**N-(4-Hydroxy-2-nitrophenyl)acetamide**

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The title compound, C₈H₈N₂O₄, differs in its degree of planarity from the 3-nitro isomer and also in its hydrogen-bonding pattern. Its NH group forms an intramolecular hydrogen bond to a nitro oxygen atom, and its OH group forms an intermolecular hydrogen bond to an amide oxygen atom, generating [101] chains in the crystal.

Structure description

The putative free-radical products of the peroxynitrite anion (PN)—CO₂ reaction (NO₂⁻ and CO₃⁻) have long been thought to constitute an important source of non-CYP450-mediated oxidative biotransformation of N-(4-hydroxyphenyl)acetamide (4-HPA; acetaminophen or paracetamol) and other xenobiotics (Babu et al., 2012; Dou et al., 2017; Gernapudi et al., 2009; Rangan et al., 2006; Uppu et al., 2005). In reactions of 4-HPA/PN/CO₂, we find that N-(4-hydroxy-3-nitrophenyl)acetamide is one of the major products formed along with N,N’-(6,6’-dihydroxy[1,1’-biphenyl]-3,3’-diyl)bisacetamide (dimer of 4-HPA) and a metastable N-acetyl-1,4-benzoquinone (NBQI; demonstrated through its binding to N-acetyl-L-cysteine; Uppu & Martin, 2005; Deere et al., 2022). It was shown that NBQI can react with electrophiles such as the nitrite ion and form yet another nitro product, N-(4-hydroxy-2-nitrophenyl)acetamide (Matsuno et al., 1989). Although we did not find evidence for the formation of this 2-nitro isomer in 4-HPA/PN/CO₂ reactions, we believe that this isomer along with other oxidation products of 4-HPA may play a role in the pharmacology and toxicology of 4-HPA (4-HPA overdose, either unintentional or intentional, is the most common cause of hepatic failure in the USA and elsewhere).

Towards a better understanding of this chemistry, we have synthesized N-(4-hydroxy-2-nitrophenyl)acetamide and N-(4-hydroxy-3-nitrophenyl)acetamide and determined their single-crystal structures. Interestingly, the 2-nitro and 3-nitro isomers have signifi-
cantly different degrees of molecular planarity in the solid-state and also differ in their hydrogen bonding patterns.

In N-(4-hydroxy-2-nitrophenyl)acetamide, Fig. 1, the molecule is nearly planar, with an r.m.s. deviation of 0.035 Å for the non-hydrogen atoms. The acetamido group has the largest deviation, with a 5.1 (2)° twist about its central C7—N2 bond. The N—H group forms an intramolecular hydrogen bond (Table 1) to O3 (part of the nitro group) having an N—O distance of 2.6363 (15) Å and N—H—O angle of 139.6 (15)°. The hydroxy group forms an intermolecular hydrogen bond to acetamido atom O4 with O—O = 2.7183 (14) Å and O—H—O = 172.0 (18)°, thereby forming chains propagating in the [101] direction (Figs. 2 and 3).

The crystal structure of N-(4-hydroxy-3-nitrophenyl)acetamide has been reported (Salahifar et al., 2015; Deere et al., 2019). It is significantly less planar than the title compound, with the acetamido group twisted out of the plane of the phenyl group by 9.0 (2)° and the nitro group twisted out of the phenyl plane by 11.8 (2)°. Its hydrogen-bonding pattern also differs, with the N—H group forming an intermolecular hydrogen bond to the acetamido O atom [N—O = 2.9079 (17) Å; N—H—O = 176.6 (19)°]. Its OH group forms a bifurcated O—H···(O,O) hydrogen bond, with intramolecular component to the adjacent nitro group [O···O = 2.6093 (17) Å] and a longer intermolecular component to a nitro oxygen atom of an adjacent molecule [O···O = 3.1421 (17) Å; Deere et al., 2019].

