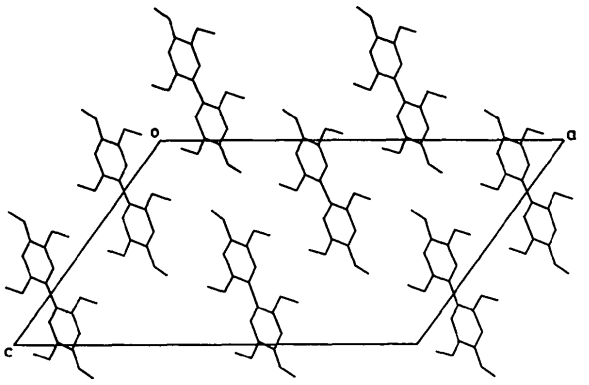

Fig. 2. View of the crystal structure.

effects of the methoxy groups (Domenicano & Murray-Rust, 1979) can be attributed to the $+R$ effect of the methoxy group (Chattopadhyay, Banerjee, Mazumdar & Podder, 1985).

The molecular packing in the crystal is shown in Fig. 2. The molecules are stacked along **b** to form a column in which the interplanar distance between the phenyl rings is 3·487 (4) Å, the intermolecular H(6)···O(1) being 2·52 (3) Å. The columns related by a centre of symmetry at $\frac{1}{4}$, $\frac{1}{4}$, 0 are held together by van der Waals interactions between the methoxyphenyl rings with an interplanar distance of 3·428 (4) Å to form a sheet in (101). The sheets related by a *c* glide plane are stacked along **c** to complete the whole structure, the shortest intermolecular distance being 2·69 (5) Å for H(92)···O(1).

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A Highly Potent Angiotensin Converting Enzyme Inhibitor: (*S,S,S*)-5-[*N*-(1-Carboxy-3-phenylpropyl)alanyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-4-carboxylic Acid Monohydrate, SBG 107

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Abstract. $C_{21}H_{24}N_2O_5S.H_2O$, $M_r = 434{\cdot}51$, orthorhombic, $P2_12_12_1$, $a = 18{\cdot}192$ (3), $b = 11{\cdot}886$ (2), $c = 10{\cdot}088$ (2) Å, $V = 2181$ (1) Å^3, $Z = 4$, $D_m = 1{\cdot}327$ (7), $D_x = 1{\cdot}323$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 16{\cdot}26$ cm^{-1}, $F(000) = 920$, $T = 295$ K, $R = 3{\cdot}8\%$ for 1763 observed reflections. The molecule is present in its zwitterionic form in the crystal. In the non-protein *C* terminal amino acid the tetrahydrothienopyridine

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ring adopts a conformation between an envelope form ^2E [C(2) out-of-plane atom] and a half-chair form ^2H_N [C(2) and N(1) out-of-plane atoms]. The thiophene ring is equatorially annulated to the tetrahydropyridine ring, the amide carbonyl C atom C(10) is in a bisectional and the carboxylic C atom C(91) is in a quasiaxial position.

Introduction. Inhibition of the physiologically important angiotensin converting enzyme (ACE) by competitive inhibitors proved to be a useful approach in the treatment of hypertension (Brunner, Turini, Waeber, Nussberger & Biollaz, 1983). Orally active ACE inhibitors have been designed on the basis of a postulated model of the active site of this enzyme (Ondetti, Rubin & Cushman, 1977).

In the course of our molecular modelling studies on ACE inhibitors we tried to improve the existing model. Thus we studied the influence of more lipophilic nonprotein condensed cyclic amino acids in the *C* terminal position on enzyme interaction. In order to obtain a suitable starting conformation the structure of the title compound, SBG 107, a new highly potent ACE inhibitor, was determined.

