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The Structure of a Prostaglandin-Analogue Precursor: 9,9-Dimethoxy-12-aza-ω-octanorprostanoic Acid Methyl Ester–L(+)-Tartaric Acid, 1:1 Adduct

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Abstract. $C_{14}H_{28}NO_4^+.C_4H_5O_6^-$, M_r = 423·46, monoclinic, $P2_1$, a = 18·510 (4), b = 7·763 (2), c = 7·528 (1) Å, β = 97·96 (2)°, V = 1071·4 Å^3, Z = 2, d_{obs} = 1·30 (flotation), d_{calc} = 1·312 Mg m^{-3}. R = 0·069 and R_w = 0·043 for 1401 observed reflexions [$I > 1\cdot5\sigma(I)$]. The prostanoid molecule has the R configuration at C(8), which corresponds to the unnatural S configuration for an unsubstituted prostaglandin. The α chain is axial rather than equatorial with respect to the ring, and is not fully extended, having a torsion angle of −63° around C(5)—C(6). The tartrate ion is close to parallel with the α chain. Hydrogen-bonded layers of tartrate ions alternate with layers of prostanoid molecules in the crystal.

Introduction. The rising interest in prostaglandins and their actions has prompted the syntheses of many analogues. One way of altering the prostanoid skeleton is by substitution of N atoms in the 8 and 12 positions, *i.e.* the chain-holding atoms. A common precursor to some of the latter compounds is the racemate of the title compound 9,9-methoxy-12-aza-ω-octanorprostanoic acid methyl ester. The optically active species investigated in this work was prepared by recrystallization with L(+)-tartaric acid, and kindly donated as the 1:1 adduct by Drs Schribner and DeFranco of E.I. du Pont de Nemours.

Crystals of satisfactory quality were obtained by slow evaporation from 1-propanol and a crystal platelet of dimensions 0·35 × 0·25 × 0·04 mm was used throughout the experiments. The space group was found to be $P2_1$. Intensity data were collected on an automatic Syntex $P\bar{1}$ diffractometer using graphite-monochromated Mo $K\alpha$ radiation (λ = 0·71069 Å). The cell parameters were determined from a least-squares fit to 25 reflexions with 20° < 2θ < 30°, measured on the same instrument. Three reflexions were measured periodically during the data collection to check the stability. 1785 reflexions with 2θ < 50° were converted to relative structure amplitudes in the usual way. 1401 reflexions having $I > 1\cdot5\sigma(I)$ were treated as observed. The programs used here, and throughout this work, are described by Groth (1973) unless stated otherwise.

The structure was solved by direct methods (Germain, Main & Woolfson, 1971) and refined by full-matrix least-squares techniques. All non-hydrogen atoms were refined with anisotropic thermal parameters; H atoms involved in hydrogen bonding were refined with isotropic thermal parameters, whereas those attached to C atoms were kept with fixed values for both positional and isotropic thermal parameters. The H atoms were placed in ideal positions, which were checked against a difference Fourier synthesis, where only diffuse peaks could be found. The fixed H atoms were not repositioned during the refinement since their inclusion gave only small shifts in the C atom positions.

Table 1. *Atomic coordinates for non-hydrogen atoms*

The coordinate refers to a left-handed axial system. $B_{eq} = \frac{1}{3}$ trace **B**.

