Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

N-Nitrosomelatonin

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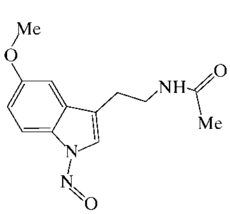
Received 18 November 1999
Accepted 23 March 2000

The title compound, *N*-[2-(5-methoxy-1-nitroso-1*H*-indol-3-yl)ethyl]acetamide, $C_{13}H_{15}N_3O_3$, an *N*-nitroso derivative of melatonin, crystallizes in the monoclinic *C*2/*c* space group. The molecules are arranged in such a way that the aromatic rings are in a planar conformation, with the alkylamide side chains in a different plane, at a dihedral angle of 108.60 (6)°. The alkylamide chains are interconnected by hydrogen bonds, constituting an infinite array.

Comment

The hormone melatonin (*N*-acetyl-5-methoxytryptamine), mainly produced by the pineal gland during the hours of darkness, mediates a variety of cellular, neuroendocrine and physiological processes (Casone, 1991). There have been multiple proposals that melatonin, as an antioxidant, can protect against damage caused by free radicals (Reiter *et al.*, 1997). Recently, we have proved the thermodynamic feasibility of melatonin reaction with the OH radical (Turjanski *et al.*, 1998). On the other hand, nitric oxide (NO) is a free radical that has been found to be involved in the regulation of a wide range of biological functions as an intercellular and



(I)

intracellular signal (Moncada *et al.*, 1991; Bredt & Snyder, 1994). Taking into account that NO may coexist with melatonin in biological media, we considered it worthwhile to analyse possible mechanisms of their interaction. The results of the present study include the characterization and X-ray

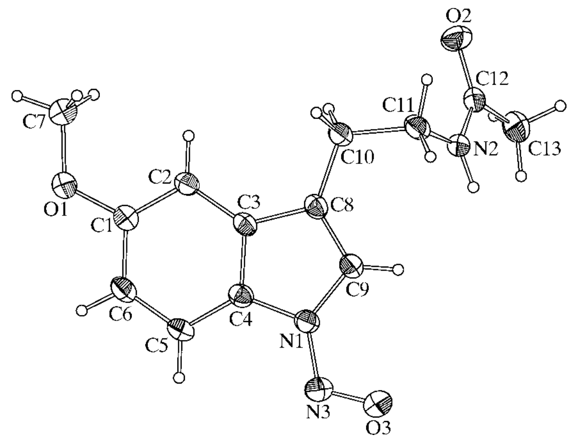


Figure 1
The molecular plot of (I) showing the atom-labelling scheme and displacement ellipsoids at the 30% probability level. H atoms are shown as spheres of arbitrary radii.

structure of the novel title compound, *N*-nitrosomelatonin, (I), the main product of the reaction of melatonin with NO.

In the molecule of (I), the N1 position is blocked by the nitroso group (Fig. 1). This results in a large difference in the crystal and molecular structures compared with melatonin (Quarles *et al.*, 1974). In the melatonin structure, atom O2 of one molecule shares a hydrogen bond with N2 and N1 of two different molecules, giving rise to an almost planar conformation of the whole molecule. In contrast, two different planes can be defined in the molecule of (I). One consists of the indol ring, the *N*-nitroso moiety and the methoxy group and is almost planar. The second plane contains the side chain (C11, N2, C12 and C13) in an extended conformation. The dihedral angle between these planes is 108.60 (6)°. The *N*-nitroso moiety is nearly coplanar with the indole ring, with a 5.5 (1)° deviation from planarity.

The methoxy group points toward atom C2. The NO moiety could crystallize in two different orientations, toward C9 or C4; a steric hindrance due to the methoxy group of the neighbouring molecule makes the conformation in which the nitroso group points to atom C9 the preferred one. Both N—N and N—O bond distances, as well as the N—N—O angle [1.339 (2) and 1.221 (2) Å, and 114.4 (2)°, respectively], are similar to those observed in other *N*-nitroso compounds (Allen & Kennard, 1993).

