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Quinoline derivatives: potential anti-parasitic and antiviral agents

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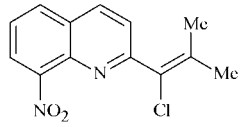
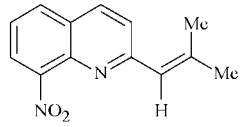
The crystal structures of closely related quinoline compounds substituted at the 2-position by a vinyl group, either including a Cl atom [2-(1-chloro-2-methylprop-1-enyl)-8-nitroquinoline, $C_{13}H_{11}ClN_2O_2$, (I)] or not [2-(2-methylprop-1-enyl)-8-nitroquinoline, $C_{13}H_{12}N_2O_2$, (II)], show an important deviation of the vinyl group from coplanarity with the quinoline ring system if the Cl atom is present. The nitro group is perpendicular [in (II)] or nearly so [in (I)] to the quinoline ring system. In (II), all non-H atoms except the nitro O atoms are located on a crystallographic mirror plane.

Comment

Recently, some 2-substituted quinoline compounds have been studied for their antiparasitic (Franck *et al.*, 2004) and antiviral (Zouhiri *et al.*, 2005) activities. Aiming at preparing original analogs with pharmacological potential in the quinoline series through a radical reaction approach, we developed a mono-electronic transfer synthesis by reacting nitrated 2-trihalomethylquinolines with 2-nitropropane salts, leading to the corresponding 2-isopropylidene-substituted products, (I) and (II), in high yields (Verhaeghe *et al.*, 2006). Such *C*-alkylation and elimination reactions have the main advantage of permitting a one-step access to tri- or tetrasubstituted vinyl derivatives through mild operating conditions. Different substrates were used for conducting this chemical work. Firstly, 8-nitro-2-(trichloromethyl)quinoline led to the expected vinyl chloride product (I) by reaction with 2-nitropropane and tetrabutylammonium hydroxide under light irradiation and under an inert atmosphere. 8-Nitro-2-(tribromomethyl)quinoline was then reacted under the same conditions and, contrary to the previous results, gave the unhalogenated vinyl product (II), previously synthesized by Nishikawa *et al.* (1980), most probably as a result of an initial *in situ* reduction of the tribromomethyl substrate into a dibromomethyl one.



(I)



(II)

The structural study of these two molecules had various objectives. It seemed important to define the relative position

