



Two orthorhombic polymorphs of hydromorphone

Jaroslaw Mazurek,^{a*} Marcel Hoffmann,^a Ana Fernandez Casares,^a D. Phillip Cox,^b Mathew D. Minardi^c and Josh Sasine^c^aCrystallics B.V., Meibergdreef 31, 1105 AZ Amsterdam, The Netherlands, ^bNoramco Inc., 503 Carr Rd, Suite 200, Wilmington, DE 19809, USA, and ^cNoramco Inc., 1440 Olympic Drive, Athens, GA 30601, USA. *Correspondence e-mail: jaroslaw.mazurek@crystallics.com

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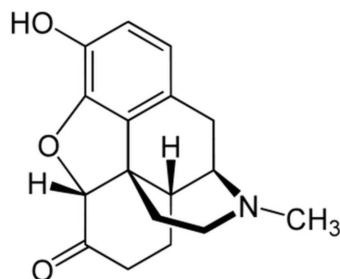
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Keywords: crystal structure; polymorphism; hydromorphone, hydrogen bonding.**CCDC references:** 1474753; 1474752**Supporting information:** this article has supporting information at journals.iucr.org/e

Conditions to obtain two polymorphic forms by crystallization from solution were determined for the analgesic drug hydromorphone [C₁₇H₁₉NO₃; systematic name: (4*R*,4*aR*,7*aR*,12*bS*)-9-hydroxy-3-methyl-1,2,4,4*a*,5,6,7*a*,13-octahydro-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-one]. These two crystalline forms, designated as I and II, belong to the *P*2₁2₁2₁ orthorhombic space group. In both polymorphs, the hydromorphone molecules adopt very similar conformations with some small differences observed only in the *N*-methyl amine part of the molecule. The crystal structures of both polymorphs feature chains of molecules connected by hydrogen bonds; however, in form I this interaction occurs between the hydroxyl group and the tertiary amine N atom whereas in form II the hydroxyl group acts as a donor of a hydrogen bond to the O atom from the cyclic ether part.

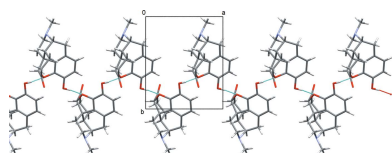
1. Chemical context

Drug polymorphism has been the subject of hundreds of publications and numerous excellent reviews (Byrn *et al.*, 1999; Grant, 1999; Singhal & Curatolo, 2004; Vippagunta *et al.*, 2001). It is well established that polymorphs with different stability may have different solubility and dissolution rates, which can affect the bioavailability. The semi-synthetic opiate drug hydromorphone is a potent derivative of morphine and despite poor bioavailability (Parab *et al.*, 1988) is commonly used to treat moderate to severe pain in the treatment of cancer (Sarhill *et al.*, 2001). To improve bioavailability of this compound a polymorph screen was performed that resulted in two solvent-free forms, designated as form I and form II.



2. Structural commentary

The molecular structure of hydromorphone in both polymorphs is nearly identical (Fig. 1) with some deviations found only for the *N*-methyl amine part of the piperidine fragment (Fig. 2). For example the C10–C11–N12–C13 torsion angle is 178.5 (2)° for form I and 169.5 (2)° for form II. The adopted



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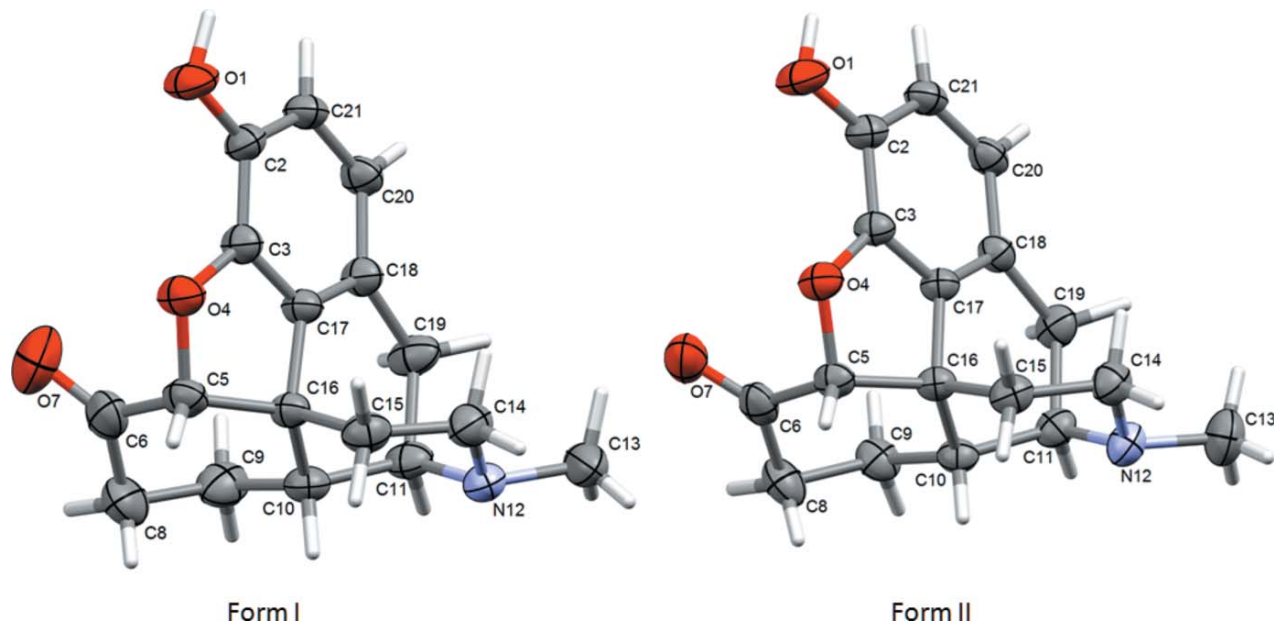


Figure 1 Molecular structure and atom-numbering scheme for hydromorphone in the crystals of form I (left) and form II (right). Displacement ellipsoids are shown at the 50% probability level.

conformation is similar to the conformation observed for morphine (Bye, 1976; Scheins *et al.*, 2005).