Experimental. Small colourless almost cube-shaped crystals, 0·2 × 0·2 × 0·3 mm, from ethanol by very slow evaporation. DEC PDP 15/40-controlled Siemens-AED diffractometer, Ni-filtered Cu $K\alpha$ radiation, lattice parameters from 24 high-order reflections ($30 \le \theta \le 50°$). One octant ($0 \le h \le 21$, $0 \le k \le 13$, $0 \le l \le 11$) of independent reflections measured, ω–2θ scan, $(\sin\theta/\lambda)_{max} = 0{\cdot}585$ Å^{-1}, 2099 reflections, 336 unobserved [$I < 2\sigma(I)$], two standard reflections indicated intensity decrease of 20% which was rescaled. No absorption or extinction correction, D_m by flotation.

Phase problem solved by direct methods (*MULTAN*, Main, Lessinger, Woolfson, Germain & Declercq, 1977). One additional water oxygen atom located in a difference synthesis, hence SBG 107 present as monohydrate in the crystal.

Least-squares refinement with isotropic, then with anisotropic temperature factors for non-hydrogen atoms, hydrogens all located from difference syntheses, isotropic (*XRAY76*, Stewart, Machin, Ammon, Dickinson, Heck & Flack, 1976); $\sum(F_o - F_c)^2$ minimized, unit weights, since ΔF showed little variation *versus* F_o and $\sin\theta$; unobserved reflections included only if $|F_c| > |F_o|$; atomic scattering factors from the standard routine of *XRAY76* (Cromer & Mann, 1968; Stewart, Davidson & Simpson, 1965); complex anomalous-dispersion correction applied for sulfur (*International Tables for X-ray Crystallography*, 1974). After convergence $R = 3{\cdot}8\%$ for observed reflections; $(\Delta/\sigma)_{max} = 1{\cdot}5$ (x coordinate of one water hydrogen atom), $(\Delta/\sigma)_{av} = 0{\cdot}08$; $\Delta\rho_{max} = 0{\cdot}16$, $\Delta\rho_{min} = -0{\cdot}21$ e Å^{-3} in final difference synthesis. Absolute configuration chosen according to the known L-alanine residue. All calculations on a CDC Cyber 175 computer (Wissenschaftliches Rechenzentrum, WRB Berlin).*

Discussion. Fractional coordinates of the title compound are listed in Table 1. Bond lengths and the chosen atomic numbering scheme are given in Fig. 1, a stereoview (*ORTEP*, Johnson, 1971) of the molecular structure is given in Fig. 2 and bond angles are listed in Table 2.

* Lists of observed and calculated structure factors, anisotropic thermal parameters, and a number of torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43424 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Atomic parameters* (U_{eq} *and* U *in* Å$^2 \times 10^2$) *of* SBG 107

U_{eq} values were calculated according to Hamilton (1959).

