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Crystal Structures of Synthetic Analgetics. II. *l*-Methadone

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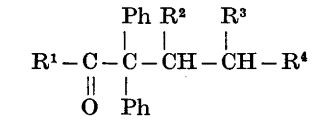
The molecular and crystal structure of *l*-methadone has been determined by X-ray methods. The crystals are orthorhombic, space group $P2_12_12_1$ with unit cell dimensions $a = 9.637$ Å; $b = 11.385$ Å; $c = 16.866$ Å. The phase problem was solved by direct methods and the model refined to an R-value of 0.038 for 1687 observed reflections. Estimated standard deviations are 0.003 – 0.004 Å in interatomic distances and 0.2 – 0.3° in angles.

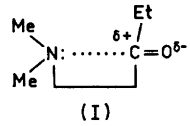
The dimethylamine group is (–)*syn clinal* relative to the quaternary carbon atom. There is a short intramolecular distance of 2.91 Å between the nitrogen atom and the carbonyl carbon atom and C3 is 0.06 Å out of the plane through C2, O and C4. The planes of the two phenyl rings make a dihedral angle of 80.6°.

The synthetic analgetic methadone may be characterized as the central compound among propylamines having morphine-like action. It belongs to a group of ketones with the general formula



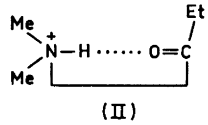
with $R^1 = Et$; $R^2 = H$; $R^3 = Me$; $R^4 = N(Me)_2$. The analgesic property of methadone and related compounds is believed to be dependent on a particular molecular conformation. Many investigations concerned with the preferred conformation of methadone have been reported.[1–4] Beckett *et al.*[1] and Beckett [2] proposed that the biologically important conformation of methadone resulted from an intramolecular interaction between the basic nitrogen atom and the carbonyl carbon atom (I).

This electrostatic attraction may bring the amine and the carbonyl group in close proximity.



(I)

Although an intramolecular hydrogen bond (II) is supposed to be present in solution,[1–4] no short distances were found between the nitrogen atom and the carbonyl group in the crystal structures of *d*-methadone hydrobromide [5] and dextropropoxyphene hydrochloride.[6]



(II)

The present structure determination was carried out to see if the particular conformation was preferred in the solid state of the free base.

EXPERIMENTAL

l-Methadone was prepared from commercially available *l*-methadone hydrochloride and single crystals were formed by recrystallization in diethyl ether by evaporation. The compound crystallizes as colourless, transparent parallelepipeds, and a crystal ground to a sphere ($r = 0.2$ mm) was used in the experiments.

Oscillation and Weissenberg photographs indicated orthorhombic symmetry. Systematically absent reflections were $h00$, $0k0$, $00l$ for odd indices; thus the space group is $P2_12_12_1$.

Unit cell dimensions were determined by least-squares methods from angular coordinates, measured on a Syntex P$\bar{1}$ diffractometer with graphite crystal monochromated Mo$K\alpha$-radiation. Three-dimensional intensity data were col-

