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On the Conformation of 8-Membered Ring Heterocycles – Dynamic and Static Conformational Analysis of Acylated Hexahydrobenzazocines

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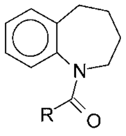
A high-field NMR analysis of several acylated hexahydrobenzazocines indicates that, surprisingly, ring methylene groups are typically diastereotopic at room temperature, as the barriers for the process of enantiomerization of the eight-membered ring are much higher than expected. It is shown that ring inversion is correlated (but not concerted) with rotation of the amide moiety, as the carbonyl is forced out of conjugation with the nitrogen in the transition state. A detailed analysis of vicinal proton-proton coupling constants, supported by molecular mechanics calculations, indicates that these compounds exist at room temperature as a mixture of fast-interconverting conformers of the octacycle. This is proved by the observation of two species in the ^{13}C NMR spectrum of the parent compound, at temperatures below –90 °C.

Introduction

Several years ago, we published a communication[1] noting a quite unusual feature in the room temperature ^{1}H NMR spectra of acylated tetrahydrobenzazepines (e.g. **1**): *one* of the protons on the N-methylene was unusual, being deshielded by at least 2 ppm more than the next most deshielded aliphatic proton signals. This suggested a rather high energy barrier between two enantiomeric species resulting from a ring flip of the seven-membered ring. Subsequently[2] we reported a detailed NMR study of several such tetrahydrobenzazepines, in which we established the ground state conformation of this class of heterocycles and explained the reason for the very large barrier for their ring epimerization. Specifically, the latter process is blocked by the interaction of the aromatic ring and the acyl substituent; in order to enable this process, the acyl group has to partially rotate out of coplanarity with the nitrogen, thus incurring a high energetic cost. The two processes, amide rotation and ring flip, are thus correlated (they *do not* occur independently), but not concerted (i.e. two aspects of a same conformational reorientation step). The above unusual ^{1}H NMR deshielding was also observed in one hexahydrobenzazocine (i.e. **2**).[1] Since little is known about the conformation of eight-membered rings we decided to examine the conformational behaviour of related acylated hexahydrobenzazocines **2**–**7**.



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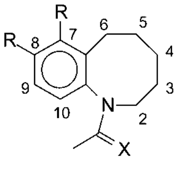
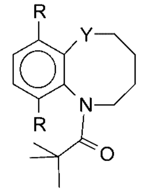


2 R = H, X = O
3 R = H, X = S
4 R = OCH$_3$, X = O



5 R = CH$_3$, Y = CH$_2$
6 R = H, Y = CO
7 R = H, Y = O

Results and Discussion

Dynamic Transformations. Some hexahydrobenzazocines were synthesized and the barriers for the ring-flip process that converts the eight-membered rings of **2**–**4**, **6** and **7** to their enantiomeric forms determined by dynamic NMR spectroscopy. The NMR results (NOE interactions) indeed indicated that there was usually a major isomer in which the carbonyl oxygen was *anti* to the aromatic ring and hence *syn* to the N-adjacent methylene group. Specifically, we simulated the coalescence of the protons of the methylene adjacent to nitrogen (see Table 1 and Exp. Sect.) in the temperature-dependent ^{1}H NMR spectra. As in the case of the benzazepines,[2] the barriers are higher than might be expected, and they must involve partial rotation of the acyl moiety. A hint that this is indeed the case is found in the ring-flip barrier for the thioamide **3**, which is several kcal·mol^{-1} higher than for the corresponding amide **2**.

In order to eliminate the possibility that ring flip and amide rotation are concerted, we measured the barriers for the rotation of the acyl and thioacyl moiety for **2** and **3**, respectively. The main technical difficulty in determining this parameter is the very low concentration (2–3%), in the

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Table 1. Dynamic NMR-derived kinetics for ring inversion of hexahydrobenzazocines.

