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Structural determination of ε-lactams by ^{1}H and ^{13}C NMR

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The thermodynamic products (ε-lactams) of the degradation of ten different spirocyclic oxaziridines were analyzed by ^{1}H and ^{13}C NMR spectroscopy. The preferred conformations were determined by examining the homonuclear spin–spin coupling constant and the chemical shift effects of the *N*-substituent and the alkyl group of the aliphatic ring on ^{1}H and ^{13}C NMR spectra.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H; ^{13}C; conformation; e-lactams

Introduction

A number of ε-lactams are of commercial interest,[1] and their syntheses have been reported.[2] The main focus of these reports was the mechanism of ε-lactam formation and the regioselectivity of the reaction. However, relatively little is known regarding the structures and preferred conformations of these compounds.

Knowledge of the substituent effect provoked by different functional groups is important in determining the preferred conformation,[3] the relative and absolute configuration[4] as well as the reactivity and stereoselectivity.[5] Here, we describe the structures and conformations of ten different azepinones, which were obtained as thermodynamic compounds from the photochemical rearrangement of the corresponding spirooxaziridines prepared by the oxidation of the C=N double bond of exocyclic ketimines.[6] We determined the preferred conformation of the heterocyclic ring, the position of substituents attached to nitrogen and the alkyl group as well as the effects of groups attached to the seven-membered ring atoms.

Mobile (R_1 = H) and anchored (R_1 = methyl or *t*-butyl) compounds were used in the structural analyses. All compounds had a seven-membered heterocyclic ring and phenyl (**1a**–**1g**) or (3-pyridyl) groups (**2a**–**2g**) bound to the lactam nitrogen atom (Fig. 1).

Results

The assignment of the ^{1}H and ^{13}C NMR spectra of the ε-lactams is based on one- and two-dimensional NMR experiments. The connectivity was established by homonuclear ^{1}H–^{1}H (COSY) and heteronuclear ^{1}H–^{13}C (HETCOR) correlation spectroscopy. Modulated coupling constant spectroscopy (APT, attached proton test) was carried out to differentiate quaternary, tertiary, secondary and primary carbons in **1b**–**1g** and **2b**–**2g**. Because of the complexity of the isomeric mixture of **1c** and **1f** or **2c** and **2f**, respectively, or their low proportion (**1g** and **2g**), the ^{1}H NMR spectra were not assigned.

The preferential conformation of the *N*-substituent (R_2) was determined based on the chemical shift effect of this group on *pseudoequatorial*/*pseudoaxial* protons at C3 and C7 in the azepinones **1a, 1b, 1d,1e, 2a, 2b, 2d** and **2e** and that of the aliphatic ring from chemical shifts and three-bond proton–proton coupling constants.

On the NMR time scale (at 20 °C), the chemical exchange of the azepinones **1a** and **2a** due to ring inversion is faster than the observed ^{1}H frequency (300 MHz), as evidenced by the chemical shifts of the protons attached to C3 and C7. Methyl or *t*-butyl groups (**1b**–**1g** and **2b**–**2g**) at the aliphatic ring prefer the *pseudoequatorial* position. Azepinones **1d, 1e, 2d** and **2e** are asymmetric and were obtained as racemic mixtures.

The rearrangement of oxaziridines obtained from the oxidation of ketimines[6] synthesized from 3- or 2-methylcyclohexanone with aniline or 3-aminopiridine were obtained as two pairs of isomers with the chiral center at C3 or C7 [2-methylcyclohexanone derivatives (**1b, 1g, 2b** and **2g**)] or C4 or C6 [3-methylcyclohexanone derivatives (**1c, 1f, 2c** and **2f**)], respectively. The relative proportions of the isomers were 10 : 1 for the 2-methylcyclohexanone derivatives (**1b** and **1g** or **2b** and **1g**) and 10 : 9 for the 3-methylcyclohexanone derivatives (**1c** and **1f** or **2c** and **2f**). These ratios were similar to those observed in oxaziridines (to be published). The orientation of the nitrogen insertion producing seven-membered rings is similar to the behavior reported for the photochemical rearrangement.[7]

The assignment of the aliphatic heterocyclic atoms was based on the inductive effects and those of the *N*-substituents. To obtain an unequivocal set of chemical shifts (Table 1) and proton–proton coupling constants (Table 2), these quantities were determined by simulation.[8]

The substituent effects of placing a methyl group at different positions on the seven-membered ring, were determined by examining the ^{13}C NMR spectral features (Table 3), and the analysis

