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ORIGINAL PAPER

Synthesis and Crystallographic Study of *N*′-(1-benzylpiperidin-4-yl)acetohydrazide

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Abstract As part of a study into new Fentanyl-derived opioid compounds with potent analgesic activity and reduced side effects the starting material title compound, $C_{14}H_{21}N_3O$ (**1**), was synthesized and characterized by NMR spectroscopy and single-crystal X-ray diffraction. The crystal structure is monoclinic *Cc* with unit cell parameters $a = 14.1480(3)$ Å, $b = 14.1720(4)$ Å, $c = 27.6701(7)$ Å, $\beta = 96.956(1)^\circ$, $\alpha = \gamma = 90^\circ$. The compound has crystallized with four crystallographically unique molecules in the asymmetric unit; each molecule has a very similar conformation and an analysis of the structure shows that although all four unique molecules overlay very well there is no evidence of *pseudo*-symmetry which would relate the molecules in the higher symmetry space group *C*2/*c*. The crystal packing consists of two separate hydrogen bonded chains which are linked together to form a thick 2D structure in the *ab* plane.

Keywords Organic compounds · $Z' > 1$ · Hydrogen bonding

Introduction

We have a long standing research interest in the synthesis and bioactivity of novel compounds for the treatment of neuropathic pain. Although morphine is a very potent and commonly used μ opioid, it has serious side effects and dependence caused by long term usage [1, 2]. Our research, therefore, aims to synthesize a range of new analgesics derived from Fentanyl, with the aim of developing compounds with reduced side effects but which remain potent analgesics [3–6]. As part of this study the title compound, **1**, was synthesized as a starting material for the synthesis of a wide variety of Fentanyl-based analgesics. We report here the synthesis and crystal structure determination of **1**.

Experimental

Synthesis

To a solution of 3.7 g (0.05 mol) of acetylhydrazide in 30 mL of ethanol was added dropwise a solution of 9.45 g (0.05 mol) of 1-(phenylmethyl)-piperidin-4-one in 30 mL of ethanol. The mixture was left overnight then the ethanol was evaporated and the remaining product was crystallized from acetone giving 11.1 g (90%) of N'-(1-benzylpiperidin-4-ylidene)acetohydrazide mp 130–131 °C. EI-MS:*m/z* 246; HRMS calcd for $C_{14}H_{20}N_3O$: 246.1606; found (ESI, $[M + H]^+$): 246.1602 (Scheme 1).

To a solution of 6.125 g (0.025 mol) of *N*′-(1-benzylpiperidin-4-ylidene)acetohydrazide dissolved in a mixture of 25 mL ethanol and 50 mL THF during 15 min was added by small aliquots 1.9 g (0.05 mol) of $NaBH_4$. The solution was left overnight then the ethanol and THF were evaporated and to the remaining residue was added 50 mL of $CHCl_3$ and with cooling and stirring was added dropwise 3 g (0.05 mol) of CH_3COOH in 10 mL of water. The organic layer was separated, dried on $MgSO_4$, and after evaporation of solvent the residue was recrystallized from hot ethanol giving 5.25 g (85%) of *N*′-(1-benzylpiperidin-4-yl)acetohydrazide, **1**, as a crystalline solid, mp 111–112 °C.

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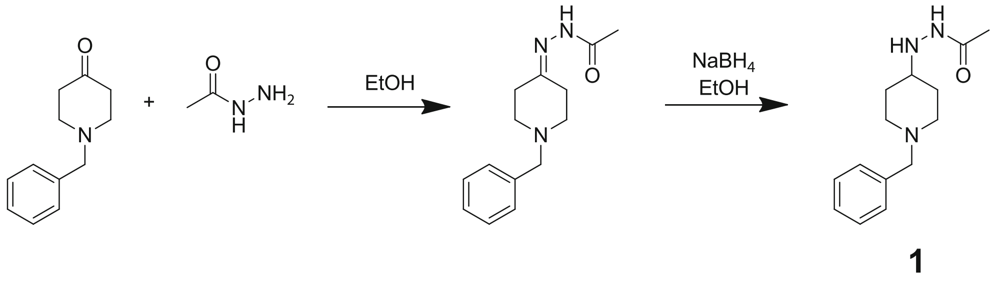

