# Crystal and molecular structure of 1-(4-methoxyphenyl)-3phthalimido-4-thiomethyl-4-phenylmethyl-2-azetidinone benzene solvate, $C_{26}H_{22}N_2O_4S + \frac{1}{2}C_6H_6$

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The crystal structure of benzene solvated 1-(4-methoxyphenyl)-3-phthalimido-4-thiomethyl-4-phenylmethyl-2-azetidinone (3) has been investigated by X-ray diffractometric methods. The compound crystallizes in the triclinic system:  $P\bar{1}, Z = 2, a = 9.068(1), b = 11.669(1), c = 13.866(1)$ Å,  $\alpha = 114.447(7), \beta = 106.777(6), \gamma = 90.790(7)^{\circ}$ . The structure was solved by direct methods and refined by full matrix, least-squares to R = 0.046 (unit weights). The solid state structure was compared with that found from nmr studies in solution.

# Introduction

Stereo-controlled syntheses of 3-amino-4-alkyl-2azetidinones attract now continuously more attention because the resulting compounds may serve as efficient synthons for a variety of mono- and bicyclic  $\beta$ -lactam antibiotics (Kirrstetter and Durckheimer, 1989). The annelation of thioformimidates with an activated acetic acid derivative in the presence of triethylamine gives the  $\beta$ -lactams in the 3,4-*trans* configuration. Conversely, when the thio group in the acyclic imino component is absent, 3,4-*cis*- $\beta$ -lactams are formed (Wagle *et al.*, 1988).

On the basis of the above literature data, we can assume that a reaction of this type leads to single 3,4*cis* or -*trans* isomers. In the cases of 3,4-disubstituted 2-azetidinones (with the presence of H at 4C) the 3,4configuration may be easily confirmed by <sup>1</sup>H nmr spectroscopy. However, in the present case, where the acyclic thioakylimidates were used as the imino components (Grochowski and Pupek, 1990), a simple <sup>1</sup>H nmr investigation cannot confirm the suspected configuration, because of the absence of hydrogen at 4C. The 3,4-configuration in **3** was investigated here instead by a series of NOE experiments. This led us to assign tentatively the 3,4-cis configuration to **3**.

The purpose of present investigation is to confirm the assumed configuration of 3,4,4-trisubstituted  $\beta$ -lactam (3) obtained in the course of annelation of S-methyl N-(4-methoxyphenyl)-phenylacet-thioimidate (1) with potassium phthalimidoacetate (2).

# Experimental

<sup>1</sup>H and <sup>13</sup>C nmr spectra were measured on a Bruker AM-500 spectrometer at 500 MHz and 125 MHz, respectively, in CDCl<sub>3</sub> solution, and are reported in ppm from internal TMS. A standard Bruker program was used to perform NOE experiments. Infrared spectra were measured on a Beckman AccuLab 1 spectrophotometer. Solvents and commercially available materials were purified by literature procedures.

# Synthesis of 3

To a suspension of 1.6 g (6.5 mmol) dry potassium phthalimidoacetate 2 in 25 cm<sup>3</sup> dichloromethane was added 1.36 g (5 mmol) thioimidate 1 and 2.1 cm<sup>3</sup> (15 mmol) triethylamine. The suspension was cooled to

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0°C, and 0.9 cm<sup>3</sup> (6 mmol) phenyl dichlorophosphate (Arrieta *et al.*, 1985) in 10 cm<sup>3</sup> dichloromethane was added. After the addition was complete, the mixture was warmed to room temperature, stirred overnight and washed first with diluted hydrochloric acid, and then by a saturated solution of sodium bicarbonate. The organic layer was dried (MgSO<sub>4</sub>) and evaporated *in vacuo*, yielding the crude  $\beta$ -lactam **3** which was then crystallized from benzene–ethanol (2.0 g, 87%). An analytical grade sample was recrystallized from pure ethanol; mp. 157–159°C. *Analysis*: calculated for C<sub>26</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S: C 68.10, H 4.84, N 6.11, S 6.99 range. *Found*: C 68.30, H 4.55, N 6.35, S 7.09.

