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Synthesis and Reactivity of Laquinimod, a Quinoline-3-carboxamide: Intramolecular Transfer of the Enol Proton to a Nitrogen Atom as a Plausible Mechanism for Ketene Formation

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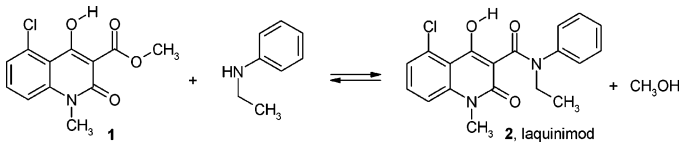
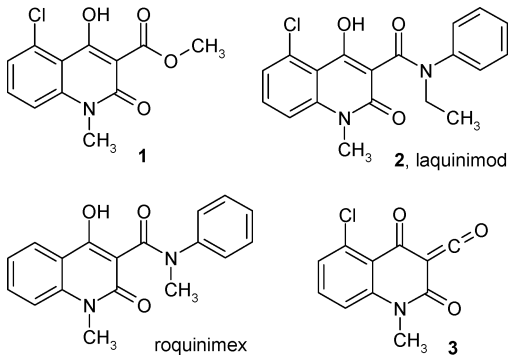


5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (laquinimod, **2**) is an oral drug in clinical trials for the treatment of multiple sclerosis. The final step in the synthesis of **2** is a high-yielding aminolysis reaction of ester **1** with *N*-ethylaniline. An equilibrium exists between **1** and **2**, and removal of formed methanol during the reaction is a prerequisite for obtaining high yields of **2** from **1**. The reactivity of **1** and **2** is explained by a mechanistic model that involves a transfer of the enol proton to the exocyclic carbonyl substituent with concomitant formation of ketene **3**. This proton transfer is especially facilitated for **2** because the intramolecular hydrogen bond to the carbonyl oxygen is weakened due to steric interactions. Both **1** and **2** undergo solvolosis reactions that obey first-order reaction kinetics, further supporting the theory that these two molecules are able to decompose unimolecularly into ketene **3**. The solvent-dependent spectroscopic features of **2** indicate that the molecule mainly resides in two conformations. One conformation is favored in nonpolar solvents and is likely the result of intramolecular hydrogen bonding. The other conformation is favored in polar solvents and probably exhibits less intramolecular hydrogen bonding.

Introduction

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS). The etiology of the disease is unknown, but the pathophysiological mechanism is similar to other autoimmune diseases where there is an infiltration of mononuclear cells into the target tissue. 5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (laquinimod, **2**, Scheme 1) was developed by Active Biotech Research AB with roquinimex as a lead compound[1,2] and has successfully undergone a clinical phase II trial as MS medication.[3] The potency of laquinimod is very high, and proof of concept was established using doses as low as 0.3 mg/person/day. The exact mechanism of action by which laquinimod exerts its effect on MS is still under investigation. The large-scale production of laquinimod utilizes the synthetic route outlined in Scheme 2. However, in this paper we will not discuss the

SCHEME 1



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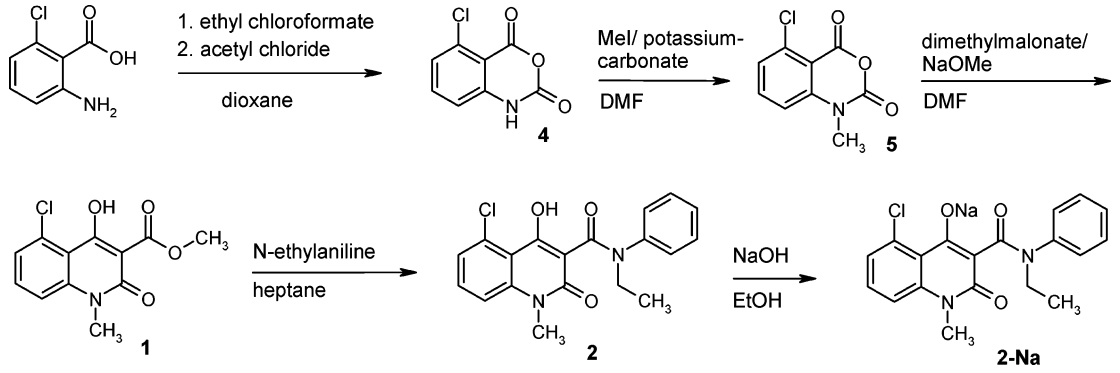
SCHEME 2. Synthetic Route for Large-Scale Production of the Sodium Salt of 2



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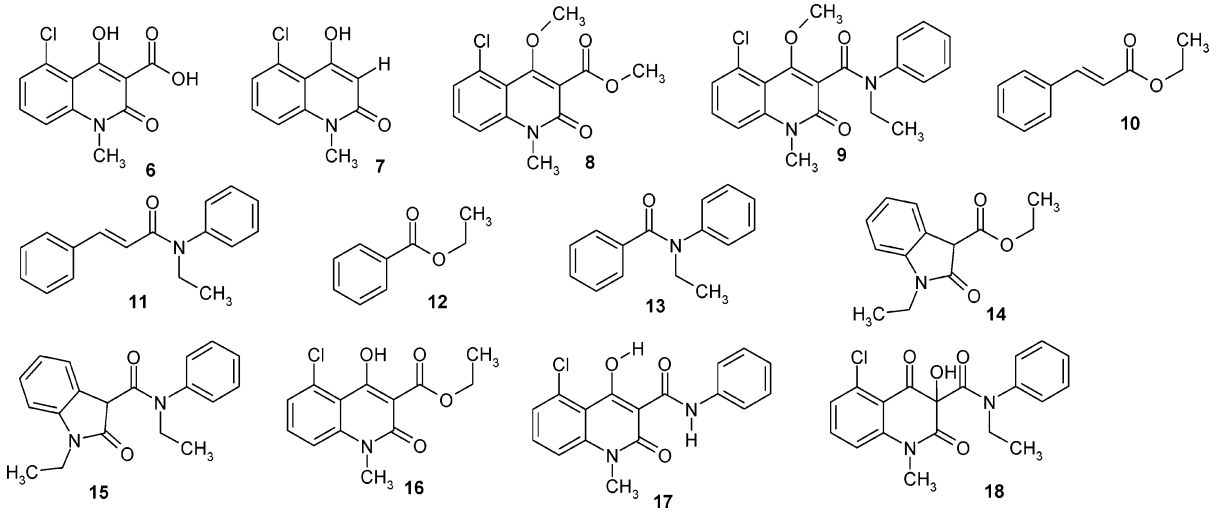

full details of large-scale synthesis such as process development and critical parameters. Instead, we will focus on the final pivotal step where ester **1** reacts with *N*-ethylaniline in heptane to afford compound **2** in almost quantitative yield. We will present evidence that this reaction occurs via the ketene intermediate **3**, rather than via a tetrahedral intermediate. Conformational analysis and solvent dependent spectroscopic properties of **2** are also discussed.

Results and Discussion

A number of synthetic routes were evaluated for the large-scale synthesis of laquinimod **2**.[2,4] The route depicted in Scheme 2 was chosen because it was reliable, easy to perform, and gave a good overall yield of **2** without the need of complicated purification methods. The nonhygroscopic sodium salt of **2** (**2-Na**) was chosen as the final drug form due to its excellent stability during storage and the fact that some minor impurities in **2** were removed in the salt-forming step. More details of the large-scale synthesis will be published later. The laboratory-scale synthesis of **2-Na** essentially follows the same route and is described in the Experimental Section. The first three steps of the synthetic route are straightforward. However, the final aminolysis step in which amide **2** is formed in almost quantitative yield from ester **1** deserves further comments. In general, amides are considered to be more stable than their corresponding esters, and a bimolecular reaction of an ester with an amine appears to be a potentially useful method for the synthesis of amides. However, relatively few examples of this kind of amide synthesis are reported in the literature, in comparison to the more common method of reacting an acyl chloride with amines or the coupling of carboxylic acids with amines using coupling reagents such as DCC. The reason for this is probably that in the bimolecular reaction of an ester with an amine, high temperature is needed to form the transition state preceding the tetrahedral intermediate. In many cases, the amide is isolated in low yield because the high reaction temperature causes unwanted side reactions. Aliphatic amines are often more reactive than aromatic amines, and very few examples of secondary aromatic amines reacting with esters are reported in the literature. During our work with the synthesis of laquinimod **2**, we realized that this amide is less stable than the corresponding ester **1** and that equilibrium exists between **1** and **2** in the aminolysis reaction. The equilibrium is probably maintained via a stabilized ketene intermediate **3** rather than via the tetrahedral intermediate.

