Acta Cryst. (1978). B34, 505–507

The Structure of the 9-Ethyl Analogue of Vitamin A Acid

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(*Received* 10 *June* 1977; *accepted* 4 *August* 1977)

The structure of the synthetic 9-ethyl analogue $C_{21}H_{30}O_2$ of vitamin A acid has been determined in order to establish its conformation. The crystals are monoclinic, space group $P2_1/c$, with $a = 13{\cdot}335$, $b = 18{\cdot}347$, $c = 8{\cdot}205$ Å, $\beta = 95{\cdot}20°$, $Z = 4$. The structure was refined to an R of 5·7% for 1393 counter reflections. The chain is slightly more curved than that of vitamin A acid and the cyclohexene ring is rotated 64° out of the *s-cis* conformation. The ring shows some conformational disorder.

Introduction

The 9-ethyl derivative of vitamin A acid (EVIT) was synthesized by Skolnik (1969). In this compound an ethyl group replaces the methyl group at C(9) in vitamin A acid. Its structural formula and the numbering of the atoms are given in Fig. 1.

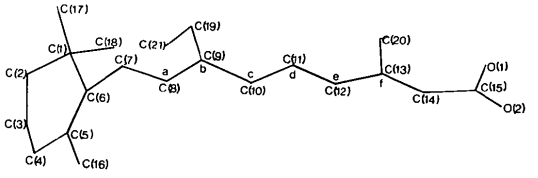

Fig. 1. Numbering of the non-hydrogen atoms of EVIT.

The growth activity of the acetate of EVIT was found to be less than 10% of that of vitamin A acetate itself (Skolnik, 1969). To find out whether this might be due to a change of conformation, a structure determination of the title compound was carried out. Stam (1972) has already reported the structures of two modifications of vitamin A acid.

Experimental

Crystals of EVIT are monoclinic. The lattice parameters were obtained from zero-layer Weissenberg photographs, calibrated with Al powder lines. Intensities were collected on a Nonius CAD-3 diffractometer with Ni-filtered Cu $K\alpha$ radiation and the θ–2θ scanning technique. In the observed part of the reciprocal lattice 1393 reflections were significantly above zero (net intensity $>2{\cdot}5\sigma$). The crystal dimensions were approximately 0·4 mm; no absorption correction was applied ($\mu = 6$ cm^{-1}).

Structure determination and refinement

All related compounds, such as the five-membered-ring analogue of vitamin A acid (Schenk, 1971), monoclinic vitamin A acid (Stam, 1972) and *retro*-vitamin A acid (Schenk, 1969), could be solved smoothly by standard direct-method techniques. The EVIT structure, however, was difficult to solve. Standard procedures for direct and Patterson methods were unsuccessful, but finally our direct-method program *SIMPEL* (Schenk, Overbeek & van der Putten, 1976) solved the phase problem, with very strict acceptance criteria and addition of symbols one by one. Finally, the Σ_2 solution with the best internal consistency revealed the complete

Table 1. *Fractional coordinates* ($\times 10^4$) *of the non-hydrogen atoms with their e.s.d.'s*

	x	y	z
C(1)	6174 (4)	1427 (3)	237 (6)
C(2)	5290 (5)	1880 (4)	721 (8)
C(3)	4321 (5)	1622 (4)	153 (9)
C(4)	4177 (4)	1519 (3)	−1686 (7)
C(5)	5091 (3)	1213 (2)	−2401 (6)
C(6)	5980 (3)	1167 (2)	−1526 (5)
C(7)	6869 (3)	829 (2)	−2184 (6)
C(8)	6932 (3)	133 (2)	−2604 (6)
C(9)	7770 (3)	−248 (2)	−3234 (6)
C(10)	7709 (3)	−986 (2)	−3387 (6)
C(11)	8448 (3)	−1472 (2)	−3968 (6)
C(12)	8317 (3)	−2196 (2)	−3967 (6)
C(13)	9009 (3)	−2752 (2)	−4413 (6)
C(14)	8748 (3)	−3455 (2)	−4248 (6)
C(15)	9311 (3)	−4103 (2)	−4619 (5)
C(16)	4899 (4)	987 (3)	−4126 (7)
C(17)	7139 (6)	1884 (5)	487 (9)
C(18)	6288 (5)	729 (4)	1377 (8)
C(19)	8686 (4)	182 (3)	−3650 (7)
C(20)	9982 (4)	−2510 (2)	−5036 (7)
C(21)	8500 (5)	542 (4)	−5284 (9)
O(1)	10097 (2)	−4105 (2)	−5273 (4)
O(2)	8872 (2)	−4700 (2)	−4166 (4)

