

The Crystal Structure of a Monoclinic Modification and the Refinement of a Triclinic Modification of Vitamin A Acid (Retinoic Acid), $C_{20}H_{28}O_2$

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The monoclinic modification of vitamin A acid investigated is in space group $P2_1/n$ with $Z=4$, $a=8.078$, $b=34.103$, $c=7.387$ Å, $\beta=118.8^\circ$. Intensities were collected on an automatic Nonius three circle diffractometer and the structure was solved by means of the symbolic addition method. Least-squares refinement reduced R to 5.7%. The molecules of this modification have an approximately planar *trans* conformation about the single bond joining the ring and side chain. They form dimers connected by hydrogen bonds, 2.67 Å in length. The previously determined structure of a triclinic modification of vitamin A acid, which has a non-planar *cis*-like conformation about the single bond joining ring and side chain, has been further refined to an R value of 6.4%.

Introduction

Vitamin A acid crystallizes in a number of modifications, of which a triclinic one was the subject of a crystal structure determination about ten years ago (Stam & MacGillavry, 1963). The molecules in the crystals of this modification have a non-planar *cis*-like conformation about the single bond C(6)–C(7) joining the cyclohexene ring and the approximately planar side chain, the angle between the ring double bond and the side chain being 35° . A similar conformation has been observed in crystals of a number of related compounds. When this investigation was started there was only one exception, namely *trans*- β -ionylidenecrotonic acid (Eichhorn & MacGillavry, 1959), which has a nearly planar *s-trans* conformation about this bond.

The most common modification of vitamin A acid is a monoclinic one. This is a metastable form which transforms irreversibly into the triclinic one at about 80°C . In order to ascertain whether the monoclinic modification is simply another packing arrangement of molecules in the same conformation as in the triclinic form, a crystal structure determination was undertaken. It turned out that the conformation about C(6)–C(7) in the monoclinic form is approximately planar *trans*.

At the same time a further refinement of the triclinic modification was carried out with new intensity data of the same accuracy as those of the monoclinic form.

In the following, the monoclinic modification is represented by 'VAAM' and the triclinic by 'VAAT'.

Experimental

VAAM

The crystals are yellow dichroic platelets parallel to (010) and elongated along [001]. The following cell constants were obtained by means of a least-squares

procedure from zero-layer Weissenberg photographs about [010] and [001], calibrated with Al powder lines:

$$\begin{aligned} a &= 8.078 (1) \text{ \AA} \\ b &= 34.103 (2) & \beta &= 118.76 (1)^\circ \\ c &= 7.387 (1) \\ V &= 1,784 \text{ \AA}^3. \end{aligned}$$

The space group is $P2_1/n$ and there are four molecules per unit cell. Intensities were collected by means of an automatic Nonius three-circle diffractometer, using the θ - 2θ scan technique with Ni-filtered Cu $K\alpha$ radiation. The instrument was equipped with a scintillation counter and a discriminator. Reflexions for which the net count was less than twice the statistical standard deviation were considered unobserved. In all, 2787 independent reflexions were obtained. The crystal dimensions were about 0.5 mm. No absorption correction was applied ($\mu=6 \text{ cm}^{-1}$).

VAAT

The crystals were obtained in the manner previously described (Stam & MacGillavry, 1963). The cell constants were redetermined using the method indicated above, resulting in:

$$\begin{aligned} a &= 8.032 (5) \text{ \AA} & \alpha &= 50.97 (7)^\circ \\ b &= 24.50 (3) & \beta &= 71.66 (6) \\ c &= 5.99 (1) & \gamma &= 95.17 (8) \\ V &= 930 \text{ \AA}^3. \end{aligned}$$

Intensities were measured in the same way as for the monoclinic modification. 2490 independent reflexions were collected. The crystal dimensions were $0.2 \times 0.3 \times 0.4$ mm. No absorption correction was applied.

Structure determination and refinement

VAAM

The structure has been determined by means of a set of programs (Schenk, 1969) based on the symbolic

Table 1. Final positional and thermal parameters for VAAM, with their estimated standard deviations

(a) Fractional coordinates $\times 10^4$; thermal parameters in $\text{\AA}^2 \times 10^3$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	2 <i>U</i> ₁₂	2 <i>U</i> ₂₃	2 <i>U</i> ₁₃
C(1)	7420 3	1955 1	14148 3	46 1	53 1	39 1	-10 2	-17 2	49 2
C(2)	7199 4	2276 1	15506 4	69 2	66 1	56 1	-25 2	-44 2	70 2
C(3)	6417 4	2115 1	16833 4	79 2	82 2	50 1	-12 3	-39 2	80 3
C(4)	4449 4	1960 1	15475 4	65 1	73 2	56 1	5 2	-23 2	86 2
C(5)	4258 3	1727 1	13658 3	47 1	60 1	47 1	2 2	-11 2	60 2
C(6)	5612 3	1709 1	13074 3	41 1	47 1	37 1	4 2	-6 2	44 2
C(7)	5269 3	1454 1	11335 3	44 1	55 1	42 1	-8 2	-18 2	49 2
C(8)	6427 3	1319 1	10654 3	44 1	53 1	39 1	-6 2	-20 2	46 2
C(9)	5864 3	1062 1	8881 3	48 1	48 1	40 1	-6 2	-16 2	47 2
C(10)	7144 3	964 1	8277 3	48 1	52 1	42 1	-4 2	-19 2	48 2
C(11)	6827 3	719 1	6502 3	53 1	49 1	43 1	-5 2	-20 2	53 2
C(12)	8156 3	685 1	5947 3	49 1	52 1	43 1	-4 2	-26 2	47 2
C(13)	7925 3	455 1	4137 3	47 1	44 1	39 1	4 2	-14 2	42 2
C(14)	9391 3	451 1	3762 3	47 1	63 1	46 1	-7 2	-38 2	49 2
C(15)	9561 3	252 1	2097 3	46 1	57 1	44 1	1 2	-25 2	49 2
C(16)	7764 4	2185 1	12566 4	70 2	62 1	57 1	-24 2	-3 2	77 2
C(17)	9138 3	1698 1	15466 4	46 1	75 2	47 1	-0 2	-2 2	40 2
C(18)	2380 4	1514 1	12543 5	56 1	120 2	82 2	-44 3	-61 3	97 3
C(19)	3847 3	925 1	7744 4	54 1	75 2	58 1	-34 2	-56 2	62 2
C(20)	6075 4	258 1	2802 4	60 1	85 2	64 2	-41 3	-76 3	75 3
O(1)	11144 2	344 1	2087 3	59 1	88 1	70 1	-34 2	-74 2	88 2
O(2)	8417 2	23 1	847 2	55 1	70 1	53 1	-16 2	-51 2	64 1

addition method of Karle & Karle (1966). The best solution, comprising 207 signed reflexions, gave an *E* Fourier map in which all non-hydrogen atoms could be located. After six cycles of isotropic and one cycle of anisotropic least-squares refinement, using a Cruickshank weighting scheme (Cruickshank, 1961) and a 30% random selection of the structure factors, *R* had dropped from 44.2 to 11.8%. From a subsequent ΔF Fourier synthesis all hydrogen atoms could be located with heights varying from 0.3 to 0.6 e. \AA^{-3} . Refinement was resumed with the hydrogen atoms included with isotropic temperature parameters. The final *R* value for the 2787 observed reflexions was 5.7%. From the last cycles 14 strong reflexions, which were apparently affected by extinction, and 47 very weak reflexions, which were given an unduly high least-squares weight by the Cruickshank scheme, were allotted zero weight. The final parameters are listed in Table 1.*

* A list of structure factors can be obtained from this laboratory.

