

On the Crystal Structure of an Analgetic Metabolite, Norpropoxyphene Maleate

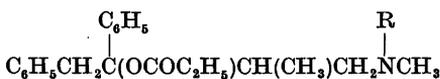
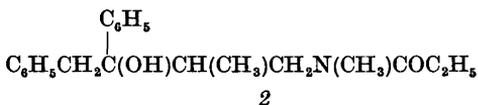
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The crystal and molecular structure of norpropoxyphene maleate has been determined by X-ray methods. The crystals are orthorhombic, space group $P2_12_12_1$, with $a=9.365(3)$, $b=9.348(3)$, $c=27.639(6)$ Å. The structure was determined by direct methods and refined by the method of full-matrix least-squares to $R=0.049$ for 1224 observed reflections. The e.s.d.'s for non-hydrogen atoms are (in average) 0.01 Å and 0.5° in bond lengths and angles, respectively.

The *N*-methylpropylamino chain is nearly fully extended with the pertinent dihedral angle of -162.0° . The present metabolite conformation closely resembles that of its congener, dextropropoxyphene. The three-dimensional structure consists of chains parallel to (100) with alternating norpropoxyphene and maleate ions, formed by $N-H^+\cdots O$ hydrogen bonds of 2.70 Å and 2.76 Å, respectively. The intramolecular $O6-H\cdots O4$ hydrogen bond of the maleate ion is 2.40 Å, both oxygen atoms being displaced by 0.2 Å to the same side of the planar carbon skeleton.

Norpropoxyphene (1a) is known to be the principal metabolite of the weak analgetic dextropropoxyphene¹ (1b). In alkaline solution ($pH > 11$) (1a) is converted to (2) by an intramolecular rearrangement which has to involve a cyclic intermediate.²

1a. $R=H$ 1b. $R=CH_3$ 

* Previous part in this series: Bye, E. *Acta Chem. Scand.* B30 (1976) 549.

Being subjected to such a reaction norpropoxyphene is of interest for structure-activity studies of morphine-like analgetics.*

Some of the present results have been reported earlier.³

EXPERIMENTAL

A single crystal of dimensions $0.1 \times 0.1 \times 0.4$ mm was selected from commercial norpropoxyphene maleate and utilized for the experiments. Rotational and Weissenberg photographs indicated orthorhombic symmetry and systematic absences are compatible with space group $P2_12_12_1$. The unit cell dimensions were determined on a SYNTEX PI diffractometer with graphite crystal monochromated $MoK\alpha$ -radiation ($\lambda=0.71069$ Å).

Three-dimensional intensity data were collected applying the $2\theta-\theta$ autocollection program with variable scan rate ($2-8^\circ \text{ min}^{-1}$). The scan range was from 0.8° below $2\theta(\alpha_1)$ to 0.8° above $2\theta(\alpha_2)$ and the backgrounds were counted for 0.35 times the scan time at each end of the scan range. Three standard reflections were measured periodically during the data collection. They did not show any systematic variation. The e.s.d.'s of the intensities were taken as the square root of the total counts with a 2% addition for instrumental instability.

Out of 2489 independently recorded reflections with $\sin \theta/\lambda \leq 0.60$, only 1224 had $I \geq 2.5\sigma(I)$. The low fraction of observed intensities to the total number (0.48) is partially caused by a small crystal volume (4×10^{-3} Å³) and partially by large thermal motion of the atoms.

All calculations were performed on a CYBER-74 computer with the programs in Ref. 4, except for the phase determinations.⁵ Atomic form factors were those of Hanson *et al.*⁶ for O, N, C and of Stewart *et al.*⁷ for H.

Table 1. Positional and thermal parameters with e.s.d.'s in parentheses. The anisotropic temperature factors are given by $\exp(-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + U_{12}hka^*b^* + U_{13}hla^*c^* + U_{23}klb^*c^*))$.