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

H=	0,K=	0																					
0	674	703	15	79	79	H=	0,K=	13	20	34	32	2	115	119	5	417	404	9	223	222	3	153	153
4	306	304	16	48	45	3	24	13	22	30	27	3	55	59	6	163	161	10	108	102	4	263	261
8	416	409	17	35	30	5	44	33	23	41	25	4	78	84	7	274	278	11	124	125	5	506	503
12	284	288	18	33	28	6	49	44	H=	1,K=	4	5	99	102	8	201	196	12	29	24	6	126	122
14	42	48	H=	0,K=	6	11	29	28	0	216	214	6	170	170	9	273	271	14	37	34	7	181	174
18	65	64	0	158	154	12	43	36	1	427	421	7	152	153	10	132	129	17	58	61	8	120	122
20	82	82	1	343	334	13	30	17	2	60	60	9	111	109	11	90	89	18	56	48	9	135	134
H=	0,K=	1	2	140	135	H=	0,K=	14	3	73	76	10	55	56	12	73	72	H=	2,K=	8	10	76	75
1	106	106	3	339	330	9	58	50	4	37	37	11	74	74	13	65	63	0	164	164	11	42	39
2	823	879	4	208	209	11	33	30	5	439	432	13	53	51	14	63	59	1	170	172	12	108	108
3	228	228	5	27	20	H=	0,K=	15	6	227	218	15	26	26	15	88	87	2	142	145	13	236	233
4	962	1026	7	82	84	4	41	40	7	252	251	16	40	38	17	88	90	3	44	36	14	113	110
5	458	454	9	89	89	6	39	32	8	205	210	19	29	15	18	31	33	4	136	139	15	81	79
6	201	195	10	52	47	9	42	37	9	196	193	H=	1,K=	10	20	35	37	5	43	39	17	33	27
7	136	138	11	124	123	10	35	35	10	77	76	0	126	128	H=	2,K=	3	6	69	74	H=	3,K=	2
8	364	360	12	138	133	11	35	34	11	87	86	1	33	38	0	88	86	7	167	174	0	217	215
9	91	91	13	101	103	H=	0,K=	16	12	57	59	2	112	118	1	330	323	8	128	132	1	56	58
10	176	172	14	62	66	3	37	29	13	89	87	3	107	108	2	249	237	9	136	138	2	177	170
11	142	143	15	56	58	7	42	39	14	36	44	4	63	68	3	341	339	10	83	84	3	201	202
14	87	87	16	32	28	8	39	39	15	66	64	5	113	108	4	582	577	11	77	79	4	138	138
15	28	21	18	32	24	H=	0,K=	17	17	50	51	6	88	85	5	437	424	12	77	79	5	465	451
17	30	24	H=	0,K=	7	1	32	20	18	28	33	7	97	99	6	330	321	13	61	52	6	454	452
18	132	132	1	198	198	H=	1,K=	0	20	28	21	8	45	45	7	51	48	15	52	52	7	206	201
19	32	36	2	92	91	1	666	677	21	39	37	9	60	55	8	161	160	H=	2,K=	9	8	186	186
20	82	79	3	70	76	2	193	192	H=	1,K=	5	11	31	30	9	64	64	0	27	22	9	48	45
H=	0,K=	2	4	128	127	3	302	304	0	191	185	12	28	36	10	66	65	1	125	129	10	102	106
0	814	839	6	55	51	4	94	93	1	87	86	14	59	55	11	58	58	2	31	28	11	68	65
1	887	964	7	94	89	5	288	293	2	77	79	H=	1,K=	11	12	75	75	3	98	96	12	61	57
2	561	565	8	247	254	7	282	279	3	241	233	1	88	84	13	27	21	4	91	90	13	84	84
3	62	61	9	68	76	8	78	74	4	22	44	2	48	44	14	65	64	5	81	85	14	62	63
4	455	448	10	148	148	9	156	158	5	346	339	3	86	89	15	141	139	6	56	57	15	140	136
5	632	626	12	53	53	10	20	24	6	216	216	4	137	137	16	57	61	7	35	43	16	56	57
6	388	384	13	23	6	12	71	71	7	81	85	5	27	33	18	47	43	8	54	53	18	57	59
7	228	219	14	71	72	14	79	79	8	105	104	6	31	33	H=	2,K=	4	9	46	45	19	42	39
8	86	82	16	51	56	16	42	38	9	157	160	8	38	39	0	434	419	16	53	49	H=	3,K=	3
9	25	26	17	34	40	17	97	99	10	60	60	9	36	35	1	41	42	H=	2,K=	10	0	102	101
11	81	74	18	32	22	18	54	49	11	114	113	10	71	66	2	44	46	0	65	67	1	243	239
12	75	73	20	59	53	20	53	46	12	115	118	11	72	69	3	254	247	1	64	69	2	121	118
13	63	61	H=	0,K=	8	H=	1,K=	1	13	72	78	12	32	41	4	211	210	2	45	38	3	132	137
14	61	53	0	89	91	0	733	756	14	47	51	14	39	34	5	315	318	3	156	161	4	479	469
15	24	20	2	100	104	1	315	306	16	41	43	15	29	23	6	418	407	4	64	66	5	291	279
16	32	27	4	28	21	2	556	566	18	30	26	16	33	31	7	67	74	5	71	67	6	198	195
17	31	41	5	53	49	3	796	818	19	30	29	H=	1,K=	12	8	174	172	8	38	31	7	56	51
18	35	32	6	354	358	4	567	567	H=	1,K=	6	0	97	95	9	134	136	11	44	32	8	50	46
20	46	41	7	181	183	5	207	207	0	139	142	1	48	48	10	65	67	15	36	32	9	100	101
H=	0,K=	3	9	41	47	6	239	233	1	160	160	2	67	69	11	70	72	H=	2,K=	11	10	165	168
1	265	267	10	53	55	7	157	159	2	130	132	3	48	46	12	128	130	0	154	154	11	30	24
2	254	260	11	65	64	8	259	260	3	99	106	4	66	65	13	40	36	1	76	78	12	109	115
3	79	76	12	65	65	9	32	31	4	147	146	5	37	40	14	119	121	3	59	59	14	39	44
