Stereochemical behaviour of κ-agonistic 2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonanones—influence of the substituent in position *N*3

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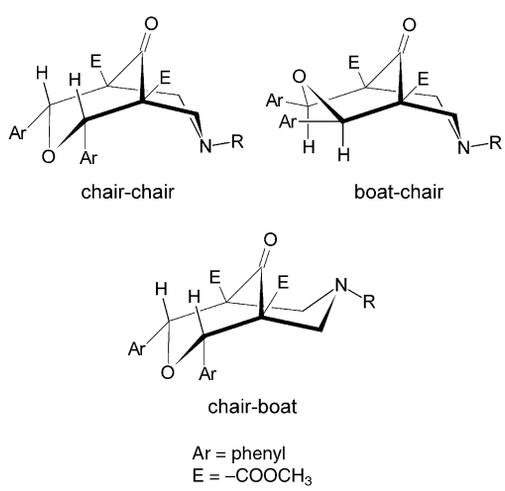
Received (in Cambridge, UK) 26th October 2000, Accepted 3rd August 2001
First published as an Advance Article on the web 12th September 2001

2,4-Diaryl substituted 3,7-diazabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylates are attracting interest as opioid-like analgesics. Since the stereochemistry is of great importance for a high affinity to the κ-receptor, the influence of substituents on the skeleton has to be considered. As a part of a greater project the influence of substituents in position *N*3 of the 3,7-diazabicyclo[3.3.1]nonanone on the conformation and configuration of the ring system was studied here. Whereas the variations of the substitution pattern of the arene rings revealed the *cis* substituted isomers in a chair–chair conformation mostly to be the thermodynamically stable form, alkyl substituents at N3 of increasing size induce the *trans* configuration of the phenyl rings often combined with a boat–chair conformation. The configuration was confirmed by X-ray analysis. Semiempirical calculations were performed to elucidate the thermodynamic stability of the isomers. However, some substituents having unsaturated bonds, such as propargyl (prop-2-enyl) and phenylethyl residues, seem to stabilise the *cis* configuration of the arene rings in a chair–chair conformation.

Introduction

2,4-Diarene substituted 3,7-diazabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylates are attracting pharmacological interest because of their antiarrhythmic[1,2] and opioid-like analgesic activity.[3–8] Recently, the usefulness of 2,4-dipyridin-2-yl substituted diazabicyclononanes as very rigid tetradentate ligands for cobalt(II),[9,10] copper(I)[11] and manganese[12] complexes was reported. In all cases the stereochemistry of the molecules is of great importance, either to bind to the receptor protein with high affinity or to complex the metals strongly.

Within the series of heterocyclic 7-azabicyclononanes, the 2,4-diphenyl substituted 3-oxa-7-aza-9-oxobicyclo[3.3.1]-nonane-1,5-dicarboxylates were found to exhibit an unexpected isomerism: commonly, both heterocyclohexanone rings take a chair conformation with the arene substituents in equatorial positions resulting in a symmetrical chair–chair conformation of the bicyclic ring system. In addition, a second symmetrical isomer was isolated which is characterized by a chair conformation of the piperidone ring and a boat conformation of the oxacyclohexanone ring with both phenyl rings in an equatorial position.[13] This is not a simple (chair–chair)–(boat–chair) conformational isomerism, because with respect to the position of the phenyl rings an additional configurational change has taken place upon isomerization (see Scheme 1): the interconversion of the chair conformation with the phenyl rings in equatorial positions into a boat conformation should have resulted in the arenes being in a quasi-axial position. However, the phenyl rings were found to be in a quasi-equatorial position in the boat. Thus, the configuration had changed by a ring-opening–ring-closure procedure (see below for the mechanism). Since the boat–chair isomer can be converted into the chair–chair isomer by refluxing in methanol, the chair–chair isomer is supposed to be thermodynamically more stable. This experimental finding was confirmed by semiempirical calculations.[14]



Scheme 1 Structure of the chair–chair, boat–chair and chair–boat isomers of the oxaazabicyclo[3.3.1]nonanone.

