References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435–436.

Belletti, D., Ugozzoli, F., Cantoni, A. & Pasquinelli, G. (1979). *Gestione on Line di Diffrattometro a Cristallo Singolo Siemens AED con Sistema General Automation Jumbo* 220. Internal Reports 1–3/79. Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma, Italy.

Caubère, P. (1974). *Acc. Chem. Res.* **7**, 301–308.

Caubère, P. (1978). *Top. Curr. Chem.* **73**, 50–124.

Caubère, P. (1991). *Rev. Heteroat. Chem.* **4**, 78–139.

Caubère, P. (1993). *Chem. Rev.* **93**, 2317–2334.

Caubère, P. & Guillaumet, G. (1972). *Bull. Soc. Chim. Fr.* pp. 4643–4649.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Jamart-Grégoire, B., Léger, C. & Caubère, P. (1990). *Tetrahedron Lett.* **31**, 7599–7602.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Lawton, S. L. & Jacobson, R. A. (1965). *The Reduced Cell and Its Crystallographic Applications*. Ames Laboratory. Available from the Clearing House for Federal Scientific and Technical Information, National Bureau of Standards, US Department of Commerce, Springfield, Virginia, USA.

Le Page, Y. (1987). *J. Appl. Cryst.* **20**, 264–269.

Mugnoli, A. (1985). *J. Appl. Cryst.* **18**, 183–184.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.

Nardelli, M. (1991a). *QCPE Bull.* **11**, p. xvii, QCMP097.

Nardelli, M. (1991b). *PARSTCIF. Program for Creating a CIF from the Output of PARST*. University of Parma, Italy.

Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.

Nardelli, M. & Mangia, A. (1984). *Ann. Chim. (Rome)*, **74**, 163–174.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Spek, A. L. (1988). *J. Appl. Cryst.* **21**, 578–579.

Tripos Associates Inc. (1992). *SYBYL. Molecular Modelling Software*. Version 6.0. Tripos Associates Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, Missouri 63144–2913, USA.

Zsolnai, L. & Pritzkow, H. (1994). *ZORTEP. ORTEP* modified for PC. University of Heidelberg, Germany.

4-(4-Chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutanamide N-Oxide Hydrate (Loperamide N-Oxide Hydrate)†

OSWALD M. PEETERS, NORBERT M. BLATON AND CAMIEL J. DE RANTER

Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium. E-mail: maurice.peeters@farm. kuleuven.ac.be

Abstract

The crystal structure of the title compound, $C_{29}H_{33}Cl\text{-}N_2O_3.2.25H_2O$, has been determined. The three C—N(piperidyl) bond lengths reflect the tetracovalency of the piperidine N atom. A strong intermolecular hydrogen bond between the hydroxyl and the N-oxide of neighbouring molecules forms endless chains in the **b** direction of the C2/c space group. The positions of the water molecules are partially occupied.

Comment

Loperamide N-oxide, (I), is a prodrug of loperamide, a specific long-acting antidiarrhoeal drug. In order to compare the structure of loperamide N-oxide with that of loperamide itself (Germain, Declercq, Van Meersche & Koch, 1977), its crystal structure has been determined.

(I)
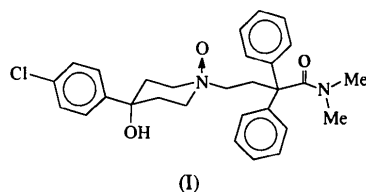
The conformation of the molecule and the atomic numbering scheme are given in Fig. 1. The overall conformation of (I) is very similar to that of loperamide. Corresponding torsion angles agree within 4° except for the N11—C16—C17—C18 torsion angle with values of 174.2 and −156.1 (2)° for loperamide and its N-oxide, respectively. The presence of the N-oxide lengthens the N—C bonds from a mean value of 1.468 Å in loperamide to a mean value of 1.505 Å in (I). These values agree well with the mean values of 1.471 and 1.509 Å found in 1,2-dipiperidinoethane mono-N-oxide

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† Internal code of the Janssen Research Foundation: R58425.

