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The Crystal Structure and Absolute Configuration of 2,9-Diacetyl-9-azabicyclo[4,2,1]non-2,3-ene*

By Carol Saunderson Huber

Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6

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The crystal structure of 2,9-diacetyl-9-azabicyclo[4,2,1]non-2,3-ene, $C_{12}H_{17}NO_2$, has been determined by direct methods from 1257 independent reflexions measured with Cu $K\alpha$ radiation on a Picker diffractometer. The title compound is the *N*-acetyl derivative of a toxin produced by *Anabaena flos-aquae* (blue-green freshwater algae). Crystal data are: space group $P4_12_12$, $D_m = 1·19$ g.cm^{-3}, $Z = 8$, $D_c = 1·21$ g.cm^{-3}, $a = 7·335$ (2), $c = 42·294$ (10) Å. The ring system is a novel one for a natural product; it is similar to that of tropane, but the piperidine ring is here replaced by an azacycloheptene ring. Two of the C–C bond lengths in the pyrrolidine ring differ significantly, the longer bond being adjacent to a C–H which appears to be involved in a weak intramolecular C–H···O hydrogen bond. The crystal packing is determined by van der Waals forces.

Introduction

Certain strains of the blue-green freshwater algal species *Anabaena flos-aquae* have been shown to produce a relatively fast acting toxin (Gorham, 1962, and references cited therein). This toxin has different properties from the one isolated from *Microcystis aeruginosa* which was shown to be a probably cyclic polypeptide (Bishop, Anet & Gorham, 1959). The difficulty of isolating sufficient quantities of the *Anabaena* toxin prevented a rigorous proof of its structure by chemical methods, and the *N*-acetyl derivative was therefore investigated by X-ray diffraction. The structure which was found is in full agreement with that which Edwards (1971) proposed and is compatible with further chemical evidence (Edwards, Gorham, Hunter & Pike, 1972).

Experimental

Well formed crystals of the title compound (hereafter referred to as DAN) were supplied by Dr O. E. Edwards of this Division. The crystals were uniaxial colourless prisms of square cross-section. The space group was deduced from systematic absences on precession and Weissenberg photographs to be $P4_12_12$ or $P4_32_12$. The density was measured by flotation in aqueous KI solution.

Crystal data

2,9-Diacetyl-9-azabicyclo[4,2,1]non-2,3-ene, $C_{12}H_{17}NO_2$, F. W. 207·3. Tetragonal, $a = 7·335$ (2), $c = 42·294$ (10) Å. $V = 2275·5$ Å^3, $D_m = 1·19$ g.cm^{-3}, $Z = 8$, $D_x = 1·21$ g.cm^{-3}. $\mu(\text{Cu } K\alpha) = 6·7$ cm^{-1}. Cell dimensions based on $\lambda(\text{Cu } K\alpha_1) = 1·54051$, $\lambda(\text{Cu } K\alpha_2) = 1·54433$ Å.

A crystal of approximate dimensions $0·25 \times 0·25 \times 0·22$ mm was mounted with its *a* axis parallel to the φ axis of a Picker four-circle diffractometer. All measurements were made at room temperature with Ni-filtered Cu radiation using a scintillation counter and pulse-height analyser. Unit-cell dimensions were obtained from 2θ values of high-angle axial reflexions. Intensities were measured by the $\theta/2\theta$ scan method; the scan ranges varied from 2·0 to 4·0° in 2θ. Background was counted for 20 sec at each end of the scans. The intensity of a standard reflexion was monitored after every 20–40 reflexions. No perceptible deterioration of the crystal occured during data collection. Only one sixteenth of the reciprocal lattice was surveyed. Of the 1257 independent reflexions accessible ($2\theta \leq 130°$) 1091 had counts above threshold. The threshold was defined as a net count of 70 or 10% of the total background count, whichever was higher. The data were corrected for Lorentz and polarization factors, but absorption corrections were considered unnecessary and therefore were not applied.

Structure determination and refinement

The structure was determined by the symbolic addition procedure and tangent refinement (Karle & Karle, 1966). Because of various computer program restrictions, these calculations were done assuming the orthorhombic sub-group ($P2_12_12_1$) symmetry rather than the tetragonal symmetry. A full octant of data was generated from the independent reflexions and normalized structure-factor amplitudes were calculated for all reflexions. Two origin-defining reflexions were chosen according to the criteria for the tetragonal space group (Hauptman & Karle, 1956), and their *khl* equivalents were also assigned the appropriate phase values to maintain the tetragonal symmetry, taking into account the shift of origin between space groups $P4_12_12$ and $P2_12_12_1$. During the symbolic addition procedure, which was done manually, equivalent pairs of reflexions (*hkl* and *khl*) were always checked as their phases were determined to ensure that the phase values were

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Table 1. *Fractional coordinates, vibration tensor components* (Å^2) *for the expression* $T=\exp[-2\pi^2(H_{11}a^{*2}h^2+\ldots\ldots.+2U_{23}b^*c^*kl+\ldots\ldots.)]$, *and their e.s.d.'s*

	x ($\times 10^4$)	y ($\times 10^4$)	z ($\times 10^5$)	U_{11} ($\times 10^4$)	U_{22} ($\times 10^4$)	U_{33} ($\times 10^4$)	$2U_{23}$ ($\times 10^4$)	$2U_{13}$ ($\times 10^4$)	$2U_{12}$ ($\times 10^4$)
C(1)	538 (4)	3921 (4)	7403 (7)	323 (14)	401 (15)	471 (18)	−104 (27)	−129 (25)	80 (26)
C(2)	−230 (4)	3157 (4)	4339 (7)	268 (13)	490 (17)	453 (9)	−162 (28)	−30 (25)	78 (24)
C(3)	−836 (4)	1435 (4)	4111 (7)	331 (15)	550 (18)	471 (18)	−269 (30)	−47 (27)	11 (29)
C(4)	−982 (5)	34 (4)	6654 (8)	517 (18)	380 (16)	680 (18)	−226 (30)	−88 (33)	−102 (28)
C(5)	623 (4)	−259 (4)	8918 (7)	494 (17)	430 (17)	616 (18)	173 (30)	123 (31)	−28 (31)
C(6)	1263 (4)	1407 (4)	10766 (7)	393 (16)	514 (17)	462 (18)	192 (28)	22 (28)	−88 (27)
C(7)	−231 (5)	2458 (5)	12452 (8)	491 (19)	759 (24)	544 (18)	−228 (38)	303 (31)	−375 (36)
C(8)	−855 (4)	3925 (5)	10179 (7)	320 (15)	686 (21)	562 (18)	−446 (33)	−57 (28)	90 (31)
N(9)	2014 (3)	2784 (3)	8631 (5)	259 (10)	461 (13)	426 (9)	113 (22)	−22 (20)	−20 (22)
C(10)	−359 (4)	4443 (4)	1685 (7)	482 (18)	585 (19)	507 (18)	86 (31)	−121 (30)	98 (32)
C(11)	−1035 (7)	3843 (7)	−1504 (8)	1187 (35)	1130 (36)	526 (18)	251 (49)	−514 (49)	−664 (62)
O(12)	102 (4)	6031 (4)	2043 (6)	1331 (26)	618 (15)	743 (18)	368 (28)	−526 (35)	−201 (34)
C(13)	3746 (4)	2753 (4)	7627 (6)	282 (13)	555 (17)	417 (18)	63 (28)	−93 (24)	7 (25)
C(14)	4315 (4)	4145 (6)	5229 (8)	379 (17)	912 (26)	598 (18)	453 (39)	19 (31)	−121 (37)
O(15)	4847 (3)	1659 (4)	8681 (6)	358 (11)	845 (17)	761 (18)	454 (28)	24 (24)	291 (22)

