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Diazocinones: Synthesis and Conformational Analysis

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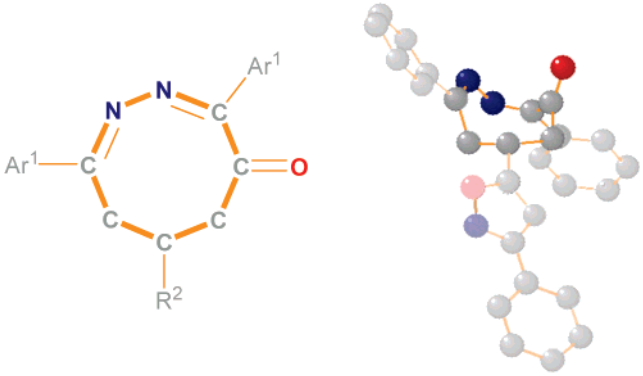

1,2,4,5-Tetrazines (prepared from aryl nitriles) condense with isoxazolylcyclobutanones (prepared from 3-benzenesulfonyl-3-vinylcyclobutanol) in methanolic KOH to give conformationally restricted 6-isoxazol-5-yl-6,7-dihydro-5*H*-[1,2]diazocin-4-ones. The solution ^{1}H NMR spectra of dihydrodiazocinone **1a** with phenyl moieties at C3 and C8 reveal two conformations of the eight-membered heterocycle that are non-interconverting on the NMR time scale at ambient temperature. The kinetics of the conversion process, followed by ^{1}H NMR between 21 and 70 °C in DMSO solution, yield an activation energy of ∼21 kcal/mol relative to the kinetic conformer and show an equilibrated ratio of ∼5:1 of the thermodynamic to the kinetic conformers. The electronic structure calculations on a model dihydrodiazocinone predict geometries for the two conformations. One of these geometries agrees with the X-ray crystallographic analysis of the thermodynamic conformation of **1a**.

Introduction

1,2,4,5-Tetrazines (**2**) are versatile precursors to semibullvalenes,[1a] homotropylidenes,[1b] diazanorcaradienes,[1c] tetraheterocyclic azepines,[1d] C60-monoadducts,[1e] azapagodanes,[1f] molecular clefts,[1g] isopyrazoles,[1h] as well as other aza-containing systems.[2] Furthermore, the various chemistries involved with 1,2,4,5-tetrazines are the subject of numerous theoretical

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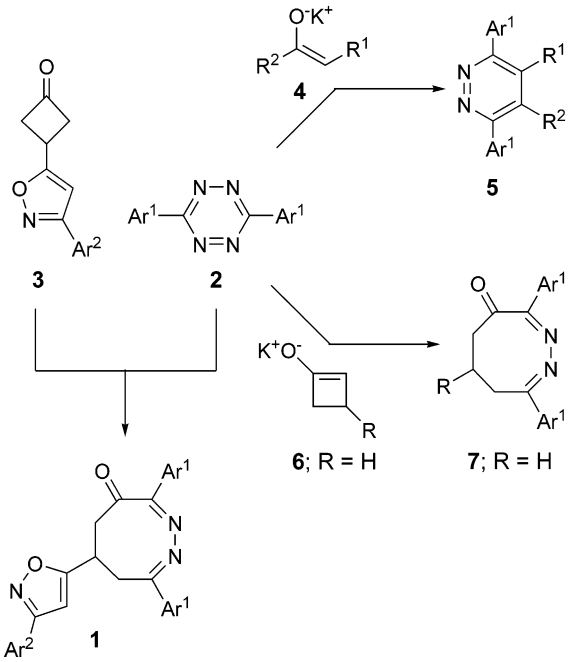
SCHEME 1. 1,2,4,5-Tetrazines as Precursors to Dihydrodiazocinone (7) and Isoxazolyl-Substituted Dihydrodiazocinone (1)



investigations.[3] In earlier work, as shown in Scheme 1, we reported that 1,2,4,5-tetrazines (**2**) condense with acyclic enolate nucleophiles (**4**) in prototic solvent to give, after nitrogen extrusion and dehydration, pyridazine **5**.[4a] Conversely, when the carbon nucleophile is derived from cyclobutanone (**6**), condensation is followed by nitrogen extrusion and [4.2.0] ring expansion to **7**.[4b]