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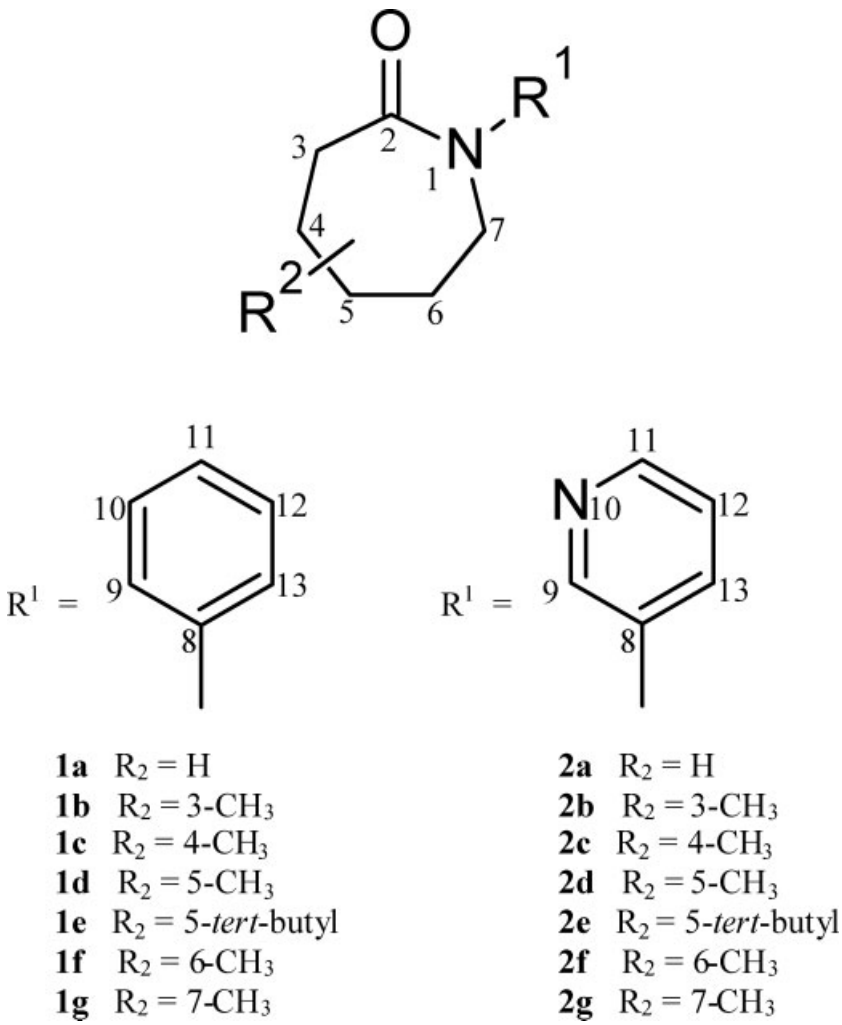

Figure 1. Structure and numbering of ε-lactams **1a–1g** and **2a–2g**.

Table 1. ^{1}H NMR chemical shifts of ε-lactams (ppm)

	3		4		5		6		7							
	Eq	Ax	Eq	Ax	Eq	Ax	Eq	Ax	Eq	Ax	9	10	11	12	13	Me
1a	2.74	2.71	1.85	1.85	1.84	1.84	1.86	1.86	3.79	3.77	7.19	7.35	7.21	7.35	7.19	–
1b	–	2.82	1.82	1.59	2.01	1.72	1.85	1.70	3.60	3.94	7.20	7.35	7.21	7.35	7.21	1.19
1d	2.67	2.73	1.93	1.42	–	1.78	1.89	1.44	3.63	3.87	7.21	7.36	7.22	7.36	7.21	1.01
1e	2.68	2.65	2.05	1.40	–	1.32	2.01	1.41	3.64	3.80	7.21	7.34	7.19	7.34	7.21	0.89
2a	2.74	2.71	1.86	1.86	1.85	1.85	1.84	1.84	3.79	3.77	8.51	–	8.46	7.08	7.60	–
2b	–	2.86	1.80	1.59	2.03	1.74	1.92	1.93	3.61	3.99	8.50	–	8.44	7.30	7.59	1.20
2d	2.68	2.75	1.95	1.41	–	1.81	1.94	1.45	3.64	3.92	8.51	–	8.45	7.31	7.60	1.03
2e	2.70	2.69	2.07	1.38	–	1.36	2.08	1.39	3.68	3.82	8.53	–	8.41	7.28	7.60	0.91

of these effects were explored using the parent compounds **1a** and **2a** as references.

Discussion

^{1}H NMR

The azepinones **1a, 1b, 1d, 1e, 2a, 2b, 2d** and **2e** give rise to complex ^{1}H NMR spectra with overlapping signals and complicated coupling patterns (most of the protons possess up to five different coupling partners). Hence, to interpret the NMR data, it was necessary to simulate the the ^{1}H NMR spectra[8] (Fig. 2). Signal assignment was performed considering the chemical shifts, multiplicity and connectivity. The root mean square (r.m.s.) error between the experimental and simulated spectra was 0.11 Hz. This excellent correlation between the experimental and simulated spectra was obtained when long-range coupling constants ($^4J_{H,H}$) were taken into account.