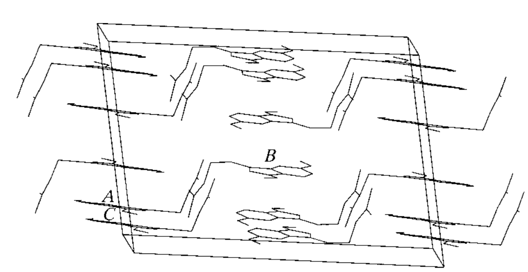


Figure 2
The crystal packing projection for (I) viewed down **b**, showing molecules *A*, *B* and *C* as referred to in the text. The *c* axis is horizontal and H atoms have been omitted for clarity.

Two different layers can be identified looking through the structure (Fig. 2), one of them containing the indole planes and the other a parallel arrangement of the alkylamide chains. Each alkylamide chain of a given molecule, *B*, is located between two alkylamide chains of molecules of (I), with their indole moieties coplanar (molecules *A* and *C*) and belonging to another plane above or below it. Hydrogen bonds maintain the linkage between the parallel alkylamide chains in the layer. There is a strong N—H···O bond between a given molecule and atom O2 of a neighbouring molecule: N···O 2.848 (3) Å and N—H···O 173.2 (1)°.

Experimental

Melatonin was purchased from Sigma and used as provided. NO was purchased from AGA and passed through NaOH pellets immediately before use. IR spectra were recorded as KBr disks with a Nicolet 510*p* FT–IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ solution with a 200 MHz Bruker AC200 instrument, using the solvent peak as the internal reference (δ 7.25 p.p.m.). A 5 m*M* solution of melatonin in acetonitrile was deoxygenated with nitrogen and stirred under an NO atmosphere. After 2 h, the yellow solution was cooled down to 253 K. Yellow crystals of (I) grew after a week. The most important bands in the IR spectrum are (KBr, cm^{-1}): 3300 (*s*) (ν_{NH} associated amine), 1636 (*s*), 1564 (*s*), 1474 (*s*), 1435 (*s*) (ν_{N-O} *N*-nitroso), 1314 (*s*) (ν_{C-N} *N*-nitroso), 1229 (*s*), 1148 (*s*) (ν_{N-N} *N*-nitroso), 1036 (*s*), 847 (*m*) and 723 (*m*); ^{1}H NMR shifts ($CDCl_3$, δ = 7.25 p.p.m.): 1.96 (*s*, 3H), 1.99 (*s*, 3H), 2.84–2.97 (*m*, 4H), 3.52–3.69 (*m*, 4H), 3.88 (*s*, 3H), 3.90 (*s*, 3H), 5.55 (*br s*, 2H), 6.90–7.04 (*m*, 2H), 7.08 (*s*, 2H), 7.54 (*s*, 1H), 7.94 (*s*, 1H), 8.04 (*d*, 1H), 8.29 (*d*, 1H). Two stable conformers, with the nitroso O atom *syn* or *anti* to the indole moiety, are found in $CDCl_3$ solution, giving rise to two sets of signals in the ^{1}H NMR spectra. Analysis calculated for $C_{13}H_{15}N_3O_3$: C 59.76, N 16.08, H 5.79%; found: C 60.14, N 15.99, H 6.19%.

Crystal data

$C_{13}H_{15}N_3O_3$	D_x = 1.349 Mg m^{-3}
M_r = 261.28	Mo $K\alpha$ radiation
Monoclinic, $C2/c$	Cell parameters from 23 reflections
a = 13.580 (5) Å	θ = 9.80–15.71°
b = 9.488 (2) Å	μ = 0.098 mm^{-1}
c = 20.266 (7) Å	T = 293 (2) K
β = 99.73 (3)°	Triangular prism, yellow
V = 2574 (1) Å^3	0.44 × 0.44 × 0.28 mm
Z = 8	

Table 1
Selected geometric parameters (Å, °).