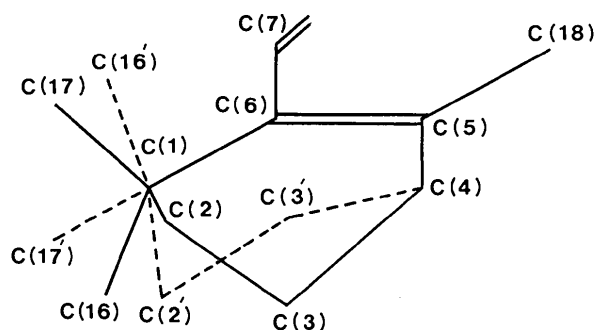


Fig. 1. Two alternative conformations of the cyclohexene ring.

Table 1 (cont.)

(b) Fractional coordinates $\times 10^3$; thermal parameters in $\text{\AA}^2 \times 10$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(1)	852 4	241 1	1644 5	42 7
H(2)	611 4	251 1	1447 4	31 6
H(3)	631 4	236 1	1773 5	43 7
H(4)	733 5	186 1	1779 5	53 8
H(5)	402 4	178 1	1630 5	42 7
H(6)	348 4	220 1	1496 5	47 8
H(7)	394 4	137 1	1057 4	35 6
H(8)	774 3	139 1	1132 3	15 4
H(9)	843 4	105 1	913 4	23 6
H(10)	556 4	61 1	568 4	28 5
H(11)	945 4	81 1	684 4	31 6
H(12)	1050 4	62 1	468 5	36 6
H(13)	654 4	235 1	1151 5	52 7
H(14)	820 5	201 1	1182 5	42 8
H(15)	880 4	240 1	1331 5	42 7
H(16)	932 3	149 1	1470 4	23 5
H(17)	1029 4	183 1	1606 5	44 7
H(18)	902 4	158 1	1657 5	45 7
H(19)	165 6	160 1	1099 7	99 12
H(20)	169 6	154 1	1324 6	81 10
H(21)	261 6	118 1	1257 7	78 12
H(22)	345 5	82 1	658 5	46 9
H(23)	363 5	77 1	874 5	56 8
H(24)	298 6	120 1	729 7	102 12
H(25)	614 5	9 1	178 5	59 9
H(26)	500 6	46 1	233 6	89 11
H(27)	581 6	4 1	356 6	62 10
H(28)	1127 5	18 1	98 6	59 9

VAAT

Starting with the previously obtained parameters (Stam & MacGillavry, 1963) three cycles of anisotropic least-squares refinement of the non-hydrogen atoms with a 30% random selection of the structure factors and weighting according to Cruickshank (1961) yielded *R* = 10.5%. In a difference Fourier synthesis all hydrogen atoms were represented by maxima of about 0.3 e. \AA^{-3} .

Table 2. Final positional and thermal parameters for VAAT, with their estimated standard deviations

(a) Fractional coordinates $\times 10^4$; thermal parameters in $\text{\AA}^2 \times 10^3$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	2 <i>U</i> ₁₂	2 <i>U</i> ₂₃	2 <i>U</i> ₁₃
C(1)	5339 4	1549 1	1093 7	59 1	66 2	66 2	63 2	-104 3	-54 2
C(2)	4734 6	991 2	1280 12	89 2	90 3	137 4	77 4	-187 6	-50 5
C(3)	3094 7	419 2	4222 14	105 3	92 3	187 5	82 5	-227 7	-99 6
C(4)	1377 5	568 2	4945 10	80 2	68 2	107 3	47 3	-135 4	-67 4
C(5)	1796 4	1182 1	4302 7	60 1	58 1	68 2	54 2	-97 3	-61 3
C(6)	3569 4	1626 1	2589 6	60 1	52 1	54 1	56 2	-81 2	-56 2
C(7)	3972 4	2228 1	1932 7	59 1	57 1	67 2	48 2	-96 3	-49 2
C(8)	3152 4	2291 1	4003 7	69 2	53 1	64 2	50 2	-91 3	-51 3
C(9)	3559 4	2901 1	3209 7	68 2	53 1	63 2	42 2	-88 3	-44 3
C(10)	2463 4	2897 1	5464 7	79 2	56 1	66 2	51 3	-95 3	-48 3
C(11)	2606 5	3456 1	5055 7	83 2	55 1	66 2	46 3	-94 3	-42 3
C(12)	1465 5	3435 1	7314 7	82 2	52 1	66 2	35 3	-89 3	-28 3
C(13)	1567 4	3991 1	9690 7	79 2	50 1	61 2	40 3	-82 3	-29 3
C(14)	336 5	3882 1	9523 8	82 2	53 2	69 2	25 3	-92 3	-6 3
C(15)	223 5	4372 2	9679 8	88 2	62 2	71 2	35 3	-103 3	-10 3
C(16)	6606 5	2164 2	-2544 9	80 2	85 2	77 2	63 4	-111 4	-18 3
C(17)	6456 6	1411 3	2938 12	99 3	188 5	133 4	197 7	-265 8	-153 6
C(18)	9 4	1245 2	5684 9	62 2	85 2	103 2	66 3	-143 4	-70 3
C(19)	5173 5	3509 2	-105 9	88 2	62 2	78 2	25 3	-105 3	-17 3
C(20)	3055 6	4649 2	3845 9	130 3	56 2	73 2	22 4	-94 4	17 4
O(1)	-1279 4	4135 1	12319 6	109 2	69 1	86 2	15 2	-123 3	31 3
O(2)	1364 4	4933 1	7687 6	112 2	67 1	95 2	2 3	-132 3	39 3

Table 2 (cont.)

