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RESEARCH ARTICLE

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

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Abstract

1-Alkyl-1,4-dihydro-4-iminoquinoline-3-carboxylates undergo neutral hydrolysis (in H_2O or H_2O–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_2O 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, ^{1}H NMR) properties are described.

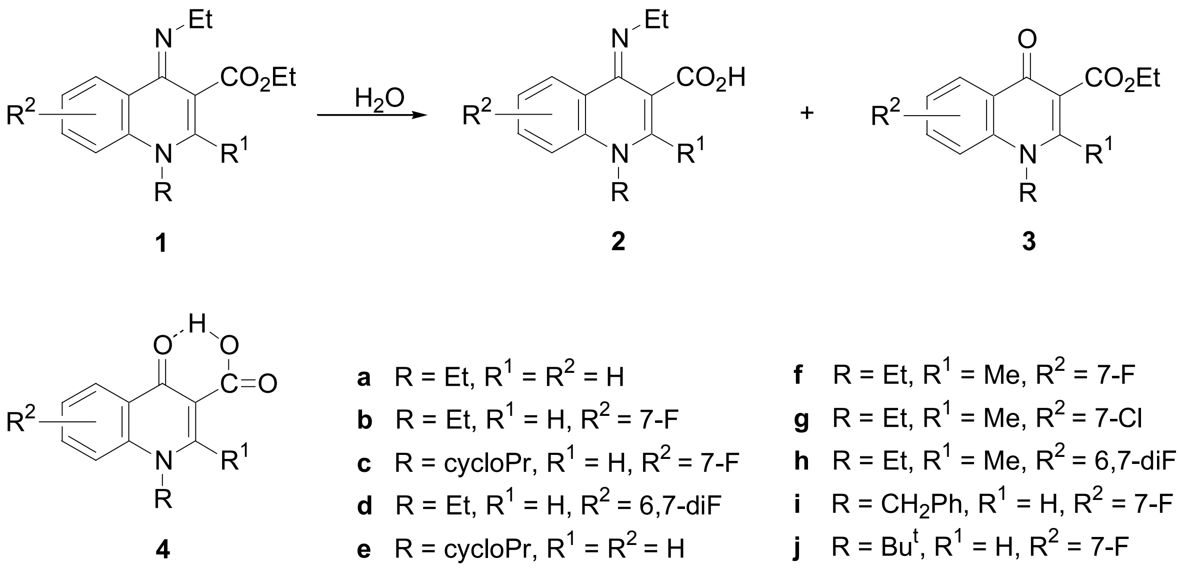
Keywords: Quinolin-4-imines; intramolecular hydrogen bonds; charge transfer structure; mechanism.

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.[2] 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[3] 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).

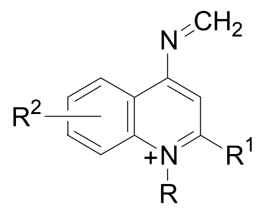


Scheme 1 The geometry of the imine group in the structures depicted above and elsewhere is not specified.

The new 4-imino acids **2** (Table 1) were obtained as colourless crystalline solids (from EtOH–Et_2O) 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 = 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)[4] for 1 h gave the 7-fluoro-4-oxo acid **4b** (86%). In exploratory studies with 4-ethylimino-7-fluoro-2-methyl acid **2f**[4] 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[5] systems.

The mass spectra of the 4-imino acids **2** (R^1 = H or Me, Scheme 1) in general showed weak peaks for the M^+ and $(M - 1)^+$ ions, with more intense ones for the $(M - CO_2)^+$ and $(M - CO_2H)^+$ fragments, and a base peak (100%) [shown from accurate mass determination to correspond to a $(M - C_2H_3O_2)^+$ 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**.



C

Examination of 4-imino acids **2** by ^{1}H NMR (200 MHz) spectroscopy provided the following general information. (i) The ^{1}H NMR ($CDCl_3$ or DMSO-d_6) spectrum of each acid **2** exhibited, *inter alia*, the 'acidic' proton as a D_2O-replaceable, broad absorption (sometimes discernible as a triplet) near δ 14, and the methylene protons of the 4-ethylimino function as a crude quintet (*J ca* 7 Hz) near δ 3.7 which collapsed to a quartet on exchange with D_2O. (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.

