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Conformational Studies of N_3-Substituted [1,3,4]-Oxadiazinan-2-ones

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Pseudoephedrine-based [1,3,4]-oxadiazinan-2-ones acylated at the N_3-position with either acetyl (**2a**), propionyl (**2b**), or phenylacetyl (**2c**) substituents are known to undergo conformational changes that are observable by ^{13}C NMR spectroscopy. The conformational properties of new [1,3,4]-oxadiazinan-2-one derivatives **2d**−**k** are examined by X-ray crystallography and variable-temperature ^{13}C NMR spectroscopy and further evaluated by semiempirical AM1 calculations. The collected data reveal that the conformational changes of the overall ring system are dependent upon the stereoelectronic factors of the N_3-substituent.

Introduction

The conformational analysis of [1,3,4]-oxadiazines[1] and [1,3,4]-oxadiazinanes[2] has been of much interest due to their conformational mobility at nitrogen.[3] In contrast, the conformational analysis of [1,3,4]-oxadiazinan-2-ones (**1**) have only recently been investigated (Scheme 1).[4a,b] We discovered that pseudoephedrine-based [1,3,4]-oxadiazinan-2-ones (**2a**−**c**) acylated at the N_3-nitrogen undergo conformational changes that are observable by ^{13}C NMR spectroscopy.[4b] The most pronounced aspect of these conformational changes is the ^{13}C NMR signal broadening of the N_4-methyl group, which is presumed to be due to pyramidal inversion. The pyramidal inversion may also be coupled with ring inversion or ring deformation processes. The exact origins of the line broadening are not entirely understood with regard to the conformational changes that they suggest.[5]

Herein, we examine the root cause of the observed line broadening in the ^{13}C NMR spectra by synthesizing and evaluating new [1,3,4]-oxadiazinan-2-one derivatives. To this end, the pseudoephedrine-based oxadiazinan-2-one **1** was alkylated with a variety of alkyl halides to afford the corresponding N_3-alkyl [1,3,4]-oxadiazinan-2-ones **3a**−**c** which did not exhibit line broadening in the ^{13}C NMR spectra at room temperature or at −50 °C. Acylation at the N_3-position gave rise to N_3-acylated derivatives **2d** (R = $-CH_2CH_2Ph$), **2e** (R = $-C(CH_3)_3$), and **2f** (R = $-OCH_3$). Derivatives **2d** and **2f** exhibited significant line broadening in their respective ^{13}C NMR spectra. The N_3-trimethylacetyl derivative **2e** did not exhibit this same characteristic. Acylation with α,β-unsaturated acyl chlorides afforded [1,3,4]-oxadiazinan-2-ones **2g**−**j,** all of which exhibited line broadening with the only exception being the N_3-methacryloyl derivative (**2j**) in addition to the N_3-trimethylacetyl derivative **2e**. In addition, acylation with benzoyl chloride gave rise to the N_3-benzoyl derivative (**2k**), which did not exhibit significant line broadening at room temperature.

These ^{13}C NMR results provide a foundation for understanding the conformational dynamics of the [1,3,4]-oxadiazinan-2-one ring system. In conjunction with X-ray crystallographic studies and semiempirical AM1 calculations, these collected results suggest that the stereoelectronic properties of the N_3-substituent dictate the overall conformation properties of the ring system.

Results and Discussion

Synthesis. Pseudoephedrine derived [1,3,4]-oxadiazinan-2-one **1** was treated with sodium hydride and subsequently alkylated with iodomethane, 1-iodopropane, and benzyl bromide to yield oxadiazinan-2-ones **3a**−**c** (Scheme 2). The yields for the 1-iodopropane and benzyl bromide reactions were 37% and 17%, respectively. The iodomethane reaction failed to generate the desired

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† Center for Structure Determination.

(1) (a) Rosling, A.; Klika, K.; Fulop, F.; Sillanpaa, R.; Mattinen, J. *Heterocycles* **1999**, *51*, 2575. (b) Rosling, A.; Hotokka, M.; Klika, K. D.; Fulop, F.; Sillanpaa, R.; Mattinen, J. *Acta Chem. Scand.* **1999**, *53*, 213. (c) Rosling, A.; Fulop, F.; Sillanpaa, R.; Mattinen, J. *Heterocycles* **1997**, *45*, 95.

