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X-Ray crystallographic and ^{13}C nuclear magnetic resonance studies of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones derived from ephedrine and pseudoephedrine☆

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Abstract—3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones derived from (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine have been synthesized and their conformational properties have been examined. The ephedrine heterocycles **5**–**7a** appear to favor one set of equilibrating conformers while the pseudoephedrine heterocycles **5**–**7b** exist as multiple conformers at room temperature. The observed conformational behavior of these heterocycles is attributed to allylic strain and a gauche effect arising from the torsional energy barrier between the lone pair electrons of the N_3- and N_4-nitrogens.

1. Introduction

3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (**1**) represent a class of heterocycles that have received little attention in terms of their structural analysis and application in organic synthesis. In 1968, Trepanier disclosed one of the first reports on 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones in the synthesis of candidates for central nervous system stimulant activity.[1] In regard to their use in synthetic transformations, Husson and co-workers[2] successfully applied this heterocycle family in asymmetric dipolar cycloadditions[2a,b] and in diastereoselective alkylations.[2c] There is the possibility that these heterocycles may be further exploited in asymmetric synthesis. This heterocycle family can be considered to be nitrogen-homologs to the Evans's oxazolidinone chiral auxiliaries which have enjoyed much success since their initial development during the 1980s.[3]

We report on the preparation of a series of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones based on (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine and conformational analysis of these heterocycles. The data collected from X-ray crystallography, variable temperature ^{13}C NMR spectroscopy and semiempirical calculations suggest that the ephedrine and pseudoephedrine heterocycles are both involved in complex conformational equilibria. The ephedrine heterocycle equilibrium appears to favor one set of equilibria whereas the pseudoephedrine heterocycle equilibrium appears to have multiple conformers present at ambient temperatures. Ultimately, understanding the fundamental conformational dynamics of this ring system would enhance any investigations into their use as chiral auxiliaries (Fig. 1).

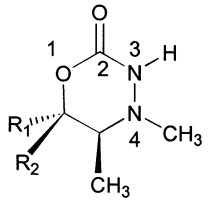

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Figure 1.

2. Results and discussion

2.1. Preparation of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones 1a and b

Both ephedrine (**2a**) and pseudoephedrine (**2b**) readily formed *N*-nitrosamines **3a** and **b** in yields of 95 and 97%, respectively, when treated with $NaNO_2$/HCl (Scheme 1).[4,5]

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Keywords: 3,4,5,6-tetrahydro-2*H*-oxadiazin-2-one; heterocycle; X-ray crystallography; allylic strain; conformation.

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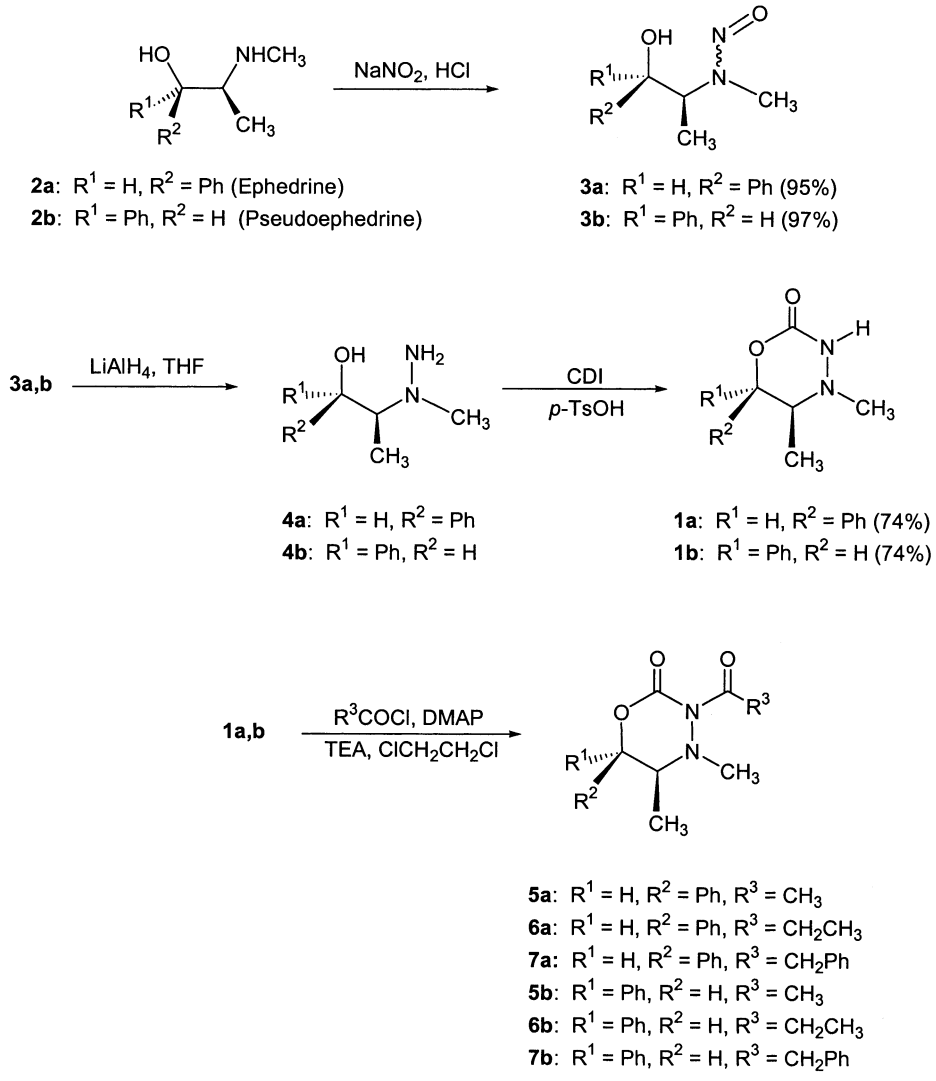


Scheme 1. Synthesis of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **5**–**7a** and **5**–**7b**.

