



Cocaethylene, the *in vivo* product of cocaine and ethanol, is a narcotic more potent than its precursors

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Received 3 August 2017

Accepted 7 September 2017

Edited by E. Y. Cheung, Amgen Inc., USA

Keywords: crystal structure; cocaethylene; cocaine; narcotic; conformation; transesterification; benzoylecgonine ester.

CCDC reference: 1573265

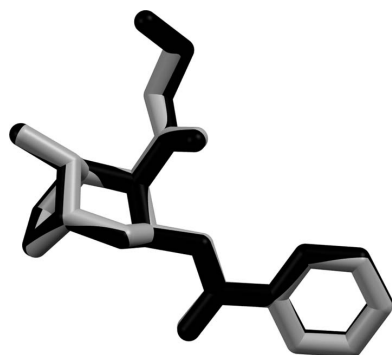
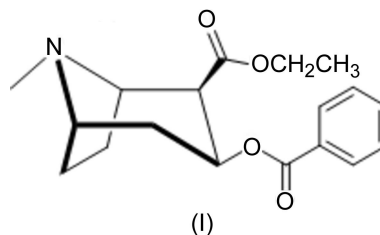
Supporting information: this article has supporting information at journals.iucr.org/c

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The molecular conformation and supramolecular architecture of cocaethylene [systematic name: ethyl (1*R*,2*R*,3*S*,5*S*)-3-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate], C₁₈H₂₃NO₄, have been determined for the first time. Cocaethylene is a narcotic produced *in vivo* when cocaine and ethanol are administered concomitantly. The intra- and intermolecular features of cocaethylene and its less potent narcotic precursor cocaine are very similar. The only molecular difference is in the conformation of the methyl group of the ethoxycarbonyl group. Similar to cocaine, the carboxylate atoms and the α -C atom are coplanar in cocaethylene, but the methyl C atom of the ethyl group is bent by *ca* 90° away from this plane in the narcotic reported here. The main supramolecular motif is a one-dimensional chain stabilized by weak C—H···O contacts.

1. Introduction

Psychoactive substances are able to cross the blood–brain barrier. When they reach the brain, they can establish their effects on the central nervous system (CNS). Abused drugs, whether illegal or prescribed legally, can produce different effects on the user according to the type of action promoted by them in the CNS. They may be CNS-depressing drugs (alcohol, cannabis, opiates, inhalers), CNS-stimulating drugs (cocaine, tobacco, amphetamines, methylphenidate) or hallucinogenic drugs (LSD, mescaline, phencyclidine). However, as varied as their effects and activation sites may seem, they all present a common denominator, *i.e.* they directly or indirectly modulate the action of dopaminergic neurotransmitters in the limbic mesocortical system (Koob & Volkow, 2009).



Cocaine is a strong inhibitor of dopamine uptake in this system. The inhibition produced by cocaine increases dopamine levels in the synaptic cleft and stimulates the nucleus accumbens, producing a pleasant and rewarding sensation (Ritz *et al.*, 1987). Since the early 2000s, an increase in the use of crack cocaine has been observed, mainly among street-involved populations (Werb *et al.*, 2010). Despite the fact that

the use of cocaine/crack, two illegal drugs, is much less than that of legal drugs such as nicotine and alcohol, its social impact is disproportionately high. Continuous use of the drug drives the individual to develop social incapacitation, followed by serious physical and psychological problems, such as cardiac arrhythmia, stroke, heart attack, difficulty breathing, hallucinations and paranoia (Kauer & Malenka, 2007).

Most individuals who use cocaine or crack also use ethanol. From the perspective of the user, concomitant cocaine and ethanol use has the effect of enhancing and prolonging the euphoria associated with cocaine while ameliorating the unwanted agitation and paranoia. In addition, low levels of ethanol and cocaine have been found to have a synergistic effect that surpasses the pleasant state felt as a result of using either one alone (McCance-Katz *et al.*, 1993). This is due to the fact that the concomitant use of cocaine and ethanol produces another psychoactive substance known as cocaethylene, which has pharmacological properties similar to those of cocaine but which has a plasma half-life three to five times longer than that of cocaine (Jatlow, 1993). From a synthetic point of view, cocaethylene is the ethyl ester of benzoylecgonine, obtained by a transesterification reaction between cocaine and ethanol.

