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The Crystal Structures of Derivatives of Tetrodotoxin. II. Diacetylanhydrotetrodotoxin Hydroiodide

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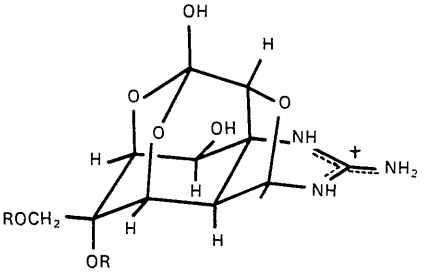
The structure of diacetylanhydrotetrodotoxin, one of the minimum changed derivatives of the toxic substance tetrodotoxin, was determined by X-ray analysis of the hydroiodide. The crystals are monoclinic with four molecules in a unit cell of dimensions $a=19{\cdot}34$, $b=14{\cdot}63$, $c=7{\cdot}18$ Å, $\beta=97{\cdot}4°$, with space group $P2_1$. There are two independent molecules in an asymmetric unit. The positions of iodine atoms were determined by three-dimensional Patterson methods. After several cycles of three-dimensional Fourier refinement, it was found that the two independent molecules have essentially the same structure,



($R=CH_3CO$), which involves an adamantane-like cage. Atomic coordinates and individual isotropic temperature factors (anisotropic for the iodine) were refined by the block-diagonal matrix least-squares method. The final R value decreased to 0·157. Intra- and intermolecular bond lengths are within the range of normal values.

Introduction

In a preliminary paper, Tsuda, Tamura, Tachikawa, Sakai, Amakasu, Kawamura & Ikuma (1963) proposed a lactam form (II) for the structure of tetrodotoxin. This was inferred from chemical considerations, taking account of an X-ray determination of the structure of tetrodonic acid hydrobromide (I) described in part I. Goto, Kishi, Takahashi & Hirata (1963) proposed independently the same structure for it on the basis of an X-ray analysis of bromoanhydrotetrodoic lactone hydrobromide (III) (Tomiie, Furusaki, Kasami, Yasuoka, Miyake, Haisa & Nitta, 1963). Further studies were required, however, since several other possible structures were not excluded definitely.

Diacetylanhydrotetrodotoxin (hereafter DAT) was prepared by alcoholysis of peracetyltetrodotoxin, and its hydroiodide (hereafter DATI) was obtained by careful control of the acidity of the mother liquor. Tetrodotoxin can be recovered from DAT or DATI by treating its alcoholic solution with a drop of aqueous hydrochloric acid (5%), but so far not from tetrodonic acid. This fact suggests that the chemical relationship between tetrodotoxin and DAT (DATI) may be very close.

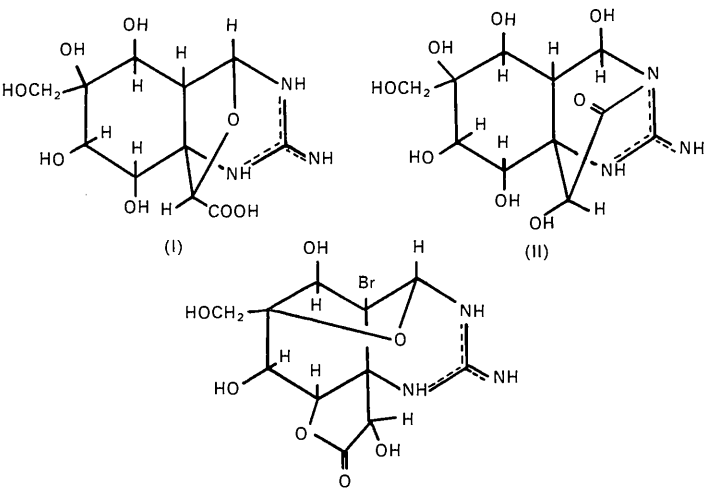
The present paper describes an X-ray determination of diacetylanhydrotetrodotoxin hydroiodide. On the basis of the structure of this compound, the structure of tetrodotoxin was established by some accompanying chemical work. The final chemical report has already been published by Tsuda, Ikuma, Kawamura, Tachikawa, Sakai, Tamura & Amakasu (1964). Meanwhile, the same structure has been presented independently by Goto, Kishi, Takahashi & Hirata (1964).

Experimental

Crystals of DATI, in the form of colourless plates, were grown by adding ether to a methanol solution containing hydroiodic acid. The unit-cell dimensions of the monoclinic crystals are:

$$a=19{\cdot}34,\ b=14{\cdot}63,\ c=7{\cdot}18\ \text{Å},\ \beta=97{\cdot}4°\ .$$

The space group was uniquely determined to be $P2_1$ from the systematic absences of $0k0$ with odd k and the fact that this compound is a naturally occurring



(I) (II) (III)

product with asymmetric carbon atoms. The density measured by the flotation method in a mixture of carbon tetrachloride and tetrabromoethane was found to be 1·69 g.cm^{-3}. From the unit-cell dimensions and the density, the molecular weight was calculated to be 1026, assuming that the number of the molecules in the unit cell is two. In a later stage of the analysis, however, it was found that there are four molecules in the unit cell, that is, two crystallographically independent molecules in an asymmetric unit. The molecular weight was therefore taken to be 513.

Equi-inclination Weissenberg photographs were taken for the zero to 12th layers about the *b* axis with Cu $K\alpha$ radiation. To obtain scaling factors among various *k* layers, the photographs around the *c* axis were taken by the same method.

Intensities were measured by visual comparison with a standard intensity scale. Strong and weak reflexions were correlated by the multiple-film technique. The maximum value of sin θ observed was 0·985, and the intensity data for 3004 reflexions were collected out of 4003 accessible *hkl*'s.

The sizes of crystals used were less than 0·1 × 0·5 × 0·8 mm. The crystals gradually became yellow and then brown, and the intensities of reflexions in higher angles decreased slightly on exposure to X-rays for some 300 hours. Three crystals were used to collect the complete set of intensity data. Corrections for Lorentz and polarization factors were made in the usual way but those for absorption were neglected. Wilson's method gave an overall temperature factor of $B=1{\cdot}8$ Å^2. This unexpectedly low value of the temperature factor might be due to the effect of absorption.

Structure determination

Four remarkable peaks were found in the three-dimensional Patterson function. These were thought to correspond to the interatomic vectors due to two iodine atoms in the asymmetric unit. The *y* coordinate of one of the iodine atoms could be put arbitrarily equal to zero. The two heavy atoms in the asymmetric unit eliminated the phase ambiguity inherent in space group $P2_1$ (Fridrichsons, Mathieson & Sutor, 1963).

The first three-dimensional Fourier synthesis, shown in Fig. 1, was calculated with the phases based on two iodine atoms. The number of peaks in this electron distribution map was much larger than that expected from the tentative chemical formula. Some of them should be ghost peaks due to the large scattering factor of the iodine atom. The clues for selecting peaks were the peak heights and their characteristic arrangement with reasonable interatomic distances. Examples of the latter are shown by connecting peaks in Fig. 2. Some thirty-six atoms were introduced into the structure factor calculation. In the second electron density distribution map, shown in Fig. 2, it was possible to connect many peaks reasonably at plausible bond distances. The structure factor calculation was made with fifty-three light atoms. The arrangement of significant peaks in the resulting Fourier map strongly suggested that there were two independent molecules in an asymmetric unit, although the detailed structures of the individual molecules were still ambiguous at this stage.

The (F_o-F_c) synthesis was computed in the next cycle of refinement with the phases calculated from fifty-eight light atoms. Some of the atoms included in the earlier stage had to be excluded later. In the structure factor calculation so far, all light atoms were treated as nitrogen, with the isotropic overall temperature factor, $B=1{\cdot}8$ Å^2. At this stage, two systems of joined six-membered rings were recognized in one molecule in the asymmetric unit. It was very difficult to explain this grouping of peaks by the hypothetical lactam form (II). After several different trial models of the skeleton had been examined, it was concluded that the orthoester model could fit the constellation of peaks in the Fourier map. Such a constellation of peaks was also found in another molecule in the asymmetric unit, and this result strongly supported the reliability

of the analysis. Other functional groups were connected to the skeleton. Thus the two molecules so built up have essentially the same structure, as shown by formula (IV).

Besides these two molecules and two iodines, a significant peak O(78) supposed to be crystallization water was observed. The measurement of magnetic resonance spectra indicated that there should be one methyl alcohol or methoxyl group per two DAT molecules. In order to find out the position of this methyl group, the $(F_o - F_c)$ synthesis was claculated, where F_c included two DAT molecules, two iodine atoms and O(78). The resulting map showed the peaks which might be bonded with O(21), O(71) and O(78) at reasonable distances. However, if the peak near O(21) is assumed to be the carbon atom, it results in unreasonably close approaches to the atoms in the neighbouring acetyl groups at distances of 2·0, 2·1 and 2·3 Å. If the carbon is assumed to attach to O(71), there results also an unreasonable contact with the iodine atom at a distance of 2·7 Å. Because of the absence of abnormal intermolecular contacts, the carbon atom was decided as bonding with O(78), forming crystallization methyl alcohol.

Some systematic disagreement between the observed and calculated structure factors was observed for the reflexions at low angles. This might have occurred from neglecting the correction for absorption. Plots of F_c/F_o for hkl with fixed k and l against $(\sin\theta/\lambda)^2$, an example of which is shown in Fig. 4, indicated a large anisotropy of the absorption effect. For convenience, we corrected the observed structure factors for this anisotropic effect by the use of the experimental curves of the type shown in Fig. 4.