	T [K]	Major rotamer k [s^{-1}]	Major rotamer $\Delta G^\dagger$ [kcal·mol^{-1}]	Minor rotamer k [s^{-1}]	Minor rotamer $\Delta G^\dagger$ [kcal·mol^{-1}]
2[a]	355.5	12	19.2		
	379.4	70	19.2		
	398.8	240	19.2		
	418.1	600	19.4		
3[a]	355.5			2.5	20.3
	379.4	0.5	22.9	10	20.6
	398.8	2.5	22.9	35	20.7
	418.1	5.5	23.3	135	20.7
4[a]	346.3	4	19.4		
	380.7	37	19.7		
	392.1	80	19.7		
	408.3	150	20.1		
	426.3	300	20.4		
6[b]	306.9	600	14.1		
	315.2	1100	14.1		
	331.0	4100	14.0		
	345.5	12000	13.9		
	355.5	20000	13.9		
7[b]	306.9	150	14.9		
	315.2	350	14.8		
	331.2	1200	14.8		
	346.5	3300	14.8		
	355.5	6200	14.8		

[a] In C_6D_5Br. [b] In $CDCl_3$.

equilibrium mixture, of the rotamer with the oxygen (or sulfur) atom positioned *syn* to the aromatic ring. As we explained in the previous paper in this series,[2] we find that the most convenient way to perform this measurement is to use the two-dimensional EXSY technique.[3] Our practice is to repeat the EXSY experiment for several values of a parameter called t_m (mixing time), and to fit the ratio of the integrals of the off-diagonal to the diagonal peaks to the theoretical curve, which depends on k_{obs} (the sum of the forward and backward reaction rates) – a typical such plot is shown in Figure 1. The results are summarized in Table 2, and the barriers turn out to be ca. 1 kcal·mol^{-1} higher than the corresponding ring-flip values. The two processes are, therefore, not concerted, but correlated; partial amide rotation is required for the topomerization of the eight-membered ring, as described in detail in ref.[2] for the seven-membered ring analogs.

Amide **4** is similar to **2**, but the extra methoxy groups make the aromatic ring more electron-rich, and therefore, the conjugation of the latter with the amide nitrogen is repressed. In such cases, the barrier for amide rotation is expected to be higher, and we notice a parallel slight increase in the barrier for ring flip (ca.19.7 instead of 19.2 kcal·mol^{-1}). In compounds **6**, in which one additional atom of the eight-membered ring is sp^2- rather than sp^3-hybridised, and **7**, in which an oxygen substitutes a methylene, the ring is more flexible and the barrier for the ring-flip process is considerably reduced (to 14.0 and 14.8 kcal·mol^{-1}, respectively).

Pivalate **5** belongs to a class of its own. We are able to measure the kinetics of amide rotation (Table 2), but it turns out that the only broadening seen in the ^{1}H spectrum, even up to 400 K, is completely described by the kinetics of the rotation of the pivalate moiety. Prof. Albrecht Mannschreck (University of Regensburg, Germany), was able to partially separate the two enantiomers of **5** by chromatography on a chiral column.[4] The (+) fraction was racemised at 119.5 °C in diglyme, a process followed by polarimetry at 365 nm. The barrier for racemisation was extremely high: 30.3 ± 0.1 kcal·mol^{-1}.

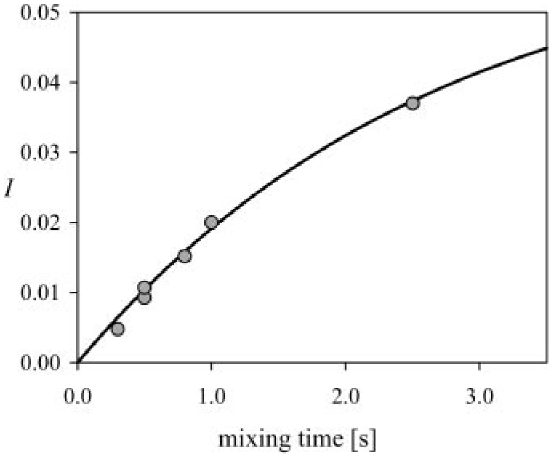

Figure 1. Results of EXSY experiments for thioacetamide **3** (see text and Table 2). In this graph I is the ratio of the sum of the volume integrals of the off-diagonal peaks to those of the diagonal peaks (see ref.[3]). As described in the text, the experiment is repeated for several values of the mixing time, t_m, and a theoretical curve is fitted for k_{obs} (the sum of the forward and backward reaction rates). The value of I tends asymptotically to $2K/(K^2 + 1)$ (the equilibrium constant is obtained from the 1D spectrum) for large mixing times, and if $t_m >> 1/k_{obs}$ the obtained I value is not useful in the fitting procedure.

