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Structural investigation on isomeric spiro-β-lactams: NMR and X-ray study

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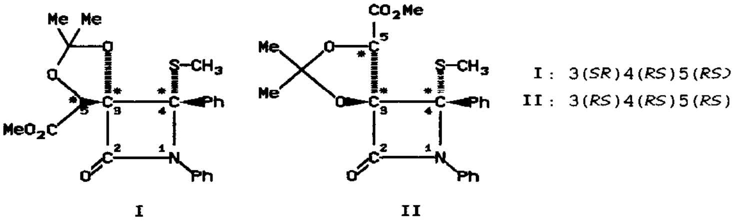
Abstract

Two diastereoisomers of 1,4-diphenyl-4-methylthio-3(4′)spiro-(2′,2′-dimethyl-5′-methoxycarbonyl-1′,3′-dioxolane)-2-azetidinone have been synthesized and investigated by ^{1}H and ^{13}C NMR, and structural X-ray diffraction methods. The isomer 3(*SR*), 4(*RS*), 5(*RS*) (**I**) crystallizes in a triclinic system, space group $P\bar{1}$, with cell dimensions a = 9.000(4), b = 9.606(2), c = 13.861(2) Å, α = 104.44(2)°; β = 107.06(2)°, γ = 100.28(3)° and Z = 2; the isomer 3(*RS*), 4(*RS*), 5(*RS*) (**II**) crystallizes in a monoclinic system, space group $P2_1/n$, with cell dimensions a = 9.642(1), b = 33.631(4), c = 12.967(1) Å, β = 96.766(8)° and Z = 8. Both structures were solved by direct methods and refined by a full-matrix, least-squares procedure to give R = 0.0670 and 0.0422 for **I** and **II**, respectively. A close investigation of the molecular geometrical parameters of **I** and **II** confirmed all the conclusions drawn from NMR (nuclear Overhauser effect) experiments.

INTRODUCTION

In the course of our investigations on the syntheses of new monocyclic β-lactam derivatives with antibiotic activity, we now direct our attention to the structures of some ring-substituted β-lactams.



Scheme 1.

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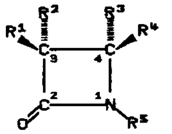
Since the discovery of the first natural representative of this class of compounds [1], they have become a center of interest in many laboratories. Suitably substituted β-lactams may serve as useful intermediates for the syntheses of bicyclic systems, such as those which occur naturally in 6-alkoxypenams, 7-alkoxycephems, cephamycins and their analogs [2].

As in our former papers [3,4], for the synthesis of 3-alkoxy-4-thioalkoxy-β-lactam derivatives, we applied the usual procedure of annelation of a ketene derivative with an imine compound. In the present investigation, the monomethyl 2,3-di-*O*-isopropylidene tartrate [5] was readily available as the ketene precursor, and we used *S*-methyl *N*-phenylbenzthioimidate [6] as the imine component. The annelation reaction led to a mixture of the 1,4-diphenyl-4-methylthio-3(4′)-spiro(2′,2′-dimethyl-5-methoxycarbonyl-1′,3′-dioxolane)-2-azetidinone stereoisomers in the ratio 6:4 (**I** and **II**).



III: R^1 = 3-phthalimid; R^2 = H;
R^3 = $S\text{-}CH_3$; R^4 = Bn; R^5 = $p\text{-}C_6H_4OCH_3$

IV: R^1 = PhO; R^2 = H; R^3 = $S\text{-}CH_3$;
R^4 = $CH{=}N\text{-}OCH_3$; R^5 = $p\text{-}C_6H_4OCH_3$

V: R^1 = Cl; R^2 = CN; R^3 = S-Ph;
R^4 = H; R^5 = C_6H_{11}

VI: R^1 = H; R^2 = N(Et)(*t*-Bu); R^3 = H;
R^4 = COOMe; R^5 = *t*-Bu

VII: R^1 = γ-glutamyl-alanylamine;
R^2 = OCH_3; R^3 = R^4 = H; R^5 = SO_3

Scheme 2.

Bose and co-workers [7,8] have reported a reaction of the above type to be completely stereoselective. However, Cassio and Palomo [9] found that the distribution of cis/trans isomers during formation of α-hydroxy-β-lactams from simple Schiff's bases depends on R^1, R^3 and R^4 substituents.

Since the ^1H NMR experiments could give no information which may be used for unambiguous structure determination of each stereoisomer of **I** and **II**, due to the absence of vicinal H atoms at C3 and C4 in the β-lactam ring, we have carried out X-ray structural investigations of **I** and **II**.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 500.135 MHz and 125.759 MHz, respectively, with internal deuterium lock in $CDCl_3$ at ambient temperature. Chemical shifts are reported relative to $\delta_{TMS} = 0$ ppm. Standard Bruker software was used to perform the $^1H\{^1H\}$ nuclear Overhauser effect (NOE), long range ^1H–^{13}C correlation (COLOC) and heteronuclear correlation (HETCOR) experiments. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1650 spectrophotometer. Low and high resolution electron impact mass spectra (HREIMS) were recorded on an AMD 604 spectrometer; peaks less than 10% were not listed. Melting points were measured in open capillary tubes and are uncorrected. Solvents and commercially available reagents were purified by literature procedures.

