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RESEARCH ARTICLE

N,1-Dialkyl-7-(alkylamino)-4-(alkylimino)-1,4-dihydroquinoline-3-carboxamides and Their 4-Oxo Derivatives: Synthesis and Properties

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Abstract

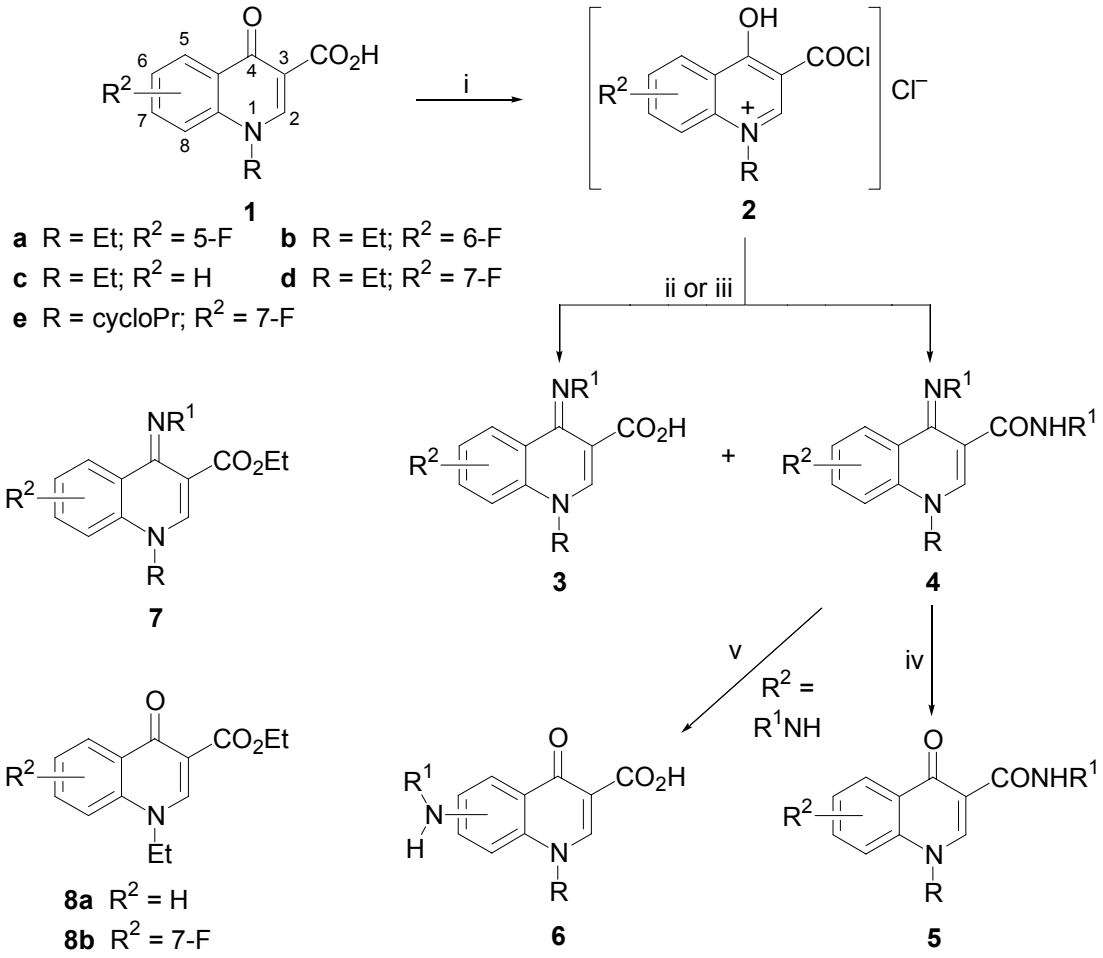
*Methods are described for accessing the little known class of 4-alkyliminoquinoline-3-carboxamide title compounds **4**; viz., from 4-oxoquinoline-3-carboxylic acids treated successively with thionyl chloride and amine, from 4-oxoquinoline-3-carboxylic esters treated likewise, and from the hydrogen chloride salt of a 4-alkyliminoquinoline-3-carboxylic ester and amine. Mechanistic aspects of the syntheses are discussed, and some spectroscopic and chemical properties of the title compounds are presented.*

Keywords Quinolin-4-ones; quinolin-4-imines; mechanism.

1. Introduction

We recently[1] showed that heating a 4-oxoquinoline-3-carboxylic acid **1** with thionyl chloride ($SOCl_2$) under reflux generates a acid chloride–hydrogen chloride complex, the structure of which is postulated as **2**.[2] When treated with aqueous amine, the complex **2**

yields a 4-iminoquinoline-3-carboxylic acid **3**, accompanied on occasion by a lesser amount of the corresponding 4-imino amide **4** (Scheme 1). When dry amine is used instead of the amine–water mixture, the product is chiefly the 4-imino amide **4**. In this paper we report on further developments relating to the synthesis, spectroscopic and chemical properties of this poorly-known class of quinolin-4(1*H*)-one derivative **4**.



Legend for compounds **3**–**7**:

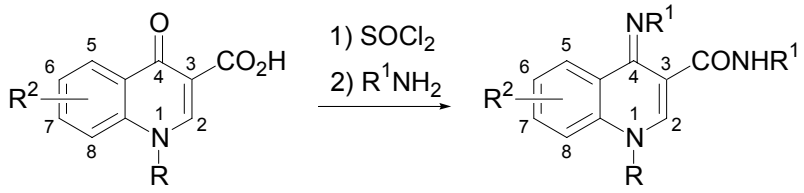
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**
R	Et	Et	Et	Et	Et	Et	Et	Et	Et	cyPr	cyPr	cyPr	cyPr	Et	Et	Et	Et
R^1	Et	Pr	Pr	Et	Pr	cyPr	cyPr	cyPr	Pr	cyPr	cyPr	Et	Bn	Bn	*p*-Tol	Pr^i	Bu^t
R^2	H	5-F	7-F	7-F	6-F	H	7-F	7-NH-cyPr	7-NH-Pr	7-F	H	H	7-F	7-F	7-F	7-F	7-F

Scheme 1 *Reagents and conditions:* i, $SOCl_2$, reflux; ii, $R^1NH_2 + H_2O$ (→ **3** > **4**); iii, dry R^1NH_2 (→ **4** > **3**); iv, $NMe_4OH–H_2O$, reflux; v, aq. NaOH, reflux. The geometry of the imines depicted above and elsewhere is not specified.