Table 2. EXSY-derived kinetics for amide rotation of hexahydrobenzazocines.[a]

	T [K]	K	G^0 [kcal·mol^{-1}]	k_{obs}[b] [s^{-1}]	k[c] [s^{-1}]	$\Delta G^\dagger$ [kcal·mol^{-1}]
2	299.4	0.021	2.31	0.45	$9.1 \cdot 10^{-3}$	20.3 ± 0.1
3	354.5	0.030	2.46	0.40	$1.21 \cdot 10^{-2}$	24.0 ± 0.1
5	337.2	0.100	1.54	16.3	1.48	19.6 ± 0.1

[a] Obtained from fitting the theoretical curve to the results of 3 to 6 values of the mixing time (see text). [b] Sum of forward and backwards reaction rates. [c] Major → minor.

In conclusion, it should be understood that the ring-flip process, which eventually converts a compound into its enantiomer, must involve a transition state in which the amide and the aromatic moieties are essentially coplanar. If C-7 is unsubstituted, this is accommodated by a partial rotation of the acyl unit out of resonance, without quite reaching the transition state for amide rotation. For **5**, the 7-methyl substituent blocks the pathway followed by the other acylated benzazocines, and, while amide rotation occurs with its expected energy barrier, enantiomerization is a very high-energy process.

Ground-State Structure. Room temperature NMR spectroscopic data for compounds **2**–**7** is presented in Table 3,

Table 4 and Table 5. Lack of proton signal overlap in the spectrum of thioacetamide **3** allowed us to do a full analysis of H-H coupling constants for this material. Since the spectral features of the other compounds in the series, and especially J_{HH}, when measurable (Table 4), are very similar, we conclude that, unless otherwise noted, we can speak in general about the whole family of these amides.

Table 3. ^{1}H NMR chemical shifts for **2**–**7**.

H	**2**[a]	**3**[a]	**4**[a,d]	**5**[a,e]	**6**[b]	**7**[c]
2α	4.76	5.63	4.73	4.72	4.65	4.74
2β	2.76	3.12	2.69	2.48	3.10	2.61
3α	1.39	1.94	1.43	1.77	1.78	1.94
3β	1.69	1.49	1.66	1.54	1.45	1.65
4α	1.55	1.69	1.58	1.65	1.94	1.50
4β	1.35	1.33	1.29	0.96	1.81	1.69
5α	1.50	1.87	1.54	1.68	2.81	4.06
5β	1.88	1.55	1.81	1.62	3.36	4.27
6α	2.64	2.48	2.26	2.67		
6β	2.64	2.65	3.06	2.73		
7	7.27	7.29			8.1	7.20
8	7.29	7.35		7.03	7.5	7.13
9	7.31	7.31	6.81	6.98	7.6	7.32
10	7.10	7.07	6.84		7.2	7.12
CH_3CO	1.76	2.18	1.82			
$(CH_3)_3CO$				0.96	0.98	0.97

[a] At 297 ± 2 K in $CDCl_3$. [b] At 210 ± 2 K in $CDCl_3$. [c] At 250 ± 2 K in $CDCl_3$. [d] 7-OMe and 8-OMe: δ = 3.69 and 3.86 ppm, respectively. [e] 7-Me and 10-Me: δ = 2.30 and 2.20 ppm, respectively.

Table 4. J_{HH} values for **2**–**7**.[a]

J_{HH}	**2**	**3**	**4**	**5**	**6**	**7**
2α,2β	13.5	13.3	13	13.2	13	13.5
2α,3α	3	3.1	3	2.5	3	3
2α,3β	8.5	8.0	8	5.9	11	6
2β,3α	8	8.1	8	10.2	3	10
2β,3β	3	2.8	3	2.2	3	2
3α,3β	15	15.4	15	15.2	13	14.5
3α,4α	1	0.8	1	1.0		1
3α,4β	10	9.9	10	10.0		10
3β,4α	11	9.7	10	10.0	12	9.5
3β,4β	1	1.0	1	0.5	3	1
4α,4β	14	14.7	14.5	12.5	15	14.5
4α,5α	4	4.2	4.5	4.5	6	4
4α,5β	6.5	6.6	6.5	6.5	12	11.5
4β,5α	10	9.8	10	10.0		3
4β,5β	3	4.2	4	4.5	6	3.5
5α,5β	12	13.7	14	12.8	13	11.5
5α,6α	4	4.3	4	4.5		
5α,6β	4	4.2	4	3.4		
5β,6α	12.5	12.7	13	12.8		
5β,6β	4	4.2	4	4.6		
6α,6β	[a]	13.7	13	13.4		
7,8	7	7.3			7.5	7.5
7,9	1	1.5			1	1.5
8,9	7	7.5		7.8	7.5	7.5
8,10		1.2			0.5	1.5
9,10	7	7.5	8.5		7.5	7.5

[a] Cannot be measured due to the close proximity of the chemical shifts of these protons.