3. Supramolecular features

Although both polymorphs crystallize in the same space group $P2_12_12_1$ with the same number of molecules in the asymmetric unit, they differ significantly in the packing features (Figs. 3 and 4). In form I, the hydrogen-bonded molecules are arranged into chains that run along the a axis with adjacent molecules in the chain related by translation. The hydroxyl

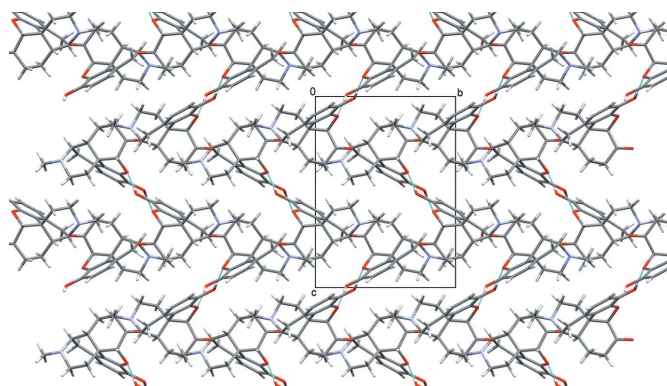


Figure 3 Crystal packing diagram of form I, viewed along the a axis. Hydrogen bonds are shown as blue lines.

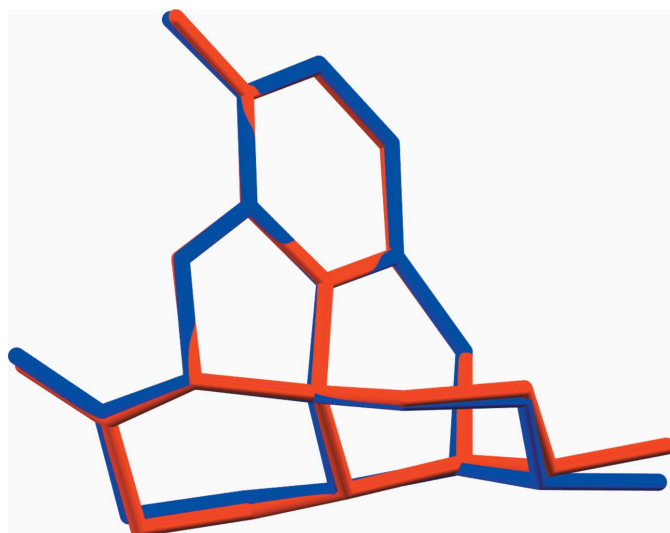


Figure 2 Superposition of the hydromorphone molecules from two polymorphic forms (red form I, blue form II) generated by fitting of the aromatic ring.

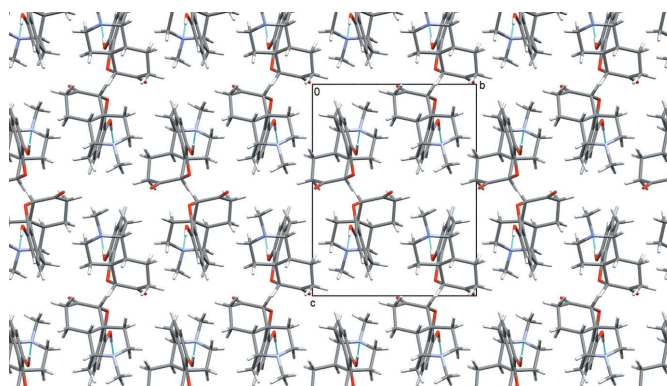


Figure 4 Crystal packing diagram of form II, viewed along the a axis. Hydrogen bonds are shown as blue lines.

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O1-H1A\cdots N12^i$	0.91 (4)	1.89 (4)	2.796 (3)	171 (3)

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

Table 2
Hydrogen-bond geometry (Å, °) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O1-H1\cdots O4^i$	0.84 (3)	1.96 (3)	2.791 (2)	167 (3)

Symmetry code: (i) $x + \frac{1}{2}, -y + \frac{3}{2}, -z + 1$.

group donates a hydrogen atom which is accepted by the free electron pair of the N atom (Fig. 5, Table 1). In the crystals of form II, intermolecular hydrogen bonds also generate a chain of molecules that propagates along the a axis; however, adjacent molecules along this chain are related by a 2_1 symmetry axis. The molecules are connected by $O-H\cdots O$ hydrogen bonds with the hydroxyl group as donor and the etheric O atom as acceptor (Table 2). These chains form a zigzag pattern, as illustrated in Fig. 6. The packing arrangement of molecules in form II is more dense than in polymorph

I, as indicated by the Kitajgorodskij (1973) packing coefficients of 0.71 and 0.69, respectively.

4. Synthesis and crystallization

10.8 mg of hydromorphone was dissolved in 1.8 mL THF/acetone (1/1, v/v) and left to evaporate slowly under ambient conditions. After several days, colorless prism-like crystals of form I (m.p. 549.8 K) appeared that were used for diffraction studies. Crystals of form II were obtained in the following way: 19.7 mg of hydromorphone was suspended in 0.3 mL of 50/50 mixture of ethanol and toluene. The suspension was heated to 333 K and stirred for about one h until it became clear. Subsequently, the vial was cooled rapidly to 278 K and colorless block-like crystals (m.p. 550.2 K) precipitated that were used for diffraction studies.

