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Crystal Structures of Synthetic Analgetics

I. Dextropropoxyphene Hydrochloride

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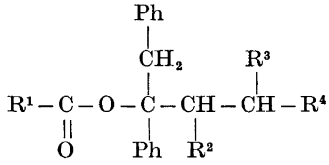
The molecular and crystal structure of dextropropoxyphene hydrochloride has been determined by X-ray methods. The crystals are orthorhombic, space group $P2_12_12_1$; with unit cell dimensions $a=11.997$ Å; $b=12.835$ Å; $c=13.830$ Å. The phase problem was solved by the heavy atom method and the model refined to an R-value of 0.032 for 1643 observed reflections. The absolute configuration has been established; estimated standard deviations are 0.003 – 0.004 Å in interatomic distances and 0.2 – 0.3° in angles.

The crystal packing is dominated by a very strong $N^+-H\cdots Cl^-$ hydrogen bond of 3.03 Å. There is no evidence of any interaction between the protonated nitrogen atom and the ester group. The latter is planar and the two phenyl rings form an angle of 86.6°.

Propoxyphene, first synthesized by Pohland *et al.* in 1953,[1] is a synthetic analgetic with morphine-like action. It belongs to a group of ester-compounds with the general formula



where $R^1=Et$; $R^2=Me$; $R^3=H$; $R^4=N(CH_3)_2$. The morphine-like action is believed to be dependent on a particular molecular conformation, resulting from an interaction between the basic nitrogen atom and the ester group. This particular conformation for synthetic analgetics was first proposed by Casy from a study of methadone .[2] The present structure determination was carried out to obtain information about the structure, and correlate this to the activity of analgetics. This is the first of several compounds related to methadone to be examined by X-ray methods in this laboratory.

Fig. 1 shows the propoxyphene molecule with the numbering scheme of the atoms (Cl and H excluded).

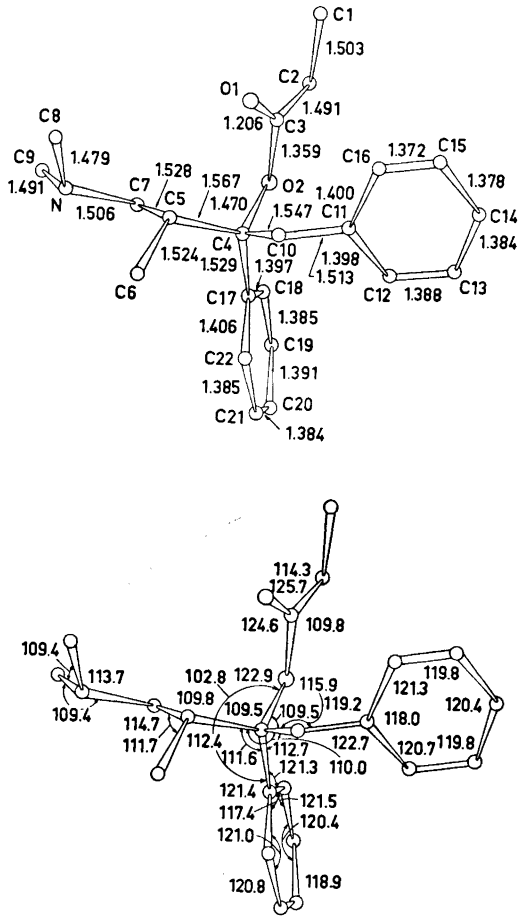


Fig. 1. Bond lengths (Å) and angles (°) in dextropropoxyphene hydrochloride.

EXPERIMENTAL

Commercially available propoxyphene hydrochloride was recrystallized from a solution of acetone/ether. The compound crystallizes as colourless, transparent parallelepipeds. Oscillation and Weissenberg photographs indicated orthorhombic symmetry, systematically absent reflections were $h00,0k0,00l$ for odd indices, and the space group is $P2_12_12_1$. Unit cell dimensions were determined from measurements on a manual Picker four-circle diffractometer with Cu$K\alpha$-radiation. The density was measured by flotation.

A crystal of dimensions 0.4 mm × 0.4 mm × 0.3 mm was used for the collection of three-dimensional intensity data on a Syntex P1 diffractometer using graphite crystal monochromated Mo$K\alpha$-radiation. The $2\theta-\theta$ autocollection program was applied with variable scan rate and a cut-off at $2\sigma_I$. The scan range was from 0.6° below $2\theta(\alpha_1)$ to 0.7° above $2\theta(\alpha_2)$, and the backgrounds were counted 0.7 times the intensity measuring time. The intensities of three standard reflections were measured periodically during the data collection. They showed an average decrease of 4 % and the intensities were corrected for this effect. Estimated standard deviations in the intensities were assigned as the square root of the total counts with a 2 % addition for instrumental instability.

A total of 1795 independent reflections were recorded within the limit of sin θ/λ 0.76, 1647 having a net count larger than $2\sigma_I$.

The data were corrected for Lorentz and polarization effects but not for absorption ($\mu = 2.01$ cm^{-1} Mo$K\alpha$) or secondary extinction.

