Crystal Structure and Absolute Configuration of Caryophyllene Chlorohydrin

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The structure of caryophyllene chlorohydrin (V) has been determined by a three-dimensional X-ray diffraction study. Crystals are trigonal, $a = 13{\cdot}1_2$, $c = 7{\cdot}1_1$ Å, space group $P3_1$, with one molecule in the asymmetric unit. Anisotropic least-squares refinement, based on 1150 visually estimated intensities, has reduced R to 0·112. The molecule is geometrically analogous to norcaryophyllene alcohol. Its constitution and absolute stereochemistry provide evidence for a novel transannular cyclisation.

THE constitution and absolute stereochemistry of caryophyllene (I) emerged partly from a series of studies by Barton *et al.*,[1-5] and partly from an X-ray study by Robertson and Todd[6] of the caryolanyl halides (II) derived from caryophyllene alcohol. Treibs[7] had shown that the oxidation of caryophyllene furnished a crystalline oxide, $C_{15}H_{24}O$, m.p. 64 °C. On further oxidation by $KMnO_4$ in acetone this was converted into a mixture of two isomeric oxidoglycols (α-, m.p. 141 °C; β-, m.p. 119 °C), and an oxidoketone, $C_{14}H_{22}O_2$, m.p. 61—62 °C. The oxidoketone played a key role in the work of Barton *et al.*[1-3] They postulated it as the epoxyketone (III), and showed that it was converted by hydrogen chloride into a chlorohydrin, $C_{14}H_{23}ClO_2$, (m.p. 147 °C), postulated as (IV).

However, the n.m.r. spectrum of the chlorohydrin showed no evidence for C–Me other than the *gem*-dimethyl group.[8a,b] The present three-dimensional X-ray study, which was undertaken to clarify the constitution of caryophyllene chlorohydrin and to supply its stereochemistry, has in fact shown it to have the tricyclic structure and absolute stereochemistry (V), analogous to norcaryophyllene alcohol (see Figure 1).[9] The bridging methylene was unexpected when it was first identified in our maps, but simultaneous studies corroborated our

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[1] D. H. R. Barton and A. S. Lindsay, *J. Chem. Soc.*, 1951, 2988.

[2] D. H. R. Barton, T. Brown, and A. S. Lindsay, *J. Chem. Soc.*, 1952, 2210.

[3] A. Aebi, D. H. R. Barton, and A. S. Lindsay, *J. Chem. Soc.*, 1953, 3124.

[4] A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsay, *J. Chem. Soc.*, 1954, 4659.

[5] D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 1954, 4665.

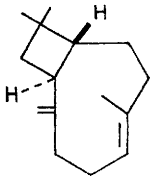
[6] J. M. Robertson and G. Todd, *J. Chem. Soc.*, 1955, 1254.

[7] W. Treibs, *Chem. Ber.*, 1947, **80**, 56.

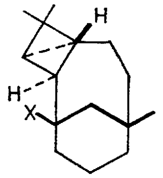
[8] (*a*) J. K. Sutherland, personal communication; (*b*) J. M. Greenwood, I. H. Qurreshi, and J. K. Sutherland, *Proc. Chem. Soc.*, 1963, 372.

[9] D. Rogers and Mazhar-ul-Haque, *Proc. Chem. Soc.*, 1963, 371.

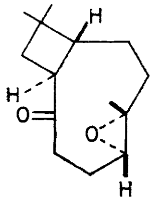
structure.[8b] The *X*-ray results and the chemical work taken together have established Barton's constitution



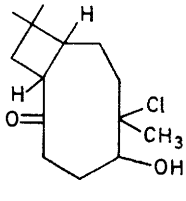
(I)



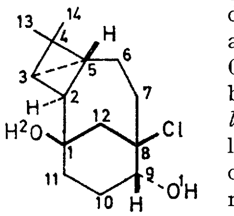
(II) a; X=OH
b; X=Cl
c; X=Br



(III)



(IV)



(V)

and stereochemistry (III) for Treib's oxidoketone, and have thrown light on the ready reversibility of the transannular cyclisation.

EXPERIMENTAL

The crystals originally supplied were very fine colourless hairs, and all attempts to grow them thicker at room temperature failed. Blocky trigonal prisms, m.p. 147 °C, were obtained accidentally from acetone solution evaporating slowly at unknown subzero temperatures: we have been unable to reproduce the crop. Both habits proved to have the same crystal structure.