4	337	334	13	38	42	10	98	102	5	43	47	8	41	41	15	30	38	4	53	54	15	64	65
5	221	221	14	72	71	11	118	118	6	188	186	9	59	55	16	35	29	5	28	30	17	78	76
7	85	84	15	43	38	12	91	94	7	92	93	12	34	41	17	65	64	6	39	34	18	54	55
8	89	89	16	66	58	13	96	93	8	23	37	H=	1,K=	13	18	25	26	8	59	64	19	27	30
9	32	27	H=	0,K=	9	14	60	63	9	145	148	1	38	43	21	43	36	9	43	38	H=	3,K=	4
10	70	67	1	28	20	15	105	105	10	21	23	5	42	41	H=	2,K=	5	11	40	40	0	216	211
11	60	62	2	32	32	16	41	38	11	71	74	7	29	35	0	144	147	12	31	28	1	180	181
12	99	100	3	176	173	17	101	102	12	60	59	11	43	34	1	125	128	13	38	34	2	143	137
13	32	26	4	107	107	19	66	67	13	32	33	H=	2,K=	0	2	222	221	H=	2,K=	12	3	114	117
14	60	56	5	87	92	20	52	48	14	73	71	0	41	42	3	164	159	1	112	109	4	94	98
15	41	50	6	84	81	H=	1,K=	2	15	37	30	1	27	29	4	227	222	2	45	45	5	108	110
16	45	48	8	114	114	0	214	219	16	39	37	2	399	399	5	142	138	3	63	68	6	45	39
17	45	39	9	55	58	1	785	823	20	27	24	3	1049	1091	6	111	114	4	29	30	7	163	166
18	41	38	11	35	34	2	599	594	H=	1,K=	7	4	210	205	7	104	107	5	38	36	8	81	82
19	35	31	12	43	41	3	544	548	1	85	81	5	266	265	8	153	158	11	59	59	10	127	129
22	28	19	13	57	52	4	292	292	2	66	67	6	159	156	9	141	146	12	44	41	11	82	84
H=	0,K=	4	14	99	94	5	96	95	3	82	84	7	156	155	10	104	104	H=	2,K=	13	12	108	110
0	286	289	15	45	45	6	276	272	4	191	191	8	224	222	11	162	164	2	55	50	13	71	72
2	90	92	17	51	45	7	253	252	6	45	50	9	63	62	12	119	121	5	26	26	14	83	90
3	56	56	18	36	30	8	98	102	7	94	96	10	44	37	13	36	36	6	48	49	15	72	71
4	151	156	19	28	16	9	104	104	8	41	46	11	37	34	14	41	34	8	43	39	16	36	38
5	63	63	H=	0,K=	10	10	189	191	9	66	68	12	23	30	15	67	69	10	47	40	18	31	30
6	114	111	0	114	114	11	120	120	10	77	73	13	73	76	17	36	32	13	32	28	20	35	44
7	214	208	1	97	100	12	132	132	11	67	66	17	25	29	19	41	40	H=	2,K=	14	H=	3,K=	5
8	142	144	2	89	90	13	45	43	12	36	42	18	46	48	22	37	36	4	44	41	0	144	143
9	231	230	4	174	176	14	103	106	13	63	63	H=	2,K=	1	H=	2,K=	6	5	36	35	1	114	114
10	41	41	6	186	190	15	104	102	14	75	76	0	640	647	0	176	181	6	40	32	2	297	283
11	37	38	7	115	117	16	38	43	16	42	43	1	385	380	1	168	164	10	32	25	3	163	162
12	24	28	8	96	102	17	46	42	17	41	35	2	675	673	2	263	256	H=	3,K=	0	4	93	97
13	24	26	10	91	87	18	49	48	19	28	25	3	842	851	3	153	151	1	140	141	5	101	95
14	61	64	12	60	56	19	37	28	21	37	17	4	247	243	4	117	113	2	205	203	6	141	141
15	56	48	13	28	22	21	36	37	H=	1,K=	8	5	212	211	5	47	48	3	793	782	7	64	61
16	23	18	15	40	34	H=	1,K=	3	0	23	23	6	235	230	6	84	83	4	99	98	8	99	100
17	30	28	H=	0,K=	11	0	161	163	1	50	56	7	167	166	7	123	126	5	950	958	9	162	166
18	47	43	1	34	31	1	516	516	2	79	79	8	69	68	8	98	95	6	214	215	10	95	97
21	33	31	2	29	21	2	351	343	3	49	49	9	37	35	9	94	90	7	456	461	11	110	109
H=	0,K=	5	3	84	86	3	247	250	4	54	58	10	124	125	10	211	214	8	92	100	12	61	67
1	24	15	5	63	59	4	311	314	5	149	149	11	87	90	11	192	198	9	34	28	14	39	42
2	32	29	7	29	17	5	261	256	6	111	109	12	121	120	13	26	17	10	27	30	15	49	55
3	218	223	10	35	40	6	232	234	7	150	149	13	36	39	14	53	60	11	102	99	16	67	68
4	146	153	11	61	60	7	256	253	8	53	47	14	81	80	15	66	67	12	43	45	H=	3,K=	6
5	68	66	12	43	40	8	217	221	9	123	122	15	112	115	16	28	18	13	48	47	0	54	48
6	66	66	15	33	37	9	55	52	10	84	80	16	35	34	H=	2,K=	7	14	32	27	1	106	107
7	19	9	19	32	27	10	80	83	11	93	89	17	50	44	0	173	175	15	54	50	2	196	199
8	75	70	H=	0,K=	12	11	93	97	12	58	58	18	37	33	1	109	105	16	56	59	3	89	86
9	29	20	0	37	29	12	52	53	13	83	81	H=	2,K=	2	2	82	83	17	43	40	4	185	183
10	40	37	1	76	81	13	56	61	15	33	28	0	102	103	4	127	127	19	63	60	5	124	129
11	52	54	4	42	42	14	27	14	17	34	38	1	147	140	5	32	35	H=	3,K=	1	6	56	57
12	75	79	8	50	50	15	38	43	H=	1,K=	9	2	298	300	6	114	116	0	434	415	7	182	186
13	43	47	12	40	27	17	95	92	0	33	33	3	583	576	7	96	98	1	179	177	8	234	236
14	46	41	14	41	41	18	48	48	1	73	74	4	516	514	8	65	64	2	162	158	9	57	58