(2) (a) Rosling, A.; Fulop, F.; Sillanpaa, R.; Mattinen, J. *Heterocycles* **1997**, *45*, 927. (b) Riddell, F. G.; Kidd, A. J. *J. Chem. Soc., Perkin. Trans. 2* **1977**, 1816. (c) Ferguson, I. J.; Katritzky, A. R.; Read, D. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1861. (d) Dorman, L. *J. Org. Chem.* **1967**, *32*, 5.

(3) Pyrazolidinones exhibit similar conformational properties in the context of lability at nitrogen. See: (a) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181. (b) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444.

(4) (a) The name formerly applied to these heterocycles is 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones. (b) Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. *Tetrahedron* **2001**, *57*, 9789.

(5) Riddell and Katrizky independently observed similar conformational dynamics of the [1,3,4]-oxadiazinanes in their respective studies. See ref 2.

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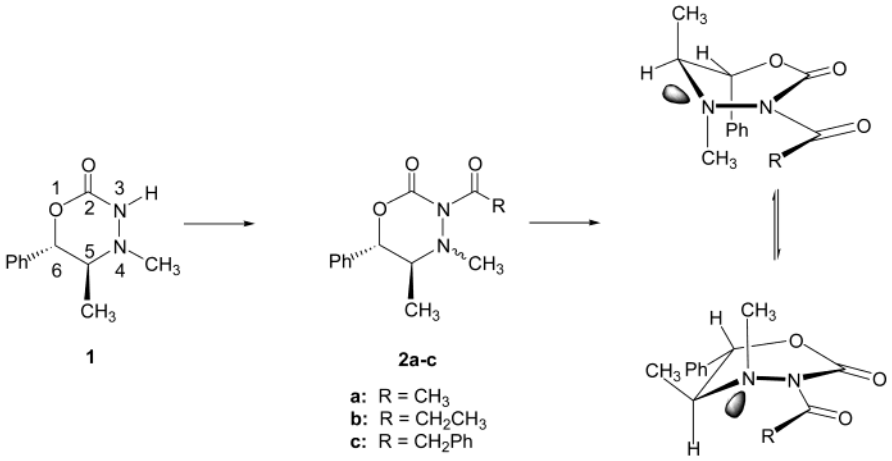
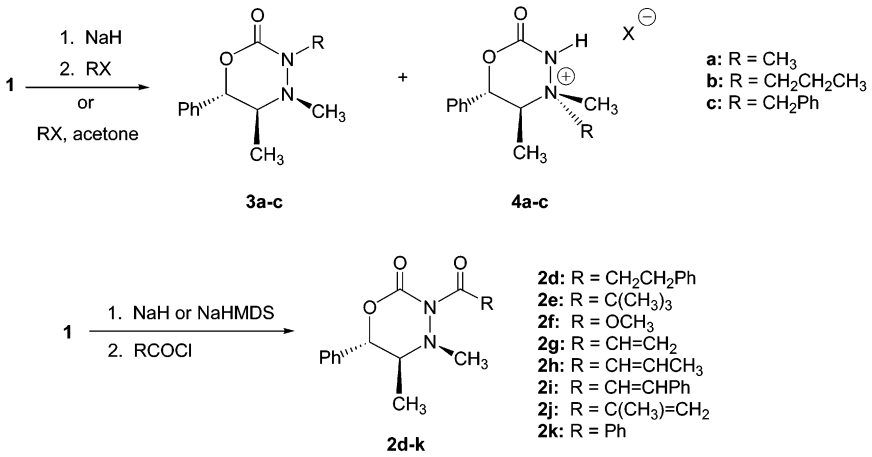
SCHEME 1. Conformational Changes of [1,3,4]-Oxadiazinan-2-ones



SCHEME 2. Synthesis of [1,3,4]-Oxadiazinan-2-ones



product **3a** in reasonable yield. We were eventually able to obtain **3a** in 5% yield by reaction of **1** with *n*-BuLi, followed by treatment with iodomethane. The low yields of **3a**−**c** that were obtained were attributed to the additional reaction to form water-soluble oxadiazinium salts **4a**−**c**.[6] Apparently, the nucleophilicity of the N_4-nitrogen can effectively compete with the nucleophilicity of the deprotonated amide N_3-nitrogen when strong electrophiles (e.g., iodomethane, benzyl bromide) are employed. Nevertheless, we were able to obtain enough material to perform low-temperature studies. We next turned our attention to the synthesis of N_3-acylated [1,3,4]-oxadiazinan-2-ones.

