

Structure of Penicillin V Benzyl Ester

BY WHANCHUL SHIN* AND SANG WOO CHO

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

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Abstract. Benzyl 3,3-dimethyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2 α -carboxylate, C₂₃H₂₄N₂O₅S, $M_r = 440.5$, monoclinic, $P2_1$, $a = 11.870$ (2), $b = 7.405$ (1), $c = 13.172$ (2) Å, $\beta = 105.98$ (1)°, $V = 1113.0$ (2) Å³, $Z = 2$, $D_x = 1.314$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 15.6$ cm⁻¹, $F(000) = 464$, $T = 294$ K, $R = 0.0418$ for 1726 reflections with $I \geq 2\sigma(I)$. The overall conformation is very similar to that of the free acid. The penam moiety assumes a closed form in which C(3) deviates by 0.517 (3) Å from the best plane formed by the four remaining atoms in the thiazolidine ring. The intramolecular N(9)—H···O(13) hydrogen bond [2.576 (4) Å] stabilizes the conformation of the molecule, placing the whole 6 β -phenoxyacetamido side chain and S(1), C(5), C(6) and N(9) atoms in a plane. Crystal packing is only by van der Waals interactions.

Introduction. It is well known that the penam moiety in the penicillin compounds has two stable conformations, *i.e.* the closed and open forms, as observed in numerous crystal structures (Domiano, Nardelli, Balsamo, Macchia & Macchia, 1979), although the open form is proposed to be the active form (Cohen, 1983; Christenson, Pruess, Talbot & Keith, 1988). Penicillin V has been used as a powerful antibiotic for several decades and the crystal structure of its free acid form in the closed conformation has been elucidated, albeit with limited accuracy (Abrahamsson, Hodgkin & Maslen, 1963). We have performed the X-ray analysis of penicillin V benzyl ester (PVBE) in order to determine whether crystal-packing forces affect the conformation of the penam moiety.

Experimental. Colourless crystals were obtained from an ethanol–acetone–water (17:4:1 *v/v*) solution saturated with PVBE (Sigma Co.) by slow evaporation at room temperature; crystal ca 0.7 × 0.5 × 0.5 mm. A Rigaku AFC diffractometer with graphite-monochromated Cu $K\alpha$ radiation was used for data collection: $2\theta \leq 120^\circ$; ω - 2θ scan; scan speed 2° min⁻¹ in 2θ ; ω -scan width (1.5 + 0.2tan θ)°; back-

ground measured for 10 s on either side of the peak. Cell parameters were determined by least-squares fit to observed 2θ values for 20 centred reflections with $27 \leq 2\theta \leq 58^\circ$. Intensity checks for three standard reflections showed little ($\pm 1.0\%$) variation. 1796 independent reflections were measured ($h - 13$ to 13, $k - 8$ to 0, $l 0$ to 14), of which 1726 (96.1%) were observed with $I \geq 2\sigma(I)$ and used in the refinement. Lp correction, but no absorption or extinction corrections were applied. The structure was solved by direct methods using *SHELXS86* (Sheldrick, 1986) and refined by full-matrix least squares on F with anisotropic thermal parameters. H atoms were identified in the difference map and refined with isotropic U values. Function $\sum w(|F_o| - |F_c|)^2$ was minimized, with $w = k/[\sigma^2(F_o) + gF_o^2]$, $\sigma(F)$ from counting statistics, k and g optimized in the least-squares procedure ($k = 1.00$, $g = 0.0053$). $wR = 0.0432$ for 1726 observed reflections, 376 variables, $R = 0.0463$ and $wR = 0.0452$ for all data, $S = 0.84$, $(\Delta/\sigma)_{\max} = 0.191$ [x coordinate of H(25b)] in the final refinement cycle; maximum and minimum heights in the final difference map were 0.18 and -0.24 e Å⁻³, respectively. All calculations were performed with *SHELX76* (Sheldrick, 1976) on an IBM PC/AT computer. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, p. 99).

Discussion. Final atomic parameters are listed in Table 1.† An *ORTEPII* (Johnson, 1976) view of the PVBE molecule with the atomic numbering scheme is presented in Fig. 1. Bond distances and angles are listed in Table 2. A stereoscopic packing diagram is shown in Fig. 2. Crystal packing consists of only van der Waals interactions.

