Crystal Structure of Penicillin V Potassium Salt

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The crystal structure of the potassium salt of penicillin *V* has been studied by the X-ray crystallographic methods. Crystal data are as follows; potassium 3,3-dimethyl-7-oxo-6-phenoxyacetoamido-4-thia-1-azabicyclo[3.2.0]-heptane-2α-carboxylate, $K^+ \cdot C_{16}H_{18}N_2O_5S^-$, $M_r = 388.5$, triclinic, $P1$, $a = 9.371$ (1), $b = 12.497$ (2), $c = 15.313$ (2) Å, $\alpha = 93.74$ (2), $\beta = 99.32$ (1), $\gamma = 90.17$ (1)°, $V = 1765.7$ (2) Å^3, $Z = 4$, $D_m = 1.461$ gcm^{-1}, λ(Cu Kα) = 1.5418 Å, $\mu = 40.1$ cm^{-1}, $F(000) = 808$, $T = 296$ K. The structure was solved by the heavy atom and difference Fourier methods with intensity data measured on an automated four-circle diffractometer. The structure was refined by the full-matrix least-squares method to a final $R = 0.081$ for 3563 observed [$I_o \geq 2\sigma(I_o)$] reflections. The four independent molecules assume different overall conformations with systematically different orientations of the phenyl groups although the penam moieties have the same closed conformations. There are intramolecular hydrogen bonds between the exocyclic amide nitrogen and phenoxy oxygen atoms. The penam moiety is conformationally very restricted although the carboxyl and exocyclic amide groups apparently have certain rotational degrees of freedom but the phenyl group is flexible about the ether bond despite the presence of the intramolecular N-H···O hydrogen bond. There are complicated pseudo symmetric relationships in the crystal lattice. The penam moieties are related by pseudo $2_{0,5}$ screw axes and the phenyl groups by pseudo centers of symmetry. The potassium ions, related by both pseudo symmetries, form an infinite zigzag planar chain parallel to the *b* axis. Each potassium ion is coordinated to seven oxygen atoms in a severely distorted pentagonal bipyramid configuration, forming the infinite hydrophilic channels which in turn form the molecular stacks. Between these stacks, there are only lipophilic interactions involving the phenyl groups.

Introduction

The β-lactam antibiotics, such as penicillins and cephalosporins, inhibit the activity of the membrane-bound enzymes that catalyze the final step of peptide cross-linking between nascent and preexisting peptidoglycans in the cell wall synthesis in bacteria.[1,2] These β-lactam antibiotics, which are structurally similar to the *C*-terminal D-Ala-D-Ala moiety of the peptidoglycans, can compete for the enzymes with the natural substrates and inhibit the enzymes by forming fairly stable acyl enzymes.[3,4]

It is well known that the penam moiety in the penicillin compounds has two stable conformations, *i.e.* the open and closed forms, as observed in numerous crystal structures[5], although the open form is proposed to be the active form[6,7]. In the closed form, C(3) deviates from the plane formed by the remaining four atoms in the thiazolidine rings, while S(1) deviates in the open form of penam. 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.[8] We recently reported the accurate crystal structure of benzyl ester of penicillin *V* which also assumes the closed conformation.[9] We have undertaken the X-ray analysis of the potassium salt of penicillin *V* (PVK) in order to analyze the conformational characteristics of penicillin *V* in a different crystal packing environment.