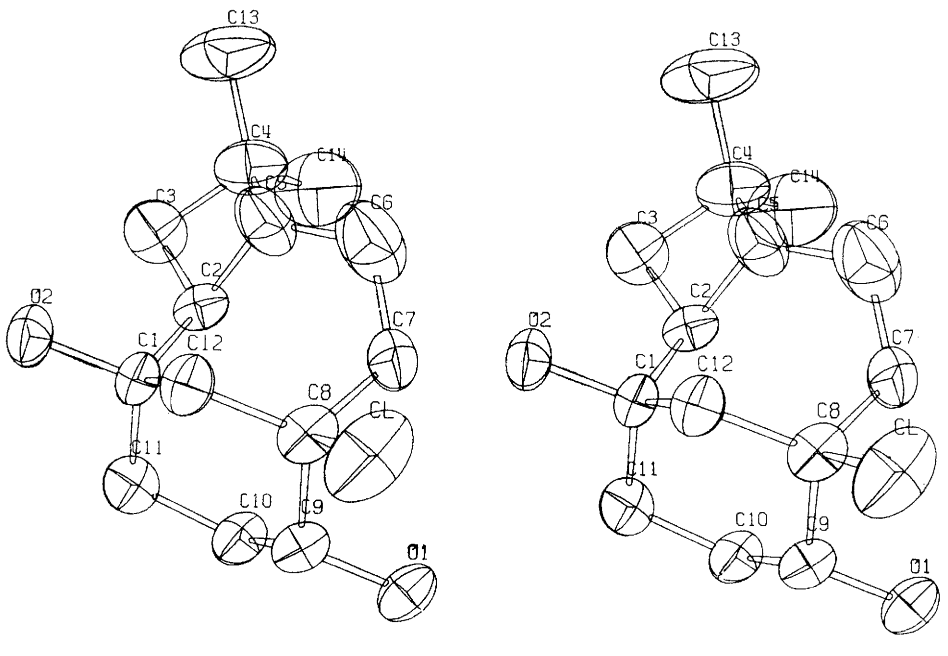


FIGURE 1 Stereopair for the molecule of caryophyllene chlorohydrin, showing the atom numbering

Crystal Data.—Caryophyllene chlorohydrin, $C_{14}H_{23}ClO_2$, $M = 258{\cdot}5$. Trigonal, $a = 13{\cdot}1_2$, $c = 7{\cdot}1_1$ Å, $U = 1060$ Å^3, $D_m = 1{\cdot}209$ g cm^{-3}, $Z = 3$, $D_c = 1{\cdot}21$ g cm^{-3}, $F(000) = 420$. Laue symmetry $\bar{3}$, and systematic absences confined to $00l$ for $l \neq 3n$. Optically active. Space group, $P3_1$ or its enantiomorph $P3_2$: the former was initially chosen arbitrarily but later shown to be correct. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å; μ(Cu-K_α) = 29·2 cm^{-1}.

Multiple-film Weissenberg photographs were taken with Cu-K_α radiation for layers $hk0$—6 for oscillation of the crystal around c, and $h0$—$2l$ for oscillation around a_2. Approximately 1150 independent intensities (of a possible 1400) were measured visually. No absorption corrections were applied as the prism used for the first set of photographs had a very regular hexagonal cross-section of diameter 0·375 mm. The crystals used for the subsidiary-axis data were trimmed to a square cross-section side *ca.* 0·42 mm. Lorentz and polarisation factors were applied by use of a program of C. K. Prout. The correlation of the l layers with layers $k = 0,1,2$ was done by hand. Preliminary estimates of scale and temperature factors were obtained by Wilson's method from the $hk0$ data, but were refined later.

Before calculating the three-dimensional Patterson the intensity data were sharpened by the empirical function, $(f_{Cl})^{-2} \exp(2 \sin^2\theta)$, which experience had shown to sharpen well without too much series-termination ripple. The chlorine positions were readily derived and their contributions to the structure factors were calculated. Only the terms $|F_{Cl}| \geqslant |F_o|/2$ were used for the first partial three-dimensional electron-density map. This was free of any pseudo-planes of symmetry, and showed ten possible peaks. The remaining atom positions emerged from the next few maps; those positions indicated by the last Fourier gave acceptable interatomic distances and angles and were adopted as the basis for refinement. The structure is depicted in (V), and Figure 1 shows the stereochemistry.