The biological connotations[5] of cyclooctyl-based compounds coupled with the rich and diverse implications of cyclooctyl-based conformational effects[6] have interested us in both the chemistry and structural implications of modifying the condensation of 1,2,4,5-tetrazines **2** with enolate **6** (route to **7**) by placing a substituent on enolate **6** (R ≠ H). To avoid regiochemical issues, this R group is best placed at C3 of the enolate, which should then deliver **7** (via **2** + **3** → **7**) with the R group at C6, as depicted. Given our experience with various isoxazolylcyclobutanone syntheses,[7] we set out to prepare a series of novel isoxazolyl-substituted dihydrodiazocinones (**2** + **3** → **1a**−**h**; Figure 1) in the belief that the eight-membered ring diaza heterocycles would have relatively few low-energy, conformationally accessible states and, in turn, limited conformational flexibility, a concept that is important in understanding small molecule-receptor interactions.[8] If correct, the rigidity of the dihydrodiazocinone skeleton would cause the adorning functional groups (Ar^1 and R^2) to be displayed in reliable spatial arrangements about the eight-membered ring.

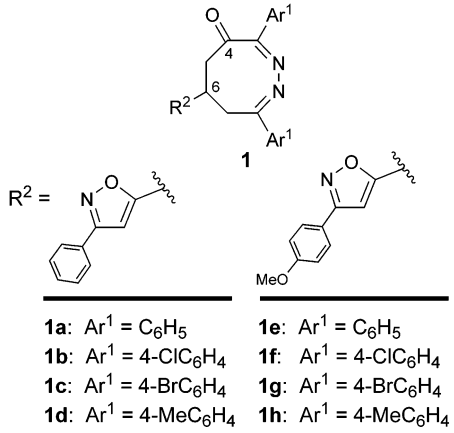


FIGURE 1. Synthesized dihydrodiazocinones **1a**−**h** were obtained in crude conformational ratios (kinetic vs thermodynamic) varying from ∼1:1 to ∼4:1.

Results and Discussion

Following literature methods,[4,5] the 1,2,4,5-tetrazine derivatives required for this study were prepared as depicted in Scheme 2. Aryl nitriles were treated with hydrazine and catalytic elemental sulfur in refluxing ethanol to give dihydro-[1,2,4,5]-tetrazines **8a**−**d**. These crude dihydro intermediates were subsequently oxidized with sodium nitrite in acetic acid to yield the vibrantly purple tetrazines **2a**−**d**.

Concurrently, the requisite isoxazolylcyclobutanones **3** were synthesized following protocols developed in our laboratory (Scheme 3).[7] Briefly, treatment of allyl phenyl sulfone with 2 equiv of *n*-butyllithium, followed by addition of epichlorohydrin, delivered 3-benzenesulfonyl-3-vinylcyclobutanol **9**. Next, employing the Huisgen method for in situ nitrile oxide generation (oxime + sodium hypochlorite),[9] the alkene moiety of **9** underwent a 1,3-dipolar cycloaddition to give **10** (phenyl- and 4-methoxyphenyl-oximes were employed). At this point, the cyclobutanol was oxidized to the cyclobutanone under Swern

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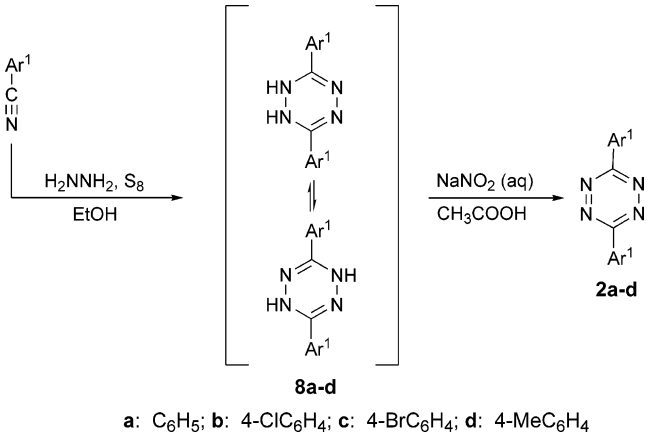
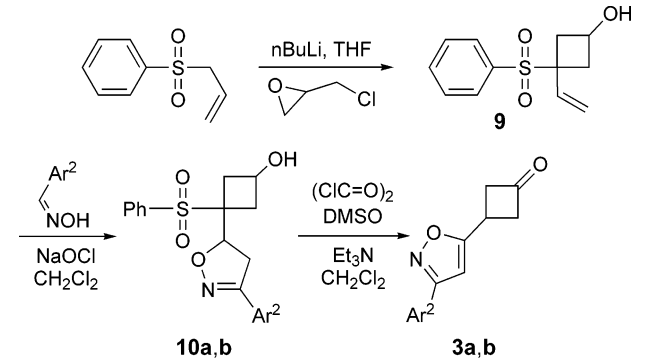
SCHEME 2. Tetrazine Synthesis