In addition to the conformational and configurational isomers discussed above, a chair–boat conformation was found when N7 carries large substituents such as *tert*-butyl or adamantyl residues.[14,15]

The 3,7-diazabicyclo[3.3.1]nonanone-1,5-dicarboxylates can be synthezised by a double Mannich reaction starting off with the condensation of 1 mole of a corresponding primary amine, and 2 moles of an arylaldehyde and dialkyl oxoglutarate. The thus obtained piperidones can be converted with formaldehyde and a corresponding primary amine to give diazabicyclononanones of a varying substitution pattern (see Fig. 1). The stereochemical behaviour observed till now is slightly different from the behaviour of the oxaazabicyclononanones. Caujolle *et al.* reported an equilibrium between a chair–chair conformation

DOI: 10.1039/b008648g

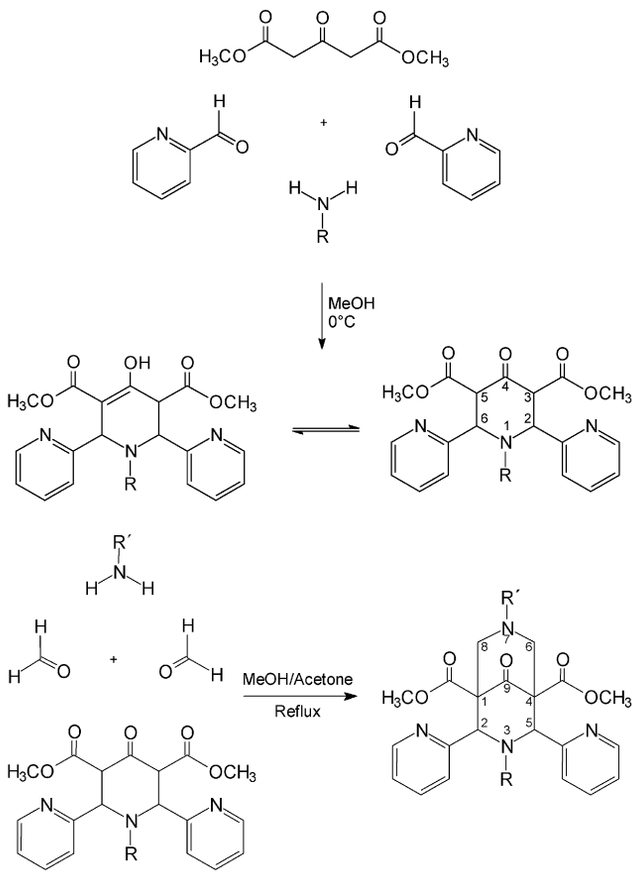


Fig. 1 Synthesis pathway giving the diazabicyclononanones.

and a chair–boat conformation with the boat in the less substituted piperidone ring (highly numbered; see Fig. 1), which depends on the size of the substituent in position N7. Diazabicyclononanes with small substituents in position 7 prefer a chair–chair conformation. With increasing steric bulk of the N7-substituent the percentage of molecules in a chair–boat conformation increases (*cf*. Scheme 1). However, even when N7 bears an adamantyl substituent, the number of molecules in the chair–chair conformation still surpasses the amount of molecules in the chair–boat conformation.[16] The chair–chair conformation could be verified for the 2,4-diphenyl substituted 3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate by X-ray analysis.[17] However, no boat–chair isomers corresponding to the oxaazabicyclononanone isomers (see Scheme 1) have yet been observed.

While synthesising a large number of 2,4-diaryl substituted diazabicyclononanones with a wide range of different substituents on the arene rings, the rotational restriction around the C2–aryl and C4–aryl axes, respectively, was observed by increasing the size of the N3-substituent from a hydrogen atom to a methyl group. Thus, in cases where *ortho*- or *meta*-substituted phenyl rings or naphthyl or quinolinyl residues were attached to C2 and C4, the substituents can either both point in the direction of the keto carbonyl group (*cf*. **I** in Scheme 2) or both to the bottom of the molecule (**III**) or in different directions (**II**).[8,18] This can be monitored spectroscopically by ^{1}H NMR by the chemical shifts of the signals for the hydrogens attached to C2 and C4 as well as the signals of the neighbouring arene substituents and confirmed by NOE experiments.[8,18] However, even the non-substituted phenyl rings show an individual set of signals for the hydrogens at each side of the phenyl ring.[3] For the bis(*m*-chlorophenyl) substituted compound the rotational barrier was determined spectroscopically by NMR to amount to 17–18 kcal mol^{-1}. The large 1-naphthyl or quinolin-4-yl rings completely restrict the rotation. Thus, the