related as required by the tetragonal space group. Several tangent refinement calculations were run, based on different starting symbol values and extending gradually down to reflexions with $E \geq 1{\cdot}50$. The convergence in one run appeared better than in the others although the resulting R_{Karle} (Karle & Karle, 1966) value, 0·28, was higher than usual for a correct structure in this laboratory. The E map which was calculated on the basis of this set of phases showed all but one of the non-hydrogen atoms in the molecule. The last atom was easily located on a difference map.

Refinement was by the block-diagonal least-squares method, minimizing $\sum w(|F_o|-|F_c|)^2$. All the hydrogen atoms were located on difference maps and were eventually included in the refinement isotropically. Scattering factor values for C, N and O were those of Hanson, Herman, Lea & Skillman (1964), and those of Stewart, Davidson & Simpson (1965) were used for bonded hydrogen.

Various weighting schemes were employed during the course of refinement to minimize variations of $\langle w\Delta^2\rangle$ with $|F_o|$ or $\sin^2\theta$. The final scheme was $w=1/[1+\{(|F_o|-P_2)/P_1\}^2]$ with $P_1=5{\cdot}0$e and $P_2=12{\cdot}0$e. Two reflexions, 2,0,16 and 215, were given zero weight during the later cycles because their observed amplitudes appear to be in error, perhaps because of contributions from double reflexions.

Anomalous scattering corrections were introduced for the oxygen atoms when the refinement was nearly complete. The values used ($\Delta f'=0$, $\Delta f''=0{\cdot}1$) were taken from *International Tables for X-ray Crystallography* (1962). Structure factors were calculated for one absolute configuration in the space group $P4_12_12$ and for the opposite absolute configuration in the enantiomorphous space group $P4_32_12$. The conventional R value was 0·0487 and the weighted $R\{=[\sum w(\Delta F)^2/\sum wF_o^2]^{1/2}\}$ was 0·0593 for space group $P4_12_12$, while for the other space group these values were 0·0491 and 0·0596 respectively. Using Hamilton's (1965) test, the ratio 0·0596/0·0593 is sufficiently greater than unity to reject at the 0·005 significance level the absolute configuration corresponding to space group $P4_32_12$. The ten reflexions showing the most significant anomalous dispersion effect, *i.e.* with the largest values of $[F_c(hkl)-F_c(\bar{h}\bar{k}\bar{l})]^2/\sigma^2(F_o)$, showed conventional R values of 0·020 and 0·025 for the accepted and rejected absolute configurations respectively. One further cycle of least-squares calculations using the correct absolute configuration concluded the refinement. The final R value for 1089 observed reflexions is 0·0483.

Final parameters and their e.s.d.'s are given in Tables 1 and 2. Observed and calculated structure amplitudes based on these parameters are listed in Table 3. A difference map calculated from the final structure factors showed no density higher than 0·17 e.Å^{-3} or lower than $-0{\cdot}15$ e.Å^{-3}. The calculated standard deviation of the difference density (Cruickshank, 1959) is 0·042 e.Å^{-3}. Of the four peaks more than 3σ in height, three are apparently spurious while one may represent π bonding density for the C(10)–O(12) bond.

Table 2. *Hydrogen atom parameters and their e.s.d.'s*

The number of the carbon atom to which the hydrogen is bonded is obtained by dropping the least significant digit of the hydrogen atom number. The e.s.d.'s of the thermal parameters have been multiplied by 10.

	x/a ($\times 10^3$)	y/b ($\times 10^3$)	z/c ($\times 10^4$)	B(Å^2)
H(11)	92 (4)	522 (4)	679 (7)	3·7 (6)
H(31)	−132 (4)	108 (4)	216 (6)	3·2 (6)
H(41)	−99 (5)	−92 (5)	552 (7)	4·5 (7)
H(42)	−215 (4)	32 (4)	796 (7)	4·6 (7)
H(51)	169 (4)	−80 (4)	764 (7)	3·8 (7)
H(52)	24 (4)	−126 (5)	1049 (7)	4·8 (7)
H(61)	216 (5)	99 (5)	1223 (7)	4·6 (8)
H(71)	−122 (5)	165 (5)	1283 (8)	5·6 (9)
H(72)	31 (5)	302 (5)	1435 (8)	6·2 (9)
H(81)	−202 (4)	367 (4)	939 (6)	4·1 (7)
H(82)	−78 (4)	506 (4)	1140 (7)	4·7 (7)
H(111)	−81 (9)	296 (8)	−195 (13)	14·6 (18)
H(112)	−91 (7)	480 (7)	−311 (10)	9·2 (13)
H(113)	−231 (9)	334 (9)	−117 (13)	11·7 (18)
H(141)	459 (7)	520 (6)	609 (11)	10·6 (13)
H(142)	546 (6)	378 (6)	464 (10)	8·3 (11)
H(143)	366 (5)	435 (5)	351 (8)	5·3 (9)

Results and discussion

A stereoscopic view of the molecule in the correct absolute configuration is given in Fig. 1, and the numbering scheme is shown in Fig. 2. The absolute configuration determined in this analysis corresponds to (1*R*, 6*R*) in the notation of Cahn, Ingold & Prelog (1956). It is interesting to note that the narcotic L-cocaine (I) also has (1*R*) absolute configuration (Fodor, 1960).

