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Ethyl 1-ethyl-7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate: X-ray and DFT studies

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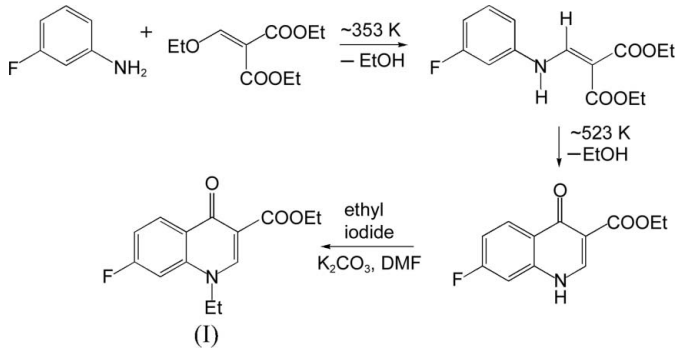
The basic building unit in the structure of the title compound, $C_{14}H_{14}FNO_3$, is pairs of molecules arranged in an antiparallel fashion, enabling weak C—H···O interactions. Each molecule is additionally involved in π–π interactions with neighbouring molecules. The pairs of molecules formed by the C—H···O hydrogen bonds and π–π interactions form ribbon-like chains running along the *c* axis. Theoretical calculations based on these pairs showed that, although the main intermolecular interaction is electrostatic, it is almost completely compensated by an exchange–repulsion contribution to the total energy. As a consequence, the dominating force is a dispersion interaction. The F atoms form weak C—F···H—C interactions with the H atoms of the neighbouring ethyl groups, with H···F separations in the range 2.59–2.80 Å.

Comment

Quinolones are known to possess a wide range of biological activities, such as antibacterial, anti-allergic, antiherpetic, anticarcinogenic *etc.*, and are used in both human and veterinary medicine (Milata *et al.*, 2000). As their antibacterial effect is enhanced with an F atom attached to the benzene ring, the majority of quinolone derivatives with medicinal applications have an F atom attached, typically in position 5, 6 or 8. The presence of a carbonyl group in position 4 and a carboxyl group in position 3 plays an important role in the interaction of a quinoline with DNA-gyrase, a key enzyme of bacterial cells in the process of DNA replication and transcription. Such a 4-oxo tautomeric form is best stabilized by an ethyl group attached to the N atom of the quinoline molecule. The skeleton of the title compound, (I), thus provides a good model for a family of potential drugs.

Compound (I) was synthesized within the framework of our continuing study (Langer *et al.*, 2009, 2010) of the structure and properties of potential drugs based on fluoroquinolones, aimed at obtaining more insight into their structure–function relationships.



(I)

The numbering scheme and the overall conformation of (I) are shown in Fig. 1. The core of (I) is essentially planar (r.m.s. deviation of 0.023 Å from the mean plane through the quinoline moiety plus the directly attached atoms F1, O1, C9 and C10), with atom C11 of the ethyl group displaced from this plane by 1.359 (3) Å. The C7—F1 bond length (Table 1) agrees with the values found previously in structurally related compounds (Langer *et al.*, 2009, 2010). A small rotation of the substituted carboxyl group along the C3—C9 bond is shown by the C2—C3—C9—O3 torsion angle [−174.7 (2)°].

The redistribution of electron density in an isolated molecule of (I) can be qualitatively described by a superposition of the resonance structures 1–4 (Fig. 3), obtained by Natural Bond Orbital (NBO) analysis (Foster & Weinhold, 1980), from which structure 1 is the most probable. The obvious consequence of the presence of resonance structure 4 is shortening of the formally single C3—C9 bond compared with the expected value (1.487 Å; Allen *et al.*, 1987). Consequently, the rigidity of the skeleton is increased, as free rotation around this bond is less favourable. The presence of resonance structures 2 and 3 is responsible for a slight lengthening of the C4═O1 and C9═O2 bonds relative to an isolated C═O bond

