

**(E)-Methyl 2-[(2-fluorophenyl)amino-
methylene]-3-oxobutanoate: X-ray
and density functional theory (DFT)
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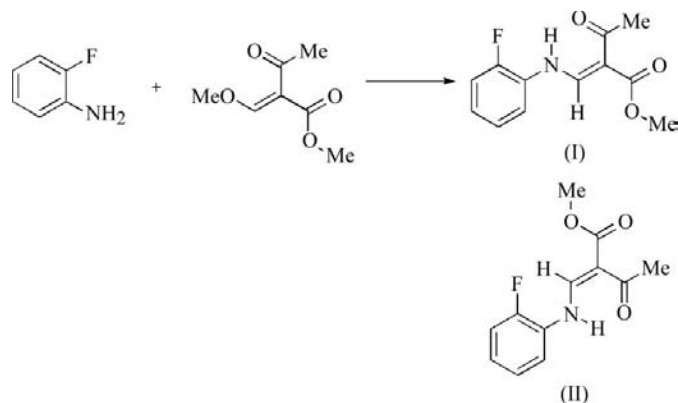
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The title compound, C₁₂H₁₂FNO₃, a potential precursor for fluoroquinoline synthesis, is essentially planar, with the most outlying atoms displaced from the best-plane fit through all non-H atoms by 0.163 (2) and 0.118 (2) Å. Molecules are arranged in layers oriented parallel to the (011) plane. The arrangement of the molecules in the structure is controlled mainly by electrostatic interactions, as the dipole moment of the molecule is 5.2 D. In addition, the molecules are linked by a weak C—H···O hydrogen bond which gives rise to chains with the base vector [1,1,1]. Electron transfer within the molecule is analysed using natural bond orbital (NBO) analysis. Deviations from the ideal molecular geometry are explained by the concept of non-equivalent hybrid orbitals.

Comment

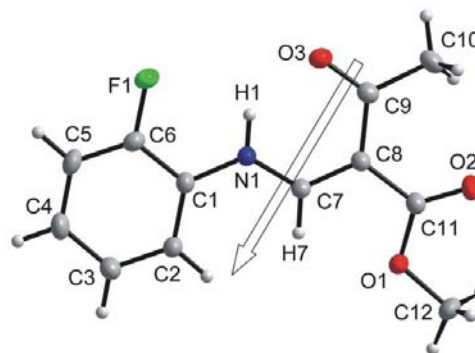
Fluoroquinolones belong to an important group of drugs with antibacterial, immunomodulating or anticancerogenic effects. However, despite their usefulness and their wide and numerous applications in medicinal practice, several objections concerning their toxicity have been raised (see, for example, www.fluoroquinolones.org). The title compound, (I), was synthesized within the framework of our ongoing study (see, for example, Kettmann *et al.*, 2004; Gróf, Milata, Kožíšek & Tokarčík, 2006; Gróf, Milata & Kožíšek, 2006; Gróf *et al.*, 2008; Langer *et al.*, 2007; Smrčok *et al.*, 2007) of the structures and properties of precursors of fluoroquinolones, because knowledge of these compounds could prove essential in reaction pathway considerations and planning. The structure of (I) is reported here to determine its solid-state conformation and molecular geometry, particularly with reference to

the relative positions of the *ortho* substituent on the benzene ring in relation to the enamino grouping and the substituents on the β -positions of the aminoethylene substituent.



Possible conformers (I) and (II) are shown in the scheme above. Both conformers would be expected to have an intramolecular hydrogen bond between the imino H atom and the acetyl carbonyl group. X-ray structure analysis establishes the preferred solid-state conformation as (I), which is shown in Fig. 1. The molecule is essentially planar and the most outlying atoms, C10 and C12, are displaced from the best-plane fit through all non-H atoms by 0.163 (2) and 0.118 (2) Å, respectively. In the crystal structure, molecules are arranged in layers oriented parallel to the (011) plane. This arrangement is proposed to be fixed mainly by long-range electrostatic interactions, as the calculated dipole moment of the molecule is as large as 5.2 D. An intermolecular C—H···O hydrogen bond links the molecules within the layers and gives rise to chains with the base vector [1,1,1] (Fig. 2 and Table 1).

