

Crystal Structures of Synthetic Analgetics. IV. Dextropropoxyphene

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The molecular and crystal structure of dextro-propoxyphene has been determined by X-ray methods. The crystals are monoclinic, space group $P2_1$, with unit cell dimensions $a = 9.257(2)$ Å; $b = 9.048(3)$ Å; $c = 12.074(7)$ Å; $\beta = 93.01(4)^\circ$. 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° . 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 morphine-like synthetic analgetics that are not narcotic.¹ It is a widely used medicinal agent against moderate pain, and related to methadone (II). These two and other analogous diphenyl-propylamines have a potential conformational flexibility in the side chain. Extensive stereochemical studies have been performed on these acyclic analgetics²⁻⁴ 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.⁵⁻⁸ So far, however, the cyclic conformation as proposed by Beckett and Casey⁹⁻¹⁰ has only been observed in the case of methadone

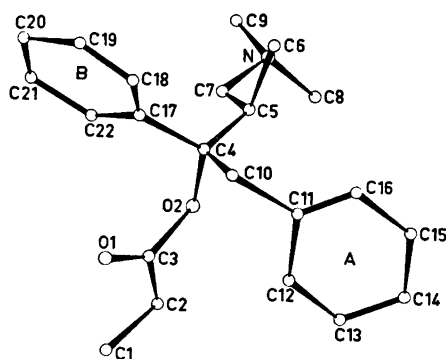
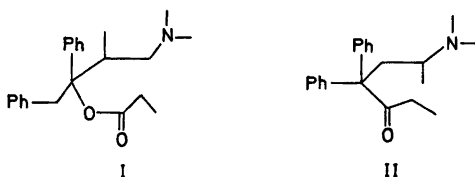


Fig. 1. The propoxyphene molecule with the numbering of the atoms indicated.

base.⁷⁻⁸ The two different conformations of methadone, found in the hydrobromide¹¹ 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 hydrochloride⁵ 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 diethyl 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.

Table 1. Positional and thermal parameters with e.s.d.'s (10⁴).

ATOM	X	Y	Z	B11	B22	B33	B12	B13	B23
O1	572(2)	2500(00)	3036(1)	131(2)	166(3)	89(1)	54(5)	63(3)	-8(4)
O2	2102(2)	3683(3)	1943(1)	106(2)	125(2)	55(1)	15(4)	23(2)	16(3)
N	3720(2)	7153(4)	216(2)	127(3)	296(6)	81(2)	66(7)	28(4)	-97(5)
C1	281(4)	85(4)	1553(3)	198(5)	126(4)	151(3)	16(8)	9(6)	28(6)
C2	1166(3)	1411(4)	1312(2)	155(4)	154(4)	110(2)	64(7)	58(5)	76(6)
C3	1221(2)	2562(4)	2208(2)	96(3)	124(3)	74(2)	-4(6)	20(4)	-3(4)
C4	2336(2)	4951(3)	2691(2)	94(3)	121(3)	82(1)	16(5)	11(3)	8(4)
C5	3367(2)	5942(3)	2036(2)	85(2)	133(4)	64(2)	8(5)	8(3)	-12(4)
C6	3822(3)	7346(4)	2654(2)	153(4)	150(4)	87(2)	72(7)	-14(4)	-10(5)
C7	2726(2)	6358(4)	882(2)	110(3)	149(4)	63(2)	17(6)	8(3)	-26(4)
C8	4739(6)	6187(10)	-234(5)	334(10)	732(22)	227(6)	-597(27)	376(14)	-522(22)
C9	2971(4)	7949(5)	-675(3)	238(6)	218(6)	91(2)	53(9)	32(6)	-103(6)
C10	3084(2)	4486(4)	3797(2)	104(3)	153(4)	53(2)	18(5)	19(3)	2(4)
C11	4403(3)	3448(4)	3709(2)	121(3)	145(4)	47(2)	9(6)	-2(3)	-25(4)
C12	4299(3)	1926(4)	3647(2)	151(4)	146(4)	90(2)	16(7)	-50(5)	-39(5)
C13	5523(4)	1053(4)	3578(3)	232(6)	140(5)	98(3)	-77(8)	-81(6)	-11(5)
C14	6874(3)	1679(4)	3583(2)	163(4)	205(6)	70(2)	-120(8)	-10(5)	-23(5)
C15	7005(3)	3179(5)	3673(2)	121(4)	227(6)	84(2)	-29(7)	2(4)	-63(6)
C16	5781(3)	4046(4)	3736(2)	128(4)	153(4)	80(2)	7(6)	7(4)	-27(5)
C17	902(2)	5727(3)	2872(2)	99(3)	130(3)	60(2)	15(5)	29(3)	10(4)
C18	706(3)	6539(4)	3362(2)	138(4)	222(5)	75(2)	-64(7)	27(4)	93(6)
C19	-564(4)	7296(5)	3970(3)	100(5)	234(6)	112(3)	-96(9)	70(6)	92(7)
C20	-1659(3)	7259(4)	3178(3)	121(3)	105(5)	152(3)	-57(7)	78(6)	14(7)
C21	-1490(3)	6460(4)	2225(3)	101(3)	171(4)	123(3)	2(6)	-3(5)	-9(6)
C22	-228(2)	5705(4)	2075(2)	96(3)	138(3)	81(2)	15(5)	17(3)	9(4)