Laboratory Trials. Synthesis of 2 Using Toluene as Solvent. Compound **2** was isolated in 90% yield when a mixture of **1** and 2.0 equiv of *N*-ethylaniline in toluene was heated to the boiling point, and most of the volatiles were distilled off during approximately 6 h. However, the purity profile of the resulting **2** was not considered to be satisfactory, as substantial amounts of unreacted ester **1** and quinoline **7** (Scheme 3) were found in the isolated crude product (see the Experimental Section and Table 1). An interesting observation is that ester **1** and amide

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TABLE 1. Yield and Purity Profile of the Isolated Product 2

			impurities in **2** (w/w, %)[a]	
solvent	yield (%)	content[a] (%)	**1**	**7**
toluene	90	94.0	4.55	0.54
heptane	98	99.4	0.02	0.03

[a] Determined by HPLC.

2 rapidly reached equilibrium at relatively low temperatures. When **1** reacted at 140 °C with 1.75 equiv of *N*-ethylaniline in sealed tubes (no volatiles can leave the reaction vessel), **2** was formed in 21% and 22% molar yield after 35 min and after 70 min, respectively (79% and 78% of **1** remained in the mixtures, see the Experimental Section for more details). The fact that the yields were almost identical indicates that equilibrium was reached. In another experiment where **2** was heated for 1 or 3 h at 100 °C with 3.0 equiv of methanol in sealed tubes, rapid methanolysis occurred and gave ester **1** in 98% molar yield in both cases (2% of **2** remained in the mixtures). Together, these experiments demonstrate the high reactivity of **1** and **2** and, unexpectedly, that ester **1** is favored in the equilibrium between **1** and **2**. They also indicate that a prerequisite for obtaining a high yield of **2** from **1** is that methanol is efficiently removed from the reaction mixture by distillation of the volatiles.

Laboratory Trials. Synthesis of 2 Using *n*-Heptane as Solvent. Apart from the finding that it was necessary to efficiently remove the formed methanol, another factor that dramatically increased the yield and purity of **2** was found. When using *n*-heptane (bp 98 °C) as solvent instead of toluene, **2** was isolated in 98% yield as white to off-white crystals with no single impurity exceeding 0.1% (Table 1). Only **1** and **7** were found in low amounts in the isolated product. This improvement in yield and purity was achieved by simply using a nontraditional solvent for synthesis such as *n*-heptane and resulted in a process patent covering the synthesis of compound **2** as well as similar structures.[4] Both reaction rate and yield are higher in heptane than in toluene, despite the lower boiling point of heptane, and this can probably be attributed to the low solubility of **2** in heptane at the reaction temperature. The solubility of **1** and **2** in heptane at room temperature was determined by means of HPLC to be 0.15 and 0.03 mg/mL respectively. The solubility at higher temperatures was not determined, but still it is expected that the solubility of **2** is lower than that of **1**. In heptane, precipitation of **2** occurs as small white needles during the reaction. In contrast, when using toluene as solvent, both **1** and **2** are fully soluble at the reaction temperature. Thus, the low solubility of **2** in heptane probably accounts for the superior yield, reaction rate, and purity in comparison to when toluene was used as a solvent. Our method was very promising and was later successfully implemented in the large-scale production of **2**. The byproduct **7** is formed in a reaction between **2** and small amounts of water present in the reaction mixture. Water may be present from the beginning of the synthesis (in solvents, etc.) or may enter the reaction vessel during the reaction. In fact, quinoline **7** was isolated in quantitative yield when **2** was heated at 140 °C with 2.0 equiv of water in toluene for 4 h (see the Experimental Section). The same reaction was also studied at 100 °C for 1 h and resulted in an almost quantitative yield of carboxylic acid **6** (contaminated with a small amount of **7**). Thus, the primary hydrolysis product of **2** is carboxylic acid **6**, which decarboxylates into **7** at elevated temperatures.

TABLE 2. Reaction of Esters with *N*-Ethylaniline[a]

ester	product	yield (%)
1	**2**	90
14	**15**	67
10	**11**	0
12	**13**	0
8	**9**	0

[a] The esters and 2.0 equiv of *N*-ethylaniline were heated in toluene, and most of the volatiles were distilled off during 6 h.

TABLE 3. Stability of Esters and Amides under Neutral or Basic Conditions

compd	conditions[a]	product	% conversion to product[b]
16	MeOH/100 °C/6 min	**1**	24
16	0.5 M NaOMe/MeOH/ 100 °C/6 min	**1**	9
16	1 M NaOH/rt/1 h	no reaction	0
16	1 M NaOH/100 °C/1 h	**7**	40
10	MeOH/100 °C/6 min	no reaction	0
10	0.5 M NaOMe/MeOH/ 100 °C/2 min	methyl ester	100
2	MeOH/100 °C/6 min	**1**	100
2	0.5 M NaOMe/MeOH/100 °C/6 min	no reaction	0
2	1 M NaOH/100 °C/1 h	no reaction	0
13	MeOH/100 °C/6 min	no reaction	0
17	MeOH/140 °C/10 min	no reaction	0

[a] Reactions in methanol were heated in sealed tubes in a microwave oven. [b] Analysis was performed by ^{1}H NMR. The remaining part was starting material.

Further Examination of the Reaction Characteristics of Esters and Amides. A study was undertaken to investigate how various esters (Scheme 3) behave in their reactions with *N*-ethylaniline (Table 2). The esters and 2.0 equiv of *N*-ethylaniline were heated in toluene, and most of the volatiles were distilled off at atmospheric pressure during 6 h. Esters **1** and **14**[5] gave their corresponding *N*-ethylanilides **2** and **15** in good yields. However, ethyl *trans*-cinnamate **10**, ethyl benzoate **12,** and the 4-*O*-methyl analogue **8** yielded no trace of their corresponding products **11**, **13**, and **9**. The activation energies for formation of **11**, **13**, and **9** are apparently much higher than can be provided by the temperature in toluene. Even when the reaction temperature was increased by using xylene (bp 138−142 °C) instead of toluene as solvent, the products **11**, **13**, and **9** could not be detected in their respective reaction mixtures. These experiments indicate that β-ketoesters such as **1** and **14**, which have enolizable protons in their structures, are reactive and that this structural feature is important for the reaction with the aniline. Therefore, the importance of pH in the methanolysis of some esters and amides under neutral or basic conditions were studied (Table 3). Thus, heating ethyl ester **16** (Scheme 3) at 100 °C in a microwave reactor for 6 min in MeOH led to formation of methyl ester **1** in 24% yield. The same experiment using 0.5 M NaOMe in MeOH yielded only 9% of **1**. The opposite result was obtained for ethyl *trans*-cinnamate **10**, which was inert in methanol at 100 °C but was completely transformed to the corresponding methyl ester under basic conditions. Ester **16** is soluble and stable in 1 M NaOH when stirred for 1 h at room temperature, in contrast to most other soluble carboxylic esters, which are hydrolyzed under such conditions. An increase of the temperature to 100 °C for 1 h gave 40% yield of compound **7**. Amide **2** is easily solvolyzed into **1** in methanol in quantitative yield but is inert at 100 °C in 0.5 M NaOMe in MeOH or when heated at 100 °C in 1 M NaOH for 1 h. The

