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Structure of Oxatomide Monohydrate: an Anti-Allergic Drug

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Abstract

The crystal structure of the monohydrate of oxatomide, 1-{3-[4-(diphenylmethyl)-1-piperazinyl]propyl}-1,3-dihydro-2*H*-benzimidazol-2-one, has been determined at 100 K. The oxatomide molecule adopts an extended conformation with a planar benzimidazolone fragment. The water molecule has a cohesive function, connecting three oxatomide molecules by intermolecular hydrogen bonds.

Comment

Oxatomide (1) is a potent broad-scale anti-allergic drug by virtue of its inhibition of both the release and the action of allergic mediators (Awouters *et al.*, 1977). The structure analysis of oxatomide was carried out as part of an investigation into the biologically active conformation of certain H_1-histamine-receptor agonists and antagonists (Richards, Brogden, Heel, Speight & Avery, 1984). A comparison of the crystal structure conformation with conformations obtained by molecular modelling of the active site could provide more insight into the actions of pharmaceuticals at the molecular level. The two central torsion angles in the propyl residue, N2—C8—C9—C10 and C8—C9—C10—N3, are 178.0(3) and 169.2(3)° respectively, resulting in an extended conformation rather than a folded one. The benzimidazolone moiety is planar and rotated through 78.8(3)° with respect to the almost planar C8—C9—C10—N3 chain. The piperazine ring has a chair conformation, with the substituents on both N atoms in equatorial positions. All hydrogen bonds are intermolecular. The cohesive role of water in the hydrogen-bond framework is embodied by its interaction as a donor to the O1 atom of the carbonyl group of an oxatomide residue at (x, y, z) and to N3 in the piperazine ring of a residue at ($1/2-x$, $1/2+y$, $1/2-z$), and as an acceptor of a hydrogen bond donated by N1—H of the residue at ($1/2-x$, $1/2-y$, $1-z$). The donor-acceptor distances are 2.801(3), 2.846(4) and 2.756(4) Å respectively, and the donor-hydrogen-acceptor angles are 173(5), 176(4) and 169(4)°.

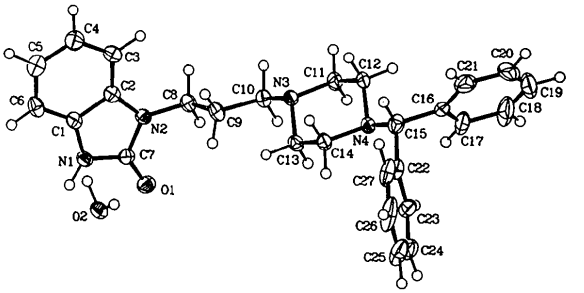
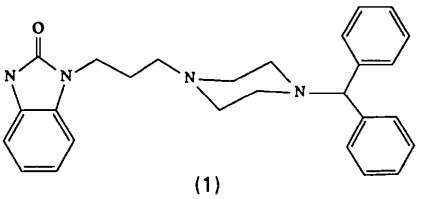


Fig. 1. View (Johnson, 1976) of oxatomide monohydrate showing the labelling of the non-H atoms. Thermal ellipsoids are shown at the 50% probability level and H atoms are drawn as small circles of arbitrary radius.



(1)

Experimental

Crystal data

$C_{27}H_{30}N_4O.H_2O$
M_r = 444.58
Monoclinic
$C2/c$
a = 31.1173 (16) Å
b = 8.9219 (6) Å
c = 19.0721 (14) Å
β = 112.853 (5)°
V = 4879.3 (6) Å^3
Z = 8
D_x = 1.210 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10.84–17.66°
μ = 0.73 mm^{-1}
T = 100 K
Platelet
0.55 × 0.20 × 0.15 mm
Colourless
Crystal source: Janssen Pharmaceutica, Beerse, Belgium

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
4793 measured reflections
4353 independent reflections
3005 observed reflections [$I>2.5\sigma(I)$]
R_{int} = 0.0409
θ_{max} = 25.37°
h = −34 → 35
k = −10 → 0
l = −22 → 0
3 standard reflections
frequency: 60 min
intensity variation: 1.2%

0108-2701/92/091712-02$06.00

Refinement

Refinement on F
Final R = 0.0581
wR = 0.0568
S = 0.94
2905 reflections
373 parameters
All hydrogen parameters were refined except those of the H atoms on the constrained phenyl ring
$w = 1/\sigma^2(F_o)$
$(\Delta/\sigma)_{max}$ = 0.20
$\Delta\rho_{max}$ = 0.64 e Å^{-3}
$\Delta\rho_{min}$ = −0.40 e Å^{-3}
Extinction correction: *SHELX76*
Extinction coefficient: 0.0005
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B)

Cell refinement: *SET4* (de Boer & Duisenberg, 1984). Data reduction: *HELENA* (Spek, 1990*a*). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1986). Program(s) used to refine structure: *SHELX76* (Sheldrick, 1976). Software used to prepare material for publication: *PLATON* (Spek, 1990*b*).