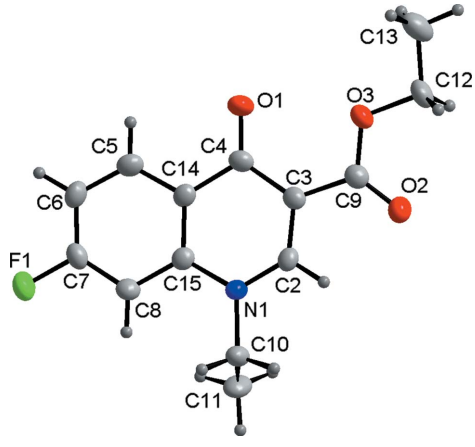


Figure 1
The structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

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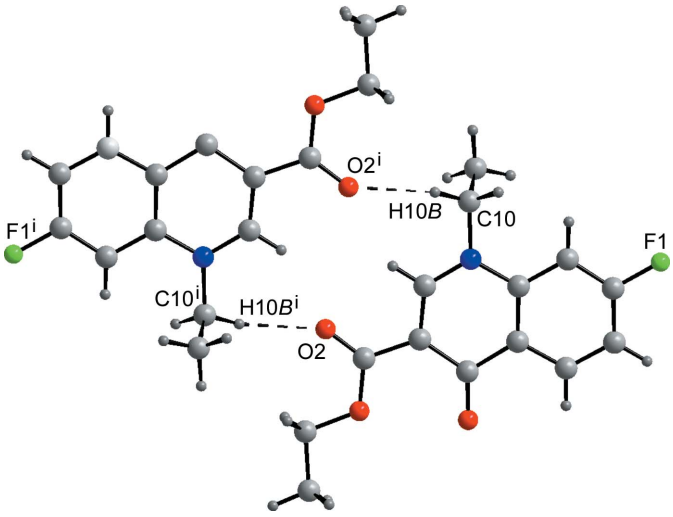

Figure 2
A pair of molecules of (I) interlinked by the C10—H10B···O2^{i} and C10^{i}—H10B^{i}···O2 hydrogen bonds (dashed lines). [Symmetry code: (i) $-x, -y+1, -z$.]

(Allen *et al.*, 1987). From Table 1 it is evident that, apart from the C12—O3 bond, the calculated Wiberg bond orders are very close to the expected values. The deviation for this bond is due the nature of NBO analysis which, in general, assumes all bonds to be covalent, and hence a value significantly lower than expected points to the significant ionicity of the bond. Deviations from expected values can also be found for polar C—O bonds in other esters. For instance, our calculations for the ethyl esters of acetic and benzoic acids give bond orders of 0.89 and 0.87, respectively. Similarly, for the C7—F1 bond, the corresponding calculated bond order is significantly smaller than 1, due to the fact that the F atom is significantly ionic.

The basic building unit in the structure of (I) is pairs of molecules arranged in an antiparallel fashion, thus enabling weak C10—H10B···O2($-x, -y+1, -z$) interactions (Fig. 2). The BSSE (basis-set superposition error) corrected binding energy calculated for an isolated model dimer, with the geometry first optimized starting from the arrangement depicted in Fig. 2, is −5.24 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}) per hydrogen bond. This value is very close to the energy of a hydrogen bond in a water dimer, for which the best theoretical estimate is −4.91 (7) kcal mol^{-1} (Halkier *et al.*, 1997); the experimentally obtained value cited in the same work is −5.4 (7) kcal mol^{-1}. Such a relatively large binding energy for a C—H···O hydrogen bond is mainly due to dispersion interactions of two large parallel atomic systems (see below) and thus has a different origin than the hydrogen bond in the above-mentioned water dimer, the origin of which is largely electrostatic.

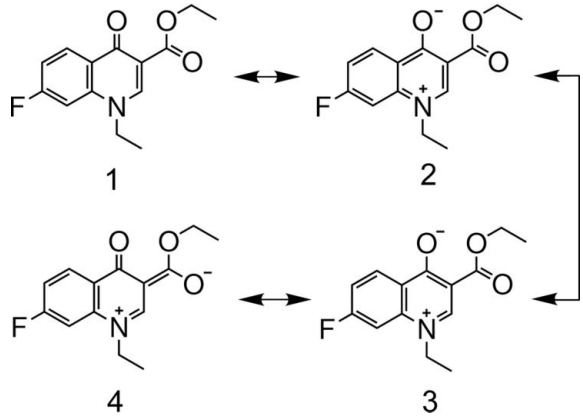

Figure 3
Possible resonance structures of the title compound.

