RESEARCH ARTICLE

1-Alkyl-1,4-dihydro-4-iminoquinoline-3-carboxylic acids: Synthesis, Structure and Properties

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Abstract

1-Alkyl-1,4-dihydro-4-iminoquinoline-3-carboxylates undergo neutral hydrolysis (in H\textsubscript{2}O or H\textsubscript{2}O–EtOH mixtures) to yield water-soluble 4-iminoquinoline-3-carboxylic acids and the corresponding 4-oxo esters. Such 4-imino acids are also accessed by treating an appropriate 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid successively with thionyl chloride and an amine–H\textsubscript{2}O mixture, or from treatment of a 4-imino ester salt with aqueous amine. In the latter procedures 7-fluoro substituted substrates gave rise to 7-alkylamino derivatives even at room temperature. The title compounds are inferred to have an intramolecularly H-bonded charge transfer structure, and some of their chemical reactions and spectral (HRMS, \textsuperscript{1}H NMR) properties are described.

Keywords: Quinolin-4-imines; intramolecular hydrogen bonds; charge transfer structure; mechanism.
1. Introduction
Despite being the 4-imino analogues of the ubiquitous quinolone antibiotics, and having a potential for biological activity, the title compounds have a surprisingly sparse chemistry literature. Only an occasional preparation of such imino acids has been reported. Here we present our findings and observations pertaining to two general syntheses of this relatively neglected class of quinoline derivatives, and discuss a likely structure for these products.

2. Results and Discussion
Neutral hydrolysis of the recently available 4-imino ester 1 afforded target product 2 in moderate (49–95%) yield (Table 1) together with the corresponding 4-oxo ester 3, derived from competitive hydrolysis of the ethoxycarbonyl and the ethylimino functions in 1, respectively (Scheme 1).

The new 4-imino acids 2 (Table 1) were obtained as colourless crystalline solids (from EtOH–Et₂O) and were readily soluble in water (ca 15-20%, w/v) at room temperature, in contrast to the sparingly soluble corresponding 4-oxo acids 4. Like its precursor 4-imino ester 1, 4-imino acid 2 was fairly stable in acidic medium. For example, heating 2 under reflux in aqueous 2.0 mol dm⁻³ HCl for 1–2 h caused little, if any, change; however, prolonged reaction (>10 h) led to 4-oxo acid 4 together with the
latter's decarboxylation product (especially for \( R^1 = \text{Me} \)). Addition of concentrated HCl to an aqueous solution of 4-imino acid 2 followed by evaporation at room temperature afforded a colourless mono(hydrogen chloride) salt 2·HCl, melting with decomposition.

Alkaline hydrolysis of 4-imino acid 2 to the corresponding 4-oxo acid 4 (as the carboxylate anion) was relatively facile. For example, refluxing 4-ethylimino-7-fluoro acid 2b with aqueous tetramethylammonium hydroxide (utilised in order to minimise nucleophilic substitution of the 7-fluoro function) for 1 h gave the 7-fluoro-4-oxo acid 4b (86%). In exploratory studies with 4-ethylimino-7-fluoro-2-methyl acid 2f in aqueous 0.10 mol dm\(^{-3}\) NaOH (20% molar excess) and conducted at room temperature, conversions into the corresponding 4-oxo acid 4f were as follows: 34% (2 days), 54% (1 week), 64% (2 weeks), while reflux for 1 h gave acid 4f in 89% yield. The two aforementioned properties of 4-imino acid 2, namely a relatively high solubility in water and a propensity to convert in alkaline medium into the corresponding 4-oxo acid 4 (anion) points to a potential for use in vivo drug delivery systems.

The mass spectra of the 4-imino acids 2, (\( R^1 = \text{H or Me, Scheme 1} \)) in general showed weak peaks for the \( M^+ \) and \((M - 1)^+ \) ions, with more intense ones for the \((M - \text{CO}_2)^+ \) and \((M - \text{CO}_2\text{H})^+ \) fragments, and a base peak (100%) [shown from accurate mass determination to correspond to a \((M - \text{C}_2\text{H}_5\text{O}_2)^+ \) ion], which is tentatively ascribed to a resonance stabilised entity such as C. Salt 2·HCl lost hydrogen chloride in the course of its HRMS determination, resulting in a spectrum identical with that of the corresponding free 4-imino acid 2.

Examination of 4-imino acids 2 by \(^1\text{H} \) NMR (200 MHz) spectroscopy provided the following general information. (i) The \(^1\text{H} \) NMR (CDCl\(_3\) or DMSO-d\(_6\) ) spectrum of each acid 2 exhibited, inter alia, the 'acidic' proton as a D\(_2\)O-replaceable, broad absorption (sometimes discernible as a triplet) near \( \delta \) 14, and the methylene protons of the 4-ethylimino function as a crude quintet (\( J \text{ ca 7 Hz} \)) near \( \delta \) 3.7 which collapsed to a quartet on exchange with D\(_2\)O. (ii) NOE experiments with representative acids 2d (Figure 1), 2e and 8a (Scheme 3) revealed, inter alia, that whereas this 'acidic' proton was distant from the 5-H (aromatic) proton (i.e., irradiation of the former signal did not enhance that of the latter, and vice versa), it was proximate to the aforementioned methylene protons, thereby supporting its spatial orientation as depicted in Figure 1.
| Substrate 4-Imino ester (mmol) | Reaction conditionsb | Product 4-Imino acid 2a | Product 4-Oxo ester 3a  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1a (1.0) H$_2$O (25 cm$^3$) reflux (1.5 h)</td>
<td>2a C$<em>{14}$H$</em>{16}$N$_2$O$_2$ Yield(%)c m.p.(°C)d δ-valuee</td>
<td>3a Yield(%)c m.p. (°C)</td>
<td></td>
</tr>
<tr>
<td>1b (4.7) H$_2$O (50 cm$^3$) reflux (1.5 h)</td>
<td>2b C$<em>{14}$H$</em>{15}$FN$_2$O$_2$ 75 198–200 14.4* (br t)</td>
<td>3b 12 127</td>
<td></td>
</tr>
<tr>
<td>1c (3.0) H$_2$O (35 cm$^3$) reflux (1.5 h)</td>
<td>2c C$<em>{15}$H$</em>{15}$FN$_2$O$_2$ 83 224–225 14.5 (br)</td>
<td>3c 7 178–180</td>
<td></td>
</tr>
<tr>
<td>1d (1.0) H$_2$O (25 cm$^3$) reflux (1.5 h)</td>
<td>2d C$<em>{14}$H$</em>{14}$F$_2$N$_2$O$_2$ 90 208–210 14.5 (br s)</td>
<td>3d 10 154</td>
<td></td>
</tr>
<tr>
<td>1g (2.0) H$_2$O (25 cm$^3$) + EtOH (10 cm$^3$) reflux (1.5 h)</td>
<td>2g C$<em>{15}$H$</em>{17}$ClN$_2$O$_2$ 49 216–218 ca12* (v br)</td>
<td>3g 47 97–98</td>
<td></td>
</tr>
<tr>
<td>1h (1.0) H$_2$O (25 cm$^3$) reflux (1.5 h)</td>
<td>2h C$<em>{15}$H$</em>{16}$F$_2$N$_2$O$_2$ 75h 204–205 (decomp.)h</td>
<td>3h 12 —</td>
<td></td>
</tr>
</tbody>
</table>