The *N*-nitrosamines were reduced with lithium aluminum hydride in THF to afford the corresponding β-hydrazino-alcohols **4a** and **b**.[2b,6] The β-hydrazino-alcohols were treated with 1,1′-carbonyldiimidazole (CDI)[2b,7] to afford the 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **1a** and **1b** in 74% yield in each case. The heterocycles were treated with 4-dimethylaminopyridine (DMAP), triethylamine and an acyl chloride [(RCOCl; R=CH_3 (**5a**, **b**); R=CH_2CH_3 (**6a**, **b**); R=CH_2Ph (**7a**, **b**)] to generate the acylated oxadiazinones **5**–**7a** and **5**–**7b**. The acylated heterocycles were isolated in fair to excellent yield (43–95%) after purification by chromatography and recrystallization.

2.2. Examination of heterocycle 7a by X-ray crystallography

The structure of **7a** was determined by single-crystal X-ray diffraction (Fig. 2).[8] The crystallographic data revealed that the conformation of **7a** is that of a twist-boat with the N(4)-methyl and C(5)-methyl substituents oriented in a *trans* 1,2-diaxial arrangement as indicated by the 169.1(6)° dihedral angle [C(13)–C(5)–N(4)–C(14)]. The orientation of the N(4)-methyl group is likely a consequence of allylic strain[9] in conjunction with a gauche effect wherein the nitrogen substituents adopt positions that diminish any interaction between the lone pairs.[10,11] As a consequence of this ordering, the N_3-acyl group may be considerably distorted from the ideal planarity with the ring system.[12]

As illustrated by the ORTEP diagram, the phenylacetyl moiety lies in the plane of the heterocycle with the imide carbonyls oriented in the same direction.[13] This was unexpected as the related oxazolidin-2-one system typically exhibits the more stable dipole minimized *anti*-conformation in which the imide carbonyls are oriented in opposite directions.[14] Semiempirical calculations (vide infra) suggest that the barrier to interconversion between the *anti*- and *syn*-conformations has a range of 2.8–5.4 kcal/mol wherein the *anti*-conformer is the more stable of the two. This arrangement would be favored as it would reduce any allylic strain induced by the nearby N(4)-methyl group.

Attempts to grow crystals suitable for X-ray crystallographic analysis for the pseudoephedrine based heterocycles **5**–**7b** were unsuccessful. It is likely that the pseudoephedrine heterocycles also adopt a similar twist boat

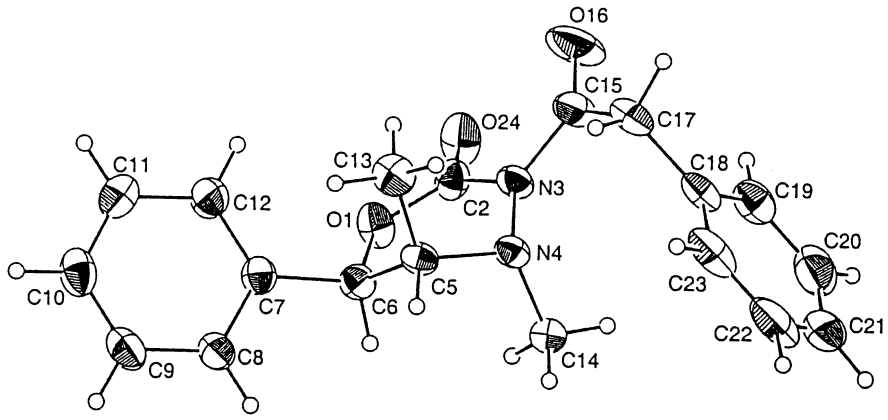


Figure 2. ORTEP diagram of **7a** (R=CH_2Ph), 30% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

conformation and contain considerable allylic stain arising from the proximity of the N_3- and N_4-substituents.

2.3. Examination of the acylated heterocycles by NMR spectroscopy

The collection of the ^{13}C NMR spectroscopic data for the ephedrine family of acylated heterocycles **5–7a** was straightforward and presented no difficulties. In contrast, the collection of ^{13}C NMR spectroscopic data for the pseudoephedrine series **5–7b** was not straightforward as some signals were significantly broadened (Table 1). There was also evidence of a broadened signal in the ^{1}H NMR spectra of pseudoephedrine derivatives **5–7b**. This signal was attributed to the C(5)-methine. The ^{13}C NMR resonance signals that were broadened were determined to be the methyl group appended to the N_4-nitrogen (–CH–N_4–*CH_3*), the methine group appended to the N_4-nitrogen (–*CH*–N_4–CH_3), the alpha carbon of the acyl group (–CO–*CH_2*R) and the urethane carbonyl group.[15] In contrast, the C-13 NMR spectrum of the *non-acylated* pseudoephedrine heterocycle **1b** does not have any resonance signals that are broadened. It stands to reason that the addition of the N_3-acyl substituent is primarily responsible for the observed conformational differences.

2.4. Variable temperature nuclear magnetic resonance studies of 5–7b

Katritzky[16] and Riddell[17] independently investigated the conformational behavior of the related ring system 3,4-dimethyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine. In the course of their variable temperature studies, they could not observe more than one discrete conformation even though there were changes in the peak shapes in the ^{1}H NMR spectra. A complex series of equilibria involving slow and fast processes was believed to be the cause of the observed phenomena. The evidence collected from this research suggested that 'passing ring inversion' was the process being observed.[17] In the case of the current family of pseudoephedrine heterocycles **5–7b**, the argument is made that there is a similar complex set of equilibria that gives rise to the broadened signals observed in the ^{1}H and C-13 NMR spectra.

In terms of the ^{1}H NMR spectra of **5–7b**, the only observable broadening was in the C(5)-methine proton at ambient temperatures. This NMR signal resolves to a doublet at −35°C. Interestingly, the C(5)-methine carbon shows virtually no sign of broadening in the ^{13}C NMR spectra of **5–7b**. The ^{13}C NMR signals **5–7b** were recorded at 50, 25 and −35°C (Table 1). The ^{13}C NMR spectrum of the propionyl pseudoephedrine heterocycle **6b** is exemplary (Fig. 3). As the temperature was increased to 50°C, the broadened signals began to resolve, although not completely. In contrast, when the temperature was lowered to −35°C, the signals became well resolved and new, smaller companion signals became apparent.

