Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(1*R*)-2-[(3*R*,4*S*)-3-Methyl-4-(*N*-phenyl-*N*-propionylamino)piperidin-1-yl]-1-phenylethyl *p*-bromobenzoate and *N*-{(3*R*,4*S*)-1-[(2*S*)-2-(4-bromophenyl)-2-hydroxyethyl]-3-methylpiperidin-4-yl}-*N*-phenylacrylamide

Jeffrey R. Deschamps,* Clifford George and Judith L. Flippen-Anderson

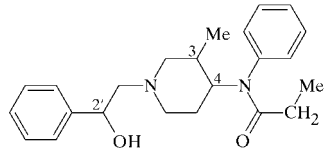
Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA
Correspondence e-mail: deschamps@nrl.navy.mil

Received 14 March 2002
Accepted 11 April 2002
Online 31 May 2002

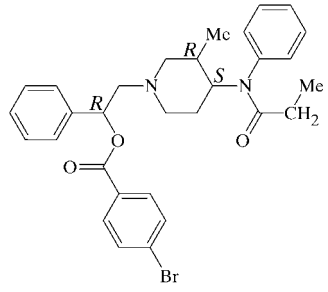
Both title compounds, $C_{30}H_{33}BrN_2O_3$ and $C_{23}H_{27}BrN_2O_2$, respectively, are brominated derivatives of the potent opioid *cis*-β-hydroxy-3-methylfentanyl (ohmefentanyl). Ohmefentanyl has three asymmetric C atoms and, therefore, has eight possible stereoisomers. The absolute configurations of the title compounds were determined to assign the proper configuration of two of these stereoisomers and the compounds have the same stereochemistry at two of the three asymmetric C atoms.

Comment

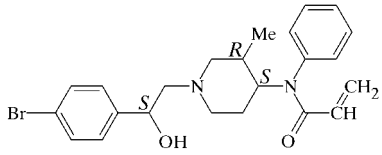
(±)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-piperidin-4-yl]-*N*-phenylpropanamide, (I), also known as ohmefentanyl or *cis*-β-hydroxy-3-methylfentanyl, is an extremely potent analgesic exhibiting high selectivity for the μ-opioid receptor (Xu *et al.*, 1987). It is one of the 'super potent' analogs of fentanyl that are more potent in producing antinocieption than was predicted on the basis of their μ-receptor affinity (Rothman *et al.*, 1991). With three asymmetric C atoms (C3, C4 and C2′), the compound has eight possible stereoisomers. Four, two pairs of optical isomers, of the eight possible stereoisomers would have *cis* arrangements of the substituents on C3 and C4. When the two pairs were separated, one pair was found to be 5.3 times more potent than the other and 6300 times more potent than morphine (Zhu *et al.*, 1983). The more active pair was referred to as ohmefentanyl. A second sample of (I), designated as RTI-4614-4, was determined to be a mixture of all four *cis* isomers (Brine *et al.*, 1992) and was shown to be 25 000 times more potent than morphine (Aceto *et al.*, 1988). In view of the differing activities and isomeric compositions of ohmefentanyl and RTI-4614-4, it was clearly necessary to resolve (I) into its four stereoisomers (Brine *et al.*, 1995). The title compounds, (II) and (III), are both brominated derivatives of (I) that were synthesized to resolve its stereochemistry. The absolute configurations of (II) and (III) are reported here.



(I)



(II)



(III)

The X-ray structure analysis of (II) indicated the absolute configuration to be 2*S*,3*R*,4*S* (Fig. 1 and Table 1). As expected, the substituents on C3 and C4 are *cis* to one another, with C3′—C3—C4—N7 torsion angles of −58.3 (4) and −56.4 (4)° for the two independent molecules. Ring *C* (see Fig. 2 for labeling) is approximately parallel to ring *A* [the angles between the least-squares planes are 33.5 (1) and 29.5 (2)° for the two molecules], while ring *B* is approximately perpendicular to the other two aromatic rings [the angles between the planes of rings *B* and *A* are 58.3 (1) and 85.1 (1)°, and between