2. Results and Discussion

Table 1 lists the 4-imino amides **4** obtained by stirring complex **2** with various (dry) primary amines at room temperature.[3] Certain outcomes in this synthesis are especially noteworthy. (i) A fully substituted product, *i.e.,* 7-alkylamino-4-imino amide **4** (R^2 = alkylamino), resulted in some instances (*e.g.,* from 7-fluoro-4-oxo acid **1d** and cyclopropylamine) under the aforementioned relatively mild[4] reaction conditions. (ii) The analogous halogen in 5-fluoro- and 6-fluoro-4-oxo acid, *i.e.,* **1a** and **1b**, respectively, was not substituted by *n*-propylamine; in each instance the end-product was the appropriate **4** (R^2 = F), thus confirming that the orientation[5] of the halogen in substrate **1** was a determinant in the reaction outcome. (iii) Neither isopropylamine[6] nor *tert*-butylamine, unlike *n*-propylamine, displaced the 7-fluoro substituent in complex **2d** under similar conditions, perhaps because of a steric difficulty in forming the requisite tetrahedral species for the substitution.

Table 1 4-Imino amides **4** from 4-oxo acids **1** treated successively with $SOCl_2$ and (dry) amine R^1NH_2.



1 **4**

4-Oxo Acid **1** (Scheme 1)	4-Imino Amide **4**[a]	Substituents			Yield (%)[b]
		R	R^1	R^2	
1a	**4b**[c]	Et	Pr	5-F	—[d,e]
1b	**4e**	Et	Pr	6-F	—[d]
1c	**4f**	Et	cycloPr	H	>80
1d	**4h**[c]	Et	cycloPr	7-NHcycloPr	>90
1d	**4i**	Et	Pr	7-NHPr	>90
1e	**4j**	cycloPr	cycloPr	7-F	>90
1e	**4m**	cycloPr	CH_2Ph	7-F	>90
1d	**4n**	Et	CH_2Ph	7-F	79
1d	**4o**	Et	4-MeC_6H_4	7-F	90
1d	**4p**	Et	Pr^i	7-F	—[d]
1d	**4q**[c]	Et	Bu^t	7-F	—[d]

[a] Crystallisations of **4** were usually from EtOAc.
[b] Yield refers to vacuum-dried crude material.
[c] Compound hydrolysed to the corresponding 4-oxo amide **5** (Experimental).
[d] Not determined.
[e] Impure product.

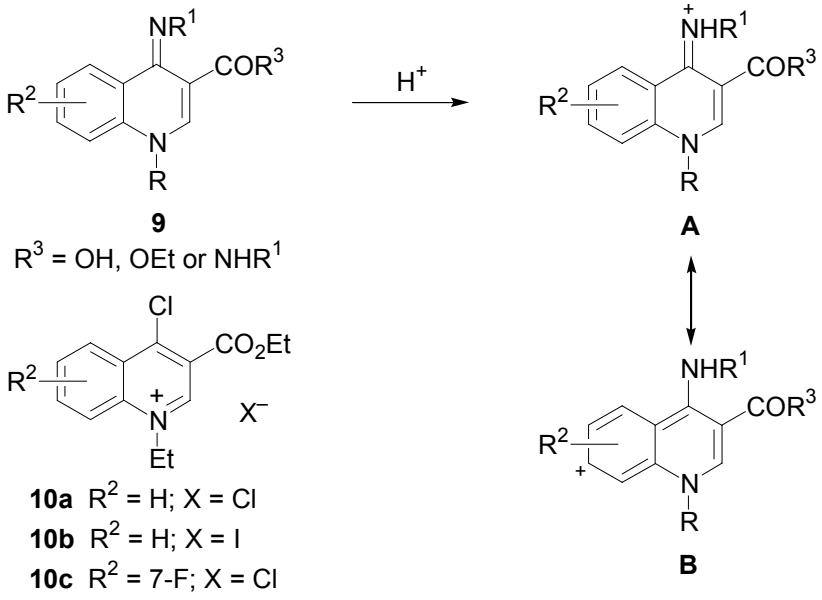
Each of the 4-imino amide products **4** (Table 1) was characterised from its spectral (^{1}H NMR and/or HRMS) properties, supplemented on occasion by alkaline hydrolysis (aqueous NMe_4OH, containing MeOH as co-solvent) to form (70–90%) the corresponding 4-oxo amide **5**,[7] which was likewise spectroscopically identified. In the instance of the 7-alkylamino-4-imino amides **4** (R^2 = alkylamino), prolonged hydrolysis with aqueous sodium hydroxide solution resulted in the formation of the corresponding 7-alkylamino-4-oxo acid **6** as end-product.[6]

The ^{1}H NMR ($CDCl_3$) spectra of the listed **4** showed the amide proton generally near δ 11–12, and the signal was removed by D_2O within one day. In comparison, the corresponding proton in the 4-oxo amides **5** (Table 1) was exhibited generally near δ 10 and was not significantly affected by D_2O under similar conditions, thereby offering a useful diagnostic ^{1}H NMR distinction between the two classes of amides.

Insight into the mechanistic aspects of the aforementioned synthesis of 4-imino amides **4** was obtained from the following observations with 7-fluoro substituted quinolone derivatives. The 4-oxo acid **1d**, 4-imino acid **3d**, 4-imino amide **4g** and 4-oxo ester **8b**, when individually mixed with an excess of dry cyclopropylamine and stored at room temperature for two days, suffered no detectable halogen substitution, and the respective substrate was recovered largely unchanged. (Compound **3d** underwent minor imino-amine exchange to give **3g**, while **8b** gave rise to some 4-oxo amide **5g**). However, addition of either hydrogen chloride, hydrochloric acid, or cyclopropylamine hydrochloride to the mixtures of cyclopropylamine and **3d** or **4g** followed by similar storage resulted in the formation of 7-cyclopropylamino derivatives **3h** and **4h**, respectively, in good yield. The two latter results (and others in Table 1) may be rationalised by postulating that the appropriate 4-iminoquinoline substrate **9** (Scheme 2) is transformed on protonation into an entity **A** providing resonance contribution **B**, which thereby enhances the tendency for nucleophilic displacement of the 7-halogen.