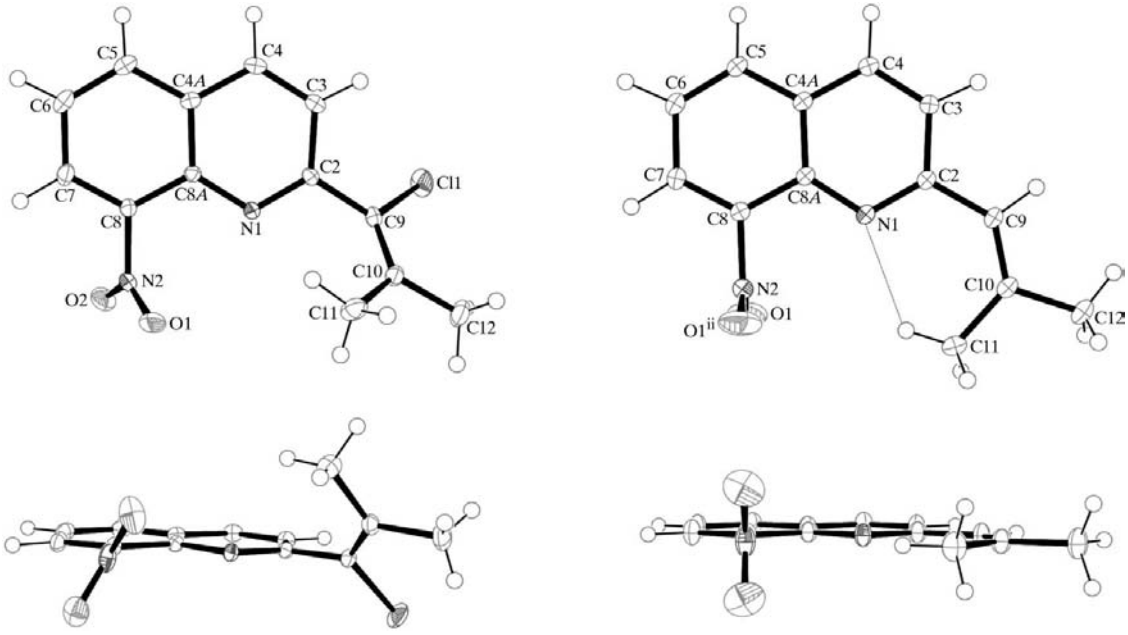


Figure 1
Mutually perpendicular views of compounds (I) and (II), showing 50% probability displacement ellipsoids and H atoms as circles of arbitrary radius. [Symmetry code: (ii) $x, y-\frac{1}{2}, z$.]

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of the substituent in the 2-position with respect to the quinoline ring system, evaluating whether the vinyl bond was conjugated with the aromatic ring or not. We also studied the coplanarity of the nitro group with respect to the quinoline ring system.

Fig. 1 shows views of the asymmetric units of 2-(1-chloro-2-methylpropenyl)-8-nitroquinoline, (I), and 2-(2-methylprop-1-enyl)-8-nitroquinoline, (II). The vinyl group at the 2-position is rigorously coplanar with the quinoline ring system in the nonhalogenated structure (II) (the dihedral angle is exactly 0.0°). In fact, in the crystal structure of (II), all non-H atoms except the nitro group O atom are located on a crystallographic mirror plane, and so the atoms of both groups lie in the same plane. In (I), the vinyl group deviates strongly from planarity with the quinoline ring system, with a dihedral angle of 51.60 (2)°. The bond lengths in the vinyl group show that in (I) the first single bond (C2—C9) is longer than the corresponding bond in (II). The vinyl double bond is shorter in (I) (Tables 1 and 3). Comparison with reference lengths for single [C—C ≃ 1.53 (2) Å] and double bonds [C═C ≃ 1.32 (1) Å] (Glusker *et al.*, 1994) indicates that the vinyl bond is conjugated with the aromatic cycle in both structures, but more strongly in (II).

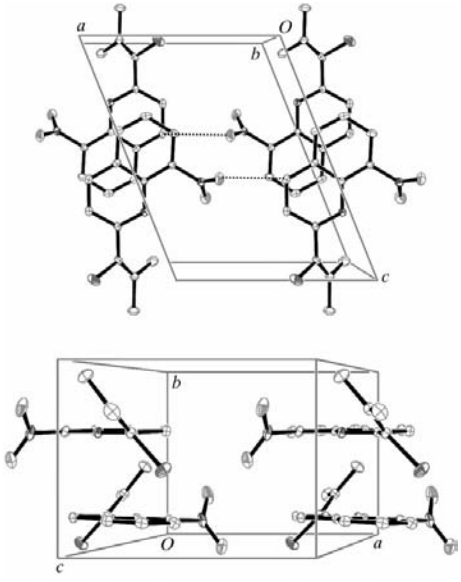

Figure 2
View of the stacking interactions and weak hydrogen bonds (dashed lines) in the halogenated compound (I).

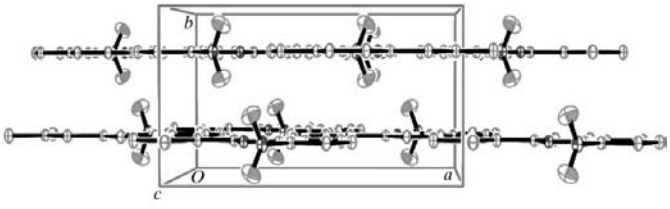

Figure 3
Stacking interactios in the nonhalogenated compound (II).

The nitro group is significantly inclined to the quinoline ring system in both structures. The dihedral angle is 90° in (II) and 61.73 (2)° in (I). Usually, nitro groups are found to be coplanar with aromatic rings, but a search among the structures deposited in the Cambridge Structural Database (CSD; Version 5.18; Allen, 2002) indicated that the nitro group attached to the benzene ring can deviate somewhat from this coplanar arrangement (by as much as 70°; Zinner *et al.*, 1994). The crystal structure of (II) shows that the vinyl group interacts through a weak hydrogen bond with the N atom of the quinoline ring system (Table 4), and so is situated on this side of the molecule. The steric encumbrance thus caused by the vinyl group obviates a coplanar orientation for the nitro fragment. In (I), the vinyl group deviates from coplanarity with the quinoline system, and so it does not introduce the steric hindrance it does in (II). Therefore, the deviation observed for the nitro group in (I) is probably caused by a weak hydrogen bond between one O atom (O2) of the nitro group and the C4—H4 group of the aromatic ring of a neighboring molecule (Table 2).