Table 3. *Observed and calculated structure amplitudes* (× 10)

An asterisk indicates an unobserved reflexion.

L	FO	FC
H= 0, K= 0		
4	709	719
8	570	567
12	742	679
16	662	621
20	491	503
24	163	179
28	427	437
32	445	452
36	230	228
40	41	35
44	29*	24
48	131	139
H= 1, K= 0		
1	821	853
2	530	530
3	635	638
4	698	702
5	1256	1283
6	470	459
7	937	923
8	491	486
9	153	155
10	323	327
11	265	267
12	463	484
13	439	445
14	267	264
15	410	393
16	56	51
17	44	51
18	66	70
19	457	429
20	259	274
21	310	307
22	78	78
23	208	208
24	67	80
25	279	262
26	83	80
27	143	143
28	50	69
29	186	186
30	115	117
31	71	77
32	122	117
33	165	169
34	70	65
35	41	47
36	210	205
37	111	109
38	149	147
39	31*	25
40	128	128
41	30*	27
42	40	35
43	30*	38
44	29*	12
45	28*	32
46	149	151
47	31	15
48	33	25
49	35	31
H= 2, K= 0		
0	1412	1445
1	643	692
2	1000	1035
3	594	599
4	516	511
5	27	20
6	78	71
7	110	109
8	147	145
9	727	657
10	295	275
11	59	59
12	83	62
13	78	83
14	19*	8
15	48	57
16	72	24
17	124	120
18	108	102
19	150	146
20	62	44
21	47	52
22	296	297
23	44	52
24	157	165
25	28*	18
26	286	291
27	47	51
28	148	141
29	28*	14
30	66	58
31	45	54
32	74	67
33	148	150
34	33*	3
35	157	161
36	159	156
37	73	71
38	106	105
39	31*	11
40	30*	19
41	98	98
42	29*	10
43	39	36
44	39	41
45	48	49
46	52	43
47	95	91
48	23*	1
H= 3, K= 0		
1	49	33
2	325	343
3	117	113
4	222	217
5	57	55
6	255	284
7	99	98
8	588	597
9	273	273
10	301	287
11	174	170
12	275	283
13	261	247
14	154	167
15	286	300
16	49	46
17	418	431
18	147	141
19	96	95
20	231	216
21	46	45
22	162	165
23	27*	39
24	27*	5
25	28*	11
26	28*	6
27	41	38
28	71	67
29	85	87
30	30*	2
31	68	56
32	77	77
33	183	197
34	156	163
35	39	37
36	94	89
37	108	102
38	30*	19
39	48	43
40	54	44
41	45	40
42	135	130
43	27*	20
44	33	20
45	25*	20
46	24*	33
H= 4, K= 0		
0	139	139
1	302	328
2	54	61
3	227	237
4	153	152
5	256	243
6	155	159
7	49	34
8	32	41
9	68	63
10	359	346
11	24*	12
12	146	143
13	63	55
14	188	182
15	215	237
16	35	37
17	108	103
18	132	136
19	27*	26
20	195	183
21	118	118
22	29*	13
23	49	46
24	292	282
25	92	98
26	125	127
27	30*	18
28	285	281
29	117	118
30	31*	12
31	31*	16
32	197	199
33	31*	7
34	70	70
35	30*	9
36	30*	11
37	29*	17
38	45	44
39	33	31
40	34	39
41	26*	15
42	41	29
43	63	52
44	35	38
H= 5, K= 0		
1	70	68
2	145	146
3	74	65
4	115	125
5	68	65
6	76	78
7	27*	20
8	186	196
9	219	231
10	28*	13
11	166	175
12	38	38
13	186	189
14	110	111
15	111	110
16	61	65
17	81	81
18	109	103
19	42	44
20	80	91
21	95	100
22	66	69
23	31*	14
24	36	37
25	41	27
26	97	101
27	104	109
28	191	192
29	61	61
30	58	62
31	43	26
32	89	83
33	58	60
34	29*	3
35	53	51
36	44	29
37	74	70
38	14	18
39	29	14
40	23*	12
H= 6, K= 0		
0	86	89
1	146	153
2	54	49
3	83	78
4	50	46
5	155	166
6	74	65
7	87	90
8	30*	16
9	71	71
10	98	97
11	33*	7
12	34*	3
13	86	81
14	113	120
15	291	302
16	78	74
17	92	97
18	149	154
19	160	102
20	31*	3
21	46	50
22	64	62
23	87	82
24	114	108
25	30*	2
26	102	101
27	88	88
28	29*	4
29	40	34
30	76	73
31	27*	28
32	44	36
33	52	53
34	61	66
35	28	31
H= 7, K= 0		
1	63	61
2	50	53
3	50	43
4	290	302
5	39	42
6	71	69
7	102	97
8	209	209
9	199	209
10	83	79
11	135	134
12	36	28
13	33*	22
14	38	44
15	74	77
16	150	146
17	35	47
18	120	117
19	39	44
20	96	103
21	45	24
22	27*	24
23	32	23
24	26*	6
25	42	34
26	25*	26
27	24*	16
28	56	60
29	38	23
H= 8, K= 0		
0	57	55
1	75	68
2	64	75
3	71	70
4	66	67
5	40	29
6	27*	19
7	49	45
8	36	26
9	71	76
10	57	61
11	26*	14
12	26*	6
13	25*	17
14	25*	1
15	31	15
16	52	40
17	24*	46
18	23*	1
H= 1, K= 1		
0	527	476
1	542	560
2	28	9
3	432	442
4	732	722
5	91	89
6	966	971
7	349	358
8	917	923
9	1022	1020
10	230	217
11	69	50
12	554	530
13	1017	997
14	304	300
15	157	157
16	381	369
17	40	57
18	246	236
19	136	139
20	465	479
21	22*	9
22	25*	31
23	92	98
24	240	255
25	37	36
26	170	167
27	26*	4
28	155	153
29	164	166
30	115	116
31	179	166
32	242	233
33	42	47
34	109	110
35	219	223
36	144	145
37	142	146
38	122	121
39	44	39
40	43	46
41	53	59
42	42	36
43	47	33
44	42	33
45	37	35
46	27*	19
47	78	73
48	45	27
49	75	69
H= 2, K= 1		
0	394	401
1	232	222
2	175	165
3	458	470
4	507	515
5	202	149
6	601	598
7	906	904
8	354	376
9	338	340
10	461	436
11	486	480
12	231	205
13	306	288
14	349	329
15	253	244
16	452	440
17	174	159
18	306	290
19	435	427
20	337	335
21	217	209
22	87	85
23	139	132
24	211	219
25	68	70
26	67	64
27	117	121
28	64	63
29	88	83
30	65	61
31	80	80
32	30	28
33	72	72
34	108	112
35	103	107
36	146	149
37	85	90
38	95	97
39	34*	22
40	91	81
41	48	55
42	58	52
43	61	57
44	44	28
45	34	10
46	25*	29
47	24*	13
48	57	47
H= 3, K= 1		
0	19*	7
1	155	152
2	576	581
3	142	138
4	232	226
5	101	106
6	244	232
7	104	97
8	344	352
9	267	282
10	306	299
11	712	701
12	245	242
13	348	339
14	339	352
15	406	398
16	271	273
17	75	81
18	207	205
19	262	259
20	106	107
21	99	95
22	172	159
23	160	164
24	110	114
25	232	227
26	80	76
27	148	151
28	101	102
29	163	161
30	82	86
31	200	212
32	130	128
33	76	68
34	37	24
35	90	93
36	58	60
37	132	139
38	115	114
39	94	84
40	47	48
41	93	97
42	62	69
43	82	69
44	36	38
45	29	25
46	50	54
H= 4, K= 1		
0	323	337
1	118	121
2	403	397
3	54	43
4	89	83
5	88	82
6	177	172
7	150	147
8	119	117
9	75	74
10	33	21
11	131	124
12	119	123
13	136	131
14	182	177
15	170	164
16	130	130
17	209	207
18	137	140
19	102	100
20	129	126
21	225	224
22	210	219
23	234	241
24	111	128
25	48	39
26	169	170
27	109	113
28	89	91
29	173	175
30	55	46
31	52	47
32	60	64
33	58	62
34	164	170
35	102	103
36	74	77
37	64	57
38	34	28
39	64	64
40	69	67
41	26*	22
42	42	40
43	30	18
H= 5, K= 1		
0	77	78
1	47	44
2	231	224
3	108	105
4	91	97
5	77	76
6	162	165
7	83	86
8	138	141
9	224	231
10	88	88
11	116	117
12	157	161
13	49	45
14	198	203
15	29*	22
16	73	78
17	125	116
18	189	190
19	185	189
20	159	161
21	71	67
22	61	59
23	131	131
24	139	145
25	111	115
26	41	50
27	128	127
28	88	91
29	128	132
30	30*	7
31	57	61
32	56	47
33	71	52
34	54	44
35	43	34
36	52	45
37	47	37
38	39	32
39	24*	18
40	60	53
H= 6, K= 1		
0	108	111
1	87	86
2	89	95
3	49	39
4	90	88
5	108	106
6	109	99
7	141	136
8	152	153
9	153	148
10	232	233
11	131	134
12	111	109
13	98	94
14	141	145
15	82	82
16	83	86
17	96	97
18	100	96
19	44	32
20	83	92
21	95	91
22	83	83
23	99	105
24	42	40
25	81	83
26	37	37
27	53	52
28	60	51
29	45	49
30	27*	30
31	80	81
32	49	41
33	40	46
34	44	41
35	44	46
H= 7, K= 1		
0	58	38
1	91	94
2	67	61
3	170	174
4	67	64
5	101	96
6	108	109
7	36	33
8	93	92
9	151	155
10	59	53
11	148	138
12	40	26
13	141	148
14	30*	6
15	109	108
16	54	57
17	41	41
18	53	50
19	42	22
20	65	62
21	78	81