*Synthesis of β-lactams **I** and **II***

To a solution of monomethyl 2,3-*O*-isopropylidene tartrate (0.82 g, 4 mmol) [5] in dichloromethane (10 ml) cooled to 0°C was consecutively added triethylamine (1.4 ml, 10 mmol), *S*-methyl *N*-phenylthiobenzimidate (0.68 g, 3 mmol) [6] and a solution of phenyldichlorophosphate (0.84 g, 4 mmol) [10] in dichloromethane (5 ml). The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then successively washed with dilute HCl and a saturated solution of $NaHCO_3$, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue which was purified by column chromatography (Merck Kieselgel 60, 230–400 mesh, 60 × 2.5 cm; eluent: hexane–ethyl acetate 85:15) affording first **I** and second **II**. Crystallographically suitable crystals were obtained by slow evaporation of the solvent from ethanolic solutions of **I** and **II**.

Compound **I**. Yield 42%. m.p. 114–115°C. IR(KBr): 1767, 1761 cm^{-1}. MS *m/z*, (%): 413(M^+, 81), 398(21), 353(11), 322(13), 308(100), 180(80), 77(22). Peak matching on $C_{22}H_{23}NO_5S$: calc. 413.1297; found 413.1294. ^1H NMR: 0.93 (s, 3H, C(12)$\underline{H}_3$), 1.49 (s, 3H, C(11)$\underline{H}_3$), 2.15 (s, 3H, S–C$\underline{H}_3$), 3.85 (s, 3H, O–C$\underline{H}_3$), 5.75 (s, 1H, C(10)$\underline{H}$), 7.28–7.36, 7.71–7.73 (m, 10H, aromatics). ^{13}C NMR: 12.53 C(5), 26.92 C(12), 26.96 C(11), 52.69 C(16), 77.20 C(10), 82.24 C(4), 99.64 C(3), 115.50 C(8), 118.48, 125.17, 127.29, 128.11, 128.54, 129.18, 136.11, 136.45 (aromatics), 163.48 C(2), 170.01 C(13).

Compound **II**. Yield 25%. m.p. 161–162°C. IR(KBr): 1769, 1763 cm^{-1}. MS *m/z*, (%): 413(M^+, 49), 397(18), 322(10), 308(100), 180(79), 77(21). Peak matching on $C_{22}H_{23}NO_5S$: calc. 413.1297; found 413.1297. ^1H NMR: 1.59 (s, 3H, C(12)$\underline{H}_3$), 1.90(s, 3H, C(11)$\underline{H}_3$), 2.12 (s, 3H, S–C$\underline{H}_3$), 3.17 (s, 3H, O–C$\underline{H}_3$), 4.87 (s, 1H, C(10)$\underline{H}$), 7.28–7.35, 7.91–7.93 (m, 10H, aromatics). ^{13}C NMR: 14.24 C(5), 25.55 C(12), 27.09 C(11), 51.93 C(16), 76.90 C(10), 84.14 C(4), 95.41 C(3), 112.68 C(8), 118.95, 125.22, 127.39, 127.76, 128.83, 129.11, 134.65, 137.16 (aromatics), 164.23 C(2), 164.83 C(13).

X-ray structural investigations

Well-shaped colorless crystals of **I** (dimensions 0.18 × 0.21 × 0.28 mm^3) and of **II** (dimensions 0.28 × 0.07 × 0.53 mm^3) were taken for X-ray diffraction measurements on a four-circle automated CAD-4 diffractometer with

TABLE 1

Crystal data and measurement conditions

	I	II
General formula	$C_{22}H_{23}NO_5S$	
Molecular weight (M_r)	413.48	
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$
Molecular multiplicity Z	2	8
Cell constants: a (Å)	9.000(4)	9.642(1)
b (Å)	9.606(2)	33.631(4)
c (Å)	13.861(2)	12.967(1)
α (deg)	104.44(2)	
β (deg)	107.06(2)	96.766(8)
γ (deg)	100.28(3)	
Cell volume V (Å^3)	1067.7(6)	4175.5(7)
Number of electrons $F(000)$	436	1744
Calculated density (g cm^{-3})	1.286	1.315
Linear absorption coeff. μ(Cu Kα) (cm^{-1})	15.17	15.52
Diffractometer	CAD-4	
Radiation	Cu Kα (λ = 1.54178 Å)	
Number of reflections		
total independently measured	4931	9511
observed ($I > 2\sigma_I$)	3246	8189
No. of unique (R_{int}) reflections	–	7699 (0.0267)
difference	1685	1322
Scan mode	$\omega/2\theta$	
Scan region ($2\theta_{max}$) (deg)	153	154
h range	−11/+11	−12/+12
k range	−12/+12	0/42
l range	0/17	0/16

graphite monochromated Cu Kα radiation. Table 1 gives the crystal data and measurement conditions for both compounds. The stability of intensities was checked on three reflections at 50 reflection intervals; no appreciable decay was observed. The cell parameters were refined by a least-squares procedure based on 25 setting angles in each case. The Lorentz and polarization corrections were applied to all collected data. No absorption corrections were performed at the measuring stage.