The N_4-methyl substituent (CH–N_4–*CH_3*) resonates at 36.9 ppm at 25°C. At −35°C, the same methyl group is represented by a signal at 35.8 and another smaller, broader signal at 46.7 ppm. The methine group appended to the N_4-nitrogen (*CH*–N_4–CH_3) resonates at 60.2 ppm at ambient

Table 1. 100 MHz ^{13}C NMR spectroscopic data for pseudoephedrine heterocycles **5–7b**

Substrate	Temperature (°C)	CH_3–CH–N–*CH_3*		CH_3–*CH*–N–CH_3		*CH_3*–CH–N–CH_3	
		Pseudoeq.	Pseudoax.	Pseudoeq.	Pseudoax.	Pseudoeq.	Pseudoax.
5b	−35	35.8	46.7 (broad)	58.8	64.9 (broad)	14.3	23.9
5b	25	36.9 (broad)	–	59.5 (broad)	–	14.3	–
5b	50	38.1 (broad)	–	60.6 (broad)	–	15.3	–
6b	−35	35.7	46.7 (broad)	58.8	65 (broad)	14.2	17.6
6b	25	37.1 (broad)	–	60.2 (broad)	–	14.9	–
6b	50	38.1 (broad)	–	60.6 (broad)	–	15.2	–
7b	−35	35.9	46.9 (broad)	59.1	65.6 (broad)	14.4	17.6
7b	25	37.3 (broad)	–	60.3 (broad)	–	14.9	–
7b	50	38.4 (broad)	–	60.9 (broad)	–	15.3	–

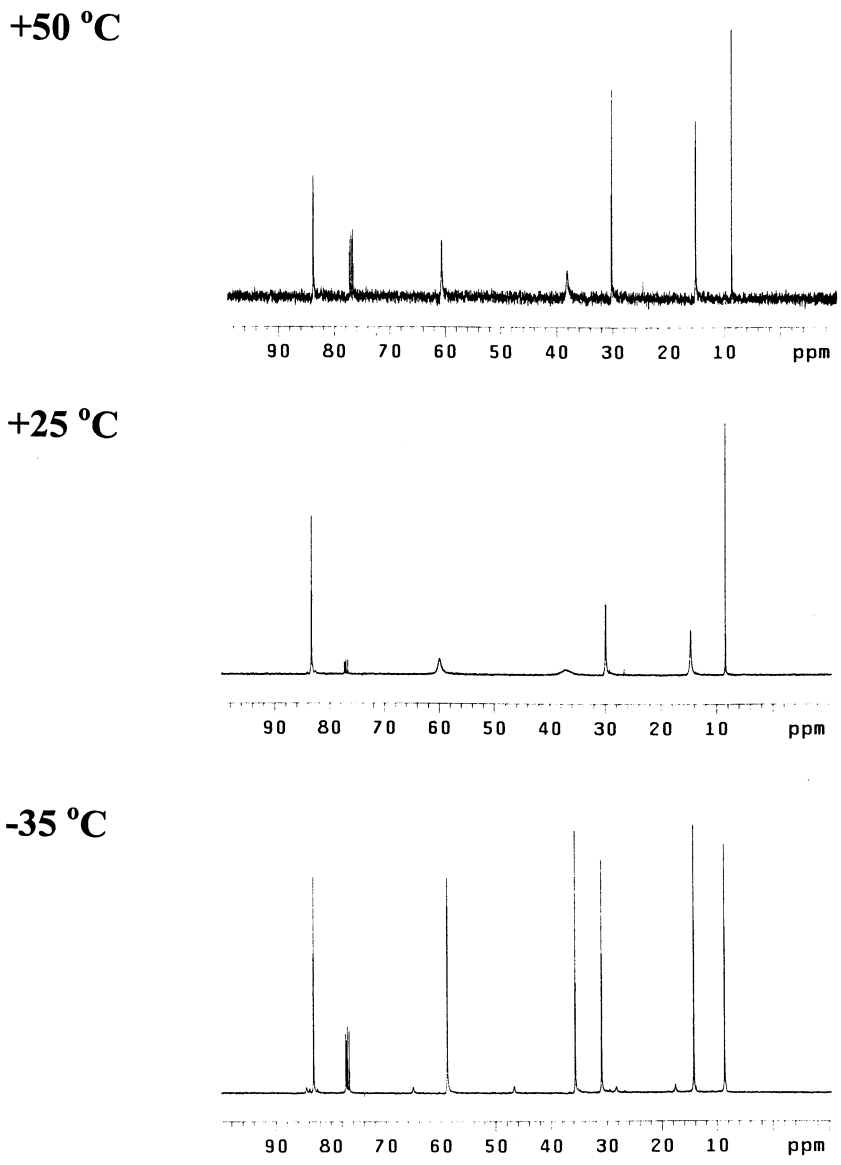


Figure 3. Comparative ^{13}C NMR temperature study for heterocycle **6b**.

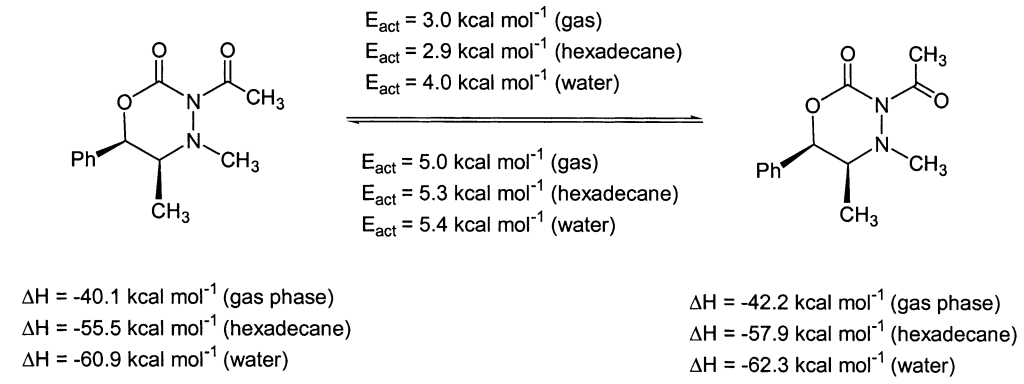
temperatures. However, when the temperature is lowered to −35°C, the same methine group is represented by a well-resolved signal at 58.8 ppm and a broadened signal at 65.0 ppm. The alpha carbon of the acyl group (–CO–CH_2R) also shows broadening but not to the same degree. The signal resolves easily when the temperature is reduced to −35°C. The urethane carbonyl NMR signal resonates at 148.3 ppm at 25°C and is significantly broadened. At lower temperatures, this signal resolves to a fine line width and occurs at 148.1 ppm. However, no companion peaks could be detected for the carbonyl. The companion signals are believed to be either too weak to observe or at nearly the same chemical shift.

