Crystal structure of ethyl 2,4-dichloroquinoline-3-carboxylate

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In the crystal structure of the title compound, $C_{12}H_9Cl_2NO_2$, the mean planes through the quinoline and carboxylate groups have r.m.s. deviations of 0.006 and 0.021 Å, respectively, and form a dihedral angle of 87.06 (19)°. In the crystal, molecules are linked *via* very weak C—H···O hydrogen bonds, forming chains, which propagate along the *c*-axis direction.

1. Related literature

For the potential of related compounds in anti-HIV treatment, see: Maartens *et al.* (2014); Hopkins *et al.* (2004). For a related structure, see: Reyes *et al.* (2013)
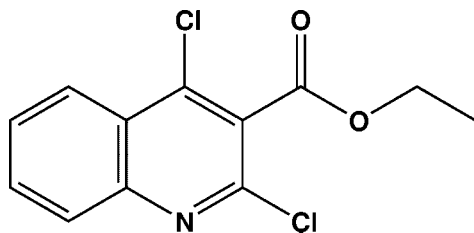
2. Experimental

2.1. Crystal data

$C_{12}H_9Cl_2NO_2$	$V = 1199.32\ (11)$ Å^3
$M_r = 270.10$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 8.5860\ (4)$ Å	$\mu = 0.53$ mm^{-1}
$b = 19.9082\ (11)$ Å	$T = 298$ K
$c = 7.1304\ (4)$ Å	$0.50 \times 0.25 \times 0.16$ mm
$\beta = 100.262\ (1)°$	

2.2. Data collection

Bruker APEXII CCD area-detector diffractometer	2197 independent reflections
	1833 reflections with $I > 2\sigma(I)$
6785 measured reflections	$R_{int} = 0.024$

2.3. Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	156 parameters
$wR(F^2) = 0.094$	H-atom parameters constrained
$S = 1.05$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
2197 reflections	$\Delta\rho_{min} = -0.21$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···O1^i	0.93	2.69	3.586 (3)	162

Symmetry code: (i) $x + 1, -y + \frac{3}{2}, z + \frac{1}{2}$.

Data collection: *APEX2* (Bruker, 2012); cell refinement: *SAINT* (Bruker, 2012); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2015); program(s) used to refine structure: *SHELXL2013* (Sheldrick, 2015); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Acknowledgements

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supporting information

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S1. Chemical context

The HIV (human immunodeficiency virus) is responsible of the acquired immunodeficiency syndrome (AIDS). The actual treatment consists of a group of several drugs known as anti-retrovirals which inhibit important proteins for virus replication, including reverse transcriptase (Maartens *et al.*, 2014).

As part of the synthesis of promising compounds as anti-retrovirals, Stammers and coworkers, maintaining as base structure a quinolone core, found compounds that showed activity in the inhibition of the reverse transcriptase. They obtained a dibromide quinolone in C2/C4 as an intermediate. After that, they were able to remove the C2 bromine in an acetic acid solution and finally, the C4 bromine was substituted by alkyl-sulfurated compounds to get the final molecules which have been proven activity against HIV (Hopkins *et al.*, 2004),

As part of our ongoing research, we have synthesized different pyridin-2 (1*H*)-one analogues (Reyes *et al.*, 2013). In this work, we developed a methodology to obtain derivatives of quinolone, with saturated and unsaturated amines in in C4 with ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxilate as a starting material. Chlorination of the quinolone core results in the dichlorinated compound ethyl 2,4-dichloroquinoline-3-carboxylate with a yield of 70% and a crystal structure was obtained. The intermediate of interest, the ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate, was obtained after treatment of the dichlorinated compound with an acetic acid solution following the methodology described by Stammers (Hopkins *et al.*, 2004) in >98% yield (see experimental section in supplementary material).

The structure of the compound is shown in Fig. 1. The two aromatic rings of quinoline are fused almost coaxially, with a dihedral angle between their planes of C8—C9—C10—C4= 179.21 (14)º. The carboxylate group is in an antiperiplanar conformation to the quinoline with a torsion angle C12—O2—C11—C3 = -179.39 (15)°, and bonded to the quinoline over the plane C3—C11—O2 by 110.46 (14)º. The deviation of the bond length values for C2—Cl1= 1.745 (2) and C4—Cl 2= 1.7248 (16) from the standard values can be attributed for the sp2 hybridization of the quinoline ring. In the crystal, molecules are linked *via* O1—H7 intermolecular hydrogen bonds forming chains propagating along the *c* axis direction. (Fig. 2).