# IR and NMR investigations

IR (KBr): 1725, 1765, 1790 cm<sup>-1</sup>. <sup>1</sup>H nmr: 2.21 (s, SCH<sub>3</sub>, 3H), 3.48, 3.71 (AB system, CH<sub>2</sub>Ph, 2H, J = 15.56), 3.80 (s, OCH<sub>3</sub>, 3H), 5.60 (s, H-3C, 1H), 6.86-6.88 (m, Ar, 2H), 6.90-6.95 (m, Ar, 3H), 7.14-7.16 (m, Ar, 2H), 7.68-7.71 (m, Ar, 4H), 7.72-7.75 (m, Ar, 2H) <sup>13</sup>C nmr: 11.34 (SCH<sub>3</sub>), 40.82 (CH<sub>2</sub>Ph), 55.40 (OCH<sub>3</sub>), 62.60 (3C), 74.51 (4C), 114.26 (Ar), 120.43 (Ar), 123.48 (Ar), 126.58 (Ar), 127.93 (Ar), 128.25 (Ar), 129.57 (Ar), 131.43 (Ar), 134.06 (Ar), 134.28 (Ar), 157.09 (Ar), 160.05 (C=O  $\beta$ -lactam), 167.12 (C=O phthalimide).

Irradiation of the S-methyl protons ( $\delta$  2.21) induced about 1.5% positive NOE at H-3C ( $\delta$  5.60). The effect induced at CH<sub>3</sub>S- by irradiation of H-3C was 9%. No change was observed at PhCH<sub>2</sub>- ( $\delta$  3.48, 3.71).

#### X-ray structural investigations

A well-shaped crystal of 3 (from benzene-ethanol, dimensions 0.35, 0.25, 0.21 mm) was chosen for dif-

fractometric measurements on a four-circle automated CAD4 diffractometer, with Cu  $K\alpha$  radiation. Cell parameters were obtained from a least-squares fit of 25 reflections: a = 9.068(1), b = 11.669(1), c = 13.866(1)Å,  $\alpha = 114.447(7)^\circ$ ,  $\beta = 106.777(6)^\circ$ ,  $\gamma = 90.790(7)^\circ$ ;  $V_c = 1263.8(2)$  Å<sup>3</sup>, Z = 2. The triclinic space group P1 was been assigned (P1 rejected early in the analysis). The calculated density (including benzene molecule in  $\frac{1}{2}$ : 1 ratio,  $M_r = 497.6$ ) is 1.34 g cm<sup>-1</sup>, and F(000) = 522;  $\mu$ (Cu  $K\alpha$ ) = 13.48 cm<sup>-1</sup>.

From a total of 5235 reflections, collected using the  $\theta/2\theta$  scan mode (4982 unique), 4915 had  $I > 2\sigma_I$ . Lorentz and polarization corrections were applied to all intensities, but no absorption correction was performed at the measuring stage. The structure was solved by direct methods (program SHELX-86, Sheldrick et al., 1986), and refined by full-matrix, least squares (Program SHELX-76, Sheldrick et al., 1976). After completion of the refinement of the non-hydrogen atoms (isotropic approximation; R = 0.145), the examination of a Fourier difference map revealed three new peaks of electron density (over four electrons each) forming an obtuse triangle (ca. 120°). The peaks with their inversion across the center at 0, 0,  $\frac{1}{2}$  gave the full benzene skeleton. Thus, three carbon atoms of benzene were included in the set of variables. Then, the positions of all H atoms were calculated from geometry, added to the set, with individual temperature factors equal to those of the adjacent atoms  $+ 1 \text{ Å}^2$ , and the total parameters refined again in the isotropic mode. At this stage an empirical, spherical absorption correction was applied to the reflections, using the DIFABS program (Walker and Stuart, 1983), resulting in minimum, maximum, and average correction coefficients of 0.783, 1.172, and 0.981, respectively. Further refinement

