Published in final edited form as:

Acta Crystallogr Sect E Struct Rep Online. 2006 July ; 62(7): o2815–o2816. doi:10.1107/S1600536806021817.

4-{N-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-phenylpropionyl]anilino}-1-phenethylpiperidinium chloride methanol disolvate

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Abstract

The structure of the title compound, a fentanyl derivative with formula $C_{36}H_{36}N_3O_3^+ \cdot Cl^- \cdot 2CH_3OH$, crystallizes as a racemic mixture. The organic cation has an extended conformation and the structure displays O–H $\cdots$ O, O–H $\cdots$ Cl and N–H $\cdots$ Cl hydrogen bonding.

Keywords

Single-crystal X-ray study; $T = 173$ K; Mean $\sigma(C-C) = 0.006$ Å; R factor = 0.067; wR factor = 0.231; Data-to-parameter ratio = 11.5

Comment

4-Anilidopiperidines represent the most powerful synthetic analgesics, which include fentanyl and related compounds (Janssen & Gardocki, 1964). Fentanyl is used for analgesia in clinical practice despite the fact that its use results in side effects such as respiratory depression, physical dependence and rapid tolerance (Bowdle, 1998). In order to decrease the toxicity profile of this compound we sought to replace the propionyl group of fentanyl with various α -substituted amino acids. Our biological tests showed that the characteristic high opioid activity of fentanyl can be retained if substitution of the propionyl group is done with hydrophobic amino acids. We found that the employment of L-phthaloylphenylalanyl chloride, prepared by treatment with thionyl chloride in refluxing toluene followed by coupling in the presence of triethylamine, gave us a completely racemized product, (I).

Compound (I) crystallized as a chloride salt with two molecules of methanol solvent. The structure of the cation is shown in Fig. 1. The cation has an extended conformation, with the piperidinium ring adopting a chair conformation with equatorial substituents. The size and

shape of the displacement ellipsoid of C30 suggests that this atom may be disordered; a disorder model brought no improvement in refinement and so the ordered model was retained. The molecular geometry is unexceptional. N–H $\cdots$ Cl, O–H $\cdots$ Cl and O–H $\cdots$ O hydrogen bonds are found between the cation, the chloride anion and the methanol molecules (Table 1).

Experimental

N-Phenyl-1-(2-phenylethyl)-4-piperidinamine (3.1 g, 11.1 mmol), prepared by the method of Maryanoff et al. (1982), and triethylamine (2.9 g, 28.9 mmol) were dissolved in dry dichloromethane (50 ml). The mixture was cooled in an ice–water bath. A solution of *L*-phthaloylphenylalanyl chloride (7.6 g, 24.2 mmol) in dry dichloromethane (50 ml) was added dropwise. The reaction mixture was stirred overnight. The mixture was then diluted with dichloromethane (100 ml) and washed with 5% aqueous K₂CO₃. The aqueous phase was extracted with dichloromethane (2 $\times$ 50 ml). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solution was concentrated *in vacuo* and chromatographed with a 1:19 methanol/dichloromethane solution. The resulting compound was dissolved in anhydrous diethyl ether and precipitated by passing dry HCl through it. The resulting precipitate was filtered off and dissolved in anhydrous methanol. The product crystallized shortly after being placed in a freezer (yield 4.1 g, 59%; m.p. 479–481 K, with loss of solvent of crystallization at 427–429 K).

Crystal data

$C_{36}H_{36}N_3O_3^+ \cdot Cl^- \cdot 2CH_4O$	$Z = 4$
$M_r = 658.21$	$D_x = 1.237 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 11.014 (2) \text{ \AA}$	$\mu = 0.15 \text{ mm}^{-1}$
$b = 17.131 (4) \text{ \AA}$	$T = 173 (2) \text{ K}$
$c = 19.055 (4) \text{ \AA}$	Block, colourless
$\beta = 100.498 (7)^\circ$	$0.45 \times 0.32 \times 0.27 \text{ mm}$
$V = 3535.3 (12) \text{ \AA}^3$	

Data collection

Bruker SMART 1000 CCD	4996 independent reflections
diffractometer	3117 reflections with $I > 2\sigma(I)$
thin-slice ω scans	$R_{\text{int}} = 0.095$
Absorption correction: none	$\theta_{\text{max}} = 23.3^\circ$
26495 measured reflections	

Refinement

Refinement on F^2	H atoms treated by a mixture of
$R[F^2 > 2\sigma(F^2)] = 0.067$	independent and constrained
$wR(F^2) = 0.231$	refinement
$S = 1.00$	$w = 1/[\sigma^2(F_o^2) + (0.1544P)^2]$
4996 reflections	where $P = (F_o^2 + 2F_c^2)/3$
434 parameters	$(\Delta/\sigma)_{\text{max}} < 0.001$
	$\Delta\rho_{\text{max}} = 0.52 \text{ e \AA}^{-3}$
	$\Delta\rho_{\text{min}} = -0.56 \text{ e \AA}^{-3}$

Despite the large crystal size the data collected were very weak and essentially unobserved at higher Bragg angles. Consequently the data were truncated at a resolution of 0.9 $\text{\AA}$. H

atoms were first located in a difference map. Aromatic, CH₂ and CH H atoms were refined as riding with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ and C–H bond lengths of 0.95, 0.99 and 1.00 Å, respectively. Methyl H atoms were refined as riding with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ and a C–H distance of 0.98 Å. O- and N-bound H atoms were refined with no constraints on geometry, giving distances as shown in Table 1, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{O,N})$.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and local programs.

Acknowledgments

The work was supported by grants from the United States Public Health Service and the National Institute on Drug Abuse. The X-ray diffractometer was purchased with funds from the National Science Foundation (grant No. CHE-9610374).

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Figure 1.
The structure of the organic cation of (I), with 50% probability displacement ellipsoids. C-bound H atoms have been omitted.

Table 1

Hydrogen-bond geometry (Å, °).

<i>D</i> – <i>H</i> ⋯ <i>A</i>	<i>D</i> – <i>H</i>	<i>H</i> ⋯ <i>A</i>	<i>D</i> ⋯ <i>A</i>	<i>D</i> – <i>H</i> ⋯ <i>A</i>
O4–H4O⋯O5	0.83(1)	2.03(4)	2.769(6)	148(7)
O5–H5O⋯Cl ¹	0.82(1)	2.34(3)	3.092(3)	152(5)
N3–H3N⋯Cl	0.98(4)	2.07(4)	3.041(4)	170(3)

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