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Semisynthetic β-Lactam Antibiotics. IV.[1] The X-Ray Analysis of Monopotassium α-Sulfophenylacetate Monohydrate. The Configuration of the Acyl Side Chain of α-Sulfobenzylpenicillin

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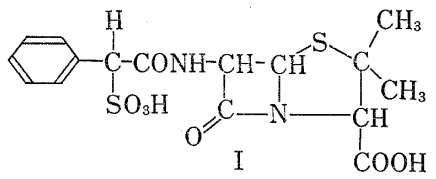
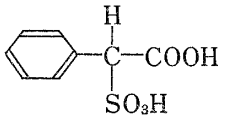
The absolute configuration of (−)-α-sulfophenylacetic acid (II), the side chain acid of a novel antipseudomonal semisynthetic penicillin, (−)-α-sulfobenzylpenicillin (I), has been determined and confirmed to be in the D-series. Accordingly, the biologically more active diastereoisomer which is derived from II has been assigned to be D(−)-α-sulfobenzylpenicillin.

α-Sulfobenzylpenicillin, discovered in these Laboratories,[1,3] has recently been in clinical use[4] for the treatment of *Pseudomonal* infections which have increased progressively during the last decade.[5]

α-Sulfobenzylpenicillin has an asymmetric α-carbon of the 6-acyl side chain and, therefore, has the two diastereoisomers. The antibacterial test of each isomer showed that the one (I) prepared by condensing (−)-α-sulfophenylacetic acid (II) with 6-aminopenicillanic acid was considerably more active than the other prepared from the (+)-acid against Gram-positive and Gram-negative bacteria.[2]



I



II

In order to assign the absolute configurations to these diastereoisomers, the X-ray analysis has been undertaken. Although I crystallizes from ethanol as fine needles, the single crystals suitable for the X-ray analysis could not be obtained. Consequently, we selected the crystalline monopotassium salt of II for this study.

Experimental

Single crystals were prepared from a mixed solution of ethanol and water. The cell dimensions and space group were determined from photographs taken with CuKα radiation ($\lambda=1.5418$ Å). They are listed in Table I together with other crystal data.

The intensities of 942 independent reflections were measured on a Hilger and Watts linear diffractometer using MoKα radiation. After the usual Lorentz and polarization corrections, intensities were put on an absolute scale by Wilson's method. In all, 889 non-zero F^2 values were thus derived and were used in the structure analysis.

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Table I. Crystal Data

Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell dimensions	$a=6.95$ Å
	$b=27.44$
	$c=5.67$
Cell volume	1831.3 Å^3
Number of molecules in the unit cell	$z=4$
Composition of asymmetric unit	$C_8H_7SO_5K\cdot H_2O$
Formula weight	272.3
Observed density	1.664 g cm^{-3} (by flotation in CCl_4/CH_2I_2)
Calculated density	1.666 g cm^{-3}
Absorption coefficient for MoKα	10.4 cm^{-1}

Determination of the Structure

The structure of II was determined by our usual procedures[6] and was refined by the least-squares method to an R value of 0.12. The atomic parameters, bond distances, bond angles, and the final structure factors are listed in Tables II, III, IV and V, respectively. The molecular structures seen down the c axis is shown in Fig. 1. Coordination to K ion, intra-(O(4)-O(5)) and intermolecular hydrogen bonds are shown in Fig. 2.

The absolute configuration was subsequently determined by the anomarous dispersion method. The dispersion terms of K and S for CuKα radiation were assumed to be $\Delta f'_K=0.3$, $\Delta f'_S=0.3$, $\Delta f''_K=1.1$ and $\Delta f''_S=0.6$. The differences between Io (hkl) and Io $(\bar{h}\bar{k}\bar{l})$ were measured visually on Weissenberg photographs taken with CuKα radiation. Of those 87 Friedel pairs, 79 showed differences in the same direction and the parameters given in Table II were found to represent the correct configuration also in an absolute sence.