Cocaethylene has an elimination half-life of 150 min (compared with approximately 90 min for cocaine), which explains the prolonged euphoric effects reported after use of cocaine and ethanol together (Boghdadi *et al.*, 1997). Both drugs increase heart rate and systolic blood pressure, but cocaethylene tends to have a greater effect on blood pressure (McCance *et al.*, 1995). The increased cardiovascular effects of cocaethylene contribute to the high mortality reported in chronic cocaine users (Farre *et al.*, 1993).

Despite the toxicological and social impact of cocaethylene, its molecular conformation and supramolecular architecture are unknown thus far. Here, we fill this gap through the first single-crystal structure determination of cocaethylene, (I), which is an even more potent narcotic than its precursor cocaine. The knowledge derived from this study will be useful

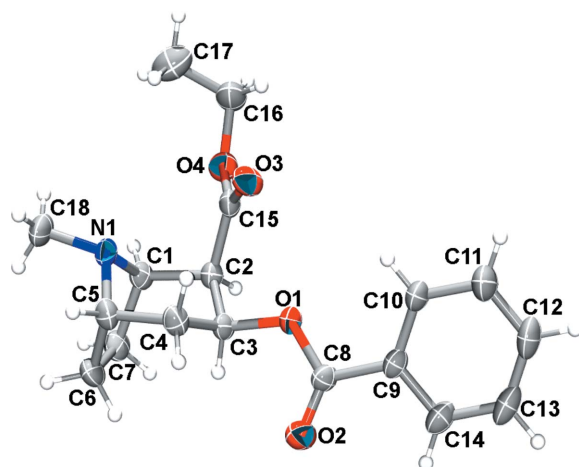


Figure 1
The molecular structure of cocaethylene, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

Table 1
Experimental details.

Crystal data	
Chemical formula	C ₁₈ H ₂₃ NO ₄
<i>M_r</i>	317.37
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	296
<i>a</i> , <i>b</i> , <i>c</i> (Å)	8.4533 (2), 10.2380 (3), 10.2552 (2)
β (°)	107.881 (1)
<i>V</i> (Å ³)	844.66 (4)
<i>Z</i>	2
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	0.72
Crystal size (mm)	0.35 × 0.15 × 0.10
Data collection	
Diffractometer	Bruker APEXII CCD area detector
Absorption correction	Multi-scan (<i>SADABS</i> ; Krause <i>et al.</i> , 2015)
<i>T_{min}</i> , <i>T_{max}</i>	0.725, 0.931
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	3969, 2133, 2026
<i>R_{int}</i>	0.024
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.595
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.036, 0.101, 1.03
No. of reflections	2133
No. of parameters	208
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å ⁻³)	0.15, -0.17
Absolute structure	Flack <i>x</i> parameter determined using 568 quotients [(<i>I</i> ⁺) - (<i>I</i> ⁻)] / [(<i>I</i> ⁺) + (<i>I</i> ⁻)] (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	-0.03 (14)

Computer programs: *APEX2* (Bruker, 2003), *SAINT* (Bruker, 2003), *SIR92* (Altomare *et al.*, 1993), *SHELXL2014* (Sheldrick, 2015), *ORTEP-3 for Windows* (Farrugia, 2012), *Mercury* (Macrae *et al.*, 2006) and *WinGX* (Farrugia, 2012).

for understanding the psychoactive profile of cocaethylene and for providing an analytical pattern for narcotic control purposes.