An indication of the sequence of events in the 4-imino amide **4** synthesis (Table 1) was obtained from TLC monitoring of the reaction between complex **2d** and (dry) *n*-propylamine. The first identifiable product to appear was 7-fluoro-*N*-propyl-4-propylimino amide **4c**. This intermediate gradually disappeared, with the concomitant production of the 7-propylamino substituted end-product **4i**. After one hour of reaction, the major product isolated was **4c**, associated with a lesser amount of **4i**. From this observation, coupled with the finding[1] that treatment of complex **2d** with aqueous amine generally

affords a mixture of 4-imino acid **3** and 4-imino amide **4**, it is surmised that the rate of nucleophilic (amine) substitution of the various pertinent functionalities in the postulated quinolinium entity **2** decreases in the order 4-OH > 3-COCl > 7-F.



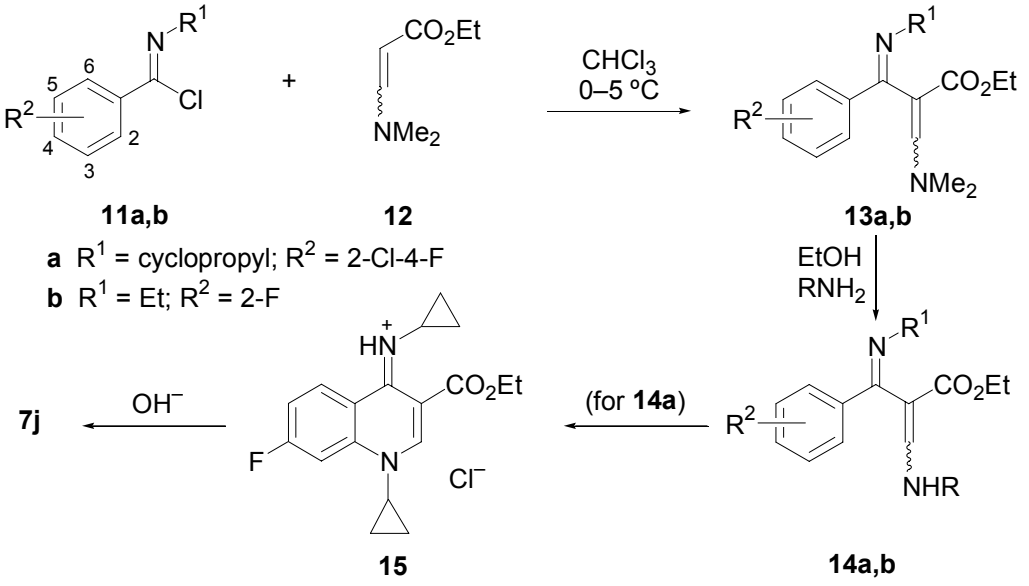
Scheme 2

In a useful modification of the above 4-imino amide synthesis, the 4-oxo acid **1** substrate was replaced by the corresponding 4-oxo ester **8** (Scheme 1). Earlier, Agui *et al.*[8] had heated 4-oxo ester **8a** under reflux with phosphorus oxychloride ($POCl_3$) to form a mixture containing what was surmised to be 4-chloro-3-ethoxycarbonyl-1-ethylquinolinium chloride **10a** (Scheme 2); this latter product was transformed into, and characterised as, its iodide derivative **10b**. In the present case, heating 4-oxo ester **8a** under reflux with $SOCl_2$ followed by addition of dry benzene to the hot solution led to separation of crystals of chloride salt **10a** in good yield. The product's assigned structure was substantiated from an elemental analysis, an IR spectrum (which revealed the absence of 4-oxo ester **8a**), conversion into the known[8] iodide salt **10b**, and a volumetric analysis that indicated the presence in the structure of one equivalent of ionic chlorine (*i.e.,* immediately available) and one equivalent of covalently-bound chlorine (*i.e.,* made available by hydrolysis). The 7-fluoro substituted quinolinium chloride **10c** was likewise accessed from 7-fluoro-4-oxo ester **8b**, $SOCl_2$ and benzene, or more conveniently by merely evaporating the $SOCl_2$ after reflux.

Quinolinium chloride **10** proved to be a useful substrate for preparing 4-imino esters of type **7**, and also 4-imino amides **4**. For example, stirring chloride **10c** with dry propylamine (three equivalents) in ethanol solution at room temperature led to only the 4-

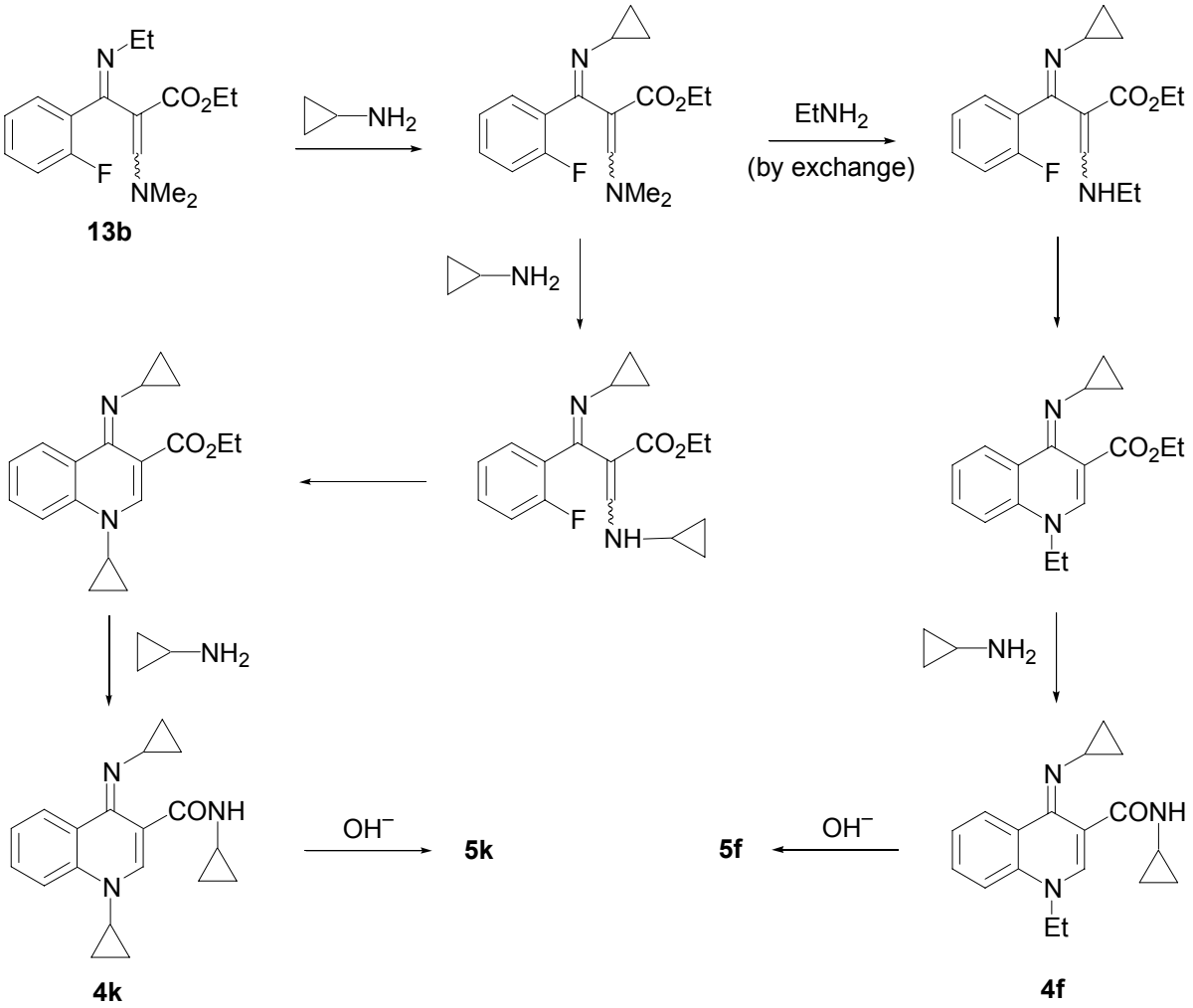
chloro function being substituted, with production of 4-propylimino ester **7c**. However, with utilisation of a very large excess of propylamine in the reaction, the ethoxycarbonyl group in **10c** also reacted, resulting, in this instance, in the corresponding 4-imino amide **4i** as end-product. TLC monitoring of the reaction between 7-fluoroquinolinium chloride **10c** and propylamine utilising **7c, 4c**, and **4i** as reference compounds revealed a rapid initial production of 4-imino ester **7c** (confirming C-4 as the site of earliest attack); as the reaction continued, this intermediate gradually disappeared and was concomitantly replaced by 7-fluoro-4-imino amide **4c**, eventuating in the latter's conversion into end-product **4i**. The adduced rate sequence 4-Cl > 3-CO_2Et > 7-F correlated well with that found from the reaction between complex **2d** and propylamine (*vide supra*).

