

## The Crystal and Molecular Structure of Prostaglandin E<sub>1</sub>

By A. L. SPEK

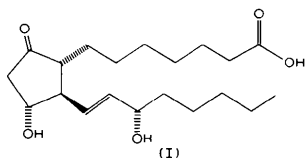
Department of Structural Chemistry, University of Utrecht, Padualaan 8, Utrecht, The Netherlands

(Received 19 July 1976; accepted 21 August 1976)

Prostaglandin E<sub>1</sub> is orthorhombic, space group  $P2_12_12_1$ , with  $a = 19.46(1)$ ,  $b = 25.83(2)$ ,  $c = 8.157(5)$  Å,  $Z = 8$ . Single-crystal X-ray diffraction data, complete to  $\theta = 68^\circ$  (Cu  $K\alpha$ ), were collected on a three-circle diffractometer. The structure was solved by direct methods and refined by block-diagonal least squares. The final discrepancy indices are  $R_F = 0.076$  and  $R_{wF} = 0.073$  for 2757 independent reflexions with  $I > 2\sigma(I)$ . The conformations of the two independent molecules are approximately the same with the alkyl and carboxyl side chains parallel. Subunits of two prostaglandin molecules, coupled through three hydrogen bonds, fit into a hydrogen-bond network that runs in a helix fashion around the screw axes in the  $c$  direction. Regions with hydrogen-bonding alternate with chain-packing regions.

### Introduction

Prostaglandin E<sub>1</sub>, 11 $\alpha$ ,15(*S*)-dihydroxy-9-oxo-13-*trans*-prostenoic acid, C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>, [(I), PGE<sub>1</sub>] is one of at least 14 known prostaglandins. These substances are found in small quantities in human and animal tissues and act as hormones. They differ chemically in the number and type of oxygen functions, and in the number of double bonds, both in the side chains and in the five-membered ring. PGE<sub>1</sub> is synthesized by the enzyme complex PG-synthetase from dihomo- $\gamma$ -linolenic acid. One of the known physiological actions of PGE<sub>1</sub> is the inhibition of blood platelet aggregation.



The first prostaglandin studied in the crystalline state was the tri-*p*-bromobenzoate of PGF<sub>1 $\beta$</sub>  methyl ester (Abrahamsson, 1963). This study settled the question of the connectivity of the prostaglandins and yielded the first evidence for the hairpin conformation of the alkyl and carboxyl side chains. Since then, several other prostaglandins have been described. PGA<sub>1</sub> (orthorhombic polymorph) was studied by Edmonds & Duax (1975), PGA<sub>1</sub> (monoclinic polymorph) by DeTitta, Edmonds & Duax (1975) and PGE<sub>2</sub> by Edmonds & Duax (1974), and several other studies are in progress. The results of eight molecules have been recently reviewed by DeTitta (1975) and DeTitta, Edmonds, Duax & Hauptman (1975).

The structure of PGE<sub>1</sub> is of interest since it adds new information to the data base on prostaglandins in order to assess the conformational stability of this type of

physiologically and pharmacologically important molecule. An additional feature of the present structure is that it contains two independent PGE<sub>1</sub> molecules.

### Experimental

A needle-shaped colourless crystal was obtained from the Unilever Research Laboratories, Vlaardingem. Weissenberg and precession photographs showed the crystals to be orthorhombic. The space group  $P2_12_12_1$  is uniquely determined from the extinctions ( $h00: h = 2n + 1; 0k0: k = 2n + 1; 00l: l = 2n + 1$ ). In addition it was found that the reflexions  $0kl$  for  $l = 2n + 1$  were nearly extinct, indicating a pseudo glide plane.

The crystal was mounted along the needle axis  $b$  on an Enraf-Nonius CAD-3 diffractometer for data collection. The cell dimensions, obtained from a least-squares treatment of 27 carefully centred reflexions, are  $a = 19.46(1)$ ,  $b = 25.83(2)$ ,  $c = 8.157(5)$  Å. The calculated density is  $1.149 \text{ g cm}^{-3}$ .

The intensities were measured with Ni-filtered Cu  $K\alpha$  radiation. A  $\theta/2\theta$  scan technique was used, with scan angle given by  $\Delta\theta = 0.50 + 0.30 \tan(\theta)$ . A reflexion was scanned up to six times in order to obtain at least

Table 1. Starting set of reflexions

$h$	$k$	$l$	Phase	Method	$h$	$k$	$l$	Phase	Method
8	0	0	$\pi$	Packing	8	0	2	0	$\Sigma_1$
0	0	2	$\pi$	Packing	0	2	2	$\pi$	$\Sigma_1$
2	1	0	$\pi$	Correlation/ quartets	10	10	0	0	Symbolic addition
2	2	0	0		10	20	0	$\pi$	
4	1	0	$\pi$		0	9	2	$\pi/2$	
6	2	0	$\pi$		3	21	1	$\pi/4$	
4	2	1	$\pm\pi/4, \pm\frac{3}{4}\pi$		4	1	1	$\pm\pi/4$	Origin
1	2	2	$\pm\pi/4, \pm\frac{3}{4}\pi$						

2000 net counts, if possible. 4227 intensities were measured. Only the set of reflexions (2761) with  $I > 2\sigma(I)$  was included in the refinement. The net intensity was scaled by the application of a smooth function to correct for fluctuations in the intensity as monitored by two reference reflexions. The fluctuations were less than 2%, and there was no indication of decay.

Table 2. *Final refined atomic coordinates ( $\times 10^4$ ) for the non-hydrogen atoms and their estimated standard deviations in parentheses*