Nine cycles of isotropic least-squares refinement reduced R to 0·171, at which level changes in R and $\Sigma w|\Delta F|^2$ became small. The temperature factors of C(3)—C(6) and C(13) and C(14) (see Figure 1 for numbering) were higher than those of the other atoms, those of C(13) and C(14) being especially high, and the later cycles were concerned mainly with adjustments of these atoms.

A difference-Fourier at this stage showed some evidence for anisotropy of the chlorine and to a lesser extent of atoms C(5), C(8), C(9), C(14), and O(1), and a few peaks in positions expected for hydrogen atoms, the strongest of which reached 0·6 eÅ^{-3}.

Two cycles of anisotropic least squares brought R to 0·144. In a third cycle allowance was made for 15 hydrogen atoms, but they were not refined. The positions of the fifteen (*i.e.* all except those in the two methyl and the two hydroxy-groups) were calculated with a program of R. A. Sparks. Twelve of them agree with fairly well-defined peaks in the ΔF map, and left nothing in that map unexplained. Ten were given an isotropic B factor in each case 1 Å^2 greater than that of the isotropic equivalent of the carbon atom to which it is attached. The remainder were attached to atoms of high B and were given an equal value; their contribution is virtually negligible. For the last three cycles of refinement a weighting scheme of the form $\sqrt{w} = 1$ for $|F_o| \leqslant P$ and $\sqrt{w} = P/|F_o|$ if $|F_o| > P$ where $P = 20$.

The co-ordinates listed in Table 1 are related to a right-handed system of axes and space group $P3_1$. Corrections were made for the anomalous dispersion of chlorine (using $\Delta f''$ values from ref. 10) and applied both to the structure of Table 1 and to its enantiomorph. The former gave R 0·112 and the latter 0·117, a difference which confirms the absolute configuration as (V) with a confidence level $\gg 99\%$.[11] This assignment also eliminates space group $P3_2$ from consideration.

TABLE 1

Fractional co-ordinates ($\times 10^4$) for the non-hydrogen atoms, with their standard deviations in parentheses

Atom	x	y	z
Cl	−408(4)	1730(3)	6667
C(1)	−2063(8)	2428(8)	2471(14)
C(2)	−1057(8)	3271(8)	1178(14)
C(3)	−1079(12)	4217(12)	−23(22)
C(4)	286(13)	4989(11)	246(20)
C(5)	34(10)	4221(12)	2116(22)
C(6)	868(12)	3951(17)	3023(30)
C(7)	431(9)	2671(10)	3340(21)
C(8)	−761(8)	1879(8)	4313(14)
C(9)	−1405(9)	637(8)	3507(14)
C(10)	−1971(9)	604(9)	1649(16)
C(11)	−2744(9)	1203(9)	1697(15)
C(12)	−1595(9)	2371(9)	4385(15)
C(13)	690(19)	6319(12)	596(35)
C(14)	948(23)	4852(21)	−1293(41)
O(1)	−654(7)	150(6)	3257(11)
O(2)	−2856(6)	2882(6)	2818(12)

TABLE 2

Calculated co-ordinates ($\times 10^4$) for hydrogen atoms

	x	y	z
H(1)–C(2)	−784	2829	418
H(2)–C(3)	−1479	4585	591
H(3)–C(3)	−1213	3943	−1399
H(4)–C(5)	−225	4619	3183
H(5)–C(6)	1188	4380	4285
H(6)–C(6)	1632	4300	2265
H(7)–C(7)	1067	2565	3922
H(8)–C(7)	477	2325	2110
H(9)–C(9)	−1975	20	4403
H(10)–C(10)	−2436	−242	1192
H(11)–C(10)	−1309	998	661
H(12)–C(11)	−3466	701	2405
H(13)–C(11)	−2993	1243	343
H(14)–C(12)	−2238	1907	5278
H(15)–C(12)	−1158	3180	4948

TABLE 3

Comparison of the bond lengths (Å) in the molecules of caryophyllene chlorohydrin (col. 2) and caryolanyl chloride (col. 3), with standard deviations in parentheses

Cl–C(8)	1·77(1)	1·8 *
C(1)–C(2)	1·53(3)	1·6
C(1)–C(11)	1·50(3)	1·5
C(1)–C(12)	1·51(2)	1·6
C(1)–O(2)	1·45(2)	
C(2)–C(3)	1·52(3)	1·6
C(2)–C(5)	1·50(4)	1·6
C(3)–C(4)	1·57(4)	1·5
C(4)–C(5)	1·60(4)	1·6
C(4)–C(13)	1·57(4)	1·6
C(4)–C(14)	1·46(5)	1·6
C(5)–C(6)	1·46(3)	1·5
C(6)–C(7)	1·50(4)	1·6
C(7)–C(8)	1·54(4)	1·6
C(8)–C(9)	1·52(3)	1·5
C(8)–C(12)	1·52(2)	1·6
C(9)–C(10)	1·50(2)	1·5
C(9)–O(1)	1·43(2)	
C(10)–C(11)	1·56(2)	1·6

* Cl–C(1).

