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Nitrated isomers of 2-(trichloromethyl)quinoline

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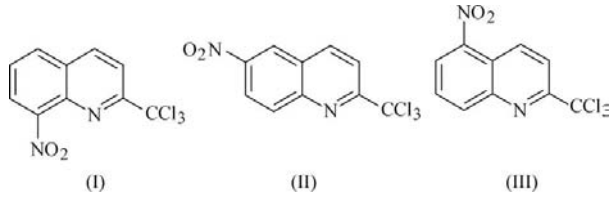
In the closely related quinoline compounds 8-nitro-2-(trichloromethyl)quinoline, (I), 6-nitro-2-(trichloromethyl)quinoline, (II), and 5-nitro-2-(trichloromethyl)quinoline, (III), all $C_{10}H_5Cl_3N_2O_2$, which are of both reactivity and pharmacological interest, and for which the biological activity and cytotoxicity appear to be based on the positions of the CCl_3 and nitro substituents, the nitro group is only coplanar with its aromatic substrate in (II). The deviation of the nitro group from coplanarity is concluded to be a function of both its position with respect to the trichloromethyl group and the intermolecular contacts in which it participates. The discrepancies between the crystal structures and the molecular shapes predicted by *ab initio* calculations are also explained in these terms. The quinoline ring is not rigorously planar in any of the structures, which may be explained by stress produced by the CCl_3 substituent.

Comment

The quinoline nucleus presents a broad spectrum of pharmacological activities. It is part of the chemotherapeutic arsenal in various medical specialities, mainly in infectiology (chloroquine, mefloquine), but also in cardiology (quinidine), and it can present analgesic properties (floctafenine). Recent research has evaluated its potential in other pharmaceutical areas, such as the central nervous system (Bromidge *et al.*, 2001), haematology (Clasby *et al.*, 2006) or virology (Polanski *et al.*, 2002). The trichloromethyl group in a position α to the Nsp^2 atom of various heteroaromatic rings has also demonstrated its own specific pharmacological activities (Liu *et al.*, 2003; Tiwari *et al.*, 2002; Sielecki *et al.*, 2001; Verhaeghe *et al.*, 2008). Furthermore, the trichloromethyl group offers interesting synthetic pathways to further products. It leads easily to the amidine function, is the main synthetic trifluoromethyl precursor and has recently been reacted with aromatic aldehydes through TDAE-initiated reactions [TDAE is tetrakis-(dimethylamino)ethylene], generating α-chloroketone derivatives (Montana *et al.*, 2006). It is also possible to involve 8- and 6-nitro-2-(trichloromethyl)quinolines, (I) and (II), in consecutive $S_{RN}1$ and $E_{RC}1$ reactions, leading to novel vinylic chloride derivatives (Verhaeghe, Rathelot, Rault & Vanelle, 2006) ($S_{RN}1$ is a nucleophilic radical substitution mechanism and $E_{RC}1$ is a unimolecular radical chain elimination reaction).



For both reaction studies and therapeutic purposes, it appeared important to establish the structures of these isomeric compounds, which were prepared efficiently in two steps from 2-methylquinoline, *via* successive nitration and microwave-assisted chlorination reactions (Verhaeghe, Rathelot, Gellis *et al.*, 2006). From a reactivity point of view, in the nitrobenzyl chloride series, Kerber *et al.* (1965) suggested that the nitro group of the aromatic substrates involved in $S_{RN}1$ reactions had to be coplanar with the benzene ring in order for the reaction to proceed correctly. However, when we reacted compounds (I) and (II) with nitroalkane salts, under single electron-transfer reaction conditions, the corresponding vinyl chloride products were obtained in similar very good yields (Verhaeghe, Rathelot, Rault & Vanelle, 2006), although the nitro group in (I) is perpendicular to the quinoline ring while the nitro group of (II) is nearly coplanar with the same quinoline ring.

Fig. 1 shows views of the asymmetric units of compounds (I), (II) and (III). The asymmetric units of compounds (I) and (II) contain one molecule, while for (III) $Z' = 2$.

In the 8-nitro isomer, (I), the nitro group is nearly perpendicular to the quinoline ring, as was initially supposed [dihedral angle = 68.42 (5)°]. An *ab initio* calculation of potential energy as a function of nitro group torsion angle [*GAUSSIAN98* (Frisch *et al.*, 2001); basis set HF/3-21G] showed that the most stable nitro group conformations are those with a deviation of about ±30° from coplanarity. The larger deviation observed in the crystal structure of (I) seems to be a consequence of intermolecular interactions. Atom O1 crowds atom O2^{i} from a neighbouring molecule [2.952 (2) Å; symmetry code: (i) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$]. At the same time, atom O1 also contacts two H atoms from aromatic C—H groups, *viz.* H5^{ii} [2.613 Å; symmetry code: (ii) $+x, \frac{3}{2}-y, -\frac{1}{2}+z$] and H6^{ii} (2.552 Å), and these electrostatic contacts are favourable to an out-of-plane twist of the nitro group.