(Jaskólski, 1987). The molecules are linked by a strong hydrogen bond between the O14 and O15 atoms forming endless chains in the **b** direction. The possible hydrogen bonds involving the H_2O molecules are summarized in Table 3.
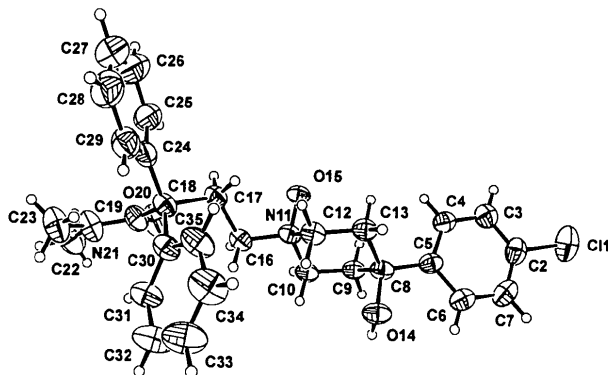

Fig. 1. Perspective view of the title compound with the atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

Experimental

Crystal data

$C_{29}H_{33}ClN_2O_3.2.25H_2O$	Cu $K\alpha$ radiation
$M_r = 533.58$	$\lambda = 1.54184$ Å
Monoclinic	Cell parameters from 41
$C2/c$	reflections
$a = 17.0543 (7)$ Å	$\theta = 11–27°$
$b = 9.6959 (6)$ Å	$\mu = 1.500$ mm^{-1}
$c = 35.025 (2)$ Å	$T = 293$ K
$\beta = 96.813 (4)°$	Prism
$V = 5750.8 (5)$ Å^3	$0.50 \times 0.20 \times 0.10$ mm
$Z = 8$	Colourless
$D_x = 1.233$ Mg m^{-3}	Crystal source: Janssen
$D_m = 1.232$ Mg m^{-3}	Research Foundation,
D_m measured by flotation in	Beerse, Belgium
n-heptane/CCl$_4$	

Data collection

Siemens $P4$ four-circle diffractometer	3030 observed reflections $[I > 2\sigma(I)]$
$\omega/2\theta$ scans	$R_{int} = 0.0225$
Absorption correction:	$\theta_{max} = 56.74°$
empirical *via* ψ scans	$h = -1 \rightarrow 18$
(*XEMP*; Siemens, 1989)	$k = -1 \rightarrow 10$
$T_{min} = 0.337$, $T_{max} = 0.464$	$l = -37 \rightarrow 37$
5226 measured reflections	3 standard reflections monitored every 100 reflections intensity decay: 3.5%
3851 independent reflections	

Refinement

Refinement on F^2	$\Delta\rho_{max} = 0.33$ e Å^{-3}
$R(F) = 0.0489$	$\Delta\rho_{min} = -0.18$ e Å^{-3}
$wR(F^2) = 0.1407$	Extinction correction:
$S = 1.057$	*SHELXL93* (Sheldrick, 1993)
3850 reflections	Extinction coefficient:
357 parameters	0.00057 (6)
H-atom parameters not refined	Atomic scattering factors from *International Tables*
$w = 1/[\sigma^2(F_o^2) + (0.0643P)^2 + 4.9738P]$	*for X-ray Crystallography*
where $P = (F_o^2 + 2F_c^2)/3$	(1974, Vol. IV, Tables
$(\Delta/\sigma)_{max} = -0.005$	2.2B and 2.3.1)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Cl1	0.49358 (6)	0.0675 (1)	0.59032 (2)	0.1005 (4)
C2	0.4530 (2)	0.0171 (4)	0.63160 (8)	0.066 (1)
C3	0.4391 (2)	0.1156 (3)	0.65793 (8)	0.063 (1)
C4	0.4058 (2)	0.0761 (3)	0.69033 (8)	0.0570 (9)
C5	0.3867 (2)	−0.0603 (3)	0.69691 (7)	0.0515 (9)
C6	0.4019 (2)	−0.1577 (3)	0.66957 (8)	0.064 (1)
C7	0.4347 (2)	−0.1192 (4)	0.63699 (9)	0.073 (1)
C8	0.3492 (1)	−0.1016 (2)	0.73260 (7)	0.0486 (8)
C9	0.2636 (1)	−0.0497 (3)	0.72898 (7)	0.0499 (9)
C10	0.2248 (2)	−0.0770 (3)	0.76459 (7)	0.0508 (9)
N11	0.2701 (1)	−0.0131 (2)	0.79972 (6)	0.0474 (7)
C12	0.3530 (1)	−0.0695 (3)	0.80420 (7)	0.0527 (9)
C13	0.3938 (2)	−0.0407 (3)	0.76942 (7)	0.0545 (9)
O14	0.3522 (1)	−0.2472 (2)	0.73796 (6)	0.0616 (7)
O15	0.2729 (1)	0.1297 (2)	0.79532 (5)	0.0528 (6)
C16	0.2284 (2)	−0.0482 (3)	0.83387 (7)	0.0570 (9)
C17	0.2615 (2)	0.0302 (3)	0.87009 (7)	0.056 (1)
C18	0.2472 (2)	−0.0399 (3)	0.90881 (8)	0.0560 (9)
C19	0.1579 (2)	−0.0276 (3)	0.91294 (9)	0.064 (1)
O20	0.1136 (1)	0.0278 (3)	0.88721 (7)	0.0870 (9)
N21	0.1283 (2)	−0.0734 (3)	0.94447 (8)	0.0761 (9)
C22	0.0433 (2)	−0.0614 (4)	0.9458 (1)	0.101 (2)
C23	0.1718 (2)	−0.1398 (4)	0.9776 (1)	0.091 (1)
C24	0.2935 (2)	0.0484 (3)	0.94086 (8)	0.063 (1)
C25	0.2775 (3)	0.1877 (4)	0.9425 (1)	0.090 (1)
C26	0.3176 (4)	0.2726 (5)	0.9695 (1)	0.127 (2)
C27	0.3753 (4)	0.2180 (7)	0.9961 (1)	0.127 (3)
C28	0.3919 (3)	0.0806 (6)	0.9954 (1)	0.111 (2)
C29	0.3513 (2)	−0.0052 (4)	0.96760 (9)	0.083 (1)
C30	0.2758 (2)	−0.1888 (3)	0.90703 (8)	0.059 (1)
C31	0.2257 (2)	−0.3014 (3)	0.90576 (9)	0.072 (1)
C32	0.2524 (2)	−0.4332 (4)	0.8994 (1)	0.098 (2)
C33	0.3286 (3)	−0.4561 (4)	0.8939 (1)	0.104 (2)
C34	0.3796 (2)	−0.3455 (4)	0.8947 (1)	0.094 (2)
C35	0.3538 (2)	−0.2151 (3)	0.9011 (1)	0.075 (1)
O36†	1/2	−0.3831 (3)	3/4	0.120 (2)
O37†	1/2	−0.6670 (9)	3/4	0.207 (8)
O38†	0.5053 (5)	−0.5274 (9)	0.6752 (2)	0.185 (4)
O39†	0.6135 (4)	−0.7222 (7)	0.6595 (2)	0.106 (3)
O40†	0.5907 (5)	−0.7157 (9)	0.6962 (6)	0.272 (9)

