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THE ALKALINE HYDROLYSIS OF 4-METHOXYCOUMARIN

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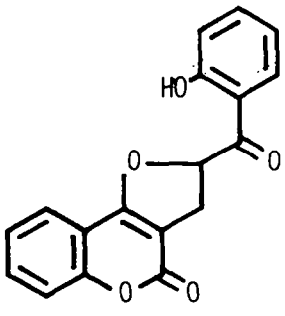
Abstract - The aqueous alkaline hydrolysis of 4-methoxycoumarin occurs in two stages. In the first, the lactone ring is opened at a rate directly proportional to the concentration of base. In the second, the methoxy group is replaced by an unusual route that depends upon the presence of an unionised phenolic hydroxy group and is therefore inversely proportional to the concentration of base. Methanolysis by methoxide ion in methanol occurs primarily at position 4 and replaces the methoxy group before the ring is opened; the difference from the aqueous hydrolysis is ascribed to solvent effects.

While investigating the dihydrofurocoumarin derivative (1) we attempted to show the presence of a lactone ring by alkaline hydrolysis but were foiled by a complex decomposition that remained unexplained.[1] During further (unpublished) work we noted that, in contrast to usual experience, the decomposition seemed more extensive in dilute than in concentrated alkali so that the derivative (1) could be regained in part from the more strongly alkaline media but never from the more dilute. Because such behaviour is rare we have returned to the problem.



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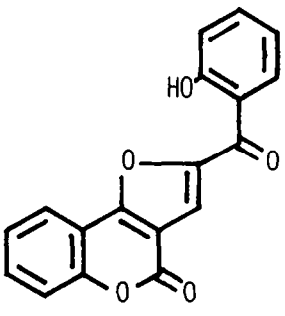

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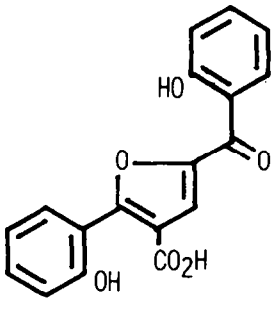


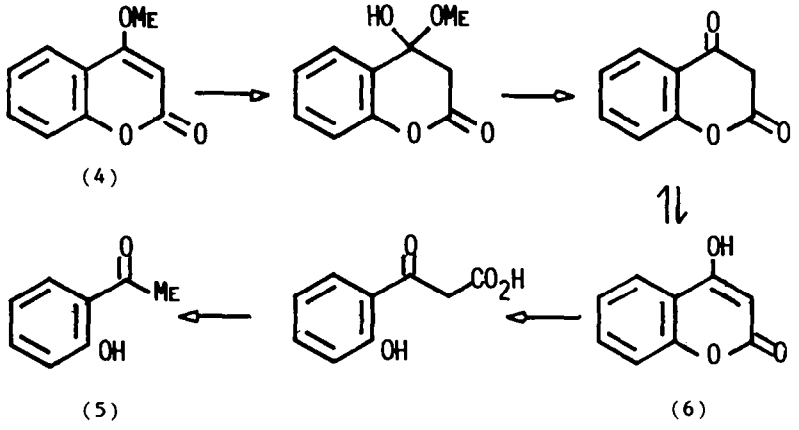
(3)

Checchi[2] hydrolysed the related furocoumarin (2) with dilute alkali and found only a normal hydrolysis giving the acid (3) which corresponds to the coumarinic acids (*cis*-2-hydroxycinnamic acids) formed by simple coumarins. A somewhat unusual feature was that the free acid was stable; most coumarinic acids relactonise when liberated from their salts and many do so even in slightly alkaline solution.[3] We have confirmed these results and attribute the stability of the acid to the geometry of the furan ring which will cause the carboxyl and hydroxy groups to be drawn away from each other.[4] There was no further hydrolysis under conditions that completely destroy the dihydrofurocoumarin (1).

We have studied 4-methoxycoumarin as a simple model for compound (1). Some other simple coumarins have been studied by various kinetic methods and have been shown to undergo hydrolysis at rates that are first order in both substrate and base and depend markedly upon the substituents.[5] The relactonisation of the resulting coumarinic acids has also been examined with respect to pH; regions of acid- and of base-catalysed cyclisation were defined, and appropriate mechanisms advanced.[6] In all this work the attack by base was at the carbonyl group, presumably under kinetic control.

However, it cannot be assumed that bases will always attack the carbonyl group. It has long been known that some nucleophiles react (add) at position 4 under appropriate conditions.[7-9] It is also known that lithium amide bases are capable of abstracting a proton from position 3 thus opening the ring in a quite different manner.[10] We have been able to exclude both these possibilities and to demonstrate that the hydrolytic opening of the lactone ring is normal and that it is in the subsequent reactions that new features appear.

4-Methoxycoumarin (4) is hydrolysed by warm, dilute alkali giving (after the usual laboratory workup) the hydroxyacetophenone (5). No trace of salicylic acid was found although vigorous hydrolysis by hot, concentrated alkali or fusion with alkali affords both products from 4-hydroxycoumarin and related compounds.[11] We assumed that the only other products of hydrolysis would be methanol and carbon dioxide but made no attempt to confirm this. The yield of hydroxyacetophenone appeared to be quantitative and neither a coumarinic acid (*cis*-methoxycinnamic acid) nor a coumaric (*trans*-methoxycinnamic) acid was detected.

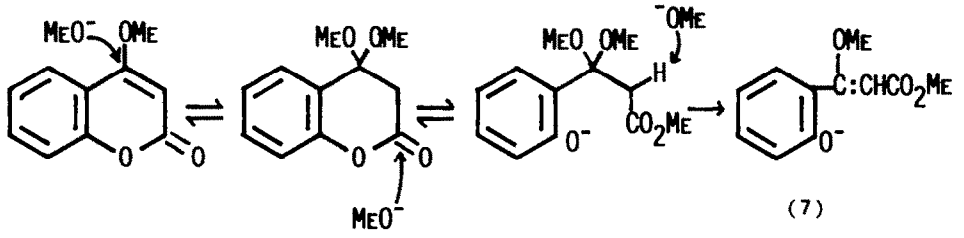


(4) (5) (6)

SCHEME 1

Scheme 1 shows a sequence of events initiated by nucleophilic attack by hydroxide ion at position 4 of the methoxycoumarin. Because such an attack could not be observed directly, we sought to support it by examining the reaction of the methoxycoumarin in d_4-methanol containing a trace of the methoxide ion. Rates were not determined, but ^{1}H-nmr spectroscopy showed that methoxy group exchange was effectively complete in three hours, and the (known[7]) 4-methoxy-d_3-coumarin was isolated and characterised by ir and mass spectral methods. However, we had to reject Scheme 1 because under our conditions of hydrolysis 4-hydroxy-coumarin (6) is stable indefinitely (it reacts in vigorous hydrolyses[11]).