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

Substrate		Product 4-Imino acid **2**[a]					Product 4-Oxo ester **3a**[a]		
4-Imino ester (mmol)	Reaction conditions[b]	Compd	Molecular Formula	Yield(%)[c]	m.p.(^{o}C)[d]	δ-value[e]	Compd	Yield(%)[c]	m.p. (^{o}C)
1a (1.0)	H_2O (25 cm^3) reflux (1.5 h)	**2a**	$C_{14}H_{16}N_2O_2$	95	220	14.2 (br s)[f]	**3a**	4	—[g]
1b (4.7)	H_2O (50 cm^3) reflux (1.5 h)	**2b**	$C_{14}H_{15}FN_2O_2$	75	198–200	14.4* (br t)[f]	**3b**	12	127
1c (3.0)	H_2O (35 cm^3) reflux (1.5 h)	**2c**	$C_{15}H_{15}FN_2O_2$	83	224–225	14.5 (br)	**3c**	7	178–180
1d (1.0)	H_2O (25 cm^3) reflux (1.5 h)	**2d**	$C_{14}H_{14}F_2N_2O_2$	90	208–210	14.5 (br s)	**3d**	10	154
1g (2.0)	H_2O (25 cm^3) + EtOH (10 cm^3) reflux (1.5 h)	**2g**	$C_{15}H_{17}ClN_2O_2$	49	216–218	*ca*12* (v br)	**3g**	47	97–98
1h (1.0)	H_2O (25 cm^3) reflux (1.5 h)	**2h**	$C_{15}H_{16}F_2N_2O_2$	75[h]	204–205 (decomp.)[h]	—[g]	**3h**	12	—[g]

[a] Crystallisation of **2** usually from EtOH–Et_2O; 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_3N 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_2O-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 ^{1}H NMR (DMSO-d_6) spectra of the mono(hydrogen chloride) salts of 4-imino acids **2f**[4] and **2g** each showed, *inter alia*, a D_2O-exchangeable, very broad absorption (1H) near δ 14.5 (attributed to a carboxylic acid proton), a D_2O-exchangeable, broad triplet (1H) near δ 9.4 (indicative of this proton being bonded to N), and a complex multiplet (2H) near δ 3.7, converted into a quartet by D_2O, for the 4-ethylimino methylene protons. NOE experiments identified the 'acidic' proton near δ 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]

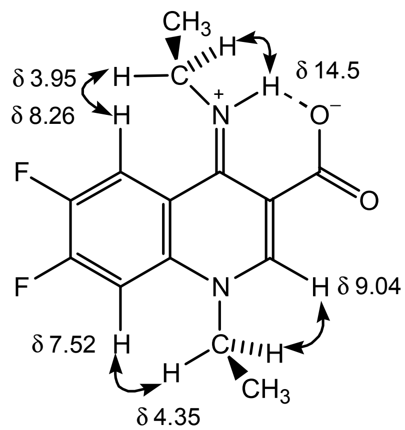
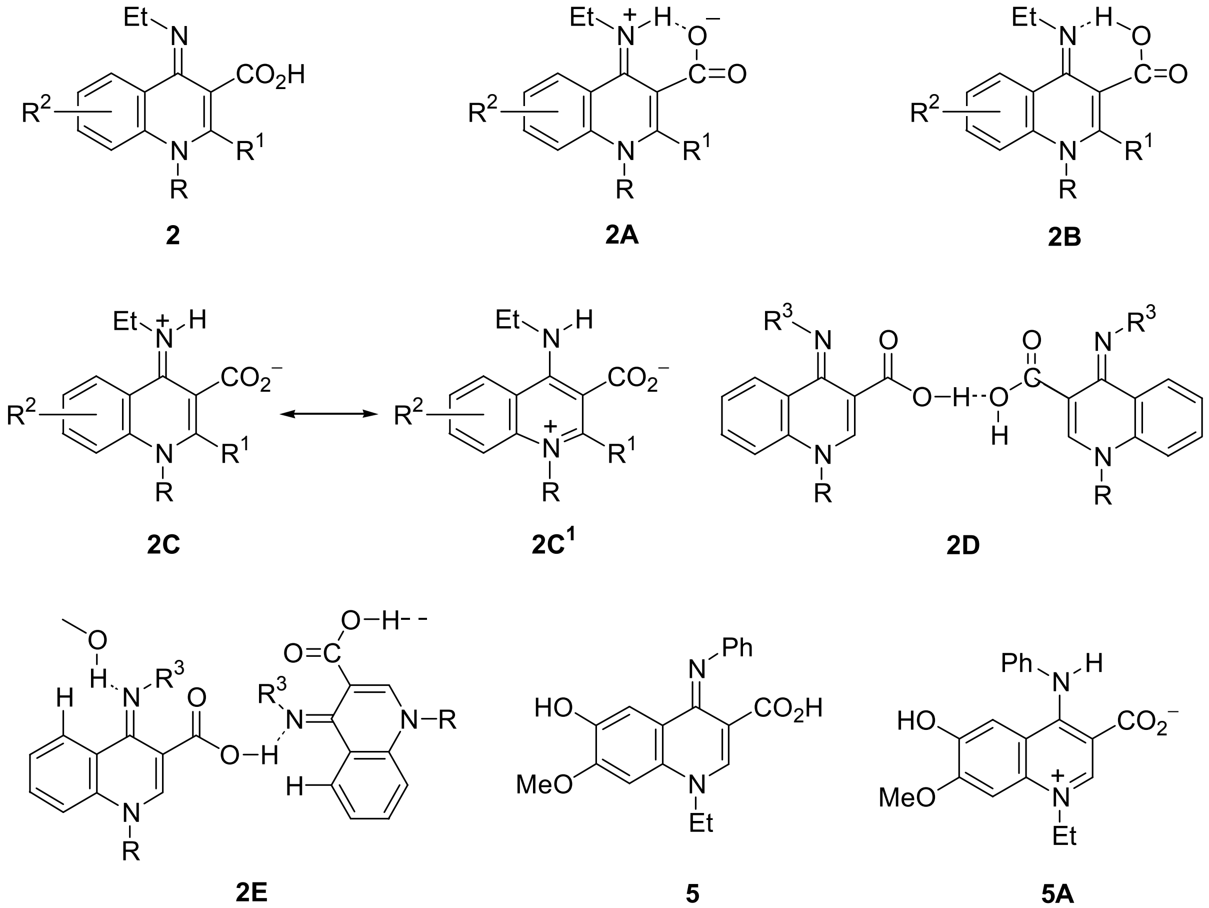


