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Conformation Analyses, Dynamic Behavior and Amide Bond Distortions of Medium-sized Heterocycles. 1. Partially and Fully Reduced 1-Benzazepines

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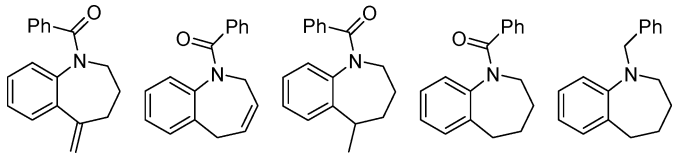

Five 1-benzazepine heterocycles were synthesized by utilizing transition-metal-catalyzed processes in key bond-forming steps. *exo*-Methylene and methyl substituents were introduced at position 5, as well as a unit of unsaturation between positions 3 and 4, with benzoyl or benzyl *N*-substituents. Solution- and solid-state structures were examined, using dynamic NMR spectroscopy and X-ray crystallography, corroborated by molecular mechanics calculations. Greater amide distortion is associated with a more stable ground-state structure, which is in turn more reluctant to undergo conformational changes.

Introduction

Broadly termed as benzazepines, benzo-fused seven-membered nitrogen heterocyclic rings are interesting structural motifs in medicinal chemistry. In recent years, 2,3,4,5-tetrahydro-1-benzazepines of types **I**[1] and **II**[2] (Figure 1) have been identified as orally active, highly potent selective nonpeptide agonists for the arginine vasopressin (AVP) V_2 receptor, which may be used in the treatment of certain diabetic conditions.[3] Subsequent

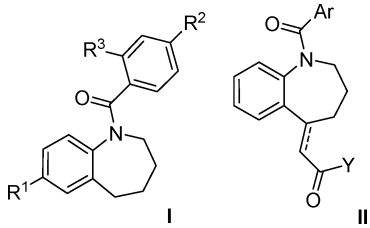

FIGURE 1. Biologically active 1-benzazepine structures.

SAR studies have revealed key structural features that are important for high potency and selectivity: (1) the presence of a *N*-benzoyl functionality; (2) a fully saturated aliphatic ring, and (3) substitution at benzylic carbon-5, which may contain an exocyclic double bond. These uniquely combine to confer a distinct conformation in the core structure, permitting highly selective binding with the receptor site.

The reactivity of benzazepine rings may also be dictated by their conformations. In an elegant study correlating the structure, chemical and cytotoxic activities of CC-1065 and Duocarmycin analogues, *N*-acylation of a 1-benzazepine intermediate was found to be dependent on the degree of hybridization at the remote carbon-5.[4]

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(1) Kondo, K.; Ogawa, H.; Shinohara, T.; Kurimura, M.; Tanada, Y.; Kan, K.; Yamashita, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Mori, T.; Tominaga, M.; Itai, A. *J. Med. Chem.* **2000**, *43*, 4388−4397.
(2) Matsuhisa, A.; Kikuchi, K.; Sakamoto, K.; Yatsu, T.; Tanaka, A. *Chem. Pharm. Bull.* **1999**, *47*, 329−339.
(3) (a) Kondo, K.; Kan, K.; Tanada, Y.; Bando, M.; Shinohara, T.; Kurimura, M.; Ogawa, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Kido, M.; Mori, T.; Tominaga, M. *J. Med. Chem.* **2002**, *45*, 3805−3808. (b) Kondo, K.; Ogawa, H.; Yamashita, H.; Miyamoto, H.; Tanaka, M.; Nakaya, K.; Kitano, K.; Yamamura, Y.; Nakamura, S.; Onogawa, T.; Mori, T.; Tominaga, M. *Bioorg. Med. Chem.* **1999**, *7*, 1743−1754. (c) Kondo, K. *Expert Opin. Ther. Pat.* **2002**, *12*, 1249−1258.

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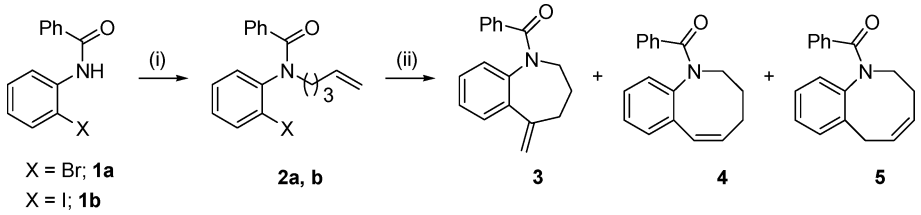
SCHEME 1. Synthesis of Benzazepine via Intramolecular Heck Reaction[a]



[a] Reagents and conditions: (i) (a) NaH, THF, rt, 3 h, (b) CH_2=$CH(CH_2)_3OTs$, reflux, 2−3 h; (ii) intramolecular Heck reaction (Table 1).

Herein, we report our studies on a series of benzazepine structures, introducing units of unsaturation, as well as specific substituents at the heteroatom and position-5. The conformation and dynamic behavior of these heterocycles were examined using a combination of dynamic NMR spectroscopy and X-ray crystal structure analysis. The results were corroborated by molecular mechanics calculations.

Results and Discussion

Synthesis. Previously, we reported an expedient synthetic route to 1-benzyl-2,3,4,5-tetrahydro-benzazepines, including nonbulky alkyl and aryl substituents at position-2 of the heterocyclic ring.[5] Herein, complementary methodologies for the synthesis of five 1-benzazepine structures from *N*-(2-iodophenyl)-benzamide **1** are described, utilizing transition-metal-catalyzed reactions for the formation of key carbon−carbon bonds (Scheme 1).

Intramolecular Heck arylation was first explored for the construction of the seven-membered ring structure.[4] Following alkylation of the *N*-2-(halo)phenyl-*N*-benzamides **1** (X = Br, I) with pent-4-enyl-4-toluenesulfonate, the products **2** were subjected to palladium catalysis, giving a mixture of 7-*exo* and 8-*endo-trig* cyclization products.[6]

The distribution of products was found to be dependent on the conditions under which palladium catalysis was effected (Table 1). The aryl bromide precursor required an elevated reaction temperature of 140 °C for cyclization to proceed, affording the 7-*exo-trig* product **3** in modest yield (entry 1). Replacement of triphenylphosphine with bidentate phosphine ligands led only to a decrease in the yield (entries 2 and 3).

By adopting the aryl iodide precursor, the reaction temperature may be lowered. Employing 3 equiv of PPh_3 ligand, competitive formation of the 8-*endo*-cyclized benzazocines **4** and **5**, as an inseparable mixture, was observed (entries 4−6).[7] Replacement of PPh_3 with the P(*o*-tolyl)$_3$ ligand led to an improvement in the yield of the benzazepine product (entry 7). Interestingly, formation of the larger ring may be avoided altogether by using 4 equiv of PPh_3 (entry 8).

