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3-Ethyl-2-methyl-5-methylene-6,7-dihydroindol-4(5H)-one

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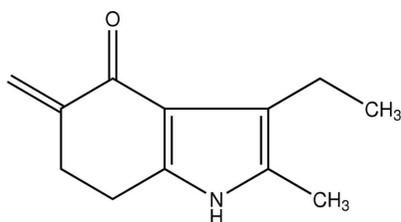
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Key indicators: single-crystal X-ray study; $T = 90$ K; mean $\sigma(\text{C}-\text{C}) = 0.002$ Å; R factor = 0.038; wR factor = 0.097; data-to-parameter ratio = 15.3.

The title compound, $\text{C}_{12}\text{H}_{15}\text{NO}$, a degradation product of molindone hydrochloride, was prepared by the reaction of molindone with methyl iodide and subsequent reaction of the resulting quaternary ammonium salt with 2*N* aqueous sodium hydroxide. The newly formed double bond is exocyclic in nature and the carbonyl group is conjugated with the π -electrons of the pyrrole ring. The six-membered ring is in the half-chair conformation. The H atom attached to the N atom is involved in an intermolecular hydrogen bond with the O atom of a screw-related molecule, thus forming a continuous chain.

Related literature

For related literature, see: Dudzinski *et al.* (1973).

Experimental

Crystal data

$\text{C}_{12}\text{H}_{15}\text{NO}$
 $M_r = 189.25$
 Monoclinic, $P2_1/n$
 $a = 9.0451$ (3) Å
 $b = 8.5840$ (3) Å
 $c = 14.3557$ (5) Å
 $\beta = 107.355$ (1)°

$V = 1063.88$ (6) Å³
 $Z = 4$
 Cu $K\alpha$ radiation
 $\mu = 0.59$ mm⁻¹
 $T = 90.0$ (2) K
 $0.15 \times 0.12 \times 0.10$ mm

Data collection

Bruker X8 Proteum diffractometer
 Absorption correction: multi-scan
 (SADABS in APEX2;
 Bruker, 2006)
 $T_{\min} = 0.837$, $T_{\max} = 0.944$

15160 measured reflections
 1972 independent reflections
 1893 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.039$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.038$
 $wR(F^2) = 0.097$
 $S = 1.05$
 1972 reflections

129 parameters
 H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.24$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.20$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{N1}-\text{H1}\cdots\text{O1}^i$	0.88	1.91	2.7749 (12)	169

Symmetry code: (i) $x - \frac{1}{2}, -y + \frac{1}{2}, z - \frac{1}{2}$.

Data collection: APEX2 (Bruker, 2006); cell refinement: APEX2; data reduction: APEX2; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: XP in SHELXTL (Sheldrick, 1995); software used to prepare material for publication: SHELX97 and local procedures.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: OM2194).

References

- Bruker (2006). APEX2. Bruker AXS Inc., Madison, Wisconsin, USA.
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 Sheldrick, G. M. (1995). XP in SHELXTL/PC. Siemens Analytical Instruments Inc., Madison, Wisconsin, USA.
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supporting information

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3-Ethyl-2-methyl-5-methylene-6,7-dihydroindol-4(5*H*)-one

Vijayakumar N. Sonar, Sean Parkin and Peter A. Crooks

S1. Comment

The Mannich condensation reaction is frequently used in the synthesis of pharmaceutical compounds. One such example is the synthesis of molindone, an antipsychotic agent. During stability studies and development of an assay for molindone hydrochloride, a degradation product was identified as 3-ethyl-2-methyl-5-methylene-6,7-dihydro-5*H*-indol-4-one (Dudzinski *et al.*, 1973). Molindone has UV absorption peaks at 255 nm and 299 nm; these UV wavelengths can be used quantitatively for quantifying the drug substance. However, preliminary studies indicated that chemical degradation (as evidenced by color and precipitate formation) was not accompanied by a decrease in UV absorption, suggesting that the degradation product had a similar chromophore to molindone. The title compound was prepared by the reaction of molindone free base with methyl iodide and subsequent reaction of the resulting quaternary ammonium salt with 2 N aqueous sodium hydroxide. The structure of the resulting compound, 3-ethyl-2-methyl-5-methylene-6,7-dihydro-5*H*-indol-4-one, was initially characterized by NMR spectroscopy and shown to be identical to the degradation product of molindone hydrochloride. To confirm the exocyclic nature of newly formed double bond and to identify chromophoric group in the molecule responsible for its UV absorption profile, its crystal structure was determined by X-ray analysis.

