Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Inter- and intramolecular C—H···π interactions in morphine bis(1-naphthoate)

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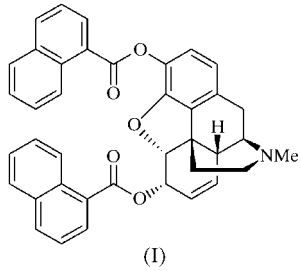
Received 16 June 2003
Accepted 15 July 2003
Online 9 August 2003

The crystal structure of morphine bis(1-naphthoate) [or 7,8-didehydro-4,5-epoxy-17-methylmorphinan-2,6-diyl bis(naphthalene-1-carboxylate)], $C_{39}H_{31}NO_5$, determined at 123 K, shows extensive C—H···π interactions in the crystal lattice. Of particular interest is an intramolecular C—H···π interaction within the unit cell between the two naphthoyl groups. Comparison of the opiate scaffolds of morphine bis(1-naphthoate) and morphine shows only a small increase in strain due to the steric bulk of the naphthoyl groups. The crystal packing shows distinct areas of packing for the naphthalene/aromatic groups and the opiate backbone. Extensive inter- and intramolecular C—H···π interactions lead to a densely packed aromatic region in the crystal lattice.

Comment

Opiate-derived compounds have been widely investigated for their medicinal properties (Schmidhammer, 1998; Rawal, 1999; Williams, 1999). During our research on the development of modified and improved synthetic pathways to pharmaceutical opiates we have encountered problems with opiate products binding to various transition metals. In particular, Fe^{II} and Fe^{III} in the Polonoski reaction and MnO_2 in oxidation protocols have been especially problematic. The improved work-up procedures we have used to tackle this problem include competitive binding (Scammells *et al.*, 2002) and ionic liquid extraction (Singer & Scammells, 2001). When using morphine as a starting material in opiate synthesis it is usual to protect either one or both of the hydroxy groups. Our latest approach for inhibiting the binding of the opiate to the transition metal is by application of suitable protecting-group methodology.

We reasoned that the O atoms of the phenol, ether and hydroxy groups (3-, 4/5- and 6-positions, respectively) of morphine and related opiates may be responsible for these interactions with transition metal ions. As a result, we were interested in employing a protecting group that addressed this issue, and we chose to investigate protection of the 3- and 6-OH groups by the 1-naphthoyl group. This protecting group not only reduces the electron density of the O atoms in the 3- and 6-positions (*via* its electron-withdrawing resonance effect) but also supplies considerable steric bulk, which further inhibits binding of transition metals to the opiate pocket. However, because of the close spatial proximity of the two alcohol groups of morphine-derived opiates, we wanted to determine the orientations of the ester groups and which of the ester groups is more distorted from its normal position. Other properties we were hoping to affect were polarity and solubility, in particular, the ease of purification of the opiate intermediates by improved column chromatography characteristics and the ease of crystallization of the product from related opiate by-products.



(I)

In the title compound, (I) (Fig. 1), the phenol naphthoyl group (Nap1) is in an orientation favouring intramolecular C—H···π interactions (Table 1) with the naphthoyl group attached to the secondary alcohol (Nap2). The distance between the Nap1 and Nap2 planes and the interplanar angle [65.22 (6)°] can be interpreted as a C—H···π non-bonding interaction.

Intermolecular C—H···π interactions between this molecule and its closest neighbours are also present (Fig. 2 and Table 1), and there are extensive intra- and intermolecular

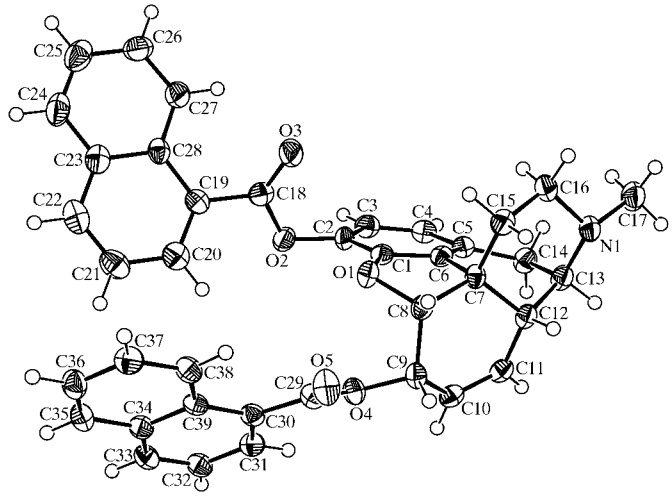


Figure 1
ORTEP-3 (Farrugia, 1997) view of (I). Displacement ellipsoids are drawn at the 50% probability level.