	<i>x</i>	<i>y</i>	<i>z</i>
<b>Molecule A</b>			
O(1A)	-66 (3)	3632 (2)	1436 (8)
O(1B)	705 (3)	3176 (2)	2799 (7)
O(9)	699 (4)	7435 (2)	-130 (9)
O(11)	1897 (4)	8073 (2)	4507 (9)
O(15)	2581 (4)	6995 (2)	8632 (8)
C(1)	405 (4)	3611 (3)	2359 (9)
C(2)	733 (5)	4075 (4)	3108 (13)
C(3)	435 (5)	4584 (3)	2564 (12)
C(4)	846 (5)	5051 (3)	3008 (12)
C(5)	571 (4)	5563 (3)	2368 (11)
C(6)	1026 (5)	6020 (3)	2669 (11)
C(7)	764 (4)	6526 (3)	1974 (10)
C(8)	1269 (4)	6972 (3)	2021 (9)
C(9)	1055 (4)	7438 (3)	1016 (10)
C(10)	1355 (5)	7915 (3)	1799 (12)
C(11)	1807 (4)	7723 (3)	3202 (10)
C(12)	1467 (4)	7205 (3)	3700 (9)
C(13)	1926 (4)	6904 (2)	4775 (9)
C(14)	1860 (4)	6834 (3)	6371 (9)
C(15)	2381 (4)	6611 (3)	7491 (9)
C(16)	2125 (5)	6151 (4)	8458 (10)
C(17)	2025 (6)	5670 (4)	7449 (11)
C(18)	1801 (6)	5199 (4)	8369 (13)
C(19)	1773 (7)	4708 (4)	7457 (16)
C(20)	1550 (9)	4243 (5)	8354 (18)
<b>Molecule B</b>			
O(1A)	959 (4)	-1822 (2)	7140 (12)
O(1B)	371 (4)	-1490 (3)	9003 (10)
O(9)	290 (3)	2370 (2)	10658 (6)
O(11)	1822 (3)	2988 (2)	6671 (7)
O(15)	2020 (4)	2147 (2)	1735 (8)
C(1)	705 (5)	-1437 (3)	7713 (14)
C(2)	731 (6)	-931 (4)	6939 (14)
C(3)	603 (6)	-467 (4)	7977 (13)
C(4)	602 (6)	43 (3)	7129 (12)
C(5)	522 (6)	501 (4)	8245 (12)
C(6)	519 (5)	1030 (3)	7446 (11)
C(7)	542 (5)	1466 (3)	8673 (10)
C(8)	554 (4)	2015 (3)	7987 (9)
C(9)	560 (4)	2421 (3)	9351 (9)
C(10)	975 (5)	2871 (3)	8768 (11)
C(11)	1176 (4)	2769 (3)	7029 (9)
C(12)	1164 (4)	2171 (3)	6910 (9)
C(13)	1169 (4)	1987 (3)	5182 (9)
C(14)	1705 (4)	1832 (3)	4339 (10)
C(15)	1717 (4)	1716 (3)	2549 (10)
C(16)	2072 (5)	1216 (4)	2145 (12)
C(17)	1718 (6)	736 (4)	2754 (13)
C(18)	2082 (7)	241 (4)	2300 (17)
C(19)	1785 (9)	-247 (5)	2836 (18)
C(20)	2164 (11)	-722 (5)	2281 (22)

### Structure determination and refinement

The reflexion data were brought to an absolute scale with a modified Wilson plot (Maslen, 1967) and  $E$  values derived. The intensities show many systematic features; for instance reflexions for which  $k$  is a multiple of ten are relatively strong. Several statistical tests wrongly indicate centrosymmetry. The Patterson function shows a large peak on  $b$ , 2.6 Å from the origin, indicating that at least the majority of the chains run along  $b$ .

The structure resisted several initial trials to solve it, both with symbolic addition (Spek, 1975) and with multi-solution methods (*MULTAN*). However, most of the more probable solutions showed C chains, although wrongly positioned with respect to the screw axes. Attention was then concentrated on the construction of a larger starting set before initiating phase extension and refinement with the tangent formula (*MULTAN*). An interpretable Fourier map was eventually found among 22 solutions generated from a starting set containing 15 reflexions. This starting set (Table 1) was obtained with various types of formulae and arguments (Spek, 1975), including the  $\Sigma_1$  formula, negative quartets (Hauptman, 1974), a correlation equation and chain-packing considerations.

All atoms were finally located after several cycles of structure factor and Fourier calculations, starting with a fragment of 18 atoms. Refinement by block-diagonal least squares, varying the coordinates and isotropic thermal parameters for the non-hydrogen atoms, converged at  $R_F = 0.23$ ,  $R_{wF} = 0.18$ . Anisotropic thermal parameters were introduced and refined to  $R_F = 0.13$  and  $R_{wF} = 0.12$ . 57 of 68 H atoms were located from a  $\Delta F$  synthesis. The other H atoms were found in a difference map after two additional cycles of refinement. Convergence was reached at  $R = 0.076$ ,  $R_{wF} = 0.073$ , for 2757 reflexions. Only the positional parameters of the H atoms were refined. Their isotropic temperature factors were fixed at the values of the carrier atoms. The blocks in the least-squares matrix were defined in such a way that they each included the parameters for the non-hydrogen atom and those for the H atoms that are bonded to it. A damping factor of 0.5 was necessary during the final cycles in order to obtain a stable and converging result. Three reflexions were excluded from the final cycles because they suffered from secondary extinction. The final parameters are shown in Tables 2 and 3.\*

A Dutch version of the X-RAY system (Stewart,

\*A table of anisotropic thermal parameters for the non-hydrogen atoms and a list of structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32110 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Positional ( $\times 10^3$ ) and thermal parameters for the hydrogen atoms*