	x	y	z	B_{eq} (Å^2)
C(1)	0·9627 (6)	0·3293 (0)	0·2929 (12)	4·8
C(2)	0·9259 (5)	0·4228 (18)	0·4276 (11)	4·2
C(3)	0·8937 (5)	0·3047 (18)	0·5562 (11)	5·2
C(4)	0·8582 (5)	0·4052 (18)	0·6922 (11)	4·0
C(5)	0·8309 (4)	0·2910 (17)	0·8355 (10)	4·0
C(6)	0·7974 (5)	0·3913 (17)	0·9781 (10)	3·2
C(7)	0·7285 (4)	0·4910 (16)	0·9016 (9)	2·8
C(8)	0·6884 (4)	0·5662 (15)	1·0487 (9)	1·9
C(9)	0·7133 (4)	0·7445 (15)	1·1181 (9)	2·3
C(10)	0·6819 (4)	0·8643 (15)	0·9711 (9)	2·3
C(11)	0·6092 (4)	0·7865 (16)	0·8946 (9)	3·0
C(12)	0·8193 (5)	0·9115 (19)	1·2228 (12)	4·6
C(13)	0·7009 (5)	0·6982 (17)	1·4302 (9)	3·4
C(14)	1·0372 (6)	0·3660 (18)	0·0641 (13)	6·0
N	0·6105 (4)	0·6059 (16)	0·9743 (11)	2·2
O(1)	0·9629 (4)	0·1783 (12)	0·2686 (9)	5·7
O(2)	0·9966 (4)	0·4370 (14)	0·1935 (9)	6·8
O(3)	0·7892 (2)	0·7455 (14)	1·1657 (6)	3·4
O(4)	0·6770 (3)	0·7922 (14)	1·2705 (6)	2·8
C(15)	0·4742 (4)	0·6976 (15)	0·2567 (9)	2·0
C(16)	0·4558 (4)	0·7547 (16)	0·4388 (9)	1·8
C(17)	0·4046 (4)	0·6176 (15)	0·5057 (9)	1·6
C(18)	0·3903 (5)	0·6661 (15)	0·6927 (9)	2·3
O(5)	0·5202 (3)	0·5789 (14)	0·2559 (6)	2·4
O(6)	0·4431 (3)	0·7742 (14)	0·1201 (6)	2·4
O(7)	0·4231 (3)	0·9170 (15)	0·4289 (7)	2·5
O(8)	0·3385 (3)	0·6044 (14)	0·3910 (7)	2·9
O(9)	0·4485 (3)	0·6476 (14)	0·8120 (7)	2·9
O(10)	0·3322 (3)	0·7818 (14)	0·7225 (6)	3·0

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Table 2. *Bond distances* (Å) *for non-hydrogen atoms*

C(1)–C(2)	1·487 (12)	C(2)–C(3)	1·514 (13)
C(3)–C(4)	1·507 (11)	C(4)–C(5)	1·535 (11)
C(5)–C(6)	1·526 (11)	C(6)–C(7)	1·533 (11)
C(7)–C(8)	1·532 (9)	C(8)–C(9)	1·528 (10)
C(9)–C(10)	1·500 (10)	C(10)–C(11)	1·515 (10)
C(8)–N	1·505 (10)	C(11)–N	1·523 (11)
C(9)–O(3)	1·402 (8)	C(12)–O(3)	1·445 (10)
C(9)–O(4)	1·456 (8)	C(13)–O(4)	1·423 (8)
C(14)–O(2)	1·421 (11)	C(1)–O(2)	1·334 (10)
C(1)–O(1)	1·187 (9)	C(18)–O(9)	1·311 (8)
C(18)–O(10)	1·207 (8)	C(15)–O(6)	1·256 (8)
C(15)–O(5)	1·256 (8)	C(16)–O(7)	1·395 (9)
C(17)–O(8)	1·400 (8)	C(15)–C(16)	1·523 (9)
C(16)–C(17)	1·555 (9)	C(17)–C(18)	1·516 (9)

Table 3. *Bond angles* (°) *for non-hydrogen atoms*

O(1)–C(1)–O(2)	121·4 (9)	O(1)–C(1)–C(2)	126·8 (9)
O(2)–C(1)–C(2)	111·9 (8)	C(1)–O(2)–C(14)	118·4 (8)
C(1)–C(2)–C(3)	113·5 (8)	C(2)–C(3)–C(4)	111·6 (8)
C(3)–C(4)–C(5)	113·3 (8)	C(4)–C(5)–C(6)	113·9 (7)
C(5)–C(6)–C(7)	113·1 (7)	C(6)–C(7)–C(8)	112·5 (6)
C(7)–C(8)–C(9)	116·0 (6)	C(7)–C(8)–N	110·2 (6)
C(8)–C(9)–O(3)	109·7 (6)	C(8)–C(9)–O(4)	110·5 (6)
C(10)–C(9)–O(3)	117·2 (6)	C(10)–C(9)–O(4)	104·5 (6)
O(3)–C(9)–O(4)	110·7 (6)	C(9)–O(3)–C(12)	114·3 (6)
C(9)–O(4)–C(13)	114·3 (6)	N–C(8)–C(9)	99·8 (6)
C(8)–C(9)–C(10)	104·0 (6)	C(9)–C(10)–C(11)	105·4 (6)
C(10)–C(11)–N	104·7 (6)	C(11)–N–C(8)	107·3 (7)
O(5)–C(15)–O(6)	125·2 (6)	O(5)–C(15)–C(16)	117·0 (6)
O(6)–C(15)–C(16)	117·8 (7)	C(15)–C(16)–O(7)	111·3 (6)
C(15)–C(16)–C(17)	108·3 (6)	O(7)–C(16)–C(17)	110·9 (6)
C(16)–C(17)–O(8)	111·8 (6)	C(16)–C(17)–C(18)	108·8 (6)
O(8)–C(17)–C(18)	110·0 (6)	C(17)–C(18)–O(9)	112·1 (7)
C(17)–C(18)–O(10)	122·4 (7)	O(9)–C(18)–O(10)	125·5 (7)

Table 4. *Dihedral angles* (°) *involving non-hydrogen atoms*

The average e.s.d. is 0·8°.