ATOM	X	Y	Z	B	ATOM	X	Y	Z	B
H1C1	241(37)	-645(43)	921(31)	8,5(.5)	H1C9	3669(44)	8519(51)	-1114(33)	9,7(.6)
H2C1	604(38)	-382(43)	2233(29)	8,5(.6)	H2C9	2390(42)	7100(49)	-1203(33)	9,7(.9)
H3C1	-718(37)	358(45)	1746(30)	8,5(.9)	H3C9	2241(43)	8611(50)	-382(34)	9,7(1.0)
H1C2	2043(36)	1225(43)	1113(27)	7,9(.6)	H1C10	3350(24)	5279(27)	4203(19)	4,1(.3)
H2C2	843(36)	1949(41)	550(28)	7,9(.8)	H2C10	2412(23)	3869(29)	4187(18)	4,1(.5)
H3C2	4236(20)	5322(23)	1973(15)	2,7(.3)	H3C12	3373(26)	1483(32)	3646(20)	5,2(.5)
H1C6	2971(31)	7962(35)	2721(23)	6,4(.7)	H3C13	5425(30)	-27(38)	3518(23)	6,4(.7)
H2C6	4241(32)	7124(37)	3367(25)	6,9(.7)	H3C14	7734(28)	1076(32)	3558(21)	5,4(.6)
H3C6	4461(34)	7933(38)	2216(26)	6,9(.7)	H3C15	7979(33)	3613(36)	3678(24)	6,5(.7)
H2C7	1914(26)	7043(30)	965(21)	5,0(.4)	H3C16	5895(24)	5042(28)	3811(18)	4,1(.5)
H1C7	2346(26)	5491(30)	498(20)	5,0(.6)	H3C18	1506(30)	6596(36)	4392(22)	6,0(.6)
H1C8	5309(49)	6672(60)	-628(39)	11,4(.8)	H3C19	-647(35)	7877(40)	4609(27)	7,7(.8)
H2C8	5249(50)	5591(61)	262(39)	11,4(1.3)	H3C20	-2593(31)	7681(38)	3742(23)	6,5(.6)
H3C8	4155(50)	5252(59)	-553(39)	11,4(.6)	H3C21	-2197(27)	6538(32)	1670(20)	5,1(.5)
					H3C22	-94(23)	5137(26)	1417(17)	3,6(.4)

The crystals are monoclinic and systematically absent reflections $0k0$ for odd indices is compatible with space group $P2_1$, for an optically active compound. Unit cell dimensions were determined on a Syntex PI diffractometer with graphite crystal monochromated $\text{MoK}\alpha$ -radiation ($\lambda = 0.71069 \text{ \AA}$).

