MAGNETIC RESONANCE IN CHEMISTRY, VOL. 28, 423–425 (1990)

Stereochemistry of Benzannelated 1,6-Diazabicyclo[4.2.1]octadienes and the Conformation of Substituents on the Methylene Bridge

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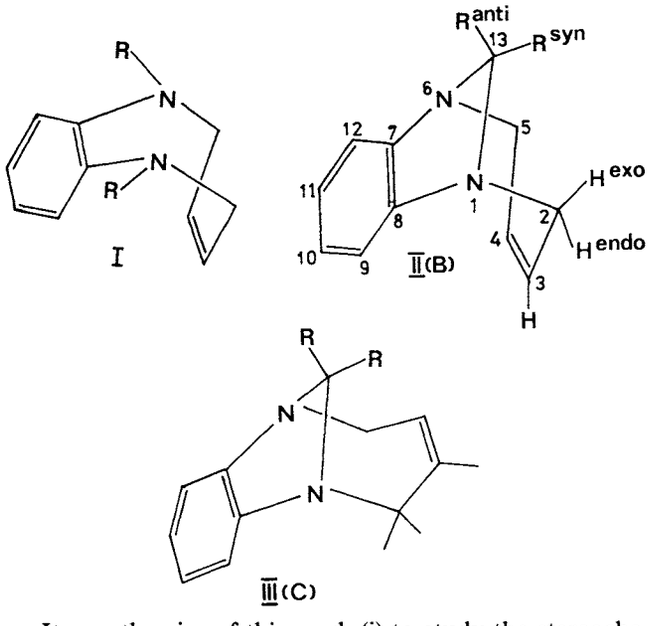
The stereochemistry of benzannelated 1,6-diazabicyclo[4.2.1]octa-3,7-dienes (the conformation of the eight-membered ring and of the variable substituents on the methylene bridge) was determined by means of NOE enhancements and stereospecific long-range H,H coupling constants in the relevant NMR spectra.

KEY WORDS Stereochemistry 1,6-Diheterobicyclo[4.2.1]octa-3,7-dienes W-coupling NOE

INTRODUCTION

Mono- and bis-benzannelated 1,6-dihetero-*cis,cis*-cycloocta-3,7-dienes prefer the boat conformation I as the ground state of the ring inversion process.[1,2] It is possible via the aminal formation reaction to overbridge 7,8-benzannelated 1,6-diaza-*cis,cis*-cycloocta-3,7-diene (I, R = H) for example, and thus to reduce the possible stereoisomers further to II(B) and III(C).



It was the aim of this work (i) to study the stereochemistry of some 13-substituted-7,8-benzannelated-1,6-diazabicyclo[4.2.1]octa-3,7-dienes **1–4** (see Scheme 1), (ii) to compare the conformational behaviour obtained (C ⇌ B of the eight-membered ring) with the monocyclic relatives[1,2] and (iii) to determine the conformation of the R substituents on the methylene bridge.

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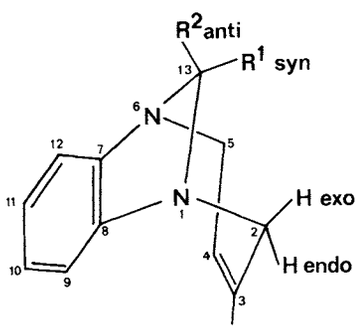


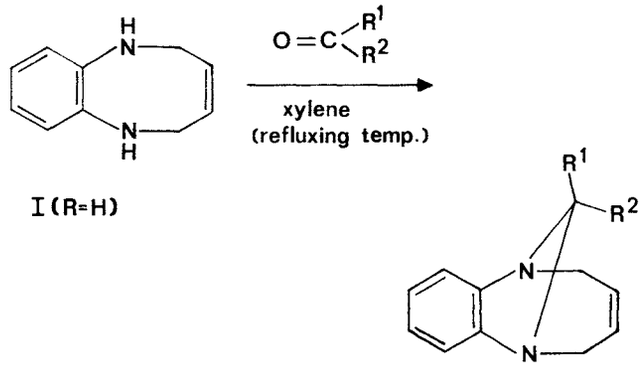
no.	R^1 ,	R^2
1	H ,	H
2	CH_3 ,	CH_3
3	H ,	Ph
4	H ,	Ph(p-NMe_2)

Scheme 1. Compounds studied.