Evidently methoxide ion attacks position 4 in preference to the carbonyl group, which reacts more slowly to give what must be formulated as the cinnamic



SCHEME 2

ester (7)(Scheme 2) because of the uv spectrum (Fig.1) which remains unchanged for several days. When followed by means of the uv absorption, the reaction gave good isosbestic points (Fig. 2) and the rate was found to be pseudo-first order with respect to methoxycoumarin (Fig. 3). With respect to methoxide ion, on the other hand, the reaction is of a higher order, log plots of rate constant against methoxide ion concentration indicating a value near 2.5, and we suggest that this arises from the sequence in Scheme 2. The first methoxide ion adds at position 4 as shown above, and the product picks up a proton from the solvent. The second methoxide ion opens the lactone ring. A third methoxide ion

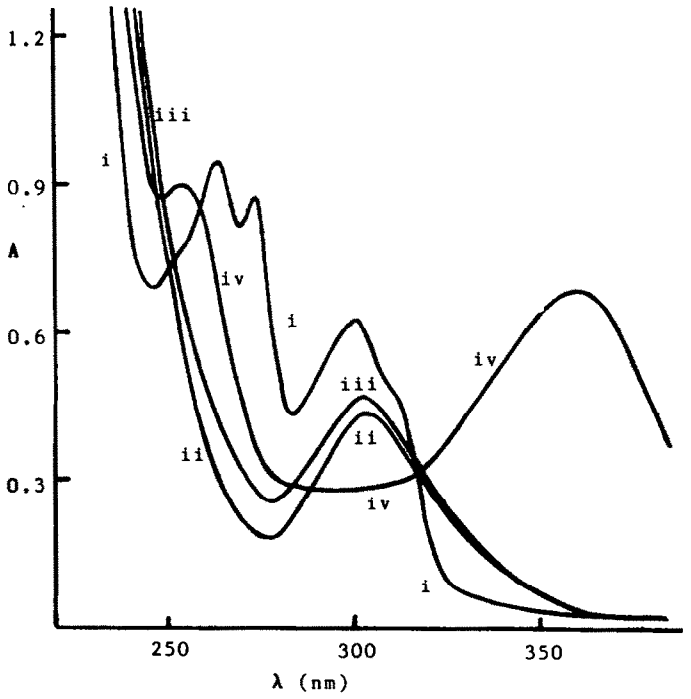


Figure 1.

Uv spectra of 4-methoxy-coumarin (c, 1.1 x 10^{-4}M)
(i) in neutral MeOH,
(ii) after 24 h in 3M-MeOK in MeOH;
(iii) after 24 h in 3M-NaOH in H_2O/MeOH
(iv) after 24 h in 0.03M NaOH in H_2O/MeOH

is required to remove a methylenic proton and so generate the cinnamic chromophore, a step that is probably the slowest because of repulsion by the phenoxide ion. Thus the last step could be rate-determining while yet dependent upon the earlier steps and give rise to some order such as that found.

Clearly, arguments based upon methoxide ion in methanol are not applicable to hydroxide ion in water in this case. This conclusion may be true for coumarins in general. Schmid and his colleagues[8] note that coumarins related to athamantin add methanol with the former reagent and that 7-methoxycoumarin does likewise although with hydroxide ion in water 7-methoxycoumarin undergoes the usual transformation into a coumarinic acid.* Since hydroxide and methoxide are very similar nucleophiles/bases the difference is probably a question of solvation effects. Strong evidence is already available (from the reverse reaction in which a coumarinic acid relactonises to a coumarin) indicating that water-solvated ortho-acid intermediates do control the rate and mechanism.[6]

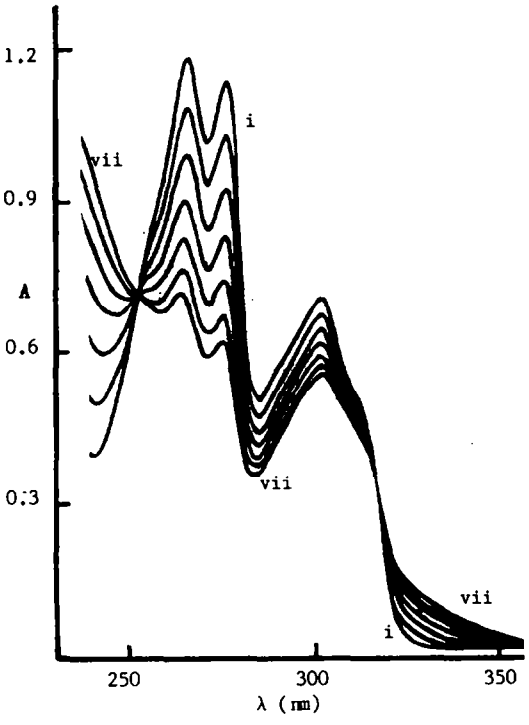


Figure 2. 4-Methoxycoumarin (1.1×10^{-4} M) with NaOMe (3M) in MeOH at 20 °C; uv scans at 1 h intervals from scan (i) at t_0.