Structure of  $C_{26}H_{22}N_2O_4S + \frac{1}{2}C_6H_6$ 

Table 1. Refined fractional coordinates ( $\times 10^4$ ) and  $B_{eq}^a$  values for non-hydrogen atoms of  $3^b$ 

	x	у	z	B <sub>eq</sub>		x	у	z	$B_{\rm eq}$
s	746(1)	1263(0)	- 844(0)	4.06(1)	C17	2546(2)	4531(2)	4139(2)	3.70(5)
N1	3823(2)	2329(1)	191(1)	3.02(4)	C18	4405(2)	2138(2)	-699(1)	3.04(5)
C2	4420(2)	2156(1)	1133(1)	3.03(4)	C19	5218(2)	1145(2)	-1066(2)	3.96(8)
C3	2907(2)	2341(1)	1415(1)	3.00(4)	C20	5798(3)	945(2)	-1929(2)	4.30(7)
C4	2252(2)	2518(2)	307(1)	3.00(4)	C21	5548(2)	1746(2)	-2444(2)	3.80(6)
C5	1496(3)	-164(2)	-887(2)	4.92(5)	C22	4748(3)	2746(2)	-2078(2)	4.17(9)
06	5671(1)	1907(1)	1546(1)	3.91(4)	C23	4186(2)	2955(2)	-1206(2)	3.79(8)
N7	3008(2)	3353(1)	2482(1)	3.04(4)	O24	6039(2)	1629(2)	-3320(1)	5.21(7)
C8	3945(2)	4553(2)	2982(1)	3.14(4)	C25	6931(4)	653(3)	-3701(2)	6.3(1)
C9	2197(2)	3263(2)	3173(2)	3.67(5)	C26	1773(2)	3813(2)	400(2)	3.33(5)
010	4845(2)	4838(1)	2593(1)	3.82(4)	C27	685(2)	4344(2)	1072(1)	3.30(5)
011	1405(2)	2300(2)	2976(1)	5.02(5)	C28	1032(2)	5598(2)	1863(2)	3.96(5)
C12	3580(2)	5309(2)	4017(1)	3.48(5)	C29	88(3)	6129(2)	2507(2)	4.71(6)
C13	4087(3)	6566(2)	4783(2)	4.53(5)	C30	-1243(3)	5402(2)	2363(2)	4.86(9)
C14	3533(3)	7019(2)	5682(2)	5.27(6)	C31	-1621(3)	4170(2)	1567(2)	5.37(8)
C15	2511(3)	6236(3)	5815(2)	5.41(7)	C32	-678(3)	3631(2)	924(2)	4.76(6)
C16	2008(3)	4982(2)	5045(2)	4.83(6)					
Benzen	e carbon atoms <sup>c</sup>	;							
C1B	1052(4)	1072(3)	5460(4)	7.7(1)	C3B	-53(5)	730(4)	4436(4)	8.0(2)
C2B	1106(4)	348(4)	6015(3)	7.8(1)					

<sup>a</sup>Calculated from anisotropic thermal parameters as  $B_{eq} = 8\pi^2 \cdot D_u^{1/3}$ , where  $D_u$  is determinant of the  $U_{ij}$  matrix in orthogonal space.

<sup>b</sup> In this and following tables the values in parentheses are estimated standard deviations.

<sup>c</sup> The second half of the benzene molecule may be generated by inversion with respect to  $(0, 0, \frac{1}{2})$ .

cycles were performed in the anisotropic mode for all non-H atoms. The final refinement converged at R = 0.046 (unit weights) at the shift/error values below 0.1. The final maximum residual electron density (from Fourier difference maps) was 0.21 e Å<sup>-3</sup>. A list of fractional nonhydrogen atomic coordinates together with their  $B_{eq}$  values is given in Table 1.

# **Results and discussion**

# Molecular spectroscopy results

The expected chemical structure and the stereochemical homogeneity of **3** were confirmed by ir, <sup>1</sup>H and <sup>13</sup>C—nmr spectroscopy, tlc, and elemental analysis. The geometrical configuration of the  $\beta$ -lactam **3** in chloroform solution was determined by measurement of nuclear Overhauser effects (NOE) in the <sup>1</sup>H—nmr spectrum. Irradiation of the S-methyl protons ( $\delta$  2.21 ppm) in the sample of **3** gave rise to a positive enhancement (about 1.5%) at 3—H ( $\delta$  5.60 ppm). The effect induced at CH<sub>3</sub>—S-protons by irradiation of 3—H was 9%. No