amide **13** was not solvolyzed to methyl benzoate when heated in MeOH at 100 °C. These experiments further underline that the enol proton, found in compounds **16** and **2**, is fundamental for the reaction with methanol and that amide **2** is more reactive than ester **16**. Apparently, the exocyclic amide bond in **2** is weak and reactive when the enol proton is present in the molecule whereas it is very stable when the molecule is in its enolate form. Compound **2** is rather acidic ($pK_a = 4.2$), and the stable enolate form dominates under physiological conditions. In vivo pharmacokinetic studies on compound **2** have not revealed any reactions related to those discussed here, and **2** is metabolized mainly by aryl hydroxylation and oxidative N-dealkylation[6] and the half-life elimination in man is 3 days. Compound **17** is similar in structure to **2** but is extremely stable when heated in MeOH at 140 °C and shows no sign of the methanolysis product or any other byproducts. Unlike compound **2**, which is readily soluble in water at pH 7.5 (100 mg/mL), compound **17** is virtually insoluble (<0.01 mg/mL). A plausible explanation of the very different chemical behavior of **2** and **17** is discussed later in the section about the possible reaction mechanism for the equilibrium between **1** and **2**.

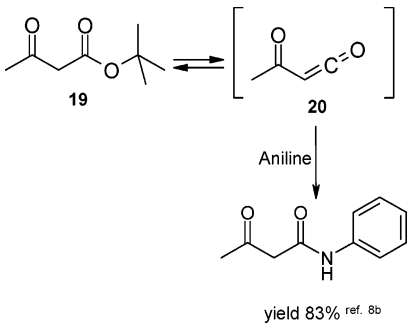
Kinetic Study of the Solvolysis of 1 and 2. The stability of the amide **2** was studied in various solvents, and it was found that the polarity of the solvent had a large impact on the stability. The ratios of the relative degradation rates in water (0.02 M HCl), DMSO, ethanol, and dichloromethane were approximately 1:5:10:40 (see the Experimental Section for details). Thus, the reactivity of **2** increases when solvent polarity decreases. Comparison of these results with the solvent dependence of UV and NMR spectra of amide **2** (discussed below) led to the assumption that compound **2** is present in two different forms in equilibrium. One form is favored in nonpolar solvents and is highly reactive, while the other form, which is much less reactive, is favored in polar solvents. Even though we expected that the reactivity of ester **1** and amide **2** would be caused by ketene formation rather than by the more common bimolecular reaction through tetrahedral intermediates, it was necessary to provide more evidence in order to exclude the latter type. Therefore, we decided to examine whether the nucleophile was involved in the rate-determining step or not. One difficulty in studying the effect of the concentration of the nucleophile was to distinguish between the direct dependence on the rate of formation and the impact of the solvent polarity. This was overcome by the using a solvent mixture (20% DMSO in acetonitrile) that was "buffered" with respect to polarity by solvents that do not enter the reaction. Kinetic experiments with amide **2** were performed using varying amounts of *n*-propanol and other alcohols in this mixed medium. In all cases, the consumption of the reactant followed first-order kinetics, obviously in favor of a reaction involving an unimolecular rate-determining step. In addition to the *n*-propyl ester, the corresponding carboxylic acid **6** was also formed but was decarboxylated to **7** before analysis. This byproduct is formed in a side-reaction with traces of moisture present in the reaction medium. In all experiments, the sum of the expected *n*-propyl ester and compound **7** corresponded well to the consumed amount of the reactant. The total rate was virtually independent of the concentration and type of alcohol used (Table 4), further indicating that the alcohol does not take part in an initial rate-determining step. In the same series, experiments were also made with solvolysis of ester **1** with two different concentrations of *n*-propanol. Although the reaction was much slower than for amide **2**, the same products were found, and reaction rate was of the first order with respect to consumption of the reactant and this rate was not dependent on the concentration of *n*-propanol. Finally, the quotients between the two final products (*n*-propyl ester and **7**) were nearly the same for both reactions (Table 4). This strongly indicates the existence of a common reactive intermediate in the reactions of **1** and **2** respectively. This intermediate could very well be the ketene **3**.

TABLE 4. Alcoholysis of Amide 2 and Trans-Esterification of Ester 1

reactant/alcohol	rate constant (h^{-1})	ester in % of products[a]
2/1.6% *n*-PrOH	0.232	91
2/0.32% *n*-PrOH	0.227	71
2/0.064% *n*-PrOH	0.226	32
2/0.32% MeOH	0.219	82
2/0.32% EtOH	0.221	66
2/0.32% *i*-PrOH	0.218	60
1/1.6% *n*-PrOH	0.00343	91
1/0.064% *n*-PrOH	0.00303	25

[a] Apart from ester, **7** was also formed from reaction with water. The found sum of **7** and ester corresponded to the consumed amount of the reactant.

SCHEME 4. Acetoacetylation of Aniline with *tert*-Butyl Acetoacetate



Possible Reaction Mechanism for the Equilibrium between 1 and 2. As previously discussed, the β-ketoesters **1** and **14** were found to be the only esters in this study that reacted with *N*-ethylaniline to give their corresponding amides in high yields (Table 2). A literature search on the subject of reactions between carboxylic esters and aromatic amines provides further support for this finding. Most references describe reactions of β-ketoesters such as malonic esters or methyl or *tert*-butyl acetoacetate with aromatic amines. A related reaction of phenyl salicylate with amines is known as the "Salol reaction".[7] Acetoacetylation of nucleophiles (alcohols or amines) with methyl or *tert*-butyl acetoacetate **19** (Scheme 4) was found to obey first-order reaction kinetics, and mechanistic studies have shown that the reaction probably proceeds via acetylketene **20** instead of via a tetrahedral intermediate.[8] Here, strong evidence for the ketene mechanism also comes from the fact that *tert*-butyl acetoacetate **19** was 15−20-fold more reactive than methyl acetoacetate. A tetrahedral intermediate is unlikely because the

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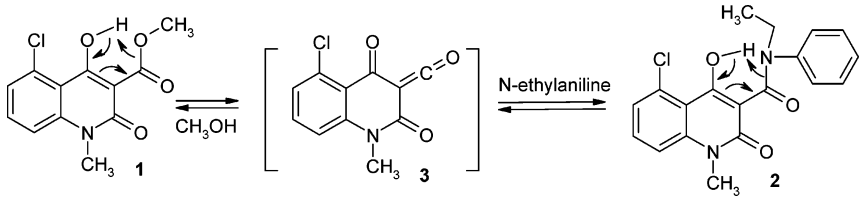
SCHEME 5. Ketene 3 Is the Common Intermediate in the Equilibrium between 1 and 2



sterically more congested *tert*-butyl ester would be more reluctant to form such intermediates. Ketenes are considered to gain stabilization from π-withdrawing groups such as carbonyl substituents.[9] The presence of one β-keto group in *tert*-butyl or methyl acetoacetate obviously makes the reaction via acetylketene more favorable than the reaction via a tetrahedral intermediate.