Three-dimensional intensity data were collected applying the $2\theta - \theta$ autocollection program with variable scan rate ($2 - 8^\circ \text{ min}^{-1}$) and a cut off for low intensities above the limit of 0.60 for $\sin \theta/\lambda$. The scan range was from 1.0° below $2\theta(\alpha_1)$ to 1.0° above $2\theta(\alpha_2)$ and the background 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.s.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 $\sin \theta/\lambda$; 1799 had a net count larger than $2.5 \sigma_I$.

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

Dextropropoxyphene, $\text{C}_{22}\text{H}_{29}\text{NO}_2$, monoclinic. $a = 9.257(2) \text{ \AA}$, $b = 9.048(3) \text{ \AA}$, $c = 12.074(7) \text{ \AA}$, $\beta = 93.01(4)^\circ$, $V = 1010.1 \text{ \AA}^3$, $M = 339.49$, $Z = 2$. $D_{\text{obs}} = 1.09 \text{ g cm}^{-3}$ (floatation), $D_{\text{calc}} = 1.11 \text{ g cm}^{-3}$. Systematic absences = $0k0$ when k is odd; space group $P2_1$.

STRUCTURE DETERMINATION

380 of the highest E -values (≥ 1.20) were used as input for MULTAN,¹³ 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 (°).

DISTANCE	(Å)	DISTANCE	(Å)	DISTANCE	(Å)
C1 = C2	1.490(5)	C2 = C3	1.501(4)	C3 = O1	1.193(3)
C3 = O2	1.351(3)	O2 = C4	1.469(3)	C4 = C5	1.556(3)
C5 = C6	1.521(4)	C5 = C7	1.533(3)	C7 = N	1.446(3)
C8 = N	1.415(7)	C9 = N	1.442(4)	C4 = C10	1.552(3)
C4 = C17	1.527(3)	C10 = C11	1.506(3)	C11 = C12	1.382(4)
C12 = C13	1.380(4)	C13 = C14	1.373(5)	C14 = C15	1.366(5)
C15 = C16	1.363(4)	C16 = C17	1.384(4)	C17 = C18	1.383(4)
C18 = C19	1.380(4)	C19 = C20	1.357(5)	C20 = C21	1.374(5)
C21 = C22	1.373(4)	C22 = C17	1.386(3)		

ANGLE	(°)	ANGLE	(°)
O1 = C3 = O2	114.6(2)	C2 = C3 = O1	124.9(2)
C3 = O2 = C4	120.8(2)	C2 = C3 = O2	110.4(2)
O2 = C4 = C10	109.9(2)	O2 = C4 = C5	102.3(2)
C5 = C4 = C10	111.2(2)	O2 = C4 = C17	110.2(2)
C10 = C4 = C17	112.0(2)	C5 = C4 = C17	111.7(2)
C4 = C5 = C7	112.6(2)	C4 = C5 = C6	113.2(2)
C5 = C7 = N	113.6(2)	C6 = C5 = C7	108.9(2)
C7 = N = C9	111.6(2)	C7 = N = C8	111.3(4)
C4 = C10 = C11	116.7(2)	C8 = N = C9	109.0(3)
C10 = C11 = C16	121.5(2)	C10 = C11 = C12	121.5(2)
C12 = C13 = C14	120.8(3)	C11 = C12 = C13	121.0(3)
C14 = C15 = C16	119.9(3)	C13 = C14 = C15	119.1(3)
C16 = C11 = C12	116.9(3)	C15 = C16 = C11	122.2(3)
C4 = C17 = C22	121.7(2)	C4 = C17 = C18	121.1(2)
C18 = C19 = C20	120.5(3)	C17 = C18 = C19	121.4(3)
C20 = C21 = C22	120.5(3)	C19 = C20 = C21	119.3(3)
C22 = C17 = C18	117.2(2)	C21 = C22 = C17	121.2(2)