Molecule <i>A</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>iso</sub>
H [O(1 <i>B</i> )]	54 (3)	296 (2)	225 (9)	5.2
H [O(11)]	147 (4)	823 (3)	457 (11)	5.9
H [O(15)]	271 (5)	722 (3)	822 (11)	5.5
H1[C(2)]	74 (4)	403 (3)	417 (10)	4.8
H2[C(2)]	115 (4)	406 (3)	294 (10)	4.8
H1[C(3)]	29 (4)	458 (3)	151 (10)	5.0
H2[C(3)]	-1 (4)	463 (3)	328 (10)	5.0
H1[C(4)]	94 (4)	510 (3)	416 (10)	4.7
H2[C(4)]	131 (4)	500 (3)	258 (9)	4.7
H1[C(5)]	41 (3)	554 (3)	112 (9)	4.1
H2[C(5)]	8 (4)	562 (2)	267 (9)	4.1
H1[C(6)]	110 (4)	605 (3)	368 (9)	3.7
H2[C(6)]	145 (3)	596 (3)	230 (9)	3.7
H1[C(7)]	67 (3)	646 (2)	75 (9)	3.7
H2[C(7)]	31 (3)	662 (2)	249 (8)	3.7
H [C(8)]	168 (3)	687 (2)	148 (8)	3.5
H1[C(10)]	161 (4)	811 (3)	109 (9)	4.5
H2[C(10)]	102 (4)	808 (3)	230 (9)	4.5
H [C(11)]	226 (3)	762 (2)	276 (8)	3.9
H [C(12)]	106 (3)	729 (2)	420 (8)	3.4
H [C(13)]	225 (3)	675 (2)	421 (8)	3.2
H [C(14)]	144 (3)	699 (2)	682 (9)	4.0
H [C(15)]	280 (3)	650 (3)	676 (9)	4.5
H1[C(16)]	245 (4)	610 (3)	920 (10)	5.0
H2[C(16)]	173 (4)	621 (3)	901 (10)	5.0
H1[C(17)]	177 (4)	574 (3)	657 (10)	5.1
H2[C(17)]	245 (4)	558 (3)	698 (10)	5.1
H1[C(18)]	205 (4)	518 (3)	945 (11)	6.5
H2[C(18)]	126 (4)	523 (3)	893 (11)	6.5
H1[C(19)]	128 (4)	478 (3)	701 (12)	7.6
H2[C(19)]	201 (5)	474 (4)	649 (12)	7.6
H1[C(20)]	189 (5)	425 (4)	932 (13)	8.8
H2[C(20)]	107 (5)	433 (4)	901 (13)	8.8
H3[C(20)]	148 (6)	400 (4)	763 (13)	8.8
<b>Molecule <i>B</i></b>				
H [O(1 <i>B</i> )]	30 (4)	-172 (3)	915 (11)	7.8
H [O(11)]	196 (4)	300 (3)	571 (9)	4.5
H [C(15)]	232 (4)	205 (3)	119 (11)	5.9
H1[C(2)]	117 (4)	-88 (3)	655 (11)	6.0
H2[C(2)]	37 (4)	-95 (3)	610 (10)	6.0
H1[C(3)]	19 (4)	-56 (3)	831 (12)	6.6
H2[C(3)]	95 (4)	-47 (3)	892 (11)	6.6
H1[C(4)]	103 (4)	12 (3)	657 (11)	6.0
H2[C(4)]	15 (4)	6 (3)	632 (10)	6.0
H1[C(5)]	13 (4)	46 (3)	880 (11)	6.0
H2[C(5)]	93 (4)	48 (3)	932 (10)	6.0
H1[C(6)]	90 (4)	107 (3)	673 (10)	5.3
H2[C(6)]	10 (4)	104 (3)	688 (10)	5.3
H1[C(7)]	13 (4)	141 (3)	937 (9)	4.9
H2[C(7)]	96 (4)	142 (3)	947 (9)	4.9
H [C(8)]	11 (3)	207 (2)	745 (8)	3.6
H1[C(10)]	80 (3)	317 (3)	898 (9)	4.0
H2[C(10)]	137 (3)	289 (3)	945 (9)	4.0
H [C(11)]	83 (3)	289 (2)	636 (9)	3.8
H [C(12)]	155 (3)	204 (2)	746 (8)	3.6
H [C(13)]	78 (3)	206 (2)	460 (8)	3.6
H [C(14)]	212 (3)	180 (3)	487 (8)	3.9
H [C(15)]	126 (3)	170 (3)	214 (9)	4.4
H1[C(16)]	208 (4)	118 (3)	96 (10)	5.5
H2[C(16)]	254 (4)	125 (3)	261 (10)	5.5
H1[C(17)]	161 (4)	74 (3)	383 (16)	5.7
H2[C(17)]	121 (4)	74 (3)	268 (11)	5.7

Table 3 (cont.)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>iso</sub>
H1[C(18)]	215 (5)	17 (3)	110 (11)	7.2
H2[C(18)]	256 (5)	23 (3)	216 (13)	7.2
H1[C(19)]	183 (6)	-16 (4)	388 (13)	9.0
H2[C(19)]	124 (5)	-19 (4)	227 (13)	9.0
H1[C(20)]	206 (5)	-68 (4)	88 (13)	9.3
H2[C(20)]	275 (5)	-69 (4)	261 (14)	9.3
H3[C(20)]	205 (6)	-99 (4)	292 (14)	9.3

Kruger, Ammon, Dickinson & Hall, 1972) was used for most of the calculations. Cromer & Mann's (1968) analytical scattering factors for C and O were used. Those for H were taken from Stewart, Davidson & Simpson (1965). The function minimized was  $\Sigma w(|F_o| - |F_c|)^2$ , with  $w = 1$  for all reflexions with  $I > 2\sigma(I)$  and  $w = 0$  otherwise. A final difference synthesis contained no peaks higher than  $0.28 \text{ e } \text{\AA}^{-3}$ .

### Results and discussion

The asymmetric unit contains two chemically identical but crystallographically independent PGE<sub>1</sub> molecules (PGE<sub>1</sub>-*A* and PGE<sub>1</sub>-*B*). Their conformations differ only in some details, originating from intermolecular hydrogen-bonding and packing.

Some results including bond distances and thermal vibrational ellipsoids are shown in the ORTEP drawing (Fig. 1). The atomic numbering is in accordance with the usual convention for prostaglandins. The standard deviations in the bonds involving non-hydrogen atoms range from 0.009 to 0.014 Å. Bond distances involving H atoms are given in Table 4.

### Molecular geometry

Most of the C(*sp*<sup>3</sup>)-C(*sp*<sup>3</sup>) distances in the side chains are considerably shorter than the normal 1.54 Å. However, this effect is rather common in this type of molecule and is generally attributed to thermal anisotropy and rotatory oscillations of the chains. This view is supported by the observation that the apparent bond distances in general shorten towards the loose end of the chains as is shown in the carboxyl side chain of PGE<sub>1</sub>-*B*. Here, going from C(8) to C(1), thermal motion increases and bond distances decrease. This decrease in the bond distances in the aliphatic chains [see C(15)-C(20) in PGE<sub>1</sub>-*A*] is usually accompanied by an increase in the bond angles (Table 5). Thus all the deviations of the bond distances and angles from standard values may be explained except for those of the carboxyl group of PGE<sub>1</sub>-*B*. Whereas the carboxyl group in PGE<sub>1</sub>-*A* has standard geometry, with the carboxyl O(1*A*) eclipsed by C(3), this is not the case in

Table 4. Bond distances involving hydrogen atoms (Å)

The labels of the hydrogen atoms have been truncated.