2. Experimental

2.1. Synthesis and crystallization

Cocaethylene was synthesized following the protocol available in the literature (Everhart *et al.*, 1999). Benzoylcocaine (500 mg), previously synthesized according to the methodology described by Findlay (1954), was stirred together with oxalyl chloride (2.5 ml) for 20 min at room temperature. Next, the mixture was cooled to 273 K prior to the dropwise addition of ethanol (5 ml). After complete addition of ethanol at 273 K, the mixture was again stirred at room temperature for 12 h. The residual solvent was then withdrawn under reduced pressure in a rotary evaporator and the obtained product was dissolved in acidified water (2 ml of water and 0.1 ml of H₂SO₄). This solution was then mixed together with a mixture of diethyl ether (4 ml) and saturated ammonium hydroxide aqueous solution (0.5 ml). The remaining aqueous phase was washed twice with diethyl ether (5 ml). The organic phases were pooled and then subjected to silica-gel column

chromatography (10:10:1 *v/v/v* ethyl acetate–hexane–triethylamine as eluent). After purification, cocaethylene was obtained as a white solid. Finally, this was dissolved in a mixture of dichloromethane and acetone (1:10 *v/v*) and allowed to evaporate slowly at 281 K, yielding acicular crystals of (I) suitable for crystal structure determination. The reaction yield was 60%.

2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. All C-bound H atoms were positioned geometrically and refined using a riding model, with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for methyl H atoms and $1.2U_{\text{eq}}(\text{C})$ otherwise. The C–H distances were fixed for CH, CH₂ and CH₃ groups at 0.98, 0.97 and 0.96 Å, respectively, and for aromatic groups at 0.93 Å.

3. Results and discussion

Cocaethylene is present with the fused six- and five-membered rings in chair and envelope conformations, respectively. According to the atom labels shown in Fig. 1, atoms C1, C2, C4 and C5 form the chair seat [r.m.s. deviation = 0.0194 Å; the atom with the greatest deviation from the plane is C5 by 0.011 (3) Å], while the legs (C3) and back (N1) deviate by –0.596 (3) and 0.8641 (19) Å, respectively, from the least-squares plane calculated for the seat. For the envelope-shaped five-membered ring, atom N1 at the flap deviates by 0.6297 (19) Å from the least-squares plane calculated for atoms C1, C5, C6 and C7 [r.m.s. deviation = 0.0115 Å; the atom with the greatest deviation from the plane is C6 by 0.008 (3) Å].

All C (C8–C14) and O atoms (O1 and O2) of the benzoate group are coplanar [r.m.s. deviation = 0.126 Å; the atom with the greatest deviation from the plane is O2 by –0.144 (3) Å], and this plane forms an angle of 70.61 (8)° with the least-squares plane calculated for the chair seat. In addition, the benzoate group adopts an *anti* conformation relative to the tropane N atom, with its carbonyl O2 atom and atom N1 projecting towards opposite sides of the chair seat. The dihedral angle between the plane formed by atoms N1, C3 and

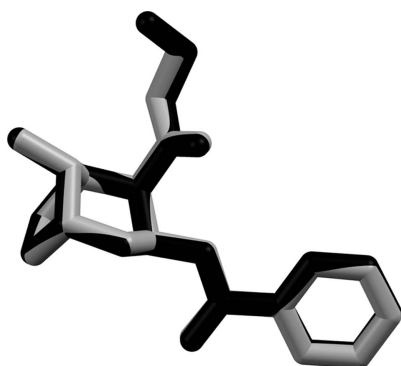


Figure 2
A molecular superposition of cocaine (grey) and cocaethylene (black). H atoms have been omitted for clarity.

Table 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>
C6–H6 <i>B</i> ···O3 ⁱ	0.97	2.71	3.618 (3)	157

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

O1 and that formed by atoms C3, O1 and C8 [160.5 (2)°] describes this conformation.

While the benzoate atoms are coplanar, the ethoxycarbonyl group is not planar. Similar to cocaine, atoms O3, C15, O4 and C16 are essentially coplanar [r.m.s. deviation = 0.0431 Å; the atom with the greatest deviation from the plane is C15 by –0.028 (3) Å] in cocaethylene. However, the methyl C atom of the ethyl group is bent by *ca* 90° away from this plane [C15–O4–C16–C17 = –90.5 (4)°], lying above the tropane nucleus. Still concerning the ethyl ester group, the least-squares plane crossing through the coplanar atoms defined above forms an angle of 74.98 (12)° with the chair seat least-squares plane. This carbonyl O atom is also projected onto the tropane nucleus, more precisely on the C2–C3 bond [C3–C2–C15–O2 = –6.0 (4)°].

