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Absolute configuration of *N*-[(−)-2-(7-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]cyclopropylcarboxamide, a highly potent and selective melatonin analogue

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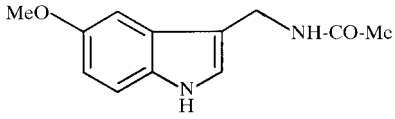
The title compound, $C_{17}H_{23}NO_2$, a tetrahydronaphthalenic analogue of melatonin, crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. The crystal structure has been determined by X-ray analysis at room temperature. The absolute configuration of this compound was determined unambiguously as *R* at the chiral naphthalene C-1 position.

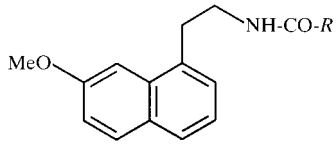
Comment

Melatonin (*N*-acetyl-5-methoxytryptamine), (I), is a hormone synthesized and secreted primarily by the pineal gland during darkness by all mammalian species (Reiter, 1991). The hormone has been the focus of considerable clinical interest in recent years. It is now well recognized as regulating circadian rhythms in humans and in different animal species (Arendt & Deacon, 1997). The effects of melatonin seem to be mediated through membrane receptors, recently classified as MT_1, MT_2 and MT_3.

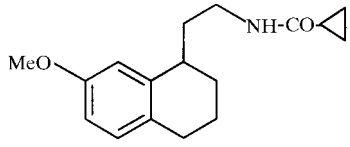
This interest prompted us to develop new melatonin receptor ligands and led us to the synthesis (Yous *et al.*, 1992) and crystallographic studies of naphthalenic bioisosteres (II) and (III) (Tinant *et al.*, 1993, 1994). Recently, we have synthesized a tetrahydronaphthalenic analogue, (IV) (Fourmaintraux *et al.*, 1998). The presence of a chiral centre in this compound, together with the pharmacological studies which showed that enantiomers of many drugs differ in activity, metabolism and toxicity, triggered the investigation of the racemic mixture (IV). Chiral direct high-pressure liquid chromatography (HPLC) has been recognized as a useful method for the resolution of racemates (Francotte & Junker-Buchheit, 1992). We obtained the two enantiomers of (IV) (Belloli *et al.*, 2001) by preparative chiral HPLC to investigate their biochemical stereoselective affinity. Preliminary results show that the (−) form has the greater affinity. Therefore, our pronounced interest was focused on the elucidation of the absolute configuration of the tetrahydronaphthalenic analogues of melatonin. A view of molecule (IV) with the atomic numbering is given in Fig. 1. The chiral centre is found to have the *R* configuration. The non-aromatic nucleus shows a half-chair conformation. Methylene atoms C7 and C8 are located



(I)



(II) $R = -Me$
(III) $R = -C_3H_5$



(IV)

at −0.475 (5) and 0.278 (5) Å, respectively, from the mean molecular plane (C5/C6/C9/C10). The amide and the naphthalene moieties are practically perpendicular: the dihedral angle between the two mean planes is 87.6 (1)°. This conformation is different from that of one of the two independent molecules of *N*-cyclopropylcarbonyl-2-(7-methoxy-1-naphthyl)ethylamine (Tinant *et al.*, 1993), in which the amide and naphthalene planes are approximately parallel. The methoxy

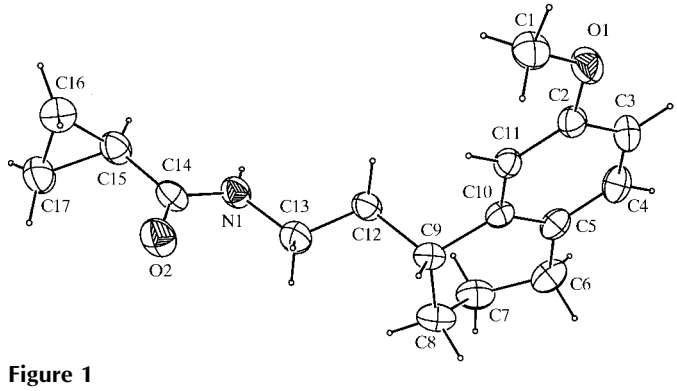


Figure 1
View of the title compound showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as small circles of arbitrary radii.