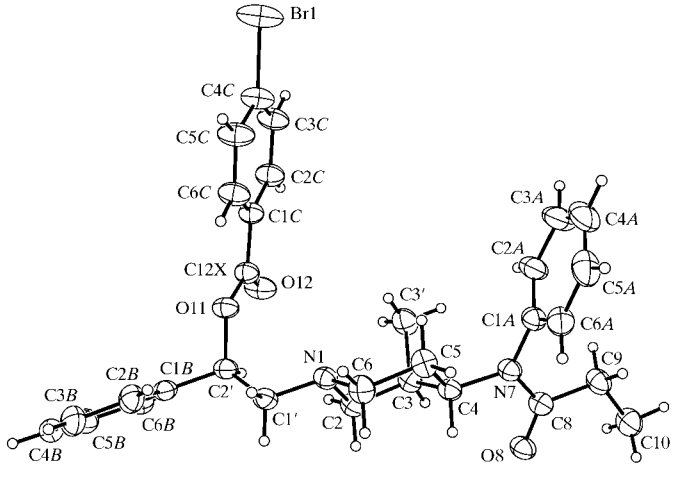


Figure 1
View of the molecule of (II), shown with 20% probability displacement ellipsoids. H atoms are shown as small spheres of arbitrary radii.

  DOI: 10.1107/S0108270102006443

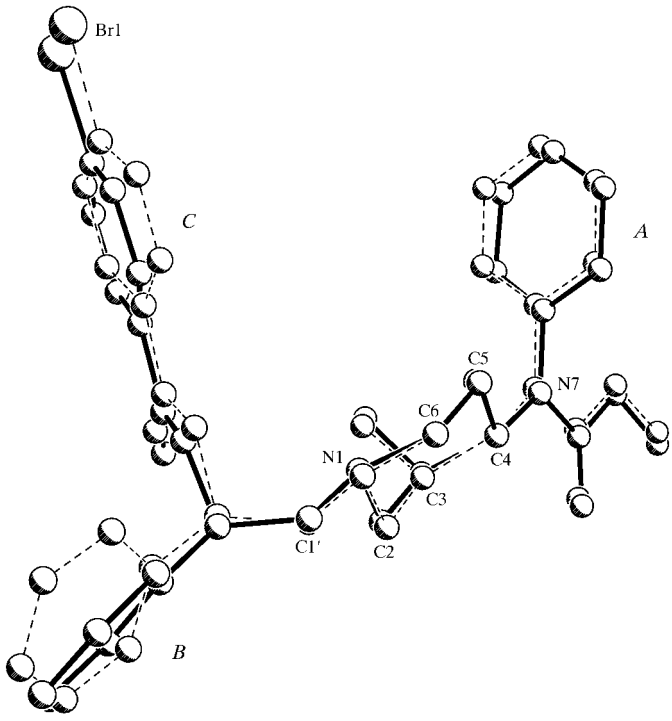


Figure 2
Least-squares fit of the two molecules in the asymmetric unit of (II). The r.m.s. deviation of the eight atoms used (six atoms in the heterocyclic ring plus N7 and C1′) is 0.097 Å.

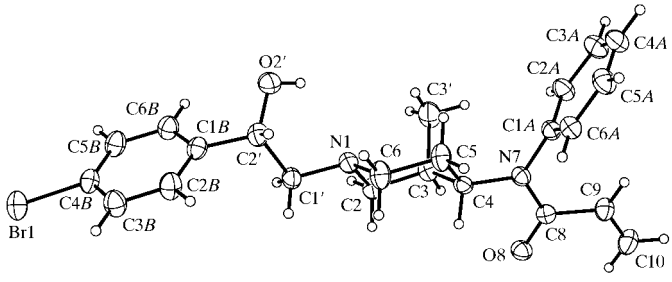


Figure 3
View of the molecule of (III), shown with 20% probability displacement ellipsoids. H atoms are shown as small spheres of arbitrary radii.

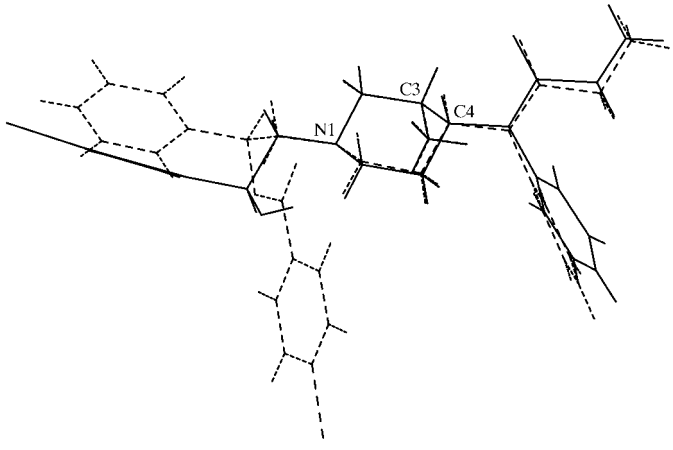


Figure 4
Superimposition of (II) and (III), showing that, despite the opposite stereochemistry at C2′, the aromatic rings on C2′ are still in close proximity. Only the labeled atoms were used to align the structures.