Table II. Atomic Coordinates and Temperature Factors with Their Standard Deviations in Parentheses

Atom	x/a	y/b	z/c	B
K	0.0182(05)	0.4878(01)	0.1500(07)	3.11(06)
S	0.5503(06)	0.4407(01)	0.1612(08)	2.77(06)
O(1)	0.0057(20)	0.3979(04)	0.4537(22)	4.33(25)
O(2)	0.6756(18)	0.4528(04)	0.9656(21)	3.56(23)
O(3)	0.6567(17)	0.4348(04)	0.3804(21)	3.51(23)
O(4)	0.3939(17)	0.4762(04)	0.1879(24)	4.06(25)
O(5)	0.2093(20)	0.4153(04)	0.8433(27)	5.09(28)
O(6)	0.3427(19)	0.3472(04)	0.7341(24)	4.77(29)
C(1)	0.4452(25)	0.3810(05)	0.0993(27)	2.91(31)
C(2)	0.3343(22)	0.3801(05)	0.8703(29)	2.52(27)
C(3)	0.6072(24)	0.3435(05)	0.1105(29)	2.88(31)
C(4)	0.6178(24)	0.3119(05)	0.3005(31)	3.19(33)
C(5)	0.7690(27)	0.2780(06)	0.3180(37)	4.22(38)
C(6)	0.9107(28)	0.2751(06)	0.1442(41)	4.73(40)
C(7)	0.9001(26)	0.3068(06)	0.9466(33)	3.62(34)
C(8)	0.7503(26)	0.3410(06)	0.9344(31)	3·46(34)

6) M. Nishikawa, K. Kamiya, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, Y. Tomiie, I. Nitta, and K. Goto, *J. Chem. Soc.* (*B*), **1968**, 652.

Table III. Bond Distances

Atoms	Distances	Atoms	Distances
S-O(2)	1.45 Å	C(1)-C(3)	1.53 Å
S-O(3)	1.46	C(3)-C(4)	1.38
S-O(4)	1.47	C(4)-C(5)	1.41
S-C(1)	1.83	C(5)-C(6)	1.40
C(1)-C(2)	1.51	C(6)-C(7)	1.42
C(2)-O(5)	1.31	C(7)-C(8)	1.40
C(2)-O(6)	1.19	C(8)-C(3)	1.41

Table IV. Bond Angles

Atoms	Angles	Atoms	Angles
O(2)-S-O(3)	112°	C(1)-C(2)-O(6)	123°
O(2)-S-O(4)	112	O(5)-C(2)-O(6)	121
O(2)-S-C(1)	107	C(1)-C(3)-C(4)	120
O(3)-S-O(4)	111	C(1)-C(3)-C(8)	122
O(3)-S-C(1)	106	C(4)-C(3)-C(8)	119
O(4)-S-C(1)	109	C(3)-C(4)-C(5)	121
S-C(1)-C(2)	113	C(4)-C(5)-C(6)	121
S-C(1)-C(3)	108	C(5)-C(6)-C(7)	119
C(2)-C(1)-C(3)	114	C(6)-C(7)-C(8)	119
C(1)-C(2)-O(5)	115	C(7)-C(8)-C(3)	121

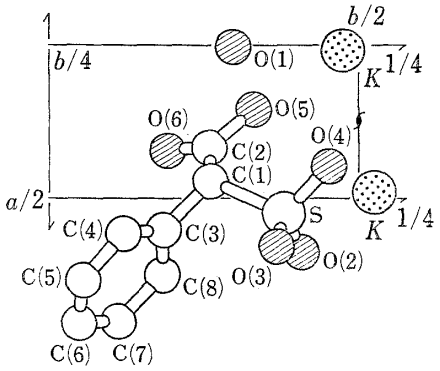

Fig. 1. Drawing of the Structure Projected along the *c* Axis

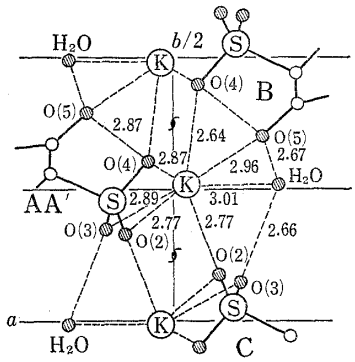

Fig. 2. Projection of Parts of Structure Coordination to K Ion and Hydrogen Bonds are shown by Dashed Lines