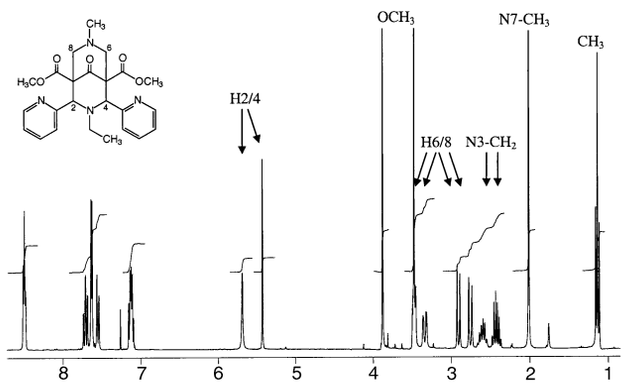


Fig. 2 ^{1}H NMR spectrum of the ethyl substituted diazabicyclononanone **1** (300 MHz, $CDCl_3$).

configurational isomers can only interconvert by cleavage of C–C bonds.[19]

In addition, Caujolle *et al.*,[16] Samhammer *et al.*,[3] and Siener *et al.*[19] observed the formation of *trans* substituted isomers with respect to arene rings when performing the last Mannich reaction of the synthesis under cooling (*cf.* **IV** in Scheme 2). Recrystallization of the *cis*–*trans* mixture of isomers from protic solvents such as methanol or ethanol always resulted in the pure *cis* isomer indicating the thermodynamic stability of this isomer. The activation enthalpy for the *trans*–*cis* isomerization was measured to be 25 kcal mol^{-1} by NMR spectroscopy. Semiempirical calculations revealed a sequence of retro-Mannich (ring-opening by breakage of the C1–C2 and C4–C5 bonds, respectively) and Mannich reaction (ring-closure) to be the mechanism of the isomerization.[19] However, in the case of the quinolin-2-yl substituted diazabicyclononane only the *trans* isomer was isolated which was found to be due to the stereochemical overcrowding of the molecule in the transition state of the reaction pathway. It was impossible to convert this *trans* isomer into the *cis* form.[19]

Summing up, it is safe to state that the stereochemistry of the diazabicyclononanones depends sensitively on the substituents in position 2 and 4 as well as in position N7. Since no systematic study has been performed with respect to substituent variation in position N3 the purpose of the investigations presented here was to systematically increase the size of this substituent in order to elucidate the stereochemical behaviour of the bicyclic system.

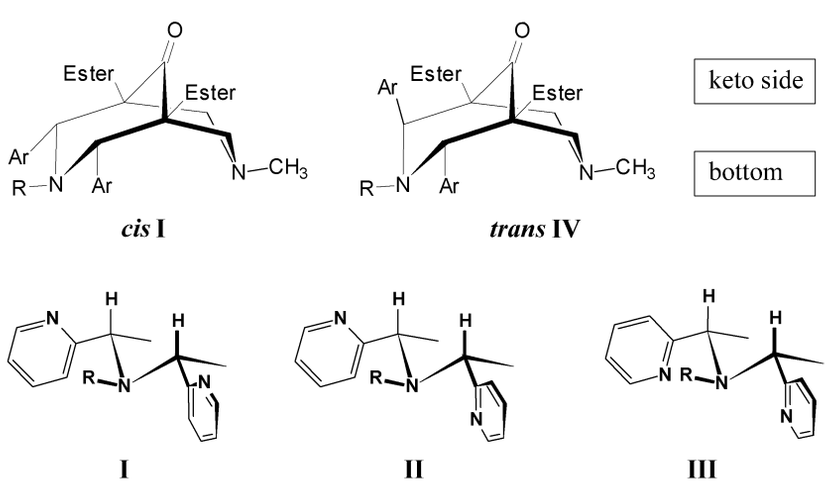
Results and discussion

A series of 2,4-dipyridin-2-yl substituted 1,5-dimethyl-3,7-diaza-9-oxobicyclo[3.3.1]nonane-1,5-dicarboxylates having substituents of increasing size attached to the nitrogen N3 has already been synthesized (see Fig. 1 and Table 1) for pharmacological purposes.[7] In contrast to HZ1 and HZ2, none of the compounds **1**–**6** showed any affinity to the κ-opioid receptor which is associated with analgesic activity.