* Crystallisation of 2 usually from EtOH–Et$_2$O; of 3 usually from EtOAc-hexane. The internal salts 2 stayed on the base-line in TLC in neutral, acidic, or basic developers; however, use of benzene–acetone (3:1, v/v) containing 5% each of Et$_3$N and HOAc led to a development.

b Refers to solvent (volume) and reflux (time) with (magnetic) stirring.

c Yield, refers to vacuum-dried crude material.

d 4-Imino acids 2 generally melted with decomposition.

e Signal is for the D$_2$O-exchangeable proton; $^1$H NMR spectra were run in CDCl$_3$, otherwise* in DMSO-d$_6$.

f br s, broad singlet; br t, broad triplet; v br, very broad.

g Not determined.

h Yield and m.p. of the hydrogen chloride salt of 2h.
Also included in Figure 1 are the chemical shifts of the various protons in 2d. In general, the other 4-imino acids 2 (Scheme 1) exhibited comparable shifts for the corresponding protons. (iii) The \( ^1H \) NMR (DMSO-\( d_6 \)) spectra of the mono(hydrogen chloride) salts of 4-imino acids 2f and 2g each showed, \textit{inter alia}, a D\(_2\)O-exchangeable, very broad absorption (1H) near \( \delta \) 14.5 (attributed to a carboxylic acid proton), a D\(_2\)O-exchangeable, broad triplet (1H) near \( \delta \) 9.4 (indicative of this proton being bonded to N), and a complex multiplet (2H) near \( \delta \) 3.7, converted into a quartet by D\(_2\)O, for the 4-ethylimino methylene protons. NOE experiments identified the ‘acidic’ proton near \( \delta \) 9.4 as the iminium proton, and as being proximate to both the (aromatic) 5-H proton and the 4-ethylimino protons. From these observations, the hydrogen chloride salt of 4-imino acid 2 was assigned structure 6 (Scheme 3), which choice was subsequently unequivocally demonstrated from a X-ray structure determination\(^6\) of the hydrochloride salt of 2f.\(^4\)

![Figure 1](image)

**Figure 1** Key NOE interactions and chemical shift values (CDCl\(_3\)) in 4-imino acid 2d.

Possible structure assignments for 4-imino acid 2 are shown in Scheme 2. The intramolecularly hydrogen-bonded charge-transfer species 2A is the only one entirely compatible with the aforementioned spectral findings and is, in the absence of a suitable crystal for X-ray analysis, our current best representation for the structure of 2. Other representations (2B, 2C and 2C\(^1\)) were separately discounted on the basis of the following evidence. (a) The neutral, intramolecularly hydrogen bonded species 2B suffers from the implication that long-range inter-proton coupling can occur (i) across six single bonds and one double bond, or (ii) across a strong (quasi-covalent) hydrogen bond and two single bonds (and with coupling constants of large magnitude, ca 6–7 Hz), neither of which \( ^1H \) NMR phenomena, as far as we are aware, has been
reported.\textsuperscript{7,8} (b) In the zwitterionic assignment 2C, which lacks hydrogen bonding, the iminium proton is comparable to the one in salt 2f·HCl (\textit{vide supra}), and could therefore be expected to resonate near $\delta$ 10 and to exhibit a positive NOE effect (signal enhancement) with the neighbouring 5-H (aromatic) proton; neither of these expectations is realised in 4-imino acid 2. In this respect, a resonance form of 2C, \textit{viz.}, 2C\textsuperscript{1}, is also not favoured in view of UV evidence\textsuperscript{2} militating against an analogous betaine structure 5A for a related 4-imino acid 5.

![Scheme 2](image)

Scheme 2 also shows two possible representative intermolecularly hydrogen-bonded assignments for 4-imino acid 2, \textit{viz.}, 2D and 2E. However, neither is compatible with the available $^1$H NMR and/or NOE spectroscopic evidence, and they are not favoured. Specifically, 2D would not exhibit coupling of the 'acidic' proton with the methylene protons of the 4-ethylimino group, as is observed in 2 (\textit{vide supra}), while in 2E a positive NOE effect that could be expected between the 'acidic' proton and the proximate 5-H (aromatic) proton is not observed in 2 (\textit{vide supra}).
Table 2  4-Imino acids 8 and 4-imino amides 9 from 4-oxo acids 4 treated successively with SOCl₂ and H₂O–R⁴NH₂ mixtures.

<table>
<thead>
<tr>
<th>Substrate 4-Oxo acid 4</th>
<th>Amine R⁴NH₂</th>
<th>Product 4-Imino acid 8ᵃ</th>
<th>Product 4-Imino amide 9ᵃᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Compd</td>
<td>Molecular Formula</td>
</tr>
<tr>
<td>4a</td>
<td>cycloPr</td>
<td>8a</td>
<td>C₁5H₁₆N₂O₂</td>
</tr>
<tr>
<td>4b</td>
<td>cycloPr</td>
<td>8b</td>
<td>C₁5H₁₅FN₂O₂</td>
</tr>
<tr>
<td>4b</td>
<td>Pr</td>
<td>8c</td>
<td>C₁₈H₂₅N₃O₂</td>
</tr>
<tr>
<td>4b</td>
<td>CH₂Ph</td>
<td>8d</td>
<td>C₂₆H₂₅N₃O₂</td>
</tr>
<tr>
<td>4c</td>
<td>cycloPr</td>
<td>8f</td>
<td>C₁₆H₁₅FN₂O₂</td>
</tr>
<tr>
<td>4c</td>
<td>CH₂Ph</td>
<td>8g</td>
<td>C₂₇H₂₅N₃O₂</td>
</tr>
<tr>
<td>4e</td>
<td>Et</td>
<td>8h</td>
<td>C₁₅H₁₆N₂O₂</td>
</tr>
<tr>
<td>4e</td>
<td>cycloPr</td>
<td>8i</td>
<td>C₁₆H₁₆N₂O₂</td>
</tr>
</tbody>
</table>

ᵃ Crystallisation of 8 usually from EtOH–Et₂O; of 9 usually from EtOAc.
ᵇ The spectral (¹H NMR, HRMS) properties of 9e and 9f are described in ref. 10.
ᶜ Yield refers to vacuum-dried crude material.
ᵈ 4-Imino acids 8 generally melted with decomposition.
ᵉ Signal is for the D₂O-exchangeable ‘acidic’ proton. ¹H NMR spectra were run in CDCl₃, otherwise* in DMSO-d₆.
ᶠ br s, broad singlet; br t, broad triplet.
ᵍ Unresolved complex product containing (TLC) 4-imino amide 9.
A second and novel general preparation of 4-imino acids 2 [and 8 (Scheme 3)] involves treating a 1-alkyl-4-oxoquinoline-3-carboxylic acid 4 (R\(^1\) = H) successively with thionyl chloride (SOCl\(_2\)) and an amine–H\(_2\)O mixture.\(^9\) For example, 4-oxo acid 4\(b\) was heated under reflux with SOCl\(_2\) for 1 h; after evaporative removal of excess reagent the residue of supposed quinolinium chloride 13\(b\) (Scheme 4) was stirred with aqueous benzylamine at room temperature to give 7-benzylamino-4-benzylimino acid 8\(d\) (56\%) together with N-benzyl-4-benzylimino-7-fluoro amide 9\(e\) (18\%). The outcomes from similar reaction between a variety of 4-oxo acids 4 and amines are listed in Table 2.