Except for the conformational preference of the terminal CH₃ group of the ethyl chain, all these intramolecular features are also observed in cocaine. Indeed, cocaethylene is isostructural with cocaine [Cambridge Structural Database

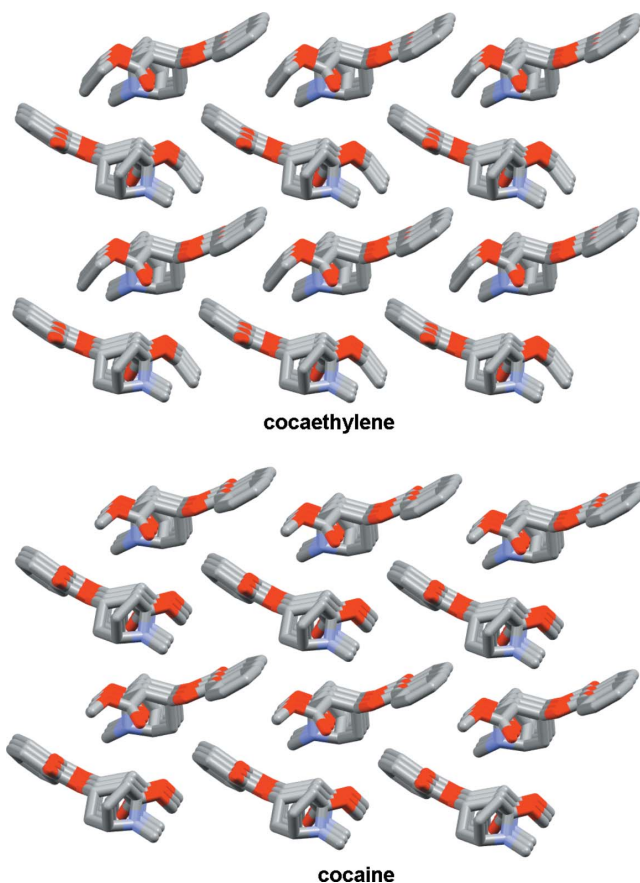


Figure 3
General packing views of cocaine and cocaethylene.

(Groom *et al.*, 2016) refcode COCAIN10; Hrynchuk *et al.*, 1983]. Their conformations are similar (Fig. 2), with an r.m.s. deviation of their corresponding non-H atoms of 0.0941 Å and with the largest atom distance being 0.198 Å for C16. Such a conformational similarity is in agreement with the same macromolecular biological target binding pattern for both narcotics, culminating in equivalent psychoactivities from a pharmacodynamic point of view. Even their crystal packings are similar (Fig. 3), which also explains the similar narcotic delivery from the solid state.

For the cocaethylene structure, the main supramolecular motif is a one-dimensional chain stabilized by weak C—H...O contacts. This chain is made up of translation symmetry-related molecules joined together through C6—H6B...O3ⁱ hydrogen bonds along the [100] direction (Fig. 4 and Table 2). Notably, several weaker contacts, such as H...H contacts, contribute to the crystal packing of this psychotropic agent.

Acknowledgements

The authors acknowledge CNPq, CAPES and FAPEG for financial support and research fellowships (to FTM and ADF).

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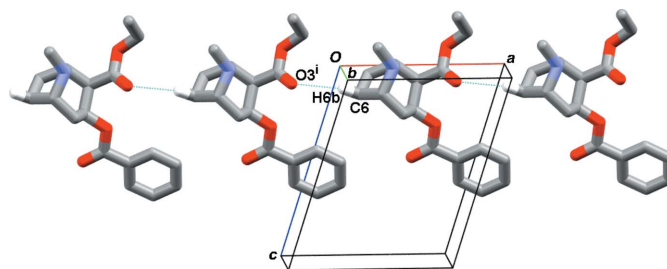


Figure 4

The infinite one-dimensional chain of cocaethylene. The C—H...O contacts are shown as dotted blue lines. [Symmetry code: (i) $x - 1, y, z$.]

supporting information

Acta Cryst. (2017). **C73**, 780-783 [https://doi.org/10.1107/S2053229617012852]