Table 2. ^{1}H NMR coupling constants of ε-lactams determined by simulation of experimental spectra (Hz)

	3	4	5	6	7	9	10	11	12
1a	$^{2}J_{3,3} = 3.4$ $^{3}J_{3,4} = 2.9$ $^{3}J_{3,4} = 1.5$ $^{4}J_{3,5} = 0.8$ $^{4}J_{3,5} = 0.4$	$^{2}J_{4,4} = 3.0$ $^{3}J_{4,5} = 2.5$ $^{3}J_{4,5} = 2.0$ $^{4}J_{4,6} = 0.5$	$^{2}J_{5,5} = 3.0$ $^{3}J_{5,6} = 3.1$ $^{3}J_{5,6} = 2.0$ $^{4}J_{5,7} = 0.8$ $^{4}J_{5,7} = 0.4$	$^{2}J_{6,6} = 3.2$ $^{3}J_{6,7} = 2.8$ $^{3}J_{6,7} = 1.9$	$^{3}J_{7,7} = 3.5$				
1b	$^{3}J_{3,me} = 6.7$ $^{3}J_{3ax,4eq} = 1.3$ $^{3}J_{3ax,4ax} = 15.6$ $^{4}J_{3ax,5eq} = 0.8$	$^{2}J_{4,4} = 14.0$ $^{3}J_{4ax,5ax} = 14.0$ $^{3}J_{4ax,5eq} = 2.5$ $^{3}J_{4eq,5eq} = 5.6$ $^{3}J_{4eq,5ax} = 3.0$ $^{4}J_{4eq,5eq} = 1.0$	$^{2}J_{5,5} = 12.8$ $^{3}J_{5eq,6eq} = 5.6$ $^{3}J_{5eq,6ax} = 3.6$ $^{3}J_{5ax,6ax} = 14.0$ $^{3}J_{5ax,6eq} = 3.3$ $^{4}J_{5eq,7eq} = 1.4$ $^{4}J_{5eq,7ax} = 0.8$	$^{2}J_{6,6} = 14.0$ $^{3}J_{6ax,7eq} = 1.3$ $^{3}J_{6ax,7ax} = 10.3$ $^{3}J_{6eq,7eq} = 5.6$ $^{3}J_{6eq,7ax} = 1.0$	$^{2}J_{7,7} = 15.4$	$^{3}J_{9o,10m} = 8.0$ $^{4}J_{9o,11p} = 1.3$	$^{3}J_{10m,11p} = 7.3$		
1d	$^{2}J_{3,3} = 14.0$ $^{3}J_{3ax,4eq} = 1.4$ $^{3}J_{3ax,4ax} = 12.3$ $^{3}J_{3eq,4eq} = 8.0$ $^{3}J_{3eq,4ax} = 1.7$ $^{4}J_{3eq,5ax} = 0.3$ $^{4}J_{3ax,5ax} = 0.3$	$^{2}J_{4,4} = 14.8$ $^{3}J_{4ax,5ax} = 11.0$ $^{3}J_{4eq,5ax} = 3.4$ $^{4}J_{4eq,6eq} = 1.9$	$^{3}J_{5ax,me} = 6.5$ $^{3}J_{5ax,6ax} = 11.1$ $^{3}J_{5ax,6eq} = 4.0$ $^{4}J_{5ax,7eq} = 0.4$ $^{4}J_{5ax,7ax} = 0.4$	$^{2}J_{6,6} = 14.0$ $^{3}J_{6ax,7eq} = 1.7$ $^{3}J_{6ax,7ax} = 10.8$ $^{3}J_{6eq,7eq} = 6.6$ $^{3}J_{6ax,7eq} = 1.1$	$^{2}J_{7,7} = 15.7$	$^{3}J_{9o,10m} = 8.0$ $^{4}J_{9o,11p} = 1.3$	$^{3}J_{10m,11p} = 7.5$		
1e	$^{2}J_{3,3} = 14.0$ $^{3}J_{3ax,4eq} = 1.9$ $^{3}J_{3ax,4ax} = 12.4$ $^{3}J_{3eq,4eq} = 8.4$ $^{3}J_{3eq,4ax} = 1.7$	$^{2}J_{4,4} = 14.2$ $^{3}J_{4ax,5ax} = 12.3$ $^{3}J_{4eq,5ax} = 2.5$ $^{4}J_{4eq,6eq} = 1.9$	$^{3}J_{5ax,6ax} = 12.4$ $^{3}J_{5ax,6eq} = 2.8$	$^{2}J_{6,6} = 14.0$ $^{3}J_{6ax,7eq} = 1.2$ $^{3}J_{6ax,7ax} = 10.1$ $^{3}J_{6eq,7eq} = 7.7$ $^{3}J_{6ax,7eq} = 1.8$	$^{2}J_{7,7} = 15.2$	$^{3}J_{9o,10m} = 8.0$ $^{4}J_{9o,11p} = 1.7$	$^{3}J_{10m,11p} = 7.3$		
2a	$^{2}J_{3,3} = 3.4$ $^{3}J_{3,4} = 2.9$ $^{3}J_{3,4} = 1.5$ $^{4}J_{3,5} = 0.8$ $^{4}J_{3,5} = 0.4$	$^{2}J_{4,4} = 3.0$ $^{3}J_{4,5} = 2.5$ $^{3}J_{4,5} = 2.0$ $^{4}J_{4,6} = 0.5$	$^{2}J_{5,5} = 3.0$ $^{3}J_{5,6} = 3.1$ $^{3}J_{5,6} = 2.0$ $^{4}J_{5,7} = 0.8$ $^{4}J_{5,7} = 0.4$	$^{2}J_{6,6} = 3.2$ $^{3}J_{6,7} = 2.8$ $^{3}J_{6,7} = 1.9$	$^{3}J_{7,7} = 3.5$	$^{4}J_{9,11} = 0.4$ $^{5}J_{9,12} = 0.8$ $^{4}J_{9,13} = 2.6$		$^{3}J_{11,12} = 4.8$ $^{4}J_{11,13} = 1.5$	$^{3}J_{12,13} = 8.2$