The coupling constants in Table 4 are unexpected. Most often, adjacent methylenes in a chain tend to be staggered. This reflects itself in one large vicinal interaction (an *anti* relationship, ca. 12 Hz) and three smaller ones (*gauche* relationships, ca. 4 Hz). The Table reveals that, except for the 5–6 methylene pair, two coupling constants are larger (but usually <12 Hz) and two are smaller. This is also reflected in NOE interactions: in the typical staggered arrangement, the two protons in the *anti* relationship show a significantly weaker NOE interaction than the other three (*gauche*) pairs. The cross-peaks detected in a NOESY spectrum show here too that the 5–6 methylene pair is conventional; for the other adjacent methylenes, however, all vicinal NOE interactions are strong. Furthermore, one expects that only the two pseudoaxial protons in a 1,3 relationship should be close in space (less than 3.5 Å) – therefore, if an NOE interaction is detected between 2α and 4α, there should not be one between 2β and 4β, or vice versa. For **3**, both pairs of protons show significant NOE cross-peaks [as a matter of

Table 5. ^{13}C NMR chemical shifts for **2**–**7**.

C	**2**[a]	**2**[a,b]	**3**[a]	**4**[a,c]	**5**[a,d]	**6**[e]	**6**[b,e]	**7**[e]
2	50.00	53.75	58.45	50.31	53.17	49.90	49.57	53.50
3	26.22	26.28[f]	25.33	26.48	26.19	22.54[f]		26.06[f]
4	26.34	27.27[f]	25.99	26.28	28.41	23.68[f]		27.79[f]
5	31.33	31.27	31.02	29.95	26.36	40.83	39.69	75.80
6	30.78	30.90	30.23	23.96	27.05	201.38	200.20	
7	130.28	129.96	130.49	147.26	134.24	131.05[g]	131.21[g]	130.53
8	128.33		129.28	152.60	129.87	130.20[g]	129.57[g]	124.99
9	128.78		128.10	110.37	128.16	134.45	135.56	130.10
10	127.49		125.06	122.78	132.57	128.94	128.05	123.04
11	141.86		143.49	135.64	142.24	141.68	142.92	139.00
12	141.28		139.17	134.96	139.30	137.26	136.43	155.35
$CH_3\mathit{C}O$	170.43		201.06[h]	170.71				
$\mathit{C}H_3CO$	22.47		33.86[h]	22.32				
$(CH_3)_3C\mathit{C}O$					177.17	178.40	178.18	177.30
$(CH_3)_3\mathit{C}CO$					41.37	42.22	40.22	40.73
$(\mathit{C}H_3)_3CCO$					29.23	29.38	27.86	28.75

[a] In $CDCl_3$ at 297 ± 2 K. [b] Minor amide rotamer. [c] 7-OMe and 8-OMe: δ = 60.97 and 55.63, respectively. [d] 7-Me and 10-Me: δ = 19.38 and 18.11, respectively. [e] In CD_2Cl_2 at 200 ± 2 K. [f] Chemical shifts with the same superscript within a column may be interchanged. [g] Chemical shifts with the same superscript within a column may be interchanged. [h] CH_3CS moiety.

Table 6. Calculated vs. experimental vicinal coupling constants for amide **2**.