ATOM	x	y	z	U11	U22	U33	U12	U13	U23
O1	.459(3)	.322(5)	.417(2)	.0815(36)	.0637(32)	.0608(31)	.0149(31)	.0084(31)	-.0142(30)
O2	.345(3)	.463(4)	.370(1)	.0520(26)	.0468(26)	.0419(25)	.0030(25)	-.0084(24)	-.0019(22)
O3	.776(1)	.484(6)	.207(2)	.0518(33)	.0694(34)	.1362(51)	.0051(29)	.0085(35)	.0156(38)
O4	.607(3)	.243(2)	.214(3)	.0713(38)	.0520(34)	.1492(56)	.0048(31)	.0056(37)	-.0152(38)
O5	.184(6)	.372(6)	.185(2)	.0491(35)	.0844(43)	.1463(52)	.0094(32)	.0026(34)	.0057(39)
O6	.352(7)	.231(1)	.204(7)	.0702(38)	.0501(34)	.1954(69)	-.0043(33)	-.0139(47)	.0007(45)
N	.035(9)	.684(5)	.295(2)	.0494(31)	.0534(33)	.0532(32)	.0061(31)	.0056(30)	.0013(32)
C1	.6954(10)	.3437(13)	.3562(4)	.0710(63)	.1421(94)	.1419(85)	.0132(71)	-.0149(62)	.0274(81)
C2	.559(9)	.394(8)	.341(3)	.0616(52)	.0629(50)	.0926(58)	.0012(50)	.0175(47)	-.0012(45)
C3	.443(8)	.395(8)	.382(3)	.0502(44)	.0455(43)	.0629(52)	.0029(44)	.0091(42)	.0050(40)
C4	.216(9)	.544(7)	.494(2)	.0615(41)	.0394(38)	.0369(35)	.0025(38)	.0020(35)	.0012(34)
C5	.122(1)	.613(7)	.372(2)	.0466(40)	.0448(38)	.0474(41)	.0043(36)	.0013(37)	.0015(34)
C6	.011(8)	.656(1)	.484(3)	.0716(52)	.0609(45)	.0657(46)	.0131(47)	.0055(42)	.0025(39)
C7	.085(3)	.562(5)	.326(3)	.0595(43)	.0309(36)	.0568(40)	.0007(33)	.0072(36)	.0101(36)
C8	.0013(10)	.846(7)	.246(1)	.0809(56)	.0708(47)	.0514(44)	.0057(52)	.0169(42)	-.0063(43)
C9	.274(8)	.562(7)	.452(2)	.0563(45)	.0546(41)	.0414(39)	.0051(41)	.0116(37)	.0009(37)
C10	.367(8)	.705(8)	.446(7)	.0692(54)	.0590(52)	.0383(39)	.0033(47)	.0117(42)	.0013(37)
C11	.5126(10)	.6857(9)	.441(8)	.0675(58)	.0671(52)	.0884(57)	.0118(52)	.0118(48)	.0220(46)
C12	.5988(10)	.8030(15)	.434(9)	.0705(63)	.1154(86)	.0964(71)	.0231(71)	.0023(50)	.0360(71)
C13	.5493(14)	.9368(14)	.432(4)	.0957(84)	.1170(96)	.0691(59)	.0538(81)	.0120(59)	.0074(61)
C14	.3967(13)	.9551(8)	.438(3)	.1286(86)	.0393(47)	.0080(59)	.0178(56)	.0369(61)	-.0104(43)
C15	.310(6)	.8375(8)	.445(3)	.0725(53)	.0492(48)	.0776(54)	.0037(47)	.0217(47)	.0041(43)
C16	.132(7)	.3619(7)	.412(2)	.0642(44)	.0374(37)	.0389(37)	.0048(39)	.0002(39)	.0001(35)
C17	.056(7)	.339(8)	.453(2)	.1168(43)	.0602(43)	.0606(40)	.0180(39)	.0262(39)	.0045(38)
C18	-.021(6)	.2155(8)	.4591(3)	.1235(94)	.0756(44)	.0659(53)	.0232(47)	.0413(47)	.0101(41)
C19	-.0182(19)	.113(8)	.4245(3)	.1042(68)	.0516(47)	.0790(57)	.0132(53)	.0144(57)	.0099(49)
C20	.0608(11)	.139(1)	.384(1)	.0810(76)	.0497(57)	.0639(51)	.0044(54)	.0086(55)	.0020(50)
C21	.1379(10)	.284(8)	.377(3)	.0547(67)	.0535(59)	.0433(50)	.0027(58)	.0004(52)	.0019(44)
C22	.648(9)	.369(4)	.208(3)	.0580(53)	.0575(52)	.0659(49)	.0020(48)	.0003(44)	.0144(43)
C23	.540(6)	.484(6)	.203(3)	.0596(52)	.0351(39)	.1291(69)	-.0009(44)	.0088(56)	.0103(47)
C24	.405(8)	.479(9)	.198(4)	.0452(48)	.0533(49)	.1476(80)	.0061(42)	.0064(52)	-.0052(56)
C25	.306(1)	.355(10)	.1955(3)	.0488(52)	.0713(62)	.0906(60)	-.0016(49)	-.0092(46)	.0131(50)