Atomic coordinates and temperature factors were refined by the block-diagonal matrix least-squares method. The temperature factors were taken as isotropic for the light atoms and as anisotropic for iodine. In the first two cycles, about 1000 reflexions for $\sin\theta$

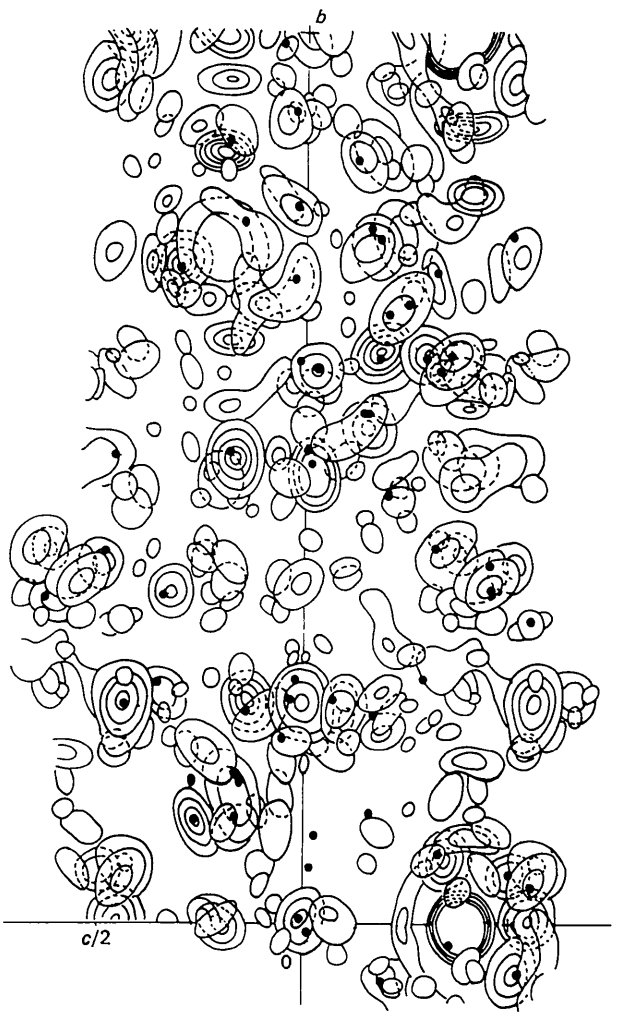


Fig. 1. The composite Fourier map projected along the a axis. Phases are based on two iodine atoms. Contour interval is arbitrary. Black circlets indicate the final atomic positions of two molecules in the asymmetric unit.

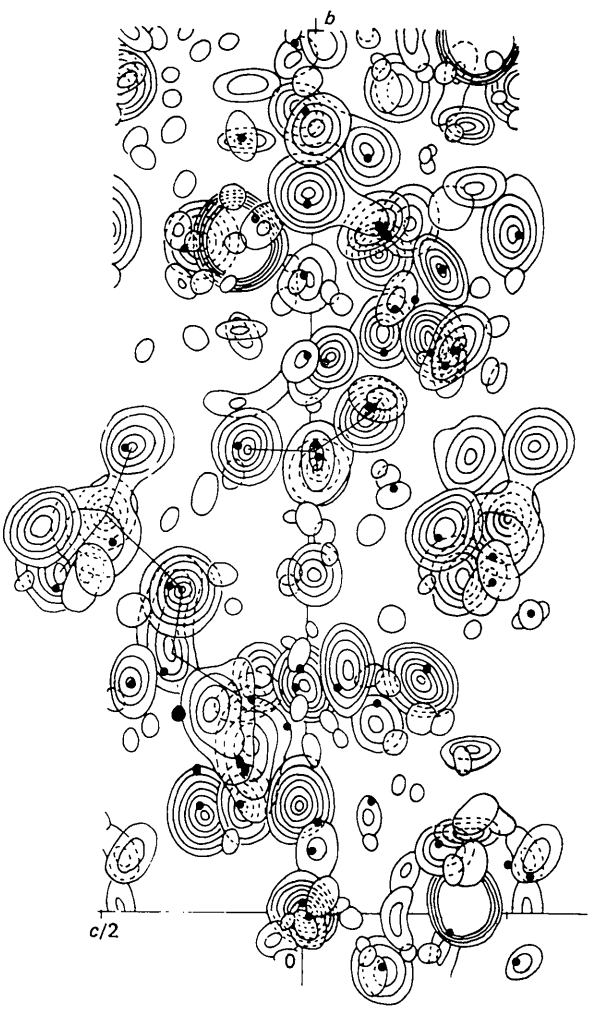


Fig. 2. The composite Fourier map projected along the a axis. Phases are based on two iodine and thirty-six light atoms. Contour interval is arbitrary. Black circlets indicate the final atomic positions of two molecules.

ranging between 0·22 and 0·42 were included. Three more cycles of refinement were made, using all the reflexions. The final R value dropped to 0·157. The final atomic coordinates and temperature factors for each atom are given in Table 1, and the observed and

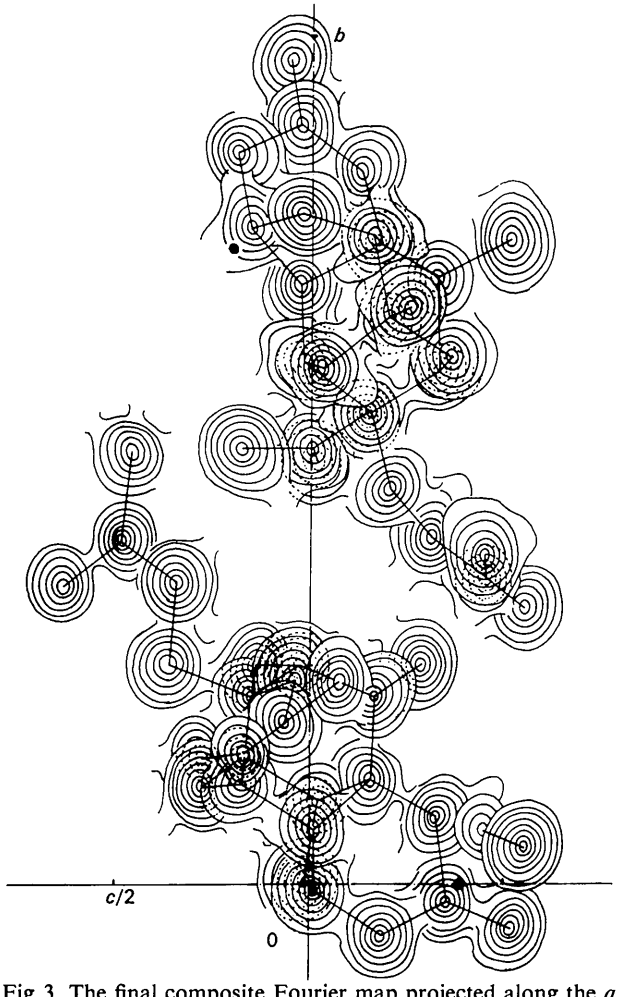


Fig. 3. The final composite Fourier map projected along the a axis, contours being drawn at intervals of 1 e.Å^{-3}. Contours for the iodine atoms are omitted and their positions are shown with black circles.

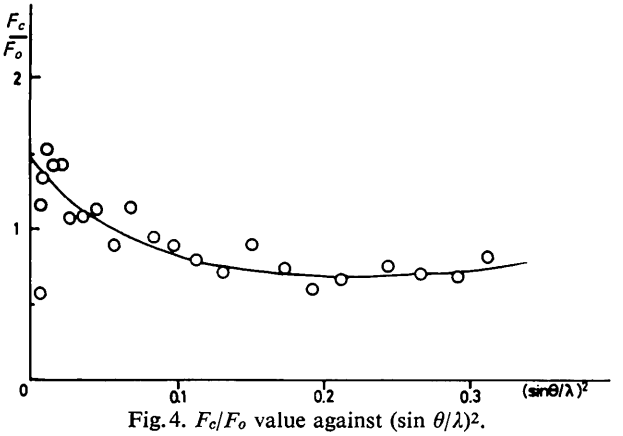


Fig. 4. F_c/F_o value against $(\sin\theta/\lambda)^2$.

Table 1. *The final atomic coordinates and temperature factors* (Å^2)

For the iodine atoms, anisotropic temperature factors in the form of exp $\{-(h^2B_{11}+k^2B_{22}+l^2B_{33}+hkB_{12}+klB_{23}+lhB_{31})\}$ were applied.

Atom	x/a	y/b	z/c	B
N(1)	0·355	0·151	−0·122	1·2
C(2)	0·362	0·107	0·033	0·7
N(3)	0·406	0·137	0·182	2·0
C(4)	0·445	0·221	0·155	1·4
C(5)	0·418	0·376	0·013	2·5
C(6)	0·377	0·437	−0·157	0·7
C(7)	0·381	0·375	−0·329	1·5
C(8)	0·346	0·280	−0·327	1·5
C(9)	0·387	0·235	−0·156	1·3
C(10)	0·392	0·284	0·029	0·9
N(11)	0·332	0·025	0·056	2·8
O(12)	0·492	0·378	−0·033	1·5
O(13)	0·304	0·436	−0·141	1·9
C(14)	0·413	0·524	−0·182	3·1
O(15)	0·364	0·585	−0·311	2·7
O(16)	0·454	0·365	−0·354	1·9
O(17)	0·346	0·224	−0·493	1·6
O(18)	0·493	0·203	0·024	1·7
C(19)	0·465	0·231	−0·160	1·6
C(20)	0·495	0·319	−0·204	1·2
O(21)	0·561	0·313	−0·237	3·4
C(22)	0·287	0·491	0·006	2·6
O(23)	0·321	0·495	0·165	3·0
C(24)	0·203	0·501	−0·020	3·2
C(25)	0·395	0·621	−0·445	1·6
C(26)	0·343	0·674	−0·559	2·9
O(27)	0·457	0·609	−0·464	3·5
N(51)	0·013	0·931	−0·329	0·5
C(52)	0·026	1·015	−0·355	1·7
N(53)	0·051	1·069	−0·198	0·9
C(54)	0·055	1·020	−0·005	1·0
C(55)	0·114	0·883	0·158	0·0
C(56)	0·128	0·776	0·146	0·7
C(57)	0·061	0·736	0·025	1·0
C(58)	0·042	0·775	−0·168	0·0
C(59)	0·029	0·887	−0·152	0·0
C(60)	0·090	0·932	−0·028	0·7
N(61)	0·011	1·055	−0·523	1·8
O(62)	0·052	0·887	0·264	0·7
O(63)	0·180	0·761	0·016	2·1
C(64)	0·146	0·736	0·338	3·0
O(65)	0·157	0·642	0·329	1·0
O(66)	0·001	0·756	0·134	0·9
O(67)	−0·013	0·736	−0·274	1·1
O(68)	−0·014	0·998	0·026	0·4
C(69)	−0·026	0·906	−0·019	0·8
C(70)	−0·009	0·852	0·175	2·0
O(71)	−0·057	0·860	0·295	1·2
C(72)	0·241	0·804	0·058	2·2
O(73)	0·267	0·858	0·166	3·8
C(74)	0·287	0·761	−0·086	2·6
C(75)	0·162	0·598	0·483	0·7
C(76)	0·165	0·497	0·462	2·5
O(77)	0·162	0·644	0·634	2·0
O(78)	0·390	0·961	−0·553	3·2
C(79)	0·433	0·949	−0·376	3·5
I(81)	0·2253	0·0000	−0·3941	*
I(82)	0·1902	0·2433	0·1903	†