	x	y	z	U_{eq} or U
O(1*W*)	0·3420 (2)	0·6231 (4)	0·4707 (5)	8·6 (2)
N(1)	0·0211 (2)	0·6012 (3)	0·3155 (4)	5·6 (1)
C(2)	0·0048 (3)	0·6610 (5)	0·4406 (5)	7·1 (2)
C(3)	−0·0395 (4)	0·5849 (8)	0·5297 (6)	9·7 (3)
C(4)	−0·1033 (3)	0·5409 (6)	0·4495 (6)	8·4 (2)
S(5)	−0·1827 (1)	0·4877 (2)	0·5173 (2)	11·95 (9)
C(6)	−0·2204 (3)	0·4650 (6)	0·3651 (8)	9·6 (3)
C(7)	−0·1734 (3)	0·4955 (5)	0·2667 (7)	7·7 (2)
C(8)	−0·1056 (3)	0·5391 (4)	0·3158 (5)	6·0 (2)
C(9)	−0·0420 (3)	0·5763 (4)	0·2312 (5)	5·3 (2)
C(91)	−0·0623 (3)	0·6774 (4)	0·1460 (5)	5·6 (2)
O(911)	−0·0396 (2)	0·7712 (3)	0·1644 (4)	7·9 (1)
O(912)	−0·1106 (2)	0·6501 (3)	0·0534 (3)	6·7 (1)
C(10)	0·0882 (3)	0·5741 (4)	0·2710 (4)	5·1 (1)
O(101)	0·0986 (2)	0·5287 (3)	0·1629 (3)	6·2 (1)
C(11)	0·1541 (3)	0·6040 (4)	0·3588 (5)	4·8 (1)
C(111)	0·1802 (4)	0·7220 (5)	0·3260 (7)	7·2 (2)
N(12)	0·2141 (2)	0·5229 (3)	0·3343 (4)	4·4 (1)
C(13)	0·1975 (2)	0·4037 (4)	0·3712 (4)	4·2 (1)
C(131)	0·2005 (2)	0·3916 (4)	0·5231 (4)	4·5 (1)
O(131)	0·2282 (2)	0·4715 (3)	0·5853 (3)	5·9 (1)
O(132)	0·1759 (2)	0·3031 (3)	0·5721 (3)	5·9 (1)
C(14)	0·2499 (3)	0·3217 (4)	0·3014 (4)	4·8 (1)
C(15)	0·3302 (3)	0·3391 (5)	0·3355 (5)	6·0 (2)
C(16)	0·3820 (2)	0·2524 (4)	0·2743 (4)	5·2 (1)
C(17)	0·3620 (3)	0·1775 (4)	0·1770 (5)	6·2 (2)
C(18)	0·4104 (3)	0·0994 (4)	0·1266 (6)	7·1 (2)
C(19)	0·4814 (3)	0·0963 (5)	0·1719 (7)	8·1 (2)
C(20)	0·5033 (3)	0·1705 (6)	0·2664 (8)	8·7 (2)
C(21)	0·4541 (3)	0·2473 (5)	0·3183 (6)	7·2 (2)
H(1*W*)	0·351 (5)	0·691 (9)	0·41 (1)	25 (5)
H(2*W*)	0·385 (5)	0·597 (8)	0·56 (1)	23 (4)
H(201)	−0·015 (3)	0·735 (5)	0·409 (5)	9 (2)
H(202)	0·052 (3)	0·691 (4)	0·483 (5)	8 (2)
H(301)	−0·062 (5)	0·658 (8)	0·59 (2)	23 (5)
H(302)	−0·012 (4)	0·501 (6)	0·558 (7)	14 (3)
H(6)	−0·269 (4)	0·412 (6)	0·360 (8)	16 (3)
H(7)	−0·182 (4)	0·497 (7)	0·176 (8)	16 (3)
H(9)	−0·028 (2)	0·511 (3)	0·176 (4)	4 (1)
H(912)	−0·134 (3)	0·736 (6)	−0·003 (7)	14 (3)
H(11)	0·143 (2)	0·600 (3)	0·454 (4)	5 (1)
H(1111)	0·143 (3)	0·771 (4)	0·339 (5)	8 (2)
H(1112)	0·190 (3)	0·729 (5)	0·226 (6)	12 (2)
H(1113)	0·221 (3)	0·740 (4)	0·386 (5)	8 (2)
H(121)	0·252 (3)	0·545 (4)	0·386 (5)	6 (1)
H(122)	0·226 (2)	0·528 (4)	0·255 (5)	6 (2)
H(13)	0·143 (3)	0·386 (4)	0·346 (5)	8 (2)
H(141)	0·232 (2)	0·238 (4)	0·321 (4)	5 (1)
H(142)	0·245 (3)	0·322 (4)	0·203 (5)	8 (2)
H(151)	0·345 (3)	0·428 (4)	0·312 (5)	7 (2)
H(152)	0·338 (3)	0·338 (5)	0·434 (6)	11 (2)
H(17)	0·308 (3)	0·174 (4)	0·141 (5)	7 (1)
H(18)	0·396 (3)	0·043 (4)	0·052 (5)	9 (2)
H(19)	0·520 (3)	0·047 (4)	0·135 (5)	8 (2)
H(20)	0·551 (3)	0·164 (5)	0·304 (6)	10 (2)
H(21)	0·467 (3)	0·301 (5)	0·386 (6)	9 (2)