† Partial occupation (see below).

Table 2. *Selected geometric parameters (Å, °)*

Cl1—C2	1.745 (3)	C18—C19	1.552 (4)
C2—C3	1.368 (4)	C18—C24	1.551 (4)
C2—C7	1.376 (5)	C18—C30	1.528 (4)
C3—C4	1.382 (4)	C19—O20	1.229 (4)
C4—C5	1.388 (4)	C19—N21	1.343 (4)
C5—C6	1.391 (4)	N21—C22	1.462 (5)
C5—C8	1.524 (4)	N21—C23	1.451 (4)
C6—C7	1.381 (4)	C24—C25	1.381 (5)
C8—C9	1.536 (3)	C24—C29	1.378 (4)
C8—C13	1.535 (3)	C25—C26	1.373 (6)
C8—O14	1.424 (3)	C26—C27	1.377 (7)

$C_{29}H_{33}ClN_2O_3.2.25H_2O$

C9—C10	1.503 (4)	C27—C28	1.363 (9)
C10—N11	1.506 (3)	C28—C29	1.399 (6)
N11—C12	1.507 (3)	C30—C31	1.383 (4)
N11—O15	1.395 (3)	C30—C35	1.394 (4)
N11—C16	1.502 (4)	C31—C32	1.382 (5)
C12—C13	1.498 (4)	C32—C33	1.355 (6)
C16—C17	1.529 (4)	C33—C34	1.379 (6)
C17—C18	1.562 (4)	C34—C35	1.367 (5)
C11—C2—C7	120.1 (2)	C17—C18—C30	107.0 (2)
C11—C2—C3	118.7 (2)	C17—C18—C24	105.7 (2)
C3—C2—C7	121.2 (3)	C17—C18—C19	107.7 (2)
C2—C3—C4	118.8 (3)	C24—C18—C30	114.5 (2)
C3—C4—C5	121.8 (3)	C19—C18—C30	113.4 (2)
C4—C5—C8	121.1 (2)	C19—C18—C24	108.1 (2)
C4—C5—C6	117.8 (2)	C18—C19—N21	121.3 (3)
C6—C5—C8	121.1 (2)	C18—C19—O20	119.4 (3)
C5—C6—C7	120.8 (3)	O20—C19—N21	119.3 (3)
C2—C7—C6	119.6 (3)	C19—N21—C23	126.7 (3)
C5—C8—O14	110.9 (2)	C19—N21—C22	118.1 (3)
C5—C8—C13	112.0 (2)	C22—N21—C23	115.2 (3)
C5—C8—C9	109.5 (2)	C18—C24—C29	123.1 (3)
C13—C8—O14	105.3 (2)	C18—C24—C25	118.9 (3)
C9—C8—O14	110.8 (2)	C25—C24—C29	118.0 (3)
C9—C8—C13	108.3 (2)	C24—C25—C26	122.1 (4)
C8—C9—C10	112.4 (2)	C25—C26—C27	119.4 (5)
C9—C10—N11	111.9 (2)	C26—C27—C28	119.9 (4)
C10—N11—C16	108.2 (2)	C27—C28—C29	120.4 (4)
C10—N11—O15	109.8 (2)	C24—C29—C28	120.3 (4)
C10—N11—C12	108.7 (2)	C18—C30—C35	119.5 (3)
O15—N11—C16	109.8 (2)	C18—C30—C31	123.3 (3)
C12—N11—C16	111.3 (2)	C31—C30—C35	116.6 (3)
C12—N11—O15	109.2 (2)	C30—C31—C32	121.4 (3)
N11—C12—C13	111.6 (2)	C31—C32—C33	120.9 (3)
C8—C13—C12	112.4 (2)	C32—C33—C34	118.8 (4)
N11—C16—C17	112.6 (2)	C33—C34—C35	120.6 (3)
C16—C17—C18	115.1 (2)	C30—C35—C34	121.7 (3)
C6—C5—C8—O14	14.8 (3)	C16—C17—C18—C19	−70.8 (3)
C5—C8—C9—C10	−175.4 (2)	C16—C17—C18—C24	173.8 (2)
O14—C8—C9—C10	61.9 (3)	C16—C17—C18—C30	51.4 (3)
C9—C10—N11—O15	61.5 (2)	C17—C18—C30—C31	−113.1 (3)
C9—C10—N11—C16	−178.7 (2)	C17—C18—C24—C29	−122.5 (3)
C10—N11—C16—C17	−170.8 (2)	C17—C18—C19—N21	−176.9 (3)
N11—C16—C17—C18	−156.1 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O14—H14···O15^i	0.82	1.78	2.596 (2)	174
O36—H36···O14	1.14	1.72	2.831 (2)	165
O37—H37···O38	1.16	1.81	2.959 (9)	172
O38—H38A···O36	0.90	2.36	2.980 (9)	126
O38—H38B···O20^i	0.91	1.98	2.852 (8)	160