Table 2. Bond lengths (Å) for 3

C4-S	1.819(1)	C15-C14	1.394(5)
C5-S	1.792(3)	C16-C15	1.377(3)
C2-N1	1.361(2)	C17-C16	1.381(4)
C4-N1	1.488(3)	C19-C18	1.377(3)
C18-N1	1.415(2)	C23-C18	1.386(4)
C3-C2	1.526(3)	C20-C19	1.378(4)
O6-C2	1.213(2)	C21-C20	1.378(4)
C4-C3	1.580(2)	C22-C21	1.375(3)
N7-C3	1.437(2)	O24-C21	1.367(3)
C26-C4	1.542(3)	C23-C22	1.377(4)
C8-N7	1.410(2)	C25-O24	1.416(4)
C9-N7	1.399(3)	C27-C26	1.515(3)
O10-C8	1.209(3)	C28-C27	1.379(3)
C12-C8	1.477(2)	C32-C27	1.395(3)
011–C9	1.210(3)	C29-C28	1.383(4)
С17—С9	1.478(3)	C30-C29	1.382(4)
C13-C12	1.379(3)	C31-C30	1.363(3)
C17-C12	1.388(3)	C32-C31	1.383(4)
C14—C13	1.382(4)		
Benzene molec	ule		
C3B-C1B	1.370(6)	C1B-C2B	1.351(8)
$C2B-C3B^{a}$	1.362(6)		

<sup>*a*</sup> Atom generated by inversion with respect to  $(0, 0, \frac{1}{2})$ .

		-	
S-C4-N1	111.5(1)	N7-C8-C12	106.1(2)
S-C4-C3	116.4(1)	N7-C9-011	124.0(2)
S-C4-C26	108.3(1)	N7-C9-C17	106.3(2)
N1-C2-C3	92.5(1)	C8-N7-C9	110.9(1)
N1-C2-O6	132.4(2)	C8-C12-C13	130.4(2)
N1-C4-C3	85.8(1)	C8-C12-C17	108.2(1)
N1-C4-C26	114.9(2)	C9-C17-C12	108.3(2)
N1-C18-C19	120.4(2)	C9-C17-C16	130.6(2)
N1-C18-C23	120.7(2)	O10-C8-C12	130.0(2)
C2-N1-C4	95.9(2)	O11-C9-C17	129.8(2)
C2-N1-C18	131.1(2)	C12-C13-C14	117.3(2)
C2-C3-C4	85.9(2)	C12-C17-C16	121.1(2)
C2-C3-N7	116.6(1)	C13-C12-C17	121.4(2)
C3-C2-O6	135.1(2)	C13-C14-C15	121.4(2)
C3-C4-C26	118.5(1)	C14-C15-C16	120.9(2)
C3-N7-C8	125.1(2)	C15-C16-C17	117.8(3)
C3-N7-C9	124.0(2)	C20-C21-O24	124.8(2)
C4-S-C5	103.1(1)	C21-O24-C25	118.2(2)
C4-N1-C18	132.0(2)	C22-C21-O24	115.6(2)
C4-C3-N7	120.7(2)	C26-C27-C28	119.1(2)
C4-C26-C27	116.6(2)	C26-C27-C32	123.3(2)
N7-C8-O10	123.9(2)		
Benzene molecule			
C3B-C1B-C2B	120.6(4)	C1B-C2B-C3B <sup>a</sup>	120.3(3)
$C2B^a - C3B - C1B$	119.1(5)		

Table 3. Valence angles (deg) in 3

<sup>*a*</sup> Atom generated by inversion with respect to  $(0, 0, \frac{1}{2})$ .

change at PhC<u>H</u><sub>2</sub>-protons ( $\delta$  3.48, 3.71 ppm) was observed. This led us to assume the 3,4-(*S*-CH<sub>3</sub>)-*trans* configuration in **3**.

# Structural X-ray diffractometric investigations

The bonding distances, valence and selected torsion angles for compound 3 are listed in Tables 2, 3, and 4, respectively. Figure 1 shows a stereo-view of 3, and Fig. 2 is a packing stereo-diagram of the crystal unit-cell, showing also the locations of the benzene inclusions.