Several 1-substituted 4-oxo acids **1** required for this work were synthesised from an aroyl chloride, an enamine ester, and an amine, by literature methods involving an enamine–amine exchange reaction.[4] We report here that utilising an imidoyl chloride in lieu of the aroyl chloride in the synthesis leads to a 4-imino ester **7** (R = R^1 or R ≠ R^1, as required). This was shown with *N*-cyclopropyl imidoyl chloride **11a**, which was condensed with ethyl 3-dimethylamino-2-propenoate **12** in chloroform to give the putative *C*-imidoylated enamine **13a** (Scheme 3). Treatment of the latter with cyclopropylamine in ethanol solution effected exchange to the 3-cyclopropylamino derivative **14a**, and this on heating gave target 4-imino ester **7j** (*via* the hydrochloride salt **15**; *ca.* 45%, based on substrate **11a**). Conducting the reaction with cyclopropylamine in larger excess and for a longer period eventuated in 4-imino amide **4j** as end-product.



Scheme 3

This route to 4-imino esters **7** is limited to the use of a primary amine bearing the same substituent on nitrogen as is present in the imidoyl chloride **11**, since otherwise a complex mixture of products arises from the operation of diverse and competing exchanges and substitution reactions. This aspect was demonstrated with the reactants *N*-ethyl imidoyl chloride **11b**, enamine ester **12**, and cyclopropylamine, which, following the aforementioned procedure, yielded a product mixture of what is assumed to be the 4-imino amides **4**. Hydrolysis of this mixture provided all four possible (separated and characterised) 4-oxo amides, *viz*., **5a**, **5f**, **5k** and **5l**. Scheme 4 outlines the exchanges and reactions envisioned to lead from the reactants to (for example) **5f** and **5k**. The overall sequence of events depicted has, to our knowledge, not previously been reported in the literature.



Scheme 4

3. Experimental

General methods are described in reference 9. Melting points were determined on a Reichert hot-stage microscope apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ solution (unless otherwise noted) with TMS as internal standard. High-resolution mass spectra were recorded on a VG70-SEQ spectrometer (by Dr P.R. Boshoff, Cape Technikon Mass Spectrometry Unit).

Samples of authentic 4-oxo acids **1**,[4] 4-imino acids **3**,[1] 4-imino amides **4**,[1] and 4-imino esters **7**[9] required for comparison/reference purposes with current products were prepared by literature methods, and included the following: *1-Ethyl-7-fluoro*-N-*propyl-4-(propylimino)-1,4-dihydroquinoline-3-carboxamide* **4c**: M.p. 94–95 ºC (hexane); δ_H ($CDCl_3$) 0.95–1.1 (6H, m), 1.43 (3H, t, *J* 7.2), 1.54–1.84 (4H, m), 3.3–3.4 (2H, m; t after addition of D_2O), 3.76 (2H, t, *J* 6.7), 3.96 (2H, q, *J* 7.2), 6.8–6.96 (2H, m), 8.02–8.09 (1H, m), 8.21 (1H, s), 11.6 (1H, br s, removed by D_2O) (Found: M^+, 317.1889. Calc. for $C_{18}H_{24}FN_3O$: *M*, 317.1903). *Ethyl 1-ethyl-7-fluoro-4-(propylimino)-1,4-dihydroquinoline-3-carboxylate* **7c**: Syrup; δ_H ($CDCl_3$) 0.98 (3H, t, *J* 7.3), 1.3–1.46 (6H, m), 1.65–1.81 (2H, m), 3.1–3.2 (2H, m), 3.92 (2H, q, *J* 7.2), 4.28 (2H, q, *J* 7.1), 6.80 (1H, dd, *J* 2.3 and 10.7), 6.9–7.0 (1H, m), 7.71 (1H, s), 8.25–8.35 (1H, m) (Found: M^+, 304.1596. Calc. for $C_{17}H_{21}FN_2O_2$: *M*, 304.1588).