2b	$^{3}J_{3,me} = 6.7$ $^{3}J_{3ax,4eq} = 2.0$ $^{3}J_{3ax,4ax} = 15.1$ $^{4}J_{3ax,5eq} = 0.4$	$^{2}J_{4,4} = 14.0$ $^{3}J_{4ax,5ax} = 14.0$ $^{3}J_{4ax,5eq} = 2.6$ $^{3}J_{4eq,5eq} = 6.0$ $^{3}J_{4eq,5ax} = 3.0$ $^{4}J_{4eq,5eq} = 1.0$	$^{2}J_{5,5} = 12.8$ $^{3}J_{5eq,6eq} = 5.6$ $^{3}J_{5eq,6ax} = 3.6$ $^{3}J_{5ax,6ax} = 14.0$ $^{3}J_{5ax,6eq} = 3.3$ $^{4}J_{5eq,7eq} = 1.4$ $^{4}J_{5eq,7ax} = 0.8$	$^{2}J_{6,6} = 14.0$ $^{3}J_{6ax,7eq} = 1.3$ $^{3}J_{6ax,7ax} = 11.5$ $^{3}J_{6eq,7eq} = 5.7$ $^{3}J_{6ax,7eq} = 1.0$	$^{2}J_{7,7} = 15.4$	$^{4}J_{9,11} = 0.3$ $^{5}J_{9,12} = 0.7$ $^{4}J_{9,13} = 2.6$		$^{3}J_{11,12} = 4.8$ $^{4}J_{11,13} = 1.5$	$^{3}J_{12,13} = 8.2$
2d	$^{2}J_{3,3} = 14.0$ $^{3}J_{3ax,4eq} = 1.4$ $^{3}J_{3ax,4ax} = 12.3$ $^{3}J_{3eq,4eq} = 8.0$ $^{3}J_{3eq,4ax} = 1.7$ $^{4}J_{3eq,5ax} = 0.4$ $^{4}J_{3ax,5ax} = 0.4$	$^{2}J_{4,4} = 14.1$ $^{3}J_{4ax,5ax} = 11.0$ $^{3}J_{4eq,5ax} = 3.4$ $^{4}J_{4eq,6eq} = 1.9$	$^{3}J_{5ax,me} = 6.5$ $^{3}J_{5ax,6ax} = 11.1$ $^{3}J_{5ax,6eq} = 4.0$ $^{4}J_{5ax,7eq} = 0.4$ $^{4}J_{5ax,7ax} = 0.4$	$^{2}J_{6,6} = 14.1$ $^{3}J_{6ax,7eq} = 1.8$ $^{3}J_{6ax,7ax} = 10.8$ $^{3}J_{6eq,7eq} = 6.6$ $^{3}J_{6ax,7eq} = 1.1$	$^{2}J_{7,7} = 15.6$	$^{4}J_{9,11} = 0.3$ $^{5}J_{9,12} = 0.8$ $^{4}J_{9,13} = 2.6$		$^{3}J_{11,12} = 4.8$ $^{4}J_{11,13} = 1.5$	$^{3}J_{12,13} = 8.2$
2e	$^{2}J_{3,3} = 13.5$ $^{3}J_{3ax,4eq} = 1.5$ $^{3}J_{3ax,4ax} = 12.3$ $^{3}J_{3eq,4eq} = 7.6$ $^{3}J_{3eq,4ax} = 1.7$	$^{2}J_{4,4} = 14.4$ $^{3}J_{4ax,5ax} = 11.0$ $^{3}J_{4eq,5ax} = 3.5$	$^{3}J_{5ax,6ax} = 11.0$ $^{3}J_{5ax,6eq} = 3.8$	$^{2}J_{6,6} = 14.5$ $^{3}J_{6ax,7eq} = 1.5$ $^{3}J_{6ax,7ax} = 9.9$ $^{3}J_{6eq,7eq} = 6.7$ $^{3}J_{6ax,7eq} = 0.9$	$^{2}J_{7,7} = 15.3$	$^{4}J_{9,11} = 0.4$ $^{5}J_{9,12} = 0.7$ $^{4}J_{9,13} = 2.6$		$^{3}J_{11,12} = 4.8$ $^{4}J_{11,13} = 1.5$	$^{3}J_{12,13} = 8.2$

The relative proportions of the structural isomers of the azepinones (**1b** and **1g** or **2c** and **2f**) were obtained from the integrals of the methyl proton signals. The chemical shifts of the C4 to C6 protons in **1a** and **2a** were similar (Table 1), indicating that the amide and *N*-substituent group have little effect on these protons.