In the 5-nitro isomer, (III), the nitro group deviates from coplanarity with the quinoline ring [dihedral angles = 36.05 (6) and 35.74 (5)°]. An *ab inito* calculation proposed, as the most

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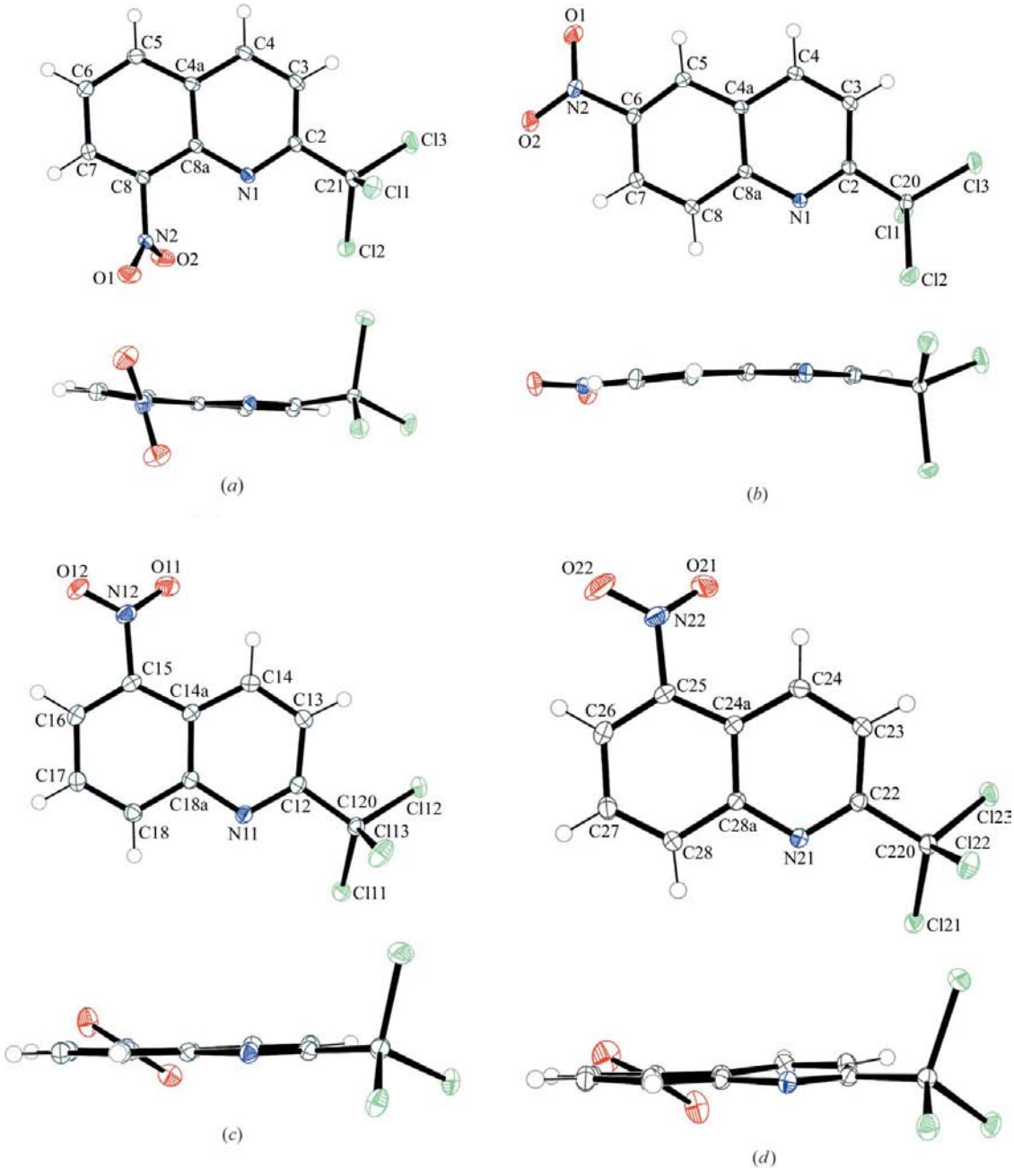

Figure 1
Views of (*a*) (I), (*b*) (II), (*c*) molecule *A* of (III) and (*d*) molecule *B* of (III), showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

stable conformation, a coplanar position for the nitro group, but with a broad minimum and only a small energy penalty of about 1 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}) for a twist of 30°. A short contact exists between atom O12 of the nitro group of one molecule and a pyridyl H atom of a neighbouring molecule [C14^{iii}—H14^{iii}···O12 = 2.51 Å; symmetry code: (iii) $1-x, -y, 1-z$], a favourable out-of-plane interaction which may be the origin of the deviation of the nitro group. The second molecule in the asymmetric unit is involved in a similar contact [C23^{iv}—H23^{iv}···O21 = 2.41 Å; symmetry code: (iv) $2-x, -y, 1-z$].