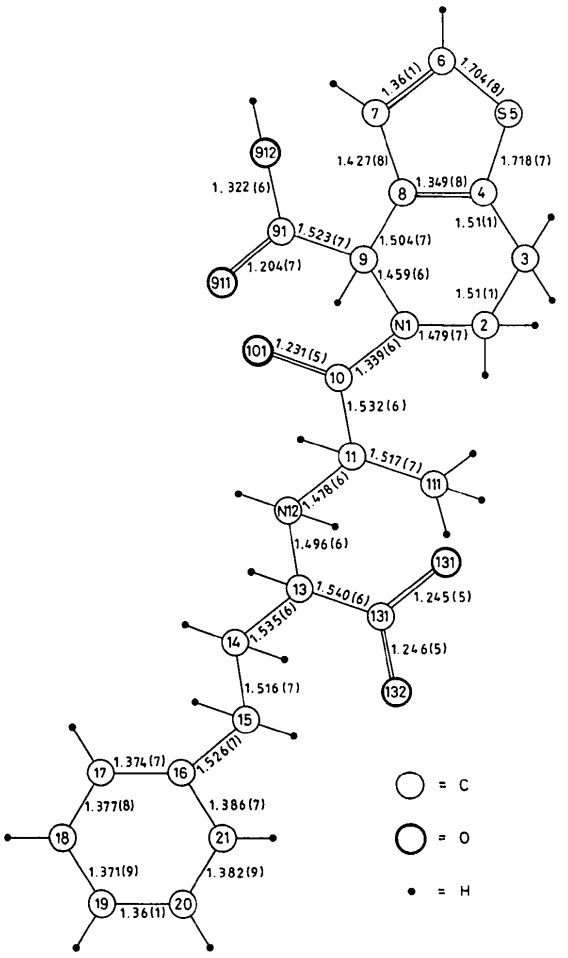

Fig. 1. Schematic drawing of the molecular skeleton, showing bond lengths (Å, e.s.d.'s in parentheses) and the numbering scheme used.

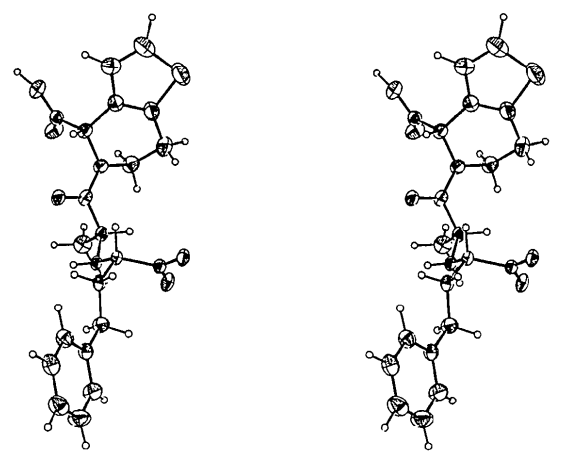

Fig. 2. Stereoview (*ORTEP*, Johnson, 1971) of the molecular structure, with the thermal ellipsoids drawn at 30% probability.

Table 2. *Bond angles* (°) *for* SBG 107 (*e.s.d.'s in parentheses*)