Ephedrine based heterocycles **5**–**7a** were also investigated using variable temperature ^{13}C NMR. Heterocycle **6a** was cooled to −35°C and its ^{13}C NMR spectrum was recorded and no change in peak shape was observed. Warming the sample to 50°C did not significantly change the appearance of the spectrum. There was no change in peak shape to suggest that the ephedrine heterocycles exist in an equilibrium condition that is exactly the same as that of the pseudoephedrine

2.5. Semi-empirical calculations

In an effort to gain insight into the observed conformational changes in the pseudoephedrine heterocycles, AM1 semi-empirical calculations were carried out.[18] From the data collected, it was determined that the *anti*-orientation of the carbonyls was consistently more stable than the *syn*-orientation in the gas phase as well as in polar and non-polar media (Scheme 2). The barrier of interconversion between the two orientations ranges from 2.8 to 5.4 kcal mol^{-1}. Although interconversion between the two conformers can readily occur, these calculations would suggest that the solution phase of the heterocycles favor the presence of the *anti*-orientation.[13]

Charts 1 and 2 illustrate potential conformations **A**–**D**



Scheme 2. Carbonyl orientation for ephedrine heterocycle **5a**.

that exist for the ephedrine heterocycle **5a** and pseudoephedrine heterocycle **5b**. These charts describe two basic conformational changes that are believed to be key to understanding the oxadiazinone ring system. These changes are ring flipping (**A** to **C** and **B** to **D**) and pyramidal inversion about the N(4)-nitrogen (**A** to **B** and **C** to **D**).

For the ephedrine class of compounds, conformer **5a**-**D**, which corresponds to X-ray crystal structure **7a**, had the greatest stability based on the AM1 predictions. The calculated barriers for interconversion of **5a**-**D** to **5a**-**B** as well as **5a**-**A** to **5a**-**C** suggest that the process of ring flipping is facile and cannot be directly observed by ^{1}H or ^{13}C NMR spectroscopy. The energy barriers for the N_4-pyramidal interconversion of **5a**-**A** to **5a**-**B** and **5a**-**C** to **5a**-**D** suggest that this process is less facile than ring flipping. However, the calculated barriers to pyramidal inversion are not high enough to warrant the existence of **5a**-**D** as the only conformer.[19] The ^{1}H and ^{13}C NMR spectra coupled with the calculated barriers lead to a number of different conclusions: (a) there is free equilibration among all four conformers; (b) the heterocycle is frozen in conformation **5a**-**D**; (c) all four conformers are in equilibrium where the only experimentally observable conformations are **5a**-**D** and **5a**-**B** (via facile ring flipping). The conclusion adopted here is that

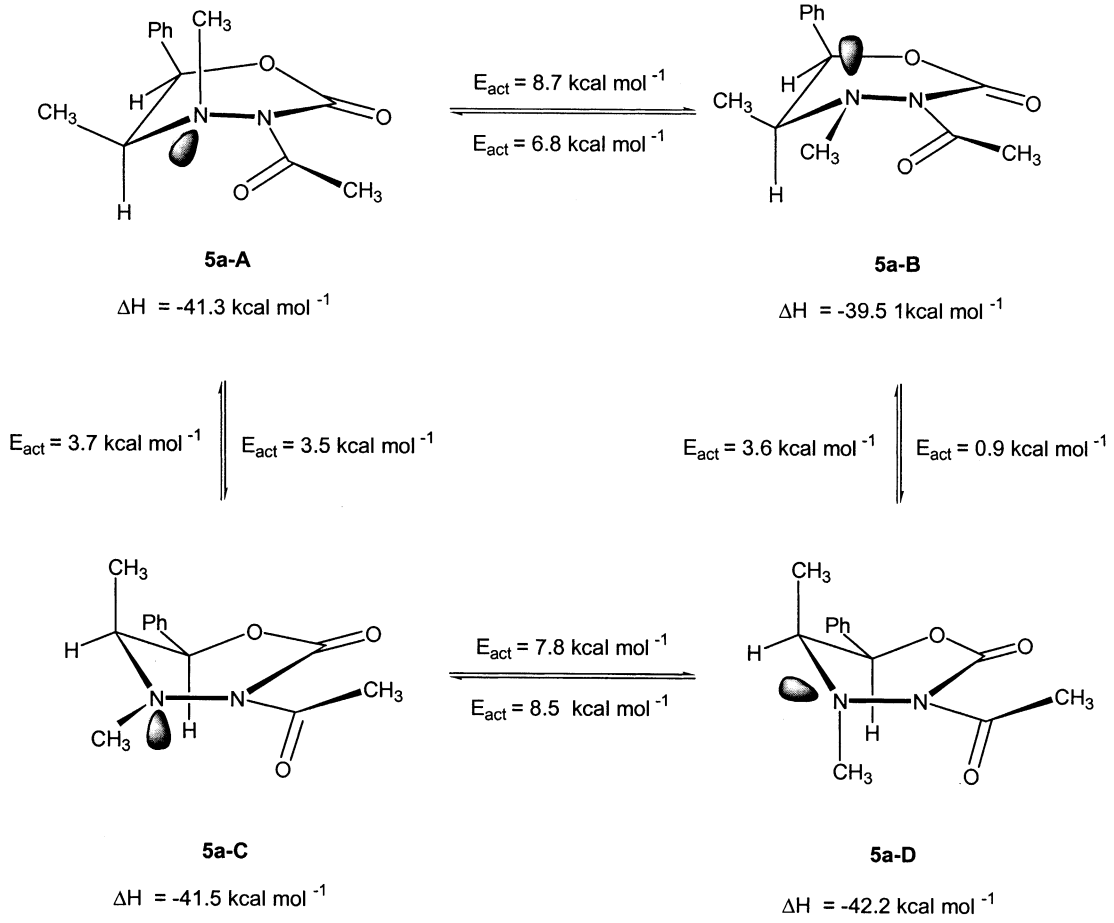


Chart 1. Potential conformations for ephedrine heterocycle **5a** (R=–CH_3).