For **I**, the space group $P1$ was chosen initially; for **II**, the systematic absences pointed to the space group $P2_1/n$. Structural analyses of the solutions were attempted using direct methods (program SHELXS 86 [14]) with scattering factors implemented in the program.

For **I**, the E-maps revealed all the non-hydrogen atoms of two molecules which were found to be reflected one onto the other with respect to a symmetry center. Thus, the atomic positions, after shifting the center to (0,0,0), were averaged in pairs and one molecule was undertaken to the refinement process in the space group $P\bar{1}$. For **II**, the E-maps also revealed all non-hydrogen atomic positions for two symmetry-independent molecules ($Z = 8$).

The refinement of all non-hydrogen atomic positional parameters were performed for **I** and **II** using the SHELX 76 program [15]. The refinements converged at $R = 0.159$ and 0.110 for **I** and **II**, respectively. At this stage the spherical, empirical absorption corrections (program DIFABS [16]) were applied to the observed reflection sets of both structures. The resulting correction factors were (maximum, minimum and average): 1.440, 0.620 and 0.989 for **I**; 1.127, 0.859 and 0.980 for **II**.

Further refinement steps in the anisotropic mode were performed in the presence of all geometrically calculated hydrogen atoms. The final refinement step involved all positional and anisotropic thermal parameters (for hydrogen isotropic) and converged with reliability factors $R = 0.0670$ and 0.0422 (unit weights) for **I** and **II**, respectively. The highest residual peaks on the final ΔF-maps were 0.33 and 0.23 eÅ^{-3} for **I** and **II**, respectively, and were located in the immediate environment of sulfur atoms in both cases.

Table 2 gives the refined positional parameters of non-hydrogen atoms together with their B_{eq} values.

RESULTS AND DISCUSSION

A general formula $C_{22}H_{23}NO_5S$ was assigned by HREIMS to the compounds **I** and **II** isolated from the reaction mixture. The structures and the stereochemical homogeneity were confirmed by IR and NMR spectroscopy. Thus, β-lactam derivatives **I** and **II** were proved to be stereoisomers with different configurations either at C(3) or C(4).

NMR results

^1H and ^{13}C NMR assignments were done on the basis of the observed chemical shifts and coupling constants (see Experimental) and then confirmed by COLOC and HETCOR experiments. COLOC experiments indicated coupling between ester methyl groups C(16)H_3 at $\delta = 3.85$ and 3.17 ppm for **I** and **II**, respectively and carbon atoms at $\delta = 170.01$ ppm (**I**) and $\delta = 164.83$ ppm (**II**), which were assigned as appropriate carboxylic carbon atoms C(13). Chemical shifts of isopropylidene methyl protons ($\delta = 0.93$, 1.49 ppm (**I**) and $\delta = 1.90$, 1.59 ppm (**II**)), were correlated with corresponding carbon shifts ($\delta = 26.92$, 26.96 ppm (**I**) and $\delta = 27.09$, 25.55 ppm (**II**) by HETCOR experiments. The relative configurations were then investigated

TABLE 2

Fractional atomic coordinates (× 10^4)[a] and B_{eq} values[b] for non-hydrogen atoms in **I** and **II**