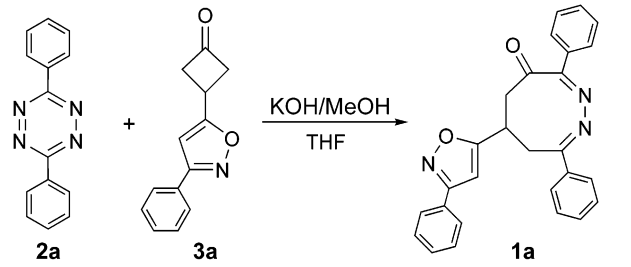


a: C_6H_5; **b**: 4-ClC_6H_4; **c**: 4-BrC_6H_4; **d**: 4-MeC_6H_4

SCHEME 3. Isoxazolylcyclobutanone Synthesis (a, Ar^2 = C_6H_5; b, Ar^2 = 4-$MeOC_6H_4$)



SCHEME 4. Synthesis of 6-Isoxazolyl-5*H*-[1,2]diazocin-4-one, 1a



conditions,[10] with concomitant base-mediated β-sulfinate elimination and isomerization of the cyclobutenone-isoxazoline to cyclobutanone-isoxazole, delivering (3-isoxazol-5-yl)cyclobutanones **3a** and **3b**.

With these tetrazines and cyclobutanones in hand, we turned our attention to creating the eight-membered dihydrodiazocinone ring systems and found that treating tetrazine **2a** with cyclobutanone **3a** in methanolic KOH in THF at room temperature gave dihydrodiazocinone **1a** in 62% yield (Scheme 4). Nitrogen evolution and the gradual discharge of the purple color of the tetrazine were indicators of the **2a** + **3a** → **1a** conversion. After completion, the reaction mixture was concentrated to remove THF, extracted with ethyl acetate, and purified by column chromatography. In similar fashion, dihydrodiazocinones **1b**−**h** were prepared in 35−62% yield.

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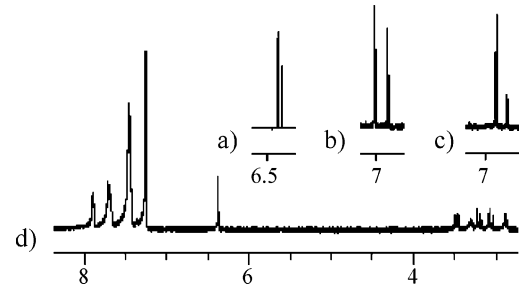

FIGURE 2. ^{1}H NMR data for dihydrodiazocinone **1a** ($J_{C4'H,C6H}$ = ~1 Hz). (a−c) Isoxazole peaks for **1a** at 25 °C ($CDCl_3$), 50 °C (DMSO-d_6), and 119 °C (DMSO-d_6), respectively. (d) Thermodynamic conformer isolated by recrystallization ($CDCl_3$).

The ^{1}H NMR spectrum of column chromatographed **1a** was suggestive of two conformations of the dihydrodiazocinone heterocycle, which were noninterconverting on the NMR time scale at ambient temperature. Indeed, this observation was strengthened by the doubling of signals in the ^{13}C NMR. The clearest indication that **1a** existed in two noninterconverting (NMR time scale) conformations was found in the proton data where two distinct singlets were observed for the proton at C4 of the isoxazole ring (viz., C4′H; Figure 2a, singlets at 6.34 and 6.38 ppm in $CDCl_3$; Figure 2b, singlets at 6.74 and 6.86 ppm in DMSO-d_6). That this doubling of signals is the consequence of conformational isomers as opposed to configurational isomers was established by variable temperature ^{1}H NMR experiments. Specifically, heating a 1.4:1 mixture of these isomers at 119 °C for 20 min led to the ^{1}H NMR spectrum depicted in Figure 2c, where the two conformations have equilibrated to a 10:1.8 mixture. Recrystallization of the crude reaction mixture (1.4:1 ratio) led to the isolation of the thermodynamic isomer in pure form (see Figure 2d).