Table 1. Continued.

10	103	100	1	263	265	5	41	42	6	59	58	2	116	113	7	147	151	7	92	95	8	28	36
11	35	39	2	142	137	6	107	110	6	85	85	3	25	15	9	44	44	8	34	31	9	62	59
12	129	134	3	308	295	7	80	81	7	86	83	4	89	89	10	36	36	9	30	30	11	63	55
13	56	65	4	168	164	8	56	56	8	197	202	5	54	59	11	94	96	10	38	39	Hz	7,Kz	10
14	37	39	5	210	206	9	23	18	9	190	194	6	96	102	13	43	32	11	47	47	4	45	46
15	26	30	6	43	55	10	52	54	10	287	296	7	38	39	16	45	42	12	86	83	7	55	60
20	40	34	7	318	319	11	69	70	11	70	72	8	37	41	Hz	6,Kz	5	13	46	47	9	69	61
21	48	41	8	207	207	12	62	62	12	60	66	9	56	55	0	143	141	14	38	34	Hz	7,Kz	11
Hz	3,Kz	7	9	155	151	13	36	28	13	29	26	10	39	38	1	116	122	15	45	41	0	39	35
0	165	168	10	173	177	Hz	4,Kz	8	14	61	63	11	48	49	2	69	72	16	35	34	6	32	34
1	241	239	11	160	162	1	47	49	15	81	80	14	74	68	3	105	108	17	33	29	Hz	8,Kz	0
2	112	116	12	212	216	2	93	90	16	29	24	Hz	5,Kz	10	4	59	62	Hz	7,Kz	2	1	22	24
3	152	151	13	92	93	3	47	45	Hz	5,Kz	3	0	27	24	5	66	70	0	51	49	2	40	40
4	58	64	14	82	83	4	67	67	0	86	85	1	61	56	6	75	78	1	93	91	3	81	82
5	22	22	16	88	90	5	37	34	1	72	69	2	42	45	7	104	102	2	55	50	4	77	73
6	135	142	17	37	34	6	85	84	2	57	54	4	83	82	10	67	71	3	30	27	5	239	246
7	49	47	Hz	4,Kz	2	8	69	67	3	154	150	5	58	54	12	48	45	4	68	74	7	57	63
8	133	135	0	60	61	9	39	40	4	70	67	6	45	45	14	48	45	5	147	151	8	79	82
9	65	69	1	108	109	10	42	46	5	77	79	7	34	32	15	40	30	6	33	33	9	60	57
10	114	120	2	198	202	11	32	27	6	100	101	8	37	45	Hz	6,Kz	6	7	172	175	13	60	53
11	60	55	3	300	293	12	31	31	7	95	92	9	48	52	0	46	45	8	74	71	15	113	106
12	30	31	4	142	141	Hz	4,Kz	9	8	59	61	10	27	21	1	90	94	9	52	56	16	37	33
13	40	38	5	139	134	0	93	88	9	165	167	12	28	28	2	87	82	10	59	59	Hz	8,Kz	1
Hz	3,Kz	8	6	190	189	1	141	142	10	93	96	Hz	5,Kz	11	3	105	110	11	33	39	0	63	62
0	48	50	7	162	158	2	74	75	11	34	42	0	52	48	4	154	153	12	30	32	1	58	60
1	185	185	8	111	114	3	94	94	12	76	75	2	46	46	5	33	26	13	70	71	2	45	43
3	48	51	9	130	133	4	130	132	15	54	58	5	48	45	6	40	46	14	50	44	3	150	153
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6	128	128	12	79	78	7	81	80	0	24	15	Hz	5,Kz	12	10	53	53	0	82	80	6	48	53
7	61	61	13	68	73	9	26	28	1	41	44	0	36	42	11	31	31	1	140	144	7	23	28
8	95	97	15	103	103	10	48	44	2	154	156	2	64	62	12	67	72	2	102	107	9	56	57
9	72	74	16	60	53	11	62	59	3	50	52	3	28	37	15	56	56	3	72	72	11	50	50
11	42	47	19	46	48	13	60	59	4	50	52	4	49	49	16	59	48	4	94	95	13	67	65
12	86	86	Hz	4,Kz	3	15	36	34	5	147	149	5	28	31	Hz	6,Kz	7	5	79	81	14	46	42
13	42	43	0	19	16	16	45	33	6	32	35	Hz	5,Kz	13	0	40	44	6	154	153	Hz	8,Kz	2
16	41	36	1	23	22	17	39	34	7	23	22	1	57	50	1	147	143	7	159	161	0	95	98
19	46	39	2	209	205	18	53	44	8	109	113	3	29	32	2	60	60	8	51	58	2	54	54
Hz	3,Kz	9	3	381	368	Hz	4,Kz	10	9	98	102	5	30	20	3	187	186	9	31	27	3	86	84
1	95	90	4	145	140	0	83	79	10	34	38	Hz	6,Kz	0	4	125	130	10	54	53	4	156	159
2	139	139	5	330	329	1	54	56	11	66	68	0	314	311	6	64	63	11	76	74	5	196	203
3	98	98	6	108	109	2	82	84	12	50	49	2	55	58	7	76	79	13	52	51	6	61	69
4	47	48	7	97	92	3	115	111	13	32	37	3	73	75	8	51	58	14	25	34	7	72	77
6	109	108	8	121	118	4	69	67	14	24	28	4	36	35	9	50	50	15	48	43	8	45	41
7	104	98	9	75	77	5	43	47	15	36	37	5	56	53	10	50	54	Hz	7,Kz	4	10	42	41
9	32	40	10	84	85	6	41	45	Hz	5,Kz	5	6	26	27	11	31	30	0	244	243	15	39	40
10	32	29	12	137	134	7	70	64	0	166	167	7	63	64	15	67	58	1	98	101	16	46	41
11	53	42	13	122	123	9	55	53	1	21	13	8	28	35	Hz	6,Kz	8	2	155	153	Hz	8,Kz	3
15	40	39	14	42	38	14	46	48	2	119	119	9	98	97	1	97	96	3	121	122	0	151	152
Hz	3,Kz	10	15	141	142	Hz	4,Kz	11	3	58	51	10	56	55	2	51	49	4	138	142	1	63	59
0	36	40	16	24	22	0	30	25	4	45	47	11	38	48	3	111	107	5	178	176	5	34	29
1	153	157	17	35	34	1	114	113	6	106	112	12	82	82	4	34	29	6	107	108	7	35	35
2	99	100	Hz	4,Kz	4	3	59	60	7	29	32	13	125	126	5	53	62	7	132	133	8	47	55
3	101	106	0	164	160	4	64	61	8	130	129	17	41	41	6	74	78	8	52	55	9	38	35