	B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{31} (×10^5)
* I(81)	121	123	543	−50	−306	51
† I(82)	94	116	1195	97	296	13

Table 2. *Observed and calculated structure factors* ($\times 10$)

h	Fo	Fc
0 8		
1	123	150
2	112	106
3	117	103
4	0	5
5	0	50
6	114	41
7	96	11
8	0	11
9	82	121
0 7		
1	430	344
2	0	47
3	433	459
4	370	308
5	0	24
6	210	237
7	0	39
8	157	239
9	116	126
10	102	65
11	0	76
12	0	3
13	57	91
0 6		
1	124	68
2	245	281
3	0	72
4	173	149
5	247	269
6	200	240
7	0	26
8	167	174
9	0	22
10	255	328
11	167	168
12	212	196
13	215	202
14	178	87
15	293	275
0 5		
1	131	50
2	185	147
3	511	541
4	261	221
5	275	298
6	346	316
7	321	379
8	217	211
9	99	81
10	187	192
11	131	134
12	96	36
13	111	59
14	165	180
15	79	95
16	85	87
0 4		
1	252	199
2	508	519
3	142	87
4	307	289
5	363	386
6	238	214
7	254	281
8	201	134
9	540	630
10	232	193
11	321	278
12	466	555
13	204	172
14	329	284
15	0	20
16	307	268
17	278	207
18	0	0
19	166	86
0 3		
1	460	541
2	300	326
3	308	259
4	281	238
5	179	191
6	145	58
7	0	55
8	102	32
9	0	38
10	0	36
11	192	131
12	0	36
13	216	199
14	361	412
15	155	127
16	277	291
17	121	69
18	257	251
19	123	144
20	181	154
21	192	235
0 2		
1	953	1046
2	358	246
3	557	512
4	653	678
5	447	453
6	415	430
7	118	87
8	577	796
9	232	242
10	268	292
11	234	231
12	171	135
13	272	312
14	127	113
15	149	77
16	201	228
17	105	40
18	99	29
19	117	135
20	0	2
21	82	12
22	0	70
23	96	118
0 1		
1	85	32
2	123	137
3	367	354
4	463	492
5	107	130
6	326	408
7	215	215
8	365	369
9	137	82
10	580	630
11	255	219
12	374	391
13	538	594
14	271	270
15	410	478
16	178	144
17	333	343
18	239	278
19	199	130
20	250	261
21	0	0
22	190	148
23	170	156
24	111	166
0 0		
2	158	5
3	147	25
4	395	409
5	944	1206
6	553	553
7	411	393
8	184	123
9	159	80
10	190	173
11	0	20
12	147	79
13	0	7
14	97	51
15	88	32
16	177	85
17	148	170
18	141	175
19	181	190
20	93	18
21	125	104
22	128	171
23	79	66
24	133	214
0 -1		
0	461	436
1	150	150
2	743	850
3	173	65
4	380	324
5	634	736
6	134	24
7	330	345
8	113	31
9	657	889
10	244	169
11	252	217
12	460	465
13	279	283
14	443	540
15	209	138
16	464	556
17	265	258
18	232	207
19	226	230
20	124	8
21	221	194
22	124	150
23	0	60
24	80	108
0 -2		
0	169	30
1	686	563
2	337	177
3	281	287
4	542	590
5	127	64
6	271	308
7	195	103
8	174	155
9	62	79
10	204	249
11	129	143
12	171	192
13	133	166
14	167	141
15	230	214
16	255	314
17	0	13
18	332	365
19	163	135
20	216	175
21	282	296
22	0	14
23	240	273
24	110	42
0 -3		
0	150	118
1	397	395
2	109	43
3	381	372
4	578	587
5	495	505
6	437	437
7	186	220
8	469	546
9	146	132
10	465	489
11	397	463
12	144	135
13	362	430
14	137	116
15	345	367
16	207	204
17	130	69
18	0	98
19	0	0
20	103	50
21	0	21
22	0	45
23	120	143
0 -4		
0	265	168
1	172	154
2	374	306
3	163	99
4	148	40
5	172	112
6	169	131
7	257	214
8	309	204
9	187	87
10	282	328
11	147	78
12	294	301
13	334	360
14	182	191
15	333	340
16	0	21
17	336	300
18	208	191
19	178	117
20	265	270
21	0	53
22	233	198
23	111	128
0 -5		
0	547	631
1	233	182
2	534	527
3	372	335
4	424	414
5	482	502
6	0	90
7	295	294
8	154	142
9	301	282
10	300	341
11	157	183
12	162	159
13	134	71
14	145	147
15	0	6
16	142	26
17	0	31
18	0	45
19	0	87
20	126	71
21	95	86
22	124	183
0 -6		
0	382	395
1	139	61
2	129	59
3	149	109
4	150	151
5	151	132
6	304	339
7	301	281
8	0	8
9	331	378
10	252	198
11	248	287
12	243	240
13	177	168
14	321	376
15	174	99
16	216	216
17	194	154
18	180	94
19	279	245
20	123	16
21	72	73
0 -7		
0	172	90
1	378	427
2	281	296
3	197	140
4	276	320
5	0	41
6	160	104
7	0	7
8	0	56
9	127	130
10	122	116
11	115	63
12	118	160
13	81	27
14	73	50
15	0	26
16	77	80
17	80	20
18	80	134
0 -8		
0	117	1
1	145	96
2	170	90
3	168	201
4	227	227
5	0	135
6	209	249
7	141	46
8	194	188
9	189	153
10	176	173
11	149	157
12	156	129
13	162	181
14	115	25
15	161	221
0 -9		
0	150	188
1	0	63
2	0	107
3	0	103
1 9		
1	0	172
2	0	112
1 8		
1	182	179
2	178	167
3	127	68
4	149	190
5	0	48
6	194	221
7	150	115
8	148	112
9	142	157
1 7		
1	171	92
2	188	156
3	127	82
4	141	112
5	250	259
6	156	130
7	210	236
8	140	136
9	193	216
10	173	124
11	176	144
12	169	145
13	131	144
1 6		
1	331	362
2	301	312
3	161	162
4	260	225
5	225	220
6	229	234
7	177	179
8	183	201
9	193	200
10	138	99
11	189	218
12	249	265
13	147	119
14	208	200
15	125	16
16	161	147
1 5		
1	351	365
2	325	306
3	153	115
4	365	355
5	278	285
6	280	285
7	285	308
8	282	315
9	166	147
10	136	138
11	226	232
12	235	236
13	214	211
14	204	167
15	104	54
16	169	168
17	207	225
18	94	58
1 4		
1	333	272
2	441	434
3	424	399
4	414	371
5	379	422
6	234	210
7	229	204
8	386	491
9	205	168
10	273	412
11	175	242
12	135	83
13	253	267
14	221	101
15	241	272
16	180	143
17	164	150
18	141	138
19	168	181
20	120	107
1 3		
1	488	507
2	368	302
3	295	240
4	456	447
5	190	167
6	489	520
7	346	340
8	218	215
9	364	379
10	227	231
11	271	251
12	226	233
13	178	145
14	194	129
15	217	206
16	190	169
17	248	261
18	119	138
19	160	168
20	137	158
21	115	97
22	88	213
1 2		
1	458	359
2	790	771
3	456	319
4	567	542
5	344	262
6	227	176
7	492	519
8	378	380
9	372	397
10	245	290
11	322	349
12	295	279
13	304	310
14	240	243
15	283	299
16	202	169
17	194	213
18	250	295
19	94	73
20	203	236
21	135	134
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7	231	220
8	225	212
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23	128	167
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23	279	235
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12	160	118
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22	123	129
23	45	183
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9	465	533
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21	170	179
22	125	134
23	134	123
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23	121	111
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Table 2 (*cont.*)