Cocaethylene, the *in vivo* product of cocaine and ethanol, is a narcotic more potent than its precursors

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Computing details

Data collection: *APEX2* (Bruker, 2003); cell refinement: *S SAINT* (Bruker, 2003); data reduction: *S SAINT* (Bruker, 2003); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997), *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *WinGX* publication routines (Farrugia, 1999).

ethyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate

Crystal data

$C_{18}H_{23}NO_4$

$M_r = 317.37$

Monoclinic, $P2_1$

$a = 8.4533$ (2) Å

$b = 10.2380$ (3) Å

$c = 10.2552$ (2) Å

$\beta = 107.881$ (1)°

$V = 844.66$ (4) Å³

$Z = 2$

$F(000) = 340$

$D_x = 1.248$ Mg m⁻³

Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å

Cell parameters from 2631 reflections

$\theta = 6.0$ – 66.1 °

$\mu = 0.72$ mm⁻¹

$T = 296$ K

Needle, colourless

$0.35 \times 0.15 \times 0.10$ mm

Data collection

Bruker APEXII CCD area-detector diffractometer

CCD scans

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

$T_{\min} = 0.725$, $T_{\max} = 0.931$

3969 measured reflections

2133 independent reflections

2026 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.024$

$\theta_{\max} = 66.5$ °, $\theta_{\min} = 6.0$ °

$h = -9 \rightarrow 9$

$k = -9 \rightarrow 12$

$l = -12 \rightarrow 11$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.036$

$wR(F^2) = 0.101$

$S = 1.03$

2133 reflections

208 parameters

1 restraint

Hydrogen site location: inferred from neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0631P)^2 + 0.0701P]$

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

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

$\Delta\rho_{\max} = 0.15$ e Å⁻³

$\Delta\rho_{\min} = -0.17$ e Å⁻³

Absolute structure: Flack x parameter
determined using 568 quotients
[(I+)-(I-)]/[(I+)+(I-)] (Parsons *et al.*, 2013).
Absolute structure parameter: -0.03 (14)

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>	$U_{\text{iso}}^*/U_{\text{eq}}$
O4	0.5751 (2)	0.4990 (2)	-0.13426 (17)	0.0664 (6)
O1	0.65669 (18)	0.5018 (2)	0.27718 (16)	0.0563 (5)
O3	0.6899 (2)	0.6327 (3)	0.0426 (2)	0.0703 (6)
N1	0.2831 (2)	0.6666 (2)	-0.0355 (2)	0.0519 (5)
C17	0.5764 (6)	0.6617 (5)	-0.2996 (4)	0.1061 (14)
H17A	0.642	0.6992	-0.3516	0.159*
H17B	0.4754	0.627	-0.3609	0.159*
H17C	0.5503	0.7277	-0.243	0.159*
C16	0.6698 (4)	0.5572 (5)	-0.2134 (3)	0.0863 (12)
H16A	0.6977	0.4911	-0.2705	0.104*
H16B	0.7727	0.592	-0.1524	0.104*
C15	0.5920 (3)	0.5498 (3)	-0.0097 (2)	0.0500 (6)
C2	0.4677 (3)	0.4846 (3)	0.0482 (2)	0.0467 (5)
H2	0.4796	0.3896	0.0436	0.056*
C3	0.4847 (3)	0.5233 (3)	0.1952 (2)	0.0487 (6)
H3	0.4143	0.4648	0.2291	0.058*
C8	0.6854 (3)	0.4519 (3)	0.4018 (2)	0.0523 (6)
C9	0.8662 (3)	0.4243 (3)	0.4680 (2)	0.0507 (6)
C14	0.9159 (4)	0.3499 (3)	0.5864 (3)	0.0677 (8)
H14	0.837	0.3186	0.625	0.081*
C13	1.0819 (5)	0.3221 (4)	0.6474 (3)	0.0780 (9)
H13	1.1148	0.271	0.7261	0.094*
C12	1.1978 (4)	0.3697 (4)	0.5917 (3)	0.0831 (11)
H12	1.3097	0.3517	0.6337	0.1*
C10	0.9846 (3)	0.4709 (3)	0.4126 (3)	0.0626 (7)
H10	0.9527	0.5209	0.333	0.075*
C11	1.1512 (4)	0.4433 (5)	0.4756 (3)	0.0825 (10)
H11	1.2312	0.4751	0.4386	0.099*
C4	0.4298 (3)	0.6621 (3)	0.2072 (2)	0.0552 (6)
H4A	0.5113	0.7227	0.1932	0.066*
H4B	0.4207	0.6766	0.2981	0.066*
C5	0.2607 (3)	0.6856 (3)	0.0992 (3)	0.0561 (6)
H5	0.2202	0.7739	0.1075	0.067*
C18	0.1473 (4)	0.7238 (4)	-0.1467 (3)	0.0772 (10)
H18A	0.1483	0.817	-0.1365	0.116*