 DOI: 10.1107/S0108270103015622

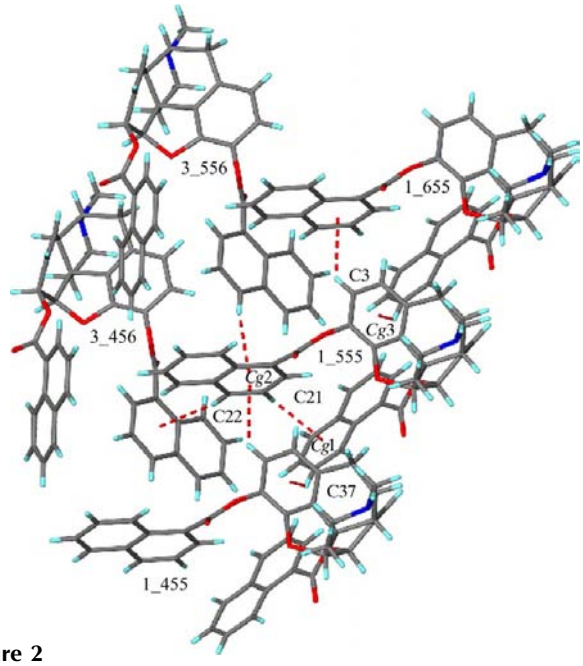


Figure 2
The C—H···π interactions in (I). Molecules are labelled by symmetry operator, where 1 is (x, y, z) and 3 is ($x+\frac{1}{2}, \frac{1}{2}-y, -z$). *Cg*1, *Cg*2 and *Cg*3 are the centroids of the C34–C39, C19–C23/C28 and C1–C6 rings, respectively.

C—H···π interactions within the crystal lattice. The interactions involving atoms C3 and C37 generate a ladder along [100], while that involving atom C22 generates a spiral chain along [100].

Several crystal structures of benzoyl-protected phenols have been solved, the simplest being phenol benzoylate (Shibakami & Sekiya, 1995). The angle between the phenol C—O bond and the benzene ring in phenol benzoylate is 3.3°, which is similar to the angle for the analogous bond in (I) [5.1 (4)°]. In phenol benzoylate, the dihedral angle between the phenol aromatic ring and the carboxylate group is 63.3° [*cf.* 76.7 (4)° for the C1—C2—O2—C18 angle in (I)] and the angle between the benzoyl aromatic ring and the carboxylate group is 8.8° [*cf.* O3—C18—C19—C20 = 41.6 (4)° and O5—C29—C30—C31 = 25.7 (4)° in (I)].

Several properties of (I) are affected by the presence of the large naphthoyl-protecting groups [*cf.* codeine methyl ether (CME) or morphine]. Compound (I) is considerably less polar than CME or morphine, and purification of (I) by column chromatography was successful using 10% methanol in dichloromethane. In this solvent system, morphine and CME had an R_F value of 0.0. Compound (I) also has a much lower solubility than morphine or CME in methanol and thus has the potential for facile purification of the desired opiate product from by-products during further synthesis.

This work has demonstrated that the bulky naphthoyl group can be attached to the morphine scaffold to give (I), which has significantly different physical properties from related opiates. Intramolecular C—H···π non-bonding interactions are present in the unit cell, and there are extensive intermolecular C—H···π interactions within the crystal lattice.

Experimental

Compound (I) was prepared by stirring (−)-morphine and 1-naphthoyl chloride together at room temperature in pyridine for 16 h, and then heating the mixture at 333 K for 4 h. The crude product was purified by column chromatography in order to remove a small amount of morphine mono(1-naphthoate). Prism-like crystals of (I) were grown by slow evaporation of a methanol solution (m.p. 462.5–464.0 K).

Crystal data

$C_{39}H_{31}NO_5$
$M_r = 593.67$
Orthorhombic, $P2_12_12_1$
$a = 7.8435$ (1) Å
$b = 9.7218$ (2) Å
$c = 39.5921$ (9) Å
$V = 3019.0$ (1) Å^3
$Z = 4$
$D_x = 1.306$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 348 reflections
$\theta = 3.5$–$27.9°$
$\mu = 0.09$ mm^{-1}
$T = 123$ (2) K
Prism, colourless
0.22 × 0.18 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
Thick-slice φ and ω scans
20 279 measured reflections
4065 independent reflections
2498 reflections with $I > 2\sigma(I)$
$R_{int} = 0.068$
$\theta_{max} = 27.9°$
$h = -10 \rightarrow 10$
$k = -12 \rightarrow 7$
$l = -52 \rightarrow 32$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.051$
$wR(F^2) = 0.112$
$S = 1.03$
4065 reflections
407 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0421P)^2 + 0.662P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}

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

*Cg*1, *Cg*2 and *Cg*3 are the centroids of the C34–C39, C19–C23/C28 and C1–C6 rings, respectively.

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3···*Cg*2^{i}	0.95	2.98	3.711 (4)	135
C21—H21···*Cg*1	0.95	2.80	3.512 (4)	132
C22—H22···*Cg*2^{ii}	0.95	2.94	3.873 (4)	166
C37—H37···*Cg*3^{iii}	0.95	3.07	3.690 (4)	124

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

H atoms were refined as riding, with C—H distances of 0.95, 0.98, 0.99 and 1.00 Å for aromatic, methyl, methylene and methine H atoms, respectively. The Flack (1983) test results were ambiguous so the Friedel pairs were merged and the absolute structure assigned by reference to (−)-morphine.

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

The authors thank the Australian Research Council for financial support and Dr J. M. White for discussions.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1262). Services for accessing these data are described at the back of the journal.

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