In a separate approach, we employed ring-closing metathesis (RCM)[8] for the preparation of unsubstituted benzazepine rings (Scheme 2). 2-Allyl-benzamide **6** was obtained from palladium-catalyzed Stille cross-coupling of *N*-(2-iodophenyl)-benzamide **1b** with allyltributyltin. Subsequent alkylation with allyl bromide gave the diene precursor **7**, which underwent RCM smoothly in the presence of Grubbs catalyst, furnishing the unsaturated benzazepine **8** in good yield (86%). Best yields of the cyclized product were obtained using a sealed Young's tube. Presumably, this prevents ethylene loss, which is critical for the stability of the ruthenium catalyst in the highly diluted solution necessary to promote intramolecular C−C bond formation.

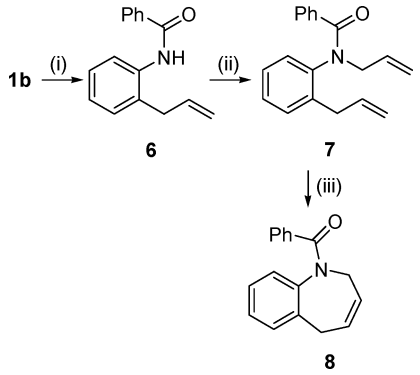
The double bonds of **3** and **8** were reduced by hydrogenation to give *N*-benzoyl-benzazepines **9** and **11**, respectively, and borane−dimethyl sulfide complex was

TABLE 1. Product Distribution Afforded by Intramolecular Heck Arylation (Scheme 1)[a]

				% yield	
entry	precursor	ligand[b]	temp	**3**[c]	**4** + **5**[d]
1	**2a**	PPh_3 (4)	140	63	
2	**2a**	dppp (2)	140	31	
3	**2a**	dppf (2)	140	35	
4	**2b**	PPh_3 (3)	120	51	17
5	**2b**	PPh_3 (3)	130	58	10
6	**2b**	PPh_3 (3)	140	60	>10
7	**2b**	(*o*-tolyl)$_3$P (3)	130	80	10
8	**2b**	PPh_3 (4)	130	88	0

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol %) or Pd_2dba_3·$CHCl_3$ (2.5 mol %), PR_3 ligand, LiCl (1.1 equiv), NEt_3 (2 equiv), DMF, 22 h. [b] Number in parentheses corresponds to equivalents of phosphine ligand employed, with respect to Pd; dppp = 1,3-bis(diphenylphosphino)propane; dppf = 1,1′-bis(diphenylphosphino)ferrocene. [c] Isolated yield following column chromatography. [d] Inseparable mixtures of **4** (major) and **5** (minor).

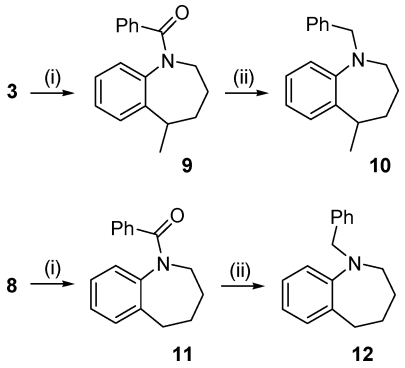
SCHEME 2. Synthesis of Benzazepine Structure by RCM[a]



[a] Reagents and conditions: (i) $Pd(OAc)_2$, PPh_3, LiCl, allyltributyltin, DMA, heat, 91%; (ii) NaH, allyl bromide, THF, reflux, 21 h, 89%; (iii) $(Cy_3P)_2Ru(=CHPh)Cl_2$, toluene, 60 °C, 86%.

(4) Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1997**, *62*, 5849−5863.
(5) Qadir, M.; Priestley, R. E.; Rising, T. W. D. F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675−3678.
(6) Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347−9350.
(7) The identity of compound **5** was verified via an independent synthesis; see Part 2 (the following paper).
(8) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

SCHEME 3. Reduction of the Benzazepine Rings[a]



[a] Reagents and conditions: (i) Pd/C, H_2; (ii) $BH_3{\cdot}SMe_2$.

employed to reduce the *N*-benzoyl moiety, affording *N*-benzyl benzazepine rings **10** and **12** (Scheme 3). Notably, 1-benzyl-2,3,4,5-tetrahydro-5-methyl-benzazepine **10** was obtained as a single diastereomeric product, i.e., the methyl and benzyl substituents have distinct relative stereochemistry.

NMR Studies of (Dynamic) Solution Structures. In previous studies, Hassner et al. proposed several interesting structural features of 1-acylated 2,3,4,5-tetrahydrobenzazepines by performing dynamic NMR and molecular mechanics calculations.[9,10]

As expected, 5-methylene-substituted benzazepine **3** undergoes slow conformational flipping in solution at ambient temperatures. This behavior was examined by recording its ^{1}H NMR spectra at variable temperatures (Supporting Information). At the slow exchange limit, one of the two diastereotopic H-2 proton resonances is located at about 5.2 ppm, some 2.5 ppm downfield from its partner. This unusual downfield shift was also previously observed by Hassner,[9] who ascribed the phenomenon to coplanarity between the exocyclic amide bond and the equatorial proton on the adjacent carbon (H-2α). Below 253 K, the spectra continued to broaden, presumably due to increased viscosity of the solution and/or slow molecular tumbling. An average $\Delta G^{\ddagger}$ of 13.7 kcal mol^{-1} was estimated from the coalescence behavior of diastereotopic methylene protons H-2, H-3 and H-4.

The reduction of the exocyclic double bond of compound **3** creates a stereogenic center and diastereomeric mixtures. The ^{1}H NMR spectrum of the 5-methyl-substituted benzazepine **9** displayed dynamic exchange between two species in a 4:1 ratio. The 2D-NOESY spectrum revealed that the major isomer contains the methyl substituent in the axial position, *syn* to the *N*-benzoyl substituent (Figure 2), as indicated by the observation of cross-peaks between H-5 with H-4α and H-4*β* resonances, while the methyl protons showed only one cross-peak with H-4α. Additionally, irradiation of the dominant methyl resonance led to a small NOE enhancement of the benzoyl aromatic protons.