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22	109	101
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21	141	99
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8	276	253
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15	148	84
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13	128	73
14	152	161
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3	307	343
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13	157	107
14	323	265
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17	171	172
18	0	56
19	180	168
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22	152	221
23	102	150
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22	191	180
23	115	32
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21	187	229
22	128	83
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24	79	26
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4	320	287
5	145	90
6	274	264
7	155	151
8	278	323
9	187	234
10	127	98
11	181	190
12	94	81
13	181	176
14	168	177
15	99	54
16	245	244
17	177	117
18	324	377
19	234	203
20	229	215
21	231	211
22	0	56
23	303	263
4 −3		
0	215	191
1	339	328
2	358	299
3	744	698
4	487	493
5	439	372
6	688	680
7	237	180
8	565	590
9	244	255
10	337	358
11	366	434
12	144	131
13	287	303
14	133	100
15	277	265
16	194	189
17	137	100
18	121	107
19	112	112
20	90	81
21	73	45
22	99	117
23	67	66
4 −4		
0	228	232
1	115	67
2	121	11
3	149	146
4	143	115
5	177	173
6	183	177
7	191	163
8	199	235
9	92	85
10	199	221
11	222	217
12	233	276
13	248	312
14	72	67
15	267	308
16	130	56
17	315	292
18	264	193
19	242	172
20	287	250
21	84	80
22	278	262
4 −5		
0	564	552
1	207	178
2	449	469
3	367	350
4	226	212
5	453	481
6	136	69
7	562	540
8	227	254
9	78	128
10	0	108
11	141	160
12	271	320
13	0	117
14	0	14
15	0	6
16	0	13
17	0	31
18	0	62
19	0	13
20	92	80
21	94	128
4 −6		
0	145	68
1	144	55
2	224	170
3	143	93
4	237	186
5	266	211
6	0	65
7	256	221
8	178	147
9	355	356
10	331	255
11	176	173
12	208	167
13	188	138
14	334	341
15	0	35
16	318	247
17	168	127
18	310	166
19	287	193
20	0	30
4 −7		
0	143	75
1	257	284
2	223	214
3	279	239
4	230	198
5	158	122
6	255	234
7	161	123
8	155	141
9	123	104
10	116	37
11	107	84
12	97	108
13	86	93
14	93	110
15	83	84
16	66	57
17	62	44
4 −8		
0	0	52
1	189	162
2	160	50
3	209	178
4	242	219
5	0	112
6	238	247
7	0	70
8	277	308
9	155	81
10	126	134
11	191	211
12	154	89
13	252	250
14	0	40
4 −9		
0	0	160
5 8		
1	157	140
2	157	156
3	0	89
4	134	152
5	113	8
6	153	164
7	149	150
8	0	135
5 7		
1	148	112
2	223	262
3	144	143
4	201	214
5	191	248
6	153	45
7	146	192
8	0	69
9	154	176
10	169	172
11	173	167
12	0	57
5 6		
1	200	164
2	200	173
3	333	318
4	0	83
5	240	214
6	120	104
7	179	236
8	0	92
9	164	155
10	157	180
11	138	155
12	154	156
13	139	131
14	195	219
15	0	58
5 5		
1	366	309
2	324	258
3	329	231
4	178	191
5	320	246
6	326	282
7	238	199
8	147	153
9	182	164
10	210	254
11	0	60
12	196	218
13	0	24
14	135	122
15	161	152
16	155	126
17	130	145
5 4		
1	353	312
2	367	321
3	426	416
4	343	277
5	248	201
6	317	315
7	151	136
8	339	359
9	247	226
10	173	161
11	229	272
12	252	228
13	333	366
14	180	136
15	157	119
16	179	148
17	170	142
18	225	214
19	156	127
5 3		
1	452	574
2	425	332
3	220	170
4	321	295
5	335	290
6	349	357
7	273	243
8	293	268
9	292	343
10	174	180
11	259	277
12	221	210
13	165	149
14	181	169
15	269	249
16	194	187
17	230	242
18	195	203
19	152	163
20	165	179
21	0	55
5 2		
1	381	310
2	628	674
3	457	357
4	450	476
5	500	522
6	170	129
7	425	457
8	223	196
9	311	402
10	274	343
11	285	265
12	308	315
13	349	376
14	128	62
15	247	228
16	218	203
17	197	174
18	162	154
19	99	73
20	194	212
21	127	75
22	95	120
5 1		
1	430	417
2	360	345
3	387	334
4	260	108
5	438	442
6	257	238
7	447	481
8	315	332
9	238	188
10	157	175
11	419	455
12	360	333
13	367	362
14	289	282
15	155	118
16	311	334
17	160	152
18	225	229
19	203	230
20	0	17
21	160	167
22	163	141
23	120	154
5 0		
1	399	724
2	278	274
3	412	423
4	586	609
5	427	373
6	381	332
7	470	463
8	361	364
9	265	242
10	268	216
11	199	156
12	362	368
13	153	142
14	266	275
15	191	200
16	215	175
17	172	172
18	0	91
19	181	179
20	155	164
21	177	189
22	141	136
23	121	105
5 −1		
0	612	639
1	436	409
2	315	268
3	289	302
4	381	354
5	257	274
6	446	509
7	204	188
8	411	445
9	164	112
10	360	360
11	358	377
12	0	44
13	401	426
14	232	206
15	367	404
16	210	187
17	294	266
18	129	119
19	0	91
20	216	224
21	0	147
22	113	101
23	155	145
5 −2		
0	500	565
1	376	351
2	339	278
3	499	483
4	462	465
5	294	258
6	321	328
7	327	301
8	244	214
9	379	421
10	235	200
11	280	294
12	301	262
13	303	288
14	296	267
15	308	228
16	0	50
17	241	220
18	193	167
19	233	253
20	209	170
21	0	51
22	188	229
23	0	12
5 −3		
0	507	451
1	220	241
2	273	261
3	297	307
4	427	364
5	434	422
6	163	97
7	467	403
8	0	41
9	373	356
10	399	401
11	201	213
12	322	372
13	233	228
14	177	185
15	336	315
16	286	271
17	191	180
18	159	145
19	0	66
20	153	166
21	134	131
22	132	158
23	100	144
5 −4		
0	196	176
1	337	353
2	337	315
3	363	351
4	108	87
5	326	351
6	318	303
7	252	207
8	337	322
9	356	297
10	312	297
11	104	214
12	226	197
13	334	364
14	180	213
15	197	130
16	312	307
17	118	106
18	180	180
19	176	157
20	0	77
21	182	191
22	101	85
5 −5		
0	132	73
1	313	281
2	203	216
3	389	338
4	332	333
5	320	225
6	323	285
7	0	109
8	338	295
9	177	168
10	269	248
11	186	202
12	186	195
13	188	199
14	214	219
15	208	210
16	158	112
17	156	139
18	102	37
19	156	115
20	117	79
21	132	137
5 −6		
0	210	171
1	253	208
2	268	222
3	179	135
4	173	177
5	173	178
6	211	179
7	150	145
8	245	239
9	214	174
10	316	385
11	168	183
12	0	125
13	113	168
14	133	28
15	206	263
16	117	131
17	170	147
18	92	87
19	135	141
5 −7		
0	250	264
1	208	203
2	205	187
3	172	199
4	308	252
5	148	151
6	201	224
7	145	151
8	116	66
9	191	199
10	133	92
11	151	183
12	144	114
13	138	132
14	174	186
15	137	89
16	121	121
17	90	40
5 −8		
0	144	146
1	166	158
2	155	175
3	211	110
4	165	145
5	144	147
6	144	71
7	183	214
8	145	90
9	145	138
10	142	125
11	165	180
12	176	172
13	0	91
6 8		
1	0	158
2	0	108
3	0	220
4	0	31
5	326	260
6	0	95
7	0	181
6 7		
1	0	94
2	0	72
3	0	44
4	0	80
5	0	98
6	0	50
7	0	116
8	0	74
9	203	164
10	225	176
11	154	98
6 6		
1	402	283
2	395	300
3	0	62
4	346	315
5	282	172
6	278	234
7	282	271
8	0	99
9	0	185
10	0	55
11	197	152
12	0	66
13	0	70
14	0	62
15	104	56
6 5		
1	266	169
2	202	141
3	409	271
4	488	401
5	0	57
6	0	170
7	0	36
8	483	421
9	357	349
10	0	89
11	264	251
12	0	54
13	339	334
14	286	251
15	258	160
16	247	215
17	127	92
6 4		
1	589	420
2	174	123
3	617	445
4	355	223
5	202	164
6	162	135
7	281	212
8	287	163
9	0	70
10	195	162
11	0	91
12	166	163
13	0	128
14	0	92
15	237	181
16	182	166
17	253	196
18	177	164
6 3		
1	470	374
2	479	355
3	575	477
4	147	94
5	653	571
6	325	250
7	416	372
8	397	422
9	232	218
10	340	433
11	150	128
12	362	420
13	191	170
14	204	162
15	199	231
16	0	43
17	120	136
18	0	43
19	77	94
20	0	92
21	0	49
6 2		
1	313	223
2	244	199
3	213	131
4	171	63
5	170	137
6	269	176
7	237	142
8	196	121
9	256	216
10	217	200
11	226	186
12	353	358
13	0	15
14	405	372
15	0	99
16	313	247
17	343	373
18	0	49
19	267	263
20	0	34
21	273	301
6 1		
1	378	322
2	1080	863
3	124	96
4	757	668
5	221	225
6	547	552
7	387	467
8	145	122
9	380	311
10	0	68
11	305	277
12	291	235
13	221	154
14	0	78
15	0	102
16	0	78
17	0	86
18	119	95
19	126	92
20	0	43
21	87	109
22	0	54
6 0		
2	332	402
3	0	15
4	508	430
5	272	179
6	525	457
7	310	220
8	391	350
9	449	375
10	386	263
11	676	612
12	229	106
13	496	454
14	380	264
15	390	301
16	479	412
17	0	36
18	435	352
19	0	98
20	256	204
21	252	211
22	0	52
23	152	124
6 −1		
0	671	479
1	710	606
2	419	289
3	889	777
4	458	375
5	463	400
6	265	320
7	187	169
8	316	315
9	297	219
10	240	137
11	186	92
12	267	218
13	192	99
14	185	137
15	201	161
16	183	68
17	230	185
18	273	237
19	0	71
20	296	247
21	0	11
22	300	223
23	260	211
6 −2		
0	399	350
1	449	420
2	383	324
3	398	353
4	359	288
5	755	771
6	255	234
7	388	462
8	261	281
9	201	255
10	457	543
11	206	115
12	647	667
13	283	260
14	407	332
15	382	309
16	0	59
17	291	272
18	175	134
19	134	144
20	116	76
21	0	65
22	0	40
23	0	40
6 −3		
0	492	498
1	191	140
2	403	329
3	217	164
4	382	318
5	301	204
6	279	183
7	0	79
8	0	31
9	274	226
10	241	161
11	319	284
12	0	97
13	0	119
14	398	338
15	0	132
16	292	229
17	332	258
18	0	28
19	315	258
20	0	81
21	304	273
22	183	148
23	0	116
6 −4		
0	358	304
1	266	225
2	418	518
3	252	204
4	413	530
5	297	265
6	259	313
7	300	372
8	224	220
9	306	410
10	157	124
11	235	313
12	0	136
13	0	122
14	0	153
15	160	201
16	148	159
17	0	53
18	0	40
19	84	59
20	0	78
21	0	20
22	0	30
6 −5		
0	123	156
1	91	96
2	0	37
3	79	63
4	91	150
5	0	60
6	105	212
7	0	57
8	97	210
9	101	256
10	0	75
11	86	361
12	0	63
13	71	307
14	56	218
15	43	181
16	43	295
17	0	46
18	26	297
19	0	36
20	4	225
6 −6		
0	419	324
1	463	386
2	301	161
3	450	372
4	280	198
5	308	268
6	329	263
7	251	135
8	0	166
9	0	76
10	0	90
11	0	109
12	0	86
13	0	43
14	0	73
15	0	44
16	0	62
17	0	59
18	141	99
19	0	45
6 −7		
0	0	61
1	240	143
2	287	184
3	0	177
4	269	72
5	268	178
6	300	103
7	289	246
8	320	289
9	0	147
10	259	218
11	0	35
12	234	285
13	176	143
14	259	207
15	256	219
16	0	104
6 −8		
0	0	174
1	198	80
2	206	251
3	0	91
4	0	125
5	0	34
6	0	144
7	0	112
8	159	48
9	0	51
10	136	120
11	0	57
12	0	41
7 8		
1	195	156
2	210	263
3	0	83
4	0	159
5	0	98
7 7		
1	166	112
2	163	154
3	0	18
4	155	200
5	86	163
6	0	145
7	120	158
8	175	119
9	0	181
10	138	44
7 6		
1	293	296
2	0	128
3	317	289
4	180	103
5	214	212
6	206	187
7	0	110
8	173	172
9	172	161
10	157	101
11	170	173
12	141	97
13	136	117
7 5		
1	278	212
2	0	110
3	192	163
4	266	282
5	239	218
6	241	196
7	291	350
8	246	230
9	166	132
10	198	260
11	156	72
12	243	293
13	171	152
14	188	187
15	162	123
16	0	35
17	0	202
7 4		
1	198	208
2	246	194
3	268	283
4	164	147
5	234	258
6	278	250
7	208	178
8	246	301
9	174	133
11	0	67
12	0	153
13	180	236
14	146	136
15	179	222
16	160	203
17	137	112
18	0	72
7 3		
1	272	282
2	314	325
3	309	290
4	350	332
5	197	122
6	463	542
7	395	369
8	273	265
9	295	313
10	204	190
11	301	291
12	240	206
13	276	236
14	299	286
15	177	122
16	234	204
17	212	200
18	0	47
19	146	139
20	100	106
7 2		
1	295	221
2	434	395
3	157	100
4	465	469
5	384	346
6	199	140
7	361	372
8	332	321
9	250	263
10	219	175
11	313	319
12	263	251
13	290	218
14	174	155
15	275	259
16	271	282
17	145	124
18	255	306
19	140	106
20	172	150
21	108	98
7 1		
1	242	255
2	312	263
3	493	544
4	264	237
5	516	561
6	335	403
7	287	301
8	342	360
9	266	256
10	367	320
11	329	313
12	187	129
13	278	203
14	262	192
15	0	45
16	279	222
17	0	24
18	185	197
19	200	246
20	179	197
21	141	172
7 0		
1	122	255
2	263	141
3	384	460
4	491	519
5	202	149
6	402	358
7	484	491
8	390	382
9	297	304
10	333	333
11	134	123
12	415	428
13	224	222
14	243	198
15	263	209
16	221	193
17	301	316
18	122	88