Experimental

Colorless crystals were obtained from an ethanol-dichloromethane solution saturated with PVK (Sigma Co.) by slow evaporation at room temperature. A crystal of the size *ca.* 0.5×0.3×0.07 mm was used for the experiment. Density was measured by floatation in cyclohexane/chloroform. Weissenberg photographs showed that the intensities of the reflections with the odd *k* indices were generally very weak. The intensity data were measured on a Rigaku AFC diffractometer with Ni-filtered, graphite-monochromated Cu Kα radiation. Cell constants were refined by least-square refinement of the 2θ angles of 25 reflections with $24° \leq 2\theta \leq 58°$. 2θ-ω scan method was used with the scan range of $(1.25 + 0.5 \tan\theta)°$ in ω and the scan speed of 8°/min. Backgroud was measured for 10 s on either side of the peak. The 5253 independent reflections (h −10 to 10, k −14 to 0, l −17 to 17) were measured to $2\theta \leq 120°$ of which 3563 (67.8%) with $I_o \geq 2\sigma(I_o)$ were considered observed. The intensities of the three standard reflections monitored every 50 reflections showed random variations of ± 2.2% with no significant trend. Lp corrections suitable for the graphite-monochromated ($2\theta_m = 26.5°$) radiation were made. No absorption and extinction corrections were applied. The structure was solved by the heavy atom and difference Fourier methods using *SHELXS*86[10] and *SHELX*76[11]. The positions of the eight heavy atoms (*K* and *S*) were initially determined from the Patterson map and the positions of the remaining 92 nonhydrogen atoms were identified in the subsequent difference Fourier maps. The structure was anisotropically refined on F by full-matrix least-squares. The positions of the hydrogen atoms were either identified in the difference map or calculated with ideal geometry (C-H: 1.08 Å). Hydrogen atoms with the idealized positions and the isotropic thermal parameters assigned to be 1.3 times those of the attached atoms were not refined but included in the structure factor calculation. $\Sigma w(|F_o| - |F_c|)^2$ was minimized with $w = k/[\sigma(F_o) + g|F_o|^2]$ where k and g were optimized in the least-squares procedure ($k = 0.57$, $g = 0$.

017); $R=0.081$ and $wR=0.084$ for 3563 observed reflections, 862 variables, S (goodness of fit)=0.87, $(\Delta/\sigma)_{max}=0.45$ [U_{13} of C(17b)] in the final refinement cycle. Maximum and minimum heights in the final difference map were 1.62 and −0.70 e Å^{-3}, respectively. Atomic scattering factors and the anomalous dispersion terms were taken from International Table for X-ray Crystallography.[12]

Table 1. Atomic Coordintes ($\times 10^4$) and Thermal Parameters (Å^2)