RESULTS

Syntheses

Compounds **1–4** were prepared via the aminal formation reaction of 1,2,5,6-tetrahydro-1,6-benzodiazocine (I, R = H)[3] with different carbonyl compounds.[4]



Received 21 November 1989
Accepted 20 December 1989

The overbridging reaction was carried out in the case of acetone (to **2**), benzaldehyde (to **3**) and *p-N,N*-dimethylaminobenzaldehyde (to **4**) in xylene, by simply refluxing the reaction mixture. Compound **1** was formed from I (R = H) and paraformaldehyde in boiling xylene under acidic catalysis conditions. The respective animals **1–4** were isolated as colourless crystals in good yields (80–95%).

NMR study

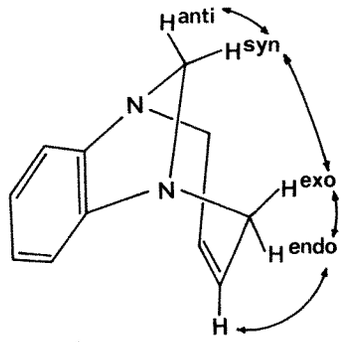
The NMR data for **1–4** (Scheme 1) studied at ambient temperature are given in Table 1. In addition, NOE experiments were carried out by irradiating the relevant ^1H NMR signals and identifying the NOE enhancements qualitatively in the difference mode.[5] These results are given in Table 1 as footnotes.

The assignments are unequivocal owing to the very characteristic absorption ranges and signal intensities for symmetry reasons. C-3,4 were differentiated from the aromatic carbon atoms by selective C,H decoupling experiments.

According to the stereochemistry of the compounds studied (**1–4**) the following NMR characteristics were noted.

(i) The NOEs obtained between H-13 (*syn*) [or CH_3 (*syn*)] and H-2,5 (*exo*) in **1–4** (see Table 1) can be expected only in the boat conformation (II-B).

(ii) The coupling pattern within the $-CH_2CH=$ moiety is as obtained for the non-bridged flexible analogues I[1,2] (^3J = 1.0–1.6 Hz), which suggests dihedral angles of *ca.* 90°. Very different coupling constants,



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according to the very different dihedral angles of *ca.* 0° and *ca.* 120°, are expected[6,7] from Dreiding models for the relevant chair conformation (III-C).

(iii) The stereospecific W-coupling between H-13 (*anti*) and H-2,5 (*endo*), obtained in **1**, is understandable only in the boat conformation of the eight-membered ring, owing to the planar precondition of all the atoms involved in the W-fragment.

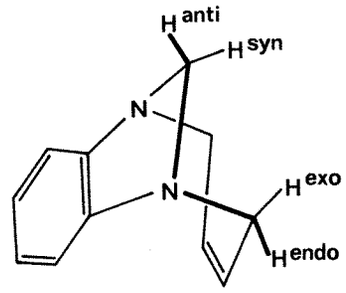

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Table 1. NMR parameters of the bridged benzannelated diazocines 1–4 in $CDCl_3$ [δ (TMS) (ppm)]