Molecular mechanics calculations revealed an energy difference of 1.2 kcal mol^{-1} between the axial and equatorial chair conformers (Figure 2), which is in good agreement with the experimental value of 0.9 kcal mol^{-1}

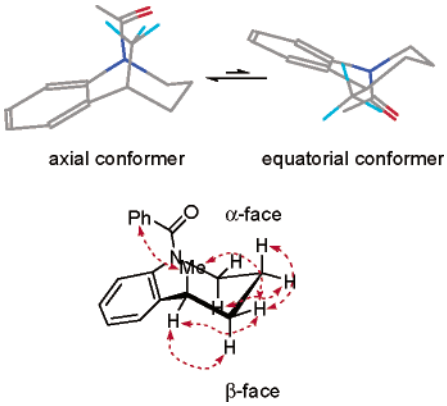


FIGURE 2. Equilibrating mixture of conformers (phenyl substituent and hydrogens omitted for clarity) and key NOE correlations for the major isomer of **9**.

(calculated from the equilibrium constant at 298 K). Subsequent line shape analysis yielded $\Delta G^{\ddagger}$ values of 14.3 kcal mol^{-1}.[11]

Benzazepine **8**, containing an endocyclic double bond, also displayed slow conformational changes at ambient temperature; the interconversion barrier is approximately 15.6 kcal mol^{-1}. When the unit of unsaturation is removed, the activation energy for benzazepine **11** to undergo conformational changes increases to 16.1 kcal mol^{-1},[12] which is comparable to that of the 5-methyl-substituted **9**. This implies that the introduction of a methyl substituent at the 5-position does not lead to significant changes in the barrier to ring inversion of the saturated ring.

Ring inversion of the unsubstituted tetrahydrobenzazepine ring **12** is rapid at ambient temperature.[5] In contrast, the ^{1}H NMR spectrum of the *N*-benzyl benzazepine **10** showed a single methyl resonance at 1.32 ppm, and distinctive resonances were observed for each of the diastereotopic protons (including the benzylic protons), which did not exhibit exchange even at 373 K. Thus impying that the reduction of the exocyclic amide functionality had led to the formation of a rigid conformational structure.

Solid-State Structures (Figure 3, Table 2). All four *N*-benzoyl benzazepines (**3**, **8**, **9**, **11**) are sufficiently crystalline to allow the solid-state structures to be determined by single-crystal X-ray diffraction. As predicted by Hassner's theoretical studies,[10] the most stable chair conformation is found to be adopted by compounds **3**, **9** and **11**; the introduction of an endocyclic double bond led to a flattening of the heterocycle in **8** to a half-chair. The carbonyl group is oriented *anti* to the fused aromatic ring in all of the solid-state structures. A small dihedral angle of −6.2° is observed between the C(2)−H(2) and N−C(O) bonds. Therefore, it would appear that the high deshielding of the H-2α resonance is largely due to its close proximity to the amide oxygen's lone pair of electrons, rather than anisotropic effects of the exocyclic amide bond as previously suggested.[9] Rather interest-

(9) Hassner, A.; Amit, B. *Tetrahedron Lett.* **1977**, *18*, 3023−3026.
(10) Hassner, A.; Amit, B.; Marks, V.; Gottlieb, H. E. *J. Org. Chem.* **2003**, *68*, 6853−6858.

(11) Eyring plot derived from the coalescence spectra yielded a $\Delta G^{\ddagger}$ value of 15.1 kcal mol^{-1} and negligible entropic contribution to the process (see Supporting Information).
(12) Hassner (ref 10) calculated an inversion barrier of 16.0 kcal mol^{-1}.

TABLE 2. Parameters Reflecting Amide Distortion[a]

structure	b[b]	θ[c]	ω_1[d]	ω_2[e]	ω_3[f]	ω_4[g]	χ_N[h]	χ_C[i]	τ[j]	α[k]
3	116.5	360.0	+187.5	+188.0	+6.3	+9.3	+1.8	+1.3	+187.8 (7.8)	1.4
8	115.3	357.3	+182.3	+200.2	+0.8	+21.7	+19.4	+1.5	+191.3 (11.3)	15.7
9	115.2	359.1	+180.7	+191.1	+0.2	+11.6	+10.9	+0.5	+185.9 (5.9)	8.6
11	116.7	358.4	+188.1	+200.0	+4.8	+23.3	+15.2	+3.3	+194.1 (14.1)	12.5

[a] ω_1, ω_2, ω_3 and ω_4 assignments are made as for *trans* amides where C1 = H. All values are in degrees. [b] Angle C1−N−C2. [c] Sum of angles around N (a + b + c). [d] ω_1 = $C_{\alpha'}$−C′−N−C2 torsion angle. [e] ω_2 = O′−C′−N−C1 torsion angle. [f] ω_3 = O′−C′−N−C2 torsion angle. [g] ω_4 = $C_{\alpha'}$−C′−N−C1 tosion angle. [h] $\chi_N = (\omega_2 - \omega_3 + \pi)(\text{mod } 2\pi)$ and has a value between 0° (planar) and 60° (complete pyramidization). [i] $\chi_C = (\omega_1 - \omega_3 + \pi)(\text{mod } 2\pi)$. [j] $\tau = [(\omega 1 + \omega 2)/2](\text{mod } 2\pi)$, where $|\omega_1 - \omega_2| < \pi$ (else τ is mod π). Value in parentheses corresponds to deviation from 180°. [k] α is the angle between the {C1−N−C2} plane and the N−C′ vector.

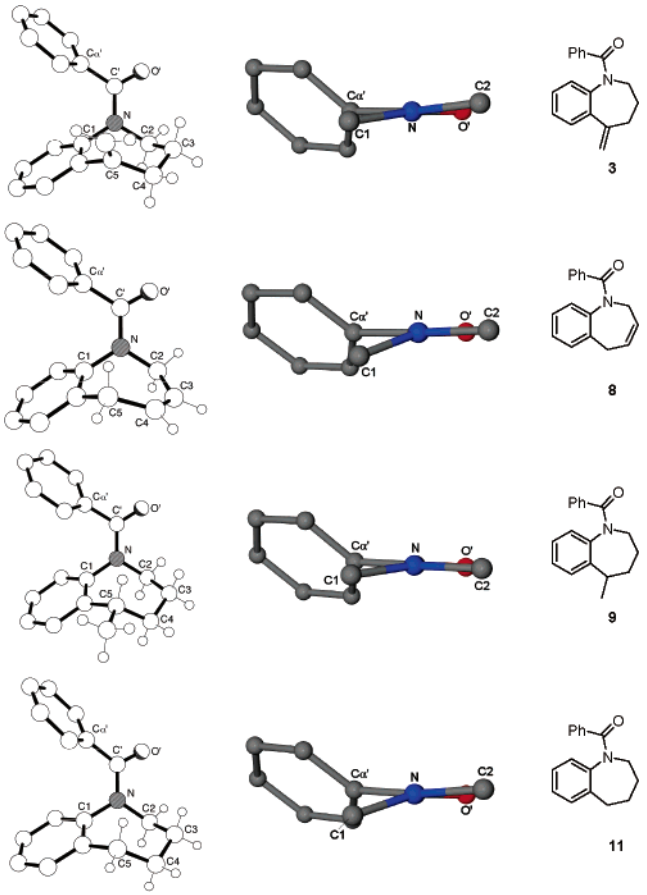


FIGURE 3. Molecular structures of benzazepines **3**, **8**, **9** and **11** (with chemical numbering scheme) and accompanying ball-and-stick models of the views along the N−C′ axes, illustrating the nature of the amide twist.

ingly, the 5-methyl substituent in the solid-state structure of compound **9** was found in the equatorial position (*anti* to the benzoyl substituent), corresponding to the minor solution conformer. Since the energy barrier between the two conformers is fairly surmountable under ambient conditions (14.3 kcal mol^{-1}), this could be the result of a better crystal packing arrangement.