The shape of the molecule is stabilized by an N1—H1···O3 hydrogen bond and two attractive intramolecular contacts (Table 1). Since 'organic' F atoms form at best only very weak nonbonded contacts (Howard *et al.*, 1996; Dunitz & Taylor, 1997), the contribution of the F1···H1 interaction to the stabilization energy is smaller than that of the O3···H1 interaction. Natural bond orbital (NBO; Foster & Weinhold,

**Figure 1**

A perspective drawing of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The arrow represents the orientation of the dipole moment vector, but not its size. The vector lies in the best-plane fit to the molecule.

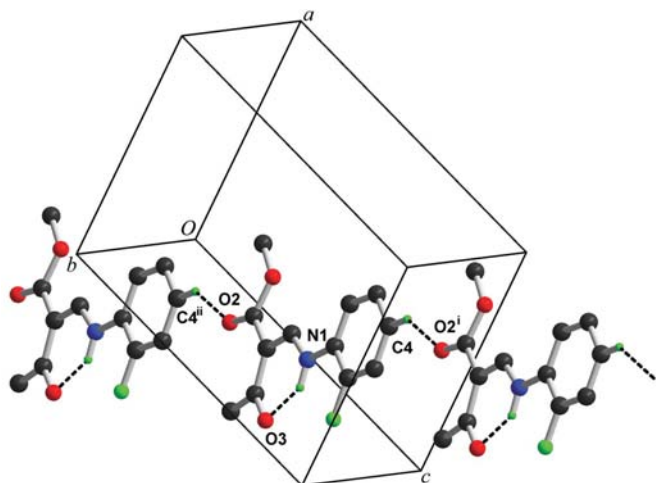


Figure 2

Weak C—H...O hydrogen bonds (broken lines) forming chains of molecules in (I). Intramolecular N—H...O hydrogen bonds are also shown as dashed lines. [Symmetry codes: (i) $x + 1, y + 1, z + 1$; (ii) $x - 1, y - 1, z - 1$.]

1980) analysis of the molecular electronic structure reveals a general delocalization pattern, which can be depicted by the resonance structures shown in Fig. 3. The N-atom lone pair is delocalized primarily into the π -antibonding orbital of the C7—C8 bond and also, due to the electron-withdrawing effect of atoms O2 and O3, to a smaller extent into the antibonding orbitals of the C9—O3 and C11—O2 bonds. The most obvious geometric consequences of such an electron redistribution are shortening of the formally single N1—C7 bond, lengthening of the formally double C7=C8 bond [see Table 2 for selected bond distances and Wiberg bond orders (Wiberg, 1968) provided by NBO analysis] and structural rigidity of the N1—C7=C8—C9=O3 moiety. This last is further enhanced by the formation of an intramolecular N1—H1...O3 (Table 1) hydrogen bond. Of the three lone electron pairs on the F atom (two sp^2 and one p), the p one contributes to the π^* antibonding orbital of the benzene ring, while the two sp^2 orbitals stay on the atom and are partially responsible for shortening the C_{ar}—F bond.

Geometric analysis also reveals a few deviations from ideal geometry for the contact of the benzene ring and the conjugated system. First, the value of the C6—C1—N1 bond angle of 117.56 (12)° is a compromise between electrostatic attraction between atoms F1 (NBO charge -0.342) and H1 (NBO charge 0.485) and repulsion of atoms H2 and H7 separated by only 2.08 Å. A simulation calculation for a model system with the F atom replaced by H clearly showed that this H—H repulsion plays a more important role than F—H attraction. The next conspicuous geometric feature of the molecule is the deviation of the C1—N1—C7 [125.73 (12)°] and N1—C7—C8 [124.65 (12)°] bond angles from the ideal value of 120°. A qualitative interpretation of this effect lies in the decreased p content of the formally sp^2 hybrid orbital, forming the σ part of the double bond (for details, see *e.g.* Bent, 1961). The main idea is that the hybrid orbital of C, which is involved in the double bond, contains more than 33% s character (the ideal

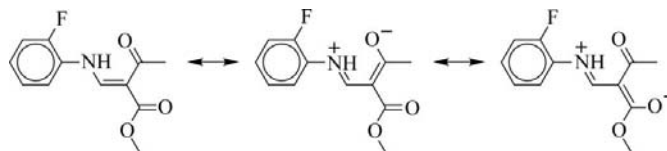


Figure 3

Possible resonance structures of (I). All principal geometric features are compatible with a superposition of these resonance structures.

