

4-Acetamido-3-chlorophenyl acetate

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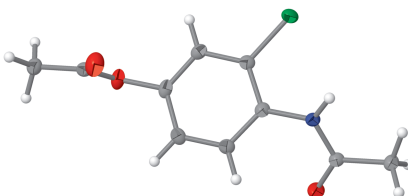
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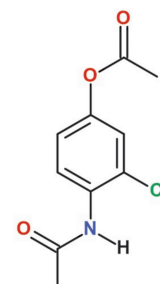
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In the title compound, C₁₀H₁₀ClNO₃, the dihedral angles between the chlorobenzene ring and the acetamide and acetate planes are 40.70 (8) and 88.07 (8)°, respectively; the acetamide and acetate planes make a dihedral angle of 51.39 (9)°. In the extended structure, the molecules are linked by N–H···O hydrogen bonds involving the acetamide group, forming C(4) chains propagating along the [010] direction.

3D view



Chemical scheme



Structure description

With approximately 25 billion doses sold annually in the United States, acetaminophen, C₈H₉NO₂ (also known as paracetamol; brand names in different countries include Tylenol, Panadol and many others) is among the most widely used analgesic and antipyretic agents (Uppu & Fronczek, 2025; Yoon *et al.*, 2016). Its metabolism is dominated by sulfation and glucuronidation, with a smaller contribution from CYP2E1-mediated oxidation (Mazaleuskaya *et al.*, 2015). In addition, non-enzymatic transformations mediated by cellular oxidants, including the peroxynitrite–CO₂ system and the myeloperoxidase–H₂O₂–Cl[−] pathway that generates HOCl/ClO[−] (pK_a ≈ 7.53), warrant consideration (Bedner & MacCrehan, 2006; Hines *et al.*, 2025; Hines *et al.*, 2026; Uppu & Martin, 2005). While CYP2E1 and related oxidants are implicated in overdose-level formation of *N*-acetyl-1,4-benzoquinone imine (NBQI), the present work focuses on low-level *in vivo* NBQI formation and the identification of chemically tractable transformation products (Manyike *et al.*, 2000).

Given the high intracellular abundance of chloride ions (*ca.* 150 mM), *N*-(4-hydroxy-2-chlorophenyl)acetamide (the 2-chloro isomer; Matsuno *et al.*, 1989) has been proposed as a chemically plausible product of NBQI–Cl[−] chemistry. Recognizing that *O*-acetylation can facilitate cellular uptake, we synthesized the title compound, C₁₀H₁₀ClNO₃ (**I**), the

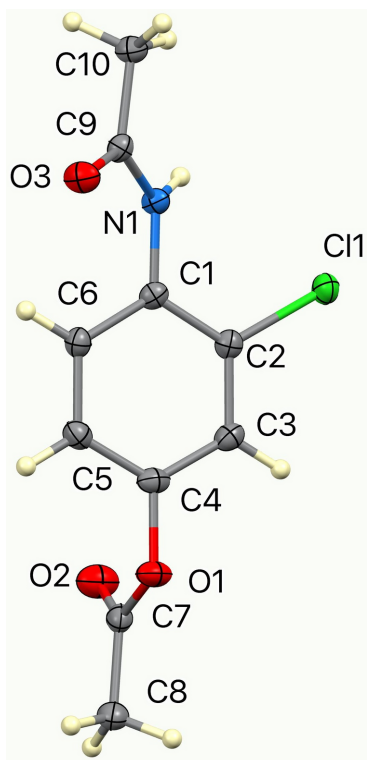


Figure 1
The molecular structure of (**I**) with displacement ellipsoids drawn at the 50% probability level.

O-acetylated derivative of *N*-(4-hydroxy-2-chlorophenyl)acetamide, and determined its crystal structure (Bai *et al.*, 2025).