As previously described, ester **1** and amide **2** react with *n*-propanol in such a manner that they obey first-order kinetics. Ketene **3** is a plausible intermediate in these reactions and is probably the common intermediate in the equilibrium between **1** and **2** (Scheme 5). According to the proposed mechanism, both ester **1** and amide **2** are capable of transferring the enol proton to the carbonyl substituent and to form ketene **3**. The hypothetical transition structures of these transformations, as shown in Scheme 5, are characterized by planarity between the exocyclic carbonyl group and the quinoline ring. Similar planar transition structures were proposed for the pseudopericyclic reactions between acetylketene and alcohols or amines, respectively.[10] However, for compounds **1** and **2**, electrostatic repulsion between the carbonyl groups is expected, and therefore, the existence of nonplanar transition structures cannot be completely ruled out. The transient ketene **3**, although stabilized by two carbonyl groups, is very reactive and reacts rapidly with either methanol or with *N*-ethylaniline. We made several attempts to isolate ketene **3** in our laboratory; however, none were successful. The surprising fact that the equilibrium favors ester **1**, as seen when the reactions were run in sealed tubes (see above), is understandable if the lowest energy conformations of **1** and **2** are considered. Theoretical calculations on **2** (see the Computational Chemistry section), show a small difference in energy between the amide *E*- and *Z*-isomers (approximately 4 kcal/mol in favor of the *E*-form). It remains uncertain whether only one or both of these two isomers are involved in the reaction mechanism. According to the calculations, there is steric repulsion in compound **2** between the *N*-ethyl group (*Z*-isomer), or the phenyl group (*E*-isomer), and the carbonyl group in (2)-position. This results in a conformation where the exocyclic carbonyl group to some extent is forced out from the ring plane. The repulsion leads to weakening of the intramolecular hydrogen bond between the enol proton and the carbonyl oxygen. In contrast, compound **1** does not suffer from a similar steric repulsion and has a stronger intramolecular hydrogen bond to the carbonyl oxygen. Thus, formation of the transition structure is easier for **2** than for **1**, and this accounts for the higher reactivity of **2**. Further evidence for the proposed mechanism is provided by the reactivity of compound **17**. In contrast to **2**, compound **17** is extremely stable, e.g., even at 140 °C in MeOH it shows no signs of methanolysis products (Table 3). Compound **17** adopts a planar structure because there are no steric constraints to prevent it, and conjugation as well as two strong intramolecular hydrogen bonds result in a structure with minimal conformational flexibility (see the Computational Chemistry section). The lack of conformational flexibility in **17** precludes decomposition into **3** via the mechanism proposed for compounds **1** and **2** and accounts for its high stability. Compound **17** is readily formed in high yield from **2** by reaction with aniline at 100 °C for 1 h. Thus, the reactivity of **1** and **2** is due to these two molecules ability to transfer the enol proton to the exocyclic carbonyl substituent and to form ketene **3**. Especially for compound **2**, steric effects make this proton-transfer easier.

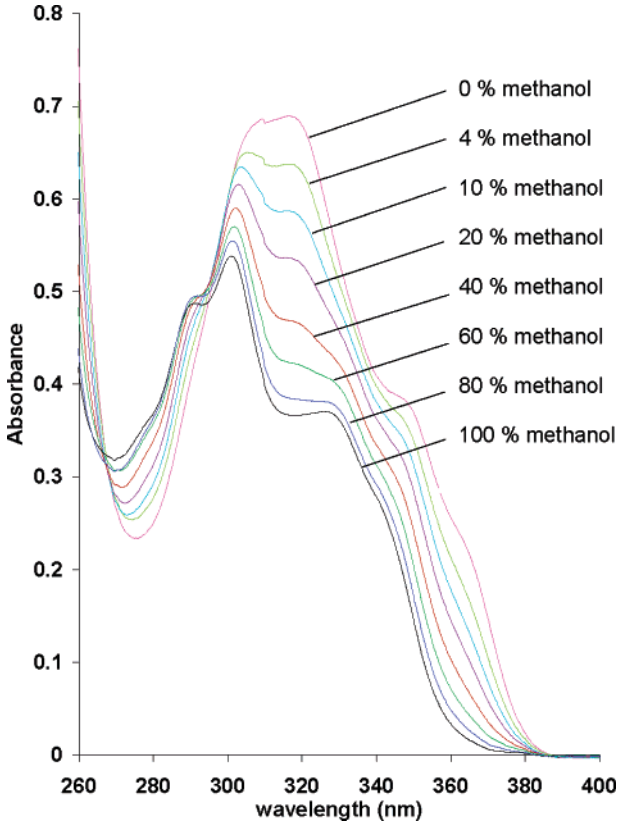


FIGURE 1. UV spectra of **2** in mixtures of methanol and dichloromethane.

Solvent-Dependent Conformation of 2. UV spectra of amide **2** were recorded in mixtures of dichloromethane and methanol (Figure 1). These spectra indicate that two different types of conformation are favored, one in polar and one in nonpolar solvents. The pattern of the overlaid spectra with converging isosbestic points[11] indicates that **2** is present in two main forms and that their relative distribution is governed by the solvent composition. It was not possible to obtain the spectra of the pure forms, and thus it was not possible to determine the ratio between the two forms in the various solvent compositions.

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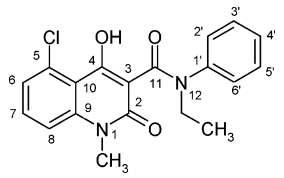
TABLE 5. ^{13}C NMR Signals of 2 Obtained in Mixtures of D_6-DMSO and $CDCl_3$



chemical ^{13}C shifts % DMSO-d_6 (v/v) in mixture with $CDCl_3$					
0	10	20	50	100	assignment
168.8	167.7	166.6	164.6	163.6	(11)
165.7	163.3	161.2	157.5	156.0	(4)
157.9	158.3	158.7	159.1	159.1	(2)
142.7	142.4	142.1	141.6	141.3	(9)
142.1	141.7	141.5	141.3	141.4	(1′)
132.8	132.3	132.1	131.5	131.0	(5)
131.7	131.5	131.2	130.8	130.8	(7)
128.5	128.5	128.5	128.4	128.6	(3′, 5′)
126.9	127.1	127.2	127.3	127.7	(4′)
126.7	126.8	126.9	127.0	127.0	(2′, 6′)
125.4	125.4	125.3	125.2	125.3	(6)
113.3	113.4	113.4	113.6	114.2	(8)
112.8	112.7	112.8	113.0	112.8	(10)
105.1	106.7	108.2	110.6	111.8	(3)
45.7	45.2	44.6	43.5	42.9	(12)
29.8	29.8	29.8	29.6	29.6	(1)
12.9	12.9	12.8	12.7	12.7	(12)

However, a rough estimate based on the spectra indicates that the methanol solution contains less than 7% of the dichloromethane-favored form, estimated at 366 nm. In dichloromethane, this form probably dominates, although the spectra indicate a content of only 32%, estimated at 280 nm.

Large solvent-dependent ^{13}C NMR spectra variations were also observed. The chemical shifts of amide **2** in $CDCl_3$ were studied after addition of various amounts of DMSO-d_6 (Table 5). In Figure 2, the shift changes for six of the most variable carbon shifts are plotted versus the shift changes of the (3)-carbon. In this way, a correlation between the signals and the ratios of the two forms could be established. A good linear relationship was demonstrated (Figure 2), and this agrees well with the presence of two distinct forms in rapid equilibrium. Several possible explanations of the occurrence of the two forms of **2** may be considered. Tautomers with the enol OH group on carbons (2), (4), or (11) and the corresponding keto tautomer are possible. Of these tautomers, the one with the OH on the (4)-carbon seems to be the most likely. A keto group in this position would have required a chemical shift of at least 185 ppm for the (4)-carbon, as seen for compound **18**. In contrast, the chemical shift for the (4)-carbon in **2** is about 166 ppm in $CDCl_3$ and about 156 ppm in DMSO-d_6. Despite that the possibility of tautomers cannot be ruled out completely, this explanation seems unlikely. Another way to explain the observed two forms would be to suppose that they correspond to the *E*- and *Z*-isomers of the exocyclic amide (see the Computational Chemistry section). This would require that the proportion between the *E*- and *Z*-isomers was very dependent on the solvent composition. However, the observed difference in ^{13}C shift between the forms is much larger (at least 10 ppm for the (4)-carbon) than that between the well separated shifts for the *E*- and *Z*-isomers obtained for the anion of **2** in alkaline D_2O solution (only 0.5 ppm for the (4)-carbon, see the Supporting Information). This excludes dependence on the *E*- and *Z*-isomers as an explanation.