We investigated the kinetics of this interconversion in DMSO-d_6 solution by monitoring the ^{1}H NMR signal of the C4′H of both conformers as a function of time at several temperatures, starting from a mixture rich in the kinetic conformer. No line broadening or evidence of an intermediate was seen in the NMR spectra. The results indicate a simple isomerization process wherein the conformers approach their equilibrium concentrations by a first-order process, with an observed rate of k_{obs} = $k_1 + k_{-1}$, where k_1 and k_{-1} are the rates for the forward and backward reactions, respectively. The latter rates are obtained from k_{obs}, given the equilibrium constant K = [thermodynamic]/[kinetic] = k_1/k_{-1}. Figure 3 (top and middle) shows the kinetic data at 21, 35, 50, and 70 °C as first-order plots of $\ln[R_t - R_\infty]$ vs time, where R = [kinetic]/{[kinetic] + [thermodynamic]}. The observed rates yield a kinetic to thermodynamic activation energy of ~21 kcal/mol (Figure 3, bottom). The equilibrium constant K does not change over the studied temperature range, within experimental uncertainties. Its value of ~10:2 indicates that the energies of the two conformers differ by ≤2 kcal/mol.

Coupling constants for the C6 methine proton to the adjacent C5 and C7 methylene protons in **1a** provide further conformational insight. These coupling constants (Table 1) indicate that the dihedral angles involving the methine proton and the adjacent methylene protons differ between the two conformers. This could result from conformer differences in the geometry of the dihydrodiazocinone ring and/or in the orientation of the isoxazole substituent (e.g., pseudo-equatorial or pseudo-axial orientation relative to the ring). To identify the explicit conformations of the eight-membered ring and the orientation of the

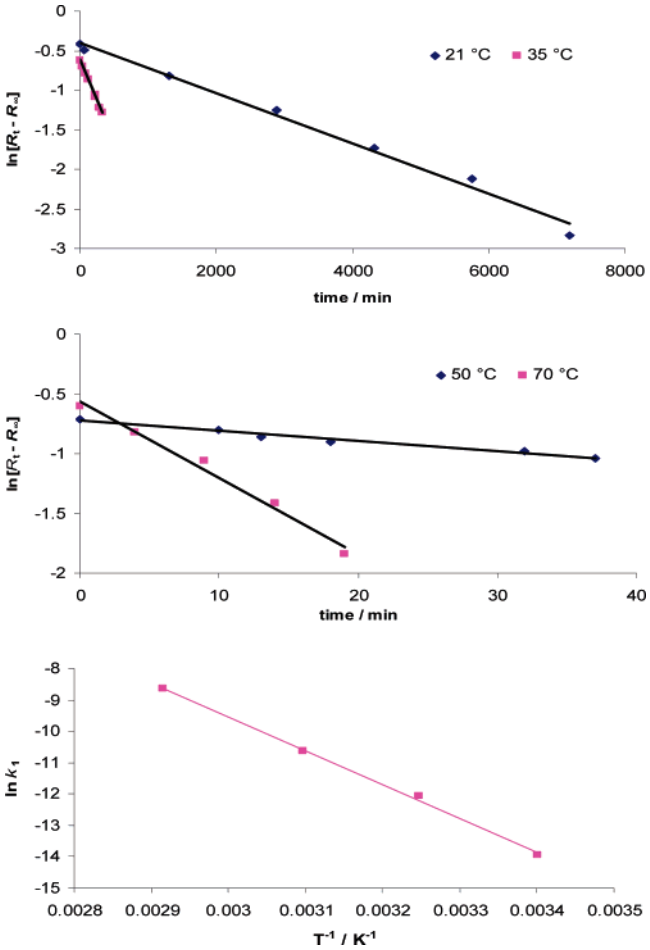

FIGURE 3. Plots of ln[$R_t - R_\infty$] vs time (top and middle), where R = [kinetic]/{[kinetic] + [thermodynamic]} at 21, 35, 50, and 70 °C, and of ln k_1 vs inverse temperature (bottom).