TABLE 4

Comparison of the valence angles (deg.), in the molecules of caryophyllene chlorohydrin (V) and caryolanyl chloride (IIb), with standard deviations in parentheses

	(V)	(IIb)
C(2)–C(1)–C(11)	112·9(8)	116
C(2)–C(1)–C(12)	110·6(8)	106
C(2)–C(1)–O(2)	109·9(8)	115 [a]
C(11)–C(1)–C(12)	108·5(8)	108
C(11)–C(1)–O(2)	109·6(9)	106 [a]
C(12)–C(1)–O(2)	105·0(9)	106 [a]
C(1)–C(2)–C(3)	124·5(8)	123
C(1)–C(2)–C(5)	116·8(9)	114
C(3)–C(2)–C(5)	88·3(9)	87
C(2)–C(3)–C(4)	88·7(10)	87
C(3)–C(4)–C(5)	83·4(10)	88
C(3)–C(4)–C(13)	112·3(11)	110
C(3)–C(4)–C(14)	112·7(13)	119
C(5)–C(4)–C(13)	114·6(12)	112
C(5)–C(4)–C(14)	119·5(14)	117
C(13)–C(4)–C(14)	111·3(13)	110
C(2)–C(5)–C(4)	88·0(10)	84
C(2)–C(5)–C(6)	120·9(12)	112
C(4)–C(5)–C(6)	125·2(13)	124
C(5)–C(6)–C(7)	115·3(15)	113
C(6)–C(7)–C(8)	121·0(12)	113
Cl–C(8)–C(7)	105·4(8)	112 [b]
Cl–C(8)–C(9)	105·9(10)	107 [b]
Cl–C(8)–C(12)	107·3(7)	110 [b]
C(7)–C(8)–C(9)	112·7(11)	110
C(7)–C(8)–C(12)	115·5(9)	110
C(9)–C(8)–C(12)	109·5(11)	108
C(8)–C(9)–C(10)	111·3(11)	110
C(8)–C(9)–O(1)	112·8(10)	
C(10)–C(9)–O(1)	108·6(10)	
C(9)–C(10)–C(11)	113·6(11)	115
C(1)–C(11)–C(10)	110·9(9)	110
C(1)–C(12)–C(8)	112·7(11)	113

[a] C–C–Cl. [b] Me–C–C.

DISCUSSION

The atomic co-ordinates and standard deviations (from the least-squares refinement) are listed in Table 1,

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[10] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1968, 214.