S2. Synthesis and crystallization

The synthesis of ethyl 2,4-dichloroquinoline-3-carboxylate and ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate includes reagents and reagent grade solvents, which were used without further purification. In a 100 mL round bottom flask equipped with a magnetic stirrer was placed 500 mg of ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (2.15 mmol) and 1.96 g of benzyltriethylammonium chloride in 15 mL of acetonitrile. Under continuous stirring, 0.88 mL of the phosphoryl chloride (9.46 mmol) was added drop by drop. The mixture was stirred at 40º C for 30 min and later at reflux for 1 h. Then, the solvent was evaporated and 15 mL of cold water was added and stirred for 1 h. Then a precipitate was obtained corresponding to a mixture of ethyl 2,4-dichloroquinoline-3-carboxylate and ethyl 4-chloro-2-oxo-1,2-di-hydroquinoline-3-carboxylate. The precipitate was dissolved in 3 mL of dichloromethane-methanol (1:1, v/v). Partial

evaporation leads to crystals (not suitable for X-ray diffraction) of ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (0.65 mmol, 30%). The rest corresponded to ethyl 2,4-dichloroquinoline-3-carboxylate (1.5 mmol, 70%). The latter compound was placed in a round bottom flask of 50 mL containing acetic acid (10 mL) and water (5 mL). The mixture was stirred under reflux for 24 h. After cooling, the product was extracted with ethyl ether to afford ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (>98%).

Ethyl 2,4-dichloroquinoline-3-carboxylate: m.p. 83-85 °C. ^{1}H RMN (DMSO-$d6$): δ 8.27 (dd, J = 8.3, 0.6 Hz, H-5), 8.09 (dd, J = 8.3, 0.6 Hz, H-8), 8.03 (ddd, J = 7.7, 6.9, 1.4 Hz, H-7), 7.89 (ddd, J = 7.7, 6.9, 1.4 Hz, H-6) 4.51 (q, J = 7.1 Hz, COOCH$_2$CH$_3$), 1.39 (t, J = 7.1 Hz, COOCH$_2$CH$_3$). ^{13}C RMN (DMSO-$d6$): δ 163.5, 147.2, 144.7, 141.1, 133.7, 130.2, 129.1, 127.1, 124.9, 124.3, 63.4, 14.3. IEMS m/e (int. rel): [M]$^+$ 269 (32), [M]$^+$+2 271 (21), [M]$^+$+4 273 (3), 241 (26), 223 (100), 195 (17), 161 (28) amu.

Crystals of the title compound suitable for X-ray diffraction were obtained by dissolving 15 mg of ethyl 2,4-dichloro-quinoline-3-carboxylate in 0.5 mL of ethanol-di-ethyl ether (1:1, v / v) and placing the solution in a glass vial. The solution was allowed to stand at room temperature for 7 days and the crystals formed were filtered.

S3. Refinement details

The C-bound H atoms were positioned geometrically and refined using a riding model with d(C—H) = 1.00 Å, U$_{iso}$ = 1.2U$_{eq}$(C) for Csp^3—H, d(C—H) = 0.99 Å, U$_{iso}$ = 1.2U$_{eq}$(C) for CH$_2$ groups, d(C—H) = 0.95 Å, U$_{iso}$ = 1.2U$_{eq}$(C) for aromatic C—H.
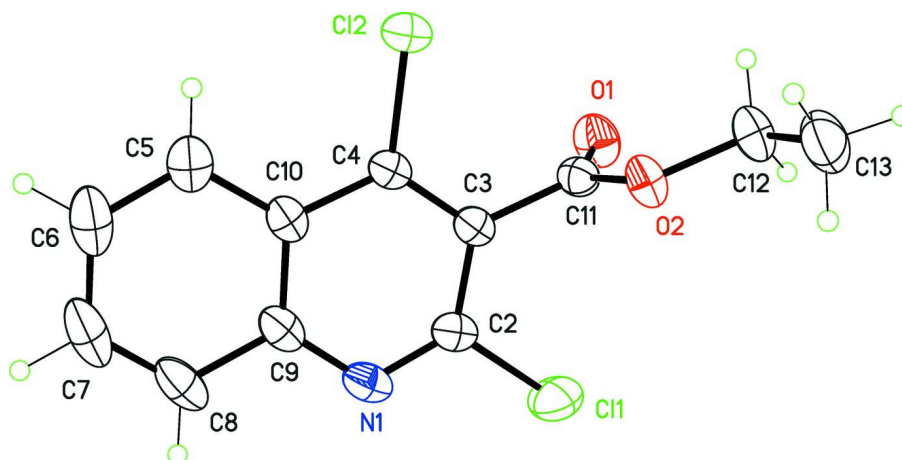