The molecular structure and the atom-numbering scheme are shown in Fig. 1. The bond length C4—C5 [1.5115 (16) Å] indicates that the newly formed double bond is exocyclic in nature. Further, it is evident from the bond lengths of C5—C6 and C6—C7 [1.5058 (15) and 1.4327 (15) Å, respectively] that the carbonyl group is conjugated with the π -electrons of pyrrole ring and not π -electrons of the exocyclic double. This explains why molindone and its degradation product, the title compound exhibit similar UV absorption. The mode of packing along the *b* direction is illustrated in Fig. 2. The H atom attached to atom N1 is involved in an intermolecular hydrogen bond [2.7749 (12) Å] with atom O1 of an inversion-related molecule, thus forming a continuous chain.

S2. Experimental

A mixture of molindone (0.276 g, 1 mmol) and excess methyl iodide (2 ml) was stirred at ambient temperature. After completion of the reaction, unreacted methyl iodide was evaporated, and the crude quaternary ammonium salt was then mixed with 2 N aqueous sodium hydroxide (10 ml) and stirred for 1 h at ambient temperature. The resulting precipitate was collected by filtration and washed with water. Recrystallization from ethanol afforded the title compound as colorless crystalline product, which was suitable for X-ray analysis. Compound I: ^1H NMR (400 MHz, CDCl_3 , p.p.m.): δ 1.15 (t, $J = 7.6$ Hz, 3H), 2.16 (s, 3H), 2.70 (q, $J = 7.6$ Hz, 2H), 2.83 (s, 4H), 5.29 (d, $J = 1.6$ Hz, 1H), 6.03 (d, $J = 1.6$ Hz, 1H), 8.43 (sb, 1H); ^{13}C NMR (75 MHz, CDCl_3 , p.p.m.): δ 10.68, 15.83, 18.41, 23.65, 32.13, 118.66, 119.16, 121.58, 124.74, 142.28, 144.84, 184.13.

S3. Refinement

All H atoms were found in difference Fourier maps and but were subsequently placed in idealized positions with constrained distances of 0.98 Å (RCH_3), 0.99 Å (R_2CH_2), 0.95 Å ($RC_{sp^2}H_2$) and 0.88 Å (NH). $U_{iso}(H)$ values were set to either $1.2U_{eq}$ or $1.5U_{eq}$ (RCH_3 only) of the attached atom.