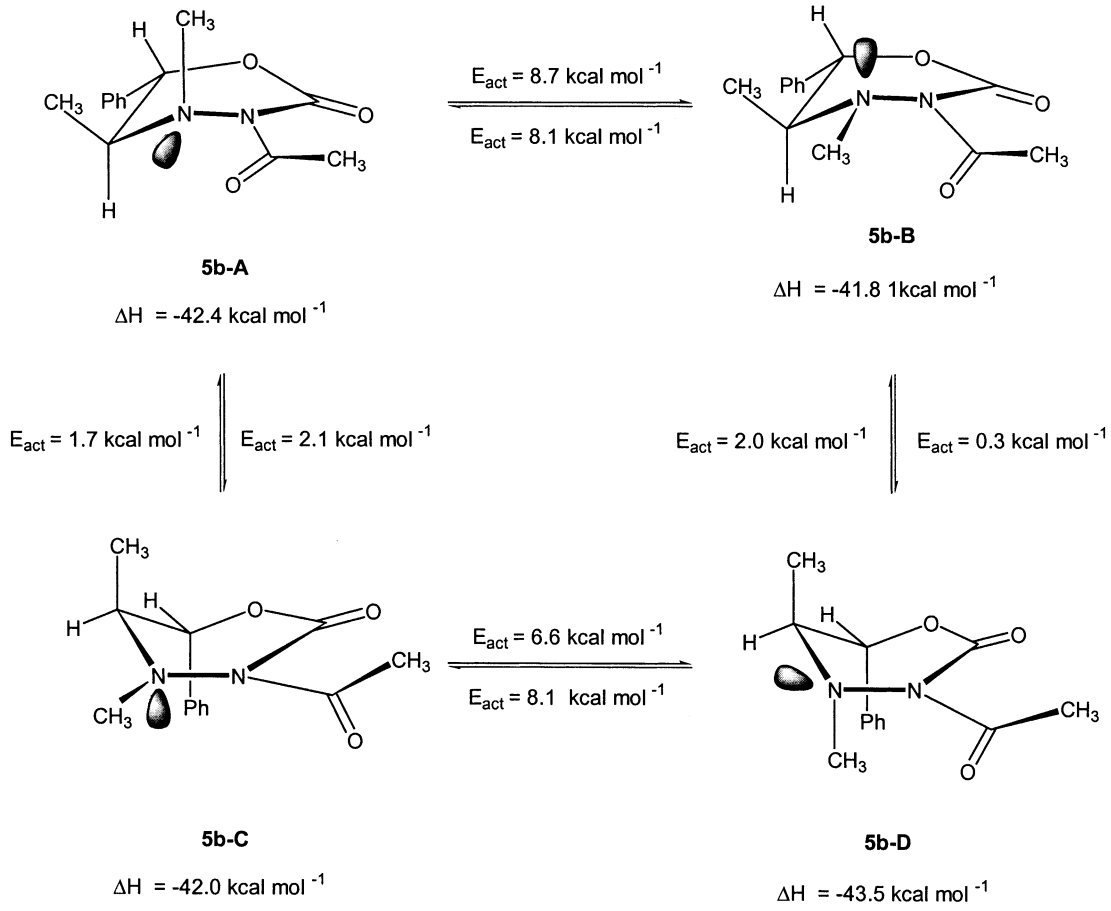


Chart 2. Potential conformations for the pseudoephedrine heterocycle **5b** (R=$-CH_3$).

there is equilibration between the conformers which marginally favors the thermodynamically more stable isomer **5a**-**D** which readily interconverts with **5a**-**B**.

The pseudoephedrine conformers **5b**-**A**–**D** have barriers for interconversion (ring flipping/pyramidal inversion) that are on the same order as the ephedrine derivatives. The conformer of highest stability predicted by AM1 calculations was determined to be **5b**-**D** conformer. However, based on the ^{1}H NMR spectra of pseudoephedrine heterocycles **5**–**7b** there is no direct evidence for the presence of conformer **5b**-**D** within the detection limits of the ^{1}H NMR spectrometer. The geometry of this conformer places the N(4)-methyl group in the region proximal the π-cloud of the aromatic residue at C(6). This would lead to a chemical shift of the N(4)-methyl group that would be highly shielded. In fact, the average chemical shift of the ephedrine and pseudoephedrine N(4)-methyl groups are at 2.97 and 2.85 ppm, respectively. This difference is not substantial enough to support the existence of conformer **5b**-**D** as the dominant conformation observed experimentally.

Calculations were also carried out to investigate the possibility of inversion at the N_4-nitrogen. The barriers for N_4-pyramidal inversion between the pseudoephedrine heterocycles **5**–**7b** are listed in Chart 2. These barriers are on the same level as that of the ephedrine heterocycles **5**–**7a** and similar ring systems.[20] The variable temperature ^{13}C NMR spectra would tend to support the idea that pyramidal inversion at the N(4)-nitrogen is the root cause of the observed line broadening. The barriers for ring flipping are too low (~2 kcal mol^{-1}) for such events to be observed. The change in position of the N_4-methyl group is more likely to be responsible for the observed signal broadening. The only ^{1}H NMR signal that is broadened is that of the C(5)-methine. If this substituent is in an environment where the N(4)-methyl is motion, then an averaged signal would be observed. In addition, the ^{13}C NMR signal that is most broadened is the N(4)-methyl substituent. The ^{13}C NMR signal for the alpha carbon of the acyl substituent is also broadened but to a smaller degree. Thus it would seem unlikely that free rotation of N(3)-acyl group is solely responsible for the observed signal broadening. The independent conformational factors active in the pseudoephedrine family cannot necessarily explain the observed phenomena. The origin of the line broadening observed in pseudoephedrine family most likely stems from a combination of factors including N(4)-pyramidal inversion, the conformational mobility of the N(3)-acyl group and other events that may have not been fully elucidated.