The nonbonding nitrogen orbital is strongly conjugated (about 84 kJ/mol) to the antibonding carbonyl π-orbital,[9] indicating that the aromatic ring is preferably perpendicular to the amide plane. This is evident because the signal of the *pseudoaxial* C7 proton exhibits a larger chemical shift than the signal of the *pseudoequatorial* proton. The preference

Table 3. ^{13}C NMR chemical shifts of ε-lactams (ppm)

		2	3	4	5	6	7	8	9	10	11	12	13	Me *t*-but
1a		175.68	37.78	23.64	29.00	29.95	53.12	144.66	126.34	129.18	126.51	–	–	–
1b	3-Me	177.27	38.81	32.64	28.54	29.39	52.08	145.02	126.50	129.04	126.32	–	–	18.54
1c	4-Me	173.88	44.77	29.23	37.83	27.42	52.54	144.21	125.91	128.74	126.05	–	–	22.66
1d	5-Me	174.97	36.31	31.31	35.84	36.82	51.68	144.25	125.97	128.82	126.13	–	–	22.48
1e	5-*t*-but	175.12	36.73	24.17	51.22	29.83	52.14	144.13	125.93	128.91	126.19	–	–	27.51
														33.01
1f	6-Me	175.07	37.24	22.39	37.92	33.67	58.73	144.44	125.96	128.76	126.05	–	–	19.72
1g	7-Me	175.70	37.48	23.32	26.59	35.80	55.97	145.02	128.49	127.24	129.14	–	–	20.28
2a		176.02	37.73	23.61	29.19	29.92	53.00	141.07	147.41	–	147.39	123.74	134.03	–
2b	3-Me	177.59	38.80	32.51	28.59	29.21	51.88	141.31	147.46	–	147.08	123.54	136.06	18.44
2c	4-Me	174.52	44.98	29.57	38.15	27.89	52.69	140.88	147.29	–	147.19	123.60	133.80	22.60
2d	5- Me	175.47	36.35	31.34	35.99	37.03	51.67	140.75	147.19	–	147.10	123.52	133.69	22.57
									147.21					
2e	5-*t*-but	174.89	36.19	23.72	50.68	29.53	51.44	140.10	146.62	146.40	123.01	132.90	–	27.13
									146.65					32.64
2f	6-Me	175.67	37.47	22.95	38.08	34.20	58.54	141.11	147.37	–	147.19	123.60	133.89	22.25
2g	7-Me	176.12	37.32	23.20	26.65	35.95	56.04	141.31	149.86	–	148.47	124.09	136.59	20.92

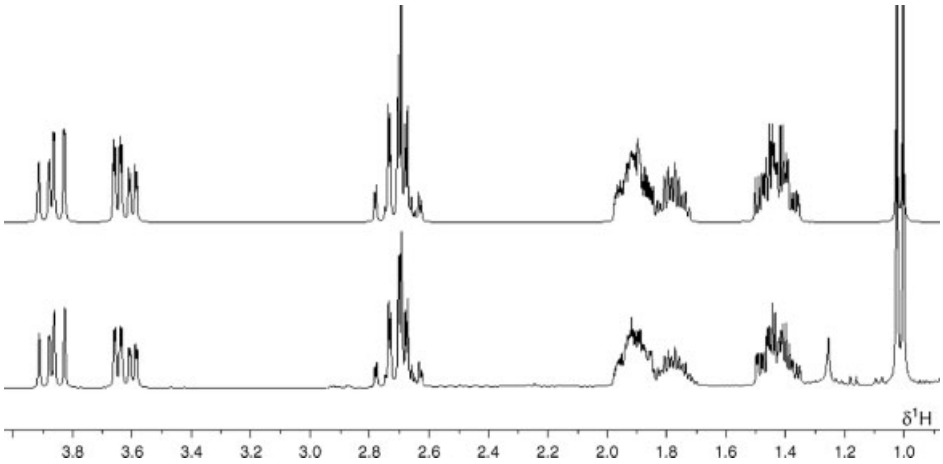

Figure 2. Aliphatic region of the ^{1}H NMR spectrum of the azepinone **1d**. Top, simulated spectrum and bottom, experimental spectrum.

of this conformation can be explained by the fact that the *pseudoaxial* proton is located in the deshielding region of the diamagnetic ring current of the aromatic group and the deshielding cones of the partial double bond produced by the conjugation between the nonbonding *n*-orbital and π^* C═O orbital (Fig. 3).[10]

The two-bond coupling constants fall into the range of 13.5–15.7 Hz; the coupling constants for the protons on C7 are about 1.5 (±0.2) Hz larger than those of the protons attached to C3. This shows that the C3 protons must have a larger geminal angle[11] (H_{ax}-C3-H_{eq}), which is a result of the conjugation of the amide group.

