N-(4-Methoxy-2-nitrophenyl)acetamide

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In the title compound, C9H10N2O4, the three substituents vary in the degree of lack of planarity with the central phenyl ring. The methoxy group is nearest to being coplanar, with a C—C—O—C torsion angle of 6.1 (5)°. The nitro group is less coplanar, with a 12.8 (5)° twist about the C—N bond and the acetamido group is considerably less coplanar with the central ring, having a 25.4 (5)° twist about the C—N bond to the ring. The NH group forms an intramolecular N—H···O hydrogen bond to a nitro-group O atom.

Structure description

The analgesic use of 4-alkoxyacetanilides, in particular 4-ethoxyacetanilide or 4-EA, predates the First World War. 4-Hydroxyacetanilide (popularly known as Tylenol or acetaminophen) and 4-EA were introduced into the markets at around the same time; however, 4-EA was withdrawn from sale some decades ago due to its carcinogenic and kidney-damaging properties (Dubach et al., 1983; Nakanishi et al., 1982). Although there has been extensive information on phase I and phase II biotransformation of 4-alkoxyacetanilides (Hinson, 1983; Kapetanović et al., 1979; Mulder et al., 1984; Veronese et al., 1985), little or no information is available on nitrated or other oxidation products that could be formed in reactions with cellular oxidants, such as hypochlorite (OCIO)/hypo- chlorous acid (HOCl; \( pK_a \approx 7.53 \)) and peroxynitrite (ONOO−)/peroxynitrous acid (ONOOH; \( pK_a \approx 6.2 \)). ONOOH and ONOO− are collectively referred to as peroxynitrite or PN. We have shown, for instance, that 4-hydroxyacetanilide forms nitrated and chlorinated products along with varying amounts of dimers when reacted with HOCl/OCIO and PN/CO2 under physiologically relevant conditions (Uppu & Martin, 2005; Deere et al., 2022). We suspect that similar products (or their positional isomers) may be formed in the reactions of 4-alkoxyacetanilides with the cellular oxidants refer-
Towards a better understanding of this and to shed light on molecular targets (Bertolini et al., 2006), we have synthesized the title compound, \( \text{C}_9\text{H}_{10}\text{N}_2\text{O}_4 \): single crystals grown from aqueous solution were analyzed by X-ray diffraction. The title compound is shown in Fig. 1. It is significantly non-planar, and its deviation from planarity may be described by torsion angles about bonds from the central C1–C6 phenyl ring to the three substituents. The methoxy group is nearest to being coplanar, with a C9—O2—C4–C3 torsion angle of 6.1 (5)°. The nitro group deviates more from coplanarity with the central ring, with the O3—N2—C2—C1 torsion angle being 12.8 (5)°. The acetamido group is considerably less coplanar with the central ring, with a C7—N1—C1—C6 torsion angle of 25.4 (5)°. These deviations are similar to those seen in the analogous 4-ethoxy compound (Uppu et al., 2020), in which the corresponding torsion angles are 0.56 (12), 14.94 (13) and 18.23 (15)°, respectively. 

\( \text{N}-(4\text{-hydroxy-2-nitrophenyl})\text{acetamide} \) (Hines et al., 2022) is considerably more planar, with torsion angles to the nitro group and to the acetamido group being 0.79 (19) and 3.1 (2)°, respectively, likely as a result of intermolecular hydrogen bonding by the OH group. The structure of \( \text{N}-(4\text{-hydroxy-3-nitrophenyl})\text{acetamide} \) (Salahifar et al., 2015; Deere et al., 2019) is also more planar than the title compound, with a torsion angle of 11.8 (2)° for the nitro group and 9.0 (2)° for the acetamido group. An intramolecular N1—H1\( \cdot \)N hydrogen bond (Table 1) is observed in the title compound.

