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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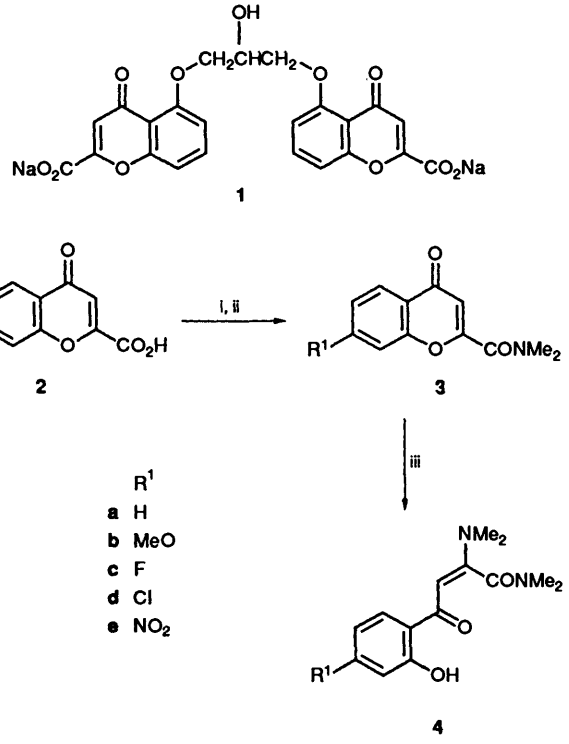
The dimethylamine-mediated ring-opening of a series of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides to the corresponding (*E*)-2-(*N,N*-dimethylamino)-3-(2-hydroxybenzoyl)acrylamides has been monitored by UV spectroscopy, and a mechanistic sequence which accommodates the observed third-order kinetics 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]

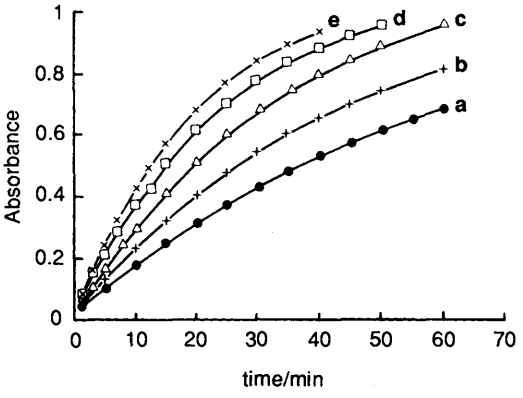


Fig. 1 Plots of absorbance *vs.* time for reaction of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamide **3a** with Me_2NH at 30 °C. [Me_2NH]/mol dm^{-3}; (*a*), 1.0; (*b*), 1.2; (*c*) 1.4; (*d*), 1.6; (*e*), 1.8.

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_a; 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^{-5} 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

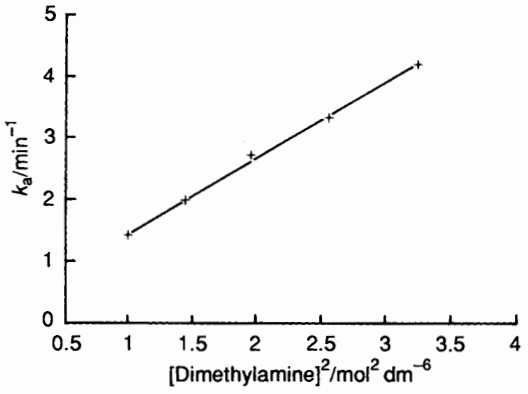


Fig. 2 Plot of pseudo-first-order rate constants k_a *vs.* [Me_2NH]^2 for the reaction of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamide **3a** with Me_2NH at 30 °C

Table 2 Pseudo-first-order rate constants (k_a) for the ring-opening of *N,N*-dimethyl-4-oxo-4*H*-chromene-2-carboxamides **3** by dimethylamine at 30 °C

R¹	[Amide]/10^{-5} mol dm^{-3}	[Me_2NH]/mol dm^{-3}	k_a[a]/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

[a] Mean value from duplicate runs.

determined from plots of pseudo-first-order rate constants (k_a) 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	$k_{obs}/10^{-4}$ dm^6 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

$$\ln (A - A_t) = -k_a t + \ln (A - A_0) \quad (1)$$

where A_0 = initial absorbance, A_t = absorbance at time, t and $A = \lim_{t\to\infty} A_t$