4-Imino amides **4** *from 4-oxo acids* **1** *treated successively with* $SOCl_2$ *and dry amine* R^1NH_2*. General Procedure*

A mixture of acid **1** (500 mg, *ca.* 2.2 mmol) and redistilled $SOCl_2$ (5 cm^3) was heated under reflux for 1 h, then evaporated to dryness (rotavapor). Anhydrous benzene was used to chase off adhering $SOCl_2$, and the residue of complex **2** was dried in high vacuum. To this was added chilled amine (*ca.* 4 cm^3; large excess) and the reaction was allowed to warm to room temperature with stirring, which was continued overnight. [In the case of $EtNH_2$ or *p*-toluidine, a solution in dioxan (*ca.* 5 cm^3) was used]. Excess amine and solvent was evaporated (rotavapor, or high vacuum for benzylamine and *p*-toluidine) to afford a residue of the putative hydrogen halide salt. This was treated with aq. 1.0 mol dm^{-3} NaOH and the sparingly soluble 4-imino amide **4** product was isolated either by filtration or by $CHCl_3$ extraction, and crystallised (usually from EtOAc). Spectral properties of selected 4-imino amides **4** so obtained (Table 1) are shown below:

1-Ethyl-6-fluoro-N-*propyl-4-(propylimino)-1,4-dihydroquinoline-3-carboxamide* **4e**

M.p. 88 ºC; δ_H ($CDCl_3$) 0.96–1.1 (6H, m), 1.42 (3H, t, *J* 7.1), 1.58–1.82 (4H, m), 3.38 (2H, q; t after addition of D_2O), 3.80 (2H, t, *J* 6.6), 4.02 (2H, q, *J* 7.1), 7.2 (2H, m), 7.82 (1H, d, *J* 10.5), 8.25 (1H, s), 11.6 (1H, br s, removed by D_2O within 1 day). (Found: M^+, 317.1906. Calc. for $C_{18}H_{24}FN_3O$: *M*, 317.1903).

N-*Cyclopropyl-4-(cyclopropylimino)-1-ethyl-1,4-dihydroquinoline*-3-*carboxamide* **4f**

M.p. 131–132 ºC; δ_H ($CDCl_3$) 0.59–0.67 (2H, m), 0.84–0.96 (4H, m), 1.1–1.17 (2H, m), 1.54 (3H, t, *J* 7.2), 2.95–3.05 (1H, 8-line m; 7-line m after addition of D_2O), 3.3–3.4 (1H, 7-line m), 4.14 (2H, q, *J* 7.2), 7.15–7.35 (2H, m), 7.57–7.65 (1H, m), 8.32 (1H, s), 8.68 (1H, dd, *J* 1,1, 8.1), 11.4 (1H, br s, removed by D_2O). (Found: M^+, 295.1695. Calc. for $C_{18}H_{21}N_3O$: *M*, 295.1685).

N-*Cyclopropyl-7-(cyclopropylamino)-4-(cyclopropylimino)-1-ethyl-1,4-dihydroquinoline-3-carboxamide* **4h**[1]

M.p. 232–234 ºC; δ_H ($CDCl_3$) 0.59–1.16 (12H, m), 1.52 (3H, t, *J* 7.1), 2.34 (1H, m), 2.86–2.95 (1H, 8-line m; 7-line m after addition of D_2O), 3.08–3.16 (1H, 8-line m; 7-line m after addition of D_2O), 4.51 (2H, q, *J* 7.1), 6.67 (1H, d, *J* 1.4), 6.81 (1H, s, removed by D_2O), 7.12 (1H, dd, *J* 2.0 and 9.4), 8.74 (1H, d, *J* 9.5), 9.78 (1H, s), 9.79 (1H, d, *J* 3.6, removed by D_2O), 11.4 (1H, s, removed by D_2O) (Found: M^+, 350.2101. Calc. for $C_{21}H_{26}N_4O$: *M*, 350.2107).

1-Ethyl-N-*propyl-7-(propylamino)-4-(propylimino)-1,4-dihydroquinoline-3-carboxamide* **4i**[1]

M.p. 187–188 ºC; δ_H ($CDCl_3$) 0.95–1.1 (9H, m), 1.41 (3H, t, *J* 7.2), 1.54–1.84 (6H, m), 3.1–3.2 (2H, *ca.* q; t after addition of D_2O), 3.32–3.42 (2H, *ca.* q; t after addition of D_2O), 3.76 (2H, t, *J* 6.6), 3.94 (2H, q, *J* 7.2), 4.12 (1H, br t, removed by D_2O), 6.25 (1H, d, *J* 2.2), 6.42 (1H, dd, *J* 2.2 and 8.9), 7.94 (1H, d, *J* 9.0), 8.17 (1H, s), 12.1 (1H, br s, removed by D_2O) (Found: M^+, 356.2576. Calc. for $C_{21}H_{32}N_4O$: *M*, 356.2576).

N*,1-Dicyclopropyl-4-(cyclopropylimino)-7-fluoro-1,4-dihydroquinoline-3-carboxamide* **4j**[1]

M.p. 151–152 ºC; δ_H ($CDCl_3$) 0.46–0.52 (2H, m), 0.73–0.84 (4H, m), 0.93–1.04 (4H, m), 1.1–1.24 (2H, m), 2.8–2.9 (1H, m), 3.1–3.2 (2H, m), 6.87–7.0 (1H, m), 7.38 (1H, d, *J* 2.6 and 10.8), 8.29 (1H, s), 8.45–8.52 (1H, m), 11.1 (1H, br peak, removed by D_2O within 1

day) (Found: M^+, 325.1588. Calc. for $C_{19}H_{20}FN_3O$: *M*, 325.1590).

N-*Benzyl-4-(benzylimino)-1-cyclopropyl-7-fluoro-1,4-dihydroquinoline-3-carboxamide* **4m**
M.p. 149–150 ºC; δ_H ($CDCl_3$) 0.96–1.04 (2H, m), 1.17–1.27 (2H, m), 3.1–3.2 (1H, m), 4.56 (2H, br s; s after addition of D_2O), 4.97 (2H, s), 6.9–7.0 (1H, m), 7.15–7.25 (*ca* 10H, m), 7.44 (1H, dd, *J* 2.5 and 10.7), 7.9–8.0 (1H, m), 8.42 (1H, s), 11.8 (1H, br s, removed by D_2O) (Found: M^+, 425.1913. Calc. for $C_{27}H_{24}FN_3O$: *M*, 425.1903).

