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

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Key indicators

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

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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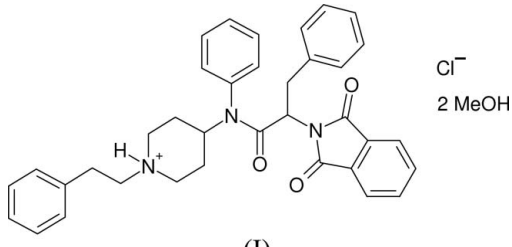
The structure of the title compound, a fentanyl derivative with formula $C_{36}H_{36}N_3O_3^+\cdot Cl^-\cdot 2CH_3OH$, crystallizes as a racemic mixture. The organic cation has an extended conformation and the structure displays O—H···O, O—H···Cl and N—H···Cl hydrogen bonding.

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).



(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···Cl, O–H···Cl and O–H···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

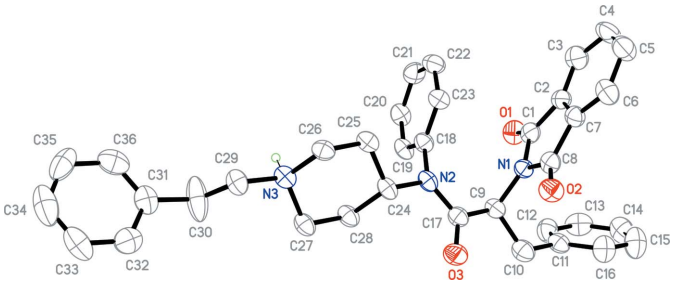


Figure 1
The structure of the organic cation of (I), with 50% probability displacement ellipsoids. C-bound H atoms have been omitted.

(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 K_2CO_3. The aqueous phase was extracted with dichloromethane (2 × 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

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

Data collection

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

Refinement

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

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4O···O5	0.83 (1)	2.03 (4)	2.769 (6)	148 (7)
O5—H5O···Cl^{i}	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) $x-1, y, z$.

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 Å. H atoms were first located in a difference map. Aromatic, CH_2 and CH H atoms were refined as riding with $U_{iso}(H) = 1.2U_{eq}(C)$ and C—H bond lengths of 0.95, 0.99 and 1.00 Å, respectively. Methyl H atoms were refined as riding with $U_{iso}(H) = 1.5U_{eq}(C)$ 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 $U_{iso}(H) = 1.2U_{eq}(O,N)$.

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.

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