Synthesis and X-ray structural investigation of (5R*,6S*)-1-benzoyl-5-methylthio-6-methoxy-1-azapenam

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Abstract

The compound $(5R^*,6S^*)$ -1-benzoyl-5-methylthio-6-methoxy-1-azapenam (3) has been synthesized and its structure investigated by X-ray diffraction. The compound crystallizes in a monoclinic system, space group Cc, Z = 4, a = 12.01(1), b = 16.51(1), c = 8.048(6) Å, $\beta = 115.87(6)^{\circ}$. The structure was solved by direct methods and refined by a full-matrix, least-squares procedure to give R = 0.070, $R_w = 0.046$, $w = 1.34/(\sigma_F^2)$. The expected cis configuration around the β -lactam ring was fully confirmed.

INTRODUCTION

The annelation of acyclic [1,2] as well as cyclic [3-6] thioimidates with acid chlorides has been noted as a stereospecific reaction leading to single isomers of β -lactams. Acyclic thioimidates give products solely with the trans configuration around the four-membered ring, while the annelation of cyclic derivatives produces single isomers (1) in which substituents formerly attached to ketene (\mathbb{R}^1) and imino carbon (\mathbb{R}^2) are cis to each other. It appears that, as a rule, (Z)-imines lead to a trans configuration, whereas (E)-imines give cis- β -lactams. This stereochemical specificity could be explained by means of a non-concerted [2 + 2] cycloaddition mechanism [7]. Surprisingly, the annelation of 1-acyl-2-methylthio-1,4,5,6tetrahydropyrimidines with different ketene precursors results in the formation of 1-azacephams (2) with the trans configuration [8,9]. The same reaction carried out with 1-benzoyl-2-methylthio-2-thiazoline failed, and

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resulted in recovery of the starting material [9]. Re-examination of the reaction with a modified separation method led us to the separation of 1-benzoyl-5-methylthio-6-methoxy-1-azapenam (3) with the cis configuration around the β -lactam ring.



EXPERIMENTAL

 1 H and 13 C NMR spectra were measured on a Bruker AM-500 spectrometer at 500 and 126 MHz, respectively, in CDCl₃ solution and are reported in p.p.m. from internal TMS. FT-IR spectra were measured on a Perkin-Elmer 1650 spectrophotometer. MS and high resolution MS spectra were recorded with an AMD 604 (AMD Intectra) spectrometer; peaks lower than 10% were not listed.

Synthesis of 1-azapenam (3)

1-Azapenam (3) was prepared by a standard method [9]. Methoxyacetyl chloride in the presence of double excess of triethylamine was used as the methoxyketene precursor, which reacts with 1-benzoyl-2-methylthio-2-imidazoline giving $(5R^*, 6S^*)$ -1-benzoyl-5-methyl-thio-6-methoxy-1-azapenam. The sole product so formed was separated by preparative HPLC (Nucleosil[®] 100-7, Macherey-Nagel No. 715026, hexane-tetrahydrofuran 85:15) in 38% yield. X-Ray suitable single crystals were obtained by the low-temperature crystallization of 3 from isopropanol at -10° C (m.p. 101-102°).

IR, NMR and MS results for 3

FT-IR (Nujol): 1784, 1640 cm⁻¹. ¹H NMR: 2.32 (s, 3H, CH₃S), 3.37 (m, 1H,

 $\frac{1}{2}$ CH₂), 3.81 (bs, 4H, CH₃O + $\frac{1}{2}$ CH₂), 3.97 (m, 2H, CH₂), 4.74 (bs, 1H, H-C6), 7.5 (m, 5H, aromatics). ¹³C NMR: 13.30 (b, CH₃S), 43.33 (b, CH₂), 50.21 (b, CH₂), 59.67 (b, CH₃O), 88.69 (C5), 90.11 (C6), 126.93, 128.39, 130.72, 135.02 (aromatics), 167.60 (CO-β-lactam). MS m/z (%): 292 M⁺ (4), 277 (86), 217 (24), 185 (13), 121 (19), 105 (100), 77 (22). Peak matching on C₁₄H₁₆N₂O₃S: calc. 292.0882; found 292.0883.

X-ray structural investigations

A colourless crystal of 3 (0.65 \times 0.40 \times 0.30 mm) was obtained as above. The reflection intensities were collected on a Syntex P2₁ diffractometer using graphite-monochromated Mo K α radiation ($\lambda = 0.71069$ Å). The cell constants were obtained from a least-squares refinement on the setting angles of 25 reflections. The data were collected with the $\omega/2\theta$ scan technique up to $2\theta_{max} = 50^{\circ}$.