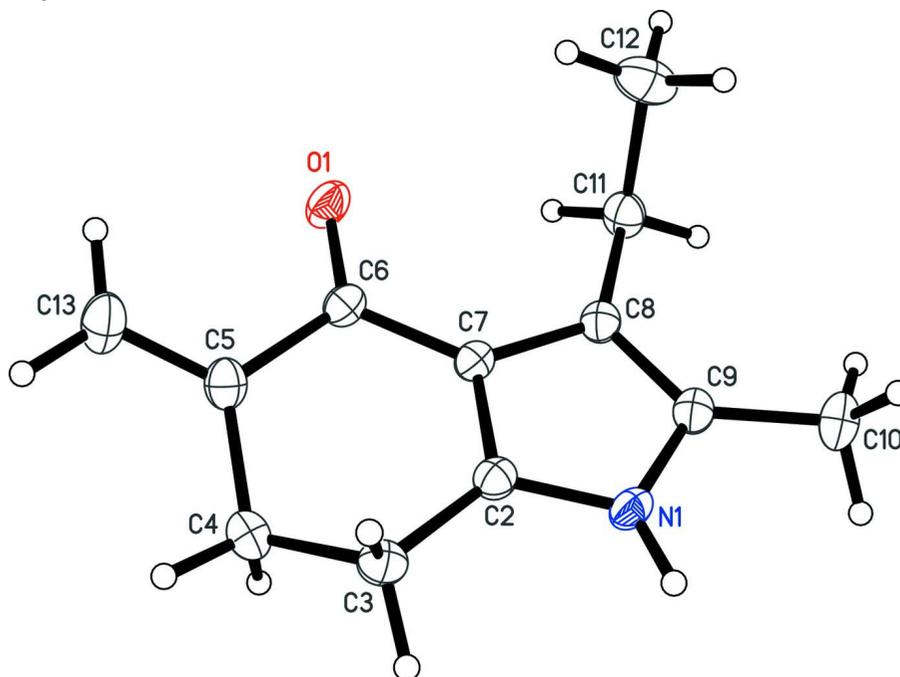
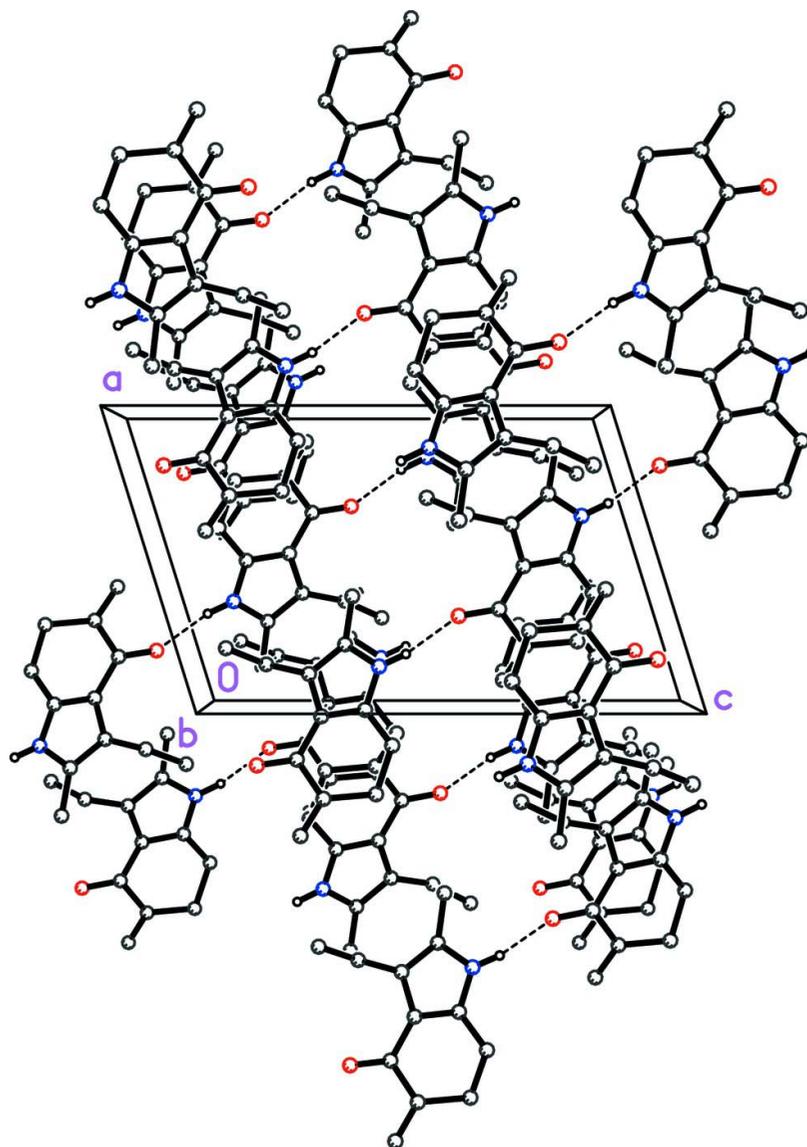
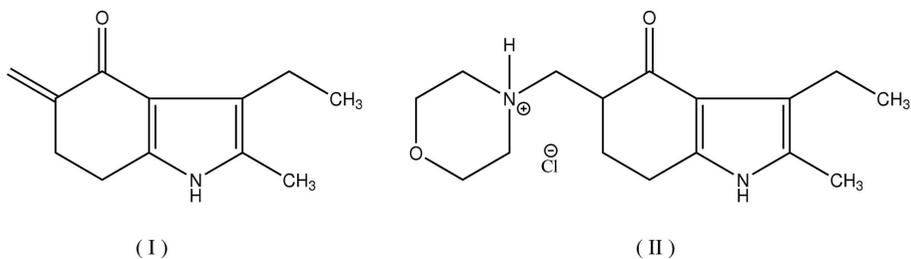


Figure 1

A view of the title compound I showing atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

**Figure 2**

A packing diagram viewed down the *b* axis, showing hydrogen bonding interactions (dashed lines). For clarity, only those H atoms involved in hydrogen bonding are shown.