All calculations were performed on a CDC 3300 computer using the programs described in Ref. 3. Atomic form factors were those of Hanson *et al.*[4] for C, O, N, and C, and of Stewart *et al.*[5] for H.

CRYSTAL DATA

Dextropropoxyphene hydrochloride, $C_{22}H_{29}NO_2$ HCl, orthorhombic.
a = 11.997 (1) Å, b = 12.835 (1) Å, c = 13.830 (1) Å.
V = 2129.6 Å^3, M = 375.94, Z = 4.
Melting point: 166.5 – 167.5°C.
D_{obs} = 1.18 g cm^{-3}, D_{calc} = 1.19 g cm^{-3}.
Systematic absences: $h00$ when h is odd, $0k0$ when k is odd, $00l$ when l is odd; space group $P2_12_12_1$.

STRUCTURE DETERMINATION

The coordinates of the chlorine ions were determined from a three-dimensional Patterson synthesis. A Fourier map revealed 18 of the 26 heavy atom positions. Two successive Fourier refinement served to establish a trial structure of all the non-hydrogen atoms. Successive cycles of full matrix least squares refinement, first with isotropic then with anisotropic thermal parameters yielded an R-value of 0.07. None of the hydrogen atoms could be localized in a difference Fourier map, and approximate positions were calculated from stereochemical considerations. A distance of 3.01 Å between Cl and N was supposed to correspond to a hydrogen bond from a protonated nitrogen atom. Giving the atoms individual isotropic thermal parameters, the block-diagonal least squares refinement converged at $R = 0.034$.

To establish the absolute configuration, the structure factors were calculated including anomalous dispersion effects for the chlorine ion. The two R-values calculated, with $\Delta f''$ positive and negative were 0.034 and 0.033, respectively. The diastereomer corresponding to the lower R-value could be assigned the configuration $4S{:}5R$, following the numbering in the present paper. This corresponds to the absolute configuration assigned to the (+)-isomer by Sullivan *et al.*[6] from chemical evidence. The R-ratio 0.034/0.033 may be accepted at a significance level better than 0.005 with Hamilton's test.[7]

The reflections 012, 023, 031, 102, and 113 were the strongest ones and had to be measured with reduced intensity of the primary beam. They showed

Table 1. Observed and calculated structure factors. The columns are h, k, l, $10|F_o|$ and $10|F_c|$.