Atom	**I**				**II**							
					Molecule A				Molecule B			
	x/a	y/b	z/c	B_{eq}	x/a	y/b	z/c	B_{eq}	x/a	y/b	z/c	B_{eq}
S	4064(1)	1191(1)	1210.9(8)	3.8(3)	1491.0(6)	2204.0(2)	4621.6(4)	3.77(1)	7091.0(6)	14.8(2)	1892.4(4)	3.96(1)
N(1)	4128(3)	4116(3)	2242(2)	3.0(8)	3031(1)	2366.5(4)	6544(1)	2.72(4)	7553(2)	660.6(4)	3227(1)	2.97(4)
C(2)	2596(4)	4179(4)	2180(3)	3.1(8)	2186(2)	2391.4(5)	7321(1)	3.02(5)	8495(2)	896.8(6)	2793(2)	3.32(5)
C(3)	2180(4)	2649(4)	2340(3)	2.8(8)	1161(2)	2082.1(5)	6812(1)	2.84(4)	7698(2)	854.6(6)	1710(1)	3.06(5)
C(4)	3945(4)	2601(3)	2332(3)	2.8(8)	2189(2)	2057.0(5)	5930(1)	2.73(5)	6769(2)	531.5(5)	2226(1)	2.92(5)
C(5)	3430(6)	1860(5)	93(3)	5.1(13)	910(3)	2708.5(7)	4751(2)	4.99(7)	8932(3)	−46.6(7)	2270(2)	5.27(9)
O(6)	1904(3)	5125(3)	2083(2)	3.9(8)	2247(2)	2585.3(4)	8107(1)	3.94(5)	9531(1)	1071.3(5)	3151(1)	4.49(5)
O(7)	2094(3)	2848(3)	3366(2)	3.3(7)	−160(1)	2241.6(4)	6482(1)	3.43(4)	8457(1)	718.3(4)	923(1)	3.79(5)
C(8)	711(4)	1794(4)	3323(3)	3.7(11)	−1228(2)	1940.7(6)	6552(2)	3.46(5)	7970(2)	911.3(7)	−53(2)	3.88(6)
O(9)	123(3)	747(3)	2278(2)	4.0(7)	−477(1)	1593.1(4)	6920(1)	3.45(3)	6826(1)	1153.1(4)	172(1)	3.80(4)
C(10)	668(4)	1399(4)	1596(3)	3.4(9)	768(2)	1733.0(5)	7482(1)	2.99(5)	7083(2)	1244.1(6)	1242(1)	3.23(5)
C(11)	1281(8)	1010(6)	4121(4)	6.5(19)	−1964(2)	1855.4(7)	5485(2)	4.47(6)	7442(3)	605.5(9)	−844(2)	5.94(9)
C(12)	−476(6)	2633(7)	3535(4)	5.8(18)	−2166(2)	2085.2(7)	7332(2)	4.48(7)	9149(3)	1163.3(9)	−374(2)	5.29(9)
C(13)	−611(4)	1945(4)	919(3)	3.5(8)	1750(2)	1391.1(6)	7784(1)	3.36(5)	5801(2)	1429.6(6)	1623(2)	3.51(5)
O(14)	−174(3)	2214(3)	128(2)	4.7(8)	2926(1)	1536.6(5)	8276(1)	4.36(4)	6087(2)	1517.8(5)	2623(1)	4.39(4)
O(15)	−1843(4)	2066(4)	1038(2)	5.3(10)	1460(2)	1049.7(4)	7671(1)	4.97(5)	4741(2)	1504.9(5)	1091(1)	4.73(5)
C(16)	−1257(7)	2821(6)	−559(4)	6.3(18)	3954(3)	1243(1)	8696(2)	5.70(9)	5001(3)	1724.4(8)	3098(2)	5.37(9)
C(17)	5453(4)	5164(4)	2254(3)	3.3(10)	4187(2)	2602.3(5)	6343(1)	2.79(5)	7565(2)	531.1(5)	4264(1)	2.95(5)
C(18)	5401(5)	6623(4)	2359(3)	4.0(12)	4818(2)	2546.0(6)	5442(1)	3.37(5)	6823(2)	197.3(6)	4500(1)	3.57(5)
C(19)	6728(6)	7644(4)	2390(4)	4.8(13)	5950(2)	2782.1(6)	5267(2)	3.79(6)	6871(2)	76.2(6)	5525(2)	3.94(6)
C(20)	8052(5)	7221(5)	2293(4)	4.6(13)	6450(2)	3069.7(7)	5974(2)	4.18(6)	7635(2)	283.0(7)	6312(2)	4.19(6)
C(21)	8098(5)	5762(5)	2175(4)	4.9(15)	5810(2)	3127.2(6)	6863(2)	4.10(6)	8367(3)	616.5(7)	6077(2)	4.51(6)
C(22)	6787(5)	4720(4)	2149(4)	4.2(12)	4683(2)	2895.7(6)	7057(1)	3.40(5)	8337(2)	742.2(6)	5057(2)	3.99(5)
C(23)	5045(4)	2472(4)	3350(3)	2.8(9)	2900(2)	1660.3(5)	5826(1)	2.92(5)	5202(2)	583.7(5)	2074(1)	2.96(5)

C(24)	5105(4)	1066(4)	3432(3)	3.4(9)	4287(2)	1597.1(6)	6201(2)	3.73(5)	4457(2)	734.6(6)	2838(1)	3.41(5)
C(25)	6060(5)	920(4)	4364(3)	4.2(13)	4881(2)	1223.0(7)	6132(2)	4.59(7)	3025(2)	788.8(7)	2641(2)	4.07(7)
C(26)	6952(5)	2166(5)	5221(3)	4.6(13)	4085(3)	910.9(7)	5701(2)	4.67(8)	2314(2)	688.2(7)	1691(2)	4.47(7)
C(27)	6899(5)	3563(5)	5152(3)	4.4(10)	2712(3)	970.8(7)	5329(2)	4.65(7)	3044(2)	533.7(8)	929(2)	4.68(7)
C(28)	5938(5)	3708(4)	4217(3)	3.7(9)	2114(2)	1345.3(6)	5377(2)	3.90(6)	4472(2)	480.4(7)	1115(2)	4.00(6)

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[a] In this and subsequent tables the values in parentheses are estimated standard deviations.

