SYNTHESIS AND X-RAY STRUCTURAL INVESTIGATION OF 1-(4-METHOXYPHENYL)-3-PHENOXY-4-METHYLTHIO-4-METHOXYIMINO-2-AZETIDINONES

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ABSTRACT

The trans- (3) and cis- (4) isomers of 1-(4-methoxyphenyl)-3-phenoxy-4-methylthio-4-methoxyimino-2-azetidinone have been synthesized. The structure of **3** has been investigated by X-ray diffraction. The compound crystallizes in a monoclinic system, space group $P2_1/a$, Z=4, a=7.377(2), b=23.790(3), c=10.724(2) Å, $\beta=95.01(2)^{\circ}$. The structure was solved by direct methods and refined by a full-matrix, least-squares procedure to R=0.0435, $R_{\rm w}=0.0597$, $w=1.92/(\sigma_{\rm F}^2+0.002F^2)$. The solid-state structure was compared with the structure found from NMR studies in solution.

INTRODUCTION

Thioimidates are convenient imino components for reaction with ketenes to form β -lactams. In almost all known cases these [2+2] cycloadditions proceed fully stereoselectively to give a single trans- β -lactam [1]. Only in one case does the thioimidate form a mixture of trans- and cis- isomers when reacted with isocyanoacetyl chloride [2].

The cyclization of a Schiff base with S-benzyl or S-phenyl thioglycolic acid derivatives also results in the *trans*-configuration of β -lactams. Van der Veen et al. [3] observed the formation of *cis*- β -lactams as single isomers in the reaction of thiophenoxyacetyl chloride and imino compounds derived from phenylglyoxal. In the absence of a thio group in the imine or ketene components, *cis*- β -lactams were formed as a rule. Such *trans*-stereospecificity in the formation of β -lactams with a thio group at C(3) or C(4), however, is not clear so far.

Previously [4] we have shown that S-methyl-N-(4-methoxyphenyl)-phenylacetothioimidate produced a single $3,4(S-CH_3)$ -trans- β -lactam (5) following cycloaddition reaction with the ketene generated from phthalimidoacetic

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acid. The purpose of the present investigation is to confirm the assumed configuration of the main β -lactam derivative **3** obtained in the course of cyclisation of S-methyl-N-(4-methoxyphenyl)-methoxyiminoacetothioimidate (**1**). The 3,4-configurations in β -lactams **3** and **4** were investigated by a series of NOE experiments. The results allowed us to assign tentatively the 3,4(S-CH₃)trans configuration to **3** and 3,4(S-CH₃)-cis to **4**.



EXPERIMENTAL

¹H and ¹³C NMR spectra were measured on a Bruker AM-500 spectrometer at 500 MHz and 125 MHz, respectively in CDCl₃ solution and are reported in ppm from internal TMS. The standard Bruker program was used to perform NOE experiments. IR spectra were measured on a Beckman AccuLab 1 spectrophotometer. Solvents and commercially available materials were purified by literature procedures.

Synthesis of **3** and **4**

To a suspension of dry 1.2 g (6.1 mmol) potassium phenoxyacetate (2) in 25 cm³ dichloromethane were added 0.7 g (3 mmol) thioimidate (1) [5] and 2.5 cm³ (18 mmol) triethylamine. The suspension was cooled to 0°C and 0.9 cm³ (6 mmol) phenyl dichlorophosphate [6] in 10 cm³ dichloromethane added. After the addition was complete, the mixture was warmed to room temperature, stirred overnight and washed with dilute hydrochloric acid, and then with a saturated solution of sodium bicarbonate. The organic layer was dried (MgSO₄) and evaporated in vacuo, yielding the crude mixture of β -lactams 3

and 4 which were separated by column chromatography $(SiO_2 230-400 \text{ mesh}, \text{hexane-ethyl acetate 4:1 system})$. Compound 3, 0.85 g (77%), was obtained as a first fraction, and 4, 0.1 g (9%), as a second. An analytical grade sample of 3 was recrystallized from pure ethanol.

Analysis: calcd. for C₁₉H₂₂N₂O₄S: C, 60.64; H, 5.94; N, 7.48; S, 8.56%; found: C, 61.24; H, 5.60; N, 7.82; S, 8.86%.