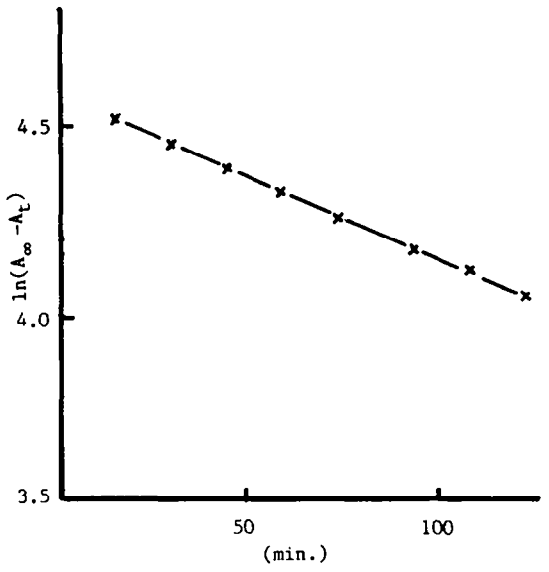


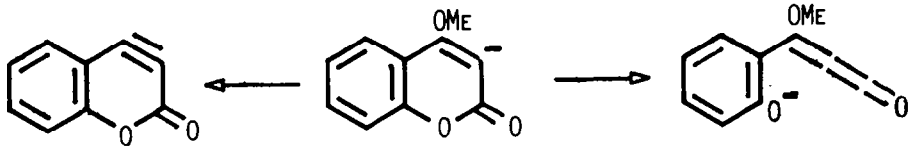
Figure 3. 4-Methoxycoumarin (1.1×10^{-4} M) with NaOMe (2M) in MeOH at 50 °C monitored at 274 nm.

It follows that hydroxide ion in a non-aqueous environment might attack at position 4 rather than at the carbonyl group. Of several solvents tried only *t*-butanol was satisfactory. Potassium *t*-butoxide in *t*-butanol did not affect 4-methoxycoumarin during several hours at 82 °C (steric hindrance ?). But after the

*When the context permits, the terms acid and phenol designate the salts as well.

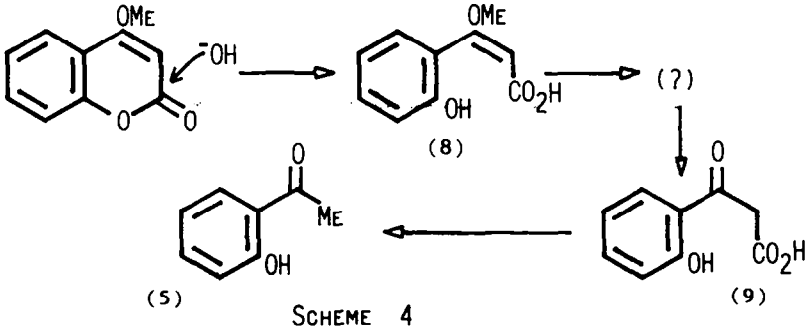
controlled addition of water (in order to provide potassium hydrocie while virtually excluding free water able to engage in solvation) the same mixture readily supplied the potassium salt of 4-hydroxycoumarin as a precipitate, Hence the route shown in Scheme 1 is valid, although not for hydroxide ion in water.

Another way of accounting for the ring opening and methoxy group removal would be to assume that the base first removes a proton from position 3 as in Scheme 3. Such reactions do occur with strong base in non-protic media as noted above, but seem most unlikely in the present hydrolysis conditions. Moreover, the experiment with d_4-methanol disclosed only the slightest exchange of the 3-proton during the time taken for complete methanolysis. Finally, the hydrolysis takes the same course when the 3-position is occupied by some group other than hydrogen as in the (naturally occurring) 3-aryl-4-methoxycoumarin glabrescin[12] and in an example discussed below. The route in Scheme 3 must be rejected.



SCHEME 3

It now seems necessary to accept that, just as with other coumarins, aqueous hydrolysis begins with attack at the carbonyl group and gives acid (8) (Scheme 4). At the outset we had also rejected this route because it seemed to offer no way in which the methoxy group could be eliminated under such mild conditions. It has long been known that 3-methoxypropionic acids are stable to prolonged alkaline hydrolysis - indeed, the usual method for making them requires prolonged heating of the esters with alkali.[13] The only new feature in the acid (8) is the phenolic hydroxy group which was never present in the earlier studies, and we now marshall evidence that the coumarin ring is opened normally and that it is indeed the phenolic group that must be responsible for the lability of the ether link. The sequence in Scheme 4 is established first, and then the manner in which the coumarinic acid (8) is transformed into ketonic acid (9) is discussed.



SCHEME 4

The hydrolysis of 4-methoxycoumarin by sodium hydroxide in 50% aqueous methanol at 50 °C was follwed spectrophotometrically. With dilute base (concentrations less than 0.1 M) the complex absorptions showed gradually shifting isosbestic points indicative of the intervention of a rate-influencing intermediate. With more concentrated base, however, the reaction furnished simpler results with well-defined isosbestic points (Fig. 4); eventually the absorption became nearly identical with that resulting from the methanolysis (Scheme 2; Figs. 1 and 4) and was assigned to the acid (8)(Scheme 4). In support, rapid acidfication of the reaction mixture provoked a return to the methoxycoumarin spectrum by lactonisation, and when the hydrolysis was run on a preparative scale (with *t*-butanol instead of methanol as co-solvent) and quenched with acetic anhydride, the acetate of acid (8) was isolated though only in poor yield.

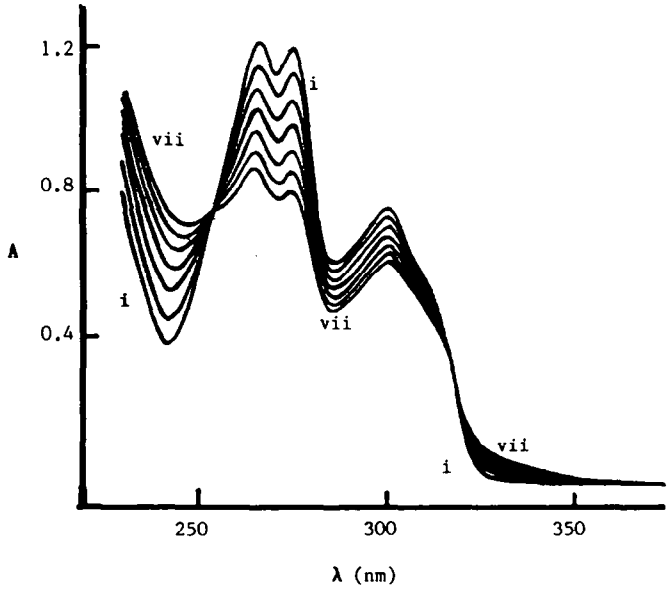


Figure 4.
4-Methoxycoumarin (1.1×10^{-4} M) with NaOH (0.1 M) in H_2O/MeOH (50%)(v/v) monitored at intervals of 2 min.