(b) Fractional coordinates $\times 10^3$; thermal parameters in $\text{\AA}^2 \times 10$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(1)	585 5	89 2	83 9	5 1
H(2)	387 12	111 4	-36 19	17 3
H(3)	274 6	3 2	435 10	7 1
H(4)	372 7	30 2	606 11	6 1
H(5)	36 5	18 2	743 9	5 1
H(6)	67 6	62 2	369 9	6 1
H(7)	495 5	259 2	-22 8	4 1
H(8)	225 5	189 2	631 8	5 1
H(9)	146 5	246 2	770 8	5 1
H(10)	356 5	386 2	303 8	4 1
H(11)	43 4	303 2	931 8	4 1
H(12)	-67 6	345 2	1145 10	6 1
H(13)	592 6	231 2	-393 11	8 1
H(14)	706 8	250 3	-281 13	11 2
H(15)	780 5	208 2	-344 9	5 1
H(16)	699 7	193 2	172 11	7 1
H(17)	764 6	140 2	188 11	7 1
H(18)	575 10	105 3	532 17	14 2
H(19)	19 4	172 1	451 7	3 1
H(20)	-106 6	102 2	567 10	7 1
H(21)	-30 6	106 2	789 10	7 1
H(22)	497 9	382 3	-68 15	13 2
H(23)	631 8	344 3	-3 13	11 2
H(24)	507 11	366 4	-217 18	15 3
H(25)	283 7	499 2	349 12	9 1
H(26)	432 8	464 3	330 14	11 2
H(27)	304 7	475 2	204 12	10 1
H(28)	-141 6	448 2	1219 11	8 1

Discussion

Disorder

Refinement was continued with the hydrogen atoms included with isotropic temperature parameters until *R* had dropped to 6.4% for the 2490 observed reflexions. Three reflexions affected by extinction and 122 very weak ones, which were given an unduly high weight by the

Cruickshank scheme, were allotted zero weight in the final least-squares cycles. The final parameters are listed in Table 2.*

* A list of structure factors can be obtained from this laboratory.

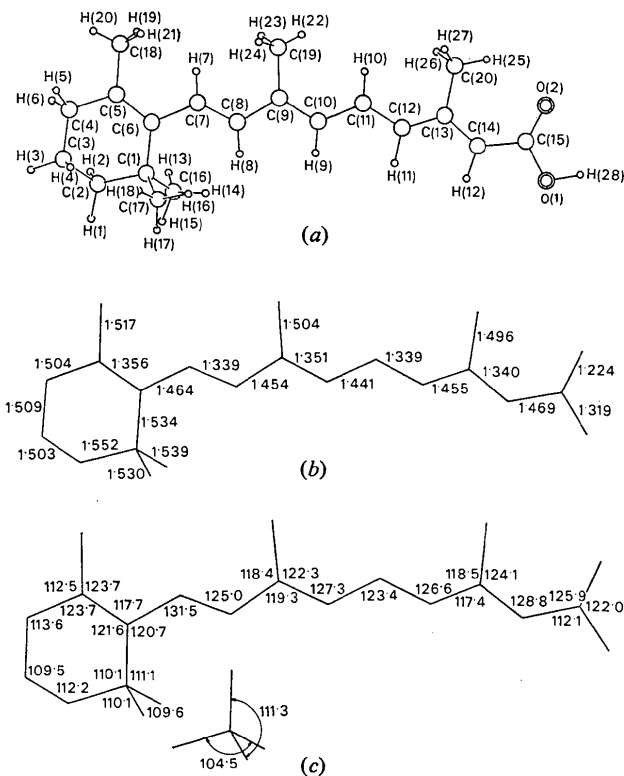


Fig. 2. (a) Numbering of the atoms in VAAM. (b) Bond distances in VAAM. (c) Bond angles in VAAM.

There is one large discrepancy between the structures of VAAM and VAAT, namely the bond length C(2)–C(3) which is 1.503 Å in VAAM against 1.43 Å in VAAT. Curiously enough, the earlier investigation of VAAT (Stam & MacGillavry, 1963) yielded a similar small value (1.45 Å) for this bond. We can give no straightforward explanation for the anomaly but it is probably connected with conformational disorder of the cyclohexene ring.

In crystal structures of a number of related compounds [15,15'-dehydrocanthaxanthin (Bart & MacGillavry, 1968*a*), canthaxanthin (Bart & MacGillavry, 1968*b*), retrovitamin A acid (Schenk, 1969), *trans*- β -ionylidene crotonic acid (Koch, 1972)] there were indications of disorder involving molecules with an alternative ring conformation obtained by reflexion in the plane of the ring double bond.

In the case of vitamin A acid, the cyclohexene ring has a planar part comprising C(4), C(5), C(6) and C(1), with C(2) and C(3) on opposite sites at 0.3 to 0.4 Å from this plane. An alternative conformation has both C(2) and C(3) switched to the other side of the plane with C(16) and C(17) also assuming new positions (Fig. 1). It is possible that a number of molecules have been included with the wrong ring conformation relative to the conformation about C(6)–C(7), thus giving rise to disorder.

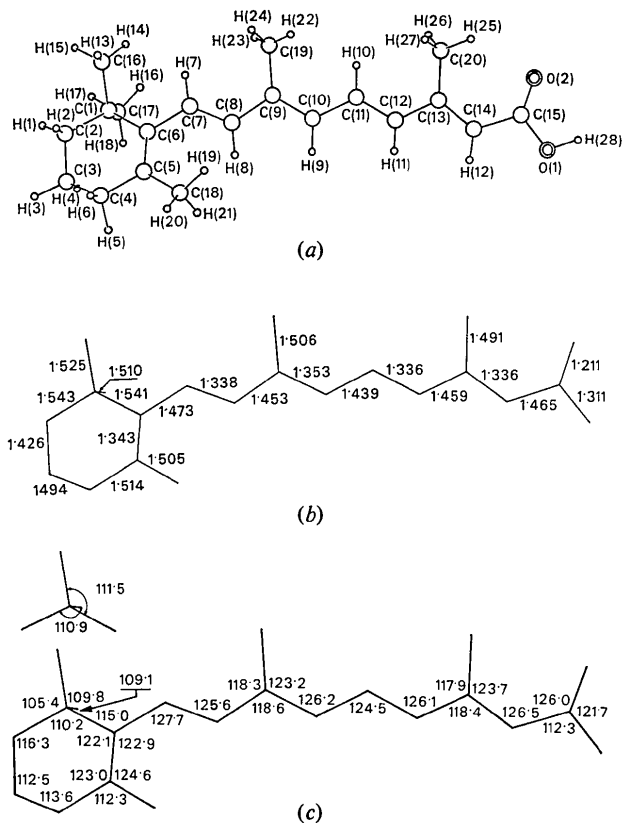


Fig. 3. (a) Numbering of the atoms in VAAT. (b) Bond distances in VAAT. (c) Bond angles in VAAT.

Indications for disorder in VAAT, apart from the anomalous C(2)–C(3) bond length, are the very large thermal parameters for C(2), C(3), C(16) and C(17) and, in the final difference Fourier map, considerable noise in the neighbourhood of the ring (up to 0.35 e.Å⁻³).

The cyclohexene ring in VAAM does not show any of these features and is presumably free of disorder.