4	49	47	1	141	138	6	54	50	9	25	27	Hz	6,Kz	1	7	60	63	9	28	16	10	27	16
5	76	74	2	289	286	7	34	45	10	26	30	0	264	270	10	53	40	10	24	33	11	24	22
6	25	20	3	42	39	9	50	47	11	49	47	1	158	158	11	45	39	11	51	56	12	42	43
7	78	73	4	178	176	11	38	34	12	38	46	2	117	118	12	42	38	12	28	26	13	27	23
8	48	50	5	209	200	Hz	4,Kz	12	13	40	41	4	178	178	13	53	52	14	47	50	Hz	8,Kz	4
10	43	40	6	88	92	1	95	95	Hz	5,Kz	6	5	77	80	14	59	51	16	37	35	0	135	135
11	69	69	7	238	235	3	37	27	0	76	77	6	68	70	Hz	6,Kz	9	17	40	28	1	55	56
13	67	62	8	112	117	8	60	47	1	154	152	7	170	177	0	33	30	Hz	7,Kz	5	2	89	91
Hz	3,Kz	11	9	98	101	9	34	38	2	174	177	8	50	53	1	61	61	0	309	314	3	55	55
1	52	58	10	79	79	Hz	4,Kz	13	3	145	150	9	222	222	2	55	49	1	134	134	4	91	93
2	59	57	11	130	128	1	51	44	4	23	31	10	110	109	3	93	96	2	82	86	5	40	33
6	27	27	12	52	54	3	48	53	5	81	83	11	80	81	4	79	83	3	83	82	6	49	59
7	54	52	13	76	82	4	53	45	6	90	91	12	48	50	5	81	77	4	70	66	7	77	80
11	72	64	14	57	58	5	48	43	7	56	53	13	68	64	7	25	26	5	45	48	8	36	40
12	37	38	15	30	44	Hz	5,Kz	0	8	48	53	14	44	45	Hz	6,Kz	10	6	103	107	10	38	36
Hz	3,Kz	12	16	44	42	1	71	68	9	39	40	Hz	6,Kz	2	0	46	45	8	67	71	11	30	32
0	28	29	17	47	46	2	370	369	10	87	87	0	251	249	2	35	39	10	29	35	14	32	27
1	56	52	19	38	33	3	40	38	11	47	48	1	108	109	3	24	23	11	31	34	Hz	8,Kz	5
2	57	53	Hz	4,Kz	5	4	137	135	13	48	41	2	171	171	5	41	37	12	39	39	0	115	120
6	45	53	0	21	19	5	118	122	17	44	35	3	49	51	6	46	46	13	32	37	1	37	31
9	30	33	1	92	89	6	55	53	18	34	26	4	102	101	8	63	59	Hz	7,Kz	6	2	37	37
Hz	3,Kz	13	2	219	211	7	119	120	Hz	5,Kz	7	5	82	79	11	43	35	0	215	218	3	101	98
0	50	48	3	112	103	8	213	216	0	30	38	6	73	78	12	46	39	1	185	185	4	70	68
4	60	55	4	45	45	10	392	399	1	87	90	7	105	111	Hz	6,Kz	11	2	68	68	5	80	79
8	53	50	5	140	140	11	199	202	2	99	98	8	86	84	0	50	53	3	63	64	6	56	53
Hz	3,Kz	14	6	86	85	12	144	150	3	92	96	9	136	135	1	49	39	4	102	105	7	44	42
0	41	43	7	101	104	14	113	111	4	117	117	10	82	88	4	56	53	5	27	24	10	65	66
1	40	36	8	135	136	16	81	77	5	54	50	11	37	37	6	66	62	7	59	62	13	34	32
2	52	54	9	106	110	17	30	37	6	174	175	12	29	34	7	32	38	12	31	30	14	57	52
5	44	36	11	161	163	19	38	32	7	89	97	13	35	29	8	52	52	14	68	65	Hz	8,Kz	6
Hz	3,Kz	15	12	57	56	Hz	5,Kz	1	8	57	60	14	69	69	10	30	22	Hz	7,Kz	7	0	85	88
5	44	41	13	64	62	0	31	25	10	55	57	18	64	52	Hz	6,Kz	12	0	93	95	2	134	132
Hz	4,Kz	0	14	25	21	1	123	119	11	29	34	Hz	6,Kz	3	2	46	35	1	107	103	3	81	79
0	152	151	15	39	43	2	308	303	12	47	50	0	163	166	7	42	31	2	45	42	4	88	88
1	44	43	16	33	38	4	40	37	14	45	48	1	181	184	Hz	7,Kz	0	3	73	73	8	52	58
2	427	425	Hz	4,Kz	6	5	90	91	16	47	40	2	135	133	1	143	147	4	62	58	10	42	42
3	327	335	1	104	105	6	194	193	Hz	5,Kz	8	3	91	94	3	141	141	5	65	62	11	40	30
4	233	227	2	147	144	7	79	78	1	41	42	4	75	73	4	26	32	6	47	46	Hz	8,Kz	7
5	106	104	3	162	158	8	241	249	2	56	55	5	74	70	6	27	37	7	39	30	0	46	44
6	178	172	4	104	107	10	291	301	3	149	151	6	92	98	8	81	80	8	59	60	1	104	101
7	31	35	5	60	63	11	72	76	4	241	245	7	228	235	9	99	102	11	50	48	2	36	38
9	24	16	6	110	111	12	58	59	5	38	41	8	119	116	10	37	37	12	60	49	4	60	57
10	117	128	7	60	61	13	26	27	6	77	78	9	84	83	11	46	53	Hz	7,Kz	8	12	37	27
11	62	63	9	93	94	14	86	84	7	70	67	10	53	59	13	25	28	1	55	60	Hz	8,Kz	8
12	46	52	11	45	48	15	45	47	8	59	63	11	67	68	15	46	42	2	28	26	1	59	54
13	98	98	12	24	23	16	48	49	9	30	33	13	52	55	16	38	34	3	35	37	2	56	56
14	30	36	13	57	57	18	53	52	10	69	72	16	42	41	Hz	7,Kz	1	4	35	36	9	39	37
15	62	56	14	38	39	Hz	5,Kz	2	11	60	61	Hz	6,Kz	4	0	142	144	8	39	36	11	68	57
16	28	33	Hz	4,Kz	7	0	220	213	12	64	68	0	45	42	1	70	57	Hz	7,Kz	9	Hz	8,Kz	9
17	36	39	0	62	68	1	105	106	15	53	48	1	109	114	2	115	116	0	38	37	1	34	32
21	52	54	1	95	94	2	188	187	16	75	66	2	24	25	4	49	51	2	59	56	3	42	47
Hz	4,Kz	1	2	51	52	3	98	98	Hz	5,Kz	9	3	87	93	5	79	77	4	37	44	7	45	39
0	55	56	4	50	52	4	112	115	0	39	43	5	181	185	6	60	59	6	71	73	8	39	32