The previous methodology developed for the acylation of the heterocycle required stoichiometric amounts of 4-(dimethylamino)pyridine (DMAP) and triethylamine, and required reflux conditions in dichloroethane.[4b] This methodology was replaced by the more effective approach of acylation with sodium hydride (NaH) or sodium hexamethyldisilazane (NaHMDS), followed by reaction with the desired acyl halide (Scheme 2).[7] Using this approach, oxadiazinan-2-one **1** was acylated to afford derivatives **2d**−**k** in 41−80% yield (Table 1).

TABLE 1. Synthesis of N_3-Acylated [1,3,4]-Oxadiazinan-2-ones 2d−k

entry	R =	reaction conditions	isolated yield (%)[a]	product
1	$-CH_2CH_2Ph$	NaH, CH_2Cl_2	63	**2d**
2	$-C(CH_3)_3$	NaH, dmf	41	**2e**
3	$-OCH_3$	NaH, dmf	75	**2f**
4	$-CH=CH_2$	NaHMDS, THF	50	**2g**
5	$-CH=CHCH_3$	NaHMDS, THF	71	**2h**
6	$-CH=CHPh$	NaHMDS, THF	80	**2i**
7	$-C(CH_3)=CH_2$	NaH, CH_2Cl_2	48	**2j**
8	$-C_6H_5$	NaH, CH_2Cl_2	76	**2k**

[a] Purification was achieved by either chromatography or recrystallization.

To further explore the conformational aspects of the N_3-acylated oxadiazinan-2-ones, **2b** (R = $-CH_2CH_3$)[4b] was converted into the corresponding trimethylsilyl enol ether **5**. It was not possible to synthesize the enol ether by direct treatment of **2b** with base [LDA, MHMDS (M = Li^+, Na^+, K^+), etc.]. In all cases, **2b** underwent acyl cleavage to afford parent heterocycle **1**. We were gratified to learn that inverse addition with trimethylsilyl chloride

(6) Trepanier prepared oxadiazinium salts earlier. Please see: (a) Trepanier, D. L.; Elbe, J. N.; Harris, G. H. *J. Med. Chem.* **1968**, *11*, 357. (b) Trepanier, D. L. Harris, J. N. U.S. patent 3,377,345, 1968; *Chem. Abstr.* **1969**, *70*, 78026c. We repeated the conditions using oxadiazinan-2-one **1** and obtained the oxadiazinium salt **4a** in 78% yield.

(7) Attempts to acylate or alkylate the parent heterocycle **1** were either marginally successful (5%) or unsuccessful when *n*-BuLi was employed.

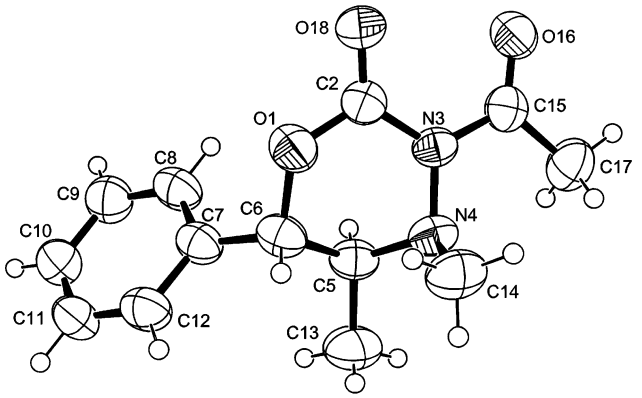


FIGURE 1. ORTEP diagram of **2a** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

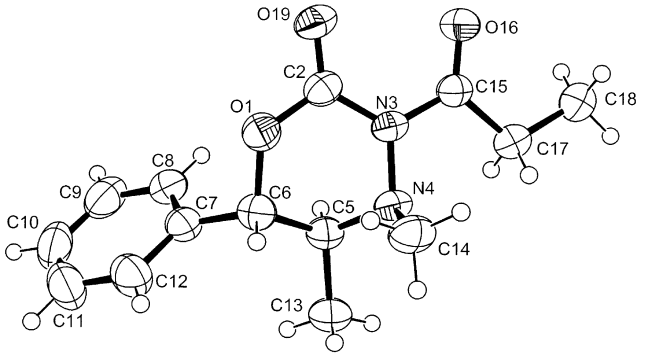
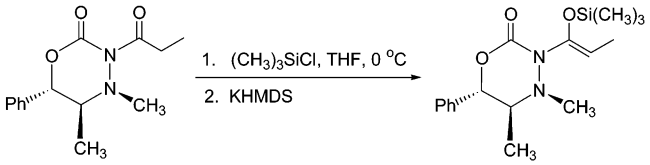