For the 6-nitro isomer, (II), the nitro group is nearly coplanar with the quinoline ring [dihedral angle = 7.49 (9)°]. The small deviation appears to be related to a contact between atom O1 of the nitro group and a neighbouring C8^{v}—H8^{v} group [symmetry code: (v) $x, -\frac{1}{2}-y, -\frac{1}{2}+z$].

In none of the three structures is the quinoline ring rigorously planar; they are all somewhat bent. The dihedral angle between the fused rings is 5.65 (5)° for the 8-nitro isomer, 5.23 (4)° for the 6-nitro isomer, and 1.80 (5) and 4.74 (4)° for the two molecules of the 5-nitro isomer. A search of quinoline structures deposited in the Cambridge Structural Database

(CSD, Version 5.29; Allen, 2002) indicates that the quinoline ring is usually planar, even if it is substituted at position 2. [Two structures with 2-chloromethyl substitution were found, namely 2-(trichloromethyl)quinoline and 2-(dichloromethyl)-quinoline (Kaluski & Golankiewicz, 1965), but no coordinates are present.] We recently reported crystal structures (Sopková-de Oliveira Santos *et al.*, 2007) in which the quinoline rings were substituted by a nitro group at position 8 and by vinyl or 1-chloro-2-methylpropenyl at position 2. In both cases, the quinoline ring was planar. Based on this comparison, it seems that it is the trichloromethyl group at position 2 that induces tension within the quinoline system.

In conclusion, the theoretical simulation predicts that the nitro group should be coplanar with the quinoline ring for the 5- and 6-nitro isomers, and twisted by about ±30° from coplanarity in the 8-nitro isomer. However, the observed deviation is about 35° for the 5-nitro isomer, 7° for the 6-nitro isomer and 68° for the 8-nitro isomer. Our *ab initio* simulations show that the deviation of 35° for the 5-nitro system involves less than a 1 kcal mol^{-1} penalty and that the deviation of about 68° in the 8-nitro compound introduces about 2.5 kcal mol^{-1} of penalty. These energy disadvantages are compensated for in the crystal structures by the intermolecular interactions involving the nitro groups.

Experimental

2-Methyl-5/6/8-nitroquinolines, obtained from commercial 2-methylquinoline through a classical nitration reaction, were reacted with a mixture of phosphorus pentachloride (4–5 equivalents) and phosphorus oxychloride, used as a solvent. The reaction was conducted under 800 W microwave irradiation in a multimode microwave reactor for 5–20 min. The crude residue was added to a solution of sodium carbonate and extracted with chloroform. Purification was performed by flash chromatography on a silica-gel column, eluting with dichloromethane–petroleum ether (1:1 *v*/*v*), leading to the chlorinated products in 83–98% yield (Verhaeghe, Rathelot, Gellis *et al.*, 2006).

Compound (I)

Crystal data

$C_{10}H_5Cl_3N_2O_2$
M_r = 291.51
Monoclinic, $P2_1/c$
a = 15.1941 (14) Å
b = 5.5843 (5) Å
c = 12.9620 (12) Å
β = 91.693 (5)°
V = 1099.33 (17) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.82 mm^{-1}
T = 150 (2) K
0.58 × 0.34 × 0.31 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
42809 measured reflections
6463 independent reflections
5214 reflections with $I > 2\sigma(I)$
R_{int} = 0.028

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.083
S = 1.11
6463 reflections
174 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.71 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Compound (II)

Crystal data

$C_{10}H_5Cl_3N_2O_2$
M_r = 291.51
Monoclinic, $P2_1/c$
a = 16.764 (3) Å
b = 5.5177 (11) Å
c = 12.313 (3) Å
β = 104.73 (3)°
V = 1101.5 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.82 mm^{-1}
T = 150 (2) K
0.41 × 0.32 × 0.28 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
53399 measured reflections
13343 independent reflections
8836 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.087
S = 0.94
13343 reflections
174 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.77 e Å^{-3}
$\Delta\rho_{min}$ = −0.78 e Å^{-3}

Compound (III)

Crystal data

$C_{10}H_5Cl_3N_2O_2$
M_r = 291.51
Triclinic, $P\overline{1}$
a = 7.7551 (6) Å
b = 11.3903 (9) Å
c = 13.6023 (11) Å
α = 69.927 (5)°
β = 87.071 (5)°
γ = 78.391 (5)°
V = 1105.25 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.82 mm^{-1}
T = 150 (2) K
0.38 × 0.28 × 0.25 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
21169 measured reflections
5900 independent reflections
5286 reflections with $I > 2\sigma(I)$
R_{int} = 0.023

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.022
$wR(F^2)$ = 0.062
S = 1.07
5900 reflections
347 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.47 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

All H atoms were determined *via* difference Fourier maps and refined with isotropic atomic displacement parameters [C—H = 0.916 (17)–0.965 (16) Å for (I) and 0.919 (11)–0.961 (14) Å for (II)].

For all compounds, data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); 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: FA3148). Services for accessing these data are described at the back of the journal.

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