Figure 1

The asymmetric unit of the title compound with displacement ellipsoids drawn at the 50% probability level.
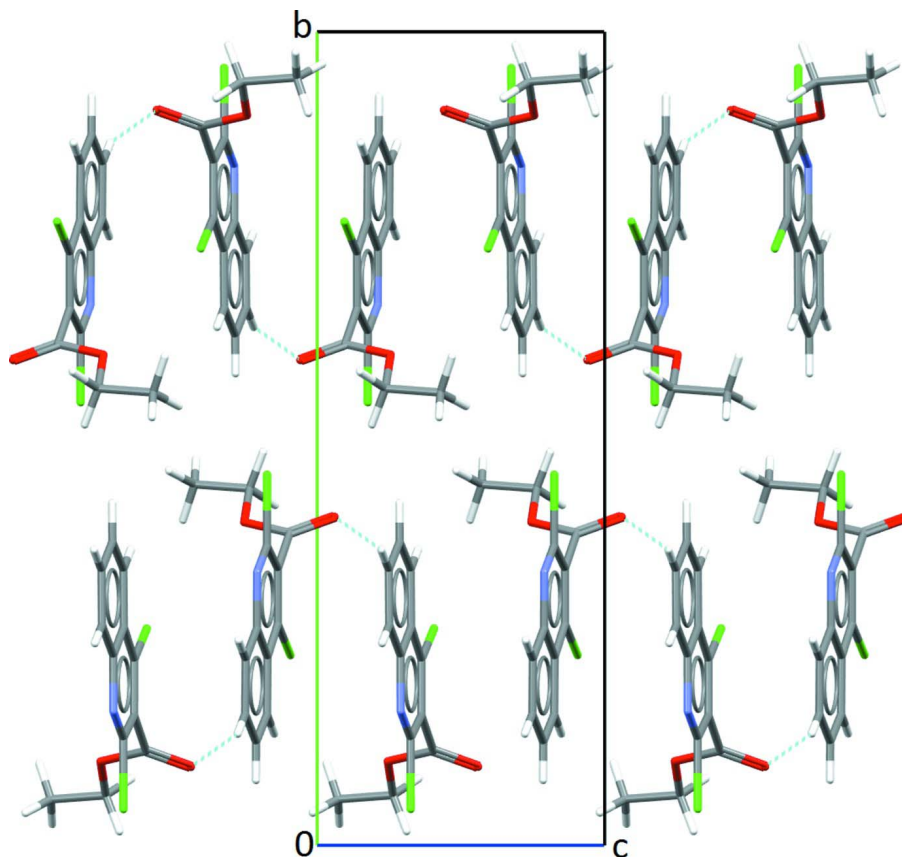
Figure 2

Crystal packing viewed along the a axis. The intermolecular C—H···O hydrogen bonds are shown as dashed lines.

Ethyl 2,4-dichloroquinoline-3-carboxylate

Crystal data

$C_{12}H_9Cl_2NO_2$	$F(000) = 552$
$M_r = 270.10$	$D_x = 1.496$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 8.5860$ (4) Å	Cell parameters from 4843 reflections
$b = 19.9082$ (11) Å	$\theta = 2.4–25.4°$
$c = 7.1304$ (4) Å	$\mu = 0.53$ mm^{-1}
$\beta = 100.262$ (1)°	$T = 298$ K
$V = 1199.32$ (11) Å^3	Prism, colourless
$Z = 4$	$0.50 \times 0.25 \times 0.16$ mm

