group has been reported to increase the acidity, *e.g.* 5-(2-hydroxypropyloxy)chromone-2-carboxylic acid and 5-(2-hydroxy-3-methoxypropyloxy)chromone-2-carboxylic acid have reported pK_a values of 1.86 and 1.92 respectively.[119] The acidity (pK_a 2.8) of 2-(1H-tetrazol-5-yl)chromone (determined by potentiometry in 50% ethanol at 20°C)[136] is comparable to chromone-2-carboxylic acid (129).

In the present study, the pK_a values (Table 11 p.121) for the chromone-2-carboxylic acids 112-118 were determined in order to explore further substituent effects on chromones. The 7-substituted chromone-2-carboxylic acids (112-117; Table 11) were chosen to elucidate electronic effects, while 6-chlorochromone-2-carboxylic acid 118 illustrates the effect of changing the substituent position.

TABLE 11. Dissociations constants of the chromone-2-carboxylic acids 112-118 at 25°C.



Compd.	R^1	pK_a[a]
112	7-H	2.69 ± 0.05[b]
113	7-OMe	2.96 ± 0.02[c]
114	7-NO_2	2.60 ± 0.03
115	7-F	2.63 ± 0.01
116	7-Cl	2.64 ± 0.04
117	7-Br	2.64 ± 0.02
118	6-Cl	2.62 ± 0.02

[a] Potentiometric titration in 0.01M-aqueous ethanol (50% v/v). [b] Lit.[143,135] 2.8 by potentiometry in 50% EtOH and 2.96 by conductimetry at 25°C. [c] Potentiometric titration in 0.005M-aqueous ethanol (50% v/v).

The pK_a values (Table 11) for the chromone-2-carboxylic acids 112-118 were determined by potentiometry in ethanol-water (50% v/v) at 25°C. 0.01M-Aqueous ethanolic solutions of the acids were titrated with 0.01M-sodium hydroxide; although, in the case of the methoxy analogue 113, 0.005M-acid and sodium hydroxide solutions were used. The recommended 0.01M-acid concentrations were generally used, since activity effects at this concentration are usually small.[137] However, precipitation of 7-methoxychromone-2-carboxylic acid 113 from a 0.01M-solution required the use of a 0.005M-solution in this case. The solvent ratio (ethanol-water; 50% v/v) was chosen to correspond to the reported[135] ratio used to determine the pK_a of the parent system 112.

In weak acids, the pK_a is equivalent to the pH at half the equivalence point,[138] and plots (*e.g.* Figure 37 p.123) of the first ($\Delta pH/\Delta V$) and second derivatives ($\Delta^2 pH/\Delta V^2$) of the pH titration curve against volume (V) were used, in each case, to determine the equivalence point.[139] All determinations were duplicated using the same standard acid solutions (solution 1), and then repeated using a second standard acid solution (solution 2).

In *para*-substituted benzoic acids, the reported[130] gradation of pK_a values is : OMe > H > F > Cl > Br > NO_2 and a similar trend was expected in the chromone-2-carboxylic acids 112-117. Electron-withdrawing substituents on chromone-2-carboxylic acids should decrease electron density at C-2 thus increasing the polarity of the O-H bond and stabilising the anion of the dissociated acid. Thus, electron withdrawing substituents should produce stronger acids (with lower pK_a values) than the parent system 112. The pK_a values (Table 11 p.121) of the 7-substituted acids 112-117 follow the expected, general trend (*i.e.* OMe > H > Cl, Br , F > NO_2) although the electronic effects of the 7-halogeno substituents on the pK_a appear to be very similar. The higher result (pK_a = 2.96) for the methoxy analogue 113, relative to the parent analogue 112, may be rationalised by electron-releasing resonance effects which increase electron density at C-2 (Figure 38 p.124). [The pK_a of the methoxy anologue 113 might have been expected to be lower than that of the parent system 112, if only inductive effects acting through the pyran oxygen were considered, as shown in the reported[130] gradation of pK_a values in *meta*-substituted benzoic acids or phenols (H > OMe > F > Cl > Br > NO_2).]

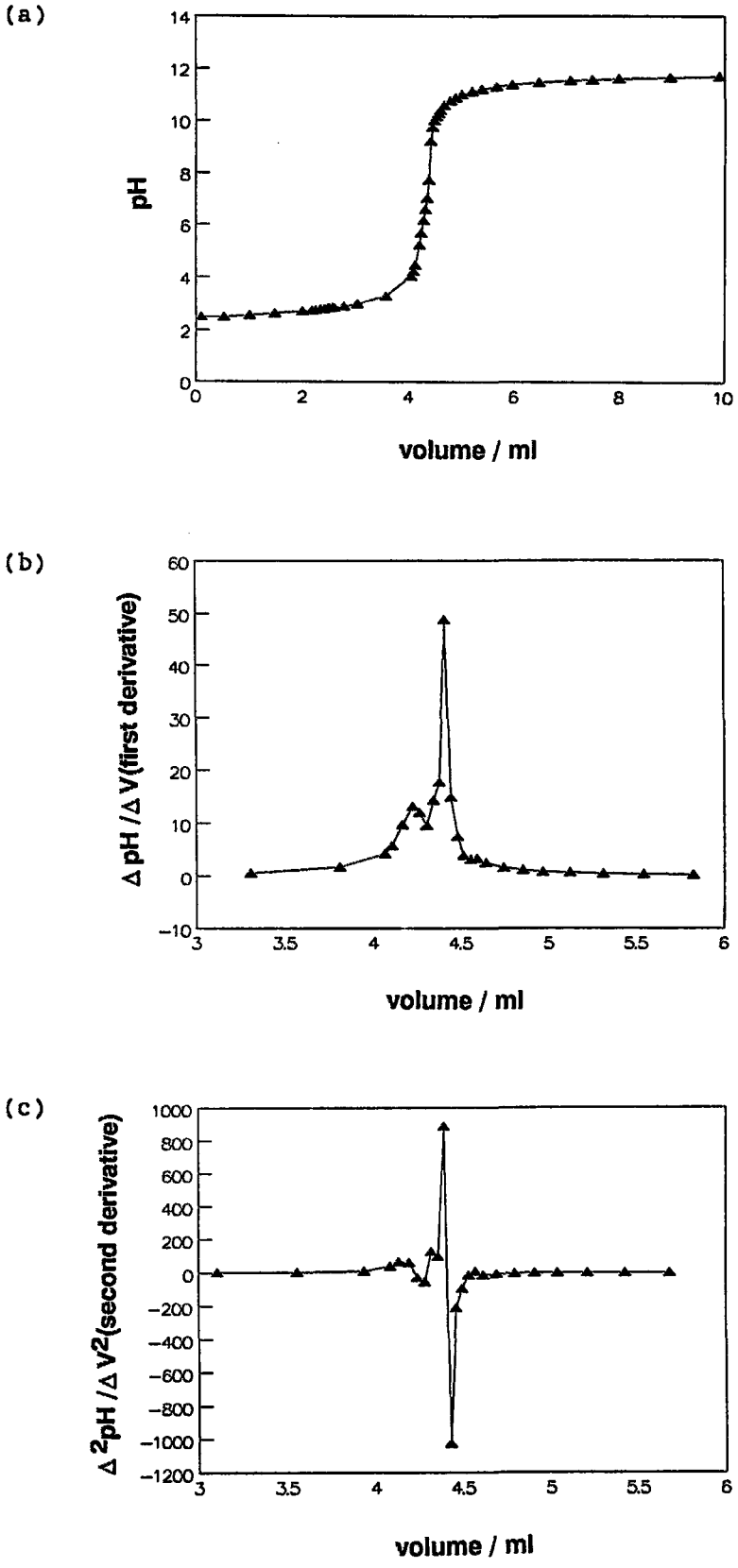


FIGURE 37. Curves for the titration of 0.01M-chromone-2-carboxylic acid 112 against 0.01M-NaOH.
(a) Titration curve;
(b) Plot of the first derivative ($\Delta pH/\Delta V$) *vs.* volume;
(c) Plot of the second derivative ($\Delta^2 pH/\Delta V^2$) *vs.* volume.

Changing the chloro substituent position from C-7 to C-6 results in a very small reduction in the pK_a, although the values are nearly identical. This apparent reduction in pK_a may be rationalised in terms of a larger net electron-withdrawing effect for the 6-chloro substituent compared to the 7-chloro substituent. Although the electron-withdrawing inductive effect of the 7-chloro substituent (Figure 39) may be expected to be stronger than that of 6-chloro substituent (since it acts over a shorter distance), mesomeric electron release is only possible with the 7-chloro substituent (Figure 39). It should be noted, however, that the difference in the pK_a values are very small and lie within the estimated experimental errors. Nevertheless, the estimated experimental errors are within the permitted scatter of ± 0.06,[140] reported for potentiometric determinations. The small, observed pK_a differences suggest that the C-7 substituents do affect the electron density at C-2. It is not surprising that the differences in this effect are small in view of the distance between the 7-substituent and the carboxylic acid group.

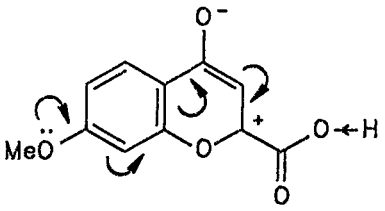


FIGURE 38.

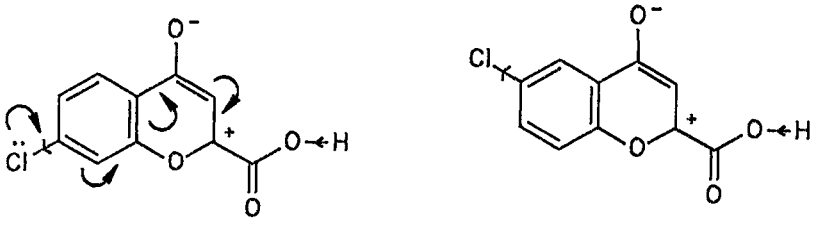


FIGURE 39.

The pK_a values were also determined in order to explore their relationship with the rate constants (k_{obs}) for the ring-opening reactions described in the previous Section (2.5). In related kinetic studies of hydroxide ion induced ring-opening reactions of chromone derivatives (Scheme 39 p.115), Szabo *et al.*[26] established a linear relationship (Equation 11) between the second-order rate constant (k) and the protonation constant (pK_{BH^+}) of the pyran carbonyl oxygen. They also suggested that this equation could be used to predict the reactivity of chromones towards other nucleophiles (*e.g.* nitrogen nucleophiles). In the present investigation, a linear relationship (Equation 12) was obtained from a plot (Figure 40) of log (k_{obs}) against the corresponding dissociation constants (pK_a) of the chromone-2-carboxylic acids **112,114-116**. This relationship is only possible provided the data for the methoxy anologue **113** is excluded. Since the pKa value of the methoxy analogue **113** follows the expected trend, this confirms that the rate constants for the ring-opening reaction do not effectively quantify the electron density at C-2 (*i.e.* C-2 electrophilicity), but rather reflect stabilising *meta*-substituent effects on the phenoxide "leaving group", as discussed in the previous Section (2.5).

$$\log (k) = -1.55pK_{BH^+} - 3.53 \qquad (11)$$

$$\log (k_{obs}) = -25.91pK_a + 65.90 \qquad (12)$$

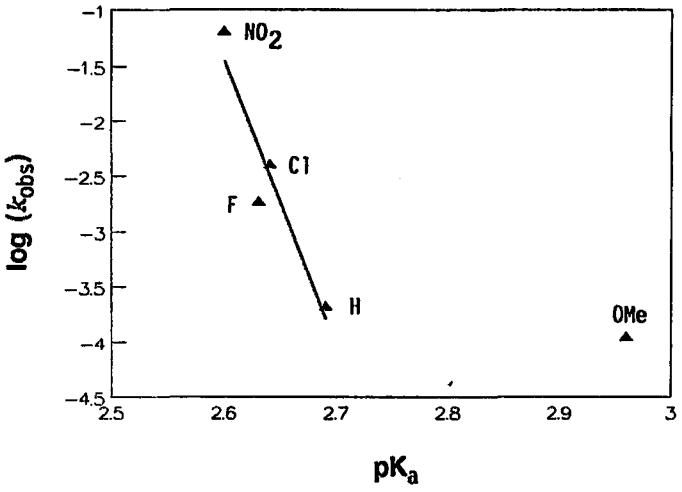


FIGURE 40. Plot of log (k_{obs}) *vs.* (pK_a) for the chromone-2-carboxylic acids 112-116.

2.6 CONCLUSION

In the chromone systems investigated, it is apparent that the C-7 substituent influences the electron density at C-2, as shown in both the NMR conformational study and the pK_a studies. Since the biological activity of anti-allergic chromones is apparently influenced by both conformation and acidity, such activity may, in turn, be related to the electron density at C-2. An involvement of ring-opening of the pyran ring in chromone pharmacology at a molecular level has been proposed. The ease of ring-opening of the chromone system may be an additional factor influencing biological activity. Future research will be concerned with verifying these proposals and is expected to involve the following.

(i) Further NMR and IR analysis of the ring-opening of DSCG with various nitrogen nucleophiles.

(ii) An extension of such analyses to include the interaction of DSCG and its analogues with proteinaceous material and mast cell extracts.

(iii) The preparation of novel DSCG analogues with enhanced ring-opening capabilities (*e.g.* a 7,7′-dinitro DSCG analogue) and the determination of their biological activities.

3. EXPERIMENTAL

3.1 GENERAL.

Melting points were determined on a Kofler hot-stage apparatus or an automatic Mettler FP1 melting point apparatus (m.p. > 230°C), and are uncorrected. NMR spectra were recorded on Bruker AM 300, AMX 400, and WM 500 MHz, or Varian Gemini 200 MHz NMR spectrometers, from $CDCl_3$ or DMSO-d_6 solutions generally using TMS as internal standard. (In the absence of TMS, the chloroform peak was used as internal standard). The spectra of disodium salts were obtained from D_2O solutions with 3-(trimethylsilyl)-propionic acid-d_6 sodium salt as internal standard for the ^1H spectra, and acetone as internal standard for the ^{13}C spectra. The ^{13}C spectra were interpreted using either off resonance decoupled (ORD) spectra or DEPT spectra, which were obtained at the frequencies used to obtain the corresponding ^{13}C spectra. Routine ^1H NMR spectra were recorded on a Perkin-Elmer R12 60 MHz NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 180 spectrophotometer using KBr discs, liquid films, or $CHCl_3$ solutions. UV spectra were recorded on a Beckmann UV 5240 spectrophotometer from dry ethanol solutions. Quartz cuvettes with a 10 mm pathlength were used. Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectra were recorded on a Varian Mat 212 spectrometer.

The common nomenclature, *viz.* chromone, for the chromone structure is chosen, in preference to the 4-oxo-4*H*-chromene nomenclature, for simplicity. The ring-opened products (**140-151** and **153**) are all referred to as 2-amino-3-(2-hydroxybenzoyl)-*N*,*N*-dialkylacrylamides for continuity. The reported nomenclature[40] of the 2-hydroxypropane

derivatives (155-156 and 158) was generally used. The atom numbering used to quote NMR signals for the different compounds generally agrees with the nomenclature. Standard atom numbering was used for the chromone structure. The benzoyl atoms of the acrylamides (140-151 and 153) are denoted by the "dashed" notation (*e.g.* 5'-H). The bridging group atoms of the 2-hydroxypropane compounds (155-159) are referred to as CHOH or OCH_2, with the appropriate atoms in italics. In bis(*o*-hydroxyacetophenone) (155) and the 1-(chromonyloxy)-3-(phenoxy)-propane compound (157), the phenoxy atoms are also represented by the "dashed" notation, thereby differentiating them from the bridge atoms and chromonyloxy atoms in the latter compound. The "aromatic" nuclei in the ring-opened compound (159) are denoted by the "dashed" notation, thereby differentiating them from the acrylic acid atoms.

Flash chromatography[141] was performed on Merck Silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)]. Preparative layer chromatography was achieved on Merck Silica gel 60 PF_{254} plates. Thin layer chromatography was performed on Merck Silica gel 60 F_{254} precoated plates. TLC plates were analysed by inspection under UV, using iodine, or using ninhydrin spray reagent.

Solvents were dried using the following prodedures[142] :

(i) Benzene and ether were dried over sodium wire and then distilled under N_2 over sodium wire using benzophenone as an indicator.

(ii) 1,2-Dichloroethane was distilled over P_2O_5.

(iii) Dimethylformamide and acetone were dried over 4A molecular sieves.

(iv) 1,2-Dioxan was dried over $CaCl_2$ and 4A molecular sieves, and then filtered through a column of basic alumina.

(v) Ethanol was distilled under N_2 over magnesium ethoxide.

(vi) Nitrobenzene was distilled under vacuum over P_2O_5.

(vii) Pyridine was dried over KOH overnight and distilled over fresh KOH.

All dry solvents were stored over 4A molecular sieves. The exact concentration of ethanolic/aqueous dimethylamine and ethanolic methylamine solutions was determined by titration with 0.1M-HCl. The purity of the ethanolic amine solutions was determined by GLC analysis on a Hewlett Packard 5980A gas chromatograph, using flame ionisation detection with N_2 carrier gas and H_2/synthetic air feeder gases. The GLC trace of ethanolic dimethylamine (25% w/w) showed an extraneous peak with a retention time equivalent to that of ethanolic methylamine. HCl gas was generated from HCl-H_2SO_4 using a standard literature procedure.[143]

Computer modelling of structures was achieved using the Tripos Associates software package, ALCHEMY II, and a CW 16 AT microcomputer and Hewlett Packard colour Pro plotter.

3.2 PREPARATION OF CHROMONE DERIVATIVES.

3-Nitrophenyl acetate (88).[103] - Ac_2O (10.9 ml, 0.118 mol) was added dropwise to a stirred solution of 3-nitrophenol (10.0 g, 72 mmol) and NaOH (4.6 g, 0.115 mol) in H_2O (*ca.* 100 ml) at 0°C, and the resulting mixture was stirred for 1 h. The mixture was extracted with EtOAc (3 x 50 ml) and the combined extracts were sequentially washed with 5% aq. $NaHCO_3$ (2 x 50 ml) and H_2O (1 x 50 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford crude 3-nitrophenyl acetate (88) (12.9 g, 99%), m.p. 53-54°C (lit.,[144] 55-56°C); δ_H (60 MHz; $CDCl_3$) 2.40 (3H, s, Me) and 7.40 - 8.30 (4H, m, ArH); ν_{max} (KBr)/cm^{-1} 1755 (CO).

3-Fluorophenyl acetate (89).[103] - Ac_2O (7.4 ml, 78 mmol) was added dropwise to a stirred solution of 3-fluorophenol (5.0 g, 55 mmol) and NaOH (3.1 g, 79 mmol) in H_2O (*ca.* 50 ml) at 0°C, and the resulting mixture was stirred for 1 h. The mixture was extracted with EtOAc (3 x 25 ml) and the combined extracts were sequentially washed with 5% aq. $NaHCO_3$ (2 x 25 ml) and saturated NaCl (1 x 50 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated to afford an oil which was distilled to give 3-fluorophenyl acetate (89) (7.4 g, 87%), b.p. 183°C/760 mmHg (lit.,[145] 77°C/16 mmHg); δ_H (60 MHz; $CDCl_3$) 2.20 (3H, s, Me) and 6.80 - 7.60 (4H, m, ArH); ν_{max} (KBr)/cm^{-1} 1760 (CO).

3-Chlorophenyl acetate (90).[103] - The experimental procedure employed for the synthesis of 3-fluorophenyl acetate (89) was followed, using Ac_2O (10.4 ml, 0.110 mol), 3-chlorophenol (10.0 g, 78 mmol), and NaOH (4.4 g, 0.110 mol) in H_2O (*ca.* 75 ml). Work-up afforded an oil which was distilled to give 3-chlorophenyl acetate (90) (11.8 g, 89%), b.p. 49°C/0.01 mmHg (lit.,[103] 105-107°C/13 mmHg); δ_H (60 MHz; $CDCl_3$) 2.20

(3H, s, Me) and 6.80 - 7.40 (4H, m, ArH); ν_{max} (KBr) /cm^{-1} 1760 (CO).

3-Bromophenyl acetate (**91**).[103] - The experimental procedure employed for the synthesis of 3-fluorophenyl acetate (**89**) was followed, using Ac_2O (8.7 ml, 93 mmol), 3-bromophenol (10.0 g, 58 mmol), and NaOH (3.7 g, 93 mmol) in H_2O (*ca.* 70 ml). Work-up afforded an oil which was distilled to give 3-bromophenyl acetate (**91**) (10.8 g, 88%), b.p. 81°C/1.5 mmHg (lit.,[146] 149°C/40 mmHg); δ_H (60 MHz; $CDCl_3$) 2.30 (3H, s, Me) and 6.90 - 7.60 (4H, m, ArH); ν_{max} (KBr) /cm^{-1} 1760 (CO).

4-Chlorophenyl acetate (**92**). - The experimental procedure employed for the synthesis of 3-fluorophenyl acetate (**89**) was followed, using Ac_2O (10.4 ml, 0.110 mol), 4-chlorophenol (10.0 g, 78 mmol), and NaOH (4.4 g, 0.110 mol) in H_2O (*ca.* 75 ml). Work-up afforded an oil which was distilled to give 4-chlorophenyl acetate (**92**) (12.3 g, 93%), b.p. 69°C/0.3 mmHg (lit.,[147] 109°C/13 mmHg); δ_H (60 MHz; $CDCl_3$) 2.25 (3H, s, Me) and 6.90 - 7.60 (4H, m, ArH); ν_{max} (liquid film) /cm^{-1} 1755 (CO).

2-Hydroxy-4-methoxyacetophenone (**93**).[100] - A mixture of resacetophenone (10.0 g, 66 mmol), dry acetone (100 ml), and Me_2SO_4 (4.8 ml, 50 mmol) was boiled under reflux over K_2CO_3 (10.2 g, 74 mmol) for 6 h. The colour of the reaction mixture changed from a dark red to orange after *ca.* 1 h. The resulting solution was cooled and the acetone removed under reduced pressure. The excess Me_2SO_4 was destroyed with a 25% ammonia-ice mixture (50 ml). The solution was then extracted with EtOAc (3 x 60 ml) and the combined organic solutions dried (anhyd. $MgSO_4$), evaporated, and distilled to afford 2-hydroxy-4-methoxyacetophenone (**93**) (9.5 g, 87%), b.p. 293°C/760 mmHg (lit.,[100] m.p. 48°C); δ_H (60 MHz; $CDCl_3$) 2.50 (3H, s, COMe), 3.80 (3H, s, OMe), 6.35 - 6.55 (2H, m , 3-H

and 5-H), 7.65 (1H, d, *J* 9 Hz, 6-H) and 12.80 (1H, br s, OH); ν_{max} (KBr) /cm^{-1} 3400 - 2500 (OH) and 1625 (CO).

2-Hydroxy-4-nitroacetophenone (**94**).[104] - A mixture of 3-nitrophenyl acetate (**88**) (20.0 g, 0.110 mol), $AlCl_3$ (28.0 g, 0.210 mol), and dry, distilled nitrobenzene (100 ml) was heated at 140°C for 8 h. After cooling overnight, a mixture of ice (80 g) and conc. HCl (32 ml) was added and the resulting mixture was steam distilled.[a] The distillate was extracted with EtOAc and the combined organic solutions were extracted with 0.5M-NaOH. The combined aqueous solutions were acidified and extracted with EtOAc (3 x 80 ml). The combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford an oil which was distilled to give 2-hydroxy-4-nitroacetophenone (**94**) (7.6 g, 38%), m.p. 60-61°C (from hexane) (lit.,[148] 67-68°C); δ_H (60 MHz; $CDCl_3$) 2.75 (3H, s, COMe), 7.60 - 8.20 (3H, m, ArH) and 12.40 (1H, br s, OH); ν_{max} (KBr) /cm^{-1} 3600 - 3300 (OH) and 1655 (CO).

4-Fluoro-2-hydroxyacetophenone (**95**).[101] - A mixture of 3-fluorophenyl acetate (**89**) (6.2 g, 40 mmol) and $AlCl_3$ (12.8 g, 96 mmol) was heated in an oil bath at 175-180°C for 1.5 h. The cooled mixture was treated with dil. HCl (*ca.* 110 ml) and then steam distilled. The distillate was extracted with $CHCl_3$ (3 x 56 ml) and the combined extracts re-extracted with 0.5M-KOH (3 x 50 ml). The combined aqueous alkali solutions were washed with $CHCl_3$ (2 x 56 ml), acidified, and extracted with $CHCl_3$ (3 x 56 ml). The $CHCl_3$ solutions were then combined, dried (anhyd. $MgSO_4$), and evaporated to afford an oil which crystallised to give crude 4-fluoro-2-hydroxyacetophenone (**95**) (4.9 g, 80%), m.p. 31-33°C

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[a] The bulk of the nitrobenzene was contained in the first two 400 ml fractions.

(from hexane) (lit.,[149] 24°C); δ_H (500 MHz; $CDCl_3$) 2.55 (3H, s, COMe), 6.54 - 6.60 (2H, m, 3-H and 5-H), 7.71 (1H, dd, *J* 9 and 6 Hz, 6-H) and 12.53 (1H, s, OH); ν_{max} (KBr) /cm^{-1} 3500 - 2600 (OH) and 1645 (CO).

4-Chloro-2-hydroxyacetophenone (**96**).[101] - The experimental procedure employed for the synthesis of 4-fluoro-2-hydroxyacetophenone (**95**) was followed, using 3-chlorophenyl acetate (**90**) (9.0 g, 53 mmol) and $AlCl_3$ (16.8 g, 0.126 mol). Work-up afforded an oil which was distilled to give 4-chloro-2-hydroxyacetophenone (**96**) (5.4 g, 60%), b.p. 77°C/1 mmHg (lit.,[101] 121-124°C/15 mmHg); δ_H (60 MHz; $CDCl_3$) 2.60 (3H, s, COMe), 6.80 - 7.15 (2H, m, 3-H and 5-H), 7.70 (1H, d, *J* 8 Hz, 6-H) and 12.45 (1H, br s, OH); ν_{max} (KBr) /cm^{-1} 3500 - 2500 (OH) and 1645 (CO).

4-Bromo-2-hydroxyacetophenone (**97**).[101] - The experimental procedure employed for the synthesis of 4-fluoro-2-hydroxyacetophenone (**95**) was followed, using 3-bromophenyl acetate (**91**) (10.0 g, 47 mmol) and $AlCl_3$ (20.3 g, 0.152 mol). In this case the reaction mixture was heated for 3 h. Work-up afforded an oil which was distilled to give 4-bromo-2-hydroxyacetophenone (**97**) (5.6g, 56%), m.p. 39-41°C (lit.,[101] 42-43°C); δ_H (60 MHz; $CDCl_3$) 2.60 (3H, s, COMe), 6.95 - 7.30 (2H, m, 3-H and 5-H), 7.65 (1H, d, *J* 8 Hz, 6-H) and 12.40 (1H, s, OH); ν_{max} (nujol mull) /cm^{-1} 3500 - 2500 (OH) and 1640 (CO).

5-Chloro-2-hydroxyacetophenone (**98**). - The experimental procedure employed for the synthesis of 4-fluoro-2-hydroxyacetophenone (**95**) was followed, using 4-chlorophenyl acetate (**92**) (11.0 g, 65 mmol) and $AlCl_3$ (20.5 g, 0.154 mol). Work-up afforded an oil which crystallised to afford 5-chloro-2-hydroxyacetophenone (**98**) (6.5 g, 59%), m.p. 51-53°C (lit.,[150] 52.5°C); δ_H (60 MHz; $CDCl_3$) 2.60 (3H, s, COMe), 6.80 - 7.80 (3H, m, ArH) and 12.20 (1H, s, OH); ν_{max} (KBr) /cm^{-1} 3600 - 2500 (OH) and

1650 (CO).

Ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**99**).[105] - Diethyl oxalate (12.0 ml, 88 mmol) and *o*-hydroxyacetophenone (7.2 ml, 60 mmol) were added dropwise to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (4.1 g, 0.180 mol) to dry EtOH (120 ml)]. The stirred, yellow mixture was gently boiled under reflux for 0.5 h becoming a thick, yellow slurry. After cooling, the mixture was poured into Et_2O (450 ml) and allowed to stand for 0.5 h. The resulting yellow, sodium salt of (3a) was then filtered off, washed (Et_2O), and added to 2M-HCl (150 ml). The resulting semi-solid was extracted with Et_2O (3 x 100 ml) and the combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford the diketone, ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**99**) which was shown, by ^1H NMR spectroscopy, to be partially enolised and was used without further purification. δ_H (60 MHz; DMSO-d_6) 1.45 (3H, t, Me), 4.50 (2H, q, CH_2Me), 6.50 (1H, br s, OH), 7.10 (2H, s, $COCH_2$) and 7.35 - 8.35 (4H, m, ArH).

Ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (**100**) and *ethyl 2-hydroxy-7-methoxychromanone-2-carboxylate* (**105**). - The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxy-chromanone-2-carboxylate (**108**) and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**) (p.137) was followed, using 2-hydroxy-4-methoxyacetophenone (**93**) (8.0 g, 48 mmol), diethyl oxalate (9.7 ml, 72 mmol), Na metal (1.7 g, 72 mmol), and dry EtOH (80 ml). In this case the reaction time was 70 min. Work-up afforded crude ethyl 4-(2-hydroxy-4-methoxyphenyl)-2,4-dioxobutanoate (**100**) (8.7 g, 68%) [δ_H (60 MHz; $CDCl_3$) 1.40 (3H, t, Me), 3.90 (3H, s, OMe), 4.40 (2H, q, CH_2Me), 6.50 (1H, br s, OH), 7.10 (2H, s, $COCH_2$) and 7.30 - 8.35 (3H, m, ArH)], which was used without further purification. During the

extraction (Et_2O, 3 x 67 ml), an insoluble interface was filtered off, dried under vacuum, acidified with 2M-HCl (50 ml), and extracted with EtOAc (3 x 67 ml). The combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford crude ethyl 2-hydroxy-7-methoxychromanone-2-carboxylate (**105**) (1.6 g, 12%); δ_H (60 MHz; $CDCl_3$/DMSO-d_6) 1.30 (3H, t, Me), 2.85 and 3.25 (2H, dd, *J* 17 Hz, $COCH_2$), 3.80 (3H, s, OMe), 4.35 (2H, q, CH_2Me), 6.40 - 7.35 (3H, m, 6-H, 8-H and OH) and 7.90 (1H, d, *J* 8 Hz, 5-H).

Ethyl 4-(2-hydroxy-4-nitrophenyl)-2,4-dioxobutanoate (**101**) and *ethyl 2-hydroxy-7-nitrochromanone-2-carboxylate* (**106**).[105,106] - A solution of 2-hydroxy-4-nitroacetophenone (**94**) (6.0 g, 33 mmol) and diethyl oxalate (50.7 ml, 0.373 mol) was added dropwise to a stirred, ethanolic solution of NaOEt [generated *in situ* by adding Na metal (2.4 g, 0.105 mol) to dry EtOH (75 ml)]. The stirred, red solution was gently boiled under reflux for 45 min. becoming a red slurry. After cooling, the mixture was poured into Et_2O (450 ml) and allowed to stand for 0.5 h. The red solid was filtered off, washed (Et_2O), and added to 2M-HCl (300 ml). The mixture was extracted with EtOAc (4 x 200 ml) and the combined organic solutions dried (anhyd. $MgSO_4$) and evaporated to afford a red solid shown, by ^1H NMR spectroscopy, to comprise a mixture of ethyl 4-(2-hydroxy-4-nitrophenyl)-2,4-dioxobutanoate (**101**) (78%) [δ_H (60 MHz; DMSO-d_6/$CDCl_3$) 1.35 (3H, t, Me), 4.35 (2H, m, CH_2Me), 7.20 (2H, s, $COCH_2$), 7.60 - 8.60 (3H, m, ArH) and 9.15 (1H, br s, OH)] and ethyl 2-hydroxy-7-nitrochromanone-2-carboxylate (**106**) (22%) [δ_H (60 MHz; DMSO-d_6/$CDCl_3$) 1.35 (3H, t, Me), 3.00 and 3.40 (2H, dd, *J* 17 Hz, $COCH_2$) 4.50 (2H, m, CH_2Me), 7.60 - 8.60 (3H, m, ArH) and 9.15 (1H, br s, OH)], which was used without further purification.

Ethyl 4-(4-fluoro-2-hydroxyphenyl)-2,4-dioxobutanoate (**102**) and *ethyl 7-fluoro-2-hydroxychromanone-2-carboxylate* (**107**). - The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**) was followed, using 4-fluoro-2-hydroxyacetophenone (**95**) (2.0 g, 13 mmol), diethyl oxalate (9.8 ml, 72 mmol), Na metal (1.2 g, 52 mmol), and dry EtOH (30 ml). Work-up afforded a solid shown, by ^{1}H NMR spectroscopy, to comprise a mixture of *ethyl 4-(4-fluoro-2-hydroxyphenyl)-2,4-dioxobutanoate* (**102**) (62%) [δ_H (60 MHz; $CDCl_3$) 1.00 - 1.65 (3H, m, Me), 4.15 - 4.75 (2H, m, C*H*$_2$Me), 6.35 (1H, br s, OH), 7.10 (2H, s, $COCH_2$), 7.25 - 7.60 (2H, m, 6-H and 8-H) and 8.30 (1H, dd, *J* 8 and 7 Hz, 5-H)] and *ethyl 7-fluoro-2-hydroxychromanone-2-carboxylate* (**107**) (38%) [δ_H (60 MHz; $CDCl_3$) 1.00 - 1.65 (3H, m, Me), 3.50 and 3.75 (2H, dd, *J* 7 Hz, CH_2CO), 4.15 - 4.75 (2H, m, C*H*$_2$Me), 6.35 (1H, br s, OH), 7.25 - 7.60 (2H, m, 6-H and 8-H) and 8.30 (1H, dd, *J* 8 and 7 Hz, 5-H)], which was used without further purification.

Ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) and *ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate* (**103**).[103] - A warm solution of 4-chloro-2-hydroxyacetophenone (**96**) (4.5 g, 26 mmol) and diethyl oxalate (19.9 ml, 0.147 mol) was added dropwise to a stirred ethanolic solution of NaOEt [generated *in situ* by adding Na metal (2.4 g, 0.105 mol) to dry EtOH (44 ml)]. The stirred, yellow mixture was gently boiled under reflux for 40 min. becoming a thick, yellow slurry. After cooling, the mixture was poured into Et_2O (108 ml) and allowed to stand for 0.5 h. The resulting yellow solid was filtered off, washed (Et_2O), and added to 2M-HCl (145 ml). The resulting semi-solid was extracted with Et_2O (3 x 50 ml) and the combined organic solutions were dried (anhyd. $MgSO_4$) and evaporated to afford a solid shown, by ^{1}H NMR

spectroscopy, to comprise a mixture of ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) (63%) [δ_H (60 MHz; $CDCl_3$/DMSO-d_6) 1.30 (3H, t, Me), 2.90 and 3.30 (2H, dd, *J* 16 Hz, $COCH_2$), 4.35 (2H, q, CH_2Me), 6.85 (1H, br s, OH), 7.00 - 7.25 (2H, m, 6-H and 8-H) and 7.85 (1H, d, *J* 9 Hz, 5-H)] and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**) (37%) [δ_H (60 MHz; $CDCl_3$/DMSO-d_6) 1.40 (3H, t, Me), 4.35 (2H, q, CH_2Me), 6.85 (1H, br s, OH), 7.00 - 7.25 (4H, m, $COCH_2$, 6-H and 8-H) and 7.85 (1H, d, *J* 9 Hz, 5-H)], which was used without further purification.

Ethyl 7-bromo-2-hydroxychromanone-2-carboxylate (**109**) and *ethyl 4-(4-bromo-2-hydroxyphenyl)-2,4-dioxobutanoate* (**104**). - The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**) was followed, using 4-bromo-2-hydroxyacetophenone (**97**) (4.5 g, 21 mmol), diethyl oxalate (15.8 ml, 0.116 mol), Na metal (2.3 g, 0.101 mol), and dry EtOH (71 ml). In this case EtOAc was used for the extraction. Work-up afforded a solid shown, by ^{1}H NMR spectroscopy, to comprise a mixture of ethyl 7-bromo-2-hydroxychromanone-2-carboxylate (**109**) (55%) [δ_H (60 MHz; $CDCl_3$/DMSO-d_6) 1.35 (3H, t, Me), 2.90 and 3.30 (2H, dd, *J* 17 Hz, $COCH_2$), 4.35 (2H, q, CH_2Me) and 7.00 - 8.25 (4H, m, ArH and OH)] and ethyl 4-(4-bromo-2-hydroxyphenyl)-2,4-dioxobutanoate (**104**) (45%) [δ_H (60 MHz; $CDCl_3$/DMSO-d_6) 1.35 (3H, t, Me), 4.35 (2H, q, CH_2Me) and 7.00 - 8.25 (6H, m, $COCH_2$, ArH and OH)], which was used without further purification.

Ethyl chromone-2-carboxylate (**110**).[105,106] - A mixture of crude ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**99**), AcOH (60 ml), and conc. HCl (1 ml) was boiled under reflux for 40 min. After cooling, a mixture of ice and water (200 ml) was added and the resulting precipitate was

filtered and dissolved in EtOAc (100 ml). The solution was then washed with 5% aq. $NaHCO_3$ (3 x 50 ml), dried (anhyd. $MgSO_4$), and evaporated to afford crude ethyl chromone-2-carboxylate (**110**) (17.9 g, 69%),[a] m.p 72°C (from EtOH) (lit.,[19] 71-72°C); δ_H (60 MHz; $CDCl_3$) 1.45 (3H, t, Me), 4.50 (2H, q, CH_2Me), 7.15 (1H, s, CH=C), 7.30 - 8.00 (3H, m, 6-H, 7-H and 8-H) and 8.25 (1H, d, *J* 8 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 1740 (CO.O) and 1650 (CO).

Ethyl 7-nitrochromone-2-carboxylate (**111**).[105,106] - A mixture (4:1) of crude ethyl 4-(2-hydroxy-4-nitrophenyl)-2,4-dioxobutanoate (**101**) and ethyl 2-hydroxy-7-nitrochromanone-2-carboxylate (**106**), AcOH (75 ml), and conc. HCl (trace, 5 drops) was boiled under reflux for 45 min. After cooling, a mixture of ice and water (150 ml) was added and the resulting precipitate was filtered and dissolved in EtOAc (500 ml). The solution was then washed with 5% aq. $NaHCO_3$ (4 x 80 ml), dried (anhyd. $MgSO_4$), and evaporated to afford crude ethyl 7-nitrochromone-2-carboxylate (**111**) (5.1 g, 58%),[b] m.p. 138°C (from EtOH) (lit.,[151] 135-137°C); δ_H (60 MHz; $CDCl_3$) 1.50 (3H, t, Me), 4.55 (2H, q, CH_2Me), 7.25 (1H, s, CH=C) and 8.20 - 8.75 (3H, m, ArH); ν_{max} (KBr) /cm^{-1} 1745 (CO.O) and 1660 (CO).

Chromone-2-carboxylic acid (**112**).[105] -

Method 1. A mixture of ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (**99**), AcOH (30 ml), and conc. HCl (30 ml) was boiled under reflux for 1 h. After cooling, the precipitated solid was filtered and recrystallized from AcOH to afford chromone-2-carboxylic acid (**112**)

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[a] Yield calculated on the basis of 2-hydroxyacetophenone.

[b] Yield calculated on the basis of 2-hydroxy-4-nitroacetophenone (**94**).

(9.6 g, 84%),[a] m.p. 251°C (decomp.) (lit.,[105] 250-251°C); δ_H (60 MHz; DMSO-d_6) 7.00 (1H, s, CH=C), 7.35 - 8.25 (4H, m, ArH) and 8.90 (1H, br s, CO_2H); ν_{max} (KBr) /cm^{-1} 3300 - 2100 (CO_2H), 1740 (CO_2H) and 1630 (CO).

Method 2.[107] A mixture of ethyl chromone-2-carboxylate (**110**), AcOH (65 ml), 8M-H_2SO_4 (28 ml), and conc. HCl (15 ml) was boiled under reflux for 14 h. After cooling, H_2O (110 ml) was added and the mixture was left to stand for 1 h. The precipitated solid was filtered off and recrystallised from AcOH to afford chromone-2-carboxylic acid (**112**) (9.9 g, 88%).[a]

7-Methoxychromone-2-carboxylic acid (**113**). - The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**116**) (p. 142) was followed, using crude ethyl 4-(4-methoxy-2-hydroxyphenyl)-2,4-dioxobutanoate (**100**) (8.7 g, 33 mmol), AcOH (64 ml), and conc. HCl (32 ml). In this case the reaction time was 1.5 h. Work-up afforded crude 7-methoxychromone-2-carboxylic acid (**113**) (6.6 g, 91%),[b] m.p. 266°C (decomp.) (from EtOH) [lit.,[152] 270°C (decomp.)]; δ_H (60 MHz; DMSO-d_6) 3.95 (3H, s, OMe), 6.90 (1H, s, CH=C), 7.00 - 7.30 (3H, m, 6-H , 8-H and OH) and 8.00 (1H, d, *J* 8Hz, 5-H); ν_{max} (KBr) /cm^{-1} 3200 - 2100 (OH), 1735 (CO_2H) and 1625 (CO).

7-Nitrochromone-2-carboxylic acid (**114**). -

Method 1.[107] A mixture of ethyl 7-nitrochromone-2-carboxylate (**111**) (0.9 g, 4 mmol), AcOH (4.0 ml), and 8M-H_2SO_4 (1.8 ml) was boiled under

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[a] Yield calculated on the basis of 2-hydroxyacetophenone.

[b] Yield calculated on the basis of 2-hydroxy-4-methoxyacetophenone (**93**).

reflux for 12 h. After cooling, H_2O (7 ml) was added and the resulting precipitate was filtered, dissolved in EtOAc (40 ml), and the solution was extracted with 5% aq. $NaHCO_3$ (3 x 50 ml). The combined aqueous solutions were acidified and extracted with EtOAc (3 x 40 ml). The organic solutions were combined, dried (anhyd. $MgSO_4$), and evaporated to afford crude 7-nitrochromone-2-carboxylic acid (**114**) (0.5 g, 65%),[a] m.p. 215°C[b] (from EtOH); δ_H (60 MHz; CD_3OD) 7.20 (1H, s, CH=C) and 8.30 - 8.70 (3H, m, ArH); ν_{max} (KBr) /cm^{-1} 3300 - 2100 (CO_2H), 1730 (CO_2H) and 1640 (CO).

Method 2.[106] A solution of ethyl 7-nitrochromone-2-carboxylate (**111**) (3.0 g, 11 mmol) and 45% HBr in AcOH (7.7 ml, 43 mmol) was boiled under reflux for 1.5 h. After cooling, H_2O (31 ml) was added and the resulting precipitate was filtered and shown, by ^1H NMR spectroscopy, to comprise a mixture of ethyl 7-nitrochromone-2-carboxylate (**111**) (72%) and 7-nitrochromone-2-carboxylic acid (**114**) (27%). The solid was dissolved in EtOAc (50 ml) and extracted with 5% aq. $NaHCO_3$ (2 x 50 ml). The combined aqueous alkali solutions were then acidified and extracted with EtOAc (3 x 50 ml). The organic solutions were combined, dried (anhyd. $MgSO_4$), and evaporated, and the residue was recrystallised from EtOH to afford 7-nitrochromone-2-carboxylic acid (**114**) (0.9 g, 33%).

7-Fluorochromone-2-carboxylic acid (**115**). - The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**116**) (p.142) was followed, using a mixture (3:2) of crude ethyl 4-(4-fluoro-2-hydroxyphenyl)-2,4-dioxobutanoate (**102**) and ethyl 7-fluoro-2-

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[a] Yield calculated on the basis of 2-hydroxy-4-nitroacetophenone (**94**).

[b] No melting point is given in the abstract[106] describing the second procedure for the synthesis of 7-nitrochromone-2-carboxylic acid (**114**).

hydroxychromanone-2-carboxylate (**107**), AcOH (10.8 ml), and conc. HCl (5.5 ml). Work-up afforded crude *7-fluorochromone-2-carboxylic acid* (**115**) (2.2 g, 81%),[a] m.p. 230°C (from EtOH); (Found : C, 57.4; H, 2.5. $C_{10}H_5FO_4$ requires : C, 57.7; H, 2.4%); δ_H (500 MHz; DMSO-d_6) 6.84 (1H, s, CH=C), 7.32 - 7.36 (1H, m, 6-H), 7.60 (1H, dd, J_m 2 Hz and $^3J_{HF}$ 10 Hz, 8-H), 8.03 (1H, dd, J_o 9 Hz and $^4J_{HF}$ 6 Hz, 5-H) and 8.9 (60 MHz; 1H, br s, CO_2H); δ_C (75 MHz; DMSO-d_6) 105.60 (d, $^2J_{CF}$ 26 Hz, C-8), 113. 67 (C-3), 114.69 (d, $^2J_{CF}$ 23 Hz, C-6), 120.92 (C-4a), 127.82 (d, $^3J_{CF}$ 11 Hz, C-5), 153.56 (C-2), 156.56 (d, $^3J_{CF}$ 14 Hz, C-8a), 161.16 (CO_2H), 165.49 (d, $^1J_{CF}$ 253 Hz, C-7) and 176.66 (C-4); ν_{max} (KBr) /cm^{-1} 3300 - 2700 (CO_2H), 1740 (CO_2) and 1630 (CO); *m/z* 208 (M^+, 100%).

7-Chlorochromone-2-carboxylic acid (**116**).[103] - A mixture (9:5) of crude ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**), AcOH (22 ml), and conc. HCl (11 ml) was boiled under reflux for 1.5 h. After cooling, H_2O (36 ml) was added and the resulting precipitated solid was filtered and recrystallised from EtOH to afford 7-chlorochromone-2-carboxylic acid (**116**) (3.5 g, 59%),[b] m.p. 236°C (decomp.) (lit.,[103] 248-250°C); δ_H (60 MHz; DMSO-d_6) 6.75 (1H, br s, CO_2H), 7.00 (1H, s, CH=C), 7.60 (1H, dd, *J* 8 and 2 Hz, 6-H), 7.90 (1H, d, *J* 2 Hz, 8-H) and 8.10 (1H, d, *J* 8 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 3200 - 2300 (CO_2H), 1710 (CO_2H) and 1650 (CO). The crude product was sublimed to yield ethyl 7-chlorochromone-2-carboxylate m.p. 106-108°C (lit.,[51] 108-109°C); δ_H (500 MHz; DMSO-d_6) 1.42 (3H, t, Me), 4.45 (2H, q, C*H*$_2$Me), 7.09 (1H, s, CH=C), 7.40 (1H, d, *J* 2 and 9 Hz, 6-H), 7.63 (1H, d, *J* 2 Hz, 8-H) and 8.12 (1H, d, *J* 9 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 1740 (CO_2H) and 1655 (CO);

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[a] Yield calculated on the basis of 4-fluoro-2-hydroxyacetophenone (**95**).

[b] Yield calculated on the basis of 4-chloro-2-hydroxyacetophenone (**96**).

m/z 252 (^{35}Cl, M^+, 100%).

7-Bromochromone-2-carboxylic acid (**117**).[51] - The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**116**) was followed, using a mixture (11:9) of crude ethyl 7-bromo-2-hydroxychromanone-2-carboxylate (**109**), and ethyl 4-(4-bromo-2-hydroxyphenyl)-2,4-dioxobutanoate (**104**) AcOH (16.4 ml), and conc. HCl (8.7 ml). Work-up afforded crude 7-bromochromone-2-carboxylic acid (**117**) (2.2 g, 81%),[a] m.p. 247°C (decomp.) (from EtOH) (lit.,[51] 252-253°C); δ_H (60 MHz; DMSO-d_6), 7.00 (1H, s, CH=C), 7.60 - 8.20 (3H, m, ArH) and 9.05 (1H, br s, CO_2H); ν_{max} (KBr) /cm^{-1} 3200 - 2100 (CO_2H), 1720 (CO_2H) and 1630 (CO).

6-Chlorochromone-2-carboxylic acid (**118**). - The experimental procedure employed for the synthesis of ethyl 7-chloro-2-hydroxychromanone-2-carboxylate (**108**) and ethyl 4-(4-chloro-2-hydroxyphenyl)-2,4-dioxobutanoate (**103**) was followed, using 5-chloro-2-hydroxyacetophenone (**98**) (4.5 g, 26 mmol), diethyl oxalate (19.9 ml, 0.147 mol), Na metal (2.4 g, 0.105 mol), and dry EtOH (44 ml). Work-up afforded a solid which was used without further purification. The experimental procedure employed for the synthesis of 7-chlorochromone-2-carboxylic acid (**116**) was then followed using the crude solid, AcOH (22 ml), and conc. HCl (11 ml). Work-up afforded a solid which was recrystallised from EtOH to afford 6-chlorochromone-2-carboxylic acid (**118**) (3.0 g, 51%),[b] m.p. 253°C (decomp.) (from EtOH) (lit.,[150,153] 275°C, 267-269°C and 262°C); δ_H (60 MHz; DMSO-d_6) 5.65 (1H, br s, CO_2H), 7.00 (1H, s, CH=C), 7.75 - 7.95 (2H, m, 7-H and 8-H) and 8.05 (1H, d, *J* 1 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 3300

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[a] Yield calculated on the basis of 4-bromo-2-hydroxyacetophenone (**97**).

[b] Yield calculated on the basis of 5-chloro-2-hydroxyacetophenone (**98**).

- 2000 (CO_2H), 1735 (CO_2H) and 1630 (CO).

Ethyl 3-methylchromone-2-carboxylate (**119**).[107] - A mixture of *o*-hydroxypropiophenone (10.0 g, 67 mmol) and diethyl oxalate (27.1 ml, 0.200 mol) was cooled in an ice-bath. NaH (50% dispersion in oil; 9.6 g, 0.200 mol) was then added portionwise to the vigorously stirred mixture. The ice-bath was removed occasionally to allow the reaction to proceed and dry Et_2O (100 ml) was then added to disperse the NaH within the slurry. After the addition of the NaH, the mixture was stirred at *ca.* 0°C for 30 min. and at room temperature for 48 h. The solid material was filtered and added portionwise to a stirred mixture of AcOH (16 ml), H_2O (50 ml), and ice (40 g). After stirring for 2h, the mixture was extracted with Et_2O (3 x 50 ml). The combined ethereal extracts were washed with H_2O (2 x 50 ml), dried (anhyd. $MgSO_4$), and evaporated. The residue was then dissolved in AcOH (20 ml) and conc. HCl (2 ml), and the resulting mixture was boiled under reflux for 0.5 h. After cooling, H_2O (20 ml) was added and the mixture was cooled in an ice-bath. The resultant precipitate was filtered, dissolved in Et_2O (125 ml), and the solution was sequentially washed with 5% aq. $NaHCO_3$ (2 x 50 ml) and H_2O (50 ml), and dried (anhyd. $MgSO_4$). The solvent was evaporated to afford crude ethyl 3-methylchromone-2-carboxylate (**119**) (7.9 g, 51%). The oil present in the filtrate was similarly extracted to afford additional crude ethyl 3-methylchromone-2-carboxylate (**119**) (1.0 g, 7%, overall 59%), m.p. 91-92°C (from EtOH) (lit.,[107] 89-90°C); δ_H (60 MHz; $CDCl_3$) 1.45 (3H, t, $CH_2\mathit{Me}$), 2.35 (3H, s, CMe=C), 4.50 (2H, q, CH_2Me) and 7.30 - 8.40 (4H, m, ArH); ν_{max} (KBr) /cm^{-1} 1730 (CO.O) and 1645 (CO).

3-Methylchromone-2-carboxylic acid (**120**).[107] - A solution of ethyl 3-methylchromone-2-carboxylate (**119**) (6.5 g, 28 mmol), AcOH (26 ml), and

7M-H_2SO_4 (22 ml) was boiled under reflux for 12 h. After cooling, H_2O (52 ml) was added and the resultant solid was filtered, dried, and recrystallised from EtOH to afford 3-methylchromone-2-carboxylic acid (**120**) (2.7 g, 49%), m.p. 230°C (lit.,[107] 233-234°C); δ_H (60 MHz; DMSO-d_6/$CDCl_3$) 2.30 (3H, s, Me), 7.30 - 8.30 (4H, m, ArH) and 10.55 (1H, br s, CO_2H); ν_{max} (KBr) /cm^{-1} 3400 - 2300 (CO_2H), 1730 (CO_2H) and 1615 (CO).

Chromone-2-carbonyl chloride (**121**).[64] -

Method 1. $SOCl_2$ (0.88 ml, 12 mmol) was added to a suspension of chromone-2-carboxylic acid (**112**) (1.8 g, 9 mmol) in dry 1,2-dichloroethane (11 ml) and *N*,*N*-dimethylformamide (0.18 ml, 2.3 mmol). The mixture was boiled under reflux for 1 h, cooled, and then concentrated under reduced pressure. Additional 1,2-dichloroethane (12 ml) was added to the concentrate and the resulting solution was evaporated to afford crude yellow chromone-2-carbonyl chloride (**121**) [m.p 92-93°C (sublimed) (lit.,[154] 104-108°C); δ_H (60 MHz; $CDCl_3$) 7.30 (1H, s, CH=C) and 7.40 - 8.40 (4H, m, ArH); ν_{max} (KBr) /cm^{-1} 1730 (CO.Cl) and 1625 (CO)], which was used without further purification.

Attempted Preparation.[154] PCl_5 (6.0 g, 29 mmol) was added to a stirred slurry of chromone-2-carboxylic acid (**112**) (5.0 g, 26 mmol) in cyclohexane (70 ml), and the resulting mixture was boiled under reflux for 1h. The solution was maintained at *ca.* 1°C for 15 h and the solvent was then evaporated to afford a solid residue shown, by ^1H NMR spectroscopy, to be starting material.

7-Methoxychromone-2-carbonyl chloride (**122**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**121**) was followed, using 7-methoxychromone-2-carboxylic acid (**113**) (1.8 g, 8 mmol), dry 1,2-dichloroethane (12 ml), *N*,*N*-dimethylformamide (0.16 ml, 2.0 mmol), and $SOCl_2$ (0.77 ml, 10.6 mmol). In this case the reaction time was 2 h. Work-up afforded crude green crystalline 7-methoxychromone-2-carbonyl chloride (**122**) [δ_H (60 MHz; DMSO-d_6/$CDCl_3$) 3.95 (3H, s, OMe), 6.95 (1H, s, CH=C), 7.00 - 7.30 (2H, m, 6-H and 8-H) and 8.05 (1H, d, *J* 8 Hz, 5-H); ν_{max} (1,2-dichloroethane) /cm^{-1} 1740 (CO.Cl) and 1620 (CO)], which was used without further purification.

7-Nitrochromone-2-carbonyl chloride (**123**). - $SOCl_2$ (0.91 ml, 12.5 mmol) was added to a suspension of 7-nitrochromone-2-carboxylic acid (**114**) (2.3 g, 10 mmol) in dry dioxan (13 ml) and *N*,*N*-dimethylformamide (0.18 ml, 2.3 mmol). The mixture was boiled under reflux for 2 h, cooled, and then concentrated under reduced pressure. Additional dry dioxan (10 ml) was added to the concentrate and the resulting solution was evaporated and dried under vacuum for 1h at 50°C to afford a brown solid shown, by ^1H NMR spectroscopy, to comprise a mixture of *7-nitrochromone-2-carbonyl chloride* (**123**) (81%) [δ_H (60 MHz; $CDCl_3$) 7.40 (1H, s, CH=C) and 8.35 - 8.70 (3H, m, ArH)] and 7-nitrochromone-2-carboxylic acid (**6c**) (19%) [(60 MHz; $CDCl_3$) 7.40 (1H, s, CH=C), 8.35 - 8.70 (3H, m, ArH) and 11.65 (1H, br s, OH)], which was used without further purification.