Scheme 1 Synthetic route to **1**

^1H NMR (600 MHz, $CDCl_3$) δ 7.32–7.20(m, 6H), 3.48 (s, 2H), 2.83 (d, J = 12.0 Hz, 3H), 2.01 (td, J = 11.5, 2.0 Hz, 2H), 1.94 (s, 3H), 1.78 (d, J = 12.3 Hz, 2H), 1.44 (dq, J = 3.8, 11.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.72, 138.53, 129.04, 128.15, 126.92, 77.24, 77.03, 76.82, 62.98, 56.89, 51.71, 30.46, 21.17. EI-MS:*m/z* 248; HRMS calcd for $C_{14}H_{20}N_3O$:248.1763; found (ESI, $[M + H]^+$): 248.1760.

X-ray Crystallography

Single-crystal X-ray diffraction data were measured on a Bruker Kappa APEXII DUO diffractometer with silicon-monochromated CuKα radiation ($\lambda = 1.54178$ Å) and a crystal temperature of 100 K. APEX2 was used for diffractometer control and unit cell determination [7]; SAINT was used for unit cell refinement and integration [7]; a numerical absorption correction was applied using SADABS [8]; the structure was solved by direct methods and refined using full-matrix least-squares on F^2 with SHELXTL [9]. ORTEP-3 for Windows [10] and Mercury 2.2 [11] were used for molecular graphics. All hydrogen atoms were located in a difference Fourier map. N-bound hydrogen atoms were freely refined; N–H distances lie in the range 0.80(2)–0.86(3) Å. C-bound H atoms were refined with $U_{iso}(H) = 1.2U_{eq}(C)$ for all hydrogen atoms except methyl hydrogen atoms which were refined with $U_{iso}(H) = 1.5\ U_{eq}(C)$. C–H distances were constrained to 1.0 Å (methine), 0.99 Å (methylene), 0.98 Å (methyl) and 0.95 Å (aromatic). The value of the absolute structure parameter is based on 3041 Friedel pairs [12] (Table 1).

Results and Discussion

Compound **1** crystallizes in the monoclinic space group *Cc* with four independent molecules in the asymmetric unit (*Z'* = 4). The four molecules are shown in Fig. 1 and have been separated for clarity. Although the ninth most common space group reported to the Cambridge Structural Database structures in space group *Cc* comprise only 1.1% of the current total (5359 out of 503348 structures as of the February 2010 update [13]). Of that 1.1%, structures with *Z'* = 4 also comprise 1.1% of all reported *Cc* structures (60 of 5359).

Table 1 Crystallographic parameters for **1**

Chemical formula	$C_{14}H_{21}N_3O$
Formula weight	247.34
Temperature	100(2) K
Radiation, wavelength	CuKα, 1.54178 Å
Crystal system, space group	Monoclinic, *Cc*
Unit cell parameters	$a = 14.1480(3)$ Å
	$b = 14.1720(4)$ Å
	$c = 27.6701(7)$ Å
	$\beta = 96.956(1)°$
Cell volume	5507.2(2) $Å^3$
Z, *Z'*	16, 4
Calculated density	1.193 g/cm^3
Absorption coefficient μ	0.609 mm^{-1}
F(000)	2144
Crystal color and size	Colorless, 0.33 × 0.25 × 0.25 mm^3
Reflections for cell refinement	9959 (θ range 4.8–70.4°)
Data collection method	ϕ and ω scans
θ range for data collection	4.4–70.5°
Index ranges	h −16 to 17, k −17 to 17, l −33 to 32
Completeness to $\theta = 70.0°$	98.8%
Reflections collected	29042
Independent reflections	8212 ($R_{int} = 0.0322$)
Reflections with $F^2 > 2\sigma$	7744
Absorption correction	Numerical
Min. and max. transmission	0.8225 and 0.8627
Structure solution	Direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters *a*, *b*	0.0456, 1.4167
Data/restraints/parameters	8212/2/686
Final *R* indices [$F^2 > 2\sigma$]	$R1 = 0.0326$, $wR2 = 0.0782$
R indices (all data)	$R1 = 0.0357$, $wR2 = 0.0799$
Goodness-of-fit on F^2	1.028
Absolute structure parameter	−0.06(15)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.16 and −0.15 e $Å^{-3}$