Compound (**I**) crystallizes as a neutral molecular species in space group *I2/a* with one molecule in the asymmetric unit (Fig. 1). The dihedral angles between the central C1–C6

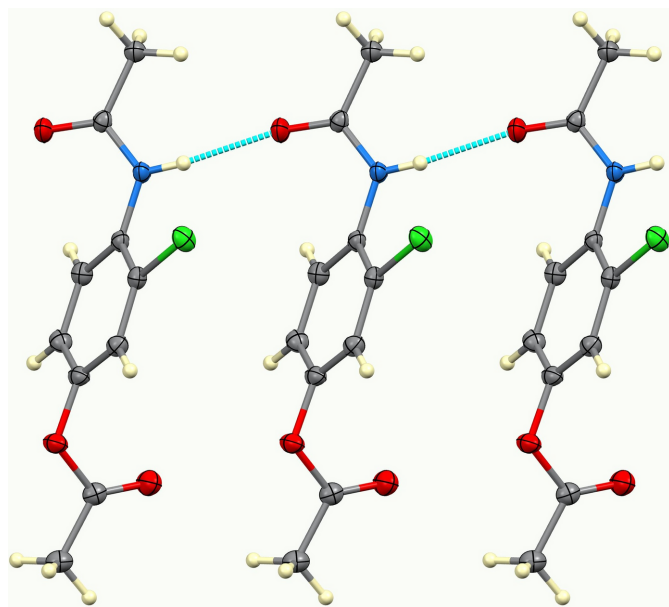


Figure 2
Fragment of a [010] hydrogen-bonded chain in (**I**).

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

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
N1–H1N···O3 ⁱ	0.87 (2)	2.01 (2)	2.8335 (17)	157.5 (17)
C8–H8A···Cl1 ⁱⁱ	0.98	2.90	3.8279 (16)	159
C8–H8C···Cl1 ⁱⁱⁱ	0.98	2.97	3.6541 (16)	128
C10–H10A···O3 ⁱ	0.98	2.46	3.2796 (18)	141

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

aromatic ring and the pendant acetamide (C9/C10/N1/O3) and acetate (C7/C8/O1/O2) mean planes are 40.70 (8) and 88.07 (8)°, respectively: the two substituents are displaced on opposite sides of the central ring. The masking of the phenolic O–H group as an ester in (**I**) suppresses phenol-based hydrogen bonding and shifts the supramolecular assembly to an amide-centered hydrogen-bonding network in which N1–H1N···O3 hydrogen bonds link the molecules into *C*(4) chains propagating in the [010] direction with adjacent molecules in the chain related by simple translation (Table 1, Fig. 2). Weak C–H···Cl and C–H···O interactions consolidate the structure (Fig. 3). This solid-state behavior is consistent with an ester that is poised for enzymatic *O*-deacetylation to *N*-(4-hydroxy-2-chlorophenyl)acetamide (Soloviev *et al.*, 2022). The molecular geometry and packing parameters reported here provide a crystallographic reference for comparison with related acetaminophen derivatives and their functionalized analogues.

Synthesis and crystallization

The title compound was synthesized by acetylation of 4-amino-3-chlorophenol with acetic anhydride following Naik *et al.* (2004) with minor modifications: 4-amino-3-chlorophenol hydrochloride (1.8 g, 10 mmol) was dissolved in ~50–75 ml water and adjusted to pH 1.5–1.7 with 1.0 *N* HCl. The cooled solution (ice bath) was treated with acetic anhydride (1.21 ml,

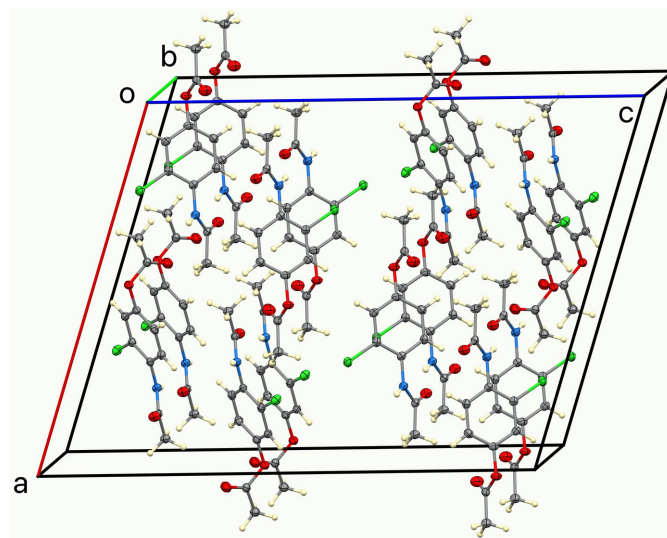


Figure 3
The unit cell of (**I**) viewed approximately down [010].