Bond distances of PVBE agree very well with the average values for other penam compounds (within 4 σ) (Domiano *et al.*, 1979). The penam moiety

† Lists of structure factors, anisotropic thermal parameters, coordinates of H atoms, molecular dimensions of the phenyl rings and dimensions involving the H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55028 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* To whom correspondence should be addressed.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters (\AA^2)
$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U_{eq}
S(1)	8017 (1)	4617†	4193 (1)	0.057
C(2)	8360 (3)	5348 (5)	5586 (3)	0.055
C(3)	7807 (3)	3856 (4)	6137 (2)	0.046
N(4)	6740 (2)	3302 (4)	5365 (2)	0.044
C(5)	6789 (3)	3219 (5)	4260 (2)	0.048
C(6)	5524 (3)	3998 (5)	3915 (2)	0.053
C(7)	5671 (3)	4213 (4)	5120 (2)	0.051
O(8)	5147 (2)	4897 (4)	5673 (2)	0.069
N(9)	5387 (3)	5640 (4)	3323 (2)	0.056
C(10)	4374 (3)	6187 (6)	2664 (2)	0.056
O(11)	3443 (2)	5421 (5)	2547 (2)	0.082
C(12)	4442 (3)	7886 (6)	2048 (3)	0.060
O(13)	5633 (2)	8376 (4)	2195 (2)	0.066
C(14)	5863 (3)	10045 (5)	1848 (2)	0.055
C(15)	7041 (3)	10527 (7)	2131 (3)	0.067
C(16)	7367 (4)	12164 (7)	1816 (4)	0.079
C(17)	6546 (4)	13338 (7)	1217 (4)	0.083
C(18)	5377 (4)	12850 (6)	955 (4)	0.078
C(19)	5035 (3)	11208 (6)	1257 (3)	0.065
C(20)	7760 (5)	7158 (6)	5666 (4)	0.082
C(21)	9687 (4)	5472 (9)	6033 (4)	0.081
C(22)	8608 (2)	2241 (4)	6454 (2)	0.047
O(23)	8741 (2)	1081 (3)	5870 (2)	0.066
O(24)	9201 (2)	2316 (3)	7481 (1)	0.058
C(25)	10037 (4)	856 (7)	7850 (3)	0.081
C(26)	10720 (2)	1281 (6)	8955 (3)	0.062
C(27)	10838 (3)	41 (8)	9739 (3)	0.083
C(28)	11493 (4)	467 (11)	10760 (4)	0.107
C(29)	12011 (3)	2051 (11)	11008 (3)	0.099
C(30)	11933 (3)	3329 (9)	10246 (4)	0.096
C(31)	11268 (3)	2952 (7)	9206 (3)	0.082

† The y coordinate of atom S(1) was fixed to define the origin of the non-centrosymmetric structure.

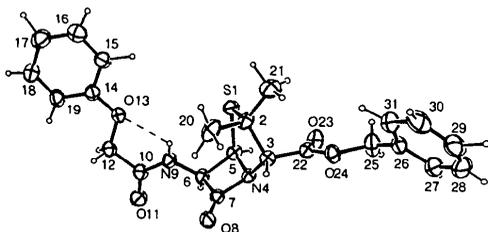


Fig. 1. ORTEP (Johnson, 1976) drawing of the PVBE molecule with atomic numbering scheme. Thermal ellipsoids are drawn at the 30% probability level. The dotted line denotes the hydrogen bond.

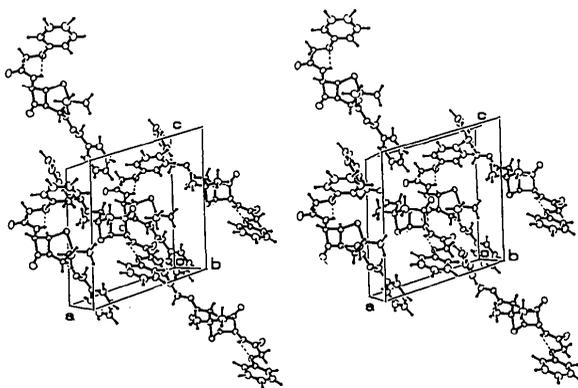


Fig. 2. Stereoscopic ORTEP (Johnson, 1976) packing drawing of PBVE. The dotted line denotes the hydrogen bond.