5. Refinement

The H atoms from the methyl group in form II were included from geometry and their isotropic displacement parameters refined. The remaining H atoms were found in a Fourier difference map and freely refined. The absolute configuration of hydromorphone was known from the synthetic route. In the

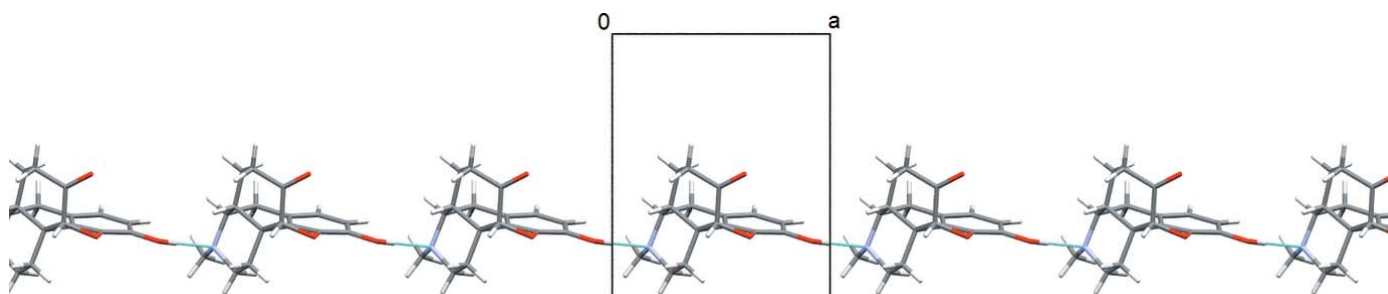


Figure 5
The chain of molecules running along the a axis formed by $O-H\cdots N$ hydrogen bonds in form I.

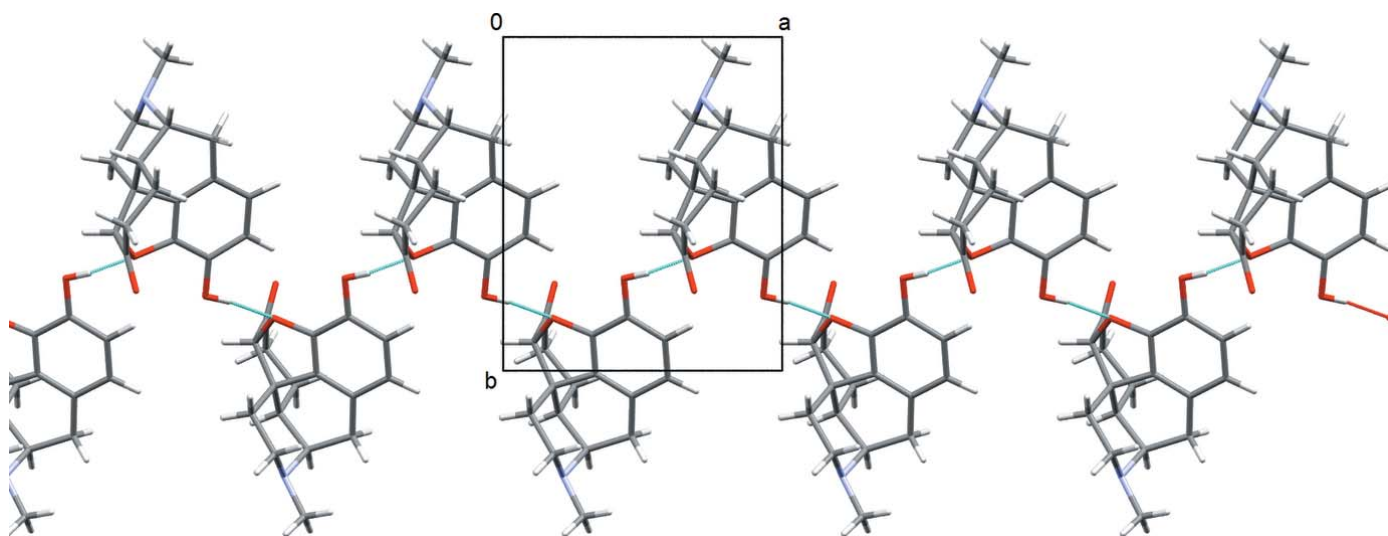


Figure 6
The zigzag chain of molecules running along the a axis formed by $O-H\cdots O$ hydrogen bonds in form II.

Table 3
Experimental details.

	(I)	(II)
Crystal data		
Chemical formula	C ₁₇ H ₁₉ NO ₃	C ₁₇ H ₁₉ NO ₃
<i>M_r</i>	285.33	285.33
Crystal system, space group	Orthorhombic, <i>P</i> 2 ₁ 2 ₁ 2 ₁	Orthorhombic, <i>P</i> 2 ₁ 2 ₁ 2 ₁
Temperature (K)	296	296
<i>a</i> , <i>b</i> , <i>c</i> (Å)	8.9497 (6), 11.0906 (6), 14.2608 (9)	8.8802 (6), 10.6208 (8), 14.4733 (9)
<i>V</i> (Å ³)	1415.49 (15)	1365.05 (16)
<i>Z</i>	4	4
Radiation type	Mo <i>K</i> α	Mo <i>K</i> α
μ (mm ⁻¹)	0.09	0.10
Crystal size (mm)	0.35 × 0.35 × 0.30	0.40 × 0.32 × 0.22
Data collection		
Diffractometer	Bruker KappaCCD	Bruker KappaCCD
Absorption correction	—	—
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	7054, 3427, 3088	15227, 4920, 4693
<i>R</i> _{int}	0.031	0.022
(sin θ/λ) _{max} (Å ⁻¹)	0.671	0.758
Refinement		
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.042, 0.096, 1.05	0.033, 0.095, 1.07
No. of reflections	3427	4920
No. of parameters	266	257
H-atom treatment	All H-atom parameters refined	H atoms treated by a mixture of independent and constrained refinement
Δρ _{max} , Δρ _{min} (e Å ⁻³)	0.19, -0.17	0.27, -0.12

Computer programs: COLLECT (Hooft, 1998), HKL DENZO and SCALEPACK (Otwinowski & Minor, 1997), SHELXT (Sheldrick, 2015a), SHELXL2014/7 (Sheldrick, 2015b), Mercury (Macrae et al., 2006) and enCIFer (Allen et al., 2004).

absence of significant anomalous scattering effects, Friedel pairs were merged. Crystal data, data collection and structure refinement details are summarized in Table 3.