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

by $^1H\{^1H\}$ NOE measurements. In compound **I** the 1.2% NOE on S–CH_3 and 2.0% NOE on isopropylidene C(11)H_3 (δ = 0.93 ppm) was observed when H–C(10) was irradiated. This was supported by the 1.5% effect on H–C(10) when the methyl protons at C(5) were irradiated. The spatial arrangement of the carbon atoms C(5) and C(10) on the same side of the β-lactam ring was additionally confirmed by a 2% NOE on C(5)H_3 when C(16)H_3 was irradiated. Conversely, in compound **II** the 1.1% NOE on C(12)H_3 was observed only when the H–C(10) proton was examined. Reverse irradiation gave a 1.3% effect on H–C(10). The weak (0.8%) enhancement was observed on the isopropylidene methyl C(11)H_3 when S–CH_3 was irradiated. Worthy of note is the considerable upfield shift of these protons in **I** and the upfield shift of H–C(10) and C(16)H_3 in **II**, suggesting the spatial proximity of the phenyl ring at C(4) to the above protons in corresponding isomers. This NMR investigation led us to assume a trans-(O7, SCH_3) configuration for **I** and a cis-(O7, SCH_3) configuration for **II**.

X-ray diffraction results

The bond lengths, valence and selected torsion angles of **I** and **II** (hydrogen atoms not involved) are presented in Tables 3, 4 and 5, respectively. Figure 1 shows stereo-diagrams of molecules **I** and **IIA**.

A simple check of configuration assignments at C(3), C(4) and C(10) in refined models of **I** and **II** allows us to establish them as C(3)(*SR*), C(4)(*RS*)

TABLE 3

Bond lengths (Å) for non-hydrogen atoms in I and II

Bond	I	II		Bond	I	II	
		Mol. A	Mol. B			Mol. A	Mol. B
C(4)–S	1.833(4)	1.818(1)	1.826(2)	C(23)–C(4)	1.516(5)	1.513(2)	1.511(3)
C(5)–S	1.802(5)	1.801(3)	1.797(3)	C(8)–O(7)	1.433(5)	1.454(2)	1.450(3)
C(2)–N(1)	1.369(5)	1.371(2)	1.376(3)	O(9)–C(8)	1.422(4)	1.427(2)	1.428(2)
C(4)–N(1)	1.476(4)	1.491(2)	1.488(2)	C(11)–C(8)	1.508(8)	1.506(3)	1.499(4)
C(17)–N(1)	1.410(5)	1.417(2)	1.412(2)	C(12)–C(8)	1.500(8)	1.514(3)	1.515(4)
C(3)–C(2)	1.538(6)	1.530(2)	1.526(3)	C(10)–O(9)	1.409(6)	1.410(2)	1.414(2)
O(6)–C(2)	1.202(5)	1.206(2)	1.204(2)	C(13)–C(10)	1.519(6)	1.512(3)	1.518(3)
C(4)–C(3)	1.601(5)	1.601(2)	1.602(3)	O(14)–C(13)	1.335(6)	1.327(2)	1.327(3)
O(7)–C(3)	1.414(5)	1.402(2)	1.400(2)	O(15)–C(13)	1.189(6)	1.187(2)	1.191(3)
C(10)–C(3)	1.527(4)	1.534(2)	1.535(3)	C(16)–O(14)	1.460(7)	1.458(3)	1.453(3)
Average bond lengths in phenyl rings							
	1.379(6)	1.386(3)	1.384(3)				

TABLE 4

Valence angles (deg) in **I** and **II** (H atoms not involved)