7-Fluorochromone-2-carbonyl chloride (**124**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**121**) was followed, using 7-fluorochromone-2-carboxylic acid (**115**) (1.2 g, 6 mmol), dry 1,2-dichloroethane (7 ml), *N*,*N*-dimethylformamide (0.11 ml, 1.4 mmol), and $SOCl_2$ (0.55 ml, 7.6 mmol). In this case the reaction

time was 1.5 h. Work-up afforded crude brown crystalline *7-fluorochromone-2-carbonyl chloride* (**124**) [m.p 113-115°C (sublimed); δ_H (60 MHz; $CDCl_3$/1,2-dichloroethane) 7.25 - 7.40 (2H, m, 6-H and 8-H), 7.50 (1H, s, CH=C) and 8.15 - 8.50 (1H, m, 5-H); ν_{max} (KBr) /cm^{-1} 1765 (CO.Cl) and 1650 (CO)], which was used without further purification.

7-Chlorochromone-2-carbonyl chloride (**125**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**121**) was followed, using 7-chlorochromone-2-carboxylic acid (**116**) (1.8 g, 8 mmol), dry 1,2-dichloroethane (13 ml), *N,N*-dimethylformamide (0.15 ml, 2.0 mmol), and $SOCl_2$ (0.76 ml, 10.4 mmol). In this case the reaction time was 1.5 h. Work-up afforded crude brown crystalline *7-chlorochromone-2-carbonyl chloride* (**125**) [m.p 179-182°C (sublimed); δ_H (60 MHz; $CDCl_3$) 7.35 (1H, s, CH=C), 7.55 (1H, dd, *J* 2 and 9 Hz, 6-H), 7.70 (1H, d, *J* 2 Hz, 8-H) and 8.20 (1H, d, *J* 9 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 1760 (CO.Cl) and 1650 (CO)], which was used without further purification.

7-Bromochromone-2-carbonyl chloride (**126**). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (**121**) was followed, using 7-bromochromone-2-carboxylic acid (**117**) (1.8 g, 7 mmol), dry 1,2-dichloroethane (8 ml), *N,N*-dimethylformamide (0.13 ml, 1.7 mmol), and $SOCl_2$ (0.65 ml, 8.9 mmol). In this case the reaction time was 1.5 h. Work-up afforded crude red crystalline *7-bromochromone-2-carbonyl chloride* (**126**) [δ_H (60 MHz; $CDCl_3$) 7.35 (1H, s, CH=C), 7.65 (1H, dd, *J* 2 and 8 Hz, 6-H), 7.90 (1H, d, *J* 2 Hz, 8-H) and 8.15 (1H, d, *J* 9 Hz, 5-H); ν_{max} (KBr) /cm^{-1} 1740 (CO.Cl) and 1640 (CO)], which was used without further purification.

3-Methylchromone-2-carbonyl chloride (127). - The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride (121) was followed, using 3-methylchromone-2-carboxylic acid (120) (0.9 g, 4 mmol), dry 1,2-dichloroethane (5 ml), *N,N*-dimethylformamide (0.08 ml, 1.1 mmol), and $SOCl_2$ (0.41 ml, 5.6 mmol). In this case the reaction time was 2 h. Work-up afforded crude yellow crystalline *3-methylchromone-2-carbonyl chloride* (127) [δ_H (60 MHz; $CDCl_3$/1,2-dichloroethane) 2.35 (3H, s, CMe=C), 7.35 - 8.40 (4H, m, ArH); ν_{max} (KBr) /cm^{-1} 1760 (CO.Cl) and 1640 (CO)], which was used without further purification.

Dimethylammonium chloride (128). - HCl gas was bubbled through a stirred solution of ethanolic Me_2NH (25% w/w; 18 ml, 77 mmol) and dry EtOH (40 ml) for 2 h at *ca.* 0°C. The solvent was evaporated and the white crystalline slurry was dried under vacuum for 1h. Dry Et_2O (*ca.* 40 ml) was added and the mixture was 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 (6 x 10 ml) by filtration under N_2 and vacuum dried for 1 h to afford crude dimethylammonium chloride (128) (6.4 g, 102%), m.p. 142-143°C (lit.,[155] 157°C); δ_H ($CDCl_3$) 2.80 (6H, t, Me) and 9.45 (1H, br s, NH).

N,N-*Dimethylchromone-2-carboxamide* (129). -

Method 1.[110] A slurry of dimethylammonium chloride (128) (1.5 g, 18 mmol) in dry pyridine (5 ml) was added slowly to a precooled (-5°C), stirred suspension of chromone-2-carbonyl chloride (121) (1.9 g, 9 mmol) in dry pyridine (15 ml), ensuring that the temperature of the resulting black mixture did not exceed 0°C. The reaction mixture was

stirred at 0°C for 2 h and at room temperature for 20 h, and was then poured into 2M-HCl (200 ml), allowed to stand for 0.5 h, and extracted with EtOAc (4 x 70 ml). The organic extracts were combined, sequentially washed with 5% aq. $NaHCO_3$ (2 x 50 ml) and saturated aqueous NaCl (1 x 50 ml), dried (anhyd. $MgSO_4$), and evaporated to afford *N,N*-dimethylchromone-2-carboxamide (**129**) (1.5 g, 76%).[a,b] The crude solid was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *N,N*-dimethylchromone-2-carboxamide (**129**) (1.2 g, 62%),[a] m.p. 115-116°C (from EtOAc) (lit.,[17] 115-116°C); δ_H (300 MHz; $CDCl_3$) 3.10 (6H, br s, NMe_2), 6.49 (1H, s, CH=C), 7.37 - 7.47 (2H, m, 6-H and 8-H), 7.64 - 7.70 (1H, m, 7-H) and 8.15 (1H, dd, *J* 2 and 8 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 35.41 and 38.27 (NMe_2), 111.58 (C-3), 118.13 (C-8), 124.20 (C-4a), 125.73 (C-5 and C-6), 134.25 (C-7), 155.66 (C-8a), 158.20 (C-2), 162.27 (CO.N) and 177.42 (C-4); ν_{max} (KBr) /cm^{-1} 3060 (CH), 1645 and 1640 (CO); λ_{max} (EtOH) /nm 215 (ε /dm^3 mol^{-1} cm^{-1} 16 929), 226 (19 907) and 301 (8 710).

Method 2.[64] Chromone-2-carbonyl chloride (**121**) (1.9 g, 9 mmol) was cautiously added to a precooled (0°C), stirred solution of aqueous Me_2NH (43% w/w; 1.14 ml, 9.6 mmol) and $NaHCO_3$ (1.3 g, 15 mmol) in ice-cold H_2O (11 ml). The mixture was stirred at *ca.* 0°C for 1h and the resulting precipitate was filtered and washed (5% aq. $NaHCO_3$). The crude solid (0.7 g) was shown, by ^1H NMR spectroscopy, to comprise a mixture (1:3) of chromone-2-carboxylic acid (**112**) and *N,N*-dimethylchromone-2-carboxamide (**129**). The mixture was dissolved in $CHCl_3$ (40 ml) and the solution was sequentially washed with 5% aq. $NaHCO_3$ (2 x 30 ml) and

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (**112**).

[b] Optimised reaction; yields using 1 and 1.5 molar equivalents of dimethylammonium chloride (**128**) were 65% and 71% respectively.

saturated aqueous NaCl (1 x 30 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated and the residue recrystallised from EtOAc to afford *N,N*-dimethylchromone-2-carboxamide (**129**) (0.2 g, 10%).[a] The crude mother liquors were chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford additional *N,N*-dimethylchromone-2-carboxamide (**129**) (0.1 g, 5%).[a]

Method 3. The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using chromone-2-carbonyl chloride (**121**) (1.9 g, 9 mmol), ethanolic Me_2NH (33% w/w; 1.75 ml, 9.6 mmol), and dry pyridine (19 ml). In this case the reaction time at room temperature was 15 h. Work-up afforded a solid (1.7 g) shown, by ^1H NMR spectroscopy, to comprise a mixture (1:2) of *N,N*-dimethylchromone-2-carboxamide (**129**) (0.6 g, *ca.* 28%) and ethyl chromone-2-carboxylate (**110**) (1.1 g, *ca.* 56%).

Attempted preparation.[17] A solution of ethyl chromone-2-carboxylate (**110**) (2.0 g, 9 mmol), ethanolic Me_2NH (33% w/w; 1.26 ml, 7.0 mmol), and dry EtOH (50 ml) was stirred at room temperature for 2 days and 21 h, and then boiled under reflux for 9 h. After cooling, the solution was evaporated to afford starting material (2.0 g).

7-Methoxy-N,N-*dimethylchromone-2-carboxamide* (**130**). - The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-methoxychromone-2-carbonyl chloride (**122**) (1.9 g, 8 mmol), dimethylammonium chloride (**128**) (1.3 g, 16 mmol), and dry pyridine (20 ml). In this case the reaction time at room temperature was 24.5 h.

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (**112**).

Work-up afforded crude *7-methoxy*-N,N-*dimethylchromone-2-carboxamide* (130) (1.8 g, 92%)[a] which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *7-methoxy*-N,N-*dimethylchromone-2-carboxamide* (130) (1.7 g, 83%),[a] m.p. 120-122°C (from EtOAc); (Found : C, 63.0; H, 5.1; N, 5.7. $C_{13}H_{13}NO_4$ requires : C, 63.15; H, 5.3; N, 5.7%); δ_H (300 MHz; $CDCl_3$) 3.10 and 3.11 (6H, 2 x s, NMe_2), 3.89 (3H, s, OMe), 6.45 (1H, s, CH=C), 6.85 (1H, d, *J* 2 Hz, 8-H), 6.98 (1H, dd, *J* 2 and 8 Hz, 6-H) and 8.10 (1H, d, *J* 8 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 35.53 and 38.50 (NMe_2), 55.91 (OMe), 100.39 (C-8), 111.68 (C-3), 115.00 (C-6), 118.05 (C-4a), 127.13 (C-5), 157.43 (C-8a), 157.50 (C-2), 162.32 (CO.N), 164.41 (C-7) and 176.69 (C-4); ν_{max} (KBr) /cm^{-1} 2995 (CH), 1660 and 1650 (CO); λ_{max} (EtOH) /nm 217 (ε /dm^3 mol^{-1} cm^{-1} 25 769), 229 (21 300) and 298 (12 277); *m/z* 247 (M^+, 100%).

N,N-*Dimethyl-7-nitrochromone-2-carboxamide* (131). - The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (129) was followed, using a mixture (4:1; 2.6 g) of crude 7-nitrochromone-2-carbonyl chloride (123) (8 mmol) and 7-nitrochromone-2-carboxylic acid (114), dimethylammonium chloride (128) (1.3 g, 16 mmol), and pyridine (20 ml). In this case the reaction time at room temperature was 13 h. Work-up afforded crude brown *N,N-dimethyl-7-nitrochromone-2-carboxamide* (131) (1.7 g, 68%)[b] which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford N,N-*dimethyl-7-nitrochromone-2-carboxamide* (131) (1.7 g, 66%),[b] m.p. 152-153°C (from EtOAc); (Found : C, 55.4; H, 3.8; N, 10.6.

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[a] Yield calculated on the basis of 7-methoxychromone-2-carboxylic acid (113).

[b] Yield calculated on the basis of 7-nitrochromone-2-carboxylic acid (114).

$C_{12}H_{10}N_2O_5$ requires : C, 55.0; H, 3.8; N, 10.7%); δ_H (300 MHz; $CDCl_3$) 3.14 and 3.15 (6H, 2 x s, NMe_2), 6.61 (1H, s, CH=C), 8.23 (1H, dd, *J* 2 and 8 Hz, 6-H) and 8.33 - 8.40 (2H, m, 5-H and 8-H); δ_C (75 MHz; $CDCl_3$) 35.65 and 38.40 (NMe_2), 112.41 (C-3), 114.55 (C-8), 119.97 (C-6), 127.86 (C-5), 150.83 (C-7), 154.99 (C-8a), 159.28 (C-2), 161.33 (CO.N) and 175.81 (C-4); ν_{max} (KBr) /cm^{-1} 1670 and 1655 (CO); λ_{max} (EtOH) /nm 212 (ε /dm^3 mol^{-1} cm^{-1} 19 846), 252 (20 137) and 322 (5 712); *m/z* 262 (M^+, 73%) and 72 (100%).

7-Fluoro-N,N-*dimethylchromone-2-carboxamide* (**132**). -

Method 1. The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-fluorochromone-2-carbonyl chloride (**115**) (1.3 g, 6 mmol), dimethylammonium chloride (**128**) (1.0 g, 12 mmol), and dry pyridine (14 ml). Work-up afforded crude brown *7-fluoro*-N,N-*dimethylchromone-2-carboxamide* (**132**) (1.0 g, 76%)[a] which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *7-fluoro*-N,N-*dimethylchromone-2-carboxamide* (**132**) (0.9 g, 64%).[a]

Method 2. The second experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-fluorochromone-2-carbonyl chloride (**124**) (1.9 g, 9 mmol), aqueous Me_2NH (43% w/w; 1.20 ml, 10.1 mmol), $NaHCO_3$ (1.2 g, 14 mmol), and H_2O (10 ml). Work-up afforded a solid (1.1 g) shown, by TLC, to comprise a mixture of two components. The mixture was chromatographed [flash

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[a] Yield calculated on the basis of 7-fluorochromone-2-carboxylic acid (**115**).

chromatography on silica gel; elution with EtOAc] to afford a solid (0.9 g, 43%)[a] which was recrystallized from EtOAc to give *7-fluoro*-N,N-*dimethylchromone-2-carboxamide* (**132**) (0.5 g, 25%),[a] m.p. 144-146°C; (Found : C, 61.85; H, 4.3; N, 6.1. $C_{12}H_{10}FNO_3$ requires : C, 61.3; H, 4.3; N, 6.0%); δ_H (300 MHz; $CDCl_3$) 3.11 (6H, s, NMe_2), 6.50 (1H, s, CH=C), 7.10 - 7.20 (2H, m, 6-H and 8-H) and 8.16 - 8.24 (1H, m, 5-H); δ_C (125 MHz; $CDCl_3$) 35.30 and 38.14 (NMe_2), 104.77 (d, $^2J_{CF}$ 26 Hz, C-8), 111.58 (C-3), 114.39 (d, $^2J_{CF}$ 23 Hz, C-6), 120.92 (C-4a), 128.14 (d, $^3J_{CF}$ 11 Hz, C-5) 156.47 (d, $^3J_{CF}$ 14 Hz, C-8a), 158.25 (C-2), 161.72 (CO.N), 165.66 (d, $^1J_{CF}$ 256 Hz, C-7) and 176.15 (C-4); ν_{max} (KBr) /cm^{-1} 1660 and 1648 (CO); λ_{max} (EtOH) /nm 223 (ε /dm^3 mol^{-1} cm^{-1} 18 558), 263 (8 687) and 296 (8 782); *m/z* 235 (M^+, 100%) and 72 (100%).

7-Chloro-N,N-*dimethylchromone-2-carboxamide* (**133**). -

Method 1. The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-chlorochromone-2-carbonyl chloride (**125**) (2.0 g, 8 mmol), dimethylammonium chloride (**128**) (1.3 g, 16 mmol), and dry pyridine (20 ml). In this case the reaction time at 0°C was 2.5 h, and at room temperature was 19.5 h. Work-up afforded crude brown *7-chloro*-N,N-*dimethylchromone-2-carboxamide* (**133**) (1.6 g, 80%)[b] which was chromatographed [flash chromatography on silica gel; elution with EtOAc]

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[a] Yield calculated on the basis of 7-fluorochromone-2-carboxylic acid (**115**).

[b] Yield calculated on the basis of 7-chlorochromone-2-carboxylic acid (**116**).

to afford *7-chloro*-N,N-*dimethylchromone-2-carboxamide* (**133**) (1.4 g, 72%).[a]

Method 2. The second experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-chlorochromone-2-carbonyl chloride (**125**) (1.9 g, 8 mmol), aqueous Me_2NH (43% w/w; 0.99 ml, 8 mmol), $NaHCO_3$ (1.2 g, 14 mmol), and H_2O (10 ml). Work-up afforded a solid (1.2 g) shown, by TLC, to comprise a mixture of two components, which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford a solid (0.8 g, 38%)[a] which was recrystallised from EtOAc to give *7-chloro*-N,N-*dimethylchromone-2-carboxamide* (**133**) (0.4 g, 22%),[a] m.p. 146-147°C; (Found : C, 57.3; H, 3.7; N, 5.5. $C_{12}H_{10}ClNO_3$ requires : C, 57.3; H, 4.0; N, 5.6%); δ_H (500 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 6.49 (1H, s, CH=C), 7.37 (1H, dd, *J* 2 and 9 Hz, 6-H), 7.47 (1H, d, *J* 2 Hz, 8-H) and 8.10 (1H, d, *J* 9 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 35.48 and 38.27 (NMe_2), 111.95 (C-3), 118.23 (C-8), 122.76 (C-4a), 126.67 and 127.17 (C-5 and C-6), 140.40 (C-7), 155.75 (C-8a), 158.23 (C-2), 161.91 (CO.N) and 176.55 (C-4); ν_{max} (KBr) /cm^{-1} 1658 and 1650 (CO); λ_{max} (EtOH) /nm 224 (ε /dm^3 mol^{-1} cm^{-1} 19 810), 274 (9 390) and 304 (9 310); *m/z* 251 (^{35}Cl, M^+, 54%) and 123 (100%).

7-Bromo-N,N-*dimethylchromone-2-carboxamide* (**134**). -

Method 1. The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using

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[a] Yield calculated on the basis of 7-chlorochromone-2-carboxylic acid (**116**).

7-bromochromone-2-carbonyl chloride (**126**) (1.9 g, 7 mmol), dimethylammonium chloride (**128**) (1.1 g, 14 mmol), and dry pyridine (20 ml). In this case the reaction time at room temperature was 14 h. Work-up afforded crude *7-bromo*-N,N-*dimethylchromone-2-carboxamide* (**134**) (1.9 g, 96%)[a] which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford *7-bromo*-N,N-*dimethylchromone-2-carboxamide* (**134**) (1.5 g, 77%).[a]

Method 2. The second experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using 7-bromochromone-2-carbonyl chloride (**126**) (1.9 g, 7 mmol), aqueous Me_2NH (43% w/w; 0.96 ml, 8.1 mmol), $NaHCO_3$ (1.0 g, 11 mmol), and H_2O (8 ml). Work-up afforded a solid (0.6 g) shown, by TLC, to comprise a mixture of two components, which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford a crude *7-bromo*-N,N-*dimethylchromone-2-carboxamide* (**134**) (0.4 g, 21%),[a] m.p. 143-145°C (from EtOAc); (Found : C, 48.8; H, 3.45; N, 4.8. $C_{12}H_{10}BrNO_3$ requires : C, 48.7; H, 3.4; N, 4.7%); δ_H (500 MHz; $CDCl_3$) 3.07 and 3.08 (6H, 2 x s, NMe_2), 6.47 (1H, s, CH=C), 7.50 (1H, dd, *J* 2 and 9 Hz, 6-H), 7.63 (1H, d, *J* 2 Hz, 8-H) and 7.99 (1H, d, *J* 9 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 35.48 and 38.26 (NMe_2), 111.93 (C-3), 121.23 (C-8), 123.06 (C-4a), 127.12 and 129.39 (C-5 and C-6), 128.51 (C-7), 155.61 (C-8a), 158.17 (C-2), 161.62 (CO.N) and 176.58 (C-4); ν_{max} (KBr) /cm^{-1} 1655 and 1635 (CO); λ_{max} (EtOH) /nm 228 (ε /dm^3 mol^{-1} cm^{-1} 19 667), 272 (10 245) and 297 (8 947); *m/z* 295 (^{79}Br, M^+, 35%) and 72 (100%).

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[a] Yield calculated on the basis of 7-bromochromone-2-carboxylic acid (**117**).

N,N-*Dimethyl-3-methylchromone-2-carboxamide* (135). -

Method 1. The first experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide (129) was followed, using 3-methylchromone-2-carbonyl chloride (127) (1.0 g, 4 mmol), dimethylammonium chloride (128) (0.7 g, 9 mmol), and dry pyridine (10 ml). In this case the reaction time at room temperature was 14 h. Work-up afforded crude N,N-*dimethyl-3-methylchromone-2-carboxamide* (135) (0.8 g, 84%)[a] which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford N,N-*dimethyl-3-methylchromone-2-carboxamide* (135) (0.7 g 71%).[a]

Method 2. The second experimental procedure for the synthesis of *N,N*-dimethylchromone-2-carboxamide (129) was followed, using 3-methylchromone-2-carbonyl chloride (127) (1.9 g, 9 mmol), aqueous Me_2NH (43% w/w; 1.22 ml, 10.2 mmol), $NaHCO_3$ (1.2 g, 15 mmol), and H_2O (7 ml). In this case the mixture was stirred at *ca.* 0°C for 2h. Work-up afforded a crude solid (1.7 g) shown, by ^1H NMR spectroscopy, to comprise a mixture (*ca.* 1:4) of 3-methylchromone-2-carboxylic acid (120) and N,N-*dimethyl-3-methylchromone-2-carboxamide* (135). The mixture was dissolved in EtOAc (60 ml), and the solution was sequentially washed with 5% aq. $NaHCO_3$ (2 x 30 ml) and saturated aqueous NaCl (1 x 30 ml), and then dried (anhyd. $MgSO_4$). The solvent was evaporated to give an oil which crystallized to afford crude N,N-*dimethyl-3-methylchromone-2-carboxamide* (135) (1.0 g, 52%).[a] Recrystallization from EtOAc afforded N,N-*dimethyl-3-methylchromone-2-carboxamide* (135) (0.1 g, 6%).[a] The crude motherliquours were chromatographed [flash chromatography on

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[a] Yield calculated on the basis of 3-methylchromone-2-carboxylic acid (120).

silica gel; elution with EtOAc] to afford additional N,N-*dimethyl-3-methylchromone-2-carboxamide* (135) (0.5 g, 24%),[a] m.p. 74-76°C (from EtOAc); [*m/z* Found : 231.090 (M^+, 100%). $C_{13}H_{13}NO_3$ requires : 231.090]; δ_H (500 MHz; $CDCl_3$) 1.96 (3H, s, 3-Me), 2.95 and 3.07 (6H, 2 x s, NMe_2), 7.31 - 7.35 (2H, m, 6-H and 8-H), 7.56 - 7.60 (1H, m, 7-H) and 8.11 (1H, dd, *J* 2 and 8 Hz, 5-H); δ_C (75 MHz; $CDCl_3$) 9.98 (3-Me), 34.56 and 37.63 (NMe_2), 117.36 (C-3), 117.88 (C-8), 122.89 (C-4a), 125.24 and 125.78 (C-5 and C-6), 133.72 (C-7), 154.39 (C-8a), 155.61 (C-2), 162.40 (CO.N) and 177.82 (C-4); ν_{max} (KBr) /cm^{-1} 1640 and 1635 (CO); *m/z* 231 (M^+, 100%).

N,N-*Diisopropylchromone-2-carboxamide* (136). -

Method 1.[64] Diisopropylamine (1.06 ml, 7.6 mmol) was added to a solution of chromone-2-carbonyl chloride (121) (1.5 g, 7 mmol) in dry pyridine (20 ml) and the resulting solution was warmed on a steam bath for 3h. After cooling, the solution was poured into 2M-HCl (200 ml) and the resulting mixture was extracted with EtOAc (3 x 50 ml). The organic extracts were combined, dried (anhyd. $MgSO_4$), and evaporated to afford a yellow oil (1.2 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc-hexane (1:1)] to afford an oil (0.8 g; 40%)[b] which crystallised on standing. Recrystallisation from EtOAc gave N,N-*diisopropylchromone-2-carboxamide* (136) (0.3 g, 15%),[b] m.p. 95-96°C (from EtOAc); (Found : C 70.65; H 7.3; N, 5.3. $C_{16}H_{19}NO_3$ requires: C 70.3; H, 7.0; N, 5.1%); δ_H (500 MHz; $CDCl_3$)

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[a] Yield calculated on the basis of 3-methylchromone-2-carboxylic acid (120).

[b] Yield calculated on the basis of chromone-2-carboxylic acid (112).

1.29 (6H, br s, $CHMe_2$), 1.55 (6H, br s, $CHMe_2$), 3.60 (1H, br s, NCH), 3.91 (1H, br s, NCH), 6.49 (1H, s, CH=C), 7.49 - 7.55 and 7.76 - 7.83 (2H, 2 x m, 6-H and 7-H), 7.57 (1H, d, *J* 8 Hz, 8-H) and 8.23 (1H d, *J* 7 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 19.94 ($CHMe_2$), 20.57 ($CHMe_2$), 46.28 (NCH), 51.12 (NCH), 109.50 (C-3), 117.96 (C-8), 124.06 (C-4a), 125.45 and 125.48 (C-5 and C-6), 133.98 (C-7), 155.46 (C-8a), 159.83 (C-2), 161.33 (CO.N) and 177.37 (C-4); ν_{max} /cm^{-1} 1655 and 1640 (CO); *m/z* 273 (M^+, 24%), 216 (100%).

Method 2. The second experimental procedure for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using chromone-2-carbonyl chloride (**121**) (1.5 g, 7 mmol), diisopropylamine (1.23 ml, 8.8 mmol), $NaHCO_3$ (1.2 g, 15 mmol), and H_2O (11 ml). The precipitated solid was filtered off and shown, by ^1H NMR spectroscopy, to be starting material (0.2 g). The filtrate was extracted with EtOAc, dried (anhyd. $MgSO_4$), and evaporated to afford crude N,N-*diisopropylchromone-2-carboxamide* (**136**) (0.1 g, 6%).[a]

1-[(Chromon-2-yl)-carbonyl]-pyrrolidine (**137**). - The second experimental procedure for the synthesis of *N,N*-dimethylchromone-2-carboxamide (**129**) was followed, using chromone-2-carbonyl chloride (**121**) (1.7 g, 8 mmol), pyrrolidine (0.746 ml, 9.0 mmol), $NaHCO_3$ (1.2 g, 14 mmol), and H_2O (10 ml). In this case, the mixture was stirred at *ca.* 0°C for 1.5 h. Work-up afforded a crude solid (0.9 g) shown, by TLC, to comprise a mixture of three components. The mixture was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford crude *1-[(chromon-2-yl)-carbonyl]-pyrrolidine* (**137**) (0.4 g, 22%),[a] m.p.103-105°C (from EtOAc); [*m/z* Found : 243.089 (M^+, 100%). $C_{14}H_{13}NO_3$

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (**112**).

requires : 243.090]; δ_H (500 MHz; $CDCl_3$) 1.83 - 1.89 [4H, m, ($CH_2(CH_2)_2CH_2$)], 3.51 (2H, t, NCH_2), 3.63 (2H, t, NCH_2), 6.62 (1H, s, CH=C), 7.27 - 7.30 and 7.56 - 7.60 (2H, 2 x m, 6-H and 7-H), 7.36 (1H, d, *J* 8 Hz, 8-H) and 8.03 (1H, dd, *J* 2 and 8 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 23.49 (CH_2), 26.09 (CH_2), 46.92 (NCH_2), 48.08 (NCH_2) 111.91 (C-3), 117.87 (C-8), 123.94 (C-4a), 125.35 and 125.47 (C-5 and C-6), 134.06 (C-7), 155.16 (C-8a), 157.86 (C-2), 159.60 (CO.N) and 177.48 (C-4); ν_{max} (KBr) /cm^{-1} 1640 and 1630 (CO); *m/z* 243 (M^+, 100%).

1-[(Chromon-2-yl)-carbonyl]-piperidine (**138**). - The first experimental procedure for the synthesis of N,N-*diisopropylchromone-2-carboxamide* (**136**) was followed, using piperidine (0.80 ml, 8.1 mmol), chromone-2-carbonyl chloride (**121**) (1.6 g, 8 mmol), and dry pyridine (20 ml). Work-up afforded a red oil (1.6 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc-hexane (3:1)] to afford an oil (1.5 g). The oil was chromatographed [flash chromatography on alumina; elution with EtOAc-hexane (2:3)] to afford an oil which crystallized on standing to afford 1-[(chromon-2-yl)-carbonyl]-piperidine (**138**) (1.5 g, 75%),[a] m.p. 66-67°C (from EtOAc) (lit.,[17] 90.5-92°C); (Found : C, 70.5; H 5.9; N, 5.6. Calc for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N 5.4%); δ_H (500 MHz; $CDCl_3$) 1.57 - 1.66 [6H, m, $(CH_2)_3$], 3.39 (2H, br s, NCH_2), 3.62 (2H, br s, NCH_2), 6.39 (1H, s, CH=C), 7.34 - 7.37 and 7.61 - 7.65 (2H, 2 x m, 6-H and 7-H), 7.41 (1H, d, *J* 9 Hz, 8-H) and 8.11 (1H, dd, *J* 2 and 8 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 24.17, 25.21, and 26.34 ($\overline{NCH_2CH_2CH_2CH_2CH_2}$), 43.21 ($NCH_2$), 48.03 ($NCH_2$), 110.96 (C-3), 118.09 (C-8), 124.09 (C-4a), 125.57 (C-5 and C-6), 134.09 (C-7), 155.61 (C-8a), 158.42 (C-2), 160.67 (CO.N)

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (**112**).

and 177.26 (C-4); ν_{max} (KBr) /cm^{-1} 1655 and 1650 (CO); *m/z* 257 (M^+, 35%) and 89 (100%).

Chromone-2-carboxamide (139). -

Method 1. The second experimental procedure for the synthesis of *N,N*-dimethylchromone-2-carboxamide (129) was followed, using chromone-2-carbonyl chloride (121) (1.2 g, 11 mmol) and aqueous NH_3 (25% w/v; 8.4 ml, 0.123 mol). In this case work-up, which excluded the extraction, afforded crude chromone-2-carboxamide (139) (1.5 g, 74%)[a] which was recrystallised from a mixture of EtOH, DMF and H_2O to afford chromone-2-carboxamide (139) (0.8 g, 41%),[a] m.p. 254°C (from EtOH) (lit.,[17] 150-151°C); δ_H (500 MHz; DMSO-d_6/$CDCl_3$) 2.06 (3H, s, impurity), 3.32 (1H, br s, $CONH_2$), 6.83 (1H, s, CH=C), 7.44 - 7.47 and 7.78 - 7.82 (2H, 2 x m, 6-H and 7-H), 7.68 (1H, dd, *J* 1 and 8 Hz, 8-H), 8.01 (1H, dd, *J* 2 and 8 Hz, 5-H) and 8.10 and 8.45 (2H, 2 x br s, impurities); δ_C (125 MHz; DMSO-d_6/$CDCl_3$) 30.45 (Me impurity), 110.42 (C-3), 118.61 (C-8), 123.51 (C-4a), 124.72 and 125.58 (C-5 and C-6), 134.49 (C-7), 155.00 (C-8a), 155.62 (C-2), 160.62 (CO.N) and 177.25 (C-4); ν_{max} (KBr) /cm^{-1} 3360 (NH), 3160 (CH), 1715 (CO.N) and 1673 and 1628 (CO). Impurities in the ^1H and ^{13}C NMR specra could not be eliminated by repeated recrystallisation from EtOH; or by purifying recrystallised material (200 mg) by chromatography [flash chromatography on alumina; elution with EtOAC and EtOH].

Method 2. The first experimental procedure for the synthesis of *N,N*-dimethylchromone-2-carboxamide (129) was followed, using chromone-2-

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (112).

carbonyl chloride (121) (2.2 g, 11 mmol), NH_4Cl (1.1 g, 21 mmol), and dry pyridine (20 ml). In this case the acidic mixture was filtered to afford a solid (0.3 g) and the extracted filtrate afforded a solid (0.9 g). Both solids were shown, by TLC, to comprise a mixture of three components. The combined material (1.2 g) was chromatographed [flash chromatography on silica gel; elution with EtOAc-hexane (50:1)] to afford crude chromone-2-carboxamide (139) (0.3 g, 17%).[a]

(E)-*2-(Dimethylamino)-3-(2-hydroxybenzoyl)*-N,N-*dimethylacrylamide* (140).

Method 1.[17,126] Ethanolic Me_2NH (25% w/w; 3.14 ml, 13.2 mmol) was added to a solution of *N,N*-dimethylchromone-2-carboxamide (129) (0.500 g, 2.3 mmol) in dry EtOH (17 ml) and the solution was stirred at room temperature for 20 h. The solution was evaporated under reduced pressure to afford a crude solid (0.53 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (140) (0.374 g, 62%).

Method 2. Crude chromone-2-carbonyl chloride (121) (1.8 g, 9 mmol) was cautiously added to precooled (0°C), stirred aqueous Me_2NH (43% w/w; 2.13 ml, 17.9 mmol), and cold water (10 ml) was then added. The mixture was stirred for 1 h at *ca.* 0°C and the resulting precipitate was filtered and washed (H_2O) to afford crude (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (140) (0.7 g, 32%),[a] m.p. 165-166°C (from EtOH) (lit.,[17] 166-167°C); δ_H (500 MHz; $CDCl_3$) 2.89 and 3.09 (6H, 2 x s, $CONMe_2$), 3.06 (6H, s, NMe_2), 5.75 (1H, s, CH=C), 6.75 -

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (112).

6.79 and 7.29 - 7.33 (2H, 2 x m, 4'-H and 5'-H), 6.88 (1H, dd, *J* 1 and 8 Hz, 3'-H), 7.67 (1H, dd, *J* 2 and 8 Hz, 6'-H) and 13.60 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.06 and 36.84 ($CONMe_2$), 39.38 and 40.11 (NMe_2), 88.81 (C-3), 117.78 and 117.88 (C-3' and C-5'), 120.18 (C-1'), 128.03 (C-6'), 133.75 (C-4'), 158.76 (C-2), 162.53 (C-2'), 166.44 (CO.N) and 189.74 (C-4); ν_{max} (KBr) /cm^{-1} 2920 and 1648; ν_{max} ($CHCl_3$) /cm^{-1} 2970 and 1650; λ_{max} (EtOH) /nm 216 (ε /dm^3 mol^{-1} cm^{-1} 16 719), 257 (7 783) and 357 (29 647); *m/z* 263 (M^+, 6%) and 72 (100%).

N-*[3-(2-Hydroxybenzoyl)-2-pyrrolidinoacryloyl]pyrrolidine* (**141**). - The second experimental procedure for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**140**) was followed, using chromone-2-carbonyl chloride (**121**) (1.7 g, 8 mmol), pyrrolidine (1.40 ml, 16.9 mmol), and H_2O (10 ml). Work-up afforded an oily solid which was dissolved in Et_2O (25 ml), and the solution was washed with H_2O (20 ml). The aqueous layer was then extracted with EtO_2 (2 x 25 ml). Yellow crystals formed during the extraction and in the combined ethereal layers which were left to stand overnight. The ethereal solution was then filtered to afford crude N-*[3-(2-hydroxybenzoyl)-2-pyrrolidinoacryloyl]pyrrolidine*(**141**) (0.2 g, 9%),[a] m.p. 161-162°C (from EtOH) (lit.,[19] 182°C); δ_H (500 MHz; $CDCl_3$) 1.77 - 1.96 [8H, m, 2 x $CH_2(CH_2)_2CH_2$], 3.06 - 3.10, 3.41 - 3.45, 3.60 - 3.61 and 3.67 - 3.69 [4H, 4 x m, $CON(CH_2)_2$], 3.22 - 3.31 [4H, m, $N(CH_2)_2$], 5.57 (1H, s, CH=C), 6.68 - 6.79 and 7.20 - 7.24 (2H, 2 x m, 4'-H and 5'-H), 6.79 (1H, dd, *J* 1 and 8 Hz, 3'-H), 7.61 (1H, dd, *J* 1 and 8 Hz, 6'-H) and 13.61 (1H, s, OH); δ_C (75 MHz; $CDCl_3$) 24.09, 24.41, 24.99 and 25.44 [$CH_2(CH_2)_2CH_2$], 44.96, 46.82, 48.11 and 48.42 (2 x CH_2NCH_2), 88.53 (C-3), 117.68 and 117.81 (C-3' and C-5'), 120.14 (C-1'),

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[a] Yield calculated on the basis of chromone-2-carboxylic acid (**112**).

123.00 (C-6'), 133.55 (C-4'), 156.78 (C-2), 162.56 (C-2'), 164.99 (CO.N) and 189.49 (C-4); ν_{max} (KBr) /cm^{-1} 1960, 1875, 1650 and 1643; *m/z* 314 (M^+, 2%) and 121 (100%).

(E)-*2-(Dimethylamino)-3-(2-hydroxy-4-methoxybenzoyl)*-N,N-*dimethylacrylamide* (142). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (140) was followed, using 7-methoxy-*N,N*-dimethylchromone-2-carboxamide (130) (0.500 g, 2.0 mmol), dry EtOH (15 ml), and ethanolic Me_2NH (25% w/w; 2.82 ml, 11.9 mmol). In this case the reaction solution was maintained at 35°C for 27 h. Work-up afforded a crude yellow oil (0.577 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to give a solid which was recrystallized from EtOAc to afford (E)-*2-(dimethylamino)-3-(2-hydroxy-4-methoxybenzoyl)*-N,N-*dimethylacrylamide* (142) (0.212 g, 36%), m.p. 154-156°C (from EtOAc); [*m/z* Found : 292.141 (M^+, 10%). $C_{15}H_{20}N_2O_4$ requires : 292.142]; δ_H (300 MHz; $CDCl_3$) 2.90 and 3.09 (6H, 2 x s, $CONMe_2$), 3.04 (6H, br s, NMe_2), 3.78 (3H, s, OMe), 5.65 (1H, s, CH=C), 6.31 - 6.37 (2H, m, 3' -H and 5' -H), 7.58 (1H, d, *J* 9 Hz, 6' -H) and 14.10 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.48 and 37.30 ($CONMe_2$), 39.47 and 40.09 (NMe_2), 55.37 (OMe), 89.12 (C-3), 101.02 and 106.43 (C-3' and C-5'), 113.95 (C-1'), 129.63 (C-6'), 157.89 (C-2), 164.26 (C-4'), 165.33 (C-2'), 166.93 (CO.N) and 189.01 (C-4); ν_{max} (KBr) /cm^{-1} 2930, 1660 and 1650; ν_{max} ($CHCl_3$) /cm^{-1} 2970 and 1650; λ_{max} (EtOH) /nm 221 (ε /dm^3 mol^{-1} cm^{-1} 16 250), 280 (8 020) and 361 (39 240); *m/z* 292 (M^+, 10%) and 220 (100%).

(E)-*2-(Dimethylamino)-3-(2-hydroxy-4-nitrobenzoyl)*-N,N-*dimethylacrylamide* (**143**) and *3-(2-hydroxy-4-nitrobenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**147**). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**140**) was followed, using *N*,*N*-dimethyl-7-nitrochromone-2-carboxamide (**131**) (0.500 g, 1.9 mmol), dry EtOH (55 ml), and ethanolic Me_2NH (25% w/w; 2.60 ml, 11.0 mmol). In this case, the solution, which rapidly turned red, was maintained at 35°C for 25 h. Work-up afforded a crude red oil (0.545 g) which was chromatographed [preparative layer chromatography; elution with EtOAc] to afford 2 crude components, viz.,

(i) (E)-*2-(dimethylamino)-3-(2-hydroxy-4-nitrobenzoyl)*-N,N-*dimethylacrylamide* (**143**) (0.305 g, 52%), m.p. 160-161°C (from EtOAc); (Found : C, 54.8; H, 5.7; N, 13.5. $C_{14}H_{17}N_3O_5$ requires : C, 54.7; H, 5.6; N, 13.7%); δ_H (300 MHz; $CDCl_3$) 2.92 and 3.11 (6H, 2 x s, $CONMe_2$), 3.07 and 3.19 (6H, 2 x s, NMe_2), 5.71 (1H, s, CH=C), 7.58 (1H, dd, *J* 2 and 9 Hz, 5'-H), 7.69 (1H, d, *J* 2 Hz, 3'-H), 7.79 (1H, d, *J* 9 Hz, 6'-H) and 13.85 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.50 and 37.14 ($CONMe_2$), 39.90 and 40.93 (NMe_2), 89.04 (C-3), 112.28 and 113.52 (C-3' and C-5'), 124.82 (C-1'), 128.87 (C-6'), 150.53 (C-4'), 160.30 (C-2), 163.09 (C-2'), 165.92 (CO.N) and 188.02 (C-4); ν_{max} (KBr) /cm^{-1} 2920 and 1645; ν_{max} ($CHCl_3$) /cm^{-1} 2930 and 1650; λ_{max} (EtOH) /nm 215 (ε /dm^3 mol^{-1} cm^{-1} 21 425), 279 (15 379) and 388 (21 087); *m/z* 307 (M^+, 11%) and 72 (100%); and

(ii) *3-(2-hydroxy-4-nitrobenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**147**) (0.041g, 7%), m.p. 222-225°C (from EtOAc); [*m/z* Found : 293.100 (M^+, 13%). $C_{13}H_{15}N_3O_5$ requires : 293.101]; δ_H (200 MHz; $CDCl_3$) 3.07 and 3.08 (3H, 2 x s, NMe), 3.12 (6H, s, $CONMe_2$), 5.76 (1H, s, CH=C), 7.58 - 7.79 (3H, m, ArH), 10.56 (1H, br s, NH) and 13.52 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 31.02 and 31.84 (NHMe), 34.27 and 37.88 ($CONMe_2$), 88.18

(C-3), 113.13 and 113.81 (C-3′ and C-5′), 125.26 (C-1′), 129.21 (C-6′), 151.20 (C-4′), 153.20 (C-2), 163.11 (C-2′), 164.07 (CO.N) and 191.18 (C-4); ν_{max} (KBr) /cm^{-1} 3235 (NH), 2930 and 1655; λ_{max} (EtOH) /nm 212 (ε /dm^3 mol^{-1} cm^{-1} 11 815), 274 (13 606) and 388 (20 043); *m/z* 293 (M^+, 13%) and 221 (100%).

(E)-*2-(Dimethylamino)-3-(4-fluoro-2-hydroxybenzoyl)*-N,N-*dimethylacrylamide* (144) and *3-(4-fluoro-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (148). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (140) was followed, using 7-fluoro-*N*,*N*-dimethylchromone-2-carboxamide (132) (0.500 g, 2.1 mmol), dry EtOH (16 ml), and ethanolic Me_2NH (25% w/w; 2.90 ml, 12.2 mmol). In this case, the reaction solution was maintained at 35°C for 26 h. Work-up afforded a crude yellow oil (0.711 g) which was recrystallized from EtOAc (0.361 g) and chromatographed [preparative layer chromatography; elution with EtOAc] to give 2 components, *viz.*,

(i) a solid which was recrystallized from EtOAc to afford (E)-*2-(dimethylamino)-3-(4-fluoro-2-hydroxybenzoyl)*-N,N-*dimethylacrylamide* (144) (0.228 g, 39%), m.p. 164-166°C (from EtOAc); (Found : C, 59.7; H, 6.3; N, 10.0. $C_{14}H_{17}N_2O_3F$ requires : C, 60.0; H, 6.1; N, 10.0%); δ_H (300 MHz; $CDCl_3$) 2.89 and 3.08 (6H, 2 x s, $CONMe_2$), 3.06 (6H, br s, NMe_2), 5.63 (1H, s, CH=C), 6.44 - 6.58 (2H, m, 3′-H and 5′-H), 7.65 (1H, dd, *J* 7 and 9 Hz, 6′-H) and 14.00 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.39 and 37.15 ($CONMe_2$), 39.59 and 40.40 (NMe_2), 88.96 (C-3), 104.73 and 105.81 (2 x d, $^2J_{CF}$ 23 Hz and $^2J_{CF}$ 24 Hz, C-3′ and C-5′), 117.25 (d, $^4J_{CF}$ 3 Hz, C-1′), 130.18 (d, $^3J_{CF}$ 11 Hz, C-6′), 159.03 (C-2), 165.27 (d, $^3J_{CF}$ 15 Hz, C-2′), 166.10 (d, $^1J_{CF}$ 254 Hz, C-4′), 166.62 (CO.N) and 189.10 (C-4); ν_{max} (KBr) /cm^{-1} 2910 and 1660; ν_{max} ($CHCl_3$) /cm^{-1} 2960, 2920 and 1655; λ_{max} (EtOH) /nm 220 (ε /dm^3 mol^{-1} cm^{-1} 17 631), 258

(7 561) and 353 (32 027); *m/z* 280 (M^+, 9%) and 208 (100%); and

(ii) crude *3-(4-fluoro-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (148) (0.039 g, 7%), m.p. 163-165°C (from EtOAc); [*m/z* Found : 266.105 (M^+, 11%). $C_{13}H_{15}N_2O_3F$ requires : 266.106]; δ_H (200 MHz; $CDCl_3$) 2.90 and 3.02 (3H, 2 x s, NMe), 3.09 (6H, s, $CONMe_2$), 5.62 (1H, s, CH=C), 6.47 - 6.63 (2H, m, 3'-H and 5'-H), 7.58 (1H, dd, J 7 and 9 Hz, 6'-H), 10.10 (1H, br s, NH) and 13.57 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 31.46 (NHMe), 34.24 and 37.90 ($CONMe_2$), 87.43 (C-3), 105.07 and 106.61 (2 x d, $^2J_{CF}$ 23 Hz and $^2J_{CF}$ 23 Hz, C-3' and C-5'), 117.28 (C-1'), 130.27 (d, $^3J_{CF}$ 11 Hz, C-6'), 161.36 (C-2), 164.74 (d, $^3J_{CF}$ 12 Hz, C-2'), 165.13 (CO.N), 166.64 (d, $^1J_{CF}$ 254 Hz, C-4') and 192.57 (C-4); ν_{max} (KBr) /cm^{-1} 3230 (NH), 2930 and 1650; λ_{max} (EtOH) /nm 215 (ε /dm^3 mol^{-1} cm^{-1} 17 067), 256 (6 117) and 253 (27 967); *m/z* 266 (M^+, 11%) and 139 (100%).

(E)-*3-(4-Chloro-2-hydroxybenzoyl)-2-(dimethylamino)*-N,N-*dimethylacrylamide* (145) and *3-(4-chloro-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (149). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-N,N-dimethylacrylamide (140) was followed, using 7-chloro-*N,N*-dimethylchromone-2-carboxamide (133) (0.500 g, 2.0 mmol), dry EtOH (20 ml), and ethanolic Me_2NH (25% w/w; 2.71 ml, 11.4 mmol). In this case the reaction solution was maintained at 35°C for 24 h. Work-up afforded a crude yellow oil (0.555 g) which was chromatographed [preparative layer chromatography; elution with EtOAc] to give 2 crude components, *viz.*,

(i) (E)-*3-(4-chloro-2-hydroxybenzoyl)-2-(dimethylamino)*-N,N-*dimethylacrylamide* (145) (0.327 g, 55%), m.p. 124-125°C (from EtOAc); [*m/z* Found : 296.092 (^{35}Cl, M^+, 12%). $C_{14}H_{17}N_2O_3Cl$ requires : 296.093]; δ_H (300 MHz; $CDCl_3$) 2.89 and 3.09 (6H, 2 x s, $CONMe_2$), 3.07 (6H, br s,

NMe_2), 5.66 (1H, s, CH=C), 6.74 (1H, dd, *J* 2 and 9 Hz, 5'-H), 6.89 (1H, d, *J* 2 Hz, 3'-H), 7.57 (1H, d, *J* 9 Hz, 6'-H) and 13.85 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.48 and 37.07 ($CONMe_2$), 39.70 and 40.60 (NMe_2), 88.88 (C-3), 118.24 and 118.39 (C-3' and C-5'), 118.85 (C-1'), 129.10 (C-6'), 139.32 (C-4'), 159.09 (C-2), 163.52 (C-2'), 166.45 (CO.N) and 188.99 (C-4); ν_{max} (KBr) /cm^{-1} 2920 and 1660; ν_{max} ($CHCl_3$) /cm^{-1} 2970, 2930 and 1650; λ_{max} (EtOH) /nm 213 (ε /dm^3 mol^{-1} cm^{-1} 17 236), 264 (10 209) and 358 (34 077); *m/z* 296 (^{35}Cl, M^+, 12%) and 224 (100%); and

(ii) crude *3-(4-chloro-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**149**) (0.032 g, 6%), m.p. 166-168°C (from EtOAc); [*m/z* Found : 282.076 (^{35}Cl, M^+, 11%). $C_{13}H_{15}N_2O_3Cl$ requires : 282.077]; δ_H (200 MHz; $CDCl_3$) 2.99 and 3.02 (3H, 2 x s, NMe), 3.09 and 3.10 (6H, 2 x s, $CONMe_2$), 5.65 (1H, s, CH=C), 6.77 (1H, dd, *J* 2 and 9 Hz, 5'-H), 6.93 (1H, d, *J* 2 Hz, 3'-H), 7.51 (1H, d, *J* 9 Hz, 6'-H), 10.30 (1H, br s, NH) and 13.41 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 31.51 (NHMe), 34.25 and 37.89 ($CONMe_2$), 87.52 (C-3), 118.61 and 119.24 (C-3' and C-5'), 119.01 (C-1'), 129.25 (C-6'), 139.88 (C-4'), 161.61(C-2), 163.41 (C-2'), 164.50 (CO.N) and 192.55 (C-4); ν_{max} (KBr) /cm^{-1} 3200 (NH), 2920 and 1640; λ_{max} (EtOH) /nm 207 (ε /dm^3 mol^{-1} cm^{-1} 17 367), 266 (8 283) and 358 (29 367); *m/z* 282 (Cl^{35}, M^+, 11%) and 210 (100%).

(E)-*3-(4-bromo-2-hydroxybenzoyl)-2-(dimethylamino)*-N,N-*dimethylacrylamide* (**146**) and *3-(4-bromo-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**150**). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**140**) was followed, using 7-bromo-*N*,*N*-dimethylchromone-2-carboxamide (**134**) (0.500 g, 1.7 mmol), dry EtOH (28 ml), and ethanolic Me_2NH (25% w/w; 2.31 ml, 9.7 mmol). In this case the reaction was maintained at 35°C for 24 h. Work-up afforded a crude red oil (0.711 g) which was chromatographed [preparative layer

chromatography; elution with EtOAc] to give 2 crude components, *viz.*, (i) an oil which crystallized and was filtered to afford (E)-*3-(4-bromo-2-hydroxybenzoyl)-2-(dimethylamino)*-N,N-*dimethylacrylamide* (**146**) (0.265 g, 46%), m.p. 124-125°C (from EtOAc); (Found : C, 49.2; H, 5.1; N, 8.4. $C_{14}H_{17}N_2O_3Br$ requires : C, 49.3; H, 5.0; N, 8.2%); δ_H (300 MHz; $CDCl_3$) 2.89 and 3.08 (6H, 2 x s, $CONMe_2$), 3.06 (6H, 2 x s, NMe_2), 5.65 (1H, s, CH=C), 6.89 (1H, dd, *J* 2 and 9 Hz, 5'-H), 7.06 (1H, d, *J* 2 Hz, 3'-H), 7.50 (1H, d, *J* 9 Hz, 6'-H) and 13.80 (60 MHz; 1H, s, OH); δ_C (75 MHz; $CDCl_3$) 34.40 and 37.11 ($CONMe_2$), 39.74 and 40.52 (NMe_2), 88.88 (C-3), 119.30 (C-1'), 121.28 and 121.40 (C-3' and C-5'), 127.63 (C-4'), 129.21 (C-6'), 159.33 (C-2), 163.56 (C-2'), 166.49 (CO.N) and 189.28 (C-4); ν_{max} (KBr) /cm^{-1} 2920 and 1660; ν_{max} ($CHCl_3$) /cm^{-1} 2970, 2930 and 1655; λ_{max} (EtOH) /nm 212 (ε /dm^3 mol^{-1} cm^{-1} 14 521), 267 (10 203) and 360 (33 131); *m/z* 340 (^{79}Br, M^+, 6%) and 72 (100%); and

(ii) *3-(4-bromo-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**150**) (0.028 g, 5%), m.p. 153-155°C (from EtOAc); [*m/z* Found : 326.025 (Br^{79}, M^+, 12%). $C_{13}H_{15}N_2O_3Br$ requires : 326.027]; δ_H (200 MHz; $CDCl_3$) 2.99 and 3.02 (3H, 2 x s, NMe), 3.08 and 3.09 (6H, 2 x s, $CONMe_2$), 5.65 (1H, s, CH=C), 6.92 (1H, dd, *J* 2 and 9 Hz, 5'-H), 7.11 (1H, d, *J* 2 Hz, 3'-H), 7.44 (1H, d, *J* 9 Hz, 6'-H), 10.30 (1H, br s, NH) and 13.36 (1H, s, OH); δ_C (50MHz; $CDCl_3$) 31.52 (NHMe), 34.26 and 37.89 ($CONMe_2$), 87.52 (C-3), 119.38 (C-1'), 121.73 and 122.11 (C-3' and C-5'), 128.29 (C-4'), 129.29 (C-6'), 161.66 (C-2), 163.31 (C-2'), 164.48 (CO.N) and 192.66 (C-4); ν_{max} (KBr) /cm^{-1} 3200 (NH), 2920 and 1640; λ_{max} (EtOH) /nm 207 (ε /dm^3 mol^{-1} cm^{-1} 18 550), 267 (9 767) and 360 (3 200); *m/z* 326 (Br^{79}, M^+, 12%) and 256 (100%).

3-(4-Bromo-2-hydroxybenzoyl)-N,N-*dimethyl-2-methylaminoacrylamide* (**150**). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**140**)

was followed, using 7-bromo-*N*,*N*-dimethylchromone-2-carboxamide (**134**) (0.502 g, 1.7 mmol), dry EtOH (25 ml), and ethanolic $MeNH_2$ (4.8% w/w; 5.44 ml, 8.4 mmol). In this case the reaction solution was maintained at 35°C for 19.5 h. Work-up afforded a crude solid (0.565 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford crude *3-(4-bromo-2-hydroxybenzoyl)*-N,N-*dimethyl-2-methylaminoacrylamide* (**150**) (0.470 g, 85%), 157-158°C (from EtOAc); δ_H (400 MHz; $CDCl_3$) 2.96 and 3.01 (3H, 2 x s, NMe), 3.08 and 3.09 (6H, 2 x s, $CONMe_2$), 5.64 (1H, s, CH=C), 6.92 (1H, dd, *J* 2 and 9 Hz, 5'-H), 7.10 (1H, d, *J* 2 Hz, 3'-H), 7.43 (1H, d, *J* 9 Hz, 6'-H), 10.28 (1H, br s, NH) and 13.37 (1H, s, OH); δ_C (100MHz; $CDCl_3$) 31.37 (NHMe), 34.10 and 37.72 ($CONMe_2$), 87.24 (C-3), 119.02 (C-1'), 121.33 and 121.70 (C-3' and C-5'), 127.86 (C-4'), 128.87 (C-6'), 161.17 (C-2), 162.81 (C-2'), 163.96 (CO.N) and 192.06 (C-4); ν_{max} (KBr) /cm^{-1} 3210 (NH), 2925 and 1640; *m/z* 326 (Br^{79}, M^+, 1%) and 72 (100%).