TABLE 1. Coupling Constants in Hz for the Proton(s) at C6[a] of the Dihydrodiazocinone

	H5a	H5b	H7a	H7b
Experimental				
thermodynamic conformer[b]	5.3	10.7	2.5	11.5
kinetic conformer[c]	11.8	3.7	1.0	3.5
Calculational				
thermodynamic conformer				
TBC (H6 ax)	5.23	11.58	1.25	11.53
TB (H6 eq)	5.97	3.11	7.05	11.52
kinetic conformer				
TB (H6 ax)	12.29	3.52	0.97	7.70
TBC (H6 eq)	2.18	6.99	7.05	1.34

[a] See TB and TBC structures in Figure 4 for H_a and H_b assignments. [b] H5 and H7 assignments based on HSQC, NOE, and ^{13}C chemical shifts. [c] H5 and H7 assignments based on the ^{13}C chemical shift correlation with the thermodynamic isomer.

C6-substituent, theoretical calculations were performed on the dihydrodiazocinone ring system.

Density functional theory calculations at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level were carried out on a model dihydrodiazocinone substituted with Ar[1] = R[2] = H (see **1** in Figure 1). The calculations show several conformations for the dihydrodiazocinone ring. The lower energy conformations have a cis,cis orientation of the two C=N double bonds. The cis,trans and trans,cis isomers are higher in energy by 7−15 kcal/mol. These results parallel the conformational isomerism in 1,3-cyclooctadiene, where the cis,cis isomer is considerably lower in energy than the cis,trans isomer.[11,12] Figure 4 shows the two conformations corresponding to energy minima and their relative energies for the cis,cis isomer of the model. These correspond roughly to the twist-boat (TB) and twist-boat-chair (TBC) conformations of *cis,cis*-1,3-cyclooctadiene, as described by Anet and Yavari.[11] The TB conformer is lower in energy by 1.5 kcal/mol in the model *cis,cis*-dihydrodiazocinone, whereas the TBC conformer is lower by 0.5 kcal/mol in *cis,cis*-1,3-cyclooctadiene. The structural parameters associated with the ring are given in Table 2 for the TB and TBC conformers of the model.

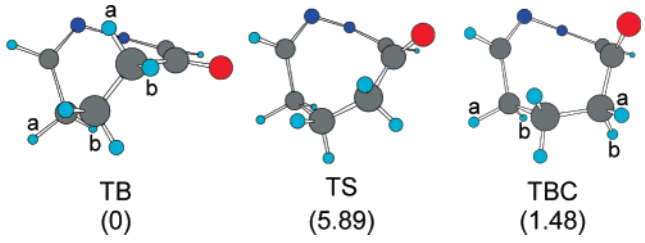

FIGURE 4. The two minimum energy (TB and TBC) conformers and the connecting TS found for the cis,cis isomer of **1a** with hydrogens in place of the aryl and isoxazolyl moieties. Energies in kcal/mol relative to TB are given in parentheses.

The two conformers are distinguished mainly by the dihedral angles. These angles for the five C−C single bonds of the ring (Table 2, D3−D7) alternate in sign for the TBC conformer but not for the TB conformer. The TBC conformer has near C_2 symmetry for the eight-membered ring, with the symmetry axis bisecting the N1−N2 and C5−C6 bonds. The TB conformer shows more extreme values for the internal ring angles: angle A7 is small at ∼109°, while angle A3 is large at ∼132°. Both the TB and TBC conformers are strongly twisted by ∼74° about the pair of C=N bonds. Although there are similarities in the geometries of these conformers and those of *cis,cis*-1,3-cyclooctadiene,[11,12] the detailed geometries of the dihydrodiazocinone and cyclooctadiene rings differ due to the shorter bonds for N relative to C and the influence of the carbonyl substituent (changed hybridization of C4).