The geometry of the  $\beta$ -lactam four-membered ring in 3 was compared with those of two other structures of  $\beta$ -lactam derivatives known from literature, namely, 4 (Parthasarathy, 1970) and 5 (Kartha and Ambady, 1973)

Table 4. Selected torsion angles (deg) in 3

C2-N1-C4-S	-116.0(1)	C2-C3-C4-S	111.3(1)
C18-N1-C4-S	52.9(2)	N7-C3-C4-S	-130.1(2)
C2-N1-C4-C3	0.8(1)	C2-C3-C4-N1	-0.7(1)
C18-N1-C4-C3	169.7(2)	N7-C3-C4-N1	118.0(2)
C2-N1-C4-C26	120.3(2)	C2-C3-C4-C26	-116.7(2)
C18-N1-C4-C26	-70.7(2)	N7-C3-C4-C26	1.9(3)
C4-N1-C2-C3	-0.8(1)	H3-C3-C4-S	-1.2(7)
C18-N1-C2-C3	-169.9(2)	C3-C4-S-C5	-45.9(2)
C4-N1-C2-O6	177.1(2)	N1-C4-S-C5	50.3(2)
C18-N1-C2-O6	8.2(3)	C26-C4-S-C5	177.6(2)
N1-C2-C3-C4	0.7(1)	C27-C26-C2-S	84.6(2)
O6-C2-C3-C4	-177.0(2)	C27-C26-C2-C3	-50.9(2)
N1-C2-C3-N7	-121.7(2)	C27-C26-C2-N1	-150.0(1)
06-C2-C3-N7	60.5(3)		



Fig. 1. Stereo-view of molecule 3 oriented at the optimal viewing. For the sake of clarity the carbon atoms of aromatic substituents are not labelled and all hydrogen atoms (except at C3) are omitted.



Fig. 2. Stereo-diagram of the triclinic unit cell of 3 (*ab*-faced), showing the packing of the molecules. The eight molecules in the diagram (with H atoms omitted) are those which contribute at least one atom to the given unit cell. Benzene molecules distinguished as black circles.

(see formula). All rings are perfectly planar: the deviations of atoms from the four-atomic least-squares planes lie in the range of 0.004–0.005 Å. Table 5 gives the geometrical data for these  $\beta$ -lactam rings, together with that of **3.** Although the deviations from regular squares may be caused partly by the presence of *N*-heteroatoms



3:  $R^{1} = 3$ -phthalimide;  $R^{2} = H$ ;  $R^{3} = S - CH_{3}$ ;  $R^{4} = Bzl$ ;  $Ar = \rho - C_{6}H_{4}OCH_{3}$ 4:  $R^{1} = i - C_{3}H_{7}$ ;  $R^{2} = R_{3} = H$ ;  $R^{4} = C_{6}H_{5}$ ;  $Ar = \rho - ClC_{6}H_{4}$ 5:  $R^{1} = R^{2} = R^{3} = R^{4} = H$ ;  $Ar = \rho - BrC_{6}H_{4}$ 

**Table 5.** Distances and angles in the monocyclic  $\beta$ -lactam rings

	3	4	5
Distances (Å)			
N1-C2	1.361(3)	1.366(4)	1.363(7)
C2-C3	1.527(3)	1.518(5)	1.518(7)
C3-C4	1.579(3)	1.575(4)	1.539(7)
C4-N1	1.488(2)	1.481(4)	1.459(7)
Angles (deg)			
C2-N1-C4	95.9(2)	95.0(3)	94.5(3)
N1-C2-C3	92.4(1)	93.0(3)	92.0(3)
C2-C3-C4	85.9(2)	85.5(3)	85.4(3)
C3-C4-N1	85.8(1)	86.5(3)	87.9(3)
Diagonal contact dis	tances (Å)		
N1-C3	2.089(2)	2.094(4)	2.080(4)
C2-C4	2.116(2)	2.100(4)	2.071(5)

and a  $C_{sp^2}$  atom, it may be seen that the rings in 3 and 4 are of a very similar shape, whereas the ring in 5 differs markedly from the others. A very significant elongation of the C3–C4 bond (av. 1.577 Å) is observed only in 3 and 4; in 5 a normal length for  $C_{sp^3}-C_{sp^3}$  is found. This may be due to the absence of bulky substituents at both C3 and C4 atoms in 5. The diagonal contact distances deviate much from those observed in cyclobutane (2.18 Å). The valence angles in the rings deviate from 90° by 4–8° causing a trapezoid rather than a rectangular shape of the rings.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60681 (30 pages).