ATOM	x	y	z	B	ATOM	x	y	z	B
H1C1	.760	.347	.327	8.2	H2C1	.735	.407	.382	8.2
H3C1	.689	.243	.368	8.2	H1C2	.569	.495	.329	5.1
H2C2	.514	.331	.316	5.1	H3C2	.181	.702	.375	3.0
H1C6	.015	.689	.438	4.8	H2C5	-.061	.736	.387	4.0
H3C6	-.077	.572	.407	4.8	H1C7	.172	.519	.311	4.0
H2C7	.008	.489	.328	4.0	H1C8	-.031	.734	.228	5.5
H2C8	.084	.607	.238	5.5	H3C8	-.076	.574	.246	5.5
H14	.105	.752	.296	4.0	H24	-.043	.722	.310	4.0
H1C9	.191	.596	.473	3.8	H2C9	.332	.494	.469	3.8
H2C11	.557	.588	.443	5.2	H2C12	.704	.790	.432	7.3
H1C13	.603	1.021	.426	6.1	H1C14	.355	1.053	.438	5.5
H1C15	.204	.851	.449	4.7	H2C17	.055	.414	.488	5.6
H1C18	-.001	.202	.489	6.3	H1C19	-.074	.020	.429	5.6
H2C20	.062	.054	.359	4.6	H2C21	.195	.267	.347	3.2
H2C23	.581	.584	.205	5.5	H2C24	.351	.574	.197	5.8
H06	.450	.236	.209	8.0					

Table 2. Bond lengths (Å) and angles (°) of norpropoxyphene maleate with e.s.d.'s in parentheses.

DISTANCE (Å)			DISTANCE (Å)			DISTANCE (Å)		
C1 = C2	1.498(12)		C2 = C3	1.496(11)		C3 = O1	1.194(8)	
C3 = O2	1.346(8)		O2 = C4	1.455(8)		C4 = C5	1.544(9)	
C5 = C6	1.521(10)		C5 = C7	1.526(9)		N = C7	1.488(8)	
N = C8	1.472(9)		C4 = C9	1.558(9)		C9 = C10	1.514(7)	
C10 = C11	1.371(11)		C11 = C12	1.375(12)		C12 = C13	1.367(14)	
C13 = C14	1.366(14)		C14 = C15	1.376(11)		C15 = C16	1.389(10)	
C4 = C16	1.538(10)		C16 = C17	1.393(9)		C17 = C18	1.383(10)	
C18 = C19	1.370(10)		C19 = C20	1.348(12)		C20 = C21	1.384(11)	
C21 = C16	1.385(9)		C22 = O3	1.237(8)		C22 = O4	1.251(9)	
C22 = C23	1.484(11)		C23 = C24	1.320(10)		C24 = C25	1.461(12)	
C25 = O5	1.221(8)		C25 = O6	1.264(10)				