Crystal data: C₁₄H₁₆N₂O₃S, $M_r = 292.44$, monoclinic, space group Cc, a = 12.014(1), b = 16.513(2), c = 8.048(1) Å, β = 115.87 (6)°, V = 1436.6(3) Å³, Z = 4, F(000) = 616, $D_x = 1.35$ g cm⁻³, μ (Cu Kα) = 1.65 mm⁻¹.

A total of 1279 reflections were collected, of which 1067 were unique; 1024 reflections were found to have $I > 2\sigma(I)$. Lorentz and polarization corrections were applied to the data. No absorption correction was applied at the measurement stage.

The phase problem was solved by direct methods (program SHELXS-86) [10]. A total of 18 atoms were found in an E-map. Initially, the positional parameters and individual isotropic temperature factors of all non-hydrogen atoms were refined to R = 0.108 (program SHELX-76) [11]. At this stage an empirical, spherical absorption correction (program DIFABS) [12] was performed. For 1024 reflections, the minimum, maximum and average corrections were 0.511, 1.544 and 1.007, respectively.

The positions of the hydrogen atoms bonded to carbon atoms were generated from assumed geometries and added with isotropic temperature factors to the set of atomic parameters. The refinement of atomic positional and thermal anisotropic parameters (isotropic for hydrogen) was performed by the least-squares, full matrix procedure using SHELX-76. The final R was 0.070, $R_w = 0.046$, $w = 1.34(\sigma_F^2)$. The highest peak in the final difference map was $0.23 e \text{\AA}^{-3}$.

The refined postional parameters for the non-hydrogen atoms of 3, together with their B_{eq} values are given in Table 1.

RESULTS AND DISCUSSION

The general formula of the compound isolated from the reaction mixture was determined as $C_{14}H_{16}N_2O_3S$ by HR-MS. The expected chemical structure

Atom	x/a	y/b	z c	$B_{ m eq}$
S(1)	0°	2020(1)	0°	5.76(5)
N(1)	-1401(5)	1122(3)	- 3046(7)	3.7(1)
C(2)	-2164(6)	1517(4)	-4862(9)	4.3(2)
C(3)	-1331(7)	2148(4)	-5087(10)	5.9(2)
N(4)	-99(5)	2023(4)	- 3511(7)	4.8(2)
C(5)	- 176(6)	1518(3)	-2064(9)	3.6(2)
C(6)	948(6)	1035(5)	-2024(11)	5.4(2)
C(7)	876(8)	1605(4)	- 3508(12)	5.4(3)
C(8)	2156(7)	425(6)	830(14)	7.7(3)
C(9)	- 1571(6)	356(4)	-2559(10)	3.4(2)
C(10)	- 1209(8)	2758(5)	-835(12)	7.3(4)
C(11)	-2788(6)	-67(4)	-3715(9)	3.9(2)
C(12)	-2727(7)	-856(4)	-4226(10)	4.8(2)
C(13)	-3849(9)	-1282(4)	-5152(10)	5.2(3)
C(14)	- 4963(9)	- 888(6)	- 5463(12)	6.7(3)
C(15)	- 5006(8)	-145(5)	- 4968(14)	6.3(2)
C(16)	- 3907(6)	285(4)	- 4091(8)	4.8(2)
O(6)	2060(5)	1056(3)	- 379(9)	6.6(2)
O(7)	1465(6)	1691(4)	- 4425(9)	6.7(3)
O(9)	- 803(4)	22(3)	- 1172(7)	4.9(3)

TABLE 1

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

^aIn this an subsequent tables the values in parentheses are estimated standard deviations. ^bCalculated from anisotropic thermal parameters as $B_{eq} = 8\pi^2 D_u^{1/3}$ where D_u is the determinant of the U_{ij} matrix in orthogonal space.

[°]Fixed coordinate.

was confirmed by IR, where the up-frequency shift of the very strong C=O band indicated the presence of the β -lactam ring. Although the measurements of nuclear Overhauser effects are recognized as a convenient method for structure determination in β -lactams [13,14], in the present case the ¹H NMR spectra exhibit the protons at 3.81 and 4.74 ppm as broad singlets, due to restricted rotation about the amide bond at N(1) at ambient temperature. Thus, partially overlapped peaks cause this technique to be useless in our case. Therefore, we selected single crystal X-ray diffraction as a method of exact structure determination.