h	k	l	10Fo	10Fc	h	k	l	10Fo	10Fc	h	k	l	10Fo	10Fc	h	k	l	10Fo	10Fc
0	0	2	153	152	0	12	3	174	184	1	7	14	80	65	2	4	4	327	325	3	1	13	44	38	3	11	9	92	85
0	0	4	442	387	0	12	4	145	144	1	7	15	42	35	2	4	5	311	303	3	1	14	78	77	3	11	10	114	119
0	0	6	968	963	0	12	7	69	69	1	8	1	121	122	2	4	6	248	247	3	1	15	54	492	3	11	11	51	57
0	0	8	64	60	0	12	10	78	67	1	8	2	60	65	2	4	7	196	184	3	1	1	376	373	3	11	12	86	82
0	0	12	70	68	0	13	0	82	82	1	8	3	228	227	2	4	8	37	43	3	1	2	512	489	3	11	13	69	65
0	1	12	26.	274	0	13	8	72	69	1	8	4	59	56	2	4	9	44	48	3	1	3	92	91	3	11	1	126	128
0	1	14	57	56	0	14	0	125	124	1	8	5	161	158	2	4	10	81	76	3	1	4	294	283	3	11	2	146	146
0	1	1	235	232	0	14	1	142	144	1	8	6	127	130	2	4	12	87	83	3	1	5	243	237	3	11	3	111	108
0	1	3	266	273	0	14	3	95	93	1	8	7	164	162	2	5	0	313	343	3	1	6	309	304	3	11	4	51	54
0	1	4	126	121	0	14	6	113	113	1	8	8	58	57	2	5	1	269	272	3	1	7	313	313	3	11	5	76	75
0	1	5	235	240	0	14	7	76	77	1	8	9	111	114	2	5	2	334	341	3	1	8	224	224	3	11	6	64	63
0	1	6	86	85	0	16	2	84	79	1	8	11	61	58	2	5	3	480	477	3	1	9	121	124	3	11	7	105	114
0	1	7	92	85	1	.	1	53	43	1	9	1	358	359	2	5	4	144	144	3	1	10	128	125	3	12	.	191	189
0	1	11	137	133	1	.	3	77	72	1	9	2	207	206	2	5	5	169	171	3	1	11	90	93	3	12	1	47	61
0	1	13	61	65	1	.	4	149	149	1	9	3	200	199	2	5	6	55	58	3	1	12	141	143	3	12	2	177	183
0	1	14	84	84	1	.	5	222	225	1	9	3	94	82	2	5	7	198	199	3	1	13	53	56	3	12	3	87	88
0	2	.	524	505	1	.	6	44	39	1	9	4	94	94	2	5	8	118	115	3	1	15	7.	6.	3	12	4	87	86
0	2	1	273	269	1	1	7	492	476	1	9	5	318	319	2	5	9	121	112	3	2	.	659	657	3	12	5	55	65
0	2	2	361	366	1	.	8	131	115	1	9	6	179	175	2	5	11	192	198	3	2	1	428	423	3	12	6	74	75
0	2	3	1344	1344	1	.	9	186	181	1	9	7	143	143	2	5	11	84	81	3	2	2	129	132	3	12	8	91	86
0	2	4	538	538	1	1	10	179	176	1	9	8	65	68	2	5	12	67	66	3	2	3	355	358	3	13	1	111	103
0	2	5	222	228	1	1	12	91	86	1	9	11	114	112	2	5	14	9.	44	3	2	4	391	387	3	13	4	59	51
0	2	6	25.	24.	1	1	14	114	113	1	9	13	64	62	2	6	.	114	108	3	2	5	248	243	3	14	.	76	72
0	2	7	555	556	1	1	15	78	84	1	10	0	147	146	2	6	1	420	417	3	2	6	178	183	3	14	1	114	98
0	2	9	211	197	1	1	.	636	664	1	10	1	63	63	2	6	2	455	461	3	2	7	65	64	3	14	3	76	73
0	2	10	83	76	1	1	1	443	45.	1	10	2	126	128	2	6	3	316	325	3	2	8	219	219	3	14	5	99	94
0	2	12	8.	8.	1	1	2	311	294	1	10	3	65	68	2	6	4	224	221	3	2	9	61	59	3	15	6	92	92
0	2	13	148	148	1	1	4	768	774	1	10	4	288	288	2	6	5	343	347	3	2	10	126	122	3	16	2	143	88
0	2	14	52	42	1	1	5	413	413	1	10	5	96	88	2	6	6	168	171	3	2	11	154	143	4	.	.	143	135
0	2	15	34	3.	1	1	6	7.	6.	1	10	6	117	114	2	6	7	179	177	3	2	12	54	54	4	.	1	395	375
0	3	2	698	691	1	1	7	332	333	1	10	7	88	85	2	6	8	46	46	3	2	14	93	93	4	.	2	55	55
0	3	3	277	262	1	1	8	57	56	1	10	9	114	108	2	6	9	69	69	3	3	.	757	746	4	.	11	364	358
0	3	4	265	255	1	1	9	236	235	1	10	9	95	91	2	6	10	92	93	3	3	1	402	404	4	.	4	221	227
0	3	5	189	188	1	1	10	69	69	1	10	10	140	97	2	6	11	121	128	3	3	2	78	79	4	.	5	734	717
0	3	6	526	516	1	1	11	133	135	1	10	12	93	94	2	6	12	129	126	3	3	3	262	264	4	.	6	142	144
0	3	7	79	75	1	1	12	180	174	1	11	1	96	99	2	7	1	168	175	3	3	4	213	214	4	.	7	148	146
0	3	8	194	192	1	1	13	138	131	1	11	2	124	123	2	7	1	112	104	3	3	5	49.	475	4	.	8	125	127
0	3	9	39	38	1	1	15	71	67	1	11	4	48	43	2	7	2	304	303	3	3	6	267	259	4	.	9	42	4.
0	3	11	167	169	1	2	.	442	424	1	11	5	90	95	2	7	3	82	8.	3	3	7	284	287	4	.	10	279	294