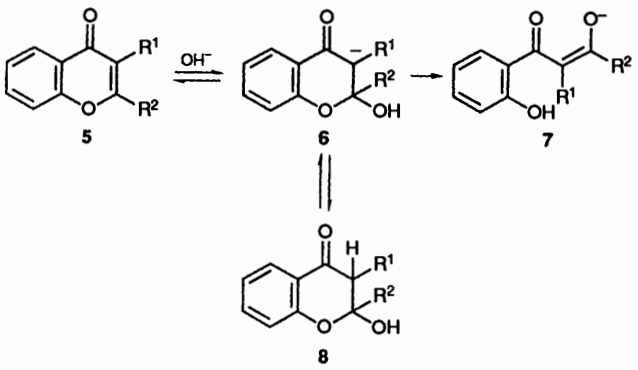
$$\text{Rate} = k_{obs}\,[\mathbf{3}]\,[Me_2NH]^2 \quad (2)$$

$$= k_a\,[\mathbf{3}] \quad (3)$$

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

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**),



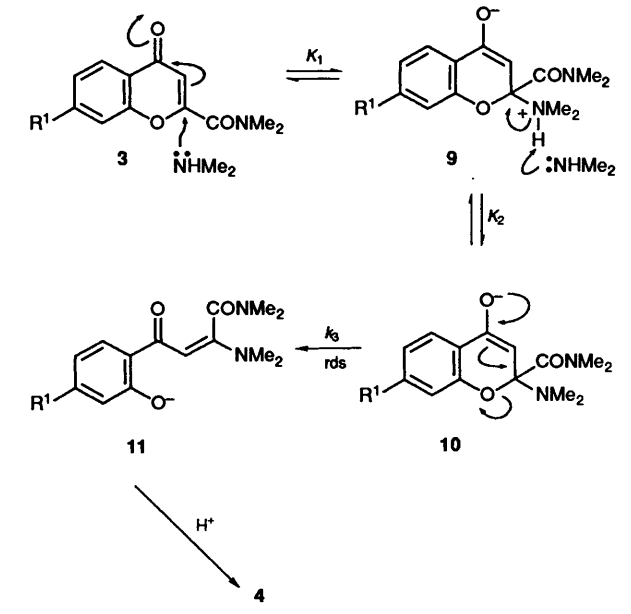
Scheme 2

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)].

$$\text{Rate} = k_3K_1K_2\,[\mathbf{3}]\,[Me_2NH]^2 \quad (4)$$

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



Scheme 3

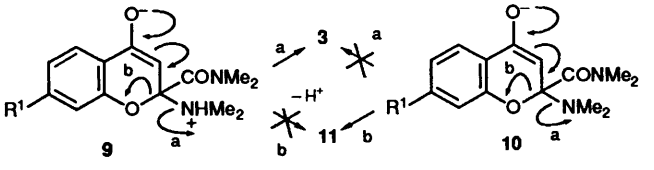


Fig. 3

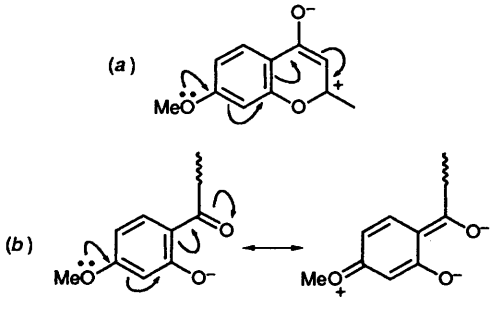


Fig. 4

base rather than a nucleophile. The resulting enolate species **10** then undergoes fission of the pyrone ring in the rate-limiting step (**10**→**11**) *via* 'loss' of the resonance stabilised phenoxide ion in preference to Me_2N^- (Fig. 3). Involvement of an intermediate addition product corresponding to compound **8** (Scheme 2) is considered unlikely since, in an NMR study, Zagorevskii *et al.*[9] have demonstrated the absence of isotope exchange in the reaction of chromone with 1-deuteriopiperidine and of 3-deuteriochromone with piperidine.

While the remote C-7 substituents may influence C-2 electrophilicity [and hence the equilibrium constant, K_1 of eqn. (4)] their contribution, as *meta*-substituents, to the relative stabilisation of the phenoxide 'leaving group' in the rate-determining step should be significant. Thus, electron-withdrawing substituents should accelerate ring-opening and, in fact, with the exception of the 7-methoxy analogue **3b**, the experimentally determined rate constants (k_{obs}; Table 3) follow the expected[10] trend (*i.e.* $k_{NO_2} > k_{Cl} > k_F > k_H$). In view of its positive MeO substituent constant ($\sigma_{m\text{-MeO}} = +0.1$)[11] the methoxy analogue **3b** might be expected to have a larger rate constant (k_{obs}) than the parent system **3a** whereas, in fact, it is smaller (Table 3). This apparent anomaly may be attributable to electron-releasing resonance effects which: (i) reduce C-2 electrophilicity [Fig. 4(*a*)] and/or (ii) inhibit *ortho*-acyl stabilisation of the phenoxide ion by competitive delocalisation [Fig. 4(*b*)].

Acknowledgements

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