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Structure of Penicillin V Benzyl Ester Sulfoxide

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Abstract. Benzyl 3,3-dimethyl-7-oxo-6-phenoxyacet-amido-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) Å^3, $Z = 2$, $D_x = 1.363$ g cm^{-3}, λ(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 preceeding 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 × 0.5 × 0.5 mm. A Rigaku AFC diffractometer with graphite-monochromated Cu $K\alpha$ radiation was used for data collection: $2\theta \leq 120°$;

ω–2θ scan; scan speed 2° min^{-1} in 2θ; ω-scan width $(1.4 + 0.4\tan\theta)°$; 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 $23 \leq 2\theta \leq 60°$. 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 *SHELXS*86 (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, $S = 0.586$, $(\Delta/\sigma)_{max} = 0.063$ [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 e Å^{-3}, respectively. All calculations were performed with *SHELX*76 (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 *ORTEP*II (Johnson, 1976) view of the PVBS molecule with the atomic numbering scheme is

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Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($\text{Å}^2 \times 10^3$)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
S(1)	2534 (1)	4115	9304 (1)	53
O(1)	2945 (3)	3190 (5)	8246 (4)	64
C(2)	1409 (3)	5051 (6)	8285 (6)	51
C(3)	772 (3)	3567 (6)	7727 (6)	45
N(4)	1037 (3)	2277 (5)	8795 (4)	46
C(5)	1815 (3)	2608 (7)	10006 (5)	48
C(6)	2137 (3)	811 (7)	9977 (5)	48
C(7)	1416 (3)	777 (7)	8522 (6)	50
O(8)	1222 (3)	−88 (5)	7502 (5)	74
N(9)	3099 (3)	410 (6)	9994 (5)	50
C(10)	3591 (3)	−734 (6)	10810 (4)	46
O(11)	3285 (3)	1526 (6)	11671 (4)	74
C(12)	4594 (3)	−994 (8)	10649 (5)	52
O(13)	4819 (2)	−164 (5)	9459 (4)	53
C(14)	4557 (3)	−874 (7)	8126 (5)	47
C(15)	4754 (4)	24 (8)	7020 (6)	61
C(16)	4523 (4)	−541 (10)	5646 (6)	68
C(17)	4093 (4)	−2080 (9)	5351 (6)	66
C(18)	3907 (4)	−2988 (8)	6484 (6)	69
C(19)	4137 (4)	−2391 (8)	7852 (6)	62
C(20)	1655 (4)	6001 (8)	7049 (6)	63
C(21)	1036 (4)	6109 (11)	9350 (7)	65
C(22)	−275 (3)	4005 (7)	7474 (5)	49
O(23)	−747 (3)	3834 (6)	8328 (4)	71
O(24)	−579 (3)	4626 (6)	6173 (4)	63
C(25)	−1574 (4)	5087 (10)	5766 (7)	70
C(26)	−1723 (4)	6858 (8)	6143 (5)	59
C(27)	−2611 (4)	7291 (10)	6247 (7)	76
C(28)	−2805 (4)	8940 (12)	6558 (7)	89
C(29)	−2083 (5)	10061 (9)	6748 (7)	79
C(30)	−1212 (4)	9606 (9)	6666 (7)	74
C(31)	−1027 (4)	8015 (9)	6327 (6)	68

Table 2. *Selected bond distances* (Å) *and angles* (°)

S(1)—O(1)	1.495 (4)	S(1)—C(2)	1.866 (5)
S(1)—C(5)	1.840 (5)	C(2)—C(3)	1.549 (7)
C(2)—C(20)	1.529 (8)	C(2)—C(21)	1.529 (8)
C(3)—N(4)	1.465 (6)	C(3)—C(22)	1.522 (7)
N(4)—C(5)	1.452 (6)	N(4)—C(7)	1.397 (7)
C(5)—C(6)	1.549 (8)	C(6)—C(7)	1.546 (7)
C(6)—N(9)	1.427 (6)	C(7)—O(8)	1.192 (7)
N(9)—C(10)	1.324 (7)	C(10)—O(11)	1.212 (6)
C(10)—C(12)	1.509 (7)	C(12)—O(13)	1.429 (6)
O(13)—C(14)	1.381 (6)	C(22)—O(23)	1.188 (6)
C(22)—O(24)	1.330 (6)	O(24)—C(25)	1.454 (7)
C(25)—C(26)	1.526 (10)		