IR and NMR results

3: (m.p. 110.0–111.5°C); IR (nujol): 1770, 1595 cm⁻¹; ¹H NMR: 2.06 (s, 3H, SC<u>H</u>₃), 3.81 (s, 3H, ArOC<u>H</u>₃), 3.84 (s, 3H, =N–OC<u>H</u>₃), 5.43 (s, 1H, C(3)– <u>H</u>), 7.60 (s, 1H, C<u>H</u>=N), 6.89–7.74 (m, 9H, Ar); ¹³C NMR: 10.17 S<u>C</u>H₃, 55.43 ArO<u>C</u>H₃, 62.57 N–O<u>C</u>H₃, 71.71 C(4), 87.65 C(3), 144.95 <u>C</u>H=N, 160.26 CO, 114.38, 116.00, 120.02, 122.87, 129.29, 129.70, 156.90, 157.34 C(Ar).

4: (m.p. 123–125°C); IR (nujol): 1760, 1590 cm⁻¹; ¹H NMR: 2.16 (s, 3H, SC<u>H₃</u>), 3.81 (s, 3H, ArOC<u>H₃</u>), 3.95 (s, 3H, =N–OC<u>H₃</u>), 5.62 (s, 1H, C(3)–<u>H</u>), 7.77 (s, 1H, C<u>H</u>=N), 6.90–7.74 (m, 9H, Ar); ¹³C NMR: 12.32 SCH₃, 55.47 ArOCH₃, 62.72 N–OCH₃, 73.47 C(4), 86.81 C(3), 145.68 CH=N, 161.50 CO, 114.54, 115.76, 119.82, 122.68, 129.20, 129.57, 145.68, 157.24, 157.27 (C)Ar.

X-ray structural investigations

A well shaped crystal of compound **3** (from benzene-cyclohexane, dimensions $0.4 \times 0.3 \times 0.2$ mm) was chosen for diffraction measurements on a fourcircle automated CAD4 diffractometer with CuK_{α} radiation. The cell parameters were obtained from a least-squares refinement on the setting angles of 25 reflections. The data were collected using the $\theta/2\theta$ scan mode up to $2\theta_{max} = 140^{\circ}$.

Crystal data are: $C_{19}H_{20}N_2O_4S$, $M_r = 372.43$, F(000) = 776, monoclinic, space group $P2_1/a$, a = 7.377(2), b = 23.790(3), c = 10.724(2) Å, $\beta = 95.01(2)^\circ$, $V_c = 1874.8(6)$ Å³, $d_c = 1.32$ Mg m⁻³, $\mu(CuK_{\alpha}) = 16.0$ cm⁻¹.

A total of 4043 reflections was collected, 3291 of them were unique and had $I > 2\sigma_{\rm I}$ ($R_{\rm int.} = 0.0245$). The Lorentz and polarization corrections were applied to all observed reflections. No absorption correction was performed at the measuring stage.

The structure was solved by direct methods (program SHELXS-86 [7]) revealing all non-hydrogen atoms of the molecule. The positional parameters and isotropic temperature factors were then refined by a full-matrix least-squares procedure (program SHELX-76 [8]). After completion of this refinement stage the empirical, spherical absorption correction was applied to all observed reflections using the DIFABS program [9], resulting in minimum, maximum, and average correction coefficients of 0.868, 1.365, and 0.994, respectively. Further refinement cycles were performed in the anisotropic mode for all non-H atoms. The positions of hydrogen atoms were calculated from