From a comparison of the bond distances and angles in both conformations it appears that the atomic coordinates mainly affected by the disorder in VAAT are those of C(2) and C(3).

Bond distances

The bond distances for both modifications are given in Figs. 2(b) and 3(b) and Table 3. Except for some of the ring distances, which for reasons already discussed are less reliable in VAAT, there are no significant differences between the two forms.

Table 3. Bond distances and angles

Bond distances VAAM		VAAT
C(1)–C(2)	1.552 (4) Å	1.543 (9) Å
C(1)–C(6)	1.534 (3)	1.541 (5)
C(1)–C(16)	1.539 (4)	1.525 (4)
C(1)–C(17)	1.530 (3)	1.510 (8)
C(2)–C(3)	1.503 (5)	1.426 (5)
C(3)–C(4)	1.509 (4)	1.494 (7)
C(4)–C(5)	1.504 (4)	1.514 (7)
C(5)–C(6)	1.356 (4)	1.343 (4)
C(5)–C(18)	1.517 (4)	1.505 (6)
C(6)–C(7)	1.464 (3)	1.473 (6)
C(7)–C(8)	1.339 (4)	1.338 (6)
C(8)–C(9)	1.454 (3)	1.453 (6)
C(9)–C(10)	1.351 (4)	1.353 (6)
C(9)–C(19)	1.504 (3)	1.506 (3)
C(10)–C(11)	1.441 (3)	1.439 (7)
C(11)–C(12)	1.339 (4)	1.336 (6)
C(12)–C(13)	1.454 (3)	1.459 (6)
C(13)–C(14)	1.340 (4)	1.336 (6)
C(13)–C(20)	1.496 (3)	1.491 (3)
C(14)–C(15)	1.469 (4)	1.465 (7)
C(15)–O(1)	1.319 (3)	1.311 (5)
C(15)–O(2)	1.224 (3)	1.211 (4)
O(1)–O(2)	2.669 (3)	2.663 (6)
Bond angles		VAAM
C(2)–C(1)–C(6)	110.1 (2)°	110.2 (3)°
C(2)–C(1)–C(16)	104.5 (2)	105.4 (4)
C(2)–C(1)–C(17)	110.1 (2)	110.9 (4)
C(6)–C(1)–C(16)	111.1 (2)	111.5 (3)
C(6)–C(1)–C(17)	111.3 (2)	109.1 (4)
C(16)–C(1)–C(17)	109.6 (2)	109.8 (3)
C(1)–C(2)–C(3)	112.2 (2)	116.3 (6)
C(2)–C(3)–C(4)	109.5 (2)	112.5 (4)
C(3)–C(4)–C(5)	113.6 (3)	113.6 (4)
C(4)–C(5)–C(6)	123.7 (2)	123.0 (3)
C(4)–C(5)–C(18)	112.5 (3)	112.3 (3)
C(6)–C(5)–C(18)	123.7 (2)	124.6 (4)
C(1)–C(6)–C(5)	121.6 (2)	122.1 (4)
C(1)–C(6)–C(7)	120.7 (2)	115.0 (2)
C(5)–C(6)–C(7)	117.7 (2)	122.9 (3)
C(6)–C(7)–C(8)	131.5 (2)	127.7 (2)
C(7)–C(8)–C(9)	125.0 (2)	125.6 (2)
C(8)–C(9)–C(10)	119.3 (2)	118.6 (2)
C(8)–C(9)–C(19)	118.4 (2)	118.3 (4)

Table 3 (cont.)

C(10)–C(9)–C(19)	122.3 (2)	123.2 (4)
C(9)–C(10)–C(11)	127.3 (2)	126.2 (2)
C(10)–C(11)–C(12)	123.4 (2)	124.5 (2)
C(11)–C(12)–C(13)	126.6 (2)	126.1 (2)
C(12)–C(13)–C(14)	117.4 (2)	118.4 (2)
C(12)–C(13)–C(20)	118.5 (3)	117.9 (4)
C(14)–C(13)–C(20)	124.1 (2)	123.7 (4)
C(13)–C(14)–C(15)	128.8 (2)	126.5 (2)
C(14)–C(15)–O(1)	112.1 (2)	112.3 (3)
C(14)–C(15)–O(2)	125.9 (3)	126.0 (4)
O(1)–C(15)–O(2)	122.0 (3)	121.7 (5)

C(2)–C(3) and C(3)–C(4) in VAAM (1.503 and 1.509 Å respectively) are rather short for sp^2 – sp^3 bonds. The carotenoidal compound of Braun, Hornstra & Leenhouts (1971) shows a similar behaviour with distances of 1.491 and 1.513 Å respectively.

The remaining bonds show more or less their expected lengths. For instance, C(5)–C(18), C(9)–C(19) and C(13)–C(20) are short (1.517, 1.504, 1.496 Å in VAAM and 1.505, 1.506, 1.49 Å in VAAT) whilst C(1)–C(16) and C(1)–C(17) are long (1.539 and 1.530 Å in VAAM, unreliable in VAAT) in agreement with the sp^2 – sp^3 character of the first three and the sp^3 – sp^3 character of the last two bonds.

Bond angles

Apart from the ring angles involving C(2) and C(3), which are the most seriously affected by the disorder in VAAT, there are some large differences between the two modifications for the angles around the point of attachment of the side chain to the ring [see Figs. 2(c) and 3(c) and Table 3]. These can be understood in terms of the different steric situations for the two modifications. The steric interaction between the ring and the side chain is between the hydrogen atoms at C(7) and C(8) on the one hand and those of the methyl groups of C(16), C(17) and C(18) on the other. In the case of VAAM, considerably more strain is present resulting in the opening up of the angles C(6)–C(7)–C(8) and C(1)–C(6)–C(7).

The side chains are very much alike except for the angles C(13)–C(14)–C(15), which differ by 2.3°. The angles opposite the chain methyl groups (117.4–119.3°) are decreased considerably relative to the value of about 125° for an unhindered conjugate chain and

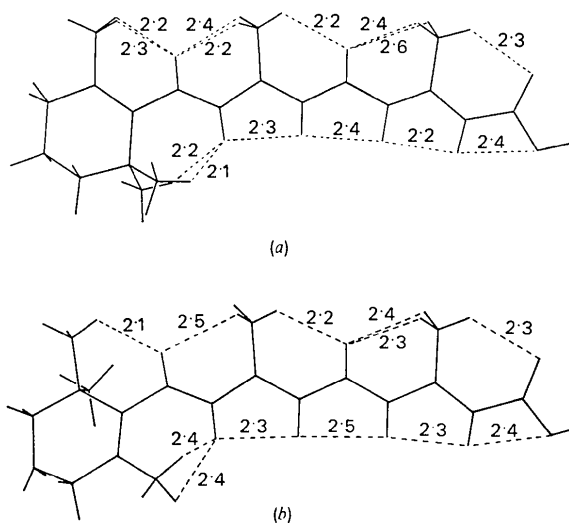


Fig. 4. Intramolecular H...H distances. (a) VAAM. (b) VAAT.

to the remaining *endo* chain angles (125.0–131.5°). This results in the typical sabre-like appearance of the molecules. The explanation for this effect, as already indicated in the earlier paper on VAAT (Stam & MacGillavry, 1963), is the steric interaction of the methyl groups of C(19) and C(20) with the side chain. Since the hydrogen atoms have now been located, the interaction can be illustrated in greater detail (see Fig. 4).