C1—O1	1.362 (2)	C5—C6	1.376 (3)
C1—C2	1.389 (3)	C8—C9	1.344 (3)
C1—C6	1.398 (3)	C8—C10	1.491 (2)
C2—C3	1.392 (3)	C9—N1	1.404 (2)
C3—C4	1.388 (2)	N1—N3	1.339 (2)
C3—C8	1.459 (2)	C12—O2	1.229 (2)
C4—C5	1.383 (3)	N3—O3	1.221 (2)
C4—N1	1.407 (2)		
O1—C1—C2	124.3 (2)	C4—C5—C6	116.6 (2)
O1—C1—C6	114.6 (2)	C5—C6—C1	121.8 (2)
C2—C1—C6	121.1 (2)	C1—O1—C7	118.0 (2)
C1—C2—C3	117.4 (2)	C9—C8—C3	107.9 (2)
C4—C3—C2	120.3 (2)	C9—C8—C10	128.8 (2)
C4—C3—C8	107.3 (2)	C3—C8—C10	123.3 (2)
C2—C3—C8	132.3 (2)	N3—N1—C9	129.2 (2)
C5—C4—C3	122.8 (2)	N3—N1—C4	121.8 (2)
C5—C4—N1	130.1 (2)	C9—N1—C4	108.8 (2)
C3—C4—N1	107.1 (2)	O3—N3—N1	114.4 (2)

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 27.96°
$\omega/2\theta$ scans	$h = -17 \rightarrow 17$
3178 measured reflections	$k = 0 \rightarrow 12$
3094 independent reflections	$l = 0 \rightarrow 26$
2015 reflections with $I > 2\sigma(I)$	1 standard reflection frequency: 30 min
R_{int} = 0.011	intensity decay: 1.1%

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.042$	$w = 1/[\sigma^2(F_o^2) + (0.0594P)^2 + 1.79P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.109$	$(\Delta/\sigma)_{max} < 0.001$
S = 1.01	$\Delta\rho_{max}$ = 0.15 e Å^{-3}
3085 reflections	$\Delta\rho_{min}$ = −0.21 e Å^{-3}
177 parameters	

Several H atoms were detected at approximate locations in a difference Fourier map. Subsequently, however, they were positioned stereochemically and refined with a riding model. During the refinement, the H atoms of the two methyl groups were allowed to rotate as rigid groups around the C—CH_3 or O—CH_3 bonds. Three U_{iso} values were refined for the H atoms, one for the methyl-H atoms, one for the CH_2-H atoms and one for the remaining H atoms.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *SDP* (Frenz, 1983); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ORTEP* (Johnson, 1965); software used to prepare material for publication: *SHELXL*93.

This work was supported by CONICET, Fundación Antorchas, University of Buenos Aires and CICPBA of Argentina. The X-ray diffraction experiments were carried out at the National Diffraction Laboratory (LANADI), La Plata, Argentina. FD, OEP and DE are members of the scientific staff of CONICET. We also thank the Cambridge Structural Database.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1515). Services for accessing these data are described at the back of the journal.

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supporting information

Acta Cryst. (2000). C**56**, 682-683   [https://doi.org/10.1107/S010827010000456X]

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Computing details

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *SDP* (Frenz, 1983); program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993); molecular graphics: *ORTEP* (Johnson, 1965); software used to prepare material for publication: *SHELXL93*.

N-nitrosomelatonin

Crystal data

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M_r = 261.28
Monoclinic, *C*2/*c*
a = 13.580 (5) Å
b = 9.488 (2) Å
c = 20.266 (7) Å
β = 99.73 (3)°
V = 2574 (1) Å^3
Z = 8
F(000) = 1104
D_x = 1.349 Mg m^{-3}
Mo *Kα* radiation, *λ* = 0.71073 Å
Cell parameters from 23 reflections
θ = 9.8–15.7°
µ = 0.10 mm^{-1}
T = 293 K
Triangular prism, yellow
0.44 × 0.44 × 0.28 mm