The preferred conformation of the seven-membered rings with an alkyl substituent is a twist chair, as determined by homonuclear (^{1}H,^{1}H) three-bond coupling constant analyses (Table 2). The *axial–axial* three-bond coupling constants range from 10.1 to 12.6 Hz. The higher values correspond to *axial* protons at C3–C4 and C6–C7, with dihedral angles of 195 ± 5° and the lower ones to *axial* protons at C4–C5 and C5–C6, with dihedral angles of 155 ± 5° or 30 ± 5°. The latter values are unusual because the

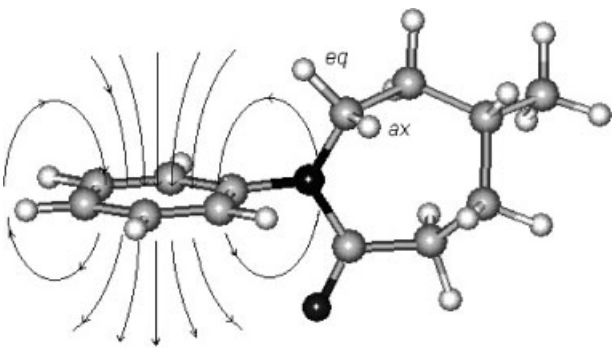

Figure 3. Preferential orientation of the aryl group and the deshielding current ring effect.

axial protons at C4–C5 or C5–C6 have *syn-diaxial* interactions. The proposed conformation is supported by the *axial–equatorial* coupling constants ranging from 1.1 to 4.0 Hz. The lower values correspond to hydrogens bonded to C3–C4 or C6–C7 and the

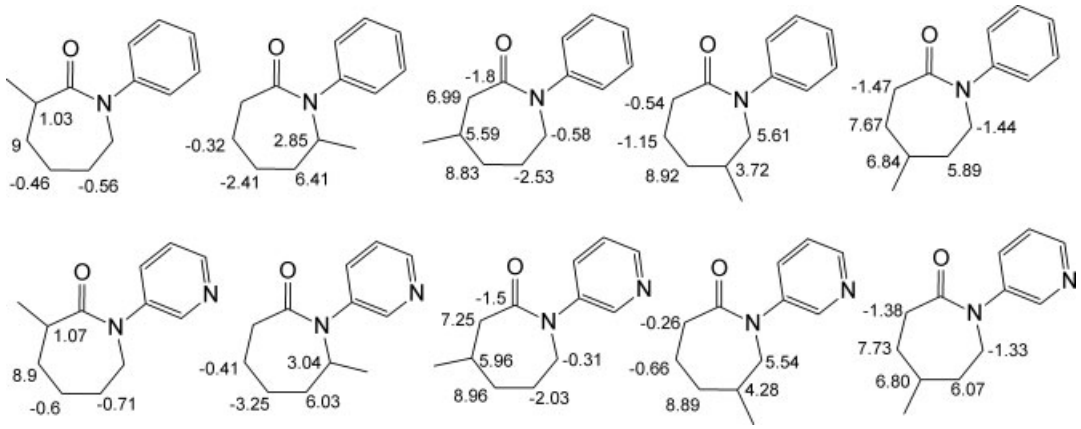

Figure 4. ^{13}C chemical shift substituent effect of the methyl group with respect to the heterocycle without the substituent: compounds **1a** and **2a**.

highest values correspond to hydrogens bonded to C4–C5–C6. The lower dihedral angle is 65 ± 10°. This angle is smaller than expected because, in azepinones derived from oxaziridines with an alkyl group on C4 of the aliphatic ring, the C4–C5–C6 structure undergoes a pseudorotation in order to minimize the steric interaction of the C5 methyl with the C4 and C6 protons.

The *equatorial–equatorial* coupling constants range from 6.6 to 8.4 Hz indicating that the dihedral angle is 35±5°. The couplings of the *equatorial* proton were lowest for protons attached to C6–C7 and highest for protons attached to C3–C4. Thus, the dihedral angle of the *equatorial* protons attached to C3–C4 is larger than that of the *equatorial* protons attached to C6–C7.

