linking N(1) in one unit cell to O(3)—C(15) in an adjacent cell. All three chiral centres were found to have the *R* configuration. Although it is the *S* configuration at C(13) which is critical for activity, the results of the present study were used to identify the other stereoisomers which were produced in the chemical synthesis so that the configurations of the active compounds were known unambiguously.

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SQ 14,225: 1-(D-3-Mercapto-2-methylpropionyl)-L-proline

BY MASAO FUJINAGA AND MICHAEL N. G. JAMES

Medical Research Council Group in Protein Structure and Function, Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2H7

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Abstract. $C_9H_{15}NO_3S$, orthorhombic $P2_12_12_1$, a = 8·811 (1), b = 17·984 (2), c = 6·837 (1) Å, Z = 4, d_m = 1·33, d_c = 1·33 Mg m^{-3}, μ_{Cu} = 2·489 mm^{-1}, R = 7·1%. The title compound is a potent inhibitor of the lung angiotensin-converting enzyme. We present the crystal structure conformation and compare it to the conformation of the molecule obtained from crystallographic studies of SQ 14,225 bound to the aspartyl protease, penicillopepsin. The molecule exhibits an unusual antiplanar conformation of the carboxyl group [O(3)—C(9)—O(2)—H(14) = −163·5°] in the single crystal due to the presence of a strong intermolecular hydrogen bond [O···O = 2·592 (6) Å].

Introduction. SQ 14,225 was designed specifically to inhibit the angiotensin-converting enzyme (kininase II, EC 3.4.15.1) (Cushman, Cheung, Sabo & Ondetti, 1977; Ondetti, Rubin & Cushman, 1977). In the design, the enzyme was assumed to have an active site similar to that of carboxypeptidase A. This assumption was based on the fact that the angiotensin-converting enzyme is a carboxypeptidase which cleaves off dipeptides and contains Zn (Das & Soffer, 1975; Bakhle, 1974). The strong inhibitory action of SQ 14,225 confirms the structural and mechanistic similarity of these two enzymes.

Plate-like crystals of the compound were grown with the vapour-diffusion technique using ethyl acetate as the solvent and petroleum ether as the precipitant. The density was measured by flotation in a mixture of monobromobenzene and monochlorobenzene. For intensity-data collection the crystal was mounted in a direction parallel to the plate surface. For experimental details, see Table 1.

The data were collected on a Picker FACS-1 diffractometer to $2\theta_{max}$ = 110° to obtain 1707 reflections. The background was measured at the beginning and at the end of each scan and was corrected for by the use of the formula $I_{net} = I_{total} - T(B1 + B2)$, where T is the ratio of the scan time to the total background time, and $B1$ and $B2$ are the two background counts. The standard deviation of the intensity was calculated from $\sigma^2(I) = I_{total} + c^2I^2_{total} + T^2[B1 + B2 + c^2(B1^2 + B2^2)]$, where c = 0·02 and represents an estimate of the instrumental instability. For reflections with $\sigma^2 \geq 2 \times 10^6$, a value of $\sigma^2(I) = 2 \times 10^6$ was used. The absorption corrections were made using the method of North, Phillips & Mathews (1968). The symmetry-equivalent reflections (hkl and $h\bar{k}l$) were

Table 1. *Experimental details*

Crystal dimensions: 0·35 × 0·12 × 0·60 mm
Extinctions: $h00$: $h = 2n + 1$; $0k0$: $k = 2n + 1$; $00l$: $l = 2n + 1$
Space group: $P2_12_12_1$
Radiation: Ni-filtered, Cu $K\alpha$, operated at 40 kV, 26 mA
Scan type: θ–2θ
Scan width, speed: 2° at 2° min^{-1} in 2θ

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averaged to give 824 reflections. The criterion $I \geq 3\sigma(I)$ was used to obtain the 799 reflections for the structure solution and refinement. The Lorentz and polarization factors were applied to derive the structure factor amplitudes.