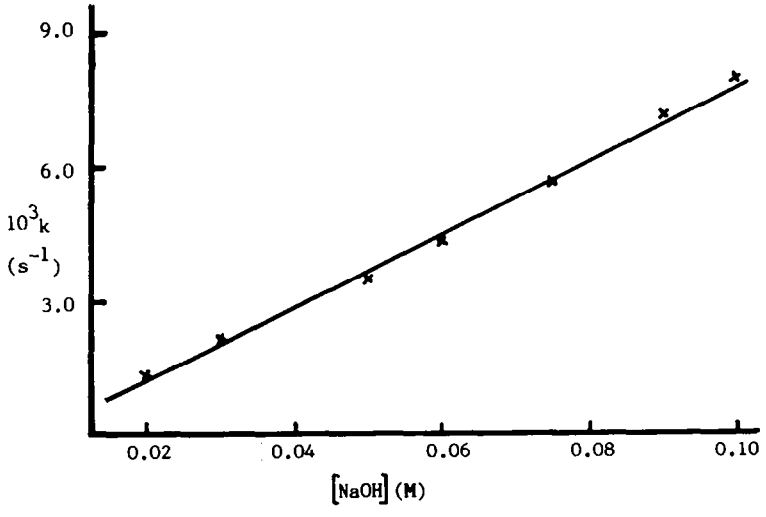


Figure 5.
Dependence of first order rate constants on [NaOH] for first stage of alkaline hydrolysis.

The next part of the problem was to isolate the second stage of hydrolysis in which the methoxycoumarinic acid collapses giving the hydroxyacetophenone chromophore. Such collapse occurs only in relatively weak alkali. When 4-methoxycoumarin is allowed to react at 75 °C in an aqueous buffer at pH 10.5 (from sodium hydroxide

mixed with sodium hydrogen carbonate) uv scanning afford good isosbestic points for the complete conversion into the hydroxyacetophenone chromophore and a pseudo-first order rate constant is readily derived. But in these circumstances the slow step must be the first, so the constant refers to that and does not yield the desired information. This we obtained by carrying out hydrolyses with the stronger alkali until all the initial methoxycoumarin had been converted into the methoxycoumarinic acid (as shown by uv), and then diluting the solution while keeping it at 50 °C and continuing the scans. A new nest of curves was obtained correponding to the second stage of hydrolysis as shown by the increasing absorption near 360 nm (Fig. 6). From a series of such dilutions we obtained reasonable pseudo-first order rate constants and found that when plotted against the reciprocal of the base concentration they gave moderate linearity (Fig. 7). Some curvature may be introduced at the lowest base concentrations because phenol ionisation is incomplete and the uv absorption no longer accurately monitors the situation. Nevertheless there is no doubt about the *inverse* proportionality between rate constant and base concentration.

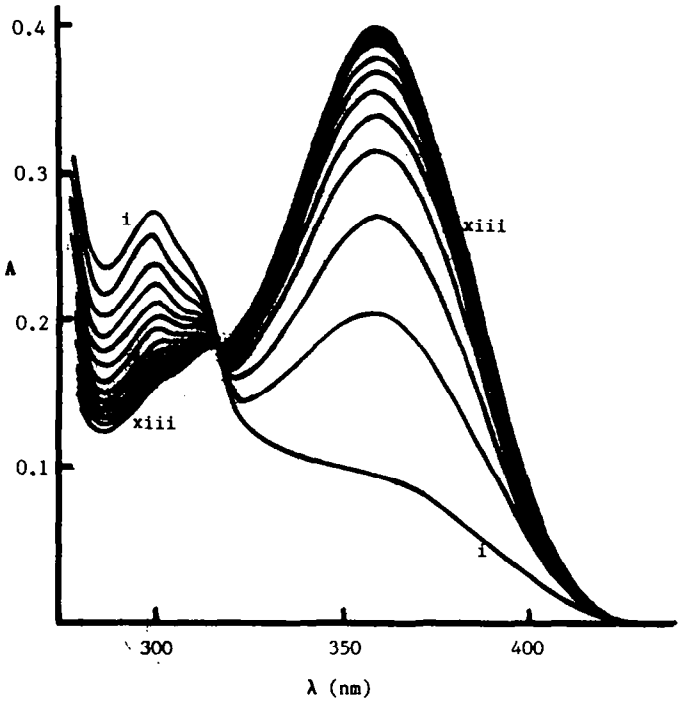


Figure 6

Hydrolysis mixture as for Fig. 4 taken after 50 min. and diluted to 0.01 M in NaOH; subsequent reaction at 50 °C scanned at intervals of 30 min.

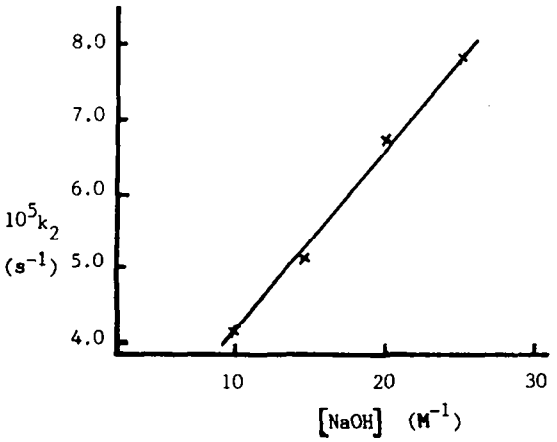


Figure 7

Dependence of pseudo-first order rate constants upon NaOH for the second stage of hydrolysis of 4-methoxycoumarin at 50 °C (monitored at 360 nm).