A low-energy transition state (TS) connecting the TB and TBC conformers of this model was found at 5.9 kcal/mol above TB. The eight-membered ring has a rough boat conformation in the TS with a near C_2 symmetry axis bisecting the N1−N2 and C5−C6 bonds. The TS structure and its geometrical parameters are included in Figure 4 and Table 2, respectively. The near-degeneracy in the calculated energies of the TB and TBC conformers agrees with the small energy difference between the kinetic and the thermodynamic conformers implied by the equilibrium constant. However, the calculated energies of the conformers and the connecting TS imply a dynamic

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TABLE 2. Selected Interatomic Distances and Angles

parameter[a]		TB	TBC	TS	crystal[b]	parameter[a]		TB	TBC	TS	crystal[b]
					Bond Lengths/Ångströms						
B1	N1N2	1.353	1.368	1.371	1.389	B5	C5C6	1.549	1.546	1.558	1.544
B2	N2C3	1.285	1.278	1.278	1.279	B6	C6C7	1.558	1.553	1.552	1.554
B3	C3C4	1.507	1.523	1.517	1.517	B7	C7C8	1.501	1.510	1.501	1.511
B3*	C4O	1.221	1.213	1.217	1.212	B8	C8N1	1.282	1.280	1.281	1.293
B4	C4C5	1.522	1.526	1.537	1.514						
					Bond Angles/Degrees						
A1	C8N1N2	121.566	120.216	118.586	118.85	A6	C5C6C7	115.458	115.557	119.688	113.80
A2	N1N2C3	124.992	119.058	119.154	118.99	A7	C6C7C8	109.188	111.902	111.965	113.16
A3	N2C3C4	131.694	125.888	127.041	122.74	A8	C7C8N1	124.894	128.119	125.603	124.95
A4	C3C4C5	121.849	114.650	123.563	114.20	A4*(3)	C3C4O	116.796	122.149	117.316	122.90
A5	C4C5C6	114.976	113.866	125.175	110.60	A4*(5)	OC4C5	121.246	123.200	118.838	122.86
					Dihedral Angles/Degrees						
D1	C8N1N2C3	−73.901	−72.644	−75.460	−72.35	D4*	OC4C5C6	−110.619	100.101	164.131	93.215
D2	N1N2C3C4	10.472	6.722	0.177	5.70	D5	C4C5C6C7	−59.432	53.713	−5.992	51.98
D3	N2C3C4C5	7.090	90.228	72.421	97.91	D6	C5C6C7C8	−40.632	−78.514	−52.213	−81.45
D3*	N2C3C4O	−176.659	−90.833	−113.771	−80.65	D7	C6C7C8N1	83.614	88.876	91.685	91.93
D4	C3C4C5C6	65.468	−80.972	−22.149	−85.35	D8	C7C8N1N2	14.203	5.906	7.346	6.635

[a] See Figure 1 for atom numbering. [b] Average of the two molecules in the unit cell.

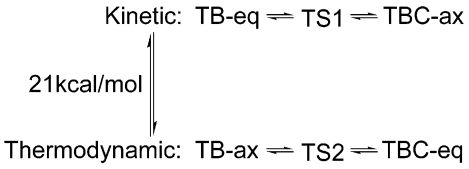

FIGURE 5. Schematic representation of the proposed interconversion between the kinetic and the thermodynamic conformers of the dihydrodiazocinone **1a**.

interconversion of the TB and TBC conformers at ambient temperature. We assume that this also holds for **1a**, even with the aryl and isoxazolyl substituents. Hence, the experimental kinetic and thermodynamic conformers cannot simply be TB and TBC conformers.

Because a substituent at C6 can assume a pseudoaxial or pseudoequatorial orientation relative to the ring, two distinct conformations for **1a** result for each of the model conformations (and TSs), depending on the orientation of the isoxazolyl substituent relative to the ring. A consideration of these geometries shows that the TB conformer with an *axial* substituent at C6 is connected by a TS to the TBC conformer with an *equatorial* substituent at C6. The energy difference between an axial or an equatorial substituent at C6 for a given conformer or TS is anticipated to be similar to the energy differences among unsubstituted TB, TBC, and TS structures. However, the conversion between the pseudoaxially (ax) and pseudoequatorially (eq) substituted isomers for a particular model conformer (TB or TBC) is expected to involve a high-energy TS. These ideas are shown schematically in Figure 5, where the top process can be associated with the kinetic conformer, and the bottom process can be associated with the thermodynamic conformer (vide infra).