**Synthesis and crystallization**

The title compound was synthesized by the acetylation of 4-hydroxy-2-nitroaniline using acetic anhydride as described by Naik et al. (2004) with some minor modification (Fig. 4). Briefly, 4-hydroxy-2-nitroaniline (3.08 g; 20 mmol) in its hydrochloride form (prepared by addition of a slight molar excess of HCl; 26 mmol) was dissolved in 125 ml of acetonitrile/water (1/4, v/v). The solution was cooled in an ice bath, followed by addition of acetic anhydride (2.43 ml; 24 mmol). Then, sodium bicarbonate (3.36–5.04 g; 40–60 mmol) was added until the mixture became pH 7, and the solution was stirred for 1 h. The precipitate was filtered, washed with methanol, and dried in a vacuum.

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

| D—H···A       | D—H | H···A | D···A  | D—H···A |
|---------------|------|-------|--------|---------|
| O1—H1O···O4  | 0.84 (2) | 1.88 (2) | 2.7183 (14) | 172.0 (18) |
| N2—H2N···O3  | 0.883 (19) | 1.901 (17) | 2.6363 (15) | 139.6 (15) |

Symmetry code: (i) x — ½, y + ½, z + ½.

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**Figure 1**
The molecular structure of the title molecule with 50% displacement ellipsoids.

**Figure 2**
The hydrogen-bonded chain.

**Figure 3**
The unit cell of the title compound.
added to the mixture with the contents being constantly stirred. Care was taken to maintain that the pH of the final reaction mixture was between 5.5 and 6.5. The yellow precipitate of N-(4-hydroxy-2-nitrophenyl)acetamide was separated by filtration and purified by recrystallization twice from aqueous solution. Single crystals were grown from methanol solution.

**Refinement**

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

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**Table 2**

| Experimental details. |
|------------------------|
| Crystal data           |
| Chemical formula       | C₈H₈N₂O₄ |
| Mᵣ                 | 196.16    |
| Crystal system, space group | Monoclinic, C2/c |
| Temperature (K)        | 90        |
| a, b, c (Å)           | 9.6643 (3), 18.5534 (5), 9.3072 (2) |
| β (°)                 | 95.5075 (14) |
| V (Å³)                | 1661.13 (8) |
| Z                     | 8         |
| Radiation type         | Cu Ka     |
| μ (mm⁻¹)              | 1.10      |
| Crystal size (mm)      | 0.21 x 0.07 x 0.02 |

**Data collection**

Diffractometer

Bruker Kappa APEXII DUO CCD

Absorption correction

Multi-scan (SADABS: Krause et al., 2015)

**T**<sub>min</sub>, **T**<sub>max</sub> 0.0872, 0.978

No. of measured, independent and observed [I > 2σ(I)] reflections 6856, 1543, 1486

R<sub>int</sub> (sin θ/λ)o max (Å⁻¹) 0.028

R<sub>int</sub> (sin θ/λ)o max (Å⁻¹) 0.607

**Refinement**

R<sub>1</sub>[F<sup>2</sup> > 2σ(F<sup>2</sup>)] wR<sub>2</sub>(F<sup>2</sup>) 0.035, 0.095, 1.13

No. of reflections 1543

No. of parameters 134

H-atom treatment H atoms treated by a mixture of independent and constrained refinement

Δρ<sub>max</sub>: Δρ<sub>min</sub> (e Å⁻³) 0.29, –0.24

**Computer programs**

APEX3 and SAINT (Brucker, 2016). SHELX97 (Sheldrick, 2008). SHELXL2014/7 (Sheldrick, 2015). Mercury (Macrae et al., 2020). ORTEP-3 (Farrugia, 2012) and pubCIF (Westrip, 2010).

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full crystallographic data

IUCrData (2022). 7, x220201  [https://doi.org/10.1107/S2414314622002012]

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

Crystal data

\( \text{C}_8\text{H}_8\text{N}_2\text{O}_4 \)

Mr = 196.16

Monoclinic, \( \text{C}2/c \)

\( a = 9.6643 \) (3) Å

\( b = 18.5534 \) (5) Å

\( c = 9.3072 \) (2) Å

\( \beta = 95.5075 \) (14)°

\( V = 1661.13 \) (8) Å\(^3\)

\( Z = 8 \)

\( F(000) = 816 \)

\( D_\lambda = 1.569 \) Mg m\(^{-3}\)

Cu K\( \alpha \) radiation, \( \lambda = 1.54184 \) Å

Cell parameters from 5235 reflections

\( \theta = 4.8–69.3 \)°

\( \mu = 1.10 \) mm\(^{-1}\)