		Calculated (MM3)					Experimental
		A		B		60% A	
H–C–C–H		dihedral angle	$^3J_{HH}$	dihedral angle	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HH}$
2α	3α	88	2.2	62	2.4	2.3	3
2α	3β	48	4.5	177	12.5	7.7	8.5
2β	3α	179	12.5	54	3.6	8.9	8
2β	3β	88	1.8	61	3.1	2.3	3
3α	4α	94	0.4	90	0.4	0.4	1
3α	4β	152	10.3	25	9.6	10.0	10
3β	4α	22	10.1	155	10.9	10.4	11
3β	4β	93	0.5	90	0.3	0.4	1
4α	5α	54	4.1	60	4.2	4.1	4
4α	5β	62	2.6	175	13.0	6.8	6.5
4β	5α	188	12.7	54	4.0	9.2	10
4β	5β	52	4.5	60	3.0	3.9	3
5α	6α	51	4.8	75	1.0	3.3	4
5α	6β	64	2.3	40	6.8	4.1	4
5β	6α	167	12.6	169	12.8	12.7	12.5
5β	6β	52	4.6	65	1.0	3.2	4
relative energy		0.00		0.32 kcal·mol^{-1}			

definition, in the tables, protons labeled "α" are positioned on the same side of the plane of the aromatic ring as the amide (or thioamide) moiety].

All these results strongly suggest that the room temperature NMR spectrum actually reflects two or more fastly equilibrating conformers (for each of the amide rotamers). In order to explore this possibility, we performed molecular mechanics calculations for amide **2**. We used the GMMX subroutine of PCModel,[5] which performs a random search for low-lying conformers. We then optimized the geometries and the energies of the latter with the MM3 force field. It turns out that two different conformations of the eight-membered ring are found, with an energy difference of 0.32 kcal·mol^{-1} (see Table 6). While in both conformers the nitrogen atom and carbons 2, 5 and 6 are roughly coplanar, in conformer "A" C-3 is below this plane (on the α-side of the molecule) and C-4 is above it (on the β-side), while in conformer "B" the orientations of the latter two carbons are reversed (see Figure 2). Furthermore, if we calculate weighted averages of the $^3J_{HH}$ values predicted for the two conformers, using weights of 0.6 and 0.4 for A and B, respectively, the results closely mimic the experimental values of the vicinal coupling constants. These estimates of ΔG_0 are in good agreement, as K = 0.6:0.4 = 1.5 corresponds, at room temperature, to an energy difference of 0.24 kcal·mol^{-1}.

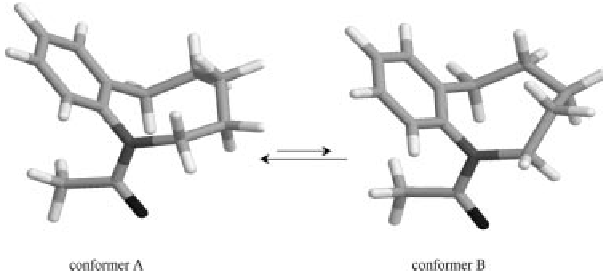

Figure 2. Calculated conformations for *N*-acetylbenzazocine (**2**).

We were able to confirm the assumption that the acylated benzazocines exist as a mixture of rapidly interconverting eight-member ring conformers by taking ^{13}C spectra of parent compound **2**, at low temperatures, in $CDCl_2F$ as a solvent (see Figure 3). Below –70 °C, several of the lines broaden considerably and eventually split into two unequal peaks in a 2.8:1 ratio (δ = 22.56 and 19.81 for the acetyl

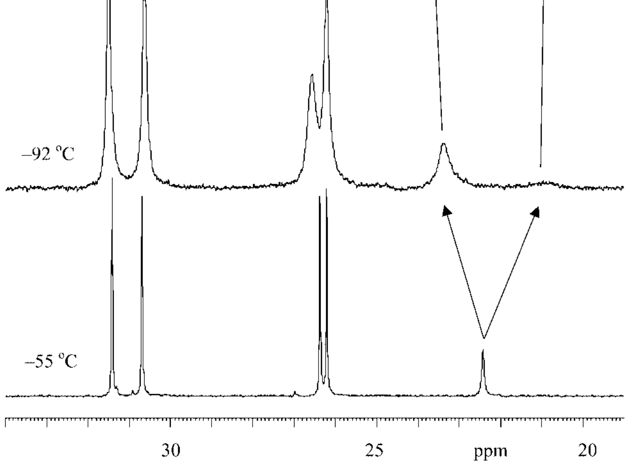

Figure 3. ^{13}C spectra of *N*-acetylbenzazocine (**2**), in $CDCl_2F$ as a solvent. As can be seen, several of the lines broaden considerably at low temperatures. Significantly, the signal for the CH_3 of the acetyl moiety at ca. δ = 22 splits into two unequal peaks corresponding to the two conformational isomers of the eight-membered ring (see text and Figure 2).

methyl group of the major and minor isomers, respectively, at –112.5 °C; ΔG^0 = 0.33 kcal·mol^{-1}). From a lineshape analysis at –92.4 °C, we obtain a major → minor rate constant of 150 s^{-1}, corresponding to an activation barrier of 8.6 kcal·mol^{-1}.