Figure 1 Key NOE interactions and chemical shift values ($CDCl_3$) in 4-imino acid **2d**.

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 ^{1}H NMR phenomena, as far as we are aware, has been reported.[7,8] (b) In the zwitterionic assignment **2C**, which lacks hydrogen bonding, the iminium proton is comparable to the one in salt **2f**·HCl (*vide supra*), and could therefore be expected to resonate near δ 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**, *viz.*, **2C^1^**, is also not favoured in view of UV evidence[2] militating against an analogous betaine structure **5A** for a related 4-imino acid **5**.



Scheme 2

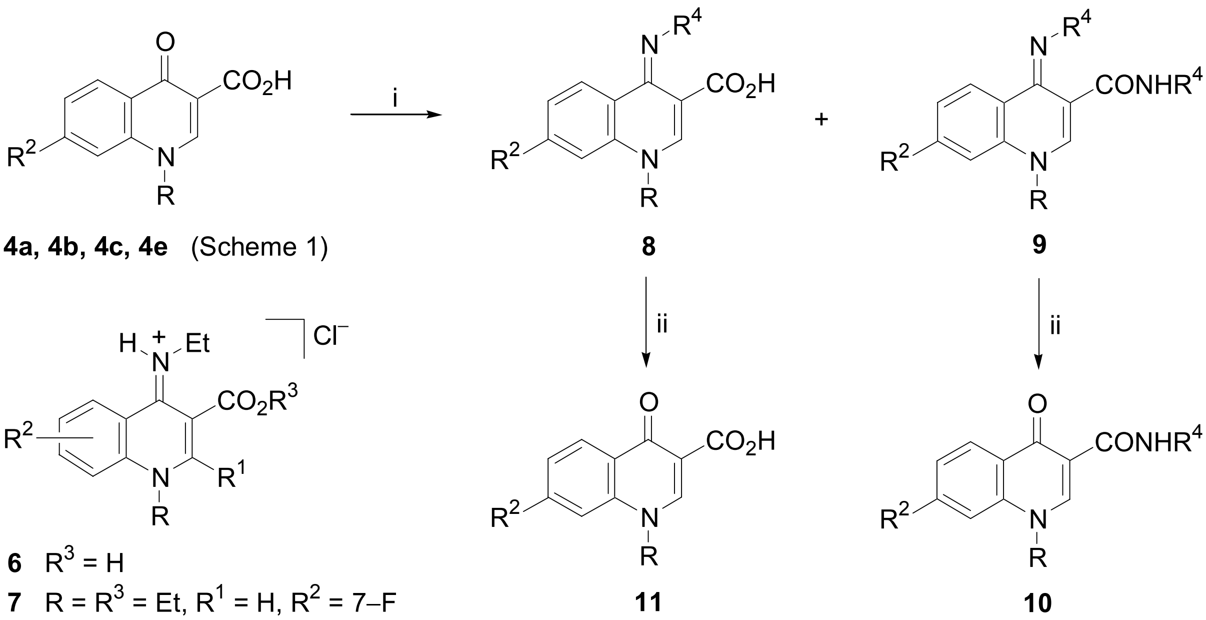
Scheme 2 also shows two possible representative intermolecularly hydrogen-bonded assignments for 4-imino acid **2**, *viz.*, **2D** and **2E**. However, neither is compatible with the available ^{1}H NMR and/or NOE spectroscopic evidence, and they are not favoured. Specifically, **2D** would not exhibit coupling of the 'acidic' proton with the methylene protons of the 4-ethylimino group, as is observed in **2** (*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** (*vide supra*).

Table 2 4-Imino acids **8** and 4-imino amides **9** from 4-oxo acids **4** treated successively with $SOCl_2$ and $H_2O–R^4NH_2$ mixtures.