Compound	C-2,5 [H-2,5]	C-3,4 [H-3,4]	C-7,8	C-9–C-12 [H-9–H-12]	C-13	R^1, R^2
1	60.0[a]	126.1[a]	148.0[a]	124.9; 117.0[a]	76.2[a]	—
	[3.89 (d, m) and 3.67 (d, m)][c]	[5.26 (m)]	—	[7.04 (s)]	[4.38 (d, t) and 4.14 (d)][b]	—
2	55.8	127.7	148.6	124.6; 117.8	82.3	29.9; 18.7
	[3.73 (m)][d]	[5.23 (s, br.)][e]	—	[7.05 (m)][f]	—	[1.59; (s) *syn*][g] [1.22; (s) *anti*][f]
3	60.0	126.7	147.1	124.9; 117.3	86.5	141.7 (*i*); 128.0 (*m*); 126.6 (*o*); 127.4 (*p*)
	[4.08 (d, m) and 3.85 (d, m)][h]	[5.38 (s, br.)][i]	—	[7.05 (m)]	[5.26 (s)]	[7.23 (m, *meta, para*) 7.52 (d, d, *ortho*)]
4	59.9	126.5	147.2	124.7; 117.2	86.3	40.5; 112.3 (*o*); 127.2 (*m*); 129.9 (*i*); 150.1 (*p*)
	[4.05 (d, m); 3.82 (d, m)][h,i]	[5.35 (s, br.)]	—	[7.03 (m)]	[5.21 (s)]	[2.85 (s); 6.61 (d, m); 7.35 (d, m)]

[a] No change in line shape down to −120 °C ($CFCl_3$).
[b] J_{gem} = 10.3 Hz; no couplings to H-3,4 but ^4J[H-13 (*anti*), H-2,5 (*endo*)] = 1.1 Hz, NOE H-13 (*syn*), H-2,5 (*exo*) and NOE H-13 (*syn*), H-13 (*anti*).
[c] J_{gem} = 16.4 Hz, only small couplings ^3J(H-2,5/H-3,4) ≈ 1–1.6 Hz; H-2,5 *exo* coupling stronger than H-2,5 *endo*; NOE H-13 (*syn*), H-2,5 (*exo*); NOE H-2,5 (*endo*), H-3,4; NOE H-2,5 (*exo*), H-2,5 (*endo*).
[d] NOE H-2,5 (*exo*)/CH_3 (*syn*); NOE H-2 (*endo*)/H-3,4.
[e] NOE H-3,4/H-2,5 (*endo*).
[f] No NOE.
[g] NOE CH_3 (*syn*), H-2,5 (*exo*).
[h] J_{gem} = 16.5 Hz, NOE H-13 (*syn*), H-2,5 (*exo*) and NOE H-13 (*syn*), H_{ortho}.
[i] NOE H-2,5 (*exo*), H-2,5 (*endo*), NOE H-2,5 (*endo*), H-3,4, NOE H-13 (*syn*), H-2,5 (*exo*).

(iv) The H-13 (*syn*)/H-2,5 NOEs were also obtained, in **3** and **4**, showing the *anti*-arrangement of the phenyl substituents in these compounds.

(v) Identical conformations are expected for the compounds studied owing to the very similar ^{1}H and ^{13}C chemical shifts; the differences parallel the normal substituent effects.

(vi) In the presence of a phenyl substituent on the methylene bridge (**3**, **4**), the ^{4}J[H-13 (*anti*), H-2,5 (*endo*)] W-coupling is no longer obtained for the remaining single H-13 absorption. The triplet structure of the latter signal is due to ^{4}J[H-13 (*syn*), H-*ortho*], which was proved by H,H decoupling experiments. This result also corroborates the *anti* conformation of the phenyl substituent in **3** and **4**.

DISCUSSION

Heteroatoms and substituents on the eight-membered ring and on the methylene bridge have a strong influence on the preferred conformation for this type of compound. With respect to the eight-membered ring, both boat[8,9] and chair conformations[8,10] have been reported as the preferred conformers, in accord with parallel force field calculations,[9] ^{1}H and ^{13}C chemical shifts[9,10] and an independent LIS study.[9]

In the case of **1**–**4** according to (i)–(iii) and (v) above, it can be unequivocally stated that only a single stereoisomer is obtained, where the eight-membered ring is in the boat conformation II(B). The phenyl substituent on the methylene bridge in **3** and **4** is in the *anti* conformation, in line with (iv)–(vi) above, obviously for steric reasons.