**Figure 3**

Compounds (I) and (II).

3-Ethyl-2-methyl-5-methylene-6,7-dihydroindol-4(5H)-one

Crystal data

C₁₂H₁₅NO $M_r = 189.25$ Monoclinic, $P2_1/n$

Hall symbol: -P 2yn

 $a = 9.0451 (3) \text{ \AA}$ $b = 8.5840 (3) \text{ \AA}$ $c = 14.3557 (5) \text{ \AA}$ $\beta = 107.355 (1)^\circ$ $V = 1063.88 (6) \text{ \AA}^3$ $Z = 4$ $F(000) = 408$ $D_x = 1.182 \text{ Mg m}^{-3}$ Cu $K\alpha$ radiation, $\lambda = 1.54178 \text{ \AA}$

Cell parameters from 9990 reflections

 $\theta = 3.2\text{--}69.4^\circ$ $\mu = 0.59 \text{ mm}^{-1}$ $T = 90 \text{ K}$

Block, colourless

 $0.15 \times 0.12 \times 0.10 \text{ mm}$

Data collection

Bruker X8 Proteum

diffractometer

Radiation source: fine-focus rotating anode

Graded multilayer optics monochromator

Detector resolution: 18 pixels mm^{-1} φ and ω scans

Absorption correction: multi-scan

(SADABS in APEX2; Bruker, 2006)

 $T_{\min} = 0.837$, $T_{\max} = 0.944$

15160 measured reflections

1972 independent reflections

1893 reflections with $I > 2\sigma(I)$ $R_{\text{int}} = 0.039$ $\theta_{\max} = 69.4^\circ$, $\theta_{\min} = 5.2^\circ$ $h = -10 \rightarrow 10$ $k = -10 \rightarrow 10$ $l = -17 \rightarrow 17$

Refinement

Refinement on F^2

Least-squares matrix: full

 $R[F^2 > 2\sigma(F^2)] = 0.038$ $wR(F^2) = 0.097$ $S = 1.05$

1972 reflections

129 parameters

0 restraints

Primary atom site location: structure-invariant

direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H-atom parameters constrained

 $w = 1/[\sigma^2(F_o^2) + (0.0464P)^2 + 0.432P]$ where $P = (F_o^2 + 2F_c^2)/3$ $(\Delta/\sigma)_{\max} < 0.001$ $\Delta\rho_{\max} = 0.24 \text{ e \AA}^{-3}$ $\Delta\rho_{\min} = -0.20 \text{ e \AA}^{-3}$

Special details

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

Refinement. Refinement of F^2 against ALL reflections. The weighted R -factor wR and goodness of fit S are based on F^2 , conventional R -factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R -factors(gt) etc. and is not relevant to the choice of reflections for refinement. R -factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger.

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

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.68573 (9)	0.20035 (10)	0.42456 (6)	0.0247 (2)
N1	0.35484 (10)	0.23361 (11)	0.11591 (6)	0.0186 (2)
H1	0.3128	0.2575	0.0540	0.022*
C2	0.49707 (13)	0.27649 (13)	0.17035 (8)	0.0181 (2)