Table 2. Selected bond distances (\AA) and angles ($^\circ$)

S(1)—C(2)	1.848 (4)	S(1)—C(5)	1.810 (4)
C(2)—C(3)	1.562 (5)	C(2)—C(20)	1.535 (6)
C(2)—C(21)	1.525 (6)	C(3)—C(4)	1.448 (4)
C(3)—C(22)	1.513 (4)	N(4)—C(5)	1.474 (4)
N(4)—C(7)	1.394 (4)	C(5)—C(6)	1.555 (5)
C(6)—C(7)	1.556 (4)	C(6)—N(9)	1.429 (4)
C(7)—O(8)	1.193 (4)	N(9)—C(10)	1.337 (5)
C(10)—O(11)	1.214 (5)	C(10)—C(12)	1.511 (6)
C(12)—O(13)	1.420 (4)	O(13)—C(14)	1.371 (5)
C(22)—O(23)	1.192 (4)	C(22)—O(24)	1.343 (3)
O(24)—C(25)	1.457 (5)	C(25)—C(26)	1.492 (5)
C(3)—C(2)—S(1)	104.4 (2)	N(4)—C(3)—C(2)	105.8 (2)
N(4)—C(5)—S(1)	106.0 (2)	C(5)—S(1)—C(2)	94.6 (1)
C(5)—N(4)—C(3)	116.1 (2)	C(6)—C(5)—S(1)	120.0 (3)
C(6)—C(5)—N(4)	88.6 (2)	C(6)—C(7)—N(4)	91.5 (2)
C(7)—N(4)—C(3)	126.2 (3)	C(7)—N(4)—C(5)	94.2 (2)
C(7)—C(6)—C(5)	84.9 (2)	O(8)—C(7)—N(4)	131.2 (3)
O(8)—C(7)—C(6)	137.3 (3)	N(9)—C(6)—C(5)	115.5 (3)
N(9)—C(6)—C(7)	115.7 (3)	C(10)—N(9)—C(6)	124.0 (3)
O(11)—C(10)—N(9)	124.4 (4)	C(12)—C(10)—N(9)	115.4 (3)
C(12)—C(10)—O(11)	120.1 (3)	O(13)—C(12)—C(10)	109.7 (3)
C(14)—O(13)—C(12)	117.8 (3)	C(15)—C(14)—O(13)	114.8 (3)
C(19)—C(14)—O(13)	125.2 (3)	C(20)—C(2)—S(1)	110.1 (3)
C(20)—C(2)—C(3)	108.9 (3)	C(21)—C(2)—S(1)	108.8 (3)
C(21)—C(2)—C(3)	112.6 (3)	C(21)—C(2)—C(20)	111.7 (4)
C(22)—C(3)—C(2)	112.0 (3)	C(22)—C(3)—N(4)	109.4 (2)
O(23)—C(22)—C(3)	125.2 (2)	O(24)—C(22)—C(3)	111.1 (2)
O(24)—C(22)—O(23)	123.6 (3)	C(25)—C(26)—C(22)	115.2 (2)
C(26)—C(25)—O(24)	107.8 (3)	C(27)—C(26)—C(25)	120.9 (4)
C(31)—C(26)—C(25)	120.7 (4)		

assumes a closed conformation in which C(3) deviates by 0.517 (3) \AA from the best plane formed by the four remaining atoms in the thiazolidine ring and N(4) retains pyramidal character as in the free acid form of penicillin V. The orientation of the phenoxyethyl side chain with respect to the penam nucleus is also very similar to that of the free acid form, despite the differences in the crystal-packing modes and the 3 α -carboxyl substituents. Relative rigidity of the apparently flexible molecule seems to originate from the N(9)—H \cdots O(13) intramolecular hydrogen bond [N(9)—H = 0.81 (5), H \cdots O(13) = 2.16 (5), N(9) \cdots O(13) = 2.576 (4) \AA , N—H—O = 112 (4) $^\circ$] which places the whole 6 β -phenoxyacetamido side chain and S(1), C(5), C(6) and N(9) atoms in a plane. There is also a relatively close contact between N(9) and S(1) [H \cdots S(1) = 2.65 (5), N(9) \cdots S(1) = 3.109 (4) \AA , N—H—S = 118 (4) $^\circ$]. However, AM1 calculation of the atomic charge indicates a slight positive charge on S(1) [0.021 and 0.059 in the open and closed penams, respectively], excluding the possibility of forming a three-centred hydrogen bond.