0	3	12	96	92	1	2	1	179	174	1	11	7	121	115	2	7	4	1.5	113	3	3	8	91	89	4	.	11	194	186
0	3	13	69	67	1	2	2	384	366	1	11	8	54	44	2	7	5	127	127	3	3	9	133	137	4	.	12	17	14
0	3	15	49	51	1	2	3	162	158	1	12	1	98	96	2	7	6	157	157	3	3	10	74	71	4	.	13	55	51
0	4	.	655	695	1	2	4	334	327	1	12	2	81	85	2	7	7	51	53	3	3	11	119	115	4	1	.	679	669
0	4	1	457	453	1	2	5	397	392	1	12	3	96	97	2	7	8	196	198	3	3	12	66	62	4	1	1	651	642
0	4	2	412	412	1	2	6	357	354	1	12	4	38	37	2	7	9	13.	13.	3	4	.	289	277	4	1	2	263	253
0	4	3	389	386	1	2	7	294	282	1	12	5	116	116	2	7	11	69	64	3	4	1	137	141	4	1	3	242	232
0	4	4	160	152	1	2	8	155	152	1	12	7	105	98	2	7	12	78	87	3	4	2	112	117	4	1	4	44	39.
0	4	5	52	52	1	2	9	161	159	1	12	9	72	68	2	8	.	1.9	111	3	4	3	266	268	4	1	5	3.5	297
0	4	6	387	395	1	2	10	94	81	1	12	10	46	52	2	8	1	22.	23.	3	4	4	442	442	4	1	6	27	2.
0	4	7	234	230	1	2	11	125	124	1	12	11	83	77	2	8	2	147	151	3	4	5	197	193	4	1	7	161	165
0	4	9	199	194	1	2	12	148	148	1	13	1	68	66	2	8	3	166	163	3	4	6	239	237	4	1	8	347	341
0	4	11	97	93	1	2	14	58	56	1	13	2	73	65	2	8	4	129	144	3	4	7	71	71	4	1	9	94	92
0	4	14	5.	46	1	2	15	47	5.	1	13	4	93	88	2	8	5	231	225	3	4	8	139	138	4	1	10	143	142
0	5	1	1221	1058	1	3	.	762	846	1	13	8	63	65	2	8	6	178	173	3	4	9	152	154	4	1	11	240	234
0	5	2	67	84	1	3	1	58.	582	1	13	9	71	69	2	8	7	158	161	3	4	10	73	72	4	1	13	88	85
0	5	3	3.5	301	1	3	2	671	689	1	14	1	87	91	2	8	8	36	36	3	4	11	44	34	4	1	15	65	88
0	5	5	223	22.	1	3	3	262	26.	1	14	4	77	72	2	8	9	148	151	3	4	13	56	51	4	2	1	297	294
0	5	6	95	94	1	3	4	395	383	1	14	8	46	54	2	8	10	98	97	3	5	.	439	435	4	2	2	3.4	297
0	5	7	152	156	1	3	5	36.	347	1	15	5	85	77	2	8	12	7.	72	3	5	1	243	233	4	2	3	748	731
0	5	9	248	243	1	3	6	286	272	1	15	6	1.3	93	2	8	14	93	87	3	5	2	314	311	4	2	4	538	515
0	5	10	78	76	1	3	7	317	327	2	.	0	5.9	523	2	9	.	31	35	3	5	3	288	278	4	2	5	156	144
0	5	11	137	142	1	3	8	76	78	2	.	1	86	76	2	9	1	156	157	3	5	4	244	245	4	2	5	183	181
0	5	12	51	47	1	3	9	88	86	2	.	2	973	977	2	9	2	149	144	3	5	5	83	9.	4	2	6	227	212
0	5	13	83	84	1	3	10	111	109	2	.	3	292	293	2	9	3	96	99	3	5	6	143	142	4	2	7	167	164
0	6	0	868	876	1	3	11	64	65	2	.	4	72.	72	2	9	4	143	146	3	5	7	71	63	4	2	8	291	294
0	6	1	719	706	1	3	12	64	62	2	0	5	267	265	2	9	5	74	72	3	5	8	159	158	4	2	9	196	202
0	6	2	41	55	1	3	13	53	58	2	.	6	348	352	2	9	6	164	158	3	5	9	151	164	4	2	10	168	168
0	6	3	321	33.	1	4	.	68.	7.1	2	.	7	410	417	2	9	7	137	141	3	5	10	138	136	4	2	11	126	126
0	6	5	17.	172	1	4	1	431	425	2	.	8	142	152	2	9	8	91	91	3	5	11	114	119	4	2	12	97	92
0	6	6	286	283	1	4	2	325	323	2	.	9	228	231	2	9	9	60	59	3	5	12	109	108	4	2	13	53	53
0	6	7	114	124	1	4	3	72	71	2	.	10	247	246	2	9	10	66	63	3	5	13	62	57	4	2	14	8.	75
0	6	8	86	86	1	4	4	91	95	2	0	11	124	114	2	10	.	104	104	3	6	1	268	266	4	3	.	308	345
0	6	11	126	122	1	4	5	324	314	2	0	12	218	218	2	10	1	104	104	3	6	2	133	129	4	3	1	167	170
0	6	12	1.1	86	1	4	6	131	131	2	0	13	117	111	2	10	2	203	201	3	6	3	69	67	4	3	2	58	52
0	7	1	319	308	1	4	7	247	241	2	1	0	91	91	2	10	3	75	71	3	6	4	54	49	4	3	3	269	264
0	7	2	164	157	1	4	8	129	126	2	1	1	66	62	2	10	4	241	195	3	6	5	241	244	4	3	4	144	138
0	7	3	340	346	1	4	9	215	214	2	1	2	681	694	2	10	5	194	181	3	6	6	94	94	4	3	5	165	162
0	7	4	211	205	1	4	10	81	84	2	1	3	426	422	2	10	6	136	128	3	6	7	136	137	4	3	6	27	3.
0	7	5	283	276	1	4	11	84	81	2	1	4	615	615	2	10	8	124	125	3	6	8	44	47	4	3	7	235	235
0	7	6	172	174	1	4	12	46	48	2	1	5	533	491	2	10	9	104	102	3	6	10	153	151	4	3	8	121	117