ANGLE (°)			ANGLE (°)		
C1 = C2 = C3	114.3(7)		C2 = C3 = O1	125.1(7)	
O1 = C3 = O2	125.0(6)		C2 = C3 = O2	109.7(6)	
C3 = O2 = C4	120.9(5)		O2 = C4 = C5	102.7(4)	
O2 = C4 = C9	109.3(5)		O2 = C4 = C16	109.7(5)	
C5 = C4 = C9	110.8(5)		C5 = C4 = C16	111.4(5)	
C9 = C4 = C16	112.4(5)		C4 = C5 = C6	113.9(5)	
C4 = C5 = C7	111.7(5)		C6 = C5 = C7	111.0(5)	
C5 = C7 = N	110.2(5)		C7 = N = C8	114.3(5)	
C4 = C9 = C10	115.4(5)		C9 = C10 = C11	119.9(7)	
C9 = C10 = C15	121.9(7)		C10 = C11 = C12	120.9(9)	
C11 = C12 = C13	120.1(8)		C12 = C13 = C14	120.1(9)	
C13 = C14 = C15	119.0(9)		C14 = C15 = C16	120.9(8)	
C15 = C16 = C17	118.2(8)		C4 = C16 = C17	120.5(5)	
C4 = C16 = C21	122.0(6)		C16 = C17 = C18	120.3(6)	
C17 = C18 = C19	120.9(7)		C18 = C19 = C20	119.6(7)	
C19 = C20 = C21	120.5(7)		C20 = C21 = C16	121.4(8)	
C21 = C16 = C17	117.3(6)		O3 = C22 = O4	123.2(7)	
O3 = C22 = C23	117.8(7)		O4 = C22 = C23	119.0(7)	
C22 = C23 = C24	131.2(8)		C23 = C24 = C25	129.8(8)	
C24 = C25 = O5	117.5(8)		C24 = C25 = O6	120.3(7)	
O5 = C25 = O6	122.1(8)				

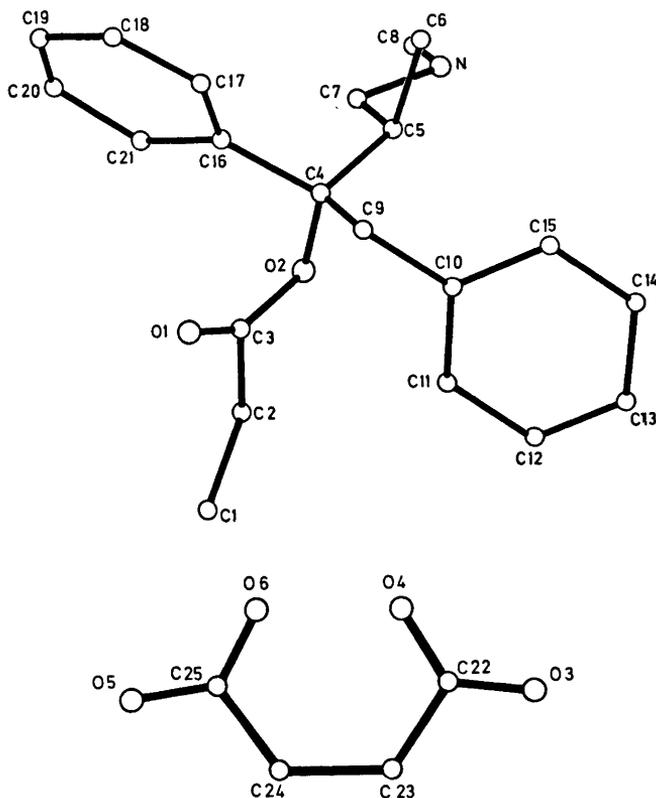


Fig. 1. The asymmetric unit of norpropoxyphene maleate with the atomic numbering.

Table 3. Torsional angles ($^{\circ}$) of norpropoxyphene maleate (I) together with those of the hydrochloride^a (II) and the free base^b (III) of propoxyphene.

Atoms	Torsional angles		
	I	II	III
C1-C2-C3-O1	-23.5	-5.4	-3.5
C2-C3-O2-C4	-179.3	175.1	180.0
C3-O2-C4-C5	178.9	64.5	-178.6
O2-C4-C5-C6	-179.7	174.5	-178.5
O2-C4-C5-C7	53.6	49.4	57.4
C4-C5-C7-N	-162.0	-176.7	-174.2
C5-C7-N-C8	178.5	173.6	-160.3
C3-O2-C4-C10	61.2	-56.3	63.6
C3-O2-C4-C17	-62.5	-176.4	-59.7
O2-C4-C10-C11	51.2	-42.1	49.8
C4-C10-C11-C12	-90.4	-76.2	-90.6
O2-C4-C17-C18	153.3	-26.1	154.5
C11-C10-C4-C17	173.2	71.8	172.1
C10-C4-C17-C18	31.5	-144.0	32.9
C6-C5-C7-N	69.7	57.8	57.4

CRYSTAL DATA

Nordextropropoxyphene* maleate, $C_{21}H_{27}NO_2$, $C_4H_4O_4$, orthorhombic.