The unit cell of the title compound is shown in Figs. 2 and 3. The closest intermolecular contact is C5—H5\( \cdot \)O2 (at -1+x, -y, 1-z), forming dimers about inversion centers with a C···O distance of 3.418 (4) Å and 171° angle about H. Molecules form a herringbone pattern in the [101] direction with alternate phenyl rings forming a dihedral angle of 65.7 (2)°.

### Synthesis and crystallization

\( \text{N}-(4\text{-methoxy-2-nitrophenyl})\text{acetamide} \) was synthesized by acetylation of 4-methoxy-2-nitroaniline using acetic anhydride in acetic acid solvent: 3.36 g (20 mmol) of 4-methoxy-2-nitroaniline in 30 ml of glacial acetic acid was allowed to react with 2.46 g (24 mmol) of acetic anhydride for 18 h at room temperature. The reaction mixture was stirred continuously during the reaction. In the end, the mixture was dried under...

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**Table 1**

Hydrogen-bond geometry (Å, °).

| D—H—A       | D—H   | H—A   | D···A | D–H···A  |
|--------------|--------|-------|-------|----------|
| N1—H1·N—O3  | 0.87 (5) | 1.92 (5) | 2.632 (4) | 137 (4)  |
| C5—H5···O2  | 0.95   | 2.48  | 3.418 (4) | 171      |
| C6—H6···O1  | 0.95   | 2.30  | 2.864 (4) | 117      |
| C8—H8B···O3  | 0.98  | 2.64  | 3.578 (4) | 160      |
| C8—H8C···O4  | 0.98  | 2.63  | 3.546 (4) | 156      |

Symmetry codes: (i) \(-x+1, -y, -z+1\); (ii) \(-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{2}\); (iii) \(x+\frac{1}{2}, -y+\frac{1}{2}, z\).
Table 2
Experimental details.

| Crystal data | Chemical formula | C_9H_{10}N_2O_4 |
|--------------|------------------|-----------------|
| M_r          |                  | 210.19          |
| Crystal system, space group | Monoclinic, P2_1/n |
| Temperature (K) |                  | 90              |
| a, b, c (Å)   |                  | 14.8713 (7), 3.9563 (2), 17.2057 (9) |
| β (°)         |                  | 114.051 (3)     |
| V (Å^3)       |                  | 924.42 (8)      |
| Z             |                  | 4               |
| Radiation type |                  | Cu Kα          |
| μ (mm⁻¹)      |                  | 1.03            |
| Crystal size (mm) |                | 0.42 × 0.06 × 0.01 |

Data collection
Diffractometer: Bruker Kappa APEXII DUO CCD
Absorption correction: Multi-scan (SADABS; Krause et al., 2015)

R_{min}, R_{max} | 0.692, 0.990 |
No. of measured, independent and observed | 11516, 1638, 1211 |
R_{free} | 0.122 |
(sin θ/λ)_{max} (Å⁻¹) | 0.595 |

Refinement
R(F^2 > 2σ(F^2)), wR(F^2), S | 0.071, 0.203, 1.09 |
No. of reflections | 1638 |
No. of parameters | 141 |
H-atom treatment: H atoms treated by a mixture of independent and constrained refinement
Δρ_{max}, Δρ_{min} (e Å⁻³) | 0.24, −0.27 |

Computer programs: APEX2 and SAINT (Bruker, 2016), SHELXT2014/5 (Sheldrick, 2008), SHELXL2017/4 (Sheldrick, 2015), Mercury (Macrae et al., 2020), and pubICIF (Westrip, 2010).

vacuum, and the N-(4-methoxy-2-nitrophenyl)acetamide in the residue was purified by recrystallization twice from aqueous solution. Single crystals in the form of yellow laths were grown in water by slow cooling of a hot and nearly saturated solution of the title compound.

Refinement
Crystal data, data collection and structure refinement details are summarized in Table 2.