Amide Distortions (Table 2). As the benzoyl substituent adopts a pseudoaxial position, this will invariably disrupt the π-interaction of the nitrogen with the adjacent aromatic ring system. On the other hand, participation of the heteroatom in π-bonding with the exocyclic carbonyl functionality (amide bond) may be interrupted by geometry constraints imposed by the heterocyclic ring and/or steric interactions between the two aromatic rings. Although the exocyclic C−N bond

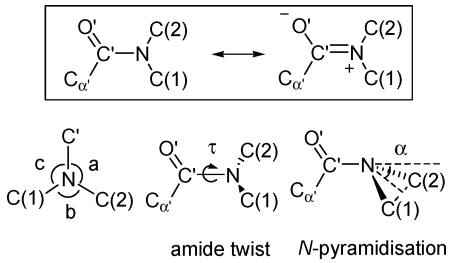


FIGURE 4. Structural parameters reflecting amide distortion.

lengths are only slightly lengthened (1.36 Å, a normal C=N amide bond is 1.33 Å), all four structures exhibit varying extents of nonplanarity around the exocyclic amide bond. Particularly, in structures **8**, **9** and **11** the nitrogen is noticeably pyramidized (χ_N up to 19.4°), while the carbonyl carbon is essentially unaffected (χ_C < 3.3°). This amide bond distortion may be delineated more closely by examining three structural parameters (Figure 4): (i) sum of the three valence angles around nitrogen (θ), (ii) the out-of-plane twist of the amide bond (τ), and (iii) the angle between the plane defined by nitrogen and its substituents with the N−C′ vector (α).[13]

Overall, these parameters are within the range previously recorded for monocyclic amides.[14] All four benzazepines have a very similar internal ring angle (*b*) at the nitrogen heteroatom of 115−116°, and there is a good overall correlation between the amide twist (τ) and the out-of-plane distortion (α). Among the four structures, benzazepine ring **3** shows the least amide pyramidization (α = 1.4°, θ = 360.0°); the planar nitrogen displays a small τ of 7.8° from planarity (Table 2, entry 1). When the double bond is hydrogenated to give benzazepine **9**, *b* becomes slightly more acute. Correspondingly, the nitrogen atom becomes slightly more pyramidal (α = 8.6°, θ = 359.1°), although there is little change in τ (5.9°). In contrast, both of the unsubstituted benzazepine rings **8** and **11** (entries 2 and 4) show substantial *N*-pyramidization (α = 15.7 and 12.5°), which is accompanied by corresponding τ values of 11° and 14°, respectively. Examining the dihedral angles around the amide bond (Figure 4), it is apparent that the distortion is due almost entirely to a torsional twist of the $C_{\alpha'}$−C′−N−C(2) moiety (ω_4), which can be as much as 23.3° for **11**.

To rationalize the above observations, molecular mechanics calculations were performed (Table 3), which

(13) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169−182.
(14) (a) Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 865−868. (b) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191−15199.

TABLE 3. Relative Energies (kcal mol^{-1}) of Benzazepines 3, 8, 9 and 11, Calculated Using Spartan Molecular Mechanics Program[a]

structure	total	torsional	electrostatic	vdW
3	+78.3	+21.9	+13.1	+46.5
8	+71.2	+17.4	−10.3	+45.0
9	+70.4	+16.6	−5.4	+46.6
11	+63.1	+15.5	−5.2	+43.6

[a] All other components are ≤7.6 kcal mol^{-1}.

revealed that structures **8** and **9** are very similar in energy. In contrast, the least distorted structure (**3**) is approximately 15 kcal mol^{-1} higher in energy than the most distorted structure (**11**). Examining the energy contributions, it is apparent that 1,4-interactions are significant in these heterocycles. Among these, the van der Waals forces, albeit sizable, showed little variance between the structures. In contrast, torsional strain is a significant contributor in all of the benzazepines (except compound **3**, which contains an additional electrostatic contribution). The relative values of the torsional energies suggest that the ring strain in tetrahydrobenzazepine **11** is effectively relieved by the ability of the amide bond to distort. A change in the hybridization at carbon-5 prohibited amide distortion, thus leading to larger torsional strain in benzazepine **3**.

It has been previously suggested that ring inversion of these heterocycles is closely associated with the amide bond rotation, where the carbonyl moiety is forced out of conjugation with the nitrogen in the transition state.[10] In the present work, a higher barrier to ring inversion was observed in the order **3** ≈ **9** > **8** > **11**. This suggests that greater amide distortion is associated with a more stable ground-state structure, which is more reluctant to undergo conformational changes.

In conclusion, solid- and solution-state structures of substituted benzazepine rings have been examined. The study revealed important effects imposed by substituents on the *N*-heteroatom and at position-5 on ring conformation, dynamic behavior and *N*-pyramidization. These insights may prove to be important for rationalization of the biological and chemical behavior of these heterocyclic rings.

Experimental Section

***N*-(2-Halophenyl)-*N*-(pent-4-en-1-yl)-benzamides (2).** An oven-dried Schlenk tube was charged with a suspension of NaH (60% dispersion in oil, 1.5 equiv) in dry THF under an argon atmosphere. While cooling in an ice-bath, *N*-(2-bromophenyl)benzamide **1a** or *N*-(2-iodophenyl)benzamide **1b** was added slowly as a solution in dry THF. When addition was completed, the ice-bath was removed and the pale yellow mixture stirred at ambient temperature for 3 h. A solution of pent-4-enyl tosylate (1.1 equiv) in dry THF was added to the yellow-colored mixture and the reaction mixture was subsequently heated to gentle reflux for 2.5 h. Excess NaH was quenched by the slow addition of water and diluted with EtOAc. The organic layer was separated and the aqueous layer extracted thrice with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration through a pad of Celite, followed by evaporation of the ensuing filtrate afforded a dark yellow oily residue that was subjected to column chromatography.