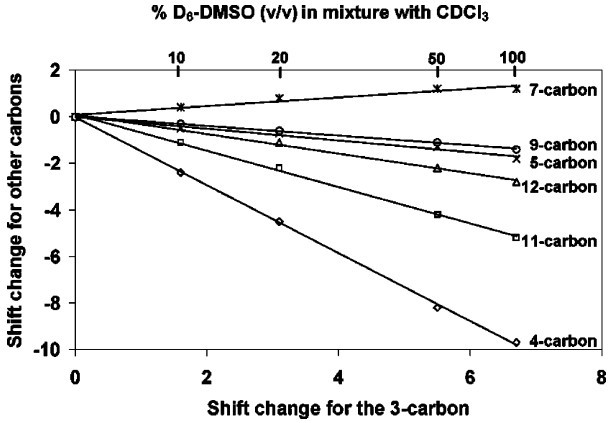


FIGURE 2. Changes of chemical shift in **2** on addition of DMSO-d_6 to $CDCl_3$ solution. The changes of six carbon shifts plotted versus the shift changes of the (3)-carbon.

A more natural explanation would be that the (4)-OH proton in nonpolar solvents is intramolecularly hydrogen bonded to the amide carbonyl group. In this way, the amide carbonyl group becomes more aligned with the quinoline ring (form A). Polar solvents, however, may solvate the 4-OH group by hydrogen bonding thus precluding intramolecular hydrogen bonding. Therefore, the amide carbonyl group forms a greater angle with the quinoline ring (form B). This conformational effect of inhibiting the intramolecular hydrogen bond is further substantiated by molecular calculations described later in the computational chemistry section. Most likely, forms A and B also exist in *E*- and *Z*-isomers. However, this does not result in visibly split signals in the NMR spectra. This is probably due to more rapid *E*/*Z* exchange compared to the corresponding exchange for the anion of **2**. This theory is borne out by the following: (1) In the UV spectrum of **2**, form A has absorption maxima at longer wavelengths than form B. This is to be expected when the amide carbonyl group is closer to the same plane as the conjugating quinoline ring. (2) In NMR, the ^{13}C-shift changes for **2** in solutions of varying polarity are large for the carbon atoms close to or directly involved in the hydrogen bonding. (3) The results of the conformation analysis made by computer calculations are in accordance with the theory.

As previously discussed (in the section Kinetic Study of the Solvolysis of **1** and **2**), compound **2** is more reactive in nonpolar solvents than in polar solvents. This effect can be explained when considering the conformational properties of **2** and the proposed mechanism for ketene formation (Scheme 5). In nonpolar solvents, intramolecular hydrogen bonds may develop between the enol proton and the carbonyl oxygen or the nitrogen atom, respectively. The latter type of binding results in ketene formation. In polar solvents, however, hydrogen bonds to the solvent dominate and this suppress ketene formation and leads to a lower reactivity.

Computational Chemistry. Ab initio quantum chemical calculations using Spartan 04 (W) were performed in order to gain information about tautomers and conformational energies for compounds **1**, **2**, and **17**.[12] For each tautomer, a conformational search was made with the semiempirical method PM3. Up to a dozen conformations for each tautomer were then chosen as starting points for further ab initio RHF calculations. After final geometry optimization at the RHF/6-31G** level, single-point MP2 calculations using the same basis set was made. Gas-

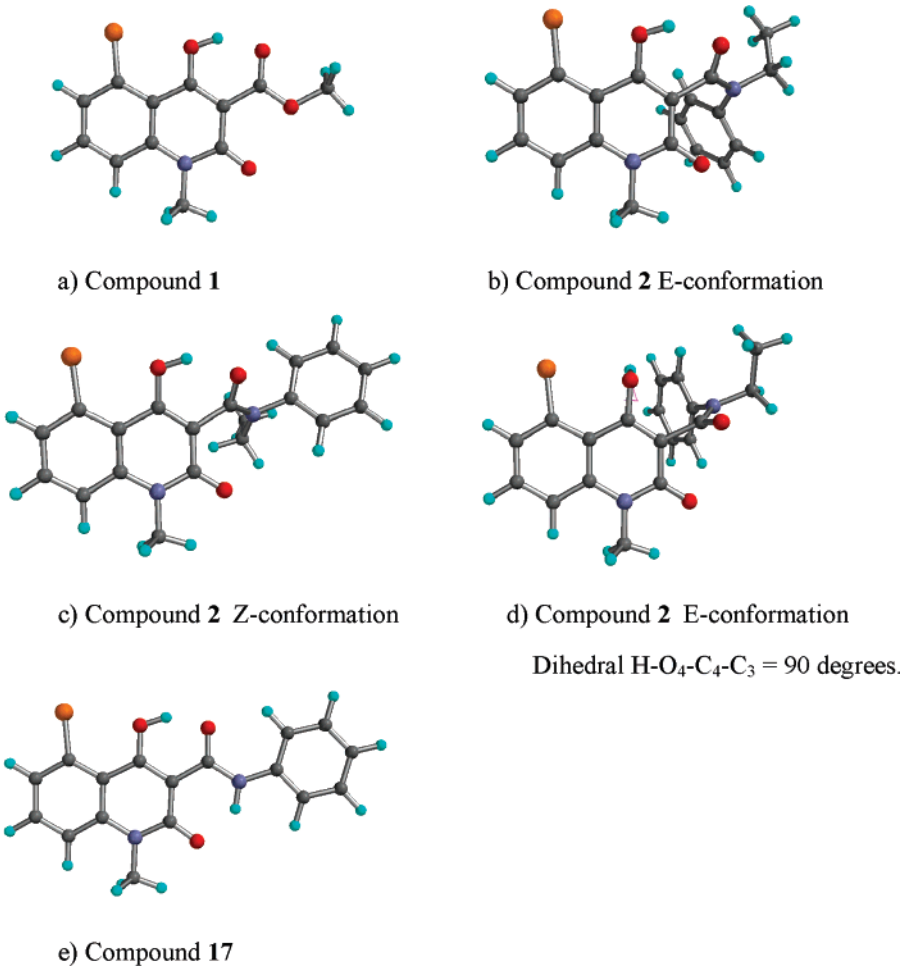


FIGURE 3. Geometry-optimized conformations with lowest energy of compound **1**, **2**, and **17**. For compound **2**, the conformations are shown for both the *E*- and *Z*-forms. Also for compound **2**, the conformation after a geometry optimization starting from the *E*-form with the dihedral H−O_4−C_4−C_3 constrained to 90° is shown.

phase calculations are assumed to be relevant for the molecules in the nonpolar solvents described in this work, and reported differences in energy refer to gas-phase energies. The geometry-optimized structure of the most stable tautomer of compound **1** adopts a planar conformation with an intramolecular hydrogen-bond between the enol group in the (4)-position and the ester carbonyl group in the (3)-position (Figure 3a). Other tautomers were at least 5 kcal/mol higher in energy.

We point out that there exist numerous energy minima for compound **2**. Therefore, the conformational search has probably not succeeded in localizing the global energy minimum conformation for the different tautomers. However, this lack in conformational search on all the tautomers is judged to be of minor importance in comparison with the obtained differences in energy between the tautomers. The conformational analysis of the most populated tautomer of **2** reveals two distinctly different low energy conformations with *E*- and *Z*-stereochemistry, respectively. The *E*-isomer is approximately 4 kcal/mol lower in energy than the *Z*-isomer (Figure 3b,c). The most populated tautomer of **2** also possesses an intramolecular hydrogen bonding between the enol proton and the amide carbonyl group which attracts the planes of the carbonyl group and the quinoline ring toward each other. However, coplanarity between the planes is prevented by steric repulsion between the amide alkyl substituent (*Z*-isomer) or the amide phenyl substituent (*E*-isomer) and the quinoline carbonyl group in the (2)-position. The dihedral angle C_4−C_3−C_{11}−O_{11} in the optimized *E*-isomer is 36.8°.