N-*Benzyl-4-(benzylimino)-1-ethyl-7-fluoro-1,4-dihydroquinoline-3-carboxamide* **4n**
M.p. 168–170 ºC; δ_H ($CDCl_3$) 1.45 (3H, t, *J* 7.2), 4.0 (2H, q, *J* 7.2), 4.56 (2H, d; s after addition of D_2O), 4.99 (2H, s), 6.88–7.02 (2H, m), 7.15–7.3 (*ca* 10H, m, overlapping $CHCR_3$ peak), 8.0–8.1 (1H, m), 8.30 (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).

1-Ethyl-7-fluoro-N-*(4-methylphenyl)-4-[(4-methylphenyl)imino]-1,4-dihydroquinoline-3-carboxamide* **4o**
M.p. 228–229 ºC; δ_H ($CDCl_3$) 1.47 (3H, t, *J* 7.2), 2.27 (3H, s), 2.32 (3H, s), 4.06 (2H, q, *J* 7.2), 6.5–6.75 (3H, m), 6.85–7.1 (5H, m), 7.5–7.65 (3H, m), 8.52 (1H, s), 13.4 (1H, br s, removed by D_2O); *m/z* 413 (M^+), 307.

1-Ethyl-7-fluoro-N-*isopropyl-4-(isopropylimino)-1,4-dihydroquinoline-3-carboxamide* **4p**
M.p 168–172 ºC; δ_H ($CDCl_3$) 1.23–1.33 (12H, m), 1.42 (3H, t, *J* 7.2), 3.95 (2H, q, *J* 7.2), 4.11–4.32 (2H, m), 6.83–6.96 (2H, m), 7.83–7.90 (1H, m), 8.15 (1H, s), 11.7 (1H, br m, removed by D_2O) (Found: M^+, 317.1903. Calc. for $C_{18}H_{24}FN_3O$: *M*, 317.1903).

N-*(*tert-*Butyl)-4-(*tert-*butylimino)-1-ethyl-7-fluoro-1,4-dihydroquinoline-3-carboxamide* **4q**
M.p. 140–142 ºC; δ_H ($CDCl_3$) 1.38–1.49 (21H, m), 3.91 (2H, q, *J* 7.2), 6.81–6.88 (2H, m), 7.82–7.90 (1H, m), 8.12 (1H, s), 11.5 (1H, br peak, removed by D_2O) (Found: M^+, 345.2220. Calc. for $C_{20}H_{28}FN_3O$: *M*, 345.2216).

Hydrolysis of 4-imino amides **4** *to 4-oxo amides* **5***. General Procedure*
A mixture of the imino amide (100 mg), H_2O (5 cm^3), MeOH (5 cm^3; or sufficient MeOH to dissolve the substrate at reflux) and NMe_4OH (1.0 cm^3 of a 25% aq. solution) was heated

under reflux for 1–2 h. Most of the solvent was evaporated (rotavapor) and the residual mass was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract provided crude 4-oxo amide **5** product which was purified by crystallisation from (generally) EtOAc. Acidification of the aq. alkaline phase with 50% HOAc (to *ca.* pH 5) provided any concomitantly produced 4-oxo acid **1** (R^2 = H or 7-F) or **6** (R^2 = 7-alkylamino), which was collected by filtration and crystallised (usually from $CH_3OCH_2CH_2OH$). Spectral details for selected 4-oxo amides **5** so obtained are shown below:

1-Ethyl-5-fluoro-4-oxo-N-*propyl-1,4-dihydroquinoline-3-carboxamide* **5b**

From (crude) **4b**; m.p. 178 ºC; δ_H ($CDCl_3$) 1.00 (3H, t, *J* 7.4), 1.54 (3H, t, *J* 7.2), 1.60–1.75 (2H, m), 3.37–3.47 (2H, m; q after addition of D_2O), 4.30 (2H, q, *J* 7.2), 7.05–7.16 (1H, m), 7.27–7.33 (1H, m), 7.61–7.72 (1H, m), 8.77 (1H, s), 9.97 (1H, br t, not removed by D_2O within 1 day) (Found: M^+, 276.1272. Calc. for $C_{15}H_{17}FN_2O_2$: *M*, 276.1274).

N-*Cyclopropyl-7-(cyclopropylamino)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5h**

From **4h**; m.p. 213–215 ºC; δ_H ($CDCl_3$) 0.6–0.9 (8H, m), 1.54 (3H, t, *J* 7.2), 2.45–2.6 (1H, m), 2.85–3.0 (1H, m), 4.24 (2H, q, *J* 7.2), 4.77 (1H, s, removed by D_2O), 6.70 (1H, d, *J* 2.0), 6.80 (1H, dd, *J* 2.0 and 9.0), 8.26 (1H, d, *J* 8.8), 8.67 (1H, s), 10.2 (1H, br s) (Found: M^+, 311.1635. Calc. for $C_{18}H_{21}N_3O_2$: *M*, 311.1634).

N-*(*tert-*Butyl)-1-ethyl-7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5q**

From **4q**; m.p. 183–184 ºC; δ_H ($CDCl_3$) 1.50 (9H, s), 1.55 (3H, t, *J* 7.3), 4.25 (2H, q, *J* 7.3), 7.16–7.24 (2H, m), 8.50–8.58 (1H, m), 8.79 (1H, s), 9.95 (1H, br peak, not removed by D_2O within 1 day) [Found: $(M - CH_3)^+$, 275.1192. Calc. for $C_{15}H_{16}FN_2O_2$: $(M - CH_3)$, 275.1196].

*Effect of cyclopropylamine on various 7-fluoroquinolin-4(1*H*)-one derivatives*

(i) To each one (100 mg) of the following derivatives: 4-oxo acid **1d**, 4-imino acid **3d**, 4-imino amide **4g**, and 4-oxo ester **8b**, was added dry cyclopropylamine (2.5 cm^3, large mmol excess), and the respective mixture was stirred at room temperature for 24 h. Following addition of H_2O and 50% HOAc, the reaction product was isolated by filtration or extracted with $CHCl_3$ as warranted, and examined by TLC and IR analysis. The

recovered material turned out to be essentially unchanged substrate, and in no instance was a nucleophilic substitution of 7-F detected; however, **8b** was mixed with 4-oxo amide **5g** from substitution of the ethoxycarbonyl function, while **3d** was associated with some 4-imino acid **3g** arising from an imine-amine exchange.