	Molecule		Molecule		
	A	B	A	B	
O(1B)—H	0.78 (6)	0.61 (8)	O(11)—H	0.93 (8)	0.83 (7)
C(2)—H1	0.87 (8)	0.93 (8)	C(12)—H	0.91 (6)	0.93 (6)
C(2)—H2	0.83 (7)	0.99 (8)	C(13)—H	0.87 (6)	0.92 (6)
C(3)—H1	0.90 (8)	0.89 (8)	C(14)—H	0.98 (6)	0.91 (7)
C(3)—H2	1.05 (7)	1.03 (9)	C(15)—H	1.06 (7)	0.96 (7)
C(4)—H1	0.97 (8)	0.97 (8)	O(15)—H	0.71 (8)	0.78 (9)
C(4)—H2	0.98 (7)	1.10 (8)	C(16)—H1	0.89 (8)	0.89 (8)
C(5)—H1	1.07 (7)	0.90 (8)	C(16)—H2	0.91 (7)	0.98 (7)
C(5)—H2	1.00 (7)	1.19 (8)	C(17)—H1	0.89 (8)	0.90 (9)
C(6)—H1	0.84 (7)	0.96 (8)	C(17)—H2	0.94 (8)	1.00 (8)
C(6)—H2	0.88 (7)	0.94 (8)	C(18)—H1	1.01 (9)	1.00 (9)
C(7)—H1	1.03 (7)	0.99 (7)	C(18)—H2	1.15 (8)	0.94 (9)
C(7)—H2	1.01 (6)	1.05 (7)	C(19)—H1	1.04 (9)	0.89 (11)
C(8)—H	0.96 (6)	0.97 (6)	C(19)—H2	0.92 (10)	1.18 (9)
C(10)—H1	0.91 (7)	0.85 (7)	C(20)—H1	1.03 (10)	1.17 (11)
C(10)—H2	0.89 (7)	0.94 (7)	C(20)—H2	1.10 (10)	1.18 (10)
C(11)—H	0.99 (6)	0.72 (7)	C(20)—H3	0.87 (10)	0.89 (10)

Table 5. Bond angles (°) involving the non-hydrogen atoms

	Molecule A	Molecule B
O(1A)—C(1)—O(1B)	123.7 (7)	116.8 (9)
O(1A)—C(1)—C(2)	123.6 (7)	124.1 (10)
O(1B)—C(1)—C(2)	112.7 (7)	119.0 (9)
C(1)—C(2)—C(3)	114.6 (8)	118.1 (9)
C(2)—C(3)—C(4)	115.4 (8)	116.6 (9)
C(3)—C(4)—C(5)	115.7 (8)	114.6 (8)
C(4)—C(5)—C(6)	115.0 (7)	116.8 (8)
C(5)—C(6)—C(7)	114.9 (7)	112.8 (8)
C(6)—C(7)—C(8)	115.4 (7)	116.8 (7)
C(7)—C(8)—C(9)	114.3 (6)	111.8 (6)
C(7)—C(8)—C(12)	118.8 (8)	117.8 (6)
C(9)—C(8)—C(12)	103.7 (6)	103.3 (5)
C(8)—C(9)—O(9)	126.3 (7)	124.7 (6)
C(10)—C(9)—O(9)	125.3 (7)	127.3 (7)
C(8)—C(9)—C(10)	108.3 (6)	107.9 (6)
C(9)—C(10)—C(11)	106.0 (6)	107.8 (6)
C(10)—C(11)—C(12)	103.3 (6)	103.4 (6)
C(10)—C(11)—O(11)	115.5 (6)	111.0 (6)
C(12)—C(11)—O(11)	114.1 (7)	113.7 (6)
C(8)—C(12)—C(11)	102.2 (6)	103.8 (5)
C(11)—C(12)—C(13)	110.7 (6)	112.2 (6)
C(8)—C(12)—C(13)	118.2 (6)	117.7 (6)
C(12)—C(13)—C(14)	126.9 (6)	126.8 (7)
C(13)—C(14)—C(15)	126.6 (7)	125.9 (7)
C(14)—C(15)—O(15)	108.8 (6)	107.8 (6)
C(14)—C(15)—C(16)	113.7 (7)	113.2 (7)
O(15)—C(15)—C(16)	107.4 (6)	112.3 (7)
C(15)—C(16)—C(17)	114.1 (7)	115.2 (8)
C(16)—C(17)—C(18)	115.9 (8)	113.7 (9)
C(17)—C(18)—C(19)	117.3 (9)	118.4 (12)
C(18)—C(19)—C(20)	117.6 (11)	115.1 (14)

Table 6. Torsion angles (°) for PGE<sub>1</sub>-A and PGE<sub>1</sub>-B

Chain	PGE <sub>1</sub> -A	PGE <sub>1</sub> -B
O(1A)—C(1)—C(2)—C(3)	-2	-161
O(1B)—C(1)—C(2)—C(3)	177	23
C(1)—C(2)—C(3)—C(4)	-168	-177
C(2)—C(3)—C(4)—C(5)	176	-176
C(3)—C(4)—C(5)—C(6)	-173	180
C(4)—C(5)—C(6)—C(7)	178	-172
C(5)—C(6)—C(7)—C(8)	-170	179
C(12)—C(13)—C(14)—C(15)	-168	-172
C(13)—C(14)—C(15)—O(15)	116	102
C(13)—C(14)—C(15)—C(16)	-124	-134
C(14)—C(15)—C(16)—C(17)	71	66
O(15)—C(15)—C(16)—C(17)	-169	-172
C(15)—C(16)—C(17)—C(18)	177	179
C(16)—C(17)—C(18)—C(19)	-174	180
C(17)—C(18)—C(19)—C(20)	180	178
Ring chain		
C(6)—C(7)—C(8)—C(9)	169	179
C(6)—C(7)—C(8)—C(12)	-69	-62
C(8)—C(12)—C(13)—C(14)	-137	-142
C(11)—C(12)—C(13)—C(14)	106	98
Ring function		
C(7)—C(8)—C(9)—C(10)	151	147
C(7)—C(8)—C(9)—O(9)	-27	-32
C(7)—C(8)—C(12)—C(11)	-165	-158
C(7)—C(8)—C(12)—C(13)	73	78
O(9)—C(9)—C(10)—C(11)	-178	-177
O(9)—C(9)—C(8)—C(12)	-158	-160
O(11)—C(11)—C(10)—C(9)	-154	-149
O(11)—C(11)—C(12)—C(8)	166	158
O(11)—C(11)—C(12)—C(13)	-67	-75
C(13)—C(12)—C(8)—C(9)	-158	-157
C(13)—C(12)—C(11)—C(10)	167	165
Ring		
C(8)—C(9)—C(10)—C(11)	5	5
C(9)—C(10)—C(11)—C(12)	-28	-26
C(10)—C(11)—C(12)—C(8)	40	37
C(11)—C(12)—C(8)—C(9)	-37	-34
C(12)—C(8)—C(9)—C(10)	20	19

PGE<sub>1</sub>-B. Here, the two C—O distances are nearly equal [1.21 (1) and 1.24 (1) Å]. The slightly longer one is interpreted to correspond to the hydroxyl group since a H atom was located near it. It is concluded that the carboxyl group has been rotated by 161° with respect to

