Crystal Structures of Synthetic Analgetics. IV. Dextropropoxyphene

ERIK BYE

Department of Chemistry, University of Oslo, Oslo 3, Norway

The molecular and crystal structure of dextropropoxyphene has been determined by X-ray methods. The crystals are monoclinic, space group $P2_1$, with unit cell dimensions $a = 9.257(2)\ \AA$; $b = 9.048(3)\ \AA$; $c = 12.074(7)\ \AA$; $\beta = 93.01(4)\degree$. The phase problem was solved by direct methods and the model refined to an $R$-value of 0.038 for 1799 observed reflections. E.s.d.'s are, in average, 0.004 Å and 0.3° in interatomic distances and angles, respectively.

The propylamine chain is nearly fully extended, the dihedral angle $C4 - C5 - C7 - N$ being $-174.2\degree$. The conformation of this side chain is similar to that in the hydrochloride of the title compound. Thus the proposed bioactive conformation is not preferred by propoxyphene in the crystalline state, as was the case for the free base of methadone.

Propoxyphene (I) is one of the few morphinelike synthetic analgetics that are not narcotic. It is a widely used medicinal agent against moderate pain, and related to methadone (II). These two and other analogous diphenylpropylamines have a potential conformational flexibility in the side chain. Extensive stereochemical studies have been performed on these acyclic analgetics with the objective to elucidate the structure-activity relationships (SAR) of these compounds. Several X-ray crystallographic determinations have been carried out (on morphine agonists) in the last years. So far, however, the cyclic conformation as proposed by Beckett and Casey has only been observed in the case of methadone.

Fig. 1. The propoxyphene molecule with the numbering of the atoms indicated.

base. The two different conformations of methadone, found in the hydrobromide and the free base itself, respectively, do not only clearly depict the conformational flexibility of these molecules but also underline the necessity of studying the molecules in different environments.

In a previous paper the author has reported the structure of the hydrochloride and here the structure of the free base is presented.

Fig. 1 shows the asymmetric unit with the numbering of the atoms.

EXPERIMENTAL

The free base of dextropropoxyphene was prepared from the commercially available hydrochloride, and single crystals were obtained by crystallization from ethyl ether by slow evaporation at room temperature. A crystal of dimensions 0.2 mm $\times$ 0.3 mm $\times$ 0.4 mm was used for the experiments.
The crystals are monoclinal and systemati-
cally absent reflections 0k0 for odd indices is
compatible with space group P2₁, for an optically
active compound. Unit cell dimensions were
determined on a Syntex P1 diffractometer with
graphite monochromated MoKα-radiation
(λ=0.71069 Å).

Three-dimensional intensity data were collected
applying the 2θ-θ autocollection program with
variable scan rate (2°-8° min⁻¹) and a cut off for low intensities above the limit of
0.60 for sin θ/λ. The scan range was from 1.0⁰
below 2θ(0) to 1.0⁰ above 2θ(0) and the back-
ground were counted 0.7 times the scan time.
The intensities of three standard reflections were
measured periodically during the collection of
data. They showed no systematic variation. E.a.
d.s. in the intensities were taken as the
square root of the total counts with a 2 %
addition for instrumental instability.

A total of 2633 independent reflections were
recorded within the limit of 0.71 for sin θ/λ;
1799 had a net count larger than 2.5 σ.
The data were corrected for Lorentz and
polarization effects.

All calculations were performed on a CDC
6600 computer utilizing the programs described
in Ref. 12, except for the phase determination.¹³
Atomic form factors were those of Hanson
et al.¹⁴ for O, N, and C and of Stewart et al.¹⁵
for H.

A complete list of the structure factors may be
obtained from the author on request.

CRYSTAL DATA

Dextrorotatory phorphyrene, C₄₂H₂₈N₂O₇, monoclinic,
α = 9.257(2) Å, b = 9.048(3) Å, c = 12.074(7) Å,
β = 93.014(4), V = 1010.1 Å³, M = 339.49, Z = 2.
D₀ = 1.09 g cm⁻³ (floation), Dcalc = 1.11 g cm⁻³.
Systematic absences = 0k0 when k is odd; space
group P2₁.

STRUCTURE DETERMINATION

380 of the highest E-values (≥ 1.20) were used
as input for MULTAN,¹⁴ and one of the resulting
E-maps gave the positions of all the 25 non-
hydrogen atoms. Successive Fourier synthesis,
isotropic and anisotropic least-squares refine-

Table 2. Interatomic distances (Å), bond angles (°) and torsional angles (°).