Table 2 (*cont.*)

h	Fo	Fc
19	168	164
20	183	185
21	157	155
22	172	179
7 -1		
0	451	401
1	375	302
2	714	716
3	330	267
4	468	479
5	304	326
6	196	164
7	218	243
8	357	394
9	289	300
10	313	333
11	264	230
12	240	170
13	321	321
14	116	96
15	294	290
16	152	139
17	186	157
18	180	196
19	217	224
20	143	58
21	176	183
22	107	86
7 -2		
0	346	279
1	391	359
2	460	386
3	377	315
4	494	469
5	223	191
6	357	440
7	368	407
8	291	321
9	333	442
10	185	118
11	262	344
12	199	129
13	287	277
14	188	161
15	208	146
16	330	362
17	166	146
18	182	171
19	143	123
20	157	126
21	146	114
22	146	165
23	0	19
7 -3		
0	324	289
1	284	273
2	298	284
3	209	173
4	333	375
5	297	278
6	158	58
7	268	283
8	169	111
9	295	401
10	282	349
11	263	319
12	0	139
13	178	126
14	304	235
15	286	289
16	238	155
17	152	147
18	225	245
19	144	59
20	211	267
21	131	119
22	128	150
7 -4		
0	425	401
1	440	372
2	249	203
3	443	454
4	172	107
5	332	323
6	336	291
7	271	323
8	329	399
9	215	163
10	345	409
11	201	172
12	224	167
13	184	171
14	221	176
15	257	253
16	187	182
17	131	76
18	136	137
19	157	182
20	119	119
21	118	114
7 -5		
0	221	123
1	328	328
2	212	173
3	295	241
4	221	186
5	259	200
6	307	246
7	0	104
8	219	190
9	265	275
10	236	220
11	0	80
12	232	295
13	180	130
14	191	180
15	219	166
16	0	76
17	192	176
18	0	70
19	256	266
20	127	97
7 -6		
0	0	113
1	274	203
2	316	320
3	0	51
4	329	341
5	0	140
6	264	257
7	257	261
8	0	133
9	0	130
10	190	186
11	221	200

h	Fo	Fc
12	0	60
13	0	125
14	0	78
15	186	150
16	157	83
17	171	111
18	136	106
7 -7		
0	309	240
1	261	159
2	226	44
3	0	88
4	225	180
5	267	216
6	207	226
7	0	136
8	213	200
9	207	185
10	0	65
11	195	188
12	0	66
13	255	235
14	242	128
15	123	65
7 -8		
0	0	111
1	194	154
2	0	108
3	163	171
4	0	84
5	162	182
6	0	131
7	0	147
8	0	42
9	139	143
10	143	148
11	0	75
8 8		
1	0	146
2	0	98
8 7		
1	280	268
2	0	44
3	266	285
4	259	256
5	186	58
6	228	223
7	259	46
8	195	235
9	203	119
8 6		
1	0	80
2	191	155
3	227	219
4	160	126
5	163	147
6	0	110
7	0	99
8	0	226
9	0	52
10	196	252
11	206	155
12	198	181
13	188	201
8 5		
1	182	164
2	322	418
3	255	248
4	189	185
5	242	300
6	184	136
7	193	233
8	0	72
9	152	132
10	147	165
11	128	51
12	133	112
13	0	36
14	0	68
15	115	40
16	82	85
8 4		
1	244	189
2	288	298
3	136	89
4	362	340
5	243	220
6	284	282
7	288	341
8	209	149
9	307	476
10	206	205
11	228	269
12	196	239
13	152	130
14	226	297
15	162	157
16	183	190
17	187	187
8 3		
1	312	374
2	231	230
3	187	155
4	169	144
5	204	140
6	269	279
7	0	18
8	178	118
9	0	62
10	0	59
11	193	158
12	207	138
13	267	250
14	289	256
15	183	117
16	197	185
17	167	59
18	286	281
19	209	195
8 2		
1	637	780
2	160	102
3	441	393
4	437	366
5	366	289
6	423	459
7	141	79
8	376	467
9	254	238

h	Fo	Fc
10	271	256
11	305	293
12	216	145
13	271	249
14	218	151
15	0	77
16	0	60
17	0	89
18	140	64
19	154	105
20	119	80
21	0	12
8 1		
1	72	90
2	94	91
3	174	152
4	185	185
5	245	325
6	212	229
7	174	168
8	273	309
9	193	139
10	380	436
11	249	192
12	324	305
13	409	424
14	294	248
15	386	439
16	200	134
17	279	284
18	187	178
19	184	175
20	159	173
21	0	54
8 0		
1	158	374
2	249	482
3	367	455
4	291	293
5	502	647
6	168	116
7	285	302
8	243	218
9	197	132
10	181	183
11	243	200
12	177	143
13	0	27
14	0	33
15	0	89
16	190	161
17	169	162
18	97	63
19	92	103
20	0	84
21	54	93
22	40	152
8 -1		
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1	316	268
2	436	436
3	376	315
4	179	147
5	255	281
6	337	362
7	378	541
8	0	51
9	429	466
10	0	84
11	483	420
12	476	429
13	315	235
14	381	364
15	0	15
16	309	309
17	299	304
18	188	155
19	183	173
20	0	75
21	162	170
22	0	89
8 -2		
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1	374	418
2	240	226
3	248	205
4	299	274
5	151	30
6	256	238
7	134	128
8	164	177
9	126	149
10	127	175
11	157	120
12	156	161
13	130	81
14	180	180
15	234	249
16	245	258
17	117	55
18	236	246
19	138	133
20	184	145
21	255	277
22	0	33
8 -3		
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1	446	443
2	159	143
3	397	443
4	405	359
5	375	331
6	503	519
7	119	45
8	357	403
9	161	86
10	362	380
11	402	452
12	168	156
13	268	297
14	211	185
15	281	270
16	187	103
17	114	104
18	132	122
19	0	67
20	0	21
21	0	37
8 -4		
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1	205	175
2	159	78
3	223	185
4	128	72
5	117	31

h	Fo	Fc
6	120	101
7	171	99
8	213	236
9	0	94
10	189	251
11	0	62
12	181	177
13	221	234
14	239	203
15	339	368
16	186	135
17	223	216
18	192	143
19	255	148
20	249	234
21	0	37
8 -5		
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1	169	75
2	346	354
3	281	239
4	268	250
5	385	455
6	0	49
7	271	274
8	203	127
9	292	257
10	203	193
11	201	150
12	197	157
13	0	85
14	0	101
15	0	62
16	0	81
17	0	34
18	159	50
19	134	112
8 -6		
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1	0	70
2	0	81
3	186	89
4	186	139
5	153	113
6	217	156
7	225	253
8	154	69
9	231	292
10	216	199
11	185	188
12	210	217
13	205	146
14	292	357
15	0	45
16	220	196
8 -7		
0	143	62
1	300	370
2	271	292
3	0	108
4	0	138
5	0	21
6	0	133
7	0	96
8	0	91
9	0	101
10	0	54
11	0	67
12	0	73
13	0	43
14	142	96
15	0	31
8 -8		
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1	0	79
2	0	69
3	170	218
4	198	222
5	137	111
6	0	217
7	177	61
8	135	204
9	0	80
10	0	204
9 8		
1	0	155
9 7		
1	0	51
2	210	214
3	0	118
4	0	140
5	189	202
6	0	48
7	193	182
8	124	131
9 6		
1	144	116
2	190	155
3	181	181
4	0	123
5	177	223
6	159	115
7	0	173
8	0	83
9	211	205
10	0	98
11	244	227
12	209	193
9 5		
1	311	287
2	280	233
3	0	136
4	212	223
5	0	79
6	212	206
7	236	246
8	181	161
9	142	131
10	147	142'
11	156	149
12	152	178
13	118	63
14	0	137
15	79	47
9 4		
1	362	290
2	156	168
3	310	304
4	350	323

h	Fo	Fc
5	279	258
6	237	223
7	219	127
8	282	352
9	168	144
10	206	243
11	265	302
12	174	164
13	204	226
14	127	98
15	190	200
16	212	194
17	97	74
9 3		
1	303	319
2	340	383
3	283	289
4	312	362
5	223	141
6	249	271
7	154	163
8	167	118
9	145	178
10	0	87
11	169	142
12	112	155
13	199	222
14	122	124
15	161	176
16	112	114
17	151	216
18	106	179
9 2		
1	253	202
2	480	503
3	533	515
4	298	303
5	275	273
6	272	201
7	365	439
8	271	265
9	294	296
10	235	247
11	298	294
12	283	299
13	211	132
14	174	114
15	201	191
16	138	109
17	166	216
18	182	217
19	111	53
20	80	154
9 1		
1	183	141
2	299	261
3	422	396
4	242	231
5	258	252
6	0	162
7	226	274
8	297	363
9	228	202
10	296	310
11	282	284
12	240	254
13	233	261
14	234	228
15	133	70
16	253	283
17	180	199
18	166	165
19	218	243
20	159	114
21	136	175
9 0		
1	219	500
2	208	247
3	312	339
4	281	303
5	152	145
6	391	424
7	312	274
8	332	327
9	227	212
10	208	203
11	198	162
12	294	287
13	161	128
14	170	156
15	153	126
16	227	229
17	202	204
18	185	142
19	135	144
20	0	128
21	182	207
9 -1		
0	247	189
1	362	244
2	465	367
3	389	366
4	265	212
5	384	362
6	347	371
7	177	123
8	571	482
9	232	112
10	608	374
11	461	263
12	222	133
13	669	411
14	0	47
15	703	388
16	328	174
17	0	70
18	299	175
19	238	102
20	286	176
21	193	118
22	0	53
9 -2		
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1	320	265
2	232	241
3	268	229
4	314	278
5	320	363
6	301	298
7	225	164
8	295	347
9	297	307
10	0	65
11	261	228
12	144	98