The bond distances and valence angles for compound 3 are listed in Tables 2 and 3, respectively. Figure 1 shows a stereoview of 3.

The arrangement of methylthio and methoxy substituents at the β -lactam ring is found to be cis, as may be seen clearly from Fig. 1 as well as from the torsion angle S(1)–C(5)–C(6)–O(6) = 3.0(9)°.

The four-membered β -lactam ring is almost flat (the average deviation of the atoms from the least-squares plane of the ring is as small as ± 0.007 Å).

TABLE 2

Bond	Distance (Å)	Bond	Distance (Å)
C(5)-S(1)	1.785(7)	0(6)-C(6)	1.413(8)
C(10)-S(1)	1.787(9)	0(7)-C(7)	1.23(1)
C(2)-N(1)	1.494(8)	0(6)-C(8)	1.40(1)
C(5)-N(1)	1.484(8)	C(11)-C(9)	1.518(9)
C(9)–N(1)	1.366(9)	O(9)-C(9)	1.226(8)
C(3)-C(2)	1.51(1)	C(12)-C(11)	1.38(1)
N(4)-C(3)	1.485(8)	C(16)-C(11)	1.37(1)
C(5)–N(4)	1.47(1)	C(13)-C(12)	1.41(1)
C(7)-N(4)	1.36(1)	C(14)-C(13)	1.41(1)
C(6)-C(5)	1.56(1)	C(15)-C(14)	1.30(1)
C(7)-C(6)	1.49(1)	C(16)-C(15)	1.39(1)

Bond distances in 3

The conformation of the five-membered imidazolidine ring may be defined as flattened ${}^{4}T_{5}$ (twist). The dihedral angle formed by the least-squares planes calculated for the four- and five-membered rings is 122.7(4)°. For both amide nitrogen atoms, the configuration of N(1) is almost flat, whereas the configuration of N(4) is apparently pyramidal. The configurations at asymmetry centres are found to be C(5) (S), C(6) (R).

The established cis configuration of the obtained 1-azapenam derivative

TABLE 3

Bond angles in 3

Angle	Value (deg)	Angle	Value (deg)
S(1)-C(5)-N(1)	112.8(6)	N(4)-C(7)-C(6)	94.1(8)
S(1)-C(5)-N(4)	116.9(4)	N(4)-C(7)-O(7)	131.3(7)
S(1)-C(5)-C(6)	118.0(4)	C(5)-C(6)-C(7)	85.0(6)
C(5)-S(1)-C(10)	102.7(4)	C(5)-C(6)-O(6)	117.6(7)
N(1)-C(2)-C(3)	105.2(5)	C(6) - C(7) - O(7)	134.7(8)
C(2)-N(1)-C(5)	111.8(5)	C(7)-C(6)-O(6)	115.8(7)
C(2)-N(1)-C(9)	125.5(5)	C(6)-O(6)-C(8)	113.1(6)
N(1)-C(5)-N(4)	102.7(5)	C(9)-C(11)-C(12)	117.1(6)
N(1)-C(5)-C(6)	115.8(5)	C(9)-C(11)-C(16)	122.0(6)
C(5)-N(1)-C(9)	119.5(5)	C(11)-C(9)-O(9)	119.5(6)
N(1)-C(9)-C(11)	118.4(5)	C(11)-C(12)-C(13)	117.8(7)
N(1)-C(9)-O(9)	122.1(6)	C(12)-C(11)-C(16)	120.6(6)
C(2)-C(3)-N(4)	105.5(6)	C(11)-C(16)-C(15)	121.2(7)
C(3)-N(4)-C(5)	111.9(6)	C(12)-C(13)-C(14)	118.6(7)
C(3)-N(4)-C(7)	127.6(6)	C(13)-C(14)-C(15)	123.0(9)
N(4)-C(5)-C(6)	87.3(6)	C(14)-C(15)-C(16)	118.8(9)
C(5)–N(4)–C(7)	93.6(6)		



Fig. 1. A stereoview of 3 oriented at optimal viewing, with crystallographic labeling of non-hydrogen atoms. For reasons of clarity, the only hydrogen atom shown is that at C(6).

3 conforms to our expectations and corresponds with the stereochemistry of annelation of thiazolidines [3–6]. However, the influence of the size of the substrate ring (6-membered instead of 5-membered) on the stereo-specificity of the annelation, when compared with the literature results [8,9], is not clear so far.

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