We thank M. Stephane Larrouture for his participation in the synthetic procedure.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1030). Services for accessing these data are described at the back of the journal.

References

Beuchet, P., Varache-Lembège, M., Neveu, A., Léger, J.-M., Larrouture, S., Deffieux, G. & Nuhrich, A. (1999). *Eur. J. Med. Chem.* In the press.
Cohen-Addad, C. (1982). *Acta Cryst.* B**38**, 1753–1757.
Cohen-Addad, C., Savariault, J.-M. & Lehmann, M. S. (1981). *Acta Cryst.* B**37**, 1703–1706.
Ekstrand, J. D. & van der Helm, D. (1977). *Acta Cryst.* B**33**, 1012–1016.
Emsley, J. (1989). In *The Elements*. Oxford: Clarendon Press.
Enraf–Nonius (1989). *CAD-4 Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Fehlmann, M. (1970). *Acta Cryst.* B**26**, 1736–1741.
Kalcheva, V., Tosheva, M. & Hadjieva, P. (1993). *Ann. Chem.* pp. 1319–1322.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Acta Cryst. (1999). C**55**, 794–796

(+)-(2*R-cis*)-Dimethyl(10-bromo-2,3,3a,8-tetrahydrodibenz[*c*,*f*]isoxazolo[2,3-*a*]azepin-2-ylmethyl)amine†

OSWALD M. PEETERS,[a] NORBERT M. BLATON,[a] CAMIEL J. DE RANTER[a] AND HANS L. DE WINTER[b]

[a]*Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium, and* [b]*Theoretical Medicinal Chemistry, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium. E-mail: maurice.peeters@farm.kuleuven.ac.be*

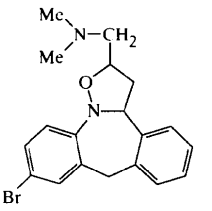
(*Received 7 December 1998; accepted 4 January 1999*)

Abstract

The title compound, $C_{19}H_{21}BrN_2O$, is a central active serotonin 5-HT_{2c} antagonist with some H_1 affinity. The (6,7,6)-tricyclic moiety is asymmetrically folded with a dihedral angle of 124.3 (1)° between the aromatic planes. The fused tetrahydroisoxazole ring adopts a conformation halfway between that of a twist and an envelope.

Comment

The structure of the title compound, (I), has been determined as part of our studies on serotonin antagonists (Peeters *et al.*, 1995, and references cited therein). The



(I)

compound is a central active serotonin 5-HT_{2c} antagonist with some H_1 affinity. *In vivo* the compound antagonizes anxiety symptoms (Meert, 1998).

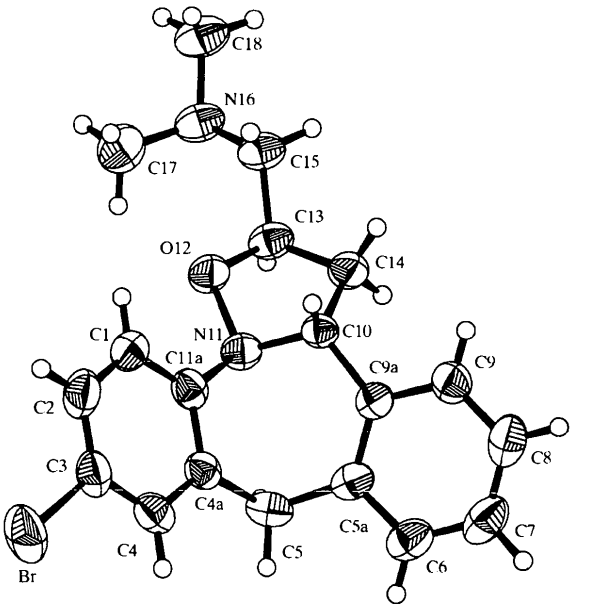


Fig. 1. Perspective view of the title compound with atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

The conformation and the atomic numbering scheme are shown in Fig. 1. The (6,7,6)-tricyclic moiety folds asymmetrically about a line through C5 and N11. The dihedral angle between the least-squares planes of the aromatic rings is 124.3 (1)°. The bond lengths do not show outstanding features. Apart from the endocyclic angles of the seven-membered ring, the bond angles have normal values. The endocyclic angles facing the non-bromo-substituted benzo ring are markedly enlarged. This enlarging and the

† Internal code of the Janssen Research Foundation: R110580.