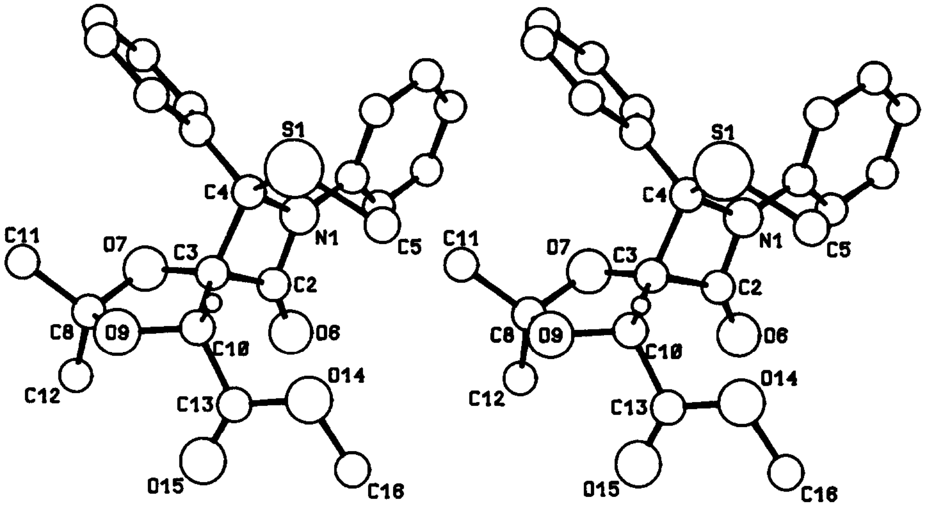
Angle	**I**	**II**		Angle	**I**	**II**	
		Mol. A	Mol. B			Mol. A	Mol. B
S–C(4)–N(1)	115.1(3)	115.3(1)	113.7(1)	C(4)–C(3)–C(10)	122.3(3)	125.4(1)	122.3(2)
S–C(4)–C(3)	117.1(2)	117.4(1)	115.2(1)	C(3)–O(7)–C(8)	111.0(2)	109.8(1)	110.3(1)
S–C(4)–C(23)	107.6(2)	106.2(2)	106.0(1)	O(7)–C(3)–C(10)	104.5(3)	100.9(1)	101.6(1)
C(4)–S–C(5)	104.7(2)	104.7(1)	103.6(1)	C(3)–C(10)–O(9)	104.5(3)	102.4(1)	102.6(1)
N(1)–C(2)–C(3)	92.6(3)	92.9(1)	92.1(1)	C(3)–C(10)–C(13)	113.3(3)	122.7(2)	120.9(2)
N(1)–C(2)–O(6)	132.3(4)	132.9(2)	133.0(2)	C(4)–C(23)–C(24)	119.7(3)	122.2(2)	122.9(1)
C(2)–N(1)–C(4)	96.1(3)	95.8(1)	96.0(1)	C(4)–C(23)–C(28)	121.6(4)	118.6(2)	118.6(2)
C(2)–N(1)–C(17)	132.0(3)	130.5(1)	129.5(2)	O(7)–C(8)–O(9)	104.9(3)	104.8(1)	104.8(2)
N(1)–C(4)–C(3)	86.3(3)	85.7(1)	85.1(1)	O(7)–C(8)–C(11)	107.9(3)	109.6(2)	109.8(2)
N(1)–C(4)–C(23)	116.4(2)	116.0(1)	118.5(1)	O(7)–C(8)–C(12)	107.8(4)	107.5(2)	108.3(2)
C(4)–N(1)–C(17)	131.9(3)	133.1(1)	133.4(2)	C(8)–O(9)–C(10)	109.8(3)	105.5(1)	105.9(1)
N(1)–C(17)–C(18)	120.0(4)	120.6(1)	120.9(1)	O(9)–C(8)–C(11)	109.1(3)	108.5(2)	108.8(2)
N(1)–C(17)–C(22)	119.6(4)	119.2(1)	119.3(2)	O(9)–C(8)–C(12)	112.9(3)	111.0(2)	111.1(2)
C(2)–C(3)–C(4)	84.8(3)	85.5(1)	85.7(1)	C(11)–C(8)–C(12)	113.8(5)	114.9(2)	113.7(2)
C(2)–C(3)–O(7)	109.6(3)	112.9(1)	116.8(2)	O(9)–C(10)–C(13)	112.5(3)	110.4(1)	110.7(1)
C(2)–C(3)–C(10)	122.8(3)	117.8(1)	114.4(2)	C(10)–C(13)–O(14)	109.3(3)	108.5(2)	109.0(2)
C(3)–C(2)–O(6)	135.1(4)	134.2(2)	134.9(2)	C(10)–C(13)–O(15)	126.2(4)	124.9(2)	125.1(2)
C(3)–C(4)–C(23)	113.5(4)	115.8(1)	117.8(1)	C(13)–O(14)–C(16)	115.3(4)	115.8(2)	116.4(2)
C(4)–C(3)–O(7)	112.0(3)	114.8(1)	116.7(2)	O(14)–C(13)–O(15)	124.5(4)	126.3(2)	125.7(2)
Average endocyclic angles in phenyl rings							
	120.0(4)	120.0(2)	120.0(2)				