C3	0.60968 (13)	0.37109 (14)	0.13708 (8)	0.0232 (3)
H3A	0.5914	0.4835	0.1445	0.028*
H3B	0.5977	0.3499	0.0674	0.028*
C4	0.77279 (13)	0.32599 (14)	0.20002 (8)	0.0239 (3)
H4A	0.7983	0.2212	0.1805	0.029*
H4B	0.8484	0.4006	0.1879	0.029*
C5	0.78799 (13)	0.32500 (13)	0.30777 (8)	0.0212 (3)
C6	0.66379 (13)	0.24233 (12)	0.33901 (8)	0.0184 (2)
C7	0.52110 (12)	0.21662 (12)	0.26362 (8)	0.0168 (2)
C8	0.38323 (12)	0.13283 (12)	0.26393 (8)	0.0179 (3)
C9	0.28372 (13)	0.14590 (12)	0.17184 (8)	0.0190 (3)
C10	0.12335 (13)	0.08583 (15)	0.12770 (9)	0.0270 (3)
H10A	0.1004	0.0069	0.1708	0.041*
H10B	0.1149	0.0391	0.0640	0.041*
H10C	0.0494	0.1719	0.1193	0.041*
C11	0.35382 (13)	0.04614 (13)	0.34712 (8)	0.0224 (3)
H11A	0.4509	-0.0057	0.3850	0.027*
H11B	0.2761	-0.0362	0.3205	0.027*
C12	0.29655 (17)	0.14824 (17)	0.41558 (10)	0.0342 (3)
H12A	0.3746	0.2276	0.4444	0.051*
H12B	0.2784	0.0839	0.4675	0.051*
H12C	0.1996	0.1991	0.3790	0.051*
C13	0.90486 (14)	0.39164 (15)	0.37417 (9)	0.0283 (3)
H13A	0.9101	0.3872	0.4412	0.034*
H13B	0.9835	0.4439	0.3548	0.034*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0246 (4)	0.0296 (5)	0.0160 (4)	-0.0050 (3)	0.0003 (3)	0.0018 (3)
N1	0.0188 (5)	0.0208 (5)	0.0137 (4)	0.0021 (4)	0.0010 (4)	-0.0001 (3)
C2	0.0186 (5)	0.0177 (5)	0.0177 (5)	0.0014 (4)	0.0046 (4)	-0.0012 (4)
C3	0.0249 (6)	0.0265 (6)	0.0184 (5)	-0.0025 (5)	0.0070 (5)	0.0024 (4)
C4	0.0204 (6)	0.0266 (6)	0.0260 (6)	-0.0032 (5)	0.0091 (5)	0.0003 (5)
C5	0.0180 (5)	0.0193 (5)	0.0245 (6)	0.0003 (4)	0.0040 (4)	0.0025 (4)
C6	0.0198 (6)	0.0166 (5)	0.0174 (5)	0.0004 (4)	0.0033 (4)	-0.0008 (4)
C7	0.0172 (5)	0.0165 (5)	0.0158 (5)	0.0003 (4)	0.0037 (4)	-0.0009 (4)
C8	0.0176 (5)	0.0163 (5)	0.0194 (5)	0.0001 (4)	0.0049 (4)	-0.0012 (4)
C9	0.0178 (5)	0.0169 (5)	0.0212 (6)	0.0005 (4)	0.0043 (4)	-0.0018 (4)
C10	0.0189 (6)	0.0272 (6)	0.0304 (6)	-0.0025 (5)	0.0002 (5)	-0.0010 (5)
C11	0.0221 (6)	0.0218 (6)	0.0233 (6)	-0.0024 (4)	0.0067 (4)	0.0028 (4)
C12	0.0415 (8)	0.0368 (7)	0.0303 (7)	0.0054 (6)	0.0200 (6)	0.0059 (5)
C13	0.0245 (6)	0.0282 (6)	0.0280 (6)	-0.0066 (5)	0.0011 (5)	0.0058 (5)

Geometric parameters (Å, °)

O1—C6	1.2377 (14)	C7—C8	1.4407 (15)
N1—C2	1.3423 (14)	C8—C9	1.3640 (15)