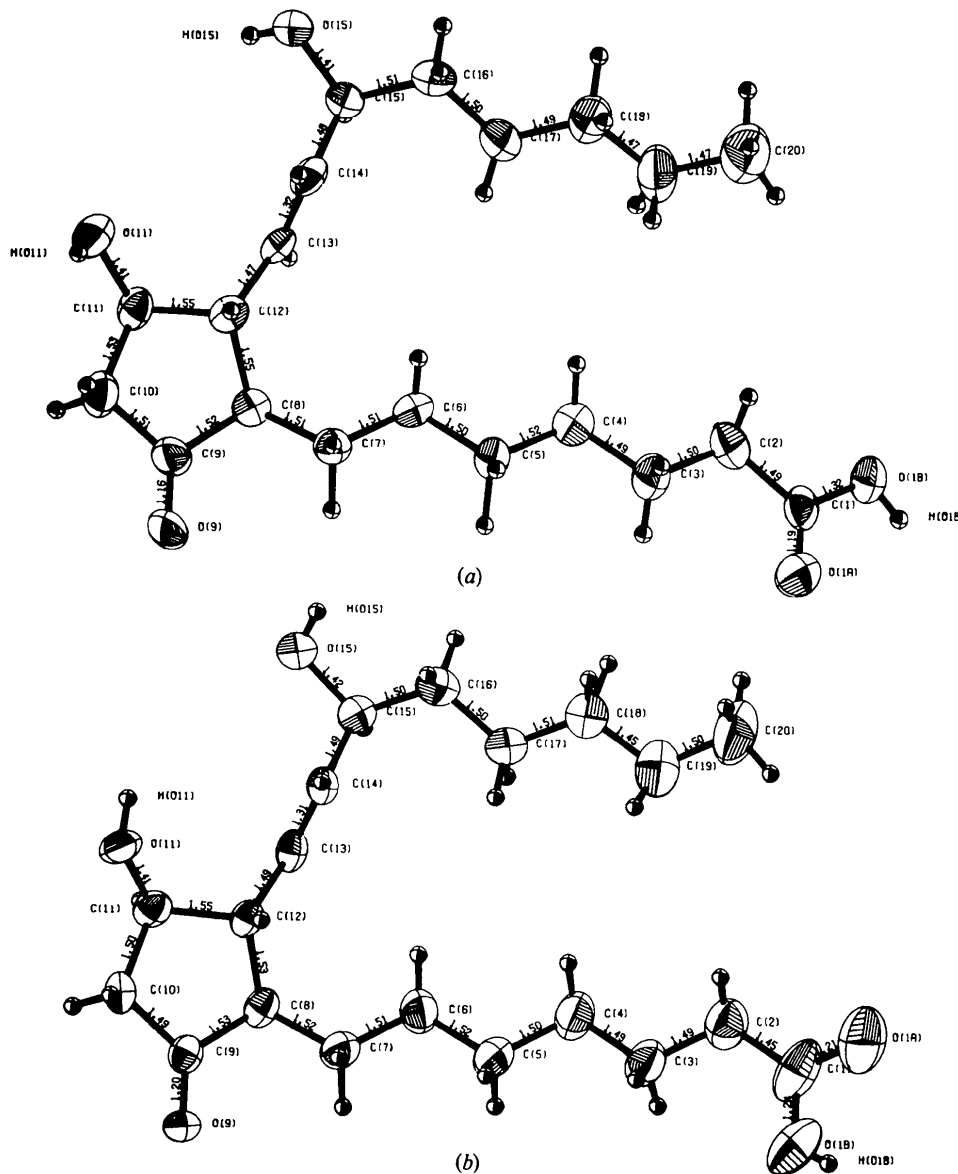


Fig. 1. ORTEP thermal ellipsoid drawings of the two independent molecules (a) PGE<sub>1</sub>-A and (b) PGE<sub>1</sub>-B. The ellipsoids are drawn at the 40% probability level. The numbering scheme and the bond distances for the non-hydrogen atoms are shown. The hydrogen atoms are represented by artificially small spheres.

the normal geometry. The reason for this change is that the carboxyl O(1A)<sub>B</sub> may now act as an acceptor and the hydroxyl O(1B)<sub>B</sub> as a donor.

Fig. 2 shows that the molecules are approximately planar with the alkyl and carboxyl side chains running parallel. The angle between the two planes through the side chains is 109° for PGE<sub>1</sub>-A and 127° for PGE<sub>1</sub>-B. The overall conformation of PGE<sub>1</sub> may be assessed from the torsion angles given in Table 6 and the deviations of the atoms from the various planes that are shown in Table 7. The geometry of PGE<sub>1</sub> is in general similar to that found in other prostaglandins and

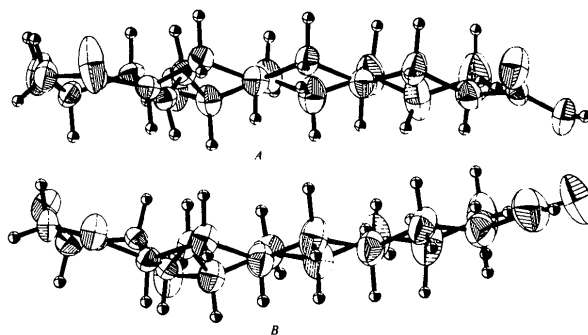


Fig. 2. Side view of the PGE<sub>1</sub> molecules showing their planarity.

Table 7. *Least-squares planes and the deviations of individual atoms from these planes*Equations of the planes are presented in fractional coordinates ( $x, y, z$ ). Atoms identified by an asterisk were given unit weight.