FIGURE 2. ORTEP diagram of **2b** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

SCHEME 3. Synthesis of Enol Silane 5



2b **5**

followed by KHMDS afforded **5** as the *Z*(O)-enolate as determined by ^{1}H NMR spectroscopy (Scheme 3).[8]

X-ray Crystallography.[9] Oxadiazinan-2-ones **2a** (R = −CH_3, Figure 1)[4b] and **2b** (R = −CH_2CH_3, Figure 2)[4b] were recrystallized to afford crystals suitable for X-ray diffraction studies.[9] The X-ray crystallographic structures revealed that the imide carbonyls in **2a** and **2b** are arranged in a parallel array that is slightly twisted out of plane as evidenced by the 3.1° and 3.3° torsion angles for [O(18)−C(2)/C(15)−O(16)] in **2a** and [O(19)−C(2)/C(15)−O(16)] in **2b**, respectively. This counterintuitive arrangement of the carbonyls in which the N_3- and the N_4-substituent are proximal may be the result of a repulsive interaction between the lone pair electrons of the N_3-carbonyl group and the lone pair electrons of the N_4-nitrogen.[10] Another argument for this parallel conformation would involve crystal packing forces. However, it appears unlikely that the orientation of the carbonyls is an artifact of crystal packing forces.[11] The closest intermolecular interactions in **2a** are H(8)−O(18), 2.59 Å, and H(11)−O(18), 2.60 Å, while the closest intermolecular interactions in **2b** are H(8)−H(18b), 2.38 Å, and H(11)−O(19), 2.58 Å. None of these intermolecular interactions would suggest that packing forces serve as an explanation of the conformation of the imide carbonyl moieties.

The near planarity of the carbonyls would indicate that there is significant resonance delocalization throughout the imide functionality. Due to the resonance interaction, the N_3-substituent is held rigidly in the plane, and as a consequence, the N_4-methyl group must adopt a position that is removed away from the allylic interaction. Based on this argument, the optimal position for the N_4-methyl group is the pseudoaxial position, although the ^{13}C NMR spectra would indicate that at room temperature multiple conformations are accessible in the solution state.

^{13}C NMR Investigation. The variable-temperature ^{13}C NMR data collected for oxadiazinan-2-ones **2a**−**d** and **2f**−**i** involved broadened signals that suggest that pyramidal inversion of the N_4-nitrogen is occurring at room temperature (Table 2). In contrast, oxadiazinan-2-ones **2e**, **2j**, and **2k** have ^{13}C NMR signals that are only marginally broadened at room temperature. It is postulated that the conformational differences between these two sets of heterocycles are made manifest by the combination of stereoelectronic effects of the N_3-substitutent. Chart 1 illustrates exemplary ^{13}C NMR spectra for oxadiazinan-2-ones **2d** (R = −CH_2CH_2Ph) and **2k** (R = −Ph).

Influence of N_3-Alkyl(alkenyl) Substituents. The N_3-alkyl-[1,3,4]-oxadiazinan-2-ones **3a**−**c** did not exhibit significant line broadening at room temperature or −50 °C. In contrast, oxadiazinan-2-ones **2a**−**c** exhibited considerable line broadening at room temperature. The X-ray diffraction studies of **2a** and **2b** revealed that the carbonyl of the N_3-acyl group is parallel and nearly coplanar with the urethane carbonyl of the ring system. It is likely that the conformation adopted in the solution phase also involves a significant resonance interaction between the carbonyls. Furthermore, the parallel arrangement may also be present in the solution phase.[12] The origin of the parallel orientation of the carbonyls may

(8) de Parrodi, C. A.; Clara-Sosa, A.; Pérez, L.; Quintero, L.; Marañón, V.; Toscano, R. A.; Aviña, J.; Rojas-Lima, S.; Juaristi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 69.

(9) Full details pertaining to data collection for **2a** and **2b** are collected in the Supporting Information along with tables of crystallographic details, atomic coordinates, bond lengths and angles, critical atom planes, torsional angles, anisotropic thermal parameters, and hydrogen atom parameters for **2a** and **2b** in CIF format.