The final spectrum is that of the (ionised) hydroxyacetophenone (5) and, as noted above, this ketone can be isolated almost quantitatively on a preparative scale. Nevertheless, the true hydrolysis product must be the ketonic acid (9) that precedes the ketone in Scheme 4. This acid would have nearly the same electronic spectrum as the ketone in mildly alkaline solution, and it would be easily decarboxylated during the usual type of work-up. Such acids have been isolated in cases where substituents would be expected to stabilise them.[14] Rapid chromatography (tlc) of an acidified hydrolysate disclosed none of the acetophenone but instead a very slow-running material that could well be the corresponding acid. The identity was confirmed by examining the hydrolysate by ^{13}C nmr spectroscopy. That the methoxycoumarinic acid (8) is the end product of hydrolysis in stronger alkali was easy to demonstrate, but the requirements for the second stage of hydrolysis in dilute alkali conflicted with the need for solutions concentrated enough to give good spectra. However, we found conditions that sufficed and observed a complete set of signals for acid (salt) (9) contaminated by only small amounts of the coumarinic acid (8) or the hydroxyacetophenone (5) (Table 1).

Table 1. ^{13}C Nmr Spectra[a] of hydrolysis products

Carbon	1	2	3	4	5	6
(A)[b]	125·66s	165·80s	119·05d	130·07d	112·07d	129·89d
(B)[c]	126·48s	169·55s	122·69d	134·54d	112·52d	129·52d
(C)[d]	128·35s	172·05s	125·15d	136·86d	114·85d	132·41d

Carbon	7	8	9	10
(A)	163·97s	98·95d	175·26s	54·56s
(B)	206·09s	29·03q		
(C)	203·68s	53·29t	178·56s	50·65q[e]

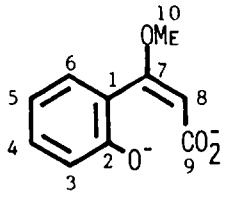
[a] At 62.89 MHz; δ scale. Hydrolyses run at 50 °C.

[b] Hydrolysis in 0.3 M NaOH (see Experimental).

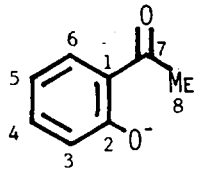
[c] Authentic sample for reference purposes.

[d] Hydrolysis in 0.03 M NaOH (see Experimental). Small peaks from stronger bands in (A) and (B) also present. A weak signal near δ 2 originating from (B) increased with time or with increase in temperature.

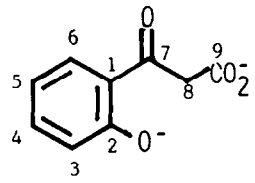
[e] Methanol liberated by hydrolysis.



(A)



(B)



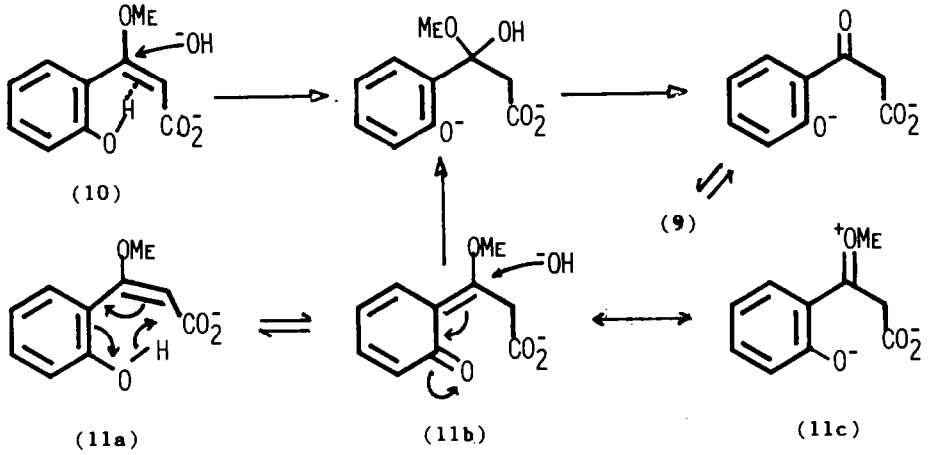
(C)

The absence of a signal from carbonate carbon (δ 171·52) confirmed the retention of its carboxyl group by the substrate.

This completes the evidence of the reaction route in Scheme 4, the only novel feature being the loss of the methoxy group under conditions in which vinyl ethers are normally completely stable. Clearly, it is the phenolic hydroxy group in acid (8) that introduces the lability since compounds without it are stable. Equally, the hydrogen atom must be in place since media basic enough to remove it prevent the loss, and what happens to this hydrogen atom is therefore the key feature. The simplest possibility is that this hydroxy group acts as a neighbouring group and promotes the addition of hydroxide ion as depicted in diagram (10) (Scheme 5). A more complex possibility is that the hydrogen atom suffers a sigmatropic shift

as indicated in (**11a**) thus leading to a quinone methide (**11b**) that will add the hydroxide ion readily (Scheme 5). After these stages, the two routes follow the same course to acid (**9**). Before choosing between these routes we note that they differ only on a time basis so that if the two discrete steps (**11a**) and (**11b**) are made simultaneous they become indistinguishable from the other route (**10**). The true mechanism might therefore lie somewhere between the two hypothetical ones thus allowing it to benefit from features in both. However, we believe that the quinone methide mechanism will be clearly dominant for the following reasons.*

Diagram (**10**) (Scheme 5) shows hydroxide adding to an alkene group in a manner normally possible only when an electron-attracting group is attached; here the carboxylate ion is more or less non-activating and the methoxy group in opposition. Neighbouring group effects may assist the addition, but in the early stages these consist only in hydrogen-bonding between the hydroxy group and the alkene bond which is known to be weak in contrast to hydrogen-bonding with various hetero-atoms. A weak effect is not likely to lower the energy barrier of an unfavourable reaction by a significant amount. Furthermore, the methoxy group in (**10**) is shown as making no contribution; it would probably be somewhat deactivating and the rate of the reaction would increase if it was not there. But then we are dealing with a simple 2-hydroxycinnamic acid and, as noted already, these are stable at all pH values accessible in aqueous solutions and undergo neither addition of water nor geometrical inversion.



SCHEME 5

At first sight it appears that the sigmatropic shift in (**11a**) will be strongly opposed by loss of much of the aromatic resonance stabilisation energy, but the quinone methide (**11b**) will itself be stabilised by the ester-type resonance indicated in diagram (**11c**) which is itself considerable and which is not present originally (quinone methides with two such stabilising effects can be stable enough for isolation and may even be found in plants and fungi). Indeed, diagram (**11c**) suggests that the isomerisation could be regarded as a polarisation instead of a loss of aromaticity. That means that the methoxy group is indispensible if the sigmatropic shift is to occur and amply explains why 2-hydroxycinnamic acids can be hydrated by base only if they contain one.