TABLE 5

Selected torsion angles (deg) in **I** and **II**

Angle	**I**	**II**		Angle	**I**	**II**	
		Mol. A	Mol. B			Mol. A	Mol. B
N(1)–C(4)–S–C(5)	−26.4(3)	−41.0(2)	−39.9(2)	C(23)–C(4)–C(3)–C(10)	−113.8(4)	−5.0(2)	10.8(2)
C(3)–C(4)–S–C(5)	72.8(3)	57.7(2)	56.0(1)	C(8)–O(7)–C(3)–C(2)	135.8(3)	−148.7(2)	−144.4(2)
C(23)–C(4)–S–C(5)	−158.0(3)	−171.0(1)	−171.8(1)	C(8)–O(7)–C(3)–C(4)	−131.8(3)	115.5(2)	116.4(2)
C(3)–C(2)–N(1)–C(4)	3.6(3)	−0.9(1)	8.5(2)	C(8)–O(7)–C(3)–C(10)	2.5(4)	−22.0(2)	−19.2(2)
O(6)–C(2)–N(1)–C(4)	−179.2(4)	178.9(2)	−172.5(2)	O(9)–C(10)–C(3)–C(2)	−140.8(4)	161.0(1)	161.8(2)
C(3)–C(2)–N(1)–C(17)	−174.4(3)	171.1(1)	177.2(2)	C(13)–C(10)–C(3)–C(2)	−18.0(6)	−74.5(2)	−74.5(2)
O(6)–C(2)–N(1)–C(17)	2.8(7)	−9.1(3)	−3.7(4)	O(9)–C(10)–C(3)–C(4)	112.9(4)	−93.6(2)	−97.3(2)
S–C(4)–N(1)–C(2)	114.8(3)	119.2(1)	107.4(1)	C(13)–C(10)–C(3)–C(4)	−124.3(4)	30.9(2)	26.4(2)
C(3)–C(4)–N(1)–C(2)	−3.5(3)	0.9(1)	−8.1(1)	O(9)–C(10)–C(3)–O(7)	−15.5(4)	37.7(1)	35.0(2)
C(23)–C(4)–N(1)–C(2)	−117.9(4)	−115.8(1)	−127.2(2)	C(13)–C(10)–C(3)–O(7)	107.3(4)	162.2(1)	158.7(2)
S–C(4)–N(1)–C(17)	−67.1(4)	−52.5(2)	−60.7(3)	C(24)–C(23)–C(4)–S	−40.1(5)	124.2(2)	126.9(2)
C(3)–C(4)–N(1)–C(17)	174.6(3)	−170.8(2)	−176.1(2)	C(28)–C(23)–C(4)–S	142.8(4)	−58.5(2)	−54.0(2)
C(23)–C(4)–N(1)–C(17)	60.1(5)	72.5(2)	64.8(3)	C(24)–C(23)–C(4)–N(1)	−171.0(4)	−5.3(2)	−2.2(2)
C(18)–C(17)–N(1)–C(2)	9.8(6)	−173.8(2)	−158.2(2)	C(28)–C(23)–C(4)–N(1)	11.9(6)	172.0(2)	176.9(2)
C(22)–C(17)–N(1)–C(2)	−169.5(4)	5.6(2)	21.6(3)	C(24)–C(23)–C(4)–C(3)	91.1(4)	−103.6(2)	−102.4(2)
C(18)–C(17)–N(1)–C(4)	−167.6(3)	−4.7(3)	6.3(3)	C(28)–C(23)–C(4)–C(3)	−86.0(5)	73.7(2)	76.7(2)
C(22)–C(17)–N(1)–C(4)	13.1(6)	174.7(2)	−173.9(2)	O(9)–C(8)–O(7)–C(3)	11.3(4)	−1.1(2)	−3.2(2)
C(4)–C(3)–C(2)–N(1)	−3.3(3)	0.8(1)	−7.8(1)	C(11)–C(8)–O(7)–C(3)	127.5(4)	−117.3(2)	−119.9(2)
O(7)–C(3)–C(2)–N(1)	108.2(3)	−114.2(1)	−125.7(2)	C(12)–C(8)–O(7)–C(3)	−109.3(4)	117.2(2)	115.4(2)
C(10)–C(3)–C(2)–N(1)	−128.7(4)	128.8(2)	115.9(2)	C(10)–O(9)–C(8)–O(7)	−22.0(4)	26.4(2)	26.8(2)
C(4)–C(3)–C(2)–O(6)	179.6(4)	−179.0(2)	173.1(3)	C(10)–O(9)–C(8)–C(11)	−137.3(4)	143.4(2)	144.2(2)
O(7)–C(3)–C(2)–O(6)	−68.8(5)	66.0(2)	55.3(3)	C(10)–O(9)–C(8)–C(12)	95.2(4)	−89.4(2)	−90.0(2)
C(10)–C(3)–C(2)–O(6)	54.2(7)	−51.0(3)	−63.2(3)	C(3)–C(10)–O(9)–C(8)	23.4(4)	−39.7(2)	−38.2(2)
S–C(4)–C(3)–C(2)	−113.3(3)	−117.1(1)	−106.6(1)	C(13)–C(10)–O(9)–C(8)	−99.9(3)	−171.9(1)	−168.6(2)
N(1)–C(4)–C(3)–C(2)	3.1(2)	−0.8(1)	7.3(1)	O(14)–C(13)–C(10)–C(3)	76.5(4)	56.9(2)	61.3(2)
C(23)–C(4)–C(3)–C(2)	120.3(3)	116.2(1)	127.0(1)	O(15)–C(13)–C(10)–C(3)	−106.2(4)	−128.7(2)	−122.8(2)
S–C(4)–C(3)–O(7)	137.7(3)	−3.9(2)	11.3(2)	O(14)–C(13)–C(10)–O(9)	−165.3(3)	177.7(1)	−178.8(2)

N(1)–C(4)–C(3)–O(7)	−105.9(3)	112.4(1)	125.2(1)	O(15)–C(13)–C(10)–O(9)	12.0(5)	−8.0(2)	−3.0(3)
C(23)–C(4)–C(3)–O(7)	11.3(4)	−130.7(1)	−115.0(2)	C(16)–O(14)–C(13)–C(10)	−177.0(3)	175.4(2)	175.8(2)
S–C(4)–C(3)–C(10)	12.6(5)	121.8(1)	137.1(1)	C(16)–O(14)–C(13)–O(15)	5.6(5)	1.1(3)	−0.0(3)
N(1)–C(4)–C(3)–C(10)	128.9(4)	−121.9(2)	−109.0(1)				