EXPERIMENTAL

Syntheses

All melting points were determined using a Boetius M melting point apparatus; they are uncorrected.

1,2,5,6-Tetrahydro-1,6-benzodiazocine (I, R = H) was prepared as described previously.[3]

1,6-Methano-1,2,5,6-tetrahydro-1,6-benzodiazocine (1). A mixture of I (R = H) (1.6 g; 0.01 mol), paraformaldehyde (1.2 g) and one drop of sulphuric acid in xylene (50 ml) was heated for 8 h while refluxing. The bulk of the solvent was removed under reduced pressure. Recrystallization from light petroleum (b.p. 70–80 °C) of the solid obtained gave **1** (1.55 g; 90%; m.p. 93–94 °C). Found: C, 76.64; H, 7.11; N, 16.53. $C_{11}H_{12}N_2$ requires C, 76.71; H, 7.02; N, 26.27%. *m/z*: 172 (M^+, 65%), 157 (88%), 144 (32%), 132 (68%), 119 (100%), 92 (36%).

13,13-Dimethyl-1,6-methano-1,2,5,6-tetrahydro-1,6-benzodiazocine (2). A solution of I (R = H) (1.6 g; 0.01 mol) in acetone (20 ml) was heated at reflux for 6 h. After evaporation of the solvent and recrystallization from light petroleum (b.p. 70–80 °C), **2** was obtained (1.9 g; 95%; m.p. 92 °C). Found: C, 77.58; H, 8.31; N, 13.94. $C_{13}H_{16}N_2$ requires C, 77.96; H, 8.05; N, 13.99%. *m/z*: 200 (M^+, 70%), 185 (95%), 170 (22%), 157 (30%), 144 (40%), 132 (37%), 119 (100%), 92 (48%).

13-Phenyl-1,6-methano-1,2,5,6-tetrahydro-1,6-benzodiazocine (3). A solution of I (R = H), (2 g; 0.012 mol) and benzaldehyde (3 g, 0.028 mol) in xylene (60 ml) was heated for 4 h at reflux. After evaporation of the solvent and recrystallization from light petroleum (b.p. 70–80 °C), **3** was obtained (2.4 g; 80%; m.p. 90–91 °C). Found: C, 82.59; H, 6.31; N, 11.47. $C_{17}H_{16}N_2$ requires C, 82.22; H, 6.50; N, 11.28%. *m/z*: 248 (M^+, 60%), 157 (35%), 144 (20%), 132 (20%), 119 (63%), 92 (26%).

13-(*p*-*N*,*N*-Dimethylamino)phenyl-1,6-methano-1,2,5,6-tetrahydro-1,6-benzodiazocine (4). Reaction of I (R = H), (1.6 g; 0.01 mol) with *p*-*N*,*N*-dimethylaminobenzaldehyde (1.68 g; 0.011 mol) in xylene (50 ml) (as described previously for **3**) gave **4** (2.3 g; 80%), m.p. 199–202 °C (from *n*-heptane). Found: C, 77.91; H, 6.96; N, 14.02. $C_{19}H_{21}N_3$ requires C, 78.31; H, 7.26; N, 14.42%. *m/z*: 291 (M^+, 69%), 157 (21%), 144 (41%), 134 (100%), 132 (30%), 119 (34%), 92 (26%).

NMR spectroscopy

The NMR spectra were obtained at 200.13 MHz (^{1}H) and 50.327 MHz (^{13}C) using a Bruker WP-200 NMR spectrometer. The solvent was $CDCl_3$ and the chemical shifts are referenced to TMS (internal).

The regular Bruker software for the Aspect 2000 was used for the H,H decoupled and NOE difference spectra in the inverse-gated mode.

Acknowledgement

We thank Mrs Renate Mühlpfordt for recording the NMR spectra.

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