The ^{1}H and ^{13}C NMR spectra of the *N*3H- and *N*3-methyl substituted compounds HZ1 and HZ2, respectively, and the *N*3-propargyl and *N*3-phenethyl substituted diazabicyclononanes **5** and **6** showed half a set of signals indicating a symmetrical *cis* configuration in a chair–chair conformation. In comparison, for the *N*3-ethyl, -propyl, -butyl and -allyl compounds **1**–**4** the set of signals was "doubled" (see Fig. 2, Tables 2 and 3). From the NMR spectra it was impossible to decide whether the molecules adopt the aforementioned nonsymmetrical *cis* conformation (*cf*. **II** in Scheme 2) or a *trans* configuration (*cf*. **IV**). In order to elucidate the stereochemistry, X-ray analysis of the *N*3-butyl substituted compound **3** was representatively performed. Fig. 3 displays the structure with the numbering used in the crystallographic study. Interestingly, the

Table 1 Calculated heats of formation ΔH_f (C/C indicates chair–chair; B/C indicates boat–chair)

Compound	Isomer isolated	Isomer calculated	ΔH_f(PM3)/ kcal mol^{-1} boat–chair	ΔH_f(PM3)/ kcal mol^{-1} chair–chair	ΔH_f(AM1)/ kcal mol^{-1} boat–chair	ΔH_f(AM1)/ kcal mol^{-1} chair–chair
HZ1 (NH)	*cis*-Sym (**III**) C/C	*cis*-Sym (**I**)	−102.23	−106.62	−85.54	−86.09
		cis-Sym (**III**)	−101.93	−100.76	−82.50	−93.36
		cis-Non-sym (**II**)	−102.64	−104.24	−84.46	−84.32
		trans	−101.42	−105.62	−84.27	−84.87
HZ2 (*N*-Methyl)	*cis*-Sym (**III**) C/C	*cis*-Sym (**I**)	−95.14	−105.34	−73.05	−78.82
		cis-Sym (**III**)	−95.65	−98.69	−67.78	−72.69
		cis-Non-sym (**II**)	−95.72	−102.53	−70.75	−76.45
		trans	−99.08	−104.36	−73.61	−77.52
1 (*N*-Ethyl)	*trans* B/C	*cis*-Sym (**I**)	−99.12	−111.26	−76.01	−84.56
		cis-Sym (**III**)	−100.37	−104.36	−73.62	−78.38
		cis-Non-sym (**II**)	−99.10	−108.26	−73.62	−82.13
		trans	−104.91	−108.04	−78.82	−81.97
2 (*N*-Propyl)	*trans* B/C	*cis*-Sym (**I**)	−102.56	−116.87	−82.22	−91.32
		cis-Sym (**III**)	−106.06	−109.64	−80.37	−85.20
		cis-Non-sym (**II**)	−105.92	−113.68	−80.37	−88.93
		trans	−110.37	−113.36	−85.58	−88.78
3 (*N*-Butyl)	*trans* B/C	*cis*-Sym (**I**)	−106.27	−121.79	−87.19	−97.38
		cis-sym (**III**)	−111.28	−114.48	−86.61	−91.17
		cis-Non-sym (**II**)	−111.15	−118.65	−86.61	−94.96
		trans	−115.33	−118.19	−91.61	−94.83
4 (*N*-Allyl)	*trans* B/C	*cis*-Sym (**I**)	−74.04	−86.14	−51.74	−59.64
		cis-Sym (**III**)	−75.14	−79.12	−48.99	−53.57
		cis-Non-sym (**II**)	−73.34	−83.03	−51.74	−57.25
		trans	−79.56	−83.21	−53.78	−56.96
5 (*N*-Progargyl)	*cis*-Sym C/C	*cis*-Sym (**I**)	−43.48	−51.52	−19.92	−21.84
		cis-Sym (**III**)	−46.75	−45.28	−18.42	−16.41
		cis-Non-sym (**II**)	−45.50	−48.89	−17.36	−19.84
		trans	−51.35	−48.90	−23.61	−18.91
6 (*N*-Phenylethyl)	*cis*-Sym C/C	*cis*-Sym (**I**)	−71.49	−83.84	−49.60	−58.43
		cis-Sym (**III**)	−73.52	−76.82	−42.75	−51.98
		cis-Non-sym (**II**)	−73.12	−80.75	−47.20	−55.94
		trans	−76.36	−80.27	−53.02	−55.90