Atom	x	y	z	Ueq
K(A)	1987 (3)	516 (2)	7222 (2)	0.034
K(B)	3994 (3)	3038 (2)	7305 (2)	0.034
K(C)	2023 (3)	5570 (2)	7313 (2)	0.036
K(D)	4082 (3)	8085 (2)	7390 (2)	0.039
S(1A)	−3955 (3)	2102 (2)	4607 (2)	0.036
C(2A)	−3967 (9)	629 (8)	4763 (5)	0.019
C(3A)	−4001 (11)	572 (8)	5781 (7)	0.033
N(4A)	−3250 (8)	1522 (7)	6204 (5)	0.029
C(5A)	−3342 (11)	2500 (8)	5766 (6)	0.027
C(6A)	−1727 (10)	2712 (9)	6095 (7)	0.031
C(7A)	−1750 (11)	1574 (10)	6442 (7)	0.036
O(8A)	−891 (9)	970 (7)	6755 (6)	0.053
N(9A)	−797 (8)	2827 (7)	5451 (5)	0.028
C(10A)	556 (11)	3165 (10)	5674 (7)	0.039
O(11A)	1158 (8)	3389 (8)	6452 (5)	0.057
C(12A)	1460 (14)	3367 (12)	4924 (7)	0.052
O(13A)	563 (10)	3206 (8)	4080 (6)	0.061
C(14A)	378 (14)	2218 (12)	3643 (8)	0.054
C(15A)	873 (15)	1316 (11)	3945 (9)	0.055
C(16A)	589 (18)	305 (14)	3395 (12)	0.081
C(17A)	−226 (21)	299 (16)	2611 (12)	0.088
C(18A)	−833 (20)	1263 (20)	2327 (12)	0.107
C(19A)	−521 (21)	2210 (15)	2836 (10)	0.087
C(20A)	−5264 (13)	134 (12)	4169 (8)	0.053
C(21A)	−2599 (13)	166 (11)	4530 (9)	0.054
C(22A)	−5576 (11)	534 (8)	6027 (7)	0.028
O(23A)	−5997 (9)	−395 (7)	6149 (5)	0.051
O(24A)	−6236 (8)	1395 (6)	6038 (5)	0.038
S(1B)	0	5000	10000	0.038
C(2B)	22 (10)	3519 (9)	9812 (7)	0.034
C(3B)	−7 (10)	3314 (8)	8780 (6)	0.025
N(4)	−784 (9)	4207 (7)	8370 (5)	0.028
C(5B)	−640 (11)	5266 (9)	8861 (6)	0.032
C(6B)	−2282 (10)	5402 (9)	8532 (7)	0.029
C(7B)	−2245 (11)	4241 (10)	8130 (6)	0.035
O(8B)	−3144 (8)	3584 (8)	7792 (6)	0.059
N(9B)	−3205 (9)	5522 (7)	9209 (6)	0.035
C(10B)	−4648 (13)	5713 (11)	8963 (8)	0.052
O(11B)	−5190 (8)	5841 (8)	8235 (5)	0.056
C(12B)	−5521 (12)	5613 (12)	9697 (8)	0.052
O(13B)	−4665 (9)	5646 (7)	10563 (5)	0.050
C(14B)	−4249 (14)	6587 (11)	11030 (7)	0.044
C(15B)	−4671 (15)	7585 (15)	10638 (10)	0.076
C(16B)	−4256 (19)	8507 (17)	11154 (17)	0.107
C(17B)	−3438 (29)	8382 (19)	11996 (18)	0.107
C(18B)	−2912 (30)	7486 (25)	12317 (14)	0.131
C(19B)	−3384 (18)	6558 (19)	11809 (10)	0.106
C(20B)	1428 (13)	3115 (10)	10325 (7)	0.046
C(21B)	−1333 (15)	3042 (10)	10071 (8)	0.056
C(22B)	1528 (12)	3215 (8)	8503 (6)	0.028