(10) For examples of conformations determined by repulsive interaction between the lone pair of a carbonyl moiety and the lone pair of a nitrogen, see: (a) Weber, M.; Morgenstern, B.; Hegetschweiler, K.; Schmalle, H. W. *Helv. Chim. Acta* **2001**, *84*, 571. (b) Srivastava, A.; Srivastava, V.; Verma, S. M. *Ind. J. Chem., B* **1997**, *36*, 236.

(11) Oxadiazinan-2-one **2a** provided an X-ray crystal structure that reinforced the idea that the conformation adopted in the solid state was due to an electronic effect as the N_3-acyl unit involved only a methyl group and a carbonyl oxygen. These two groups are nearly isosteric but the carbonyl oxygen has two sets of nonbonding electrons that would have a repulsive interaction with the lone pair electrons of the N_4-nitrogen thus giving rise to the parallel array.

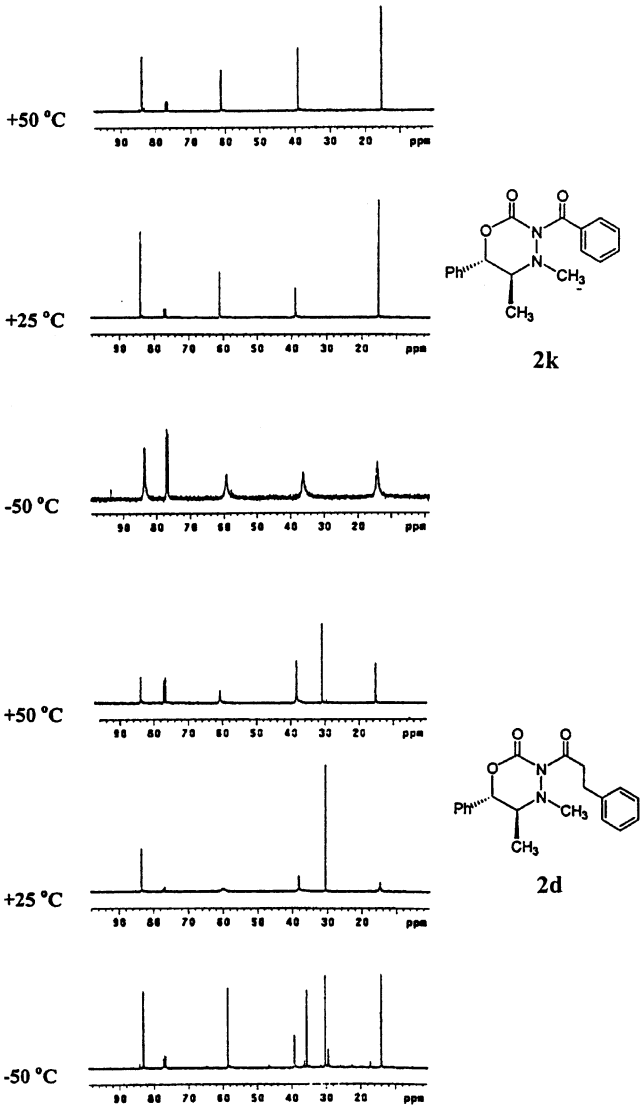
(12) Solvation phenomena must also be taken into account in arguments of the solution phase. We maintain that the conformation adopted in solution closely resembles that of the solid-state X-ray crystal structures based on observed signal broadening observed in oxadiazinan-2-ones **2d**−**k**.

TABLE 2. Collected ^{13}C NMR Spectra for [1,3,4]-Oxadiazinan-2-ones 2a−j

entry	compd	R =	N_4-methyl δ (ppm) t = 25 °C	appearance t = 25 °C	N_4-methyl δ (ppm) t = −50 °C	appearance t = −50 °C
1	**2a**[4b]	CH_3−	36.9	broadened	35.8[a]	sharp
2	**2b**[4b]	CH_3CH_2−	37.1	broadened	35.7$_a$	sharp
3	**2c**[4b]	$PhCH_2$−	37.3	broadened	35.9[a]	sharp
4	**2d**	$PhCH_2CH_2$−	38.2	broadened	38.2	sharp
5	**2e**	$(CH_3)_3C$−	37.8	sharp	38.0	broadened
6	**2f**	CH_3O-	38.0	broadened	35.8	sharp
7	**2g**	CH_2=CH−	37.9	broadened	36.1	sharp
8	**2h**	CH_3CH=CH−	38.4	broadened	38.1	sharp
9	**2i**	PhCH=CH−	38.4	broadened	36.2	sharp
10	**2j**	CH_2=C(CH_3)−	38.4	sharp	37.9	broadened
11	**2k**	Ph−	39.1	sharp	36.4	broadened

[a] The temperature of the NMR experiment was set at −35 °C for [1,3,4]-oxadiazinan-2-ones. See ref 4b.