Table 1. Continued.

9	55	49	7	63	65	6	27	24	H=	9,K=	6	5	31	31	1	62	56	4	50	46	1	53	48
10	44	37	8	56	54	7	29	21	0	29	28	6	41	36	2	69	73	5	67	54	3	44	44
H=	8,K=	10	9	45	44	8	61	70	1	96	94	8	49	45	3	44	45	6	36	46	4	43	40
6	45	38	11	33	35	H=	9,K=	4	2	58	53	12	86	73	4	50	42	7	51	44	H=	11,K=	4
8	33	37	12	64	60	0	47	43	3	52	59	H=	10,K=	1	6	68	67	H=	10,K=	7	0	41	29
H=	9,K=	0	14	39	32	1	52	50	4	59	58	0	70	68	H=	10,K=	4	4	72	71	1	53	51
1	25	31	H=	9,K=	2	2	54	53	H=	9,K=	7	1	58	56	0	52	47	6	58	44	3	49	47
2	46	45	0	78	79	3	134	134	0	44	34	2	47	42	1	94	92	H=	10,K=	8	4	31	32
3	36	39	1	55	54	4	72	72	1	76	74	4	43	40	2	44	39	0	61	51	H=	11,K=	5
4	67	70	2	50	46	5	27	12	2	40	45	5	53	56	4	39	41	4	36	39	5	43	36
5	31	26	3	72	74	6	54	54	4	57	48	7	59	59	5	51	41	H=	11,K=	0	H=	11,K=	6
6	117	116	4	57	62	8	60	58	6	53	50	8	46	45	6	36	31	1	51	60	3	36	32
7	30	23	5	106	107	9	28	36	9	46	36	10	59	49	H=	10,K=	5	10	98	87	H=	11,K=	7
8	50	46	6	44	42	10	30	28	10	35	25	H=	10,K=	2	0	55	52	H=	11,K=	1	2	35	33
9	94	89	8	64	64	H=	9,K=	5	H=	9,K=	8	0	146	140	1	50	48	1	38	36	H=	12,K=	0
10	38	31	9	54	57	0	80	76	3	37	31	1	46	43	2	48	42	2	40	44	4	33	31
13	64	61	12	32	30	1	72	71	6	35	29	2	104	104	3	38	38	4	34	22	6	43	32
H=	9,K=	1	13	49	47	2	75	71	H=	9,K=	9	3	61	59	5	55	47	7	37	39	H=	12,K=	2
1	99	102	H=	9,K=	3	3	65	62	4	42	33	4	45	48	H=	10,K=	6	8	75	72	1	53	46
2	83	80	0	81	74	4	43	43	H=	10,K=	0	8	58	60	0	42	30	H=	11,K=	2	2	35	30
3	39	34	2	92	90	5	50	49	0	93	97	12	80	70	1	41	39	10	59	51	5	43	43
4	107	106	3	91	93	8	42	39	2	58	61	H=	10,K=	3	2	31	34	H=	11,K=	3	H=	12,K=	3
5	108	109	4	96	94	10	36	25	4	45	40	0	99	96	3	51	45	0	41	43	4	28	30
6	39	37	5	102	104	12	38	35															

lected using the $2\theta-\theta$ autocollection program with variable scan rate and a cut-off for low intensities. The scan range was from 0.7° 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 no systematic variation. The 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 1911 independent reflections were recorded within the limit of 0.66 for sin θ/λ, 1687 having a net count larger than 2 σ_I.

The data were corrected for Lorentz and polarization effects but not for absorption or secondary extinction.

All calculations were performed on a CDC 6600 computer using the programs described in Ref. 7, except for the phase determination which was done with the program MULTAN, written by Main *et al.*[8] Atomic form factors were those of Hanson *et al.*[9] for O, N, and C and of Stewart *et al.*[10] for H.

CRYSTAL DATA

(6:*R*)-6-Dimethylamino-4,4-diphenyl-3-heptanone, (*l*-methadone), $C_{21}H_{27}NO$, orthorhombic.

$a=9.637$ (1) Å, $b=11.385$ (2) Å, $c=16.866$ (2) Å.

$V=1850.4$ Å^3, M = 309.20, $Z=4$.

Melting point: 79 – 80°C.

$D_{obs}=1.10$ gcm^{-3} (flotation), $D_{calc}=1.11$ gcm^{-3}.

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

STRUCTURE DETERMINATION

The structure was determined by direct methods. Preliminary scale and overall isotropic thermal vibration factor ($B=3.11$ Å^2) were derived by Wilson's statistical method and normalized structure factors were calculated. The phase determination was carried out by the program MULTAN, using the 344 highest E-values (≥ 1.25), and a total of 1400 relations of the $\sum_2$ formula.[11] The set of phases with the third highest figure of merit gave an E-map where 20 of the 23 non-hydrogen atoms could be located. Two successive Fourier refinement served to establish a trial structure of all the heavy atoms. Successive cycles of full matrix least-squares refinement, first with isotropic then with anisotropic thermal parameters gave an R-value of 0.09. Approximate positions of all the hydrogen atoms were calculated from stereochemical considerations. Giving these 27 atoms individual isotropic thermal parameters, the refinement converged at $R=0.038$ ($R_w=0.033$).

Inspection of the structure factor values of strong reflections, showed that nine probably were affected by secondary extinction. The differences $|F_o-F_c|$ for these reflections were less than 10 % of the F_c's, and the effect turned out to be negligible, both in the atomic parameters and the R-value.

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

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

The e.s.d.'s in bond lengths and angles were calculated to be 0.003 – 0.004 Å and 0.2 – 0.3°, respectively.

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}
C1	64536	2111	33978	1256	1105	468	138	−549	−173
	33	32	21	40	33	13	60	42	36
C2	51829	7272	30097	1146	796	311	175	−113	−72
	29	24	15	32	23	9	48	32	26
C3	45648	−558	23784	773	629	299	−37	52	93
	22	20	12	24	19	8	39	26	23
C4	35029	5093	17984	729	486	299	35	−8	−14
	22	17	12	23	16	8	36	25	20
C5	41499	15653	13408	969	540	370	8	−136	116
	25	21	15	28	18	10	41	29	24
C6	53441	12585	7896	1276	731	316	−406	165	19
	26	22	14	34	22	9	47	32	24
C7	56281	22630	2047	1725	1727	578	−475	177	917
	47	43	26	57	50	19	95	60	54
C8	74416	836	8109	1885	1352	1120	773	1338	−35
	54	43	39	63	45	31	91	80	65
C9	73801	18503	15567	1133	1796	662	−676	141	−104
	39	44	27	41	52	20	78	52	56
C10	29192	−3389	11696	811	529	288	−46	25	96
	21	17	12	24	18	8	34	26	19
C11	16452	−814	8204	908	693	357	205	−81	−87
	24	22	14	29	21	9	45	29	25
C12	11306	−7336	1975	991	961	393	7	−316	−86
	27	24	16	31	26	11	50	32	29
C13	18638	−16688	−964	1459	786	344	−132	−156	−222
	30	22	15	37	23	10	52	34	26
C14	31222	−19488	2402	1390	704	396	306	46	−155
	29	22	15	38	22	11	51	36	26
C15	36428	−12987	8629	938	752	358	282	−111	−44
	26	21	14	30	23	10	43	31	25
C16	23099	9151	23492	776	728	324	73	−88	−113
	22	20	13	24	20	9	39	26	22
C17	19429	20728	24685	1066	778	565	127	81	−293
	28	25	18	31	24	14	50	37	31
C18	8614	23676	29718	1179	1251	680	517	46	−799
	31	27	20	34	32	17	60	45	38
C19	1306	15263	33618	981	1869	504	284	118	−831
	27	36	18	34	42	13	69	36	42
C20	4854	3662	32588	1140	1653	452	−279	341	−81
	28	30	17	35	41	12	62	38	36
C21	15631	631	27544	1033	1038	416	42	232	−51
	25	24	15	29	24	10	53	33	30
O	47886	−10987	23922	1614	536	508	179	−594	125
	18	13	10	25	13	8	31	24	16
N	65606	8915	12503	1022	873	512	299	321	89
	21	18	13	25	19	10	41	30	23