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Computing details

For both compounds, data collection: *COLLECT* (Hooft, 1998). Cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997) for (I); *HKL SCALEPACK* (Otwinowski & Minor, 1997) for (II). Data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997) for (I); *HKL DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997) for (II). For both compounds, program(s) used to solve structure: *SHELXT* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2014/7* (Sheldrick, 2015b); molecular graphics: *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *enCIFer* (Allen *et al.*, 2004).

(I) (4*R*,4*aR*,7*aR*,12*bS*)-9-Hydroxy-3-methyl-1,2,4,4*a*,5,6,7*a*,13-octahydro-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-one]

Crystal data

C₁₇H₁₉NO₃

M_r = 285.33

Orthorhombic, *P*2₁2₁2₁

a = 8.9497 (6) Å

b = 11.0906 (6) Å

c = 14.2608 (9) Å

V = 1415.49 (15) Å³

Z = 4

F(000) = 608

D_x = 1.339 Mg m⁻³

Melting point < 549.8 K

Mo *Kα* radiation, λ = 0.71073 Å

Cell parameters from 9169 reflections

θ = 1.0–32.6°

μ = 0.09 mm⁻¹

T = 296 K

Prism, colorless

0.35 × 0.35 × 0.30 mm

Data collection

Bruker KappaCCD

diffractometer

Radiation source: fine-focus sealed tube

Horizontally mounted graphite crystal

monochromator

CCD scans

7054 measured reflections

3427 independent reflections

3088 reflections with *I* > 2σ(*I*)

*R*_{int} = 0.031

θ_{max} = 28.5°, θ_{min} = 3.4°

h = -11 → 11

k = -11 → 14

l = -17 → 19

Refinement

Refinement on *F*²

Least-squares matrix: full

R[*F*² > 2σ(*F*²)] = 0.042

wR(*F*²) = 0.096

S = 1.05

3427 reflections

266 parameters

0 restraints

Primary atom site location: difference Fourier map

Secondary atom site location: difference Fourier map

Hydrogen site location: difference Fourier map

All H-atom parameters refined

$$w = 1/[\sigma^2(F_o^2) + (0.0361P)^2 + 0.2726P]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.005$

$$\Delta\rho_{\max} = 0.19 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.17 \text{ e } \text{\AA}^{-3}$$

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.

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

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.91711 (18)	0.7664 (2)	0.17051 (12)	0.0513 (5)
H1A	0.993 (4)	0.774 (3)	0.213 (2)	0.069 (10)*
C2	0.7893 (2)	0.7337 (2)	0.21531 (15)	0.0337 (4)
C3	0.6543 (2)	0.73164 (19)	0.16755 (13)	0.0318 (4)
O4	0.63079 (17)	0.74990 (16)	0.07223 (10)	0.0409 (4)
C5	0.4813 (3)	0.7006 (2)	0.05538 (15)	0.0369 (5)
H5A	0.439 (3)	0.745 (2)	0.0007 (18)	0.034 (6)*
C6	0.4906 (3)	0.5664 (3)	0.03355 (16)	0.0455 (6)
O7	0.6063 (3)	0.5185 (2)	0.00966 (16)	0.0692 (6)
C8	0.3484 (4)	0.4980 (3)	0.0485 (2)	0.0555 (7)
H8A	0.362 (4)	0.413 (3)	0.031 (2)	0.073 (10)*
H8B	0.271 (4)	0.541 (3)	0.006 (2)	0.063 (9)*
C9	0.3038 (3)	0.5078 (2)	0.1523 (2)	0.0464 (6)
H9A	0.387 (4)	0.480 (3)	0.193 (2)	0.057 (8)*
H9B	0.220 (3)	0.455 (3)	0.166 (2)	0.055 (8)*
C10	0.2671 (2)	0.6384 (2)	0.17446 (16)	0.0334 (4)
H10A	0.175 (3)	0.660 (2)	0.1390 (16)	0.034 (6)*
C11	0.2315 (2)	0.6636 (2)	0.27875 (16)	0.0365 (5)
H11A	0.147 (3)	0.610 (2)	0.2993 (18)	0.043 (7)*
N12	0.1698 (2)	0.78799 (19)	0.28457 (13)	0.0381 (4)
C13	0.1274 (3)	0.8219 (3)	0.3807 (2)	0.0555 (7)
H13A	0.072 (4)	0.750 (3)	0.410 (2)	0.068 (9)*
H13B	0.216 (4)	0.844 (3)	0.417 (2)	0.054 (8)*
H13C	0.060 (4)	0.893 (3)	0.373 (2)	0.073 (10)*
C14	0.2738 (3)	0.8808 (2)	0.24843 (19)	0.0426 (6)
H14A	0.221 (3)	0.956 (3)	0.251 (2)	0.051 (8)*
H14B	0.359 (3)	0.888 (2)	0.291 (2)	0.046 (7)*
C15	0.3324 (3)	0.8528 (2)	0.15154 (17)	0.0377 (5)
H15A	0.251 (3)	0.862 (3)	0.105 (2)	0.048 (7)*
H15B	0.414 (3)	0.912 (2)	0.1341 (18)	0.043 (7)*
C16	0.3942 (2)	0.72389 (19)	0.14723 (13)	0.0291 (4)
C17	0.5225 (2)	0.70844 (19)	0.21381 (14)	0.0289 (4)
C18	0.5145 (2)	0.6740 (2)	0.30675 (14)	0.0315 (4)
C19	0.3642 (2)	0.6356 (3)	0.34492 (17)	0.0417 (5)
H19A	0.364 (3)	0.548 (3)	0.356 (2)	0.058 (9)*
H19B	0.341 (3)	0.672 (3)	0.406 (2)	0.058 (8)*