DIMEDRAL ANGLE	(°)	DIMEDRAL ANGLE	(°)
C1 = C2 = C3 = O1	-3.5(4)	C1 = C2 = C3 = O2	176.9(2)
O1 = C3 = O2 = C4	.4(3)	C2 = C3 = O2 = C4	180.0(2)
C3 = O2 = C4 = C5	-178.6(2)	C3 = O2 = C4 = C10	63.6(2)
C5 = O2 = C4 = C17	-59.7(2)	C12 = C11 = C10 = C4	-98.6(3)
C11 = C10 = C4 = O2	49.8(3)	C11 = C10 = C4 = C17	172.1(2)
C11 = C10 = C4 = C5	-62.2(3)	C18 = C17 = C4 = C5	-92.6(3)
C18 = C17 = C4 = O2	154.5(2)	C18 = C17 = C4 = C10	32.9(3)
C16 = C11 = C10 = C4	92.3(3)	C22 = C17 = C4 = O2	-28.5(3)
O2 = C4 = C5 = C6	-178.5(2)	O2 = C4 = C5 = C7	57.4(2)
C4 = C5 = C7 = N	-174.2(2)	C6 = C5 = C7 = N	59.4(3)
C5 = C7 = N = C8	77.7(4)	C5 = C7 = N = C9	-160.3(2)

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 (*R_w* = 0.039). The final parameters are listed in Table 1, where the anisotropic temperature factor is given by

$$\exp - (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$$

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,¹⁶ 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

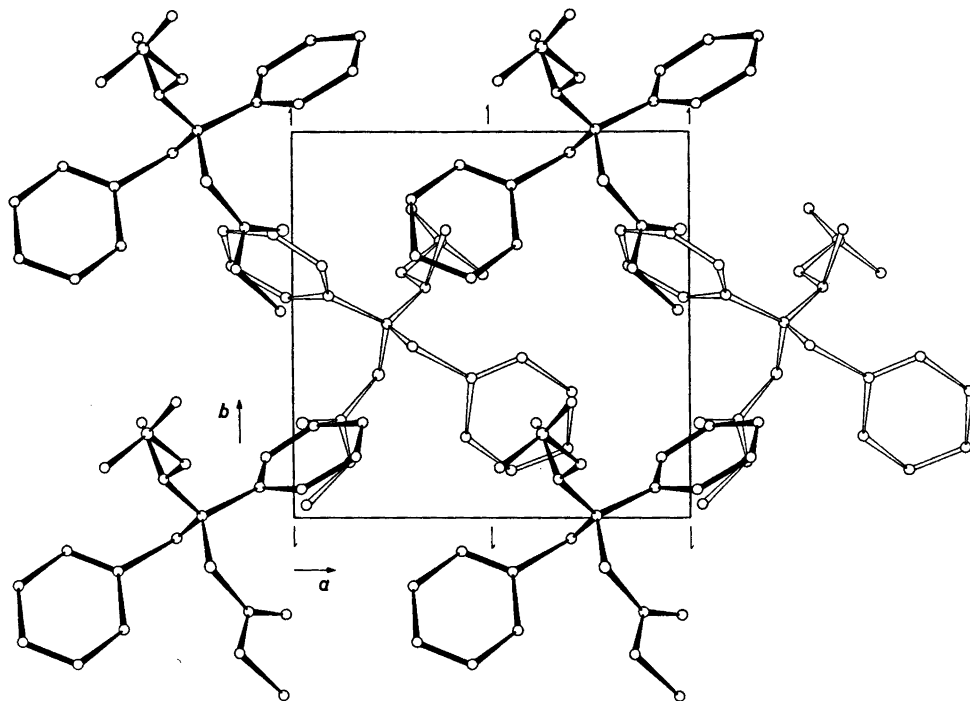


Fig. 2. The crystal packing of dextropropoxyphene as seen along the *c*-axis.

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 hydrochloride⁵ and other related compounds.^{6-8,17}

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(*sp*³)-C(*sp*³)-C(*sp*³) 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 conforma-

tion in the crystalline state resembling that of the hydrochloride.⁵ This may indicate a less degree of conformational flexibility as compared to the methadone molecule.^{6,11} In this manner propoxyphene seems to be similar to isomethadone. Recent spectroscopic investigations on methadone and isomethadone in solution⁴ 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.

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