0	7	7	183	185	1	4	13	66	61	2	1	6	143	149	2	10	10	67	62	3	6	13	75	62	4	3	9	93	84
0	7	10	66	59	1	4	14	91	93	2	1	6	353	345	2	11	13	63	61	3	7	0	195	192	4	3	10	75	77
0	7	11	159	149	1	5	.	93	98	2	1	7	41	40	2	11	.	104	105	3	7	1	242	241	4	3	11	148	145
0	7	12	147	134	1	5	1	577	597	2	1	8	91	92	2	11	1	100	108	3	7	2	298	311	4	3	12	55	53
0	7	13	67	61	1	5	2	414	412	2	1	9	319	311	2	11	2	93	94	3	7	3	109	114	4	3	13	70	64
0	8	2	154	152	1	5	3	124	121	2	1	10	149	153	2	11	3	88	91	3	7	4	230	226	4	3	14	74	59
0	8	5	225	219	1	5	4	226	223	2	1	11	129	126	2	11	4	134	140	3	7	5	199	198	4	4	.	88	92
0	8	8	94	97	1	5	5	279	272	2	1	12	72	73	2	11	5	118	114	3	7	6	202	199	4	4	1	279	278
0	8	11	214	209	1	5	6	162	156	2	1	14	127	121	2	11	6	71	68	3	7	7	194	188	4	4	2	137	133
0	8	14	174	171	1	5	7	196	190	2	2	0	752	781	2	11	8	73	74	3	7	8	94	95	4	4	3	275	264
0	8	12	69	55	1	5	8	151	154	2	2	1	827	829	2	12	.	148	154	3	7	9	127	122	4	4	4	195	178
0	9	1	232	234	1	5	9	97	98	2	2	2	212	221	2	12	1	133	127	3	7	10	116	117	4	4	5	346	294
0	9	2	425	425	1	5	10	53	54	2	2	3	561	567	2	12	2	94	83	3	7	11	45	45	4	4	6	246	241
0	9	3	126	134	1	6	.	244	243	2	2	4	526	526	2	12	3	94	91	3	8	.	247	242	4	4	8	45	45
0	9	4	145	143	1	6	1	575	569	2	2	5	172	173	2	12	6	89	86	3	8	1	165	177	4	4	9	136	135
0	9	5	287	282	1	6	2	238	229	2	2	6	170	171	2	12	7	77	87	3	8	2	81	78	4	4	10	36	34
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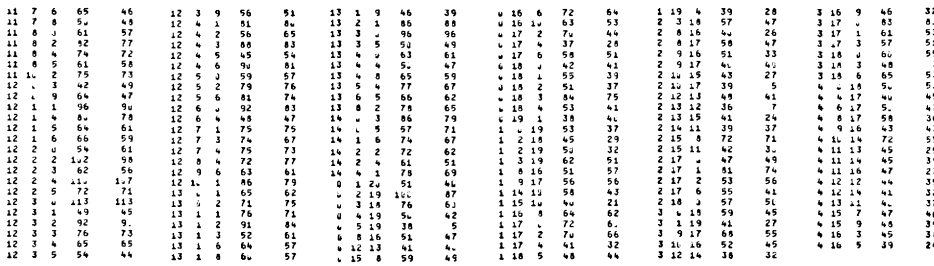
0	9	7	274	271	1	6	4	233	234	2	2	8	152	143	2	12	9	77	69	3	8	4	75	68	4	4	12	62	67
0	9	8	323	317	1	6	5	162	155	2	2	9	161	154	2	12	11	66	66	3	8	5	157	143	4	4	14	75	71
0	9	9	143	138	1	6	6	133	133	2	2	10	96	96	2	13	4	66	64	3	8	6	88	88	4	5	.	146	145
0	9	10	73	81	1	6	7	35	29	2	2	11	91	85	2	13	6	149	86	3	8	7	192	194	4	5	1	69	74
0	10	.	194	196	1	6	8	91	83	2	2	12	67	58	2	13	7	7.	6.	3	8	8	123	125	4	5	2	214	214
0	10	1	93	91	1	6	9	64	61	2	3	0	748	717	2	14	1	57	51	3	8	9	68	72	4	5	3	191	190
0	10	2	94	89	1	6	10	139	136	2	3	1	324	324	2	14	2	53	56	3	8	11	81	84	4	5	4	87	92
0	10	3	218	220	1	6	12	7.	6.	2	3	2	338	338	2	14	3	111	108	3	9	.	17.	169	4	5	5	175	179
0	10	4	117	116	1	6	13	97	96	2	3	3	252	257	2	14	4	72	64	3	9	1	59	54	4	5	6	185	187
0	10	6	198	202	1	6	14	70	68	2	3	4	331	331	2	14	5	76	68	3	9	2	234	246	4	5	7	194	189
0	10	7	103	109	1	7	.	105	102	2	3	5	377	363	2	15	3	99	96	3	9	3	13.	121	4	5	8	84	85
0	10	8	74	66	1	7	1	531	532	2	3	6	153	148	2	15	4	123	96	3	9	4	147	144	4	5	9	166	164
0	10	10	112	112	1	7	2	215	195	2	3	7	224	218	2	16	1	98	87	3	9	5	262	259	4	5	10	84	88
0	10	14	102	90	1	7	3	377	365	2	3	8	133	132	3	0	2	29	16	3	9	6	57	60	4	5	11	78	78
0	11	1	172	174	1	7	4	258	258	2	3	9	144	139	3	.	3	5.3	497	3	9	7	75	74	4	5	12	90	87
0	11	2	82	85	1	7	5	159	164	2	3	10	125	118	3	1	4	151	150	3	9	8	119	124	4	5	13	59	59
0	11	9	2.5	2.3	1	7	6	211	198	2	3	11	117	116	3	1	5	64	61	3	9	10	59	54	4	6	.	49	54
0	11	7	69	70	1	7	7	59	62	2	3	12	60	64	3	1	6	252	255	3	9	11	86	79	4	6	1	36	23
0	11	8	45	41	1	7	8	92	92	2	3	13	72	79	3	1	7	44	41	3	10	.	88	84	4	6	2	33.	336
0	11	9	74	66	1	7	9	88	88	2	4	0	801	812	3	1	9	61	64	3	10	1	111	116	4	6	3	149	148
0	11	11	96	83	1	7	10	51	49	2	4	1	342	335	3	1	10	157	151	3	10	2	139	138	4	6	4	32	48
0	12	.	127	114	1	7	12	65	61	2	4	2	521	521	3	1	11	92	95	3	10	3	77	77	4	6	5	117	112
0	12	2	78	85	1	7	13	64	73	2	4	3	386	379	3	1	12	297	294	3	10	4	15.	156	4	6	6	48	48