C20	0.6499 (2)	0.6686 (2)	0.35428 (14)	0.0335 (4)
H20A	0.655 (3)	0.640 (2)	0.4198 (18)	0.039 (6)*
C21	0.7821 (2)	0.6994 (2)	0.30952 (15)	0.0350 (5)
H21A	0.871 (3)	0.693 (2)	0.3430 (17)	0.038 (6)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0239 (8)	0.0907 (15)	0.0393 (9)	−0.0080 (8)	0.0014 (7)	0.0059 (9)
C2	0.0235 (9)	0.0427 (12)	0.0349 (10)	0.0002 (9)	0.0009 (8)	−0.0005 (9)
C3	0.0293 (10)	0.0393 (11)	0.0269 (9)	−0.0021 (8)	0.0004 (8)	0.0035 (8)
O4	0.0315 (8)	0.0656 (11)	0.0256 (7)	−0.0051 (7)	0.0000 (6)	0.0068 (7)
C5	0.0321 (10)	0.0511 (13)	0.0276 (9)	−0.0006 (10)	−0.0047 (9)	0.0035 (9)
C6	0.0490 (14)	0.0573 (15)	0.0301 (10)	0.0061 (12)	−0.0004 (11)	−0.0045 (10)
O7	0.0662 (14)	0.0728 (14)	0.0687 (14)	0.0171 (11)	0.0256 (11)	−0.0007 (11)
C8	0.0547 (16)	0.0505 (16)	0.0615 (17)	−0.0015 (14)	−0.0071 (14)	−0.0212 (14)
C9	0.0390 (13)	0.0362 (12)	0.0640 (16)	−0.0067 (10)	−0.0001 (12)	−0.0024 (11)
C10	0.0262 (9)	0.0360 (11)	0.0380 (11)	−0.0030 (8)	−0.0044 (9)	0.0015 (9)
C11	0.0257 (10)	0.0438 (12)	0.0398 (11)	−0.0059 (9)	0.0004 (9)	0.0046 (10)
N12	0.0266 (8)	0.0487 (11)	0.0389 (9)	−0.0015 (8)	0.0005 (8)	−0.0058 (8)
C13	0.0374 (13)	0.084 (2)	0.0448 (14)	−0.0071 (15)	0.0034 (12)	−0.0195 (14)
C14	0.0357 (12)	0.0383 (13)	0.0536 (14)	0.0002 (10)	0.0000 (11)	−0.0055 (10)
C15	0.0339 (11)	0.0353 (11)	0.0438 (12)	0.0003 (9)	−0.0037 (10)	0.0064 (9)
C16	0.0257 (9)	0.0340 (10)	0.0275 (9)	−0.0015 (8)	−0.0034 (8)	0.0024 (8)
C17	0.0247 (9)	0.0340 (10)	0.0281 (9)	−0.0015 (8)	−0.0033 (8)	0.0024 (8)
C18	0.0281 (9)	0.0391 (11)	0.0274 (9)	−0.0019 (8)	0.0000 (8)	0.0040 (8)
C19	0.0291 (11)	0.0599 (15)	0.0363 (12)	−0.0029 (10)	0.0027 (10)	0.0144 (11)
C20	0.0335 (11)	0.0414 (11)	0.0256 (9)	−0.0002 (9)	−0.0037 (8)	0.0035 (8)
C21	0.0260 (9)	0.0441 (12)	0.0350 (10)	−0.0003 (9)	−0.0074 (9)	−0.0006 (9)

Geometric parameters (Å, °)

O1—C2	1.360 (3)	C11—C19	1.548 (3)
O1—H1A	0.91 (4)	C11—H11A	1.01 (3)
C2—C3	1.387 (3)	N12—C13	1.472 (3)
C2—C21	1.398 (3)	N12—C14	1.480 (3)
C3—C17	1.376 (3)	C13—H13A	1.03 (4)
C3—O4	1.390 (2)	C13—H13B	0.98 (3)
O4—C5	1.465 (3)	C13—H13C	1.00 (4)
C5—C6	1.523 (4)	C14—C15	1.510 (3)
C5—C16	1.546 (3)	C14—H14A	0.96 (3)
C5—H5A	1.00 (3)	C14—H14B	0.98 (3)
C6—O7	1.212 (3)	C15—C16	1.534 (3)
C6—C8	1.498 (4)	C15—H15A	0.99 (3)
C8—C9	1.537 (4)	C15—H15B	1.01 (3)
C8—H8A	0.99 (3)	C16—C17	1.500 (3)
C8—H8B	1.03 (3)	C17—C18	1.381 (3)
C9—C10	1.519 (3)	C18—C20	1.390 (3)