Each product (Tables 1, 2) was characterized from its spectral (\(^1\)H NMR and/or HRMS) properties, supplemented on occasion by alkaline hydrolysis to the appropriate 4-oxo derivative. In the instance of 7-propylamino-4-propylimino acid 8\(c\), hydrolysis gave 7-propylamino-4-oxo acid 11\(c\). Treatment of the latter acid 11\(c\) successively with SOCl\(_2\) and dry propylamine afforded N-propyl-7-propylamino-4-propylimino amide 9\(c\),\(^10\) a reaction of potential synthetic utility.
Currently, it is surmised that the production of 4-imino acid 8 and 4-imino amide 9 from quinolinium chloride 13 and aqueous amine (Table 2) occurs by (i) the amine substituting 13 initially at C-4, eventuating in (ii) an intermediate species, such as a 4-imino carbonyl chloride 14 (or its hydrogen chloride complex), which (iii) then undergoes competitive hydrolysis and aminolysis, resulting in the aforementioned end-products.

Evidence supportive of 4-imino carbonyl chloride 14 being an intermediate in the above sequence of events was obtained from the following reaction outcomes: 4-Ethylimino-7-fluoro acid 2b, when treated successively with SOCl₂ and EtOH, yielded 4-ethylimino-fluoro ester 1b; while from 4-ethylimino acid 2a, SOCl₂ and dry cyclopropylamine, N-cyclopropyl-4-cyclopropylimino amide 9a was formed by way of a participating imine–amine exchange.

A limitation in the synthesis of 4-imino acid 2 from 4-oxo acid 4 (R¹ = H), SOCl₂ and aqueous amine (vide supra) lies in the nature of the 1-substituent in 4. This was shown with 1-benzyl-7-fluoro-4-oxo acid 4i which, when heated under reflux with SOCl₂, eliminated benzyl chloride. Treatment of the residual product with H₂O gave 7-fluoro-4-oxoquinoline-3-carboxylic acid 15a (Scheme 4), while with dry cyclopropylamine the product was N-cyclopropyl-4-cyclopropylamino-7-fluoroquinoline-3-carboxamide 16a. The residual product was identified as 4-chloroquinoline-3-carbonyl chloride 16b from its reaction with aqueous cyclopropylamine to provide 4-chloro-N-cyclopropyl-7-fluoroquinoline-3-carboxamide 16c, hydrolysis of which gave 4-oxo amide 15b.

Another limitation in the aforementioned 4-imino acid 2 synthesis procedure, is the inability to utilise a 2-methyl- or 2-ethyl substituted 4-oxo acid 4 as substrate, since this reacts with SOCl₂ to form a thieno [3,4-b]quinoline derivative.

In a further development, we acted on the surmise that the protonated form of 4-imino ester 1 resembles that of salt 6, and would exhibit quinolinium-like enhanced susceptibility of the 7-fluoro substituent to nucleophilic displacement. Accordingly, a mixture of the hydrogen chloride salt of 7-fluoro-4-ethylimino ester 1b (i.e., 7) and an excess of propylamine was stirred at room temperature for 3–4 days, when following on expectation, the products were 7-propylamino-4-propylimino acid 8c (80%) and N-propyl-7-propylamino-4-propylimino amide 9c (16%). In comparison, a similar reaction employing 4-imino ester 1b in lieu of its salt yielded little, if any, of either product. Analogous 4-imino acids 8 were obtained from other amines (Table 3); reaction at 40–50 ºC for 6 h led to comparable yields. This procedure using a 4-imino ester salt 1·HCl
offers access to 4-imino acids 2 and 8 under especially mild conditions. Thus, 
N-methylpiperazine, a secondary amine, likewise reacted with 1b·HCl in water, forming 
7-(4-methylpiperazinyl)-4-ethylimino acid 8k (50–70%), which on hydrolysis gave the 
known\textsuperscript{16} 7-(4-methylpiperazinyl)-4-oxo acid 11k. A significant concentration of H\textsuperscript{+} in the 
reaction appears to be a requirement for success in this particular synthesis of 4-imino 
acids. In principle, the production of a 2-methyl substituted 4-imino acid 2 (R\textsuperscript{1} = Me) by 
this method appears to be feasible and this aspect is being studied.

![Chemical structures](image)

**Scheme 4**

**Table 3** 4-Imino acids 8 and 4-imino amides 9 from 4-imino ester 1 hydrochlorides 
and H\textsubscript{2}O–amine (R\textsuperscript{4}NH\textsubscript{2}) mixtures.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Amine R\textsuperscript{4}NH\textsubscript{2}</th>
<th>Product(s),\textsuperscript{a} (Yield, %),\textsuperscript{b} m.p., °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b·HCl</td>
<td>Et\textsuperscript{c}</td>
<td>8l (80) &gt;250\textsuperscript{d} e</td>
</tr>
<tr>
<td>1b·HCl</td>
<td>Pr</td>
<td>8c (80) 236–238\textsuperscript{d} 9c (16) 187–188</td>
</tr>
<tr>
<td>1b·HCl</td>
<td>CH\textsubscript{2}Ph</td>
<td>8d (70-80) &gt;240\textsuperscript{d} e</td>
</tr>
<tr>
<td>1b·HCl</td>
<td>1-Methylpiperazine</td>
<td>8k (50-70) 210–211</td>
</tr>
<tr>
<td>1b</td>
<td>Et\textsuperscript{c,f}</td>
<td>8l (95) &gt;250\textsuperscript{d} e</td>
</tr>
<tr>
<td>2b</td>
<td>1-Methylpiperazine</td>
<td>8k (95) 210–211</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Identified from \textsuperscript{1}H NMR and mixture m.p. comparison with material prepared by the 4-oxo acid 
4b/SOCl\textsubscript{2}/H\textsubscript{2}O-amine reaction (ref. 9), and/or by a literature method (ref. 10).

\textsuperscript{b} Yield refers to vacuum-dried crude material. \textsuperscript{c}EtNH\textsubscript{2} added as a 70% aqueous solution.

\textsuperscript{d} Melted with decomposition.

\textsuperscript{e} Not isolated or obtained.