C(2)—S(1)—O(1)	106.7 (2)	C(3)—C(2)—S(1)	103.8 (3)
N(4)—C(3)—C(2)	106.5 (4)	N(4)—C(5)—S(1)	103.4 (3)
C(5)—S(1)—O(1)	104.6 (2)	C(5)—S(1)—C(2)	88.3 (2)
C(5)—N(4)—C(3)	117.4 (4)	C(6)—C(5)—S(1)	115.9 (3)
C(6)—C(5)—N(4)	89.4 (4)	C(6)—C(7)—N(4)	91.6 (4)
C(7)—N(4)—C(3)	124.0 (4)	C(7)—N(4)—C(5)	92.8 (4)
C(7)—C(6)—C(5)	83.6 (4)	O(8)—C(7)—N(4)	130.6 (5)
O(8)—C(7)—C(6)	137.8 (5)	N(9)—C(6)—C(5)	121.1 (4)
N(9)—C(6)—C(7)	117.7 (4)	C(10)—N(9)—C(6)	124.3 (4)
O(11)—C(10)—N(9)	123.7 (4)	C(12)—C(10)—N(9)	116.2 (4)
C(12)—C(10)—O(11)	120.1 (5)	O(13)—C(12)—C(10)	114.3 (4)
C(14)—O(13)—C(12)	118.5 (4)	C(15)—C(14)—O(13)	115.4 (5)
C(19)—C(14)—O(13)	125.0 (5)	C(20)—C(2)—S(1)	106.8 (4)
C(20)—C(2)—C(3)	110.9 (4)	C(21)—C(2)—S(1)	106.3 (4)
C(21)—C(2)—C(3)	114.0 (4)	C(21)—C(2)—C(20)	114.1 (5)
C(22)—C(3)—C(2)	111.3 (4)	C(22)—C(3)—N(4)	112.1 (4)
O(23)—C(22)—C(3)	124.6 (4)	O(24)—C(22)—C(3)	110.4 (4)
O(24)—C(22)—O(23)	125.0 (4)	C(25)—O(24)—C(22)	116.9 (4)
C(26)—C(25)—O(24)	111.6 (5)	C(27)—C(26)—C(25)	117.0 (6)
C(31)—C(26)—C(25)	123.6 (5)		

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 only of van der Waals interactions.

Molecular dimensions of PVBS agree well with those of other penam sulfoxide compounds. The overall conformation of PVBS is quite different from that of the parent compound PVBE as is the case for other pairs of penams and their sulfoxide derivatives. The penam moiety of the PVBS molecule assumes an open conformation in which S(1) deviates 0.884 (1) Å from the plane formed by the remaining four atoms while PVBE assumes a closed conformation. It has been pointed out that the sulfoxide compound cannot assume a closed form because O(1) becomes too close to N(9) and the 2β-methyl group (Labischinski *et al.*, 1987). The conformations of the 6β-phenoxyacetamido side chains are also different in the two structures. The phenoxy group is almost perpendicular to the acetamido group in PVBS while the two planar groups form a good plane in PVBE. These differences in the conformation seem to originate from the different intramolecular hydrogen-bonding schemes. While the amide N(9) forms a weak intramolecular hydrogen bond with O(13) in PVBE, there is no hydrogen-bonding interaction between these two atoms in PVBS [N(9)—H = 0.79 (7), H···O(13) = 2.46 (6), N(9)···O(13) = 2.692 (5) Å, N—H—O = 99 (6)°]. Instead, N(9) forms a stronger intramolecular hydrogen bond with O(1) [H···O(1) = 2.13 (8), N(9)···O(1) = 2.813 (6) Å, N—H—O = 145 (7)°].
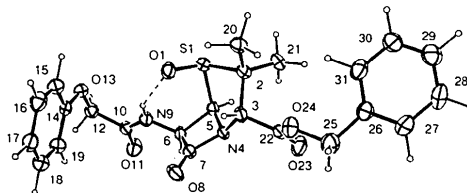