C9—H9A	1.00 (3)	C18—C19	1.512 (3)
C9—H9B	0.97 (3)	C19—H19A	0.99 (3)
C10—C16	1.531 (3)	C19—H19B	0.98 (3)
C10—C11	1.546 (3)	C20—C21	1.387 (3)
C10—H10A	1.00 (2)	C20—H20A	0.99 (3)
C11—N12	1.488 (3)	C21—H21A	0.93 (3)
C2—O1—H1A	110 (2)	C14—N12—C11	113.08 (18)
O1—C2—C3	120.43 (18)	N12—C13—H13A	108.1 (19)
O1—C2—C21	124.26 (19)	N12—C13—H13B	110.6 (17)
C3—C2—C21	115.31 (18)	H13A—C13—H13B	111 (3)
C17—C3—C2	120.96 (17)	N12—C13—H13C	105 (2)
C17—C3—O4	111.48 (17)	H13A—C13—H13C	111 (3)
C2—C3—O4	127.56 (18)	H13B—C13—H13C	110 (3)
C3—O4—C5	104.13 (15)	N12—C14—C15	113.2 (2)
O4—C5—C6	110.4 (2)	N12—C14—H14A	106.6 (17)
O4—C5—C16	105.03 (16)	C15—C14—H14A	112.8 (17)
C6—C5—C16	111.35 (19)	N12—C14—H14B	109.2 (16)
O4—C5—H5A	106.7 (14)	C15—C14—H14B	108.4 (16)
C6—C5—H5A	110.2 (14)	H14A—C14—H14B	106 (2)
C16—C5—H5A	113.0 (14)	C14—C15—C16	110.72 (18)
O7—C6—C8	122.9 (3)	C14—C15—H15A	109.5 (16)
O7—C6—C5	122.2 (3)	C16—C15—H15A	109.6 (17)
C8—C6—C5	114.8 (2)	C14—C15—H15B	110.0 (15)
C6—C8—C9	108.8 (2)	C16—C15—H15B	109.6 (15)
C6—C8—H8A	110 (2)	H15A—C15—H15B	107 (2)
C9—C8—H8A	110 (2)	C17—C16—C10	109.73 (16)
C6—C8—H8B	104.6 (18)	C17—C16—C15	110.92 (17)
C9—C8—H8B	110.7 (18)	C10—C16—C15	107.40 (17)
H8A—C8—H8B	112 (3)	C17—C16—C5	97.53 (16)
C10—C9—C8	108.9 (2)	C10—C16—C5	119.10 (18)
C10—C9—H9A	109.6 (18)	C15—C16—C5	111.80 (17)
C8—C9—H9A	110.5 (18)	C3—C17—C18	123.80 (18)
C10—C9—H9B	111.4 (18)	C3—C17—C16	109.37 (17)
C8—C9—H9B	110.3 (18)	C18—C17—C16	126.82 (18)
H9A—C9—H9B	106 (2)	C17—C18—C20	115.76 (18)
C9—C10—C16	112.16 (19)	C17—C18—C19	118.01 (18)
C9—C10—C11	114.6 (2)	C20—C18—C19	125.99 (18)
C16—C10—C11	106.56 (17)	C18—C19—C11	113.97 (18)
C9—C10—H10A	107.5 (14)	C18—C19—H19A	109.8 (18)
C16—C10—H10A	109.8 (14)	C11—C19—H19A	107.0 (18)
C11—C10—H10A	106.0 (14)	C18—C19—H19B	113.1 (19)
N12—C11—C10	107.31 (18)	C11—C19—H19B	107.2 (18)
N12—C11—C19	115.9 (2)	H19A—C19—H19B	105 (2)
C10—C11—C19	113.08 (19)	C21—C20—C18	120.57 (18)
N12—C11—H11A	104.9 (15)	C21—C20—H20A	118.2 (16)
C10—C11—H11A	109.1 (15)	C18—C20—H20A	121.2 (16)
C19—C11—H11A	106.1 (15)	C20—C21—C2	123.27 (19)

C13—N12—C14	108.0 (2)	C20—C21—H21A	118.1 (15)
C13—N12—C11	112.6 (2)	C2—C21—H21A	118.5 (15)
C10—C11—N12—C13	178.5 (2)		

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>
O1—H1A...N12 ⁱ	0.91 (4)	1.89 (4)	2.796 (3)	171 (3)

Symmetry code: (i) $x+1, y, z$.**(II) (4R,4aR,7aR,12bS)-9-hydroxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro[3,2-*e*]isoquinoline-7-one***Crystal data*

$C_{17}H_{19}NO_3$	$D_x = 1.388 \text{ Mg m}^{-3}$
$M_r = 285.33$	Melting point < 550.2 K
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
$a = 8.8802 (6) \text{ \AA}$	Cell parameters from 7368 reflections
$b = 10.6208 (8) \text{ \AA}$	$\theta = 0.4\text{--}32.6^\circ$
$c = 14.4733 (9) \text{ \AA}$	$\mu = 0.10 \text{ mm}^{-1}$
$V = 1365.05 (16) \text{ \AA}^3$	$T = 296 \text{ K}$
$Z = 4$	Block, colorless
$F(000) = 608$	$0.40 \times 0.32 \times 0.22 \text{ mm}$

Data collection

Bruker KappaCCD diffractometer	4920 independent reflections
Radiation source: fine-focus sealed tube	4693 reflections with $I > 2\sigma(I)$
Horizontally mounted graphite crystal monochromator	$R_{\text{int}} = 0.022$
CCD scans	$\theta_{\text{max}} = 32.6^\circ$, $\theta_{\text{min}} = 3.8^\circ$
15227 measured reflections	$h = -13 \rightarrow 13$
	$k = -16 \rightarrow 16$
	$l = -21 \rightarrow 16$

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: mixed
$R[F^2 > 2\sigma(F^2)] = 0.033$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.095$	$w = 1/[\sigma^2(F_o^2) + (0.0623P)^2 + 0.0509P]$
$S = 1.07$	where $P = (F_o^2 + 2F_c^2)/3$
4920 reflections	$(\Delta/\sigma)_{\text{max}} = 0.011$
257 parameters	$\Delta\rho_{\text{max}} = 0.27 \text{ e \AA}^{-3}$
0 restraints	$\Delta\rho_{\text{min}} = -0.12 \text{ e \AA}^{-3}$
Primary atom site location: difference Fourier map	

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.