Substrate 4-Oxo acid **4**	Amine R^4NH_2 R^4	Product 4-Imino acid **8**[a]					Product 4-Imino amide **9**[a,b]		
		Compd	Molecular Formula	Yield (%)[c]	m.p. (°C)[d]	δ-value[e]	Compd	Molecular Formula	Yield (%)[c]
4a	cycloPr	**8a**	$C_{15}H_{16}N_2O_2$	60	228–230	14.2 (br s)[f]			*ca* 20[g]
4b	cycloPr	**8b**	$C_{15}H_{15}FN_2O_2$	56	219–221	14.3 (br s)	**9b**	$C_{18}H_{20}FN_3O$	38
4b	Pr	**8c**	$C_{18}H_{25}N_3O_2$	85	236–238	13.2 (br t)[f]			*ca* 10[g]
4b	CH_2Ph	**8d**	$C_{26}H_{25}N_3O_2$	56	248–249	13.9* (br t)	**9e**	$C_{26}H_{24}FN_3O$	18
4c	cycloPr	**8f**	$C_{16}H_{15}FN_2O_2$	82	235–236	14.6 (br s)	**9f**	$C_{19}H_{20}FN_3O$	16
4c	CH_2Ph	**8g**	$C_{27}H_{25}N_3O_2$	>90	231–233	14.0* (br t)			*ca* 10[g]
4e	Et	**8h**	$C_{15}H_{16}N_2O_2$	70	214–215	14.3 (br s)			*ca* 20[g]
4e	cycloPr	**8i**	$C_{16}H_{16}N_2O_2$	70	>220	14.4 (br s)			*ca* 20[g]

[a] Crystallisation of **8** usually from EtOH–Et_2O; 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 D_2O-exchangeable 'acidic' proton. ^1H NMR spectra were run in $CDCl_3$, otherwise* in DMSO-d_6.
[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_2O mixture.[9] For example, 4-oxo acid **4b** was heated under reflux with $SOCl_2$ for 1 h; after evaporative removal of excess reagent the residue of supposed quinolinium chloride **13b** (Scheme 4) was stirred with aqueous benzylamine at room temperature to give 7-benzylamino-4-benzylimino acid **8d** (56%) together with *N*-benzyl-4-benzylimino-7-fluoro amide **9e** (18%). The outcomes from similar reaction between a variety of 4-oxo acids **4** and amines are listed in Table 2.



4a, 4b, 4c, 4e (Scheme 1) **8** **9**

6 R^3 = H
7 R = R^3 = Et, R^1 = H, R^2 = 7–F

11 **10**

a R = Et, R^2 = H, R^4 = cycloPr
b R = Et, R^2 = F, R^4 = cycloPr
c R = Et, R^2 = NHPr, R^4 = Pr
d R = Et, R^2 = $NHCH_2Ph$, R^4 = CH_2Ph
e R = Et, R^2 = F, R^4 = CH_2Ph
f R = R^4 = cycloPr, R^2 = F
g R = cycloPr, R^2 = NCH_2Ph, R^4 = CH_2Ph
h R = cycloPr, R^2 = H, R^4 = Et
i R = R^4 = cycloPr, R^2 = H
j R = Et, R^2 = NHcycloPr, R^4 = cycloPr
k R = R^4 = Et, R^2 = 4-methylpiperazinyl

Scheme 3 *Reagents and conditions:* (i) $SOCl_2$, reflux, 1 h, evaporation, then R^4NH_2–H_2O mixture, rt, 12h; (ii) H_2O, MeOH, NMe_4OH, reflux, 1 h.

Each product (Tables 1, 2) was characterized from its spectral (^1H 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 **8c**, hydrolysis gave 7-propylamino-4-oxo acid **11c**. Treatment of the latter acid **11c** successively with $SOCl_2$ and dry propylamine afforded *N*-propyl-7-propylamino-4-propylimino amide **9c**,[10] a reaction of potential synthetic utility.