CHART 1. ^{13}C NMR Spectra of [1,3,4]-Oxadiazinan-2-ones 2d and 2k



be the result of lone pair repulsion between the N_4-nitrogen and the N_3-acyl carbonyl oxygen. Alternatively, it is possible that this orientation is a manifestation of dipole minimization. *It is postulated that it is the parallel array and planarity of the N_3-acyl group that is responsible for the observable line broadening.* This argument is supported by the fact that trimethylsilyl enol ether **5** does not exhibit any line broadening in the ^{13}C NMR either at room temperature or at −50 °C whereas oxadiazinan-2-one **2b** does. The N_3-[1-trimethylsilyloxy-(*Z*)-propenyl] moiety is free to rotate and adopt a conformation that does not perturb the N_4-methyl substituent (Scheme 4). The N_3-alkyl substituents of **3a**−**c** most likely exhibit the same characteristic of conformational freedom to adopt a position that does not perturb the N_4-methyl substituent.

Influence of N_3-Acyl Substituents of Low Steric Demand. Oxadiazinan-2-one derivatives **2a**−**d** and **2f** have substituents that include $-CH_3$ (**2a**), $-CH_2CH_3$ (**2b**), $-CH_2Ph$ (**2c**), $-CH_2CH_2Ph$ (**2d**), and $-OCH_3$ (**2f**). Oxadiazinan-2-ones **2g**−**i** have substituents that are of the variety $-CH=CH_2$ (**2g**), $-CH=CHCH_3$ (**2h**), and −CH=CHPh (**2i**). When evaluated together, these substituents are similar in that they do not have high steric requirements. In fact, the room temperature ^{13}C NMR spectra of these heterocycles all share the common feature of broadened signals for the N_4-methyl group. This was especially true in the case of the hydrocinnamoyl derivative **5a** where line broadening was extensive enough so that some of the ^{13}C NMR signals were difficult to discern from the baseline until the temperature was lowered to −50 °C.[13] In fact, the ^{13}C NMR signal for the benzylic methylene ($-CH_2\mathbf{CH_2}Ph$) of the N_3-acyl group is one of the broadened signals. This evidence would support the close proximity of the N_3-acyl group and N_4-methyl group in the solution phase.

Influence of N_3-Acyl Substituents of High Steric Demand. Oxadiazinan-2-ones **2e** (R = $-C(CH_3)_3$), **2j** (R = $-C(CH_3)=CH_2$), and **2k** (R = $-C_6H_5$) did not exhibit significant line broadening features in their respective room temperature ^{13}C NMR spectra. However, when the temperature was lowered to −50 °C, the NMR signals began to undergo line broadening. These results suggested that the process of N_4-pyramidal inversion is facile at room temperature but is slowed at lower temperatures. This was in stark contrast to the oxadiazinan-2-ones where the N_3-acyl substituents had low steric demand. The steric requirements of the N_3-acyl substituents of **2e**,

(13) The hydrocinnamoyl derivative **2d** also has anomalous behavior at high temperature. At elevated temperatures (50 °C), the N_4-methyl signal is still significantly broadened.