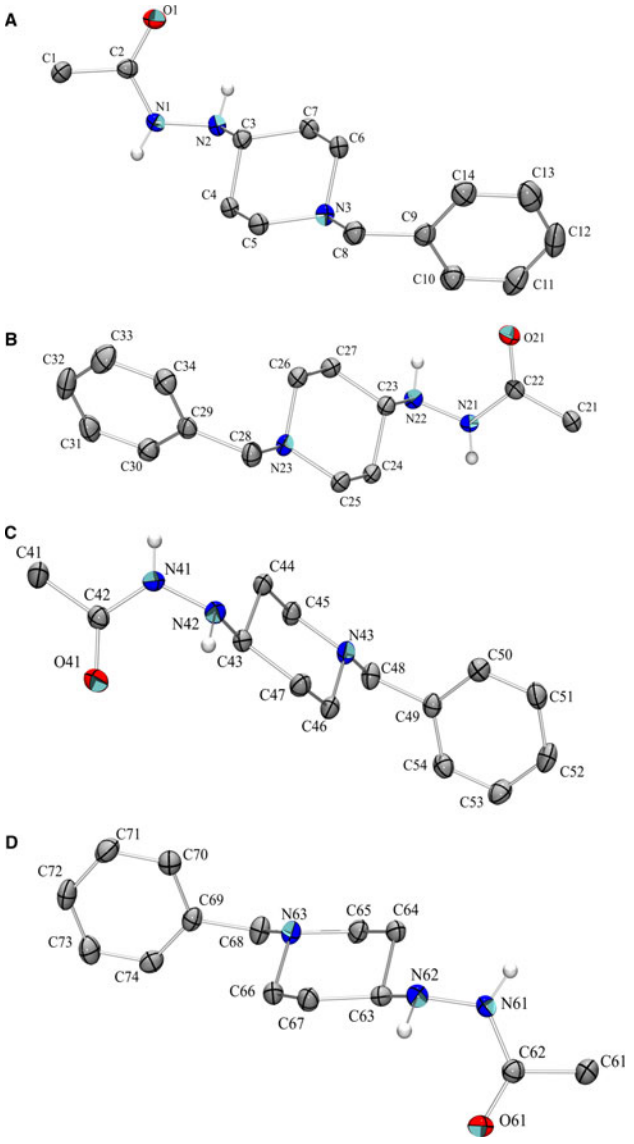

Fig. 1 The four unique molecules in **1**. Displacement ellipsoids are at the 50% probability level and C-bound hydrogen atoms are omitted

The subject of multiple molecules in the asymmetric unit is one of much recent interest and debate in the literature [14]. Researchers often describe such structures in terms of packing "frustration" caused by competing strong intermolecular interactions, or by some inherent chemical property forcing molecules to crystallize with lower than expected symmetry; witness the inability of chiral carboxylic acids to pack around a crystallographic inversion center as an example of such chemical *vs* crystallographic frustration [15]. In other examples molecules with conformational flexibility may crystallize with $Z' > 1$ and the crystallographically unique molecules adopt very different conformations. Other $Z' > 1$ structures are those which are apparently related by symmetry elements not present in the space group. The phrase "crystal on the way", coined to describe some high $Z' > 1$ structures as a kinetic product of crystallization [16], has recently been applied to this class of structure [17–19]. The structure of **1** does not appear to fall into any of these categories.

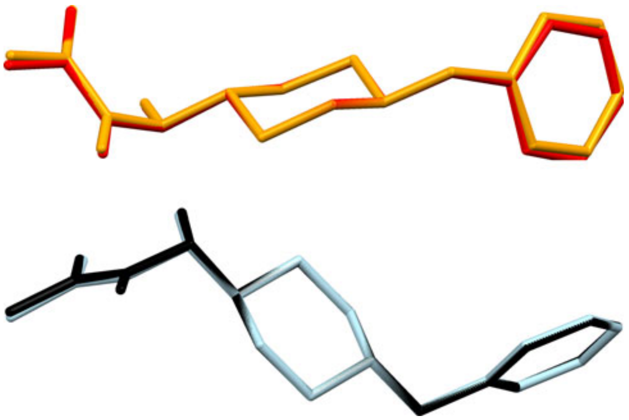

Fig. 2 Least-squares overlays of molecules A with C (top, A = orange, C = red, rms deviation = 0.0051 Å) and B with D (bottom, B = light blue, D = black, rms deviation = 0.007 Å). In both cases the six atoms which comprise the piperidine ring were used for the overlay. In the printed version of the journal molecules A and B appear as pale gray

The four unique molecules in **1** can be split into two pairs; by using a least-squares overlay of the six atoms which comprise the piperidine ring we show in Fig. 2 that molecules A and C overlay very well, as do molecules B and D. In the case of A with C there are some small differences between the hydrazide and phenyl groups but in the case of B with D the overlay is excellent.