sp^2 value). An increase in the s content of one hybrid orbital means in turn an increase in the p character of the other two hybrid orbitals, thus decreasing the angle between them from the ideal value of 120°. Indeed, the hybridization pattern of the natural orbitals shows increasing p content in both C—H and N—H bonds, and decreasing content in the C—N and C—C bonds. Consequently, bond angles involving H atoms should be less than the ideal value of 120° and the angles in the conjugated system should of course be larger.

Another interesting question is the existence of the hypothetical conformer, (II), related to (I) by rotation of the benzene ring about the exocyclic C1—N1 bond. Our molecular calculations show that, although it would be stabilized by the formation of an intramolecular attractive contact formed by the moderately acidic atom H7 with atom F1 (H...F = 2.14 Å), its total energy *in vacuo* is 2.5 kJ mol⁻¹ (1 kcal mol⁻¹ = 4.184 kJ mol⁻¹) higher than that of (I), the interconversion barrier height being 13.4 kJ mol⁻¹. Moreover, due to its smaller dipole moment (4.10 D), the existence of (II) is even further disfavoured in such a polar environment as that used in the present synthesis. Calculation of the solvent effect by means of the PCM continuum model (Miertuš *et al.*, 1981; Foresman *et al.*, 1996) revealed that ethanol further stabilizes conformation (I), conformation (II) being less stable by 4.6 kJ mol⁻¹. Additionally, in this environment the barrier for the interconversion of (II) to (I) is reduced to 9.2 kJ mol⁻¹, thus making crystallization of (II) even less probable.

Experimental

The title compound could be easily prepared by nucleophilic vinylic substitution of equimolar amounts of (*E*)-methyl 2-methoxymethylene-3-oxobutanoate with 2-fluoroaniline in boiling ethanol (Leyva *et al.*, 1999).

Crystal data

C ₁₂ H ₁₂ FNO ₃	$\gamma = 91.827$ (3)°
$M_r = 237.23$	$V = 554.58$ (14) Å ³
Triclinic, P $\bar{1}$	$Z = 2$
$a = 7.6772$ (11) Å	Mo K α radiation
$b = 7.7591$ (11) Å	$\mu = 0.11$ mm ⁻¹
$c = 9.9774$ (14) Å	$T = 153$ K
$\alpha = 100.718$ (3)°	$0.11 \times 0.09 \times 0.07$ mm
$\beta = 107.473$ (3)°	

Data collection

Siemens SMART CCD area-detector diffractometer	7912 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	3743 independent reflections
$T_{\min} = 0.497, T_{\max} = 0.992$	2388 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.030$

Table 1

Hydrogen-bonding and short attractive contact geometry (Å, °).

For intramolecular dimensions, both the experimentally determined (*a*) and theoretically (B3LYP) calculated values (*b*) are given.

<i>D</i> — <i>H</i> ··· <i>A</i>	<i>D</i> — <i>H</i>	<i>H</i> ··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> — <i>H</i> ··· <i>A</i>	
N1—H1···O3	0.88	1.92	2.5945 (15)	132	<i>a</i>
	1.029	1.806	2.613	132.48	<i>b</i>
C4—H4···O2 ⁱ	0.95	2.40	3.2076 (17)	142	
N1—H1···F1	0.88	2.29	2.6710 (13)	106	<i>a</i>
	1.029	2.316	2.690	99.83	<i>b</i>
C7—H7···O1	0.95	2.24	2.6308 (15)	104	<i>a</i>
	1.083	2.219	2.653	101.36	<i>b</i>

Symmetry code: (i) $x + 1, y + 1, z + 1$.**Table 2**

Selected bond distances and Wiberg bond orders (WBO) (Wiberg, 1968).