[11] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

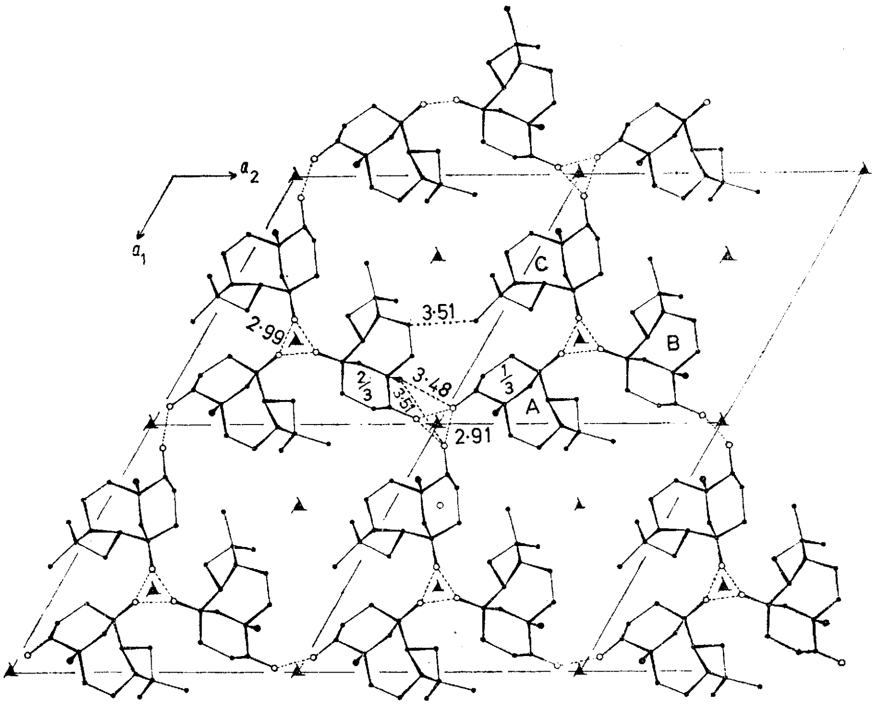


FIGURE 2 The [001] projection showing the two distinct spirals of hydrogen bonds and the large tubular cavity surrounding the third screw axis. The co-ordinates quoted in Table 1 are for the molecule marked A. The other two (B and C) facilitate correlation with Figure 3.

and the calculated hydrogen co-ordinates in Table 2. The bond lengths and valence angles are listed (with their standard deviations) in Tables 3 and 4, and the torsion and dihedral angles in Table 5. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20881 (2 pp., 1 microfiche),* which also includes a Table of the anisotropic thermal parameters of the atoms in Table 1.

Figure 1 depicts one molecule and shows the atomic numbering used. Figures 2 and 3 show the [001] and [100] projections of the structure, and together present four different views of the molecule. A comparison of the three different views (at 120° intervals) in Figure 3 shows that: (*a*) the six-membered ring, though slightly flattened, has a regular chair form (see also Figure 1), and its three free substituents are all equatorial; (*b*) the seven-membered ring, despite its fusion with two other rings, is surprisingly regular and adopts a boat conformation; and (*c*) the cyclobutane ring is *trans*-fused as expected and non-planar.

Bond lengths and valence angles are almost all as expected. C(5)–C(6) and C(4)–C(14) are shorter and C(4)–C(5) longer than expected, but in view of their standard deviations the abnormalities are not statistically significant. However, the 'long' bond, C(4)–C(5), is accompanied by enlargements of the angles at C(4) and C(5) (Figure 4). Together they suggest a consistent pattern of strains arising from the non-bonded contact C(6) · · · C(14) 3·27 Å.

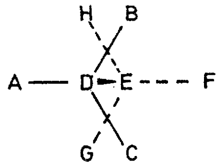
TABLE 5

Comparison of the dihedral angles (deg.), in the molecules of caryophyllene chlorohydrin (V) and caryolanyl chloride (IIb)

		(V)	(IIb)			(V)	(IIb)
O(2) (*1*, 2)	*11*	−123	−124	*6* (*7*, 8)	9	146	153
	12	117	117		12	20	34
	3	−19	−20		Cl	−99	−89
	5	89	82	*7* (*8*, 9)	*12*	−129	−120
1 (*2*, 3)	*5*	122	116		Cl	115	108
	4	149	145		10	−76	−65
2 (*3*, 4)	5	−25	−29		O(1)	46	
	13	−136	−141	*8* (*9*, 10)	O(1)	125	
	14	98	91		11	−50	−58
3 (*4*, 5)	*13*	−113	−110	*9* (*10*, 11)	1	51	60
	14	115	122	*10* (*11*, 1)	2	68	62
	2	26	29		12	−52	−56
	6	150	141		O(2)	−169	−170
1 (*2*, 5)	*3*	−128	−124	*2* (*1*, 12)	*11*	−122	−124
	4	−154	−152		O(2)	119	
	6	77	84		8	−63	−65
2 (*5*, 6)	*4*	109	98	*1* (12, 8)	7	68	64
	7	−13	−8		9	−59	−57
5 (*6*, 7)	8	−53	−71		Cl	174	187

Average standard deviations are *ca.* 1°.

All dihedral angles are denoted as follows:



A(*D*,E) X when viewing from atom D to E. *A*,*D* are in italics to denote the nearer group and so too is X if it is connected to D, *i.e.* B or C. All rotations are quoted from the position of A and reckoned positive if clockwise.