The non-hydrogen-atom positions were obtained with Patterson and Fourier methods. Six low-2θ reflections (002, 040, 130, 141, 210, 231), for which $|F_c| \gg |F_o|$, were deemed to suffer from the effects of secondary extinction and were omitted from the least-squares refinement (Stout & Jensen, 1968). The positions of H(6) and H(13) were obtained directly from a difference Fourier synthesis. The remaining H-atom positions, except for the one bonded to S(1), were calculated from geometry, and were found to occcupy positions in the difference map having positive electron densities of 0·2 to 0·4 e Å^{-3}. The refinement was performed by the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962), with weights $w = 1/\sigma^2(I)$. All the non-hydrogen atoms were refined anisotropically while the H atoms were refined isotropically. The final value of the R factor was 7·1%.* The scattering curves for the non-hydrogen atoms were taken from Cromer & Mann (1968) and that for H was from Mason & Robertson (1966).

Discussion. The atomic coordinates for SQ 14,225 are given in Table 2, and a perspective drawing of the molecule is shown in Fig. 1. The bond lengths and angles are shown in Fig. 2. The crystal is stabilized by hydrogen bonding between atoms O(1) and O(2) of the molecules related by 2_1 screw axes at $x, \frac{1}{4}, 0$ and $x, \frac{3}{4}, \frac{1}{2}$

* Lists of structure factors, anisotropic thermal parameters, and hydrogen-atom positions with their isotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35525 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Atomic coordinates and equivalent isotropic temperature factors of the non-hydrogen atoms*

The parameters have been multiplied by 10^4.

	x	y	z	U_{eq} (Å^2)
C(1)	10608 (7)	1588 (3)	4690 (9)	580 (19)
C(2)	9576 (5)	1074 (2)	5864 (9)	439 (14)
C(3)	10463 (8)	514 (4)	7081 (12)	705 (22)
C(4)	8652 (6)	1547 (3)	7283 (8)	405 (17)
C(5)	6300 (6)	829 (3)	6467 (10)	478 (17)
C(6)	4718 (6)	1088 (4)	6746 (15)	799 (27)
C(7)	4686 (6)	1524 (3)	8630 (11)	582 (18)
C(8)	6287 (6)	1778 (2)	9036 (9)	431 (17)
C(9)	6812 (6)	1559 (3)	11088 (9)	485 (17)
S(1)	11539 (2)	1104 (1)	2670 (3)	676 (9)
N(1)	7211 (4)	1396 (2)	7530 (6)	407 (13)
O(1)	9260 (4)	2050 (2)	8299 (6)	582 (13)
O(2)	6386 (5)	2000 (3)	12489 (6)	679 (16)
O(3)	7588 (5)	1022 (2)	11391 (7)	663 (17)

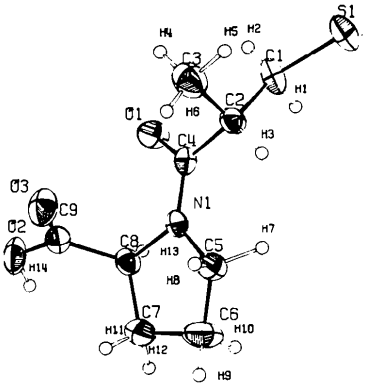

Fig. 1. *ORTEP* drawing (Johnson, 1976) of the SQ 14,225 molecule. The thermal ellipsoids enclose 36% probability. The H atoms were given an arbitrary radius of 0·1 Å.

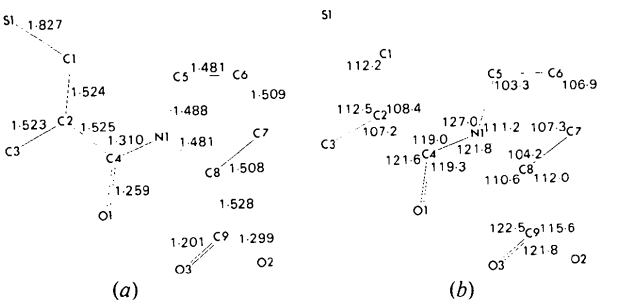

Fig. 2. (*a*) Bond lengths (Å); standard deviations are 0·006–0·012 Å. (*b*) Bond angles (°); standard deviations are 0·3–0·6°.