TABLE	1

Atom	x/a	y/b	z/c	$B_{ m eq}$
s	407.6(6)	9265.2(2)	9176.7(4)	3.46(1)
N(1)	1816(2)	8168(1)	9123(1)	2.86(4)
C(2)	1016(3)	7825(1)	8210(2)	3.20(4)
C(3)	343(2)	8328(1)	7410(2)	3.33(5)
C(4)	1525(2)	8698(1)	8408(1)	2.97(3)
C(5)	-1485(3)	8897(1)	9741(2)	4.31(4)
0(6)	930(2)	7319(1)	8104(1)	3.25(4)
C(7)	3264(2)	8899(1)	7934(2)	3.74(5)
N(8)	3764(2)	9397(1)	8074(2)	4.66(5)
0(9)	5424(2)	9489(1)	7557(2)	5.98(9)
C(10)	6008(4)	10046(1)	7796(4)	3.57(3)
0(11)	891(2)	8310(1)	6194(1)	3.15(4)
C(12)	187(2)	8711(1)	5348(2)	4.39(6)
C(13)	-959(3)	9142(1)	5642(2)	5.19(7)
C(14)	-1598(4)	9508(1)	4682(2)	4.86(6)
C(15)	-1084(4)	9448(1)	3480(2)	4.43(6)
C(16)	75(3)	9021(1)	3222(2)	3.79(5)
C(17)	711(3)	8645(1)	4148(2)	2.69(4)
C(18)	2675(2)	8066(1)	10331(1)	2.93(4)
C(19)	2500(2)	7536(1)	10867(2)	3.20(4)
C(20)	3268(2)	7437(1)	12058(2)	3.09(4)
C(21)	4189(2)	7861(1)	12752(2)	3.44(5)
C(22)	4403(3)	8383(1)	12217(2)	3.33(4)
C(23)	3652(3)	8482(1)	10997(2)	4.29(4)
O(24)	4804(2)	7714(1)	13943(1)	5.07(7)
C(25)	5726(4)	8121(1)	14725(2)	4.66(6)

Fractional coordinates ($\times 10^4$) and B_{eq}^a of non-hydrogen atoms in 3^b

 ${}^{a}B_{eq} = 8\pi^{2} \cdot D_{u}^{1/3}$, where D_{u} is the determinant of the U_{ij} matrix in orthogonal space. ^bIn this and following Tables the figures in parentheses are estimated standard deviations.

the geometry and added to the atomic set with isotropic temperature factors equal to the $B_{\rm eq}$ of the adjacent atoms +1 Å². The final refinement step, involving all atomic positional and thermal parameters (anisotropic for non-H atoms and isotropic for H atoms), converged at R=0.0435 [$R_{\rm w}=0.0597$, $w=1.98/\sigma_{\rm F}^2+0.002F^2$)] at shift/error values below 0.1. The final maximum residual electron density (from Fourier difference maps) was 0.24 eÅ⁻³. A list of fractional non-hydrogen atomic parameters together with their $B_{\rm eq}$ values is given in Table 1.

RESULTS AND DISCUSSION

Molecular spectroscopy results

The expected chemical structures of **3** and **4** were confirmed by IR, ¹H and ¹³C NMR spectroscopy and elemental analysis. The geometrical configuration

of the substituents at C(3) and C(4) in β -lactams **3** and **4** in chloroform solution could be determined by measurement of nuclear Overhauser effects (NOE). When the proton at C(3) in **3** was irradiated, positive NOE effects at CH₃S-protons (8.6%) and at ortho-protons in the phenoxy group (13.6%) were observed. Irradiation of the CH₃S-protons in this sample gave rise to a positive enhancement (1.2%) at C(3)-H. On the other hand, irradiation of the C(3)-H proton in **4** gave positive effect only at ortho-protons in the phenoxy group at C(3) (24.4%). No change at CH₃S-protons was observed. Irradiation of the S-methyl protons in **4** had no effect. This allowed us to assume the 3,4(SCH₃)trans configuration in **3** and 3,4(SCH₃)-cis in **4**.

Structural X-ray 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**.

The geometry of the four-membered ring in **3** was compared with that of **5** [4], and with two other structures of β -lactam derivatives known from the literature, namely **6** [10] and **7** [11] (Table 5). The geometry of these rings in **3** and **5** [4] is almost isomorphic in the range of 2 e.s.d.'s.



3:
$$R^{1} = PhO$$
, $R^{2} = H$, $R^{3} = SCH_{3}$
 $R^{4} = CH = N - OCH_{3}$, $Ar = p - CH_{3}OC_{6}H_{4}$
4: $R^{1} = H$, $R^{2} = PhO$, $R^{3} = SCH_{3}$
 $R^{4} = CH = N - OCH_{3}$, $Ar = p - CH_{3}OC_{6}H_{4}$
5: $R^{1} = Pht$, $R^{2} = H$, $R^{3} = SCH_{3}$
 $R^{4} = Bz1$, $Ar = p - CH_{3}OC_{6}H_{4}$
6: $R^{1} = i - C_{3}H_{7}$, $R^{2} = R^{3} = H$
 $R^{4} = C_{6}H_{5}$, $Ar = p - C1C_{6}H_{4}$
7: $R^{1} = R^{2} = R^{3} = R^{4} = H$, $Ar = p - BrC_{6}H_{4}$