***N*-(2-Bromophenyl)-*N*-(pent-4-en-1-yl)-benzamide (2a).** Yield: 77% as a pale yellow syrup, R_f = 0.21, hexanes/EtOAc (5/1). Found: C, 62.90; H, 5.45; N, 4.20. Calcd for $C_{18}H_{18}NOBr$: C, 62.79; H, 5.28; N, 4.07. ν_{max}(thin film)/cm^{-1} 1651 s (CO); δ_H (360 MHz; $CDCl_3$) 1.57−1.62 (1H, m, CH_2CH$_2$N), 1.65−1.85 (1H, m, CH_2CH$_2$N), 2.05 (2H, br m, CH_2CH$_2$CH$_2$N), 3.42 (1H, ddd, *J* 3.1, 5.2 and 10.5, CH_2N), 4.15 (1H, ddd, *J* 3.0, 5.1 and 10.5, CH_2N), 4.88−4.97 (2H, m, CH_2=CH), 5.68−5.79 (1H, m, CH$_2$=C*H*), 6.97−7.01 (2H, m Ar-H), 7.04−7.28 (6H, Ar-H), 7.45 (1H, d, *J* 7.9, Ar-H); δ_C (90.6 MHz; $CDCl_3$) 26.8 (*C*H$_2$CH$_2$N), 31.6 (*C*H$_2$CH$_2$CH$_2$N), 49.3 (CH$_2$N), 115.4 (*C*H$_2$=CH), 123.8 (Ar-C), 128.0 (Ph-C$_{ortho}$), 128.4 (Ph-C$_{meta}$), 128.5 (Ar-C), 129.3 (Ar-C), 130.0 (Ph-C$_{para}$), 132.2 (Ar-C), 134.2 (Ar-C), 136.5 (Ph-C$_{ipso}$), 138.1 (CH$_2$=*C*H), 142.4 (Ar-C), 169.6 (CO); *m/z* (EI) 343/345 (M$^+$, 19/19%), 301/303 (6/6), 288/290 (21/21), 275/277 (37/37), 264 (96), 196 (32), 105 (100), 77 (96).

***N*-(2-Iodophenyl)-*N*-(pent-4-en-1-yl)-benzamide (2b).** Yield: 83% as a colorless syrup that slowly crystallized upon standing, R_f = 0.23, hexanes/EtOAc (5/1). Found: C, 55.40; H, 4.75; N, 3.75. Calcd for $C_{18}H_{18}NIO$: C, 55.25; H, 4.65; N, 3.58. ν_{max}(thin film)/cm^{-1} 1647 s (CO); δ_H (360 MHz; $CDCl_3$) 1.58−1.65 (1H, br m, CH_2CH$_2$N), 1.81−1.87 (1H, br m, CH_2CH$_2$N), 1.97−2.12 (2H, br m, CH_2CH$_2$CH$_2$N), 3.31 (1H, ddd, *J* 2.9, 5.0 and 10.7, CH_2N), 3.57 (br s, rotamer), 4.22 (1H, ddd, *J* 2.8, 5.6 and 10.7, CH_2N), 4.88−4.98 (2H, br m, CH_2=CH), 5.69−5.80 (1H, m, CH$_2$=C*H*), 5.52 (br s, rotamer), 6.65−6.80 (1H, Ar-H), 6.97 (1H, d, *J* 7.0, Ar-H), 7.06−7.74 (6H, m, Ar-H), 7.73 (1H, d, *J* 7.4, Ar-H), 7.90 (br s, rotamer); δ_C (90.6 MHz; $CDCl_3$) 26.8 (1C, *C*H$_2$CH$_2$N), 31.6 (1C, *C*H$_2$CH$_2$CH$_2$N), 49.6 (1C, CH$_2$N), 100.5 (Ar-C), 115.5 (1C, *C*H$_2$=CH), 128.0 (Ph-C$_{ortho}$), 128.6 (Ph-C$_{meta}$), 129.3 (Ar-C), 129.4 (Ph-C$_{para}$), 130.0 (Ar-C), 131.9 (Ar-C), 136.5 (Ph-C$_{ipso}$), 138.1 (CH$_2$=*C*H), 140.7 (Ar-C), 145.5 (Ar-C), 170.7 (CO); *m/z* (EI) 391 (M$^+$, 5%), 323 (14), 264 (100), 230 (5), 196 (21), 105 (68), 77 (33).

1-Benzoyl-5-methylene-2,3,4,5-tetrahydro-1*H*-benzazepine (3). An oven-dried Young's tube was charged with $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %) and LiCl (1.1 equiv) under a N_2 atmosphere. Triethylamine (2 equiv) was added, followed by anhydrous DMF (4 mL) and the mixture was stirred at ambient temperature for 15 min. The amide precursor **2b** (0.50 g) was added as a solution in anhydrous DMF (1 mL), after which the Young's tube was sealed and heated in a thermostated oil bath at 130 °C for 22 h. The reaction mixture was filtered through a small pad of Celite, which was washed repeatedly with EtOAc. The collected filtrate was concentrated in vacuo to give a dark, viscous oil that was subjected to column chromatography. The 7-*exo-trig* cyclized product **3** was obtained as a colorless, viscous oil which crystallized upon standing for a few hours. The solids were recrystallized from EtOH to yield colorless prisms for X-ray crystallography. Yield: 88%, R_f = 0.18, hexanes/EtOAc (3/1); mp 108.5−109.5 °C (from EtOAc/hexanes). Found: C, 81.85; H, 6.30; N, 5.25. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.52; N, 5.32. ν_{max}(KBr)/cm^{-1} 1636 s (CO); δ_H (360 MHz; $CDCl_3$; 253 K) 2.00 (1H, br s, *H*-3*β*), 2.07−2.16 (1H, br m, *H*-3α), 2.43 (1H, br m, *H*-4α), 2.76−2.82 (1H, br m, *H*-4*β*), 3.00−3.06 (1H, br m, *H*-2*β*), 5.00−5.03 (1H, br m, *H*-2α), 5.33 (1H, s, CH_2=C), 5.25 (1H, s, CH_2=C), 6.64 (1H, dd, *J* 1.0 and 7.9, Ar-H), 6.95−6.99 (1H, m, Ar-H), 7.14−7.24 (6H, m, Ar-H), 7.35 (1H, dd, *J* 1.3 and 7.6, Ar-H); δ_C (90.6 MHz; $CDCl_3$) 29.0 (*C*-3), 34.9 (1C, *C*-4), 47.5 (1C, *C*-2), 116.4 (*C*H$_2$=C), 127.6 (Ar-C), 128.0 (Ph-C$_{ortho}$), 128.3 (Ph-C$_{meta}$), 128.4 (Ar-C), 128.8 (Ar-C), 129.2 (Ar-C), 129.8 (Ar-C), 136.8 (Ph-C$_{ipso}$), 140.6 (Ar-C), 141.3 (Ar-C), 149.9 (*C*-5), 170.2 (CO); *m/z* (EI) 263 (M$^+$, 86%), 249 (6), 235 (10), 158 (15), 143 (23), 130 (10), 105 (100), 77 (37). **Crystal data for 3** (CCDC 251225): $C_{18}H_{17}NO$, MW = 263.33, monoclinic, $P2_1/c$ (No. 14), a = 14.6421(5), b = 7.4495(4), c = 14.4893(7) Å, β = 116.974(2)°, V = 1408.51(11) Å^3, Z = 4, D_c = 1.242 g cm^{-3}, μ(Mo Kα) = 0.077 mm^{-1}, T = 120 K, colorless blocks; 3219 independent measured reflections, F^2 refinement, R_1 = 0.044, wR_2 = 0.095, 2082 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 55°$], 250 parameters.