Conclusion

We are able to identify three different dynamic processes in the title compounds. In ascending order of energies, the first ($\Delta G^{\ddagger}$ = 8.6 kcal mol^{-1} for parent amide **2**) involves a fast interconversion between two distinct conformers of the eight-membered ring, which differ in ground state energy by ca. 0.3 kcal·mol^{-1}. The next process ($\Delta G^{\ddagger}$ = 19.2 kcal mol^{-1}) is the enantiomerization of the heterocyclic ring, which is correlated, but not concerted with the highest-energy process, amide rotation ($\Delta G^{\ddagger}$ = 20.3 kcal mol^{-1}).

Experimental Section

Molecular Mechanics Calculations: Initial ground state conformations were obtained with PCModel;[5] the structures were optimized with the MMX force field included in this package, which is based on Allinger's MM2. More accurate calculations were then performed with the MM3 force field (versions 1994 and 1996).

NMR Spectroscopy: NMR spectra were run at 600.1 (^{1}H) and 150.9 MHz (^{13}C) on a Bruker DMX-600 instrument. Probe temperatures were measured with a calibrated digital thermometer; we estimate temperatures to be accurate to ±0.5 K. Peak assignments in Table 3 and Table 5 were unambiguously determined with the aid of two-dimensional techniques such as COSY, HMQC and HMBC. NOE interactions were detected in NOESY spectra. NMR lineshape analyses were performed using computer programs based on the equations of Alexander[6] for the case of two spin-coupled exchanging protons (in the ring-flip process, see text) or of Sutherland[7] for the case of two exchanging singlets. For more details on the EXSY technique (2D-NMR Exchange Spectroscopy), used to determine the rates of amide (or thioamide) rotation, see ref.[3].

Synthesis of Hexahydrobenzazocines

1-Acetyl-1,2,3,4,5,6-hexahydro-1-benzazocine (2) has been reported in the literature.[8] For this study, we prepared it starting from benzosuberone, via a Schmidt rearrangement followed by LAH reduction and acylation. $C_{13}H_{17}NO$ (203) calcd. C 76.81, H 8.43; found C 76.77, H 8.47.

1-Thioacetyl-1,2,3,4,5,6-hexahydro-1-benzazocine (3) was prepared by the reaction of **2** (0.2 g, 1.2 mmol) with an equivalent amount of 2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide (Lawesson's reagent) in HMPA (2 mL), for 9 h at 85 °C, according to the established procedure.[9] **3** (0.1 g, 0.5 mmol, 47%) was purified by column chromatography (silica gel, 1:1 ether/pentane) and obtained as pale yellow crystals; m.p. 75–78 °C. HRMS: *m*/*z* calcd. for $[C_{13}H_{17}NS+H]^+$ 220.1159; found 220.1159.