We consider gas-phase calculations not to be relevant for the structure of **2** in polar solvents such as DMSO. In polar solvents, another tautomer may be lower in energy or the intramolecular hydrogen bond may be replaced by an intermolecular hydrogen bond to the solvent. We have investigated what consequences such an intermolecular hydrogen bond may have on the conformation of **2**. To make a rough simulation of a polar solvent, we chose the minimum energy conformation of the *E*-isomer (Figure 3b) as the initial conformation, with the difference that the dihedral angle H−O_4−C_4−C_3 was constrained to 90°. A geometry optimization with this constraint resulted in a markedly different conformation (Figure 3d). To minimize the electrostatic repulsion between oxygen atoms, the dihedral angle C_4−C_3−C_{11}−O_{11} becomes 96.4°. It is of interest to note that a similar structure results from the gas-phase minimization of **2-Na** (unpublished results).

Despite a seemingly large structural similarity between compounds **2** and **17**, their conformations are quite different. The steric repulsive interactions between amide substituents and the quinoline (2)-carbonyl group is absent in **17** and is replaced

(12) Spartan 04 Windows, Wavefunction, Inc., 18401 Von Karman Ave, Suite 370, Irvine, CA 92612.

by an intramolecular hydrogen bond between the amide hydrogen and the (2)-carbonyl group. The cooperative forces of the two intramolecular hydrogen bonds result in an energy minimized conformer with a rigid planar structure (Figure 3e). Other tautomers than the (4)-OH tautomer of **17** were roughly 4 kcal/mol higher in energy. The differences in conformation and exposure of polar groups give **2** and **17** markedly different physicochemical properties such as a considerably lower aqueous solubility of **17**.

Conclusions

The reactivity of laquinimod **2**, a compound currently being evaluated as a potential drug for the treatment of multiple sclerosis, and some analogues were studied. Compounds **1** and **2** undergo solvolysis reactions that obey first-order reaction kinetics, and ketene **3** was postulated as a transient intermediate in the synthesis of **2** from **1**. The enol protons in compounds **1** and **2** appear to play a crucial role for the reactivity, and a possible mechanism involving an intramolecular transfer of the enol protons to the exocyclic carbonyl substituents with concomitant formation of ketene **3** was presented. The solvent dependence of ^{13}C NMR and UV spectra of compound **2** was rationalized in terms of two different mean conformations. One form is favored in nonpolar solvents and exhibits intramolecular hydrogen bonding, the other form is more abundant in polar solvents and exhibits less intramolecular hydrogen bonding. The reactivity of **2** was found to be dependent on solvent polarity. In nonpolar solvents, an intramolecular hydrogen bond is developed more easily, and this facilitates the transfer of the enol proton to the exocyclic carbonyl substituent. Steric effects in **2** make such a proton transfer especially feasible since a strong hydrogen bond to the carbonyl oxygen is prohibited. The reactivity of **2** decreases when solvent polarity increases because intramolecular bonding becomes more difficult. Other enolizable β-ketoamides besides **2** may also react via ketene intermediates in substitution reactions. In fact, a preliminary investigation (unpublished results) has revealed that compound **15** shows similar characteristics to that of **2**. Thus, the solvolysis rate of **15** in ethanol is even faster than that of **2**. Furthermore, the degradation rate is similar to that of **2**, i.e., more rapid in nonpolar than in polar solvents and theoretical calculations corroborate that steric interactions in the enol form of **15** prevents a strong hydrogen bond to the exocyclic carbonyl oxygen. Finally, a process was developed that provides **2** in very high yield (98%) from **1**. We found that the solvent was important for the process. Thus, using *n*-heptane instead of toluene as solvent significantly improved the process with respect to reaction rate, yield, and purity. This was attributed to the low solubility of **2** in *n*-heptane.

Experimental Section

Syntheses of compounds **4**, **5**, and **1** were performed using the published methods.[2a,b,4] Analytical data follows.

5-Chloroisatoic anhydride (4): ^{1}H NMR (DMSO) δ 7.09 (dd, J = 8.2 and 0.9 Hz, 1H), 7.29 (dd, J = 7.9 and 0.9 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 11.8 (s broad, 1H); ^{13}C NMR (DMSO) δ 108.1 (C), 114.6 (CH), 125.7 (CH), 135.0 (C), 136.5 (CH), 144.0 (C), 146.7 (C), 156.5 (C); MS-ESI *m*/*z* 196 $[M - H]^-$. Anal. ($C_8H_4NO_3Cl$): C, 48.63; H, 2.04; N, 7.09. Found: C, 48.7; H, 2.06; N, 7.08.

5-Chloro-*N*-methylisatoic anhydride (5): ^{1}H NMR (DMSO) δ 3.45 (s, 3H), 7.36−7.44 (m, 2H), 7.77 (t, J = 8.2 Hz, 1H); ^{13}C NMR (DMSO) δ 32.4 (CH_3), 109.4 (C), 114.1 (CH), 126.0 (CH), 135.4 (C), 136.6 (CH), 144.6 (C), 147.4 (C), 155.5 (C); MS-ESI *m*/*z* 212 $[MH]^+$. Anal.($C_9H_6NO_3Cl$): C, 51.09; H, 2.86; N, 6.62. Found: C, 51.3; H, 2.98; N, 6.52.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic acid methyl ester (1): ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 4.04 (s, 3H), 7.24 (dd, J = 8.6 and 1.0 Hz, 1H), 7.27 (dd, J = 7.7 and 1.0 Hz, 1H), 7.50 (dd, J = 8.6 and 7.7 Hz, 1H), 14.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1 (CH_3), 53.2, (CH_3), 98.1 (C), 112.5 (C), 113.3 (CH), 126.1 (CH), 133.4 (CH), 134.6 (C), 143.6 (C), 158.8 (C), 172.7 (C), 173.4 (C); MS-ESI *m*/*z* 268 $[MH]^+$. Anal. ($C_{12}H_{10}NO_4Cl$): C, 53.85; H, 3.77; N, 5.23. Found: C, 54.0; H, 3.78; N, 5.34.

5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide Sodium Salt (2-Na). 5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic acid methyl ester **1** (3.00 g, 11.2 mmol), *N*-ethylaniline (2.88 mL, 22.4 mmol), and *n*-heptane (60 mL) were heated, and the volatiles, mainly heptane and formed methanol (32 mL), distilled off during 6 h and 35 min. After the mixture was cooled to room temperature, the crystalline suspension was filtered, and the crystals were washed with *n*-heptane and dried in a vacuum to yield crude 5-chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide **2** as white to off-white crystal needles (3.94 g, 98%, purity data are reported in Table 1). This compound has been described before,[2a,b,4] and ^{13}C NMR ($CDCl_3$, DMSO-d_6) is reported in Table 5 above. Compound **2** (2.48 g, 6.95 mmol) was suspended in ethanol (99.5%, 18.6 mL), and NaOH (10.0 M, 0.70 mL, 7.0 mmol) was added. The suspension was stirred for 2 h and the crystalline precipitate was collected, washed with cold ethanol (99.5%) and dried to afford **2-Na** as small white crystals (2.55 g, 96%): ^{1}H NMR (D_2O + NaOD, 21 mg/mL) δ 1.20 (t, J = 7.2 Hz, 3H), 3.14 (s, 3H), 3.86 (m, 2H), 6.56 (d, J = 7.5 Hz, 1H), 6.83 (m, 2H), 6.99 (t, J = 7.4 Hz, 1H), 7.18 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H); ^{13}C NMR (D_2O+NaOD) δ 14.9 (CH_3), 32.2 (CH_3), 46.8 (CH_2), 111.5 (C), 116.4 (CH), 121.3 (C), 127.3 (CH), 129.3 (2CH), 130.5 (CH), 131.2 (2CH), 132.3 (CH), 134.3 (C), 144.4 (C), 144.4 (C), 164.2 (C), 173.6 (C), 173.7 (C); MS-ESI *m*/*z* 379 $[MH]^+$. Anal. ($C_{19}H_{16}N_2O_3ClNa$): C, 60.25; H, 4.26; N, 7.40; O, 12.67. Found: C, 60.1; H, 4.26; N, 7.35; O, 12.5.