	PGE <sub>1</sub> -A					PGE <sub>1</sub> -B				
	I	II	III	IV	V	VI	VII	VIII	IX	X
O(1A)	-0.32*	0.49	—	—	—	0.44*	0.46*	—	—	—
O(1B)	0.71*	0.45	—	—	—	0.10*	-0.53	—	—	—
O(9)	-0.15*	—	—	—	0.01*	0.07*	—	—	—	0.00*
O(11)	-0.08*	—	—	—	-0.47*	1.09*	—	—	—	0.61
O(15)	0.07*	—	0.40	1.26	—	-0.35*	—	-0.21	1.39	—
C(1)	0.16*	0.32*	—	—	—	0.17*	0.04*	—	—	—
C(2)	0.24*	-0.03*	—	—	—	-0.15*	0.09*	—	—	—
C(3)	-0.30*	-0.12*	—	—	—	-0.03*	-0.05*	—	—	—
C(4)	0.03*	-0.18*	—	—	—	-0.43*	-0.05*	—	—	—
C(5)	-0.43*	-0.17*	—	—	—	-0.20*	-0.10*	—	—	—
C(6)	0.03*	-0.08*	—	—	—	-0.58*	-0.10*	—	—	—
C(7)	-0.39*	-0.03*	—	—	—	-0.13*	0.06*	—	—	—
C(8)	0.25*	0.29*	—	-0.87	0.00*	-0.45*	0.09*	—	-0.80	0.00*
C(9)	0.04*	0.63*	—	—	0.01*	0.03*	0.23	—	—	-0.01*
C(10)	0.05*	—	—	—	0.00*	0.45*	—	—	—	0.00*
C(11)	0.40*	—	—	1.46	0.10	0.15*	—	—	1.49	-0.09
C(12)	-0.13*	-0.76	—	0.06*	-0.54	0.16*	1.23	—	0.05*	0.50
C(13)	0.40*	—	—	-0.06*	—	-0.47*	—	—	-0.05*	—
C(14)	-0.26*	—	-1.24	-0.06*	—	0.15*	—	1.21	-0.04*	—
C(15)	0.32*	—	0.05*	0.06*	—	-0.50*	—	-0.02*	0.05*	—
C(16)	-0.26*	—	0.01*	-1.07	—	0.03*	—	0.01*	-0.96	—
C(17)	0.15*	—	-0.07*	—	—	-0.28*	—	0.00*	—	—
C(18)	-0.36*	—	-0.05*	—	—	0.23*	—	0.02*	—	—
C(19)	0.15*	—	0.02*	—	—	-0.00*	—	0.01*	—	—
C(20)	-0.35*	—	0.04*	—	—	0.50*	—	-0.02*	—	—

Equations of the planes

I	17.08x - 4.496y - 3.641z = -1.953	VI	17.16x - 1.362y + 3.828z = +4.185
II	9.848x - 3.306y - 6.958z = -2.753	VII	19.40x + 0.9519y + 0.6089z = +1.657
III	18.50x - 5.804y + 1.756z = +1.833	VIII	10.50x + 1.183y + 6.859z = +3.776
IV	8.955x + 22.52y + 1.369z = +17.99	IX	3.916x + 24.45y - 2.051z = +4.301
V	15.77x - 2.535y - 4.715z = -0.7155	X	16.17x - 10.72y + 3.025z = +1.150

Table 8. *Geometry of the hydrogen bonds and some short C—H...O interactions*Symmetry operations are coded by the combination  $ijks$ . The first three digits code a lattice translation of  $(i-5)a + (j-5)b + (k-5)c$ . The last digit denotes one of the three following operations.  $s = 1: x, y, z$ ;  $s = 2: \frac{1}{2} - x, -y, \frac{1}{2} + z$ ;  $s = 4: -x, \frac{1}{2} + y, \frac{1}{2} - z$ .

D	H	A	Symmetry transformation of A	D—H (Å)	H...A (Å)	D...A (Å)	∠C—O—H (°)	∠D—H...A (°)	∠H...A—C (°)
O(1B) <sub>A</sub>	H(1) <sub>A</sub>	O(9) <sub>B</sub>	5541	0.78	2.06	2.83	105	169	112
O(11) <sub>B</sub>	H(11) <sub>B</sub>	O(15) <sub>A</sub>	5442	0.83	1.91	2.74	120	171	136
O(15) <sub>A</sub>	H(15) <sub>A</sub>	O(15) <sub>B</sub>	5452	0.71	2.11	2.81	111	171	116
O(15) <sub>B</sub>	H(15) <sub>B</sub>	O(11) <sub>A</sub>	5442	0.78	2.07	2.84	109	168	120
O(11) <sub>A</sub>	H(11) <sub>A</sub>	O(1A) <sub>B</sub>	5651	0.93	2.33	2.83	102	114	118
O(1B) <sub>B</sub>	H(1) <sub>B</sub>	O(9) <sub>A</sub>	5461	0.61	2.40	2.94	113	148	113
C(2) <sub>B</sub>	H2[C(2)] <sub>B</sub>	O(1A) <sub>A</sub>	5454	0.99	2.41	3.25	—	142	139
C(11) <sub>A</sub>	H[C(11)] <sub>A</sub>	O(11) <sub>B</sub>	5642	0.99	2.54	3.47	—	157	108

largely consistent with the previously predicted conformation on the basis of extended Hückel calculations (Hoyland & Kier, 1972). The observed hair-pin configuration of the parallel side chains is stabilized by dispersion forces (Rabinowitz, Ramwell & Davison, 1971) and is usually found in prostaglandins. It is

probable that particularly in the present structure this configuration is further stabilized because the chains are in a region of the structure with chain packing alone. The conformation of the cyclopentane ring is of the envelope type with the puckering at C(12). In fact, the largest conformational differences between the

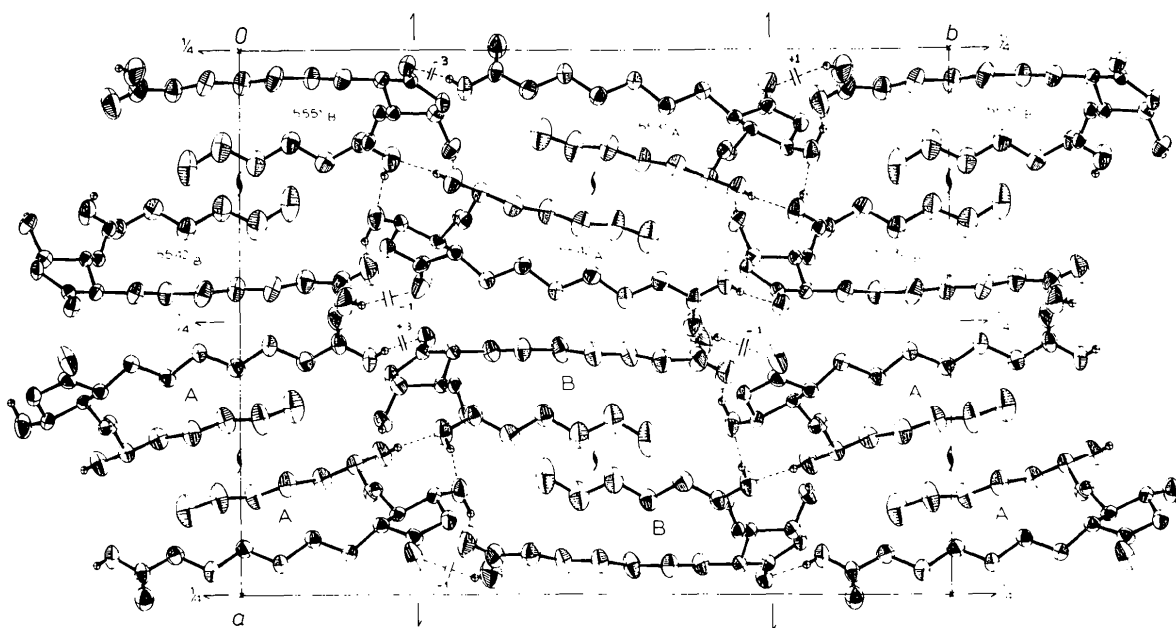


Fig. 3. Projection of the structure as viewed down *c* showing the helix type of hydrogen-bonding along the screw axes. For symmetry code see Table 8.