The calculated coupling constants for the protons on C6 to the protons on C5 and C7 for the minimum-energy conformations of the model are included in Table 1, with the two protons on C6 in the model distinguished by their pseudoaxial or pseudoequatorial orientation relative to the ring. The best agreement between the calculated results for a single conformer and the experimental data occurs if the thermodynamic conformer is assigned to TBC with H6 axial (rms difference, 1.5 Hz), and the kinetic conformer to TB with H6 axial (rms difference, 4.2 Hz). These correspond to TBC-eq and TB-eq for **1a**, respectively, where ax and eq refer to the orientation of the isoxazolyl substituent at C6. Better agreement is obtained if the thermodynamic conformer is assigned as 0.85 TBC-eq and 0.15 TB-ax (rms difference, 0.55 Hz) and the kinetic conformer as 0.15 TBC-ax and 0.85 TB-eq (rms difference, 3.5 Hz), following the system proposed in Figure 5. The experimental and calculated coupling constants are in significantly better agreement for the thermodynamic conformer than the kinetic conformer and may be associated with a greater contribution of the axially substituted conformer in the kinetic isomer and/or the inherent dihedral angle changes implicated by placement of the isoxazole substituent in the TBC-ax, TB-ax, and TB-eq conformers. An equatorial orientation of the isoxazolyl substituent at C6 in TBC should not cause large changes in the dihedral angles at C6 compared to the corresponding angles of the model dihydrodiazocinone ring; consequently, the calculated coupling constants agree well with the experimental values. However, an axial orientation of the isoxazolyl substituent in TBC and either an axial or equatorial orientation of the substituent in TB should cause greater geometry changes; consequently, the coupling constants calculated for the unperturbed dihydrodiazocinone ring show poorer agreement with experiment.

Finally, X-ray crystallography analysis of **1a** yields the TBC-eq conformation (Figure 6), in agreement with the major contributor of the thermodynamic conformer. The data in Table 2 show that the calculated internal ring bond distances, bond angles, and dihedral angles in the model are in good agreement with the crystallography results. The average rms differences are 0.009 Å, 1.6°, and 3.8°, respectively.

Conclusions

We have achieved a general route to novel isoxazole-substituted dihydrodiazocinones (**1**), which proceeds by the condensation of tetrazines (**2**) with cyclobutanones (**3**) in methanolic KOH in THF at room temperature. These eight-membered ring diaza heterocycles exist in relatively few low-energy, conformationally accessible states and experience limited conformational flexibility. Conformational analyses of these dihydrodiazocinones by spectral, crystallographic, kinetic,

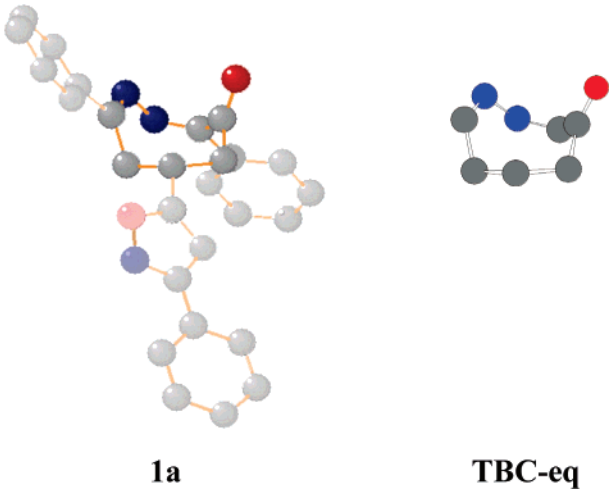

FIGURE 6. X-ray crystal structure of the thermodynamic conformer of **1a** and, for comparison, the calculated structure of the model TBC-eq.

and computational means allow us to confidently assign the conformation TBC as the major contributor to the thermodynamic isomer.

Experimental Section

5-(1-Benzenesulfonyl-3-hydroxycyclobutyl)-3-phenyl-4,5-dihydroisoxazole (10a). The allylcyclobutanol **9** (1.5 g, 6.25 mmol) and benzaldehyde oxime (3.025 g, 25 mmol) were dissolved in CH_2Cl_2 (60 mL) at 0 °C, and aqueous NaOCl (35 mL, 25 mmol, 5.25% of solution) was added dropwise with stirring at 6 drops/sec. The solution was warmed to room temperature overnight, and the organic layer was separated, dried ($MgSO_4$), vacuum filtered, and concentrated. The crude reaction mixture was recrystallized from ethyl acetate and hexanes to yield **10a** as a white powder (1.4 g, 60% yield): mp 170−171 °C; IR (neat) 1445, 1302, 1245, 1130, 1147; ^{1}H NMR δ 2.58−2.64 (m, 2H), 2.76−2.83 (m, 2H), 3.42−3.45 (d, 2H, J = 9.9 Hz), 4.37−4.41 (m, 1H), 4.64−4.68 (t, 1H, J = 9.9 Hz), 7.38−7.44 (m, 4H), 7.60−7.65 (m, 2H), 7.71−7.75 (m, 2H), 7.88−7.90 (dd, 2H, J = 1.3, 8.4 Hz; d, 1H), 5.32 (d, 1H), 5.91 (m, 1H), 7.53 (m, 2H), 7.59 (t, 1H), 7.78 (d, 2H); ^{13}C NMR δ 136.1, 134.8, 130.8, 129.8, 129.7, 129.1, 128.8, 127.0, 62.1, 61.8, 38.4, 38.2, 33.6.[7]