Angles not quoted above are readily deducible, *e.g.* *12*, (*1*, 2) 5 is 89 − 117, − 28°

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* See Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

The cyclobutane ring is markedly nonplanar. The average deviation of its atoms is 0·17 Å; the two diagonals miss each other by 0·35 Å, and the dihedral (fold) angles across these diagonals are 36·5° [across C(2)–C(4)] and 35·8° [across C(3)–C(5)]. The torsion angles around this ring are given in Table 5. There is one large ring angle (121°) at C(7), probably due to strain reflected from the cyclobutane ring.

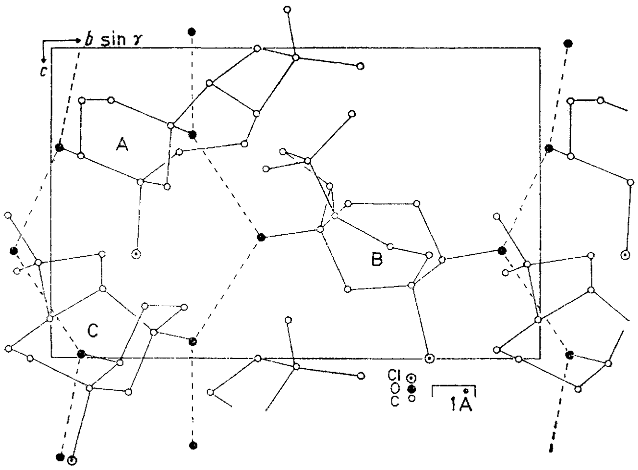

FIGURE 3 The [100] projection showing the packing of the molecules and the hydrogen bonds. Three different aspects of the molecule (A,B,C) appear

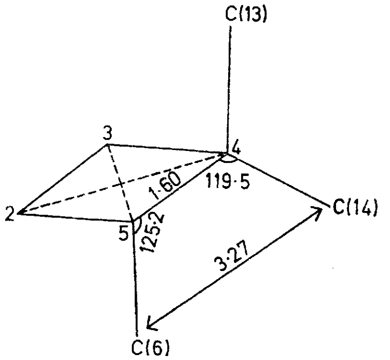

FIGURE 4 Details of the interaction between the *gem*-dimethyl group and C(6)

The most noteworthy feature of the molecule is the close similarity of its tricyclic nucleus to that found by Robertson and Todd [6] in caryolanyl chloride (IIb). This was unexpected in view of the very different processes of cyclisation. A comparison of the measured bonds, valence and dihedral angles (Tables 3—5) suggests that this system is relatively rigid and only slightly affected by variations in its substituents. Robertson and Todd's work was only two-dimensional, and the atomic coordinates were not refined as thoroughly as they would be today. Nevertheless, the correspondence applies even to details. Thus, in the cyclobutane ring their diagonals fail to intersect by 0·44 Å [*cf.* 0·35 Å in (V)] and the same one is uppermost [shown dotted in both (II) and (V)].

Figures 2 and 3 show how the molecules are linked together to form two distinct hydrogen-bonded spirals, leaving a large cylindrical cavity (6—7 Å in diameter) around the third screw, which may explain the difficulties met in growing thick prisms. There is nothing in this hole in our maps, and the atoms that line it [notably C(3), C(5), C(6), C(13), and C(14)] have β_{ij} values which indicate vigorous oscillation mainly parallel to the c axis, which doubtless explains the rather large standard deviations of these atoms.

The only intermolecular contacts <3·6 Å are shown in Figure 2. They are (i) C(6) · · · C(13) 3·51; (ii) O(1) · · · O(1′) 2·99, and O(2) · · · O(2′) 2·91 Å, which represent relatively weak hydrogen bonds; and (iii) two between Cl and OH [Cl · · · O(2′) 3·48 and Cl · · · O(2″) 3·51 Å] both of which must be van der Waals contacts (sum of Pauling radii 3·20 Å) as there are no hydrogen atoms in these gaps. The low-density packing is, therefore, controlled principally by the O · · · O hydrogen bonds. Angles (deg.) involved in the hydrogen spirals are

(i) around $00z$:
C(9,A)–O(1,A) · · · O(1,B) 116·6
C(9,A)–O(1,A) · · · O(1,C) 121·5
O(1,B) · · · O(1,A) · · · O(1,C) 119·8

(ii) around $\frac{2}{3}\frac{1}{3}z$:
C(1,A)–O(2,A) · · · O(2,B) 127·5
C(1,A)–O(2,A) · · · O(2,C) 115·1
O(2,B) · · · O(2,A) · · · O(2,C) 116·1

They are consistent with hydrogen bonding.

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