asymmetric folding is common to almost all crystal structures of dihydrodibenzoheteroepines (Bandoli *et al.*, 1984). The C4a—C11a—N11 endocyclic angle [114.9 (4)°] is rather small for a C atom with sp^2 hybridization. The corresponding angle in Mianserin (van Rij & Feil, 1973) is 117.2°. The squeezing is probably due to the extra intramolecular hydrogen bond between the H(—C1) atom and the isoxazole O atom [H1···O12 = 2.38, C1···O12 = 2.694 (6) Å, C1—H1···O12 = 99°]. The central seven-membered ring adopts a distorted boat–sofa conformation with a pseudo mirror plane through C9a and the centre of the C4a—C11a bond [puckering parameters for the sequence N11,C11a,C4a,C5,C5a,C9a,C10: q_2 = 0.812 (4), q_3 = 0.321 (4), Q_T = 0.873 (4) Å, φ_2 = 19.6 (3), φ_3 = −45.1 (7)°; asymmetry parameter: Δ_s(C9a) = 0.057 (2)]. The tetrahydroisoxazole ring has a conformation halfway between a twist and an envelope, with the flap at the N11 atom [puckering parameters for the sequence O12,N11,C10,C14,C13: q_2 = 0.487 (3) Å, φ_2 = −153.0 (6)°; asymmetry parameters: Δ_s(N11) = 0.066 (2), Δ_2(C14) = 0.044 (2)]. There are no unusual intermolecular contacts.

Experimental

A sample of the title compound was obtained from the Janssen Research Foundation, Beerse, Belgium. Suitable crystals were obtained from an isopropyl ether solution at 277 K.

Crystal data

$C_{19}H_{21}BrN_2O$
M_r = 373.29
Monoclinic
$C2$
a = 22.07 (2) Å
b = 4.419 (6) Å
c = 22.29 (3) Å
β = 127.18 (8)°
V = 1732. (4) Å^3
Z = 4
D_x = 1.432 Mg m^{-3}
D_m = 1.429 Mg m^{-3}
D_m measured by flotation in aqueous KI solution

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 24 reflections
θ = 9.35–11.15°
μ = 2.380 mm^{-1}
T = 293 K
Prism
0.48 × 0.30 × 0.24 mm
Colourless

Data collection

Stoe Stadi4 four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1992*a*)
T_{min} = 0.383, T_{max} = 0.565
9380 measured reflections
1750 independent reflections (plus 1315 Friedel-related reflections)

2394 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.021
θ_{max} = 25°
h = −26 → 26
k = −5 → 5
l = −26 → 26
3 standard reflections
frequency: 60 min
intensity decay: 6.0%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.091
S = 1.056
3065 reflections
211 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0478P)^2 + 0.355P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001

$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0035 (5)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.01 (1)

Table 1. *Selected geometric parameters (°)*

C5—C4a—C11a	118.4 (3)	C10—N11—C11a	114.2 (4)
C4a—C5—C5a	115.6 (4)	C1—C11a—C4a	121.0 (3)
C5—C5a—C9a	123.9 (4)	C1—C11a—N11	124.1 (4)
C5a—C9a—C10	125.3 (3)	C4a—C11a—N11	114.9 (4)
C9a—C10—N11	114.5 (3)		
C11a—C4a—C5—C5a	65.3 (5)	C14—C10—N11—O12	−45.8 (3)
C5—C4a—C11a—N11	1.1 (6)	N11—C10—C14—C13	22.4 (4)
C4a—C5—C5a—C9a	−48.8 (6)	C10—N11—C11a—C4a	−81.3 (4)
C5—C5a—C9a—C10	−0.4 (6)	C10—N11—O12—C13	53.2 (3)
C5a—C9a—C10—N11	−8.5 (6)	N11—O12—C13—C14	−37.5 (4)
C9a—C10—N11—C11a	72.4 (4)	O12—C13—C14—C10	8.9 (4)

Data were collected using a variable scan speed between 0.5 and 2 s per step. The scan width was 1.08° (36 steps of 0.03°) plus α_1–α_2 dispersion. The structure was solved by Patterson and direct methods. Refinement with full-matrix least squares on F^2 for all reflections. H atoms were calculated at geometrical positions and allowed to ride on their parent atom.

Data collection: *DIF*4 (Stoe & Cie, 1992*b*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1992*c*). Program(s) used to solve structure: *DIRDIF*92 (Beurskens *et al.*, 1992). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *DIAMOND* (Bergerhoff, 1996). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1399). Services for accessing these data are described at the back of the journal.