(E)-*3-(2-Hydroxybenzoyl)*-N,N-*dimethyl-2-pyrrolidinoacrylamide* (**151**). - The first experimental procedure employed for the synthesis of (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**140**) was followed, using *N*,*N*-dimethylchromone-2-carboxamide (**129**) (0.500 g, 2.3 mmol), dry EtOH (10 ml), and pyrrolidine (0.95 ml, 11.5 mmol). In this case the reaction solution was maintained at 35°C for 6.5 h. Work-up afforded a crude solid (0.669 g) which was chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford (E)-*3-(2-hydroxybenzoyl)*-N,N-*dimethyl-2-pyrrolidinoacrylamide* (**151**) (0.594 g, 90%), m.p. 183-184°C (from EtOH); (Found : C, 66.3; H, 7.05; N, 9.2. $C_{16}H_{20}N_2O_3$ requires : C, 66.65; H, 7.0; N, 9.7%); δ_H (200 MHz, $CDCl_3$) 1.86 - 2.11 [4H, m, $CH_2(CH_2)_2CH_2$], 2.94 and 3.11 (6H, 2 x s, NMe_2), 3.36 - 3.45 and 3.65 - 3.72 [3H and 1H, 2 x m, $N(CH_2)_2$], 5.72 (1H, s, CH=C), 6.76 - 6.93 (2H, m, 4'-H and 5'-H), 7.28 - 7.37 (1H, m,

3'-H), 7.69 (1H, dd, *J* 2 and 8 Hz, 6'-H) and 13.70 (60 MHz; 1H, s, OH); δ_C (50 MHz, $CDCl_3$) 24.82 and 25.39 [$CH_2(CH_2)_2CH_2$], 34.41 and 37.24 (NMe_2), 48.57 and 48.78 [$N(CH_2)_2$], 89.84 (C-3), 118.30 and 118.61 (C-3' and C-5'), 120.70 (C-1'), 128.62 (C-6'), 134.35 (C-4'), 156.74 (C-2), 163.31 (C-2'), 167.65 (CO.N) and 190.44 (C-4); ν_{max} (KBr) /cm^{-1} 2930, 2870 and 1650; *m/z* 288 (M^+, 2%) and 121 (100%).

Glycine ethyl ester hydrochloride (**152**).[156] - HCl gas was bubbled through a mixture of glycine (7.5 g, 10 mmol) and EtOH (40 ml) on a boiling water bath until all the glycine was dissolved (*ca.* 1 h) and then for an additional 5 min. After cooling, the solution rapidly crystallised and was cooled on an ice bath. The crystals were filtered, washed (cold EtOH), and dried under vacuum for 1 h to afford crude glycine ethyl ester hydrochloride (**152**) (13.0 g, 93%) m.p. 141-143°C (lit.,[156] 143-144°C); δ_H (60 MHz, $CDCl_3$) 1.30 (3H, t, CH_2Me), 3.80 (2H, br s, CH_2CO), 4.30 (2H, q, CH_2Me) and 8.80 (3H, br s, NH_3^+).

2-(N-Carbethoxymethylamino)-3-(2-hydroxybenzoyl)-N,N-dimethylacrylamide (**153**). - Ethanolic glycine ethyl ester (2.5 mmol) [generated by adding a solution of KOH (0.14 g, 2 mmol) in dry EtOH (2 ml) dropwise to a solution of glycine ethyl ester hydrochloride (**152**) (0.35 g, 2.5 mmol) in dry EtOH (5 ml)] was added dropwise to a solution of *N,N*-dimethylchromone-2-carboxamide (**129**) (0.50 g, 2.3 mmol) in dry EtOH (10 ml). The resulting mixture was warmed at 35°C for 24 h. Additional glycine ethyl ester (9.2 mmol) [generated by adding a solution of KOH (0.60 g, 11 mmol) in dry EtOH (4 ml) dropwise to a solution of glycine ethyl ester hydrochloride () (1.29 g, 9.2 mmol) in dry EtOH (5 ml)] was added and the mixture was warmed at 35°C for 4 days, and at room temperature for 23 days. After cooling, the mixture was filtered and the filtrate was evaporated to give a red oil (1.53 g) which was

chromatographed [flash chromatography on silica gel; elution with EtOAc] to afford 3 fractions, *viz.*,

i) an oil (0.28 g, 37%) which crystallized and was recrystallized from EtOAc to afford *2-(N-carbethoxymethylamino)-3-(2-hydroxybenzoyl)*-N,N-*dimethylacrylamide* (153) (0.19 g, 25%), m.p. 134-135°C (from EtOH); (Found : C, 59.8; H, 6.2; N, 8.6. $C_{16}H_{20}N_2O_5$ requires : C, 60.0; H, 6.3; N, 8.7%); δ_H (400 MHz; $CDCl_3$) 1.30 (3H, t, CH_2Me), 3.05 and 3.12 (6H, 2 x s, NMe_2), 4.07 (2H, d, *J* 6 Hz, CH_2NH), 4.24 (2H, q, CH_2Me), 5.80 (1H, s, CH=C), 6.81 (1H, t, *J* 7 Hz, 5'-H), 6.93 (1H, d, *J* 8 Hz, 3'-H), 7.36 (1H, t, *J* 8 Hz, 4'-H), 7.61 (1H, d, *J* 8 Hz, 6'-H), 10.50 (1H, br s, NH) and 13.01 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 14.10 (CH_2Me), 34.36 and 38.51 (NMe_2), 45.82 ($NHCH_2$), 61.86 (CH_2Me), 89.20 (C-3), 118.37 and 118.40 (C-3' and C-5'), 120.09 (C-1'), 128.04 (C-6'), 134.46 (C-4'), 158.15 (C-2), 162.35 (C-2'), 164.13 (CO.N), 168.82 (CO.O) and 193.62 (C-4); ν_{max} (KBr) /cm^{-1} 3230 (NH), 2990 (CH), 1743 (CO.O) and 1640 (CO); *m/z* 320 (M^+, 24%) and 248 (100%);

ii) starting material (0.03 g); and

iii) an oil (0.11 g).

1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (155).[40] - A solution of KOH (85% pellets; 2.3 g, 35 mmol), *i*-PrOH (25 ml), and H_2O (*ca.* 1 ml) was added to a stirred solution of 2,6-dihydroxyacetophenone (9.7 g, 64 mmol), epichlorohydrin (2.75 ml, 35 mmol), and *i*-PrOH (250 ml). The mixture was then boiled under reflux for 96 h, and stirred for 2 days. Half the *i*-PrOH was distilled off and H_2O (50 ml) was then added. After cooling, the precipitated solid was filtered off, washed (*i*-PrOH and Et_2O), and recrystallized from *i*-PrOH to afford 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (155) (4.6 g, 40%), m.p. 167-169°C (lit.,[40] 165-166°C); δ_H (400 MHz; $CDCl_3$) 1.57 (3H, s, impurity), 2.73 (6H, s, CO*Me*), 4.23 - 4.33 (5H, sept, C*H*OH and 2 x

OCH_2), 4.55 - 4.62 (1H, ses, CHO*H*), 6.40 and 6.63 (4H, 2 x d, *J* 8 Hz, 2 x 4'-H and 6'-H), 7.35 (2H, t, *J* 8 Hz, 2 x 5'-H) and 13.17 (2H, s, 2 x ArOH); δ_C (100 MHz; $CDCl_3$) 33.92 (CO*Me*), 68.73 (CHOH), 70.02 (2 X OCH_2), 101.80 and 111.80 (C-4' and C-6'), 111.45 (C-2'), 136.13 (C-5'), 159.92 (C-3'), 164.78 (C-1') and 204.37 (CO); ν_{max} (KBr) /cm^{-1} 3600 - 3400 (OH) and 1618 (CO).

1,3-Bis(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane (**156**) and *3-(2-acetyl-3-hydroxyphenoxy)-1-(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane* (**157**).[40] - An ethanolic solution of NaOEt was generated *in situ* by adding Na metal (1.1 g, 48 mmol) to dry EtOH (14 ml) with stirring and heating under reflux. After cooling, Et_2O (28 ml) was added. A warm solution of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (**155**) (4.0 g, 11 mmol), diethyl oxalate (6.94 ml, 51 mmol), dry EtOH (14 ml), and dry benzene (14 ml) was then added, and the resulting yellow mixture was boiled under reflux overnight (*ca.* 16 h). After cooling, dry Et_2O (56 ml) was added and the resulting precipitate was filtered off, washed (Et_2O, 28 ml), and dried. The solid was then added to H_2O (67 ml) with stirring, and the mixture was acidified with conc. HCl. The H_2O was decanted off, and the remaining syrupy solid was dissolved in dry EtOH (14 ml) and dry benzene (14 ml). The solvent was evaporated off to azeotrope off any H_2O. Conc. HCl (0.14 ml), dry EtOH (5 ml), and dry benzene (5 ml) was added to the red oil, and the mixture was boiled under reflux for 5 min. Since no precipitation occurred, the mixture was azeotroped with additional dry EtOH-benzene (1:1; 28 ml). The resulting oil was dissolved in dry EtOH-benzene (1:1; 10 ml) and conc. HCl (0.28 ml), and boiled under reflux for 5 min. After cooling, the solution was evaporated and azeotroped with dry EtOH-benzene (1:1; 40 ml) to afford a red oil (3.4 g), half of which was repeatedly chromatographed [flash chromatography on silica

gel; elution with EtOAc-hexane (2:1)] to afford three components, *viz.*,

i) starting material (0.22 g) m.p. 171-172°C;

ii) a solid which was recrystallised from EtOH to afford 1,3-bis(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane (**156**) (0.151 g), m.p 186-188°C (lit.,[40] 180-182°C); δ_H (400 MHz; $CDCl_3$) 1.42 (6H, t, 2 x CH_2*Me*), 4.34 - 4.38 and 4.49 - 4.59 (5H, 2 x m, C*H*OH and 2 x OCH_2), 4.45 (4H, q, 2 x C*H*$_2$Me), 4.86 (1H, d, *J* 6 Hz, CHO*H*), 6.96 (2H, s, 2 x CH=C), 6.97 and 7.16 (4H, 2 x d, *J* 8 Hz, 2 x 6-H and 8-H) and 7.60 (2H, t, *J* 8Hz, 2 x 7-H); δ_C (100 MHz; $CDCl_3$) 14.06 (CH_2*Me*), 62.89 (*C*H_2Me), 67.76 (CHOH), 70.36 (2 X OCH_2), 109.64 and 111.13 (C-6 and C-8), 115.66 (C-4a), 116.21 (C-3), 134.88 (C-7), 150.66 (C-2), 157.69 (C-8a), 158.83 (C-5), 160.46 (CO.O) and 178.19 (C-4); ν_{max} (KBr) /cm^{-1} 3600 - 3200 (OH), 1748 (CO.O) 1666 and 1650 (CO); and

iii) a mixture (0.73 g), shown, by TLC, to comprise two components, of which 70 mg was chromatographed [preparative layer chromatography; elution with EtOAc-hexane (2:1)] to afford 3-(2-acetyl-3-hydroxyphenoxy)-1-(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane (**157**) (0.038 g), m.p. 140-142°C (from EtOH);[a] δ_H (400 MHz; $CDCl_3$) 1.43 (3H, t, CH_2*Me*), 2.72 (3H, s, CO*Me*), 4.26 - 4.33 and 4.36 - 4.39 (4H, 2 x m, 2 x OCH_2), 4.46 (3H, q, C*H*OH and C*H*$_2$Me), 4.83 (1H, d, *J* 6 Hz, CHO*H*), 6.44 and 6.57 (2H, 2 x d, *J* 8 Hz, 4' - and 6' -H), 6.90 and 7.25 (2H, 2 x d, *J* 8 and 9 Hz, 6-H and 8-H), 6.99 (1H, s, CH=C), 7.32 (1H, t, *J* 8 Hz, 5' -H), 7.64 (1H, t, *J* 8Hz, 7-H) and 13.18 (1H, s, ArOH); δ_C (100 MHz; $CDCl_3$) 14.06 (CH_2*Me*), 33.96 (CO*Me*), 63.03 (*C*H_2Me), 68.03 (CHOH), 69.32 (*C*H_2OPh), 72.25 (*C*H_2OChromonyl), 102.03 and 111.14 (C-4' and C-6'), 110.59 and 112.07 (C-6 and C-8), 111.40 (C-2'), 115.99 (C-4a), 116.13 (C-3), 134.96 (C-7), 136.09 (C-5'), 150.99 (C-2), 157.64 (C-8a), 158.79 (C-5), 160.25 and 160.32 (C-3' and CO.O), 164.62 (C-1'), 178.55 (C-4)

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[a] No melting point is given in the abstract.[157]

and 204.88 (CO); ν_{max} (KBr) /cm^{-1} 3600 - 3300 (OH), 1725 (CO.O), 1660 (CO) and 1625 (COMe).

1,3-Bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt [disodium cromoglycate (DSCG)] (**158**).[40] - 2N-NaOH (0.233 ml, 0.8 mmol) was added dropwise to a stirred suspension of 1,3-bis(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane (**156**) (0.122 g, 0.2 mmol) in absolute EtOH (0.58 ml). Three drops of H_2O was added to the yellow/red paste and the mixture was boiled under reflux for 1 h. The solid dissolved after *ca.* 5 min. After cooling, EtOH (1.16 ml) was added and the precipitate was filtered, washed (absolute EtOH), and dried under vacuum at 50°C for 3 h to afford crude 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt (**158**) (0.109 g, 91%);[a] δ_H (400 MHz; D_2O/acetone) 4.17 - 4.32 (5H, m, C*H*OH and 2 x OCH_2), 4.55 - 4.71 (10H, m, HDO), 6.37 (2H, s, 2 x CH=C), 6.71 and 6.80 (4H, 2 x d, *J* 7 Hz, 2 x 6-H and 8-H) and 7.14 (2H, t, *J* 7Hz, 2 x 7-H); δ_C (100 MHz; D_2O) 67.92 (CHOH), 70.89 (2 X OCH_2), 109.56 and 111.21 (C-6 and C-8), 112.70 (C-3), 113.74 (C-4a), 135.98 (C-7), 156.87 (C-2), 157.49 (C-8a), 158.25 (C-5), 165.63 (CO.ONa) and 181.58 (C-4); ν_{max} (KBr) /cm^{-1} 3700 - 2800 (OH and H_2O of crystallisation) and 1635 (CO).

Ring-opening of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt [disodium cromoglycate (DSCG)] (**158**). - A solution of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt (**158**) (0.031 g, 0.05 mmol) in D_2O (0.7 ml) was added to aqueous Me_2NH (43% w/w, 74 μl, 0.62 mmol) in an NMR tube. After 0.5 h, the resulting red solution was examined by NMR spectroscopy and showed no evidence of

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[a] Yield calculated of the basis of the unhydrated product.

starting material, as illustrated in Figures 25 and 26 (p.105 and 106).[a] [Both ^{1}H and ^{13}C spectra of the reaction mixture correspond essentially with the ring-opened *disodium 1,3-bis[2-(3-carboxy-3-dimethylaminoacryloyl)-3-hydroxyphenoxy]-2-hydroxypropane* (**159**).] After 24 h, the spectra of the reaction solution were essentially the same. After 32 h, the red solution was poured into a round bottomed flask, and dry benzene (5 ml) was added.[b] The solution was warmed under vacuum to azeotrope off the H_2O. This process was repeated several times in an attempt to reduce the volume of H_2O, and the resulting solution was dried under vacuum for 2h at *ca.* 70°C to afford crude starting material (0.033 g, 100%).

---

[a] The ^{1}H and ^{13}C spectra of DSCG (**158**) were calibrated against acetone. The spectra of the reaction mixture were calibrated against the HDO signal at 4.5 - 4.7 ppm for the ^{1}H spectrum, and by the Me_2NH *N*-methyl signal at *ca.* 36.9 ppm in the ^{13}C spectrum. [The Me_2NH chemical shift was calibrated from a reference solution of aqueous Me_2NH (40% w/w) in D_2O using acetone as reference material.]

[b] The isolation procedure did not involve acidification, since this may have resulted in formation of the dimethylammonium salt.

3.3 NMR CONFORMATIONAL STUDIES.

Variable-temperature ^1H spectra were recorded on a Bruker AM 300 MHz NMR spectrometer, from $CDCl_3$ solutions of the chromone-2-carboxamides, and temperature errors are estimated at ±1K. The n.O.e difference spectra were recorded on a Bruker AM 300 MHz NMR spectrometer, from a $CDCl_3$ solution at 298K.

The coalescence temperatures (T_c) were obtained from the variable-temperature spectra (Figure 41) with an estimated ±2K accuracy. The estimated error of the T_c values, *viz.*, ±3K is the sum of this error and the accuracy of the NMR spectrometer temperature, *viz.*, ±1K. The ^1H NMR frequency separations measured at slow site-exchange ($\Delta\nu_o$) are either maximum frequency separations ($\Delta\nu_o$) or separations corresponding to the minimum temperature below which precipitation of material precluded further measurement. The frequency differences at coalescence ($\Delta\nu_c$) were obtained from the variable-temperature spectra by extrapolation of linear plots of the frequency separations ($\Delta\nu$) against temperature (T). Extrapolation data and plots are included after the variable temperature spectra (Figure 41). The estimated error of the $\Delta\nu_c$ values is the sum of the measurement error [±0.5 mm (for 1 mm = 1 Hz) and ±0.3 mm (for 2 mm = 1 Hz)] and the linear extrapolation error. The latter error was calculated by substituting T_c ±3K into the respective linear equation. The rotational energy barriers (ΔG^*) were calculated from the coalescence temperatures (T_c) and the frequencies at coalescence ($\Delta\nu_c$). The estimated errors of the ΔG^* data were calculated from the separate effects of the errors in T_c and $\Delta\nu_c$, and the maximum scatter incorporating both effects was quoted.

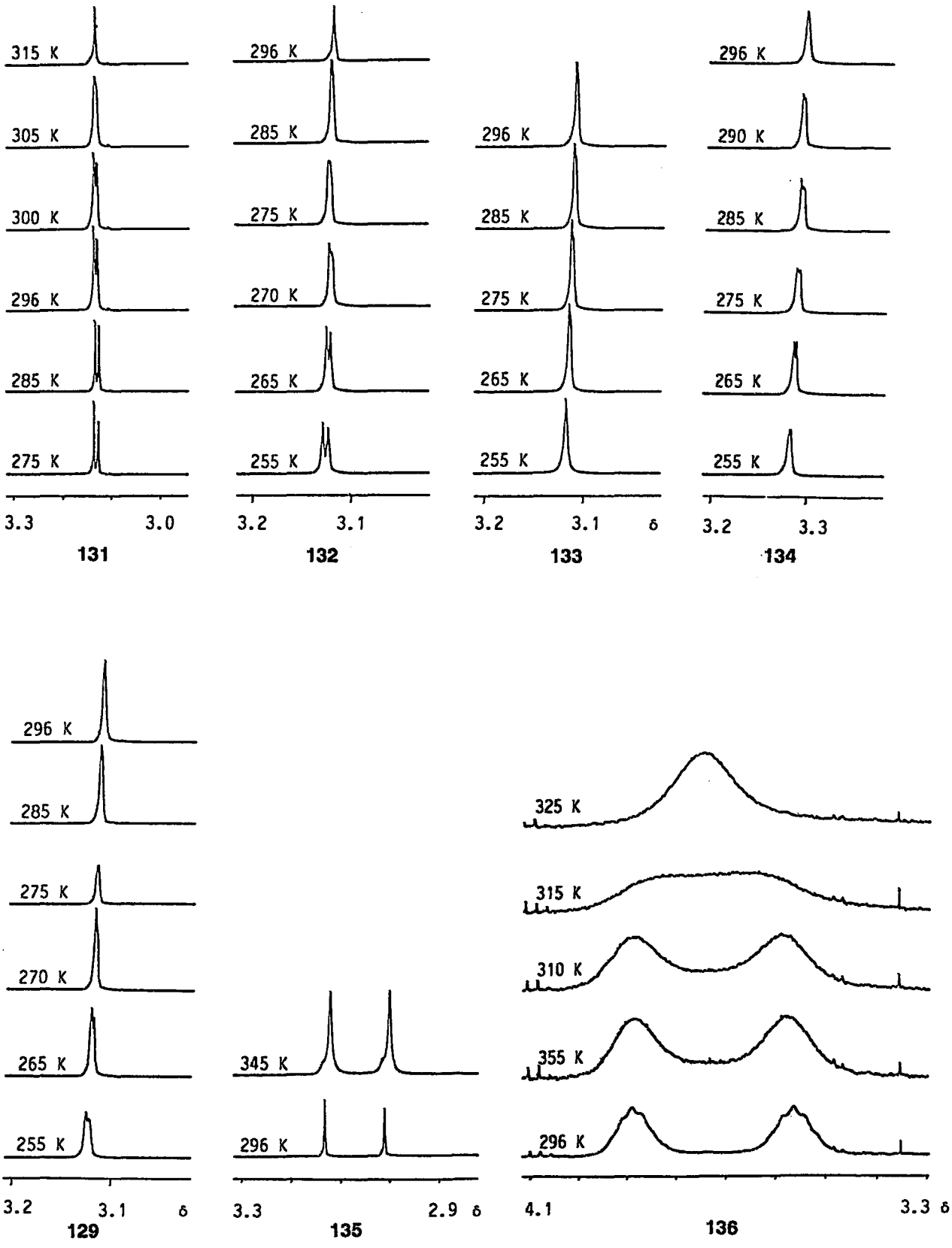


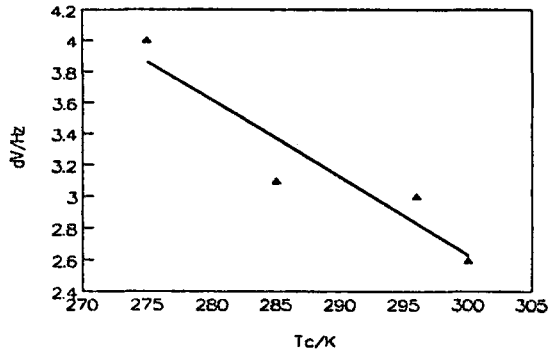
FIGURE 41. Variable temperature ^{1}H NMR spectra showing *N*-alkyl signals for selected chromone-2-carboxamides 129-138.

130

No.	Tc/K	dV/Hz	Y(CALC)
1	275	4.0	3.9
2	285	3.1	3.4
3	296	3.0	2.8
4	300	2.6	2.6

Regression Output:

Constant	17.39826
Std Err of Y Est	0.247249
R Squared	0.88328
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-0.0492154
Std Err of Coef.	0.0126503729

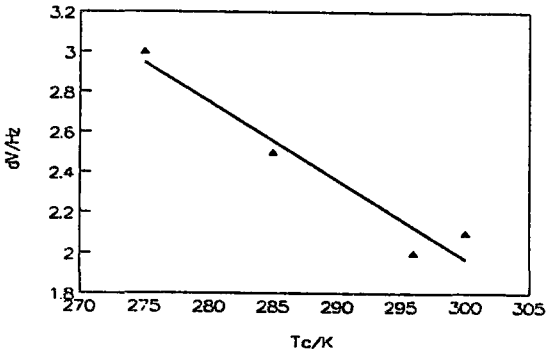


131

No.	Tc/K	dV/Hz	Y(CALC)
1	275	3.0	2.9
2	285	2.5	2.6
3	296	2.0	2.1
4	300	2.1	2.0

Regression Output:

Constant	13.67263
Std Err of Y Est	0.139323
R Squared	0.937384
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-0.03900562
Std Err of Coef.	0.00712840252

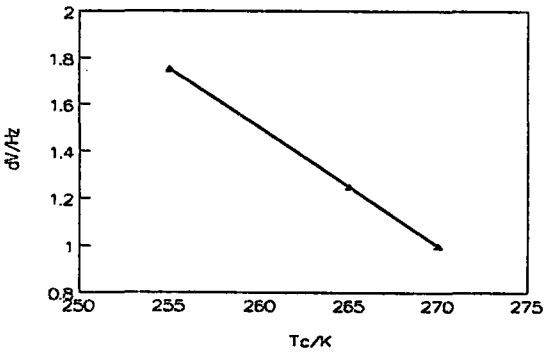


132

No.	Tc/K	dV/Hz	Y(CALC)
1	255	1.75	1.75
2	265	1.25	1.25
3	270	1.00	1.00

Regression Output:

Constant	14.5
Std Err of Y Est	1.11E-06
R Squared	1
No. of Observations	3
Degrees of Freedom	1
X Coefficient(s)	-0.0500
Std Err of Coef.	0.0000

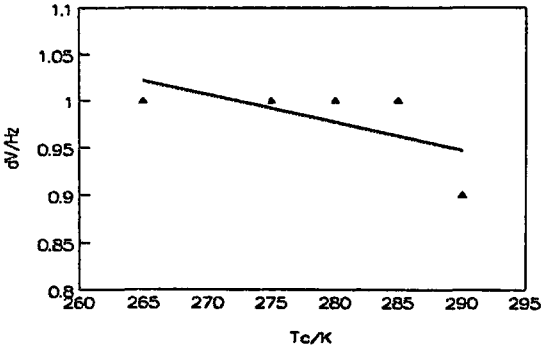


134

No.	Tc/K	dV/Hz	Y(CALC)
1	265	1.0	1.0
2	275	1.0	1.0
3	280	1.0	1.0
4	285	1.0	1.0
5	290	0.9	0.9

Regression Output:

Constant	1.80946
Std Err of Y Est	0.03971
R Squared	0.40878
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.0029729730
Std Err of Coef.	0.00206422329

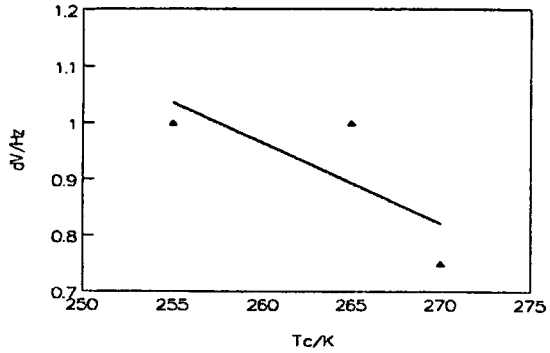


129

No.	Tc/K	dV/Hz	Y(CALC)
1	255	1.00	1.04
2	265	1.00	0.89
3	270	0.75	0.82

Regression Output:

Constant	4.678571
Std Err of Y Est	0.133631
R Squared	0.571429
No. of Observations	3
Degrees of Freedom	1
X Coefficient(s)	-0.01428571
Std Err of Coef.	0.0124

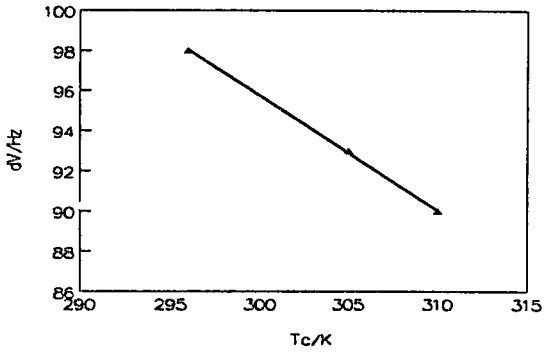


136

No.	Tc/K	dV/Hz	Y(CALC)
1	296	98	98
2	305	93	93
3	310	90	90

Regression Output:

Constant	266.6159
Std Err of Y Est	0.115087
R Squared	0.999595
No. of Observations	3
Degrees of Freedom	1
X Coefficient(s)	-0.5695365
Std Err of Coef.	0.0115

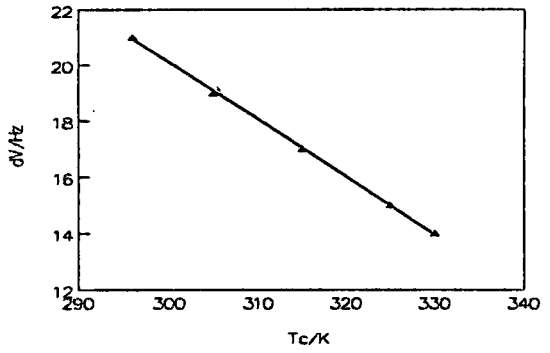


137

No.	Tc/K	dV/Hz	Y(CALC)
1	296	21	21
2	305	19	19
3	315	17	17
4	325	15	15
5	330	14	14

Regression Output:

Constant	81.50103
Std Err of Y Est	0.070885
R Squared	0.99954
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.20464997
Std Err of Coef.	0.00253355

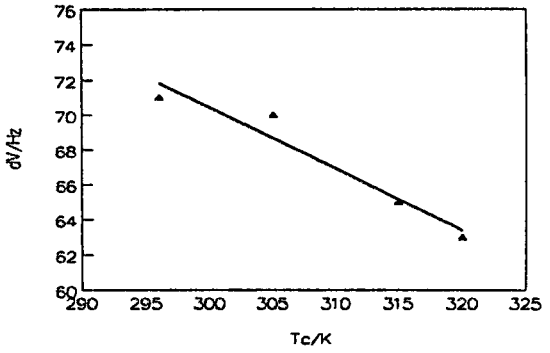


138

No.	Tc/K	dV/Hz	Y(CALC)
1	296	71	72
2	305	70	69
3	315	65	65
4	320	63	63

Regression Output:

Constant	175.6711
Std Err of Y Est	1.149943
R Squared	0.9409
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-0.3508772
Std Err of Coef.	0.062181785



Calculation of the percentage n.O.e.

The percentage n.O.e for each interaction was calculated using equation 13, where A_S, B_S, C_S, and D_S represent the height, in mm, of a particular peak in a trace divided by the scale for the trace of the spectra A, B, C, and D respectively (figure 42).

$$\% \text{ n.O.e} = (A_S/B_S) \times 100 \times (D_S/C_S) \qquad (13)$$

Calculations : a) Irradiation at ν_1 : $D_S = 144$, $C_S = 104$

Peak 2 : $A_S = .9375$, $B_S = 150$, % n.O.e = .87

Peak 3 : $A_S = .3125$, $B_S = 144$, % n.O.e = .30

b) Irradiation at ν_2 : $D_S = 144$, $C_S = 110$

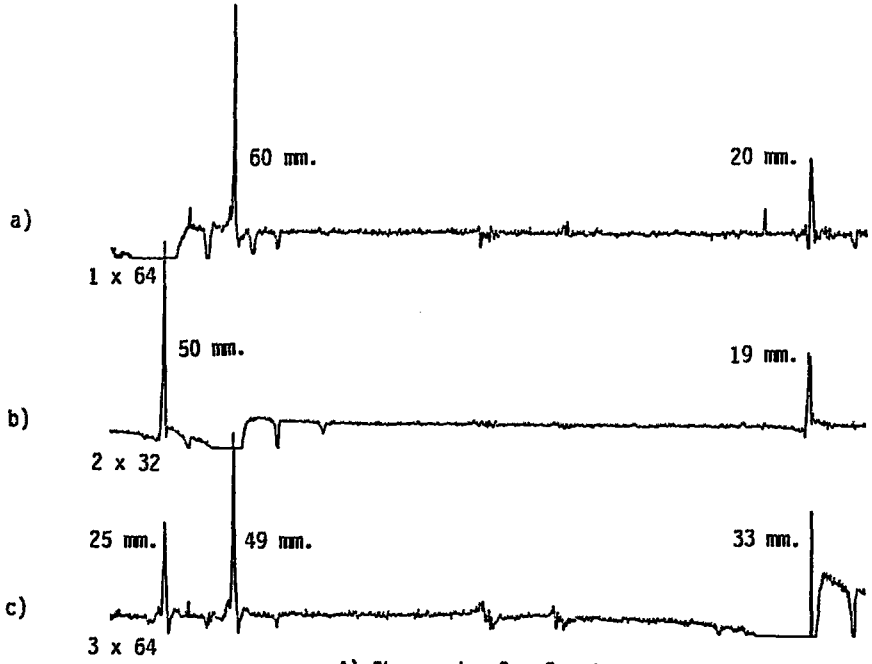
Peak 1 : $A_S = 1.5625$, $B_S = 144$, % n.O.e = 1.42

Peak 3 : $A_S = .59375$, $B_S = 144$, % n.O.e = .54

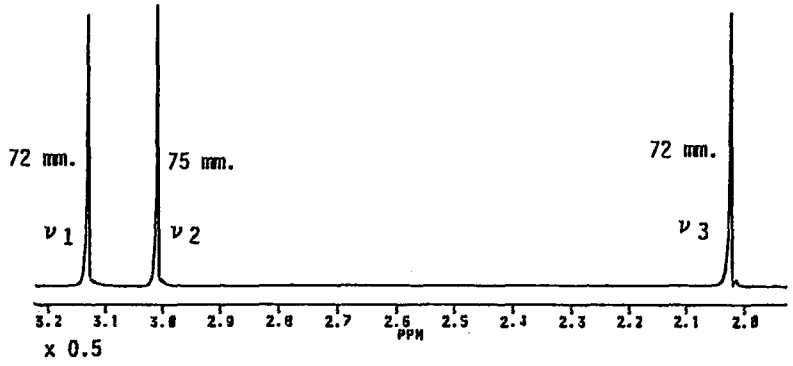
c) Irradiation at ν_3 : $D_S = 144$, $C_S = 104$

Peak 1 : $A_S = .390625$, $B_S = 144$, % n.O.e = .38

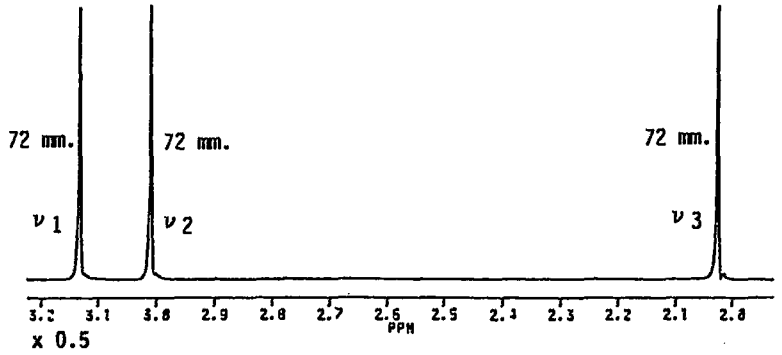
Peak 2 : $A_S = .76565$, $B_S = 150$, % n.O.e = .71



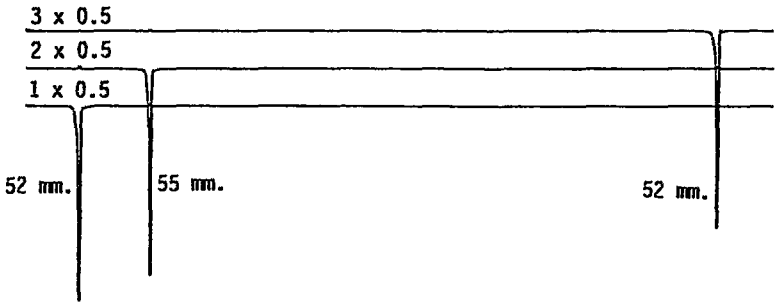
A) Observed n.O.e Specta.



B) Reference Spectum of A.



D) Reference Spectum of C.



C) Negative Specta of A.

FIGURE 42

3.4 CRYSTAL STRUCTURE DETERMINATION OF 2-DIMETHYLAMINO-3-(2-HYDROXYBENZOYL)-*N*,*N*-DIMETHYLACRYLAMIDE.

Collection and reduction of intensity data.

The crystal used for data collection was grown from 95% ethanol. Preliminary investigation was carried out using a Stoe reciprocal lattice explorer. The absence of symmetry in the oscillation photograph and the de Jong-Bouman photograph of the reciprocal lattice plane *hk0* indicated that the crystal was triclinic with the space group *P*1 or $P\bar{1}$. Crystal density calculation indicated that there were two molecules per unit cell, suggesting $P\bar{1}$ as the correct group. The structure was successfully refined in $P\bar{1}$ which confirmed this assignment. X-ray intensity data were measured on an Enraf-Nonius CAD4 diffractometer at 298K using graphite-monochromated *Mo* K^{α} radiation (λ = 0.70930 Å). The data were corrected for Lorenz and polarization effects and for absorption.

Structure solution and refinement.

Automatic centrosymmetric direct methods were used to determine the positions of the non-hydrogen atoms. The structure was refined using full matrix least-squares; 190 parameters were refined using 3260 observed ($I > \sigma(I)$) reflections. All the non-hydrogen atoms were assigned anisotropic temperature factors. Hydrogen atoms [with the exception of the hydroxy hydrogen H(0)] were placed at calculated positions based on the corresponding carbon atoms and refined with common isotropic temperature factors. The position of H(0) was determined from the difference Fourier map and refined in subsequent cycles. H(0) is involved in an intramolecular hydrogen bond : O(1)-H(0) 0.87(3)Å; O(2)...H(0) 1.69(3)Å; and O(1)-H(0)...O(2) 150.0(2)°. The final refinement converged to an R factor of 0.069 with

unit weights for the reflection data. *SHELX* [158] was used for the structure solution and refinement.

Structure Analysis.

The crystal data are summarised in tables 12-23 (Appendix 5.2). The program *XANADU* [159] was used to calculate dihedral angles of the amide and enamine functionalities (table 17) and the hydrogen bond (table 18), mean planes through various groups of atoms (tables 19-22) and the angles between the normals of the planes (table 23). The plotting program *PLUTO* [160] was used to obtain the molecular structure (figure 21 p.97) and packing diagram (figure 22 p.98) viewed in the direction of minimum overlap. Crystal data are summarised in table 12, the atomic co-ordinates and equivalent isotropic temperature factors for the non-hydrogen atoms and the atomic co-ordinates and isotropic temperature factor for H(0) in table 13, the atomic co-ordinates and isotropic temperature factors for the hydrogen atoms in table 16, bond lengths and angles for non-hydrogen atoms and H(0) in table 14, and the anisotropic temperature factors for non-hydrogen atoms in table 15. Observed and calculated structure factors are available from the Department of Chemistry and Biochemistry, Rhodes University, Grahamstown, South Africa.

3.5 KINETIC STUDIES.

Standard ethanolic chromone-2-carboxamide solutions were prepared by the following illustrative procedure : *N*,*N*-dimethylchromone-2-carboxamide **129** (5.0 mg, 23.0 mmol) was dissolved in dry EtOH (10 ml) in a 10 ml volumetric flask and the resulting solution (0.46 ml, 1.05 x 10^{-3} mmol) was diluted in a 10 ml volumetric flask. This solution (1.00 ml, 1.05 x 10^{-3} mmol) was then diluted in a 3 ml reaction volumetric flask to the required initial concentration. The volumes and corresponding dimethylamine concentrations used are summarised in Table 24.

Dilution and triggering of the reaction were carried out in a 3 ml volumetric flask [for the chromone-2-carboxamides (**129**,**130**,**132**, and **133**) standard amide solutions (1.00 ml) were added to the volumetric flask containing the required ethanolic dimethylamine (33% w/w; 0.22 - 1.43 ml); while ethanolic dimethylamine (33% w/w; 32.54 - 54.23 μl) was added to the flask containing *N*,*N*-dimethyl-7-nitro-chromone-2-carboxamide **131** (1.00 ml)]. The stopwatch was started after combining the reagents and mixing was achieved by inverting the flask five times. The reaction was then transferred to the curvette and initial readings were taken after 1 - 2 min.

Concentrations and corresponding absorptions required for the Beer's Law determinations of the acrylamides (**140**,**142-143**) were calculated using molar absorption coefficients [e.g. for the parent acrylamide (**140**), λ_{max} 357 (ε 29 647 dm^3 mol^{-1} cm^{-1})]. Standard ethanolic acrylamide solutions were prepared by the following procedure : (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**140**) (5.35 mg, 20.4 mmol) was dissolved in dry EtOH (10 ml) in a 10 ml volumetric flask and the resulting solution (0.50 ml, 1.02 x 10^{-4} mmol) was diluted in a 10 ml

volumetric flask. This solution was then diluted in a 3 ml volumetric flask. The volumes used for the final dilution, and the concentrations, calculated absorptions (A_c), and measured absorptions (A_m) are summarised in table 25 p.186. The linear regression data is summarised below Table 25.

TABLE 24. Ethanolic dimethylamine concentrations.

R^1	Volume[a] (ml)	$[Me_2NH]$ ($mol.l^{-1}$)	R^1	Volume[b] (μl)	$[Me_2NH]$ ($10^{-2}mol.l^{-1}$)
H	0.55	1.00	NO_2	32.54	5.9
	0.66	1.20		37.96	6.9
	0.77	1.40		43.38	7.9
	0.88	1.60		48.81	8.9
OMe	0.99	1.80		54.23	9.9
	1.10	2.00			
	1.21	2.20			
	1.32	2.40			
	1.43	2.60			
F	0.22	0.40			
	0.27	0.50			
	0.33	0.60			
	0.38	0.70			
	0.44	0.80			
Cl	0.11	0.20			
	0.17	0.30			
	0.22	0.40			
	0.27	0.50			
	0.33	0.60			

[a] ± 0.1 ml. [b] ± 0.4 μl.

TABLE 25. Beer's Law data for 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide **140**.

[acrylamide] (10^{-5} mol.l^{-1})	volume (ml)	A_c	A_m
0.7	0.20	0.2	0.233
1.4	0.40	0.4	0.440
2.0	0.59	0.6	0.639
2.7	0.79	0.8	0.858
3.4	0.99	1.0	1.083
4.0	1.19	1.2	1.305

The linear regression data are summarised below :

(i) determinations of Beer's law p.187-189;

(ii) determinations of the pseudo first order rate constants (k_a) p.190-214;

(iii) determinations of the observed rate constants (k_{obs}) p. 215-217.

(iv) Hammett plot p.217.

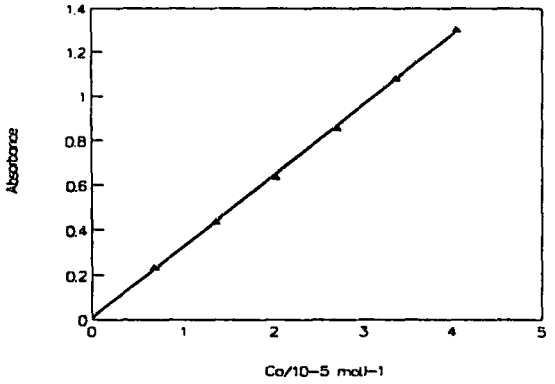
(i) Determinations of Beer's law.

140 R-H

No.	Ca/10-5	Absorbance	Y(calc)
1	0.68	0.233	0.224
2	1.35	0.440	0.438
3	2.02	0.639	0.651
4	2.70	0.858	0.867
5	3.37	1.083	1.081
6	4.05	1.305	1.297

Regression Output:

Constant		0.00799
Std Err of Y Est		0.00972
R Squared		0.99953
No. of Observations		6
Degrees of Freedom		4
X Coefficient(s)	0.31828	
Std Err of Coef.	0.00345	

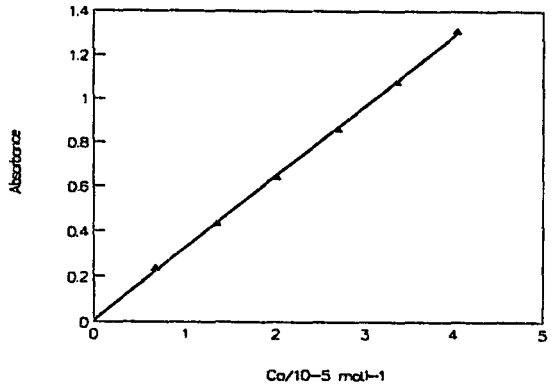


R-H

No.	Ca/10-5	Absorbance	Y(calc)
1	0.68	0.235	0.222
2	1.35	0.432	0.437
3	2.02	0.641	0.651
4	2.70	0.862	0.868
5	3.37	1.080	1.083
6	4.05	1.311	1.300

Regression Output:

Constant		0.00478
Std Err of Y Est		0.01055
R Squared		0.99945
No. of Observations		6
Degrees of Freedom		4
X Coefficient(s)	0.31985	
Std Err of Coef.	0.00374	

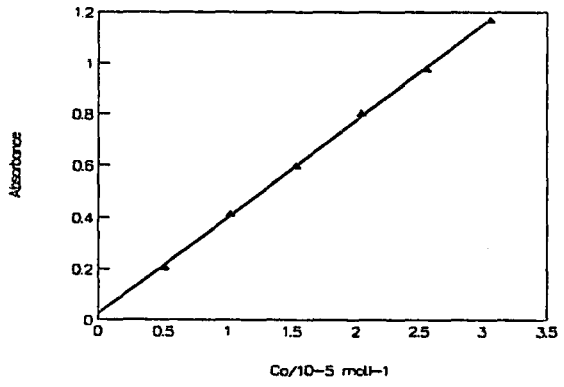


142 R-OMe

No.	Ca/10-5	Absorbance	Y(calc)
1	0.51	0.207	0.216
2	1.02	0.416	0.408
3	1.53	0.599	0.599
4	2.04	0.802	0.791
5	2.56	0.978	0.986
6	3.06	1.171	1.173

Regression Output:

Constant		0.02513
Std Err of Y Est		0.00937
R Squared		0.99945
No. of Observations		6
Degrees of Freedom		4
X Coefficient(s)	0.37521	
Std Err of Coef.	0.00439	

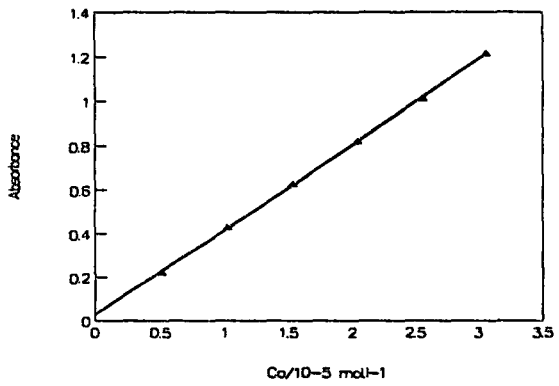


R-OMe

No.	Ca/10-5	Absorbance	Y(calc)
1	0.51	0.221	0.227
2	1.02	0.429	0.424
3	1.53	0.626	0.621
4	2.04	0.821	0.819
5	2.56	1.011	1.020
6	3.06	1.216	1.213

Regression Output:

Constant		0.02962
Std Err of Y Est		0.00652
R Squared		0.99975
No. of Observations		6
Degrees of Freedom		4
X Coefficient(s)	0.38678	
Std Err of Coef.	0.00305	

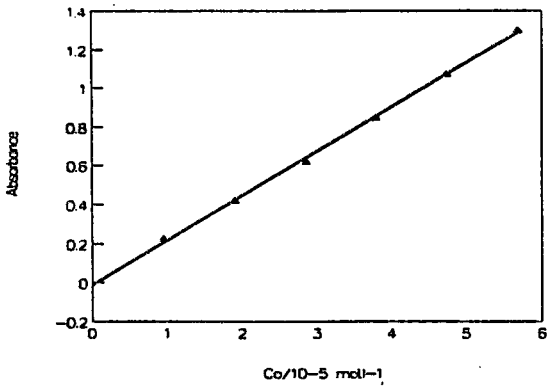


143 R-NO2

No.	Ca/10-5	Absorbance	Y(calc)
1	0.95	0.224	0.206
2	1.90	0.419	0.423
3	2.85	0.620	0.640
4	3.79	0.848	0.855
5	4.74	1.072	1.072
6	5.69	1.302	1.289

Regression Output:

Constant	-0.01110
Std Err of Y Est	0.01550
R Squared	0.99883
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.22849
Std Err of Coef.	0.00391

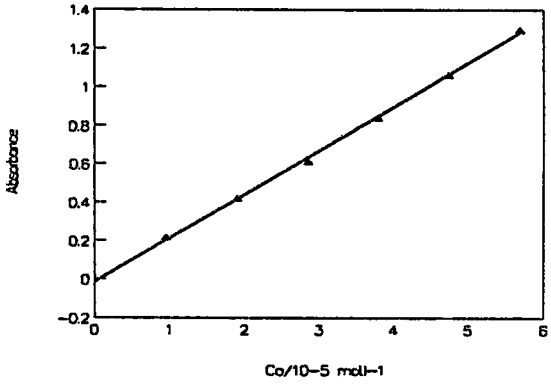


R-NO2

No.	Ca/10-5	Absorbance	Y(calc)
1	0.95	0.215	0.201
2	1.90	0.420	0.417
3	2.85	0.612	0.634
4	3.79	0.840	0.847
5	4.74	1.062	1.064
6	5.69	1.294	1.280

Regression Output:

Constant	-0.01530
Std Err of Y Est	0.01518
R Squared	0.99887
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.22765
Std Err of Coef.	0.00383

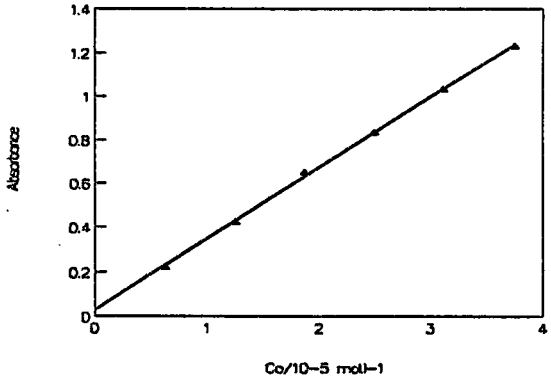


144 R-F

No.	Ca/10-5	Absorbance	Y(calc)
1	0.62	0.221	0.229
2	1.25	0.426	0.431
3	1.87	0.651	0.631
4	2.50	0.835	0.835
5	3.12	1.033	1.035
6	3.75	1.233	1.238

Regression Output:

Constant	0.02712
Std Err of Y Est	0.01129
R Squared	0.99929
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.32303
Std Err of Coef.	0.00432

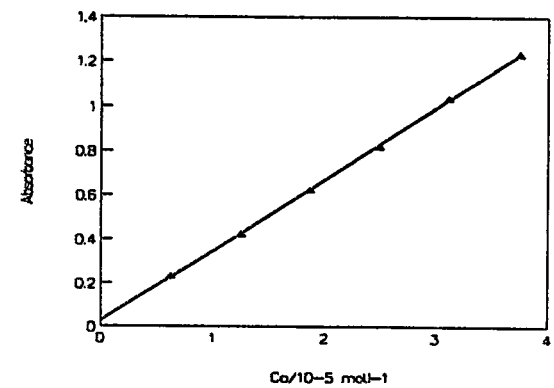


R-F

No.	Ca/10-5	Absorbance	Y(calc)
1	0.62	0.231	0.225
2	1.25	0.423	0.426
3	1.87	0.624	0.625
4	2.50	0.818	0.828
5	3.12	1.033	1.027
6	3.75	1.232	1.230

Regression Output:

Constant	0.02437
Std Err of Y Est	0.00682
R Squared	0.99974
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.32139
Std Err of Coef.	0.00261

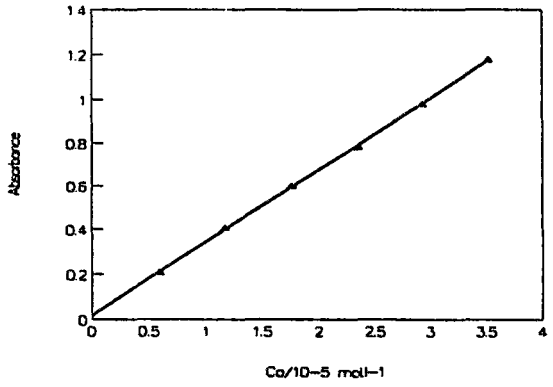


145 R=Cl

No.	Ca/10-5	Absorbance	Y(calc)
1	0.59	0.207	0.210
2	1.17	0.406	0.401
3	1.76	0.600	0.596
4	2.35	0.783	0.790
5	2.93	0.978	0.981
6	3.52	1.179	1.175

Regression Output:

Constant	0.01584
Std Err of Y Est	0.00554
R Squared	0.99981
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.32938
Std Err of Coef.	0.00226

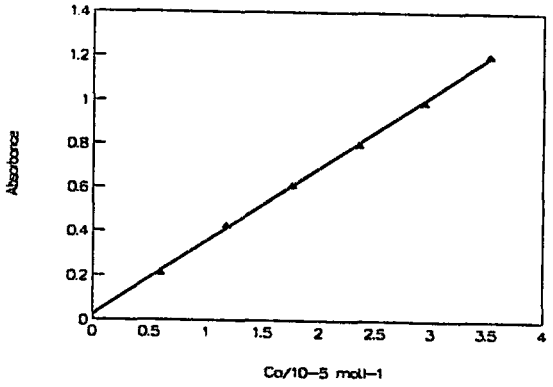


R=Cl

No.	Ca/10-5	Absorbance	Y(calc)
1	0.59	0.214	0.221
2	1.17	0.427	0.414
3	1.76	0.613	0.611
4	2.35	0.801	0.808
5	2.93	0.994	1.002
6	3.52	1.206	1.199

Regression Output:

Constant	0.02384
Std Err of Y Est	0.00967
R Squared	0.99944
No. of Observations	6
Degrees of Freedom	4
X Coefficient(s)	0.33376
Std Err of Coef.	0.00394



(ii) Determinations of pseudo first order rate constants (k_a).