	Bond distance	WBO
F1—C6	1.3584 (16)	0.89
C1—N1	1.4096 (16)	1.06
N1—C7	1.3290 (16)	1.30
C7—C8	1.3864 (17)	1.47
C8—C9	1.4545 (18)	1.11
C9—O3	1.2427 (16)	1.64
C8—C11	1.4685 (17)	1.09
C11—O1	1.3453 (17)	0.99
C11—O2	1.2075 (16)	1.68
C9—C10	1.5077 (18)	1.03

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$

$wR(F^2) = 0.155$

$S = 1.00$

3743 reflections

162 parameters

H atoms treated by a mixture of constrained and independent refinement

$\Delta\rho_{\max} = 0.39 \text{ e } \text{Å}^{-3}$

$\Delta\rho_{\min} = -0.26 \text{ e } \text{Å}^{-3}$

For the X-ray data, H atoms were constrained to ideal geometry using an appropriate riding model, with C—H = 0.95–0.98 Å and N—H = 0.88 Å. For methyl groups, the C—H distances and C—C—H or O—C—H angles (109.5°) were kept fixed, while the torsion angles were allowed to refine, with their starting positions based on the circular Fourier synthesis averaged using a local threefold symmetry. $U_{\text{iso}}(\text{H})$ values were fixed at $1.5U_{\text{eq}}(\text{C})$ for the methyl groups or refined in all other cases. Molecular calculations were carried out at the B3LYP/6-31+G** level of theory using GAUSSIAN98 (Frisch *et al.*, 1998). Natural bond orbital (Foster & Weinhold, 1980) calculations were carried out using the NBO program (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: SHELXTL (Sheldrick, 2008); program(s) used to refine structure: SHELXTL; molecular graphics: DIAMOND (Brandenburg, 2008); software used to prepare material for publication: PLATON (Spek, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3082). Services for accessing these data are described at the back of the journal.

References

- Bent, H. A. (1961). *Chem. Rev.* **61**, 275–311.
- Brandenburg, K. (2008). *DIAMOND*. Version 3.1f. Crystal Impact GbR, Bonn, Germany.
- Bruker (2003). *SMART* (Version 5.63) and *SAINTE* (Version 6.45). Bruker AXS Inc., Madison, Wisconsin, USA.
- Dunitz, J. D. & Taylor, R. (1997). *Chem. Eur. J.* **3**, 89–98.
- Foresman, J. B., Keith, T. A., Wiberg, K. B., Snoonian, J. & Frisch, M. J. (1996). *J. Phys. Chem.* **100**, 16098–16104.
- Foster, J. P. & Weinhold, F. (1980). *J. Am. Chem. Soc.* **102**, 7211–7218.
- Frisch, M. J., *et al.* (1998). *GAUSSIAN98*. Revision A.7. Gaussian Inc., Pittsburgh, Pennsylvania, USA.
- Glendening, E. D., Reed, A. D., Carpenter, J. E. & Weinhold, F. (1993). *NBO*. Version 3.1. Theoretical Chemistry Institute, University of Wisconsin, Madison, Wisconsin, USA.
- Gróf, M., Kožíšek, J., Milata, V. & Gatial, A. (2008). *Acta Cryst.* **E64**, o998.
- Gróf, M., Milata, V. & Kožíšek, J. (2006). *Acta Cryst.* **E62**, o4464–o4465.
- Gróf, M., Milata, V., Kožíšek, J. & Tokarčík, M. (2006). *Acta Cryst.* **E62**, o4060–o4061.
- Howard, J. A. K., Hoy, V. J., O'Hagan, D. & Smith, G. T. (1996). *Tetrahedron*, **32**, 12613–12622.
- Kettmann, V., Lokaj, J., Milata, V., Marko, M. & Štvrtecká, M. (2004). *Acta Cryst.* **C60**, o252–o254.
- Langer, V., Scholtzová, E., Milata, V. & Solčan, T. (2007). *Acta Cryst.* **C63**, o552–o554.
- Leyva, E., Montreal, E. & Hernández, A. (1999). *J. Fluorine Chem.* **94**, 7–10.
- Miertuš, S., Scrocco, E. & Tomasi, J. (1981). *Chem. Phys.* **55**, 117–129.
- Sheldrick, G. M. (2003). *SADABS*. Version 2.10. University of Göttingen, Germany.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Smrčok, Ľ., Jorík, V., Scholtzová, E. & Milata, V. (2007). *Acta Cryst.* **B63**, 477–484.
- Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.
- Wiberg, K. (1968). *Tetrahedron* **24**, 1083–1096.