Fig. 1. *ORTEP*II (Johnson, 1976) drawing of the PVBS molecule with atomic numbering scheme. Thermal ellipsoids are drawn at the 30% probability level. The dotted line denotes the hydrogen bond.
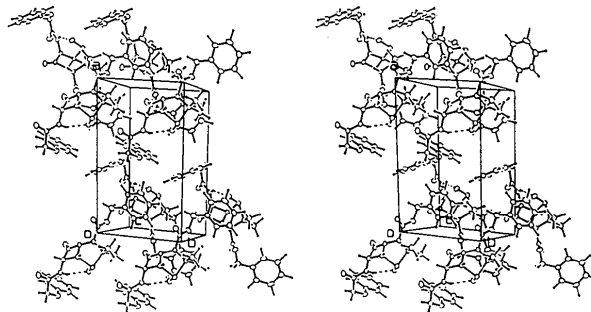

Fig. 2. Stereoscopic *ORTEP*II (Johnson, 1976) packing drawing of PVBS. The dotted line denotes the hydrogen bond.

It has been proposed that the open form of penam is the active one from the consideration of the relative three-dimensional orientation of the β-lactam carbonyl and 3α-carboxyl groups (Cohen, 1983). Penam molecules can assume either an open or a closed conformation in the crystalline state which may be interconvertable in solution, while the sulfoxide derivatives assume only the open conformation. Therefore, the oxygen functionality on S(1) and/or the intramolecular N(9)—H···O(1) hydrogen bond which limits the flexibility of the 6β side chain seems to be the major factor for the loss of activity in penam sulfoxide derivatives.

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Structure of Diphenylmethyl 7β-Amino-7α-methoxy-3-[(1-methyl-1H-tetrazol-5-ylthio)methyl]-3-cephem-4-carboxylate

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Abstract. Diphenylmethyl 7β-amino-7α-methoxy-3-[(1-methyl-1H-tetrazol-5-ylthio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, $C_{24}H_{24}$-$N_6O_4S_2$, $M_r = 524.61$, orthorhombic, $P2_12_12_1$, $a = 9.829$ (1), $b = 13.290$ (2), $c = 18.864$ (3) Å, $V = 2464.2$ (6) Å^3, $Z = 4$, $D_x = 1.414$ g cm^{-3}, λ(Cu $K\alpha$) $= 1.5418$ Å, $\mu = 22.8$ cm^{-1}, $F(000) = 1096$, $T = 295$ K, $R = 0.048$ for 1654 reflections with $I \geq 2\sigma(I)$. The S(1)—C(2) bond is similar to the S(1)—C(6) bond in cephamycin while the former bond is always longer by *ca* 0.02 Å in cephalosporin. The orientation of the carboxyl group with respect to the 3-cephem nucleus is not affected by the presence of the bulky diphenylmethyl group. The 7α-methoxy group assumes the same conformation in cephamycin and oxacephalosporin. The (1-methyl-1H-tetrazol-5-yl-thio)methyl moiety is perpendicular to the dihydrothiazine ring. Crystal packing consists only of van der Waals interactions.

Introduction. Cephamycins are derivatives of cephalosporin which contain a methoxy group at the

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7α position. The 7α-methoxy group contributes to protection of the β-lactam ring against enzymatic inactivation by β-lactamase with little reduction in intrinsic activity (Hoover, 1983). The title compound (DPMCEP) is an intermediate for syntheses of cephamycin analogues with various 7β side chains. Its structure is compared with related compounds.

Experimental. Pale-yellow needles were obtained from a dichloromethane–methanol solution; crystal *ca* 0.5 × 0.2 × 0.2 mm. A Rigaku AFC diffractometer with graphite-monochromated Cu $K\alpha$ radiation was used for data collection; $2\theta \leq 120°$, ω–2θ scan; scan speed 2° min^{-1} in 2θ, ω-scan width (2.0 + 0.1tanθ)°; 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 $22 \leq 2\theta \leq 51°$. Intensity checks for three standard reflections showed little ($\pm 1.0\%$) variation. 2114 independent reflections were measured (h 0 to 11, k −14 to 0, l −21 to 0), of which 1654 (78.2%) were observed with $I \geq 2\sigma(I)$ and used in the refinement. Lp corrections, but no absorption or extinction corrections were applied. The structure