h	Fo	Fc
13	251	220
14	267	206
15	227	193
16	168	193
17	248	245
18	138	140
19	155	123
20	159	143
21	120	111
9 -3		
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1	311	217
2	312	308
3	284	230
4	429	448
5	448	459
6	167	129
7	416	402
8	167	114
9	301	252
10	295	258
11	348	348
12	334	330
13	237	203
14	208	185
15	139	110
16	213	208
17	136	111
18	161	134
19	92	69
20	135	143
21	60	51
9 -4		
0	336	367
1	298	326
2	162	130
3	262	236
4	116	75
5	297	327
6	181	196
7	220	237
8	204	192
9	228	256
10	180	214
11	131	59
12	147	145
13	192	216
14	252	108
15	0	81
16	171	189
17	151	137
18	205	186
19	198	191
20	0	108
9 -5		
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1	323	296
2	0	94
3	383	368
4	378	398
5	0	86
6	260	221
7	0	48
8	289	280
9	273	288
10	0	130
11	196	130
12	0	116
13	0	129
14	168	180
15	121	149
16	121	93
17	116	84
18	114	78
19	44	146
9 -6		
0	173	195
1	0	68
2	160	166
3	176	146
4	0	100
5	176	165
6	248	216
7	144	134
8	177	210
9	141	149
10	188	225
11	0	130
12	0	123
13	156	173
14	0	50
15	248	232
9 -7		
0	18'	223
1	[illegible]	44
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3	207	223
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5	0	112
6	0	70
7	185	204
8	147	121
9	0	156
10	0	38
11	0	125
12	0	87
9 -8		
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1	0	92
2	0	136
10 7		
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2	0	79
10 6		
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2	325	321
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4	260	248
5	211	134
6	220	251
7	202	176
8	0	100
9	182	181
10	0	23
10 5		
1	175	116
2	170	117
3	206	203
4	318	274

h	Fo	Fc
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6	247	255
7	123	85
8	246	270
9	205	238
10	0	76
11	205	231
12	172	15
13	282	256
14	208	195
10 4		
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2	255	218
3	273	272
4	0	98
5	238	228
6	0	95
7	189	186
8	193	176
9	0	62
10	0	84
11	0	47
12	111	112
13	104	56
14	104	67
15	144	146
16	0	78
10 3		
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2	206	205
3	252	236
4	249	195
5	479	591
6	260	199
7	370	385
8	189	196
9	199	178
10	430	497
11	0	90
12	334	346
13	218	203
14	179	179
15	178	188
16	108	44
17	123	125
18	53	83
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2	126	74
3	218	217
4	110	66
5	243	225
6	211	262
7	317	351
8	151	184
9	214	262
10	228	235
11	0	133
12	332	344
13	129	76
14	309	295
15	203	158
16	197	198
17	173	222
18	172	76
19	198	246
10 1		
1	318	323
2	671	632
3	186	129
4	485	494
5	220	193
6	388	454
7	362	404
8	134	113
9	255	300
10	0	36
11	230	241
12	191	185
13	106	63
14	0	101
15	136	94
16	121	127
17	0	51
18	61	72
19	54	50
20	55	110
10 0		
1	73	132
2	99	94
3	134	146
4	226	265
5	217	196
6	312	315
7	266	216
8	355	348
9	362	318
10	318	241
11	482	498
12	181	89
13	282	270
14	223	151
15	381	324
16	346	322
17	0	48
18	255	254
19	0	60
20	223	207
10 -1		
0	268	244
1	445	432
2	231	112
3	515	540
4	330	312
5	247	218
6	227	245
7	204	173
8	277	263
9	0	47
10	213	116
11	0	109
12	176	112
13	209	120
14	0	63
15	0	51
16	0	66
17	198	191
18	172	162
19	126	84
20	182	212
21	0	48
10 -2		
0	450	420

h	Fo	Fc
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2	360	302
3	393	390
4	329	226
5	424	427
6	291	237
7	315	366
8	283	314
9	220	202
10	445	477
11	163	106
12	327	359
13	248	164
14	308	259
15	297	245
16	0	96
17	209	207
18	0	74
19	189	122
20	105	91
21	0	56
10 -3		
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1	251	217
2	231	265
3	234	131
4	209	240
5	133	102
6	113	107
7	169	139
8	216	202
9	0	92
10	192	88
11	214	162
12	192	179
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16	233	199
17	247	251
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19	303	304
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10 -4		
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1	225	207
2	419	379
3	178	114
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6	431	433
7	337	306
8	204	135
9	355	437
10	0	66
11	257	324
12	188	161
13	0	128
14	109	129
15	0	86
16	96	82
17	0	35
18	0	21
10 -5		
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1	144	100
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3	0	75
4	162	183
5	121	34
6	137	138
7	178	147
8	217	263
9	227	223
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11	219	333
12	0	44
13	233	252
14	181	159
15	235	152
16	3[illegible]	264
17	179	92
18	0	181
10 -6		
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2	0	17
3	294	344
4	0	85
5	264	238
6	200	159
7	197	74
8	158	210
9	0	77
10	181	96
11	0	91
12	0	70
10 -7		
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1	0	102
2	170	62
3	0	186
4	0	34
5	0	179
6	159	92
7	169	201
8	136	216
9	130	103
11 7		
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2	0	171
11 6		
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2	0	101
3	304	281
4	0	86
5	0	190
6	0	137
11 5		
1	252	191
2	190	128
3	228	191
4	0	68
5	213	180
6	229	5
7	220	210
8	224	210
9	223	198
10	251	232
11	0	27
12	232	243
13	159	148

h	Fo	Fc
11 4		
1	202	161
2	387	424
3	311	243
4	178	123
5	202	166
6	186	184
7	186	181
8	195	224
9	0	27
10	0	147
11	0	116
12	0	134
13	159	131
14	208	193
15	149	188
11 3		
1	486	476
2	332	277
3	343	176
4	351	360
5	190	131
6	360	362
7	273	270
8	199	163
9	196	207
10	113	62
11	257	291
12	176	143
13	194	160
14	181	185
15	125	75
16	0	130
17	87	175
11 2		
1	266	208
2	389	356
3	460	330
4	164	130
5	247	188
6	328	247
7	367	407
8	134	128
9	248	171
10	214	202
11	229	175
12	241	176
13	270	252
14	183	107
15	259	262
16	289	285
17	131	117
18	169	210
11 1		
1	518	468
2	111	92
3	461	456
4	173	63
5	467	411
6	273	253
7	146	121
8	268	263
9	208	161
10	331	333
11	268	227
12	124	95
13	196	230
14	0	122
15	0	89
16	162	140
17	0	77
18	167	158
19	136	140
11 0		
1	110	214
2	177	172
3	247	190
4	259	239
5	329	258
6	302	240
7	326	303
8	308	244
9	225	200
10	298	238
11	232	198
12	364	432
13	239	186
14	243	250
15	262	289
16	195	124
17	236	255
18	156	85
19	194	173
11 -1		
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1	294	187
2	459	453
3	240	193
4	406	329
5	287	274
6	224	170
7	221	209
8	207	190
9	202	137
10	190	134
11	216	185
12	236	159
13	231	210
14	222	131
15	193	144
16	141	132
17	189	193
18	185	116
19	171	173
20	0	67
11 -2		
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1	324	299
2	224	157
3	403	308
4	395	331
5	156	91
6	306	323
7	263	210
8	258	284
9	270	321
10	0	90
11	330	340
12	254	80
13	301	273
14	344	302
15	141	86
16	212	179

h	Fo	Fc
17	179	119
18	241	173
19	160	118
20	0	72
11 -3		
0	339	271
1	445	454
2	207	184
3	307	169
4	0	120
5	294	213
6	157	92
7	287	273
8	235	141
9	247	214
10	165	174
11	273	256
12	266	219
13	266	200
14	0	69
15	287	238
16	236	193
17	187	130
18	236	220
19	0	12
11 -4		
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1	344	276
2	314	221
3	440	448
4	251	134
5	342	320
6	270	193
7	0	65
8	222	196
9	214	154
10	251	289
11	0	63
12	0	85
13	216	160
14	233	230
15	224	189
16	222	168
17	0	48
18	0	115
11 -5		
0	227	137
1	240	142
2	0	86
3	233	177
4	275	250
5	0	97
6	206	183
7	198	166
8	202	171
9	0	125
10	0	160
11	176	133
12	122	214
13	0	109
14	210	205
15	0	135
16	166	162
17	38	210
11 -6		
0	0	130
1	241	206
2	261	298
3	0	22
4	0	246
5	0	106
6	0	187
7	0	161
8	0	103
9	0	135
10	0	137
11	181	139
12	0	67
11 -7		
0	192	96
1	0	134
2	0	86
3	0	159
12 6		
1	0	96
2	0	128
12 5		
1	200	139
2	300	313
3	182	173
4	163	185
5	203	253
6	170	61
7	191	205
8	193	91
9	0	147
12 4		
1	219	162
2	220	226
3	248	62
4	273	258
5	247	213
6	225	204
7	283	377
8	0	35
9	250	293
10	200	139
11	239	258
12	200	209
13	0	75
14	151	229
12 3		
1	307	388
2	199	155
3	103	111
4	117	121
5	174	162
6	0	53
7	182	190
8	0	137
9	152	115
10	0	90
11	168	174
12	161	108
13	155	201
14	135	140
15	0	95
16	100	214