C(2)–N(1)–C(9)	115·9 (4)	O(101)–C(10)–C(11)	119·6 (4)
C(2)–N(1)–C(10)	125·8 (4)	C(10)–C(11)–C(111)	109·5 (4)
C(9)–N(1)–C(10)	118·2 (4)	C(10)–C(11)–N(12)	109·3 (4)
N(1)–C(2)–C(3)	109·1 (5)	C(111)–C(11)–N(12)	109·6 (4)
C(2)–C(3)–C(4)	107·4 (5)	C(11)–N(12)–C(13)	115·2 (3)
C(3)–C(4)–S(5)	124·1 (5)	N(12)–C(13)–C(131)	109·2 (3)
C(3)–C(4)–C(8)	124·4 (5)	N(12)–C(13)–C(14)	111·2 (3)
S(5)–C(4)–C(8)	111·5 (4)	C(131)–C(13)–C(14)	112·0 (3)
C(4)–S(5)–C(6)	92·2 (3)	C(13)–C(131)–O(131)	116·5 (4)
S(5)–C(6)–C(7)	111·3 (5)	C(13)–C(131)–O(132)	117·4 (4)
C(6)–C(7)–C(8)	112·8 (6)	O(131)–C(131)–O(132)	126·1 (4)
C(4)–C(8)–C(7)	112·3 (5)	C(13)–C(14)–C(15)	114·1 (4)
C(4)–C(8)–C(9)	122·6 (5)	C(14)–C(15)–C(16)	114·3 (4)
C(7)–C(8)–C(9)	125·1 (5)	C(15)–C(16)–C(17)	124·2 (4)
N(1)–C(9)–C(8)	109·5 (4)	C(15)–C(16)–C(21)	118·9 (4)
N(1)–C(9)–C(91)	111·1 (4)	C(17)–C(16)–C(21)	116·8 (5)
C(8)–C(9)–C(91)	111·4 (4)	C(16)–C(17)–C(18)	122·0 (5)
C(9)–C(91)–O(911)	124·1 (4)	C(17)–C(18)–C(19)	119·9 (5)
C(9)–C(91)–O(912)	111·5 (4)	C(18)–C(19)–C(20)	119·4 (6)
O(911)–C(91)–O(912)	124·3 (5)	C(19)–C(20)–C(21)	120·4 (6)
N(1)–C(10)–O(101)	122·8 (4)	C(16)–C(21)–C(20)	121·4 (5)
N(1)–C(10)–C(11)	117·6 (4)		

SBG 107 exists in its zwitterionic form in the crystal. This is supported by a number of observations. First, two protons were located unambiguously at the nitrogen N(12); second, both N(12)–C bonds are longer than normal N–C bonds of unprotonated nitrogens; third, a comparison of bond lengths for the two carboxyl groups at C(9) and C(13) shows the group at C(13) to be deprotonated. This follows from the almost equal bond lengths C(131)–O(131) and C(131)–O(132), the unequal C–O bonds at C(91) and the fact that no proton was located either at O(131) or at O(132), but one was found at O(912).

In the bicyclic tetrahydrothienopyridine ring, the five-membered ring is planar with an average deviation of the ring atoms from a least-squares plane of $\sigma = 0{\cdot}006$ Å. The S–C bond lengths and the bond angle at S(5) are in the normal range for a thiophene ring; the same holds for the neighbouring C=C double bonds C(4)–C(8) and C(6)–C(7).

The six-membered ring is *not* planar. A calculation (Luger & Bülow, 1983) of puckering parameters after Cremer & Pople (1975) based on a choice of N(1) and C(2) as ring atoms 1 and 2 indicates this ring to have a conformation between an envelope form ^2E [C(2) as the out-of-plane atom] and a half-chair form ^2H_N with C(2) and N(1) as the out-of-plane atoms [$Q = 0{\cdot}502$ (6) Å, $\theta = 126{\cdot}9$ (7), $\varphi = 225{\cdot}6$ (9)°]. C(7) and S(5) are equatorially substituted on the six-membered ring whereas C(10) is in a bisectional and C(91) in a quasiaxial position (Jeffrey & Yates, 1979).

The N–C bond lengths at N(1) are in good agreement with values previously found in cyclic amino acids. From a comparative study on proline derivatives, Benedetti, Bavoso, de Blasio, Pavone & Pedone (1983) report an average length for the N–C_α bond of 1·462 Å; for SBG 107 the N(1)–C(9) distance is 1·459 (6) Å. In the same study N–C_δ was 1·474 Å; the comparable bond N(1)–C(2) is 1·479 (7) Å.

Further, the peptide bond to the alanine residue N(1)–C(10) = 1·339 (6) Å and the C=O bond C(10)–O(101) [1·231 (5) Å] have comparable lengths to those reported by Benedetti *et al.* (1983) for a *trans* peptide bond (1·337 and 1·230 Å).

In the alanine residue bond lengths and angles are in the range normally found in alanine parts of oligopeptides (Mohana & Mamannamana, 1980; Kojima, Tanaka & Ashida, 1982) with the following exceptions [caused probably by the protonation of N(12)]: C(11)–N(12) = 1·478 (6) Å is longer than a normal alanine N–C_α bond, which is about 1·455 Å; the bond angles at C(11) (C′–C–N) and N(12), having values of 109·3 (4) and 115·2 (3)°, are smaller than normal (114 and 120°).