\textsuperscript{f} Conc. HCl (1–2 drops) added to reaction mixture.
3. Experimental

General methods have been described previously. All reagents and solvents were of reagent grade quality and were used without further purification. $^1$H NMR spectra were obtained on a Bruker AC 200 spectrometer operating at 200.13 MHz, using CDCl$_3$ as a solvent (unless otherwise stated), with tetramethylsilane as internal standard. Mass spectra were recorded on a VG70-SEQ instrument, and high resolution measurements were made on a Kratos MS9/50 instrument (by Dr P. R. Bosshoff, Cape Technikon). IR spectra were determined using a Bruker IFS 25 Fourier Transform Spectrophotometer. No serious attempts were made to optimise yields. The reaction products described below were obtained as colourless solids/crystals.

4-Iminoquinoline-3-carboxylates $^1$ (Table 1), 4-oxo acids $^4$ and their precursor 4-oxo esters $^3$ (Scheme 1) required for this work were synthesised by literature methods. In illustration, ethyl 1-benzyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate $^{3i}$ was accessed from the C-acylated enamine $^{17a}$ derived from 2-chloro-4-fluorobenzoyl chloride and ethyl 3-dimethylamino-2-propenoate; this product enamine was treated with benzylamine in EtOH to effect exchange to the 3-benzylamino enamine $^{17b}$, which was then cyclised to title ester $^{3i}$. Crystals, m.p. 190–192 °C (from EtOAc); $\delta_H$ (CDCl$_3$) 1.42 (3H, t, $J$ 7.2), 4.40 (2H, q, $J$ 7.2), 5.34 (2H, s), 6.95–7.2 (4H, m), 7.35–7.4 (3H, m), 8.50–8.58 (1H, m), 8.59 (1H, s). Acid hydrolysis$^{17}$ gave the corresponding 4-oxo acid $^{4i}$; crystals, m.p. 225–228 °C; $\delta_H$ (CDCl$_3$) 5.47 (2H, s), 7.15–7.47 (7H, m), 8.5–8.6 (1H, m) 8.91 (1H, s), 14.7 (1H, s, removed by D$_2$O).

4-Imino acids $^2$ and 4-oxo esters $^3$ from neutral hydrolysis of 4-imino esters $^1$.

General procedure.

This is illustrated with imino ester $^{1b}$. A mixture of ester $^{1b}$ (1.37 g, 4.72 mmol) and H$_2$O (50 cm$^3$) was heated at reflux with stirring for 1.5 h. The resulting solution was evaporated (rotavapor) and the residue was dried azeotropically (benzene–EtOH). The dry product mixture (of $^{2b}$ and $^{3b}$) was placed on a tared sintered funnel and triturated with warm (ca 40–50 °C) EtOAc (ca 3 cm$^3$), after which the sparingly soluble 1-ethyl-4-ethylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid $^{2b}$ was filtered, washed with EtOAc (2 x 2 cm$^3$) and finally with hexane to give crystals (0.93 g, 75%), m.p. 198–200 °C (decomp.); $\delta_H$ (DMSO-d$_6$) 1.3–1.4 (6H, m), 3.92–3.99 (2H, m; simplifies to q, $J$ 7.1,
on treatment with D₂O), 4.51 (2H, q, J 7.1), 7.46–7.51 (1H, br t), 7.91–7.95 (1H, m), 8.55–8.65 (1H, m), 8.89 (1H, d, J 2.7), 14.4 (1H, br t, removed by D₂O), m/z 262 (M⁺, 39%), 261 (M – 1, 60), 247 (M – CH₃, 15), 218 (M – CO₂, 30), 217 (M – CO₂H, 53), 203 (M – C₂H₃O₂, 100) [Found: (M – C₂H₃O₂)⁺, 203.0989. Calc. for C₁₂H₁₂FN₂: 203.0985. Found: M⁺, 262.1121. Calc. for C₁₄H₁₅FN₂O₂ M, 262.1118]. Evaporation of the combined aforementioned EtOAc filtrate and washings gave ethyl 1-ethyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate 3b (149 mg, 12%); crystals, m.p. 127 ºC (EtOAc–hexane); δₜ (CDCl₃) 1.42 (3H, t, J 7.1), 1.55 (3H, t, J 7.2), 4.20 (2H, q, J 7.3), 4.40 (2H, q, J 7.1), 7.09–7.17 (2H, m), 8.48 (1H, s), 8.53–8.57 (1H, m), and identical (¹H NMR) with 4-oxo ester 3b synthesised by a literature¹⁷ method. Other 4-imino acids 2 and 4-oxo esters 3 similarly obtained are listed in Table 1.

Several of the product 4-imino acids 2 were converted into their hydrogen chloride salts, as shown in the following procedure with 2b. To a solution of 2b (100 mg) in H₂O (2 cm³) was added aq. conc. HCl (1 cm³); evaporation gave the salt 2b·HCl; crystals, m.p. 210–212 ºC (decomp.); δₜ (DMSO-d₆) 1.42–1.46 (6H, m), 4.06 (2H, m; simplifies to q on treatment with D₂O), 4.65 (2H, q, J 7.0), 7.67 (1H, br t), 8.14 (1H, m), 8.7 (1H, br t), 9.21 (1H, s), 10.95 (1H, br s, removed by D₂O), 13.9 (1H, v br peak, removed by D₂O); m/z identical with that of the free acid 2b.

Spectroscopic properties of the following additional compounds, prepared by the above procedures, are given below.

1-Ethyl-4-ethylimino-1,4-dihydroquinoline-3-carboxylic acid 2a
δₜ (CDCl₃) 1.53–1.59 (6H, m), 3.95–4.03 (2H, m; simplifies to q on treatment with D₂O), 4.40 (2H, q, J 7.2), 7.52–7.56 (1H, m), 7.70–7.73 (1H, m), 7.8–7.9 (1H, m), 8.43 (1H, m), 9.05 (1H, s), 14.2 (1H, br s, removed by D₂O); m/z 244 (M⁺, 61%), 243 (M – 1, 100), 229 (M – CH₃, 21), 200 (M – CO₂, 26), 199 (M – CO₂H, 70), 185 (M – C₂H₃O₂, 69) (Found: M⁺, 244.1213. Calc. for C₁₄H₁₆N₂O₂: M, 244.1219).

Hydrochloride salt: δₜ (DMSO-d₆) 1.32 (3H, t, J 7.0), 1.42 (3H, t, J 7.0), 2.77 (3H, s), 3.61 (simplifies to q on treatment with D₂O), 4.61 (2H, q, J 7.1), 7.76 (1H, t, J 7.8), 8.03 (1H, t, J 7.7), 8.21 (1H, d, J 8.8), 8.80 (1H, d, J 8.4), 9.2 (1H, br t, removed by D₂O), 14.5 (1H, v br peak, removed by D₂O).
1-Cyclopropyl-4-ethylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid 2c
\[ \delta_H \text{ (CDCl}_3 \text{)} 1.20–1.26 (2H, m), 1.38–1.43 (2H, m), 1.56 (3H, t, J 7.1), 3.46–3.52 (1H, m), 3.92–3.99 (2H, m; simplifies to q on treatment with D}_2O\), 7.28–7.33 (1H, m), 7.80–7.84 (1H, m), 8.40–8.44 (1H, m), 9.08 (1H, s), 14.5 (1H, br s, removed by D}_2O\); m/z 274 (M\(^+\), 60%), 273 (M – 1, 93), 259 (M – CH\(_3\), 26), 230 (M – CO\(_2\), 34), 229 (M – CO\(_2\)H, 70), 215 (M – C\(_2\)H\(_3\)O\(_2\), 100) [Found: (M – C\(_2\)H\(_3\)O\(_2\))\(^+\), 215.0990. Calc. for C\(_{13}\)H\(_{12}\)FN\(_2\): 215.0985. Found: M\(^+\), 274.1120. Calc. for C\(_{15}\)H\(_{15}\)FN\(_2\)O\(_2\): M, 274.1118].