H18B	0.1618	0.7019	-0.2333	0.116*
H18C	0.0429	0.6899	-0.1428	0.116*
C1	0.2916 (3)	0.5243 (3)	-0.0423 (2)	0.0511 (6)
H1	0.2727	0.4956	-0.1371	0.061*
C7	0.1534 (3)	0.4726 (3)	0.0128 (3)	0.0659 (8)
H7A	0.0516	0.4574	-0.0613	0.079*
H7B	0.187	0.392	0.0634	0.079*
C6	0.1309 (3)	0.5823 (4)	0.1068 (3)	0.0694 (8)
H6A	0.152	0.551	0.1999	0.083*
H6B	0.0193	0.6179	0.0746	0.083*
O2	0.5794 (3)	0.4319 (3)	0.45504 (19)	0.0812 (8)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O4	0.0741 (11)	0.0762 (15)	0.0519 (9)	0.0089 (11)	0.0238 (9)	-0.0017 (10)
O1	0.0401 (8)	0.0775 (13)	0.0467 (8)	0.0054 (8)	0.0066 (6)	0.0137 (9)
O3	0.0495 (9)	0.0973 (18)	0.0612 (11)	-0.0194 (10)	0.0129 (8)	-0.0028 (10)
N1	0.0381 (9)	0.0570 (13)	0.0533 (11)	0.0001 (9)	0.0031 (8)	0.0101 (10)
C17	0.148 (4)	0.081 (3)	0.091 (3)	-0.004 (3)	0.039 (3)	0.010 (2)
C16	0.0776 (19)	0.127 (4)	0.0625 (17)	0.017 (2)	0.0336 (15)	0.0166 (19)
C15	0.0386 (11)	0.0581 (16)	0.0491 (12)	0.0082 (11)	0.0076 (10)	0.0042 (11)
C2	0.0445 (11)	0.0451 (13)	0.0475 (11)	0.0018 (9)	0.0095 (9)	-0.0012 (10)
C3	0.0360 (10)	0.0625 (16)	0.0431 (11)	-0.0004 (10)	0.0057 (9)	0.0045 (11)
C8	0.0524 (13)	0.0618 (16)	0.0396 (11)	-0.0022 (12)	0.0097 (10)	0.0005 (11)
C9	0.0560 (13)	0.0515 (15)	0.0371 (10)	0.0033 (11)	0.0034 (10)	-0.0004 (10)
C14	0.0776 (18)	0.070 (2)	0.0447 (13)	0.0009 (15)	0.0035 (13)	0.0063 (13)
C13	0.092 (2)	0.070 (2)	0.0501 (14)	0.0138 (19)	-0.0109 (15)	0.0072 (14)
C12	0.0645 (17)	0.093 (3)	0.0682 (19)	0.0173 (18)	-0.0145 (15)	0.0024 (19)
C10	0.0512 (13)	0.080 (2)	0.0485 (12)	0.0065 (13)	0.0028 (10)	0.0136 (13)
C11	0.0534 (15)	0.112 (3)	0.0719 (18)	0.0078 (18)	0.0046 (13)	0.0153 (19)
C4	0.0485 (12)	0.0642 (17)	0.0500 (12)	0.0018 (12)	0.0110 (10)	-0.0096 (12)
C5	0.0456 (12)	0.0595 (17)	0.0614 (14)	0.0089 (11)	0.0139 (11)	-0.0031 (12)
C18	0.0526 (15)	0.093 (3)	0.0732 (19)	0.0075 (16)	0.0009 (13)	0.0305 (18)
C1	0.0406 (11)	0.0598 (16)	0.0477 (12)	-0.0054 (10)	0.0058 (9)	-0.0045 (11)
C7	0.0422 (12)	0.070 (2)	0.0772 (16)	-0.0127 (12)	0.0063 (11)	0.0089 (15)
C6	0.0391 (12)	0.101 (2)	0.0691 (16)	0.0041 (14)	0.0180 (12)	0.0147 (16)
O2	0.0612 (11)	0.129 (2)	0.0524 (10)	-0.0048 (13)	0.0163 (9)	0.0109 (12)