N1—C9	1.3905 (14)	C8—C11	1.4968 (15)
N1—H1	0.8800	C9—C10	1.4911 (15)
C2—C7	1.3894 (15)	C10—H10A	0.9800
C2—C3	1.4883 (15)	C10—H10B	0.9800
C3—C4	1.5322 (16)	C10—H10C	0.9800
C3—H3A	0.9900	C11—C12	1.5185 (17)
C3—H3B	0.9900	C11—H11A	0.9900
C4—C5	1.5115 (16)	C11—H11B	0.9900
C4—H4A	0.9900	C12—H12A	0.9800
C4—H4B	0.9900	C12—H12B	0.9800
C5—C13	1.3237 (17)	C12—H12C	0.9800
C5—C6	1.5058 (15)	C13—H13A	0.9500
C6—C7	1.4327 (15)	C13—H13B	0.9500
C2—N1—C9	109.90 (9)	C9—C8—C7	106.11 (9)
C2—N1—H1	125.1	C9—C8—C11	126.25 (10)
C9—N1—H1	125.1	C7—C8—C11	127.64 (10)
N1—C2—C7	107.88 (10)	C8—C9—N1	108.61 (9)
N1—C2—C3	126.27 (10)	C8—C9—C10	131.34 (11)
C7—C2—C3	125.85 (10)	N1—C9—C10	120.05 (10)
C2—C3—C4	107.68 (9)	C9—C10—H10A	109.5
C2—C3—H3A	110.2	C9—C10—H10B	109.5
C4—C3—H3A	110.2	H10A—C10—H10B	109.5
C2—C3—H3B	110.2	C9—C10—H10C	109.5
C4—C3—H3B	110.2	H10A—C10—H10C	109.5
H3A—C3—H3B	108.5	H10B—C10—H10C	109.5
C5—C4—C3	112.49 (9)	C8—C11—C12	113.92 (10)
C5—C4—H4A	109.1	C8—C11—H11A	108.8
C3—C4—H4A	109.1	C12—C11—H11A	108.8
C5—C4—H4B	109.1	C8—C11—H11B	108.8
C3—C4—H4B	109.1	C12—C11—H11B	108.8
H4A—C4—H4B	107.8	H11A—C11—H11B	107.7
C13—C5—C6	119.71 (11)	C11—C12—H12A	109.5
C13—C5—C4	122.95 (11)	C11—C12—H12B	109.5
C6—C5—C4	117.34 (10)	H12A—C12—H12B	109.5
O1—C6—C7	123.12 (10)	C11—C12—H12C	109.5
O1—C6—C5	121.31 (10)	H12A—C12—H12C	109.5
C7—C6—C5	115.57 (9)	H12B—C12—H12C	109.5
C2—C7—C6	121.18 (10)	C5—C13—H13A	120.0
C2—C7—C8	107.51 (9)	C5—C13—H13B	120.0
C6—C7—C8	131.31 (10)	H13A—C13—H13B	120.0
C9—N1—C2—C7	0.04 (12)	C5—C6—C7—C2	-5.13 (15)
C9—N1—C2—C3	179.92 (10)	O1—C6—C7—C8	-5.42 (19)
N1—C2—C3—C4	-152.52 (11)	C5—C6—C7—C8	174.62 (10)
C7—C2—C3—C4	27.34 (15)	C2—C7—C8—C9	0.04 (12)
C2—C3—C4—C5	-48.30 (13)	C6—C7—C8—C9	-179.74 (11)
C3—C4—C5—C13	-133.03 (12)	C2—C7—C8—C11	179.14 (10)

C3—C4—C5—C6	47.57 (14)	C6—C7—C8—C11	-0.63 (19)
C13—C5—C6—O1	-18.54 (17)	C7—C8—C9—N1	-0.02 (12)
C4—C5—C6—O1	160.88 (10)	C11—C8—C9—N1	-179.14 (10)
C13—C5—C6—C7	161.42 (11)	C7—C8—C9—C10	-179.29 (11)
C4—C5—C6—C7	-19.16 (14)	C11—C8—C9—C10	1.6 (2)
N1—C2—C7—C6	179.76 (9)	C2—N1—C9—C8	-0.01 (12)
C3—C2—C7—C6	-0.13 (17)	C2—N1—C9—C10	179.35 (10)
N1—C2—C7—C8	-0.05 (12)	C9—C8—C11—C12	-96.71 (14)
C3—C2—C7—C8	-179.93 (10)	C7—C8—C11—C12	84.36 (14)
O1—C6—C7—C2	174.83 (10)		

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—H1...O1 ⁱ	0.88	1.91	2.7749 (12)	169

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