O(23B)	1929 (8)	2256 (6)	8367 (5)	0.041
O(24B)	2214 (8)	4032 (6)	8440 (5)	0.039
S(1C)	−3932 (3)	7106 (2)	4666 (2)	0.035
S(2C)	−4017 (11)	5636 (9)	4807 (6)	0.028
C(3C)	−4016 (11)	5623 (9)	5851 (6)	0.030
N(4C)	−3194 (8)	6526 (7)	6276 (5)	0.024
C(5C)	−3280 (11)	7516 (9)	5811 (6)	0.030
C(6C)	−1654 (11)	7745 (9)	6156 (7)	0.036
C(7C)	−1707 (11)	6619 (10)	6537 (7)	0.036
O(8C)	−854 (9)	5967 (8)	6849 (6)	0.064
N(9C)	−726 (9)	7743 (8)	5486 (6)	0.035
C(10C)	713 (10)	7998 (9)	5721 (6)	0.028
O(11C)	1234 (8)	8325 (7)	6457 (5)	0.052
C(12C)	1535 (12)	7859 (10)	4953 (7)	0.038
O(13C)	649 (9)	7439 (9)	4192 (5)	0.067
C(14C)	1259 (14)	6961 (13)	3546 (8)	0.058
C(15C)	2417 (17)	7459 (13)	3219 (9)	0.064
C(16C)	2954 (17)	6936 (13)	2455 (10)	0.067
C(17C)	2406 (20)	6033 (16)	2113 (10)	0.081
C(18C)	1352 (23)	5500 (18)	2457 (13)	0.115
C(19C)	750 (19)	6038 (19)	3158 (11)	0.116
C(20C)	−5392 (13)	5176 (10)	4259 (8)	0.047
C(21C)	−2677 (12)	5120 (9)	4583 (9)	0.054
C(22C)	−5506 (10)	5538 (9)	6106 (7)	0.031
O(23C)	−6006 (8)	4622 (6)	6201 (5)	0.041
C(24C)	−6170 (7)	6400 (6)	6188 (5)	0.037
S(1D)	−57 (3)	10046 (2)	10019 (2)	0.038
C(2D)	148 (11)	8578 (9)	9896 (6)	0.032
C(3D)	226 (11)	8313 (9)	8870 (7)	0.036
N(4D)	−683 (9)	9175 (7)	8418 (6)	0.033
C(5D)	−643 (11)	10235 (8)	8867 (7)	0.029
C(6D)	−2297 (11)	10322 (10)	8491 (7)	0.040
C(7D)	−2131 (11)	9133 (10)	8211 (7)	0.042
O(8D)	−3034 (9)	8431 (8)	7890 (6)	0.066
N(9D)	−3201 (9)	10582 (7)	9137 (6)	0.032
C(10D)	−4586 (11)	10879 (10)	8837 (7)	0.036
O(11D)	−5088 (8)	10942 (8)	8110 (5)	0.056
C(12D)	−5486 (14)	11170 (14)	9571 (8)	0.064
O(13D)	−4580 (10)	11178 (9)	10431 (6)	0.076
C(14D)	−5154 (13)	11707 (10)	11104 (6)	0.042
C(15D)	−4606 (18)	12722 (16)	11472 (14)	0.096
C(16D)	−5139 (26)	13223 (19)	12131 (17)	0.144
C(17D)	−6191 (19)	12742 (22)	12504 (11)	0.114
C(18D)	−6678 (20)	11717 (13)	12153 (10)	0.083
C(19D)	−6138 (18)	11233 (15)	11476 (13)	0.093
C(20D)	1617 (14)	8310 (11)	10434 (7)	0.059
C(21D)	−1168 (16)	8023 (11)	10137 (10)	0.080
C(22D)	1685 (11)	8316 (10)	8607 (7)	0.037
O(23D)	2200 (9)	7381 (7)	8520 (5)	0.047
O(24D)	2298 (8)	9147 (6)	8498 (5)	0.042