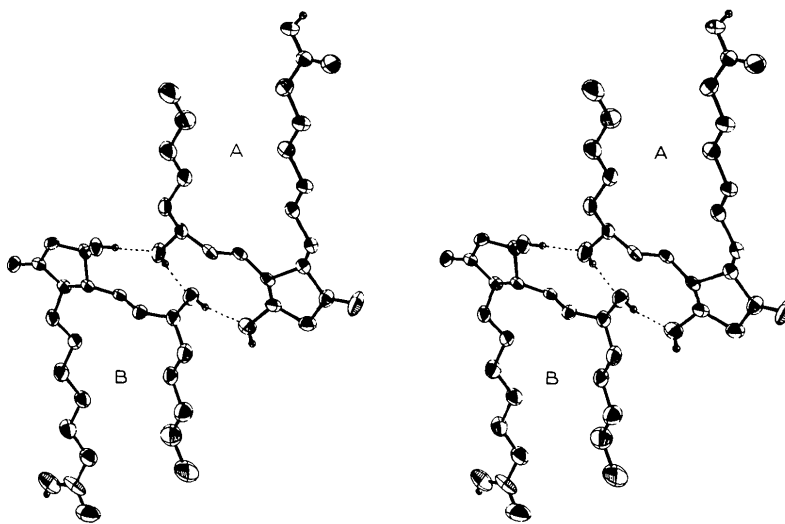


Fig. 4. Stereoscopic drawing illustrating the 'dimeric unit' PGE<sub>1</sub>-A/PGE<sub>1</sub>-B.

prostaglandins are found in this five-membered ring which seems to be rather easily deformed in order to bring the two side chains in an appropriate parallel configuration.

The conformation around both C(14)–C(15) and C(12)–C(13) is *gauche-gauche*, and the junction of the carboxyl chain with the ring is *trans* to C(8)–C(9) as is commonly found in other prostaglandins.

The observed overall conformation for PGE<sub>1</sub> resembles that found for the monoclinic modification of PGA<sub>1</sub> (DeTitta, Edmonds & Duax, 1975) and to a somewhat lesser extent PGF<sub>1β</sub> (Abrahamsson, 1963).

### Hydrogen-bonding

The hydrogen-bonding network is given in Table 8 and shown in Fig. 3. From this it can be seen that the PGE<sub>1</sub> molecules are not dimerized through the two carboxyl groups, as is often the case in carboxylic acids. Nevertheless some kind of dimerization is present in this structure if one considers the threefold hydroxyl interactions between two PGE<sub>1</sub> molecules, involving O(11)<sub>A</sub>, O(15)<sub>A</sub>, O(11)<sub>B</sub> and O(15)<sub>B</sub>. All other hydrogen-bond interactions between two molecules are single. The stereoscopic drawing, Fig. 4, shows such a

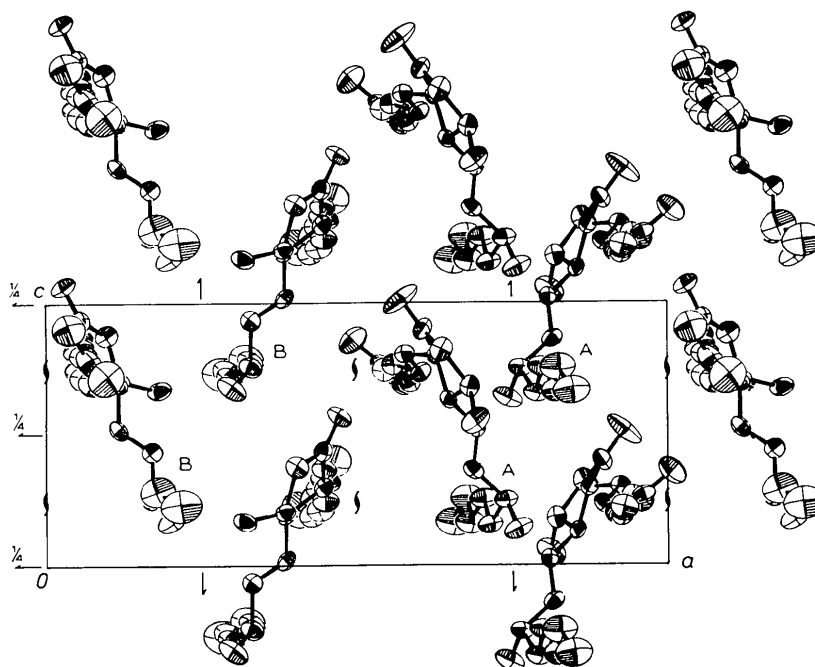


Fig. 5. Projection of part of the structure down  $b$  illustrating the chain packing. Only the molecules that pass through the plane at  $y = 0$  are shown.

dimeric  $AB$  unit. These subunits fit in a hydrogen-bond network that coils in a helical fashion around the two-fold screw axes in the  $c$  direction (Fig. 3). The bonds involved are the two carboxyl hydroxyl-carbonyl interactions [ $O(1B)_A-O(9)_B$  and  $O(1B)_B-O(9)_A$ ] and the interaction  $O(11)_A-O(14)_B$ . The interactions through hydrogen bonds of the type  $O-H \cdots O$  only extend over two dimensions, since there are no bonds of this type across the planes at  $x = 0$  or  $x = \frac{1}{2}$ . However, there is probably a weak interaction between these layers of the type  $C-H \cdots O$  involving the carbonyl  $O(14)_A$ , which is not involved in hydrogen-bonding otherwise, and the side-chain proton  $H2[C(2)]_B$ . In addition a  $C-H \cdots O$  interaction is found that is 'in line' with the previously mentioned triple hydroxyl-hydroxyl interaction between  $PGE_1-A$  and  $PGE_1-B$ .