3. Conclusion

In summary, we have synthesized a series of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones from commercially available (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine.

Based on the evidence gathered from the ^{13}C NMR spectra, X-ray crystallography and semiempirical calculations, it appears that the ephedrine heterocycles exist in a complex equilibria that favors one set of conformers (**5a-B/5a-D**). The corresponding pseudoephedrine heterocycles exhibit a complex series of equilibria that involve free equilibration among all conformers. The conformation flexibility is most likely due to the combination of several factors including allylic strain and the gauche effect, dynamic mobility of the N(3)-acyl group and other molecular events yet to be recognized.

4. Experimental

4.1. Crystal structure determination of 7a[8]

A single crystal suitable for X-ray diffraction was obtained by layering an ethyl acetate solution of **7a** with hexanes. The colorless prismatic crystal was mounted on a glass fiber and used for data collection at 298 K on an Enraf-Nonius MACH3 automatic diffractometer, Mo Kα (λ=0.70930 Å). Cell constants and an orientation matrix for data collection were obtained by least squares refinements of the diffraction data from 25 reflections. **7a** was found to crystallize in the monoclinic crystal system with the following unit cell parameters: a=9.383(2), b=10.639(2), c=9.519(1) and β=116.72(1)°, Z=2. A total of 1719 reflections were collected of which 1575 were unique and 1113 were observed ($I>3\sigma I$).

Data reduction and refinement were performed using maXus 2.0 package of programs.[21] The space group was determined to be $P2_1$. The structure was solved with direct methods and all non-hydrogen atoms were refined with anisotropic temperature factors. The H atoms of CH were fixed at d=0.96 Å, allowed to ride on the C atoms and assigned fixed isotropic temperature factor, U=0.05 Å^2. Scattering factors are from Wassmaire and Kirfel.[22] Full-matrix least-squares refinement on F led to convergence with R=3.51% and wR=4.29%. A final difference Fourier synthesis showed features in the range of +0.11 to −0.12 eÅ^{-3}. Details of the X-ray data collection and of the crystal structure determination can be obtained from the Cambridge Crystallographic Data Center.[8]

4.2. General remarks

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium amalgam with benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. All reactions were run under a nitrogen atmosphere. Lithium aluminum hydride (LAH) was purchased from Aldrich chemicals. Flash chromatography was conducted with silica gel purchased from Selecto scientific (32–63 mesh). Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded at 25°C on a Varian spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). Tetramethylsilane (TMS) was used as an internal standard (δ=0.00 ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Low-resolution gas chromatography–mass spectrometry was performed on a Hewlett-Packard Instrument (G1800A/GCD) with an ionization voltage of 70 eV; peaks are reported as m/z (% intensity relative to the base peak). High-resolution mass spectra were obtained from the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign. The 70-VSE mass spectrometer used for sample analysis was purchased in part with a grant from the Division of Research Resources, National Institutes of Health (RR 04648). Elemental analyses were conducted by either Galbraith Laboratories, Inc. Knoxville, TN or by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

4.2.1. (1*R*,2*S*)–2-Amino-*N*-nitroso-*N*-methyl-1-phenyl-1-propanol (3a). This material was prepared as described in an earlier report.[4] Mp: 92–94°C (lit. mp: 92–94°C). R_f=0.55 (EtOAc–hexanes, 1:1). ^1H NMR ($CDCl_3$/TMS): 1.47 (d, 3H, J=7.0 Hz), 2.40 (bs, 1H), 2.96 (s, 3H), 4.69 (quintet, 1H, J=7.0 Hz), 5.07 (d, 1H, J=5.1 Hz), 7.35–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.4, 31.4, 65.3, 74.6, 126.4, 128.4, 128.8, 141.0.

4.2.2. (1*S*,2*S*)–2-Amino-*N*-methyl-*N*-nitroso-1-phenyl-1-propanol (3b). In a round bottom flask equipped with a stir bar was placed (1*S*,2*S*)-(+)-pseudoephedrine **3b** (20.0 g, 121 mmol) and THF (50 mL). An aqueous solution of HCl (50.8 mL, 2.74 M, 139 mmol) was then added followed by the addition of sodium nitrite (9.60 g, 139 mmol) in small portions over a period of 10 min. The reaction was stirred for 24 h and the cloudy mixture was then diluted with a saturated aqueous solution of sodium bicarbonate. The reaction mixture was then extracted with EtOAc (3×75 mL) and the extract was washed with a saturated aqueous solution of brine (50 mL). The resulting solution was dried (Na_2SO_4) followed by the removal of the solvent by rotary evaporation. This yielded a yellow solid which was recrystallized with EtOAc and hexanes to give **4b** as a yellow crystalline solid (22.9 g). Yield: 97%. Mp: 85–86°C. R_f=0.47 (EtOAc–hexanes, 1:1). ^1H NMR ($CDCl_3$): 1.29 (d, 3H, J=6.6 Hz), 2.44 (bs, 1H), 3.07 (s, 3H), 4.75–4.86 (m, 2H), 7.32–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): 16.0, 30.2, 65.1, 76.4, 126.8, 128.6, 128.9, 140.4. IR (KBr): 3480, 3032, 1465 (N=O stretch). m/z (EI): 107 (70, $M^+-C_8H_{11}$), 77 (35), 58 (100, $M^+-C_9H_{12}0$).