Table 2. *Parameters of the hydrogen atoms with their e.s.d.'s*

Fractional coordinates are $\times 10^3$, thermal parameters in Å^2.

	x	*y*	*z*	*B*
H(1)	565 (5)	44 (3)	99 (8)	15 (2)
H(2)	not found			
H(3)	700 (5)	41 (4)	94 (9)	17 (3)
H(4)	714 (7)	208 (5)	164 (11)	23 (4)
H(5)	697 (3)	232 (2)	−21 (5)	7 (1)
H(6)	787 (9)	142 (7)	26 (15)	33 (6)
H(7)	544 (4)	194 (3)	183 (7)	12 (2)
H(8)	535 (4)	243 (3)	2 (7)	13 (2)
H(9)	428 (5)	107 (3)	72 (7)	15 (2)
H(10)	383 (6)	198 (4)	47 (9)	19 (3)
H(11)	384 (4)	196 (3)	−235 (7)	13 (2)
H(12)	357 (3)	121 (3)	−207 (5)	8 (1)
H(13)	460 (4)	138 (3)	−479 (6)	12 (2)
H(14)	434 (3)	61 (2)	−416 (6)	9 (1)
H(15)	565 (4)	91 (3)	−457 (7)	12 (2)
H(16)	741 (3)	114 (2)	−241 (5)	8 (1)
H(17)	631 (4)	−13 (3)	−252 (7)	12 (2)
H(18)	894 (4)	55 (3)	−284 (7)	13 (2)
H(19)	936 (4)	−12 (3)	−363 (7)	14 (2)
H(20)	797 (4)	95 (3)	−510 (6)	10 (2)
H(21)	841 (4)	11 (3)	−596 (6)	13 (2)
H(22)	919 (6)	74 (4)	−562 (9)	18 (3)
H(23)	719 (3)	−121 (2)	−312 (5)	7 (1)
H(24)	910 (3)	−127 (2)	−429 (5)	7 (1)
H(25)	771 (3)	−237 (3)	−351 (6)	10 (2)
H(26)	1037 (4)	−290 (3)	−536 (6)	9 (2)
H(27)	1000 (4)	−218 (3)	−565 (6)	11 (2)
H(28)	1024 (4)	−211 (3)	−423 (7)	14 (2)
H(29)	818 (4)	−357 (3)	−374 (7)	12 (2)
H(30)	907 (4)	−510 (3)	−437 (7)	13 (2)

Table 3. *Bond lengths* (Å) *of the non-hydrogen atoms with their e.s.d.'s*

C(1)–C(2)	1·523 (9)	C(9)–C(10)	1·360 (6)
C(1)–C(6)	1·523 (7)	C(9)–C(19)	1·519 (7)
C(1)–C(17)	1·533 (10)	C(10)–C(11)	1·442 (7)
C(1)–C(18)	1·586 (9)	C(11)–C(12)	1·339 (6)
C(2)–C(3)	1·415 (10)	C(12)–C(13)	1·444 (7)
C(3)–C(4)	1·515 (9)	C(13)–C(14)	1·346 (6)
C(4)–C(5)	1·509 (9)	C(13)–C(20)	1·505 (8)
C(5)–C(6)	1·331 (9)	C(14)–C(15)	1·453 (6)
C(5)–C(16)	1·475 (8)	C(15)–O(1)	1·220 (7)
C(6)–C(7)	1·482 (8)	C(15)–O(2)	1·311 (6)
C(7)–C(8)	1·327 (6)	C(19)–C(21)	1·495 (9)
C(8)–C(9)	1·453 (7)		