Scheme 2 Structures of isomers of the diazabicyclo[3.3.1]nonanones: the *cis*-symmetrical **I**, *cis*-non-symmetrical **II**, the *cis*-symmetrical **III** and the *trans* isomer **IV**.

crystal structure revealed a boat–chair conformation of the *N*3-butyl substituted diazabicycle with a boat in the higher substituted piperidone ring and, additionally, a *trans* configuration of the pyridine rings. The butyl group attached to position N3 is in an unexpected quasi-axial position and the methyl group attached to the nitrogen N7 in an equatorial position. Thus, a second *trans* isomer was found. This is the first time that such a boat–chair conformation was found in the series of diazabicyclononanones. To the best of our knowledge a *trans* configuration of the arene rings in a boat form was neither observed for 3,7-diaza- nor for 3-oxa-7-aza- or any other bicyclononanone of corresponding substitution pattern.

The "configurational switch" of one of the pyridine rings from an equatorial position to an axial one may have occurred with the piperidone which is the intermediate in the synthesis pathway (Fig. 1). For piperidones an equilibrium between the *cis*-keto and *trans*-enol form was observed (see Fig. 4). When the double bond is introduced into the ring system to give the enol form, the equatorial position of the neighbouring substituent becomes energetically unfavourable[20] and the system avoids this high energy state by a corresponding configurational change of this substituent to the axial position. The *trans*-enol isomers are likely to be the starting compound for the synthesis of diazabicyclononanones characterized by a *trans* configuration.

The lack of symmetry of the diazabicyclononane **3** explains the "doubled" set of signals observed in the NMR spectra (see Tables 2 and 3). In comparison to the symmetrical *cis* isomers in the chair–chair conformation both signals due to the hydrogens attached to C2 and C4 are downfield shifted which can be

Table 2 ^{1}H NMR spectroscopic data of the diazabicyclononanones studied (δ (ppm), J/Hz in brackets, $CDCl_3$)

Compound	Configuration	H2/4	H6/8	*N*7-CH_3	OCH_3
HZ1 (NH)	*cis*-sym	4.45	2.57/3.18	1.83	3.70
HZ2 (*N*-Methyl)	*cis*-Sym	4.70	2.47/2.97 (12)	2.00	3.80
HZ2 (*N*-Methyl)	*trans*	4.90	2.87/3.37 (12)	2.07	3.50
		5.14	3.10/3.70 (11)		3.82
1 (*N*-Ethyl)	*trans*	5.43	2.76/3.33 (12)	2.02	3.48
		5.69	2.91/3.47 (11)		3.88
2 (*N*-Propyl)	*trans*	5.41	2.75/3.34 (12)	2.03	3.49
		5.63	2.91/3.49 (11)		3.88
3 (*N*-Butyl)	*trans*	5.42	2.75/3.34 (12)	2.03	3.49
		5.66	2.92/3.48 (11)		3.88
4 (*N*-Allyl)	*trans*	5.41	2.75/3.32 (12)	2.04	3.48
		5.69	2.92/3.49 (11)		3.88
5 (*N*-Propargyl)	*cis*-Sym	4.97	2.67/3.08[a]	2.27	3.78
6 (*N*-Phenethyl)	*cis*-Sym	5.29	2.56–2.68[b]	2.26	3.83

[a] Broad signals. [b] Hidden by NCH_2CH_2.