the planes of rings *B* and *C* are 61.7 (1) and 70.9 (1)°]. The differences are due to rotation about the C2′—C1*A* bond for ring *B* (Fig. 2).

In compound (III), which crystallized with a single molecule in the asymmetric unit, the absolute configuration is 2*R*,3*R*,4*S* (Fig. 3 and Table 2), with a C3′—C3—C4—N7 torsion angle of −63.2 (3)°. The molecule of (III) has only two aromatic rings, which are approximately parallel to one another [the angle between the planes is 45.2 (1)°], and one intramolecular hydrogen bond [H···N 2.31 (4) Å, O···N 2.775 (3) Å and O—H···N 117 (4)°; Table 3].

Compounds (II) and (III) differ in the stereochemistry only at C2′. Superimposition of the two compounds using atoms N1, C3 and C4 shows that there is good agreement in the conformation of the central six-membered ring and the substituents on C4 (Fig. 4). Despite a change in the C2—N1—C1′—C2′ torsion angle [−80.4 (3) and −156.3 (3)° for compounds (II) and (III), respectively], the *C* rings are still in close proximity and could still bind in a similar manner to a receptor. The change in this torsion angle may be caused by the substitution at O2′ in compound (II). Thus, the large difference in potency reported by Brine *et al.* (1995) can only be attributed to the opposite stereochemistry at C2′, which places the hydroxyl group in ohmefentanyl on the opposite side of the molecule.

Experimental

The title compounds were synthesized at the Research Triangle Institute in North Carolina (Brine *et al.*, 1992). Crystals of both compounds were grown by slow evaporation from a diisopropyl ether solution.

Compound (II)

Crystal data

$C_{30}H_{33}BrN_2O_3$
M_r = 549.49
Monoclinic, $P2_1$
a = 10.8806 (2) Å
b = 22.4670 (5) Å
c = 11.5313 (3) Å
β = 92.208 (1)°
V = 2816.78 (11) Å^3
Z = 4
D_x = 1.296 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 6392 reflections
θ = 3.9–66.8°
μ = 2.24 mm^{-1}
T = 153 (2) K
Prism, colorless
0.56 × 0.44 × 0.24 mm

Table 1
Selected geometric parameters (Å, °) for (II).

Br1—C4*C*	1.904 (4)	N11—C16	1.446 (5)
N1—C6	1.449 (4)	N11—C12	1.453 (5)
N1—C1′	1.465 (4)	N11—C11′	1.459 (4)
N1—C2	1.466 (4)	Br11—C14*C*	1.910 (4)
C4—N7	1.494 (3)	C14—N17	1.483 (4)
N7—C8	1.362 (4)	N17—C18	1.364 (4)
N7—C1*A*	1.431 (4)	N17—C11*A*	1.444 (4)
C6—N1—C1′	111.4 (2)	C16—N11—C12	110.6 (3)
C6—N1—C2	109.0 (2)	C16—N11—C11′	114.7 (3)
C1′—N1—C2	111.2 (2)	C12—N11—C11′	112.3 (3)
C8—N7—C1*A*	121.8 (2)	C18—N17—C11*A*	120.7 (2)
C8—N7—C4	117.1 (2)	C18—N17—C14	117.1 (3)
C1*A*—N7—C4	120.8 (2)	C11*A*—N17—C14	121.7 (2)

Data collection

Bruker CCD area-detector diffractometer
ω scans
Absorption correction: by integration (Bruker, 2001)
T_{min} = 0.608, T_{max} = 0.931
13 643 measured reflections
7419 independent reflections
6654 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
θ_{max} = 67.0°
$h = -12 \rightarrow 12$
$k = -23 \rightarrow 26$
$l = -12 \rightarrow 13$
88 standard reflections
frequency: variable
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.122
S = 1.07
7419 reflections
650 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0803P)^2 + 0.1540P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.45 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0386 (10)
Absolute structure: Flack (1983); 2687 Friedel pairs
Flack parameter = 0.032 (15)