Hydrogen bonds

The molecules in both modifications form dimers across centres of symmetry by means of hydrogen bonds between the carboxylic groups. The chains of both molecules in a dimer are practically coplanar. The distances between the best planes of both chains are 0.28 and 0.12 Å for VAAM and VAAT respectively.

The hydrogen bonds have lengths of 2.669 (3) and 2.663 (6) Å for VAAM and VAAT respectively. The geometry of the COOH groups is very similar in both forms. Because of the influence of the neighbouring methyl group of C(20) the C–O lengths and the O–C–O angle do not fit in with the correlation be-

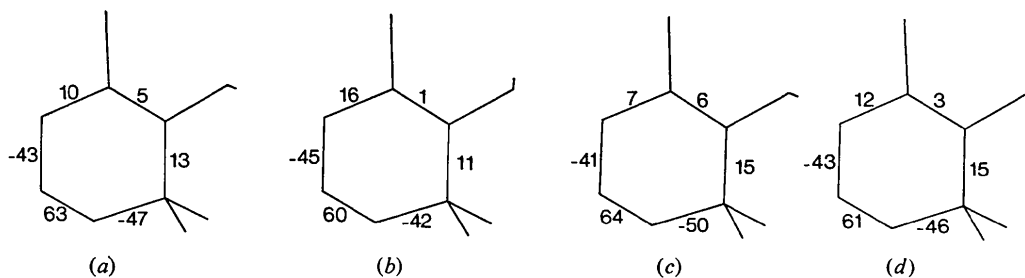


Fig. 5. Dihedral angles for the cyclohexene ring. (a) VAAM, (b) VAAT, (c) carotenoidal compound of Braun *et al.* (1971), (d) *trans*- β -ionylidene crotonic acid (Koch, 1972).

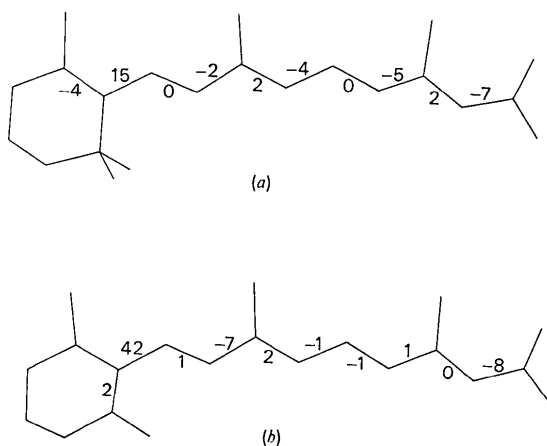


Fig. 6. Dihedral angles for the conjugated chain. (a) VAAM. (b) VAAT.

tween these quantities as noticed by Hahn (1957). The system C(14) C(15) O(1) O(2) is planar within 0.005 Å in both cases. The distances between the planes of the two hydrogen-bonded COOH groups are 0.06 and 0.04 Å in VAAM and VAAT respectively.

Conformational aspects

Cyclohexene ring. In both modifications of VAA and also in the carotenoidal compound of Braun *et al.* (1971) and in *trans*- β -ionylidene crotonic acid (Koch, 1972) the cyclohexene rings have virtually the same half-chair conformation. This is illustrated in Fig. 5, in which the dihedral angles for the bonds in the four rings have been indicated. The double bond system of C(5)–C(6) is only approximately planar (Table 4).

Conjugated chain. The conjugated chains in VAAM and in VAAT [C(5)–C(6) excluded] are not completely planar (Table 4). The deviations from planarity are perhaps most clearly demonstrated by the dihedral angles about the various bonds as indicated in Fig. 6. The separate double-bond systems are reasonably planar (see also Table 4); the deviations from planarity in the chain are mainly caused by twists about the single bonds.

Attachment of ring to chain. The main difference between VAAM and VAAT is in the way the cyclohexene ring is joined to the conjugated chain. In VAAM the angle between the plane of the ring double bond C(5)–C(6) and the mean plane of the chain is 6°, representing a nearly planar *s-trans* conformation

Table 4. Distances ($\text{Å} \times 10^3$) from the planes through various double-bond systems

M=VAAM, T=VAAT.

Plane	1		2		3		4		5		6		7		8	
	M	T	M	T	M	T	M	T	M	T	M	T	M	T	M	T
C(1)	-47	19														
C(4)	41	-5														
C(5)	3	-16														
C(6)	11	-12														
C(7)	40	-6	2	-10									-123	-113	-186	-151
C(8)			-2	11									-114	-83	-159	-107
C(9)			-1	10	-19	-13							71	86	47	69
C(10)			2	-10	16	8							58	69	47	65
C(11)					24	20	-13	0					181	107	192	110
C(12)					-21	-16	12	0					112	42	140	58
C(13)							15	0	6	3			167	50	216	72
C(14)							-14	0	2	-3			51	-14	116	21
C(15)									-15	-2	1	2	22	33	107	73
C(18)	-48	20							10	2	-4	-5	-56	-7	51	58
C(19)					0	1							-137	-4	-158	-3
C(20)									-3	0			-46	-118	14	-76
O(1)											1	2	-197	-114	-74	-58
O(2)											1	2	12	67	121	128

Coefficients of planes $Ax + By + Cz + D = 0$ relative to standard axes according to Cruickshank (1959)

Plane	Atoms	VAAM				VAAT			
		A	B	C	D	A	B	C	D
1	C(1, 4, 5, 6, 7, 18)	0.1492	-0.7728	0.6169	-0.6904	-0.5249	-0.0896	-0.8465	3.1641
2	C(6, 7, 8, 9)	-0.0896	-0.7995	0.5939	-0.3765	0.9590	-0.0506	0.2790	-3.3267
3	C(8, 9, 10, 11, 19)	-0.0279	-0.8113	0.5840	-0.3596	0.9240	-0.0052	-0.3823	-3.8343
4	C(10, 11, 12, 13)	0.0147	-0.8340	0.5516	-0.2698	0.9240	0.0292	0.3812	-4.0946
5	C(12, 13, 14, 15, 20)	-0.0809	-0.8288	0.5537	-0.5943	0.9320	0.0231	0.3618	-3.9791
6	C(14, 15), O(1, 2)	0.1936	-0.7637	0.6159	-1.5347	0.8680	0.0067	0.4966	-4.1057
7	C(6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 19, 20), O(1, 2)	0.0840	-0.7803	0.6197	-0.8126	0.9187	-0.0047	0.3949	-3.6721
8	Atoms of plane 7 plus the same atoms inverted at 1,0,0 and 0,½,1 respectively	0.0787	-0.7963	0.5998	-0.6359	0.9077	-0.0023	0.4195	-3.6981

about C(6)–C(7). In VAAT this angle is 35° with respect to the planar *s-cis* conformation about C(6)–C(7). The possibly more significant angles between the double bonds C(5)–C(6) and C(7)–C(8) are 15 and 42° respectively.

