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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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