Data collection

Enraf-Nonius CAD4 diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
ω/2*θ* scan
3178 measured reflections
3094 independent reflections
2015 reflections with $I > 2\sigma(I)$
R_{int} = 0.011
θ_{max} = 28.0°, θ_{min} = 2.0°
h = −17→17
k = 0→12
l = 0→26
1 standard reflections every 30 min
intensity decay: 1.1%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.109$
S = 1.08
3085 reflections
177 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0594P)^2 + 1.79P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement on F^2 for ALL reflections except for 0 with very negative F^2 or flagged by the user for potential systematic errors. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2\sigma(F^2)$ is used only for calculating R factor obs *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	y	z	U_{iso}*/U_{eq}
C1	0.87455 (14)	0.2415 (2)	0.59395 (9)	0.0417 (4)
C2	0.88099 (13)	0.2435 (2)	0.52626 (9)	0.0391 (4)
H2	0.88781 (13)	0.3277 (2)	0.50398 (9)	0.051 (3)*
C3	0.87684 (13)	0.1146 (2)	0.49309 (8)	0.0361 (4)
C4	0.86632 (13)	−0.0097 (2)	0.52732 (9)	0.0382 (4)
C5	0.85724 (14)	−0.0128 (2)	0.59424 (9)	0.0445 (4)
H5	0.84818 (14)	−0.0968 (2)	0.61607 (9)	0.051 (3)*
C6	0.8623 (2)	0.1148 (2)	0.62691 (9)	0.0465 (5)
H6	0.8574 (2)	0.1169 (2)	0.67213 (9)	0.051 (3)*
O1	0.87852 (12)	0.35842 (15)	0.63327 (7)	0.0552 (4)
C7	0.8877 (2)	0.4916 (2)	0.60300 (11)	0.0563 (5)
H7A	0.8868 (14)	0.5647 (2)	0.6356 (3)	0.093 (4)*
H7B	0.8330 (7)	0.5048 (8)	0.5668 (6)	0.093 (4)*
H7C	0.9496 (6)	0.4953 (7)	0.5861 (8)	0.093 (4)*
C8	0.88287 (13)	0.0770 (2)	0.42409 (8)	0.0380 (4)
C9	0.87660 (14)	−0.0640 (2)	0.41879 (9)	0.0413 (4)
H9	0.87845 (14)	−0.1156 (2)	0.38001 (9)	0.051 (3)*
N1	0.86679 (12)	−0.1208 (2)	0.48136 (8)	0.0413 (4)
C10	0.8950 (2)	0.1828 (2)	0.37167 (9)	0.0433 (4)
H10A	0.9575 (2)	0.2324 (2)	0.38548 (9)	0.050 (3)*
H10B	0.8415 (2)	0.2514 (2)	0.36917 (9)	0.050 (3)*
C11	0.8943 (2)	0.1224 (2)	0.30197 (9)	0.0454 (5)
H11A	0.9152 (2)	0.1952 (2)	0.27370 (9)	0.050 (3)*
H11B	0.9427 (2)	0.0465 (2)	0.30501 (9)	0.050 (3)*
N2	0.79779 (13)	0.0692 (2)	0.27069 (7)	0.0421 (4)
H2A	0.78426 (13)	−0.0183 (2)	0.27553 (7)	0.051 (3)*
C12	0.7294 (2)	0.1507 (2)	0.23482 (9)	0.0456 (5)
C13	0.6325 (2)	0.0817 (3)	0.20683 (11)	0.0620 (6)
H13A	0.6306 (6)	−0.0110 (8)	0.2255 (7)	0.093 (4)*
H13B	0.6264 (6)	0.0750 (17)	0.15904 (14)	0.093 (4)*
H13C	0.5783 (2)	0.1368 (10)	0.2180 (8)	0.093 (4)*
O2	0.74487 (14)	0.2758 (2)	0.22447 (9)	0.0688 (5)
N3	0.86643 (14)	−0.2560 (2)	0.50033 (9)	0.0500 (4)
O3	0.87183 (13)	−0.3404 (2)	0.45566 (8)	0.0644 (5)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0428 (10)	0.0445 (10)	0.0380 (9)	0.0015 (8)	0.0071 (8)	0.0021 (8)
C2	0.0399 (9)	0.0409 (9)	0.0359 (9)	−0.0030 (8)	0.0049 (7)	0.0055 (7)
C3	0.0336 (8)	0.0426 (9)	0.0312 (8)	−0.0015 (7)	0.0027 (6)	0.0051 (7)
C4	0.0346 (9)	0.0424 (10)	0.0371 (9)	−0.0025 (7)	0.0042 (7)	0.0045 (8)
C5	0.0502 (11)	0.0457 (11)	0.0387 (10)	−0.0001 (9)	0.0108 (8)	0.0116 (8)
C6	0.0536 (11)	0.0539 (12)	0.0339 (9)	0.0007 (9)	0.0129 (8)	0.0066 (8)
O1	0.0809 (11)	0.0457 (8)	0.0406 (7)	−0.0011 (7)	0.0151 (7)	−0.0015 (6)
C7	0.0720 (14)	0.0437 (11)	0.0531 (12)	−0.0030 (10)	0.0102 (10)	−0.0004 (9)
C8	0.0371 (9)	0.0434 (10)	0.0323 (8)	−0.0026 (7)	0.0024 (7)	0.0019 (7)
C9	0.0457 (10)	0.0441 (10)	0.0335 (9)	−0.0029 (8)	0.0045 (7)	0.0020 (8)
N1	0.0439 (9)	0.0407 (8)	0.0385 (8)	−0.0033 (7)	0.0050 (6)	0.0056 (6)
C10	0.0515 (11)	0.0436 (10)	0.0341 (9)	−0.0066 (8)	0.0050 (8)	0.0045 (8)
C11	0.0538 (11)	0.0478 (11)	0.0366 (9)	0.0025 (9)	0.0136 (8)	0.0071 (8)
N2	0.0594 (10)	0.0324 (8)	0.0341 (7)	0.0027 (7)	0.0067 (7)	0.0014 (6)
C12	0.0663 (13)	0.0378 (10)	0.0316 (9)	0.0057 (9)	0.0050 (8)	−0.0021 (7)
C13	0.0700 (15)	0.0652 (14)	0.0456 (12)	0.0000 (12)	−0.0055 (10)	0.0015 (11)
O2	0.0976 (13)	0.0358 (8)	0.0649 (10)	0.0057 (8)	−0.0095 (9)	0.0075 (7)
N3	0.0577 (10)	0.0395 (9)	0.0526 (10)	−0.0032 (8)	0.0091 (8)	0.0049 (8)
O3	0.0900 (12)	0.0437 (8)	0.0608 (10)	−0.0044 (8)	0.0163 (9)	−0.0018 (7)