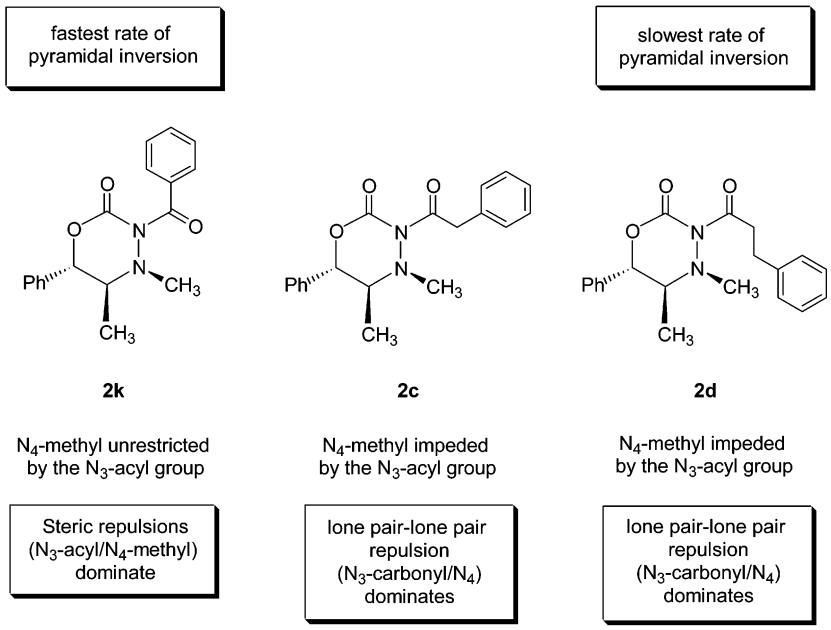
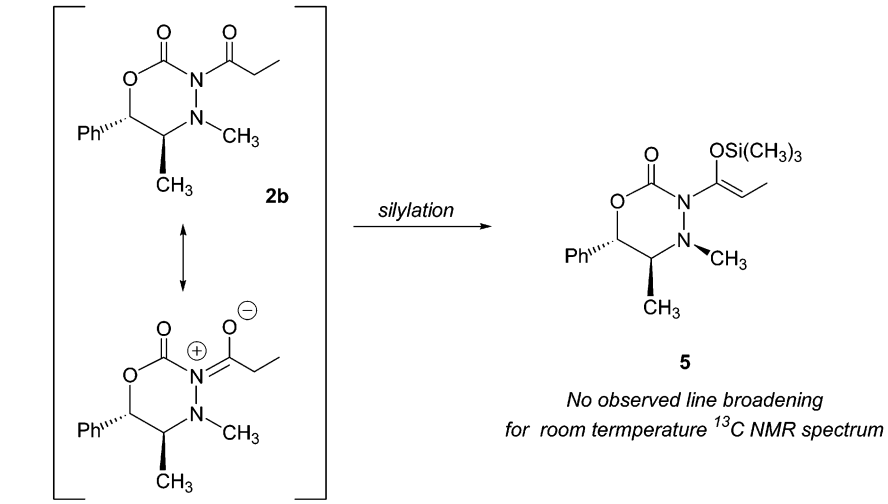


FIGURE 3. Conformational modes for N_3-substituted [1,3,4]-oxadiazinan-2-ones.

SCHEME 4. Conformational Freedom of the N_3-[1-Trimethylsilyloxy-(*Z*)-propenyl] Moiety



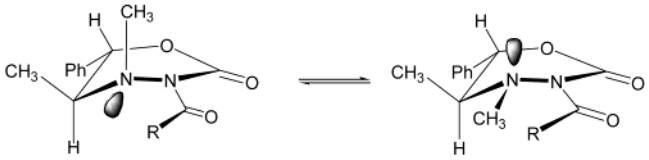
2j, and **2k**[14] are considerably greater than that of **2a**−**d**, **2f**, and **2g**−**i**, so that the conformational equilibria would no longer favor the parallel, coplanar array of the carbonyls where the N_3- and N_4-substituent are proximal.

Computational Studies.[15] The evidence collected from the variable-temperature ^{13}C NMR studies suggested that the dominant conformational event was pyramidal inversion at the N_4-nitrogen as this was the signal that was most broadened. The barrier to this inversion was investigated with oxadiazinan-2-ones **2a**, **2e**, **2f**, **2g**, **2j**, and **2k** using semiempirical AM1 calculations. In nearly all cases the calculated energies of the conformational structures most similar to those observed in the X-ray crystal studies were more stable than the conformation wherein the N_4-nitrogen had undergone pyramidal inversion. However, this difference was not substantial enough to warrant the clear dominance of one structure over another (Table 3). In addition, the barrier to the N_4-nitrogen inversion from the conformation observed in X-ray crystal studies was typically greater than the barrier for the reverse process. This result can be explained in the context of the conformational preference of the N_3-acyl group. The presumed parallel arrangement of the imide carbonyls in solution is most likely responsible for the observable line broadening wherein the heterocycle is engaged in complex confor-

(14) The aryl substituent is likely coplanar with the carbonyl. See: Leardini, R.; Lunazzi, L.; Mazzanti, A.; Nanni, D. *J. Org. Chem.* **2001**, *66*, 7879 and references therein.