4.2.3. (1*R*,2*S*)-*N*-Amino-2-methylamino-1-phenyl-1-propanol (4a). In a flame-dried, nitrogen-purged 5 L, 3-neck round bottom flask fitted with an addition funnel and a condenser was placed lithium aluminum hydride (12.3 g, 325 mmol) and freshly distilled THF (300 mL). The mixture was then heated to reflux and (1*R*,2*S*)-*N*-nitrosoephedrine **3a** (21.0 g, 108 mmol), dissolved in freshly distilled THF (250 mL), was added slowly through the addition funnel for 30 min. Once the addition was completed, the reaction mixture was maintained under reflux for an additional 5 h. The reaction mixture was cooled to 0°C followed by the cautious addition of NaOH (6 M) until the remaining lithium aluminum hydride was consumed. The mixture was diluted with a saturated aqueous solution of sodium

potassium tartrate (Rochelle's salt, 150 mL) and stirred for 45 min. The mixture was then extracted with EtOAc (4×125 mL), washed with saturated aqueous brine solution (100 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation. This process afforded a viscous yellow oil that was determined to be ca. 95% pure by ^{1}H NMR spectroscopy (18.0 g). Yield: 93%. R_f=0.22 (EtOAc). ^{1}H NMR ($CDCl_3$): 0.83 (d, 3H, J=6.6 Hz), 2.59 (s, 3H), 2.76 (dq, 1H, J=6.8, 1.5 Hz), 5.21 (s, 1H), 7.21–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): 3.1, 48.7, 64.9, 77.7, 125.9, 126.70, 142.4. IR (KBr): 3313, 2978, 1046.

4.2.4. (1*S*,2*S*)-*N*-Amino-2-methylamino-1-phenyl-1-propanol (4b). (1*S*,2*S*)-*N*-Nitrosopseudoephedrine **3b** (22.9 g, 118 mmol) was treated in a similar fashion as **3a**. This process afforded the title compound as a viscous yellow oil (21.1 g). Yield: 99%. R_f=0.19 (EtOAc). ^{1}H NMR ($CDCl_3$): 0.79 (d, 3H, J=6.6 Hz), 2.58 (s, 3H), 2.63–2.69 (m, 1H), 4.42 (d, 1H, J=9.2 Hz), 7.27–7.38 (m, 5H). IR (neat): 3333, 2975, 754, 701. *m/z* (EI): 133 (1), 91 (5), 73 (100).

4.2.5. (5*S*,6*R*)-4,5-Dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (1a). In a flame-dried, nitrogen-purged 500 mL round bottom flask was placed (1*R*,2*S*)-ephedrine hydrazine **5a** (14.3 g, 79.4 mmol) and freshly distilled THF (200 mL). To this solution was added *p*-toluenesulfonic acid monohydrate (15.1 g, 87.4 mmol) and 1,1′-carbonyldiimidazole (14.2 g, 87.4 mmol). After the addition was completed, the resulting mixture was heated to reflux. The reaction mixture was cooled to room temperature after 3 h and an aqueous saturated solution of sodium bicarbonate (50 mL) was added. The resulting mixture was extracted with EtOAc (3×50 mL) and the extract was washed with saturated brine (50 mL), dried (Na_2SO_4), and the solvent was removed by rotary evaporation. This process yielded a yellow oil which was purified by column chromatography on silica gel (EtOAc, column dimensions=22×5 cm) to yield **1a** (12.1 g) as a white solid. Yield: 74%. Mp: 118–120°C. R_f=0.52 (EtOAc). ^{1}H NMR ($CDCl_3$): 0.93 (d, 3H, J=7.0 Hz), 2.89 (s, 3H), 3.13 (bs, 1H), 5.81 (s,1H), 6.88 (bs, 1H), 7.32–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.5, 46.5, 56.9, 74.1, 125.2, 127.9, 128.5, 136.2, 152.3. IR (KBr): 3228, 2943, 1686. *m/z* (EI): 118 (75), 91 (33), 77 (100). Anal. calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.10; H, 6.90; N, 13.51.

4.2.6. (5*S*,6*S*)-4,5-Dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine-2-one (1b). (1*S*,2*S*)-pseudoephedrine hydrazine **4b** (2.86 g, 15.9 mmol) was treated in a similar fashion as **4a**. This reaction yielded a yellow oil which was purified by column chromatography on silica (EtOAc, R_f=0.30, column dimensions=5×16 cm) to yield 2.40 g of the title compound as a white solid. Yield: 74%. Mp: 97–98°C; R_f=0.48 (EtOAc). ^{1}H NMR ($CDCl_3$/TMS): 1.03 (d, 3H, J=7.0 Hz), 2.78 (s, 3H), 3.32 (dq, 1H, J=10.1, 7.0 Hz), 5.34 (d, 1H, J=9.9 Hz), 7.32–7.42 (m, 5H) 7.45 (bs, 1H). ^{13}C NMR ($CDCl_3$/TMS): 13.9, 39.8, 58.4, 80.3, 126.8, 128.4, 128.7, 136.4, 152.9. IR (KBr): 3240, 1699, 755, 700. *m/z* (EI): 191 (19), 117 (19), 57 (100). HRMS calcd for $C_{11}H_{14}N_2O_2$ 206.1055, found 206.1051. Anal. calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 63.80; H, 6.69; N, 13.33.

4.3. (5*S*,6*R*)-3-Acyl-4,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (5a–7a) and (5*S*,6*S*)-3-acyl-4,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (5b–7b): typical procedure

In a flame dried, nitrogen-purged round bottom flask equipped with a reflux condenser and stir bar was placed ephedrine heterocycle **1a** (1.00 g, 4.86 mmol) and 4-(dimethylamino)pyridine (0.593 g, 4.86 mmol) followed by the addition of 1,2-dichloroethane (18 mL). Once the solids were dissolved triethylamine (1.35 mL, 9.72 mmol) were added. The acyl chloride (5.83 mmol) was added via syringe and the reaction mixture was heated to reflux and stirred for 15 h. The reaction mixture was then cooled to room temperature and was diluted with a saturated aqueous solution of sodium bicarbonate (50 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvents were removed by rotary evaporation to afford the title compound.

4.3.1. (5*S*,6*R*)-3-Acetyl-4,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (5a). The crude product was then purified by flash chromatography on silica (column dimensions: 14×5 cm, R_f=0.39, 55:45 hexanes/ethyl acetate, 42 fractions at 3 mL each) to yield 1.15 g of **5a**. Yield: 95%. Mp: 107–108°C. ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 3H, J=7.0 Hz), 2.59 (s, 3H), 2.97 (s, 3H), 3.41 (dq, 1H, J=7.0, 4.4 Hz), 6.05 (d, 1H, J=4.4 Hz), 7.28–7.42 (5H, m). ^{13}C NMR ($CDCl_3$) δ 12.6, 26.4, 43.5, 56.9, 78.1, 125.1, 128.4, 128.9, 135.8, 148.7, 170.9. IR (KBr) 2978, 1760, 1731 cm^{-1}. HRMS calcd for $C_{13}H_{16}N_2O_3$ 248.1161, found 248.1156. Anal. calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.87; H, 6.48; N, 11.14.