12 mmol), then sodium bicarbonate (2.16–3.02 g, 25–35 mmol) was added with continuous stirring, maintaining the reaction pH between 5.5 and 6.5. The off-white precipitate was collected by filtration. Crystals were grown from a hot, near-saturated ethanolic aqueous solution by slow cooling and evaporation to form colorless needles of (**I**).

Refinement

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

Funding information

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Table 2

Experimental details.

Crystal data	
Chemical formula	C ₁₀ H ₁₀ ClNO ₃
<i>M_r</i>	227.64
Crystal system, space group	Monoclinic, <i>I2/a</i>
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	19.2482 (7), 4.7223 (2), 24.3718 (11)
β (°)	111.222 (2)
<i>V</i> (Å ³)	2065.06 (15)
<i>Z</i>	8
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	3.19
Crystal size (mm)	0.40 × 0.03 × 0.02
Data collection	
Diffractometer	Bruker D8 Venture DUO with Photon III C14
Absorption correction	Multi-scan (<i>SADABS</i> ; Krause <i>et al.</i> , 2015)
<i>T_{min}</i> , <i>T_{max}</i>	0.795, 0.939
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	20794, 2190, 1953
<i>R_{int}</i>	0.049
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.638
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.031, 0.079, 1.06
No. of reflections	2190
No. of parameters	141
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.28, -0.31

Computer programs: *APEX5* and *SAINT* (Bruker, 2016), *SHELXT2018/2* (Sheldrick, 2015a), *SHELXL2019/1* (Sheldrick, 2015b) and *Mercury* (Macrae *et al.*, 2020).

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full crystallographic data

IUCrData (2026). **11**, x260076 [<https://doi.org/10.1107/S2414314626000763>]

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Crystal data

$C_{10}H_{10}ClNO_3$

$M_r = 227.64$

Monoclinic, $I2/a$

$a = 19.2482$ (7) Å

$b = 4.7223$ (2) Å

$c = 24.3718$ (11) Å

$\beta = 111.222$ (2)°

$V = 2065.06$ (15) Å³

$Z = 8$

$F(000) = 944$

$D_x = 1.464$ Mg m⁻³

Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å

Cell parameters from 7338 reflections

$\theta = 5.1$ – 78.8 °

$\mu = 3.19$ mm⁻¹

$T = 100$ K

Needle, colourless

$0.40 \times 0.03 \times 0.02$ mm

Data collection

Bruker D8 Venture DUO with Photon III C14 diffractometer

Radiation source: $I\mu S$ 3.0 microfocus

φ and ω scans

Absorption correction: multi-scan (SADABS; Krause *et al.*, 2015)

$T_{\min} = 0.795$, $T_{\max} = 0.939$

20794 measured reflections

2190 independent reflections

1953 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.049$

$\theta_{\max} = 79.5$ °, $\theta_{\min} = 3.9$ °

$h = -23 \rightarrow 24$

$k = -5 \rightarrow 5$

$l = -30 \rightarrow 30$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.031$

$wR(F^2) = 0.079$

$S = 1.06$

2190 reflections

141 parameters

0 restraints

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0352P)^2 + 2.3982P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.28$ e Å⁻³