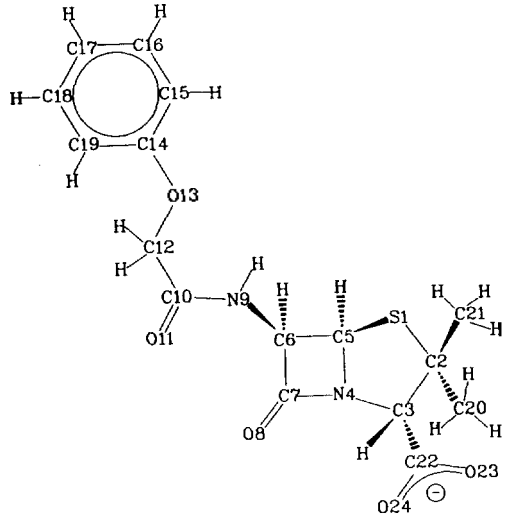

Figure 1. Atomic numbering scheme of the penicillin V molecule.

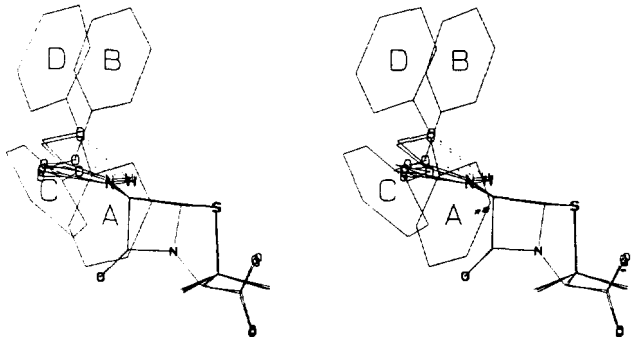

Figure 2. Stereoscopic drawing of the superimposed molecules. The dotted line denotes the intramolecular hydrogen bond.

Results and Discussion

The final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1. The atomic numbering scheme is shown in Figure 1. Bond lengths and bond angles are listed in Table 2.

The structure could not be determined accurately enough for a detailed discussion of the molecular dimensions due to poor diffracting quality of the crystal and weak intensities of a substantial portion of the intensity data originated from pseudo symmetry. However, those of the four independent molecules are in agreement with each other and also with those of the related compounds within experimental error. It has been suggested that the ease of base hydrolysis of the lactam amide bond, owing to pyramidal character of the lactam N(4) atom, is important to biological activities of the β-lactam compounds.[13] Deviations of N(4) from the C(3)-C(5)-C(7) planes are 0.37-0.40 Å in PVK showing similar pyramidalities to the other penam compounds.

