Crystal Structure of α -Bicyclo[2.2.1]hept-5-en-2-yl- α -phenyl-1-piperidine-propanol (Biperiden)

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Biperiden (Fig. 1) is an anticholinergic drug used for treatment of the Parkinson syndrome.¹ The crystal structures of (+)-biperiden and (+)-biperiden L-(+)-mandelate were determined by X-ray crystallography.² The conformations of (+)-biperiden are markedly different in the ion and in the free base. The title compound is the free base of the racemate. The X-ray analysis of the title compound was undertaken in order to compare the three-dimensional structures of the free base forms of the (+)-enantiomer and the racemate.

Fig. 1 Chemical structures.

A colorless platelike crystal with the dimensions of 0.40×0.35×0.25 mm was obtained from an ethanol solution at 293(1)K and was used for the diffraction experiments. The crystal and experimental data are given in Table 1. The structure was solved by direct methods and refined by full-matrix least-squares methods with anisotropic temperature factors for non-H atoms. All H atoms were found from difference Fourier maps and refined isotropically. Atomic parameters for non-hydrogen atoms are listed in Table 2.

Selected bond distances and angles are listed in Table 3. An ORTEP II⁵ drawing of the title compound together with the atomic numbering is shown in Fig. 2. Bond distances and angles are within the expected ranges. The conformation of the title compound is very similar to that of the free base of the (+)-biperiden. The alkyl chain connecting the C8 atom and the piperidinyll ring is folded. The torsion angle along this chain

Table 1 Crystal and experimental data

Formula: C ₂₁ H ₂₉ NO
Formula weight=311.47
Crystal system: monoclinic
Space group: <i>P</i> 2 ₁ / <i>n</i> <i>Z</i> =4
<i>a</i> =16.175(3)Å
<i>b</i> =5.789(6)Å <i>β</i> =106.79(7)°
<i>c</i> =20.363(8)Å
<i>V</i> =1825(2)Å ³
<i>D_x</i> =1.133 g/cm ³
No. of reflections used=2363
2 θ _{max} =120° with Cu K α
<i>R</i> =0.053
(Δ / σ) _{max} =0.066
($\Delta\rho$) _{max} =0.18 eÅ ⁻³
($\Delta\rho$) _{min} =-0.08 eÅ ⁻³
Measurement: Enraf-Nonius CAD-4 Turbo
Program system: Structure Determination Package for Windows ³
Structure determination: MULTAN ⁴
Refinement: full-matrix

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (*B*_{eq})

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
O	0.7286(1)	0.0544(3)	0.03306(9)	3.80(4)
N	0.6495(1)	0.2952(4)	0.1163(1)	3.54(5)
C1	0.5569(2)	0.3082(6)	0.0772(2)	4.48(7)
C2	0.5084(2)	0.0959(7)	0.0895(2)	5.02(8)
C3	0.5173(2)	0.0661(8)	0.1655(2)	5.61(9)
C4	0.6125(2)	0.0682(7)	0.2063(2)	5.27(9)
C5	0.6587(2)	0.2785(7)	0.1903(1)	4.64(8)
C6	0.6984(2)	0.4935(6)	0.1015(2)	4.36(7)
C7	0.7173(2)	0.4726(5)	0.0329(2)	3.98(7)
C8	0.7738(2)	0.2626(5)	0.0278(1)	3.35(6)
C9	0.7928(2)	0.2606(5)	-0.0422(1)	3.60(6)
C10	0.7120(2)	0.2198(6)	-0.1071(2)	4.29(7)
C11	0.7456(3)	0.2998(7)	-0.1666(2)	5.96(9)
C12	0.8023(2)	0.1477(7)	-0.1747(2)	5.79(9)
C13	0.8090(2)	-0.0406(6)	-0.1223(2)	4.94(8)
C14	0.8559(2)	0.0661(6)	-0.0507(2)	4.48(7)
C15	0.7156(2)	-0.0426(6)	-0.1178(2)	4.62(7)
C16	0.8605(2)	0.2733(5)	0.0844(1)	3.62(6)
C17	0.8860(2)	0.0997(6)	0.1325(2)	4.63(8)
C18	0.9653(2)	0.1124(7)	0.1825(2)	5.98(9)
C19	1.0198(2)	0.2946(8)	0.1850(2)	5.98(9)
C20	0.9955(2)	0.4683(8)	0.1378(2)	6.2(1)
C21	0.9159(2)	0.4595(6)	0.0878(2)	5.12(8)

$$B_{eq}=8\pi^2/3 \sum_i \sum_j U_{ij} a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j).$$

Table 3 Selected bond distances(Å) and angles(°)

O---C8	1.429(3)	N---C1	1.482(3)
N---C5	1.474(4)	N---C6	1.474(4)
C1---N---C5	109.9(2)	C1---N---C6	111.7(2)
C5---N---C6	111.0(2)	N---C1---C2	111.1(2)
N---C5---C4	111.2(2)	N---C6---C7	112.9(2)
O---C8---C7	109.5(2)	O---C8---C9	107.8(2)
O---C8---C16	110.7(2)		

(N-C6-C7-C8) is $-62.1(3)^\circ$, this angle is $-63.2(2)^\circ$ in the free base of the (+)-enantiomer. The positions of the other substituents on the C8 atom, relative to the C6-C7 bond, in the title compound are similar to those in the free base of the (+)-enantiomer. As in the free base of the (+)-enantiomer, there is an intramolecular hydrogen bond between the O and N atoms. The distances are O...N 2.776(3) and H...N 2.18(3) Å, and the angle O-H...N is $148(1)^\circ$. This intramolecular hydrogen bond contributes to determine the conformation of the molecule. The conformation of the piperidine ring is flattened around the C3 atom. The torsion angles of C1-C2-C3-C4 and C2-C3-C4-C5 are $-53.2(4)$ and $52.8(4)^\circ$, respectively. Such flattening which is also found in the free base of the (+)-enantiomer decreases the 1,3-diaxial interactions of H atoms with the lone pair on the N atom. There is no intermolecular contact shorter than the sum of the van der Waals radii. As the low D_x value of 1.133 indicates, the molecules are loosely packed in the crystal.

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Fig. 2 ORTEP drawing of the molecule, representing heavy atoms as 50% probability ellipsoids and H atoms as spheres of arbitrary radius.

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(Received March 9, 1999)

(Accepted April 27, 1999)