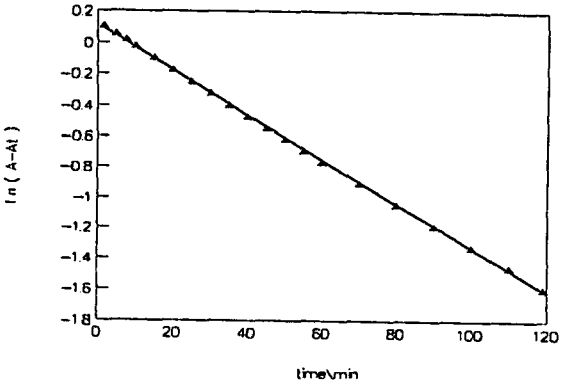
129

RUN 1 R-H Ca=3.5 Cb=1.0 A=1.163 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.58	0.050	1.113	0.107	0.092
2	5.02	0.106	1.057	0.055	0.042
3	7.50	0.146	1.017	0.017	0.006
4	10.00	0.185	0.978	-0.022	-0.030
5	15.00	0.255	0.908	-0.097	-0.102
6	20.00	0.322	0.841	-0.173	-0.174
7	25.00	0.383	0.780	-0.248	-0.246
8	30.00	0.439	0.724	-0.323	-0.318
9	35.00	0.491	0.672	-0.397	-0.390
10	40.00	0.539	0.624	-0.472	-0.462
11	45.02	0.583	0.580	-0.545	-0.535
12	50.00	0.624	0.539	-0.618	-0.607
13	55.00	0.662	0.501	-0.691	-0.679
14	60.00	0.697	0.466	-0.764	-0.751
15	70.00	0.759	0.404	-0.906	-0.895
16	80.03	0.812	0.351	-1.047	-1.040
17	90.00	0.858	0.305	-1.187	-1.184
18	100.02	0.897	0.266	-1.324	-1.328
19	110.00	0.930	0.233	-1.457	-1.472
20	120.00	0.960	0.203	-1.595	-1.616

Regression Output:

Constant	0.1147
Std Err of Y Est	0.0111
R Squared	0.9996
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0144
Std Err of Coef.	0.0001

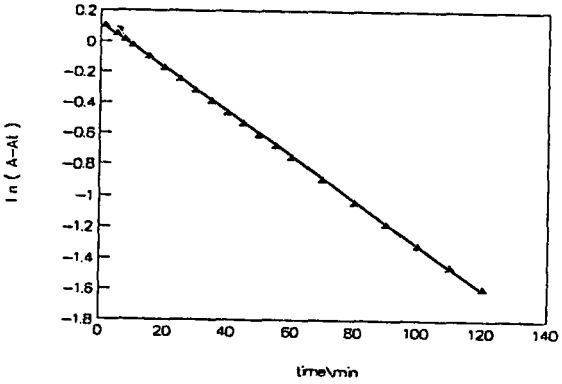


RUN 2 R-H Ca=3.5 Cb=1.0 A=1.156 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.15	0.043	1.113	0.107	0.099
2	5.00	0.101	1.055	0.054	0.044
3	7.50	0.140	1.016	0.016	0.008
4	10.00	0.178	0.978	-0.022	-0.028
5	15.00	0.248	0.908	-0.097	-0.099
6	20.00	0.313	0.843	-0.171	-0.171
7	25.00	0.372	0.784	-0.243	-0.242
8	30.00	0.428	0.728	-0.317	-0.314
9	35.00	0.479	0.677	-0.390	-0.385
10	40.00	0.527	0.629	-0.464	-0.457
11	45.00	0.570	0.586	-0.534	-0.528
12	50.00	0.611	0.545	-0.607	-0.600
13	55.00	0.649	0.507	-0.679	-0.671
14	60.00	0.684	0.472	-0.751	-0.743
15	70.00	0.747	0.409	-0.894	-0.886
16	80.00	0.801	0.355	-1.036	-1.029
17	90.00	0.847	0.309	-1.174	-1.172
18	100.02	0.887	0.269	-1.313	-1.315
19	110.00	0.921	0.235	-1.448	-1.458
20	120.02	0.951	0.205	-1.585	-1.601

Regression Output:

Constant	0.1152
Std Err of Y Est	0.0076
R Squared	0.9998
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0143
Std Err of Coef.	0.0000

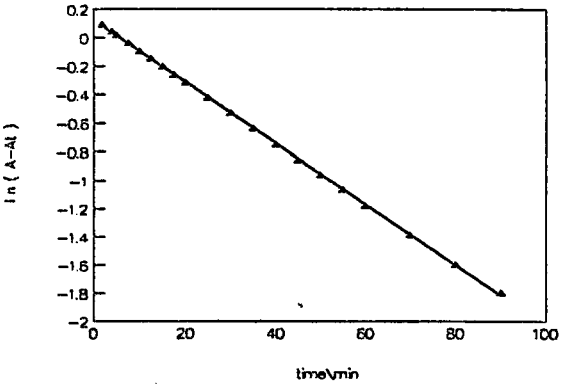


RUN 1 R=H Ca=3.5 Cb=1.2 A=1.163 %R=85

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.77	0.068	1.095	0.091	0.083
2	3.97	0.118	1.045	0.044	0.036
3	5.00	0.143	1.020	0.020	0.014
4	7.50	0.198	0.965	-0.036	-0.040
5	10.00	0.255	0.908	-0.097	-0.094
6	12.50	0.299	0.864	-0.146	-0.148
7	15.00	0.344	0.819	-0.200	-0.201
8	17.50	0.389	0.774	-0.256	-0.255
9	20.02	0.430	0.733	-0.311	-0.309
10	25.00	0.506	0.657	-0.420	-0.417
11	30.00	0.573	0.590	-0.528	-0.524
12	35.00	0.634	0.529	-0.637	-0.632
13	40.00	0.689	0.474	-0.747	-0.739
14	45.00	0.738	0.425	-0.856	-0.847
15	50.02	0.781	0.382	-0.962	-0.955
16	55.00	0.819	0.344	-1.067	-1.062
17	60.00	0.855	0.308	-1.178	-1.170
18	70.00	0.913	0.250	-1.386	-1.385
19	80.00	0.960	0.203	-1.595	-1.600
20	90.00	0.997	0.166	-1.796	-1.815

Regression Output:

Constant	0.1213
Std Err of Y Est	0.0072
R Squared	0.9999
No. of Observations	20
Degrees of Freadom	18
X Coefficient(s)	-0.0215
Std Err of Coef.	0.0001

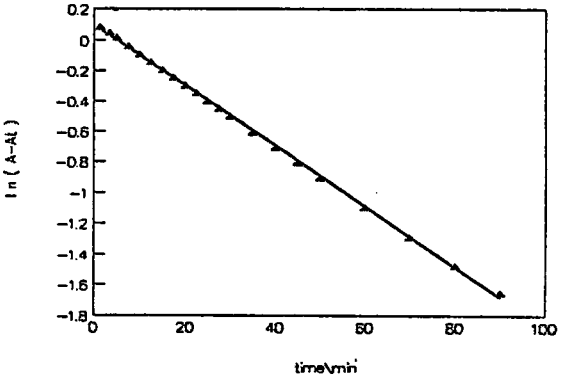


RUN 2 R=H Ca=3.5 Cb=1.2 A=1.146 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.40	0.056	1.090	0.086	0.072
2	3.40	0.099	1.047	0.046	0.033
3	5.00	0.133	1.013	0.013	0.001
4	7.50	0.185	0.961	-0.040	-0.048
5	10.00	0.234	0.912	-0.092	-0.098
6	12.50	0.280	0.866	-0.144	-0.147
7	15.00	0.324	0.822	-0.196	-0.197
8	17.50	0.365	0.781	-0.247	-0.246
9	20.00	0.404	0.742	-0.298	-0.296
10	22.50	0.441	0.705	-0.350	-0.345
11	25.00	0.476	0.670	-0.400	-0.395
12	27.50	0.509	0.637	-0.451	-0.444
13	30.00	0.541	0.605	-0.503	-0.494
14	35.00	0.602	0.544	-0.609	-0.593
15	40.00	0.653	0.493	-0.707	-0.692
16	45.00	0.699	0.447	-0.805	-0.791
17	50.00	0.741	0.405	-0.904	-0.890
18	60.00	0.811	0.335	-1.094	-1.088
19	70.00	0.871	0.275	-1.291	-1.286
20	80.00	0.917	0.229	-1.474	-1.484
21	90.00	0.954	0.192	-1.650	-1.682

Regression Output:

Constant	0.1002
Std Err of Y Est	0.0122
R Squared	0.9995
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.0198
Std Err of Coef.	0.0001

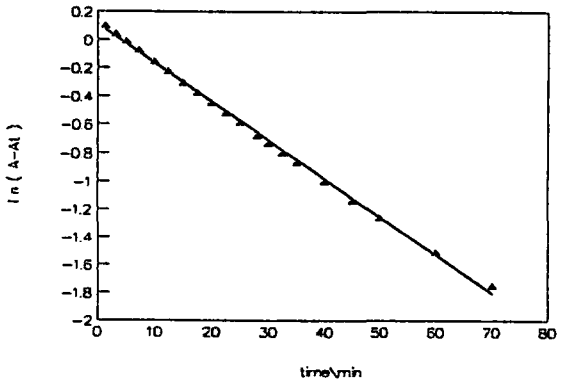


RUN 1 R=H Cb=3.5 Cb=1.4 A=1.170 %R=85

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.38	0.066	1.104	0.099	0.072
2	3.17	0.127	1.043	0.042	0.024
3	5.00	0.177	0.993	-0.007	-0.026
4	7.15	0.238	0.932	-0.070	-0.085
5	10.00	0.312	0.858	-0.153	-0.163
6	12.38	0.370	0.800	-0.223	-0.228
7	15.03	0.430	0.740	-0.301	-0.300
8	17.50	0.481	0.689	-0.373	-0.368
9	20.00	0.528	0.642	-0.443	-0.436
10	22.50	0.573	0.597	-0.516	-0.504
11	25.00	0.613	0.557	-0.585	-0.572
12	28.00	0.660	0.510	-0.673	-0.654
13	30.00	0.688	0.482	-0.730	-0.709
14	32.52	0.720	0.450	-0.799	-0.778
15	35.00	0.750	0.420	-0.868	-0.845
16	40.02	0.803	0.367	-1.002	-0.982
17	45.02	0.849	0.321	-1.136	-1.119
18	50.00	0.887	0.283	-1.262	-1.255
19	60.02	0.949	0.221	-1.510	-1.528
20	70.13	0.996	0.174	-1.749	-1.804

Regression Output:

Constant	0.1102
Std Err of Y Est	0.0212
R Squared	0.9985
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0273
Std Err of Coef.	0.0003

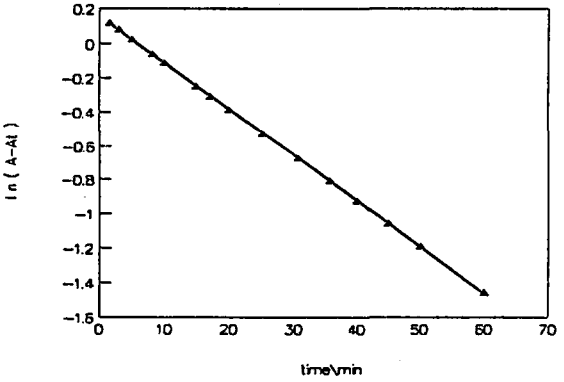


RUN 2 R=H Ca=3.5 Cb=1.4 A=1.190 %R=80

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.55	0.063	1.127	0.120	0.117
2	3.00	0.105	1.085	0.082	0.077
3	5.02	0.163	1.027	0.027	0.023
4	8.20	0.249	0.941	-0.061	-0.063
5	10.02	0.295	0.895	-0.111	-0.112
6	14.98	0.410	0.780	-0.248	-0.246
7	17.18	0.455	0.735	-0.308	-0.305
8	20.03	0.510	0.680	-0.386	-0.382
9	25.15	0.599	0.591	-0.526	-0.520
10	30.67	0.680	0.510	-0.673	-0.669
11	35.67	0.744	0.446	-0.807	-0.804
12	40.02	0.793	0.397	-0.924	-0.922
13	45.02	0.842	0.348	-1.056	-1.056
14	50.02	0.885	0.305	-1.187	-1.191
15	60.06	0.957	0.233	-1.457	-1.462

Regression Output:

Constant	0.1584
Std Err of Y Est	0.0038
R Squared	0.9999
No. of Observations	15
Degrees of Freedom	13
X Coefficient(s)	-0.0270
Std Err of Coef.	0.0001

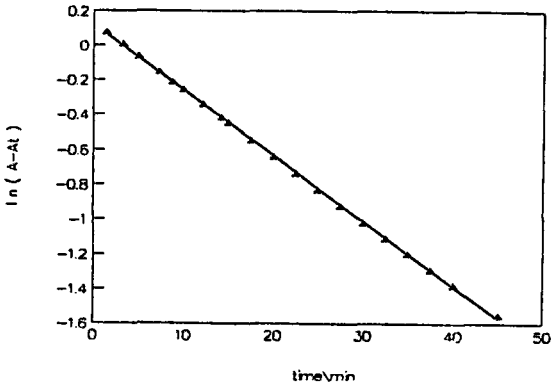


RUN 1 R-H Ca=3.5 Cb=1.6 A=1.16 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.38	0.079	1.081	0.078	0.067
2	3.25	0.153	1.007	0.007	-0.003
3	5.00	0.220	0.940	-0.062	-0.069
4	7.32	0.302	0.858	-0.153	-0.156
5	8.82	0.350	0.810	-0.211	-0.212
6	10.00	0.387	0.773	-0.257	-0.257
7	12.25	0.450	0.710	-0.342	-0.341
8	14.22	0.503	0.657	-0.420	-0.415
9	15.00	0.522	0.638	-0.449	-0.445
10	17.50	0.581	0.579	-0.546	-0.539
11	20.00	0.633	0.527	-0.641	-0.633
12	22.53	0.681	0.479	-0.736	-0.728
13	25.00	0.723	0.437	-0.828	-0.820
14	27.50	0.762	0.398	-0.921	-0.914
15	30.00	0.798	0.362	-1.016	-1.008
16	32.50	0.829	0.331	-1.106	-1.102
17	35.00	0.858	0.302	-1.197	-1.196
18	37.50	0.884	0.276	-1.287	-1.290
19	40.00	0.908	0.252	-1.378	-1.384
20	45.00	0.948	0.212	-1.551	-1.572

Regression Output:

Constant	0.1190
Std Err of Y Est	0.0081
R Squared	0.9997
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0376
Std Err of Coef.	0.0001

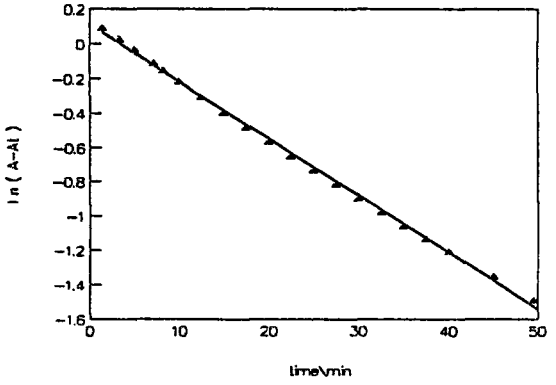


RUN 2 R-H Ca=3.5 Cb=1.6 A=1.180 %R=81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.42	0.084	1.096	0.092	0.067
2	3.38	0.154	1.026	0.026	0.002
3	5.00	0.213	0.967	-0.034	-0.051
4	7.13	0.286	0.894	-0.112	-0.122
5	8.23	0.321	0.859	-0.152	-0.158
6	10.00	0.373	0.807	-0.214	-0.217
7	12.50	0.442	0.738	-0.304	-0.299
8	15.00	0.505	0.675	-0.393	-0.382
9	17.50	0.560	0.620	-0.478	-0.465
10	20.00	0.612	0.568	-0.566	-0.547
11	22.50	0.658	0.522	-0.650	-0.630
12	25.00	0.699	0.481	-0.732	-0.713
13	27.50	0.737	0.443	-0.814	-0.795
14	30.00	0.772	0.408	-0.896	-0.878
15	32.50	0.803	0.377	-0.976	-0.961
16	35.00	0.833	0.347	-1.058	-1.044
17	37.50	0.858	0.322	-1.133	-1.126
18	40.00	0.881	0.299	-1.207	-1.209
19	45.00	0.921	0.259	-1.351	-1.374
20	50.00	0.954	0.226	-1.487	-1.540

Regression Output:

Constant	0.1143
Std Err of Y Est	0.0204
R Squared	0.9983
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0331
Std Err of Coef.	0.0003

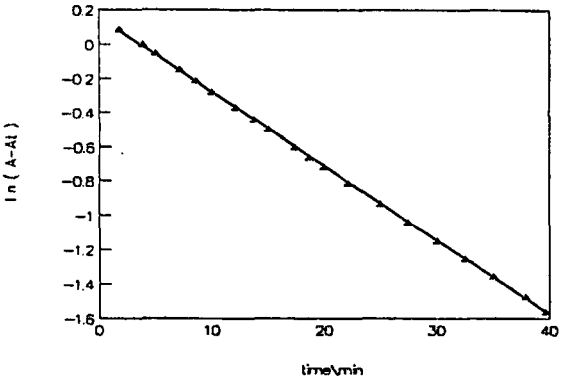


RUN 1 R-H Ca=3.5 Cb=1.8 A=1.193 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.78	0.104	1.089	0.085	0.078
2	3.85	0.195	0.998	-0.002	-0.011
3	5.00	0.245	0.948	-0.053	-0.061
4	7.12	0.330	0.863	-0.147	-0.153
5	8.55	0.385	0.808	-0.213	-0.215
6	10.00	0.435	0.758	-0.277	-0.277
7	12.13	0.503	0.690	-0.371	-0.369
8	13.72	0.550	0.643	-0.442	-0.438
9	15.00	0.586	0.607	-0.499	-0.494
10	17.32	0.645	0.548	-0.601	-0.594
11	18.68	0.676	0.517	-0.660	-0.653
12	20.00	0.705	0.488	-0.717	-0.710
13	22.18	0.750	0.443	-0.814	-0.804
14	25.02	0.800	0.393	-0.934	-0.927
15	27.53	0.840	0.353	-1.041	-1.036
16	30.02	0.876	0.317	-1.149	-1.144
17	32.53	0.907	0.286	-1.252	-1.252
18	35.00	0.935	0.258	-1.355	-1.359
19	37.85	0.964	0.229	-1.474	-1.483
20	40.00	0.983	0.210	-1.561	-1.576

Regression Output:

Constant	0.1555
Std Err of Y Est	0.0072
R Squared	0.9998
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0433
Std Err of Coef.	0.0001

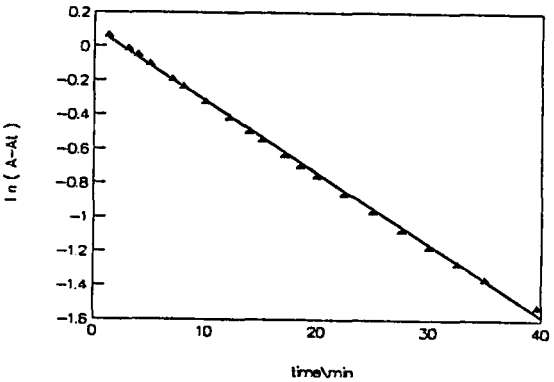


RUN 2 R-H Ca=3.5 Cb=1.8 A=1.151 %R=81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.23	0.082	1.069	0.067	0.046
2	3.00	0.161	0.990	-0.010	-0.028
3	3.90	0.200	0.951	-0.050	-0.065
4	5.00	0.246	0.905	-0.100	-0.111
5	7.00	0.324	0.827	-0.190	-0.195
6	8.00	0.360	0.791	-0.234	-0.237
7	9.98	0.427	0.724	-0.323	-0.320
8	12.12	0.492	0.659	-0.417	-0.409
9	13.87	0.540	0.611	-0.493	-0.483
10	15.02	0.570	0.581	-0.543	-0.531
11	17.05	0.619	0.532	-0.631	-0.616
12	18.50	0.651	0.500	-0.693	-0.677
13	20.00	0.681	0.470	-0.755	-0.739
14	22.48	0.727	0.424	-0.858	-0.843
15	25.00	0.769	0.382	-0.962	-0.949
16	27.55	0.809	0.342	-1.073	-1.055
17	30.00	0.840	0.311	-1.168	-1.158
18	32.50	0.869	0.282	-1.266	-1.263
19	35.00	0.894	0.257	-1.359	-1.367
20	40.00	0.932	0.219	-1.519	-1.577

Regression Output:

Constant	0.0979
Std Err of Y Est	0.0189
R Squared	0.9985
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0419
Std Err of Coef.	0.0004



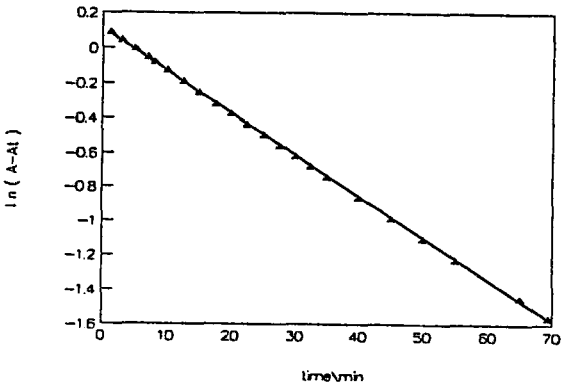
130

RUN 1 R-OMe Ca-3.0 Cb-1.8 A-1.152 %R-82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.22	0.060	1.092	0.088	0.080
2	3.00	0.107	1.045	0.044	0.037
3	5.00	0.157	0.995	-0.005	-0.011
4	7.00	0.204	0.948	-0.053	-0.059
5	8.00	0.228	0.924	-0.079	-0.084
6	10.00	0.272	0.880	-0.128	-0.132
7	12.50	0.326	0.826	-0.191	-0.192
8	15.00	0.376	0.776	-0.254	-0.252
9	17.70	0.426	0.726	-0.320	-0.318
10	20.00	0.465	0.687	-0.375	-0.373
11	22.50	0.506	0.646	-0.437	-0.433
12	25.00	0.545	0.607	-0.499	-0.494
13	27.50	0.581	0.571	-0.560	-0.554
14	30.00	0.615	0.537	-0.622	-0.614
15	32.50	0.646	0.506	-0.681	-0.675
16	35.00	0.676	0.476	-0.742	-0.735
17	40.00	0.730	0.422	-0.863	-0.856
18	45.00	0.778	0.374	-0.983	-0.976
19	50.00	0.820	0.332	-1.103	-1.097
20	55.00	0.858	0.294	-1.224	-1.218
21	65.00	0.916	0.236	-1.444	-1.459
22	70.00	0.942	0.210	-1.561	-1.579

Regression Output:

Constant	0.1095
Std Err of Y Est	0.0078
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0241
Std Err of Coef.	0.0001

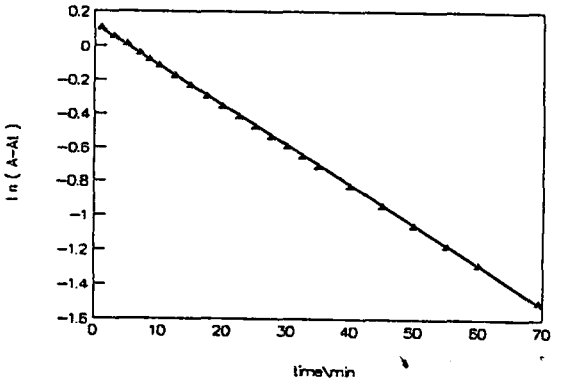


RUN 2 R-OMe Ca-3.0 Cb-1.8 A-1.166 %R-81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.03	0.052	1.114	0.108	0.098
2	3.00	0.103	1.063	0.061	0.052
3	5.00	0.153	1.013	0.013	0.005
4	7.00	0.202	0.964	-0.037	-0.042
5	8.50	0.236	0.930	-0.073	-0.078
6	10.00	0.270	0.896	-0.110	-0.113
7	12.50	0.323	0.843	-0.171	-0.171
8	15.00	0.372	0.794	-0.231	-0.230
9	17.52	0.419	0.747	-0.292	-0.289
10	20.00	0.463	0.703	-0.352	-0.347
11	22.50	0.504	0.662	-0.412	-0.406
12	25.00	0.542	0.624	-0.472	-0.465
13	27.50	0.578	0.588	-0.531	-0.523
14	30.00	0.612	0.554	-0.591	-0.582
15	32.50	0.644	0.522	-0.650	-0.641
16	35.00	0.674	0.492	-0.709	-0.699
17	40.00	0.728	0.438	-0.826	-0.817
18	45.00	0.775	0.391	-0.939	-0.934
19	50.00	0.818	0.348	-1.056	-1.051
20	55.00	0.855	0.311	-1.168	-1.169
21	60.00	0.888	0.278	-1.280	-1.286
22	70.00	0.942	0.224	-1.496	-1.521

Regression Output:

Constant	0.1219
Std Err of Y Est	0.0087
R Squared	0.9997
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0235
Std Err of Coef.	0.0001

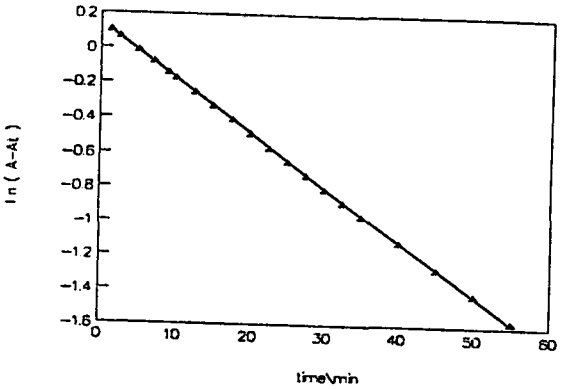


RUN 1 R-OMe Ca=3.0 Cb=2.0 A=1.182 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.32	0.072	1.110	0.104	0.098
2	2.50	0.112	1.070	0.068	0.062
3	5.00	0.194	0.988	-0.012	-0.016
4	7.00	0.255	0.927	-0.076	-0.079
5	9.00	0.313	0.869	-0.140	-0.141
6	10.00	0.340	0.842	-0.172	-0.172
7	12.58	0.406	0.776	-0.254	-0.253
8	15.00	0.463	0.719	-0.330	-0.329
9	17.52	0.518	0.664	-0.409	-0.407
10	20.00	0.568	0.614	-0.488	-0.485
11	22.50	0.615	0.567	-0.567	-0.563
12	25.00	0.658	0.524	-0.646	-0.641
13	27.50	0.697	0.485	-0.724	-0.719
14	30.00	0.733	0.449	-0.801	-0.797
15	32.50	0.767	0.415	-0.879	-0.875
16	35.00	0.798	0.384	-0.957	-0.953
17	40.00	0.853	0.329	-1.112	-1.109
18	45.00	0.900	0.282	-1.266	-1.265
19	50.02	0.939	0.243	-1.415	-1.422
20	55.02	0.973	0.209	-1.565	-1.578

Regression Output:

Constant	0.1397
Std Err of Y Est	0.0051
R Squared	0.9999
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0312
Std Err of Coef.	0.0001

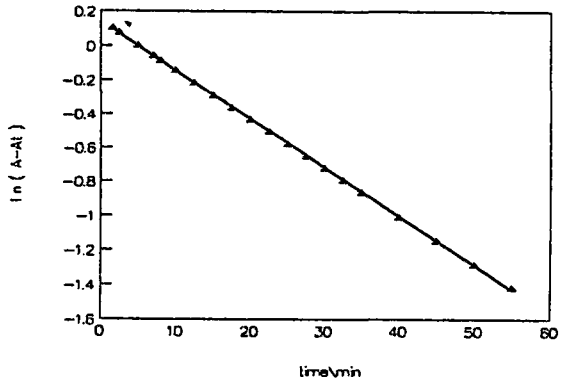


RUN 2 R-OMe Ca=3.0 Cb=2.0 A=1.195 %R=80

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.58	0.086	1.109	0.103	0.097
2	2.50	0.114	1.081	0.078	0.071
3	5.00	0.191	1.004	0.004	-0.001
4	7.00	0.248	0.947	-0.054	-0.058
5	8.00	0.276	0.919	-0.084	-0.087
6	10.00	0.328	0.867	-0.143	-0.144
7	12.50	0.389	0.806	-0.216	-0.215
8	15.00	0.446	0.749	-0.289	-0.287
9	17.50	0.499	0.696	-0.362	-0.358
10	20.00	0.547	0.648	-0.434	-0.429
11	22.50	0.592	0.603	-0.506	-0.501
12	25.00	0.634	0.561	-0.578	-0.572
13	27.50	0.673	0.522	-0.650	-0.644
14	30.02	0.709	0.486	-0.722	-0.716
15	32.50	0.742	0.453	-0.792	-0.787
16	35.00	0.773	0.422	-0.863	-0.858
17	40.00	0.829	0.366	-1.005	-1.001
18	45.00	0.876	0.319	-1.143	-1.144
19	50.00	0.917	0.278	-1.280	-1.287
20	55.00	0.952	0.243	-1.415	-1.430

Regression Output:

Constant	0.1420
Std Err of Y Est	0.0060
R Squared	0.9998
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0286
Std Err of Coef.	0.0001

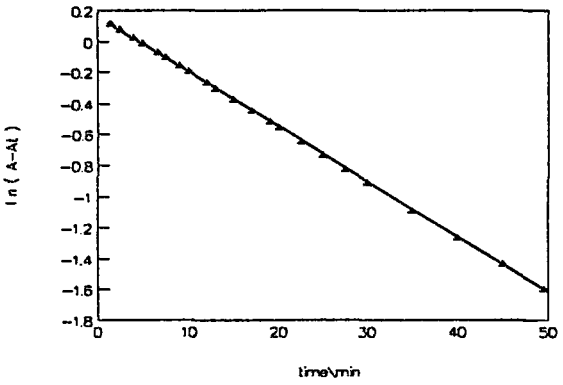


RUN 1 R=OMe Ca=3.0 Cb=2.2 A=1.227 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.42	0.100	1.127	0.120	0.113
2	2.50	0.142	1.085	0.082	0.074
3	4.02	0.201	1.026	0.026	0.020
4	5.00	0.237	0.990	-0.010	-0.014
5	6.62	0.292	0.935	-0.067	-0.072
6	7.50	0.322	0.905	-0.100	-0.103
7	9.00	0.371	0.856	-0.155	-0.157
8	10.05	0.403	0.824	-0.194	-0.194
9	12.02	0.460	0.767	-0.265	-0.264
10	13.00	0.487	0.740	-0.301	-0.299
11	15.00	0.538	0.689	-0.373	-0.370
12	17.00	0.586	0.641	-0.445	-0.441
13	19.00	0.631	0.596	-0.518	-0.512
14	20.00	0.652	0.575	-0.553	-0.547
15	22.52	0.702	0.525	-0.644	-0.637
16	25.00	0.747	0.480	-0.734	-0.725
17	27.50	0.787	0.440	-0.821	-0.814
18	30.00	0.824	0.403	-0.909	-0.902
19	35.00	0.889	0.338	-1.085	-1.080
20	40.00	0.943	0.284	-1.259	-1.258
21	45.00	0.987	0.240	-1.427	-1.435
22	50.00	1.024	0.203	-1.595	-1.613

Regression Output:

Constant	0.1631
Std Err of Y Est	0.0069
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0355
Std Err of Coef.	0.0001

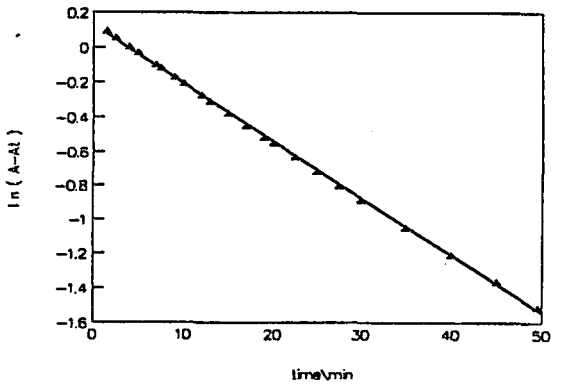


RUN 2 R=OMe Ca=3.0 Cb=2.2 A=1.191 %R=81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.45	0.095	1.096	0.092	0.079
2	2.50	0.134	1.057	0.055	0.044
3	4.00	0.188	1.003	0.003	-0.006
4	5.00	0.222	0.969	-0.031	-0.040
5	6.92	0.285	0.906	-0.099	-0.104
6	7.50	0.303	0.888	-0.119	-0.123
7	9.02	0.349	0.842	-0.172	-0.174
8	10.00	0.378	0.813	-0.207	-0.206
9	12.02	0.432	0.759	-0.276	-0.274
10	13.00	0.458	0.733	-0.311	-0.306
11	15.00	0.507	0.684	-0.380	-0.373
12	17.00	0.552	0.639	-0.448	-0.440
13	19.00	0.594	0.597	-0.516	-0.506
14	20.00	0.614	0.577	-0.550	-0.540
15	22.50	0.660	0.531	-0.633	-0.623
16	25.00	0.703	0.488	-0.717	-0.706
17	27.50	0.742	0.449	-0.801	-0.790
18	30.00	0.778	0.413	-0.884	-0.873
19	35.00	0.840	0.351	-1.047	-1.040
20	40.01	0.892	0.299	-1.207	-1.206
21	45.00	0.935	0.256	-1.363	-1.373
22	50.00	0.970	0.221	-1.510	-1.539

Regression Output:

Constant	0.1269
Std Err of Y Est	0.0109
R Squared	0.9995
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0333
Std Err of Coef.	0.0002

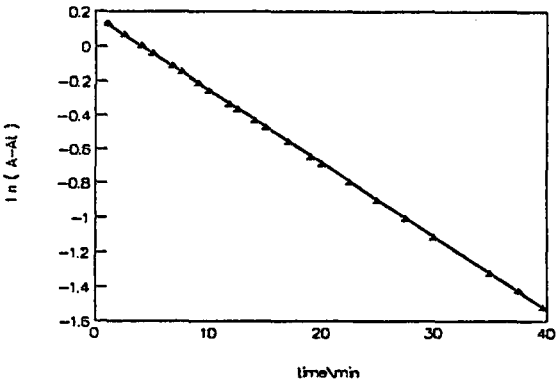


RUN 1 R=OMe Ca=3.0 Cb=2.4 A=1.225 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.05	0.083	1.142	0.133	0.126
2	2.50	0.151	1.074	0.071	0.065
3	4.00	0.219	1.006	0.006	0.001
4	5.00	0.262	0.963	-0.038	-0.042
5	6.70	0.330	0.895	-0.111	-0.114
6	7.50	0.361	0.864	-0.146	-0.148
7	9.00	0.416	0.809	-0.212	-0.212
8	10.00	0.450	0.775	-0.255	-0.255
9	11.78	0.508	0.717	-0.333	-0.331
10	12.50	0.530	0.695	-0.364	-0.361
11	14.00	0.574	0.651	-0.429	-0.425
12	15.00	0.602	0.623	-0.473	-0.468
13	17.00	0.653	0.572	-0.559	-0.553
14	19.00	0.700	0.525	-0.644	-0.638
15	20.00	0.722	0.503	-0.687	-0.680
16	22.50	0.773	0.452	-0.794	-0.787
17	25.00	0.818	0.407	-0.899	-0.893
18	27.50	0.858	0.367	-1.002	-1.000
19	30.00	0.895	0.330	-1.109	-1.106
20	35.00	0.957	0.268	-1.317	-1.319
21	37.52	0.983	0.242	-1.419	-1.426
22	40.00	1.006	0.219	-1.519	-1.532

Regression Output:

Constant	0.1710
Std Err of Y Est	0.0058
R Squared	0.9999
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0426
Std Err of Coef.	0.0001

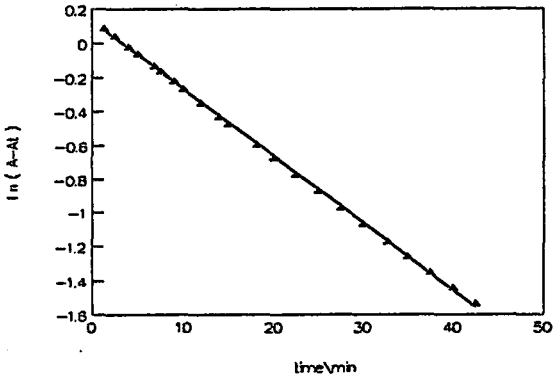


RUN 2 R=OMe Ca=3.0 Cb=2.4 A=1.191 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.35	0.097	1.094	0.090	0.080
2	2.50	0.147	1.044	0.043	0.034
3	4.00	0.209	0.982	-0.018	-0.025
4	5.00	0.249	0.942	-0.060	-0.065
5	6.78	0.314	0.877	-0.131	-0.136
6	7.50	0.339	0.852	-0.160	-0.164
7	9.00	0.390	0.801	-0.222	-0.224
8	10.00	0.423	0.768	-0.264	-0.263
9	11.98	0.484	0.707	-0.347	-0.342
10	14.00	0.539	0.652	-0.428	-0.422
11	15.02	0.566	0.625	-0.470	-0.463
12	18.12	0.639	0.552	-0.594	-0.586
13	20.00	0.680	0.511	-0.671	-0.660
14	22.50	0.728	0.463	-0.770	-0.759
15	25.00	0.771	0.420	-0.868	-0.858
16	27.50	0.811	0.380	-0.968	-0.958
17	30.00	0.846	0.345	-1.064	-1.057
18	32.77	0.881	0.310	-1.171	-1.167
19	35.00	0.906	0.285	-1.255	-1.255
20	37.52	0.932	0.259	-1.351	-1.355
21	40.00	0.954	0.237	-1.440	-1.454
22	42.50	0.975	0.216	-1.532	-1.553

Regression Output:

Constant	0.1334
Std Err of Y Est	0.0090
R Squared	0.9997
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0397
Std Err of Coef.	0.0001

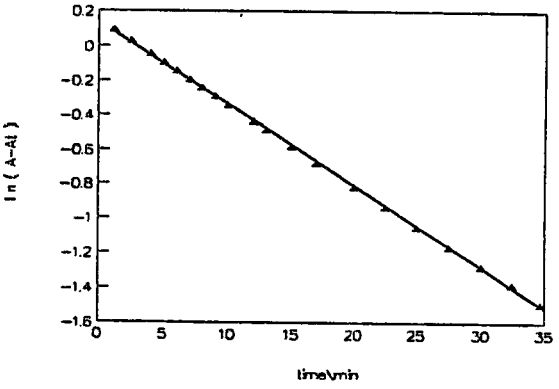


RUN 1 R=OMe Ca=3.0 Cb=2.6 A=1.197 %R=81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.18	0.100	1.097	0.093	0.080
2	2.50	0.168	1.029	0.029	0.018
3	4.00	0.242	0.955	-0.046	-0.053
4	5.00	0.287	0.910	-0.094	-0.100
5	6.00	0.330	0.867	-0.143	-0.147
6	7.00	0.372	0.825	-0.192	-0.194
7	8.00	0.412	0.785	-0.242	-0.242
8	9.00	0.449	0.748	-0.290	-0.289
9	10.00	0.486	0.711	-0.341	-0.336
10	12.00	0.552	0.645	-0.439	-0.430
11	13.00	0.582	0.615	-0.486	-0.477
12	15.00	0.638	0.559	-0.582	-0.571
13	17.00	0.690	0.507	-0.679	-0.666
14	20.02	0.756	0.441	-0.819	-0.808
15	22.50	0.805	0.392	-0.936	-0.925
16	25.00	0.847	0.350	-1.050	-1.043
17	27.50	0.885	0.312	-1.165	-1.161
18	30.00	0.918	0.279	-1.277	-1.278
19	32.50	0.946	0.251	-1.382	-1.396
20	35.00	0.972	0.225	-1.492	-1.514

Regression Output:

Constant	0.1354
Std Err of Y Est	0.0102
R Squared	0.9996
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0471
Std Err of Coef.	0.0002

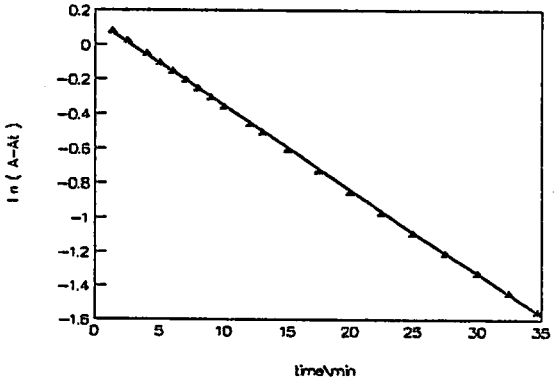


RUN 2 R=OMe Ca=3.0 Cb=2.6 A=1.198 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.35	0.112	1.086	0.083	0.071
2	2.50	0.172	1.026	0.026	0.015
3	4.00	0.246	0.952	-0.049	-0.058
4	5.03	0.296	0.902	-0.103	-0.108
5	6.00	0.340	0.858	-0.153	-0.156
6	7.00	0.382	0.816	-0.203	-0.205
7	8.00	0.422	0.776	-0.254	-0.253
8	9.00	0.461	0.737	-0.305	-0.302
9	10.00	0.498	0.700	-0.357	-0.351
10	12.00	0.564	0.634	-0.456	-0.449
11	13.00	0.595	0.603	-0.506	-0.497
12	15.00	0.652	0.546	-0.605	-0.595
13	17.50	0.715	0.483	-0.728	-0.717
14	20.00	0.771	0.427	-0.851	-0.839
15	22.50	0.819	0.379	-0.970	-0.961
16	25.00	0.861	0.337	-1.088	-1.083
17	27.50	0.899	0.299	-1.207	-1.205
18	30.00	0.932	0.266	-1.324	-1.327
19	32.50	0.961	0.237	-1.440	-1.449
20	35.00	0.986	0.212	-1.551	-1.571

Regression Output:

Constant	0.1371
Std Err of Y Est	0.0091
R Squared	0.9997
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0488
Std Err of Coef.	0.0002



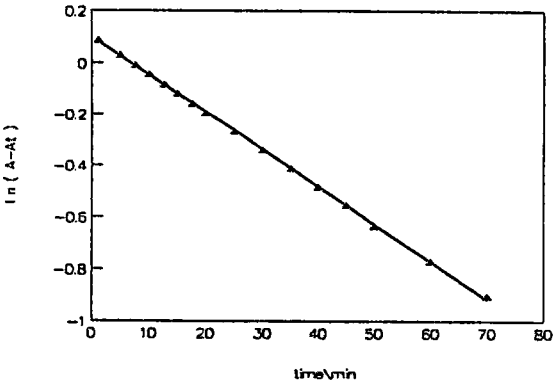
131

RUN 1 R=NO2 Ca=5.5 Cb=0.059 A=1.160 %R=65

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.18	0.069	1.091	0.087	0.082
2	5.00	0.129	1.031	0.031	0.027
3	7.65	0.169	0.991	-0.009	-0.012
4	10.02	0.203	0.957	-0.044	-0.046
5	12.75	0.241	0.919	-0.084	-0.086
6	15.00	0.272	0.888	-0.119	-0.118
7	17.65	0.307	0.853	-0.159	-0.157
8	20.00	0.337	0.823	-0.195	-0.191
9	25.02	0.395	0.765	-0.268	-0.264
10	30.02	0.448	0.712	-0.340	-0.336
11	35.00	0.497	0.663	-0.411	-0.408
12	40.00	0.543	0.617	-0.483	-0.481
13	45.00	0.585	0.575	-0.553	-0.553
14	50.02	0.629	0.531	-0.633	-0.626
15	60.00	0.697	0.463	-0.770	-0.770
16	70.02	0.755	0.405	-0.904	-0.915

Regression Output:

Constant	0.0990
Std Err of Y Est	0.0047
R Squared	0.9998
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.0145
Std Err of Coef.	0.0001

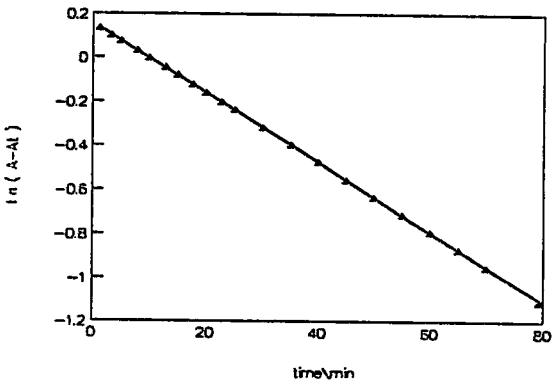


RUN 2 R=NO2 Ca=5.5 Cb=0.059 A=1.208 %R=73

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.25	0.066	1.142	0.133	0.136
2	3.28	0.100	1.108	0.103	0.104
3	5.00	0.130	1.078	0.075	0.076
4	7.85	0.176	1.032	0.031	0.031
5	10.00	0.210	0.998	-0.002	-0.003
6	12.82	0.253	0.955	-0.046	-0.047
7	15.00	0.285	0.923	-0.080	-0.082
8	17.67	0.323	0.885	-0.122	-0.124
9	20.00	0.357	0.851	-0.161	-0.161
10	22.77	0.393	0.815	-0.205	-0.205
11	25.00	0.421	0.787	-0.240	-0.240
12	30.00	0.481	0.727	-0.319	-0.319
13	35.00	0.536	0.672	-0.397	-0.398
14	40.00	0.587	0.621	-0.476	-0.477
15	45.00	0.635	0.573	-0.557	-0.556
16	50.00	0.678	0.530	-0.635	-0.635
17	55.00	0.718	0.490	-0.713	-0.714
18	60.00	0.754	0.454	-0.790	-0.793
19	65.00	0.790	0.418	-0.872	-0.872
20	70.00	0.822	0.386	-0.952	-0.951
21	80.00	0.879	0.329	-1.112	-1.109

Regression Output:

Constant	0.1554
Std Err of Y Est	0.0014
R Squared	1.0000
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.0158
Std Err of Coef.	0.0000

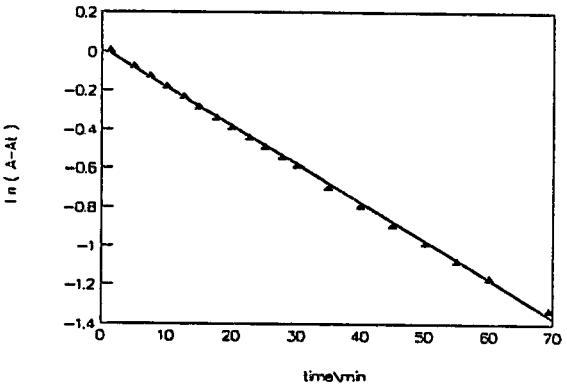


RUN 1 R=NO2 Ca=5.5 Cb=0.069 A=1.087 %R=76

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.33	0.082	1.005	0.005	-0.012
2	5.00	0.157	0.930	-0.073	-0.084
3	7.50	0.203	0.884	-0.123	-0.134
4	10.00	0.247	0.840	-0.174	-0.183
5	12.68	0.292	0.795	-0.229	-0.236
6	15.00	0.333	0.754	-0.282	-0.282
7	17.67	0.373	0.714	-0.337	-0.335
8	20.00	0.407	0.680	-0.386	-0.381
9	22.75	0.444	0.643	-0.442	-0.435
10	25.12	0.475	0.612	-0.491	-0.482
11	27.77	0.505	0.582	-0.541	-0.534
12	30.00	0.530	0.557	-0.585	-0.578
13	35.00	0.589	0.498	-0.697	-0.677
14	40.00	0.635	0.452	-0.794	-0.776
15	45.00	0.677	0.410	-0.892	-0.875
16	50.02	0.713	0.374	-0.983	-0.974
17	55.02	0.746	0.341	-1.076	-1.073
18	60.03	0.775	0.312	-1.165	-1.172
19	70.00	0.822	0.265	-1.328	-1.369

Regression Output:

Constant	0.0147
Std Err of Y Est	0.0148
R Squared	0.9987
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	-0.0198
Std Err of Coef.	0.0002

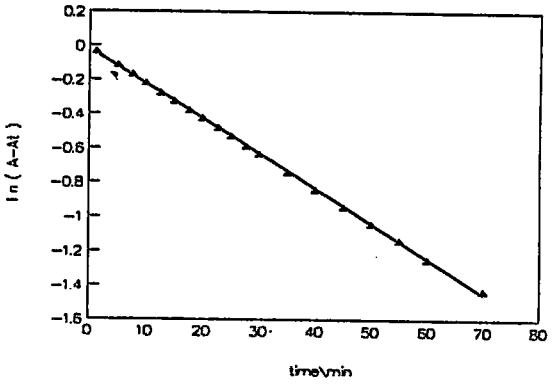


RUN 2 R=NO2 Ca=5.5 Cb=0.069 A=1.042 %R=77

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.22	0.076	0.966	-0.035	-0.043
2	5.00	0.148	0.894	-0.112	-0.121
3	7.62	0.196	0.846	-0.167	-0.174
4	10.00	0.239	0.803	-0.219	-0.223
5	12.60	0.284	0.758	-0.277	-0.276
6	15.00	0.322	0.720	-0.329	-0.325
7	17.62	0.360	0.682	-0.383	-0.378
8	20.00	0.389	0.653	-0.426	-0.427
9	22.67	0.425	0.617	-0.483	-0.481
10	25.00	0.455	0.587	-0.533	-0.529
11	27.65	0.487	0.555	-0.589	-0.583
12	30.00	0.512	0.530	-0.635	-0.631
13	35.00	0.567	0.475	-0.744	-0.733
14	40.00	0.611	0.431	-0.842	-0.835
15	45.00	0.652	0.390	-0.942	-0.937
16	50.00	0.688	0.354	-1.038	-1.039
17	55.00	0.721	0.321	-1.136	-1.142
18	60.00	0.755	0.287	-1.248	-1.244
19	70.02	0.803	0.239	-1.431	-1.448

Regression Output:

Constant	-0.0184
Std Err of Y Est	0.0070
R Squared	0.9997
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	-0.0204
Std Err of Coef.	0.0001

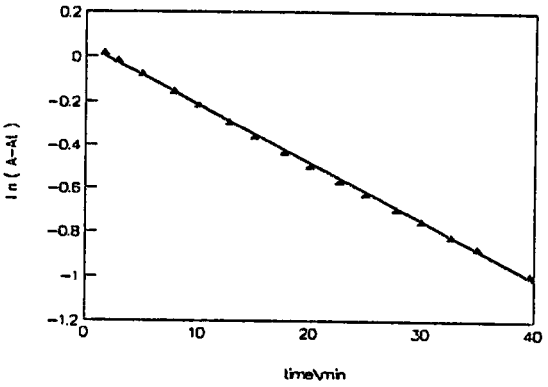


RUN 1 R=NO2 Ca=5.5 Cb=0.079 A=1.135 %R=67

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.65	0.117	1.018	0.018	0.005
2	2.83	0.151	0.984	-0.016	-0.027
3	5.00	0.210	0.925	-0.078	-0.084
4	7.77	0.278	0.857	-0.154	-0.158
5	10.00	0.330	0.805	-0.217	-0.217
6	12.77	0.389	0.746	-0.293	-0.291
7	15.00	0.437	0.698	-0.360	-0.350
8	17.70	0.486	0.649	-0.432	-0.421
9	20.00	0.525	0.610	-0.494	-0.483
10	22.70	0.567	0.568	-0.566	-0.554
11	25.00	0.600	0.535	-0.625	-0.615
12	27.73	0.636	0.499	-0.695	-0.688
13	30.00	0.663	0.472	-0.751	-0.748
14	32.65	0.694	0.441	-0.819	-0.819
15	35.00	0.717	0.418	-0.872	-0.881
16	40.00	0.763	0.372	-0.989	-1.014

Regression Output:

Constant	0.0486
Std Err of Y Est	0.0109
R Squared	0.9989
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.0266
Std Err of Coef.	0.0002

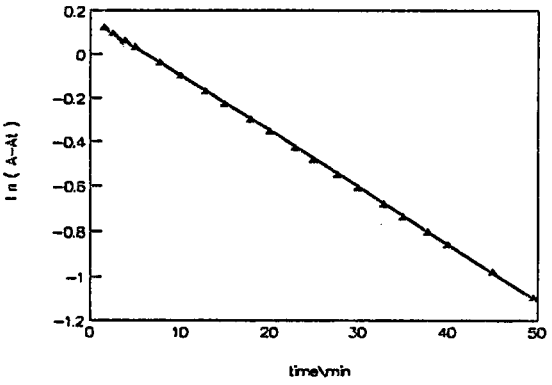


RUN 2 R=NO2 Ca=5.5 Cb=0.079 A=1.232 %R=78

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.52	0.097	1.135	0.127	0.119
2	2.50	0.128	1.104	0.099	0.094
3	3.88	0.165	1.067	0.065	0.059
4	5.00	0.197	1.035	0.034	0.031
5	7.70	0.268	0.964	-0.037	-0.038
6	10.00	0.324	0.908	-0.097	-0.096
7	12.82	0.387	0.845	-0.168	-0.168
8	15.00	0.435	0.797	-0.227	-0.223
9	17.87	0.491	0.741	-0.300	-0.296
10	20.00	0.531	0.701	-0.355	-0.350
11	22.92	0.581	0.651	-0.429	-0.424
12	25.00	0.615	0.617	-0.483	-0.477
13	27.72	0.656	0.576	-0.552	-0.546
14	30.00	0.688	0.544	-0.609	-0.603
15	32.87	0.725	0.507	-0.679	-0.676
16	35.02	0.753	0.479	-0.736	-0.731
17	37.77	0.783	0.449	-0.801	-0.801
18	40.00	0.808	0.424	-0.858	-0.857
19	45.00	0.856	0.376	-0.978	-0.984
20	50.00	0.897	0.335	-1.094	-1.111

Regression Output:

Constant	0.1574
Std Err of Y Est	0.0062
R Squared	0.9997
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0254
Std Err of Coef.	0.0001

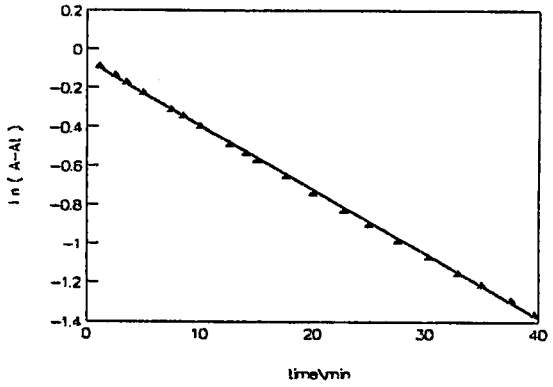


RUN 1 R=NO2 Ca=5.5 Cb=0.089 A=1.013 %R=75

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.13	0.096	0.917	-0.087	-0.100
2	2.50	0.139	0.874	-0.135	-0.145
3	3.50	0.169	0.844	-0.170	-0.178
4	5.00	0.212	0.801	-0.222	-0.228
5	7.47	0.277	0.736	-0.307	-0.309
6	8.50	0.303	0.710	-0.342	-0.343
7	10.00	0.339	0.674	-0.395	-0.392
8	12.57	0.395	0.618	-0.481	-0.477
9	14.00	0.424	0.589	-0.529	-0.524
10	15.00	0.444	0.569	-0.564	-0.557
11	17.55	0.490	0.523	-0.648	-0.641
12	20.00	0.535	0.478	-0.738	-0.722
13	22.75	0.575	0.438	-0.826	-0.812
14	25.00	0.606	0.407	-0.899	-0.886
15	27.57	0.640	0.373	-0.986	-0.971
16	30.32	0.669	0.344	-1.067	-1.062
17	32.95	0.696	0.317	-1.149	-1.148
18	35.00	0.714	0.299	-1.207	-1.216
19	37.57	0.736	0.277	-1.284	-1.300
20	40.00	0.756	0.257	-1.359	-1.380

Regression Output:

Constant	-0.0630
Std Err of Y Est	0.0112
R Squared	0.9993
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0329
Std Err of Coef.	0.0002

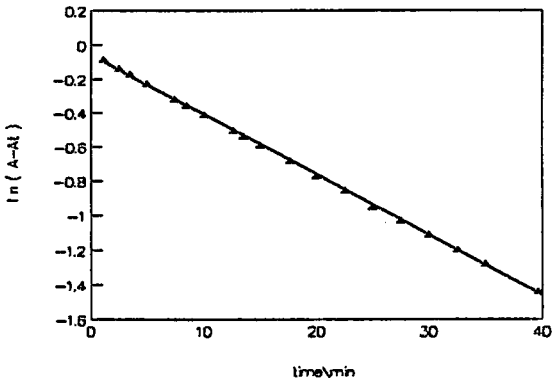


RUN 2 R=NO2 Ca=5.5 Cb=0.089 A=1.016 %R=76

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.13	0.098	0.918	-0.086	-0.098
2	2.50	0.143	0.873	-0.136	-0.146
3	3.50	0.174	0.842	-0.172	-0.181
4	5.00	0.220	0.796	-0.228	-0.233
5	7.47	0.289	0.727	-0.319	-0.320
6	8.50	0.316	0.700	-0.357	-0.356
7	10.02	0.353	0.663	-0.411	-0.409
8	12.62	0.413	0.603	-0.506	-0.500
9	13.50	0.433	0.583	-0.540	-0.531
10	15.00	0.462	0.554	-0.591	-0.584
11	17.62	0.511	0.505	-0.683	-0.676
12	20.00	0.552	0.464	-0.768	-0.759
13	22.58	0.591	0.425	-0.856	-0.849
14	25.00	0.630	0.386	-0.952	-0.934
15	27.53	0.658	0.358	-1.027	-1.023
16	30.00	0.687	0.329	-1.112	-1.110
17	32.52	0.714	0.302	-1.197	-1.198
18	35.00	0.737	0.279	-1.277	-1.285
19	40.00	0.778	0.238	-1.435	-1.460

Regression Output:

Constant	-0.0580
Std Err of Y Est	0.0099
R Squared	0.9995
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	-0.0350
Std Err of Coef.	0.0002