Result and Discussion

Intermolecular Contact

Features of intermolecular short contacts and packing of the molecules in the crystal are given in Fig. 2 and 3. Hydrogen bonding and coordination to potassium play an important role in the molecular packing, that is, the connection of acid molecules with one another by these interactions results in the formation of infinite networks perpendicular to the *b* axis.

Absolute Configuration

Introduction of α-sulfo group in benzylpenicillin creates a new asymmetric center in the acyl side chain. The higher activity is present in one of the two diastereoisomers. Since levorotatory α-sulfophenylacetic acid (II) was proved to be in the D-series by the present

TABLE V. Observed and Calculated Structure Factors

H	K	L	FO	FC
0	6	0	17	21
0	8	0	23	25
0	10	0	12	8
0	12	0	9	12
0	14	0	32	32
0	16	0	22	18
0	18	0	45	42
0	20	0	10	11
0	22	0	23	22
0	24	0	33	32
0	26	0	7	4
0	28	0	30	28
1	1	0	10	15
1	2	0	58	73
1	3	0	23	23
1	4	0	46	47
1	5	0	60	59
1	6	0	13	11
1	7	0	74	77
1	8	0	61	58
1	9	0	59	62
1	10	0	47	48
1	11	0	37	38
1	12	0	77	82
1	14	0	68	73
1	15	0	9	10
1	16	0	32	34
1	17	0	25	28
1	18	0	5	7
1	19	0	22	22
1	20	0	7	7
1	21	0	8	11
1	22	0	4	8
1	23	0	5	5
1	24	0	17	22
1	25	0	7	10
1	26	0	10	14
1	28	0	13	17
2	0	0	65	61
2	1	0	11	10
2	2	0	75	80
2	3	0	57	61
2	4	0	46	50
2	5	0	55	61
2	6	0	27	26
2	7	0	36	40
2	8	0	35	37
2	9	0	41	40
2	10	0	47	45
2	11	0	60	58
2	13	0	17	21
2	14	0	3	2
2	15	0	16	18
2	16	0	36	37
2	17	0	3	4
2	18	0	14	19
2	19	0	5	5
2	20	0	6	9
2	21	0	18	20
2	22	0	9	10
2	23	0	16	19
2	24	0	21	25
2	25	0	9	10
2	26	0	15	20
2	27	0	6	4
2	28	0	6	9
3	2	0	52	50
3	3	0	21	23
3	4	0	15	14
3	5	0	17	18
3	6	0	7	7
3	7	0	70	66
3	8	0	53	48
3	9	0	48	45
3	10	0	33	33
3	12	0	31	34
3	13	0	4	3
3	14	0	28	28
3	15	0	25	24
3	16	0	13	15
3	17	0	15	14
3	18	0	10	9
3	19	0	4	5
3	20	0	19	19
3	21	0	14	16
3	22	0	15	20
3	23	0	7	8
3	24	0	2	5
3	25	0	8	8
4	0	0	13	12
4	1	0	4	4
4	2	0	34	34
4	3	0	7	6
4	4	0	17	17
4	5	0	4	7
4	6	0	4	5
4	7	0	13	12
4	8	0	30	30
4	9	0	12	13
4	10	0	26	26
4	11	0	16	13
4	12	0	25	21
4	13	0	4	7
4	14	0	15	11
4	15	0	4	3
4	17	0	8	4
4	18	0	17	17
4	19	0	19	18
4	20	0	5	4
4	21	0	28	26
4	23	0	12	14
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5	3	0	15	19
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5	7	0	9	12
5	8	0	11	10
5	9	0	22	22
5	10	0	12	10
5	11	0	23	23
5	12	0	27	26
5	13	0	4	8
5	14	0	31	32
5	16	0	21	19
6	0	0	9	12
6	1	0	5	3
6	2	0	21	26
6	3	0	19	23
6	5	0	23	28
6	6	0	4	4
6	7	0	11	15
6	8	0	12	15
6	9	0	4	4
6	10	0	9	9
6	12	0	5	5
6	15	0	4	5
6	16	0	6	7
0	1	1	64	71
0	2	1	42	42
0	3	1	45	50
0	4	1	47	56
0	5	1	23	22
0	6	1	123	117
0	7	1	74	67
0	8	1	16	15
0	9	1	54	49
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0	14	1	3	4
0	15	1	5	5
0	16	1	8	12
0	17	1	8	12
0	18	1	53	51
0	19	1	22	20
0	20	1	48	45
0	21	1	24	20
0	22	1	35	35
0	23	1	8	5
0	24	1	24	24
0	25	1	16	14
0	26	1	11	7
0	27	1	27	26
0	28	1	6	4
1	0	1	21	20
1	1	1	76	78
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1	3	1	28	33
1	4	1	46	44
1	5	1	85	82
1	6	1	50	51
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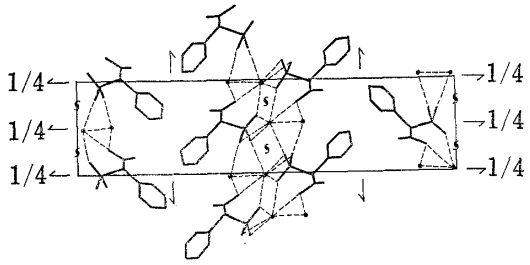