\( T = 90 \) K

Lath, yellow

0.21 × 0.07 × 0.02 mm

Data collection

Bruker Kappa APEXII DUO CCD
diffractometer

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

QUAZAR multilayer optics monochromator

\( \phi \) and \( \omega \) scans

Absorption correction: multi-scan

(SADABS; Krause et al., 2015)

\( T_{\text{min}} = 0.872, T_{\text{max}} = 0.978 \)

6856 measured reflections

1543 independent reflections

1486 reflections with \( I > 2\sigma(I) \)

\( R_{\text{int}} = 0.028 \)

\( \theta_{\text{max}} = 69.3\)°, \( \theta_{\text{min}} = 4.8\)°

\( h = -11 \rightarrow 7 \)

\( k = -22 \rightarrow 20 \)

\( l = -11 \rightarrow 10 \)

Refinement

Refinement on \( F^2 \)

Least-squares matrix: full

\( R[F^2 > 2\sigma(F^2)] = 0.035 \)

\( wR(F^2) = 0.095 \)

\( S = 1.13 \)

1543 reflections

134 parameters

0 restraints

\( \Delta \rho_{\text{max}} = 0.29 \) e Å\(^{-3}\)

\( \Delta \rho_{\text{min}} = -0.23 \) e Å\(^{-3}\)

Special details

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. The coordinates of the N—H and O—H hydrogen atoms were refined. \( U_{\text{eq}}(\text{H}) \) values were assigned as \( 1.2U_{\text{eq}} \) for the attached atom (1.5 for OH and methyl).
Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

|     | x          | y          | z          | \(U_{iso}^{*}/U_{eq}^{*}\) |
|-----|------------|------------|------------|-----------------------------|
| O1  | 0.49965 (11) | 0.11112 (5) | 0.49610 (11) | 0.0180 (2) |
| H1O | 0.435 (2) | 0.1126 (10) | 0.551 (2) | 0.027* |
| O2  | 0.36347 (11) | 0.35035 (5) | 0.64809 (11) | 0.0240 (3) |
| O3  | 0.47807 (11) | 0.43019 (5) | 0.53985 (12) | 0.0239 (3) |
| O4  | 0.79942 (10) | 0.37109 (5) | 0.17917 (10) | 0.0208 (3) |
| N1  | 0.44852 (12) | 0.36642 (6) | 0.56392 (12) | 0.0163 (3) |
| N2  | 0.65588 (12) | 0.39184 (6) | 0.35604 (12) | 0.0149 (3) |
| H2N | 0.6134 (17) | 0.4246 (10) | 0.4050 (18) | 0.018* |
| C1  | 0.53400 (14) | 0.18008 (7) | 0.46502 (14) | 0.0143 (3) |
| C2  | 0.47727 (13) | 0.23927 (7) | 0.52723 (13) | 0.0146 (3) |
| H2  | 0.4113 | 0.2327 | 0.5955 | 0.018* |
| C3  | 0.51647 (13) | 0.30877 (7) | 0.49012 (13) | 0.0138 (3) |
| C4  | 0.61410 (13) | 0.32179 (7) | 0.39015 (13) | 0.0137 (3) |
| C5  | 0.66952 (13) | 0.26010 (7) | 0.32904 (13) | 0.0140 (3) |
| H5  | 0.7536 | 0.2659 | 0.2606 | 0.017* |
| C6  | 0.63082 (13) | 0.19119 (7) | 0.36548 (13) | 0.0143 (3) |
| H6  | 0.6708 | 0.1509 | 0.3220 | 0.017* |
| C7  | 0.74622 (13) | 0.41291 (7) | 0.25993 (14) | 0.0152 (3) |
| C8  | 0.77664 (15) | 0.49227 (7) | 0.26014 (16) | 0.0211 (3) |
| H8A | 0.8474 | 0.5036 | 0.3395 | 0.032* |
| H8B | 0.6914 | 0.5192 | 0.2729 | 0.032* |
| H8C | 0.8109 | 0.5058 | 0.1681 | 0.032* |