Comparison between Toluene and *n*-Heptane as Solvent for the Synthesis of 2, Table 1. Compound **1** (3.00 g, 11.2 mmol), *N*-ethylaniline (2.88 mL, 22.4 mmol), and toluene (60 mL) were heated, and the volatiles, mainly toluene and formed methanol (32 mL), distilled off during 6 h and 35 min. After cooling to room temperature and precipitation of the product with heptane (40 mL), the precipitate was filtered, washed with heptane, and dried in a vacuum to yield crude **2** as off-white crystals (3.58 g, 90%). This product and the crude **2** isolated from the reaction in *n*-heptane described above were analyzed using HPLC and reference compounds; see Table 1 in Results and Discussion. Only ester **1** and 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline **7** were detected in the products. Peaks with area % below 0.02% are not reported in Table 1. Preparation of **7** is described below.

Studies on the Equilibrium between 1 and 2. Aminolysis of 1 with *N*-Ethylaniline. Compound **1** (200 mg, 0.75 mmol), *N*-ethylaniline (163 mg, 1.12 mmol), and $CDCl_3$ (2.0 mL) were heated in sealed tubes at 140 °C in a microwave reactor for 35 and 70 min, respectively. Analysis of the mixtures by means of ^{1}H NMR revealed that apart from **1** and *N*-ethylaniline only **2** and methanol were present. The molar yields were estimated by measuring the integrals of representative signals in compounds **1** and **2**. The yield of **2** was 21% and 22%, respectively, after 35 and 70 min of heating. The corresponding yields of **1** were 79% and 78%.

Methanolysis of 2. Compound **2** (90 mg, 0.25 mmol), methanol (31 μL, 0.76 mmol), and $CDCl_3$ (3.0 mL) were heated in sealed tubes at 100 °C for 1 and 3 h, respectively. According to ^{1}H NMR analysis, only **1**, **2**, methanol, and *N*-ethylaniline were present in

the reaction mixtures. The molar yields of **1** after 1 or 3 h were 98% in both cases. 2% of **2** remained in the mixtures.

Determination of the Solubility of 1 and 2 in *n*-Heptane. Saturated solutions of **1** and **2** in *n*-heptane at room temperature were prepared by shaking and ultrasonication of an excess amount of the respective compound in *n*-heptane. The solutions were filtered and analyzed using HPLC with use of reference solutions for quantification. The solubility at room temperature was 0.15 mg/mL for **1** and 0.03 mg/mL for **2**.

Reaction of 2 with Water in Toluene. Compound **2** (357 mg, 1.0 mmol), toluene (4.0 mL), and water (36 mg, 2.0 mmol) were heated in sealed tubes for 4 h at 140 °C or 1 h at 100 °C, respectively. After concentration of the mixtures, they were analyzed by ^{1}H NMR and TLC. The mixture that was heated for 4 h at 140 °C gave exclusively 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline **7** (212 mg, 100%). The mixture that was heated for 1 h at 100 °C gave 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic acid **6** (253 mg, 100%, contaminated with less than 5% of compound **7**). Compound **6** is preferably prepared as described[2a] by cleavage of ester **1** with anhydrous HCl in acetic acid at 60 °C for 6 h and has the following analytical data: ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 7.42 (dd, J = 8.8 and 0.8 Hz, 1H), 7.45 (dd, J = 8.0 and 0.8 Hz, 1H), 7.65 (dd, J = 8.8 and 8.0 Hz, 1H), 15.77 (s, 1H), 15.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.5 (CH_3), 95.3 (C), 113.8 (C), 114.0 (CH), 127.7 (CH), 134.1 (CH), 135.4 (C), 142.1 (C), 164.3 (C), 172.9 (C), 174.0 (C); MS-ESI m/z 254 $[MH]^+$. Anal. ($C_{11}H_8NO_4Cl$): C, 52.09; H, 3.18; N, 5.52. Found: C, 52.2; H, 3.17; N, 5.56.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline (7). Compound **6** (5.0 g, 19.7 mmol) and DMSO (25 mL) were heated at 70 °C for 90 min and then cooled. Water (20 mL) was added, the suspension was stirred for 30 min, and the precipitate was collected, washed with water, and dried to give **7** (4.04 g, 98%): ^{1}H NMR (DMSO) δ 3.53 (s, 3H), 5.92 (s, 1H), 7.27 (dd, J = 7.7 and 0.9 Hz, 1H), 7.46 (dd, J = 8.5 and 0.9 Hz, 1H), 7.53 (dd, J = 8.5 and 7.7 Hz, 1H), 11.46 (s broad, 1H); ^{13}C NMR (DMSO) δ 99.6 (C), 113.3 (C), 114.4 (CH), 124.9 (CH), 130.5 (C), 131.1 (CH), 142.5 (C), 161.7 (2C); MS-ESI m/z 210 $[MH]^+$. Anal. ($C_{10}H_8NO_2Cl$): C, 57.30; H, 3.85; N, 6.68. Found: C, 57.1; H, 3.84; N, 6.62.

Reaction Studied and Reported in Table 2. Aminolysis of ester **1** with *N*-ethylaniline was described above and gave **2** in 90% yield. The other esters were treated as follows: The ester (3.0 g), *N*-ethylaniline (2.0 equiv), and toluene (60 mL) were heated, and approximately 50 mL of the volatiles was distilled off during 6 h. The reaction mixtures corresponding to ester **8**, ethyl *trans*-cinnamic acid **10**, and ethyl benzoate **12** were concentrated, and ^{1}H NMR and TLC on the residues revealed that none of them were able to give even a trace of the corresponding *N*-ethylanilides. Increasing the temperature by using xylene instead of toluene as solvent did not change the outcome for these esters. Apart from ester **1**, only ester **14**[5] gave the corresponding product **15** which precipitated upon cooling the reaction mixture.

5-Chloro-1,2-dihydro-4-methoxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Methyl Ester (8). Compound **1** (15.0 g, 56.0 mmol) and DBU (9.2 mL, 60.0 mmol) were dissolved in dimethylacetamide (80 mL), and methyl iodide (4.4 mL, 70.0 mmol) was added at 0 °C. After being stirred for 20 h at room temperature, the mixture was poured onto HCl/ice and extracted with chloroform. The organic extract was dried, concentrated, and subjected to chromatography (EtOAc/*n*-heptane 1:1) to give first the 3-C-methylated ester.

5-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-3-carboxylic acid methyl ester (6.2 g, 39%): ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H), 3.49 (s, 3H), 3.73 (s, 3H), 7.13 (dd, J = 8.5 and 0.8 Hz, 1H), 7.23 (dd, J = 7.9 and 0.9 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 30.9 (CH_3), 53.5 (CH_3), 65.8 (C), 114.0 (CH), 118.7 (C), 126.6 (CH), 134.8 (CH), 135.3 (C), 144.6 (C), 167.4 (C), 167.4 (C), 189.3 (C); MS-ESI m/z 282 $[MH]^+$. Anal. ($C_{13}H_{12}NO_4Cl$): C, 55.43; H, 4.29; N, 4.97. Found: C, 55.6; H, 4.23; N, 5.06. Eluted next was compound **8** (5.8 g, 37%): ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 7.30−7.32 (m, 2H), 7.48 (dd, J = 8.8 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 53.0 (CH_3), 61.3 (CH_3), 113.5 (CH), 114.6 (C), 115.6 (C), 126.4 (CH), 131.5 (CH), 132.3 (C), 142.1 (C), 160.3 (C), 161.2 (C), 165.5 (C); MS-ESI m/z 282 $[MH]^+$. Anal. ($C_{13}H_{12}NO_4Cl$): C, 55.43; H, 4.29; N, 4.97. Found: C, 55.7; H, 4.05; N, 5.10.