$\Delta\rho_{\min} = -0.31$ 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. The N-bound H atom was located in a difference map and its position was freely refined. The C-bound H atoms were geometrically placed (C—H = 0.95–0.98 Å) and refined as riding atoms. The constraint $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ or $1.5U_{\text{eq}}(\text{methyl C or N})$ was applied in all cases.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
Cl1	0.29945 (2)	1.05930 (8)	0.43887 (2)	0.02274 (12)
O1	0.51347 (6)	0.4581 (2)	0.42785 (5)	0.0234 (2)
O2	0.54882 (6)	0.7934 (3)	0.37753 (5)	0.0311 (3)
O3	0.16631 (6)	0.3467 (2)	0.29322 (5)	0.0240 (2)
N1	0.21473 (7)	0.7825 (3)	0.32425 (5)	0.0166 (3)
H1N	0.2050 (11)	0.961 (4)	0.3252 (8)	0.025*
C1	0.29024 (8)	0.6998 (3)	0.34951 (6)	0.0164 (3)
C2	0.33611 (8)	0.8169 (3)	0.40297 (6)	0.0175 (3)
C3	0.41082 (8)	0.7434 (3)	0.42888 (6)	0.0193 (3)
H3	0.441580	0.827008	0.464947	0.023*
C4	0.43917 (8)	0.5462 (3)	0.40099 (6)	0.0198 (3)
C5	0.39561 (8)	0.4239 (3)	0.34806 (7)	0.0206 (3)
H5	0.416175	0.287458	0.329626	0.025*
C6	0.32145 (8)	0.5039 (3)	0.32240 (6)	0.0189 (3)
H6	0.291440	0.423692	0.285717	0.023*
C7	0.56449 (8)	0.5943 (3)	0.41004 (6)	0.0196 (3)
C8	0.63895 (8)	0.4550 (4)	0.43598 (7)	0.0236 (3)
H8A	0.675565	0.561234	0.424852	0.035*
H8B	0.635720	0.260647	0.421143	0.035*
H8C	0.654427	0.451599	0.478961	0.035*
C9	0.15738 (8)	0.6016 (3)	0.29791 (6)	0.0169 (3)
C10	0.08112 (8)	0.7331 (3)	0.27509 (6)	0.0203 (3)
H10A	0.084987	0.934742	0.285256	0.031*
H10B	0.049155	0.638463	0.292905	0.031*
H10C	0.059499	0.711821	0.232210	0.031*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.02477 (19)	0.0215 (2)	0.01999 (18)	0.00295 (13)	0.00569 (13)	-0.00444 (13)
O1	0.0159 (5)	0.0289 (6)	0.0251 (5)	0.0034 (4)	0.0071 (4)	0.0090 (4)
O2	0.0261 (6)	0.0313 (6)	0.0364 (6)	0.0010 (5)	0.0119 (5)	0.0116 (5)
O3	0.0240 (5)	0.0134 (5)	0.0315 (6)	0.0002 (4)	0.0063 (4)	-0.0009 (4)
N1	0.0171 (6)	0.0118 (6)	0.0186 (6)	0.0003 (4)	0.0039 (4)	-0.0005 (4)
C1	0.0178 (7)	0.0139 (7)	0.0167 (6)	-0.0007 (5)	0.0051 (5)	0.0030 (5)
C2	0.0203 (7)	0.0148 (7)	0.0173 (7)	-0.0006 (5)	0.0069 (5)	0.0011 (5)
C3	0.0186 (7)	0.0208 (7)	0.0167 (7)	-0.0025 (6)	0.0040 (5)	0.0020 (5)
C4	0.0152 (6)	0.0230 (8)	0.0212 (7)	0.0007 (5)	0.0064 (5)	0.0071 (6)
C5	0.0220 (7)	0.0207 (7)	0.0217 (7)	0.0025 (6)	0.0110 (6)	0.0017 (6)
C6	0.0214 (7)	0.0187 (7)	0.0167 (7)	-0.0003 (5)	0.0071 (5)	0.0001 (5)
C7	0.0198 (7)	0.0221 (7)	0.0173 (7)	-0.0017 (6)	0.0073 (5)	-0.0030 (6)
C8	0.0188 (7)	0.0283 (8)	0.0235 (8)	-0.0005 (6)	0.0076 (6)	-0.0014 (6)
C9	0.0189 (7)	0.0158 (7)	0.0155 (6)	-0.0011 (5)	0.0057 (5)	0.0013 (5)
C10	0.0175 (7)	0.0182 (7)	0.0234 (7)	-0.0001 (5)	0.0050 (5)	0.0004 (6)

Geometric parameters (Å, °)