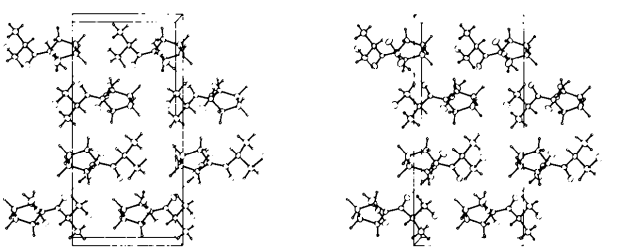

Fig. 3. Stereographic packing diagram (Johnson, 1976) viewed down **c**; **a** is across, **b** is up. The hydrogen bonds are shown by the dotted lines. The antiplanar O=C–OH conformation of the O–H group and the zigzag interconnections of the molecules can be seen.

(Fig. 3). These hydrogen bonds connect the molecules in a zigzag fashion thus forming an infinite chain. The distance between O(1) and O(2) is 2·592 (6) Å which indicates that the interaction is relatively strong. The strength of this interaction is also reflected in the lengthening of the C(4)–O(1) bond and the shortening of the N(1)–C(4) bond which normally have distances of about 1·24 and 1·32 Å respectively (Marsh & Donohue, 1967).

This strong hydrogen bonding seems to be responsible for the antiplanar O=C–OH conformation adopted by the O–H group. Such conformations of the

OH of carboxyl groups have been observed in cases where the O—H bond participates in an intramolecular hydrogen bond, but the present study appears to be the first in which an intermolecular interaction is responsible for the antiplanar conformation of the OH group (Leiserowitz, 1976). The possibility of an intramolecular hydrogen bond between O(3) and O(1) is eliminated because the shortness of the C(9)—O(3) bond [1·201 (7) Å], compared to the C(9)—O(2) bond [1·299 (7) Å], clearly shows that O(3) is the carbonyl oxygen.

The carboxyl group adopts a synplanar conformation with the torsion angle N(1)—C(8)—C(9)—O(3) = −17·0°. This appears to be a preferred conformation for such groups, as it has been observed in a number of other peptides and amino acids (Lakshminarayanan, Sasisekharan & Ramachandran, 1967). In addition, the synplanar arrangement of C^{β}—C^{α}—C=O is the preferred conformation in a number of α,β-saturated carboxylic acids (Dunitz & Strickler, 1968).

The reaction mechanism of aspartyl proteases has a predominantly electrophilic character (Fruton, 1974). As the title compound was specifically designed to inhibit metalloproteases which also have a predominantly electrophilic mechanism (Lipscomb *et al.*, 1968), we decided to examine the possible binding of SQ 14,225 to penicillopepsin in the crystal of that enzyme (James, Hsu & Delbaere, 1977). The resulting difference electron density map, obtained from intensity data collected after soaking a crystal of penicillopepsin in a solution of SQ 14,225, shows an excellent fit for the 3-mercapto-2-D-methylpropionyl group but poor density for the L-proline moiety of the inhibitor (James, Hsu, Hofmann & Sielecki, 1980). The major site of binding of the inhibitor to penicillopepsin is the extended binding cleft which contains the two active-centre aspartyl residues, Asp 32 and Asp 215 (James, Hsu & Delbaere, 1977). The current model of SQ 14,225 bound to the active site of penicillopepsin indicates that its inhibitory action may derive from its binding in a direction in which the polarity of the peptide bond is reversed to that which we have observed for oligopeptide inhibitors and products (James *et al.*, 1980). This reason for inhibition differs from that advanced in the metalloprotease case, where SQ 14,225 is deemed to chelate the Zn^{2+} (Cushman *et al.*, 1977). The fitting of a model of the inhibitor to the observed electron density on the difference map was carried out on an MMS-X interactive graphics system. The resultant independently derived conformation is very similar to that we have observed in the single crystals of SQ 14,225 (Table 3). The pucker of the proline ring and ψ for the carboxyl group have not been determined for the enzyme-bound inhibitor, because of the poor electron density for those groups.

Table 3. *Torsion angles* (°) *of* SQ 14,225

For the single crystal, the e.s.d.'s of the last figures are given in parentheses. For the molecule bound to penicillopepsin, the value in parentheses represents an estimate of the accuracy of the model fitting.