(ii) Repetition of the above procedure with the **3d**–cycloPrNH$_2$ mixture (+ 4 cm^3 H$_2$O) and the aforementioned **4g**–cycloPrNH$_2$ mixture, each now containing 1–2 drops conc HCl, yielded 7-cyclopropylamino-4-cyclopropylimino acid **3h**[6] and 7-cyclopropylamino-4-cyclopropylimino amide **4h** *(vide supra*), respectively, as evidenced from spectral (IR, ^{1}H NMR) comparison with the respective reference compound.

4-Chloro-3-ethoxycarbonyl-1-ethylquinolinium chloride **10a** *and iodide* **10b**

4-Oxo ester **8a** (1.00 g, 4.01 mmol) was heated under reflux with $SOCl_2$ (10 cm^3) for 1 h. Solvent was evaporated (rotavapor) and residual $SOCl_2$ was chased off with benzene. The solid product **10a** was dried *in vacuo* over KOH overnight and was identical (IR spectrum) with that prepared by treating the hot $SOCl_2$ reaction solution with benzene. Chloride **10a** was dissolved in ice-cold H_2O (5 cm^3) and treated with a chilled solution of a large excess of KI (1.25 g) in H_2O (5 cm^3). A red oil separated immediately, which solidified on scratching. This product **10b** was collected by filtration, washed with ice-water, and dried *in vacuo* (960 mg, 2.67 mmol). Red crystals (from acetone) m.p. 138–139 ºC) (lit.[8] m.p. 145–146 ºC dec.); ν_{max} (KBr)/cm^{-1} 1740, 1610, 1556, 1510, and identical (IR spectrum) with the quinolinium iodide **10b** prepared by a literature[8] method. *4-Chloro-3-ethoxycarbonyl-1-ethyl-7-fluoroquinolinium chloride* **10c** was likewise obtained as colourless crystals from 4-oxo ester **8b** and $SOCl_2$. The IR spectra of **10a** and **10c** exhibited strong absorptions near 1600 cm^{-1} and revealed the absence in each of either 4-oxo ester **8** or 4-oxo acid **1** contaminants. To **10c** (34.9 mg, 0.11 meq) was added 0.50 mol dm^{-3} aq. NaOH (6 cm^3) and the solution was stirred overnight, then kept at 65–70 ºC for 6 h. The reaction was acidified (HOAc), chilled, and filtered to obtain 4-oxo acid **1d** (27.6 mg, 0.12 mmol); the filtrate was analysed for Cl ion by volumetric titration ($AgNO_3$/NH_4CNS): Found: Cl, 1.93 equivalents. Calc. for $C_{14}H_{14}Cl_2FNO_2$: Cl, 2.00 equivalents.

Formation of 4-imino esters **7** *from 4-chloroquinolinium chloride* **10** *and amines*

The method is illustrated for the preparation of *ethyl 1-ethyl-4-(ethylimino)-1,4-*

dihydroquinoline-3-carboxylate **7a**. To quinolinium ester **10a** [from 4-oxo ester **8a** (750 mg, 3.01 mmol)] was added ice-cold $EtNH_2$ in EtOH (3.0 mol dm^{-3}; 6 cm^3, i.e. 18 mmol $EtNH_2$) and the mixture was stirred at room temperature for 2.5–5 h or until the reaction was complete [TLC, benzene–acetone (3:1) + Et_3N]. Solvent was evaporated (rotavapor) and the residual mass was basified with 2.0 mol dm^{-3} NaOH and extracted with $CHCl_3$. Evaporation of the H_2O-washed $CHCl_3$ phase gave crude imino ester **7a**. Crystals (520 mg, 64.%) (EtOAc–hexane), m.p. 117–118 ºC, and identical (mixture mp and IR) with **7a** prepared by a literature[9] method. Similar reaction of ester **10c** [from 4-oxo ester **8b** (790 mg, 3.00 mmol)] and propylamine (600 mg, 10.2 mmol) in absolute EtOH (5 cm^3) gave *1-ethyl-7-fluoro-4-(propylimino)-1,4-dihydroquinoline-3-carboxylate* **7c** (*vide supra*).

Formation of 4-imino amide **4i** *from quinolinium chloride* **10c** *and propylamine*

To substrate **10c** (500 mg, 1.58 mmol) was added dry propylamine (4 cm^3, large mmol excess) and the mixture was stirred at room temperature for *ca.* 20 h. Propylamine was evaporated (rotavapor) and the residual syrup was treated with aq. 1.0 mol dm^{-3} NaOH and extracted with $CHCl_3$. Evaporation of the organic extract gave a residue which was washed with warm EtOAc. The sparingly soluble *1-ethyl*-N-*propyl-7-(propylamino)-4-(propylimino)-1,4-dihydroquinoline-3-carboxamide* **4i** was collected by filtration [430 mg (crude), 77.%]; crystals from EtOAc, m.p. 187–188 ºC] and identical (IR/^{1}H NMR) with 4-imino amide **4i** prepared from 4-oxo acid **1d** treated successively with $SOCl_2$ and propylamine (*vide supra*). Similar reaction between **10c** (500 mg, 1.58 mmol) and cyclopropylamine (4cm^3) gave N-*cyclopropyl-7-(cyclopropylamino)-4-(cyclopropylimino)-1-ethyl-1,4-dihydroquinoline-3-carboxamide* **4h** [410 mg (crude), 75%; crystals from EtOAc, m.p. 232–234 ºC], and identical (IR/^{1}H NMR) with the product from 4-oxo acid **1d**, $SOCl_2$, and cyclopropylamine (*vide supra*).

TLC monitoring of the reaction of propylamine with (a) quinolinium chloride **10c** *and (b) with acid chloride complex* **2d**

To **10c** (25 mg) was added chilled (neat) propylamine (*ca.* 200 mg) and the reaction was allowed to proceed at room temperature to completion (*ca.* 20 h), during which period aliquots were taken at intervals for TLC monitoring [silica gel, benzene–acetone (3:1) containing 5% Et_3N]. 4-Imino ester **7c** was the first to form and reached maximum production after *ca.* 1 h, with only minor 4-imino amide **4c** present. The amount of the

latter product increased with time while that of ester **7c** concomitantly diminished. With further progress of the reaction, intermediate imino amide **4c** likewise was replaced (after *ca.* 20 h) by end-product **4i**. Similar monitoring of the reaction between propylamine and complex **2d** provided an indication of the sequence of events in the 4-imino amide synthesis (*vide supra*).