4.3.2. (5*S*,6*R*)-4,5-Dimethyl-6-phenyl-3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (6a). The crude product was recrystallized from hexanes/ethyl acetate to yield **6a** as white needles. Yield: 86%. Mp: 94–95°C; R_f=0.68 (EtOAc). ^{1}H NMR ($CDCl_3$): 0.85 (d, 3H, J=6.6 Hz), 1.20 (t, 3H, J=7.3 Hz), 2.97 (s, 3H), 2.97 (m, 2H), 3.41 (dq, 1H, J=7.0, 4.7 Hz), 6.04 (d, 1H, J=4.4 Hz), 7.29–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): 9.2, 12.6, 31.5, 43.5, 56.9, 77.9, 125.1, 128.3, 128.8, 135.9, 148.5, 174.7. IR (KBr): 3064, 2981, 1779, 1724 cm^{-1}. HRMS calcd for $C_{14}H_{18}N_2O_3$ 262.1317, found 262.1309. Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.10; H, 6.94; N, 10.68.

4.3.3. (5*S*,6*R*)-4,5-Dimethyl-6-phenyl-3-phenylacetyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (7a). Chromatography of the crude reaction mixture on silica (column dimensions: 14×5 cm, R_f=0.41, 65:35 hexanes/ethyl acetate, 79 fractions at 3 mL each, fractions 45–78 collected) afforded the title compound **7a**. Yield: 60%. Mp: 125–126°C. ^{1}H NMR ($CDCl_3$): 0.68 (d, 3H, J=7.0 Hz), 2.93 (s, 3H), 3.37 (dq, 1H, J=7.0, 4.4 Hz), 4.31 (*AB* spin system, 2H, $\Delta\nu$=35, J=15 Hz), 6.01 (d, 1H, J=4.8 Hz), 7.22–7.39 (m, 10H). ^{13}C NMR (75 MHz; $CDCl_3$): 12.4, 43.4, 44.1, 57.0, 78.0, 125.0, 127.2, 128.3, 128.5, 128.8, 129.6, 134.1, 135.7, 148.3, 172.0. IR (KBr): 2972, 1763 (broad C=O stretch) cm^{-1}. HRMS calcd for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1465. Anal. calcd for

$C_{19}H_{20}N_2O_2$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.00; H, 6.29; N, 8.53.

4.3.4. (5*S*,6*S*)-3-Acetyl-4,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (5b). Chromatography of the crude reaction mixture on silica (column dimensions: 12×5 cm, R_f=0.53, 50:50 hexanes/THF, 30 fractions at 3 mL each) afforded the title compound **5b**. Yield: 89%. Mp: 90.0–90.5°C. ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 3H, J=7.0 Hz), 2.55 (s, 3H), 2.79 (s, 3H), 3.32 (dq, 1H, J=7.0, 4.0 Hz), 5.21 (bs, 1H), 7.29–7.41 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 24.6, 36.9, 59.5, 83.0, 126.1, 128.1, 128.3, 135.3, 148.3, 169.5. IR (KBr) 2984, 1782, 1731, 1057 cm^{-1}. HRMS calcd for $C_{13}H_{16}N_2O_3$ 248.1161, found 248.1165. Anal. calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.82; H, 6.45; N, 11.18.

4.3.5. (5*S*,6*S*)-4,5-Dimethyl-6-phenyl-3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (6b). Chromatography of the crude reaction mixture on silica (column dimensions: 15×5 cm, R_f=0.28, 70:30 hexanes/ethyl acetate, 47 fractions at 4 mL each) afforded 1.52 g of the title compound **6b** as a viscous oil. Yield: 78%. ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, J=6.6 Hz), 1.19 (t, 2H, J=7.3 Hz), 2.78 (s, 3H), 2.86 (m, 2H), 3.30 (dq, 1H, J=6.6, 4.4 Hz), 5.24 (d, 1H, J=9.5 Hz), 7.29–7.42 (5H, m). ^{13}C NMR ($CDCl_3$) δ 8.9, 14.9, 30.3, 37.2, 60.2, 83.8, 126.7, 128.8, 129.3, 135.9, 148.8, 173.9. IR (KBr) 2981, 1780, 1726, 1209 cm^{-1}. *m/z* (EI): 206 (32), 118 (100), 91 (22), 77 (20). HRMS calcd for $C_{14}H_{18}N_2O_3$ 262.1317, found 262.1323.

4.3.6. (5*S*,6*S*)-4,5-Dimethyl-6-phenyl-3-phenylacetyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (7b). Chromatography of the crude reaction mixture on silica (column dimensions: 14×5 cm, R_f=0.19, 45:55 hexanes/ethyl acetate, 40 fractions at 4 mL each followed by 15 fractions at 50 mL each, fractions 46–55 collected) afforded 1.015 g of the title compound **7b** as a yellow oil. Yield: 43%. ^{1}H NMR ($CDCl_3$/TMS) δ 1.24 (d, 3H, J=7.0 Hz), 2.94 (s, 3H), 2.97 (s, 3H), 3.27 (dq, 1H, J=7.0, 2.9 Hz), 4.41 (*AB* spin system, 2H, $\Delta\nu$=57.5 Hz, J=14.7 Hz), 5.28 (bs, 1H), 7.26–7.28 (4H, m), 7.49–7.56 (6H, m). ^{13}C NMR ($CDCl_3$) δ 14.9, 37.3, 43.3, 60.3, 83.8, 126.5, 126.9, 128.4, 128.6, 129.0, 129.2, 133.8, 135.6, 148.6, 171.1. IR (KBr) 2981, 1775, 1722, 1207 cm^{-1}. Anal. calcd for $C_{19}H_{20}N_2O_2$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.38; H, 6.12; N, 8.70.

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