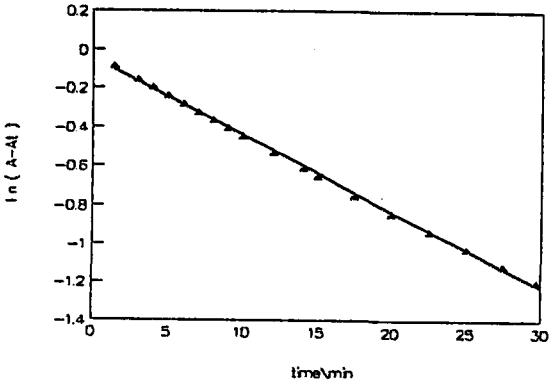


RUN 1 R=NO2 Ca=5.5 Cb=0.099 A=1.037 %R=71

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.40	0.120	0.917	-0.087	-0.104
2	3.00	0.181	0.856	-0.155	-0.167
3	4.00	0.216	0.821	-0.197	-0.206
4	5.00	0.250	0.787	-0.240	-0.245
5	6.00	0.282	0.755	-0.281	-0.284
6	7.00	0.313	0.724	-0.323	-0.323
7	8.00	0.343	0.694	-0.365	-0.362
8	9.00	0.370	0.667	-0.405	-0.402
9	10.00	0.397	0.640	-0.446	-0.441
10	12.00	0.450	0.587	-0.533	-0.519
11	14.02	0.495	0.542	-0.612	-0.598
12	15.00	0.516	0.521	-0.652	-0.636
13	17.48	0.564	0.473	-0.749	-0.733
14	20.00	0.606	0.431	-0.842	-0.832
15	22.52	0.645	0.392	-0.936	-0.930
16	25.00	0.678	0.359	-1.024	-1.027
17	27.50	0.708	0.329	-1.112	-1.125
18	30.00	0.735	0.302	-1.197	-1.223

Regression Output:

Constant	-0.0496
Std Err of Y Est	0.0125
R Squared	0.9988
No. of Observations	18
Degrees of Freedom	16
X Coefficient(s)	-0.0391
Std Err of Coef.	0.0003

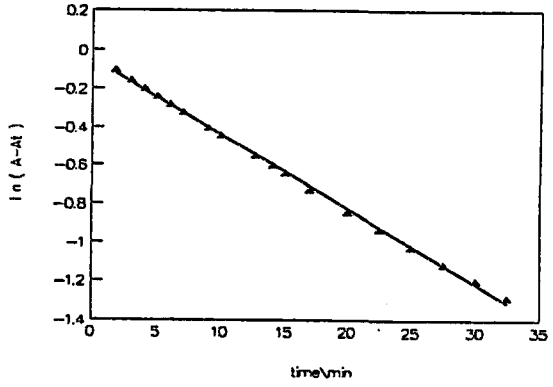


RUN 2 R=NO2 Ca=5.5 Cb=0.099 A=1.042 %R=73

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.77	0.139	0.903	-0.102	-0.119
2	3.02	0.187	0.855	-0.157	-0.167
3	4.07	0.222	0.820	-0.198	-0.208
4	5.00	0.254	0.788	-0.238	-0.244
5	6.00	0.286	0.756	-0.280	-0.283
6	7.00	0.317	0.725	-0.322	-0.322
7	9.00	0.374	0.668	-0.403	-0.400
8	10.00	0.400	0.642	-0.443	-0.438
9	12.65	0.465	0.577	-0.550	-0.541
10	14.02	0.495	0.547	-0.603	-0.595
11	15.02	0.516	0.526	-0.642	-0.634
12	17.00	0.560	0.482	-0.730	-0.710
13	20.00	0.613	0.429	-0.846	-0.827
14	22.52	0.650	0.392	-0.936	-0.925
15	25.00	0.684	0.358	-1.027	-1.021
16	27.50	0.715	0.327	-1.118	-1.119
17	30.00	0.741	0.301	-1.201	-1.216
18	32.50	0.765	0.277	-1.284	-1.313

Regression Output:

Constant	-0.0498
Std Err of Y Est	0.0132
R Squared	0.9989
No. of Observations	18
Degrees of Freedom	16
X Coefficient(s)	-0.0389
Std Err of Coef.	0.0003



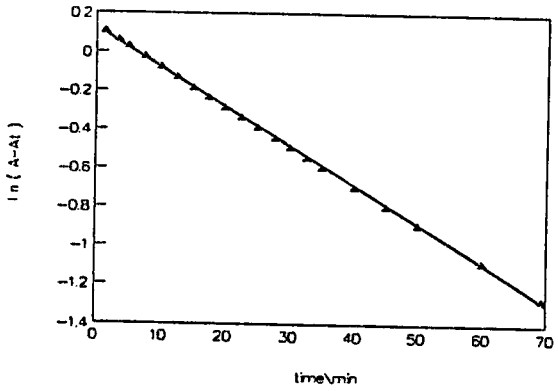
132

RUN 1 R-F Ca=3.0 Cb=0.4 A=1.168 %R=76

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.38	0.053	1.115	0.109	0.097
2	3.52	0.102	1.066	0.064	0.053
3	5.02	0.136	1.032	0.031	0.023
4	7.50	0.188	0.980	-0.020	-0.027
5	10.00	0.239	0.929	-0.074	-0.078
6	12.52	0.288	0.880	-0.128	-0.129
7	15.02	0.334	0.834	-0.182	-0.179
8	17.50	0.376	0.792	-0.233	-0.229
9	20.00	0.416	0.752	-0.285	-0.280
10	22.52	0.453	0.715	-0.335	-0.331
11	25.00	0.489	0.679	-0.387	-0.381
12	27.73	0.526	0.642	-0.443	-0.436
13	30.00	0.555	0.613	-0.489	-0.482
14	32.52	0.586	0.582	-0.541	-0.533
15	35.00	0.615	0.553	-0.592	-0.583
16	40.00	0.668	0.500	-0.693	-0.684
17	45.00	0.715	0.453	-0.792	-0.785
18	50.00	0.757	0.411	-0.889	-0.886
19	60.00	0.829	0.339	-1.082	-1.088
20	70.00	0.886	0.282	-1.266	-1.290

Regression Output:

Constant	0.1245
Std Err of Y Est	0.0093
R Squared	0.9994
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0202
Std Err of Coef.	0.0001

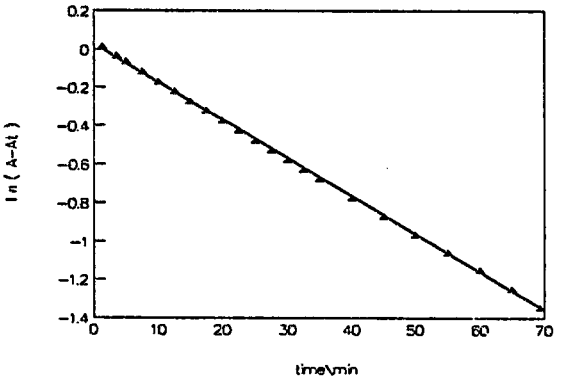


RUN 2 R-F Ca=3.0 Cb=0.4 A=1.058 %R=75

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.25	0.046	1.012	0.012	0.001
2	3.50	0.091	0.967	-0.034	-0.043
3	5.00	0.121	0.937	-0.065	-0.073
4	7.50	0.168	0.890	-0.117	-0.122
5	10.00	0.213	0.845	-0.168	-0.172
6	12.50	0.255	0.803	-0.219	-0.221
7	15.00	0.295	0.763	-0.270	-0.270
8	17.50	0.333	0.725	-0.322	-0.320
9	20.00	0.370	0.688	-0.374	-0.369
10	22.50	0.403	0.655	-0.423	-0.418
11	25.00	0.436	0.622	-0.475	-0.468
12	27.50	0.466	0.592	-0.524	-0.517
13	30.00	0.495	0.563	-0.574	-0.566
14	32.50	0.522	0.536	-0.624	-0.616
15	35.00	0.548	0.510	-0.673	-0.665
16	40.00	0.597	0.461	-0.774	-0.764
17	45.00	0.638	0.420	-0.868	-0.862
18	50.00	0.677	0.381	-0.965	-0.961
19	55.00	0.711	0.347	-1.058	-1.060
20	60.00	0.741	0.317	-1.149	-1.158
21	65.00	0.771	0.287	-1.248	-1.257
22	70.00	0.797	0.261	-1.343	-1.356

Regression Output:

Constant	0.0258
Std Err of Y Est	0.0076
R Squared	0.9997
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0197
Std Err of Coef.	0.0001

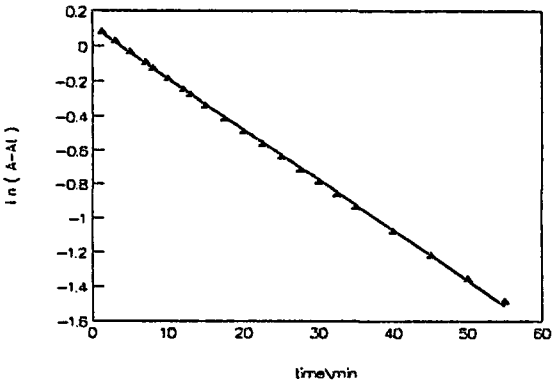


RUN 1 R=F Ca=3.0 Cb=0.5 A=1.156 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.25	0.066	1.090	0.086	0.072
2	3.00	0.122	1.034	0.033	0.021
3	5.00	0.184	0.972	-0.028	-0.038
4	7.00	0.243	0.913	-0.091	-0.097
5	8.00	0.270	0.886	-0.121	-0.126
6	10.00	0.324	0.832	-0.184	-0.185
7	12.02	0.373	0.783	-0.245	-0.245
8	13.00	0.397	0.759	-0.276	-0.274
9	15.00	0.442	0.714	-0.337	-0.332
10	17.50	0.495	0.661	-0.414	-0.406
11	20.00	0.542	0.614	-0.488	-0.480
12	22.50	0.586	0.570	-0.562	-0.553
13	25.00	0.627	0.529	-0.637	-0.627
14	27.50	0.666	0.490	-0.713	-0.701
15	30.00	0.700	0.456	-0.785	-0.774
16	32.50	0.732	0.424	-0.858	-0.848
17	35.00	0.762	0.394	-0.931	-0.921
18	40.00	0.814	0.342	-1.073	-1.069
19	45.00	0.859	0.297	-1.214	-1.216
20	50.00	0.897	0.259	-1.351	-1.363
21	55.00	0.929	0.227	-1.483	-1.510

Regression Output:

Constant	0.1092
Std Err of Y Est	0.0109
R Squared	0.9995
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.0294
Std Err of Coef.	0.0002

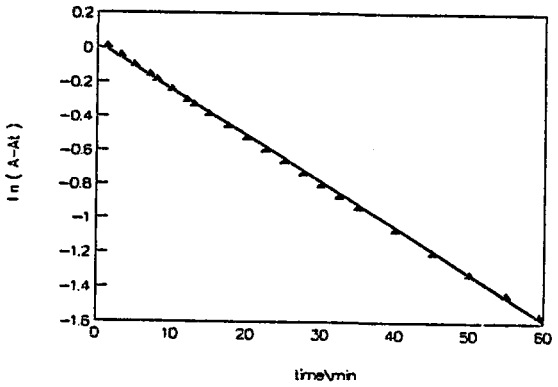


RUN 2 R=F Ca=3.0 Cb=0.5 A=1.077 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.37	0.066	1.011	0.011	-0.011
2	3.17	0.118	0.959	-0.042	-0.059
3	5.00	0.168	0.909	-0.095	-0.109
4	7.00	0.219	0.858	-0.153	-0.163
5	8.00	0.243	0.834	-0.182	-0.189
6	10.00	0.290	0.787	-0.240	-0.243
7	12.00	0.337	0.740	-0.301	-0.297
8	13.00	0.355	0.722	-0.326	-0.324
9	15.00	0.395	0.682	-0.383	-0.378
10	17.50	0.442	0.635	-0.454	-0.446
11	20.00	0.484	0.593	-0.523	-0.513
12	22.50	0.524	0.553	-0.592	-0.580
13	25.00	0.561	0.516	-0.662	-0.648
14	27.50	0.595	0.482	-0.730	-0.715
15	30.00	0.627	0.450	-0.799	-0.782
16	32.50	0.656	0.421	-0.865	-0.850
17	35.00	0.683	0.394	-0.931	-0.917
18	40.00	0.732	0.345	-1.064	-1.052
19	45.00	0.774	0.303	-1.194	-1.187
20	50.00	0.809	0.268	-1.317	-1.321
21	55.00	0.839	0.238	-1.435	-1.456
22	60.00	0.866	0.211	-1.556	-1.591

Regression Output:

Constant	0.0261
Std Err of Y Est	0.0149
R Squared	0.9990
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0270
Std Err of Coef.	0.0002

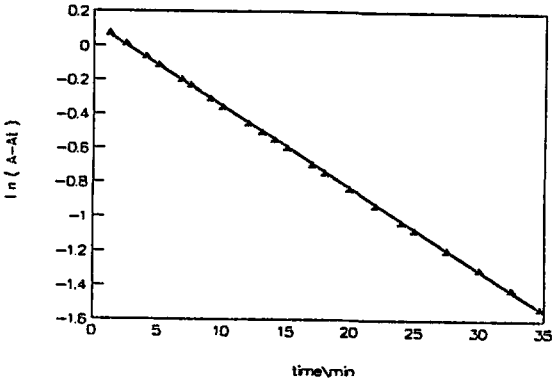


RUN 1 R-F Ca=3.0 Cb=0.6 A=1.167 %R=81

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.25	0.090	1.077	0.074	0.064
2	2.50	0.154	1.013	0.013	0.004
3	4.00	0.226	0.941	-0.061	-0.067
4	5.00	0.271	0.896	-0.110	-0.115
5	6.77	0.345	0.822	-0.196	-0.199
6	7.50	0.374	0.793	-0.232	-0.234
7	9.02	0.431	0.736	-0.307	-0.306
8	10.00	0.466	0.701	-0.355	-0.353
9	12.00	0.531	0.636	-0.453	-0.448
10	13.07	0.564	0.603	-0.506	-0.499
11	14.00	0.590	0.577	-0.550	-0.544
12	15.00	0.617	0.550	-0.598	-0.591
13	17.00	0.667	0.500	-0.693	-0.687
14	18.00	0.691	0.476	-0.742	-0.734
15	20.00	0.734	0.433	-0.837	-0.829
16	22.00	0.774	0.393	-0.934	-0.925
17	24.00	0.809	0.358	-1.027	-1.020
18	25.00	0.825	0.342	-1.073	-1.068
19	27.50	0.862	0.305	-1.187	-1.187
20	30.02	0.894	0.273	-1.298	-1.307
21	32.50	0.924	0.243	-1.415	-1.425
22	35.00	0.950	0.217	-1.528	-1.544

Regression Output:

Constant	0.1232
Std Err of Y Est	0.0076
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0476
Std Err of Coef.	0.0002

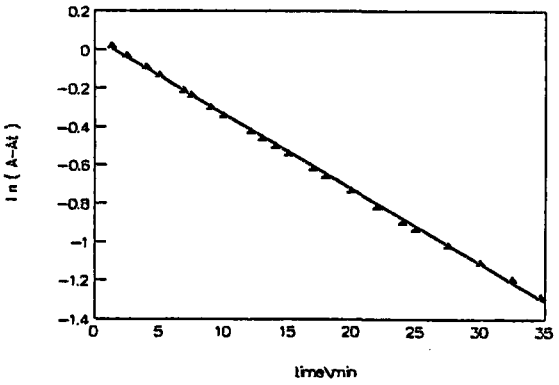


RUN 2 R-F Ca=3.0 Cb=0.6 A=1.104 %R=75

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.35	0.081	1.023	0.023	0.005
2	2.50	0.130	0.974	-0.026	-0.040
3	4.00	0.188	0.916	-0.088	-0.098
4	5.00	0.227	0.877	-0.131	-0.137
5	6.88	0.292	0.812	-0.208	-0.211
6	7.50	0.312	0.792	-0.233	-0.235
7	9.00	0.360	0.744	-0.296	-0.294
8	10.00	0.390	0.714	-0.337	-0.333
9	12.08	0.448	0.656	-0.422	-0.414
10	13.00	0.471	0.633	-0.457	-0.450
11	14.00	0.495	0.609	-0.496	-0.489
12	15.00	0.519	0.585	-0.536	-0.528
13	17.00	0.564	0.540	-0.616	-0.606
14	18.00	0.584	0.520	-0.654	-0.645
15	20.00	0.623	0.481	-0.732	-0.723
16	22.00	0.662	0.442	-0.816	-0.802
17	24.00	0.695	0.409	-0.894	-0.880
18	25.00	0.710	0.394	-0.931	-0.919
19	27.50	0.743	0.361	-1.019	-1.016
20	30.00	0.773	0.331	-1.106	-1.114
21	32.50	0.801	0.303	-1.194	-1.212
22	35.00	0.826	0.278	-1.280	-1.309

Regression Output:

Constant	0.0579
Std Err of Y Est	0.0122
R Squared	0.9991
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0391
Std Err of Coef.	0.0003

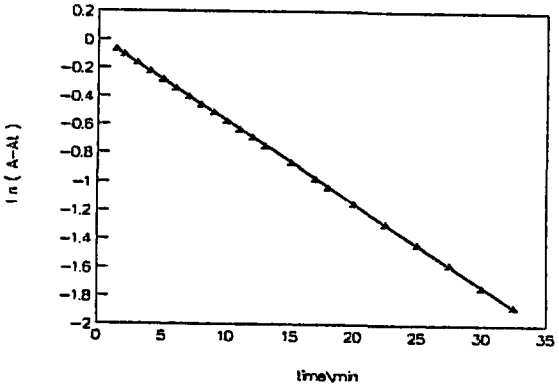


RUN 1 R-F Ca=3.0 Cb=0.7 A=1.056 %R=85

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.37	0.121	0.935	-0.067	-0.072
2	2.00	0.156	0.900	-0.105	-0.108
3	3.00	0.205	0.851	-0.161	-0.166
4	4.00	0.254	0.802	-0.221	-0.224
5	5.00	0.300	0.756	-0.280	-0.282
6	6.00	0.343	0.713	-0.338	-0.340
7	7.00	0.384	0.672	-0.397	-0.398
8	8.00	0.423	0.633	-0.457	-0.456
9	9.00	0.458	0.598	-0.514	-0.513
10	10.00	0.493	0.563	-0.574	-0.571
11	11.00	0.525	0.531	-0.633	-0.629
12	12.00	0.555	0.501	-0.691	-0.687
13	13.00	0.584	0.472	-0.751	-0.745
14	15.00	0.635	0.421	-0.865	-0.861
15	17.00	0.681	0.375	-0.981	-0.977
16	18.00	0.702	0.354	-1.038	-1.034
17	20.00	0.740	0.316	-1.152	-1.150
18	22.50	0.782	0.274	-1.295	-1.295
19	25.00	0.818	0.238	-1.435	-1.440
20	27.50	0.849	0.207	-1.575	-1.584
21	30.00	0.879	0.177	-1.732	-1.729
22	32.50	0.902	0.154	-1.871	-1.874

Regression Output:

Constant	0.0076
Std Err of Y Est	0.0040
R Squared	0.9999
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0579
Std Err of Coef.	0.0001

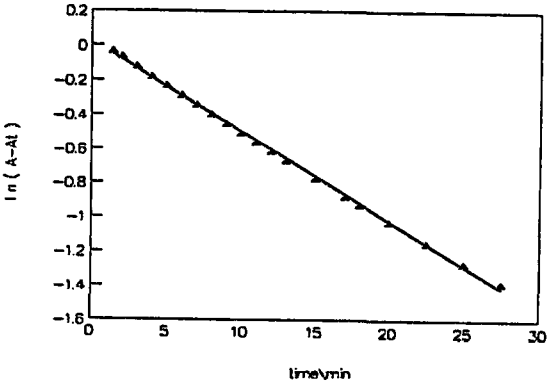


RUN 2 R-F Ca=3.0 Cb=0.7 A=1.080 %R=77

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.40	0.112	0.968	-0.033	-0.048
2	2.00	0.143	0.937	-0.065	-0.080
3	3.00	0.193	0.887	-0.120	-0.132
4	4.00	0.242	0.838	-0.177	-0.184
5	5.00	0.287	0.793	-0.232	-0.236
6	6.00	0.330	0.750	-0.288	-0.289
7	7.00	0.370	0.710	-0.342	-0.341
8	8.00	0.408	0.672	-0.397	-0.393
9	9.00	0.444	0.636	-0.453	-0.445
10	10.00	0.478	0.602	-0.507	-0.497
11	11.00	0.509	0.571	-0.560	-0.550
12	12.00	0.539	0.541	-0.614	-0.602
13	13.00	0.567	0.513	-0.667	-0.654
14	15.00	0.618	0.462	-0.772	-0.758
15	17.00	0.663	0.417	-0.875	-0.863
16	18.00	0.683	0.397	-0.924	-0.915
17	20.00	0.721	0.359	-1.024	-1.019
18	22.50	0.763	0.317	-1.149	-1.150
19	25.00	0.798	0.282	-1.266	-1.280
20	27.50	0.829	0.251	-1.382	-1.411

Regression Output:

Constant	0.0247
Std Err of Y Est	0.0125
R Squared	0.9991
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0522
Std Err of Coef.	0.0004

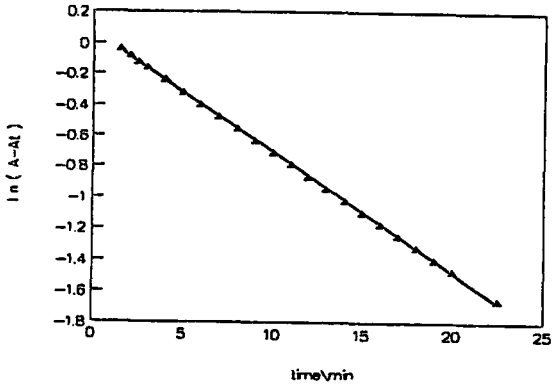


RUN 1 R-F Ca=3.0 Cb=0.8 A=1.123 %R=83

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.48	0.160	0.963	-0.038	-0.047
2	2.02	0.201	0.922	-0.081	-0.088
3	2.50	0.236	0.887	-0.120	-0.125
4	3.00	0.271	0.852	-0.160	-0.164
5	4.00	0.335	0.788	-0.238	-0.241
6	5.00	0.395	0.728	-0.317	-0.318
7	6.00	0.450	0.673	-0.396	-0.395
8	7.00	0.501	0.622	-0.475	-0.472
9	8.02	0.548	0.575	-0.553	-0.551
10	9.00	0.591	0.532	-0.631	-0.626
11	10.00	0.632	0.491	-0.711	-0.704
12	11.00	0.668	0.455	-0.787	-0.781
13	12.00	0.703	0.420	-0.868	-0.858
14	13.00	0.733	0.390	-0.942	-0.935
15	14.02	0.763	0.360	-1.022	-1.013
16	15.00	0.788	0.335	-1.094	-1.089
17	16.00	0.813	0.310	-1.171	-1.166
18	17.00	0.835	0.288	-1.245	-1.243
19	18.00	0.855	0.268	-1.317	-1.320
20	19.00	0.875	0.248	-1.394	-1.397
21	20.00	0.892	0.231	-1.465	-1.474
22	22.50	0.931	0.192	-1.650	-1.667

Regression Output:

Constant	0.0672
Std Err of Y Est	0.0070
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0771
Std Err of Coef.	0.0002

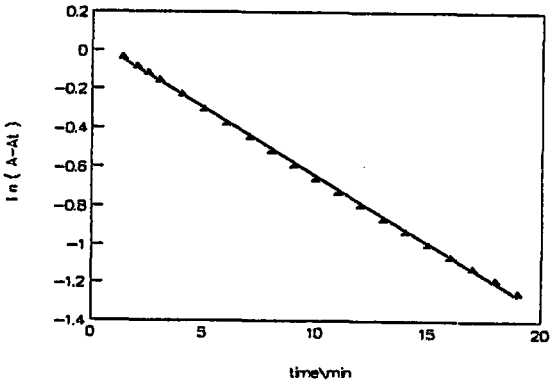


RUN 2 R-F Ca=3.0 Cb=0.8 A=1.105 %R=74

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.38	0.137	0.968	-0.033	-0.047
2	2.00	0.181	0.924	-0.079	-0.090
3	2.50	0.213	0.892	-0.114	-0.124
4	3.00	0.246	0.859	-0.152	-0.159
5	4.00	0.307	0.798	-0.226	-0.228
6	5.02	0.364	0.741	-0.300	-0.299
7	6.00	0.416	0.689	-0.373	-0.367
8	7.02	0.464	0.641	-0.445	-0.438
9	8.00	0.508	0.597	-0.516	-0.506
10	9.02	0.549	0.556	-0.587	-0.577
11	10.00	0.587	0.518	-0.658	-0.645
12	11.00	0.621	0.484	-0.726	-0.714
13	12.00	0.653	0.452	-0.794	-0.783
14	13.00	0.683	0.422	-0.863	-0.853
15	14.00	0.710	0.395	-0.929	-0.922
16	15.00	0.735	0.370	-0.994	-0.991
17	16.00	0.759	0.346	-1.061	-1.061
18	17.00	0.779	0.326	-1.121	-1.130
19	18.00	0.799	0.306	-1.184	-1.200
20	19.00	0.818	0.287	-1.248	-1.269

Regression Output:

Constant	0.0492
Std Err of Y Est	0.0108
R Squared	0.9993
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.0694
Std Err of Coef.	0.0004



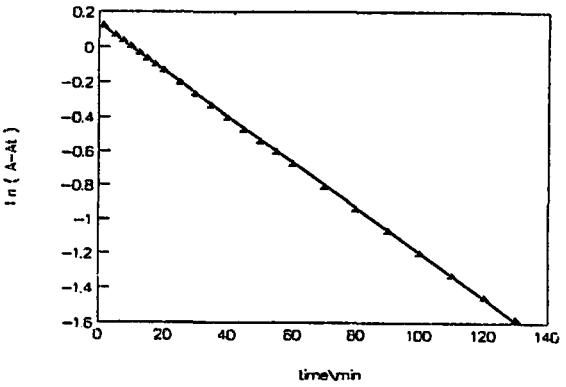
133

RUN 1 R=Cl Ca=3.5 Cb=0.2 A=1.174 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.18	0.039	1.135	0.127	0.119
2	5.00	0.097	1.077	0.074	0.068
3	7.50	0.133	1.041	0.040	0.035
4	10.00	0.168	1.006	0.006	0.001
5	12.50	0.202	0.972	-0.028	-0.032
6	15.00	0.235	0.939	-0.063	-0.065
7	17.53	0.266	0.908	-0.097	-0.099
8	20.00	0.297	0.877	-0.131	-0.132
9	25.00	0.355	0.819	-0.200	-0.198
10	30.00	0.408	0.766	-0.267	-0.265
11	35.00	0.458	0.716	-0.334	-0.331
12	40.00	0.505	0.669	-0.402	-0.397
13	45.02	0.549	0.625	-0.470	-0.464
14	50.02	0.590	0.584	-0.538	-0.531
15	55.00	0.627	0.547	-0.603	-0.597
16	60.00	0.663	0.511	-0.671	-0.663
17	70.00	0.727	0.447	-0.805	-0.796
18	80.00	0.782	0.392	-0.936	-0.929
19	90.00	0.829	0.345	-1.064	-1.062
20	100.00	0.872	0.302	-1.197	-1.195
21	110.00	0.908	0.266	-1.324	-1.328
22	120.00	0.940	0.234	-1.452	-1.461
23	130.00	0.968	0.206	-1.580	-1.594

Regression Output:

Constant	0.1342
Std Err of Y Est	0.0063
R Squared	0.9999
No. of Observations	23
Degrees of Freedom	21
X Coefficient(s)	-0.0133
Std Err of Coef.	0.0000

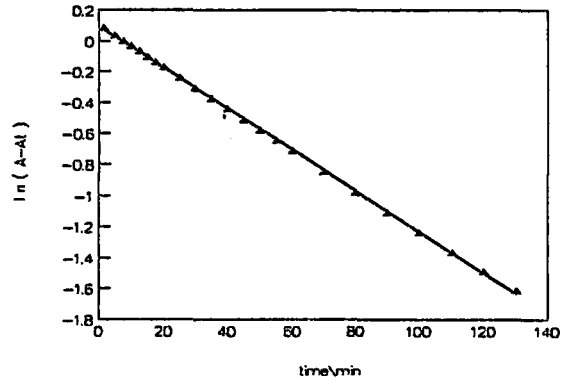


RUN 2 R=Cl Ca=3.5 Cb=0.2 A=1.130 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.48	0.042	1.088	0.084	0.072
2	5.00	0.094	1.036	0.035	0.026
3	7.52	0.130	1.000	-0.000	-0.008
4	10.00	0.163	0.967	-0.034	-0.041
5	12.50	0.196	0.934	-0.068	-0.074
6	15.00	0.229	0.901	-0.104	-0.107
7	17.50	0.259	0.871	-0.138	-0.140
8	20.00	0.288	0.842	-0.172	-0.173
9	25.00	0.344	0.786	-0.241	-0.239
10	30.00	0.396	0.734	-0.309	-0.306
11	35.00	0.444	0.686	-0.377	-0.372
12	40.00	0.489	0.641	-0.445	-0.438
13	45.00	0.531	0.599	-0.512	-0.504
14	50.00	0.570	0.560	-0.580	-0.571
15	55.00	0.606	0.524	-0.646	-0.637
16	60.00	0.640	0.490	-0.713	-0.703
17	70.00	0.702	0.428	-0.849	-0.835
18	80.00	0.754	0.376	-0.978	-0.968
19	90.00	0.800	0.330	-1.109	-1.100
20	100.00	0.839	0.291	-1.234	-1.233
21	110.10	0.874	0.256	-1.363	-1.367
22	120.00	0.904	0.226	-1.487	-1.498
23	130.23	0.930	0.200	-1.609	-1.633

Regression Output:

Constant	0.0917
Std Err of Y Est	0.0095
R Squared	0.9997
No. of Observations	23
Degrees of Freedom	21
X Coefficient(s)	-0.0132
Std Err of Coef.	0.0001

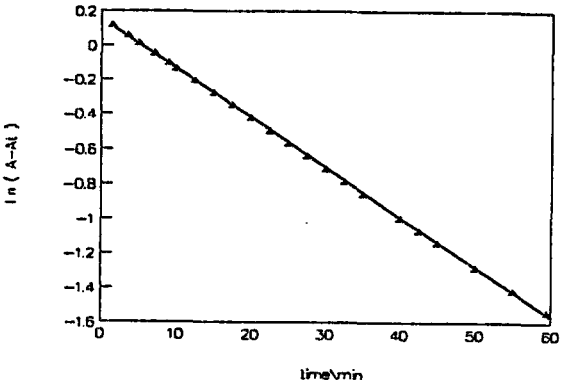


RUN 1 R=Cl Ca=3.5 Cb=0.3 A=1.208 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.40	0.080	1.128	0.120	0.112
2	3.50	0.147	1.061	0.059	0.052
3	5.00	0.193	1.015	0.015	0.009
4	7.00	0.250	0.958	-0.043	-0.048
5	9.00	0.305	0.903	-0.102	-0.105
6	10.00	0.332	0.876	-0.132	-0.134
7	12.50	0.393	0.815	-0.205	-0.205
8	15.00	0.451	0.757	-0.278	-0.277
9	17.50	0.504	0.704	-0.351	-0.348
10	20.00	0.553	0.655	-0.423	-0.419
11	22.50	0.599	0.609	-0.496	-0.491
12	25.00	0.642	0.566	-0.569	-0.562
13	27.50	0.681	0.527	-0.641	-0.634
14	30.00	0.717	0.491	-0.711	-0.705
15	32.50	0.752	0.456	-0.785	-0.777
16	35.00	0.782	0.426	-0.853	-0.848
17	40.00	0.838	0.370	-0.994	-0.991
18	42.53	0.864	0.344	-1.067	-1.063
19	45.00	0.887	0.321	-1.136	-1.134
20	50.00	0.930	0.278	-1.280	-1.276
21	55.00	0.965	0.243	-1.415	-1.419
22	60.00	0.993	0.215	-1.537	-1.562

Regression Output:

Constant		0.1519
Std Err of Y Est		0.0077
R Squared		0.9998
No. of Observations		22
Degrees of Freedom		20
X Coefficient(s)	-0.0286	
Std Err of Coef.	0.0001	

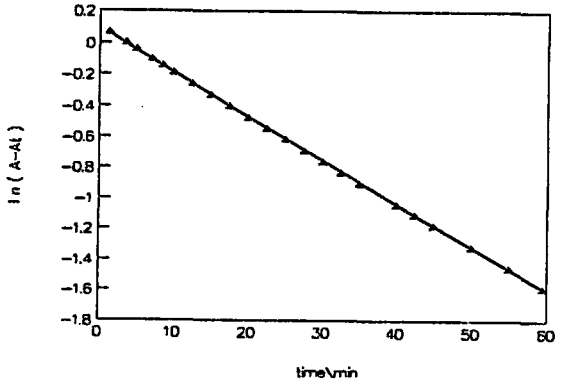


RUN 2 R=Cl Ca=3.5 Cb=0.3 A=1.138 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.28	0.069	1.069	0.067	0.058
2	3.50	0.134	1.004	0.004	-0.004
3	5.00	0.178	0.960	-0.041	-0.047
4	7.07	0.234	0.904	-0.101	-0.105
5	8.50	0.271	0.867	-0.143	-0.146
6	10.00	0.309	0.829	-0.188	-0.188
7	12.50	0.366	0.772	-0.259	-0.259
8	15.00	0.420	0.718	-0.331	-0.329
9	17.50	0.470	0.668	-0.403	-0.400
10	20.00	0.516	0.622	-0.475	-0.471
11	22.50	0.559	0.579	-0.546	-0.541
12	25.00	0.599	0.539	-0.618	-0.612
13	27.50	0.636	0.502	-0.689	-0.683
14	30.00	0.671	0.467	-0.761	-0.753
15	32.50	0.702	0.436	-0.830	-0.824
16	35.00	0.732	0.406	-0.901	-0.895
17	40.00	0.785	0.353	-1.041	-1.036
18	42.50	0.808	0.330	-1.109	-1.107
19	45.02	0.830	0.308	-1.178	-1.178
20	50.00	0.870	0.268	-1.317	-1.319
21	55.00	0.904	0.234	-1.452	-1.460
22	60.00	0.933	0.205	-1.585	-1.601

Regression Output:

Constant		0.0946
Std Err of Y Est		0.0065
R Squared		0.9998
No. of Observations		22
Degrees of Freedom		20
X Coefficient(s)	-0.0283	
Std Err of Coef.	0.0001	

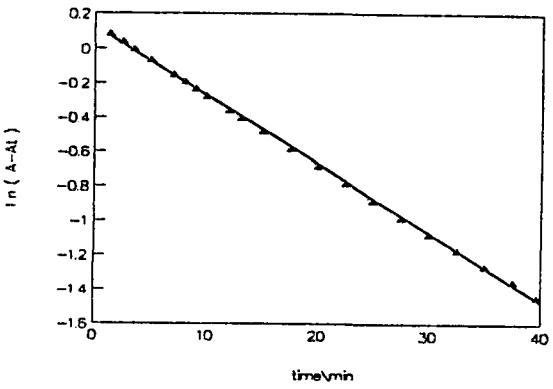


RUN 1 R-Cl Ca=3.5 Cb=0.4 A=1.195 %R=80

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.37	0.104	1.091	0.087	0.069
2	2.50	0.155	1.040	0.039	0.024
3	3.50	0.198	0.997	-0.003	-0.015
4	5.00	0.260	0.935	-0.067	-0.075
5	7.02	0.336	0.859	-0.152	-0.155
6	8.00	0.371	0.824	-0.194	-0.194
7	9.00	0.405	0.790	-0.236	-0.234
8	10.00	0.438	0.757	-0.278	-0.274
9	11.98	0.497	0.698	-0.360	-0.353
10	13.02	0.527	0.668	-0.403	-0.394
11	15.00	0.578	0.617	-0.483	-0.473
12	17.50	0.639	0.556	-0.587	-0.572
13	20.00	0.692	0.503	-0.687	-0.672
14	22.50	0.739	0.456	-0.785	-0.771
15	25.00	0.782	0.413	-0.884	-0.871
16	27.50	0.821	0.374	-0.983	-0.970
17	30.00	0.854	0.341	-1.076	-1.070
18	32.50	0.885	0.310	-1.171	-1.169
19	35.00	0.912	0.283	-1.262	-1.269
20	37.50	0.936	0.259	-1.351	-1.368
21	40.00	0.958	0.237	-1.440	-1.468

Regression Output:

Constant	0.1240
Std Err of Y Est	0.0129
R Squared	0.9993
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.0398
Std Err of Coef.	0.0002

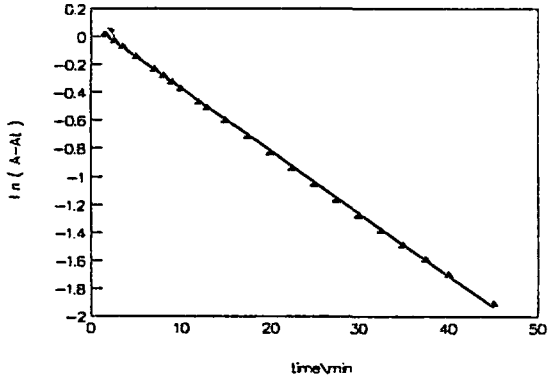


RUN 2 R-Cl Ca=3.5 Cb=0.4 A=1.148 %R=87

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.58	0.127	1.021	0.021	0.008
2	2.57	0.172	0.976	-0.024	-0.036
3	3.50	0.213	0.935	-0.067	-0.078
4	5.00	0.278	0.870	-0.139	-0.145
5	7.00	0.354	0.794	-0.231	-0.235
6	8.00	0.390	0.758	-0.277	-0.279
7	9.00	0.424	0.724	-0.323	-0.324
8	10.00	0.457	0.691	-0.370	-0.369
9	12.07	0.520	0.628	-0.465	-0.461
10	13.00	0.546	0.602	-0.507	-0.503
11	15.02	0.599	0.549	-0.600	-0.593
12	17.50	0.658	0.490	-0.713	-0.704
13	20.00	0.711	0.437	-0.828	-0.816
14	22.50	0.757	0.391	-0.939	-0.927
15	25.00	0.799	0.349	-1.053	-1.039
16	27.50	0.836	0.312	-1.165	-1.151
17	30.00	0.868	0.280	-1.273	-1.263
18	32.50	0.897	0.251	-1.382	-1.374
19	35.00	0.922	0.226	-1.487	-1.486
20	37.50	0.944	0.204	-1.590	-1.598
21	40.00	0.965	0.183	-1.698	-1.710
22	45.00	0.999	0.149	-1.904	-1.933

Regression Output:

Constant	0.0784
Std Err of Y Est	0.0113
R Squared	0.9997
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0447
Std Err of Coef.	0.0002

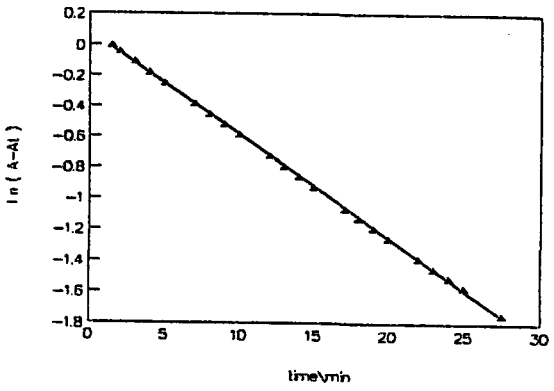


RUN 1 R=Cl Ca=3.5 Cb=0.5 A=1.141 %R=85

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.48	0.148	0.993	-0.007	-0.017
2	2.00	0.184	0.957	-0.044	-0.051
3	3.00	0.246	0.895	-0.111	-0.118
4	4.00	0.306	0.835	-0.180	-0.184
5	5.00	0.361	0.780	-0.248	-0.251
6	7.00	0.460	0.681	-0.384	-0.384
7	8.00	0.506	0.635	-0.454	-0.451
8	9.00	0.547	0.594	-0.521	-0.518
9	10.00	0.586	0.555	-0.589	-0.584
10	12.00	0.657	0.484	-0.726	-0.718
11	13.01	0.688	0.453	-0.792	-0.785
12	14.00	0.717	0.424	-0.858	-0.851
13	15.00	0.745	0.396	-0.926	-0.918
14	17.10	0.796	0.345	-1.064	-1.058
15	18.00	0.817	0.324	-1.127	-1.118
16	19.00	0.837	0.304	-1.191	-1.184
17	20.00	0.856	0.285	-1.255	-1.251
18	22.02	0.890	0.251	-1.382	-1.386
19	23.02	0.906	0.235	-1.448	-1.452
20	24.00	0.920	0.221	-1.510	-1.518
21	25.00	0.933	0.208	-1.570	-1.584
22	27.50	0.966	0.175	-1.743	-1.751

Regression Output:

Constant	0.0821
Std Err of Y Est	0.0072
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0667
Std Err of Coef.	0.0002

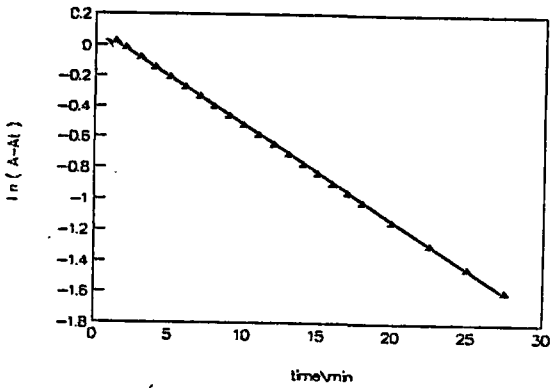


RUN 2 R=Cl Ca=3.5 Cb=0.5 A=1.157 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.38	0.131	1.026	0.026	0.017
2	2.00	0.171	0.986	-0.014	-0.022
3	3.00	0.231	0.926	-0.077	-0.084
4	4.00	0.288	0.869	-0.140	-0.146
5	5.00	0.342	0.815	-0.205	-0.208
6	6.00	0.393	0.764	-0.269	-0.269
7	7.00	0.440	0.717	-0.333	-0.331
8	8.00	0.484	0.673	-0.396	-0.393
9	9.00	0.525	0.632	-0.459	-0.455
10	10.00	0.564	0.593	-0.523	-0.517
11	11.00	0.599	0.558	-0.583	-0.579
12	12.00	0.633	0.524	-0.646	-0.641
13	13.00	0.664	0.493	-0.707	-0.703
14	14.00	0.695	0.462	-0.772	-0.765
15	15.00	0.722	0.435	-0.832	-0.827
16	16.00	0.749	0.408	-0.896	-0.889
17	17.00	0.772	0.385	-0.955	-0.951
18	18.00	0.795	0.362	-1.016	-1.013
19	20.00	0.837	0.320	-1.139	-1.136
20	22.50	0.882	0.275	-1.291	-1.291
21	25.00	0.919	0.238	-1.435	-1.446
22	27.50	0.952	0.205	-1.585	-1.601

Regression Output:

Constant	0.1021
Std Err of Y Est	0.0067
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0619
Std Err of Coef.	0.0002

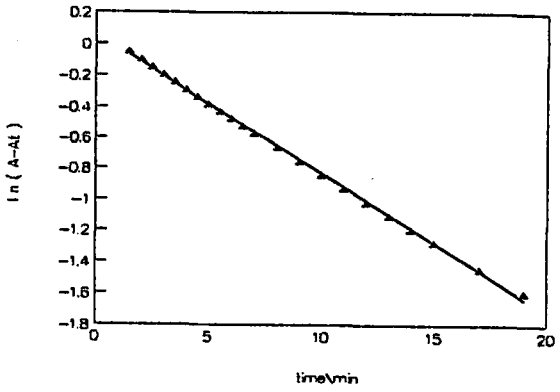


RUN 1 R=Cl Ca=3.5 Cb=0.6 A=1.154 %R=82

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.45	0.203	0.951	-0.050	-0.066
2	2.00	0.250	0.904	-0.101	-0.115
3	2.50	0.292	0.862	-0.149	-0.160
4	3.00	0.332	0.822	-0.196	-0.204
5	3.50	0.369	0.785	-0.242	-0.249
6	4.00	0.406	0.748	-0.290	-0.294
7	4.50	0.439	0.715	-0.335	-0.338
8	5.00	0.473	0.681	-0.384	-0.383
9	5.50	0.504	0.650	-0.431	-0.428
10	6.00	0.534	0.620	-0.478	-0.472
11	6.50	0.563	0.591	-0.526	-0.517
12	7.00	0.589	0.565	-0.571	-0.562
13	8.00	0.638	0.516	-0.662	-0.651
14	9.00	0.684	0.470	-0.755	-0.740
15	10.00	0.724	0.430	-0.844	-0.830
16	11.00	0.759	0.395	-0.929	-0.919
17	12.00	0.794	0.360	-1.022	-1.008
18	13.00	0.824	0.330	-1.109	-1.097
19	14.00	0.851	0.303	-1.194	-1.187
20	15.00	0.875	0.279	-1.277	-1.276
21	17.00	0.918	0.236	-1.444	-1.455
22	19.00	0.951	0.203	-1.595	-1.633

Regression Output:

Constant	0.0637
Std Err of Y Est	0.0133
R Squared	0.9992
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0893
Std Err of Coef.	0.0006

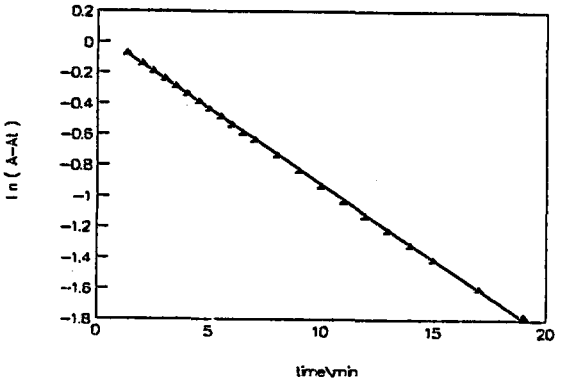


RUN 2 R=Cl Ca=3.5 Cb=0.6 A=1.110 %R=85

No.	time	Absorbance	A-At	ln(A-At)	Y(calc)
1	1.33	0.179	0.931	-0.071	-0.079
2	2.00	0.238	0.872	-0.137	-0.144
3	2.50	0.280	0.830	-0.186	-0.193
4	3.00	0.321	0.789	-0.237	-0.242
5	3.50	0.359	0.751	-0.286	-0.290
6	4.00	0.395	0.715	-0.335	-0.339
7	4.52	0.430	0.680	-0.386	-0.389
8	5.00	0.463	0.647	-0.435	-0.436
9	5.50	0.495	0.615	-0.486	-0.484
10	6.00	0.525	0.585	-0.536	-0.533
11	6.50	0.554	0.556	-0.587	-0.581
12	7.00	0.580	0.530	-0.635	-0.630
13	8.00	0.630	0.480	-0.734	-0.727
14	9.00	0.675	0.435	-0.832	-0.824
15	10.00	0.715	0.395	-0.929	-0.921
16	11.00	0.752	0.358	-1.027	-1.018
17	12.00	0.785	0.325	-1.124	-1.116
18	13.00	0.815	0.295	-1.221	-1.213
19	14.00	0.841	0.269	-1.313	-1.310
20	15.00	0.865	0.245	-1.406	-1.407
21	17.00	0.907	0.203	-1.595	-1.601
22	19.00	0.940	0.170	-1.772	-1.795

Regression Output:

Constant	0.0498
Std Err of Y Est	0.0080
R Squared	0.9998
No. of Observations	22
Degrees of Freedom	20
X Coefficient(s)	-0.0971
Std Err of Coef.	0.0003



(iii) Determinations of the observed rate constants (k_{obs}).

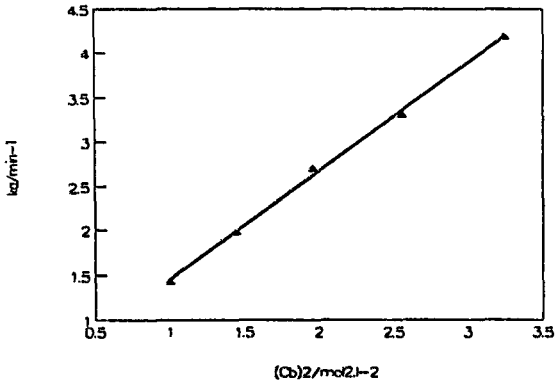
129

RUN 1 R=H

No.	Cb	(Cb)2	ka	Y(calc)
1	1.00	1.00	1.43	1.45
2	1.20	1.44	1.98	1.99
3	1.40	1.96	2.70	2.62
4	1.60	2.56	3.31	3.36
5	1.80	3.24	4.19	4.19

Regression Output:

Constant		0.230
Std Err of Y Est		0.053
R Squared		0.998
No. of Observations		5
Degrees of Freedom		3
X Coefficient(s)	1.22	
Std Err of Coef.	0.03	

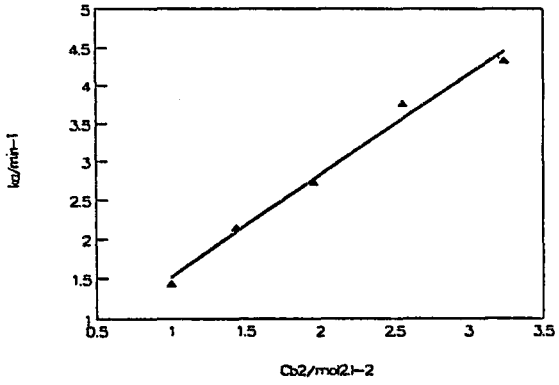


RUN 2 R=H

No.	Cb	(Cb)2	ka	Y(calc)
1	1.00	1.00	1.44	1.52
2	1.20	1.44	2.15	2.09
3	1.40	1.96	2.73	2.78
4	1.60	2.56	3.76	3.56
5	1.80	3.24	4.33	4.46

Regression Output:

Constant		0.205
Std Err of Y Est		0.148
R Squared		0.988
No. of Observations		5
Degrees of Freedom		3
X Coefficient(s)	1.31	
Std Err of Coef.	0.08	



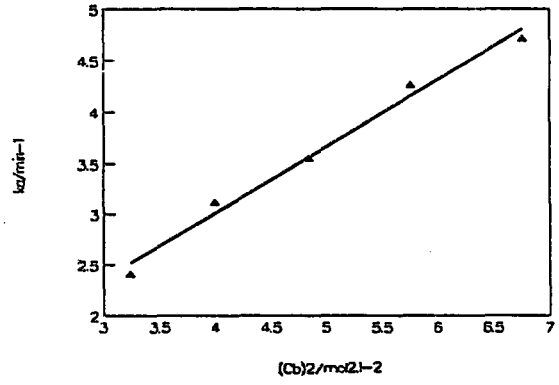
130

RUN 1 R=OMe

No.	Cb	(Cb)2	ka	Y(calc)
1	1.80	3.24	2.41	2.52
2	2.00	4.00	3.12	3.01
3	2.20	4.84	3.55	3.56
4	2.40	5.76	4.26	4.16
5	2.60	6.76	4.71	4.80

Regression Output:

Constant		0.416
Std Err of Y Est		0.120
R Squared		0.987
No. of Observations		5
Degrees of Freedom		3
X Coefficient(s)	0.65	
Std Err of Coef.	0.04	

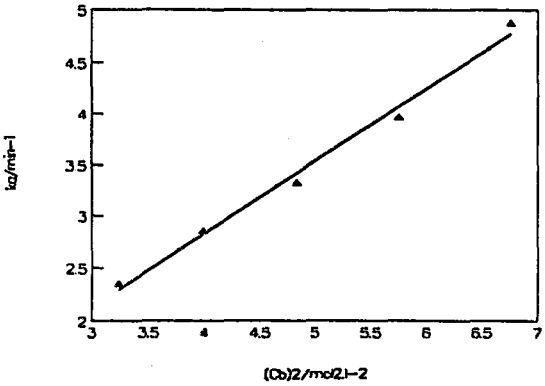


RUN2 R=OMe

No.	Cb	(Cb)2	ka	Y(calc)
1	1.80	3.24	2.35	2.30
2	2.00	4.00	2.86	2.83
3	2.20	4.84	3.33	3.42
4	2.40	5.76	3.97	4.07
5	2.60	6.76	4.88	4.77

Regression Output:

Constant		0.014
Std Err of Y Est		0.106
R Squared		0.991
No. of Observations		5
Degrees of Freedom		3
X Coefficient(s)	0.70	
Std Err of Coef.	0.04	



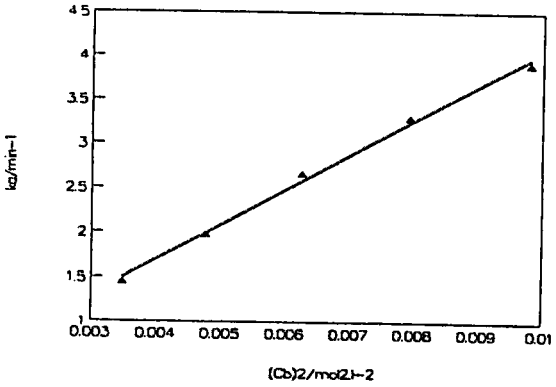
131

RUN 1 R-NO2

No.	Cb	(Cb)2	ka	Y(calc)
1	0.059	0.003	1.450	1.496
2	0.069	0.005	1.980	1.998
3	0.079	0.006	2.660	2.579
4	0.089	0.008	3.290	3.239
5	0.099	0.010	3.910	3.977

Regression Output:

Constant	0.129
Std Err of Y Est	0.073
R Squared	0.996
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	392.6
Std Err of Coef.	14.6

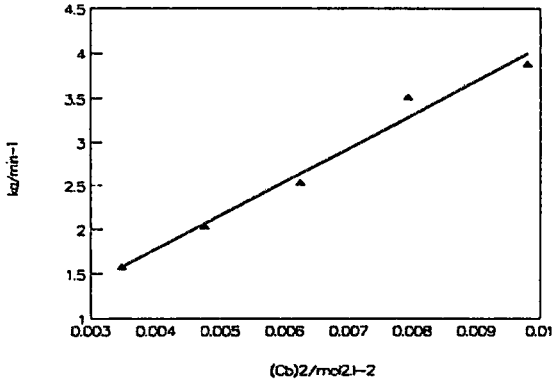


RUN 2 R-NO2

No.	Cb	(Cb)2	ka	Y(calc)
1	0.059	0.003	1.580	1.574
2	0.069	0.005	2.040	2.066
3	0.079	0.006	2.540	2.635
4	0.089	0.008	3.510	3.281
5	0.099	0.010	3.890	4.004

Regression Output:

Constant	0.235
Std Err of Y Est	0.158
R Squared	0.980
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	384.5
Std Err of Coef.	31.6



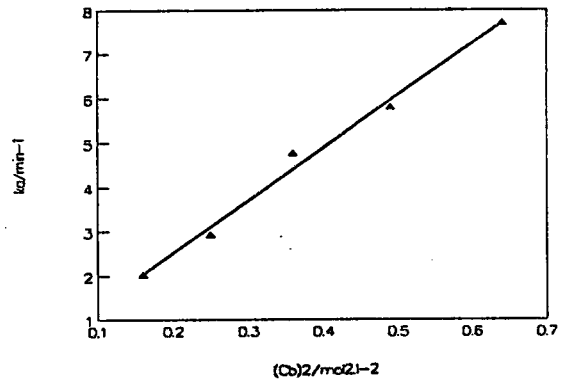
132

RUN 1 R-F

No.	Cb	(Cb)2	ka	Y(Calc)
1	0.40	0.16	2.02	2.04
2	0.50	0.25	2.94	3.11
3	0.60	0.36	4.76	4.41
4	0.70	0.49	5.79	5.95
5	0.80	0.64	7.71	7.72

Regression Output:

Constant	0.150
Std Err of Y Est	0.243
R Squared	0.991
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	11.83
Std Err of Coef.	0.64

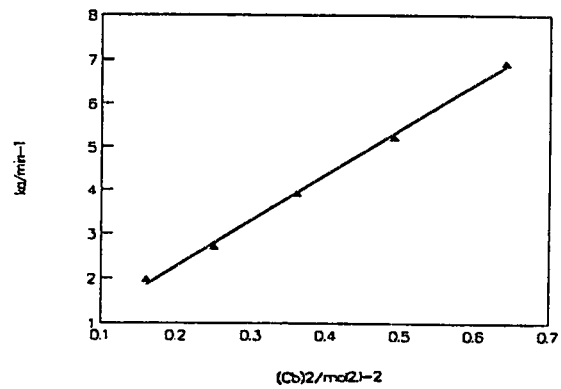


RUN 2 R-F

No.	Cb	(Cb)2	ka	Y(calc)
1	0.40	0.16	1.97	1.85
2	0.50	0.25	2.70	2.79
3	0.60	0.36	3.91	3.94
4	0.70	0.49	5.22	5.29
5	0.80	0.64	6.94	6.86

Regression Output:

Constant	0.186
Std Err of Y Est	0.108
R Squared	0.998
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	10.43
Std Err of Coef.	0.28



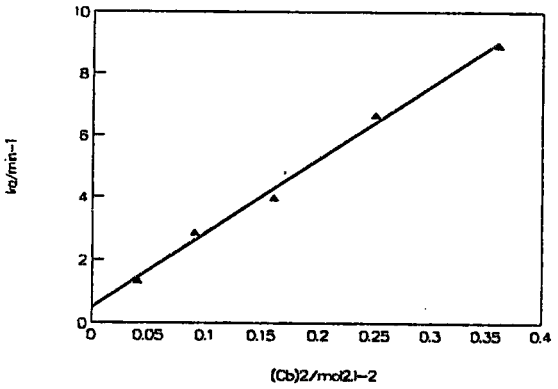
133

RUN 1 R-Cl

No.	Cb	(Cb)2	ka	Y(calc)
1	0.20	0.04	1.33	1.43
2	0.30	0.09	2.86	2.62
3	0.40	0.16	3.98	4.28
4	0.50	0.25	6.67	6.41
5	0.60	0.36	8.93	9.02

Regression Output:

Constant	0.485
Std Err of Y Est	0.278
R Squared	0.994
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	23.72
Std Err of Coef.	1.09

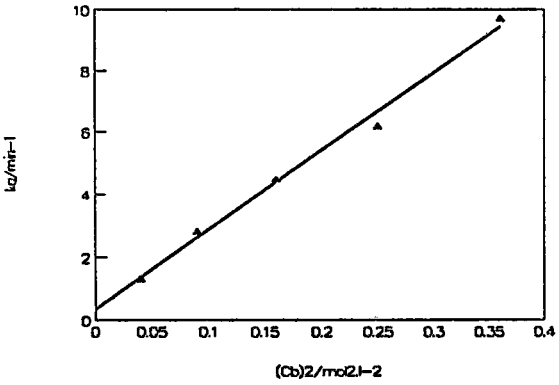


RUN 2 R-Cl

No.	Cb	(Cb)2	ka	Y(calc)
1	0.20	0.04	1.32	1.37
2	0.30	0.09	2.83	2.63
3	0.40	0.16	4.47	4.40
4	0.50	0.25	6.19	6.67
5	0.60	0.36	9.71	9.45

Regression Output:

Constant	0.357
Std Err of Y Est	0.340
R Squared	0.992
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	25.26
Std Err of Coef.	1.33

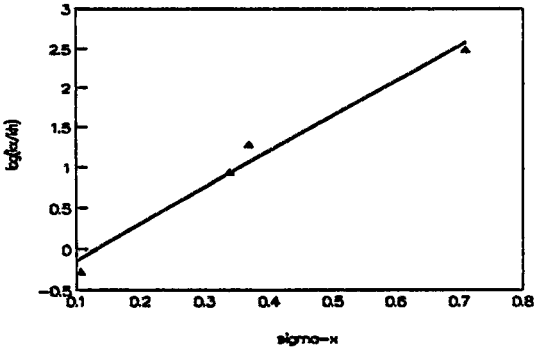


(iv) Hammett plot.