Geometric parameters (Å, º)

C1—O1	1.362 (2)	C8—C9	1.344 (3)
C1—C2	1.389 (3)	C8—C10	1.491 (2)
C1—C6	1.398 (3)	C9—N1	1.404 (2)
C2—C3	1.392 (3)	N1—N3	1.339 (2)
C3—C4	1.388 (2)	C10—C11	1.523 (3)
C3—C8	1.459 (2)	C11—N2	1.447 (3)
C4—C5	1.383 (3)	N2—C12	1.327 (2)
C4—N1	1.407 (2)	C12—O2	1.229 (2)
C5—C6	1.376 (3)	C12—C13	1.493 (3)
O1—C7	1.419 (2)	N3—O3	1.221 (2)
O1—C1—C2	124.3 (2)	C9—C8—C10	128.8 (2)
O1—C1—C6	114.6 (2)	C3—C8—C10	123.3 (2)
C2—C1—C6	121.1 (2)	C8—C9—N1	108.9 (2)
C1—C2—C3	117.4 (2)	N3—N1—C9	129.2 (2)
C4—C3—C2	120.3 (2)	N3—N1—C4	121.8 (2)
C4—C3—C8	107.3 (2)	C9—N1—C4	108.80 (15)
C2—C3—C8	132.3 (2)	C8—C10—C11	115.0 (2)
C5—C4—C3	122.8 (2)	N2—C11—C10	113.6 (2)
C5—C4—N1	130.1 (2)	C12—N2—C11	122.4 (2)
C3—C4—N1	107.1 (2)	O2—C12—N2	122.1 (2)
C4—C5—C6	116.6 (2)	O2—C12—C13	121.6 (2)
C5—C6—C1	121.8 (2)	N2—C12—C13	116.3 (2)

C1—O1—C7	118.0 (2)	O3—N3—N1	114.4 (2)
C9—C8—C3	107.9 (2)		