Geometric parameters (Å, °)

O4—C15	1.346 (3)	C14—C13	1.379 (4)
O4—C16	1.434 (4)	C14—H14	0.93
O1—C8	1.328 (3)	C13—C12	1.367 (6)
O1—C3	1.456 (3)	C13—H13	0.93
O3—C15	1.192 (3)	C12—C11	1.361 (5)
N1—C1	1.462 (4)	C12—H12	0.93
N1—C5	1.463 (3)	C10—C11	1.387 (4)

N1—C18	1.468 (3)	C10—H10	0.93
C17—C16	1.456 (7)	C11—H11	0.93
C17—H17A	0.96	C4—C5	1.535 (3)
C17—H17B	0.96	C4—H4A	0.97
C17—H17C	0.96	C4—H4B	0.97
C16—H16A	0.97	C5—C6	1.543 (4)
C16—H16B	0.97	C5—H5	0.98
C15—C2	1.511 (3)	C18—H18A	0.96
C2—C3	1.522 (3)	C18—H18B	0.96
C2—C1	1.548 (3)	C18—H18C	0.96
C2—H2	0.98	C1—C7	1.539 (4)
C3—C4	1.512 (4)	C1—H1	0.98
C3—H3	0.98	C7—C6	1.529 (5)
C8—O2	1.202 (3)	C7—H7A	0.97
C8—C9	1.497 (3)	C7—H7B	0.97
C9—C10	1.379 (4)	C6—H6A	0.97
C9—C14	1.385 (4)	C6—H6B	0.97
C15—O4—C16	117.5 (3)	C11—C12—H12	119.6
C8—O1—C3	117.99 (17)	C13—C12—H12	119.6
C1—N1—C5	101.5 (2)	C9—C10—C11	119.9 (3)
C1—N1—C18	113.5 (2)	C9—C10—H10	120
C5—N1—C18	112.5 (2)	C11—C10—H10	120
C16—C17—H17A	109.5	C12—C11—C10	120.0 (3)
C16—C17—H17B	109.5	C12—C11—H11	120
H17A—C17—H17B	109.5	C10—C11—H11	120
C16—C17—H17C	109.5	C3—C4—C5	109.2 (2)
H17A—C17—H17C	109.5	C3—C4—H4A	109.8
H17B—C17—H17C	109.5	C5—C4—H4A	109.8
O4—C16—C17	110.9 (3)	C3—C4—H4B	109.8
O4—C16—H16A	109.5	C5—C4—H4B	109.8
C17—C16—H16A	109.5	H4A—C4—H4B	108.3
O4—C16—H16B	109.5	N1—C5—C4	107.42 (19)
C17—C16—H16B	109.5	N1—C5—C6	104.9 (2)
H16A—C16—H16B	108.1	C4—C5—C6	112.0 (2)
O3—C15—O4	124.0 (2)	N1—C5—H5	110.8
O3—C15—C2	127.5 (2)	C4—C5—H5	110.8
O4—C15—C2	108.6 (2)	C6—C5—H5	110.8
C15—C2—C3	114.1 (2)	N1—C18—H18A	109.5
C15—C2—C1	107.80 (19)	N1—C18—H18B	109.5
C3—C2—C1	107.85 (18)	H18A—C18—H18B	109.5
C15—C2—H2	109	N1—C18—H18C	109.5
C3—C2—H2	109	H18A—C18—H18C	109.5
C1—C2—H2	109	H18B—C18—H18C	109.5
O1—C3—C4	111.83 (19)	N1—C1—C7	105.7 (2)
O1—C3—C2	107.86 (18)	N1—C1—C2	106.57 (19)
C4—C3—C2	112.8 (2)	C7—C1—C2	112.9 (2)
O1—C3—H3	108.1	N1—C1—H1	110.5