Table 1. Continued.

Table 1. Continued.



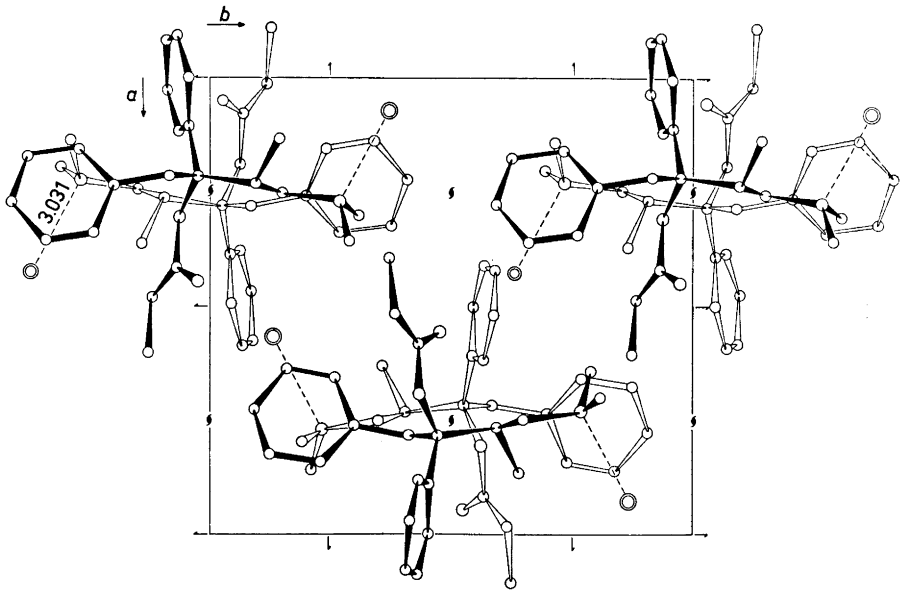


Fig. 2. The crystal structure of dextropropoxyphene hydrochloride as seen along the *c*-axis.

great differences ($F_o - F_c$) and were excluded from the further refinement.

Final block-diagonal least squares refinement, including anomalous dispersion effects gave an R-value of 0.032 ($R_w = 0.032$). In the last cycle the average shift in the parameters were 0.1σ for the 1643 observed reflections.

A total difference Fourier map showed electron densities in the range ± 0.2 eÅ^{-3}.

Observed and calculated structure factors are listed in Table 1, and the atomic parameters in Tables 2 and 3. The anisotropic temperature factor is given by

Table 2. Fractional atomic coordinates and thermal parameters with standard deviations (10^5) for non-hydrogen atoms.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	44808	−37286	6017	872	674	959	371	133	210
	7	7	7	7	5	7	11	13	11
N	22449	−26439	7777	647	410	515	−56	−125	11
	18	15	16	17	14	14	27	30	25
O1	4785	2717	18542	627	833	559	−292	−82	−311
	15	16	14	15	16	12	28	25	24
O2	19313	6478	8602	492	452	443	19	15	−45
	13	13	12	13	10	10	21	21	20
C1	−10477	13028	6017	671	1419	824	553	−28	−365
	27	34	26	26	37	25	56	46	55
C2	1644	11802	3593	651	661	567	49	31	−139
	23	24	21	23	21	19	39	36	36
C3	8386	6512	11201	535	425	484	−141	88	164
	21	20	18	20	16	16	33	31	31
C4	28210	2555	14942	524	415	387	6	29	5
	21	19	18	21	17	15	32	23	27
C5	26550	−9410	16661	682	411	402	−40	−113	−32
	22	20	19	22	17	15	34	33	28
C6	36101	−14228	22381	1214	507	678	202	590	−23
	29	24	23	32	20	21	47	47	37
C7	24782	−14938	6994	730	373	455	−116	−58	−17
	22	20	19	24	16	16	33	35	29
C8	13405	−29022	14640	1135	604	930	−408	−771	−147
	30	26	26	32	22	26	48	54	43
C9	19621	−30635	−1969	1280	566	629	−286	171	257
	29	24	23	35	21	21	48	48	37
C10	27871	8435	24706	502	502	401	−42	−106	97
	21	20	18	20	17	15	33	33	29
C11	25933	20030	24103	594	476	372	45	130	172
	21	21	18	21	17	15	33	32	29
C12	34187	26995	21334	788	514	633	7	16	301
	24	23	23	25	19	20	39	39	35
C13	32227	37612	21427	1175	526	642	−217	237	29
	28	24	23	33	20	21	47	44	37
C14	22051	41337	24349	1508	547	644	740	761	261
	32	24	22	38	21	21	51	53	38
C15	13794	34577	27151	890	767	795	705	402	466
	27	26	24	28	25	24	47	46	43
C16	15710	24064	26963	631	700	623	299	57	403
	23	23	22	23	22	20	39	38	38
C17	38751	4836	9145	543	358	476	76	−86	104
	21	18	19	20	16	16	31	35	30
C18	38502	5533	−871	637	673	428	−200	−106	67
	23	23	19	23	21	16	39	36	34
C19	48077	7323	−6169	917	830	489	−96	−352	−53
	26	26	21	29	25	18	47	39	38
C20	58223	8554	−1573	623	804	687	−77	−473	12
	23	25	22	24	24	21	42	39	40
C21	58658	7818	8357	506	856	711	226	−86	136
	23	25	23	21	24	20	40	39	43
C22	49114	5937	13679	564	618	531	154	−96	60
	23	23	20	21	22	17	38	34	35