	Single crystal	Bound to penicillopepsin
N(1)—C(4)—C(2)—C(3)	−100·1 (8)	−134 (5)
C(3)—C(2)—C(1)—S(1)	71·1 (6)	50 (5)
N(1)—C(8)—C(9)—O(3)	−17·0 (6)	
C(9)—C(8)—N(1)—C(4)	−67·3 (8)	
C(8)—N(1)—C(4)—C(2)	173·3 (7)	
C(4)—N(1)—C(5)—C(6)	−159·0 (9)	
N(1)—C(5)—C(6)—C(7)	−26·9 (7)	
C(5)—C(6)—C(7)—C(8)	22·0 (7)	
C(6)—C(7)—C(8)—N(1)	−7·4 (8)	
O(3)—C(9)—O(2)—H(14)	−164 (6)	

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10,10-Divanillyl-9(10*H*)-anthracenone

BY KEVIN L. BROWN

Chemistry Division, Department of Scientific and Industrial Research, Private Bag, Petone, New Zealand

AND TERRY J. FULLERTON

Forest Research Institute, Private Bag, Rotorua, New Zealand

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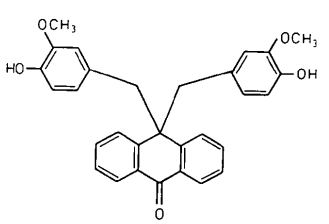
Abstract. $C_{30}H_{26}O_5$, $M_r = 466{\cdot}5$, monoclinic, $P2_1/n$, $a = 11{\cdot}205$ (1), $b = 9{\cdot}332$ (2), $c = 22{\cdot}804$ (3) Å, $\beta = 100{\cdot}70$ (1)°, λ (Cu $K\alpha$) = 1·5418 Å, $Z = 4$, $D_c = 1{\cdot}32$ Mg m^{-3}, $\mu = 0{\cdot}64$ mm^{-1}. $R = 0{\cdot}065$ for 1759 diffractometer data. Strong shielding effects in the proton NMR spectrum are explained by the disposition of the substituted vanillyl rings with respect to the anthrone ring.

Introduction. During a study of the mechanism of anthraquinone wood pulping (Fullerton, 1978), the title compound (I) was isolated from the reaction of anthrahydroquinone with vanillyl alcohol (Fullerton, 1980). The proton NMR spectrum was unusual, with none of the expected resonances of a vanillyl substituent. The methoxy and aromatic protons showed strong shielding, which was assumed to be because the vanillyl rings have a preferred orientation above and below the anthrone ring. To elucidate the exact nature of this orientation, an X-ray analysis was undertaken.



(I)

Crystals obtained from $CHCl_3$ were found to contain occluded chloroform and subsequently proved unsuitable for data collection. Suitable crystals were then obtained from toluene. The crystals are thin colourless plates and intensities and cell dimensions were obtained from a plate 0·52 × 0·25 × 0·03 mm. The systematic absences $0k0$, $k \neq 2n$ and $h0l$, $h + l \neq 2n$ indicated space group $P2_1/n$. Cell dimensions were determined by least squares from the parameters of 12 reflections centred on a Hilger & Watts automated diffractometer. Data were collected to a maximum of $\theta = 57°$ (Ni-filtered Cu $K\alpha$ radiation, θ–2θ scan, scan width = 0·70°, scan time = 70 s). Three standard reflections measured periodically showed only random fluctuations of ±2%.

Intensity measurements were obtained for 3959 reflections which, after averaging of equivalent forms, yielded 1759 reflections which were considered observed ($I > 2{\cdot}5\sigma_I$). Absorption corrections were applied (de Meulenaer & Tompa, 1965), the correction ranging from 1·05 to 1·12. The structure was solved by direct methods and refined by full-matrix least squares with experimental weights ($W = 2{\cdot}97/\sigma_F^2$; a weighting analysis confirmed the validity of this function). The non-hydrogen parameters were refined with anisotropic thermal parameters and the positional parameters of the H atoms with a common temperature factor [U_H = 0·066 (4) Å^2]. All the H atoms, except that bonded to O(25), were found from difference syntheses. It proved impossible to locate H(25), even on the final difference synthesis. The high-resolution mass spectrum confirmed the formula $C_{30}H_{26}O_5$; therefore it was assumed that H(25) is disordered to the point where the electron density did not show on a difference map. Consequently, H(25) has not been included in the final model which converged at $R = 0{\cdot}065$, $R_w = 0{\cdot}060$. A final difference synthesis showed no unusual features.

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