R	sigma	k(obs)	log(kx/kh)	Y(calc)
OMe	0.10	0.000113	-0.273	-0.14
NO2	0.71	0.064800	2.485	2.59
F	0.34	0.001850	0.941	0.93
Cl	0.37	0.004080	1.284	1.06

Regression Output:

Constant	-0.59
Std Err of Y Est	0.19
r	0.98
No. of Observations	4.00
Degrees of Freedom	2.00
X Coefficient(s)	4.48
Std Err of Coef.	0.45



3.6 POTENTIOMETRIC DETERMINATION OF DISSOCIATION CONSTANTS.

Aqueous ethanolic chromone-2-carboxylic acid standard solutions (50% v/v; 0.01M and 0.005M) were obtained by dissolving the appropriate masses (m_c) in 95% ethanol (half the volume of the volumetric flask used) with heating and stirring, and on cooling, diluting with water to the required volume (Table 26). Aqueous benzoic acid and salicylic acid standard solutions (0.01M) were obtained by respectively dissolving benzoic acid (0.12230 g, 1.00 mmol) and salicylic acid (0.13833 g, 1.00 mmol) in water (100 ml). Standard NaOH solutions (0.01M and 0.005M) were obtained by diluting standard 0.1M-NaOH. The pH buffers 2, 4, and 6, were obtained using commercial vials or tablets with dilution to the appropriate volumes. A British Drug House (B.D.H) pH buffer 3.1, devised by Prideaux and Ward,[161] was also obtained by dilution in the appropriate volume.

Table 26. Standard chromone-2-carboxylic acid solutions.

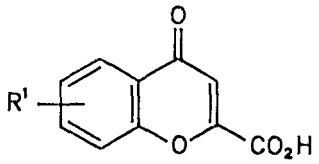
R^1	Volume (ml)	mass(m_c) (g)
H	250	0.4754
	50	0.0474
OMe	50	0.05505
NO_2	25	0.05879
F	25	0.05204
Cl	25	0.05615
Br	25	0.06726

The pH was measured using a Knick Digital-pH-meter 646 and an Ingold combined electrode; and the pH meter was calibrated with pH buffers 4 and 7 using standard procedures.[162] Once calibrated, the pH region of the expected pK_a (*ca.* pH 2.7) was checked using pH buffers 2 and 3.1, which consistently gave readings of 2.01 and 3.16 respectively. It was then assumed that the meter would read accurately in the pH range 2-4. The 0.01M-chromone-2-carboxylic acid solutions (5ml) were maintained at 25 (±0.2)°C, using a waterbath, and titrated with 0.01M-NaOH (*ca.* 10 ml). The titrations were done slowly to ensure that the temperature was maintained throughout the titration. In the case of the methoxy analogue **113**, 0.005M-acid and NaOH solutions were used. Magnetic stirring was stopped while the pH readings were taken.

This procedure was also validated by initially determining the pK_a values of benzoic acid (pK_a = 4.21 ± 0.02 *cf* lit.,[163] 4.19 at 25°C) and salicylic acid (pK_a = 3.07 ± 0.01 *cf* lit.,[163] 2.97 at 19°C), by potentiometry in 0.01M-aqueous solutions of the appropriate acids at 25°C.

In each case, the determination was duplicated using the same standard solution (solution 1), and then repeated using a second standard acid solution (solution 2). The pK_a values are summarised in table 27. The reported pK_a value, in each case, is the logarithm of the mean of the dissociation constants obtained using solution 1 (average of two determinations) and the dissociation constant obtained using solution 2. Linear regression data for the plots of pK_a against log (k_{obs}) and sample titration curves for each acid are summarised after Table 27 p.220.

TABLE 27. Dissociations constants of the chromone-2-carboxylic acids 112-118 at 25°C.



Compd.	R^1	pK_a[a] Solution 1		Solution 2	Mean value
112	7-H	2.74	2.74	2.64	2.69 ± 0.05
113	7-OMe[b]	2.96	2.99	2.94	2.96 ± 0.02
114	7-NO_2	2.65	2.59	2.57	2.60 ± 0.03
115	7-F	2.62	2.62	2.64	2.63 ± 0.01
116	7-Cl	2.67	2.67	2.60	2.64 ± 0.04
117	7-Br	2.65	2.67	2.63	2.64 ± 0.02
118	6-Cl	2.65	2.55	2.63	2.62 ± 0.02

[a] Potentiometric titration in 0.01M-aqueous ethanol (50% v/v).

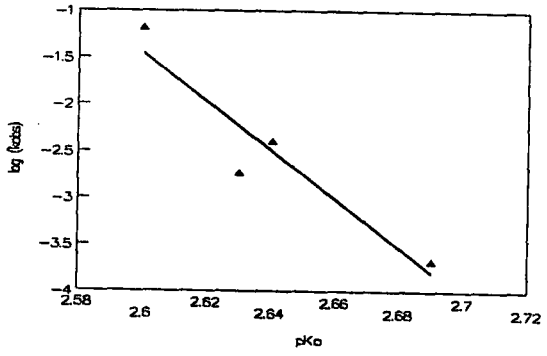
[b] Potentiometric titration in 0.005M-aqueous ethanol (50% v/v).

Determination of the relationship between pK_a and $\log(k_{obs})$.

R	pKa	k(obs)	log(kobs)	Y(calc)
H	2.69	0.000212	-3.674	-3.79
NO2	2.60	0.064800	-1.188	-1.46
F	2.63	0.001850	-2.733	-2.24
Cl	2.64	0.004080	-2.389	-2.50

Regression Output:

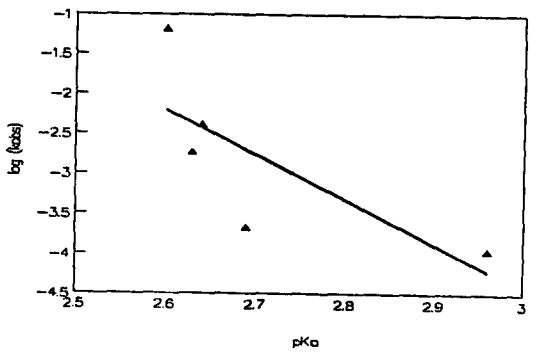
Constant	65.90
Std Err of Y Est	0.42
R Squared	0.89
No. of Observations	4.00
Degrees of Freedom	2.00
X Coefficient(s)	-25.91
Std Err of Coef.	6.41



R	pKa	k(obs)	log(kobs)	Y(calc)
H	2.69	0.000212	-3.674	-2.71
OMe	2.96	0.000113	-3.947	-4.21
NO2	2.60	0.064800	-1.188	-2.21
F	2.63	0.001850	-2.733	-2.37
Cl	2.64	0.004080	-2.389	-2.43

Regression Output:

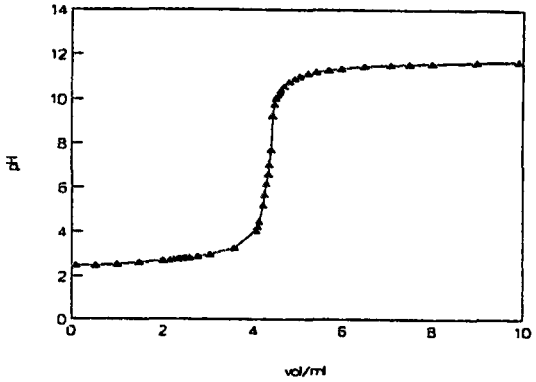
Constant	12.29
Std Err of Y Est	0.85
R Squared	0.55
No. of Observations	5.00
Degrees of Freedom	3.00
X Coefficient(s)	-5.58
Std Err of Coef.	2.90

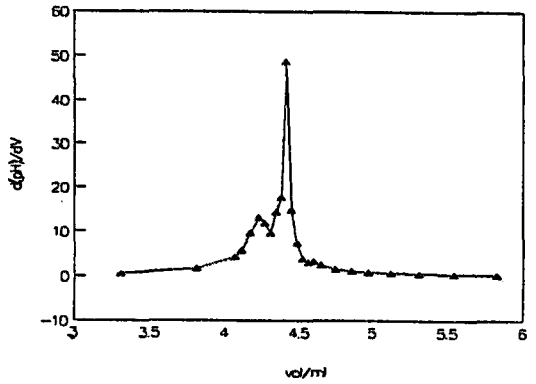


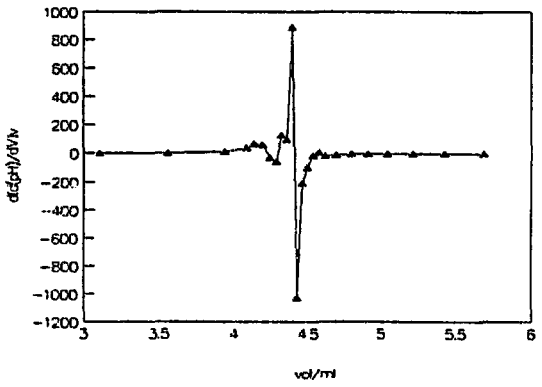
112

R=H

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.47				
2	0.520	2.49	0.260	0.038		
3	1.005	2.55	0.762	0.124	0.511	0.170
4	1.485	2.62	1.245	0.146	1.004	0.046
5	2.000	2.71	1.742	0.175	1.494	0.058
6	2.185	2.74	2.093	0.162	1.917	-0.036
7	2.255	2.76	2.220	0.286	2.156	0.969
8	2.330	2.78	2.292	0.267	2.256	-0.263
9	2.357	2.79	2.344	0.370	2.318	2.033
10	2.395	2.79	2.376	0.000	2.360	-11.396
11	2.435	2.80	2.415	0.250	2.396	6.410
12	2.475	2.82	2.455	0.500	2.435	6.250
13	2.510	2.82	2.493	0.000	2.474	-13.333
14	2.555	2.84	2.533	0.444	2.513	11.111
15	2.590	2.85	2.573	0.286	2.553	-3.968
16	2.775	2.90	2.683	0.270	2.628	-0.140
17	3.035	2.99	2.905	0.346	2.794	0.341
18	3.575	3.28	3.305	0.537	3.105	0.477
19	4.045	4.06	3.810	1.660	3.557	2.223
20	4.085	4.23	4.065	4.250	3.938	10.159
21	4.125	4.46	4.105	5.750	4.085	37.500
22	4.205	5.23	4.165	9.625	4.135	64.583
23	4.240	5.69	4.223	13.143	4.194	61.180
24	4.280	6.17	4.260	12.000	4.241	-30.476
25	4.325	6.60	4.302	9.556	4.281	-57.516
26	4.355	7.03	4.340	14.333	4.321	127.407
27	4.394	7.72	4.375	17.692	4.357	97.362
28	4.425	9.23	4.410	48.710	4.392	886.211
29	4.460	9.75	4.443	14.857	4.426	-1025.834
30	4.495	10.01	4.478	7.429	4.460	-212.245
31	4.534	10.16	4.514	3.846	4.496	-96.822
32	4.575	10.29	4.554	3.171	4.534	-16.886
33	4.605	10.39	4.590	3.333	4.572	4.580
34	4.680	10.58	4.643	2.533	4.616	-15.238
35	4.800	10.77	4.740	1.583	4.691	-9.744
36	4.905	10.89	4.853	1.143	4.796	-3.915
37	5.025	10.99	4.965	0.833	4.909	-2.751
38	5.215	11.11	5.120	0.632	5.043	-1.302
39	5.405	11.20	5.310	0.474	5.215	-0.831
40	5.680	11.29	5.542	0.327	5.426	-0.630
41	5.970	11.36	5.825	0.241	5.684	-0.304
42	6.485	11.45	6.228	0.175	6.026	-0.166
43	7.074	11.52	6.779	0.119	6.503	-0.101
44	7.497	11.55	7.285	0.071	7.032	-0.095
45	7.995	11.59	7.746	0.080	7.516	0.020
46	8.975	11.64	8.485	0.051	8.115	-0.040
47	9.975	11.68	9.475	0.040	8.980	-0.011



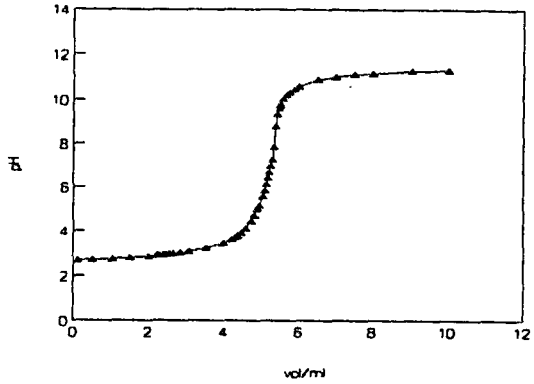


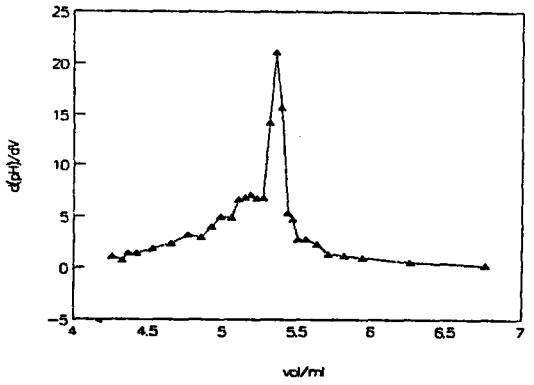


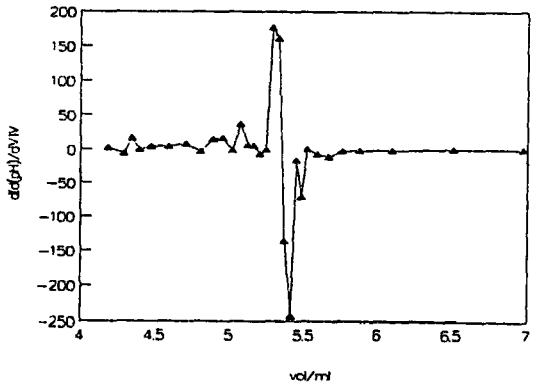
113

R-OMe

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.68				
2	0.519	2.71	0.260	0.058		
3	1.044	2.75	0.782	0.076	0.520	0.035
4	1.514	2.80	1.279	0.106	1.030	0.061
5	2.019	2.87	1.767	0.139	1.523	0.066
6	2.244	2.91	2.131	0.178	1.949	0.107
7	2.278	2.92	2.261	0.294	2.196	0.898
8	2.318	2.92	2.298	0.000	2.280	-7.949
9	2.401	2.94	2.360	0.241	2.329	3.918
10	2.464	2.95	2.433	0.159	2.396	-1.126
11	2.509	2.96	2.487	0.222	2.460	1.176
12	2.558	2.96	2.534	0.000	2.510	-4.728
13	2.599	2.97	2.579	0.244	2.556	5.420
14	2.674	2.99	2.637	0.267	2.607	0.392
15	2.859	3.03	2.767	0.216	2.702	-0.388
16	3.080	3.09	2.970	0.271	2.868	0.272
17	3.549	3.24	3.315	0.320	3.142	0.140
18	3.999	3.45	3.774	0.467	3.544	0.320
19	4.219	3.63	4.109	0.818	3.942	1.049
20	4.299	3.72	4.259	1.125	4.184	2.045
21	4.351	3.76	4.325	0.769	4.292	-5.390
22	4.379	3.80	4.365	1.429	4.345	16.484
23	4.464	3.92	4.421	1.412	4.393	-0.297
24	4.584	4.14	4.524	1.833	4.473	4.113
25	4.719	4.46	4.652	2.370	4.588	4.212
26	4.799	4.72	4.759	3.250	4.705	8.183
27	4.900	5.02	4.850	2.970	4.804	-3.091
28	4.940	5.18	4.920	4.000	4.885	14.606
29	5.024	5.60	4.982	5.000	4.951	16.129
30	5.077	5.86	5.050	4.906	5.016	-1.377
31	5.119	6.14	5.098	6.667	5.074	37.074
32	5.161	6.43	5.140	6.905	5.119	5.669
33	5.199	6.70	5.180	7.105	5.160	5.013
34	5.240	6.98	5.220	6.829	5.200	-6.987
35	5.284	7.28	5.262	6.818	5.241	-0.261
36	5.324	7.85	5.304	14.250	5.283	176.948
37	5.369	8.80	5.346	21.111	5.325	161.438
38	5.404	9.35	5.386	15.714	5.367	-134.921
39	5.454	9.62	5.429	5.400	5.408	-242.689
40	5.479	9.74	5.466	4.800	5.448	-16.000
41	5.511	9.83	5.495	2.812	5.481	-69.737
42	5.589	10.05	5.550	2.821	5.523	0.146
43	5.664	10.22	5.627	2.267	5.588	-7.240
44	5.751	10.34	5.708	1.379	5.667	-10.955
45	5.879	10.49	5.815	1.172	5.761	-1.930
46	6.001	10.61	5.940	0.984	5.878	-1.506
47	6.518	10.91	6.260	0.580	6.100	-1.262
48	6.994	11.03	6.756	0.252	6.508	-0.661
49	7.494	11.13	7.244	0.200	7.000	-0.107
50	8.000	11.18	7.747	0.099	7.495	-0.201
51	9.039	11.28	8.520	0.096	8.133	-0.003
52	10.019	11.32	9.529	0.041	9.024	-0.055



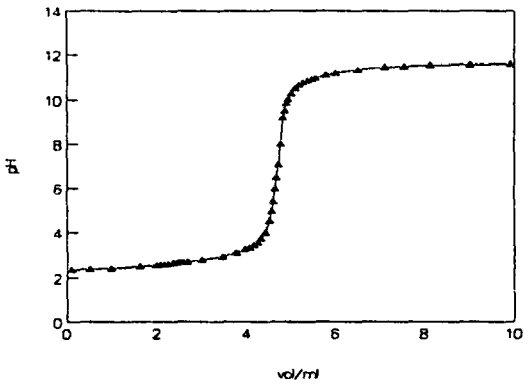


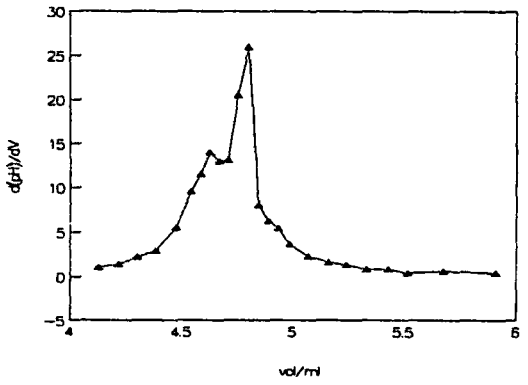


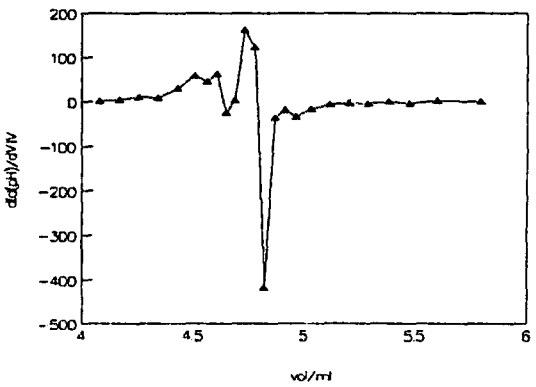
114

R=NO2

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.36				
2	0.515	2.38	0.258	0.039		
3	1.000	2.43	0.758	0.103	0.508	0.129
4	1.630	2.51	1.315	0.127	1.036	0.043
5	2.001	2.57	1.815	0.162	1.565	0.069
6	2.099	2.59	2.050	0.204	1.933	0.181
7	2.180	2.60	2.139	0.123	2.095	-0.901
8	2.265	2.62	2.223	0.235	2.181	1.347
9	2.359	2.64	2.312	0.213	2.267	-0.252
10	2.400	2.65	2.380	0.244	2.346	0.461
11	2.440	2.66	2.420	0.250	2.400	0.151
12	2.480	2.67	2.460	0.250	2.440	-0.000
13	2.522	2.67	2.501	0.000	2.481	-6.098
14	2.565	2.68	2.543	0.233	2.522	5.472
15	2.615	2.69	2.590	0.200	2.567	-0.700
16	2.700	2.71	2.658	0.235	2.624	0.523
17	3.010	2.79	2.855	0.258	2.756	0.115
18	3.475	2.95	3.243	0.344	3.049	0.222
19	3.778	3.11	3.627	0.528	3.434	0.479
20	3.995	3.28	3.886	0.783	3.756	0.982
21	4.080	3.36	4.037	0.941	3.962	1.045
22	4.175	3.46	4.128	1.053	4.082	1.238
23	4.260	3.58	4.218	1.412	4.173	3.990
24	4.341	3.76	4.300	2.222	4.259	9.765
25	4.430	4.02	4.385	2.921	4.343	8.225
26	4.520	4.52	4.475	5.556	4.430	29.432
27	4.565	4.95	4.542	9.556	4.509	59.259
28	4.605	5.41	4.585	11.500	4.564	45.752
29	4.645	5.97	4.625	14.000	4.605	62.500
30	4.685	6.49	4.665	13.000	4.645	-25.000
31	4.730	7.08	4.708	13.111	4.686	2.614
32	4.775	8.00	4.753	20.444	4.730	162.963
33	4.820	9.17	4.798	26.000	4.775	123.457
34	4.861	9.50	4.841	8.049	4.819	-417.470
35	4.915	9.84	4.888	6.296	4.864	-36.894
36	4.950	10.03	4.932	5.429	4.910	-19.499
37	5.021	10.29	4.986	3.662	4.959	-33.332
38	5.118	10.51	5.070	2.268	5.027	-16.594
39	5.202	10.65	5.160	1.667	5.115	-6.645
40	5.282	10.76	5.242	1.375	5.201	-3.557
41	5.385	10.85	5.333	0.874	5.288	-5.478
42	5.479	10.93	5.432	0.851	5.383	-0.231
43	5.555	10.96	5.517	0.395	5.474	-5.369
44	5.800	11.11	5.678	0.612	5.597	1.355
45	6.021	11.20	5.911	0.407	5.794	-0.880
46	6.525	11.35	6.273	0.298	6.092	-0.302
47	7.119	11.45	6.822	0.168	6.548	-0.235
48	7.558	11.50	7.338	0.114	7.080	-0.105
49	8.125	11.55	7.841	0.088	7.590	-0.051
50	9.020	11.58	8.572	0.034	8.207	-0.075
51	9.975	11.61	9.497	0.031	9.035	-0.002



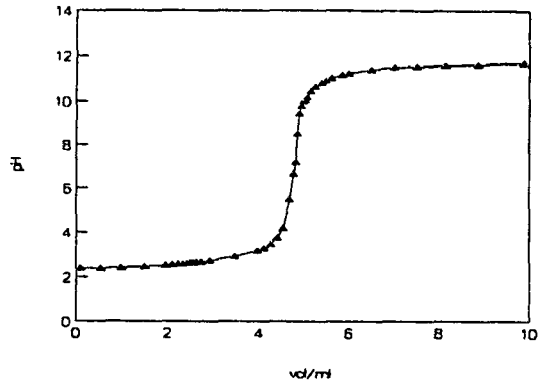


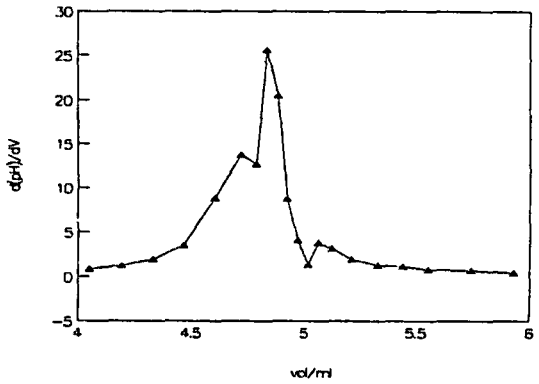


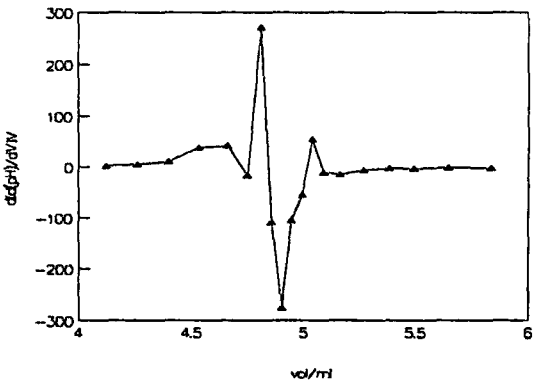
115

R-F

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.39				
2	0.540	2.39	0.270	0.000		
3	0.980	2.41	0.760	0.045	0.515	0.093
4	1.501	2.47	1.240	0.115	1.000	0.145
5	1.980	2.53	1.740	0.125	1.490	0.020
6	2.115	2.56	2.047	0.222	1.894	0.316
7	2.255	2.59	2.185	0.214	2.116	-0.058
8	2.345	2.61	2.300	0.222	2.242	0.069
9	2.440	2.62	2.393	0.105	2.346	-1.264
10	2.490	2.63	2.465	0.200	2.429	1.307
11	2.530	2.64	2.510	0.250	2.487	1.111
12	2.570	2.65	2.550	0.250	2.530	-0.000
13	2.610	2.66	2.590	0.250	2.570	0.000
14	2.660	2.67	2.635	0.200	2.612	-1.111
15	2.750	2.69	2.705	0.222	2.670	0.317
16	2.941	2.74	2.846	0.262	2.775	0.282
17	3.490	2.93	3.216	0.346	3.030	0.228
18	3.980	3.21	3.735	0.571	3.475	0.434
19	4.122	3.33	4.051	0.845	3.893	0.866
20	4.261	3.50	4.191	1.223	4.121	2.690
21	4.401	3.77	4.331	1.929	4.261	5.058
22	4.530	4.22	4.465	3.488	4.398	11.597
23	4.677	5.52	4.603	8.844	4.534	38.806
24	4.760	6.66	4.718	13.735	4.661	42.534
25	4.805	7.23	4.782	12.667	4.750	-16.692
26	4.855	8.51	4.830	25.600	4.806	272.281
27	4.900	9.43	4.878	20.444	4.854	-108.538
28	4.940	9.78	4.920	8.750	4.899	-275.163
29	4.989	9.98	4.965	4.082	4.942	-104.907
30	5.041	10.05	5.015	1.346	4.990	-54.168
31	5.078	10.19	5.059	3.784	5.037	54.778
32	5.160	10.45	5.119	3.171	5.089	-10.303
33	5.259	10.64	5.210	1.919	5.164	-13.829
34	5.398	10.82	5.329	1.295	5.269	-5.246
35	5.480	10.91	5.439	1.098	5.384	-1.786
36	5.621	11.02	5.551	0.780	5.495	-2.847
37	5.859	11.18	5.740	0.672	5.645	-0.569
38	6.000	11.24	5.929	0.426	5.835	-1.302
39	6.499	11.40	6.250	0.321	6.090	-0.328
40	7.030	11.51	6.764	0.207	6.507	-0.220
41	7.505	11.55	7.267	0.084	7.016	-0.244
42	8.142	11.61	7.823	0.094	7.545	0.018
43	8.860	11.64	8.501	0.042	8.162	-0.077
44	9.882	11.72	9.371	0.078	8.936	0.042



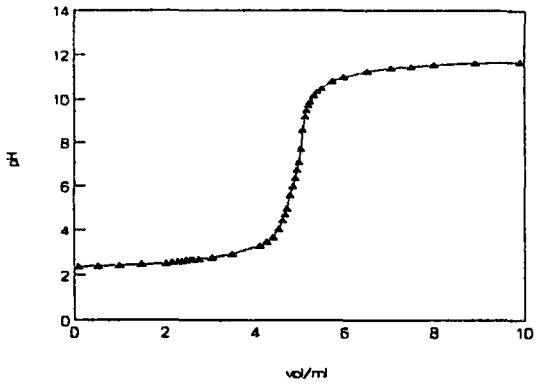


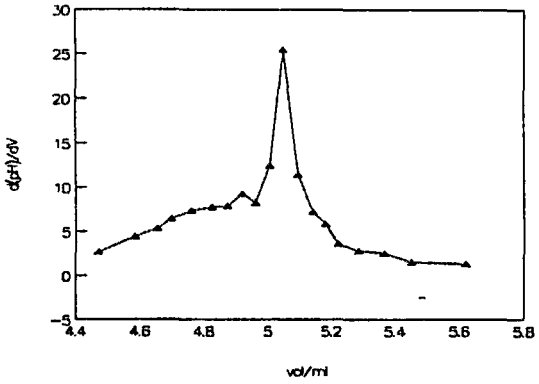


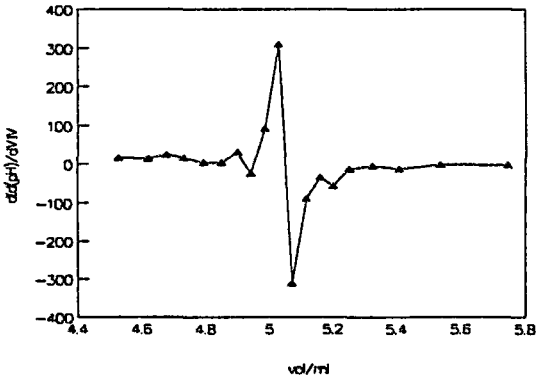
116

R-Cl

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.37				
2	0.522	2.40	0.261	0.057		
3	1.002	2.43	0.762	0.063	0.511	0.010
4	1.490	2.47	1.246	0.082	1.004	0.040
5	2.030	2.52	1.760	0.093	1.503	0.021
6	2.160	2.58	2.095	0.462	1.927	1.101
7	2.295	2.61	2.228	0.222	2.161	-1.806
8	2.380	2.62	2.337	0.118	2.282	-0.951
9	2.460	2.64	2.420	0.250	2.379	1.604
10	2.500	2.66	2.480	0.500	2.450	4.167
11	2.550	2.67	2.525	0.200	2.502	-6.667
12	2.598	2.68	2.574	0.208	2.550	0.170
13	2.640	2.69	2.619	0.238	2.596	0.661
14	2.760	2.71	2.700	0.167	2.659	-0.882
15	3.050	2.78	2.905	0.241	2.803	0.364
16	3.502	2.94	3.276	0.354	3.091	0.304
17	4.123	3.32	3.813	0.612	3.544	0.481
18	4.270	3.48	4.196	1.088	4.005	1.241
19	4.405	3.70	4.337	1.630	4.267	3.838
20	4.540	4.07	4.472	2.741	4.405	8.230
21	4.630	4.47	4.585	4.444	4.529	15.144
22	4.680	4.74	4.655	5.400	4.620	13.651
23	4.720	5.00	4.700	6.500	4.678	24.444
24	4.802	5.61	4.761	7.439	4.731	15.394
25	4.851	5.99	4.827	7.755	4.794	4.826
26	4.899	6.37	4.875	7.917	4.851	3.331
27	4.940	6.75	4.919	9.268	4.897	30.374
28	4.981	7.09	4.960	8.293	4.940	-23.795
29	5.030	7.70	5.005	12.449	4.983	92.362
30	5.065	8.59	5.047	25.429	5.026	309.038
31	5.120	9.22	5.092	11.455	5.070	-310.534
32	5.160	9.51	5.140	7.250	5.116	-88.517
33	5.199	9.74	5.179	5.897	5.160	-34.242
34	5.240	9.89	5.220	3.659	5.200	-55.972
35	5.330	10.15	5.285	2.889	5.252	-11.750
36	5.400	10.33	5.365	2.571	5.325	-3.968
37	5.502	10.49	5.451	1.569	5.408	-11.660
38	5.741	10.81	5.622	1.339	5.536	-1.347
39	6.000	11.01	5.870	0.772	5.746	-2.276
40	6.521	11.25	6.261	0.461	6.066	-0.799
41	7.050	11.40	6.786	0.284	6.523	-0.337
42	7.492	11.47	7.271	0.158	7.028	-0.258
43	8.002	11.54	7.747	0.137	7.509	-0.044
44	8.915	11.63	8.459	0.099	8.103	-0.054
45	9.919	11.68	9.417	0.050	8.938	-0.051



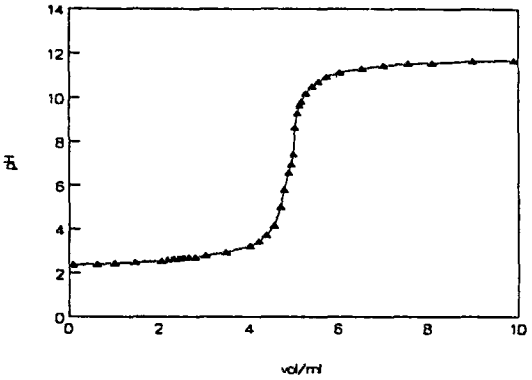


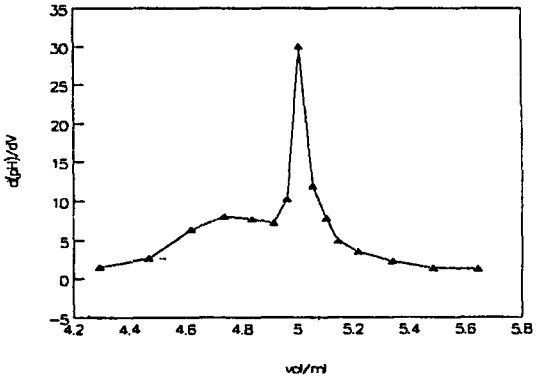


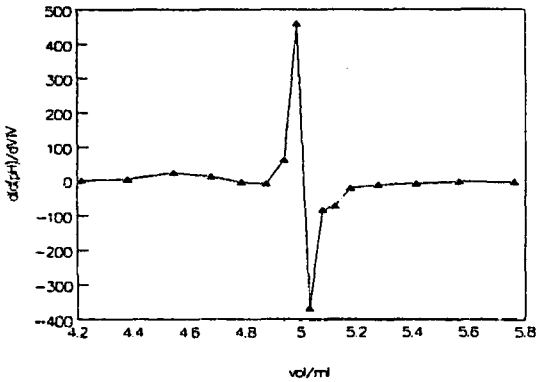
117

R=Br

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.36				
2	0.636	2.40	0.318	0.063		
3	1.023	2.42	0.829	0.052	0.574	-0.022
4	1.468	2.48	1.245	0.135	1.037	0.200
5	2.062	2.55	1.765	0.118	1.505	-0.033
6	2.193	2.60	2.127	0.382	1.946	0.728
7	2.303	2.62	2.248	0.182	2.188	-1.659
8	2.345	2.63	2.324	0.238	2.286	0.740
9	2.442	2.65	2.393	0.206	2.359	-0.459
10	2.483	2.66	2.462	0.244	2.428	0.547
11	2.528	2.67	2.505	0.222	2.484	-0.504
12	2.573	2.68	2.550	0.222	2.528	0.000
13	2.673	2.70	2.623	0.200	2.587	-0.307
14	2.805	2.71	2.739	0.076	2.681	-1.071
15	3.043	2.79	2.924	0.336	2.832	1.407
16	3.493	2.94	3.268	0.333	3.096	-0.008
17	4.021	3.24	3.757	0.568	3.512	0.480
18	4.203	3.43	4.112	1.044	3.934	1.340
19	4.384	3.71	4.293	1.547	4.203	2.771
20	4.553	4.16	4.468	2.663	4.381	6.376
21	4.688	5.02	4.620	6.370	4.544	24.392
22	4.784	5.79	4.736	8.021	4.678	14.290
23	4.885	6.57	4.835	7.723	4.785	-3.026
24	4.938	6.95	4.912	7.170	4.873	-7.181
25	4.984	7.42	4.961	10.217	4.936	61.567
26	5.024	8.62	5.004	30.000	4.982	460.061
27	5.082	9.31	5.053	11.897	5.028	-369.458
28	5.123	9.63	5.102	7.805	5.078	-82.660
29	5.164	9.83	5.143	4.878	5.123	-71.386
30	5.265	10.18	5.214	3.465	5.179	-19.897
31	5.413	10.51	5.339	2.230	5.277	-9.925
32	5.558	10.71	5.486	1.379	5.412	-5.805
33	5.728	10.93	5.643	1.294	5.564	-0.541
34	6.025	11.14	5.877	0.707	5.760	-2.514
35	6.528	11.33	6.276	0.378	6.076	-0.823
36	7.018	11.46	6.773	0.265	6.525	-0.226
37	7.563	11.54	7.290	0.147	7.032	-0.229
38	8.103	11.59	7.833	0.093	7.562	-0.100
39	9.003	11.66	8.553	0.078	8.193	-0.021
40	9.983	11.70	9.493	0.041	9.023	-0.039



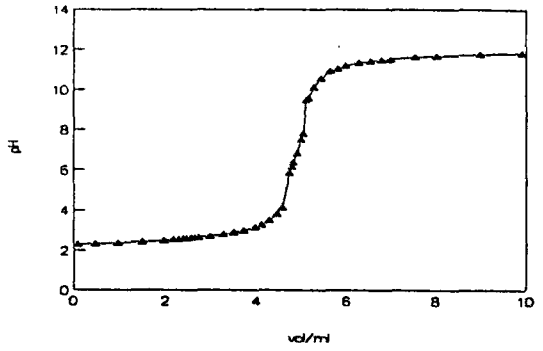


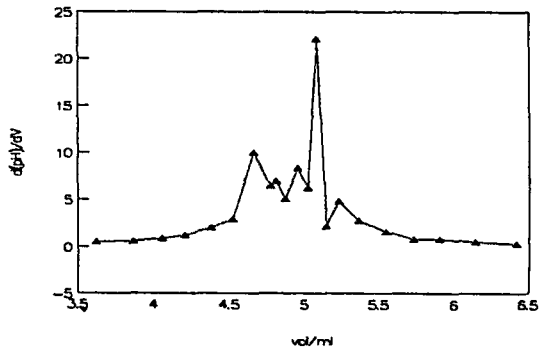


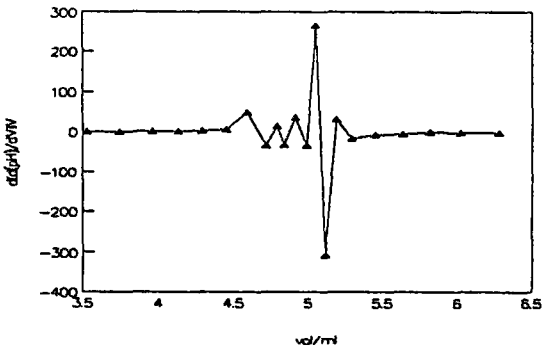
118

R-6-Cl R-6-Cl

No.	Vol/ml	pH	V1(Ave)	d(pH)/dV	V2(Ave)	d[d(pH)/dV]V
1	0.000	2.31				
2	0.480	2.35	0.240	0.083		
3	0.975	2.39	0.728	0.081	0.484	-0.005
4	1.505	2.46	1.240	0.132	0.984	0.100
5	1.980	2.53	1.743	0.147	1.491	0.030
6	2.195	2.57	2.088	0.186	1.915	0.112
7	2.315	2.59	2.255	0.167	2.171	-0.116
8	2.405	2.61	2.360	0.222	2.308	0.529
9	2.480	2.62	2.442	0.133	2.401	-1.077
10	2.575	2.64	2.527	0.211	2.485	0.908
11	2.656	2.66	2.615	0.247	2.571	0.413
12	2.735	2.68	2.696	0.253	2.655	0.078
13	3.000	2.75	2.867	0.264	2.781	0.064
14	3.285	2.84	3.143	0.316	3.005	0.188
15	3.515	2.92	3.400	0.348	3.271	0.124
16	3.735	3.03	3.625	0.500	3.513	0.676
17	3.994	3.19	3.865	0.618	3.745	0.492
18	4.117	3.30	4.056	0.894	3.960	1.448
19	4.295	3.52	4.206	1.236	4.131	2.270
20	4.465	3.86	4.380	2.000	4.293	4.391
21	4.575	4.18	4.520	2.909	4.450	6.494
22	4.745	5.88	4.660	10.000	4.590	50.649
23	4.790	6.17	4.768	6.444	4.714	-33.075
24	4.820	6.38	4.805	7.000	4.786	14.815
25	4.910	6.84	4.865	5.111	4.835	-31.481
26	4.995	7.55	4.952	8.353	4.909	37.049
27	5.040	7.83	5.018	6.222	4.985	-32.780
28	5.115	9.49	5.077	22.133	5.047	265.185
29	5.170	9.61	5.143	2.182	5.110	-306.946
30	5.280	10.14	5.225	4.818	5.184	31.956
31	5.445	10.60	5.362	2.788	5.294	-14.766
32	5.645	10.93	5.545	1.650	5.454	-6.235
33	5.820	11.07	5.732	0.800	5.639	-4.533
34	5.990	11.21	5.905	0.824	5.819	0.136
35	6.290	11.37	6.140	0.533	6.022	-1.235
36	6.545	11.45	6.418	0.314	6.279	-0.791
37	6.795	11.52	6.670	0.280	6.544	-0.134
38	6.993	11.55	6.894	0.152	6.782	-0.574
39	7.545	11.66	7.269	0.199	7.082	0.127
40	8.015	11.71	7.780	0.106	7.524	-0.182
41	8.985	11.80	8.500	0.093	8.140	-0.019
42	9.995	11.85	9.490	0.050	8.995	-0.044







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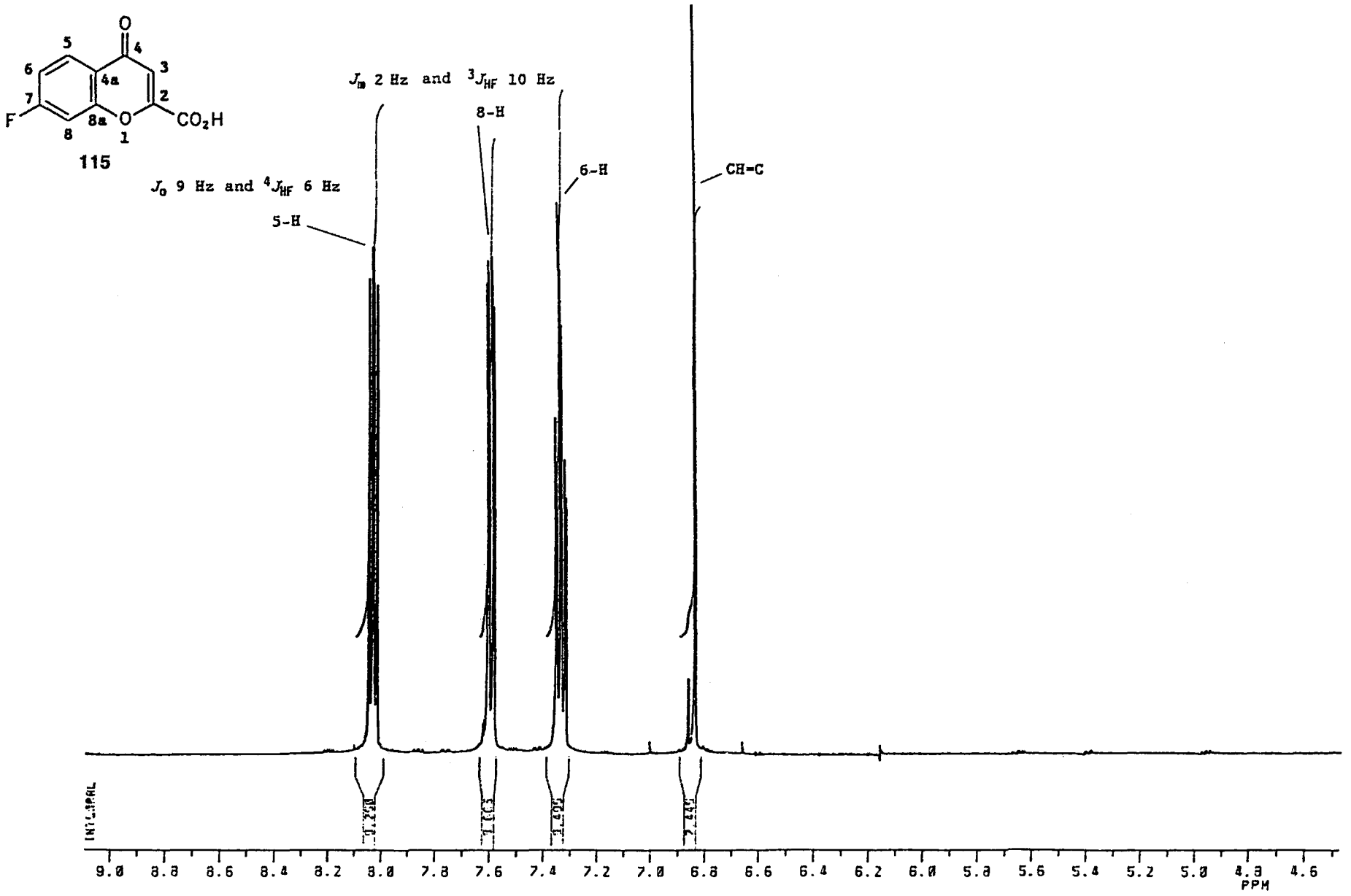
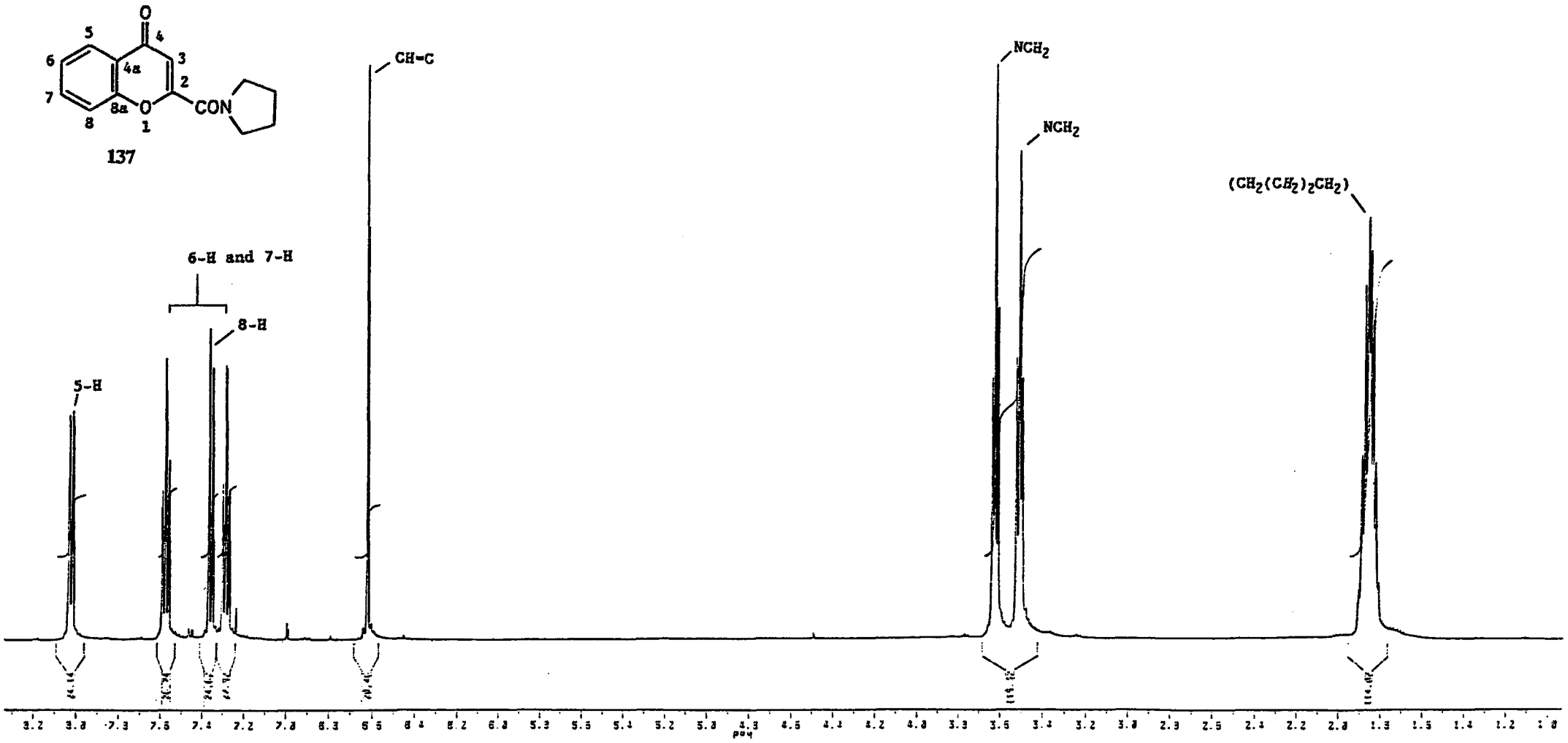
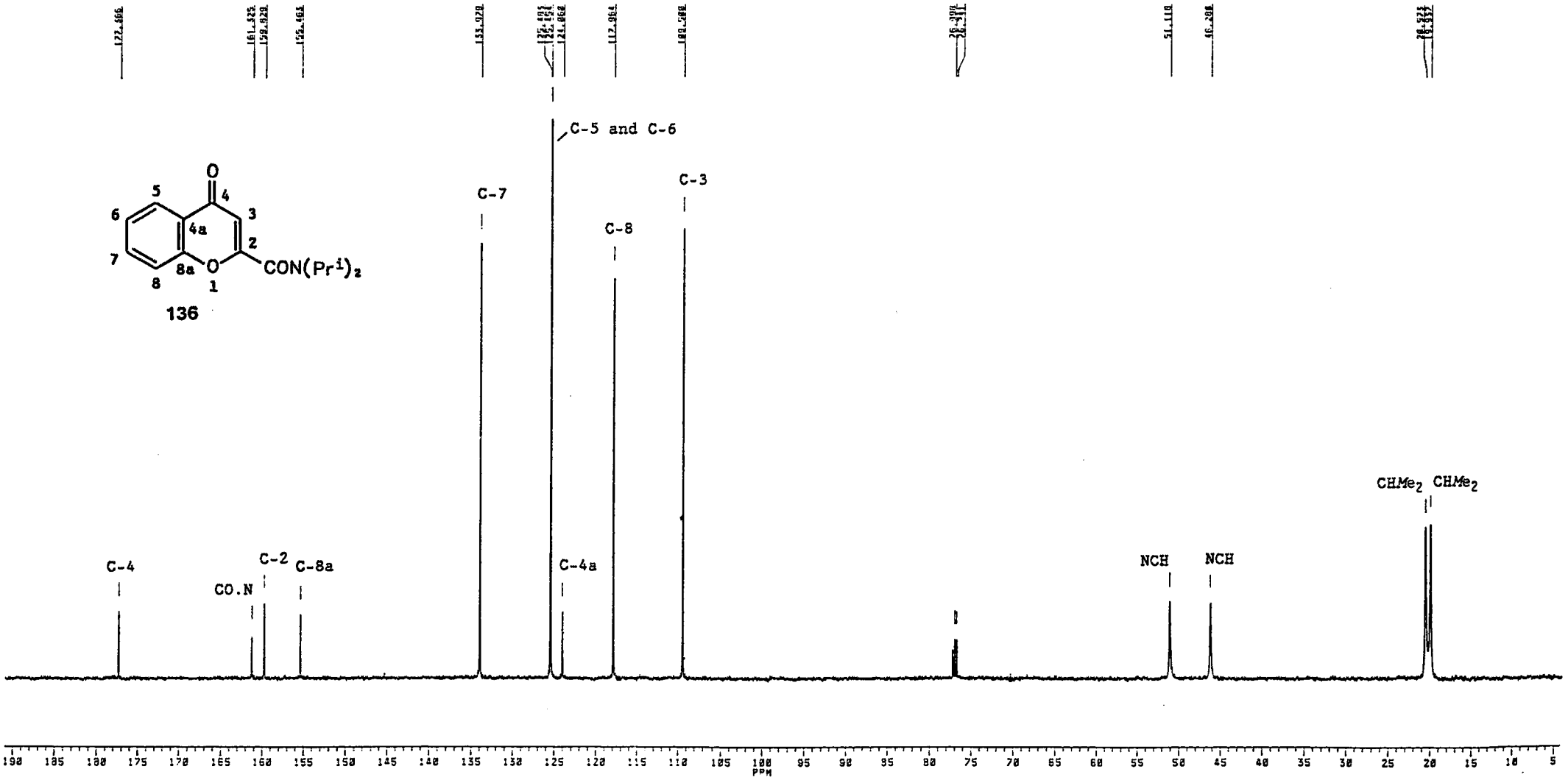
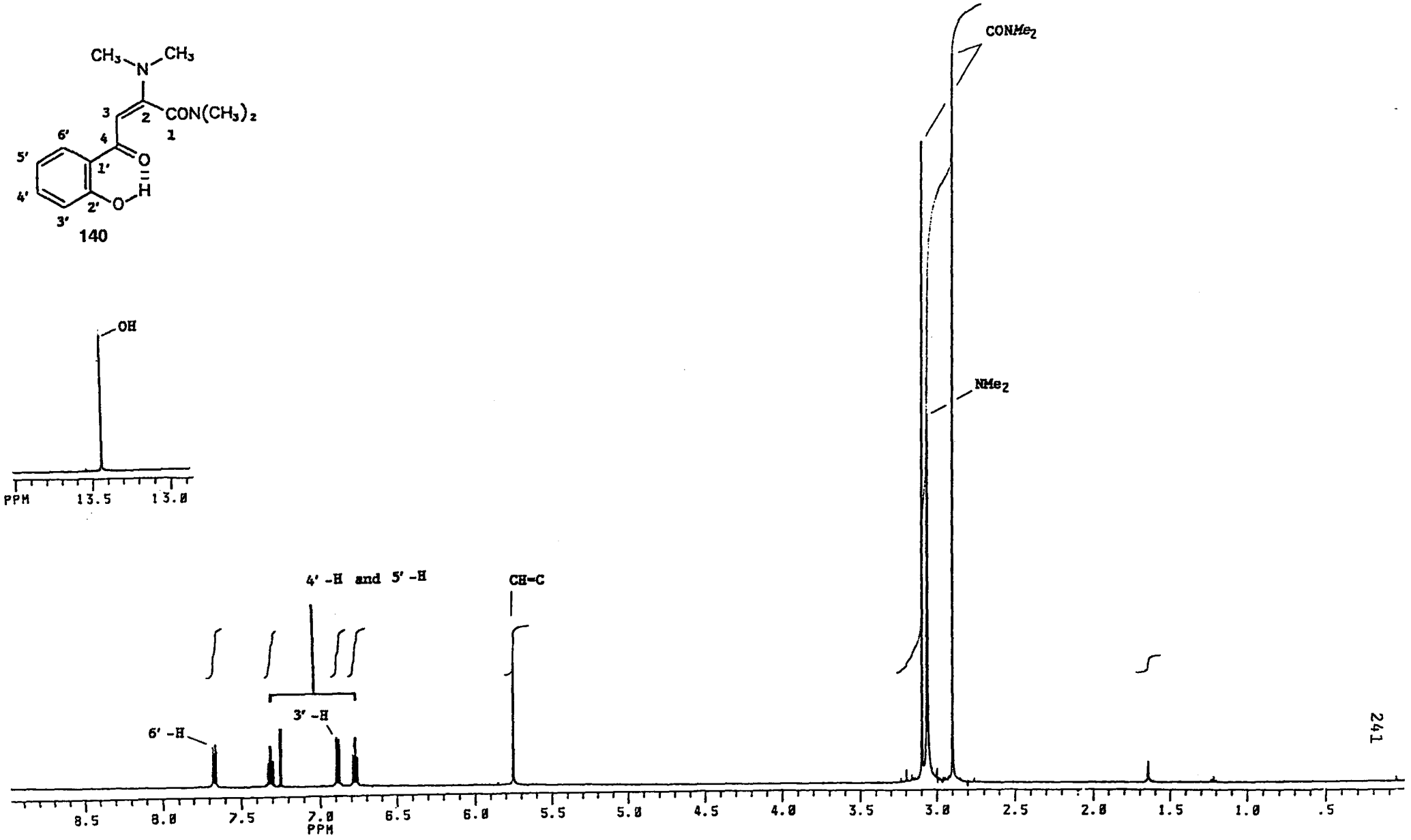
5. APPENDICES

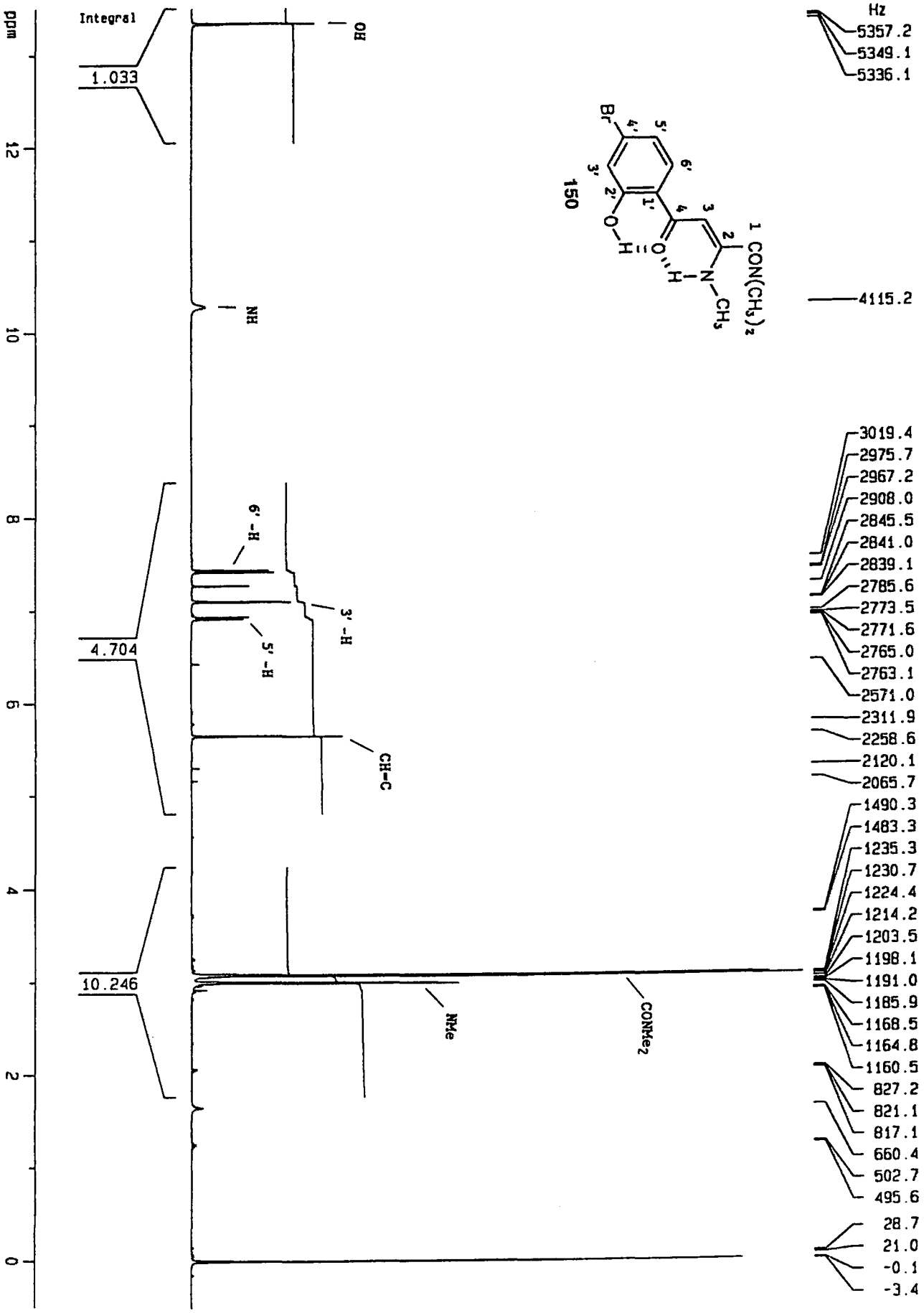
5.1 SPECTRAL DATA.