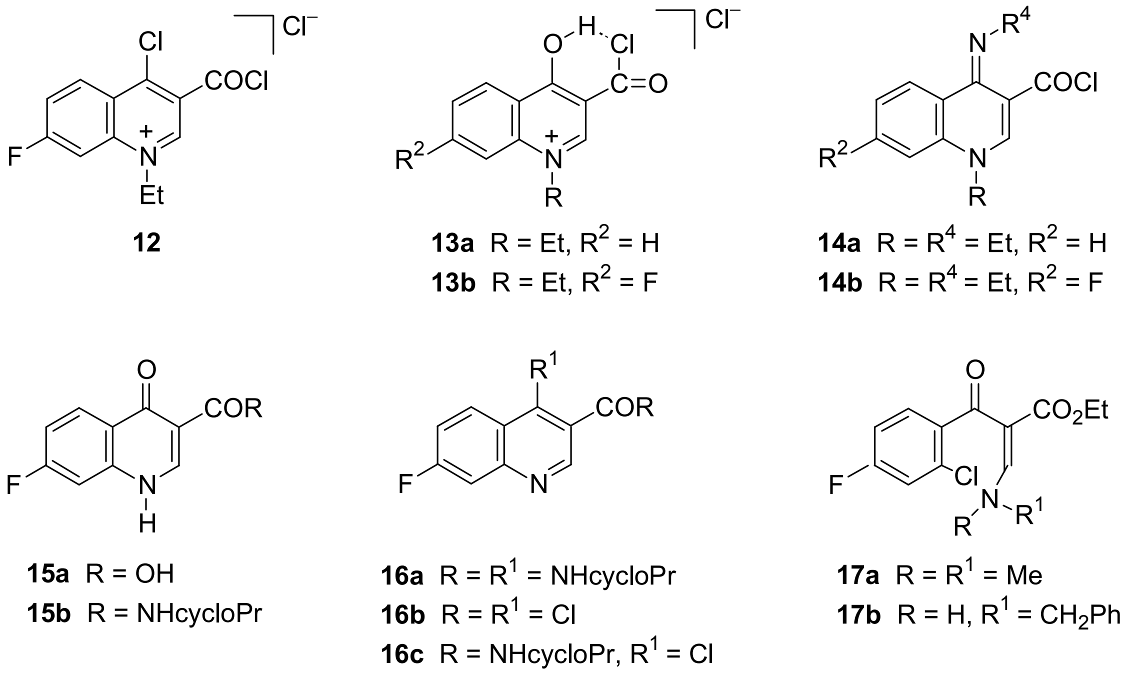
Currently, it is surmised that the production of 4-imino acid **8** and 4-imino amide **9** from quinolinium chloride **13** and aqueous amine (Table 2) occurs by (i) the amine substituting **13** initially at C-4, eventuating in (ii) an intermediate species, such as a 4-imino carbonyl chloride **14** (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 $SOCl_2$ and EtOH, yielded 4-ethylimino-fluoro ester **1b**; while from 4-ethylimino acid **2a**, $SOCl_2$ and dry cyclopropylamine, *N*-cyclopropyl-4-cyclopropylimino amide **9a** was formed by way of a participating imine–amine[10,11] exchange.

A limitation in the synthesis of 4-imino acid **2** from 4-oxo acid **4** (R^1 = H), $SOCl_2$ 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 $SOCl_2$, eliminated benzyl chloride.[12] Treatment of the residual product with H_2O 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-fluoro-quinoline-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-[13] or 2-ethyl-[14] substituted 4-oxo acid **4** as substrate, since this reacts with $SOCl_2$ 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[15] 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[16] 7-(4-methylpiperazinyl)-4-oxo acid **11k**. A significant concentration of H^+ 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^1 = Me) by this method appears to be feasible and this aspect is being studied.



Scheme 4

Table 3 4-Imino acids **8** and 4-imino amides **9** from 4-imino ester **1** hydrochlorides and H_2O–amine (R^4NH_2) mixtures.

Substrate	Amine R^4NH_2	Product(s);[a] (Yield, %);[b] m.p., °C	
	R^4	4-Imino acid **8**	4-Imino amide **9**
1b·HCl	Et [c]	**8l** (80) >250 [d]	— [e]
1b·HCl	Pr	**8c** (80) 236–238 [d]	**9c** (16) 187–188
1b·HCl	CH_2Ph	**8d** (70-80) >240 [d]	— [e]
1b·HCl	1-Methylpiperazine	**8k** (50-70) 210–211	— [e]
1b	Et [c,f]	**8l** (95) >250 [d]	— [e]
2b	1-Methylpiperazine	**8k** (95) 210–211	— [e]

[a] Identified from ^1H NMR and mixture m.p. comparison with material prepared by the 4-oxo acid **4b**/$SOCl_2$/H_2O-amine reaction (ref. 9), and/or by a literature method (ref. 10).
[b] Yield refers to vacuum-dried crude material. [c] $EtNH_2$ added as a 70% aqueous solution.
[d] Melted with decomposition.
[e] Not isolated or obtained.
[f] Conc. HCl (1–2 drops) added to reaction mixture.

3. Experimental

General methods have been described previously.[3] All reagents and solvents were of reagent grade quality and were used without further purification. ^1H 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. Boshoff, 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**[3] (Table 1), 4-oxo acids **4** and their precursor 4-oxo esters **3** (Scheme 1) required for this work were synthesised by literature[11,17] 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;[17] this product enamine was treated with benzylamine in EtOH to effect exchange[11] to the 3-benzylamino enamine **17b**, which was then cyclised to title ester **3i**. Crystals, m.p. 190–192 ºC (from EtOAc); δ_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 ºC; δ_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_2O).