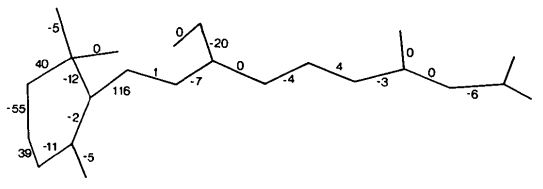

Fig. 2. Dihedral angles for the C–C bonds of EVIT. For the methyl groups and methylene C(19) the rotations are given with respect to their reference conformation, which for an sp^3–sp^3 system is staggered and for an sp^2–sp^3 system is such that a H atom eclipses the double bond.

structure. A comparison with former failures showed that in this case a few incorrect Σ_2 relations with rather large $N^{-1/2}EEE$ values generated a large number of incorrect signs. In the final procedure these Σ_2 relations were not used in the phasing process.

The refinement of EVIT was carried out with the XRAY system (Stewart, 1972). As a result of the disorder in the hexene ring, to be discussed later, one of the H atoms could not be located. The final R was 5·7% for 1393 reflections. The parameters of the atoms are given in Tables 1 and 2.* The bond lengths, the valence angles and torsion angles are given in Tables 3, 4 and 5, and Fig. 2.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33076(9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond angles* (°) *between non-hydrogen atoms with their e.s.d.'s*

C(2)–C(1)–C(6)	110·5 (4)	C(7)–C(8)–C(9)	128·7 (4)
C(2)–C(1)–C(17)	109·1 (5)	C(8)–C(9)–C(10)	118·1 (4)
C(2)–C(1)–C(18)	108·8 (5)	C(8)–C(9)–C(19)	119·3 (4)
C(6)–C(1)–C(17)	111·5 (5)	C(10)–C(9)–C(19)	122·6 (4)
C(6)–C(1)–C(18)	107·8 (4)	C(9)–C(10)–C(11)	127·6 (4)
C(17)–C(1)–C(18)	109·1 (5)	C(10)–C(11)–C(12)	121·4 (4)
C(1)–C(2)–C(3)	115·9 (6)	C(11)–C(12)–C(13)	127·9 (4)
C(2)–C(3)–C(4)	113·5 (6)	C(12)–C(13)–C(14)	118·4 (4)
C(3)–C(4)–C(5)	113·6 (4)	C(12)–C(13)–C(20)	117·8 (4)
C(4)–C(5)–C(6)	121·6 (4)	C(14)–C(13)–C(20)	123·8 (4)
C(4)–C(5)–C(16)	113·7 (4)	C(13)–C(14)–C(15)	128·3 (4)
C(6)–C(5)–C(16)	124·7 (5)	C(14)–C(15)–O(1)	125·0 (4)
C(1)–C(6)–C(5)	124·0 (4)	C(14)–C(15)–O(2)	111·8 (4)
C(1)–C(6)–C(7)	113·8 (4)	O(1)–C(15)–O(2)	123·1 (4)
C(5)–C(6)–C(7)	122·2 (4)	C(9)–C(19)–C(21)	111·1 (4)
C(6)–C(7)–C(8)	124·6 (4)		