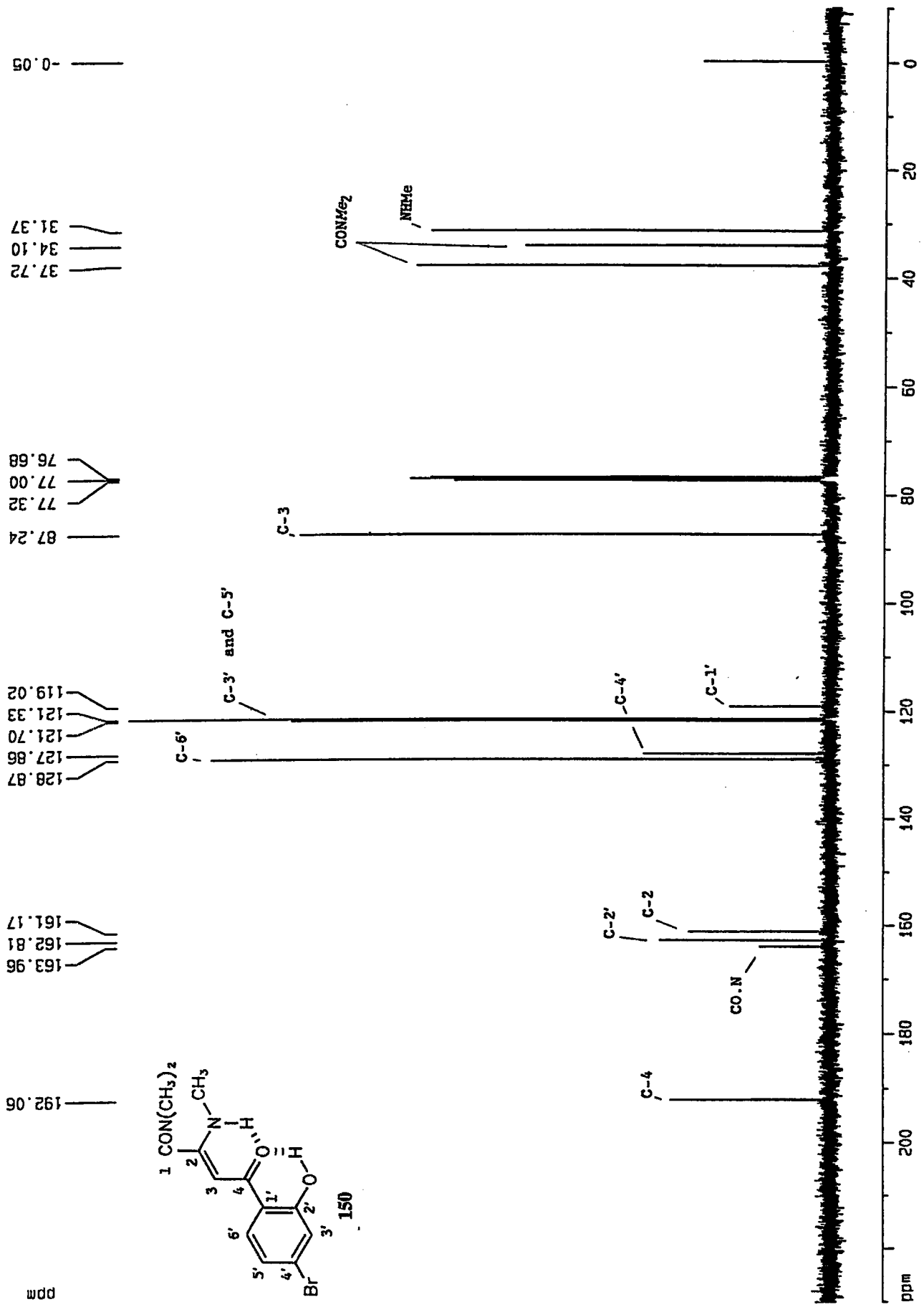

O
4
5
3
6
4a
2
7
F
8a
O
CO2H
8
1
115
J_m 2 Hz and $^3J_{HF}$ 10 Hz
8-H
6-H
CH=C
J_o 9 Hz and $^4J_{HF}$ 6 Hz
5-H
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
PPM

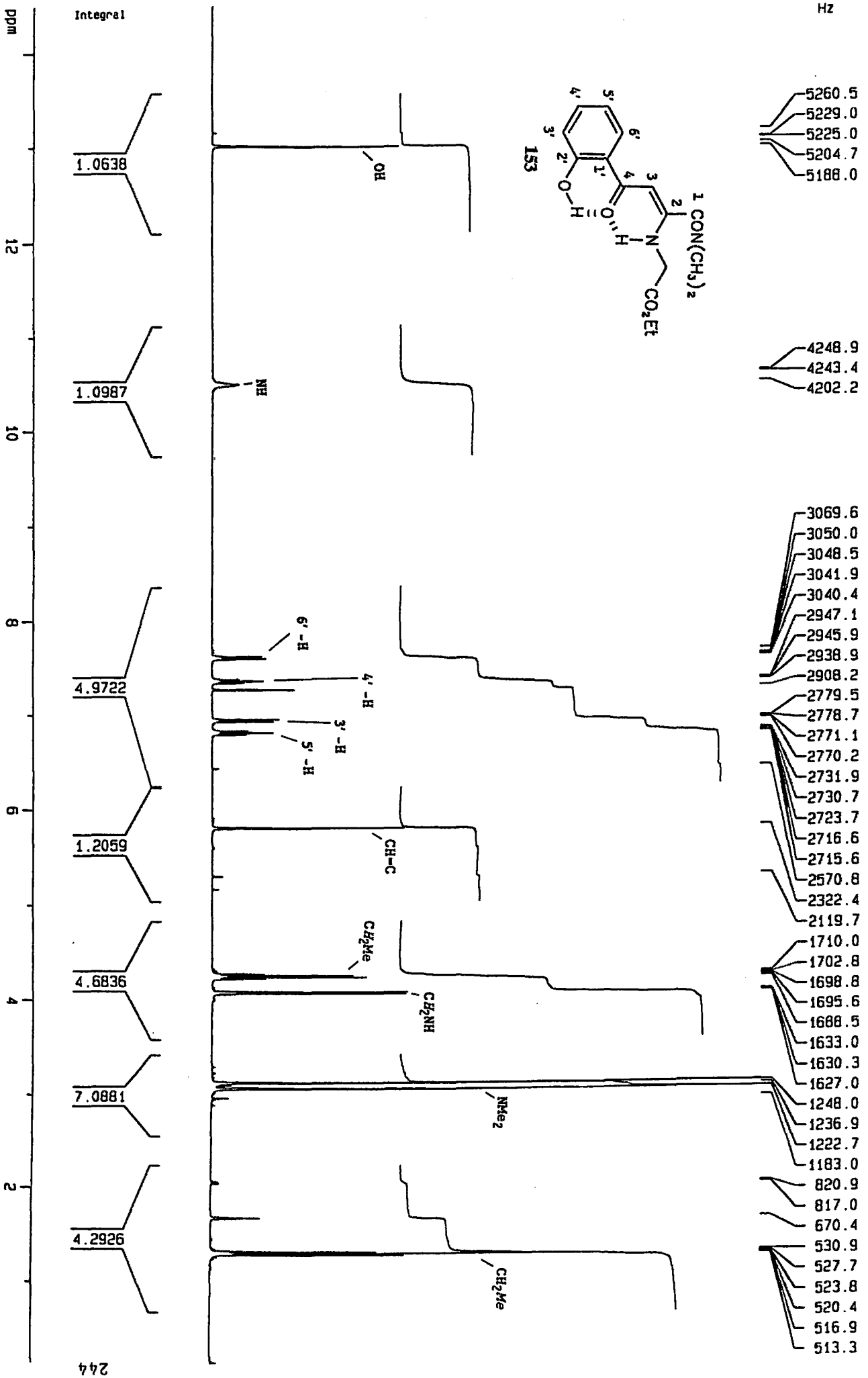

O
4
5
3
6
4a
2
7
8a
O
CON
8
1
137
CH=C
NCH2
NCH2
(CH2(CH2)2CH2)
6-H and 7-H
8-H
5-H
ppm

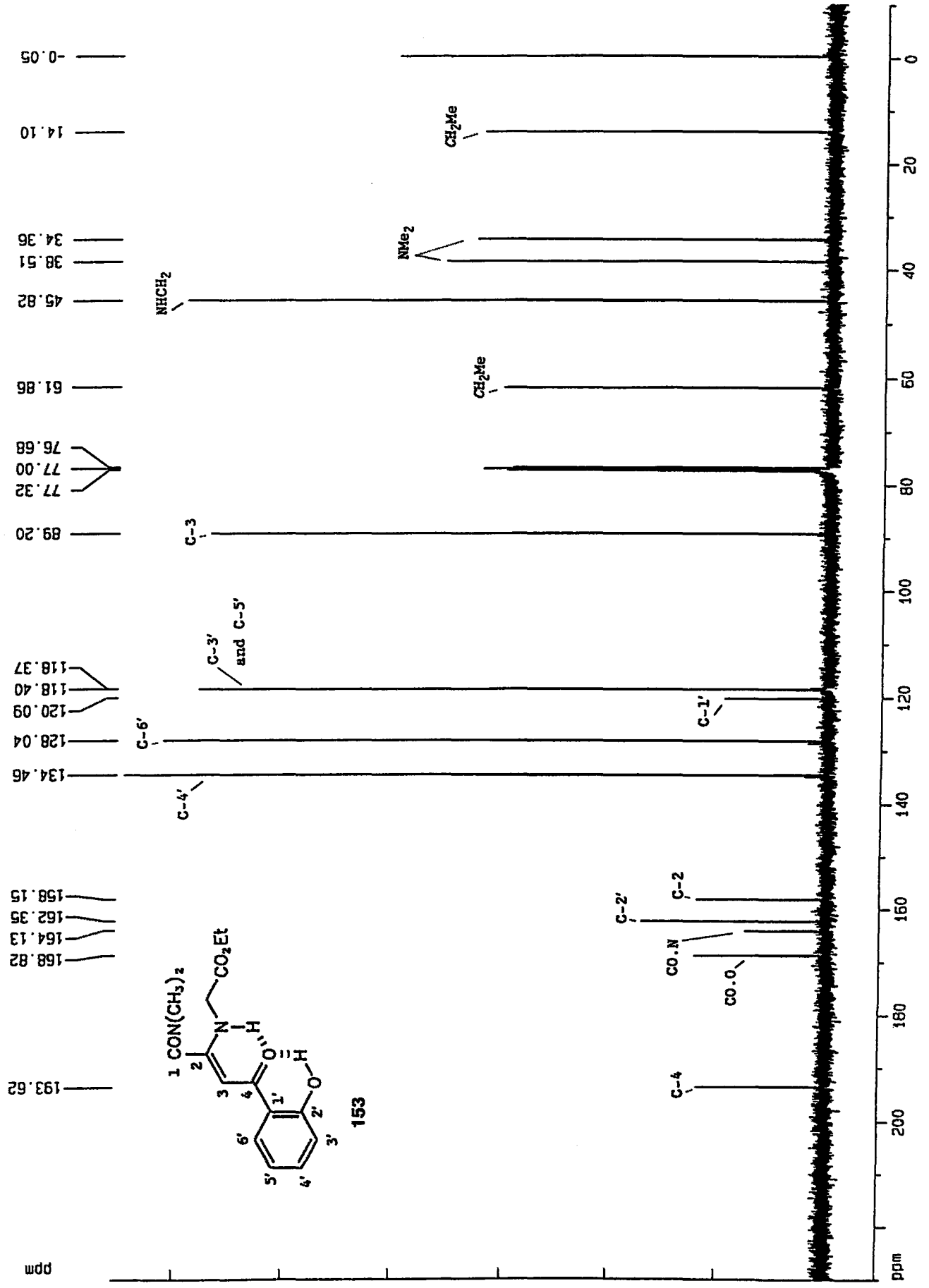

C-5 and C-6
C-7
C-3
C-8
C-4
CO.N
C-2
C-8a
C-4a
NCH
NCH
CHMe2
CHMe2
CON(Pri)2
136
PPM

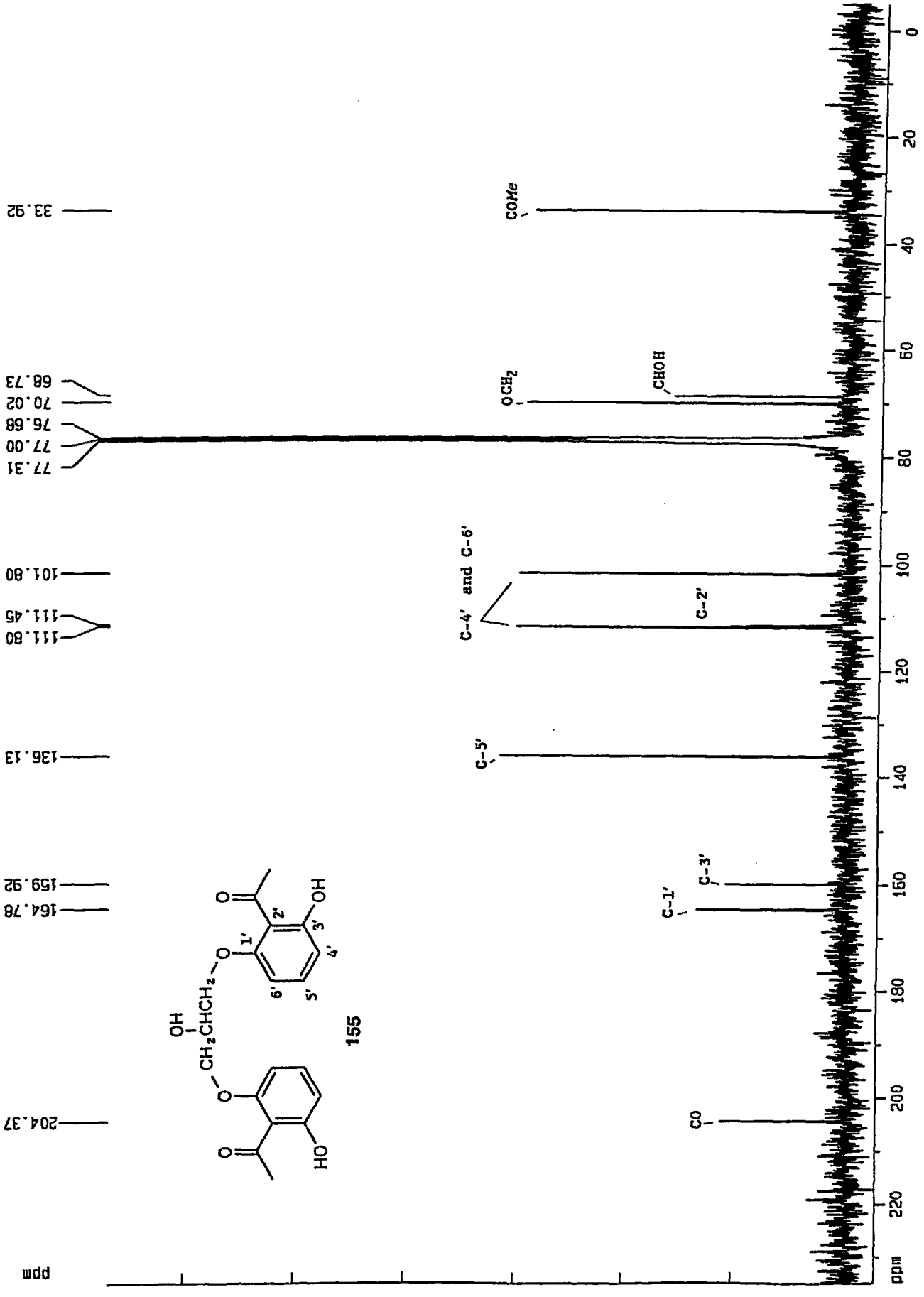

CH3
N
CH3
3
2
CON(CH3)2
1
6'
4
5'
1'
O
4'
H
2'
O
3'
140
OH
PPM
13.5
13.0
CONMe2
NMe2
4'-H and 5'-H
CH=C
3'-H
6'-H
8.5
8.0
7.5
7.0
PPM
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5


Integral
1.033
4.704
10.246
ppm
12
10
8
6
4
2
0
OH
NH
6'-H
3'-H
5'-H
CH=C
NMe
CONMe2
Hz
5357.2
5349.1
5336.1
4115.2
3019.4
2975.7
2967.2
2908.0
2845.5
2841.0
2839.1
2785.6
2773.5
2771.6
2765.0
2763.1
2571.0
2311.9
2258.6
2120.1
2065.7
1490.3
1483.3
1235.3
1230.7
1224.4
1214.2
1203.5
1198.1
1191.0
1185.9
1168.5
1164.8
1160.5
827.2
821.1
817.1
660.4
502.7
495.6
28.7
21.0
-0.1
-3.4
Br
O
H
N
CH3
1 CON(CH3)2
150


-0.05
31.37
34.10
37.72
76.68
77.00
77.32
87.24
119.02
121.33
121.70
127.86
128.87
161.17
162.81
163.96
192.06
CONMe2
NHMe
C-3
C-3' and C-5'
C-6'
C-4'
C-1'
C-2'
C-2
CO.N
C-4
1 CON(CH3)2
150
Br
ppm

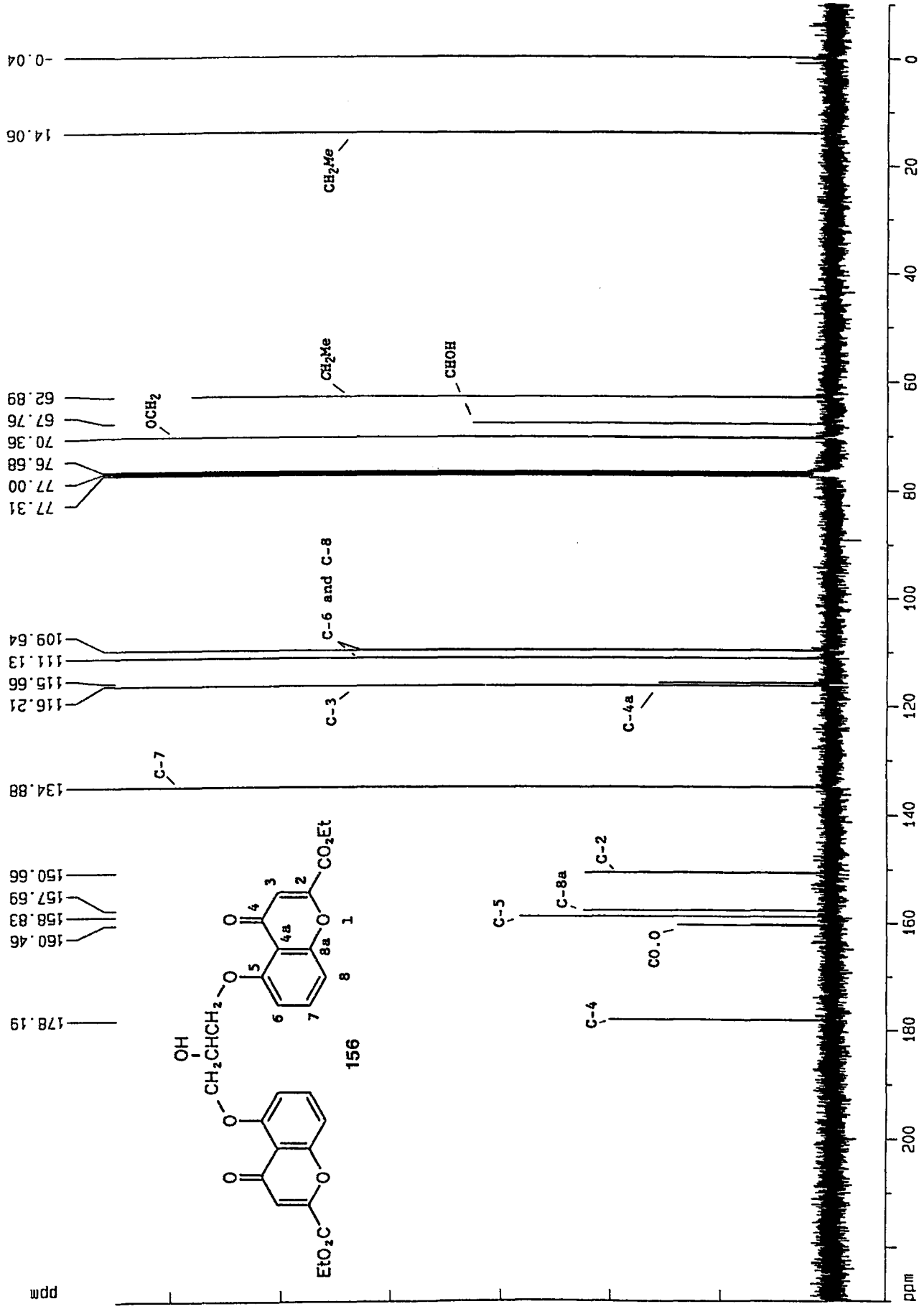

Integral
Hz
ppm
1.0638
1.0987
4.9722
1.2059
4.6836
7.0881
4.2926
OH
NH
6'-H
4'-H
3'-H
5'-H
CH=C
CH2Me
CH2NH
NMe2
CH2Me
153
1 CON(CH3)2
CO2Et
5260.5
5229.0
5225.0
5204.7
5188.0
4248.9
4243.4
4202.2
3069.6
3050.0
3048.5
3041.9
3040.4
2947.1
2945.9
2938.9
2908.2
2779.5
2778.7
2771.1
2770.2
2731.9
2730.7
2723.7
2716.6
2715.6
2570.8
2322.4
2119.7
1710.0
1702.8
1698.8
1695.6
1688.5
1633.0
1630.3
1627.0
1248.0
1236.9
1222.7
1183.0
820.9
817.0
670.4
530.9
527.7
523.8
520.4
516.9
513.3


-0.05
14.10
34.36
38.51
45.82
61.86
76.68
77.00
77.32
89.20
118.37
118.40
120.09
128.04
134.46
158.15
162.35
164.13
168.82
193.62
CH2Me
NMe2
NHCH2
CH2Me
C-3
C-3' and C-5'
C-6'
C-4'
C-1'
C-2'
C-2
CO.N
CO.O
C-4
1 CON(CH3)2
CO2Et
153
ppm


33.92
68.73
70.02
76.68
77.00
77.31
101.80
111.45
111.80
136.13
159.92
164.78
204.37
COMe
OCH2
CHOH
C-4' and C-6'
C-2'
C-5'
C-3'
C-1'
CO
ppm
0
20
40
60
80
100
120
140
160
180
200
220
OH
CH2CHCH2
O
O
O
O
HO
OH
1'
2'
3'
4'
5'
6'

155

ppm
Hz
159
7-H
6-H and 8-H
CH=C
CHOH
CH2Me
2 x OCH2
CHOH and
CH2Me
3048.2
3039.9
3031.5
2908.0
2870.7
2862.2
2791.9
2784.0
1943.5
1836.1
1831.4
1827.2
1822.6
1798.2
1789.5
1782.4
1775.3
1768.1
1751.4
1745.5
1742.6
1736.7
1490.7
720.5
632.9
577.0
569.8
562.7
503.6
496.6
489.6
58.5
40.8
29.6
21.3
0.0
-19.8
-24.4
-59.8


-0.04
14.06
CH2Me
62.89
67.76
70.36
76.68
77.00
77.31
OCH2
CH2Me
CHOH
109.64
111.13
115.66
116.21
C-6 and C-8
C-3
C-4a
134.88
C-7
150.66
157.69
158.83
160.46
178.19
C-2
C-8a
C-5
CO.O
C-4
CO2Et
EtO2C
OH
CH2CHCH2
156
ppm
0
20
40
60
80
100
120
140
160
180
200
ppm

5.2 CRYSTALLOGRAPHIC DATA.

Table 12. Crystal data for (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 140.[a]

Formula	$C_{14}H_{18}N_2O_3$
Molar mass	262.31
Crystal system	triclinic
Space group	$P\bar{1}$
a(Å)	6.8745(6)
b(Å)	9.353(1)
c(Å)	10.872(1)
α(°)	94.536(8)
β(°)	99.245(8)
γ(°)	91.223(8)
V(Å^3)	698.38(21)
Z	2
D_c(g.cm^{-1})	1.2637(4)
F(000)	280
μ(cm^{-1})	0.71
Number of reflections ($2 < \theta < 30°$)	4195
Observed reflections [$I > \sigma(I)$]	3260
R(unit weights)	0.069
$N_{parameters}$	190

[a] Estimated standard deviations in parentheses.

Table 13. Fractional coordinates ($x10^4$) and equivalent isotropic temperature factors ($Å^2$, $x10^3$) for (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide **140**.[a,b]

atom	x/a	y/b	z/c	U_{eq}
C(1)	3746(3)	2544(2)	7544(2)	40(1)
C(2)	4446(3)	1354(2)	8181(2)	44(1)
C(3)	3164(4)	227(3)	8319(3)	54(1)
C(4)	1200(4)	271(3)	7832(3)	60(1)
C(5)	472(4)	1427(3)	7209(3)	62(1)
C(6)	1730(3)	2549(3)	7066(3)	53(1)
O(1)	6362(3)	1258(2)	8686(2)	66(1)
H(0)	6934(51)	2084(37)	8613(32)	98(12)*
O(2)	6909(2)	3670(2)	7972(2)	61(1)
C(7)	5145(3)	3749(2)	7440(2)	42(1)
C(8)	4480(3)	4935(2)	6764(2)	43(1)
C(9)	5709(3)	6084(2)	6666(2)	40(1)
C(10)	7921(3)	6067(2)	7141(2)	42(1)
N(1)	5105(3)	7253(2)	6094(2)	47(1)
C(11)	3046(4)	7375(3)	5518(3)	57(1)
C(12)	6442(4)	8452(3)	5964(3)	60(1)
O(3)	8996(2)	5627(2)	6412(2)	56(1)
N(2)	8558(3)	6626(2)	8313(2)	50(1)
C(13)	10644(4)	6488(3)	8826(3)	71(1)
C(14)	7234(5)	7056(4)	9187(3)	76(1)

* isotropic temperature factor

$U_{eq} = 1/3 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* (a_i . a_j)$

[a] For atom labelling see figure 21 p.97 (Section 2.3).

[b] Estimated standard deviations in parentheses.

Table 14. Bond lengths (Å) and angles (°) for (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide **140**.[a,b,c]

C(1)-C(2)	1.410(3)	C(1)-C(6)	1.400(3)
C(1)-C(7)	1.489(3)	C(2)-C(3)	1.392(3)
C(2)-O(1)	1.351(3)	C(3)-C(4)	1.371(3)
C(4)-C(5)	1.381(4)	C(5)-C(6)	1.380(3)
O(1)-H(0)	0.87(3)	O(2)-C(7)	1.263(2)
C(7)-C(8)	1.422(3)	C(8)-C(9)	1.374(3)
C(9)-C(10)	1.526(3)	C(9)-N(1)	1.340(3)
C(10)-O(3)	1.222(3)	C(10)-N(2)	1.339(3)
N(1)-C(11)	1.464(3)	N(1)-C(12)	1.465(3)
N(2)-C(13)	1.465(3)	N(2)-C(14)	1.458(3)

C(2)-C(1)-C(6)	117.7(2)	C(2)-C(1)-C(7)	119.3(2)
C(6)-C(1)-C(7)	123.0(2)	C(1)-C(2)-C(3)	120.6(2)
C(1)-C(2)-O(1)	122.1(2)	C(3)-C(2)-O(1)	117.3(2)
C(2)-C(3)-C(4)	119.9(2)	C(3)-C(4)-C(5)	120.8(2)
C(4)-C(5)-C(6)	119.9(2)	C(1)-C(6)-C(5)	121.2(2)
C(2)-O(1)-H(0)	106.0(2)	C(1)-C(7)-O(2)	117.6(2)
C(1)-C(7)-C(8)	120.1(2)	O(2)-C(7)-C(8)	122.3(2)
C(7)-C(8)-C(9)	122.1(2)	C(8)-C(9)-C(10)	121.3(2)
C(8)-C(9)-N(1)	123.6(2)	C(10)-C(9)-N(1)	115.0(2)
C(9)-C(10)-O(3)	118.2(2)	C(9)-C(10)-N(2)	117.1(2)
O(3)-C(10)-N(2)	124.5(2)	C(9)-N(1)-C(11)	121.1(2)
C(9)-N(1)-C(12)	123.0(2)	C(11)-N(1)-C(12)	115.9(2)
C(10)-N(2)-C(13)	117.8(2)	C(10)-N(2)-C(14)	123.1(2)
C(13)-N(2)-C(14)	117.5(2)		

[a] For atom labelling see figure 21 p.97 (Section 2.3).

[b] Estimated standard deviations in parentheses.

[c] Bond Lengths and angles involving hydrogen atoms, excepting the phenolic hydrogen, are not listed as their positions were calculated and not refined.

Table 15. Anisotropic temperature factors ($Å^2$, $x10^3$) for (*E*)-2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide 140.[a,b]

atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
C(1)	37(1)	39(1)	42(1)	4(1)	6(1)	2(1)
C(2)	42(1)	42(1)	47(1)	5(1)	2(1)	3(1)
C(3)	53(1)	40(1)	68(2)	12(1)	2(1)	0(1)
C(4)	52(1)	48(1)	80(2)	11(1)	5(1)	-11(1)
C(5)	40(1)	58(2)	85(2)	17(1)	-1(1)	-6(1)
C(6)	40(1)	49(1)	69(2)	15(1)	1(1)	2(1)
O(1)	44(1)	59(1)	93(2)	31(1)	-10(1)	0(1)
O(2)	40(1)	55(1)	84(1)	24(1)	-8(1)	-4(1)
C(7)	37(1)	41(1)	47(1)	5(1)	4(1)	0(1)
C(8)	37(1)	43(1)	50(1)	9(1)	2(1)	1(1)
C(9)	40(1)	41(1)	38(1)	3(1)	3(1)	1(1)
C(10)	41(1)	36(1)	47(1)	4(1)	3(1)	-2(1)
N(1)	47(1)	41(1)	51(1)	9(1)	-1(1)	-1(1)
C(11)	52(1)	51(1)	63(2)	12(1)	-7(1)	6(1)
C(12)	66(2)	45(1)	69(2)	16(1)	4(1)	-10(1)
O(3)	45(1)	63(1)	59(1)	-1(1)	15(1)	-1(1)
N(2)	50(1)	48(1)	46(1)	1(1)	-4(1)	-3(1)
C(13)	55(2)	77(2)	72(2)	15(2)	-19(1)	-10(1)
C(14)	84(2)	89(2)	51(2)	-11(1)	8(1)	17(2)

[a] For atom labelling see figure 21 p.97 (Section 2.3).

[b] Estimated standard deviations in parentheses.

Table 16. Fractional coordinates ($x10^4$) for hydrogen atoms for (*E*)-2-(dimethylamino)-3-(2-hydroxybenzloyl)-*N*,*N*-dimethylacrylamide 140.[a,b]

	x/a	y/b	z/c	U
H(3)	3715(4)	-679(3)	8809(3)	82(4)
H(4)	212(4)	-607(3)	7938(3)	82(4)
H(5)	-1079(4)	1451(3)	6834(3)	82(4)
H(6)	1149(3)	3448(3)	6577(3)	82(4)
H(0)	6934(51)	2084(37)	8613(32)	98(12)
H(8)	2961(3)	4932(2)	6312(2)	82(4)
H(11A)	2818(4)	8447(3)	5231(3)	176(6)
H(11B)	2095(4)	7161(3)	6187(3)	176(6)
H(11C)	2704(4)	6607(3)	4711(3)	82(4)
H(12A)	5614(4)	9168(3)	5362(3)	176(6)
H(12B)	7712(4)	8105(3)	5565(3)	176(6)
H(12C)	6924(4)	9005(3)	6876(3)	176(6)
H(13A)	10942(4)	7148(3)	9700(3)	176(6)
H(13B)	11647(4)	6801(3)	8219(3)	176(6)
H(13C)	10840(4)	5376(3)	9001(3)	176(6)
H(14A)	8074(5)	7683(4)	9980(3)	176(6)
H(14B)	6618(5)	6102(4)	9496(3)	176(6)
H(14C)	6056(5)	7685(4)	8753(3)	176(6)

[a] For atom labelling see figure 21 p.97 (Section 2.3).

[b] Estimated standard deviations in parentheses.

Table 17. Torsion angles (°) of the amide and β-amino-vinyl ketone functionalities.[a]

O3	C10	N2	C13	-10.55
O3	C10	N2	C14	-175.88
C9	C10	N2	C13	173.99
C9	C10	N2	C14	8.65
N1	C9	C10	N2	90.65
N1	C9	C10	O3	-85.11
C8	C9	C10	N2	-92.96
C8	C9	C10	O3	91.29
C8	C9	N1	C11	0.00
C8	C9	N1	C12	-178.11
C10	C9	N1	C11	175.93
C10	C9	N1	C12	-1.81

Table 18. Torsion angles (°) in the vicinity of the intra-molecular hydrogen-bond.[a]

C6	C1	C7	C8	-4.10
C6	C1	C7	O2	175.75
C2	C1	C7	C8	177.77
C2	C1	C7	O2	-2.37
C7	C1	C2	O1	-1.07
C7	C1	C2	C3	178.44
C6	C1	C2	O1	180.00
C6	C1	C2	C3	0.00
C1	C2	O1	H0	7.16
C3	C2	O1	H0	-172.37

[a] For atom labelling see figure 21 p.97 (Section 2.3).

Table 19. Deviations from the mean plane 1 defined by C1-C12, H0, N1, O1, and O2.[a]

C1	-0.0219	O2	0.0576
C2	-0.0229	C7	-0.0031
C3	-0.0078	C8	-0.0496
C4	0.0077	C9	-0.0058
C5	0.0146	C10	-0.0796
C6	-0.0004	N1	0.0263
O1	-0.0287	C11	0.0082
H0	0.0732	C12	0.0323

Table 20. Deviations from the mean plane 2 of the amide functionality defined by C9, C10, O3, N2, and C14.[a]

C9	-0.0192	N2	0.0820
C10	-0.0065	C14	-0.0399
O3	0.0025		

Table 21. Deviations from the mean plane 3 of the β-amino-vinyl ketone functionality defined by C8, C9, N1, C11 and C12.[a]

C8	-0.0087	C11	-0.0019
C9	0.0066	C12	-0.0101
N1	0.0141		

[a] For atom labelling see figure 21 p.97 (Section 2.3).

Table 22. Deviations from the mean plane 4 of the hydrogen-bond chelation defined by C1, C2, O1, HO, O2, and C7.[a]

C1	0.0110	HO	0.0375
C2	0.0094	O2	0.0013
O1	-0.0401	C7	-0.0191

[a] For atom labelling see figure 21 p.97 (Section 2.3).

Table 23. The angles (°) between the normals to the planes.

1 and 2	85.14
1 and 3	1.28
1 and 4	2.17
2 and 3	86.40

5.2 PUBLICATIONS.

Manuscript as published in *Synth. Commun.*, 1990, 20, 727, by courtesy of Marcel Dekker, Inc.

CHROMONE STUDIES. PART 2.[1] AN EFFICIENT SYNTHESIS OF N,N-DIMETHYLCHROMONE-2-CARBOXAMIDES

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ABSTRACT: Chromone-2-carboxylic acids are efficiently transformed into the N,N-dimethylcarboxamides, without concomitant formation of unwanted products, by reacting the corresponding acid chlorides with dimethylammonium chloride in pyridine.

The potential of chromone derivatives in asthma therapy is well illustrated by the established action of compounds such as khellin, a naturally-occuring furochromone, and the widely used synthetic drug, disodium cromoglycate.[2] Certain chromone carboxamides have also been shown to exhibit some antiallergic activity.[3] In order to explore the conformational properties of such compounds, we required a range of model carboxamides, including the N,N-dimethylchromone-2-carboxamides[3(a-f); Scheme]. However, the preparation of these (latter) compounds, from the corresponding acid chlorides (2), was complicated by:-

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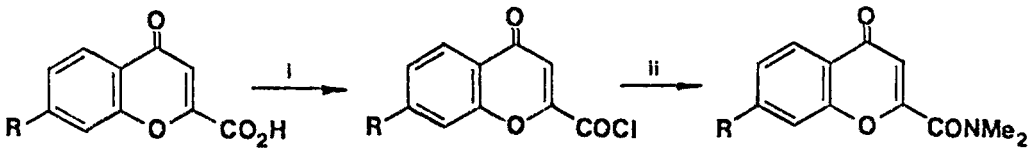
i) competitive formation of the ethyl carboxylate analogues, when using ethanolic dimethylamine;[4]

ii) heterogeneous reaction mixtures with hydrolytic potential, when using aqueous dimethylamine;[5]

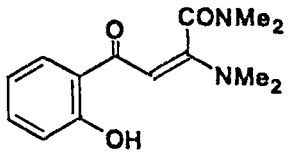
iii) the susceptibility of chromones to nucleophilic attack at C-2 by excess dimethylamine and consequent ring opening to afford products such as (4);[6]

iv) the difficulties associated with handling and metering pure dimethylamine (b.p.7°C);[7] and

v) unacceptably low yields.[4,5]



1 2 3



4

	R
a	H
b	OMe
c	NO_2
d	F
e	Cl
f	Br

SCHEME

Reagents i) $SOCl_2$, DMF, $ClCH_2CH_2Cl$;

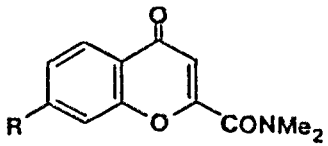
ii) Me_2NH_2Cl, pyridine, 0°C.

The foregoing difficulties were obviated by the simple but effective expedient of generating dimethylamine *in situ* from the amine salt, dimethylammonium chloride, in pyridine. The pyridine thus serves as reaction solvent; as base, releasing nucleophilic dimethylamine from its hydrochloride salt and neutralising the HCl liberated during acyl substitution; and, presumably, as nucleophilic catalyst, enhancing acyl substitution.[8] Previous applications involving ammonium salts include the acid catalysed ammonolysis of ethyl benzoate;[9] the acylation of amines by carboxamides;[10] and, recently, Schotten-Baumann acylation of 1,3,5-tris(aminomethyl)benzene trihydrochloride.[11]

In our method, the acid chlorides (2) were reacted with two equivalents of dimethylammonium chloride in pyridine, at *ca.* 0°C, to afford the corresponding chromone-2-carboxamides (3) in overall yields ranging from moderate to excellent (Table). The general procedure is illustrated by the following example.

> A slurry of dimethylammonium chloride[12] (1.50g, 18.4 mmol) in dry pyridine (5 ml) was added slowly to a pre-cooled (- 5°C), stirred solution of chromone-2-carbonyl chloride (2a)[generated[3] from the acid (1a)(1.75 g, 9.2 mmol)] in dry pyridine (15 ml), ensuring that the temperature of the resulting mixture did not exceed 0°C. After stirring for 2 h at 0°C and then for a further 20 h at room temperature, the black mixture was poured into 2M-HCl

TABLE Data for N,N-dimethylaminochromone-2-carboxamides(3)



Compd.	R	Crude Yield[a] (%)	Chromotographed Yield[b] (%)	Melting Point (°C)	Microanalytical Data (%) Found C	H	N	Molecular Formula	Requires C	H	N
3a	H	76	62	115-116[c]							
3b	OMe	92	83	120-122[d]	63.0	5.1	5.7	$C_{13}H_{13}NO_4$	63.15	5.3	5.7
3c	NO2	68	66	152-153[d]	55.4	3.8	10.6	$C_{12}H_{10}N_2O_5$	55.0	3.8	10.7
3d	F	76	64	144-146[d]	61.85	4.3	6.1	$C_{12}H_{10}FNO_3$	61.3	4.3	6.0
3e	Cl	80	72	146-147[d]	57.3	3.7	5.5	$C_{12}H_{10}ClNO_3$	57.3	4.0	5.6
3f	Br	96	77	143-145[d]	48.8	3.45	4.8	$C_{12}H_{10}BrNO_3$	48.7	3.4	4.7

[a] Overall yield from the corresponding acids (1); the crude material was essentially clean by ^1H NMR spectroscopy. [b] Overall yield from acid (1) after flash chromatography. [c] Lit.[6] 115-116°C. [d] New compound which gave satisfactory spectroscopic (^1H and ^{13}C NMR, IR, and MS) analyses.

(200 ml). After standing for 0.5 h, the resulting mixture was extracted (EtOAc) and the organic extracts were washed (*ca.*5% aq. $NaHCO_3$ and then satd.aq.NaCl), dried (anhyd. $MgSO_4$), and evaporated. The residue (1.51 g) was chromatographed (flash chromatography on silica gel; elution with EtOAc) to afford N,N-dimethylchromone-2-carboxamide (3a) (1.24 g).

ACKNOWLEDGEMENTS

The authors thank AECI Ltd for a post-graduate fellowship (to D.N.D.) and Rhodes University and the Foundation for Research Development for generous support.

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4. For example, reaction of the acid chloride (2a) with 33% ethanolic Me_2NH (1 eq.) in pyridine gave a 1:2 mixture of the chromone-2-carboxamide [(3a), 28%] and the corresponding ethyl carboxylate ester.

5. Reaction of various acid chlorides (2) with 40% aq. Me_2NH (1 eq.), in the presence of $NaHCO_3$, gave the carboxamides (3) (15 - 61%) and the corresponding carboxylic acids (1).

6. We obtained the known enamine (4), in 37% yield, from a reaction of the acid chloride (2a) with excess (2 eq.) 40% aq. Me_2NH. Cyclisation of this enamine (4) to the chromone-2-carboxamide (3a) has been reported by Jerzmanowska, Z. and Kostka, K., *Roczniki Chem.*, 1963, 37, 413.

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12. Dimethylammonium chloride was obtained by bubbling dry HCl through 33% ethanolic Me_2NH at *ca.* 0°C for 2 h. The solvent was evaporated *in vacuo* and the crystalline salt was washed (Et_2O) under N_2 and dried *in vacuo*.

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Chromone Studies. Part 3.[1] NMR Analysis of Rotational Isomerism in 4-Oxo-4*H*-chromene-2-carboxamides

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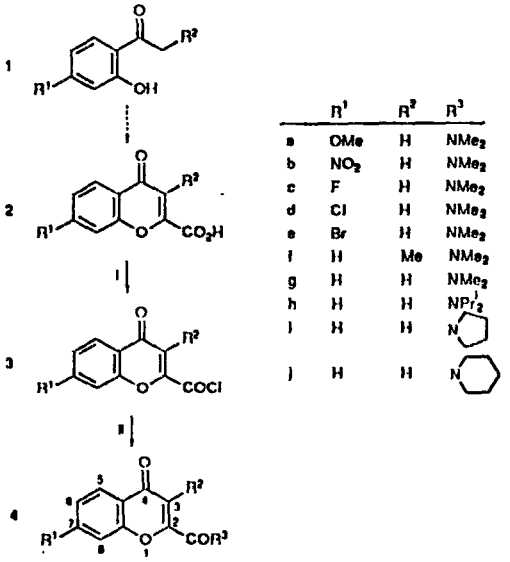
Temperature dependent splitting of *N*-alkyl ^{1}H and ^{13}C NMR signals in a series of 4-oxo-4*H*-chromene-2-carboxamides has been analysed in terms of rotation of the amide group. Rotational barriers have been calculated from dynamic ^{1}H NMR data and the conformational options have been explored.

Various 4-oxo-4*H*-chromene derivatives are known to exhibit anti-allergic activity; these include the widely used synthetic drug, disodium cromoglycate[2] and certain 4-oxo-4*H*-chromene carboxamides.[3] In an earlier communication[4] we described an IR study of rotational isomerism in a series of 4-oxo-4*H*-chromene-2-carboxylate esters. As part of an investigation into electronic and conformational effects in chromone systems with medicinal potential, we now report the results of NMR studies of rotational isomerism in a series of 4-oxo-4*H*-chromene-2-carboxamides.

Results and Discussion

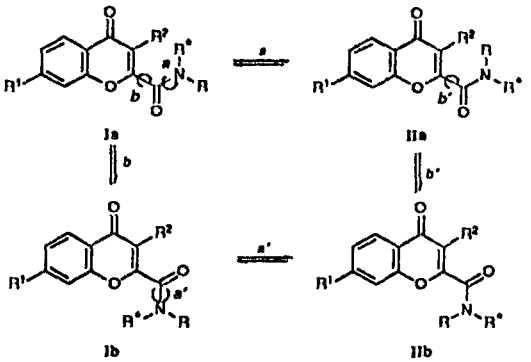
The 4-oxo-4*H*-chromene-2-carboxamides (4) were obtained by reacting the acid chlorides (3) with the appropriate secondary amine or, in the case of the *N*,*N*-dimethylcarboxamides, with dimethylammonium chloride in pyridine[5] (Scheme 1). Symmetrically substituted amides were used in order to simplify analysis of the dynamic NMR data, while the *N*-alkyl and ring substituents were chosen to elucidate electronic and steric effects on the rotameric equilibria.



	R^1	R^2	R^3
a	OMe	H	NMe_2
b	NO_2	H	NMe_2
c	F	H	NMe_2
d	Cl	H	NMe_2
e	Br	H	NMe_2
f	H	Me	NMe_2
g	H	H	NMe_2
h	H	H	NPr^i_2
i	H	H	N
j	H	H	N

Scheme 1 *Reagents*: i, $SOCl_2$, DMF $ClCH_2CH_2Cl$; ii, Me_2NH_2Cl-pyridine or R^{3}H aq. $NaHCO_3$ or R^{3}H-pyridine

In the 4-oxo-4*H*-chromene-2-carboxamides [4 R* = R (Scheme 2)], the conformational energy minima associated



Scheme 2

with simultaneous rotation about the N–CO and C-2–CO bonds may be expected to correspond to two equivalent pairs of quasi-planar † conjugated conformers (Ia ≡ IIa and Ib ≡ IIb). In two recent investigations[6,7] of systems exhibiting simultaneous rotation about separate bonds, the site-exchange processes were sufficiently slow for dynamic NMR analysis of individual rotational barriers. In the 4-oxo-4*H*-chromene-2-carboxamides (4), however, at ambient temperature C-2–CO rotation is expected to be rapid, relative to the NMR time-scale,‡ and to require analysis by an alternative technique. The sensitivity of IR carbonyl absorption bands to conformational change often makes IR spectroscopy (with its very much shorter time-scale) a useful probe for studying rapid rotations involving carbonyl groups.[4] Unfortunately, the amide and 4-oxo-4*H*-chromene IR carbonyl absorption bands of the 4-oxo-4*H*-chromene-2-carboxamides (4) overlap extensively (at *ca.* 1650 cm^{-1}), precluding use of IR spectroscopy for analysing rotation about the C-2–CO bond. Rotation about the N–CO bond, on the other hand, should be sufficiently inhibited by delocalisation effects (Fig. 2), [*i.e.* k_a, $k_{a'} \ll k_b$, $k_{b'}$ (Scheme 2)] to permit analysis by dynamic NMR methods. The observed splitting of *N*-alkyl ^{1}H (Fig. 1 and Table 1) and ^{13}C NMR signals is thus attributed to slow site-exchange of the *N*-alkyl substituents§ and variable temperature ^{1}H NMR spectroscopy has been used to explore rotation about the N–CO bond in the title compounds (4).