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**[3] (1.37 g, 4.72 mmol) and H_2O (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 ºC) 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 × 2 cm^3) and finally with hexane to give crystals (0.93 g, 75%), m.p. 198–200 ºC (decomp.); δ_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 D_2O), 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 D_2O), *m/z* 262 (M^+, 39%), 261 (M – 1, 60), 247 (M – CH_3, 15), 218 (M – CO_2, 30), 217 (M – CO_2H, 53), 203 (M – $C_2H_3O_2$, 100) [Found: (M – $C_2H_3O_2$)$^+$, 203.0989. Calc. for $C_{12}H_{12}FN_2$: 203.0985. Found: M^+, 262.1121. Calc. for $C_{14}H_{15}FN_2O_2$ *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); δ_H ($CDCl_3$) 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 (^{1}H NMR) with 4-oxo ester **3b** synthesised by a literature[17] 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 H_2O (2 cm^3) was added aq. conc. HCl (1 cm^3); evaporation gave the salt **2b**·HCl; crystals, m.p. 210–212 ºC (decomp.); δ_H (DMSO-d_6) 1.42–1.46 (6H, m), 4.06 (2H, m; simplifies to q on treatment with D_2O), 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 D_2O), 13.9 (1H, v br peak, removed by D_2O); *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**

δ_H ($CDCl_3$) 1.53–1.59 (6H, m), 3.95–4.03 (2H, m; simplifies to q on treatment with D_2O), 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 D_2O); *m/z* 244 (M^+, 61%), 243 (M – 1, 100), 229 (M – CH_3, 21), 200 (M – CO_2, 26), 199 (M – CO_2H, 70), 185 (M – $C_2H_3O_2$, 69) (Found: M^+, 244.1213. Calc. for $C_{14}H_{16}N_2O_2$: *M*, 244.1219).

Hydrochloride salt: δ_H (DMSO-d_6) 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 D_2O), 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 D_2O), 14.5 (1H, v br peak, removed by D_2O).

1-Cyclopropyl-4-ethylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid **2c**

δ_H ($CDCl_3$) 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_2H, 70), 215 (M – $C_2H_3O_2$, 100) [Found: (M – $C_2H_3O_2$)$^+$, 215.0990. Calc. for $C_{13}H_{12}FN_2$: 215.0985. Found: M^+, 274.1120. Calc. for $C_{15}H_{15}FN_2O_2$: *M*, 274.1118].

1-Ethyl-4-ethylimino-6,7-difluoro-1,4-dihydroquinoline-3-carboxylic acid **2d**.

δ_H ($CDCl_3$), 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 ($CDCl_3$) (*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_2H), 48), 221 (M – $C_2H_3O_2$, 100) [Found: (M – $C_2H_3O_2$)$^+$, 221.0889. Calc. for $C_{12}H_{11}F_2N_2$: 221.0890. Found: M^+, 280.1025. Calc. for $C_{14}H_{14}F_2N_2O_2$: *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 ºC (decomp.) (from EtOH-Et_2O); δ_H (DMSO-d_6) 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 $C_{15}H_{17}FN_2O_2$ (*i.e.*, $C_{15}H_{18}ClFN_2O_2$ – HCl), 276.1274].

7-Chloro-1-ethyl-4-ethylimino-1,4-dihydro-2-methylquinoline-3-carboxylic acid **2g**

δ_H (DMSO-d_6) 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_2H, 18), 233 (M – $C_2H_3O_2$, 100) [Found: (M – $C_2H_3O_2$)$^+$, 233.0850. Calc. for $C_{13}H_{14}ClN_2$: 233.0846. Found: M^+, 292.0973. Calc. for $C_{15}H_{17}ClN_2O_2$: *M*, 292.0979].

Hydrochloride salt: δ_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_2O), 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_2O), 14.6 (1H, v br peak, removed by D_2O); *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: δ_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_2O), 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_2O), 14.6 (1H, v br peak, removed by D_2O); *m/z* 294 [$(M - HCl)^+$, 4%], 293 [$(M - HCl - 1)^+$, 3], 250 [$(M - HCl - CO_2)$, 25], 249 [$(M - HCl - CO_2H)$, 22], 235 [$(M - HCl - C_2H_3O_2)$, 100] [Found: $(M - HCl)^+$, 294.1180. Calc. for $C_{15}H_{16}F_2N_2O_2$ (*i.e.*, $C_{15}H_{17}CClF_2N_2O_2 - HCl$), 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_2O (5 cm^3) containing sodium acetate (1 g) and benzylamine (2 cm^2) 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_2O (*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 ºC; δ_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_2O), 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_2O) (Found: M^+, 413.1903. Calc. for $C_{26}H_{24}FN_3O$: *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_2SO_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 ºC; δ_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_2O), 5.06 (2H, d; simplifies to s on treatment with D_2O), 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_2O), 8.19 (1H, d, *J* 9.5), 8.68 (1H, s), 13.9 (1H, br t, removed by D_2O) (Found: M^+, 411.1869. Calc. for $C_{26}H_{25}N_3O_2$: *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**

δ_H ($CDCl_3$) 0.97–1.26 (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_2O), 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_2O); *m/z* 256 (M^+, 5%), 229 (M – 27, 41), 228 (M – 28, 100) (Found: M^+, 256.1211. Calc. for $C_{15}H_{16}N_2O_2$: *M*, 256.1212).

4-Cyclopropylimino-1-ethyl-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid **8b**

δ_H ($CDCl_3$) 0.8–1.2 (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_2O), 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_2O); *m/z* 274 (M^+, 4%), 247 (M – CHN, 41), 246 (M – CH_2N, 100), 230 (M – CO_2, 6), 229 (M – CO_2H, 17) (Found: M^+, 274.1125. Calc. for $C_{15}H_{15}FN_2O_2$: *M*, 274.1118).