1-Ethyl-4-ethylimino-6,7-difluoro-1,4-dihydroquinoline-3-carboxylic acid 2d.
\[ \delta_H \text{ (CDCl}_3 \text{)} , 1.55–1.60 (6H, m), 3.92–3.98 (2H, m; simplifies to q on treatment with D}_2O\), 4.35 (2H, q, J 7.3), 7.49–7.54 (1H, m), 8.24–8.29 (1H, m), 9.04 (1H, s), 14.5 (1H, br s, removed by D}_2O). NOE (CDCl}_3 \text{) (cf. Figure 1), signal irradiated (δ) [NOE observed (δ): 14.5 [9.1 (minor), 4.0, 1.6], 9.1 [4.4, 1.6], 8.3 [4.0, 1.6], 7.5 [4.4, 1.6], 4.4 [9.1, 7.6, 1.6], 4.0 [8.3, 14.5, 1.6], 1.6 [14.5, 9.1, 8.3 (v w), 7.6, 4.3, 4.0]; m/z 280 (M\(^+\), 36%), 279 (M – 1, 51), 265 (M – CH\(_3\), 13), 236 (M – CO\(_2\), 27), 235 (M – CO\(_2\)H, 48), 221 (M – C\(_2\)H\(_3\)O\(_2\), 100) [Found: (M – C\(_2\)H\(_3\)O\(_2\))\(^+\), 221.0889. Calc. for C\(_{12}\)H\(_{11}\)F\(_2\)N\(_2\): 221.0890. Found: M\(^+\), 280.1025. Calc. for C\(_{14}\)H\(_{14}\)F\(_2\)N\(_2\)O\(_2\): M, 280.1023].

1-Ethyl-4-ethylimino-7-fluoro-1,4-dihydro-2-methylquinoline-3-carboxylic acid 2f\(^4\)
Hydrochloride salt: M.p. 200–203 °C (decomp.) (from EtOH-Et\(_2\)O); \[ \delta_H \text{ (DMSO-d}_6 \text{)} 1.31 (3H, t, J 7.1), 1.39 (3H, t, J 7.0), 2.76 (3H, s), 3.61 (2H, m; simplifies to q on treatment with D}_2O\), 4.56 (2H, q, J 7.0), 7.71 (1H, br t), 8.11 (1H, m), 8.97 (1H, m), 9.4 (1H, br t, removed by D}_2O), ca 14.5 (1H, v br peak, removed by D}_2O); m/z 276 ((M – HCl\(^+\), 3.4%) [Found: (M – HCl\(^+\), 276.1265. Calc. for C\(_{15}\)H\(_{17}\)FN\(_2\)O\(_2\) (i.e., C\(_{15}\)H\(_{18}\)ClFN\(_2\)O\(_2\) – HCl), 276.1274].

7-Chloro-1-ethyl-4-ethylimino-1,4-dihydro-2-methylquinoline-3-carboxylic acid 2g
\[ \delta_H \text{ (DMSO-d}_6 \text{)} 1.28 (3H, t, J 7.1), 1.35 (3H, t, J 7.1), 2.81 (3H, s), 3.85 (2H, m; simplifies to q, J 7.1, on treatment with D}_2O\), 4.50 (2H, q, J 7.0), 7.62 (1H, m), 8.15 (1H m), 8.44 (1H, m), ca 12 (1H, v br peak, removed by D}_2O); m/z 292 (M\(^+\), 2%), 291 (M – 1, 2), 248 (M – CO\(_2\), 24), 247 (M – CO\(_2\)H, 18), 233 (M – C\(_2\)H\(_3\)O\(_2\), 100) [Found: (M – C\(_2\)H\(_3\)O\(_2\))\(^+\), 233.0850. Calc. for C\(_{13}\)H\(_{14}\)ClN\(_2\): 233.0846. Found: M\(^+\), 292.0973. Calc. for C\(_{15}\)H\(_{17}\)ClN\(_2\)O\(_2\): M, 292.0979].
Hydrochloride salt: $\delta^H$ (DMSO-d$_6$) 1.31 (3H, t, $J$ 7.0), 1.39 (3H, t, $J$ 7.0), 2.76 (3H, s), 3.61 (2H, m; simplifies to q on treatment with D$_2$O), 4.60 (2H, q, $J$ 7.0), 7.82 (1H, d, $J$ 8.4), 8.30 (1H, d, $J$ 1.7), 8.89 (1H, d, $J$ 9.0), 9.4 (1H, s, removed by D$_2$O), 14.6 (1H, v br peak, removed by D$_2$O); $m/z$ identical with that of free base 2g.

1-Ethyl-4-ethylimino-6,7-difluoro-1,4-dihydro-2-methyquinoline-3-carboxylic acid 2h

Hydrochloride salt: $\delta^H$ (DMSO-d$_6$) 1.32 (3H, t, $J$ 7.1), 1.37 (3H, t, $J$ 7.1), 2.74 (3H, s), 3.60 (2H, m; simplifies to q, $J$ 7.0, on treatment with D$_2$O), 4.57 (2H, q, $J$ 7.1), 8.4–8.5 (1H, m), 9.1–9.2 (1H, m), 9.3 (1H, br t, removed by D$_2$O), 14.6 (1H, v br peak, removed by D$_2$O); $m/z$ 294 [(M – HCl)$^+$, 4%], 293 [(M – HCl – 1)$^+$, 3], 250 [(M – HCl – CO$_2$), 25], 249 [(M – HCl – CO$_2$H), 22], 235 [(M – HCl – C$_2$H$_3$O$_2$), 100] [Found: (M – HCl)$^+$, 294.1180. Calc. for C$_{15}$H$_{16}$F$_2$N$_2$O$_2$ (i.e., C$_{15}$H$_{17}$CClF$_2$N$_2$O$_2$ – HCl), 294.1180].

4-Imino acids 8 and 4-imino amides 9 from 4-oxo acids 4 treated successively with SOCl$_2$ and aqueous amine. General procedure.