Fatty-acid chain			
C(14)–O(2)–C(1)–C(2)	−177·1	O(1)–C(1)–C(2)–C(3)	−7·3
O(2)–C(1)–C(2)–C(3)	173·8	C(1)–C(2)–C(3)–C(4)	−178·9
C(2)–C(3)–C(4)–C(5)	174·9	C(3)–C(4)–C(5)–C(6)	−177·9
C(4)–C(5)–C(6)–C(7)	−63·4	C(5)–C(6)–C(7)–C(8)	−170·5
C(6)–C(7)–C(8)–C(9)	−87·6	C(6)–C(7)–C(8)–N	160·0
Methoxy groups			
C(12)–O(3)–C(9)–C(8)	−176·3	C(12)–O(3)–C(9)–C(10)	−58·1
C(13)–O(4)–C(9)–C(8)	−71·2	C(13)–O(4)–C(9)–C(10)	177·5
Exocyclic			
C(7)–C(8)–C(9)–O(3)	51·2	C(7)–C(8)–C(9)–O(4)	173·5
C(7)–C(8)–C(9)–C(10)	−75·6	C(7)–C(8)–N–C(11)	86·6
O(3)–C(9)–C(8)–N	169·4	O(3)–C(9)–C(10)–C(11)	−156·3
O(4)–C(9)–C(8)–N	−68·3	O(4)–C(9)–C(10)–C(11)	80·9
Endocyclic			
C(8)–C(9)–C(10)–C(11)	35·0	C(9)–C(10)–C(11)–N	12·2
C(10)–C(11)–N–C(8)	15·0	C(11)–N–C(8)–C(9)	−36·0
N–C(8)–C(9)–C(10)	43·3		
Tartaric acid			
O(5)–C(15)–C(16)–C(17)	76·4	O(5)–C(15)–C(16)–O(7)	−161·5
O(6)–C(15)–C(16)–C(17)	−104·6	O(6)–C(15)–C(16)–O(7)	17·5
C(15)–C(16)–C(17)–C(18)	−175·9	C(15)–C(16)–C(17)–O(8)	62·4
O(7)–C(16)–C(17)–C(18)	61·7	O(7)–C(16)–C(17)–O(8)	−59·9
C(16)–C(17)–C(18)–O(9)	69·7	C(16)–C(17)–C(18)–O(10)	−107·7
O(8)–C(17)–C(18)–O(9)	−167·6	O(8)–C(17)–C(18)–O(10)	15·0

The least-squares refinement converged with final $R = 0{\cdot}069$, $R_w = 0{\cdot}043$ and the e.s.d. of an observation of unit weight $S = 1{\cdot}4$ for the 1401 observed reflexions. Inclusion of all 1785 reflexions yielded $R = 0{\cdot}095$. The atomic scattering factors used were those of Doyle & Turner (1968) for C, N and O, and those of Stewart, Davidson & Simpson (1965) for H. The final positional parameters for the non-hydrogen atoms are given in Table 1 together with isotropic thermal parameters.* A final difference Fourier synthesis revealed no peaks with absolute values greater than 0·3 e Å^{-3}.

Bond distances, angles and torsion angles are given in Tables 2, 3 and 4, respectively.

Discussion. The most interesting aspect of prostaglandin-like structures is probably the conformation and particularly the relative orientation of the side chains (DeTitta, 1976). The latter aspect is not relevant to this compound, as the ω chain is missing. It may be of interest, however, that the tartrate ion is oriented parallel to the α chain, thus making the overall conformation of the adduct resemble that of natural prostaglandins (Abrahamsson, 1963; Edmonds & Duax, 1974, 1975; Detitta, Edmonds & Duax, 1975). There are, however, some important differences: (1) the side chain is axial rather than equatorial with respect to the ring, (2) the side chain is not fully extended, having a torsion angle of −63° around C(5)–C(6), and (3) the absolute configuration at C(8) is *R*, which corresponds to the unnatural *S* configuration in an unsubstituted prostaglandin. The last feature was discovered by adapting the structure to the known absolute configuration of L(+)-tartaric acid.