1-Ethyl-1,4-dihydro-7-propylamino-4-propyliminoquinoline-3-carboxylic acid **8c**

δ_H ($CDCl_3$) 1.0–1.13 (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_2O), 3.72–3.82 (2H, q; simplifies to t, *J* 7.0, on treatment with D_2O), 4.22 (2H, q, *J* 7.1), 6.1 (1H, br t, removed by D_2O), 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_2O) (Found: M^+, 315.1928. Calc. for $C_{18}H_{25}N_3O_2$: *M*, 315.1945).

1-Cyclopropyl-4-cyclopropylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid **8f**

δ_H ($CDCl_3$) 0.97–1.47 (8H, m), 3.15–3.24 (1H, 8-line m; simplifies to 7-line m on treatment with D_2O), 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_2O); *m/z* 286

(M^+, 3%), 259 (M – 27, 41), 258 (M – 28, 100), 241 (M – CO_2H, 13) (Found: M^+, 286.1117. Calc. for $C_{16}H_{15}FN_2O_2$: *M*, 286.1118).

7-Benzylamino-4-benzylimino-1-cyclopropyl-1,4-dihydroquinoline-3-carboxylic acid **8g**
δ_H (DMSO-d_6) 0.75–0.85 (2H, m), 1.0–1.15 (2H, m), *ca* 3.5 (1H, overlapping DMSO-d_6 peak), 4.48 (2H, d; simplifies to s on treatment with D_2O), 5.04 (2H, d; simplifies to s on treatment with D_2O), 6.9–7.0 (2H, m), 7.2–7.4 (10H, m) 7.93 (1H, br t, removed by D_2O), 8.17 (1H, d, *J* 9.6), 8.56 (1H, s), 14.0 (1H, br t, removed by D_2O); *m/z* 379 (M – CO_2, 39%), 378 (M – CO_2H, 100), 302, 274, 91 [Found: $(M – CO_2H)^+$, 378.1969. Calc. for $C_{27}H_{25}N_3O_2$ – CO_2H: *M*, 378.1970].

1-Cyclopropyl-4-ethylimino-1,4-dihydroquinoline-3-carboxylic acid **8h**
δ_H ($CDCl_3$) 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 D_2O), 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 D_2O); *m/z* 256 (M^+, 63), 255 (M – 1, 100), 241 (M – CH_3, 20), 212 (M – CO_2, 30), 211 (M – CO_2H, 79), 197 (M – $C_2H_3O_2$, 68) (Found: M^+, 256.1210. Calc. for $C_{15}H_{16}N_2O_2$: *M*, 256.1212).

1-Cyclopropyl-4-cyclopropylimino-1,4-dihydroquinoline-3-carboxylic acid **8i**
δ_H ($CDCl_3$), 0.97–1.46 (8H, m), 3.19–3.29 (1H, 8 line m; simplifies to 7-line m on treatment with D_2O), 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 D_2O); *m/z* 268 (M^+, 6%), 241(M – 27, 45), 240 (M – 28, 100), 223 (M – CO_2H, 15) (Found: M^+, 268.1199. Calc. for $C_{16}H_{16}N_2O_2$: *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), H_2O (5 cm^3), MeOH or dioxane (5 cm^3, or sufficient organic solvent to dissolve the substrate at reflux), and NMe_4OH (1 cm^3 of a 25% aqueous solution) was heated at reflux for 1 h. The solvent was evaporated and the residue was treated with H_2O (*ca* 2 cm^3), and extracted with $CHCl_3$. 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 known[4] *1-ethyl-1,4-dihydro-7-fluoro-4-oxoquinoline-3-carboxylic acid* **4b** (77 mg, 86%),

m.p. 302–304 ºC (from $MeOCH_2CH_2OH$); ν_{max} (KBr)/cm^{-1} 3500–3200, 1610, 1570, 1450; δ_H (DMSO-d_6) 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 D_2O). In the case of an amphoteric product **11** (R^2 = 7-alkylamino) arising from certain substrates **8**, this was isolated by exhaustive extraction of the acidified (pH *ca* 5) hydrolysis mixture with $CHCl_3$. Each product 4-oxo acid **4**[17] or **11** was identified from its spectral (^{1}H NMR and/or IR) properties, and on occasion, (*e.g.*, **11c**) by comparison with authentic material synthesised by a literature[18] method.