$a = 9.365(3) \text{ \AA}$, $b = 9.348(3) \text{ \AA}$, $c = 27.639(5) \text{ \AA}$.

$V = 2419.6 \text{ \AA}^3$, $M = 441.5$, $Z = 4$.

$D_o = 1.22 \text{ g cm}^{-3}$ (floatation), $D_c = 1.21 \text{ g cm}^{-3}$.

Systematic absences: $h00$, $0k0$, $00l$ for odd indices, space group $P2_12_12_1$.

STRUCTURE DETERMINATION

A preliminary scale factor and an overall isotropic temperature factor ($B = 3.2 \text{ \AA}^2$) were determined by Wilson's statistical method and used to calculate normalized structure factors. The phase determination was carried out with MULTAN⁵ utilizing the 320 highest E 's

* The dextro-form of norpropoxyphene is studied.

normal. Large atomic thermal vibrations may explain the short terminal C1–C2 distance of 1.490 Å and the C–N⁺ distances of 1.472 and 1.480 Å, respectively, which are slightly shorter than expected for charged amino groups.

C4 bridges four large groups and the lengthening of the bond distances and distortions of the angles involving this atom indicate the significance of non-bonded interactions in the molecule. The observed values of bond lengths and angles are consistent with those reported for dextropropoxyphene.HCl⁸ and the free base.⁹

The intramolecular strain is evident as C9 and C4 are displaced by 0.07 and 0.09 Å from least-squares planes of the two phenyl rings A and B, respectively (see Fig. 1). The interplanar angle between plane A and B is 59.9°, close to 61.3° reported for dextropropoxyphene.⁹

In Fig. 1 it may be seen that the propylamino chain is *extended* in the present case. The pertinent dihedral angle C4–C5–C7–N is –162.0°, close to the values –176.7 and –174.2° found in the hydrochloride and the free base of dextropropoxyphene,^{8,9} respectively. Some of these torsional angles are listed in Table 3.

There are only minor differences in the overall conformations of the three compounds, particularly between I and III (see Table 3). The present *extended* propylamine chain seems to confirm earlier suggestions about a reduced conformational flexibility for compounds with the methyl group at C5, as compared to those with C6–Me substituents.¹⁰

The maleate ion. Ionization of only one carboxyl group is evident from the two equal C–O bond distances C22–O3 [1.237(8) Å] and C22–O4 [1.251(9) Å], whereas the other end of the acid is non-symmetrical. O6 and O4 are engaged in a short intramolecular hydrogen bond of 2.402 Å, close to the values listed by James *et al.*¹¹ In the present ion, however, the oxygen atoms O4 and O6 are displaced to the same side by 0.18 Å from the planar carbon skeleton C22–C23–C24–C25 (see Table 4). This situation is somewhat different as compared with that normally encountered for maleic acid/maleates,¹¹ in which the two oxygen atoms most currently are found at opposite sides. This may be due to crystal packing effects (see below).

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Molecular packing. The crystal structure is illustrated in Fig. 2 which shows the chains running along the *a*-axis with alternate nor-propoxyphene and maleate ions. Each nor-propoxyphene unity is linked to two different maleate ions through N–H⁺...O hydrogen bonds of 2.707 and 2.760 Å. Some of the hydrogen bond parameters are given in Table 5. The molecular chains are connected through v. d. Waals forces only. The slightly short contacts O3...C8 (3.27 Å) and O5...C8 (3.34 Å) may probably force the oxygen atoms O3 and O5 (or O4 and O6) to the same side of the planar backbone of the maleate ion.

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