Until recently, the non-planar *s-cis* conformation was the common one for vitamin A related and carotenoid compounds, the only exception being β -ionylidene crotonic acid (Eichhorn & MacGillavry, 1959; Koch, 1972) with an almost planar *s-trans* conformation. Recently Braun *et al.* (1971) have found the planar *s-trans* conformation in a carotenoid compound and 3-(1,1,5-trimethyl-5-cyclohexene-6-yl)propenoic acid also appears to have this conformation (Schenk, 1972). So in all there are now four cases in which an almost planar *s-trans* conformation has been found.

The question of the relative stability of the two conformations has been treated by Pullman and collaborators (Pullman, Langlet & Berthod, 1969; Langlet, Pullman & Berthod, 1970) by means of quantum mechanical (extended Hückel and PCILO) calculations on retinal, the aldehyde of vitamin A. They have calculated the molecular energy as a function of the angle of rotation of the ring about C(6)–C(7), using the geometry as found for VAAT (Stam & MacGillavry, 1963). The most stable conformation was found to be an *s-cis*-like one in which the plane of the ring double bond makes an angle of 40° with the plane of the side chain, in good agreement with the situation in VAAT. A nearly planar *s-trans* form also represents a minimum in the energy but is 2.5–2.8 kcal.mol⁻¹ less stable. In these calculations the angle C(6)–C(7)–C(8) was kept fixed at 128°, the value for VAAT. The results for VAAM show that this angle is opened up to 131.5° in the planar *s-trans* conformation [corresponding values for the carotenoid compound of Braun *et al.* (1971) 130.4°, for *trans*- β -ionylidene crotonic acid 131.9° (Koch, 1972)]. Although this would imply that the planar *s-trans* conformation is more stable if C(6)–C(7)–C(8) 131.5° than with C(6)–C(7)–C(8) 128°, it does not necessarily invalidate the result of Pullman *et al.* that the *s-cis* conformation has the lower energy, since their result applies to the isolated molecule. The smaller volume per molecule in the monoclinic crystals (446 Å³ against 465 Å³ in the triclinic modification) indicates that the packing of the planar *s-trans* molecules is more efficient. So it may well be that there is an increase in the internal energy when a molecule is going from the *s-cis* to the planar *s-trans* conformation, which is offset by a decrease of the intermolecular interaction energy.

Methyl groups. The side chain methyl groups have one hydrogen atom eclipsing the double bond thus showing the usual behaviour of a methyl group attached to a double bond (Herschbach & Krisher, 1958). The methyl group of C(18) attached to the ring double bond, however, has a hydrogen atom eclipsing a single bond. Here, eclipsing of the double bond would

mean a very short approach of one of the methyl hydrogen atoms to H(7) in VAAT and H(8) in VAAM.

Thermal behaviour

The vibration ellipsoids are listed in Table 5. The thermal behaviour of the atoms in both modifications is similar especially for the side chain atoms, the anisotropy in VAAT (in part accounting for the disorder) being more marked than in VAAM. The side-chain atoms have their largest vibration roughly perpendicular to the plane of the chain and their smallest vibration roughly along the length of the chain. The ring atoms, except the *gem* methyl groups, have their largest motion roughly perpendicular to the plane of the ring double bond. The *gem* methyl groups have their largest motion approximately perpendicular to the C–CH₃ bonds and in the plane C(1)–C(16)–C(17).

Table 5. *R.m.s. amplitudes of vibration along the axes of the vibration ellipsoids, and their angles relative to standard axes according to Cruickshank (1961)*

	VAAM			VAAT				
	$(\bar{u}^2)^{1/2}$	φ_1	φ_2	φ_3	$(\bar{u}^2)^{1/2}$	φ_1	φ_2	φ_3
C(1)	0.24 Å	77°	149°	62°	0.20 Å	115°	34°	68°
	0.21	145	115	113	0.26	69	103	25
	0.18	122	73	38	0.26	33	59	102
C(2)	0.29	71	136	52	0.43	50	85	40
	0.25	24	66	91	0.30	46	68	128
	0.19	104	55	38	0.19	109	22	80
C(3)	0.18	117	69	35	0.46	58	82	33
	0.30	78	148	61	0.33	32	89	122
	0.28	150	113	108	0.21	85	172	84
C(4)	0.17	137	72	53	0.35	54	86	36
	0.28	90	153	63	0.29	37	103	124
	0.26	133	110	131	0.22	98	167	79
C(5)	0.18	146	77	59	0.21	102	13	86
	0.25	93	161	71	0.26	72	90	18
	0.23	124	104	142	0.25	22	77	108
C(6)	0.18	134	73	49	0.19	105	19	79
	0.22	104	162	80	0.25	151	108	68
	0.20	133	88	137	0.23	115	87	155
C(7)	0.25	84	150	61	0.20	103	17	79
	0.21	138	113	123	0.27	45	89	45
	0.18	131	72	46	0.24	48	73	133
C(8)	0.24	90	152	62	0.20	97	8	85
	0.21	149	104	117	0.28	21	86	69
	0.18	121	67	41	0.25	70	83	159
C(9)	0.18	113	63	36	0.29	24	89	66
	0.23	76	142	56	0.24	66	84	156
	0.22	152	115	101	0.20	93	6	85
C(10)	0.18	116	62	40	0.31	17	86	74
	0.24	91	149	59	0.25	75	80	162
	0.22	154	102	112	0.20	96	10	82
C(11)	0.18	114	59	41	0.32	17	88	73
	0.24	76	137	51	0.25	74	81	161
	0.23	152	116	100	0.20	95	9	82
C(12)	0.18	110	56	41	0.34	21	87	69
	0.25	100	146	57	0.24	69	85	158
	0.22	158	93	112	0.21	94	6	86

Table 5 (cont.)