Quinolinium chloride **13b** *from 7-fluoro-4-oxo acid* **4b** *and* $SOCl_2$

A mixture of 4-oxo acid **4b** (500 mg) and redistilled $SOCl_2$ (5 cm^3) 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 $C_{12}H_{10}Cl_2FNO_2$: C, 49.68; H, 3.47; N, 4.83; Cl, 24.44%); ν_{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 $SOCl_2$ (5 cm^3) at reflux for 1 h and merely evaporating off (rotavapor) the excess $SOCl_2$. Product **13b** dissolved readily in H_2O; 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 ºC, 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 cm^3) 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 $CHCl_3$ to yield 7-fluoro-4-oxo ester **3b** (92.3 mg, 64%); crystals (from EtOAc–hexane), m.p. 127 ºC, and identified from its ^{1}H-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 $SOCl_2$ (5 cm^3) for 1 h, after which solvent was evaporated and adhering $SOCl_2$ was ‘chased off’ with benzene. To the residue of supposed **14b** was added ice-cold absolute EtOH (3 cm^3)

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**. $CHCl_3$ was added and the organic phase was washed with aq. $NaHCO_3$. Evaporation of the $CHCl_3$ extract gave target ester **1b** (136 mg); m.p. 135–137 ºC (from EtOAc–hexane) and identical (IR, mixture m.p.) with literature[3] material.

(b) With cyclopropylamine. 4-Imino acid **2a** (75 mg) was treated with $SOCl_2$ (5 cm^3) 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 (^{1}H NMR, m.p. and mixture m.p.) with that obtained from 4-oxo acid **4a**, $SOCl_2$ and cyclopropylamine.[10]

(c) With propylamine. 7-Propylamino-imino acid **11c** (160 mg) was treated successively with $SOCl_2$ 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 (^{1}H NMR, m.p. and mixture m.p.) with that obtained from 7-fluoro-4-oxo acid **4b**, $SOCl_2$ and propylamine.[10]

Reaction of 1-benzyl-7-fluoro-4-oxo acid **4i** *with* $SOCl_2$

Acid **4i** (500 mg) was heated under reflux with $SOCl_2$ (10 cm^3) as for 4-oxo acid **4b** (*vide supra*); following evaporation of $SOCl_2$ the residue of **13b** was treated with H_2O to give sparingly soluble *7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* **15a**; crystals, m.p. 267–268 ºC (decomp.) (from MeOH) [lit.,[19] 267–268 ºC (decomp.)]; δ_H (DMSO-d_6) 7.4–7.6 (2H, m), 8.3–8.4 (1H, m), 8.95 (1H, s), 13.4 (1H, v br peak, removed by D_2O), 15.2 (1H, br s, removed by D_2O); *m*/*z* 207 (M^+). 1-*tert*-Butyl-7-fluoro acid **4j**[14] similarly afforded the same product **15a**. Treatment of the aforementioned residue with H_2O–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 ºC (from EtOAc); δ_H ($CDCl_3$) 0.6–1.0 (4H, m), 2.92–3.04 (1H, m), 6.54 (1H, br s, removed by D_2O), 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^+, ^{35}Cl), 208, 180, 153. With dry cyclopropylamine in lieu of the H_2O–amine mixture the product was N-*cyclopropyl-4-cyclopropylamino-7-fluoroquinoline-3-carboxamide* **16a**; crystals, m.p. 213–217 ºC (from MeOH–H_2O); δ_H ($CDCl_3$) 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 D_2O), 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 D_2O); *m/z* 285 (M^+, 11%), 229 (M – C_3H_6N, 100%), 201 (69%) (Found: M^+, 285.1255. Calc. for $C_{16}H_{16}FN_3O$: *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 ºC (from MeOH); δ_H ($CDCl_3$) 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 D_2O), 10.4 (1H, br peak, removed by D_2O), 11.6 (1H, br peak, removed by D_2O); *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 H_2O (4 cm^3) was added the amine (6–10 mmol) ($EtNH_2$ in the form of 1 cm^3 of 70% $EtNH_2$ in H_2O) and the mixture was stirred at room temperature for 2–4 d, or at 40 ºC for 6 h when, generally, TLC [benzene–acetone (3:1) + 5% Et_3N] showed the reaction to be complete. For most amines the free imino ester **1b** initially separated; this dissolved (R^1 = H, within 5–10 min; R^1 = Me, within 0.5–1 h) to give a yellow solution. Exhaustive extraction of the reaction mixture with $CHCl_3$ 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 (^{1}H NMR, m.p. and mixture m.p.) with the respective preparations from 4-oxo acid **4b** treated successively with $SOCl_2$ 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–Et_2O, gave the title acid, m.p. 134–136 ºC; δ_H ($CDCl_3$) 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 D_2O), 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 D_2O); *m/z* 342 (M^+, 5%), 341 (M – 1, 4), 298 (M – CO_2, 25), 297 (M – CO_2H, 18), 283 (M – $C_2H_3O_2$,100) [Found: $(M – C_2H_3O_2)^+$, 283.1911. Calc. for $C_{17}H_{23}N_4$: 283.1923. Found: M^+, 342.2031. Calc. for $C_{19}H_{26}N_4O_2$: *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 ºC; (lit.,[16] 215 ºC); δ_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_2O); *m/z* 315 (M^+, 68%), 272 (M – CO_2, 19), 271 (M – CO_2H, 100) (Found: M^+, 315.1589. Calc. for $C_{17}H_{21}N_3O_3$: M, 315.1583).

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