Fig. 3. The Structure Viewed along the *c* Axis
Dashed lines Represent Intermolecular Contact

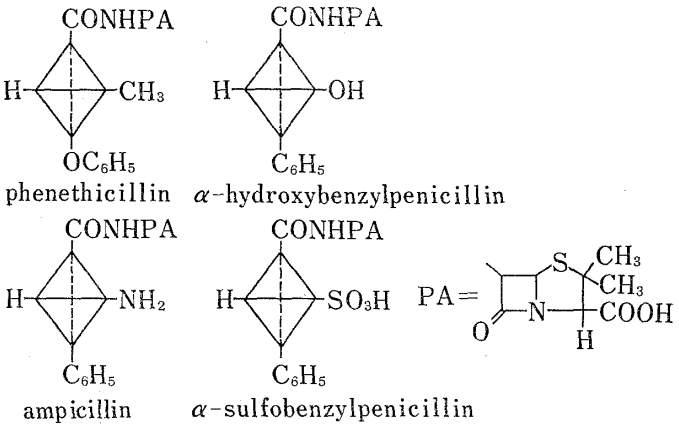

Fig. 4. Projection Formulae of the Acid Side Chains of Penicillins

study, the biologically more active diastereoisomer prepared from II was determined to be the D-series of the Fisher-Rosanoff convention,[7] while the one derived from the (+)-acid, having the lower activity, was assigned to be the L-isomer.

Comparing the antibacterial activities between each pair of the diastereoisomers of the penicillins derived from D- and L-α-phenoxypropionic, α-aminophenylacetic and α-hydroxyphenylacetic acids, and relating them to the structural features of the molecules, Gourevitch, *et al.*[8] have suggested that when the side chain acids of the biologically more active diastereoisomers are similarly oriented with respect to their bulky (phenyl or phenoxy) groups, the remaining substituents have the same spatial relationships. Projection formulae of these penicillins including I are given in Fig. 4. The spatial relationship of D(−)-α-sulfophenylacetic acid was consistent with their suggestion. Difference in the stereochemistry of the penicillin side chain may effect on the accessibility of the molecule to the active site of the bacterial cell wall,[9] resulting in the different antibacterial activity (interference with the cell wall synthesis) of the isomers.

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