Table 2 (*cont.*)

h	Fo	Fc
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2	201	177
3	450	512
4	284	269
5	262	237
6	372	446
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8	201	272
9	293	287
10	277	313
11	214	203
12	0	71
13	191	172
14	0	75
15	168	193

h	Fo	Fc
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12	1	
1	181	186
2	142	71
3	210	170
4	154	149
5	167	175
6	189	163
7	217	225
8	293	280
9	182	134
10	269	276
11	264	227
12	269	309
13	187	209

h	Fo	Fc
14	150	119
15	272	336
16	0	17
17	231	246
12	0	
1	180	298
2	312	471
3	280	283
4	317	298
5	436	432
6	237	158
7	263	261
8	152	175
9	235	233
10	174	180

h	Fo	Fc
11	130	73
12	0	82
13	60	95
14	21	113
12	-1	
0	121	70
1	187	155
2	233	230
3	186	153
4	185	250
5	172	179
6	156	213
7	306	453
8	0	75
9	291	359

h	Fo	Fo
10	0	132
11	332	345
12	253	258
13	153	53
14	336	295
15	0	63
16	270	275
17	190	161
18	184	129
19	165	192
12	-2	
0	251	196
1	335	383
2	224	236
3	235	219

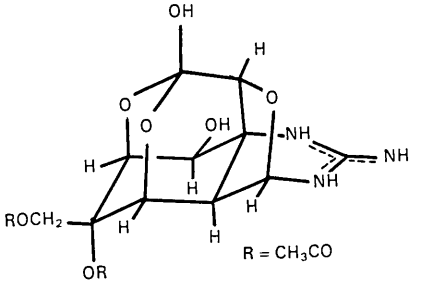
h	Fo	Fc
4	212	204
5	171	100
6	200	167
7	122	138
8	173	184
9	151	113
10	0	81
11	0	35
12	113	94
13	130	121
14	138	126
15	124	95
16	148	230
17	0	54
18	74	149
12	-3	

h	Fo	Fc
0	204	162
1	197	217
2	156	80
3	389	390
4	293	274
5	172	161
6	334	425
7	229	156
8	303	386
9	210	213
10	192	290
11	199	265
12	0	43
13	198	240
14	139	113
15	156	184

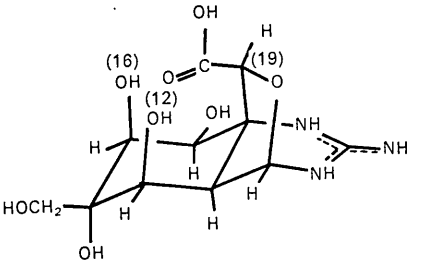
h	Fo	Fc
16	168	154
17	134	78
18	0	18
12	-4	
0	112	143
1	0	62
2	209	111
3	233	198
4	264	250
5	143	45
6	0	69
7	122	31
8	216	201
9	199	187
11	134	161

h	Fo	Fc
12	209	226
13	220	244
14	0	84
15	238	202
16	172	61
12	-5	
0	319	340
1	196	141
2	241	267
3	192	207
4	240	179
5	265	283
6	222	54
7	277	318
8	215	167

h	Fo	Fc
9	0	181
10	0	129
11	142	62
12	0	154
13	0	62
14	0	59
12	-6	
0	0	71
1	0	13
2	0	109
3	0	125
4	0	90
5	0	111
6	0	61



(IV)



(V)

calculated structure factors are listed in Table 2. Computations were done on an IBM 7090 computer with programs written by the authors.

Discussion

Fig. 3 shows the superimposed sections of the electron density distribution cut through the atomic centres of DATI and methyl alcohol. It is conceived that the general structure of the DAT molecule is now established, except its absolute configuration. The fact that essentially the same structure has been deduced from the two independent molecules in the asymmetric unit is additional evidence of the reliability of the present analysis. In the present paper, except in Figs. 1, 2 and 3, the molecules are drawn with the correct absolute configuration, by taking account of the result by Tomiie, Furusaki, Kasami, Yasuoka, Miyake, Haisa & Nitta (1964) who have determined the absolute configuration of bromoanhydrotetrodoic lactone hydrobromide, another derivative of tetrodotoxin.

The present compound and tetrodonic acid have the same perhydroquinazoline skeleton. The conformation of substituent atoms to the cyclohexane ring is the same for these two compounds; O(17) and C(14) are in equatorial positions and O(13) is in axial position. The structural relationship between DAT and tetrodonic acid may be described as follows: Let us start from the hypothetical epitetrodonic acid (V), in which the configuration at C(19) is antipodal to that in tetrodonic acid. The ortho-ester may, then, be formed by combining the acid carbonyl with the hydroxyl groups, O(12) and O(16). The skeletal structure of DAT so built up is similar to that of adamantane, which is a cage molecule consisting of four six-membered rings in the chair form.

Intramolecular bond lengths and angles in the two independent molecules are shown in Fig. 5 and Table 3 respectively. The estimated standard deviations in the atomic coordinates are approximately 0·004 Å for the iodine and 0·07 Å for the light atoms. Hence, the standard deviation of the bond lengths between the light

Table 3. *Bond angles*

C(2)—N(1) –C(9)	126°	C(52)–N(51) C(59)	123°
N(1) –C(2)—N(3)	121	N(51)–C(52)–N(53)	119
N(1) –C(2)—N(11)	124	N(51)–C(52)–N(61)	122
N(3) –C(2)—N(11)	115	N(53)–C(52)–N(61)	119
C(2)—N(3) –C(4)	117	C(52)–N(53)–C(54)	115
N(3) –C(4)—C(10)	105	N(53)–C(54)–C(60)	106
N(3) –C(4)—O(18)	109	N(53)–C(54)–O(68)	108
C(10)–C(4)—O(18)	99	C(60)–C(54)–O(68)	106
C(6)—C(5)—C(10)	115	C(56)–C(55)–C(60)	117
C(6)—C(5)—O(12)	102	C(56)–C(55)–O(62)	103
C(10)–C(5)—O(12)	113	C(60)–C(55)–O(62)	105
C(5)—C(6)—C(7)	102	C(55)–C(56)–C(57)	105
C(5)—C(6)—O(13)	109	C(55)–C(56)–O(63)	108
C(5)—C(6)—C(14)	112	C(55)–C(56)–C(64)	116
C(7)—C(6)—O(13)	102	C(57)–C(56)–O(63)	100
C(7)—C(6)—C(14)	110	C(57)–C(56)–C(64)	116
O(13)–C(6)—C(14)	120	O(63)–C(56)–C(64)	115
C(6)—C(7)—C(8)	117	C(56)–C(57)–C(58)	117
C(6)—C(7)—O(16)	108	C(56)–C(57)–O(66)	110
C(8)—C(7)—O(16)	110	C(58)–C(57)–O(66)	107
C(7)—C(8)—C(9)	102	C(57)–C(58)–C(59)	109
C(7)—C(8)—O(17)	117	C(57)–C(58)–O(67)	116
C(9)—C(8)—O(17)	111	C(59)–C(58)–O(67)	110
N(1) –C(9)—C(8)	109	N(51)–C(59)–C(58)	114
N(1) –C(9)—C(10)	104	N(51)–C(59)–C(60)	113
N(1) –C(9)—C(19)	115	N(51)–C(59)–C(69)	113
C(8)—C(9)—C(10)	118	C(58)–C(59)–C(60)	111
C(8)—C(9)—C(19)	115	C(58)–C(59)–C(69)	110
C(10)–C(9)—C(19)	95	C(60)–C(59)–C(69)	96
C(4)—C(10)–C(5)	113	C(54)–C(60)–C(55)	114
C(4)—C(10)–C(9)	101	C(54)–C(60)–C(59)	96
C(5)—C(10)–C(9)	111	C(55)–C(60)–C(59)	115
C(5)—O(12)–C(20)	108	C(55)–O(62)–C(70)	116
C(6)—O(13)–C(22)	113	C(56)–O(63)–C(72)	116

Table 3 (*cont.*)

C(6)—C(14)–O(15)	108	C(56)–C(64)–O(65)	111
C(14)–O(15)–C(25)	112	C(64)–O(65)–C(75)	117
C(7)—O(16)–C(20)	114	C(57)–O(66)–C(70)	115
C(4)—O(18)–C(19)	111	C(54)–O(68)–C(69)	108
C(9)—C(19)–O(18)	105	C(59)–C(69)–O(68)	102
C(9)—C(19)–C(20)	113	C(59)–C(69)–C(70)	112
O(18)–C(19)–C(20)	110	O(68)–C(69)–C(70)	105
O(12)–C(20)–O(16)	106	O(62)–C(70)–O(66)	109
O(12)–C(20)–C(19)	106	O(62)–C(70)–C(69)	107
O(12)–C(20)–O(21)	109	O(62)–C(70)–O(71)	107
O(16)–C(20)–C(19)	112	O(66)–C(70)–C(69)	109
O(16)–C(20)–O(21)	111	O(66)–C(70)–O(71)	109
C(19)–C(20)–O(21)	113	C(69)–C(70)–O(71)	116
O(13)–C(22)–O(23)	125	O(63)–C(72)–O(73)	139
O(13)–C(22)–C(24)	107	O(63)–C(72)–C(74)	103
O(23)–C(22)–C(24)	120	O(73)–C(72)–C(74)	118
O(15)–C(25)–C(26)	106	O(65)–C(75)–C(76)	114
O(15)–C(25)–O(27)	125	O(65)–C(75)–O(77)	118
C(26)–C(25)–O(27)	129	C(76)–C(75)–O(77)	128

atoms is about 0·1 Å, and that of the bond angles is about 6°. None of the bond lengths and angles deviate significantly from their normal values. The average values of the bond lengths are 1·53 Å for C–C, 1·33 Å for C–N (in the guanidine group), 1·46 Å for C–N, 1·42 Å for C–O and 1·23 Å for C=O. It should be pointed out that the corresponding bond lengths and angles in the two independent molecules are in good agreement as seen from Fig. 5 and Table 3.