Atomic displacement parameters (Å²)

|     | \(U_{11}^{*}\) | \(U_{22}^{*}\) | \(U_{33}^{*}\) | \(U_{12}^{*}\) | \(U_{13}^{*}\) | \(U_{23}^{*}\) |
|-----|----------------|----------------|----------------|----------------|----------------|----------------|
| O1  | 0.0214 (5) | 0.0120 (5) | 0.0220 (5) | −0.0007 (4) | 0.0096 (4) | 0.0002 (4) |
| O2  | 0.0279 (6) | 0.0189 (5) | 0.0287 (6) | 0.0003 (4) | 0.0202 (4) | 0.0005 (4) |
| O3  | 0.0298 (6) | 0.0121 (5) | 0.0327 (6) | −0.0014 (4) | 0.0180 (5) | −0.0002 (4) |
| O4  | 0.0256 (5) | 0.0158 (5) | 0.0234 (5) | 0.0000 (4) | 0.0141 (4) | −0.0013 (4) |
| N1  | 0.0175 (6) | 0.0143 (6) | 0.0182 (6) | 0.0003 (4) | 0.0073 (4) | −0.0003 (4) |
| N2  | 0.0148 (6) | 0.0129 (5) | 0.0179 (6) | 0.0009 (4) | 0.0061 (4) | −0.0006 (4) |
| C1  | 0.0142 (6) | 0.0132 (6) | 0.0155 (6) | −0.0010 (5) | 0.0005 (5) | 0.0010 (5) |
| C2  | 0.0143 (6) | 0.0159 (7) | 0.0143 (6) | −0.0002 (5) | 0.0041 (5) | 0.0001 (5) |
| C3  | 0.0140 (6) | 0.0141 (7) | 0.0136 (6) | 0.0017 (5) | 0.0026 (5) | −0.0019 (5) |
| C4  | 0.0124 (6) | 0.0153 (6) | 0.0133 (6) | −0.0002 (5) | 0.0004 (5) | 0.0004 (5) |
| C5  | 0.0122 (6) | 0.0165 (7) | 0.0138 (6) | 0.0003 (5) | 0.0031 (5) | −0.0003 (5) |
| C6  | 0.0134 (6) | 0.0152 (6) | 0.0145 (6) | 0.0016 (5) | 0.0025 (5) | −0.0013 (5) |
| C7  | 0.0142 (6) | 0.0143 (6) | 0.0173 (6) | 0.0006 (5) | 0.0028 (5) | 0.0010 (5) |
| C8  | 0.0245 (7) | 0.0142 (7) | 0.0266 (7) | −0.0006 (5) | 0.0125 (6) | −0.0002 (5) |

Geometric parameters (Å, °)

|     |     |     |     |
|-----|-----|-----|-----|
| O1—C1 | 1.3599 (16) | C2—C3 | 1.3966 (18) |
| O1—H1O | 0.84 (2) | C2—H2 | 0.9500 |

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| Bond Lengths (Å) |  | Bond Angles (°) |  |
|------------------|------------------|------------------|------------------|
| C1—O1 | 1.080 (12) | O1—C1—C2—C3 | −179.68 (11) |
| C2—C1 | 1.187 (12) | C2—C1—C2—C3 | 0.19 (19) |
| N1—C3 | 1.4608 (17) | O3—N1—C3—C4 | −0.79 (19) |
| C5—C6 | 1.3835 (18) | C5—C6—C7—N2 | 3.1 (2) |
| H5 | 0.9500 | C4—C5—C6—H6 | 0.9500 |
| H6 | 0.9500 | N2—C4—C5—C6 | 178.36 (11) |
| H8A | 0.9800 | N2—C4—C5—C6 | 178.36 (11) |
| H8B | 0.9800 | N2—C4—C5—C6 | 178.36 (11) |
| H8C | 0.9800 | N2—C4—C5—C6 | 178.36 (11) |

Hydrogen-bond geometry (Å, °)

| D—H···A | D—H | H···A | D···A | D—H···A |
|----------|------|-------|-------|---------|
| O1—H1O···O4i | 0.84 (2) | 1.88 (2) | 2.7183 (14) | 172.0 (18) |
| N2—H2N···O3  | 0.883 (19) | 1.901 (17) | 2.6363 (15) | 139.6 (15) |

Symmetry code: (i) x−1/2, −y+1/2, z+1/2.