This is illustrated with 4-oxo acid 4b and aqueous benzylamine. A mixture of acid 4b (500 mg) and redistilled SOCl$_2$ (5 cm$^3$) was heated under reflux for 1 h, then evaporated to dryness (rotavapor). Adhering SOCl$_2$, was ‘chased off’ with anhydrous benzene, and the residue of 13b was dried in high vacuum. An ice-cold mixture of H$_2$O (5 cm$^3$) containing sodium acetate (1 g) and benzylamine (2 cm$^3$) was added and the reaction mixture was allowed to warm to room temperature with stirring, which was continued overnight. Solvent and excess amine were evaporated (rotavapor generally, or high vacuum for benzylamine), after which H$_2$O (ca 5 cm$^3$) was added and the sparingly soluble N-benzyl-4-benzylimino-1-ethyl-7-fluoro-1,4-dihydroquinoline-3-carboxamide 9e was collected by filtration (158 mg, 18%); m.p. 168–170 $^\circ$C; $\delta^H$ (CDCl$_3$) 1.45 (3H, t, $J$ 7.2), 4.01 (2H, q, $J$ 7.2), 4.56 (2H, d; simplifies to s on treatment with D$_2$O), 4.99 (2H, s), 6.85–7.0 (2H, m), 7.15–7.35 (ca 10H, m), 8.0–8.1 (1H, m), 8.31 (1H, s), 11.9 (1H, br s, removed by D$_2$O) (Found: M$^+$, 413.1903. Calc. for C$_{26}$H$_{24}$FN$_3$O: M, 413.1903). The aqueous filtrate (pH adjusted to ca 5 with 50% aq. HOAc) was repeatedly extracted with CHCl$_3$ and the combined dried (Na$_2$SO$_4$) extract was evaporated to yield ETOAc-insoluble material which was mainly 7-benzylamino-4-benzylimino-1-ethyl-1,4-dihydro-quinoline-3-carboxylic acid 8d (490 mg, 56%); m.p. >240 $^\circ$C; $\delta^H$ (DMSO-d$_6$) 1.14 (3H, t, $J$ 6.9), 4.2–4.35 (2H, q, $J$ 6.9), 4.50 (2H, d;
simplifies to s on treatment with D$_2$O), 5.06 (2H, d; simplifies to s on treatment with D$_2$O), 6.56 (1H, s), 6.93 (1H, d, J 8.0), 7.2–7.5 (10H, m), 7.81 (1H, br t, removed by D$_2$O), 8.19 (1H, d, J 9.5), 8.68 (1H, s), 13.9 (1H, br t, removed by D$_2$O) (Found: M$^+$, 411.1869. Calc. for C$_{26}$H$_{28}$N$_3$O$_2$: M, 411.1867). Other 4-imino acids 8 similarly obtained are listed in Table 2.

Spectroscopic properties of the following additional compounds, prepared by the above procedure, are given below.

1-Ethyl-4-cyclopropylimino-1,4-dihydroquinoline-3-carboxylic acid 8a
\[ \delta_H (\text{CDCl}_3) \]
(4H, m), 1.58 (3H, t, J 7.2), 3.18–3.28 (1H, 8-line m; simplifies to 7-line m on treatment with D$_2$O), 4.43 (2H, q, J 7.2), 7.5–7.62 (1H, m), 7.7–7.8 (1H, m), 7.85–7.95 (1H, m), 9.07 (1H, s), 9.24 (1H, d, J 8.6), 14.2 (1H, br s, removed by D$_2$O); m/z 256 (M$^+$, 5%), 229 (M – 27, 41), 228 (M – 28, 100) (Found: M$^+$, 256.1211. Calc. for C$_{15}$H$_{16}$N$_2$O$_2$: M, 256.1212).

4-Cyclopropylimino-1-ethyl-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid 8b
\[ \delta_H (\text{CDCl}_3) \]
(4H, m), 1.58 (3H, t, J 7.3), 3.15–3.3 (1H, 8-line m; simplifies to 7-line m on treatment with D$_2$O), 4.38 (2H, q, J 7.3), 7.3–7.45 (2H, m), 9.05 (1H, s), 9.2–9.3 (1H, m), 14.3 (1H, br s, removed by D$_2$O); m/z 274 (M$^+$, 4%), 247 (M – CHN, 41), 246 (M – CH$_2$N, 100), 230 (M – CO$_2$, 6), 229 (M – CO$_2$H, 17) (Found: M$^+$, 274.1125. Calc. for C$_{15}$H$_{15}$FN$_2$O$_2$: M, 274.1118).

1-Ethyl-1,4-dihydro-7-propylamino-4-propyliminoquinoline-3-carboxylic acid 8c
\[ \delta_H (\text{CDCl}_3) \]
(6H, m), 1.50 (3H, t, J 7.2), 1.68–1.93 (4H, m), 3.18–3.28 (2H, q; simplifies to t, J 7.2, on treatment with D$_2$O), 3.72–3.82 (2H, q; simplifies to t, J 7.0, on treatment with D$_2$O), 4.22 (2H, q, J 7.1), 6.1 (1H, br t, removed by D$_2$O), 6.56 (1H, d, J 2.0), 6.89 (1H, dd, J 2.1 and 9.4), 8.10 (1H, d, J 9.4), 8.78 (1H, s), 13.2 (1H, br t, removed by D$_2$O) (Found: M$^+$, 315.1928. Calc. for C$_{18}$H$_{25}$N$_3$O$_2$: M, 315.1945).

1-Cyclopropyl-4-cyclopropylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid 8f
\[ \delta_H (\text{CDCl}_3) \]
(8H, m), 3.15–3.24 (1H, 8-line m; simplifies to 7-line m on treatment with D$_2$O), 3.47–3.57 (1H, 7-line m), 7.29–7.38 (1H, m), 7.84 (1H, dd, J 2.6 and 10.2), 9.11 (1H, s), 9.20–9.27 (1H, m), 14.6 (1H, br s, removed by D$_2$O); m/z 286
7-Benzylamino-4-benzylimino-1-cyclopropyl-1,4-dihydroquinoline-3-carboxylic acid 8g
δH (DMSO-d6) 0.75–0.85 (2H, m), 1.0–1.15 (2H, m), ca 3.5 (1H, overlapping DMSO-d6 peak), 4.48 (2H, d; simplifies to s on treatment with D2O), 5.04 (2H, d; simplifies to s on treatment with D2O), 6.9–7.0 (2H, m), 7.2–7.4 (10H, m) 7.93 (1H, br t, removed by D2O), 8.17 (1H, d, J 9.6), 8.56 (1H, s), 14.0 (1H, br t, removed by D2O); m/z 379 (M – CO2, 39%), 378 (M – CO2H, 100), 302, 274, 91 [Found: (M – CO2H)+, 378.1969. Calc. for C27H25N3O2 – CO2H: M, 378.1970].