<table>
<thead>
<tr>
<th>Distance (Å)</th>
<th>Distance (Å)</th>
<th>Distance (Å)</th>
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<tbody>
<tr>
<td>C1 = C2</td>
<td>1.409(5)</td>
<td>C2 = C3</td>
</tr>
<tr>
<td>C3 = O2</td>
<td>1.361(3)</td>
<td>C2 = C4</td>
</tr>
<tr>
<td>C6 = C7</td>
<td>1.521(4)</td>
<td>C5 = C7</td>
</tr>
<tr>
<td>C9 = N</td>
<td>1.415(7)</td>
<td>C9 = C10</td>
</tr>
<tr>
<td>C17 = C18</td>
<td>1.527(3)</td>
<td>C18 = C19</td>
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<tr>
<th>Angle (°)</th>
<th>Angle (°)</th>
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<tbody>
<tr>
<td>C1 = C2 = C3</td>
<td>114.6(1)</td>
</tr>
<tr>
<td>C3 = C2</td>
<td>124.6(1)</td>
</tr>
<tr>
<td>C2 = C1</td>
<td>126.8(1)</td>
</tr>
<tr>
<td>C4 = C1</td>
<td>111.2(1)</td>
</tr>
<tr>
<td>C8 = C4</td>
<td>112.4(1)</td>
</tr>
<tr>
<td>C6 = C5</td>
<td>118.6(1)</td>
</tr>
<tr>
<td>C5 = C7</td>
<td>113.6(1)</td>
</tr>
<tr>
<td>C6 = C7</td>
<td>108.9(2)</td>
</tr>
<tr>
<td>C5 = C6</td>
<td>110.5(3)</td>
</tr>
<tr>
<td>C4 = C5</td>
<td>110.3(3)</td>
</tr>
<tr>
<td>C3 = C4</td>
<td>117.1(3)</td>
</tr>
<tr>
<td>C2 = C3</td>
<td>127.1(3)</td>
</tr>
<tr>
<td>C1 = C2</td>
<td>129.8(1)</td>
</tr>
<tr>
<td>C2 = C1</td>
<td>117.2(2)</td>
</tr>
</tbody>
</table>

ments gave an R-factor of 0.08. Approximate positional parameters of all the 29 hydrogen atoms were calculated from stereochemical considerations. Hydrogen atoms positioned at the same carbon atom were given common B-values, and all the light atoms were refined isotropically.

Inclusion of the three hydrogen atoms at C8 in the refinement tends to move C8 towards the nitrogen atom, decreasing the C – N distance by about 0.03 Å. This indicates a correlation between the carbon and the hydrogen atom parameters. But due to an improvement of the R-factor of 0.5 % and in spite of a large B-value, these three hydrogen atoms were included in the refinement, which converged at R = 0.038 (Rw = 0.039). The final parameters are listed in Table 1, where the anisotropic temperature factor is given by

\[
\exp\left(-\frac{(B11h^2 + B22k^2 + B33l^2 + B12hk + B13hl + B23kl)}{2}\right)
\]

The mean e.s.d.'s in the positional parameters of the heavy atoms are 0.004, 0.006, and 0.003 in the x-, y-, and z-coordinates.

**DISCUSSION**

Interatomic distances, bond angles and dihedral angles are given in Table 2. The listed e.s.d.'s are calculated from the correlation matrix.

The bond lengths and angles found in this molecule are normal and do not deviate from standard values, except for the short C8 – N distance (discussed above) and the molecular dimensions at C4. The lengthening of the C4–C5, C4–C10, C4–C17 and C4–O2 single

bonds clearly demonstrate the crowded situation around C4. This, together with the corresponding angular distortions, is mainly attributed to nonbonded interactions. This somewhat distorted molecular geometry is in agreement with results reported for the hydrochloride and other related compounds.

The two phenyl rings A and B (Fig. 1) are strictly planar. C10 is essentially coplanar with plane A (0.011 Å out of the plane), whereas C4 is elevated as much as 0.065 Å out of B. As reported for dextropropoxyphene hydrochloride the angle C4–C10–C11 is somewhat opened as compared to the accepted value for C(sp³)–C(sp³)–C(sp³) bond angles. The two planes A and B form an angle of 61.3°. The plane through C4, C10, C11 is nearly perpendicular to plane A whereas the dihedral angle C18–C17–C4–C10 is as small as 32.9°.

The torsional angle C4–C5–C7–N is −174.2° and the propylamine chain is thus almost fully extended. Hence the free base of propoxyphene prefers a side chain conformation in the crystalline state resembling that of the hydrochloride. This may indicate a less degree of conformational flexibility as compared to the methadone molecule. In this manner propoxyphene seems to be similar to isomethadone. Recent spectroscopic investigations on methadone and isomethadone in solution suggested a predominant conformational homogeneity for isomethadone.

The structure reports on analgetics so far seem to confirm that intermolecular forces, for example hydrogen bonds, play an important part in the selection of the preferred conformation in compounds having a quaternary ammonium group. Compounds with an uncharged nitrogen atom and a methyl group on the β carbon atom in the side chain may be more rigid than those having the s-methyl group at the α carbon atom.

The crystal structure as seen along the c-axis is shown in Fig. 2. There are no short intermolecular distances in the crystal.
REFERENCES


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