Production of (A) 4-imino esters **7***, and (B) of 4-oxo amides* **4** *by C-imidoylation of ethyl 3-dimethylamino-2-propenoate* **12**

Procedure (A) is illustrated for *ethyl 1-cyclopropyl-4-(cyclopropylimino)-7-fluoro-1,4-dihydroquinoline-3-carboxylate* **7j**. To a chilled solution of imidoyl chloride **11a** (4.62 g, 20.0 mmol) in dry $CHCl_3$ (30 cm^3) was added enamine ester **12** (2.86 g, 20.0 mmol) and the reaction was kept at 0–5 ºC overnight and then at room temperature for a further 3 d. Solvent was evaporated (<40 ºC, rotavapor) and the residue was rapidly extracted several times with warm (<40 ºC) aq. 1.0 mol dm^{-3} HCl, each extract being cooled[9] soon after. The combined acidic solution was then repeatedly extracted with $CHCl_3$ until no further material was removed. This extract was then washed successively with aq. 1.0 mol dm^{-3} NaOH and H_2O, dried (Na_2SO_4), and evaporated to give the crude (assumed) C-imidoylated enamine **13a** as a syrup (*ca.* 70%). To the latter was added an EtOH solution of cyclopropylamine (2.0 mol dm^{-3}, *ca.* 20 cm^3) and the mixture was stirred at room temperature overnight to effect enamine–amine exchange[4] to the target C-imidoylated enamine **14a**. Evaporation of EtOH gave a residual syrup, which was kept at 60–70 ºC overnight to give the putative hydrochloride salt **15** (*ca.* 45%, based on imidoyl chloride **11a**) of target imino ester **7j**. Basification with aq. 1.0 mol dm^{-3} NaOH gave title ester **7j**, mp 92 ºC (hexane); δ_H ($CDCl_3$) 0.74–1.22 (8H, m), 1.34 (3H, t, *J* 7.1), 2.7–2.8 (1H, m), 3.1–3.2 (1H, m), 4.28 (2H, q, *J* 7.1), 6.88–6.98 (1H, m), 7.18–7.25 (1H, dd, *J* 2.4 and 10.6), 7.81 (1H, s), 8.11–8.19 (1H, m) (Found: M^+, 314.1421. Calc. for $C_{18}H_{19}FN_2O_2$: *M*, 314.1431).

Procedure (B) is shown with the C-imidoylated enamine **13b** prepared from *N*-ethyl-2-fluoro imidoyl chloride **11b** (3.70 g, 20.0 mmol) and enamine **12** (2.86 g, 20.0 mmol) following procedure (A). A mixture of crude product **13b** (10 mmol) and cyclopropylamine (4 cm^3) was stirred initially at room temperature overnight, and finally kept at 60–70 ºC overnight to maximise the formation of the 4-imino amide **4** precursors. Evaporation of

unchanged cyclopropylamine followed by hydrolysis of the residue with NMe_4OH *(vide supra)* yielded a mixture of target 4-oxo amides **5** which was separated (silica gel, benzene–acetone, 3:1) to provide the following four components:

N*,1-Diethyl-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5a**

M.p. 136–137 ºC; δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.3), 1.56 (3H, t, *J* 7.2), 3.44–3.58 (2H, m), 4.35 (2H, q, *J* 7.2), 7.45–7.6 (2H, m), 7.7–7.8 (1H, m), 8.55 (1H, dd, *J* 1.5 and 8.2), 8.83 (1H, s), 10.0 (1H, br s, slowly removed by D_2O); *m/z* (FAB) 245 (MH^+), 200.

N-*Cyclopropyl-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5f**

M.p. 175–176 ºC; δ_H ($CDCl_3$) 0.64–0.87 (4H, m), 1.56 (3H, t, *J* 7.2), 2.95–3.05 (1H, m), 4.35 (2H, q, *J* 7.2), 7.45–7.6 (2H, m), 7.7–7.8 (1H, m), 8.52 (1H, dd, *J* 1.5 and 8.1), 8.83 (1H, s), 10.1 (1H, br s) (Found: M^+, 256.1215. Calc. for $C_{15}H_{16}N_2O_2$: *M*, 256.1212).

N*,1-Dicyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5k**

M.p.160–161 ºC; δ_H ($CDCl_3$) 0.67–0.89 (4H, m), 1.1–1.4 (4H, m), 2.9–3.05 (1H, m), 3.45–3.6 (1H, m), 7.45–7.55 (1H, m), 7.7–7.8 (1H, m), 8.02 (1H, d, *J* 8.3), 8.46 (1H, dd, *J* 1.5 and 8.0), 8.93 (1H, s), 10.0 (1H, br s) (Found: M^+, 268.1217. Calc. for $C_{16}H_{16}N_2O_2$: *M*, 268.1212).

1-Cyclopropyl-N-*ethyl-4-oxo-1,4-dihydroquinoline-3-carboxamide* **5l**

M.p. 136 ºC; δ_H ($CDCl_3$) 1.15–1.41 (7H, m), 3.43–3.58 (3H, m), 7.47–7.54 (1H, m), 7.72–7.81 (1H, m), 8.02 (1H, d, *J* 8.7), 8.49 (1H, dd, *J* 1.5 and 8.0), 8.93 (1H, m), 9.95 (1H, br s) (Found: M^+, 256.1212. Calc. for $C_{15}H_{16}N_2O_2$: *M*, 256.1212).

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References

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2 Structural representation **2** (Scheme 1) for the complex is currently preferred to that shown in Reference 1.

3 4-Imino amides **4h**, **4i** and **4j** (Table 1) which appear in Reference 1 are here represented for spectral structure verifications (Experimental).

4 More vigorous reaction conditions are generally utilised to effect nucleophilic substitution of the 7-F in 1-alkyl-4(1*H*)-quinolone derivatives, as exemplified in the contributions by (a) K. Grohe and H. Heitzer, *Liebigs Ann. Chem.,* 1987, 29; and (b) K. Grohe, *J. Prakt. Chem.,* 1993, **335**, 397.

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7 Other methods for preparing related 4-oxo amides **5** include (i) converting the appropriate quinolone-3-carboxylic acid into its acylimidazole derivative, followed by treatment with the requisite amine, and (ii) amidating a quinolone-3-carboxylic ester in a stainless steel bomb containing the amine. M.P. Wentland, R.B. Perni, P.H. Dorff, R.P. Brundage, M.J. Castaldi, T.R. Bailey, P.M. Carabateas, E.R. Bacon, D.C. Young, M.G. Woods, D. Rosi, M.L. Drozd, R.K. Kullnig and F.J. Dutko, *J. Med. Chem.,* 1993, **36**, 1580.

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