(15) Full details including choice of method via correlation to X-ray crystallographic data of **2a** are collected in the Supporting Information.

TABLE 3. Calculated Barriers (kcal mol^{-1}) for Pyramidal Inversion



entry	R	compd	$\Delta H°_A$	$\Delta H°_B$	$\Delta H^{\ddagger}_{A\rightarrow B}$	$\Delta H^{\ddagger}_{B\rightarrow A}$
1	$-CH_3$	**2a**	−40.7	−34.0	10.5	3.8
2	$-OCH_3$	**2f**	−77.5	−74.9	8.0	5.3
3	$-CH{=}CH_2$	**2g**	−13.5	–	10.4	–
4	$-C(CH_3)_3$	**2e**	−51.3	−48.5	12.9	10.0
5	$-C(CH_3){=}CH_2$	**2j**	−20.2	−19.3	10.4	9.5
6	$-C_6H_5$	**2k**	−3.8	−3.8	9.8	9.8

[a] The entries denoted with "–" indicate conformations that could not be located using the AM1 method.

mational equilibria represented in part by the pyramidal inversion of the N_4-nitrogen.

The calculations appear to suggest that the energy barriers for the pyramidal inversions where the substituent is small ($-CH_3$, $-OCH_3$, $-CH{=}CH_2$) are on the same order as those where the substituent is large ($-C(CH_3)_3$, $-C(CH_3){=}CH_2$, $-C_6H_5$). This is counterintuitive as the ^{13}C NMR spectra indicated that the oxadiazinan-2-ones with N_3-acyl substituents of low steric demand have broadened signals at room temperature and sharpened signals at low temperature. In contrast, oxadiazinan-2-ones with large N_3-acyl substituents have signals that are not significantly broadened at room temperature but are considerably broadened at low temperature. This would suggest that when the substituent is large, the equilibrium between conformers is more rapid than when the substituent is small. A potential argument that unifies the results of the observed ^{13}C NMR data and the semiempirical AM1 calculations relies on the conformation of the N_3-acyl group. The conformational arrangement of parallel carbonyls adopted by **2a**−**d**, **2f**, and **2g**−**i** (small N_3-acyl substituents) would be costly in energetic terms for **2e**, **2j**, and **2k** (large N_3-acyl substituents). The result is that the large N_3-acyl groups would be driven from the parallel, coplanar conformation and into a conformation that must allow the N_4-methyl group to undergo inversion more readily. It is likely that the N_3-acyl group would adopt an *anti*-parallel arrangement with regard to the carbonyl moieties. Semiempirical AM1 calculations show that oxadiazinan-2-one **2e** (R = $-C(CH_3)_3$) would have the carbonyl moiety pointed in a direction that is 118° away from planarity. Figure 3 summarizes the conclusions drawn from the observed ^{13}C NMR spectra and the associated calculations.

Conclusions

In summary, we have synthesized a series of pseudoephedrine-based [1,3,4]-oxadiazinan-2-ones that have conformational properties that are dependent on the substituent at the N_3-position. X-ray crystallographic, variable-temperature ^{13}C NMR spectroscopic studies, and semiempirical AM1 calculations suggested that the conformation adopted by the oxadiazinan-2-ones is dependent on the balance between repulsive interactions. When the N_3-acyl group does not have high steric requirements, the parallel arrangement of the carbonyls is favored due to the repulsive force of lone pair electrons of the N_4-position and the N_3-acyl group carbonyl, although arguments for dipole minimization and solvation effects are also relevant. Conversely, when the N_3-acyl group has high steric requirements, the *anti*-parallel arrangement of the carbonyls is favored so that the N_3- and N_4-substituents are separated by the greatest distance.

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Supporting Information Available: Experimental details for compounds **2d**−**k**, copies of ^{1}H and ^{13}C NMR (25 and −50 °C) spectra for compounds **2d**−**k**, X-ray crystal data for compounds **2a** and **2b**, and semiempirical AM1 calculation methodology, as well as tables of crystallographic details, atomic coordinates, bond lengths and angles, critical atom planes, torsional angles, anisotropic thermal parameters, and hydrogen atom parameters for **2a** and **2b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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