1-Cyclopropyl-4-ethylimino-1,4-dihydroquinoline-3-carboxylic acid 8h
δH (CDCl3) 1.18–1.45 (4H, m), 1.55 (3H, t, J 7.1), 3.5–3.6 (1H, m), 3.93–4.06 (2H, m; simplifies to q on treatment with D2O), 7.5–7.6 (1H, m) 7.8–7.9 (1H, m), 8.15–8.25 (1H, d, J 8.8), 8.35–8.45 (1H, m), 9.11 (1H, s), 14.3 (1H, br s, removed by D2O); m/z 256 (M*, 63), 255 (M – 1, 100), 241 (M – CH3, 20), 212 (M – CO2, 30), 211 (M – CO2H, 79), 197 (M – C2H3O2, 68) (Found: M*, 256.1210. Calc. for C15H16N2O2: M, 256.1212).

1-Cyclopropyl-4-cyclopropylimino-1,4-dihydroquinoline-3-carboxylic acid 8i
δH (CDCl3), 0.97–1.46 (8H, m), 3.19–3.29 (1H, 8 line m; simplifies to 7-line m on treatment with D2O), 3.52–3.61 (1H, 7-line m), 7.55–7.64 (1H, m), 7.87–7.95 (1H, m), 8.22 (1H, d, J 8.8), 9.15 (1H, s), 9.19 (1H, d, J 8.6), 14.4 (1H, br s, removed by D2O); m/z 268 (M*, 6%), 241(M – 27, 45), 240 (M – 28, 100), 223 (M – CO2H, 15) (Found: M*, 268.1199. Calc. for C16H16N2O2: M, 268.1212).

Hydrolysis of 4-imino acids 2 and 8 to 4-oxo acids 4 and 11. General procedure.
A mixture of 4-imino acid 2 (100 mg), H2O (5 cm³), MeOH or dioxane (5 cm³, or sufficient organic solvent to dissolve the substrate at reflux), and NMe4OH (1 cm³ of a 25% aqueous solution) was heated at reflux for 1 h. The solvent was evaporated and the residue was treated with H2O (ca 2 cm³), and extracted with CHCl3. The aqueous phase was acidified to pH ca 5 with 50% aq. HOAc, chilled, and the product 4-oxo acid 4 was collected by filtration. Thus, from 4-imino acid 2b (100 mg) was obtained the known⁴ 1-ethyl-1,4-dihydro-7-fluoro-4-oxoquinoline-3-carboxylic acid 4b (77 mg, 86%).
m.p. 302–304 °C (from MeOCH₂CH₂OH); ν\text{max} (KBr)/cm⁻¹ 3500–3200, 1610, 1570, 1450; δ\text{H} (DMSO-d₆) 1.40 (3H, t, J 7.2), 4.57 (2H, q, J 7.2), 7.5–7.6 (1H, m), 7.95–8.05 (1H, dd, J 2.2 and 10.4), 8.4–8.5 (1H, m), 9.08 (1H, s), 15.1 (1H, br s, removed by D₂O). In the case of an amphoteric product 11 (R² = 7-alkylamino) arising from certain substrates 8, this was isolated by exhaustive extraction of the acidified (pH ca 5) hydrolysis mixture with CHCl₃. Each product 4-oxo acid 4¹⁷ or 11 was identified from its spectral (¹H NMR and/or IR) properties, and on occasion, (e.g., 11c) by comparison with authentic material synthesised by a literature¹⁸ method.

Quinolinium chloride 13b from 7-fluoro-4-oxo acid 4b and SOCl₂
A mixture of 4-oxo acid 4b (500 mg) and redistilled SOCl₂ (5 cm³) was heated at reflux for 1 h. To the hot solution dry benzene was added portionwise to cause precipitation of title product 13b. The mixture was chilled and the colourless crystals were collected by filtration, washed with cold benzene, and dried in vacuo over KOH (Found: C, 47.48; H, 3.40; N, 4.55; Cl, 22.09. Calc. for C₁₂H₁₀Cl₂FNO₂: C, 49.68; H, 3.47; N, 4.83; Cl, 24.44%); ν\text{max}(KBr)/cm⁻¹ 1700 (s), 1620 (s), 1565. The identical (IR spectrum) quinolinium chloride 13b resulted also after heating 4-oxo acid 4b (500 mg) with SOCl₂ (5 cm³) at reflux for 1 h and merely evaporating off (rotavapor) the excess SOCl₂. Product 13b dissolved readily in H₂O; on standing at room temperature, crystals of 4-oxo acid 4b (IR spectrum) separated from solution within 15 min. Crystalline 13b decomposed slowly at room temperature, and more rapidly on heating; when placed on a hot-plate at 220–240 °C, it melted with effervescent evolution of hydrogen chloride and resolidified to 4-oxo acid 4b (IR spectrum). Freshly prepared 13b (160 mg) was stirred with absolute EtOH (5 cm³) at room temperature for 48 h. A small amount (10.3 mg) of 4-oxo acid 4b (IR) was removed by filtration. The filtrate was basified (with 1.0 mol dm⁻³ NaOH) and extracted with CHCl₃ to yield 7-fluoro-4-oxo ester 3b (92.3 mg, 64%); crystals (from EtOAc–hexane), m.p. 127 °C, and identified from its ¹H-NMR spectrum (vide supra).

Preparation and reactions of the putative 4-imino carbonyl chloride 14
(a) With EtOH. Imino acid 2b (126 mg) was heated under reflux with SOCl₂ (5 cm³) for 1 h, after which solvent was evaporated and adhering SOCl₂ was ‘chased off’ with benzene. To the residue of supposed 14b was added ice-cold absolute EtOH (3 cm³)
and the reaction was kept at room temperature for 2 h, when TLC monitoring showed complete conversion of the substrate 2b into the 4-imino ester 1b. CHCl₃ was added and the organic phase was washed with aq. NaHCO₃. Evaporation of the CHCl₃ extract gave target ester 1b (136 mg); m.p. 135–137 °C (from EtOAc–hexane) and identical (IR, mixture m.p.) with literature³ material.

(b) With cyclopropylamine. 4-Imino acid 2a (75 mg) was treated with SOCl₂ (5 cm³) as in (a) above. To the chilled residue of supposed 14a was added dry cyclopropylamine (200 mg, excess) and the mixture was allowed to remain overnight at room temp. Work-up (vide supra) afforded crude N-cyclopropyl-4-cyclopropylimino amide 9a (80 mg). The product after purification was identical (¹H NMR, m.p. and mixture m.p.) with that obtained from 4-oxo acid 4a, SOCl₂ and cyclopropylamine.¹⁰

(c) With propylamine. 7-Propylamino-imino acid 11c (160 mg) was treated successively with SOCl₂ and dry propylamine (1.5 g, excess) as in (b). Work-up (vide supra) gave crude N-propyl-7-propylamino-4-propylimino amide 9c (ca 60%). The product after purification was identical (¹H NMR, m.p. and mixture m.p.) with that obtained from 7-fluoro-4-oxo acid 4b, SOCl₂ and propylamine.¹⁰