#### Packing of the molecules

Going from  $y = 0$  to  $y = 1$ , regions in the structure with mainly chain packing alternate with regions with hydrogen bonds (Fig. 3). Fig. 5 shows a cross-section at  $y = 0$ . Because the chains are relatively short and because they are restricted in their rotation around the chain axes, they are not expected to pack in the same degree of order as they do in paraffin-like structures. Nevertheless a considerable amount of regularity is observed that may be described roughly by an orthorhombic subcell. In fact two of the three dimensions of the unit cell are determined by the dimensions of this subcell.

The author thanks Dr T. C. van Soest for providing the crystal and for preliminary work, Dr H. van Koningsveld for the collection of the data, Professor A. F. Peerdeman, Dr J. Kroon and Dr H. Krabbendam for their help and interest and Dr G. DeTitta for some valuable suggestions.

#### References

- ABRAHAMSSON, S. (1963). *Acta Cryst.* **16**, 409-418.  
 CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* **A24**, 321-324.  
 DETITTA, G. T. (1975). *Molecular Conformations of the Prostaglandins. A Review of the Crystallographic Results*. Internal Report, Medical Foundation of Buffalo, New York.  
 DETITTA, G. T., EDMONDS, J. W. & DUAX, W. L. (1975). *Prostaglandins*, **9**, 659-665.  
 DETITTA, G. T., EDMONDS, J. W., DUAX, W. L. & HAUPTMAN, H. (1975). Proc. 2nd Int. Prostaglandin Conf. Florence, Italy.  
 EDMONDS, J. W. & DUAX, W. L. (1974). *Prostaglandins*, **5**, 275-281.  
 EDMONDS, J. W. & DUAX, W. L. (1975). *J. Amer. Chem. Soc.* **97**, 413-417.  
 HAUPTMAN, H. (1974). *Acta Cryst.* **A30**, 472-476.  
 HOYLAND, J. R. & KIER, L. B. (1972). *J. Med. Chem.* **15**, 84-86.  
 MASLEN, E. N. (1967). *Acta Cryst.* **A22**, 945-946.  
 RABINOWITZ, I., RAMWELL, P. & DAVISON, P. (1971). *Nature, New Biol.* **233**, 88-89.  
 SPEK, A. L. (1975). Thesis, Univ. of Utrecht, The Netherlands.



STEWART, J. M., KRUGER, G. J., AMMON, H. L., DICKINSON, C. & HALL, S. R. (1972). The X-RAY system. Tech. Rep. TR192. Computer Science Center, Univ. of Maryland, College Park, Maryland.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

*Acta Cryst.* (1977). **B33**, 824–829

## The Crystal and Molecular Structure of 1-(Diphenylmethyl)azetidin-3-ol

BY S. RAMAKUMAR AND K. VENKATESAN

*Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, India*

AND S. T. RAO

*Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin, Madison, Wisconsin 53706, USA*

(Received 20 July 1976; accepted 27 August 1976)

1-(Diphenylmethyl)azetidin-3-ol is triclinic, space group  $P\bar{1}$ , with  $a = 8.479(2)$ ,  $b = 17.294(4)$ ,  $c = 10.606(3)$  Å,  $\alpha = 118.59(2)^\circ$ ,  $\beta = 100.30(2)^\circ$ ,  $\gamma = 89.63(2)^\circ$ ,  $Z = 4$ . The structure was solved by multi-solution methods and refined to an  $R$  of 0.044 for 2755 reflexions. The four-membered rings in the two independent molecules are puckered with dihedral angles of 156 and 153°. The two molecules differ in conformation with respect to rotation of the phenyl rings about the C–C bonds. The structure is stabilized by a network of O–H...N intermolecular hydrogen bonds.

### Introduction

A fundamental assumption in the analysis of structure–activity relationships is that the structure of the substrate molecule is complementary to that of the receptor. In order to obtain information about the mode of binding of acetylcholine and related compounds at its cholinergic receptor, X-ray investigations of many cholinergic agents have been carried out (Baker, Chothia, Pauling & Petcher, 1971). During the synthesis of rigid or semi-rigid analogues of acetylcholine, Chatterjee & Triggler (1968) obtained the title compound and an X-ray investigation was undertaken to establish the conformation and stereochemistry. The problem of the geometry of four-membered rings is a fascinating one. For example, the cyclobutane ring is found to occur in both planar and puckered forms (Moriarty, 1974; Cotton & Frenz, 1974). Results on the azetidine ring are limited and the title compound provides an opportunity to study its geometry.

### Experimental

Crystals were supplied by Dr S. Chatterjee. That used for data collection was  $0.3 \times 0.2 \times 0.6$  mm. The data were collected at Wisconsin on a Picker FACS-I

computer-controlled diffractometer with Cu  $K\alpha$  radiation. The intensities were measured in the  $\theta$ – $2\theta$  scan mode at a scan rate of  $2^\circ \text{ min}^{-1}$  and a scan width of  $(2 + 0.285 \tan \theta)^\circ$  for  $4^\circ \leq 2\theta \leq 125^\circ$ . The agreement between 600 inverse reflexions [ $2\sum |F_1 - F_2| / \sum (F_1 + F_2)$ ] was 0.02. The cell constants were determined by a least-squares fit on 12 reflexions with  $40^\circ \leq 2\theta \leq 50^\circ$ . Crystal data are summarized in Table 1. The final data set contained 3845 independent reflexions excluding the reflexions for which the net count was less than the net background. Reflexions with  $F_o < 2.0\sigma(F_o)$  were treated as unobserved. The data were corrected for the Lorentz–polarization factor but not for absorption ( $\mu r < 0.30$ ).

Table 1. *Crystal data*

$C_{16}H_{17}NO$	F.W. 239.32
Triclinic	$Z = 4$
Space group $P\bar{1}$	$F(000) = 512$
$a = 8.479(2)$ Å	$\alpha = 118.59(2)^\circ$
$b = 17.294(4)$	$\beta = 100.30(2)^\circ$
$c = 10.606(3)$	$\gamma = 89.63(2)^\circ$
$V = 1338(2)$ Å <sup>3</sup>	$\lambda(\text{Cu } K\alpha) = 1.5418$ Å
$D_m = 1.24$ g cm <sup>-3</sup>	$D_x = 1.188$ g cm <sup>-3</sup>
$\mu(\text{Cu } K\alpha) = 4.93$ cm <sup>-1</sup>	