As can be seen from the bond distances in Table 2, as well as from Fig. 1, the C–C distances of the α chain are probably seriously affected by thermal motion.

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* Lists of structure factors, anisotropic thermal parameters for the non-hydrogen atoms and positional and thermal parameters for the H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35770 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

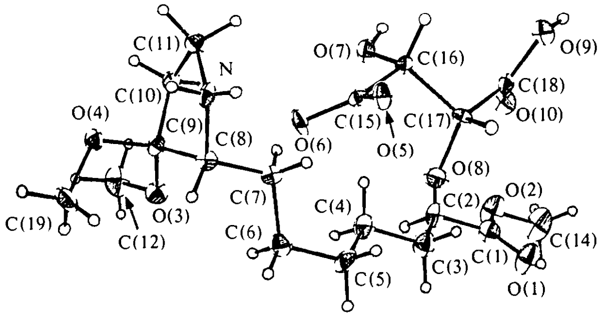

Fig. 1. Perspective drawing (Johnson, 1976) of the molecule, with atomic notation and thermal ellipsoids scaled to 30% probability.

Table 5. *Details of the hydrogen-bonding system*

E.s.d.'s are 0·07 Å for *D*–H and H···*A*, 0·008 Å for *D*···*A* and 8° for the angles.

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*	H–*D*–*X*	H···*A*–*Y*	Symmetry code for *A*
N–H(N)1···O(5)	1·04	1·85	2·882	168	109*	111	$x, y, z+1$
N–H(N)2···O(6)	0·66	2·25	2·815	146	109*	131	$1-x, -\frac{1}{2}+y, 1-z$
O(7)–H(O7)···O(5)	0·71	2·11	2·761	153	111	126	$1-x, \frac{1}{2}+y, 1-z$
O(8)–H(O8)···O(10)	0·86	2·14	2·674	120	104	79	x,y,z
O(9)–H(O9)···O(6)	0·77	1·79	2·533	162	109	119	$x, y, z+1$

* Average value for all valence angles involving this H atom.

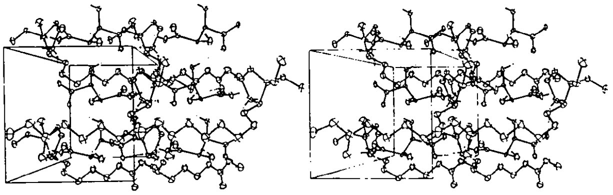

Fig. 2. Stereodrawing (Johnson, 1976) of the unit-cell content and some neighbouring molecules displaying the hydrogen-bonding system. The view is down the *a* axis, with *b* pointing up and *c* to the right (thus constituting a left-handed axial system).

However, attempts to fit rigid-body models to the thermal motion (Schomaker & Trueblood, 1968) failed. The average C–C distance for the bonds involving C(1) to C(4) is 1·503 Å, whereas for the rest of the α chain it is 1·532 Å. The high e.s.d. (0·01 Å) precludes any conclusion about the possible significance of this difference. In the tartaric acid the central C–C bond is significantly longer than the outer ones due to the different hybridizations involved.

The two C–O bonds of the deprotonated carboxyl group of the tartaric acid are identical, whereas those in the other carboxyl group differ by 0·104 Å; those of the ester differ by 0·147 Å. The alcoholic C–OH bonds in the acid are equal (1·40 Å), and although the variance for the ether C–O bonds of the prostanoid is rather large, none of the individual bonds differs by more than 3σ from the average value of 1·432 Å.

The unit-cell content, plus some neighbouring molecules included to display the hydrogen-bonding system, is shown in Fig. 2, and details of the individual hydrogen bonds are given in Table 5. There are five isolated bonds, each having a carbonyl O atom as acceptor. One of the bonds is intramolecular [O(8)–H···O(10)]. The other two O–H···O bonds form a two-dimensional network of tartaric acid molecules parallel to the *bc* plane. The prostanoid molecules form bimolecular layers parallel to those of the tartrate groups through van der Waals interactions between the fatty-acid chains. The two kinds of layers alternate and are held together by hydrogen bonds from the N atom to the deprotonated carboxyl group. All the hydrogen bonds are rather strong, especially that from O(9) to O(6).

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