22	50	43
23	43	44
24	65	72
25	44	40
26	72	73
27	24*	18
28	63	56
H= 8, K= 1		
0	27*	21
1	27*	1
2	86	82
3	27*	14
4	34	3
5	57	58
6	86	98
7	53	55
8	26*	28
9	31	32
10	36	39
11	53	55
12	25*	17
13	25*	26
14	36	42
15	24*	20
16	24*	5
17	71	64
H= 2, K= 2		
0	278	298
1	122	116
2	280	278
3	62	40
4	219	244
5	19*	4
6	138	137
7	19*	6
8	211	224
9	155	158
10	412	419
11	90	92
12	606	587
13	343	325
14	308	306
15	283	273
16	154	155
17	199	202
18	417	427
19	260	270
20	31	22
21	25*	11
22	207	211
23	92	91
24	247	249
25	170	172
26	228	238
27	42	56
28	118	113
29	217	210
30	60	61
31	162	171
32	67	62
33	31*	24
34	168	152
35	34*	22
36	94	97
37	109	106
38	101	102
39	57	61
40	96	93
41	47	46
42	70	70
43	99	94
44	26*	28
45	48	41
46	36	34
H= 3, K= 2		
0	183	188
1	150	141
2	101	97
3	92	85
4	195	194
5	376	368
6	213	209
7	256	282
8	356	350
9	183	192
10	108	115
11	121	123
12	304	302
13	138	125
14	184	179
15	148	151
16	216	240
17	150	154
18	259	252
19	108	103
20	124	126
21	80	79
22	187	188
23	170	173
24	197	194
25	193	193
26	72	72
27	264	261
28	87	98
29	118	123
30	123	116
31	44	52
32	144	149
33	91	89
34	31*	23
35	31*	19
36	91	84
37	49	52
38	63	63
39	29*	18
40	28*	30
41	51	53
42	39	37
43	57	47
44	81	65
45	34	23
H= 4, K= 2		
0	341	331
1	185	199
2	108	117
3	236	228
4	25*	27
5	63	59
6	255	253
7	200	192
8	142	140
9	218	215
10	69	52
11	222	223
12	47	41
13	313	220
14	244	248
15	221	235
16	139	135
17	83	75
18	91	92
19	248	245
20	98	99
21	227	227
22	51	42
23	178	176
24	69	67
25	119	125
26	205	211
27	173	175
28	39	43
29	114	119
30	107	106
31	91	90
32	34*	10
33	51	46
34	135	129
35	59	56
36	34	37
37	83	83
38	27*	6
39	31	17
40	69	28
41	25*	26
42	26*	28
H= 5, K= 2		
0	86	87
1	135	141
2	71	72
3	218	212
4	305	298
5	217	221
6	62	57
7	110	97
8	205	208
9	138	142
10	127	132
11	55	42
12	37	19
13	63	76
14	117	108
15	55	53
16	201	206
17	43	46
18	110	109
19	117	117
20	57	47
21	238	241
22	63	65
23	50	36
24	41	48
25	55	46
26	94	99
27	153	156
28	61	67
29	125	124
30	59	49
31	29*	11
32	48	38
33	33	29
34	39	25
35	41	24
36	60	44
37	29	13
38	24*	19
H= 6, K= 2		
0	136	138
1	48	49
2	169	172
3	129	134
4	49	100
5	45	49
6	178	178
7	74	69
8	92	85
9	84	93
10	273	267
11	157	154
12	59	57
13	44	34
14	39	23
15	85	90
16	120	119
17	98	105
18	105	104
19	51	38
20	49	48
21	38	12
22	57	57
23	51	46
24	105	107
25	90	82
26	42	66
27	28*	38
28	87	77
29	71	73
30	37	28
31	32	42
32	51	31
33	30	6
H= 7, K= 2		
0	30*	10
1	99	99
2	74	70
3	41	32
4	66	66
5	83	81
6	102	106
7	52	45
8	71	70
9	180	179
10	30*	11
11	78	77
12	57	55
13	106	104
14	53	43
15	41	49
16	55	40
17	79	76
18	28*	22
19	53	66
20	54	56
21	55	51
22	38	34
23	104	96
24	49	38
25	24*	20
26	68	70
H= 8, K= 2		
0	59	59
1	89	86
2	80	73
3	90	95
4	36	26
5	89	80
6	66	61
7	70	72
8	90	94
9	25*	13
10	55	57
11	65	66
12	26*	10
13	23*	22
14	36	25
H= 3, K= 3		
0	451	457
1	200	208
2	97	94
3	53	47
4	147	144
5	64	63
6	272	238
7	57	47
8	117	121
9	307	299
10	275	212
11	152	187
12	38	27
13	131	128
14	89	90
15	57	57
16	171	183
17	211	205
18	63	61
19	92	87
20	28*	15
21	162	167
22	61	63
23	77	79
24	115	119
25	52	50
26	113	117
27	77	79
28	46	40
29	37	37
30	41	19
31	31*	17
32	91	88
33	36	29
34	118	129
35	30*	16
36	79	77
37	66	51
38	74	74
39	107	107
40	26*	6
41	34	4
42	24*	19
43	59	64
H= 4, K= 3		
0	101	106
1	120	127
2	105	100
3	54	52
4	27*	17
5	65	52
6	57	67
7	42	33
8	211	215
9	43	35
10	166	169
11	105	102
12	86	88
13	112	107
14	183	184
15	173	169
16	74	80
17	222	225
18	121	119
19	128	124
20	148	148
21	33*	30
22	156	157
23	53	48
24	46	48
25	86	95
26	76	81
27	60	65
28	81	78
29	43	41
30	30*	27
31	30*	3
32	35	27
33	29*	19
34	38	38
35	45	41
36	52	42
37	26*	11
38	56	50
39	25*	5
40	30	36
H= 5, K= 3		
0	172	166
1	196	195
2	93	94
3	152	162
4	87	91
5	54	50
6	77	75
7	67	66
8	113	116
9	99	102
10	209	211
11	56	53
12	85	77
13	56	54
14	70	75
15	55	41
16	166	167
17	34*	35
18	158	163
19	57	51
20	31*	36
21	144	144
22	70	73
23	36	43
24	86	93
25	30*	28
26	140	139
27	56	50
28	51	40
29	87	84
30	73	72
31	30*	38
32	75	69
33	56	58
34	54	52
35	27*	24
36	46	42
H= 6, K= 3		
0	90	83
1	124	123
2	63	55
3	182	193
4	59	63
5	86	83
6	146	145
7	153	151
8	106	101
9	89	80
10	139	141
11	111	119
12	130	129
13	155	155
14	180	181
15	78	72
16	72	68
17	77	81
18	40	40
19	56	57
20	56	38
21	29*	20
22	83	87
23	40	34
24	66	61
25	27*	33
26	84	93
27	47	35
28	47	42
29	53	53
30	24*	20
31	31	30
H= 7, K= 3		
0	43	52
1	32*	10
2	29*	17
3	78	72
4	135	140
5	74	65
6	48	39
7	77	70
8	29*	23
9	103	99
10	28*	21
11	84	85
12	96	101
13	28*	27
14	27*	29
15	42	34
16	45	19
17	51	34
18	55	64
19	74	74
20	31	31
21	49	41
22	46	37
23	73	70
H= 8, K= 3		
0	63	55
1	41	29
2	75	76
3	71	68
4	43	48
5	34	43
6	51	48
H= 4, K= 4		
0	29*	19
1	39	34
2	61	54
3	54	50
4	126	118
5	89	89
6	160	151
7	37	20
8	265	273
9	42	44
10	42	36
11	104	103
12	197	199
13	272	274
14	51	48
15	142	144
16	39	32
17	36	34
18	83	88
19	78	80
20	170	179
21	179	175
22	60	63
23	95	96
24	31*	4
25	67	70
26	106	104
27	36	12
28	30*	36
29	39	34
30	29*	10
31	28*	24
32	28*	9
33	38	35
34	26*	44
35	25*	26
36	27*	19
37	39	21
H= 5, K= 4		
0	108	109
1	105	120
2	41	46
3	60	64
4	90	88
5	147	137
6	86	85
7	152	187
8	119	112
9	50	66
10	138	136
11	90	95
12	73	80
13	96	95
14	101	98
15	115	124
16	100	105
17	79	75
18	128	128
19	188	190
20	78	79
21	40	42
22	74	64
23	130	132
24	58	58
25	101	104
26	50	36
27	28*	7
28	86	82
29	43	31
30	80	76
31	25*	28
32	39	35
33	23*	23
H= 6, K= 4		
0	30*	27
1	49	48
2	85	90
3	30*	30
4	41	31
5	145	153
6	72	63
7	120	116
8	57	55
9	57	43
10	83	90
11	53	44
12	53	58
13	76	67
14	83	73
15	41	22
16	57	55
17	31*	38
18	55	56
19	61	58
20	62	70
21	36	47
22	26*	20
23	68	62
24	57	63
25	59	44
26	24*	12
27	42	50
H= 7, K= 4		
0	66	61
1	70	61
2	43	34
3	81	86
4	27*	7
5	49	48
6	75	73
7	41	46
8	93	86
9	31	22
10	34	13
11	38	28
12	25*	27
13	38	40
14	54	50
15	42	28
16	24*	39
17	23*	18
H= 5, K= 5		
0	232	240
1	265	266
2	45	42
3	39	2
4	118	115
5	157	164
6	41	49
7	45	49
8	118	120
9	30*	5
10	80	86
11	38	12
12	151	156
13	97	95
14	117	118
15	29*	26
16	63	66
17	52	38
18	131	134
19	47	41
20	28*	8
21	30*	10
22	27*	1
23	53	52
24	37	31
25	73	76
26	29	23
27	26*	21
28	25*	19
H= 6, K= 5		
0	97	97
1	33	9
2	97	93
3	52	46
4	28*	22
5	65	60
6	125	120
7	58	52
8	65	58
9	44	37
10	57	58
11	38	43
12	27*	15
13	43	45
14	47	41
15	58	50
16	71	62
17	55	36
18	56	61
19	36	35
20	31	5
21	23*	2
H= 7, K= 5		
0	36	36
1	53	35
2	68	67
3	84	74
H= 6, K= 6		
0	24*	4
1	32	35
2	40	32
3	40	44
4	24*	8
5	32	44
6	41	46
7	23*	39
8	33	28