Table 5. *Bond distances* (Å) *of the hydrogen atoms with their e.s.d.'s*

C(2)–H(7)	0·93 (6)	C(17)–H(4)	1·02 (9)
C(2)–H(8)	1·16 (6)	C(17)–H(5)	0·99 (4)
C(3)–H(9)	1·11 (6)	C(17)–H(6)	1·32 (13)
C(3)–H(10)	0·98 (8)	C(18)–H(1)	1·03 (7)
C(4)–H(11)	1·05 (6)	C(18)–H(2)	not found
C(4)–H(12)	1·01 (4)	C(18)–H(3)	1·19 (7)
C(7)–H(16)	0·95 (4)	C(19)–H(18)	1·00 (6)
C(8)–H(17)	0·97 (6)	C(19)–H(19)	1·05 (6)
C(10)–H(23)	0·85 (4)	C(20)–H(26)	0·93 (5)
C(11)–H(24)	1·01 (4)	C(20)–H(27)	0·79 (5)
C(12)–H(25)	0·98 (5)	C(20)–H(28)	1·02 (6)
C(14)–H(29)	0·92 (6)	C(21)–H(20)	1·04 (5)
C(16)–H(13)	0·97 (5)	C(21)–H(21)	0·97 (5)
C(16)–H(14)	1·01 (5)	C(21)–H(22)	1·04 (8)
C(16)–H(15)	1·11 (6)	O(2)–H(30)	0·80 (6)

Discussion

Disorder

As in most vitamin A derivatives (Stam, 1972 and references therein) the bond lengths and angles of EVIT deviate from the values of an idealized cyclohexene ring; in particular, C(2)–C(3) is about 0·10 Å shorter than expected. Most probably this anomaly is connected with conformational disorder of the cyclohexene ring. The conformation of the ring is a half chair, with C(2) and C(3) on opposite sides of the plane through C(1), C(6), C(5) and C(4) at approximately 0·3 Å from that plane. A small fraction of the molecules have C(2) and C(3) switched to the other side of the plane, giving rise to alternative positions of C(17) and C(18). As a result of packing, the remaining ring atoms of the alternative conformation will be slightly shifted. In a difference map indications could be found for the alternative C(17) and C(18) atoms with peak heights in the range of those of H atoms. One of these gave overlap with H(2) so that H(2) was not stable in the refinement. Other indications for the disorder are the large thermal parameters for C(2), C(3), C(17), C(18) and, to a lesser degree, for C(1), C(4) and C(16).

Bond lengths and angles

The bond lengths in and around the cyclohexene ring are unreliable as a result of the disorder. All other bonds have expected lengths.

The steric interactions between the H atoms of C(7), C(19), C(11) and C(20) force the chain to have a sabre-like form. In Fig. 1 the angles which are affected by the steric hindrance are indicated by a to f and the extent of curvature is then given by $\Delta = a - b + c - d + e - f$ (Bart & MacGillavry, 1968). For EVIT $\Delta = 26°$ which is about 6° larger than for most of the related compounds. To a good approximation the chain can be considered to be planar as the torsion angles of the chain bonds (Fig. 2) are small. The largest deviations from planarity are 0·14 Å.

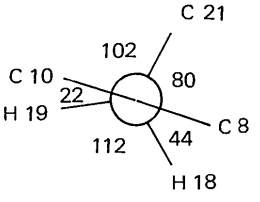

Fig. 3. Newman projection along C(9)–C(19). Angles are in degrees.

Conformational aspects

The cyclohexene ring is rotated by 64° from the *s-cis* position, approximately 15° more than in most of the related structures.

Fig. 2 shows that all the methyl groups have approximately normal conformations. Fig. 3 shows that the methylene C(19) is rotated 20° from the conformation in which a H atom eclipses the double bond C(9)–C(10); the plane through C(9), C(19) and C(21) is nearly perpendicular to the conjugated chain.

The molecules form centrosymmetric dimers through hydrogen bonds of 2·650 (5) Å.

Comparison of EVIT and vitamin A acid

The main differences between the conformations of EVIT and vitamin A acid concern the ring–chain attachment (15° more rotated for EVIT) and the curvature of the chain (6° larger for EVIT). However, both differences give rise to only small changes in the shape of the molecule. Therefore, the decrease in growth activity of 9-ethyl vitamin A is probably due to the space requirements of the extra methyl group C(21).

The authors thank Dr S. Skolnik and Professor H. O. Huisman for providing the crystals, Mr D. Heijdenrijk for his assistance in the experimental part and Dr C. H. Stam and Professor B. O. Loopstra for criticizing the manuscript.

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