Compounds **1g** and **2g** with the methyl on C7 have this group in the *pseudoaxial* position as determined from the magnitude of the three-bond coupling constants $^{3}J(CH,CH_3) = 7.2$ Hz.[12]

^{13}C NMR

Complete assignments of the ^{13}C NMR signals of all azepinones isomers **1a**–**1g** and **2a**–**2g** are listed in Table 3. They were made considering the effects of the substituents, orientations, connectivities and the isomeric abundance for 2- or 3-methylcyclohexanone derivatives (**1b** and **1g, 1c** and **1f** or **2b** and **2g, 2c** and **2f**).

The chemical shifts of the signals observed for **1a** and **2a** are very similar indicating that the heteroaromatic nitrogen atom does not have an important inductive effect on the atoms of the seven-membered ring.

Because of the conjugation between the nonbonding nitrogen orbital and π^* orbital, the amide group and the atoms directly attached must be almost coplanar in the compounds analyzed. When a substituent is attached to any other atom of the ring (C3, C4, C5, C6 or C7), only the bonds C3–C4–C5–C6 have the possibility to undergo a significant pseudorotation. As a result, the γ effect between the atoms of the ring depends on the position of the substituent. This is evident from variations in the magnitude of methyl substituent effects at different positions. The normal substitution effect of a methyl group is $\alpha = 9.1$, $\beta = 9.4$ and $\gamma = 2.5$ ppm when the group is in the *anti* position,[13] whereas we observed values of $\alpha = 4.1 \pm 2.1$, $\beta = 6.5 \pm 2.8$ and $\gamma = -1.5 \pm 0.6$ ppm (Fig. 4).

The lowest α substituent effect arises when the methyl group is on C3 (1.05 ± 0.02 ppm) or C7 (2.95 ± 0.1 ppm), because these atoms are bound to the amide group and the dihedral angle between these atoms (C3–C2–N1–C7) is small. This generates a big negative γ_{syn} effect.[13] The α substituent effect is largest when the methyl group is on C5 (6.82 ± 0.02 ppm); the largest effect for this configuration is because this carbon (C5) has the highest mobility, with an average dihedral angle between C5–C4–C3–C2 or C5–C6–C7–N1 of nearly 60°. The largest β substituent effect is observed on C3, C4 and C5 (about 8.91 ± 0.08 ppm) when the methyl is attached to C2, C3 or C6. This shows that the average dihedral angle between these carbons with the ring atoms is larger than 60°.

Conclusions

A complete conformational and structural description of ε-lactams has been made by the ^{1}H and ^{13}C NMR analysis. Aryl groups prefer rotamers in which they are orthogonal to the seven-membered ring plane. The azepinone rings exchange conformation rapidly when they are unsubstituted; in substituted rings, they prefer conformations with an alkyl group at *pseudoequatorial* position. However, when the methyl group is at C7, it prefers the *pseudoaxial* position.

Experimental

The NMR spectra of compounds **1a** to **2e** were recorded at ±18 °C with a Bruker 300 Avance spectrometer equipped with a 5-mm multinuclear broadband probe. All spectra were obtained in $CDCl_3$ solution (0.9 mmol in 0.4 ml of solvent), with chemical shifts referenced[14] to internal $(CH_3)_4Si$; $\delta(^{1}H) = 0$ and $\delta(^{13}C) = 0$ ppm. ^{1}H NMR spectra were recorded at 300 MHz (spectral width 6188.1 Hz, acquisition time 2.648 s, 16 384 data points, recycle delay of 1 s, equivalent to 30° pulse duration, 16 scans). The dihedral angles were calculated using a generalized Karplus-type equation.[15]

The ^{13}C{^{1}H} NMR spectra were recorded at 75.47 MHz (spectral width 17361.1 Hz, 32 768 data points, recycle delay of 0.01 s, equivalent to 30° pulse duration, 257 scans). Similar conditions were used to record APT and INEPT spectra.

The H,H-COSY spectra were obtained with the cosy45 pulse sequence[16] using a 1024 × 512 data point matrix and a 751.20 × 751.20 Hz frequency matrix; the recycle delay was 2 s. Fourier transformations were carried out using a sine function for F1 and F2, in absolute value mode.

The ^{13}C,^{1}H-COSY spectra were obtained with the hxco pulse sequence for the aliphatic region[9] using a 2048 × 256 data point

matrix and a 6265 × 751 Hz frequency matrix; pulse time intervals 1 and 2 were set to $2 \times 1/4J = 1.85$ ms and the recycle delay was 2 s. Fourier transformations were carried out using a square-sine function for F1 and F2, in absolute value mode.

Mass spectra were determined using a Hewlett-Packard 5890 spectrometer at 70 eV coupled with a gas chromatograph in electron ionization (EI) mode.

Syntheses

The oxaziridine precursors of the lactams were prepared by mixing 1.5 molar equivalents of *m*-chloroperbenzoic acid and 1 equivalent of the corresponding imine[17] in 25 ml of methylene chloride. The reaction was carried out at 0 °C under constant stirring for 1 hour. Then, 250 ml of water was added to the solution and extracted three times with 150 ml of CH_2Cl_2. The portions were combined and dried over $MgSO_4$. Oxaziridines were purified by using a flash chromatography alumina (**1a**–**1g**) or a silica gel (**2a**–**2g**) column and 90% hexane/10% ethyl acetate as an eluting agent. To synthesize the lactams, oxaziridines were left at room temperature and atmosphere during 4 weeks.