***N*-(2-Allylphenyl)benzamide (6).** An oven-dried Young's tube was charged with $Pd(OAc)_2$ (33.6 mg, 0.31 mmol, 4 mol

%), PPh_3 (0.33 g, 1.24 mmol, 4 equiv with respect to Pd) and LiCl (0.36 g, 8.51 mmol). Anhydrous DMA (5 mL) was added and the mixture stirred at ambient temperature for 20 min in order to generate the catalyst. To the ensuing yellow solution was added **1b** (2.50 g, 7.74 mmol) as a solution in DMA (7 mL) and allyltributyltin (3.60 mL, 11.6 mmol, 1.5 equiv). The Young's tube was sealed and subsequently heated in an oil bath at 100 °C for 21 h. Filtration through Celite followed by evaporation, yielded a viscous, yellow residue that was purified by column chromatography to furnish white solids. Further purification was achieved by recrystallization from EtOAc–Et_2O. Yield: 91% as translucent, feathery needles, $R_f = 0.23$, hexanes/EtOAc (4/1); mp 120.8–121.9 °C (from EtOAc/Et_2O) (lit.[15] 118–119 °C). Found: C, 80.70; H, 6.20; N, 5.75. Calcd for $C_{16}H_{15}NO$: C, 80.97; H, 6.38; N, 5.90. ν_{max}(KBr)/cm^{-1} 1651 s (CO); δ_H (400 MHz; $CDCl_3$) 3.51 (2H, close doublets, ArC*H*$_2$), 5.14–5.19 (1H, m, CH=C*H*$_2$), 5.28–5.31 (1H, m, CH=C*H*$_2$), 6.05–6.15 (1H, m, C*H*=CH$_2$), 7.18–7.22 (1H, m, Ar-H), 7.27 (1H, dd, *J* 1.5 and 7.5, Ar-H), 7.35–7.40 (1H, m, Ar-H), 7.51–7.62 (3H, Ph-H$_{meta}$ and Ph-H$_{para}$), 7.89–7.91 (2H, m, Ph-H$_{ortho}$), 8.03 (1H, br s, NH), 8.11 (1H, d, *J* 8.0, Ar-H); δ_C (100.6 MHz; $CDCl_3$) 37.5 (ArCH$_2$), 117.3 (CH=*C*H$_2$), 123.8 (Ar-C), 125.7 (Ar-C), 127.4 (Ph-C$_{ortho}$), 128.1 (Ar-C), 129.2 (Ph-C$_{meta}$), 130.2 (Ar-C), 130.3 (Ar-C), 132.3 (Ph-C$_{para}$), 135.4 (Ph-C$_{ipso}$), 136.7 (*C*H=CH$_2$ and Ar-C), 165.9 (CO); *m/z* (EI) 237 (M$^+$, 31%), 197 (10), 105 (100), 76 (75).

Preparation of *N*-Allyl-*N*-(2-allylphenyl)benzamide (7). To a suspension of NaH (60% dispersion in oil, 0.66 g, 16.5 mmol, 1.5 equiv) in dry THF (15 mL) was added *N*-(2-allylphenyl)benzamide **6** (3.00 g, 11.0 mmol) portionwise. Additional THF (15 mL) was added and the pale colored suspension stirred rapidly at ambient temperature for 3 h, after which allyl bromide (1.42 mL, 16.5 mmol, 1.5 equiv) was added, and the reaction subsequently was refluxed for 21 h. After dilution with water (20 mL), the organic layer was separated. The remaining aqueous phase was extracted with EtOAc (3 × 30 mL), and the organic fractions washed with brine, dried over $MgSO_4$, filtered and evaporated. The dark yellow oily residue was purified by column chromatography. Yield: 89% as a pale yellow oil, $R_f = 0.35$, hexanes/EtOAc (4/1). Found: C, 82.45; H, 7.10; N, 5.15. Calcd for $C_{19}H_{19}NO$: C, 82.26; H, 6.92; N, 5.05. ν_{max}(thin film)/cm^{-1} 1645 s (CO); δ_H (360 MHz; $CDCl_3$) 3.15 (1H, dd, *J* 6.6 and 9.5, ArC*H*$_2$), 3.35 (1H, dd, *J* 6.6 and 9.1, ArC*H*$_2$), 3.45 (br m, rotamer), 3.98–4.02 (br m, rotamer), 4.12 (1H, dd, *J* 6.0 and 7.4, C*H*$_2$N), 4.17 (br m, rotamer), 4.76 (1H, dd, *J* 6.0 and 8.4, C*H*$_2$N), 4.89 (br m, rotamer), 5.04–5.19 (4H, m, C*H*$_2$=CHCH$_2$N and ArCH$_2$-CH=C*H*$_2$), 5.68–5.75 (1H, m, ArCH$_2$C*H*=CH$_2$), 5.77 (br m, rotamer), 5.98–6.08 (1H, m, CH$_2$=C*H*CH$_2$N), 6.09–6.20 (br m, rotamer), 7.11–7.59 (9H, m, Ar-H); δ_C (90.6 MHz; $CDCl_3$) 35.4 (ArCH$_2$), 53.7 (CH$_2$N), 117.4 (ArCH$_2$CH=*C*H$_2$), 118.9 (*C*H$_2$=CHCH$_2$N), 127.4 (Ar-C), 127.9 (Ar-C), 128.2 (Ar-C), 128.9 (Ar-C), 130.0 (Ar-C), 130.1 (Ar-C), 130.8 (Ar-C), 133.1 (CH$_2$=*C*HCH$_2$N), 136.3 (ArCH$_2$*C*H=CH$_2$ and Ph-C$_{ipso}$), 137.4 (Ar-C), 141.8 (Ar-C), 170.6 (CO); *m/z* (EI) 277 (M$^+$, 64%), 262 (5), 236 (93), 218 (11), 172 (61), 105 (100), 91 (10), 77 (70).