References

Bandoli, G., Nicolini, M. & Tollenaere, J. P. (1984). *J. Crystallogr. Spectrosc. Res.* **14**, 401–446.
Bergerhoff, G. (1996). *DIAMOND. Visual Crystal Information System.* Bonn, Germany.
Beurskens, P. T., Admiraal, G., Beurskens, G., Bosman, W. P., Garcia-Granda, S., Gould, R. O., Smits, J. M. M. & Smykalla, C. (1992). *The DIRDIF Program System.* Technical Report. Crystallography Laboratory, University of Nijmegen, The Netherlands.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Meert, T. (1998). Personal communication.
Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.
Peeters, O. M., Blaton, N. M. & De Ranter, C. J. (1995). *Acta Cryst.* C**51**, 1435–1438
Rij, C. van & Feil, D. (1973). *Tetrahedron*, **29**, 1891–1893.
Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Stoe & Cie (1992a). *EMPIR. Empirical Absorption Correction Program.* Version 1.03. Stoe & Cie, Darmstadt, Germany.
Stoe & Cie (1992b). *DIF4. Diffractometer Control Program.* Version 7.09. Stoe & Cie, Darmstadt, Germany.
Stoe & Cie (1992c). *REDU4. Data Reduction Program.* Version 7.03. Stoe & Cie, Darmstadt, Germany.

Acta Cryst. (1999). C**55**, 796–798

The highly solvated structure of theonellapeptolide Id, a tridecapeptide lactone from the Okinawa marine sponge *Theonella swinhoei*

MITSUNOBU DOI,[a] TOSHIMASA ISHIDA,[a] MOTOMASA KOBAYASHI,[b] JEFFREY R. DESCHAMPS[c] AND JUDITH L. FLIPPEN-ANDERSON[c]

[a]*Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-11, Japan,* [b]*Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan, and* [c]*Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA. E-mail: doit@oysun01.oups.ac.jp*

(*Received 9 September 1997; accepted 4 November 1998*)

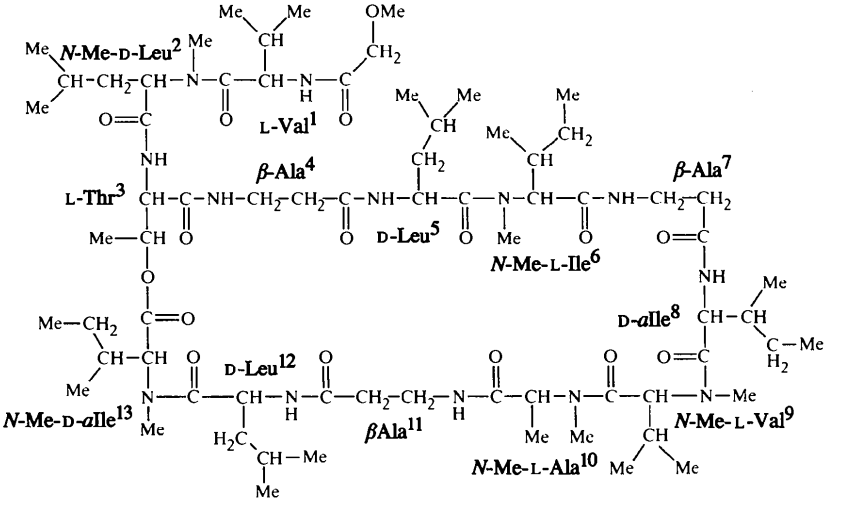
Abstract

Theonellapeptolide Id (TNLP-Id), $C_{70}H_{125}N_{13}O_{16}\cdot 12H_2O$, was crystallized from an aqueous methanol solution. This crystalline cyclic tridecapeptide is solvated by 12 water molecules, which interact with the backbone. All the solvent molecules are located on one face of the hydrophobic peptide. This suggests that the molecule also has unanticipated amphipathic properties. The uniquely folded cyclic backbone is composed of short and long turn units.

Comment

Theonellapeptolide Id (TNLP-Id) is the tridecapeptide lactone isolated from the Okinawa marine sponge *Theonella swinhoei*, and it shows potent cytotoxicity (Kobayashi *et al.*, 1991). The TNLP family has high hydrophobicity and is extracted by ethyl acetate with related peptides and macrolides (Kobayashi, Kanzaki *et al.*, 1994; Kobayashi, Kawazoe *et al.*, 1994). Their chemical structures contain unusual amino acids and most of the amide bonds are methylated. In TNLP-Id, the terminal N atom is capped by the methoxyacetate, and the terminal C atom bonds through an ester linkage to the hydroxyl group of the threonine[3] residue.

The highly hydrophobic title polypeptide was crystallized from aqueous methanol solution in a solvated form (Bernardinelli *et al.*, 1992). The 12 independent water molecules are associated with one face of TNLP-Id. The alkyl groups of the hydrophobic residues (Val, Leu and Ile) are assembled on the opposing face, as shown in Fig. 1. Previously, only hydrophobic properties were presumed to be associated with this molecule; selective hydration of a single surface, however, suggests that TNLP-Id also has amphipathic characteristics. Solvation occurs through hydrogen bonding with the amide bonds (Table 1) and networks are observed among the solvent molecules (not indicated). No direct interaction is observed between neighboring peptides, except for van der Waals contacts and water-mediated indirect connections that stabilize the molecular packing in the crystal. The intermolecular hydrogen bonds contribute to the formation of turn segments, which have



TNLP-Id