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full crystallographic data

IUCrData (2022). 7, x220277  [https://doi.org/10.1107/S2414314622002772]

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N-(4-Methoxy-2-nitrophenyl)acetamide

Crystal data

\[ \text{C}_{9}\text{H}_{10}\text{N}_{2}\text{O}_{4} \]

\[ M_r = 210.19 \]

Monoclinic, \( P2_1/n \)

\[ a = 14.8713 (7) \AA \]

\[ b = 3.9563 (2) \AA \]

\[ c = 17.2057 (9) \AA \]

\[ \beta = 114.051 (3)\degree \]

\[ V = 924.42 (8) \AA^3 \]

\[ Z = 4 \]

\[ F(000) = 440 \]

\[ D_x = 1.510 \text{ Mg m}^{-3} \]

\[ \text{Cu K\alpha radiation, } \lambda = 1.54184 \AA \]

Cell parameters from 2102 reflections

\[ \theta = 3.3–66.3\degree \]

\[ \mu = 1.03 \text{ mm}^{-1} \]

\[ T = 90 \text{ K} \]

Lath, yellow

\[ 0.42 \times 0.06 \times 0.01 \text{ mm} \]

Data collection

Bruker Kappa APEXII DUO CCD diffractometer

Radiation source: I\( \mu \)S microfocus

QUAZAR multilayer optics monochromator

\( \varphi \) and \( \omega \) scans

Absorption correction: multi-scan

(SADABS; Krause et al., 2015)

\( T_{\text{min}} = 0.692, T_{\text{max}} = 0.990 \)

11516 measured reflections

1638 independent reflections

1211 reflections with \( I > 2\sigma(I) \)

\( R_{\text{int}} = 0.122 \)

\( \theta_{\text{max}} = 66.7\degree, \theta_{\text{min}} = 3.3\degree \)

\( h = -17\rightarrow17 \)

\( k = -4\rightarrow4 \)

\( l = -20\rightarrow20 \)

Refinement

Refinement on \( F^2 \)

Least-squares matrix: full

\[ R[F^2 > 2\sigma(F^2)] = 0.071 \]

\[ wR(F^2) = 0.203 \]

\[ S = 1.09 \]

1638 reflections

141 parameters

0 restraints

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

\[ (\Delta\sigma)_{\text{max}} < 0.001 \]

\[ \Delta\rho_{\text{max}} = 0.24 \text{ e Å}^{-3} \]

\[ \Delta\rho_{\text{min}} = -0.27 \text{ e Å}^{-3} \]

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

Refinement. All H atoms were located in difference maps and those on C were thereafter treated as riding in geometrically idealized positions with C—H distances 0.95 Å for phenyl and 0.98 Å for methyl. Coordinates of the N—H hydrogen atom were refined. \( U_{\text{iso}}(\text{H}) \) values were assigned as 1.2\( U_{\text{eq}} \) for the attached atom (1.5 for methyl).
### Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