group is close to the plane of the aromatic ring and the conformation about the C2—O1 bond is staggered (*sp*) with a C11—C2—O1—C1 torsion angle of 3.3 (3)°. The distance between the methoxy O1 atom and the amide H1 atom, *i.e.* the two presumed polar anchoring points on the receptor (Lesieur, 1992), is 7.36 Å. By comparison, this distance is 7.34 Å in melatonin (Mostad & Romming, 1974) and 6.98 Å in molecule *A* of *N*-cyclopropylcarbonyl-2-(7-methoxy-1-naphthyl)ethylamine (Tinant *et al.*, 1993).

Experimental

For details of the preparation of the title compound, see Fourmaintraux *et al.* (1998).

Crystal data

$C_{17}H_{23}NO_2$
M_r = 273.36
Monoclinic, $P2_1$
a = 6.6653 (6) Å
b = 5.0767 (4) Å
c = 22.615 (2) Å
β = 95.262 (2)°
V = 762.0 (2) Å^3
Z = 2
D_x = 1.191 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5338 reflections
θ = 4.41–25.26°
μ = 0.077 mm^{-1}
T = 293 (2) K
Needle, colourless
0.20 × 0.18 × 0.08 mm

Data collection

Bruker SMART CCD diffractometer
ω scans
9999 measured reflections
2673 independent reflections
2422 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 25.26°
$h = -7 \rightarrow 7$
$k = -6 \rightarrow 6$
$l = -27 \rightarrow 27$
Intensity decay: none

Table 1
Selected geometric parameters (Å, °).

C1—O1	1.417 (3)	C14—C15	1.484 (3)
O1—C2	1.369 (2)	C15—C16	1.496 (4)
C13—N1	1.450 (3)	C15—C17	1.500 (3)
N1—C14	1.322 (3)	C16—C17	1.475 (3)
C14—O2	1.228 (2)		
C2—O1—C1	118.43 (14)	N1—C14—C15	115.91 (18)
O1—C2—C3	115.41 (15)	C14—C15—C16	117.9 (2)
O1—C2—C11	125.00 (16)	C14—C15—C17	117.01 (18)
C14—N1—C13	121.12 (19)	C16—C15—C17	58.97 (16)
O2—C14—N1	122.95 (19)	C17—C16—C15	60.65 (16)
O2—C14—C15	121.15 (18)	C16—C17—C15	60.38 (16)
C1—O1—C2—C3	−176.73 (17)	C9—C12—C13—N1	−179.57 (19)
C1—O1—C2—C11	3.3 (3)	C12—C13—N1—C14	−152.2 (2)
C10—C9—C12—C13	−156.68 (19)	C13—N1—C14—O2	1.0 (3)
C8—C9—C12—C13	75.5 (2)	C13—N1—C14—C15	−179.08 (19)

Refinement

Refinement on F^2
$R(F)$ = 0.036
$wR(F^2)$ = 0.107
S = 1.062
2673 reflections
191 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0703P)^2 + 0.0399P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = 0.01 (14)

The absolute configuration was determined by refinement of the Flack (1983) parameter, based on 1143 Friedel pairs. The reported configuration yielded x = 0.01 (14) while the inverse configuration yielded x = 1.01 (14). The NH and CH H atoms were included in observed positions and refined. Other H atoms were placed in calculated positions with C—H distances of 0.93 (Csp^2), 0.97 (CH_2) and 0.96 Å (CH_3). All H atoms were assigned an isotropic displacement parameter corresponding to 1.2U_{eq} of the attached parent atom.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1106). Services for accessing these data are described at the back of the journal.

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