Compound (III)

Crystal data

$C_{23}H_{27}BrN_2O_2$
M_r = 443.38
Orthorhombic, $P2_12_12_1$
a = 6.1932 (1) Å
b = 10.7461 (1) Å
c = 33.0458 (3) Å
V = 2199.29 (5) Å^3
Z = 4
D_x = 1.339 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 7464 reflections
θ = 2.7–67.2°
μ = 2.70 mm^{-1}
T = 295 (2) K
Rod, colorless
0.48 × 0.08 × 0.03 mm

Data collection

BrukerCCD area-detector diffractometer
ω scans
Absorption correction: a face-indexed absorption correction was followed by a *SADABS* correction (Bruker, 2001)
T_{min} = 0.395, T_{max} = 0.876
9443 measured reflections
3605 independent reflections
3330 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 67.2°
$h = -7 \rightarrow 7$
$k = -12 \rightarrow 12$
$l = -39 \rightarrow 36$
61 standard reflections
frequency: variable
intensity decay: none

Table 2
Selected geometric parameters (Å, °) for (III).

Br1—C4*B*	1.906 (3)	N7—C8	1.368 (3)
N1—C6	1.455 (4)	N7—C1*A*	1.442 (3)
N1—C2	1.465 (3)	C9—C10	1.300 (4)
N1—C1′	1.466 (3)	C2′—O2′	1.421 (4)
C4—N7	1.475 (3)		
C6—N1—C2	110.5 (2)	C8—N7—C1*A*	120.7 (2)
C6—N1—C1′	111.2 (2)	C8—N7—C4	117.20 (19)
C2—N1—C1′	111.1 (2)	C1*A*—N7—C4	122.1 (2)

Table 3
Hydrogen-bonding geometry (Å, °) for (III).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2′—H2′···N1	0.81 (4)	2.31 (4)	2.775 (3)	117 (4)

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.105
S = 1.09
3605 reflections
254 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0689P)^2 + 0.0827P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.39 e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0194 (8)
Absolute structure: Flack (1983); 1377 Friedel pairs
Flack parameter = 0.004 (19)

The H atoms of compound (II) were refined as riding (C—H = 0.93–0.98 Å), as were the H atoms of compound (III), except for the hydroxy H atom, which was refined freely.

For compounds (II) and (III), data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2001); software used to prepare material for publication: *SHELXTL* (Bruker, 2001).

The NRL authors wish to acknowledge financial support from the Office of Naval Research (ONR), Mechanics Division and the National Institutes on Drug Abuse (NIDA).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1544). Services for accessing these data are described at the back of the journal.

References

Aceto, M. D., Bowman, E. R., Harris, L. S. & May, E. L. (1988). *Problems of Drug Dependence*. Proceedings of the 50th Annual Scientific Meeting. NIDA Research Monograph 90, pp. 468–515.
Brine, G. A., Sawyer, D. K., Huag, P. T., Stark, P. A., Gaetano, K. D. & Carroll, F. I. (1992). *J. Heterocycl. Chem.* **29**, 1773–1779.
Brine, G. A., Stark, P. A., Liu, Y., Carroll, F. I., Singh, P., Xu, H. & Rothman, R. B. (1995). *J. Med. Chem.* **38**, 1547–1557.
Bruker (2001). *SMART* (Version 5.624) and *SAINT* (Version 6.04) for Windows NT, and *SADABS* (Version 2.03) and *SHELXTL* (Version 5.10) for UNIX. Bruker AXS Inc., Madison, Wisconsin, USA.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Rothman, R. B., Xu, H., Seggel, M., Jacobosn, A. E., Rice, K. C., Brine, G. A. & Carroll, F. I. (1991). *Life Sci.* **48**, PL111–116.
Sheldrick, G. M. (1997). *SHELXTL*. Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Xu, H., Yao, Y. H., Zhu, Y. C., Chan, J. & Chi, Z. Q. (1987). *Acta Pharm. Sin.* **8**, 289–292.
Zhu, Y. C., Wu, R. Q., Chou, D. P. & Huang, Z. M. (1983). *Acta Pharm. Sci.* **18**, 900–904.