5-(3-Oxocyclobutyl)-3-phenylisoxazole (3a). Oxalyl chloride (284 μL, 24 mmol) and DMSO (520 μL, 6.75 mmol) were dissolved in CH_2Cl_2 (20 mL) with stirring at −78 °C for 40 min. In 10 mL of CH_2Cl_2, cyclobutanol **10a** (1.0 g, 2.7 mmol) was added dropwise to the solution and stirred for 15 min, followed by the addition of Et_3N (1.87 mL, 13.5 mmol). The reaction was monitored by TLC (50% EtOAc in hexanes) and quenched by the addition of water after 20 min. The organic layer was diluted with CH_2Cl_2, and the aqueous layer was washed once with 60 mL CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), vacuum filtered, and concentrated. The crude material was purified by column chromatography (50% EtOAc in hexanes) to give the isoxazolylcyclobutanone **3a** (470 mg, 75%): mp 95−96 °C; IR 1783, 1442, 1290; ^{1}H NMR δ 3.49−3.57 (d, 4H), 3.82 (m, 1H), 6.43 (s, 1H), 7.42 (d, 2H), 7.44 (t, 2H), 7.8, (t, 1H); ^{13}C NMR δ 203.9, 174.21, 162.9, 130.4, 129.2, 126.9, 99.3, 53.7, 21.6.[7]

General Route to Dihydrodiazocinones: 3,8-Diphenyl-6-(3-phenylisoxazol-5-yl)-6,7-dihydro-5*H*-[1,2]diazocin-4-one (1a). Cyclobutanone **3a** (0.1 g, 0.46 mmol) and tetrazine **2a** (0.109 g, 0.46 mmol) were dissolved in THF. To this solution was added KOH/MeOH (1.5 equiv), and the resulting mixture was stirred at room temperature for 3 h. The workup consisted of a dilution with ethyl acetate (40 mL) and washing sequentially with water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (hexanes/ethyl acetate, 9:1) and recrystallized from MeOH to give compound **1a** (0.116, 62%): mp 125−126 °C; IR (neat) 1714, 1599, 1428, 1252 cm^{-1}; ^{1}H NMR δ 2.86−2.90 (dd, 1H, J = 5.3, 12.3 Hz), 3.05−3.11 (dd, 1H, J = 10.4, 12.5 Hz), 3.17−3.23 (dd, 1H, J = 10.9, 13.2 Hz), 3.28−3.35 (m, 1H), 3.46−3.51 (dd, 1H, J = 2.56, 13.4 Hz), 6.37−6.38 (d, 1H, J = 1 Hz), 7.44−7.46 (m, 9H), 7.66−7.71 (m, 4H), 7.87−7.89 (m, 2H); ^{13}C NMR δ 203.8, 173.3, 162.9, 153.6, 150.4, 135.0, 131.4, 131.2, 130.8, 130.5, 129.4, 129.2, 129.0, 128.8, 127.5, 127.2, 127.0, 99.6, 45.2, 31.244, 31.1. ESI MS (M + H) *m*/*z* calcd, 419.16; found, 420.08. Purity was determined to be 95% by HPLC analysis on the basis of the absorption at 220 nm.

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Supporting Information Available: Detailed experimental procedures for **2a**−**d**, **3b**, **9**, **8a**−**d**, and **10b**, spectra for **1a**−**h**, **3a**, and **10a** (^{1}H NMR, ^{13}C NMR, and HPLC), crystallographic data for **1a**, and details of the electronic structure calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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