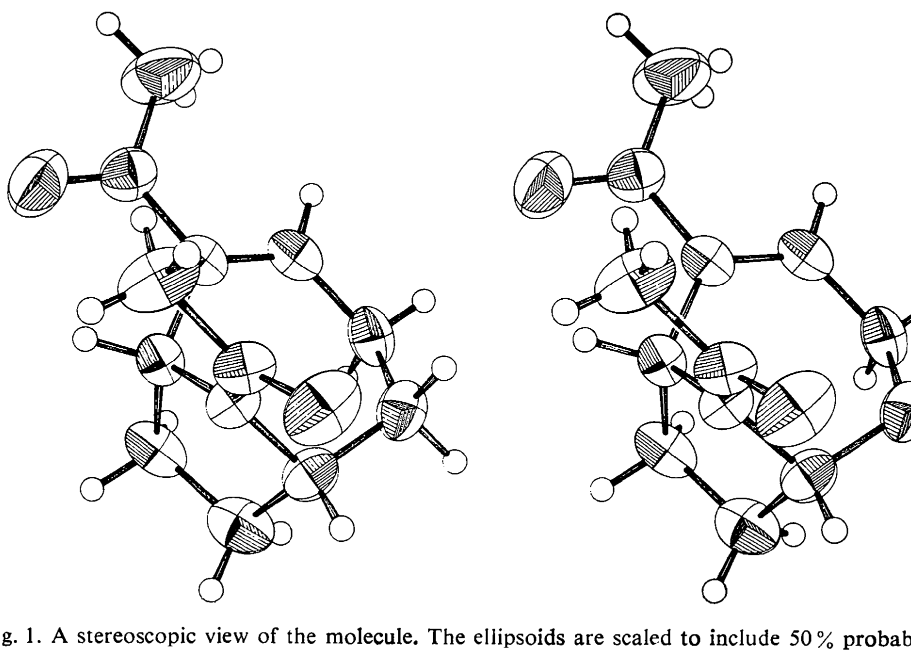
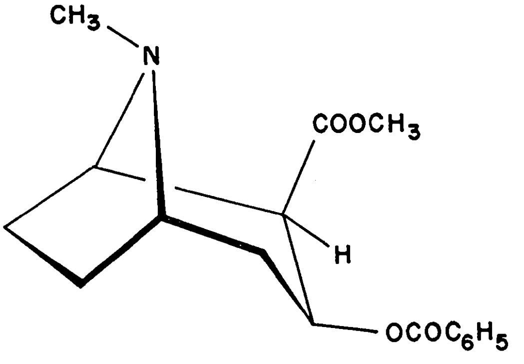