Table 3. Fractional coordinates (10^3) and isotropic thermal parameters ($Å^2$) for hydrogen atoms.

Atom	x	y	z	B
H1C1	682	75	380	5.3
H2C1	717	2	301	7.0
H3C1	631	−56	363	6.9
H1C2	534	152	279	5.0
H2C2	445	83	339	4.7
H1C5	448	218	172	2.3
H2C5	338	194	102	3.5
HC6	511	56	48	3.9
H1C7	577	299	50	7.9
H2C7	480	233	−12	7.9
H3C7	652	210	−9	7.7
H1C8	681	−61	65	11.2
H2C8	821	−17	117	11.8
H3C8	785	45	33	10.1
H1C9	684	239	184	7.7
H2C9	791	225	110	8.8
H3C9	805	153	194	13.0
HC11	111	55	103	4.0
HC12	32	−52	−3	4.5
HC13	155	−213	−53	4.4
HC14	370	−259	2	4.6
HC15	450	−151	108	3.9
HC17	244	267	222	5.5
HC18	59	319	303	7.2
HC19	−61	171	375	5.7
HC20	3	−26	352	6.4
HC21	184	−74	268	4.1

DISCUSSION

Interatomic distances and bond angles are given in Tables 4 and 5, and shown in Fig. 1. The absolute configuration (6:*R*) of *l*-methadone has been chosen according to earlier reports.[5,12]

The analysis of the thermal parameters showed that the two aromatic rings could be regarded as rigid bodies, and the positional parameters of these atoms, including C4, were corrected for librational effects. The corrected bond lengths are also listed in Table 4.

The crystal structure as seen down the *b*-axis is illustrated in Fig. 2. There are no particularly short intermolecular distances in the structure.

The distance C1 – C2 (1.508 Å) is found to be shorter than normal, 1.537.[13] This is probably due to the thermal motion of the methyl carbon atom, also reported for dextropropoxyphene hydrochloride.[7]

The mean C – N bond length is 1.455 Å, in agreement with the mean value for amines (1.456 Å) reported by Falkenberg.[14]

The expected lengthening of C – C single bonds in a compound having a quaternary carbon atom is shown by the bond lengths 1.555 Å (C3 – C4), 1.559 Å (C4 – C5), 1.544 Å (C4 – C10), and 1.552 Å (C4 – C16). Owing to the four large groups attached to C4, there is considerable deviations from tetrahedral values in the bond angles involving this atom. Similar distortions are reported in *d*-methadone. HBr [5] and dextropropoxyphene.HCl.[6]

Each of the two phenyl rings A (C10,C15) and B (C16,C21) is found to be planar. C4 is coplanar with ring B, whereas it is 0.16 Å out of plane A. This latter deviation from planarity is probably caused by the strain around C4. The two planes form an angle of 80.6°. The dihedral angles C5 – C4 – C16 – C17 and C3 – C4 – C10 – C15 are as small as −4.9° and −29.8°, respectively, and

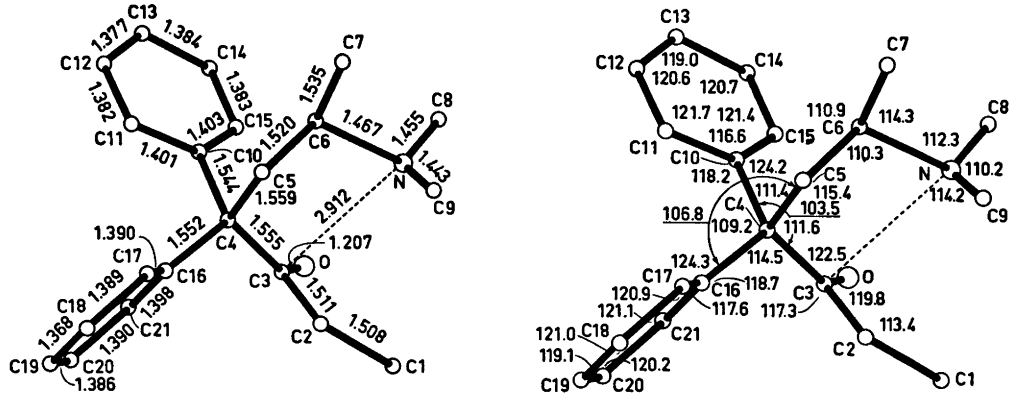

Fig. 1. (a) Bond lengths (Å). (b). Angles (°) in *l*-methadone.