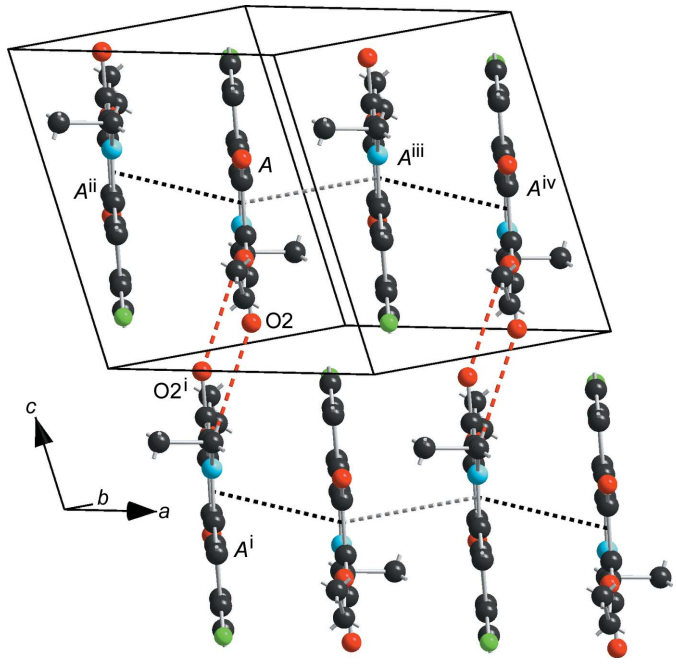

Figure 4
The packing of the molecules of (I) in the crystal structure. The pairs of molecules formed by the C—H···O hydrogen bonds (long-dashed lines) and π–π interactions (short-dashed lines) form ribbon-like chains running along the c axis. [Symmetry codes: (i) $-x, -y+1, -z$; (ii) $-x, -y+1, -z+1$; (iii) $-x+1, -y+1, -z+1$; (iv) $x+1, y, z$.]

Each molecule of (I) is additionally involved in π–π interactions with neighbouring molecules (Fig. 4). The strength of the pair interactions was estimated using a simple model involving just three neighbouring molecules taken from the structure, *viz.* A, A^{ii} and A^{iii} [symmetry codes: (ii) $-x, -y+1, -z+1$; (iii) $-x+1, -y+1, -z+1$]. Although the planes fitted to the molecules are almost parallel, the distance between the centres of gravity (Cg) of the heterocycles (N1/C2–C4/C14/C15) of molecules A and A^{ii} is significantly shorter than that for the pair of A and A^{iii}: $Cg(A)\cdots Cg(A^{ii})$ = 3.456 (2) Å *versus* $Cg(A)\cdots Cg(A^{iii})$ = 3.999 (2) Å. The difference in packing is also emphasized by the values of the mutual shift of the heterocycles (slippage) calculated with respect to the positions of the centres of gravity: 2.003 Å for A and A^{iii}, compared with 1.041 Å for the $A\cdots A^{ii}$ pair. Theoretical calculations based on these pairs showed that, although the main intermolecular interaction is electrostatic (the dipole moment of an isolated molecule calculated at the B3LYP/cc-pvTZ level is 4.5 D), it is almost completely compensated by the exchange–repulsion contribution to the total energy. As a consequence, the

dominating force is a dispersion interaction. The sizes of the interaction energies between molecule *A* and its close neighbours A^{ii} and A^{iii}, *viz.* −18.8 and −22 kcal mol^{-1}, respectively, are then comparable with the values characteristic for medium–strong hydrogen bonds.

The pairs of molecules formed by the C—H···O hydrogen bonds and π–π interactions form ribbon-like chains running along the *c* axis (Fig. 4). The intermolecular interactions are completed by weak C—H···F contacts (H···F < 3 Å) with H12*B*($-x$, $-y+1$, $-z+1$)···F1 = 2.69 Å, H11*C*(x, y, $z+1$)···F1 = 2.81 Å, H11*B*(x, $-y+\frac{3}{2}$, $z+\frac{1}{2}$)···F1 = 2.84 Å, H12*A*($-x+1$, $-y+1$, $-z+1$)···F1 = 2.95 Å and H11*A*(x, $-y+\frac{3}{2}$, $z+\frac{1}{2}$)···F1 = 2.99 Å. These H···F separations are within the limits for this type of contact (Shimoni & Glusker, 1994).