Superposition of the four independent molecules, in which the seven ring atoms are least-squares fitted, is shown in Figure 2. It vividly shows that the orientations of the phenyl groups are systematically different while the penam moieties have the same closed conformation as its free acid and benzyl ester forms. The phenyl groups of the molecules A and

Table 2. Selected Bond Distances (Å) and Bond Angles (°)

	A	B	C	D
S(1)-C(2)	1.87 (1)	1.86 (1)	1.87 (1)	1.85 (1)
S(1)-C(5)	1.81 (1)	1.80 (1)	1.80 (1)	1.79 (1)
C(2)-C(3)	1.57 (1)	1.58 (1)	1.60 (1)	1.60 (1)
C(2)-C(20)	1.50 (2)	1.53 (2)	1.51 (2)	1.54 (2)
C(2)-C(21)	1.49 (2)	1.52 (2)	1.49 (2)	1.52 (2)
C(3)-N(4)	1.44 (1)	1.46 (1)	1.42 (1)	1.51 (1)
C(3)-C(22)	1.58 (1)	1.57 (1)	1.53 (1)	1.49 (1)
N(4)-C(5)	1.43 (1)	1.47 (1)	1.46 (1)	1.45 (1)
N(4)-C(7)	1.39 (1)	1.36 (1)	1.39 (1)	1.34 (1)
C(5)-C(6)	1.53 (1)	1.55 (1)	1.55 (1)	1.57 (1)
C(6)-C(7)	1.55 (2)	1.54 (2)	1.56 (2)	1.54 (2)
C(6)-N(9)	1.43 (1)	1.46 (1)	1.45 (1)	1.43 (1)
C(7)-O(8)	1.17 (1)	1.21 (1)	1.21 (2)	1.24 (2)
N(9)-C(10)	1.32 (1)	1.37 (2)	1.37 (1)	1.37 (1)
C(10)-O(11)	1.25 (1)	1.17 (1)	1.20 (1)	1.14 (1)
C(10)-C(12)	1.57 (2)	1.51 (2)	1.51 (1)	1.54 (2)
C(12)-O(13)	1.43 (1)	1.43 (1)	1.39 (1)	1.45 (2)
O(13)-C(14)	1.36 (2)	1.36 (2)	1.33 (2)	1.37 (1)
C(22)-O(23)	1.26 (1)	1.27 (1)	1.26 (1)	1.27 (2)
C(22)-C(24)	1.24 (1)	1.22 (1)	1.26 (1)	1.22 (1)
C(3)-C(2)-S(1)	103.7 (6)	104.6 (7)	101.3 (7)	105.3 (7)
N(4)-C(3)-C(2)	105.7 (8)	106.2 (8)	108.1 (8)	103.3 (8)
N(4)-C(5)-S(1)	104.9 (6)	105.4 (7)	105.2 (7)	105.7 (7)
C(5)-S(1)-C(2)	95.2 (4)	96.1 (5)	96.9 (5)	96.6 (4)
C(5)-N(4)-C(3)	120.4 (8)	118.1 (7)	117.6 (8)	118.2 (8)
C(6)-C(5)-S(1)	119.4 (7)	120.2 (7)	121.7 (7)	120.3 (7)
C(6)-C(5)-N(4)	89.8 (7)	86.9 (7)	90.1 (7)	87.9 (8)
C(6)-C(7)-N(4)	90.3 (8)	91.5 (8)	92.4 (8)	93.4 (9)
C(7)-N(4)-C(3)	122.5 (9)	124.7 (9)	128.4 (9)	124.5 (9)
C(7)-N(4)-C(5)	94.6 (8)	95.6 (8)	93.4 (8)	94.4 (8)
C(7)-C(6)-C(5)	84.5 (7)	85.5 (8)	83.7 (8)	82.6 (8)
O(8)-C(7)-N(4)	133.2 (11)	133.2 (11)	129.7 (11)	135.0 (11)
O(8)-C(7)-C(6)	136.4 (10)	135.0 (10)	137.5 (10)	131.6 (10)
N(9)-C(6)-C(5)	118.4 (8)	116.7 (8)	115.9 (8)	115.3 (9)
N(9)-C(6)-C(7)	114.4 (9)	113.0 (8)	111.2 (9)	117.8 (9)
C(10)-N(9)-C(6)	122.2 (8)	119.4 (9)	120.2 (8)	117.5 (9)
O(11)-C(10)-N(9)	124.2 (10)	123.9 (11)	122.6 (9)	125.7 (10)
C(12)-C(10)-N(9)	119.0 (9)	113.7 (10)	112.8 (8)	114.6 (9)
C(12)-C(10)-O(11)	116.7 (9)	122.0 (11)	124.5 (9)	119.7 (10)
O(13)-C(12)-C(10)	109.6 (10)	113.7 (9)	111.2 (9)	110.0 (10)
C(14)-O(13)-C(12)	121.6 (11)	121.9 (10)	118.7 (9)	114.4 (10)
C(15)-C(14)-O(13)	126.4 (12)	119.0 (11)	121.3 (13)	121.0 (12)
C(19)-C(14)-O(13)	113.8 (13)	118.6 (14)	120.4 (13)	120.3 (13)
C(20)-C(2)-S(1)	108.1 (7)	108.3 (7)	108.9 (7)	107.3 (8)
C(20)-C(2)-C(3)	114.4 (8)	110.5 (8)	112.9 (9)	108.0 (8)
C(21)-C(2)-S(1)	108.5 (7)	109.3 (7)	109.7 (8)	109.7 (9)
C(21)-C(2)-C(3)	110.6 (8)	109.9 (8)	109.4 (9)	109.8 (9)
C(21)-C(2)-C(20)	111.1 (9)	113.9 (9)	113.8 (9)	116.2 (10)
C(22)-C(3)-C(2)	114.2 (8)	114.1 (7)	114.3 (8)	117.0 (9)
C(22)-C(3)-N(4)	109.5 (8)	110.6 (8)	113.6 (8)	109.8 (9)
O(23)-C(22)-C(3)	113.7 (9)	114.4 (9)	118.8 (9)	113.1 (10)
O(24)-C(22)-C(3)	116.8 (9)	119.0 (9)	116.5 (9)	121.8 (10)
O(24)-C(22)-O(23)	129.4 (10)	126.6 (10)	124.7 (9)	125.1 (10)