Data collection

Bruker APEXII CCD area-detector diffractometer	1833 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.024$
Detector resolution: 0.83 pixels mm^{-1}	$\theta_{max} = 25.4°$, $\theta_{min} = 2.1°$
ω scans	$h = -10 \rightarrow 10$
6785 measured reflections	$k = -23 \rightarrow 23$
2197 independent reflections	$l = -8 \rightarrow 8$

Refinement

Refinement on F^2	H-atom parameters constrained
Least-squares matrix: full	$w = 1/[\sigma^2(F_o^2) + (0.052P)^2 + 0.1257P]$
$R[F^2 > 2\sigma(F^2)] = 0.035$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.094$	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.05$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
2197 reflections	$\Delta\rho_{min} = -0.21$ e Å^{-3}
156 parameters	Extinction correction: *SHELXL2013* (Sheldrick,
0 restraints	2015), Fc*=kFc[1+0.001xFc$^2\lambda^3$/sin(2θ)]$^{-1/4}$
Hydrogen site location: inferred from	Extinction coefficient: 0.010 (2)
neighbouring sites	

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
Cl1	0.85142 (7)	0.95554 (3)	0.67524 (10)	0.0847 (2)
Cl2	0.49224 (5)	0.73357 (2)	0.59388 (7)	0.05637 (19)
O1	0.48324 (17)	0.90370 (7)	0.44065 (18)	0.0701 (4)
O2	0.48524 (14)	0.89699 (6)	0.75480 (17)	0.0565 (3)
N1	0.96891 (17)	0.83536 (9)	0.7101 (2)	0.0567 (4)
C2	0.8376 (2)	0.86809 (9)	0.6757 (2)	0.0514 (4)
C3	0.68405 (18)	0.84036 (8)	0.6379 (2)	0.0435 (4)
C4	0.67539 (18)	0.77181 (8)	0.6378 (2)	0.0415 (4)
C5	0.8137 (3)	0.66071 (10)	0.6754 (3)	0.0621 (5)
H5	0.7187	0.6372	0.6505	0.075*
C6	0.9535 (3)	0.62696 (13)	0.7135 (3)	0.0816 (7)
H6	0.9531	0.5802	0.7143	0.098*
C7	1.0976 (3)	0.66121 (14)	0.7514 (3)	0.0838 (8)
H7	1.1918	0.6371	0.7779	0.101*
C8	1.1014 (2)	0.72928 (13)	0.7498 (3)	0.0705 (6)
H8	1.1981	0.7516	0.7748	0.085*
C9	0.9593 (2)	0.76660 (10)	0.7105 (2)	0.0511 (5)
C10	0.81366 (19)	0.73162 (9)	0.6738 (2)	0.0451 (4)
C11	0.5396 (2)	0.88399 (9)	0.5963 (2)	0.0478 (4)
C12	0.3434 (2)	0.93853 (11)	0.7367 (3)	0.0674 (5)
H12A	0.2575	0.9182	0.6481	0.081*
H12B	0.3638	0.9828	0.6897	0.081*
C13	0.3010 (3)	0.94358 (13)	0.9279 (3)	0.0858 (7)
H13A	0.2721	0.9000	0.9681	0.129*
H13B	0.2133	0.9738	0.9235	0.129*
H13C	0.3900	0.9602	1.0166	0.129*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0773 (4)	0.0613 (3)	0.1107 (5)	−0.0197 (3)	0.0034 (3)	−0.0015 (3)
Cl2	0.0445 (3)	0.0641 (3)	0.0597 (3)	−0.01024 (19)	0.0070 (2)	−0.0018 (2)
O1	0.0713 (9)	0.0848 (10)	0.0506 (8)	0.0213 (7)	0.0009 (7)	0.0096 (7)
O2	0.0498 (7)	0.0681 (8)	0.0529 (7)	0.0183 (6)	0.0129 (6)	0.0081 (6)
N1	0.0395 (8)	0.0795 (11)	0.0508 (9)	−0.0050 (7)	0.0070 (6)	−0.0022 (8)
C2	0.0455 (10)	0.0606 (11)	0.0475 (10)	−0.0066 (8)	0.0064 (8)	−0.0016 (8)
C3	0.0393 (9)	0.0544 (10)	0.0367 (8)	0.0011 (7)	0.0069 (7)	0.0000 (7)
C4	0.0377 (8)	0.0548 (10)	0.0325 (8)	−0.0016 (7)	0.0073 (6)	−0.0002 (7)
C5	0.0719 (13)	0.0630 (12)	0.0520 (11)	0.0133 (10)	0.0128 (9)	0.0027 (9)
C6	0.0980 (19)	0.0785 (15)	0.0680 (14)	0.0429 (14)	0.0143 (13)	0.0066 (11)
C7	0.0768 (16)	0.118 (2)	0.0564 (13)	0.0554 (16)	0.0110 (11)	0.0060 (13)
C8	0.0445 (11)	0.120 (2)	0.0476 (11)	0.0239 (11)	0.0085 (8)	−0.0009 (11)
C9	0.0412 (9)	0.0793 (13)	0.0337 (9)	0.0101 (8)	0.0090 (7)	−0.0001 (8)
C10	0.0451 (9)	0.0608 (11)	0.0301 (8)	0.0100 (8)	0.0088 (7)	0.0016 (7)
C11	0.0440 (9)	0.0499 (9)	0.0481 (10)	−0.0006 (7)	0.0042 (8)	0.0018 (8)
C12	0.0544 (11)	0.0706 (12)	0.0778 (13)	0.0229 (10)	0.0136 (10)	0.0079 (11)
C13	0.0641 (14)	0.1089 (19)	0.0878 (16)	0.0215 (13)	0.0227 (12)	−0.0130 (14)