Furthermore when A and C are inverted they fit very well onto the overlay of B with D (Fig. 3) and it is clear that the molecules do not differ significantly in terms of their conformation. Despite this the molecules have not crystallized with *pseudo*-symmetry elements which would relate the molecules to one-another (with a possibility of some disorder) in the higher symmetry space group *C*2/*c*; the structure does not solve in space group *C*2/*c* and the *Cc* model cannot be converted to *C*2/*c* by applying extra symmetry operations and deleting redundant atoms. The value of the Flack parameter also confirms the correctness of the space group as *pseudo*-inversion symmetry, for example, would likely increase the value of the Flack parameter.

The crystal packing consists of two hydrogen-bonded chains which are linked together to form a thick 2D structure. Part of the crystal packing is shown in Fig. 4. A $\mathbf{C}_2^2(8)$ chain [20] linking A with molecule B by virtue of two unique N–H···O interactions is observed; a second $\mathbf{C}_2^2(8)$ chain links molecule C with molecule D in a similar fashion. These two unique chains are connected to one-another by two unique **D**(3) N–H···N interactions thus

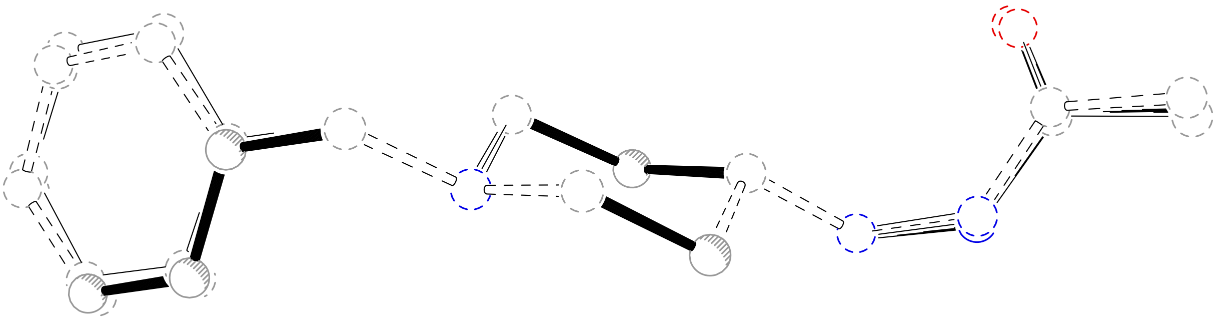

Fig. 3 A composite overlay of all four unique molecules. *Key*: A, open bonds; B, dashed open bonds; C, line bonds; D, full bonds

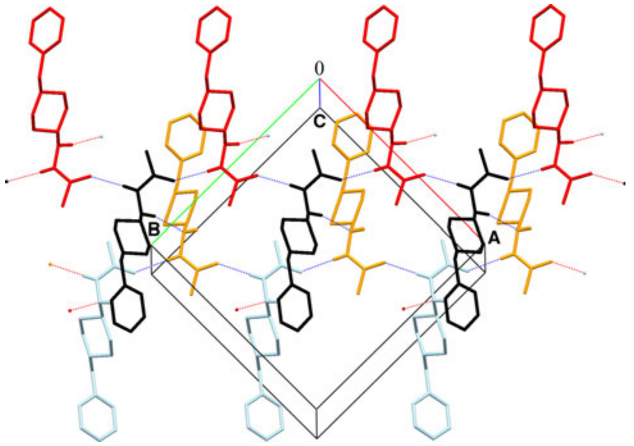

Fig. 4 Part of the crystal packing of **1**. Hydrogen bonding interactions are shown as *dotted lines* and the molecular color scheme is the same as Fig. 2

forming a thick 2D hydrogen bonded sheet structure in the *ab* plane.

Supplementary Information

CCDC 751146 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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