1-Acetyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydro-1-benzazocine (4): A mixture of 2,3-dimethoxybenzaldehyde (15 g, 90 mmol) and of methyl crotonate (18 g, 180 mmol) was added dropwise to a cooled suspension of potassium *tert*-butoxide (30 g, 267 mmol) in *tert*-butyl alcohol (250 mL, temp. kept below 20 °C), and the reaction mixture was stirred overnight at room temp. The reaction mixture was acidified (AcOH) and extracted with $CHCl_3$. The oily residue of the extraction was saponified with NaOH (40 g) in H_2O (100 mL) and EtOH (200 mL). The basic solution was washed with Et_2O, acidified with concd. HCl and the yellow precipitate was washed with H_2O and dried under high vacuum. The crude **5-(2′,3′-dimethoxyphenyl)pentadienoic acid** (19 g, 81 mmol, 90%) was used without purification in the next step. This acid (10 g, 43 mmol) was dissolved in AcOH (200 mL) with the addition of 10% Pd/C (1 g) and the mixture hydrogenated overnight at 25 psi. After filtration and evaporation an oily product was left. Distillation gave pure **5-(2′,3′-dimethoxyphenyl)pentanoic acid** (9 g, 38 mmol, 88%; b.p. 161–164 °C at 0.2 Torr). This acid (27 g, 113 mmol) was mechanically stirred with of polyphosphoric acid (PPA, 550 g) for 40 h at 40 °C; the obtained mass was treated with ice water, and extracted with CH_2Cl_2 (300 mL). The organic solvent was dried (Na_2SO_4) and evaporated, and the residue recrystallized from petroleum ether to yield **6,7-dimethoxybenzosuberone** (16 g, 73 mmol, 65%; m.p. 47 °C). This ketone (11 g, 50 mmol) was dissolved in concd. HCl (180 mL), the solution was cooled and NaN_3 (4.9 g, 75 mmol) was added in small portions, so as to keep the temp. below 8 °C. The reaction mixture was then stirred for 90 h at room temp, poured into H_2O (500 mL) and extracted with $CHCl_3$ (2×200 mL). After the organic solvent was dried (Na_2SO_4) and evaporated, the residue was shown by TLC to consist of a mixture of two isomeric lactams. The first band to elute from a silica gel column ($CHCl_3$) was crystallized from MeOH to yield **7,8-dimethoxy-3,4,5,6-tetraahydro-1-benzazocin-2(1*H*)-one** (7 g, 30 mmol, 41%, m.p. 183–184 °C); $C_{13}H_{17}NO_3$ (235) calcd. C 66.36, H 7.28, N 5.95; found C 66.41, H 7.30, N 5.95. This lactam (7 g, 30 mmol) was added in small portions to a slurry of $LiAlH_4$ (4 g, 105 mmol) in anhydrous ether (250 mL). The mixture was refluxed for 40 h, after which the excess hydride was decomposed with $Na_2SO_4·10H_2O$. The solids were extracted with boiling ethyl acetate(2×250 mL); the combined organic phases were evaporated to dryness, and the resulting oil purified by distillation to yield **7,8-dimethoxy-1,2,3,4,5,6-hexahydro-1-benzazocine** (5 g, 23 mmol, 77%; b. p. 161–164 °C at 0.2 Torr). This amine (5 g) was dissolved in a mixture of benzene (40 mL), acetic anhydride (40 mL) and triethylamine (5 mL) and stirred overnight at room temp. Ether (400 mL) was then added, and the red solution was extracted with 1 N HCl until the washings were colourless, then washed with satd. NaCl and ammonia. The organic layer was dried (Na_2SO_4), then all volatile components were evaporated. The resulting red oil was treated with charcoal in boiling ligroin. The now colourless oil treated with ether/petroleum ether at 0 °C to yield crystalline **4**, (4 g, 15 mmol, 65%; m.p. 85–86 °C). $C_{15}H_{21}NO_3$ (263) calcd. C 68.41, H 8.04, N 5.32; found C 68.43, H 8.10, N 5.31. HRMS: *m*/*z* calcd. 263.1521; found 263.1517.

7,10-Dimethyl-1-pivaloyl-1,2,3,4,5,6-hexahydro-1-benzazocine (5): 6,9-Dimethylbenzosuberone[10] (19 g, 93 mmol, prepared from 2,5-dimethylbenzaldehyde in a sequence of reactions similar to the one in the previous paragraph), $NH_2OH·HCl$ (14 g, 201 mmol), pyridine (200 mL) and EtOH (100 mL) were refluxed for 25 h. The solvents were then evaporated and the residue was dissolved in ether/water. The organic layer was washed with satd. citric acid, then satd. NaCl and evaporated to yield an oil, which was triturated with petroleum ether to give crude **6,9-dimethylbenzosuberone oxime** (10 g, 46 mmol, 49%, as an amorphous white powder) which was used without purification in the next step. The oxime (9 g, 41 mmol) and PPA (200 g) were stirred for 15 min at 130 °C; after cooling and treatment with ice water(1 L), the mixture was extracted with $CHCl_3$ (2×200 mL). The organic layer was washed with H_2O, dried and evaporated, and the residue was shown by TLC to consist of a mixture of two isomeric lactams. The first band to elute from a silica gel column ($CHCl_3$) was crystallized from