Fig. 1. A stereoscopic view of the molecule. The ellipsoids are scaled to include 50% probability.



(I)

Thermal motion

The anisotropic thermal parameters were used in an analysis of rigid-body motion with the procedure described by Schomaker & Trueblood (1968). Various rigid-body models were used, comprising different combinations of atoms. The best fit between the observed U_{ij}'s and those calculated from the translation and libration tensors was obtained for the 7-atom model C(1)···C(6), N(9). For this calculation the r.m.s. ΔU_{ij} was 0·0023 Å^2, roughly the same as the e.s.d.'s of the observed U_{ij}'s (see Table 1). Some of the results obtained from this calculation are listed in Table 4. Maximum libration occurs about an axis nearly parallel with the C(4)–C(5) bond. Libration corrections have been calculated for the bond lengths and angles not involving hydrogen atoms; those for the bond angles were in all cases less than the corresponding e.s.d.'s and were therefore omitted. Uncorrected bond lengths and angles with their e.s.d.'s are given in Table 5, while the corrected bond lengths, on which further discussion is based, are shown in Fig. 2. The C(10)–C(11), C(10)–O(12), C(13)–C(14) and C(13)–O(15) bond lengths have been corrected for 'riding motion' using the procedure of Busing & Levy (1964). It appears that the corrections to the C(10)–C(11) and C(10)–O(12) bond lengths may be overestimated. The average C–H bond length is 0·94 Å (e.s.d. 0·04 Å) and the average of the C–C–H angles [excluding those at C(3)] is 108·9° (e.s.d. about 2°).

Table 4. *Rigid-body vibrational tensors*

The **L** (libration) tensor is referred to the crystal axes *a*, *b*, *c*, while the reduced **T** (translation) and reduced **S** (screw) tensors, obtained after **S** was symmetrized, are referred to the directions of the principal axes of **L**.

L and direction cosines	4·86°	−0·766	0·260	−0·588
	4·01	−0·638	−0·423	0·644
	2·13	−0·081	0·868	0·490
T and direction cosines	0·209 Å	0·525	−0·833	0·175
	0·192	0·312	−0·003	−0·950
	0·161	0·792	0·554	0·258
S and direction cosines	0·004	0·725	−0·400	−0·561
	0·000	0·499	0·866	0·027
	−0·004	0·475	−0·299	0·828
E.s.d. of U_{ij}			0·0017 Å^2	
$[\langle\{U_{ij}(\text{meas})-U_{ij}(\text{calc})\}^2\rangle]^{1/2}$			0·0023 Å^2	

Table 5. *Bond lengths and angles*

(*a*) Uncorrected bond lengths (Å) and their e.s.d.'s.

