Chromone Studies. Part 3.[1] NMR Analysis of Rotational Isomerism in 4-Oxo-4*H*-chromene-2-carboxamides

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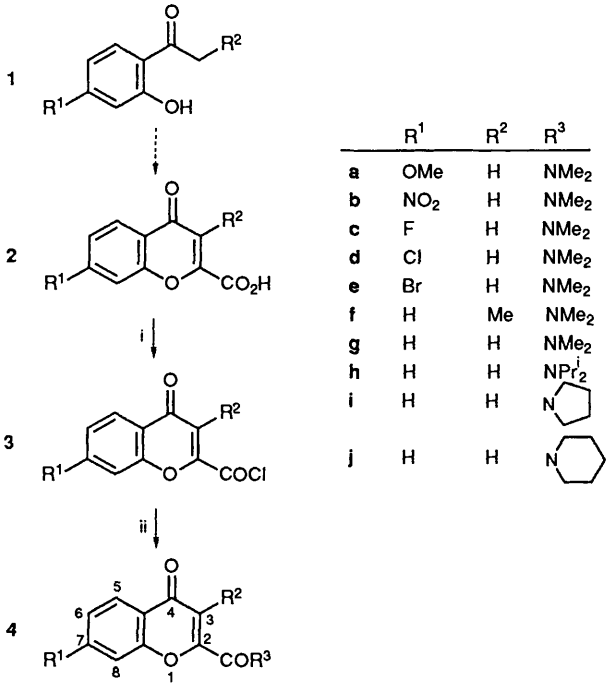
Temperature dependent splitting of *N*-alkyl ^{1}H and ^{13}C NMR signals in a series of 4-oxo-4*H*-chromene-2-carboxamides has been analysed in terms of rotation of the amide group. Rotational barriers have been calculated from dynamic ^{1}H NMR data and the conformational options have been explored.

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.

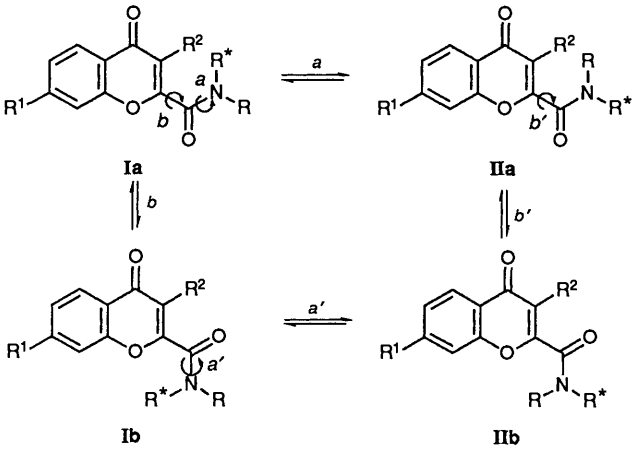
Results and Discussion

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[1] (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.



Scheme 1 *Reagents:* i, $SOCl_2$–DMF–$ClCH_2CH_2Cl$; ii, Me_2NH_2Cl–pyridine or R^3H–aq. $NaHCO_3$ or R^3H–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**).

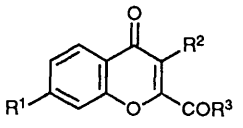
It should be noted that rotation of the amide group in a

† Steric interactions in analogous benzamides appear to interfere with the co-planarity of the aromatic and carboxamide systems.[5]

‡ 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]



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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.

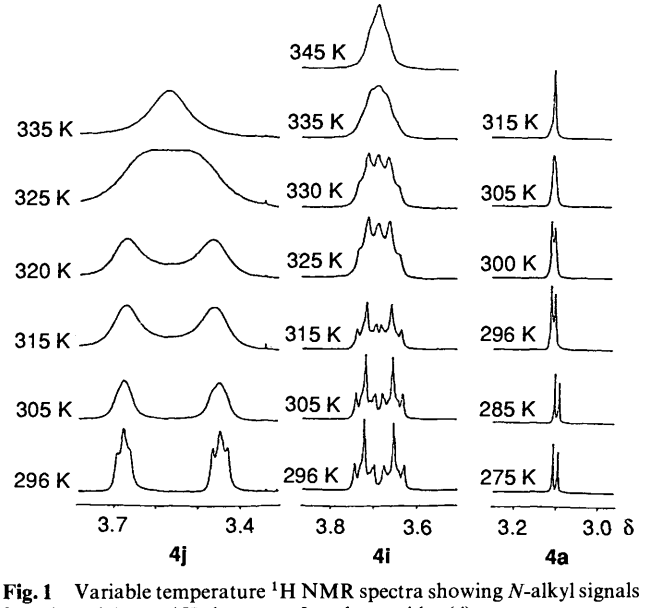

Fig. 1 Variable temperature ^{1}H NMR spectra showing *N*-alkyl signals for selected 4-oxo-4*H*-chromene-2-carboxamides (**4**)

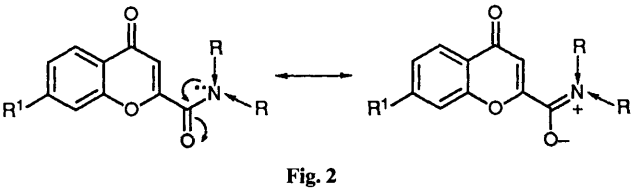

Fig. 2

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**.

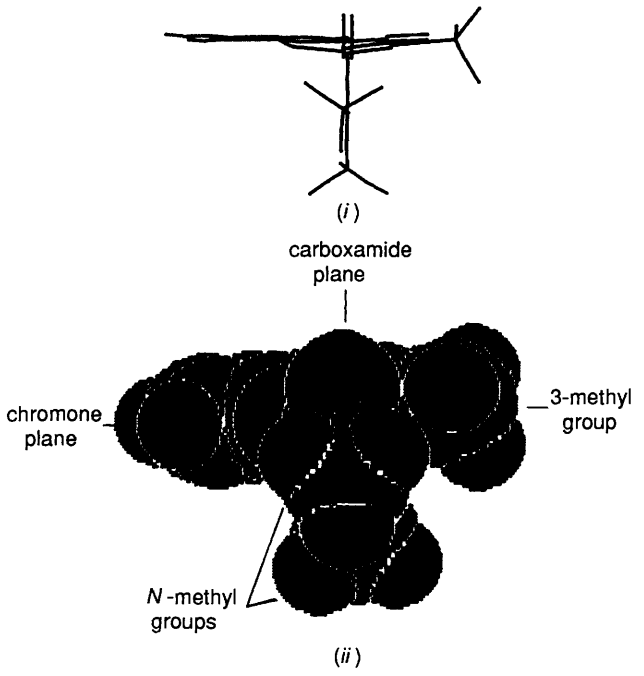

Fig. 3 Proposed conformation of compound **4f** based on computer-modelled structure; (*i*) 'wire-frame' and (*ii*) 'spacefill' representations

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. $C_{15}H_{15}NO_3$ 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%).

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