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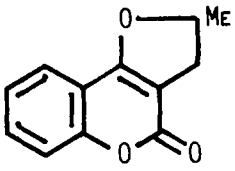
* A Referee takes the opposite view.

The stability of Checchi's acid (3) can be attributed to the fact that there is an ether oxygen in the right place but only as part of a furan ring stabilised both by its intrinsic resonance energy and by interactions with the benzoyl group all of which would be upset, without recompense, by the sigmatropic shift. The routes shown in Schemes 4 and 5 might be expanded to include another in which the carboxyl group is lost before instead of after the methoxy group but we have been unable to find any evidence that this occurs although we cannot exclude it altogether.

As a closer model for the dihydrofurocoumarin (1) the tricyclic compound[15] (12) was examined briefly. Alkaline hydrolysis furnished the ketonic alcohol (13) and a limited kinetic study again indicated a two-stage mechanism through a gradually shifting isosbestic point near 265 nm and a fairly stable isosbestic point near 328 nm (Fig. 8). The rates were very like those from 4-methoxycoumarin (Table 2) so the extra ring makes little difference. The original compound (1), however, shows further complexities that must now be attributed to the presence of the 2-hydroxybenzoyl group and remain to be elucidated.



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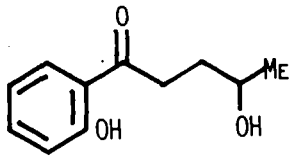

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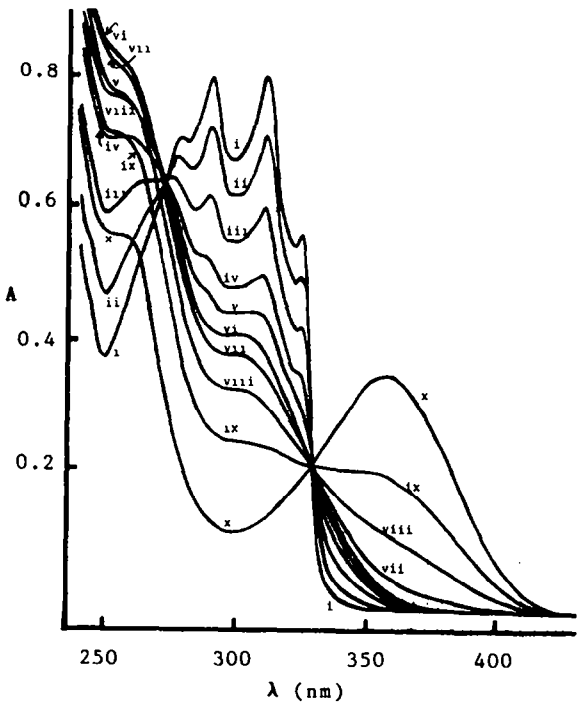

Figure 8. Hydrolysis of dihydrofurocoumarin (12) (0.75 x 10^{-4} M) by NaOH (0.30 M) in 50% H_2O-EtOH at 25 °C monitored by uv scans after (i) 3 min., (ii) 9 min., (iii) 15 min., (iv) 30 min., (v) 45 min., (vi) 90 min., (vii) 24 h, (viii) 95 h, (ix) 316 h, and (x) 30 days.

Table 2. Selected rate constants[a]

Substrate	Base	Conc. (M)	Solvent	Temp. (°C)	k_1 (s^{-1})	k_2 (s^{-1})
Methoxy-coumarin	NaOMe	1.00	MeOH	50	1.0×10^{-5}	
Coumarin[b]	NaOH/$NaCO_3$	pH 10.5	H_2O	31	2.5×10^{-4}	
Methoxy-coumarin	NaOH/$NaCO_3$	pH 10.5	H_2O	75	1.05×10^{-4}	(large)
Coumarin	NaOH/$NaCO_3$	pH 10.5	H_2O	75	6.3×10^{-3}	
Methoxy-coumarin	NaOH	0.10	H_2O/MeOH[c]	50	7.2×10^{-4}	3.4×10^{-5}
Methoxy-coumarin	NaOH	0.03	H_2O/MeOH[c]	50	1.05×10^{-5}	7.9×10^{-5}
Dihydrofuro-benzopyrone	NaOH	0.30	H_2O/EtOH[c]	25	2.3×10^{-3}	3.8×10^{-7}
"	NaOH	0.03	"	25	2.0×10^{-4}	6.0×10^{-6}
"	NaOH	0.30	"	72	2.3×10^{-3}	8.5×10^{-4}
"	NaOH	0.03	"	75	5.3×10^{-5}	5.0×10^{-3}

[a] Pseudo-first order derivation; k_1 refers to stage 1 (opening of lactone ring), and k_2 refers to stage 2 (hydrolysis of methoxycoumarinic acid to ketone).

[b] Following ref. 5b.

[c] 50% by volume.

EXPERIMENTAL

Some rates were obtained by the use of a Unicam SP500 spectrophotometer, but most by the use of a Perkin Elmer Lambda 5 machine. Nmr spectra were obtained from a Bruker WM 250 spectrometer (for carbon) and from a Varian R12 spectrometer (for protons) operating at 200 MHz.

Methanol and ethanol were refluxed with sodium hydroxide pellets for 2 h and then distilled; they were dried when necessary by refluxing with magnesium and redistillation. *t*-Butanol was purified and dried by repeated chilling to crystallisation point and taking only the solid. Methanol-d_4 was used as supplied (Aldrich) and contained 99.5 atom % of deuterium.

4-Methoxycoumarin was prepared by heating 4-hydroxycoumarin with methanolic hydrogen chloride and purified by several crystallisations from small amounts of methanol.[16] 2,3-Dihydro-2-methyl-4*H*-furo [3,2-c][1] benzopyran-4-one was prepared and purified by published methods.[15] Coumarin and 2-hydroxyacetophenone were commercial samples that had adequate spectroscopic properties and were used without further purification.

Solutions for kinetic studies were renewed weekly and kept and used under nitrogen.