O39—H39A···O38	1.18	1.66	2.74 (1)	150
O39—H39B···O15^{ii}	1.20	1.57	2.755 (7)	168

Symmetry codes: (i) $\frac{1}{2} - x, y - \frac{1}{2}, \frac{3}{2} - z$; (ii) $1 - x, y - 1, \frac{3}{2} - z$.

The structure was solved using direct methods. Isotropic refinement and subsequent electron-density synthesis revealed five extra atomic peaks, two of which were at a special position. Although two positions are at a bonding distance of ca 1.40 Å and could represent a methanol molecule, the electron density in this region was finally assigned to two partially occupied H_2O molecules suggested by the hydrogen-bonding scheme. Based on the measured density, which indicates 2.25 molecules of H_2O in the asymmetric unit, and on the electron density, the O36–O40 atoms were included in the full-matrix least-squares anisotropic refinement (on F^2) with fixed site-occupation factors of 0.50, 0.25, 0.50, 0.50 and 0.50, respectively. The H atoms of the loperamide N-oxide molecule were positioned geometrically and allowed to ride on their parent atoms. The H atoms of the H_2O molecules were located from ΔF maps, except for those of O40 which could not be found.

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEX*2.1 (McArdle, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: NA1244). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Germain, G., Declercq, J.-P., Van Meersche, M. & Koch, M. H. J. (1977). *Acta Cryst.* B33, 942–944.
Jaskólski, M. (1987). *Acta Cryst.* C43, 2391–2393.
McArdle, P. (1994). *J. Appl. Cryst.* 27, 438–439.
Nardelli, M. (1983). *Comput. Chem.* 7, 95–98.
Sheldrick, G. M. (1985). *SHELXS86. Program for the Solution of Crystal Structures.* University of Göttingen, Germany.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.
Siemens (1989). *XEMP. Empirical Absorption Correction Program.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1994). *XSCANS. X-ray Single Crystal Analysis Software.* Version 2.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

2-Ethyl-3-(3-pyridyl)-5(2H)-isoxazolone

Karla Frydenvang, Lotte Brehm, Roberto di Biase† and Erik Falch

PharmaBiotec Research Center, Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark. E-mail: karla@medchem.dfh.dk

Abstract

The 3-isoxazoline ring in the title compound, $C_{10}H_{10}N_2O_2$, adopts a flattened envelope conformation. The interplanar angle between the two ring systems is 31.71 (5)°, but the connecting single bond may indicate a certain degree of conjugation. The crystal packing is