Table 3. Fractional coordinates (10^4) and isotropic thermal parameters (Å^2) with standard deviations for hydrogen atoms.

Atom	x	y	z	B
H1C1	−1378	1681	86	8.0
	2:	27	23	.9
H2C1	−1100	1728	1222	9.7
	34	30	24	1.1
H3C1	−1379	683	847	11.0
	33	33	27	1.2
H1C2	294	752	−254	5.7
	21	22	18	.7
H2C2	506	1802	260	4.5
	20	20	18	.6
HC5	1998	−992	2055	3.5
	20	20	18	.6
H1C6	3723	−1044	2817	8.5
	29	28	23	1.0
H2C6	3424	−2145	2410	6.5
	25	26	21	.8
H3C6	4334	−1405	1820	7.1
	24	26	21	.8
H1C7	3202	−1446	242	5.0
	20	22	19	.7
H2C7	1875	−1195	332	3.6
	19	19	17	.6
HN	2964	−2948	931	5.9
	22	22	20	.7
H1C8	1209	−3618	1509	6.4
	24	24	19	.7
H2C8	678	−2489	1227	8.5
	28	28	23	1.0
H3C8	1604	−2726	2197	5.9
	23	24	21	.8
H1C9	1819	−3804	−169	4.0
	18	19	17	.6
H2C9	2624	−2996	−572	6.0
	22	23	21	.7
H3C9	1604	−2722	−506	8.7
	31	30	24	1.0
H1C10	3559	744	2835	3.6
	19	19	16	.6
H2C10	2193	525	2860	2.1
	17	16	15	.5
HC12	4151	2384	1962	4.8
	21	21	18	.6
HC13	3828	4248	3935	5.6
	22	22	19	.7
HC14	2065	4868	2444	7.1
	24	25	21	.8
HC15	693	3767	2919	6.2
	23	24	20	.7
HC16	939	1921	2887	5.1
	23	22	19	.7
HC18	3148	547	−389	3.2
	18	18	16	.5
HC19	4800	760	−1303	4.9
	21	21	18	.6
HC20	6552	971	−524	4.4
	19	19	17	.6
HC21	6583	863	1208	4.7
	20	20	16	.6
HC22	4930	575	2059	4.5
	23	22	18	.7

Table 4. Bond lengths (Å) and bond angles (°) for the nonhydrogen atoms, with standard deviations.

	Bond length			
	Uncorrected	Corrected	Angles	
C1 –C2	1.503 (4)		C1 –C2 –C3	114.3 (.3)
C2 –C3	1.491 (4)		C2 –C3 –O1	125.7 (.2)
C3 –O1	1.206 (3)		C2 –C3 –O2	109.8 (.2)
C3 –O2	1.359 (3)		O1 –C3 –O2	124.6 (.2)
O2 –C4	1.470 (3)		C3 –O2 –C4	122.9 (.2)
C4 –C5	1.567 (4)		O2 –C4 –C5	109.5 (.2)
C5 –C6	1.524 (4)		O2 –C4 –C10	109.5 (.2)
C5 –C7	1.528 (4)		O2 –C4 –C17	102.8 (.2)
C7 –N	1.506 (3)		C4 –C5 –C6	112.4 (.2)
C8 –N	1.479 (4)		C4 –C5 –C7	109.8 (.2)
C9 –N	1.491 (4)		C6 –C5 –C7	111.7 (.2)
C4 –C10	1.547 (3)		C5 –C7 –N	114.7 (.2)
C10–C11	1.509 (4)	1.513	C7 –N –C8	113.7 (.2)
C11–C12	1.388 (4)	1.398	C7 –N –C9	109.4 (.2)
C12–C13	1.383 (4)	1.388	C8 –N –C9	109.4 (.2)
C13–C14	1.372 (5)	1.384	C5 –C4 –C10	110.0 (.2)
C14–C15	1.373 (5)	1.378	C5 –C4 –C17	111.6 (.2)
C15–C16	1.369 (4)	1.372	C4 –C10–C11	115.9 (.2)
C16–C11	1.389 (4)	1.400	C10–C11–C12	122.7 (.2)
C4 –C17	1.527 (4)	1.529	C11–C12–C13	120.7 (.3)
C17–C18	1.389 (4)	1.397	C12–C13–C14	119.8 (.3)
C18–C19	1.382 (4)	1.385	C13–C14–C15	120.4 (.3)
C19–C20	1.382 (4)	1.391	C14–C15–C16	119.8 (.3)
C20–C21	1.378 (4)	1.384	C15–C16–C11	121.3 (.3)
C21–C22	1.382 (4)	1.385	C16–C11–C12	118.0 (.3)
C22–C17	1.400 (4)	1.406	C16–C11–C10	119.2 (.2)
			C5 –C4 –C17	111.6 (.2)
			C10–C4 –C17	112.7 (.2)
	Hydrogen bond length		C4 –C17–C18	121.3 (.2)
N–H···Cl^-	3.031 (2)		C17–C18–C19	121.5 (.3)
			C18–C19–C20	120.4 (.3)
			C19–C20–C21	118.9 (.3)
			C20–C21–C22	120.8 (.3)
			C21–C22–C17	121.0 (.3)
			C22–C17–C18	117.4 (.2)
			C22–C17–C4	121.4 (.2)