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Structure of Penicillin V Benzyl Ester Sulfoxide

BY WHANCHUL SHIN,* JAHEON KIM AND JOOHYUN KIM

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

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Abstract. Benzyl 3,3-dimethyl-7-oxo-6-phenoxyacetamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide, $C_{23}H_{24}N_2O_6S$, $M_r = 456.5$, monoclinic, $P2_1$, $a = 14.467$ (5), $b = 8.212$ (1), $c = 9.608$ (2) Å, $\beta = 102.96$ (3)°, $V = 1112.4$ (5) Å³, $Z = 2$, $D_x = 1.363$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 16.1$ cm⁻¹, $F(000) = 480$, $T = 294$ K, $R = 0.0583$ for 1648 reflections with $I \geq 3\sigma(I)$. The overall conformation of the sulfoxide derivative is quite different from that of the parent compound. The penam moiety assumes an open form in which S deviates 0.884 (1) Å from the best plane formed by the four remaining atoms in the thiazolidine ring. The exocyclic amide N atom forms an intramolecular hydrogen bond with the sulfoxide O atom [2.813 (6) Å] instead of the phenoxy O atom. Crystal packing is only by van der Waals interactions.

Introduction. Oxidation of penam to its sulfoxide results in an inactive derivative with the *S* configuration (Cooper, DeMarco, Cheng & Jones, 1969). It has been shown in three cases that the sulfoxide derivatives of penam assume different conformations from their parent compounds. These include pairs of penicillin V (Abrahamsson, Hodgkin & Maslen, 1963; Cooper *et al.*, 1969), cloxacillin (Blanpain & Durant, 1976), penamecillin (Labischinski, Naumann, Barnickel, Dreissig, Gruszecki, Hofer & Bradaczek, 1987) and their corresponding sulfoxides. We have reported the crystal structure of penicillin V benzyl ester in the preceding paper (PVBE; Shin & Cho, 1992) and now present the crystal structure of its sulfoxide derivative (PVBS) for comparison.

Experimental. Colourless crystals were obtained from an aqueous acetone solution saturated with PVBS (Sigma Co.) by slow evaporation at room temperature; crystal ca $0.2 \times 0.5 \times 0.5$ mm. A Rigaku AFC diffractometer with graphite-monochromated Cu $K\alpha$ radiation was used for data collection: $2\theta \leq 120^\circ$;

ω - 2θ scan; scan speed 2° min^{-1} in 2θ ; ω -scan width $(1.4 + 0.4 \tan \theta)^\circ$; background measured for 10 s on either side of the peak. Cell parameters were determined by least-squares fit to observed 2θ values for 20 centred reflections with $23 \leq 2\theta \leq 60^\circ$. Intensity checks for three standard reflections showed little ($\pm 1.8\%$) variation. 1790 independent reflections were measured ($h - 16$ to 15 , $k - 9$ to 0 , $l 0$ to 10), of which 1648 (92.1%) were observed with $I \geq 3\sigma(I)$ and used in the refinement. Lp corrections but no absorption or extinction corrections were applied. The structure was solved by direct methods using *SHELXS86* (Sheldrick, 1986) and refined by full-matrix least squares on F with anisotropic thermal parameters. Eight H atoms were identified in the difference map and their positions were refined, other H-atom positions were calculated with ideal geometry and included in the structure-factor calculation. Function $\sum w(|F_o| - |F_c|)^2$ was minimized, with $w = k/[\sigma^2(F_o) + gF_o^2]$, $\sigma(F)$ from counting statistics, k and g optimized in the least-squares procedure ($k = 1.00$, $g = 0.020$); $wR = 0.0568$ for 1648 observed reflections, 312 variables, $R = 0.0656$ for all data, $S = 0.586$, $(\Delta/\sigma)_{\text{max}} = 0.063$ [y coordinate of H(9)] in the final refinement cycle; maximum and minimum heights in the final difference map were 0.26 and $-0.63 \text{ e } \text{Å}^{-3}$, respectively. All calculations were performed with *SHELX76* (Sheldrick, 1976) on an IBM PC/AT computer. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, p. 99).

Discussion. Final atomic parameters are listed in Table 1.† An *ORTEPII* (Johnson, 1976) view of the PVBS molecule with the atomic numbering scheme is

† Lists of structure factors, anisotropic thermal parameters, coordinates of H atoms, molecular dimensions of the phenyl rings and dimensions involving the H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55029 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* To whom correspondence should be addressed.