1-Benzoyl-2,5-dihydro-1*H*-1-benzazepine (8). A dry Young's tube was charged with Grubbs catalyst (5–10 mol %) and the corresponding diene **7** (0.50 g) as a 0.1 M solution in dry toluene. The ensuing dark purple colored solution was stirred at ambient temperature for 10 min. The Young's tube was then sealed and heated in an oil bath at 60 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by column chromatography, to afford the product as a viscous oil that crystallized upon standing overnight. For X-ray crystallography, recystallisation was carried out with EtOH to obtain colorless prisms. Yield: 86%, $R_f = 0.36$, hexanes/EtOAc (3/1); mp 96.6–97.3 °C. Found: C, 82.00; H, 6.20; N, 5.55. Calcd for $C_{17}H_{15}NO$: C, 81.89; H, 6.08; N, 5.62. ν_{max}(KBr)/cm^{-1} 1644 s (CO); δ_H (400 MHz; Tol-d_8; 243 K) 2.53 (1H, dd, *J* 8.5 and 16.2, *H*-5*β*), 3.27–3.31 (1H, br m, *H*-2*β*), 3.71 (1H, br d, *J* 16.2, *H*-5α), 5.21–5.24 (1H, m, *H*-3), 5.52–5.57 (1H, m, *H*-2α), 5.73–5.78 (1H, br m, *H*-4), 6.36 (1H, d, *J* 7.6, Ar-H), 6.51 (1H, td, *J* 2.5 and 7.8, Ar-H), 6.65–6.69 (2H, m, Ar-H), 6.76–6.82 (3H, m, Ar-H), 7.32–7.34 (2H, m, Ar-H); δ_C (100.6 MHz; $CDCl_3$) 31.2 (*C*-5), 44.4 (*C*-2), 123.0 (*C*-4), 125.2 (*C*-3), 126.0 (Ar-C), 126.1 (Ar-C), 126.3 (Ar-C), 126.5 (Ar-C), 127.2 (Ar-C), 127.3 (Ar-C), 128.4 (Ar-C), 134.2 (Ph-C$_{ipso}$), 137.4 (Ar-C), 141.4 (Ar-C), 167.8 (CO); *m/z* (EI) 249 (M$^+$, 91%), 144 (22), 129 (37), 105 (100), 91 (4) 77 (41). **Crystal data for 8** (CCDC 251226): $C_{17}H_{15}NO$, MW = 249.30, monoclinic, $P2_1/n$ (No. 14), a = 10.2478(3), b = 10.1404(2), c = 12.6013(3) Å, β = 95.2080(10)°, V = 1304.08(6) Å^3, Z = 4, D_c = 1.270 g cm^{-3}, μ(Mo Kα) = 0.079 mm^{-1}, T = 120 K, colorless blocks; 2927 independent measured reflections, F^2 refinement, $R_1 = 0.038$, $wR_2 = 0.093$, 2498 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 55°$], 233 parameters.

Typical Procedure for Hydrogenation of Endocyclic/Exocyclic Double Bond (Synthesis of 9 and 11). To a solution of unsaturated benzazepine (0.50 g) in MeOH (15 mL) was added 10% Pd/C (10 mol %). The suspension was stirred vigorously at room temperature under a hydrogen atmosphere for 2 days. The reaction mixture was then filtered through a thin pad of Celite, washing the residue with a mixture of EtOAc and MeOH. The collected filtrate was evaporated to a crude viscous oil that was purified by column chromatography.

1-Benzoyl-5-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9). The product was isolated as a colorless syrup that crystallized upon standing overnight. The solids were recrystallized from EtOAc/hexanes to obtain colorless prisms suitable for X-ray crystallography. Yield: 86%, R_f = 0.29, hexanes/EtOAc (3/1); mp 87.8–88.6 °C (from EtOAc/hexanes). Found: C, 81.45; H, 7.35; N, 5.30. Calcd for $C_{18}H_{19}NO$: C, 81.46; H, 7.23; N, 5.28. ν_{max}(KBr)/cm^{-1} 1638 s (CO). *m/z* (EI) 256 (M$^+$, 74%), 222 (7), 160 (66), 144 (19), 130 (12), 105 (100), 77 (46). **Axial conformer:** δ_H (360 MHz; $CDCl_3$) 1.34–1.39 (1H, br m, *H*-4*β*), 1.48 (3H, d, *J* 7.0, CH_3), 1.68–1.73 (1H, br m, *H*-3*β*), 1.95–2.06 (2H, br m, *H*-3α and *H*-4α), 3.02–3.08 (1H, br m, *H*-2*β*), 3.27–3.72 (1H, br m, *H*-5), 4.70 (1H, ddd, *J* 3.1, 7.0 and 13.2, *H*-2α), 6.64 (1H, d, *J* 7.7, Ar-H), 6.90–6.94 (1H, m, Ar-H), 7.07–7.31 (7H, m, Ar-H); δ_C (125.8 MHz; $CDCl_3$) 18.8 (CH_3), 25.8 (*C*-3), 33.2 (*C*-4), 33.6 (1C, *C*-5), 45.8 (*C*-2), 124.0 (Ar-C), 125.3 (Ar-C), 125.9 (Ar-C), 126.3 (Ph-C$_{ortho}$), 126.4 (Ph-C$_{meta}$), 126.9 (Ar-C), 128.3 (Ar-C), 135.0 (Ph-C$_{ipso}$), 140.7 (Ar-C), 141.4 (Ar-C), 168.3 (CO). **Equatorial conformer**: δ_H (360 MHz; $CDCl_3$) 1.34–1.39 (1H, br m, *H*-4), 1.53 (3H, d, *J* 7.4, CH_3), 1.79–1.86 (1H, br m, *H*-3α), 1.95–2.06 (1H, br m, *H*-4), 2.29–2.33 (1H, br m, *H*-3*β*), 2.70–2.76 (1H, br m, *H*-2α), 3.27–3.72 (1H, br m, *H*-5), 5.14–5.18 (1H, br m, *H*-2*β*), 6.57 (1H, d, *J* 7.6, Ar-H), 6.86–6.88 (1H, m, Ar-H), other aromatic protons overlapped by resonances of the axial conformer; δ_C (125.8 MHz; $CDCl_3$) 17.5 (CH_3), 22.9 (*C*-4), 31.1 (*C*-3), 39.6 (*C*-5), 47.1 (*C*-2), 125.5 (Ar-C), 126.1 (Ar-C), 127.3 (Ar-C), 127.7 (Ar-C), 128.2 (Ar-C), 129.4 (Ar-C), (1C, Ar-C). **Crystal data for 9** (CCDC 251227): $C_{18}H_{19}NO$, MW = 265.34, monoclinic, $P2_1/n$ (No. 14), a = 10.1500(2), b = 8.3473(2), c = 16.6953(4) Å, β = 92.6330(10)°, V = 1413.02(6) Å^3, Z = 4, D_c = 1.247 g cm^{-3}, μ(Mo Kα) = 0.077 mm^{-1}, T = 120 K, colorless prisms; 3221 independent measured reflections, F^2 refinement, $R_1 = 0.046$, $wR_2 = 0.110$, 2813 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 55°$], 183 parameters.