C(13)	0.18	113	55	44	0.33	19	84	72
	0.23	129	138	75	0.24	73	81	160
	0.21	133	69	130	0.20	98	11	83
C(14)	0.28	98	147	58	0.38	26	86	64
	0.22	155	96	114	0.23	66	76	152
	0.18	114	58	42	0.20	100	15	79
C(15)	0.26	102	149	62	0.38	24	87	66
	0.22	145	97	125	0.25	71	62	145
	0.18	123	60	47	0.20	104	29	65
C(16)	0.28	46	124	63	0.38	32	69	68
	0.24	97	136	133	0.29	92	40	130
	0.21	135	115	55	0.22	121	58	48
C(17)	0.27	91	178	88	0.44	106	133	48
	0.23	40	92	130	0.29	123	118	134
	0.21	50	89	40	0.23	143	56	76
C(18)	0.37	83	150	61	0.33	69	89	21
	0.26	99	120	148	0.27	58	36	103
	0.19	169	92	79	0.24	140	54	74
C(19)	0.31	84	143	54	0.38	26	90	64
	0.22	7	84	91	0.25	64	87	153
	0.19	93	54	36	0.23	91	3	87
C(20)	0.34	84	142	53	0.47	19	86	71
	0.23	163	104	99	0.24	73	76	157
	0.19	106	56	39	0.21	98	15	78
O(1)	0.34	85	141	51	0.47	26	88	64
	0.23	137	119	119	0.25	70	56	139
	0.18	133	66	53	0.19	106	34	60
O(2)	0.30	89	144	54	0.49	28	89	62
	0.23	152	106	112	0.24	65	69	146
	0.17	118	59	44	0.19	100	21	72

within a sheet is pictured in Fig. 7(a). The packing of molecules in consecutive sheets is indicated in Fig. 7(b). Both figures are projections on to the mean plane of the double-bond system of a double molecule. The shorter distances involved are listed in Table 7.

Table 6. Shorter intermolecular distances in VAAM

C-C < 3.6, C-O < 3.3, C-H < 3.0, O-H < 2.7, H-H < 2.6 Å.

C(10)—C(15)	i	3.52 Å
C(12)—C(15)	ii	3.58
C(13)—C(15)	ii	3.50
C(14)—C(14)	ii	3.47
C(19)—H(12)	iii	2.76
H(1)—H(2)	iv	2.2
H(1)—H(13)	iv	2.6
H(3)—H(6)	iv	2.3
H(3)—H(15)	v	2.4
H(5)—H(24)	i	2.4
H(12)—H(22)	vi	2.2
H(13)—H(15)	vii	2.5
H(16)—H(20)	vi	2.6
H(23)—H(26)	i	2.6
H(25)—H(25)	viii	2.5

i	x	y	1+z
ii	2-x	-y	1-z
iii	-1+x	y	z
iv	$\frac{1}{2}+x$	$\frac{1}{2}-y$	$\frac{1}{2}+z$
v	$-\frac{1}{2}+x$	$\frac{1}{2}-y$	$\frac{1}{2}+z$
vi	1+x	y	z
vii	$-\frac{1}{2}+x$	$\frac{1}{2}-y$	$-\frac{1}{2}+z$
viii	1-x	-y	-z

Packing

In a crystal of VAAT all conjugated side chains are parallel, forming sheets parallel to (201). The packing

in VAAM crystals, the packing of the double molecules is fishbone-like as illustrated in Fig. 8 in which a projection along [100] is given. As can be seen from this figure, crystals of VAAM consist of slabs per-

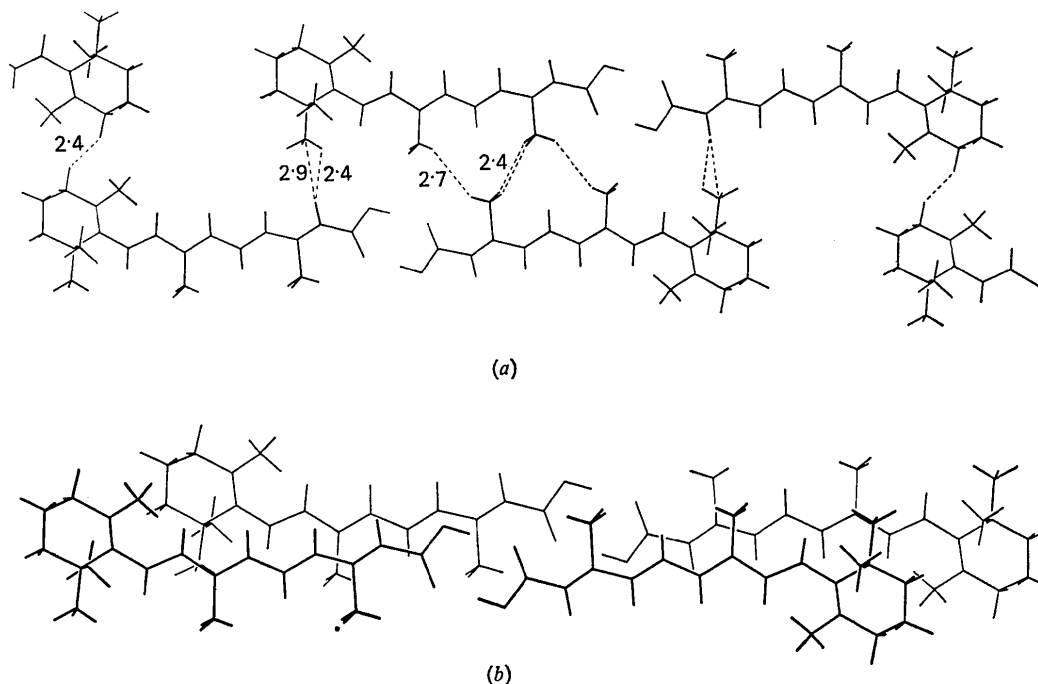


Fig. 7. (a) Packing within one layer in VAAT. (b) Packing of consecutive layers in VAAT.

pendicular to [010] of thickness $\frac{1}{2}b$, composed of parallel double molecules. Consecutive slabs are related by the n -glide plane. They make contact through the ring hydrogen atoms (shortest H-H approach 2.2 Å).

A slab can be considered as consisting of strips parallel to [100] in which the distance between the mean planes of consecutive double molecules is 0.64 Å. The packing within a strip is indicated in Fig. 9(a) where a projection is given on to the mean plane of the