Geometric parameters (Å, º)

Cl1—C2	1.745 (2)	C6—C7	1.396 (4)
Cl2—C4	1.7248 (16)	C6—H6	0.9300
O1—C11	1.195 (2)	C7—C8	1.356 (4)
O2—C11	1.323 (2)	C7—H7	0.9300
O2—C12	1.459 (2)	C8—C9	1.413 (3)
N1—C2	1.287 (2)	C8—H8	0.9300
N1—C9	1.371 (3)	C9—C10	1.414 (2)
C2—C3	1.411 (2)	C12—C13	1.476 (3)
C3—C4	1.367 (2)	C12—H12A	0.9700
C3—C11	1.500 (2)	C12—H12B	0.9700
C4—C10	1.417 (2)	C13—H13A	0.9600
C5—C6	1.360 (3)	C13—H13B	0.9600
C5—C10	1.412 (3)	C13—H13C	0.9600
C5—H5	0.9300		
C11—O2—C12	116.84 (14)	C9—C8—H8	119.8
C2—N1—C9	117.06 (15)	N1—C9—C8	118.38 (18)
N1—C2—C3	126.55 (18)	N1—C9—C10	122.85 (15)
N1—C2—Cl1	116.62 (14)	C8—C9—C10	118.77 (19)
C3—C2—Cl1	116.83 (14)	C5—C10—C9	119.45 (16)
C4—C3—C2	116.09 (15)	C5—C10—C4	124.43 (17)
C4—C3—C11	122.35 (14)	C9—C10—C4	116.12 (16)
C2—C3—C11	121.55 (15)	O1—C11—O2	125.64 (16)
C3—C4—C10	121.33 (15)	O1—C11—C3	123.90 (16)
C3—C4—Cl2	119.25 (12)	O2—C11—C3	110.46 (14)

C10—C4—Cl2	119.42 (13)	O2—C12—C13	107.24 (16)
C6—C5—C10	119.7 (2)	O2—C12—H12A	110.3
C6—C5—H5	120.2	C13—C12—H12A	110.3
C10—C5—H5	120.2	O2—C12—H12B	110.3
C5—C6—C7	121.2 (2)	C13—C12—H12B	110.3
C5—C6—H6	119.4	H12A—C12—H12B	108.5
C7—C6—H6	119.4	C12—C13—H13A	109.5
C8—C7—C6	120.5 (2)	C12—C13—H13B	109.5
C8—C7—H7	119.7	H13A—C13—H13B	109.5
C6—C7—H7	119.7	C12—C13—H13C	109.5
C7—C8—C9	120.4 (2)	H13A—C13—H13C	109.5
C7—C8—H8	119.8	H13B—C13—H13C	109.5

Hydrogen-bond geometry (Å, º)

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···O1[i]	0.93	2.69	3.586 (3)	162

Symmetry code: (i) $x+1$, $-y+3/2$, $z+1/2$.