1-Ethyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic Acid Ethylphenylamide (15). Ethyl ester **14**[5] (3.0 g, 12.8 mmol) was treated with *N*-ethylaniline in toluene as described above. The precipitate was filtered, washed with heptane, and dried to give crude **15** (3.32 g, 10.7 mmol). This was dissolved in a mixture of ethanol (99.5%, 30 mL), 10 M NaOH (1.07 mL, 10.7 mmol), and water (15.0 mL). Then, 5 M HCl (aq) (2.4 mL, 12.0 mmol) was added. The crystalline precipitate was collected, washed with ethanol/water 1:1 and dried to afford compound **15** (2.65 g, 67%): ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 3.53 (m, 1H), 3.71 (m, 2H), 3.95 (m, 1H), 4.45 (s, 1H), 6.73 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.30−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.6 (CH_3), 12.9 (CH_3), 34.9 (CH_2), 44.9 (CH_2), 51.6 (CH), 108.4 (CH), 122.4 (CH), 123.8 (CH), 126.2 (C), 128.3 (CH), 128.6 (CH), 129.2 (CH), 129.7 (CH), 141.3 (C), 144.1 (C), 166.4 (C), 172.0 (C); MS-ESI m/z 309 $[MH]^+$. Anal. ($C_{19}H_{20}N_2O_2$): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.4; H, 6.23; N, 9.22.

Compounds Studied and Reported in Table 3. Esters and amides were heated under the conditions reported in Table 3. A microwave reactor was used for reactions with methanol as solvent. An oil bath was used for reactions in 1 M NaOH. The reaction mixtures from ethyl ester **16**[2] and amide **2** were diluted with excess 1 M HCl, and the precipitates were collected and dried prior to ^{1}H NMR analysis. The reaction mixtures from ester **10** were passed through a short silica gel column (in order to neutralize NaOMe) prior to concentration and analysis. The reaction mixtures of amide **13** and **17** were concentrated prior to analysis. The molar yields were estimated by measuring the integrals of representative signals in the ^{1}H NMR spectrum.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (17). Compound **2** (819 mg, 2.27 mmol), aniline (414 μL, 4.54 mmol), and toluene (10.0 mL) were heated at 100 °C for 1 h. Upon cooling the reaction mixture to room temperature and the addition of heptane (10 mL), the precipitate was collected, washed with toluene/heptane 1:1, and dried to afford **17** (693 mg, 92%): ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 7.17 (t, J = 7.5 Hz, 1H), 7.31 (m, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.52 (t, J = 8.2 Hz, 1H), 7.66 (d, J = 7.9 Hz, 2H), 12.59 (s, 1H), 17.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3 (CH_3), 96.9 (C), 113.5 (CH), 114.0 (C), 121.4 (CH), 125.0 (CH), 126.7 (CH), 129.0 (CH), 132.9 (CH), 134.6 (C), 137.0 (C), 142.2 (C), 162.2 (C), 169.7 (C), 173.9 (C); MS-ESI m/z 329 $[MH]^+$. Anal. ($C_{17}H_{13}N_2O_3Cl$): C, 62.11; H, 3.99; N, 8.52. Found: C, 62.3; H, 3.99; N, 8.56.

Impact of the Solvent Polarity on the Reactivity of 2. Solutions of **2** were prepared in a concentration of about 1 mg/mL in DMSO, ethanol, and dichloromethane and in a concentration of about 0.0075 mg/mL in 0.02 M HCl. 1.00 mL portions were dispensed into glass-stoppered tubes and stored at room temperature in the dark for different times. After storage, the degradation of the samples dissolved in organic solvents was stopped by change of solvent. Solutions in DMSO and ethanol were directly diluted with 0.02 M sodium hydroxide to 10.00 mL. Solutions in dichloromethane were evaporated by means of a gentle stream of nitrogen without heating, and the residues were then dissolved in 0.02 M sodium hydroxide to 10.00 mL. The samples stored in 0.02 M HCl were analyzed directly without dilution. Quantification of **2** was made by HPLC by comparison with a standard solution. Quantification of formed degradation products **6**, **7**, and **16** was made by HPLC with use of predetermined conversion factors for weight %.

The rate constant was determined by the slope of the fitted straight line in a diagram with the natural logarithm of (initial

concentration of **2**/concentration of **2** at time *t* calculated from formed products) versus time. These diagrams showed straight lines in all cases, as expected for first-order kinetics, except for neat dichloromethane, which showed a curved behavior. This nonlinear behavior in neat dichloromethane is explained by the limited amount of nucleophilic reactants available for reaction with ketene **3**, which is formed from **2**. In this solvent, the rate constant was roughly estimated from the initial degradation after day 1 instead. The determined rate constants (day^{-1}) in water (0.02 M HCl), DMSO, ethanol, and dichloromethane were 0.2, 1.0, 2.0 and 8.3, respectively (see the Supporting Information for tables and figures).

Kinetic Study of the Solvolysis of 1 and 2. Acetonitrile (8.00 mL), containing 0.1% trifluoroacetic acid and an appropriate addition of the alcohol to be used, was preheated in the thermostat bath at 50 °C. Then 2.00 mL of DMSO, containing either compound **1** or **2**, was added. The final concentration of the alcohol in the reaction medium was 1.6, 0.32, or 0.064% (v/v). The added concentration of compound **2** was 0.0011 M in the reaction medium, and that of compound **1** was 0.0013 M. The mixture was left in the thermostat bath for the time desired. The reaction was stopped by the addition of 2.0 mL 1 M NH_3 (aq). After dilution of the final solution to 50.0 mL with water, it was allowed to stand for at least 24 h in the dark to achieve complete decarboxylation of the carboxylic acid **6** to compound **7**. Finally, the solutions were analyzed by means of HPLC. Calibration was made with solutions of compound **1**, **2** and **7**. The factor obtained for compound **1** for conversion from peak area to molar concentration, was applied also for the other alkyl-esters. The reaction times were 0, 1, 2, 3, and 4 h for amide **2**, and 0, 2, 4, 6, and 24 h for ester **1**. The rate constant was determined in the same way as described above (see the Supporting Information for tables and figures).

5-Chloro-3-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylic Acid Ethylphenylamide (18). Compound **2-Na** (1.00 g, 2.64 mmol), disodium hydrogenphosphate dihydrate (1.15 g, 6.4 mmol), Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 1.97 g, 3.20 mmol), and water (20 mL) were stirred for 30 min, and the precipitate was collected, washed with ethanol/water 2:8, and dried to give compound **18** (939 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 1.16 (t, $J = 7.0$ Hz, 3H), 3.21 (s, 3H), 3.79 (m, 2H), 5.71 (s, 1H), 6.84 (d, $J = 8.5$ Hz, 1H), 7.00−7.25 (m, 6H), 7.35 (t, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 30.6 (CH_3), 47.0 (CH_2), 78.0 (C), 113.8 (CH), 117.3 (C), 126.8 (CH), 128.9 (CH), 129.1 (CH), 131.6 (CH), 134.9 (CH), 136.2 (C), 137.2 (C), 144.5 (C), 165.4 (C), 167.9 (C), 188.9 (C); MS-ESI *m*/*z* 373 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4Cl$): C, 61.21; H, 4.60; N, 7.52. Found: C, 61.4; H, 4.47; N, 7.52.

Supporting Information Available: General experimental procedures, NMR spectra for compounds described in the Experimental Section, kinetic data, and Cartesian coordinates for calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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