Table 3 ^{13}C NMR spectroscopic data of the diazabicyclononanones studied (δ (ppm), $CDCl_3$)

Compound	Configuration	C1/5	C2/4	C6/8	C9	C=O	NCH_3
HZ1 (NH)	*cis*-Sym	61.2	66.1	59.9	204.7	168.9	44.5
HZ2 (*N*-Methyl)	*cis*-Sym	61.8	73.0	60.1	203.1	167.6	43.9
1 (*N*-Ethyl)	*trans*	62.4	67.1	61.1	205.6	170.0	43.7
		62.8	65.9	65.9		170.8	
2 (*N*-Propyl)	*trans*	62.4	67.5	61.2	205.5	170.0	43.7
		62.6	67.6	65.9		170.8	
3 (*N*-Butyl)	*trans*	62.4	67.6	61.2	205.5	170.0	43.7
		62.7	67.7	65.9		170.8	
4 (*N*-Allyl)	*trans*	62.3	67.2	61.2	205.4	169.8	43.7
		62.9	67.4	65.9		170.2	
5 (*N*-Propargyl)	*cis*-sym	61.6	67.5	61.3	202.3	169.5	44.2
		62.4	68.7	65.9		169.8	
6 (*N*-Phenethyl)	*cis*-Sym	62.3	69.7	60.9	203.2	168.5	44.5

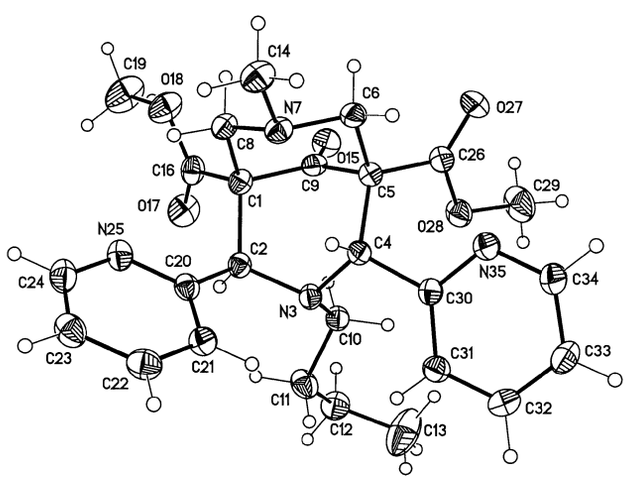


Fig. 3 Molecular structure of **3** showing the atomic numbering scheme (thermal ellipsoids at 50% probability). Hydrogen atoms are shown with an arbitrary radius.

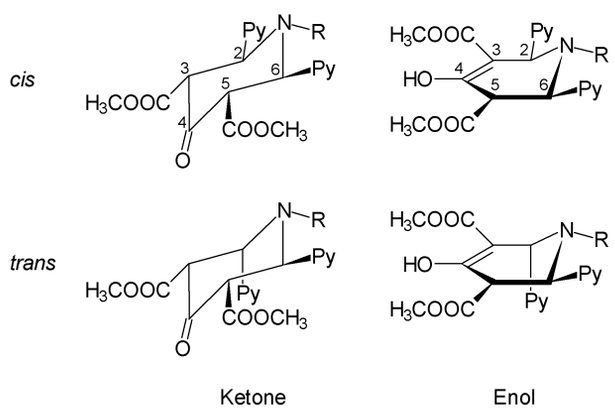


Fig. 4 Isomerism and tautomerism of the piperidones.

explained by the configurational change of *one* hydrogen from the axial to the equatorial position and by the influence of the deshielding part of the ring current of the axial pyridine ring on the *other* hydrogen in the axial position.

Due to the almost identical ^{1}H and ^{13}C NMR data of the compounds **1**–**4** (*cf.* Tables 2 and 3) it is likely that diazabicyclononanes having an alkyl substituent larger than a methyl group in position N3 are characterized by a structure similar to the one found for **3**. Interestingly, the ^{1}H NMR data of the "*trans*" isomer of HZ2 are quite different from the data observed for **1**–**4** (see Table 2), which may indicate that the *trans* isomer of HZ2 is characterised by a chair–chair conformation. As mentioned above, the ^{1}H and ^{13}C NMR spectra (*cf.* Tables 2 and 3) of the *N*3-propargyl and *N*3-phenylethyl substituted compounds **5** and **6** exhibit the symmetry of the molecule clearly indicating the *cis* chair–chair configuration. This is in accordance with the corresponding *N*7-hydroxyethyl substituted 3,7-diazabicyclononanone whose *cis* chair–chair configuration was confirmed by means of X-ray analysis.[21]