All other bond lengths and angles in the chain C(13) to C(16) and in the phenyl ring C(16) to C(21) are as expected.

The overall molecular conformation can best be described by the selected torsion angles displayed as Newman projections in Fig. 3. The carboxyl group at C(9) adopts an almost synplanar conformation with a torsion angle N(1)–C(9)–C(91)–O(911) of $\psi = -14{\cdot}0\ (7)°$. This has also been found for the carboxyl group of captopril (Fujinaga & James, 1980), a further ACE inhibitor. In this compound the torsion angle φ along the N–C_α bond was found at −67·3°; this angle is larger in the present structure, $\varphi = C(10)–N(1)–C(9)–C(91) = -93{\cdot}6\ (6)°$. The torsion angle along N(1)–C(10) [$\omega = C(9)–N(1)–C(10)–C(11) = 178{\cdot}1\ (4)°$] shows the presence of a *trans* peptide bond.

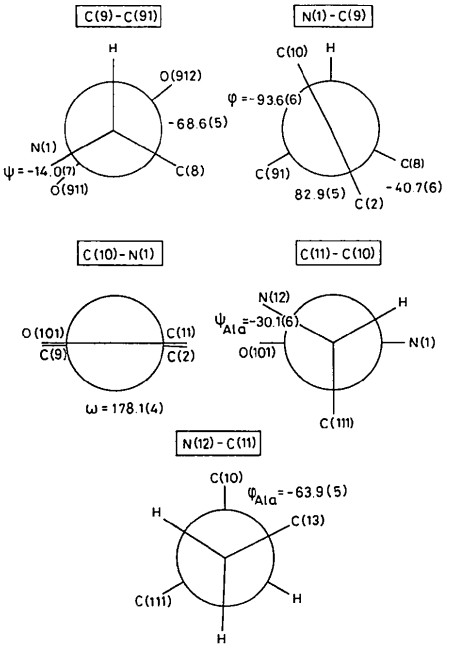

Fig. 3. Illustration of the molecular conformation by a number of Newman projections.

This is also the case for captopril so that both structures have similar conformations in that the amide carbonyl points in the same direction as the carboxyl group at C(9). This does not hold for a captopril analogue {*S*,*S*-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic acid} investigated by Vrieling & Codding (1984). These authors report an opposite orientation, *i.e.* a *cis* peptide bond.

In the alanine part the torsion angles of interest are ψ_{ala} [= O(101)–C(10)–C(11)–N(12)] = −30·1 (6)° and φ_{ala} [= C(10)–C(11)–N(12)–C(13)] = −63·9°. These conformational angles cause the methyl group C(111) to point in the same direction as the carboxyl group at C(9) whereas the carboxyl group at C(13) points in the opposite direction. The linear chain N(12)···C(15) has a *trans–gauche–trans* conformation. The deprotonated carboxyl group is synplanar with the nitrogen atom N(12) of the alanine residue, as was also found for the carboxyl group at C(9).

Table 3. *Summary of hydrogen-bond distances* (Å, °) *with e.s.d.'s in parentheses*

X–H···*Y*	*X*···*Y*	*X*–H	H···*Y*	*X*–H···*Y*	Symmetry operation for *Y*
N(12)–H(121)···O(1*W*)	2·954 (6)	0·90 (5)	2·07 (5)	167 (8)	*x*, *y*, *z*
N(12)–H(121)···O(131)	2·618 (5)	0·90 (5)	2·23 (5)	105 (4)	*x*, *y*, *z*
N(12)–H(122)···O(131)	2·723 (5)	0·83 (5)	1·90 (5)	168 (5)	$\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$
O(1*W*)–H(2*W*)···O(101)	2·861 (6)	1·2 (1)	1·9 (1)	136 (9)	$\frac{1}{2}-x, 1-y, \frac{1}{2}+z$
O(912)–H(912)···O(132)	2·514 (5)	1·24 (7)	1·31 (7)	161 (6)	$-x, \frac{1}{2}+y, \frac{1}{2}-z$