|   | x         | y         | z          | \(U_{eq}\)/*\(U_{eq}\) |
|---|-----------|-----------|------------|----------------------|
| O1| 0.58485 (18) | 0.7604 (7) | 0.81731 (16) | 0.0512 (7) |
| O2| 0.36866 (18) | 0.2368 (6) | 0.43490 (15) | 0.0455 (6) |
| O3| 0.23210 (18) | 0.9412 (7) | 0.61788 (16) | 0.0529 (7) |
| O4| 0.16683 (18) | 0.9595 (6) | 0.53559 (16) | 0.0480 (7) |
| N1| 0.4165 (2) | 0.7462 (7) | 0.75182 (18) | 0.0447 (7) |
| H1N| 0.363 (4) | 0.830 (11) | 0.753 (3) | 0.054* |
| N2| 0.2326 (2) | 0.8718 (7) | 0.60286 (18) | 0.0416 (7) |
| C1| 0.4018 (3) | 0.6185 (9) | 0.6716 (2) | 0.0428 (8) |
| C2| 0.3144 (2) | 0.6751 (8) | 0.5992 (2) | 0.0420 (8) |
| C3| 0.3005 (2) | 0.5555 (8) | 0.5182 (2) | 0.0415 (8) |
| H3A| 0.241073 | 0.602472 | 0.470197 | 0.050* |
| C4| 0.3736 (3) | 0.3699 (8) | 0.5092 (2) | 0.0417 (8) |
| C5| 0.4605 (3) | 0.3057 (8) | 0.5806 (2) | 0.0431 (8) |
| H5| 0.511084 | 0.176401 | 0.574482 | 0.052* |
| C6| 0.4740 (3) | 0.4264 (9) | 0.6593 (2) | 0.0442 (8) |
| H6| 0.533915 | 0.378381 | 0.706654 | 0.053* |
| C7| 0.5054 (3) | 0.8178 (8) | 0.8187 (2) | 0.0435 (8) |
| C8| 0.4928 (3) | 0.9743 (9) | 0.8926 (2) | 0.0475 (8) |
| H8A| 0.473964 | 0.799894 | 0.923540 | 0.071* |
| H8B| 0.441299 | 1.147414 | 0.872021 | 0.071* |
| H8C| 0.554993 | 1.078496 | 0.930706 | 0.071* |
| C9| 0.2843 (3) | 0.3245 (9) | 0.3589 (2) | 0.0488 (9) |
| H9A| 0.224837 | 0.228708 | 0.361637 | 0.073* |
| H9B| 0.292327 | 0.233462 | 0.309172 | 0.073* |
| H9C| 0.278101 | 0.571021 | 0.354165 | 0.073* |

### Atomic displacement parameters (Å²)

|   | \(U_{11}\) | \(U_{22}\) | \(U_{33}\) | \(U_{12}\) | \(U_{13}\) | \(U_{23}\) |
|---|-----------|-----------|-----------|-----------|-----------|-----------|
| O1| 0.0331 (14) | 0.0634 (15) | 0.0497 (14) | 0.0015 (10) | 0.0093 (11) | −0.0066 (11) |
| O2| 0.0413 (14) | 0.0494 (13) | 0.0439 (13) | −0.0005 (10) | 0.0154 (10) | −0.0013 (10) |
| O3| 0.0419 (14) | 0.0706 (16) | 0.0434 (14) | 0.0026 (12) | 0.0145 (11) | −0.0053 (11) |
| O4| 0.0361 (13) | 0.0553 (14) | 0.0444 (13) | 0.0047 (10) | 0.0079 (10) | 0.0026 (10) |
| N1| 0.0398 (17) | 0.0513 (16) | 0.0424 (15) | 0.0000 (12) | 0.0162 (13) | 0.0006 (12) |
| N2| 0.0308 (15) | 0.0465 (15) | 0.0425 (16) | −0.0030 (11) | 0.0097 (13) | −0.0028 (12) |
| C1| 0.0376 (18) | 0.0453 (17) | 0.0429 (18) | −0.0019 (13) | 0.0140 (15) | 0.0030 (13) |
| C2| 0.0354 (18) | 0.0430 (17) | 0.0458 (19) | −0.0024 (13) | 0.0148 (15) | 0.0032 (13) |
| C3| 0.0342 (17) | 0.0411 (17) | 0.0432 (17) | −0.0037 (13) | 0.0095 (14) | 0.0033 (13) |
| C4| 0.0381 (18) | 0.0425 (17) | 0.0446 (18) | −0.0025 (13) | 0.0170 (15) | −0.0011 (13) |
| C5| 0.0331 (18) | 0.0454 (17) | 0.0469 (19) | −0.0008 (13) | 0.0125 (15) | −0.0009 (14) |
| C6| 0.0366 (18) | 0.0437 (17) | 0.0495 (19) | 0.0007 (13) | 0.0146 (15) | 0.0033 (14) |
| C7| 0.0342 (19) | 0.0449 (17) | 0.0452 (18) | −0.0005 (13) | 0.0099 (15) | 0.0039 (13) |
| C8| 0.0412 (19) | 0.0501 (19) | 0.0462 (18) | 0.0005 (15) | 0.0126 (15) | −0.0017 (15) |
| C9| 0.045 (2) | 0.0517 (19) | 0.0416 (18) | 0.0030 (16) | 0.0089 (16) | −0.0008 (14) |
### Geometric parameters (Å, °)