The crystal structure viewed along the *c* axis is illustrated in Fig. 6, where anticipated hydrogen bonds are shown by the broken lines. The hydrogen bond lengths and short intermolecular contacts are listed in Table 4. The donors of the hydrogen bonds in Table 4 are the atoms at *x*, *y*, *z*. There are six NH···O, three OH···N and one OH···O hydrogen bond per asymmetric unit, and these hydrogen bonds connect the

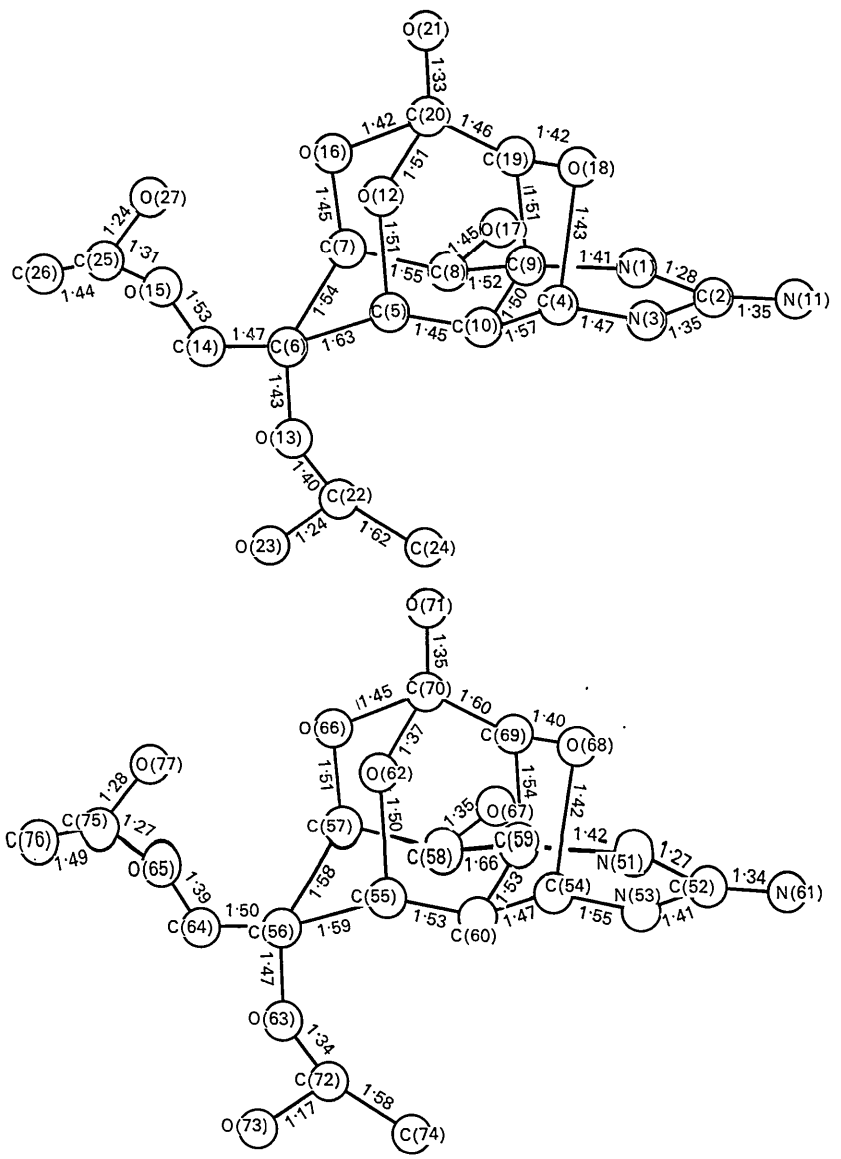


Fig. 5. Bond lengths (Å).

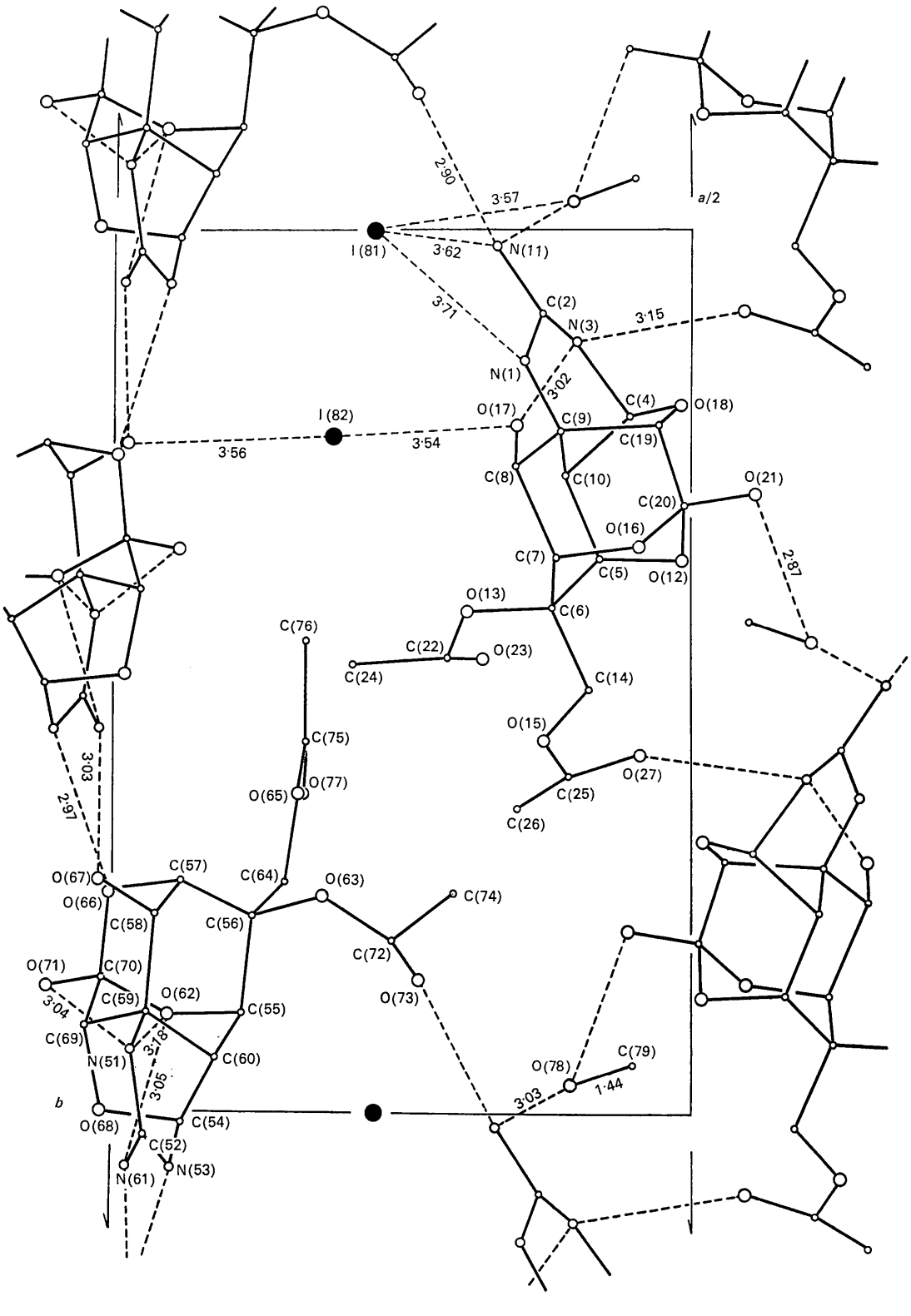


Fig. 6. Crystal structure viewed along the *c* axis.

DAT and methyl alcohol molecules to form an infinite three-dimensional network. The iodine atoms are in the interstices of the three-dimensional network and short contacts are found for I(81)···N(1), I(81)···N(11), I(82)···O(17) and I(82)···O(67). It may be suggested that the iodine atoms interact with the hydrogen atoms bonded with these nitrogen or oxygen atoms.

Table 4. *Possible hydrogen bonds and short intermolecular distances*

From atom at *x*, *y*, *z*	To atom	At position	Distance
	(*a*) Possible hydrogen bonds		
N(3)	O(27)	11	3·15 Å
N(11)	O(73)	4	2·90
O(17)	N(3)	2	3·02
O(21)	O(78)	12	2·87
N(51)	O(62)	2	3·18
N(53)	O(66)	9	2·97
N(61)	O(62)	2	3·05
N(61)	O(67)	10	3·03
O(71)	N(51)	3	3·04
O(78)	N(11)	5	3·03
	(*b*) Short intermolecular contacts		
I(81)	N(1)	1	3·71
I(81)	N(11)	1	3·62
I(81)	O(78)	4	3·57
I(81)	N(53)	4	3·95
I(81)	C(52)	4	3·91
I(81)	O(73)	6	3·95
I(82)	O(17)	3	3·54
I(82)	O(67)	7	3·56
O(15)	C(74)	1	3·48
C(24)	O(65)	1	3·45
C(24)	C(76)	1	3·63
C(26)	C(74)	1	3·91
O(17)	C(4)	2	3·36
C(24)	C(75)	2	3·83
C(24)	C(76)	2	3·70
C(24)	O(77)	2	3·27
C(25)	O(23)	2	3·50
C(26)	O(23)	2	3·28
C(26)	C(64)	2	3·89
C(26)	C(72)	2	3·70
C(26)	O(73)	2	3·54
C(26)	C(75)	2	3·72
C(52)	O(62)	2	3·41
C(58)	O(77)	2	3·45
N(61)	O(68)	2	3·32
N(61)	O(71)	2	3·34
O(63)	O(77)	2	3·21
O(67)	O(71)	2	3·59
C(74)	O(77)	2	3·40
O(78)	O(73)	2	3·28
O(78)	N(3)	5	3·24
C(24)	C(69)	7	3·74
C(57)	N(53)	7	3·59
C(57)	C(54)	7	3·87
C(75)	C(52)	7	3·83
C(75)	N(61)	7	3·45
C(76)	N(51)	7	3·58
C(76)	C(52)	7	3·68
C(76)	N(61)	7	3·59
O(77)	N(61)	7	3·58
C(76)	O(71)	8	3·52
C(4)	C(14)	11	3·97
C(4)	C(25)	11	3·79
C(4)	O(27)	11	3·18
C(5)	C(79)	11	3·78
O(12)	C(79)	11	3·27
O(18)	C(14)	11	3·30
O(18)	C(27)	11	3·47
O(21)	O(73)	11	3·36
O(21)	C(74)	11	3·58
O(16)	O(78)	12	3·47
O(16)	C(79)	12	3·34
C(20)	C(79)	12	3·97
O(21)	C(26)	12	3·23
O(21)	C(79)	12	3·43
O(27)	C(79)	12	3·46

Position								
1	x	y	z	7	$-x$	$-\frac{1}{2}+y$	$-z$
2	x	y	$-1+z$	8	$-x$	$-\frac{1}{2}+y$	$1-z$
3	x	y	$1+z$	9	$-x$	$\frac{1}{2}+y$	$-z$
4	x	$-1+y$	z	10	$-x$	$\frac{1}{2}+y$	$-1-z$
5	x	$1+y$	$-1+z$	11	$1-x$	$-\frac{1}{2}+y$	$-z$
6	x	$-1+y$	$-1+z$	12	$1-x$	$-\frac{1}{2}+y$	$-1-z$

All distances less than 4·0 Å between the reference molecules at *x*, *y*, *z* and the neighbouring molecules were calculated. Only those less than 4·0 Å for C···C and C···I pairs and those less than 3·6 Å for the other pairs are listed.

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