C4—C3—H3	108.1	C7—C1—H1	110.5
C2—C3—H3	108.1	C2—C1—H1	110.5
O2—C8—O1	124.2 (2)	C6—C7—C1	103.6 (2)
O2—C8—C9	124.2 (2)	C6—C7—H7A	111
O1—C8—C9	111.65 (19)	C1—C7—H7A	111
C10—C9—C14	119.3 (2)	C6—C7—H7B	111
C10—C9—C8	121.1 (2)	C1—C7—H7B	111
C14—C9—C8	119.6 (2)	H7A—C7—H7B	109
C13—C14—C9	120.2 (3)	C7—C6—C5	104.1 (2)
C13—C14—H14	119.9	C7—C6—H6A	110.9
C9—C14—H14	119.9	C5—C6—H6A	110.9
C12—C13—C14	119.8 (3)	C7—C6—H6B	110.9
C12—C13—H13	120.1	C5—C6—H6B	110.9
C14—C13—H13	120.1	H6A—C6—H6B	109
C11—C12—C13	120.8 (3)		
C15—O4—C16—C17	-90.5 (4)	C8—C9—C10—C11	-179.6 (3)
C16—O4—C15—O3	-6.1 (4)	C13—C12—C11—C10	0.1 (6)
C16—O4—C15—C2	173.6 (2)	C9—C10—C11—C12	0.3 (6)
O3—C15—C2—C3	-6.0 (4)	O1—C3—C4—C5	169.50 (19)
O4—C15—C2—C3	174.3 (2)	C2—C3—C4—C5	47.7 (3)
O3—C15—C2—C1	113.7 (3)	C1—N1—C5—C4	75.8 (3)
O4—C15—C2—C1	-66.0 (3)	C18—N1—C5—C4	-162.6 (3)
C8—O1—C3—C4	95.5 (3)	C1—N1—C5—C6	-43.6 (2)
C8—O1—C3—C2	-139.9 (2)	C18—N1—C5—C6	78.1 (3)
C15—C2—C3—O1	-53.0 (3)	C3—C4—C5—N1	-61.3 (3)
C1—C2—C3—O1	-172.69 (19)	C3—C4—C5—C6	53.3 (3)
C15—C2—C3—C4	71.1 (2)	C5—N1—C1—C7	43.2 (2)
C1—C2—C3—C4	-48.7 (3)	C18—N1—C1—C7	-77.8 (3)
C3—O1—C8—O2	-5.6 (4)	C5—N1—C1—C2	-77.1 (2)
C3—O1—C8—C9	174.8 (2)	C18—N1—C1—C2	161.9 (2)
O2—C8—C9—C10	-168.0 (3)	C15—C2—C1—N1	-59.9 (2)
O1—C8—C9—C10	11.6 (4)	C3—C2—C1—N1	63.8 (2)
O2—C8—C9—C14	12.5 (4)	C15—C2—C1—C7	-175.5 (2)
O1—C8—C9—C14	-167.9 (3)	C3—C2—C1—C7	-51.8 (3)
C10—C9—C14—C13	-0.5 (5)	N1—C1—C7—C6	-25.7 (3)
C8—C9—C14—C13	179.0 (3)	C2—C1—C7—C6	90.4 (3)
C9—C14—C13—C12	1.0 (5)	C1—C7—C6—C5	-1.1 (3)
C14—C13—C12—C11	-0.8 (6)	N1—C5—C6—C7	27.4 (3)
C14—C9—C10—C11	-0.1 (5)	C4—C5—C6—C7	-88.8 (3)

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>
C6—H6B...O3 ⁱ	0.97	2.71	3.618 (3)	157

Symmetry code: (i) *x*-1, *y*, *z*.