Table 5. Bond lengths (Å) involving hydrogen atoms.

C1–H1C1	0.96	C9 –H1C9	0.97
C1–H2C1	1.01	C9 –H2C9	0.95
C1–H3C1	0.95	C9 –H3C9	1.02
C2–H1C2	1.02	C10–H1C10	1.06
C2–H2C2	0.94	C10–H2C10	0.98
C5–HC5	0.96	C12–HC12	1.00
C6–H1C6	0.95	C13–HC13	1.00
C6–H2C6	0.98	C14–HC14	0.96
C6–H3C6	1.04	C15–HC15	0.96
C7–H1C7	1.08	C16–HC16	1.02
C7–H2C7	0.96	C18–HC18	0.94
N –HN	0.97	C19–HC19	0.95
C8–H1C8	0.93	C20–HC20	1.02
C8–H2C8	1.01	C21–HC21	1.00
C8–H3C8	1.09	C22–HC22	0.96

Standard deviations are in the range 0.02–0.03 Å.

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

The e.s.d. in bond lengths and angles were calculated to be 0.003 – 0.004 Å and 0.3°, respectively.

DISCUSSION

Interatomic distances and bond angles are given in Tables 4 and 5, and are shown in Fig. 1. The analysis of the thermal parameters showed that the two benzyl parts of propoxyphene could be regarded as rigid bodies, and the positional parameters of these atoms were corrected for librational effects. The corrected bond lengths are also listed in Table 4.

Fig. 2 illustrates the crystal structure which is dominated by a very strong hydrogen bond (3.03 Å) between the protonated nitrogen atom and the chlorine ion; the distance between the hydrogen atom (HN) and the chlorine ion being 2.08 Å.

There are no other particularly short intermolecular distances in the structure.

The distance C1 – C2 (1.503 Å) is found to be shorter than the normal, 1.537 Å.[8] This is probably due to the considerable thermal motion of the methyl carbon atom.

The mean C – N bond length is 1.492 Å, in agreement with the value reported by Marsh *et al.* (1.487 Å).[9] The mean aromatic C – C distance is 1.383 Å (1.389 Å corrected).

Owing to the two large aromatic groups at C4, the angle O2 – C4 – C17 is as small as 102.8°. To compensate the strain around C4, the angle C4 – C10 – C11 is 115.9°. Both values are significantly different from the normal tetrahedral angle.

The phenyl rings A and B are planar. C4 is co-planar with plane B, whereas C10 is 0.09 Å out of plane A. This deviation from planarity may be caused by the repulsions around C4 mentioned above. The two planes A and B form an angle of 86.6°. The dihedral angles C12 – C11 – C10 – C4 and C18 – C17 – C4 – O2 are 76.2° and – 28.3°, respectively.

The ester group (C2,C3,O1,O2) is planar to within 0.004 Å, the planes through C1,C2,C3 and C3,O2,C4 form angles of 5.4° and 5.6° with this plane, respectively, C1 and C4 being on the same side.

The butylamine part of the molecule is nearly fully extended, the torsional angles around the bonds C10 – C4, C4 – C5 and C5 – C7 being – 162.6°, 169.8° and – 176.7°. Owing to the strong hydrogen bond between the nitrogen atom and the chlorine ion there is no interaction between the $NH^+(CH_3)_2$ and the ester groups. The bond N – H is pointing away from the ester group, and the suggested morphine-like conformation is not found in this hydrochloride of dextropropoxyphene. In the present structure the distance H1C7 – O1 is 3.27 Å, and a rotation about the bonds C5 – C7 and C7 – N may thus bring the nitrogen atom in close contact with the carbonyl group. This rotation may take place in the free molecule or related compounds; the crystal structure of methadone now being under investigation in this laboratory may give an answer to this.

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