In all compounds discussed, the β -lactam rings are perfectly planar (the deviations of atoms from the four-atomic least-squares planes are in the range of 0.004–0.005 Å). Although the deviations from regular squares may be caused partly by the presence of N-heteroatoms and a C_{sp^2} atom, it may be seen that the rings in **3** and **6** are of very similar shape, whereas the ring in **7** differs distinctly from the others. A very significant elongation of the C(3)–C(4) bond

TABLE 2

Atoms	Bond length	Atoms	Bond length
<u> </u>	1.816(2)	C(17)-C(12)	1.385(3)
C(5)-S	1.797(2)	C(14)-C(13)	1.398(3)
C(2) - N(1)	1.368(3)	C(15)-C(14)	1.382(3)
C(4) - N(1)	1.482(3)	C(16)-C(15)	1.371(4)
C(18) - N(1)	1.413(2)	C(17)-C(16)	1.387(3)
C(3)-C(2)	1.530(3)	C(19)-C(18)	1.396(3)
O(6)-C(2)	1.210(3)	C(23)-C(18)	1.385(3)
C(4) - C(3)	1.587(3)	C(20)-C(19)	1.372(3)
O(11)-C(3)	1.399(2)	C(21)-C(20)	1.395(3)
C(7) - C(4)	1.499(2)	C(22)-C(21)	1.383(3)
N(8)-C(7)	1.246(2)	O(24) - C(21)	1.363(2)
O(9) - N(8)	1.405(2)	C(23)-C(22)	1.396(3)
C(10) - O(9)	1.410(3)	C(25)-O(24)	1.416(3)
C(12)-O(11)	1.386(3)	H(3)-C(3)	1.033(5)
C(13)-C(12)	1.383(3)	H(7)-C(7)	0.943(9)

Bond lengths (Å) in 3

TABLE 3

Bond angles (deg) in 3

Atoms	Angle	Atoms	Angle	
$\overline{S-C(4)-N(1)}$	116.64(9)	O(11)-C(12)-C(13)	124.3(2)	
S-C(4)-C(3)	118.3(1)	O(11)-C(12)-C(17)	114.3(2)	
S-C(4)-C(7)	110.6(2)	C(12)-C(13)-C(14)	117.9(2)	
C(4)-S-C(5)	100.8(1)	C(13)-C(12)-C(17)	121.5(2)	
N(1)-C(2)-C(3)	91.9(2)	C(12)-C(17)-C(16)	119.2(2)	
N(1)-C(2)-O(6)	132.6(2)	C(13)-C(14)-C(15)	121.3(2)	
C(2)-N(1)-C(4)	95.9(1)	C(14)-C(15)-C(16)	119.4(2)	
C(2)-N(1)-C(18)	133.2(2)	C(15)-C(16)-C(17)	120.7(2)	
N(1)-C(4)-C(3)	85.6(2)	C(18)-C(19)-C(20)	119.5(2)	
N(1)-C(4)-C(7)	110.9(2)	C(19)-C(18)-C(23)	119.7(2)	
C(4)-N(1)-C(18)	130.8(2)	C(18)-C(23)-C(22)	120.6(2)	
N(1)-C(18)-C(19)	118.8(2)	C(19)-C(20)-C(21)	121.0(2)	
N(1)-C(18)-C(23)	121.4(2)	C(20)-C(21)-C(22)	119.7(2)	
C(2)-C(3)-C(4)	85.6(2)	C(20) - C(21) - O(24)	114.9(2)	
C(2)-C(3)-O(11)	113.1(2)	C(21)-C(22)-C(23)	119.4(2)	
C(3)-C(2)-O(6)	135.5(2)	C(22)-C(21)-O(24)	125.3(2)	
C(3)-C(4)-C(7)	112.6(1)	C(21)-O(24)-C(25)	118.9(2)	
C(4)-C(3)-O(11)	117.3(2)	C(2)-C(3)-H(3)	110.8(6)	
C(3)-O(11)-C(12)	117.8(2)	C(4)-C(3)-H(3)	113.7(5)	
C(4)-C(7)-N(8)	121.0(2)	O(11)-C(3)-H(3)	113.2(4)	
C(7)-N(8)-O(9)	111.1(2)	C(4)-C(7)-H(7)	118.3(6)	
N(8)-O(9)-C(10)	109.7(2)	N(8)-C(7)-H(7)	120.7(6)	