Experimental

To a flask containing ethyl 7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1.00 g, 4.81 mmol) suspended in dimethylformamide (10 ml) was added K_2CO_3 (2.35 g, 19.5 mmol). The reaction mixture was heated for 10 min in an oil bath at 333 K and ethyl iodide (0.78 ml, 9.2 mmol) was added. After 3.5 h, the reaction mixture was poured into water (40 ml) and the resulting solution was extracted with chloroform (3 × 40 ml). The organic phases were collected, dried with sodium sulfate and evaporated to dryness, and the product obtained was purified using column chromatography (ethyl acetate/hexane, 20:1 *v*/*v*) to give the title compound, (I), as a white powder (999 mg, 89%) [m.p. 388–393 K (uncorrected)]. A small amount of the product was dissolved in chloroform and the solution allowed to evaporate slowly over a period of 2 d at room temperarure, after which time crystals of (I) suitable for X-ray analysis were obtained.

Crystal data

$C_{14}H_{14}FNO_3$
M_r = 263.26
Monoclinic, $P2_1/c$
a = 7.1426 (18) Å
b = 21.156 (5) Å
c = 8.623 (2) Å
β = 108.510 (5)°
V = 1235.6 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.11 mm^{-1}
T = 153 K
0.22 × 0.16 × 0.07 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan *SADABS*; Sheldrick, 2003
T_{min} = 0.976, T_{max} = 0.992
9173 measured reflections
2199 independent reflections
1447 reflections with $I > 2\sigma(I)$
R_{int} = 0.069

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.132
S = 0.99
2199 reflections
174 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Aromatic and secondary H atoms were refined isotropically, with U_{iso}(H) = 1.2U_{eq}(C), and their positions were constrained to an ideal geometry using an appropriate riding model (C—H = 0.95 Å for aromatic or 0.99 Å for secondary H atoms). For methyl groups, C—C—H angles (109.5°) were kept fixed, while the torsion angle was allowed to refine with the starting positions based on the circular Fourier synthesis averaged using the local threefold axis, with U_{iso}(H) = 1.5U_{eq}(C) and a constrained C—H distance of 0.98 Å.

Table 1
Selected bond distances (Å) and Wiberg bond orders (WBO; Wiberg, 1968).

	Distance	WBO		Distance	WBO
C2—N1	1.336 (3)	1.231	C9—O3	1.333 (3)	1.075
C15—N1	1.389 (3)	1.077	C10—C11	1.518 (4)	1.029
C10—N1	1.478 (3)	0.934	C12—O3	1.446 (3)	0.872
C2—C3	1.367 (3)	1.529	C12—C13	1.484 (4)	1.045
C3—C9	1.478 (3)	1.021	C4—O1	1.233 (3)	1.654
C9—O2	1.215 (3)	1.665	C7—F1	1.361 (3)	0.889

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C10—H10*B*···O2^{i}	0.99	2.36	3.336 (3)	169

Symmetry code: (i) $-x, -y+1, -z$.

Basic molecular calculations were carried out at the B3LYP/6-31+G** and B3LYP/cc-pvTZ levels of theory (*GAUSSIAN98*; Frisch *et al.*, 1998). Dispersion calculations were carried out at the B97-d/cc-pvTZ level of theory using *TURBOMOLE* (Version 5.10; Ahlrichs *et al.*, 1989) employing the *RI* DFT module (Treutler & Ahlrichs, 1995). Natural Bond Orbital (Foster & Weinhold, 1980) calculations were carried out using the *NBO* program (Version 3.1; Glendening *et al.* 1993) included in the *GAUSSIAN98* package.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT* and *SADABS* (Sheldrick, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg, 2010); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008) and *PLATON* (Spek, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: EM3044). Services for accessing these data are described at the back of the journal.

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