CH_2Cl_2/petroleum ether to yield **7,10-dimethyl-3,4,5,6-tetraahydro-1-benzazocin-2(1*H*)-one** (6 g, 27 mmol, 66%, m.p. 162 °C). This lactam (4 g, 18 mmol) was added in small portions to a slurry of $LiAlH_4$ (3 g, 79 mmol) in anhydrous ether (200 mL). The mixture was refluxed for 40 h, and workup as described above yielded **7,10-dimethyl-1,2,3,4,5,6-hexahydro-1-benzazocine** (b.p. 77–80 °C at 0.03 Torr). $C_{13}H_{19}N$ (189) calcd. C 82.48, H 10.12, N 7.34; found C 82.39, H 10.12, N 7.39. To a solution of this amine (2.3 g, 12 mmol) in anhydrous benzene (50 mL), pivaloyl chloride (1.2 g, 10 mmol) was added while stirring, and a precipitate formed immediately. Triethylamine (2 mL) was then added and the mixture was stirred for 24 h at room temp. 300 mL of ether was then added, and the solution was washed with satd. NaCl, 1 *N* HCl and again satd. NaCl. The organic layer was dried (Na_2SO_4), and evaporated, resulting in a red oil, which was treated with charcoal in boiling ligroin. On evaporation of the solvent and cooling, crystals of **5** were formed (2 g, 7 mmol, 58%), m.p. 42 °C. $C_{18}H_{27}NO$ (273) calcd. C 79.07, H 9.95, N 5.12; found C 79.03, H 9.96, N 5.11. HRMS: *m*/*z* calcd. 273.1779; found 273.1780. From Prof. Albrecht Mannschreck (University of Regensburg, vide supra) we learnt that for the pure (–)-enantiomer the m.p. is 46–50 °C, and $[a]_{365}^{16.5} = -133 \pm 5$.

1-Pivaloyl-2,3,4,5-tetrahydro-1-benzazocin-6(1*H*)-one (6): The known 1,2,3,4,5,6-hexahydro-1-benzazocin-6-ol[11] (1.77 g, 10 mmol) was added to a solution of pivaloyl chloride (1.44 g, 12 mmol) in benzene (60 mL) at room temp. After 2 min, a precipitate started to appear, and triethylamine (1.5 g) was added to the solution, which was then stirred for a further 40 min. Ether was added (200 mL) and the organic the mixture was washed with dilute citric acid and then H_2O. The residue from the organic layer was recrystallized from petroleum ether to yield of **1-pivaloyl-1,2,3,4,5,6-hexahydro-1-benzazocin-6-ol** (1.7 g, 7 mmol, 70%); m.p. 186–188 °C, $C_{16}H_{23}NO_2$ (261) calcd. C 73.56, H 8.81; found C 73.48, H 8.87. This alcohol (1.4 g, 5.4 mmol) was dissolved in pyridine (20 mL) and added to CrO_3/pyridine reagent [prepared by slowly adding CrO_3 (1.7 g) to pyridine (30 mL) at 0 °C; it took about 30 min until the orange complex was formed]. The alcohol solution was added with cooling so as to keep the temp. below 15 °C, and the final mixture was stirred overnight at room temp. It was then diluted with $CHCl_3$, filtered through Celite and washed with 2 N HCl and H_2O. The residue of the organic phase was purified by column chromatography (silica gel, $CHCl_3$). The resulting oil solidified on trituration with ether and was recrystallized from CH_2Cl_2/ether to give **6** (1.2 g, 4.6 mmol, 85%, m.p. 120–121 °C), $C_{16}H_{21}NO_2$ (259) calcd. C 74.13, H 8.10; found C 74.12, H 8.14. HRMS: *m*/*z* calcd. 259.1573; found 259.1560.

1-Pivaloyl-2,3,4,5-tetrahydro-6*H*-1,6-benzoxazocine (7): The known 2,3,4,5-tetrahydro-6*H*-1,6-benzoxazocine[12] (2.48 g, 14.5 mmol) was treated with pivaloyl chloride (1.56 g, 12.9 mmol) as described in the previous paragraph. The resulting oil solidified on standing and was purified by a double recrystallization from hexane to yield **7** (2.5 g, 10.1 mmol, 78%, m.p. 108–109 °C), $C_{15}H_{21}NO_2$ (247) calcd. C 72.84, H 8.56, N 5.66; found C 72.88, H 8.58, N 5.65. HRMS: *m*/*z* calcd. 247.1572; found 247.1595.

Supporting Information (see footnote on the first page of this article): ^{13}C NMR spectrum of 1-thioacetyl-1,2,3,4,5,6-hexahydro-1-benzazocine (**3**) in $CDCl_3$.

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