Reaction of 1-benzyl-7-fluoro-4-oxo acid 4i with SOCl₂

Acid 4i (500 mg) was heated under reflux with SOCl₂ (10 cm³) as for 4-oxo acid 4b (vide supra); following evaporation of SOCl₂ the residue of 13b was treated with H₂O to give sparingly soluble 7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid 15a; crystals, m.p. 267–268 °C (decomp.) (from MeOH) [lit.,¹⁹ 267–268 °C (decomp.)]; δH (DMSO-d₆) 7.4–7.6 (2H, m), 8.3–8.4 (1H, m), 8.95 (1H, s), 13.4 (1H, v br peak, removed by D₂O), 15.2 (1H, br s, removed by D₂O); m/z 207 (M⁺). 1-tert-Butyl-7-fluoro acid 14 similarly afforded the same product 15a. Treatment of the aforementioned residue with H₂O–cyclopropylamine mixture as described with 4-oxo acid 4b (vide supra) gave sparingly soluble 4-chloro-N-cyclopropyl-7-fluoroquinoline-3-carboxamide 16c; crystals, m.p. 178–180 °C (from EtOAc); δH (CDCl₃) 0.6–1.0 (4H, m), 2.92–3.04 (1H, m), 6.54 (1H, br s, removed by D₂O), 7.4–7.5 (1H, m), 7.72 (1H, dd, J 2.5 and 9.5), 8.2–8.3 (1H, m), 8.97 (1H, s); m/z 264 (M⁺, ³⁵Cl), 208, 180, 153. With dry cyclopropylamine in lieu of the H₂O–amine mixture the product was N-cyclopropyl-4-cyclopropylamino-7-fluoroquinoline-3-carboxamide 16a; crystals, m.p. 213–217 °C (from MeOH–H₂O); δH (CDCl₃) 0.6–1.06 (8H, m), 2.79–2.91 (1H, m) 3.07–3.19 (1H,
m), 6.6 (1H, br s, removed by D₂O), 7.05–7.18 (1H, m), 7.49 (1H, dd, J 2.7 and 10.1), 8.54 (1H, s), 8.95–9.05 (1H, m), 10.0 (1H, br s, removed by D₂O); m/z 285 (M⁺, 11%), 229 (M – C₆H₃N, 100%), 201 (69%) (Found: M⁺, 285.1255. Calc. for C₁₆H₁₆FN₃O: M, 285.1277). Hydrolysis of 4-chloro-7-fluoro amide 16c as described for 4-imino acid 2 (vide supra) gave N-cyclopropyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxamide 15b; crystals, m.p. >250 °C (from MeOH); δₓ (CDCl₃) 0.7–0.95 (4H, m), 2.95–3.08 (1H, m), 7.1–7.2 (1H, m), 7.38 (1H, dd, J 2.3 and 9.1), 8.4–8.5 (1H, m), 8.88 (1H, d; simplifies to s on treatment with D₂O), 10.4 (1H, br peak, removed by D₂O), 11.6 (1H, br peak, removed by D₂O); m/z 246 (M⁺), 218, 190, 152.

4-Imino acids 8 from hydrochloride salts of 4-imino ester 1b treated with aqueous amine. General procedure.

To a solution of 1b·HCl (1 mmol) dissolved in H₂O (4 cm³) was added the amine (6–10 mmol) (EtNH₂ in the form of 1 cm³ of 70% EtNH₂ in H₂O) and the mixture was stirred at room temperature for 2–4 d, or at 40 °C for 6 h when, generally, TLC [benzene–acetone (3:1) + 5% Et₃N] showed the reaction to be complete. For most amines the free imino ester 1b initially separated; this dissolved (R¹ = H, within 5–10 min; R¹ = Me, within 0.5–1 h) to give a yellow solution. Exhaustive extraction of the reaction mixture with CHCl₃ followed by evaporation of the organic solvent and excess amine provided a major portion of the title acid 8 and all of any aqueous ammonia-insoluble 7-alkylamino-4-alkylimino amide 9 by-product.¹⁰ Products 8c (from propylamine), and 8d (from benzylamine) were identical (¹H NMR, m.p. and mixture m.p.) with the respective preparations from 4-oxo acid 4b treated successively with SOCl₂ and the appropriate amine (vide supra). Other 4-imino acids 8 similarly obtained are listed in Table 3.

In the case of 1-ethyl-4-ethylimino-1,4-dihydro-7-(4-methylpiperazinyl)quinoline-3-carboxylic acid 8k (from 4-methylpiperazine), liquid–liquid extraction overnight of the reaction provided the product as a semi-solid mass which, on crystallisation from MeOH–Et₂O, gave the title acid, m.p. 134–136 °C; δₓ (CDCl₃) 1.47–1.56 (6H, m), 2.39 (3H, s), 2.58–2.64 (4H, m), 3.46–3.51 (4H, m), 3.85–3.91 (2H, m; simplifies to q on treatment with D₂O), 4.26 (2H, q, J 7.2), 6.69 (1H, d, J 2.3), 7.06 (1H, dd, J 2.4 and 9.6), 8.20 (1H, d, J 9.6), 8.86 (1H, s), 13.5 (1H, br peak, removed by D₂O); m/z 342 (M⁺, 5%), 341 (M – 1, 4), 298 (M – CO₂, 25), 297 (M – CO₂H, 18), 283 (M – C₂H₃O₂,100) [Found: (M – C₂H₃O₂)⁺, 283.1911. Calc. for C₁₇H₂₁N₄: 283.1923. Found: M⁺, 342.2031. Calc. for C₁₉H₂₆N₄O₂: M, 342.2056].
Hydrolysis (*vide supra*) of acid **8k** gave 1-ethyl-1,4-dihydro-7-(4-methyl-piperazinyl)-4-oxoquinoline-3-carboxylic acid **11k**. Crystals, m.p. 210–211 °C; (lit.,\(^1\) 215 °C); \(\delta_H\) (CDCl\(_3\)) 1.58 (3H, t, \(J\, 7.1\)), 2.39 (3H, s), 2.55-2.65 (4H, m), 3.40–3.50 (4H, m), 4.29 (2H, q, \(J\, 7.2\)), 6.67 (1H, d, \(J\, 1.9\)), 7.13 (1H, dd, \(J\, 2.0\) and 9.2), 8.30 (1H, d, \(J\, 9.2\)), 8.61 (1H, s), 15.5 (1H, br peak, removed by D\(_2\)O); \(m/z\) 315 (M\(^+\), 68%), 272 (M – CO\(_2\), 19), 271 (M – CO\(_2\)H, 100) (Found: M\(^+\), 315.1589. Calc. for C\(_{17}\)H\(_{21}\)N\(_3\)O\(_3\): M, 315.1583).

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**References**

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6 We thank Professor D.C. Levendis and Ms. L. Cook, University of the Witwatersrand, for the X-ray crystal structure determination of salt **2f**·HCl, details of which will be reported elsewhere.
8 It is noteworthy that the related \(N,N\)-dimethylanthranilic acid in the solid state is reported to have a structure analogous to **2A**, which changes in solution to a
structure related to 2B, as evidenced from an IR study (K.R.K. Rao and C.I. Jose, *Spectrochim. Acta*, 1974, **30A**, 859). We thank a Referee for valuable input relating to the structure of 4-imino acid 2.


14 T. van Es and B. Staskun, unpublished work.