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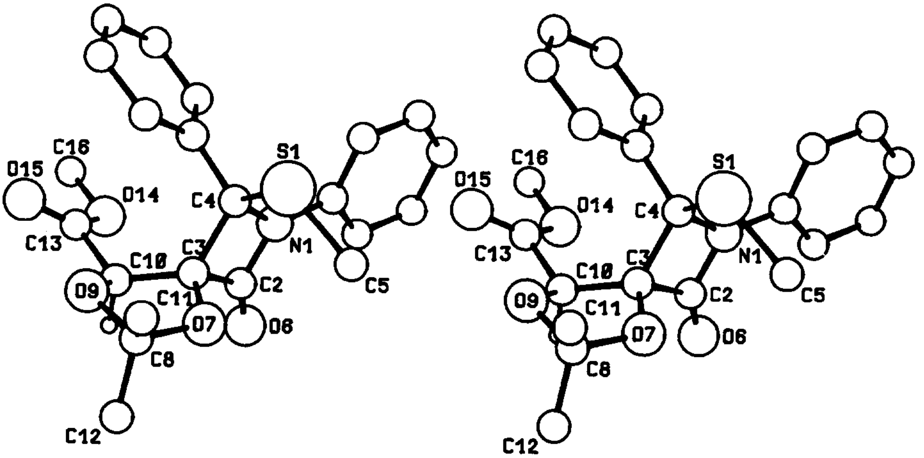

IIA

Fig. 1. Stereo-views of molecules of **I** and **IIA** with crystallographic labelling of non-hydrogen atoms. All hydrogen atoms except for H(10) are omitted for clarity. Orientations to give optimal viewings are approximately the same for both molecules with respect to the β-lactam rings.

TABLE 6

Comparison of the bond distances and bond angles in the monocyclic β-lactam rings[a] in related compounds

Parameter	I	IIA	IIB	III[b]	IV[c]	V[d]	VI[e]	VII[f]
Bond distance (Å)								
N(1)–C(2)	1.369(5)	1.371(2)	1.376(3)	1.368(3)	1.361(3)	1.348(5)	1.355(2)	1.375(7)
C(2)–C(3)	1.538(6)	1.530(2)	1.526(3)	1.530(3)	1.527(3)	1.561(6)	1.545(3)	1.553(8)
C(3)–C(4)	1.601(5)	1.601(2)	1.602(3)	1.587(3)	1.579(3)	1.566(5)	1.603(2)	1.556(7)
C(4)–N(1)	1.476(4)	1.491(2)	1.488(3)	1.482(3)	1.488(2)	1.452(5)	1.464(2)	1.477(7)
Bond angle (deg)								
C(2)–N(1)–C(4)	96.1(3)	95.8(1)	96.0(1)	95.9(1)	95.9(2)	97.9(3)	96.4(2)	95.5(4)
N(1)–C(2)–C(3)	92.6(3)	92.9(1)	92.1(1)	91.9(2)	92.4(1)	90.4(3)	92.9(1)	90.7(4)
C(2)–C(3)–C(4)	84.8(3)	85.5(1)	85.7(1)	85.6(1)	85.9(2)	85.0(3)	83.7(1)	85.5(4)
C(3)–C(4)–N(1)	86.3(3)	85.7(1)	85.1(1)	85.6(2)	85.8(1)	86.5(3)	86.6(1)	86.9(4)
Diagonal contact distance (Å)								
N(1)···C(3)	2.110(3)	2.110(2)	2.090(3)	2.089(2)	2.086(2)	2.071(6)	2.105(3)	2.088(7)
C(2)···C(4)	2.120(3)	2.130(2)	2.130(3)	2.116(2)	2.118(3)	2.112(7)	2.102(2)	2.111(8)
Folding angles (deg) by diagonal lines								
N(1)···C(3)	4.7(3)	1.19(8)	11.0(2)	1.0(1)	10.4(1)	5.3(1)	5.2(1)	12.3(5)
C(2)···C(4)	4.8(3)	1.2(1)	11.3(2)	1.0(2)	10.58(8)	5.4(3)	4.9(1)	12.5(5)

[a] The atom numbering conforms to that of the present paper. [b] Ref. 3. [c] Ref. 4. [d] Ref. 11. [e] Ref. 12. [f] Ref. 13.

and C(10)(*RS*) for **I**, and C(3)(*RS*), C(4)(*RS*) and C(10)(*RS*) for **II**. Thus, compound **I** differs from compound **II** by opposite configuration at C(3), in agreement with our conclusions from the NMR experiments. Furthermore, the two symmetry independent molecules of **II** found in the asymmetric unit are proved to be the same enantiomorphs, although they are not isomorphic. As a matter of fact, they differ by the geometry of the β-lactam ring, which is almost planar in **IIA** and folded in **IIB** (see Table 6).

The distances and valence angles in the β-lactam rings of **I** and **II** do not differ significantly from those observed in numerous other β-lactam derivatives investigated so far. The distance C(3)–C(4) is significantly elongated (up to 1.6 Å), causing a rather trapezoidal shape of the ring. The observed folding of the ring seems to be an important feature from the point of view of the biological activity of β-lactam derivatives [17]. In all known biologically active derivatives (particularly in all antibiotics) this ring reveals a considerable folding (up to 19° in penicillins). A ring geometry comparison of some β-lactam derivatives is shown in Table 6.

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