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

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O1	0.22002 (7)	0.2642 (2)	0.3400 (1)	0.0313 (6)
N1	0.29023 (9)	0.1433 (3)	0.4106 (2)	0.027 (1)
N2	0.27849 (8)	0.2210 (3)	0.2950 (1)	0.0239 (6)
N3	0.19488 (8)	0.1118 (3)	0.0200 (1)	0.0221 (6)
N4	0.12599 (8)	−0.0347 (3)	−0.1117 (1)	0.0248 (8)
C1	0.3304 (1)	0.1088 (3)	0.3983 (2)	0.025 (1)
C2	0.3225 (1)	0.1552 (3)	0.3243 (2)	0.024 (1)
C3	0.3557 (1)	0.1334 (4)	0.2940 (2)	0.030 (1)
C4	0.3971 (1)	0.0662 (4)	0.3398 (2)	0.036 (1)
C5	0.4056 (1)	0.0233 (4)	0.4147 (2)	0.034 (1)
C6	0.3716 (1)	0.0446 (4)	0.4445 (2)	0.031 (1)
C7	0.2587 (1)	0.2138 (3)	0.3482 (2)	0.026 (1)
C8	0.2545 (1)	0.2812 (4)	0.2187 (2)	0.026 (1)
C9	0.2340 (1)	0.1577 (4)	0.1598 (2)	0.028 (1)
C10	0.2078 (1)	0.2248 (3)	0.0815 (2)	0.026 (1)
C11	0.1732 (1)	0.1869 (4)	−0.0543 (2)	0.029 (1)
C12	0.1599 (1)	0.0733 (4)	−0.1181 (2)	0.029 (1)
C13	0.1611 (1)	0.0029 (3)	0.0264 (2)	0.025 (1)
C14	0.1479 (1)	−0.1099 (3)	−0.0379 (2)	0.025 (1)
C15	0.1132 (1)	−0.1455 (4)	−0.1742 (2)	0.029 (1)
C16	0.08845 (8)	−0.0712 (3)	−0.2509 (1)	0.037 (1)
C17	0.05696 (8)	0.0456 (3)	−0.2596 (1)	0.048 (1)
C18	0.03262 (8)	0.1073 (3)	−0.3314 (1)	0.084 (2)
C19	0.03978 (8)	0.0523 (3)	−0.3944 (1)	0.124 (3)
C20	0.07127 (8)	−0.0644 (3)	−0.3857 (1)	0.122 (3)
C21	0.09561 (8)	−0.1262 (3)	−0.3139 (1)	0.076 (2)
C22	0.0828 (1)	−0.2694 (3)	−0.1629 (2)	0.026 (1)
C23	0.0429 (1)	−0.2362 (4)	−0.1507 (2)	0.032 (1)
C24	0.0155 (1)	−0.3496 (4)	−0.1404 (2)	0.047 (1)
C25	0.0276 (1)	−0.4973 (5)	−0.1428 (3)	0.058 (1)
C26	0.0671 (2)	−0.5318 (4)	−0.1558 (2)	0.056 (2)
C27	0.0949 (1)	−0.4189 (4)	−0.1656 (2)	0.040 (1)
O2	0.22301 (8)	0.4473 (3)	0.4611 (1)	0.0281 (6)

Table 2. *Geometric parameters* (Å, °)

O1—C7	1.237 (4)	N4—C12	1.469 (4)
N1—C1	1.393 (5)	N4—C14	1.467 (4)
N1—C7	1.367 (5)	N4—C15	1.479 (4)
N2—C2	1.392 (4)	C8—C9	1.525 (5)
N2—C7	1.378 (4)	C9—C10	1.519 (5)
N2—C8	1.456 (4)	C11—C12	1.513 (5)
N3—C10	1.479 (4)	C13—C14	1.515 (4)
N3—C11	1.473 (4)	C15—C16	1.516 (4)
N3—C13	1.471 (4)	C15—C22	1.524 (5)
C1—N1—C7	110.0 (3)	N1—C7—N2	106.7 (3)
C2—N2—C7	109.6 (2)	N2—C8—C9	112.0 (3)
C2—N2—C8	126.8 (3)	C8—C9—C10	110.5 (3)
C7—N2—C8	123.4 (3)	N3—C10—C9	112.8 (2)
C10—N3—C11	109.6 (2)	N3—C11—C12	110.4 (3)
C10—N3—C13	111.6 (2)	N4—C12—C11	110.7 (3)
C11—N3—C13	107.8 (2)	N3—C13—C14	110.5 (3)
C12—N4—C14	107.4 (2)	N4—C14—C13	110.6 (2)
C12—N4—C15	110.4 (2)	N4—C15—C16	111.2 (3)
C14—N4—C15	110.3 (2)	N4—C15—C22	111.0 (3)
N1—C1—C2	106.7 (3)	C16—C15—C22	110.1 (3)
N1—C1—C6	131.5 (3)	C15—C16—C17	120.8 (2)
N2—C2—C1	106.9 (3)	C15—C16—C21	119.1 (2)
N2—C2—C3	132.2 (3)	C15—C22—C23	121.1 (3)
O1—C7—N1	127.7 (3)	C15—C22—C27	119.9 (3)
O1—C7—N2	125.5 (3)		

All non-H atoms in the structure were found by direct methods except for three C atoms in one of the phenyl rings. During initial refinements, these missing C atoms were located in difference electron density syntheses. In subsequent refinements, anisotropic thermal parameters were used for all non-H atoms. The H atoms on the benzimidazolone moiety and those on the sp^3 C atoms were located from difference electron density syntheses and included in the refinement. The C atoms of the terminal phenyl rings display a high thermal motion which is possibly the cause of deviating geometries upon refinement. Since no satisfactory disorder model could be derived, one of the phenyl rings was constrained to a regular hexagon during refinement and the H atoms of the phenyl rings were placed at calculated positions. The H atoms were given overall isotropic U values according to their different types (phenyl-ring, benzimidazolone-ring, Csp^3 and water H atoms).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55233 (32 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB1009]

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