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

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.93240 (13)	0.77706 (10)	0.49050 (9)	0.0470 (3)
H1	1.015 (3)	0.792 (2)	0.517 (2)	0.069 (8)*
C2	0.94522 (14)	0.66225 (11)	0.44868 (8)	0.0314 (2)
C3	0.82077 (12)	0.60798 (11)	0.40680 (7)	0.02819 (19)
O4	0.67658 (10)	0.65856 (9)	0.39772 (7)	0.03425 (18)
C5	0.60923 (12)	0.58599 (11)	0.32226 (8)	0.0299 (2)
H5	0.500 (2)	0.586 (2)	0.3283 (14)	0.039 (4)*
C6	0.64963 (14)	0.64991 (13)	0.23020 (10)	0.0362 (2)
O7	0.68419 (15)	0.76008 (11)	0.22794 (10)	0.0516 (3)
C8	0.6488 (2)	0.56607 (16)	0.14696 (10)	0.0455 (3)
H8A	0.549 (3)	0.528 (2)	0.1420 (15)	0.048 (5)*
H8B	0.681 (3)	0.615 (2)	0.0937 (18)	0.058 (6)*
C9	0.75507 (16)	0.45421 (14)	0.16230 (8)	0.0366 (3)
H9A	0.856 (2)	0.486 (2)	0.1784 (15)	0.048 (5)*
H9B	0.759 (3)	0.396 (3)	0.1098 (19)	0.065 (7)*
C10	0.69690 (13)	0.37489 (11)	0.24255 (7)	0.0289 (2)
H10	0.601 (2)	0.3431 (18)	0.2251 (13)	0.035 (4)*
C11	0.79909 (14)	0.26306 (11)	0.26841 (8)	0.0322 (2)
H11	0.810 (2)	0.2131 (17)	0.2157 (12)	0.033 (4)*
N12	0.71416 (14)	0.18458 (10)	0.33458 (8)	0.0359 (2)
C13	0.7868 (2)	0.06280 (15)	0.35203 (14)	0.0513 (4)
H13A	0.8072	0.0217	0.2943	0.075 (8)*
H13B	0.8796	0.0760	0.3847	0.090 (9)*
H13C	0.7212	0.0110	0.3885	0.081 (8)*
C14	0.68139 (17)	0.24994 (12)	0.42125 (9)	0.0367 (2)
H14A	0.617 (3)	0.1946 (18)	0.4586 (14)	0.044 (5)*
H14B	0.769 (3)	0.2710 (19)	0.4580 (15)	0.046 (5)*
C15	0.59734 (14)	0.37270 (12)	0.40416 (8)	0.0323 (2)
H15A	0.496 (2)	0.3593 (17)	0.3840 (13)	0.034 (4)*
H15B	0.592 (2)	0.4201 (18)	0.4616 (15)	0.044 (5)*
C16	0.67804 (11)	0.45335 (10)	0.33092 (7)	0.02580 (18)
C17	0.83077 (12)	0.49110 (10)	0.36541 (7)	0.02626 (19)
C18	0.96269 (12)	0.42399 (11)	0.35670 (8)	0.02859 (19)
C19	0.95925 (15)	0.30434 (12)	0.30011 (10)	0.0356 (2)
H19A	1.020 (3)	0.318 (2)	0.2452 (17)	0.055 (6)*
H19B	1.006 (3)	0.233 (3)	0.3363 (19)	0.071 (7)*
C20	1.09004 (13)	0.47869 (12)	0.39737 (8)	0.0325 (2)
H20	1.191 (2)	0.4392 (19)	0.3896 (13)	0.039 (4)*
C21	1.07953 (14)	0.59403 (12)	0.44358 (8)	0.0334 (2)
H21	1.170 (2)	0.6333 (17)	0.4688 (15)	0.043 (5)*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0399 (5)	0.0442 (5)	0.0569 (6)	-0.0038 (4)	-0.0079 (5)	-0.0219 (5)

C2	0.0304 (5)	0.0351 (5)	0.0289 (5)	-0.0049 (4)	-0.0020 (4)	-0.0040 (4)
C3	0.0249 (4)	0.0316 (5)	0.0281 (4)	-0.0005 (4)	0.0002 (4)	-0.0050 (4)
O4	0.0277 (4)	0.0350 (4)	0.0400 (4)	0.0037 (3)	-0.0007 (3)	-0.0119 (3)
C5	0.0232 (4)	0.0327 (5)	0.0337 (5)	0.0021 (3)	-0.0005 (4)	-0.0050 (4)
C6	0.0263 (5)	0.0402 (6)	0.0421 (6)	0.0046 (4)	-0.0030 (4)	0.0064 (5)
O7	0.0452 (6)	0.0432 (6)	0.0663 (7)	-0.0039 (5)	-0.0079 (5)	0.0138 (5)
C8	0.0511 (8)	0.0538 (8)	0.0316 (5)	0.0087 (7)	-0.0034 (5)	0.0080 (5)
C9	0.0400 (6)	0.0445 (6)	0.0254 (4)	0.0030 (5)	0.0035 (4)	-0.0002 (4)
C10	0.0285 (5)	0.0334 (5)	0.0248 (4)	-0.0008 (4)	0.0007 (3)	-0.0048 (3)
C11	0.0352 (5)	0.0305 (5)	0.0310 (5)	0.0001 (4)	0.0044 (4)	-0.0064 (4)
N12	0.0415 (6)	0.0285 (4)	0.0378 (5)	-0.0021 (4)	0.0036 (4)	-0.0025 (4)
C13	0.0601 (10)	0.0338 (6)	0.0602 (9)	0.0061 (6)	0.0052 (7)	0.0034 (6)
C14	0.0438 (6)	0.0357 (6)	0.0306 (5)	-0.0041 (5)	0.0038 (5)	0.0024 (4)
C15	0.0314 (5)	0.0369 (5)	0.0285 (4)	-0.0044 (4)	0.0065 (4)	-0.0038 (4)
C16	0.0228 (4)	0.0295 (4)	0.0251 (4)	-0.0013 (3)	0.0012 (3)	-0.0042 (3)
C17	0.0237 (4)	0.0291 (4)	0.0260 (4)	-0.0012 (3)	-0.0001 (3)	-0.0029 (3)
C18	0.0248 (4)	0.0308 (5)	0.0301 (4)	0.0018 (4)	0.0008 (3)	0.0003 (4)
C19	0.0296 (5)	0.0331 (5)	0.0441 (6)	0.0039 (4)	0.0046 (5)	-0.0060 (4)
C20	0.0240 (4)	0.0387 (5)	0.0350 (5)	0.0014 (4)	-0.0020 (4)	0.0045 (4)
C21	0.0272 (5)	0.0412 (6)	0.0320 (5)	-0.0054 (4)	-0.0056 (4)	0.0014 (4)