Table 3. Geometry of Intramolecular Hydrogen Bonds and Selected Torsion Angles

	A	B	C	D
O(13)···N(9) (Å)	2.69 (1)	2.66 (1)	2.54 (1)	2.61 (1)
O(13)···H(9) (Å)	2.24 (1)	2.20 (1)	2.07 (1)	2.15 (1)
O(13)···H(9)-N(9) (°)	102.7 (8)	102.8 (8)	102.9 (8)	102.2 (8)
N(9)-C(10)-C(12)-O(13) (°)	4 (1)	17 (1)	−4 (1)	7 (1)
C(10)-C(12)-O(13)-C(14) (°)	−87 (1)	85 (1)	−159 (1)	163 (2)
C(12)-O(13)-C(14)-C(15) (°)	5 (1)	0 (1)	−49 (1)	−107 (2)

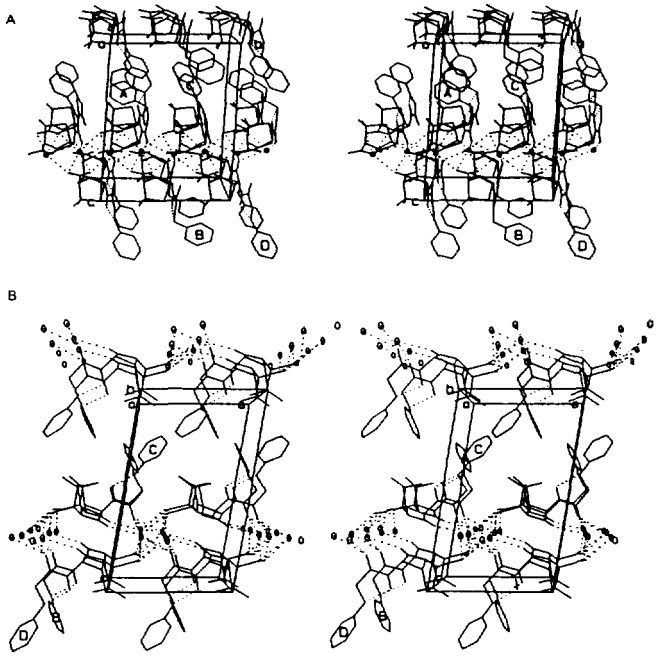

Figure 3. Stereoscopic packing diagrams viewed along the *a* (A) and *b* (B) axes. The hydrogen atoms except H(N9) are omitted for clarity. The small circles represent the potassium ions. The dotted and dashed lines denote the hydrogen bond and K···O interaction, respectively.

B and those of C and D are pseudo mirror-related with respect to the exocyclic amide plane. The orientations of the phenyl groups are also quite different from those of the free acid and benzyl ester forms in which the phenyl groups are approximately parallel to the exocyclic amide planes.[8,9] There are intramolecular hydrogen bonds between exocyclic amide N(9) and phenoxy O(13) in all four independent molecules, as observed in the free acid and benzyl ester forms of penicillin *V*. These indicate that this side chain is flexible about the ether bond despite the presence of intramolecular N-H··· O hydrogen bond. The hydrogen-bonding geometry and the selected torsion angles involving the phenoxymethyl side chains are listed in Table 3. Although the carboxyl and the exocyclic amide groups apparently have certain rotational degrees of freedom, their orientations with respect to the penam nucleus are almost identical in the penicillin *V* compounds, suggesting that the penam moiety is conformationally very restricted.

PVK crystal has an interesting packing mode. Stereoscopic

Table 4. K···O and K···K Distances (Å)

	K(A)	K(B)	K(C)	K(D)
O(8)	2.747 (9) Ai*	2.737 (8) Bii	2.730 (9) Ci	2.712 (9) Dii
O(11)	2.887 (8) Div	2.814 (8) Ai	2.769 (8) Bii	2.838 (9) Ci
O(11)	2.944 (9) Ciii	3.035 (10) Div	2.999 (10) Ai	3.194 (10) Bii
O(23)	2.888 (9) Aii	2.926 (8) Bi	2.913 (8) Cii	2.841 (8) Di
O(23)	2.709 (8) Bi	2.686 (8) Cii	2.814 (9) Di	2.766 (9) Avi
O(24)	2.914 (8) Aii	2.831 (8) Bi	2.842 (7) Cii	2.841 (8) Di
O(24)	2.662 (8) Diii	2.715 (8) Aii	2.653 (8) Bi	2.689 (8) Cii
K(A)···K(B)	3.650 (4)	K(B)···K(C)	3.669 (4)	
K(C)···K(D)	3.668 (4)	K(D)···K(A)v	3.623 (4)	

*A, B, C and D represent the molecule designator for the O atoms and the Roman numbers denote the following symmetry codes.

i. x, y, z; ii. $1+x, y, z$; iii. $x, 1-y, z$; iv. $1+x, 1-y, z$; v. $x, 1+y, z$; vi. $1+x, 1+y, z$.