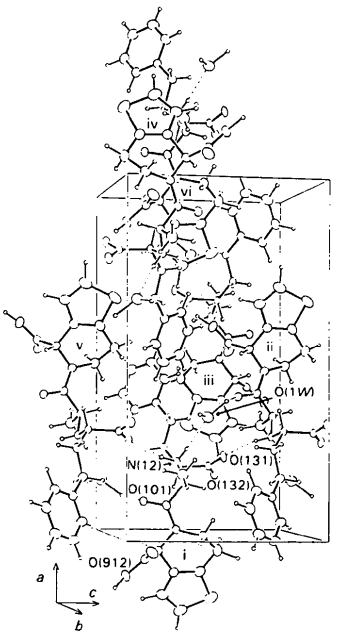

Fig. 4. The contents of the unit cell of SBG 107. Dotted lines indicate intermolecular hydrogen bonds. Molecules generated by the following symmetry operations are drawn: (i) *x*, *y*, *z*; (ii) $\frac{1}{2}-x$, $1-y$, $\frac{1}{2}+z$; (iii) $\frac{1}{2}+x$, $\frac{1}{2}-y$, $1-z$; (iv) $1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$; (v) $\frac{1}{2}-x$, $1-y$, $-\frac{1}{2}+z$; (vi) $1+x$, *y*, *z*.

The crystal structure comprises molecules of SBG 107 and water linked by a complex system of intermolecular hydrogen bonds (see Table 3). There is one strong hydrogen bond [O(912)—H(912)···O(132)'] between the two carboxyl groups where the O—H [1·24 (7) Å] and H···O [1·31 (7) Å] distances are almost equal with respect to the standard deviations.

The above-mentioned hydrogen bond causes a connection along the **b** direction, all further bonds of that type contribute to a network in the *ac* plane (see Fig. 4). N(12) has intramolecular N···O contacts to O(101) and O(131) of 2·723 (5) and 2·618 (5) Å. The corresponding H···O contacts of the protons H(122) and H(121) are 2·50 (4) and 2·23 (5) Å. The H(122)···O(101) contact is rather large; however, at least the N(12)—H(121)···O(131) contact can be coded as an intramolecular hydrogen bond.

The high inhibitory potency of SBG 107 suggests that an additional hydrophobic pocket can be integrated in the postulated model of the ACE at the position of the thiophene ring found in this X-ray analysis.

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1,2,3,4-Tetrachlorodibenzo-*p*-dioxin*

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Abstract. $C_{12}H_4Cl_4O_2$, $M_r = 321{\cdot}98$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 4{\cdot}820$ (1), $b = 14{\cdot}666$ (2), $c = 16{\cdot}917$ (2) Å, $V = 1196{\cdot}0$ Å^3, $Z = 4$, $D_x = 1{\cdot}79$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 0{\cdot}98$ mm^{-1}, $F(000) = 640$, $T = 296$ K, final $R = 0{\cdot}037$ for 543 unique observed reflections. The large size of the molecule does not allow it to fit into the dioxin receptor and therefore it does not have similar toxic effects to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Molecular dimensions are: maximum length 9·405 (3) Å [Cl(3)—H(10)], maximum height 6·182 (3) Å [Cl(1)—Cl(4)]. A small deviation from planarity occurs; the maximum distance from the least-squares plane is 0·081 (4) Å [Cl(2)].

Introduction. It has been suggested that the extreme toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is related to its molecular structure. The dioxin receptor theory as proposed by Poland & Knutson (1982) and Gillner, Fernström, Gustafsson, Cambilleau & Bergman (1985) proposes that the dimensions of the TCDD molecule allow it to fit exactly into a particular liver cell receptor (now called the dioxin receptor) and cause cytochrome-488 induction. This induction is the manifestation of the extreme toxicity of TCDD. The purpose of our study was to solve the molecular

* 1,2,3,4-Tetrachlorodibenzo[*b*,*e*][1,4]dioxin.

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