Mass spectra data, Karplus-type plots and an example of assignment are collected in the Supporting information.

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Supporting information

Supporting information may be found in the online version of this article.

References

[1] (a) P. A. Tuthill, P. R. Seida, W. Barker, J. A. Cassel, S. Belanger, R. N. DeHaven, M. Koblish, S. L. Gottshall, P. J. Little, D. L. DeHaven-Hudkins, R. E. Dolle, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5693; (b) J. A. Robl, R. Sulsky, E. Sieber-McMaster, D. E. Ryono, M. P. Cimarusti, L. M. Simpkins, D. S. Karanewsky, S. Chao, M. M. Asaad, A. A. Seymour, M. Fox, P. L. Smith, N. C. Trippodo, *J. Med. Chem.* **1999**, *42*, 305; (c) L. Jia, L. Gang, N. Fa-Jun, X. Chuan-Ming, M. Yi-Ming, T. Wan-Yi, L. Yu-Li, *ChemMedChem* **2008**, *3*, 74.

[2] (a) R. O. Hutchins, W. Y. Su, R. Sivakurmar, F. Cistone Y. P. Stercho, *J. Org. Chem.* **1983**, *48*, 3412; (b) E. Oliveros, M. Rivière, A. Lattes, *J. Heterocycl. Chem.* **1983**, *17*, 1025; (c) H. Rao, Y. Jin, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2006**, *12*, 3636; (d) H. Krimm, *Chem. Ber.* **1958**, *91*, 1057; (e) L. Wang, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2008**, *14*, 10722.

[3] R. Montalvo-González, A. Ariza-Castolo, *J. Mol. Struct.* **2003**, *655*, 375.

[4] (a) A. Ariza-Castolo, A. Montalvo-González, R. Montalvo-González, *Magn. Reson. Chem.* **2005**, *43*, 975; (b) J. A. Guerrero-Alvarez, A. Moncayo-Bautista, A. Ariza-Castolo, *Magn. Reson. Chem.* **2004**, *42*, 524.

[5] E. Juaristi, *Introduction to Stereochemistry and Conformational Analysis*, Wiley: New York, USA, **1991**.

[6] D. R. Boyd, D. C. Neill, C. G. Watson, W. B. Jennings, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1813.

[7] (a) M. Fischer, *Tetrahedron Lett.* **1969**, *27*, 2281; (b) E. Oliveros, M. Riviere, J. P. Malrieu, C. Teichteil, *J. Am. Chem. Soc.* **1979**, *101*, 318; (c) M. E. Kuehne, W. H. Parsons, *Tetrahedron* **1983**, *39*, 3763; (d) J. Aubé, Y. Wang, S. Ghosh, K. L. Langhans, *Synth. Commun.* **1991**, *21*, 693; (e) J. Aubé, S. Ghosh, M. Tanol, *J. Am. Chem. Soc.* **1994**, *116*, 9009.

[8] (a) Nuts NMR utility transform software, **2009**, http://www.acornnmr.com. (accessed February 2009); (b) K. Marat, *Spin Works*, version 3.0, University of Manitoba, **2009**, http://www.umanitoba.ca/chemistry/nmr/spinworks/index.html. (accessed May 2009).

[9] N. G. Akhmedov, E. M. Myshakin, C. D. Hall, *Magn. Reson. Chem.* **2004**, *42*, 39.

[10] C. S. Wannere, P. V. R. Schleyer, *Org. Lett.* **2003**, *5*, 605.

[11] R. S. Macomber, *NMR Spectroscopy: Basic Principles and Applications*, Wiley-Interscience Publication: New York, **1998**.

[12] E. Oliveros, M. Riviere, A. Lattes, *Org. Magn. Reson.* **1976**, *8*, 601.

[13] H. O. Kalinowski, S. Berger, S. Braun, *Carbon-13 NMR Spectroscopy*, Wiley: Chichester, **1991**.

[14] R. K. Harris, E. D. Becker, S. M. Cabral de Menezes, R. Goodfellow, P. Granger, *Magn. Reson. Chem.* **2002**, *40*, 489.

[15] (a) C. A. G. Hassnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783; (b) C. M. Cerda-García-Rojas, L. G. Zepeda, P. Joseph-Nathan, *Tetrahedron Comp. Method.* **1990**, *3*, 113.

[16] S. Braun, H. O. Kalinowski, S. Berger, *200 and More Basic NMR Experiments, a Practical Course*, Wiley-VCH: Weinheim, **2004**.

[17] R. Montalvo-González, A. Montalvo-González, A. Ariza-Castolo, *Magn. Reson. Chem.* **2008**, *46*, 907.