C(1)—C(2)	1·520 (4)
C(1)—C(8)	1·556 (4)
C(1)—N(9)	1·462 (4)
C(2)—C(3)	1·343 (4)
C(2)—C(10)	1·469 (4)
C(3)—C(4)	1·491 (4)
C(4)—C(5)	1·532 (5)
C(5)—C(6)	1·525 (4)
C(6)—C(7)	1·518 (5)
C(6)—N(9)	1·463 (4)
C(7)—C(8)	1·514 (5)
N(9)—C(13)	1·339 (3)
C(10)-C(11)	1·503 (5)
C(10)-O(12)	1·223 (4)
C(13)-C(14)	1·498 (5)
C(13)-O(15)	1·223 (4)

(*b*) Bond angles (°) and their e.s.d.'s.

C(2)—C(1)—C(8)	113·6 (2)
C(2)—C(1)—N(9)	111·5 (2)
C(8)—C(1)—N(9)	102·7 (2)
C(1)—C(2)—C(3)	122·1 (3)
C(1)—C(2)—C(10)	116·0 (2)
C(3)—C(2)—C(10)	121·9 (3)
C(2)—C(3)—C(4)	128·3 (3)
C(3)—C(4)—C(5)	119·5 (3)
C(4)—C(5)—C(6)	116·4 (3)
C(5)—C(6)—C(7)	115·2 (3)
C(5)—C(6)—N(9)	110·7 (2)
C(7)—C(6)—N(9)	102·2 (2)
C(6)—C(7)—C(8)	106·3 (3)
C(1)—C(8)—C(7)	106·2 (3)
C(1)—N(9)—C(6)	109·5 (2)
C(1)—N(9)—C(13)	126·8 (2)
C(6)—N(9)—C(13)	122·8 (2)
C(2)—C(10)-C(11)	121·3 (3)
C(2)—C(10)-O(12)	120·0 (3)
C(11)-C(10)-O(12)	118·8 (3)
N(9)—C(13)-C(14)	117·8 (3)
N(9)—C(13)-O(15)	121·5 (3)
C(14)-C(13)-O(15)	120·7 (3)

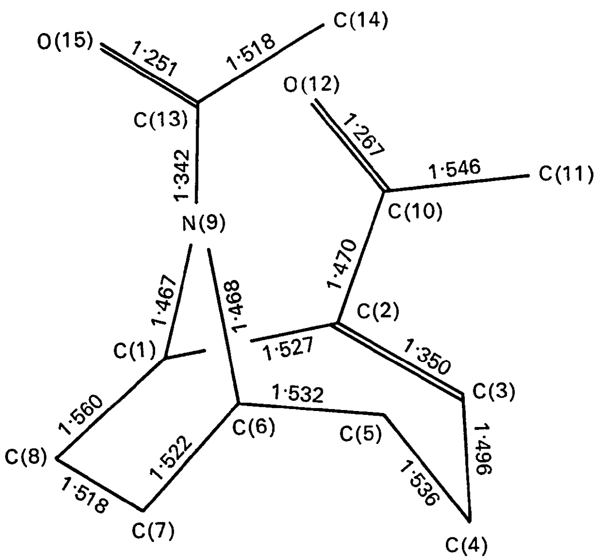


Fig. 2. Bond lengths (Å) including libration corrections.

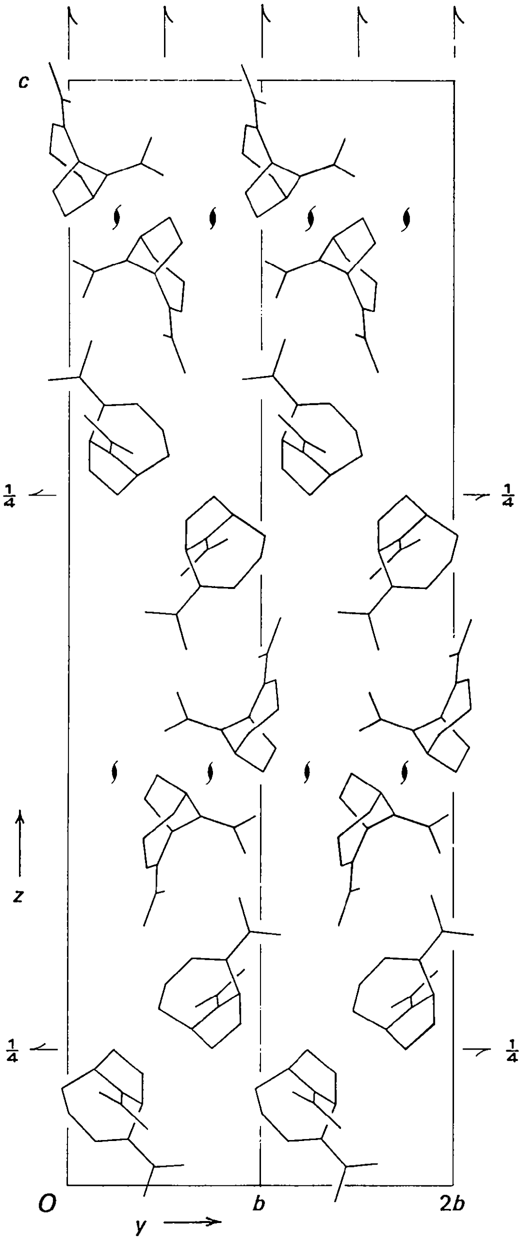


Fig. 3. Projection of the structure down the *a* axis.

Bond lengths and angles

Most of the bond lengths and angles found in this structure (DAN) are quite normal, but a few require comment. C(1)–C(8) (1·560 Å) is significantly ($\sim 6\sigma$) longer than C(6)–C(7) (1·522 Å), whereas one might have expected them to be equal. A comparable difference has been found in the structure of L-cocaine hydrochloride (Gabe & Barnes, 1963) where the corresponding bond lengths are 1·562 and 1·525 Å. Whether this effect is due to the electron-withdrawing groups (acetyl in the present case, carbomethoxy in cocaine) at C(2) is not clear. The equivalent bond lengths in the pyrrolidine ring of scopolamine *N*-oxide hydrobromide (Huber, Fodor & Mandava, 1971) do not differ significantly. That structure, like cocaine, also has a tropane nucleus, but does not have a side chain on the carbon atom adjacent to the bridgehead. The stretching of the C(1)–C(8) bond is probably not because of H(11)···H(82) repulsion in the present case, as the H(61)···H(72) and H(72)···H(82) distances, 2·20 and 2·11 Å respectively, are both less than the H(11)···H(82) distance (2·32 Å).