ORTEP[14] packing drawings along the *a* and *b* axes are shown in Figure 3. Although the salt crystallizes in the space group without any crystallographic symmetry, there are various pseudo symmetry elements relating two parts of the penicillin molecule separately. The penam nuclei of the molecules A, B, C and D are related by pseudo 2-fold rotational and 1/4*b*-translational symmetry operations successively. These result in the pseudo $2_{0.5}$ screw axes parallel to the *b*-axis and there are four such axes related by 1/2*a* or 1/2*c* translation ($x=0.30$ or 0.80 and $z=0.23$ or 0.73) in the unit cell. As a result of these pseudo symmetric relationships, the penam moieties of the molecules A and C and those of B and D are related by a half unit cell translation along the *b* axis. In contrast, the two phenyl groups of A and B and those of C and D are related by pseudo centers of symmetry which locate on the $2_{0.5}$ axes at $y=0.43$ and 0.93. The potassium ions form an infinite zigzag planar chain parallel to the *b* axis. They are related by the pseudo $2_{0.5}$ axis at $x=0.30$ and $z=0.73$ and also by the pseudo centers of symmetry on the $2_{0.5}$ axis at $y=0.18$, 0.43, 0.68 and 0.93. Each potassium ion is coordinated to seven oxygen atoms in a severely distorted pentagonal bipyramid configuration, forming an infinite channel that involves only the $K^{+}\cdots O^{\delta-}$ interactions. Geometric details of the K···O interactions are listed in Table 4.

For each penicillin V molecule, β-lactam keto O(8) and amide keto O(11) interacts with one and two potassium ions, respectively, in one K···O channel while each of carboxyl O(23) and O(24) interacts with two ions in the other channel translated by one unit cell along the *a* axis. Two layers of the penam moieties related by translation along the *b* axis form a molecular stack in the *ac* plane mediated by the hydrophilic potassium channels. Between these molecular stacks, there are only lipophilic interactions involving the phenyl groups. When the phenyl groups are disregarded, each half of the present triclinic unit cell along the *b* axis is approximately equivalent to a monoclinic cell with the space group $P2_1$ due to the pseudo symmetry elements. These pseudo symmetric relationships present in the crystal lattice explain the reason why the intensities of the reflections with the odd *k* indices are generally very weak.

Supplementary Materials. Lists of structure factors, anisotropic thermal parameters, coordinates of the H atoms and molecular dimensions of the phenyl rings are available from the author.

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Synthesis and Herbicidal Activities of *N*-Phenyl Oxadiazolidinedione Derivatives

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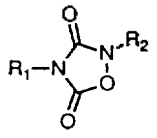
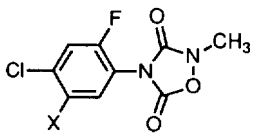
N-Phenyl oxadiazolidinedione derivatives **II** were synthesized and their herbicidal activities were measured against grass weeds. A parabolic relationship between molar refractivity (MR) of meta substituents of dione **II** and their herbicidal activities was observed. With the substituents having MR value = ~15, the higher activities were obtained. Especially, the highest herbicidal activity (97% inhibition of weeds at 0.25 kg/ha) was observed by propyne **IIr** containing propargyloxy group as meta substituent.

Introduction

Disubstituted oxadiazolidinedione derivatives **I**, a class of *N*-phenylimide, have been well known as their herbicidal activities.[1] The structural derivatization of oxadiazolidine **I** by modification of substituents R_1, R_2 and the heterocyclic ring itself affects their herbicidal activities and selectivity on the plants. The herbicidal activities of oxadiazolidine **I** are usually increased with the halogenated phenyl groups at R_1 and R_2. However, no clear structure activity relationship (SAR) is available yet. We have been interested in providing the SAR data of oxadiazolidine **I** since it is useful for the design of new herbicides such as *N*-phenyl pyrimidone and phthalimide derivatives. The herbicidal biomechanism of Methazole (**III**),[2] a well known oxadiazolidinedione, includes the cleavage of oxadiazolidine ring as a key step to give a potent urea **IV** (Scheme 1). When a phenyl ring is adjacent to the bond breaking or formation center, the electronic effect of meta substituent is not important on the reaction. Rather, it might have significant bulk effect on its binding to a receptor or an enzyme during the action as a biomolecule.

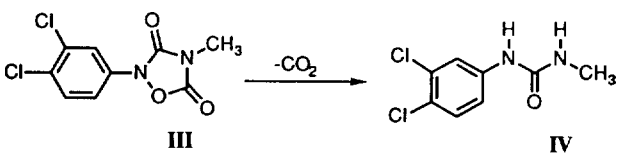


I



II

In this regard, we designed oxadiazolidine derivatives **II** in which *N*-2-fluoro-4-chlorophenyl group with various meta



III **IV**

Scheme 1.