| Bond/Angle                  | Value      |
|----------------------------|------------|
| O1—C7                      | 1.214 (4)  |
| O2—C4                      | 1.357 (4)  |
| O2—C9                      | 1.438 (4)  |
| O3—N2                      | 1.239 (4)  |
| O4—N2                      | 1.222 (4)  |
| N1—C7                      | 1.383 (5)  |
| N1—H1N                     | 0.87 (5)   |
| N2—C2                      | 1.467 (4)  |
| C1—C6                      | 1.400 (5)  |
| C1—C2                      | 1.405 (5)  |
| C2—C3                      | 1.404 (5)  |
| C3—C4                      | 1.372 (5)  |
| C4—O2—C9                   | 117.1 (3)  |
| C7—N1—C1                   | 127.4 (3)  |
| C7—N1—H1N                  | 118 (3)    |
| C1—N1—H1N                  | 113 (3)    |
| O4—N2—O3                   | 122.6 (3)  |
| O4—N2—C2                   | 117.9 (3)  |
| O3—N2—C2                   | 119.6 (3)  |
| C6—C1—N1                   | 121.6 (3)  |
| C6—C1—C2                   | 116.2 (3)  |
| N1—C1—C2                   | 122.2 (3)  |
| C3—C2—C1                   | 122.4 (3)  |
| C3—C2—N2                   | 115.6 (3)  |
| C1—C2—N2                   | 122.0 (3)  |
| C4—C3—C2                   | 119.2 (3)  |
| C4—C3—H3A                  | 120.4      |
| C2—C3—H3A                  | 120.4      |
| O2—C4—C3                   | 124.9 (3)  |
| O2—C4—C5                   | 115.7 (3)  |
| C3—C4—C5                   | 119.4 (3)  |
| C6—C5—C4                   | 121.0 (3)  |
| C7—N1—C1                   | 25.4 (5)   |
| C7—N1—C1                   | −154.6 (3) |
| C6—C1—C2                   | −1.8 (5)   |
| N1—C1—C2                   | 178.2 (3)  |
| C6—C1—C2—N2                | 180.0 (3)  |
| N1—C1—C2—N2                | −0.1 (5)   |
| O4—N2—C2                   | −10.9 (4)  |
| O3—N2—C2                   | 168.8 (3)  |
| O4—N2—C2                   | 167.5 (3)  |
| O3—N2—C2                   | −12.8 (5)  |
| C1—C2—C3                   | 1.5 (5)    |

*Note: Values in parentheses indicate standard deviations.*
N2—C2—C3—C4 179.9 (3)

Hydrogen-bond geometry (Å, °)

|                | D—H  | H···A  | D···A  | D—H···A |
|----------------|------|--------|--------|---------|
| N1—H1N···O3   | 0.87 (5) | 1.92 (5) | 2.632 (4) | 137 (4) |
| C5—H5···O2i   | 0.95  | 2.48   | 3.418 (4) | 171     |
| C6—H6···O1    | 0.95  | 2.30   | 2.864 (4) | 117     |
| C8—H8B···O3ii | 0.98  | 2.64   | 3.578 (4) | 160     |
| C8—H8C···O4iii| 0.98  | 2.63   | 3.546 (4) | 156     |

Symmetry codes: (i) −x+1, −y, −z+1; (ii) −x+1/2, y+1/2, −z+3/2; (iii) x+1/2, −y+5/2, z+1/2.