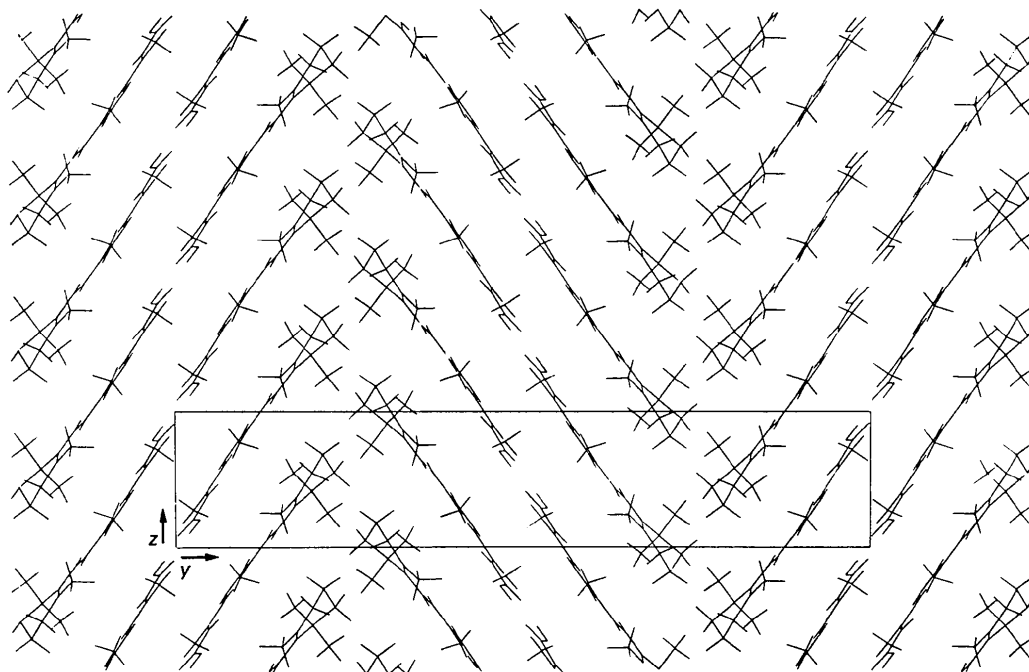


Fig. 8. Projection of the structure of VAAM along [100].

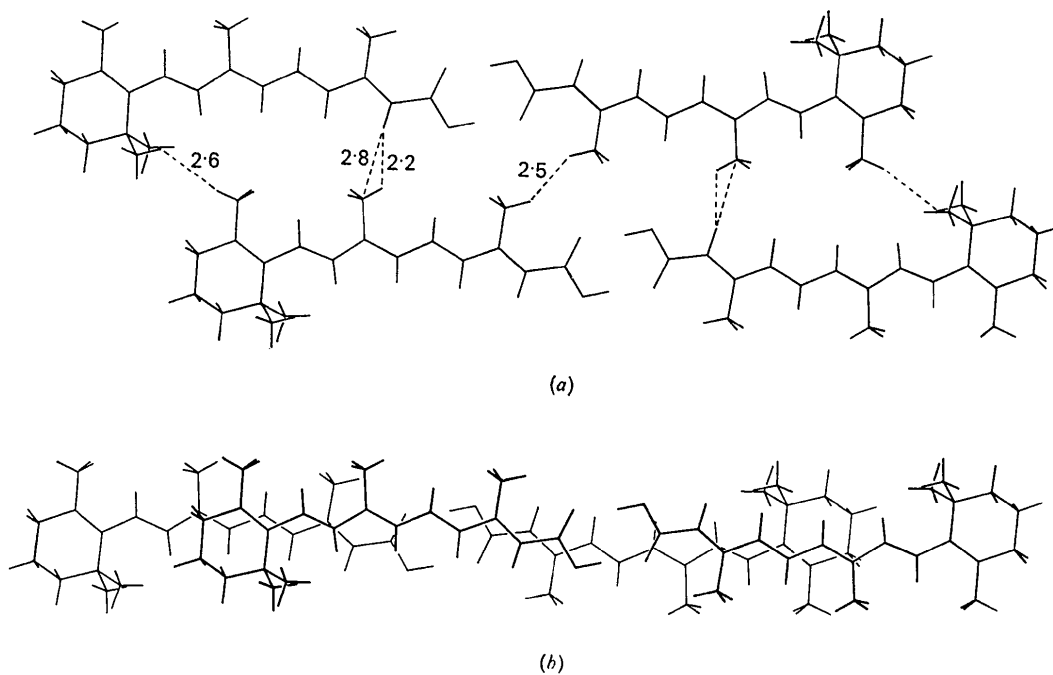


Fig. 9. (a) Packing within a strip in VAAM. (b) Packing in the direction perpendicular to a strip in VAAM.

Table 7. Shorter intermolecular distances in VAAT

C-C < 3.6, C-O < 3.3, C-H < 3.0, O-H < 2.7, H-H < 2.6 Å.

C(8)—H(13)	i	2.87	Å
C(9)—H(13)	i	2.89	
C(16)—H(12)	ii	2.86	
C(17)—H(20)	iii	2.85	
H(3)—H(6)	iv	2.6	
H(5)—H(5)	v	2.4	
H(12)—H(14)	vi	2.4	
H(15)—H(19)	vii	2.6	
H(17)—H(20)	iii	2.5	
H(18)—H(20)	iii	2.6	
H(26)—H(27)	viii	2.4	
i	x	y	1+z
ii	1+x	y	-2+z
iii	1+x	y	z
iv	-x	-y	1-z
v	-x	-y	2-z
vi	-1+x	y	2+z
vii	1+x	y	-1+z
viii	1-x	1-y	-z

double-bond system of a double molecule. The molecules in adjacent strips within a slab, which are separated by a translation \mathbf{c} , are practically on top of each other as illustrated in Fig. 9(b). Contacts are mainly between the carbon atoms (see Table 6). The distance between the mean planes of consecutive molecules is 3.60 Å, a normal value for the thickness of a planar conjugated system. The lateral contacts between the molecules in a strip is through the H atoms, with shortest distances of 2.5 Å.

The disorder in VAAT is understandable in terms of its packing. In VAAT the rings have more freedom of motion than in VAAM in which the ring double bond interacts with the double-bond system of an adjacent

molecule (Fig. 8). The closer packing of the molecules in VAAM is also evident from the intermolecular contacts, of which there are more in VAAM than in VAAT (Tables 6 and 7).

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The Molecular Structure and Absolute Configuration of Chaetocin

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Chaetocin, $C_{30}H_{28}N_6O_6S_4$, a fungal metabolite dimer with an epidithiodiketopiperazine nucleus, crystallizes in $P2_12_12_1$, with $a = 23.30$, $b = 7.31$, and $c = 17.31$ Å, and four formula units in the cell. The structure was solved by direct methods with three-dimensional diffractometer data (graphite monochromated Mo $K\alpha$ radiation) and refined by block-diagonal least-squares methods to $R = 0.042$ for 1704 reflexions. The absolute configuration was determined by measuring the anomalous dispersion effect of sulphur with Cu $K\alpha$ radiation.

Introduction

Chaetocin, a fungal metabolite with antibacterial and cytostatic activity, has been isolated from the fermentation broth of *Chaetomium minutum* (Hauser, Weber

& Sigg, 1970). This new natural product belongs to the class of 3,6-epidithio-diketopiperazines of which chaetomin (Safe & Taylor, 1972), gliotoxin (Fridrichsons & Mathieson, 1967), sporidesmin (Fridrichsons & Mathieson, 1965), aranotin (Nagarajan, Huckstep,