In (I), the quinoline ring systems stack in a nearly parallel orientation (with a dihedral angle of 3.06°), forming columns along *b*. Considering the interaction between the C_6 and C_5N rings, successive pairs along the stack have *Cg*···*Cg* distances of 3.5749 (3) [from the C_6 ring at (x, y, z) to the C_5N ring at ($-x$, $y-\frac{1}{2}$, $-z+1$)] and 3.5911 (3) Å [C_6(x, y, z) to C_5N($-x$, $y+\frac{1}{2}$, $-z+1$)] (Fig. 2). Each interaction in the column includes a slight slip in the *c*-axis direction. Thus, atom C4*A* is situated approximately facing the center of gravity of the benzene ring at ($-x$, $y-\frac{1}{2}$, $-z+1$), and atom C6 lies over the center of gravity of the pyridine ring at ($-x$, $y-\frac{1}{2}$, $-z+1$). These columns are related to one another in the *a*-axis direction through the weak hydrogen bond described above.

In (II), columns are formed in the *b* direction through stacking interactions with an interplanar distance of *b*/2 (approximately 3.45 Å; Fig. 3). The rings are rigorously parallel and, as in (I), alternate rings in the column are slipped (here, in the *a* direction). In this case, atom C4*A* is situated exactly facing the center of gravity of the benzene ring, and atom C6 faces the center of gravity of the pyridine ring of the neighboring molecule at ($-x+2$, $y+\frac{1}{2}$, $-z+1$).

Experimental

Compound (I)

Crystal data

$C_{13}H_{11}ClN_2O_2$
M_r = 262.69
Monoclinic, $P2_1$
a = 8.6278 (2) Å
b = 6.6525 (2) Å
c = 11.3284 (3) Å
β = 111.658 (1)°
V = 604.31 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.31 mm^{-1}
T = 150 (2) K
0.59 × 0.34 × 0.23 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
45955 measured reflections
9975 independent reflections
8940 reflections with $I > 2\sigma(I)$
R_{int} = 0.023

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.029$
$wR(F^2) = 0.082$
$S = 1.06$
9975 reflections
207 parameters
1 restraint
All H-atom parameters refined
$\Delta\rho_{max} = 0.55$ e Å^{-3}
$\Delta\rho_{min} = -0.44$ e Å^{-3}
Absolute structure: Flack (1983), 4595 Friedel pairs
Flack parameter: 0.02 (2)

Table 1
Selected bond lengths (Å) for (I).

Cl1—C9	1.7514 (5)	C9—C10	1.3394 (7)
C2—C9	1.4819 (6)		

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

D—H···A	D—H	H···A	D···A	D—H···A
C4—H4···O2^{i}	0.976 (12)	2.482 (13)	3.2098 (7)	131.2 (10)

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

Compound (II)

Crystal data

$C_{13}H_{12}N_2O_2$
$M_r = 228.25$
Orthorhombic, *Pnma*
$a = 11.5578$ (5) Å
$b = 6.8987$ (3) Å
$c = 13.9900$ (6) Å
$V = 1115.48$ (8) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.09$ mm^{-1}
$T = 150$ (2) K
0.54 × 0.25 × 0.20 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
53490 measured reflections
2280 independent reflections
1973 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.129$
$S = 1.09$
2280 reflections
132 parameters
All H-atom parameters refined
$\Delta\rho_{max} = 0.53$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Table 3
Selected bond lengths (Å) for (II).

C2—C9	1.4668 (13)	C9—C10	1.3472 (13)

Table 4
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C11—H11B···N1	0.97 (2)	2.33 (2)	3.0097 (13)	126.6 (16)

All H-atom parameters were refined freely [C—H = 0.85 (2)–1.022 (12) Å in (I) and 0.965 (14)–1.029 (19) Å in (II)].

For both compounds, data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXTL* (Bruker, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3106). Services for accessing these data are described at the back of the journal.

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