1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11). Yield: 90% as colorless, needlelike crystals, R_f = 0.26, hexanes/EtOAc (3/1); mp 94.2–95.4 °C (from Et_2O/hexanes; lit.[16] 86–87 °C, from *n*-hexane). Found: C, 81.40; H, 6.90; N, 5.45. Calcd for $C_{17}H_{17}NO$: C, 81.23; H, 6.83; N, 5.57. ν_{max}(KBr)/cm^{-1} 1640 s (CO); δ_H (400 MHz; $CDCl_3$) 1.41–1.47 (1H, m, *H*-4*β*), 1.87–2.03 (3H, br m, *H*-4α, *H*-3α and *H*-3*β*), 2.66–2.69 (1H, m,

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H-2β), 2.72−2.82 (1H, m, *H*-5β), 2.94−3.00 (1H, m, *H*-5α), 4.94−4.97 (1H, br m, *H*-2α), 6.54 (1H, d, *J* 7.7, Ar-H), 6.79−6.83 (1H, m, Ar-H), 6.96−7.19 (7H, m, Ar-H); δ_C (100.6 MHz; $CDCl_3$) 26.8 (*C*-4), 30.1 (*C*-3), 35.3 (*C*-5), 48.0 (*C*-2), 127.3, 127.5 (Ar-C), 128.1 (Ph-C_{ortho}), 128.5 (Ph-C_{meta}), 128.8 (Ar-C), 129.6 (Ar-C), 130.4 (Ar-C), 136.7 (Ph-C_{ipso}), 139.7 (Ar-C), 144.5 (Ar-C), 169.5 (CO); *m/z* (EI) 251 (M^+, 65%), 145 (15), 130 (26), 105 (100), 77 (38). **Crystal data for 11** (CCDC 251228): $C_{17}H_{17}NO$, MW = 251.32, monoclinic, $P2_1/c$ (No. 14), a = 6.19210(10), b = 15.5228(3), c = 14.0870(3) Å, β = 99.3150(10)°, V = 1336.17(4) Å^3, Z = 4, D_c = 1.249 g cm^{-3}, μ(Mo Kα) = 0.077 mm^{-1}, T = 120 K, colorless shards; 3038 independent measured reflections, F^2 refinement, R_1 = 0.050, wR_2 = 0.117, 2470 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 55°$], 173 parameters.

1-Benzyl-5-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (10). To a solution of the benzazepine **9** (0.50 g) in dry THF (15 mL) was added BH_3·SMe_2 (2 M solution in THF, 1.1 equiv) dropwise under an inert atmosphere. The reaction mixture was then heated to gentle reflux for 3 h, after which the solvent was removed in vacuo. DCM (15 mL) and water (10 mL) were added and the organic layer separated. The remaining aqueous layer was extracted with DCM (2 × 15 mL). The combined organic extracts were washed with saturated, aqueous $NaHCO_3$ (15 mL) solution, brine (10 mL) and dried over $MgSO_4$. Filtration, followed by evaporation of the solvent afforded a crude, pale yellow oil which was purified by column chromatography. The furnished product was obtained in 84% yield as a colorless oil, R_f = 0.6, hexanes/EtOAc (3/1). Found: C, 85.95; H, 8.55; N, 5.45. Calcd for $C_{18}H_{21}N$: C, 86.00; H, 8.44; N, 5.57. δ_H (360 MHz; $CDCl_3$) 1.20−1.28 (1H, br m, *H*-4β), 1.32 (3H, d, *J* 7.1, CH_3), 1.45−1.51 (2H, br m, *H*-3), 1.65−1.70 (1H, br m, *H*-4α), 2.62 (1H, ddd, *J* 3.8, 6.6 and 12.0, *H*-2α), 2.87−2.93 (1H, br m, *H*-2β), 3.22−3.26 (1H, br m, *H*-5), 4.12 (1H, d, *J* 13.6, PhCH_2), 4.33 (1H, d, *J* 13.6, PhCH_2), 6.87−6.93 (2H, m, ArH), 7.07−7.12 (2H, m, ArH), 7.16−7.20 (1H, m, ArH), 7.24−7.28 (2H, m, ArH), 7.35 (2H, d, *J* 7.4, ArH); δ_C (90.6 MHz; $CDCl_3$) 20.3 (CH_3), 27.2 (*C*-3), 33.6 (*C*-4), 35.9 (*C*-5), 53.3 (1C, *C*-2), 59.1 (Ph*C*H_2), 118.3 (Ar-C), 121.9 (Ar-C), 126.5 (Ph-C_{para}), 126.8 (Ar-C), 127.3 (Ar-C), 128.7 (Ph-C_{ortho}), 128.8 (Ph-C_{meta}), 139.8 (C_2), 140.2 (Ph-C_{ipso}), 151.5 (C_1); *m/z* (EI) 251 (M^+, 22%), 160 (57), 118 (5), 84 (100).

Fully reduced benzazepine **12** was prepared similarly from compound **11**. Characterization data for **12** was identical to a genuine sample previously prepared via a complementary route.[5] δ_H (500 MHz, $CDCl_3$, free amine): 1.52−1.54 (4H, m, CH_2); 2.80−2.83 (4H, m, CH_2); 4.24 (2H, s, CH_2Ph); 6.80−6.83 (1H, m, Ar-H); 6.89−6.92 (1H, m, Ar-H); 7.05−7.09 (2H, m, Ar-H); 7.16−7.17 (1H, m, Ar-H); 7.24−7.28 (2H, m, Ar-H); 7.35−7.37 (2H, d, *J* 7.1, Ar-H).

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Supporting Information Available: Thermal ellipsoid plots of compounds **3**, **8**, **9** and **11**; ^{1}H NMR of the mixture of compounds **4** and **5**; and Eyring plot for benzazepine **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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