TABLE 4

Selected torsion angles (deg) in 3

Atoms	Angle	Atoms	Angle
$\overline{N(1)-C(4)-S-C(5)}$	-47.7(1)	S-C(4)-C(3)-C(2)	-124.8(1)
C(3)-C(4)-S-C(5)	52.3(2)	N(1)-C(4)-C(3)-C(2)	-6.8(1)
C(7) - C(4) - S - C(5)	-175.7(1)	C(7)-C(4)-C(3)-C(2)	104.1(2)
C(3)-C(2)-N(1)-C(4)	-7.9(1)	S-C(4)-C(3)-O(11)	121.4(2)
O(6)-C(2)-N(1)-C(4)	171.1(3)	N(1)-C(4)-C(3)-O(11)	-120.6(2)
C(3)-C(2)-N(1)-C(18)	173.4(2)	C(7)-C(4)-C(3)-O(11)	-9.7(3)
O(6)-C(2)-N(1)-C(18)	-7.6(4)	C(12)-O(11)-C(3)-C(2)	172.9(2)
S-C(4)-N(1)-C(2)	127.2(1)	C(12)-O(11)-C(3)-C(4)	-89.8(2)
C(3)-C(4)-N(1)-C(2)	7.6(1)	N(8)-C(7)-C(4)-S	-0.8(2)
C(7)-C(4)-N(1)-C(2)	-104.9(2)	N(8)-C(7)-C(4)-N(1)	-131.9(2)
S-C(4)-N(1)-C(18)	-54.1(2)	N(8)-C(7)-C(4)-C(3)	134.1(2)
C(3)-C(4)-N(1)-C(18)	-173.6(2)	O(9)-N(8)-C(7)-C(4)	-179.9(2)
C(7)-C(4)-N(1)-C(18)	73.8(2)	C(10)-O(9)-N(8)-C(7)	-176.5(2)
C(4)-C(3)-C(2)-N(1)	7.3(1)	H(3)-C(3)-C(2)-N(1)	-106.4(6)
O(11)-C(3)-C(2)-N(1)	125.2(2)	S-C(4)-C(3)-H(3)	-14.0(6)
C(4)-C(3)-C(2)-O(6)	-171.6(3)	H(7)-C(7)-C(4)-S	-179.9(3)
O(11)-C(3)-C(2)-O(6)	-53.7(3)	H(7)-C(7)-C(4)-N(1)	49.0(5)



Fig. 1. A stereo-view of 3 at an orientation providing optimal viewing. For clarity the labels of the phenyl carbons and all hydrogen atoms except H(3) are omitted.

TABLE 5

	3	5 ^b	6 ^c	7^{d}
Distances (Å)		** <u>***********************************</u>		
N(1)-C(2)	1.368(3)	1.361(3)	1.366(4)	1.363(7)
C(2)-C(3)	1.530(3)	1.527(3)	1.518(5)	1.518(7)
C(3)-C(4)	1.587(3)	1.579(3)	1.575(4)	1.539(7)
C(4)-N(1)	1.482(3)	1.488(2)	1.481(4)	1.459(7)
Angles (deg)				
C(2)-N(1)-C(4)	95.9(1)	95.9(2)	95.0(3)	94.5(3)
N(1)-C(2)-C(3)	91.9(2)	92.4(1)	93.0(3)	92.0(3)
C(2)-C(3)-C(4)	85.6(1)	85.9(2)	85.5(3)	85.4(3)
C(3)-C(4)-N(1)	85.6(2)	85.8(1)	86.5(3)	87.9(3)
Diagonal contact distan	uces (Å)			
$N(1)\cdots C(3)$	2.089(2)	2.086(2)	2.094(4)	2.080(4)
$C(2)\cdots C(4)$	2.116(2)	2.118(3)	2.100(4)	2.071(5)

Comparison of interatomic distances and angles in the monocyclic β -lactam rings^a

^aThe numbering of atoms in **5**, **6**, and **7** conforms to that in **3**. ^bRef. 4. ^cRef. 10. ^dRef. 11.

(average 1.577 Å) is observed only in **3** and **6**, in **7** a rather normal length for $C_{sp^3}-C_{sp^3}$ atoms is found. This may be due to the absence of bulky substituents at both C(3) and C(4) atoms in **7**. 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° producing a trapezoid rather than a rectangular shape for the rings.

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