Methanolysis in Methanol-d_4. - 4-Methoxycoumarin (20 mg; 1 mol. prop.) was dissolved in methanol-d_4 (0.3 ml) and to it was added methanol-d_4 (0.2 ml) containing dissolved potassium (0.05 mol. prop) all in an nmr tube flushed with nitrogen. The proton spectrum showed a steady diminution of the methoxy signal over 5 h at ambient temperature, after which there was little further change. The aromatic protons appeared to be unaffected; there was very slight loss in the signal from the 3-proton. After a total of 8 h, the the reaction mixture was exposed to a stream of nitrogen to remove solvents leaving a solid that was washed with a little ice-cold methanol and dried in air to give 4-methoxy-d_3-coumarin, m.p. 125-126 °C (lit.[7] 125-126 °C), exhibiting in the mass spectrometer peaks at *m/e* 179 (M^+), 151 (M^+-CO), and 133 (M^+-CO-CD_3) where the undeuteriated compound exhibited peaks at 176, 148, and 133, respectively.

Methanolysis: Kinetics. Methanolic solutions of 4-methoxycoumarin (2.20×10^{-4} M) and sodium methoxide (6.0 M) were prepared, equilibrated at 50±0.2 °C, and mixed in equal volumes in a quartz cell(1 cm) flushed with nitrogen and thermostatted at the sametemperature. One uv scan was made immediately (Fig. 2, run i) and others at regular intervals until half the substrate had been consumed. For analysis absorbance values at 274 nm were used to give a first order plot. Various concentrations (M) of base gave the following values for $10^4 k$ (s^{-1}): 3,2.7; 2.5, 1.35; 2, 0.75; 1.5, 0.27; 1.0, 0.10). These values correspond to no simple order in methoxide ion but a plot of log k against log [NaOMe] was linear with slope 2.5.

Reactions in t-Butanol.-(i) *In dry t-butanol.* Potassium (1 g) was dissolved in dry t-butanol (25 ml) at the b.p. and under nitrogen, and 4-methoxycoumarin (1.0 g) was added. Heating was continued for 4 h during which time the solution became somewhat yellowish. The cooled solution was poured into a large volume of sodium

hydrogen carbonate solution saturated with carbon dioxide and with a layer of ether above. The ether was removed and the aqueous layer extracted several times with ether; the combined ether solutions were washed with water, dried ($MgSO_4$), and the solvents removed under reduced pressure. The residue crystallised from methanol to give 4-methoxycoumarin (0.9 g),

(ii) *With restricted water.* Potassium (1.2 g; 31 mmol.)was dissolved in refluxing *t*-butanol (25 ml) under nitrogen and then water (28 mmol.) was added followed by 4-methoxycoumarin (1 g; 5.7 mmol.). Refluxing was continued for 8 h but only a pale yellow colour was produced , followed by a thick white precipitate after about 2 h had elapsed. Thin layer chromatography showed that no methoxycoumarin remained. The mixture was filtered but no organic material could be recovered from the filtrate. the gummy solid dissolved easily in water and after acidification gave a precipitate identified spectroscopically with 4-hydroxycoumarin.

(iii) *Hydrolysis with acetylation.* 4-Methoxycoumarin (1 g) dissolved in *t*-butanol (100 ml) was treated with acetic anhydride (25 ml) and shaken with sodium carbonate (100 g) dissolved in the minimum water for 24 h. The upper layer was removed and the lower layer was extracted with dichloromethane; this extract was combined with the upper layer and all solvents removed under vacuum. The residue was identified in the usual way as 4-methoxycoumarin (0.45 g). The water layer was made acid to Congo Red and the product isolated into ether in the usual way; an oil resulted that deposited a solid when kept under vacuum over solid potassium hydroxide. This solid was recrystallised from trichloromethane-benzene giving 3-(*2-acetoxyphenyl*)-3-*methoxypropenoic acid* (**8**; OAc for OH) as clusters of tiny needles, m.p. 113 °C (decomp.) $\nu_{max.}$ (KBr) 3 000 (br, CO_2H), 1 1710 (ArOAc), and 1 685 cm^{-1} (br, CO_2H), δ 2.19 (3H, s, OAc), 3.74 (3H, s, OMe), 5.32 (1H, s, $=C\underline{H}CO_2H$), 7.13 (1H, d, *J* 7 Hz, ArH), 7.23 (1H, d, *J* 7 Hz, ArH), *ca.* 7.35 (2H, m, ArH), and 9.15 (1H, Br s, removed by D_2O, CO_2H)(Found: C, 61.2; H, 4.8. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%). Although the mass spectrum displayed a peak at *m/e* 236 as expected for the molecular ion,the peak was very small; a major peak at 192 corresponds to loss of CO_2 from the molecular ion. To confirm the molecular weight a small amount of the acid was briefly treated with diazomethane in ether and the residue after evaporation of volatile materials was again examined by mass spectrometry;a clear molecular ion was apparent at *m/e* 250 ($C_{13}H_{14}O_5$ requires *m/e* 250).

Aqueous Hydrolysis of 4-Methoxycoumarin; Identification of Hydrolysis Products: (i) 4-Methoxycoumarin (0.66 g) in aqueous methanol (50% v/v)(500 ml) was treated with 0.01 **M** sodium hydroxide also in aqueous methanol (200 ml) at 50 °C under nitrogen. When the uv spectra of samples showed no further change the solution was adjusted to pH 6 and a sample then showed the absorption peaks characteristic of 2-hydroxyacetophenone. The solution was extracted with dichloromethane (3 x 100 ml) and the extracts were combined and dried ($MgSO_4$) and concentrated under reduced pressure leaving an oil (0.47 g) that was divided into two parts. One part had the ir and pmr characteristics of 2-hydroxyacetophenone and showed no additional peaks; the other part was treated for 5 min. with diazomethane in ether and subjected to glc analysis on a column of Celite coated with Reoplex 100 and held at 200 °C with nitrogen as carrier gas; the sisngle peak observed corresponded to 2-hydroxyacetophenone and there was no trace of methyl salicylate which in separate experiments was shown to be readily detected by these conditions.

(ii) A hydrolysis as in (i) was conducted but with a buffer composed of sodium hydroxide (6.0 g) and sodium hydrogen carbonate (15.0 g) in water (100 ml) as the base. The results were identical; only 2-hydroxyacetophenone was produced.