In the present structure, bond length C(1)–C(2) (1·527 Å) is significantly longer than C(3)–C(4) (1·496 Å), probably because the C(1)–C(2) bond is between more highly substituted atoms. The N(9)–C(13) bond (1·342 Å) is considerably shorter than the 1·393 Å quoted by Birnbaum (1970) as representing a C_{sp^2}–N single-bond length, but it is much closer to the value 1·333 Å quoted by Sutton (1965) as a typical value for the C–N bond length in a N–C=O group. This suggests that considerable double-bond character, which the N(9)–C(13) bond clearly shows, is usually found in such cases. The partial double bond character of the N(9)–C(13) bond is also suggested by the near-coplanarity of the C(13), C(14), O(15) acetyl group with C(1), C(6), N(9).

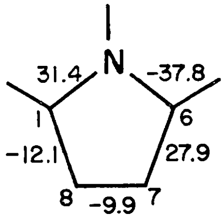
The substitution of the piperidine ring in cocaine by the azacycloheptene ring in DAN increases the distance across the ring at the bridge only slightly, from 2·35 Å in L-cocaine hydrochloride (Gabe & Barnes, 1963) to 2·39 Å [C(1)···C(6)] here. This slight increase is reflected in small increases, averaging 2·9°, of the C(1)–C(8)–C(7), C(6)–C(7)–C(8), and C(1)–N(9)–C(6) angles in DAN from values of the corresponding angles in the cocaine structure.

There appears to be considerable attraction between H(11) and O(12) in the present structure. The H(11)···O(12) distance is only 2·18 Å, significantly less than a normal H···O van der Waals contact (2·6 Å). Although the C(1)–C(2)–C(10) angle (116·0°) is comparable with the corresponding C–C–C angle in isobutylene [115·3° (Scharpen & Laurie, 1963)], it is significantly less than the corresponding two angles (118·3 and 118·4°) in all-*trans*-retinal$_1$ (Hamanaka, Mitsui, Ashida & Kakudo, 1972). Also, the combined electron-withdrawing effects of the *N*-acetyl group and the conjugated double bond and carbonyl group mean that the hydrogen at C(1) is relatively acidic in nature. These factors together suggest that the interaction between H(11) and O(12) is attraction rather than repulsion. H(11)–C(1)–C(2) and H(11)–C(1)–C(8) angles, 103 and 112° respectively, are at least consistent with this hypothesis, although they cannot be considered very significant proof. The C(1)–H(11)···O(12) angle is 115°; a similar value (112·9°) has been observed in the structure of hydroxyproline determined by neutron diffraction (Koetzle, Lehmann & Hamilton, 1972; Koetzle, 1971) for the N–H···O angle. In that structure the H···O distance is 2·08 Å, and an intramolecular hydrogen bond is quite definitely present. In the L-cocaine hydrochloride structure (Gabe & Barnes, 1963) there is also a relatively short intramolecular H···O distance (2·41 Å) between the hydrogen atom attached to C(1) and the ether oxygen of the adjacent carbomethoxy group. It may be that this H···O interaction in the two structures is also a factor in the difference of the two C–C bond lengths in the pyrrolidine ring discussed earlier.

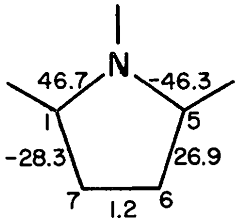
The opening of the C(2)–C(3)–C(4) angle in DAN (to 128·3°) serves to increase the H(42)···H(71) distance to a normal van der Waals contact value, 2·37 Å. The H(42)···H(81) distance is 2·53 Å. O(15) in the *N*-acetyl group does not seem to be attracted towards H(61). The H(61)···O(15) distance is 2·52 Å, the C(6)–N(9)–C(13) angle is 122·8°, and the N(9)–C(6)–H(61) angle is 111°.

Conformation

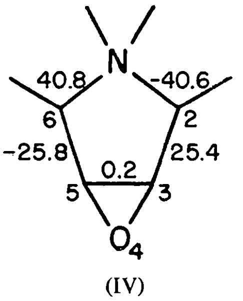
The pyrrolidine ring is approximately envelope-shaped, with C(1), C(6), C(7), C(8) coplanar within 0·06 Å and N(9) displaced 0·49 Å from the mean plane. The azacycloheptene ring has a distorted chair form. C(1), C(2), C(3), C(4) are significantly non-planar ($\chi^2 = 63{\cdot}1$) and the dihedral angle between that mean plane and the plane defined by C(5), C(6), N(9) is 20·0°. Torsional angles within the pyrrolidine ring show more asymmetry in the DAN structure (II) than in cocaine hydrochloride (III) or scopolamine *N*-oxide hydrobromide (IV). Torsional angles for the azacycloheptene ring in DAN are also shown (V). The sign convention is that of Klyne & Prelog (1960).



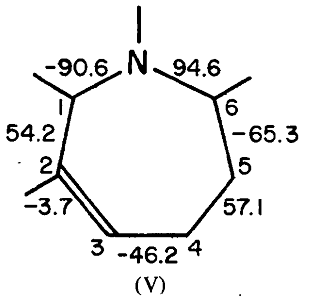
(II)



(III)



(IV)



(V)

As expected in a conjugated double-bond system, the C(10), C(11), O(12) acetyl group is nearly coplanar with C(1), C(2), C(3). The dihedral angle between those two planes is 3·9°, while the other acetyl group is bent out of the C(1), C(6), N(9) plane by 6·9°, toward C(3).

Packing arrangement

The molecular packing is shown in Fig. 3. None of the intermolecular contacts is shorter than the corresponding van der Waals distance.

The computer programs of Ahmed, Hall, Huber & Pippy (1966), Johnson (1965) and Schomaker & Trueblood (1968) were used for this analysis. The author wishes to thank Dr O. E. Edwards for suggesting the problem, supplying the crystals, and for many valuable discussions. She would also like to thank Dr T. F. Koetzle for supplying information on the hydroxyproline structure prior to publication, and Dr M. Przybylska for her continued encouragement.

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