C11—C2	1.7378 (15)	C4—C5	1.385 (2)
O1—C7	1.3692 (18)	C5—C6	1.388 (2)
O1—C4	1.4033 (17)	C5—H5	0.9500
O2—C7	1.1958 (19)	C6—H6	0.9500
O3—C9	1.2271 (18)	C7—C8	1.494 (2)
N1—C9	1.3592 (18)	C8—H8A	0.9800
N1—C1	1.4129 (17)	C8—H8B	0.9800
N1—H1N	0.87 (2)	C8—H8C	0.9800
C1—C6	1.393 (2)	C9—C10	1.5027 (19)
C1—C2	1.3965 (19)	C10—H10A	0.9800
C2—C3	1.389 (2)	C10—H10B	0.9800
C3—C4	1.376 (2)	C10—H10C	0.9800
C3—H3	0.9500		
C7—O1—C4	116.09 (11)	C5—C6—H6	119.4
C9—N1—C1	124.31 (12)	C1—C6—H6	119.4
C9—N1—H1N	118.6 (13)	O2—C7—O1	122.79 (14)
C1—N1—H1N	117.1 (13)	O2—C7—C8	126.87 (14)
C6—C1—C2	118.04 (13)	O1—C7—C8	110.33 (12)
C6—C1—N1	121.95 (12)	C7—C8—H8A	109.5
C2—C1—N1	120.01 (13)	C7—C8—H8B	109.5
C3—C2—C1	121.72 (13)	H8A—C8—H8B	109.5
C3—C2—C11	118.56 (11)	C7—C8—H8C	109.5
C1—C2—C11	119.72 (11)	H8A—C8—H8C	109.5
C4—C3—C2	118.35 (13)	H8B—C8—H8C	109.5
C4—C3—H3	120.8	O3—C9—N1	122.91 (13)
C2—C3—H3	120.8	O3—C9—C10	121.46 (13)
C3—C4—C5	121.84 (13)	N1—C9—C10	115.63 (13)
C3—C4—O1	119.30 (13)	C9—C10—H10A	109.5
C5—C4—O1	118.81 (13)	C9—C10—H10B	109.5
C4—C5—C6	118.91 (14)	H10A—C10—H10B	109.5
C4—C5—H5	120.5	C9—C10—H10C	109.5
C6—C5—H5	120.5	H10A—C10—H10C	109.5
C5—C6—C1	121.12 (13)	H10B—C10—H10C	109.5
C9—N1—C1—C6	41.6 (2)	C7—O1—C4—C5	86.39 (17)
C9—N1—C1—C2	-138.86 (14)	C3—C4—C5—C6	0.3 (2)
C6—C1—C2—C3	0.2 (2)	O1—C4—C5—C6	177.91 (13)
N1—C1—C2—C3	-179.30 (13)	C4—C5—C6—C1	-1.2 (2)
C6—C1—C2—C11	-179.28 (11)	C2—C1—C6—C5	0.9 (2)
N1—C1—C2—C11	1.21 (18)	N1—C1—C6—C5	-179.57 (13)
C1—C2—C3—C4	-1.0 (2)	C4—O1—C7—O2	6.4 (2)
C11—C2—C3—C4	178.46 (11)	C4—O1—C7—C8	-172.55 (12)
C2—C3—C4—C5	0.8 (2)	C1—N1—C9—O3	-0.6 (2)
C2—C3—C4—O1	-176.80 (12)	C1—N1—C9—C10	178.72 (12)
C7—O1—C4—C3	-95.97 (16)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
N1—H1N \cdots O3 ⁱ	0.87 (2)	2.01 (2)	2.8335 (17)	157.5 (17)
C8—H8A \cdots C11 ⁱⁱ	0.98	2.90	3.8279 (16)	159
C8—H8C \cdots C11 ⁱⁱⁱ	0.98	2.97	3.6541 (16)	128
C10—H10A \cdots O3 ⁱ	0.98	2.46	3.2796 (18)	141

Symmetry codes: (i) $x, y+1, z$; (ii) $x+1/2, -y+2, z$; (iii) $-x+1, -y+2, -z+1$.