Geometric parameters (Å, °)

O1—C2	1.3660 (15)	C11—C19	1.5574 (18)
O1—H1	0.84 (3)	C11—H11	0.934 (17)
C2—C3	1.3860 (15)	N12—C14	1.4629 (17)
C2—C21	1.3975 (18)	N12—C13	1.467 (2)
C3—C17	1.3813 (14)	C13—H13A	0.9600
C3—O4	1.3948 (14)	C13—H13B	0.9600
O4—C5	1.4643 (14)	C13—H13C	0.9600
C5—C6	1.5379 (18)	C14—C15	1.5225 (19)
C5—C16	1.5407 (16)	C14—H14A	0.98 (2)
C5—H5	0.98 (2)	C14—H14B	0.97 (2)
C6—O7	1.2101 (18)	C15—C16	1.5398 (15)
C6—C8	1.498 (2)	C15—H15A	0.958 (19)
C8—C9	1.533 (2)	C15—H15B	0.97 (2)
C8—H8A	0.97 (2)	C16—C17	1.4998 (14)
C8—H8B	0.97 (2)	C17—C18	1.3770 (15)
C9—C10	1.5249 (17)	C18—C20	1.4010 (16)
C9—H9A	0.98 (2)	C18—C19	1.5122 (16)
C9—H9B	0.98 (3)	C19—H19A	0.97 (2)
C10—C16	1.5356 (14)	C19—H19B	1.01 (3)
C10—C11	1.5409 (17)	C20—C21	1.3988 (18)
C10—H10	0.954 (19)	C20—H20	1.00 (2)
C11—N12	1.4767 (16)	C21—H21	0.98 (2)
C2—O1—H1	107.5 (18)	C13—N12—C11	112.62 (12)
O1—C2—C3	119.90 (11)	N12—C13—H13A	109.5

O1—C2—C21	123.87 (11)	N12—C13—H13B	109.5
C3—C2—C21	116.22 (10)	H13A—C13—H13B	109.5
C17—C3—C2	120.81 (11)	N12—C13—H13C	109.5
C17—C3—O4	111.37 (9)	H13A—C13—H13C	109.5
C2—C3—O4	127.81 (10)	H13B—C13—H13C	109.5
C3—O4—C5	104.03 (8)	N12—C14—C15	111.38 (10)
O4—C5—C6	108.58 (10)	N12—C14—H14A	107.6 (12)
O4—C5—C16	104.99 (9)	C15—C14—H14A	108.4 (12)
C6—C5—C16	112.43 (9)	N12—C14—H14B	114.9 (13)
O4—C5—H5	109.9 (12)	C15—C14—H14B	106.6 (12)
C6—C5—H5	108.1 (12)	H14A—C14—H14B	107.7 (17)
C16—C5—H5	112.8 (13)	C14—C15—C16	111.10 (10)
O7—C6—C8	123.66 (14)	C14—C15—H15A	112.6 (11)
O7—C6—C5	120.62 (14)	C16—C15—H15A	108.1 (11)
C8—C6—C5	115.67 (11)	C14—C15—H15B	109.2 (12)
C6—C8—C9	109.94 (11)	C16—C15—H15B	108.9 (12)
C6—C8—H8A	107.9 (13)	H15A—C15—H15B	106.8 (17)
C9—C8—H8A	104.6 (13)	C17—C16—C10	108.88 (9)
C6—C8—H8B	108.7 (15)	C17—C16—C15	109.91 (9)
C9—C8—H8B	110.4 (15)	C10—C16—C15	108.80 (9)
H8A—C8—H8B	115 (2)	C17—C16—C5	98.12 (8)
C10—C9—C8	109.26 (11)	C10—C16—C5	118.14 (9)
C10—C9—H9A	108.6 (13)	C15—C16—C5	112.34 (9)
C8—C9—H9A	109.0 (13)	C18—C17—C3	124.03 (10)
C10—C9—H9B	104.8 (15)	C18—C17—C16	126.91 (10)
C8—C9—H9B	113.6 (16)	C3—C17—C16	109.05 (9)
H9A—C9—H9B	111.5 (19)	C17—C18—C20	115.70 (10)
C9—C10—C16	111.81 (10)	C17—C18—C19	117.86 (10)
C9—C10—C11	114.29 (10)	C20—C18—C19	126.32 (10)
C16—C10—C11	106.27 (9)	C18—C19—C11	114.49 (9)
C9—C10—H10	107.3 (11)	C18—C19—H19A	107.6 (14)
C16—C10—H10	108.4 (11)	C11—C19—H19A	108.1 (15)
C11—C10—H10	108.6 (12)	C18—C19—H19B	110.0 (16)
N12—C11—C10	106.97 (10)	C11—C19—H19B	108.4 (16)
N12—C11—C19	115.74 (11)	H19A—C19—H19B	108 (2)
C10—C11—C19	113.10 (9)	C21—C20—C18	120.67 (11)
N12—C11—H11	105.2 (11)	C21—C20—H20	118.9 (12)
C10—C11—H11	107.5 (11)	C18—C20—H20	120.3 (12)
C19—C11—H11	107.8 (12)	C2—C21—C20	122.43 (11)
C14—N12—C13	110.99 (12)	C2—C21—H21	117.6 (11)
C14—N12—C11	112.94 (9)	C20—C21—H21	119.8 (12)
C10—C11—N12—C13	169.5 (2)		

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
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O1—H1 \cdots O4 ⁱ	0.84 (3)	1.96 (3)	2.791 (2)	167 (3)
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Symmetry code: (i) $x+1/2, -y+3/2, -z+1$.