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

Bond lengths		Corrected	Bond angles	
C1 – C2	1.508(4)		C1 – C2 – C3	113.3(.2)
C2 – C3	1.511(3)		C2 – C3 – C4	117.3(.2)
C3 – O	1.207(3)		O – C3 – C4	122.5(.2)
C3 – C4	1.555(3)		C3 – C4 – C5	111.6(.2)
C4 – C5	1.559(3)		C3 – C4 – C10	114.4(.2)
C4 – C10	1.541(3)	1.544	C3 – C4 – C16	103.6(.2)
C4 – C16	1.549(3)	1.552	C5 – C4 – C10	106.8(.2)
C5 – C6	1.520(3)		C5 – C4 – C16	111.3(.2)
C6 – C7	1.535(4)		C10 – C4 – C16	109.2(.2)
C6 – N	1.467(3)		C4 – C5 – C6	115.4(.2)
C8 – N	1.455(4)		C5 – C6 – C7	110.9(.3)
C9 – N	1.443(4)		C5 – C6 – N	110.3(.2)
C10 – C11	1.393(3)	1.401	C7 – C6 – N	114.2(.2)
C11 – C12	1.379(3)	1.382	C6 – N – C8	112.1(.3)
C12 – C13	1.371(3)	1.377	C6 – N – C9	114.3(.3)
C13 – C14	1.376(4)	1.384	C8 – N – C9	110.0(.3)
C14 – C15	1.379(3)	1.383	C4 – C10 – C11	118.7(.2)
C15 – C10	1.396(3)	1.403	C4 – C10 – C15	124.3(.2)
C16 – C17	1.379(3)	1.390	C10 – C11 – C12	121.7(.2)
C17 – C18	1.385(4)	1.389	C11 – C12 – C13	120.6(.3)
C18 – C19	1.359(4)	1.368	C12 – C13 – C14	119.0(.2)
C19 – C20	1.375(4)	1.386	C13 – C14 – C15	120.7(.3)
C20 – C21	1.386(4)	1.390	C14 – C15 – C10	121.4(.2)
C21 – C16	1.388(3)	1.398	C15 – C10 – C11	116.6(.2)
			C4 – C16 – C17	124.3(.2)
			C4 – C16 – C21	118.2(.2)
			C16 – C17 – C18	120.9(.3)
			C17 – C18 – C19	121.0(.3)
			C18 – C19 – C20	119.1(.2)
			C19 – C20 – C21	120.2(.3)
			C20 – C21 – C16	121.1(.3)
			C21 – C16 – C17	117.6(.2)
Intramolecular interaction			C2 – C3 – O	119.8(.2)
N···C3	2.912(3)			

Table 5. Bond lengths (Å) involving hydrogen atoms. Standard deviations are in the range 0.02 – 0.04 Å.

C1 – H1C1	0.98	C9 – H1C9	0.94
C1 – H2C1	0.97	C9 – H2C9	1.03
C1 – H3C1	0.97	C9 – H3C9	0.98
C2 – H1C2	0.99	C11 – HC11	0.95
C2 – H2C2	0.96	C12 – HC12	0.91
C5 – H1C5	0.99	C13 – HC13	0.95
C5 – H2C5	1.02	C14 – HC14	0.99
C6 – HC6	0.98	C15 – HC15	0.94
C7 – H1C7	0.98	C17 – HC17	0.93
C7 – H2C7	0.97	C18 – HC18	0.98
C7 – H3C7	1.01	C19 – HC19	0.99
C8 – H1C8	1.04	C20 – HC20	0.95
C8 – H2C8	1.01	C21 – HC21	0.96
C8 – H3C8	0.99		

the opening of the trigonal angles O – C3 – C4 (122.5°), C4 – C10 – C15 (124.3°), and C4 – C16 – C17 (124.3°) decreases the repulsions between C5 and C17, and between O and C15, respectively.

An interesting short intramolecular distance is that between N and C3 which are separated by 2.912 Å, approximately 0.1 Å shorter than the sum of the van der Waals radii. This close proximity of N and C_{co} may be explained by an interaction between the lone pair of the nitrogen atom and the electropositive carbonyl carbon atom, as discussed in the introduction (I). The carbonyl carbon atom is elevated 0.06

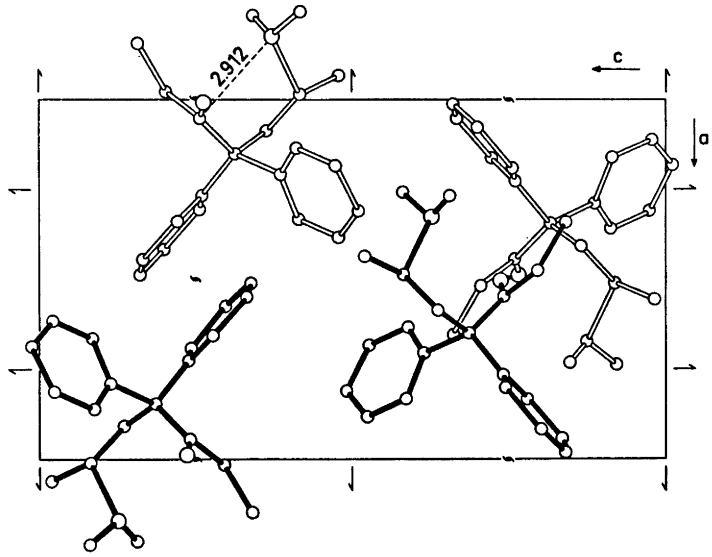

Fig. 2. The crystal structure of *l*-methadone as seen down the *b*-axis.

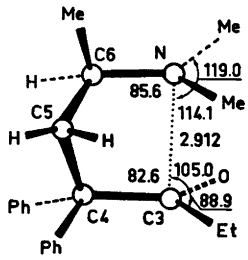

Fig. 3. Schematic drawing of the conformation of *l*-methadone.

Å out of the plane through the atoms to which it is bonded (towards the nitrogen atom.) The conformation of *l*-methadone, as seen perpendicular to a plane through C3,C4,C6 is shown in Fig. 3.

The conformation of methadone [1,2,4] proposed as necessary for analgesic activity is thus confirmed by this X-ray analysis. In the present structure the dimethylamine group is *gauche* relative to C4, the dihedral angle C4 – C5 – C6 – N being – 68.5°. It may be of great interest to see if other synthetic analgetics related to methadone are preferring a similar conformation in the solid state.

Note. The author has been made aware of the structure determination of the same compound carried out by H. B. Bürgi, E. Shefter and J. D. Dunitz, to be published in *Nature*. (The First European Crystallographic Meeting, Bordeaux, August 1973).

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