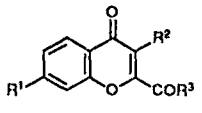
It should be noted that rotation of the amide group in a

† Steric interactions in analogous benzamides appear to interfere with the co-planarity of the aromatic and carboxamide systems.[8]

‡ Even in sterically hindered *ortho*-substituted benzamides, C-1–CO rotational barriers are less than 60 kJ mol^{-1}.[8]

§ Dynamic rate processes involving nitrogen inversion and ring reversal are considered to be significantly faster than N–CO rotation.[9]

Table 1 Data from dynamic NMR study of 4-oxo-4*H*-chromene-2-carboxamides (4)[a]



4

Compound	R^1	R^2	R^3	T_c[b]/K	$\Delta\nu_c$[c]/Hz	$\Delta G^{\ddagger}$[d]/kJ mol^{-1}	k_{298}[e]/s^{-1}
4a	OMe	H	NMe_2	302	2.5 ± 0.7	69.7 ± 1.5	4
4b	NO_2	H	NMe_2	305	1.8 ± 0.6	71.2 ± 1.9	2
4c	F	H	NMe_2	270	1.0 ± 0.5	64.1 ± 2.3	36
4d	Cl	H	NMe_2	<255[f]	—	—	—
4e	Br	H	NMe_2	290	1.0 ± 0.3	69.0 ± 1.6	5
4f	H	Me	NMe_2	>345[g]	—	>72.3 ± 0.2	<1
4g	H	H	NMe_2	270	0.8 ± 0.3	64.6 ± 1.9	29
4h	H	H	NPr^i_2	315	87.2 ± 2.2	63.5 ± 0.7	46
4i	H	H		332	13.6 ± 1.1	72.2 ± 0.9	1
4j	H	H		325	61.6 ± 1.6	66.5 ± 0.9	14

[a] Variable temperature 300 MHz ^{1}H NMR spectra recorded using solutions in $CDCl_3$. [b] Coalescence temperature (± 3 K). [c] Frequency separation at coalescence (see reference 12). [d] Free energy of activation for N–CO rotation; $\Delta G^{\ddagger} = RT_c(22.96 + \ln T_c/\Delta\nu_c)$. [e] First-order rate constant at 298 K for N–CO rotation; $\ln k = \ln(k_bT/h) - \Delta G^{\ddagger}/RT$. [f] No splitting of NMe_2 signal observed. [g] No coalescence of the NMe signals observed; $\Delta\nu$ at 345 K = 36.5 ± 0.5 Hz.

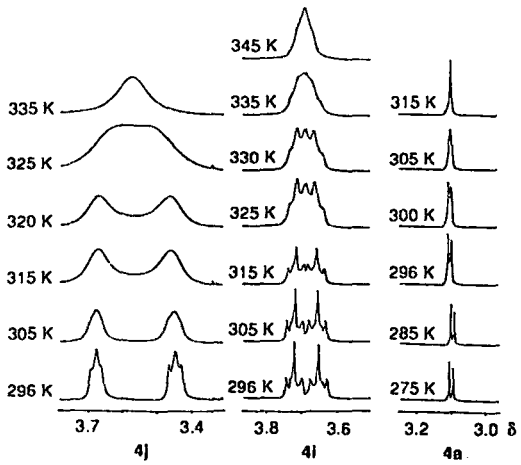


Fig. 1 Variable temperature ^{1}H NMR spectra showing *N*-alkyl signals for selected 4-oxo-4*H*-chromene-2-carboxamides (4)

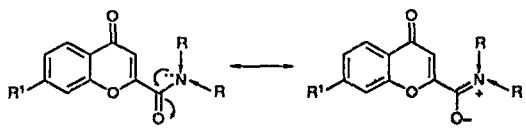


Fig. 2

symmetrically substituted benzamide, for example, effectively involves site-exchange between a pair of equivalent quasi-planar conformers.[5] In the 4-oxo-4*H*-chromene-2-carboxamides (4), however, the situation is complicated by the non-equivalence of rotamer types (*a*) and (*b*) (Scheme 2) and the measured rates of site-exchange must represent some combination of the individual rates, k_a [**Ia**] and k_a [**Ib**].[10]

The ^{1}H NMR frequency separations measured at slow site exchange* ($\Delta\nu_0$) vary widely (1–99 Hz), the separations being smallest for the *N*,*N*-dimethylcarboxamides. For each compound examined $\Delta\nu_0$ must reflect the difference in the average magnetic environment of the nuclei concerned and, more specifically, their average spatial orientation relative to the magnetically anisotropic 4-oxo-4*H*-chromene and carboxamide[8] moieties.

Factors which contribute to such orientation of the relevant nuclei undoubtedly include: dipole–dipole and steric[5] interactions; 'gear-meshing'[11] of the isopropyl groups in compound **4h**; and ring-conformational constraints in the heterocyclic analogues **4f** and **4j**. Thus, comparable deshielding of the *N*-methyl groups in the *N*,*N*-dimethylcarboxamides (**4a–c**, **e** and **g**) accounts for their remarkably small $\Delta\nu_0$ values; in fact, in the case of the 8-chloro-*N*,*N*-dimethylcarboxamide (**4d**), splitting of the *N*-methyl ^{1}H NMR signals could not be achieved within the accessible temperature range†—an observation which undoubtedly reflects the chemical shift equivalence of these signals at slow site exchange rather than an unusually low rotational barrier.‡

Rotational energy barriers ($\Delta G^{\ddagger}$, 64–72 kJ mol^{-1}; Table 1), determined for the 4-oxo-4*H*-chromene-2-carboxamides **4 a–c**, **e**, **g–j** from the coalescence data,[12] lie within the typical amide range (50–100 kJ mol^{-1}). More pertinent is the correspondence between these results and the $\Delta G^{\ddagger}$ data obtained for comparable *N*,*N*-dialkylbenzamides.[13,14] The tendency towards slightly higher rotational barriers in the 4-oxo-4*H*-chromene analogues is consistent with the expectation that the electron-withdrawing 4-oxo-4*H*-chromene system should reduce competitive delocalisation[8] and, hence, increase the

* At maximum separation ($\Delta\nu_0$) or at the minimum temperature below which precipitation of material precluded further measurement.

† Material precipitated below 255 K.

‡ Splitting of *N*-alkyl signals was observed in the ambient ^{13}C NMR spectra of all the 4-oxo-4*H*-chromene-2-carboxamides (**4**) examined, including **4d**.

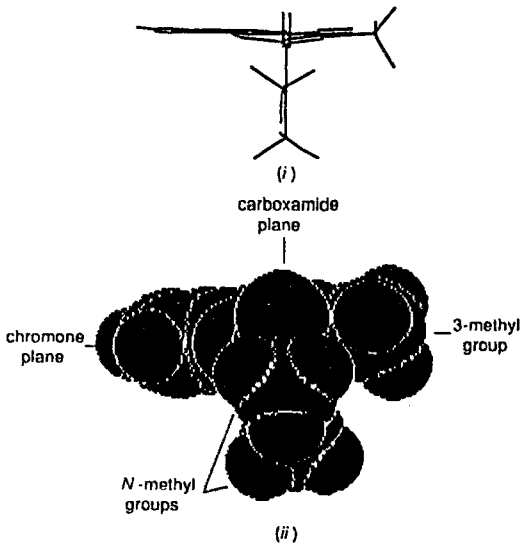


Fig. 3 Proposed conformation of compound 4f based on computer-modelled structure; (*i*) 'wire-frame' and (*ii*) 'spacefill' representations

π-character of the N–CO bond and the magnitude of the rotational barrier. Similar arguments, based on the net electron-withdrawing properities of substituent R[1] may well explain the gradation of $\Delta G^{\ddagger}$ values in the series of *N*,*N*-dimethylcarboxamides R[1] = F (4c) < Br (4e) < NO_2 (4b)—a trend which parallels results obtained for the corresponding *para*-substituted *N*,*N*-dimethylbenzamides.[13] The anomalous result for the 7-methoxy analogue (4a), while possibly reflecting the influence of changing conformer populations on the overall rate of rotation, nevertheless emphasises the complexity of the rotameric equilibria and the need for caution in interpreting the $\Delta G^{\ddagger}$ data, particularly when $\Delta G^{\ddagger}$ differences are comparable with the estimated errors.

The influence of electron-releasing inductive effects on nitrogen lone-pair delocalisation (Fig. 2) appears to be illustrated by the higher rotational barrier (relative to compound 4g) observed for the pyrrolidine derivative (4i) and, to a lesser extent, for the piperidine analogue (4j). The difference in $\Delta G^{\ddagger}$ for carboxamides 4i and 4j is consistent with the greater ease with which a pyrrolidine nitrogen is expected to adopt the planar sp^2 arrangement necessary for effective lone-pair delocalisation. In spite of an electron-releasing inductive effect, such delocalisation may, of course, be inhibited by steric destabilisation of the carboxamide ground-state[15]—a situation which presumably obtains in the case of *N*,*N*-diisopropyl-4-oxo-4*H*-chromene-2-carboxamide (4h). (Rotational barriers for benzamide analogues are reported to follow a similar pattern: *N*,*N*-diisopropylbenzamide ≤ *N*,*N*-dimethylbenzamide[14] ≈ 1-benzoylpiperidine.[16])

In 4-oxo-4*H*-chromene-2-carboxylate esters, bulky 3-substituents appear to prevent co-planarity of the ester and chromene planes[4] and similar conformational constraints were expected to operate in the 3-methyl-4-oxo-4*H*-chromene-2-carboxamide (4f)—an expectation which is supported both by computer modelling and by earlier studies of benzamide analogues.[5] ^{1}H NMR analysis of this compound (4f) reveals *N*-methyl signals which are well separated (37 Hz) and which, even at 345 K, show no sign of coalescence. These observations, which indicate significant inhibition of *N*-methyl site-exchange, are accommodated by the proposed conformation (Fig. 3), in which: (*i*) the essentially planar *N*,*N*-dimethylcarboxamide group occupies an average position perpendicular, or quasi-perpendicular, to the chromone plane; (*ii*) the *N*-methyl groups are diastereotopic; and (*iii*) there is significant steric hindrance to rotation about *both* the C-2–CO *and* N–CO bonds.

Experimental

The 4-oxo-4*H*-chromene-2-carboxamides (4) were obtained by treating the acid chlorides (3)[3] [obtained from the corresponding carboxylic acids (2)[4]]: with dimethylammonium chloride in pyridine[1] (4a–g); with the appropriate amine in aq. $NaHCO_3$ (4i)[3] or in pyridine (4h,j).[3]

^{13}C NMR spectra were edited with the aid of DEPT (75 MHz) and ORD (125 MHz) techniques. All coupling constants are in Hz. Variable temperature ^{1}H NMR data were obtained from $CDCl_3$ solutions of the 4-oxo-4*H*-chromene-2-carboxamides (4) on a Bruker AM 300 NMR spectrometer and temperatures are judged to be correct within ± 1 K. Computer modelling for compound 4f was effected using the Tripos Associates software package, ALCHEMY II.

Analytical data for new compounds are as follows:

7-Fluoro-4-oxo-4H-chromene-2-carboxylic acid (2c) m.p. 230 °C (EtOH) (Found: C, 57.4; H, 2.5. $C_{10}H_5FO_4$ requires: C, 57.7; H, 2.4%); δ_H(500 MHz; [$^2H_6$]DMSO) 6.84 (1 H, s, CH=C), 7.32–7.36 (1 H, m, 6-H), 7.60 (1 H, dd, J_m 2 and $^3J_{HF}$ 10, 8-H), 8.03 (1 H, dd, J_o 9 and $^4J_{HF}$ 6, 5-H) and 8.9 (60 MHz; 1 H, br s, CO_2H); δ_C (75 MHz; [$^2H_6$]DMSO) 105.60 (d, $^2J_{CF}$ 26, C-8), 113.67 (C-3), 114.69 (d, $^2J_{CF}$ 23, C-6), 120.92 (C-4a), 127.82 (d, $^3J_{CF}$ 11, C-5), 153.56 (C-2), 156.56 (d, $^3J_{CF}$ 14, C-8a), 161.16 (CO_2H), 165.49 (d, $^1J_{CF}$ 253, C-7) and 176.66 (C-4); ν_{max}(KBr) 3300–2700 (OH), 1740 (CO·OH) and 1630 (CO) cm^{-1}; *m*/*z* 208 (M^+, 100%).

N,N,3-*methyl-4-oxo-4H-chromene-2-carboxamide* (4f) m.p. 74–76 °C (EtOAc) (Found: M^+ 231.090. $C_{13}H_{13}NO_3$ requires *M*, 231.090); δ_H(500 MHz; $CDCl_3$) 1.96 (3 H, s, 3-Me), 2.95 (3 H, s, NMe), 3.07 (3 H, s, NMe), 7.31–7.35 (2 H, m, 6-H and 7-H), 7.56–7.60 (1 H, m, 8-H) and 8.11 (1 H, dd, *J* 2 and 8, 5-H); δ_C(75 MHz; $CDCl_3$) 9.98 (3-Me), 34.56 (NMe), 37.63 (NMe), 117.36 (C-3), 117.88 (C-8), 122.89 (C-4a), 125.24 and 125.78 (C-5 and C-6), 133.72 (C-7), 154.39 (C-8a), 155.61 (C-2), 162.40 (CO·N) and 177.82 (C-4); ν_{max}(KBr) 1640 and 1635 (CO) cm^{-1}; *m*/*z* 231 (M^+, 100%).

N,N-*Diisopropyl-4-oxo-4H-chromene-2-carboxamide* (4h) m.p. 95–96 °C (EtOAc) (Found: C, 70.65; H, 7.3; N, 5.3. $C_{16}H_{19}NO_3$ requires: C, 70.3; H, 7.0; N, 5.1%); δ_H(500 MHz; $CDCl_3$) 1.29 (6 H, br s, $CHMe_2$), 1.55 (6 H, br s, $CHMe_2$), 3.60 (1 H, br s, NCH), 3.91 (1 H, br s, NCH), 6.49 (1 H, s, CH=C), 7.49–7.55 and 7.76–7.83 (2 H, 2 × m, 6-H and 7-H), 7.57 (1 H, d, *J* 8, 8-H) and 8.23 (1 H, d *J* 7, 5-H); δ_C(125 MHz; $CDCl_3$) 19.94 ($CHMe_2$), 20.57 ($CHMe_2$), 46.28 (NCH), 51.12 (NCH), 109.50 (C-3), 117.96 (C-8), 124.06 (C-4a), 125.45 and 125.48 (C-5 and C-6), 133.98 (C-7), 155.46 (C-8a), 159.83 (C-2), 161.33 (CO·N) and 177.37 (C-4); ν_{max} 1655 and 1640 (CO) cm^{-1}; *m*/*z* 273 (M^+, 24%), 216 (100%).

1-(*4-Oxo-4H-chromen-2-ylcarbonyl*)*pyrrolidine* (4i) m.p. 103–105 °C (EtOAc) (Found: M^+ 243.089. $C_{14}H_{13}NO_3$ requires: *M*, 243.090); δ_H(500 MHz; $CDCl_3$) 1.83–1.89 ([4 H, m, $CH_2(CH_2)_2CH_2$], 3.51 (2 H, t, NCH_2), 3.63 (2 H, t, NCH_2), 6.62 (1 H, s, CH=C), 7.27–7.30 and 7.56–7.60 (2 H, 2 × m, 6-H and 7-H), 7.36 (1 H, d, *J* 8, 8-H) and 8.03 (1 H, dd, *J* 2 and 8, 5-H); δ_C(125 MHz; $CDCl_3$) 23.49 (CH_2), 26.09 (CH_2), 46.92 (NCH_2), 48.08 (NCH_2), 111.91 (C-3), 117.87 (C-8), 123.94 (C-4a), 125.35 and 125.47 (C-5 and C-6), 134.06 (C-7), 155.16 (C-8a), 157.86 (C-2), 159.60 (CO·N) and 177.48 (C-4); ν_{max}(KBr) 1640 and 1630 (CO) cm^{-1}; *m*/*z* 243 (M^+, 100%).

1-(*4-Oxo-4H-chromen-2-yl*)-*carbonyl*)*piperidine* (4j) m.p. 65–

66 °C (EtOAc) (lit.,[17] 90.5–92 °C) (Found: C, 70.5; H, 5.9; N, 5.6. $C_{13}H_{15}NO_3$ requires: C, 70.0; H, 5.9; N, 5.4%); δ_H(500 MHz; $CDCl_3$) 1.57–1.66 [6 H, m, $(CH_2)_3$], 3.39 (2 H, br s, NCH_2), 3.62 (2 H, br s, NCH_2), 6.39 (1 H, s, CH=C), 7.34–7.37 and 7.61–7.65 (2 H, 2 × m, 6-H and 7-H), 7.41 (1 H, d, *J* 9, 8-H) and 8.11 (1 H, dd, *J* 2 and 8, 5-H); δ_C(125 MHz; $CDCl_3$) 24.17, 25.21 and 26.34 ($\overline{NCH_2CH_2CH_2CH_2CH_2}$), 43.21 ($NCH_2$), 48.03 ($NCH_2$), 110.96 (C-3), 118.09 (C-8), 124.09 (C-4a), 125.57 (C-5 and C-6), 134.09 (C-7), 155.61 (C-8a), 158.42 (C-2), 160.67 (CO·N) and 177.26 (C-4); ν_{max}(KBr) 1655 and 1650 (CO) cm^{-1}; *m/z* 257 (M^+, 35%) and 89 (100%).

Acknowledgements

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Chromone Studies. Part 4.[1] Structural Analysis of Chromone-derived 2-Amino-3-(2-hydroxybenzoyl)acrylamides

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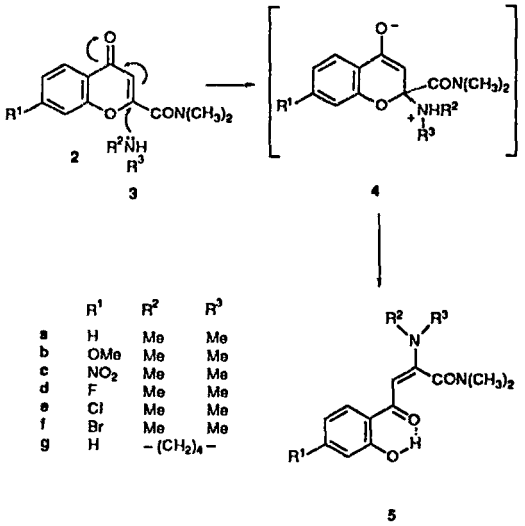
A combination of X-ray crystallographic, ^1H, ^{13}C NMR and IR spectroscopic, and computer-modelling techniques have been used to explore both configurational and conformational aspects of the structures of a series of substituted 2-amino-3-(2-hydroxybenzoyl)acrylamides.

Chromone derivatives such as disodium cromoglycate (DSCG 1),[2] and certain chromone-2-carboxamides[3] are known to exhibit anti-allergic activity. In fact, DSCG 1 is widely used[4] in asthma therapy, its mode of action apparently involving, amongst other things, stabilisation of mast cells in the bronchial mucosa.[5,6] To our knowledge, however, the molecular basis for such action has yet to be established.[4,7] The susceptibility of chromones to ring opening, *via* C-2 attack by various nitrogen,[8] and oxygen nucleophiles,[9] has prompted us to explore the possible implication of this molecular process in chromone pharmacology. Thus, appropriate chromones may block or modify receptor interactions by binding covalently, through C-2, to biogenetic nucleophiles such as mast-cell proteins or inflammatory mediators like histamine[10] (Fig. 1). Consequently, we have begun a detailed examination of the reactions of chromone-2-carboxamides (**2**, Scheme 1) with amines as models for *in vivo* nucleophiles.



	R^1	R^2	R^3
a	H	Me	Me
b	OMe	Me	Me
c	NO_2	Me	Me
d	F	Me	Me
e	Cl	Me	Me
f	Br	Me	Me
g	H	$-(CH_2)_4-$	

Scheme 1

In principle, ring opening of chromones may afford products having either *E*- or *Z*-double-bond configurations. Zagorevskii *et al.*,[11] in an earlier investigation of related systems, used ^1H NMR $J_{1,3}$ vinyl coupling constants and IR spectroscopy to establish: the *E*-configuration of *N,N*-disubstituted β-amino-vinylketones **6**; the *Z*-configuration of *N*-monosubstituted analogues **7**; and the significance of intra-molecular hydrogen bonding in both series. However, they were unable to determine the double-bond geometry in the products of reactions of 2-substituted chromones with secondary amines. In this communication we describe the use of X-ray crystallographic, spectroscopic and computer-modelling methods in elucidating the stereochemistry of such compounds **5**.

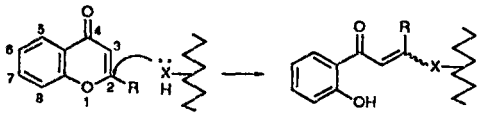
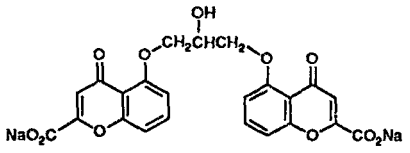


Fig. 1 Putative interaction of biogenetic nucleophiles (*e.g.* X = N, O, S) with chromone systems



1

6 7

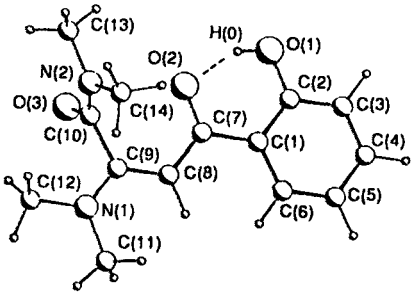


Fig. 2 X-Ray crystal structure of 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N,N*-dimethylacrylamide (**5a**), showing the crystallographic numbering

A definitive determination of the solid-state structure of the parent system **5a** was achieved by single crystal X-ray diffraction analysis. The crystal structure (Fig. 2) clearly indicates the *E*-geometry of the double bond in this compound. Other significant features of the solid state structure are: (i) intra-

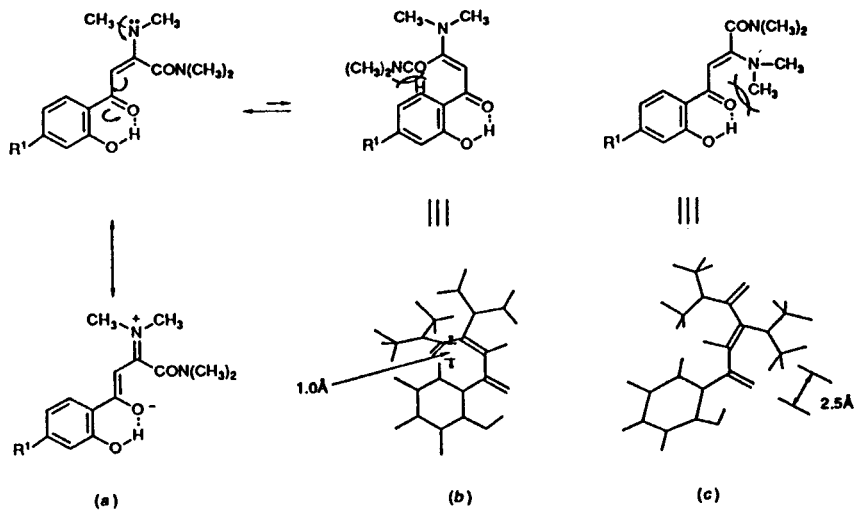


Fig. 3 (*a*) Favoured *E*-configuration of compounds **5a–f** illustrating delocalisation and hydrogen-bonded chelation. (*b*) Unfavourable steric interaction (see footnote * on p. 1183) in the alternative rotamer of the *E*-diastereoisomer. (*c*) Unfavourable steric interaction (see footnote * on p. 1183) in a planar conformation of the *Z*-diastereoisomer.

Table 1 Comparative ^1H and ^{13}C NMR chemical shifts for compounds **5a–f** (see Fig. 4)

^{13}C Nucleus	δ **5a**	$\Delta\delta^a$
CON*Me*$_2$	34.06	0.44
	36.84	0.46
NMe_2	39.38	0.52
	40.11	0.82
C-1	166.44	0.52
C-2	158.76	1.54
C-3	88.81	0.31
C-4	189.74	1.72
3-H[b]	5.75	0.12

[a] Maximum variation from value for compound **5a** in the series **5b–f**. [b] ^1H nucleus.

molecular hydrogen bonding between the phenolic hydroxy and the *syn*-orientated ketone carbonyl groups; (ii) the orthogonal (*ca.* 85°) arrangement of the planar* carboxamide moiety with respect to the rest of the molecule; and (iii) the remarkable co-planarity* of all of the remaining crystallographically determined atoms. The observed co-planarity is consistent with significant delocalisation of the dimethylamino nitrogen lone pair into the extended conjugated system, an effect which is, undoubtedly, enhanced by the hydrogen-bonding chelation (Fig. 3).

It is apparent, from IR and NMR spectroscopic data, that the solid-state (crystal) conformation of the parent system **5a** is essentially maintained in solution (in chloroform at least) and it may also be argued that the same configurational and conformational features, in fact, characterise all of the 2-amino-3-(2-hydroxybenzoyl)acrylamides **5a–g** examined. Thus the NMR data, obtained for $CDCl_3$ solutions, provide compelling evidence for *E*-geometry in each of the 2-amino-3-(2-hydroxybenzoyl)acrylamides **5a–g**. Firstly, the chemical shifts for the vinyl protons (3-H) and the non-aromatic carbons exhibit only marginal variations within the series (Table 1; Fig. 4), and the 3-

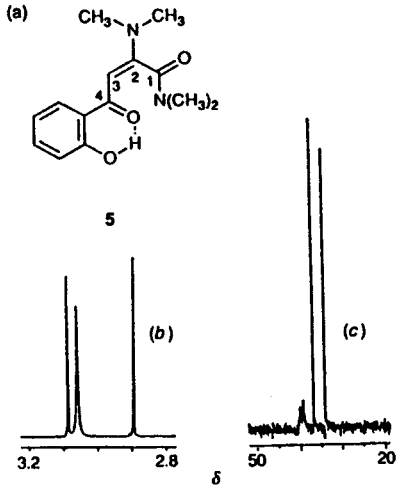


Fig. 4 (*a*) Compounds **5** with numbering (see Table 1 for NMR data); (*b*) partial ^1H NMR spectrum for **5d** (R^1 = F); (*c*) partial ^{13}C NMR spectrum for **5d** (R^1 = F)

H chemical shifts are closer to the calculated[12] value for the *E*-isomer (5.51 ppm) than for the *Z*-isomer (6.08 ppm). Secondly, in each of the compounds **5a–f**, both the amino- and carboxamido ^{13}C *N*-methyl signals are split [in the ^1H NMR spectra only the corresponding carboxamido signals are clearly split, the amino *N*-methyl signals typically appearing, at ambient temperature, as broad, post-coalescence singlets (Fig. 4)].† While slow site-exchange of *N*-alkyl groups is typical of *N,N*-disubstituted carboxamides, the parallel splitting of the dimethylamino ^{13}C signals is particularly significant, the implication being hindered rotation between resonance-stabilised

* Maximum deviations from the least-square planes were: 0.0820 Å (carboxamide moiety) and 0.0796 Å (rest of the molecule).

† The assignment of ^1H and ^{13}C NMR *N*-methyl signals is based on comparisons between the relevant spectra of the dimethylamino (**5a–f**) and pyrrolidino (**5g**) analogues.

planar conformers in which the *N*-methyl groups are diastereotopic. Such an arrangement is only possible if the acrylamides **5a–g** adopt the *E*-configuration illustrated in Fig. 3(*a*), since molecular modelling studies* clearly indicate that in the *Z*-diastereoisomer [Fig. 3(*c*)], co-planarity of the dimethylamino and vinyl ketone moieties is sterically prohibited. [Unfavourable steric interactions* would also destabilise the alternative planar rotamer, Fig. 3(*b*), even when the carboxamide moiety is perpendicular to the rest of the molecule.] The significance of these steric constraints is further illustrated by the orthogonal orientation of the carboxamide group in the crystal structure of the parent system **5a**. This orientation, which is presumably maintained in solution, obviates unfavourable steric interaction with the vinyl ketone oxygen without inhibiting lone-pair delocalisation in the independently planar carboxamide group.

IR carbonyl absorption band frequencies tend to be sensitive to structural change and it is noteworthy that, in the solid (KBr disc) and solution (chloroform) spectra of compounds **5a–g**, these bands exhibit minimal frequency variation (*ca.* ±10 cm^{-1}). Moreover, the general superposition of both ketone and carboxamide carbonyl absorption bands at low (*ca.* 1650 cm^{-1}) frequencies reflects effective delocalisation and concomitant reduction in the double-bond character of both carbonyl groups. Such frequency shifts are characteristic of planar carboxamide moieties but, more pertinently in this instance, argue independently for the essential co-planarity of the dimethylamino and aryl vinyl ketone systems. Furthermore, in both the solid state and solution IR spectra of each compound **5a–g**, the hydroxyl stretching band is shifted below 3000 cm^{-1}. This observation [together with the low field resonance (*ca.* δ 14) of the phenolic proton in the 60 MHz ^1H NMR spectrum of each compound] is indicative[11] of the strongly hydrogen-bonded chelate conformation illustrated in Fig. 3.

C-2 nucleophilic attack is, of course, equally likely at either face of the chromone-2-carboxamides (**2**, Scheme 1) and ring-opening (*via* racemic intermediates **4**) to the corresponding (*E*)-dimethylaminoacrylamides **5** may be attributed either to product development control or, in view of the reported[13] *E*/*Z*-configurational lability of related systems, to predominance of the more stable diastereoisomer. Effective π-participation by the dimethylamino nitrogen lone pair is expected to account for stabilisation of the essentially planar, conjugated *E*-products **5**, relative to the corresponding *Z*-isomers. In the mono-substituted amino analogues **7** examined by Zagorevskii *et al.*,[11] however, *syn*-orientated amino and vinyl ketone groups can achieve co-planarity without steric strain, and the configuration which permits 'double hydrogen bonding' is apparently favoured.

Experimental

^1H and ^{13}C NMR spectra were obtained from $CDCl_3$ solutions on Bruker AM 300 and WM 500 MHz or Varian Gemini 200 MHz spectrometers. Computer modelling was effected using Tripos Associates' software package, ALCHEMY II. The title compounds **5a–g** were obtained by treating the corresponding chromone-2-carboxamides **2a–f**[14] with ethanolic dimethylamine as illustrated in the following example (all coupling constant values *J* are given in Hz).

Dimethylamine (25% w/w solution in EtOH, 3.14 cm^3; 13.2 mmol) was added to a solution of *N*,*N*-dimethylchromone-2-carboxamide **2a** (0.500 g, 2.3 mmol) in dry EtOH (17 cm^3). After being stirred at room temperature (35 °C for the preparation of compounds **5b–g**) for 20 h, the solution was cooled and evaporated under reduced pressure to afford a crude solid (0.53 g) which was chromatographed† on silica (elution with EtOAc) to afford 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide (**5a**) (0.374 g, 62%), m.p. 165–166 °C (from EtOH) (lit.,[15] 166–167 °C); δ_H(500 MHz; $CDCl_3$) 2.89 and 3.09 (6 H, 2 × s, $CONMe_2$), 3.06 (6 H, s, NMe_2), 5.75 (1 H, s, CH=C), 6.75–6.79 and 7.29–7.33 (2 H, 2 × m, 4′-H and 5′-H), 6.88 (1 H, dd, *J* 1 and 8, 3′-H), 7.67 (1 H, dd, *J* 2 and 8, 6′-H) and 13.60 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.06 and 36.84 ($CONMe_2$), 39.38 and 40.11 (NMe_2), 88.81 (C-3), 117.78 and 117.88 (C-3′ and C-5′), 120.18 (C-1′), 128.03 (C-6′), 133.75 (C-4′), 158.76 (C-2), 162.53 (C-2′), 166.44 (CO·N) and 189.74 (C-4); ν_{max}(KBr)/cm^{-1} 2920 and 1648.

Analytical data for new compounds are as follows. 2-(*Dimethylamino*)-3-(*2-hydroxy-4-methoxybenzoyl*)-N,N-*dimethylacrylamide* (**5b**) (0.212 g, 36%), m.p. 154–156 °C (from EtOAc); [*m*/*z* Found: 292.141 (M^+, 10%). $C_{15}H_{20}N_2O_4$ requires: 292.142]; δ_H(300 MHz; $CDCl_3$) 2.90 and 3.09 (6 H, 2 × s, $CONMe_2$), 3.04 (6 H, br s, NMe_2), 3.78 (3 H, s, OMe), 5.65 (1 H, s, CH=C), 6.31–6.37 (2 H, m, 3′-H and 5′-H), 7.58 (1 H, d, *J* 9, 6′-H) and 14.10 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.48 and 37.30 ($CONMe_2$), 39.47 and 40.09 (NMe_2), 55.37 (OCH_3), 89.12 (C-3), 101.02 and 106.43 (C-3′ and C-5′), 113.95 (C-1′), 129.63 (C-6′), 157.89 (C-2), 164.26 (C-4′), 165.33 (C-2′), 166.93 (CO·N) and 189.01 (C-4); ν_{max}(KBr)/cm^{-1} 2930, 1660 and 1650; *m*/*z* 292 (M^+, 10%) and 220 (100%).

2-(*Dimethylamino*)-3-(*2-hydroxy-4-nitrobenzoyl*)-N,N-*dimethylacrylamide* (**5c**) (0.305 g, 52%), m.p. 160–161 °C (from EtOAc) (Found: C, 54.8; H, 5.7; N, 13.5. $C_{14}H_{17}N_3O_5$ requires: C, 54.7; H, 5.6; N, 13.7%); δ_H(300 MHz; $CDCl_3$) 2.92 and 3.11 (6 H, 2 × s, $CONMe_2$), 3.07 and 3.19 (6 H, 2 × s, NMe_2), 5.71 (1 H, s, CH=C), 7.58 (1 H, dd, *J* 2 and 9, 5′-H), 7.69 (1 H, d, *J* 2, 3′-H) 7.79 (1 H, d, *J* 9, 6′-H) and 13.85 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.50 and 37.14 ($CONMe_2$), 39.90 and 40.93 (NMe_2), 89.04 (C-3), 112.28 and 113.52 (C-3′ and C-5′), 124.82 (C-1′), 128.87 (C-6′), 150.53 (C-4′), 160.30 (C-2), 163.09 (C-2′), 165.92 (CO·N) and 188.02 (C-4); ν_{max}(KBr)/cm^{-1} 2920 and 1645; *m*/*z* 307 (M^+, 11%) and 72 (100%).

2-(*Dimethylamino*)-3-(*4-fluoro-2-hydroxybenzoyl*)-N,N-*dimethylacrylamide* (**5d**) (0.228 g, 39%), m.p. 164–166 °C (from EtOAc) (Found: C, 59.7; H, 6.3; N, 10.0. $C_{14}H_{17}N_2O_3F$ requires: C, 60.0; H, 6.1; N, 10.0%); δ_H(300 MHz; $CDCl_3$) 2.89 and 3.08 (6 H, 2 × s, $CONMe_2$), 3.06 (6 H, br s, NMe_2), 5.63 (1 H, s, CH=C), 6.44–6.58 (2 H, m, 3′-H and 5′-H), 7.65 (1 H, dd, *J* 7 and 9, 6′-H) and 14.0 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.39 and 37.15 ($CONMe_2$), 39.59 and 40.40 (NMe_2), 88.96 (C-3), 104.73 and 105.81 (2 × d, $^2J_{CF}$ 23 and $^2J_{CF}$ 24, C-3′ and C-5′), 117.25 (d, $^4J_{CF}$ 3, C-1′), 130.18 (d, $^3J_{CF}$ 11, C-6′), 159.03 (C-2), 165.27 (d, $^3J_{CF}$ 15, C-2′), 166.10 (d, $^1J_{CF}$ 254, C-4′), 166.62 (CO·N) and 189.10 (C-4); ν_{max}(KBr)/cm^{-1} 2910 and 1660; *m*/*z* 280 (M^+, 9%) and 208 (100%).

3-(*4-Chloro-2-hydroxybenzoyl*)-2-(*dimethylamino*)-N,N-*dimethylacrylamide* **5e** (0.327 g, 55%), m.p. 124–125 °C (from EtOAc); [*m*/*z* Found: 296.092 (M^+, 12%). $C_{14}H_{17}N_2O_3Cl$ requires: 296.093]; δ_H(300 MHz; $CDCl_3$) 2.89 and 3.09 (6 H, 2 × s, $CONMe_2$), 3.07 (6 H, br s, NMe_2), 5.66 (1 H, s, CH=C), 6.74 (1 H, dd, *J* 2 and 9, 5′-H), 6.89 (1 H, d, *J* 2, 3′-H), 7.57 (1 H, d, *J* 9, 6′-H) and 13.85 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.48 and 37.07 ($CONMe_2$), 39.70 and 40.60 (NMe_2), 88.88 (C-3), 118.24 and 118.39 (C-3′ and C-5′), 118.85 (C-1′), 129.10 (C-6′), 139.32 (C-4′), 159.09 (C-2), 163.52 (C-2′), 166.45

* The required structures were modelled, and the resulting interatomic distances measured, using the software package, ALCHEMY II. The planar arrangements were obtained by altering the relevant torsion angles of energy-minimised structures.

† Preparative layer chromatography was typically employed to obtain analytical samples.

Table 2 Fractional coordinates ($\times 10^4$) for 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide[a,b]

Atom	*x/a*	*y/b*	*z/c*
C(1)	3 746(3)	2 544(2)	7 544(2)
C(2)	4 446(3)	1 354(2)	8 181(2)
C(3)	3 164(4)	227(3)	8 319(3)
C(4)	1 200(4)	271(3)	7 832(3)
C(5)	472(4)	1 427(3)	7 209(3)
C(6)	1 730(3)	2 549(3)	7 066(3)
O(1)	6 362(3)	1 258(2)	8 686(2)
H(0)	6 934(51)	2 084(37)	8 613(32)
O(2)	6 909(2)	3 670(2)	7 972(2)
C(7)	5 145(3)	3 749(2)	7 440(2)
C(8)	4 480(3)	4 935(2)	6 764(2)
C(9)	5 709(3)	6 084(2)	6 666(2)
C(10)	7 921(3)	6 067(2)	7 141(2)
N(1)	5 105(3)	7 253(2)	6 094(2)
C(11)	3 046(4)	7 375(3)	5 518(3)
C(12)	6 442(4)	8 452(3)	5 964(3)
O(3)	8 996(2)	5 627(2)	6 412(2)
N(2)	8 558(3)	6 626(2)	8 313(2)
C(13)	10 644(4)	6 488(3)	8 826(3)
C(14)	7 234(5)	7 056(4)	9 187(3)

[a] For atom labelling, see Fig. 2. [b] Estimated standard deviations in parentheses.

Table 3 Selected bond lengths/Å and angles/° for 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide[a,b]

C(1)–C(7)	1.489(3)	C(2)–O(1)	1.351(3)
O(1)–H(0)	0.87(3)	O(2)–C(7)	1.263(2)
C(7)–C(8)	1.422(3)	C(8)–C(9)	1.374(3)
C(9)–C(10)	1.526(3)	C(9)–N(1)	1.340(3)
C(10)–O(3)	1.222(3)	C(10)–N(2)	1.339(3)
N(1)–C(11)	1.464(3)	N(1)–C(12)	1.465(3)
N(2)–C(13)	1.465(3)	N(2)–C(14)	1.458(3)
C(2)–C(1)–C(7)	119.3(2)	C(6)–C(1)–C(7)	123.0(2)
C(1)–C(2)–O(1)	122.1(2)	C(3)–C(2)–O(1)	117.3(2)
C(2)–O(1)–H(0)	106.0(2)	C(1)–C(7)–O(2)	117.6(2)
C(1)–C(7)–C(8)	120.1(2)	O(2)–C(7)–C(8)	122.3(2)
C(7)–C(8)–C(9)	122.1(2)	C(8)–C(9)–C(10)	121.3(2)
C(8)–C(9)–N(1)	123.6(2)	C(10)–C(9)–N(1)	115.0(2)
C(9)–C(10)–O(3)	118.2(2)	C(9)–C(10)–N(2)	117.1(2)
O(3)–C(10)–N(2)	124.5(2)	C(9)–N(1)–C(11)	121.1(2)
C(9)–N(1)–C(12)	123.0(2)	C(11)–N(1)–C(12)	115.9(2)
C(10)–N(2)–C(13)	117.8(2)	C(10)–N(2)–C(14)	123.1(2)
C(13)–N(2)–C(14)	117.5(2)		

[a] For atom labelling, see Fig. 2. [b] Estimated standard deviations in parentheses.

(CO·N) and 188.99 (C-4); ν_{max}(KBr)/cm^{-1} 2920 and 1660; *m/z* 296 (^{35}Cl, M$^+$, 12%) and 224 (100%).

3-(4-*Bromo*-2-*hydroxybenzoyl*)-2-(*dimethylamino*)-N,N-*dimethylacrylamide* (**5f**) (0.265 g, 46%), m.p. 124–125 °C (from EtOAc) (Found: C, 49.2; H, 5.1; N, 8.4. $C_{14}H_{17}N_2O_3Br$ requires: C, 49.3; H, 5.0; N, 8.2%); δ_H(300 MHz; $CDCl_3$) 2.89 and 3.08 (6 H, 2 × s, $CONMe_2$), 3.06 (6 H, 2 × s, NMe_2), 5.65 (1 H, s, CH=C), 6.89 (1 H, dd, *J* 2 and 9, 5′-H), 7.06 (1 H, d, *J* 2, 3′-H), 7.50 (1 H, d, *J* 9, 6′-H) and 13.80 (60 MHz; 1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 34.40 and 37.11 ($CONMe_2$), 39.74 and 40.52 (NMe_2), 88.88 (C-3), 119.30 (C-1′), 121.28 and 121.40 (C-3′ and C-5′), 127.63 (C-4′), 129.21 (C-6′), 159.33 (C-2), 163.56 (C-2′), 166.49 (CO·N) and 189.28 (C-4); ν_{max}(KBr)/cm^{-1} 2920 and 1660; *m/z* 340 (^{79}Br, M$^+$, 6%) and 72 (100%).

3-(2-*Hydroxybenzoyl*)-N,N-*dimethyl*-2-*pyrrolidinoacrylamide* (**5g**) (0.594 g, 90%), m.p. 183–184 °C (from EtOH) (Found: C, 66.3; H, 7.05; N, 9.2. $C_{16}H_{20}N_2O_3$ requires: C, 66.65; H, 7.0; N, 9.7); δ_H(200 MHz; $CDCl_3$) 1.86–2.11 [4 H, m, $CH_2(CH_2)_2CH_2$], 2.94 and 3.11 (6 H, 2 × s, $CONMe_2$), 3.36–3.45 and 3.65–3.72 [3 H and 1 H, 2 × m, $N(CH_2)_2$], 5.72 (1 H, s, CH=C), 6.76–6.93 (2 H, m, 4′-H and 5′-H), 7.28–7.37 (1 H, m, 3′-H), 7.69 (1 H, dd, *J* 2 and 8, 6′-H) and 13.70 (60 MHz; 1 H, s, OH); δ_C(50 MHz; $CDCl_3$) 24.82 and 25.39 [$CH_2(CH_2)_2CH_2$], 34.41 and 37.24 (2 × NMe), 48.57 and 48.78 [$N(CH_2)_2$], 89.84 (C-3), 118.30 and 118.61 (C-3′ and C-5′), 120.70 (C-1′), 128.62 (C-6′), 134.35 (C-4′), 156.74 (C-2), 163.31 (C-2′), 167.65 (CO·N) and 190.44 (C-4); ν_{max}(KBr)/cm^{-1} 2930, 2870 and 1650; *m/z* 288 (M$^+$, 2%) and 121 (100%).

Crystal Data.—$C_{14}H_{18}N_2O_3$, M = 262.31. Triclinic, a = 6.8745(6), b = 9.353(1), c = 10.872(1) Å, α = 94.536(8), β = 99.245(8), γ = 91.223(8)°, V = 687.4(1) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.7093 Å), space group $P\bar{1}$, Z = 2, D_x = 1.264 g cm^{-3}, yellow blocks, μ = 0.71 cm^{-1}.

Data Collection and Processing.—CAD4 diffractometer, ω–2θ mode with ω scan width = 0.5 + 0.35 tan θ, variable ω scan speed (max = 5.49° min^{-1}), graphite-monochromated Mo-$K\alpha$ radiation: 4195 reflections measured ($2 \leq \theta \leq 30°$, h:$\bar{9}$–9, k:$\bar{1}$3–13, l:0–15), 3260 observed with $I > \sigma(I)$. No crystal decay observed.

Structure Analysis and Refinement.—Direct methods[16] followed by full-matrix least-squares refinement with all non-hydrogen atoms anisotropic, and hydrogen atoms (with the exception of the phenolic hydrogen) in calculated positions with common isotropic temperature factors. The phenolic hydrogen [H(0)] was located from a difference Fourier map and its position refined. H(0) is involved in an intramolecular hydrogen bond: O(1)–H(0) 0.87(3) Å; O(2)···H(0) 1.69(3) Å; and O(1)–H(0)···O(2) 150.0(2)°. Unit weights were used. The final R value was 0.069 (190 parameters). Final fractional atomic coordinates are given in Table 2, and some selected bond lengths and angles are presented in Table 3. A diagram of the molecule appears in Fig. 2. Full lists of bond lengths and bond angles, thermal parameters and hydrogen atom coordinates have been deposited at the Cambridge Crystallographic Data Centre (CCDC).*

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* For details, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1991, Issue 1.

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Chromone Studies. Part 5.[1] Kinetics and Mechanism of the Reaction of 4-Oxo-4*H*-chromene-2-carboxamides with Dimethylamine

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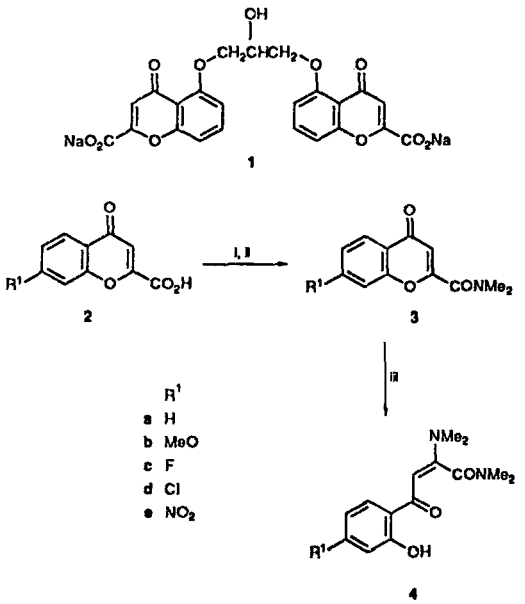
The dimethylamine-mediated ring-opening of a series of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides to the corresponding (*E*)-2-(*N,N*-dimethylamino)-3-(2-hydroxybenzoyl)acrylamides has been monitored by UV spectroscopy, and a mechanistic sequence which accommodates the observed third-order kinetics is presented.

In our investigations of substituent effects in chromone (4-oxo-4*H*-chromene) systems we have previously examined the internal rotation of 4-oxo-4*H*-chromene-2-carboxylate esters by IR spectroscopy[2] and *N*-methyl site-exchange in 4-oxo-4*H*-chromene-2-carboxamides by DNMR techniques.[3] The susceptibility of chromone derivatives to ring-opening *via* nucleophilic attack at C-2 is well illustrated by the amine-mediated formation of (*E*)-2-(*N,N*-dimethylamino)-3-(2-hydroxybenzoyl)acrylamides **4** from 4-oxo-4*H*-chromene-2-carboxamide precursors **3**,[1] and the possible implication of such



Scheme 1 *Reagents*: i, $SOCl_2$–DMF–$ClCH_2CH_2Cl$; ii, Me_2NH_2Cl–pyridine; iii, ethanolic Me_2NH–EtOH

reactions in the molecular-level pharmacology of anti-allergic drugs such as disodium cromoglycate (DSCG, **1**) has prompted the present kinetic study of substituent effects on the ring-opening process.

Experimental

Materials.—The *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides **3a–e** were prepared from the corresponding 4-oxo-4*H*-chromene-2-carboxylic acids **2a–e** as described previously[4] and the identity of the ring-opened products as (*E*)-2-(*N,N*-dimethylamino)-3-(2-hydroxybenzoyl)acrylamides **4** has already been established.[1] The exact concentration of the ethanolic dimethylamine (supplied by Fluka as a 33% w/w solution) was determined by titration against 0.1 mol dm^{-3} HCl. Ethanol, used as a solvent for the reactions, was dried by distillation from magnesium ethoxide.[5]

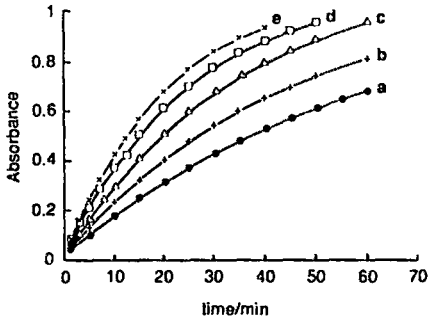


Fig. 1 Plots of absorbance *vs.* time for reaction of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamide **3a** with Me_2NH at 30 °C. [Me_2NH]/mol dm^{-3}; (*a*), 1.0; (*b*), 1.2; (*c*) 1.4; (*d*), 1.6; (*e*), 1.8.

Kinetic Procedure.—The formation of the acrylamides **4** was followed on a Beckmann UV 5240 spectrophotometer, the absorbance changes being measured, in each case, at the wavelength corresponding to the absorption maximum of the particular acrylamide **4** (*e.g.* Fig. 1). In all cases, the absorption maxima of reactants and products were well separated. The wavelength, initial concentrations of 4-oxo-4*H*-chromene-2-carboxamide **3** and dimethylamine, and the duration of each reaction are summarised in Table 1. Quartz cuvettes with 10 mm pathlength were used, and the cuvette chamber, reaction flask, and reagent solutions were maintained at 30 (±0.2) °C. Initial 4-oxo-4*H*-chromene-2-carboxamide **3** concentrations were chosen to produce maximum acrylamide **4** absorbances of *ca.* 1.0–1.2 absorbance units and dimethylamine concentrations were chosen to ensure *ca.* 80% transformation within 1–1.5 h (Table 1). The final absorbance readings ($\lim_{t\to\infty} A_t$) were taken after 15–24 h. All determinations were duplicated. The linear (Beer's Law) relationship between acrylamide **4** concentration and absorbance was confirmed over the corresponding ranges used for each system.

Use of large excesses of dimethylamine {$> 10^3$ [3]} permitted pseudo-first-order analysis of the reactions, linear plots of ln ($A - A_t$) against time [eqn. (1)] affording pseudo-first-order rate constants [k_ψ; eqn. (3)] at different dimethylamine concentrations. The ring-opening reactions were shown to be third-order overall [eqn. (2)] and the rate constants (k_{obs}) were

Table 1 Reaction parameters

R¹	λ/ nm	[Amide]/10⁻³ mol dm⁻³	[Me_2NH]/ mol dm⁻³	Completion (%)	Reaction time (min)
H	357	3.5	1.0–1.8	80–85	40–120
OMe	361	3.0	1.8–2.6	65–76	32–80
NO_2	388	5.5	0.059–0.099	80–82	35–70
F	353	3.5	0.4–0.8	74–85	19–70
Cl	358	3.5	0.2–0.6	80–87	17.5–130

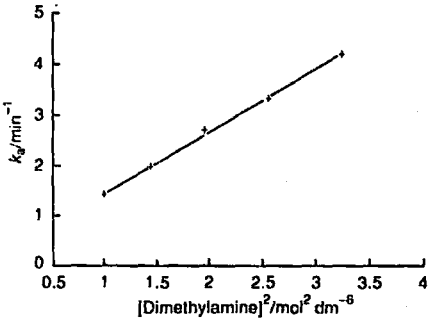


Fig. 2 Plot of pseudo-first-order rate constants k_s vs. $[Me_2NH]^2$ for the reaction of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamide **3a** with Me_2NH at 30 °C

Table 2 Pseudo-first-order rate constants (k_s) for the ring-opening of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides **3** by dimethylamine at 30 °C

R¹	[Amide]/ 10⁻³ mol dm⁻³	[Me_2NH]/ mol dm⁻³	k_s*/10⁻⁴ s⁻¹
H	3.5	1.00	2.40 ± 0.02
		1.20	3.45 ± 0.15
		1.40	4.53 ± 0.03
		1.60	5.90 ± 0.38
		1.80	7.10 ± 0.12
OMe	3.0	1.80	3.97 ± 0.05
		2.00	4.98 ± 0.22
		2.10	5.73 ± 0.18
		2.40	6.87 ± 0.25
		2.60	7.97 ± 0.15
NO_2	5.5	0.059	2.53 ± 0.12
		0.069	3.35 ± 0.05
		0.079	4.33 ± 0.10
		0.089	5.67 ± 0.18
		0.099	6.50 ± 0.02
F	3.5	0.40	3.33 ± 0.05
		0.50	4.70 ± 0.20
		0.60	7.23 ± 0.72
		0.70	9.18 ± 0.48
		0.80	12.22 ± 0.65
Cl	3.5	0.20	2.22 ± 0.02
		0.30	4.75 ± 0.03
		0.40	7.05 ± 0.42
		0.50	10.72 ± 0.40
		0.60	15.53 ± 0.65

* Mean value from duplicate runs.

determined from plots of pseudo-first-order rate constants (k_s) against $[Me_2NH]^2$ (*e.g.* Fig. 2). The relevant data are summarised in Tables 2 and 3. Best straight line fits were obtained by linear regression analysis of the experimental data.

Table 3 Rate constants (k_{obs}) for the ring-opening of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides **3** by dimethylamine at 30 °C

R¹	k_{obs}/10⁻⁴ dm⁶ mol⁻² s⁻¹
H	2.12 ± 0.08
OMe	1.13 ± 0.05
NO_2	648 ± 7
F	18.5 ± 1.2
Cl	40.8 ± 1.3

$$\ln (A - A_t) = -k_s t + \ln (A - A_0) \quad (1)$$

where A_0 = initial absorbance, A_t = absorbance at time, t and $A = \lim_{t\to\infty} A_t$

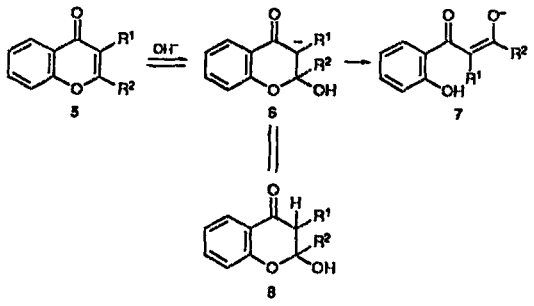
$$\text{Rate} = k_{obs}\,[3]\,[Me_2NH]^2 \quad (2)$$

$$= k_s\,[3] \quad (3)$$

where $k_s = k_{obs}[Me_2NH]^2$

Results and Discussion

In related kinetic studies, Szabo *et al.* have shown that hydroxide-ion-induced cleavage of the pyrone ring in chromone[6] and isoflavonoid derivatives[7,8] follows second-order kinetics {Rate ∝ [substrate][OH^-]}. They proposed a mechanistic sequence (Scheme 2) in which the first step (**5**→**6**),



Scheme 2

involving hydroxide ion attack at C-2, is considered to be rate-determining, and suggested[6] that the measured rate constants reflect the electron density at C-2 and, hence, the susceptibility of chromone derivatives to C-2 nucleophilic attack.

Consequently, we expected the reactions of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides **3** with dimethylamine to follow second-order kinetics with C-2 attack by dimethylamine being rate-determining. In the event, our results clearly show that these ring-opening reactions follow *third-order* (rather than second-order) kinetics overall and require formulation of the rate equation as indicated in eqn. (2). The mechanism which we are now proposing is detailed in Scheme 3 and is consistent with a rate expression [eqn. (4)] which, for $k_3K_1K_2 = k_{obs}$, is identical to the experimentally determined relationship [eqn. (2)].

$$\text{Rate} = k_3K_1K_2\,[3]\,[Me_2NH]^2 \quad (4)$$

The proposed mechanism (Scheme 3) comprises two consecutive equilibria followed by a rate-determining ring-opening step. In the first equilibrium, readily reversible nucleophilic attack by the amine at C-2 of the 4-oxo-4*H*-chromene-2-carboxamide **3** affords the dipolar species **9** in which loss of the *neutral* amine (**9**→**3**; Fig. 3) occurs more readily than ring-fission (**9**→**11**). The next step is simply an acid–base equilibrium, the second molecule of amine now acting as a