(iii) 4-Methoxycoumarin (0.5 g) was dissolved in a mixture of ethanol (10 ml) and 3 **M**-aqueous sodium hydroxide (10 ml) and held at 50 °C until samples showed by their uv spectra that no coumarin remained (5-7 min.). The whole was then chilled in ice and quickly acidified to pH 4-5. Samples withdrawn at intervals showed the regeneration of the uv spectrum of the original coumarin; when this seemed to be complete, the whole solution was extracted with dichloromethane and the product isolated in the usual manner as a somewhat oily solid shown by the ^1H nmr spectrum to consist mainly of 4-methoxycoumarin with some 2-hydroxyacetophenone. Recrystallisation of the solid from a little methanol furnished this coumarin identical with an authentic specimen.

(iv) 4-Methoxycoumarin (90 mg) was finely powdered and shaken with 0.3 **M**-aqueous sodium hydroxide (5 ml) until no more appeared to dissolve (2 days). The solution was filtered and its ^{13}C-nmr spectrum determined using a 5 mm tube and an insert containing acetonitrile-d_3 to provide lock signal and external reference. The results (Table 1) indicate the presence of a methoxycoumarinic acid (**8**).

The solution was then diluted ten times and held at 55°C for 2 h. The solution was now yellow, and to it was added a drop of D_2O to act as internal reference and provide a lock signal and the ^{13}C spectrum determined using a 10 mm tube. The results (Table 1) indicated the presence of the ketoacid (**10**).

Hydrolysis in Buffer: Kinetics. - The buffer used consisted of sodium hydroxide (0.03 **M**) and sodium hydrogen carbonate (0.04 **M**) solutions mixed in equal amounts according to the method of Garrett *et al.*[5b] A solution of coumarin (7.5×10^{-5} **M**) in aqueous ethanol (50% v/v) was mixed with an equal volume of buffer at 31±2 °C and maintained at that temperature until the uv spectrum showed no further change, scans being made every 6 min. The rate constant was then determined by monitoring a similar hydrolysis at 280 nm for 150 min., after which the reaction was considered to be complete. A least squares analysis based on 18 data points gave a

first order rate constant listed in Table 2. The rate constant for coumarin and also that for 4-methoxycoumarin were determined at about 75 °C. Again good isosbestic points were obtained by regular uv scanning; for 4-methoxycoumarin these were at 256 and 320 nm. The rate constants so derived are listed in Table 2.

Kinetics in Aqueous Sodium Hydroxide at 50 °C. - A stock solution of 4-methoxycoumarin was prepared, 2.20 M in substrate. Solutions of sodium hydroxide in freshly re-distilled water were prepared, stored under nitrogen, and made available in a range of concentrations from 0.2 to 0.02 M. All solutions were equilibrated at 50 ± 0.2 °C before use and all runs were made at the same temperature.

For each run, equal volumes of substrate and sodium hydroxide solutions were mixed , placed in a quartz cell (usually 1 cm) flushed with nitrogen and stoppered. Uv scans were made at requisite intervals for all reactions; for rate studies the reactions were also monitored at selective wavelengths, usually 274 nm for the first stage (opening of the lactonering). Often infinity readings could not be obtained because of the incursion of the second stagec(collapse to ketone) and were therefore determined under similar conditions but using alkali concentrations at or above 1.0 M. Infinity readings were made for the second stage of hydrolysis were usually made 24 h after initiation; longer periods were rendered inadvisable because of further, unrelated changes that might be either slight oxidation of aldol condensation. Typical rate constants are listed in Table 2.

Hydrolysis of 2,3-*Dihydro*-2-*methyl*-4H-*furo* 3,2-c 1 *benzopyran*-4-*one*. - (i) *Identification of Product*. Prepared according to the published method,[15] the title compound had δ ($CDCl_3$) 1.58 (3H, d, *J* 6.5 Hz; Me), 2.83 (1H, dd, *J* 7,15 Hz, methylenic H_A), 3.40 (1H, dd, *J* 9,15 Hz; methylenic H_B), 5.20 (1H, m, C<u>H</u>Me), and *ca.* 7.5 (4H, m, ArH). A sample (0.5 g) was kept at 80 °C with 5% aqueous sodium hydroxide (10 ml) for 6 h. Acidification, ether extraction, and chromatography furnished 4-*hydroxy*-1-(2-*hydroxyphenyl*)*pentan*-1-*one* (**13**) as a straw oil (0.41 g), λ (EtOH) 225 and 350 nm (log ε 3.98 and 3.54), $\nu_{max.}$ (Nujol) 3 400br (OH), 1 640 (H-bonded C=O), 1 490, 1 160, and 760 cm^{-1}, δ ($CDCl_3$) 1.25 (3H, d, *J* 6.5 Hz; Me), 1.87 (2H, q, *J* 6.5 Hz; $CH_2C\underline{H}_2CHOH$), 3.12 (2H, t, *J* 6.5 Hz; $O{:}C\underline{CH}_2CH_2$), 3.8 (1H, dt, *J* 6.5 Hz; C<u>H</u>OH), *ca.* 7.5 (4H, m, ArH), and 11.16 (2H, s, bonded OH). AS is usual with alcohols, the mass spectrum (electron impact) did not display a clear molecular ion but only the fragment ion after loss of H_2O (Found: M^+, *m/e* 176. $C_{11}H_{14}O_3 - H_2O$ requires *m/e* 176).

(ii) *Kinetics*. - Solutions of the title compound (7.5×10^{-5} M) containing sodium hydroxide (0.30 M) in aqueous methanol (50% v/v) were held at 25 °C under nitrogen and the reaction monitored by the uv spectrum (Fig. 8). The final solution had the absorption characteristics of the phenol (**13**) in aqueous alkali of the same concentration, and one good isosbestic point was noted at 328 nm with another cross-over point near 262 nm that varied with time. The absorbance at 262 nm when plotted against time reached a maximum after about 1 h and then slowly fell during 300 h. A plot of ln (A_{262}-A_{328}) against time after the initial 2 h gave a straight line yielding a value for k_2, the rate constant for ketone formation. The value for k_1 (corresponding to the opening of the lactone ring) was then obtained from the relation $t_{max.} = \ln(k_1/k_2)(k_1 - k_2)^{-1}$. The results are given in Table 2.

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