In order to elucidate the reason for the stereochemical behaviour of the diazabicyclononanones studied here, the heats of formation of each possible isomer, the *cis*-symmetrical **I**, *cis*-symmetrical **II**, the *cis*-non-symmetrical **III** and the *trans* isomers **IV** in chair–chair and boat–chair conformation, respectively, (see Scheme 2 and Fig. 3) were computed. The isomers were separately built up using the X-ray structure of **3** for the boat–chair isomers and an X-ray structure of a corresponding *N*7-*tert*-butyl-*N*3-methyldiazabicyclononanone[22] for

the symmetrical chair–chair isomers. A random search was performed to find low energy conformations, and the subsequent force field (MMFF94) and semiempirical calculations (AM1 and PM3) were carried out to compute the heats of formation which are depicted in Table 1.

The AM1 and PM3 semiempirical calculations gave almost the same picture. In the case of the boat–chair geometry, for all *N*3-alkyl substituted diazabicyclononanones the *trans* configuration was found to be energetically more favourable than the boat–chair *cis* configuration ($\Delta\Delta H > 4$ kcal mol^{-1}) which nicely mirrors the experimental finding for **1**–**4**, where the boat–chair *trans* isomer was isolated. However, the pairwise comparison of the heats of formation of the boat–chair isomers with the chair–chair isomers revealed the chair–chair conformations to be energetically always superior to the corresponding boat–chair forms (the propargyl substituted compound **5** is the only exception †). Moreover, the symmetrical chair–chair form (**I**) was always found to be the thermodynamically most stable form, which is in contrast to the experimental findings for **1**–**4** but in accordance with the findings for HZ1, HZ2 as well as **5** and **6**. This contradicting result indicates that one has to be careful to consider only the thermodynamic stability of the end-point of the Mannich reaction. In a previous study,[19] the reaction pathway of the *trans*–*cis*-isomerisation, a retro-Mannich reaction, was semiempirically and NMR-spectroscopically studied. Depending on the nature of the arene substituent transition states were found which led to both isomers, *i.e.* the *trans* and *cis* configurations. Taken together, the stereochemistry of the diazabicyclononanone skeleton is governed by both thermodynamic and kinetic effects.

Conclusion

Taking the findings of the studies on the influence of substituents in the N3 position of the 3,7-*diaza*bicyclononanones together, it can be stated that residues larger than a methyl group can induce both a configurational change from *cis* to *trans* with respect to the arene rings and a conformational change from a chair–chair to a boat–chair. Whereas HZ1 and HZ2 bearing a hydrogen atom and a methyl group, respectively, always stay in a chair–chair conformation with an energetically favourable *cis* configuration, the elongation of the alkyl chain at position N3 induced an epimerization in position 2 or 4 in combination with a flip of the piperidone ring from a chair to a boat conformation. In comparison, the symmetrical chair–chair and boat–chair configurational isomers of 3-*oxa*-7-azabicyclo[3.3.1]nonanones are one configurational step further down the isomerisation route. Herein, both arene rings have changed their positions from quasi-axial to quasi-equatorial. However, diazabicyclononanones with N3 substituents bearing unsaturated moieties were found to be symmetrical with a chair–chair conformation and *cis* conformation of the pyridine rings. Previous molecular modelling studies revealed the pharmacophoric conformation of the κ-agonistic diazabicyclononanones to be a chair–boat conformation with protonation of the nitrogen N7, a parallel orientation of the carbonyl function and the N^+–H and at least one aromatic ring.[5] Since the compounds **1**–**4** cannot fulfil this model, especially with respect to the position of the arene rings, it is easy to understand that no affinity to the κ-receptor was observed[7] which, in turn, supports the pharmacophore model.

† In comparison to all other compounds, calculation of the propargyl substituted compound is difficult for both AM1 and PM3 semiempirical methods. The calculations are extremely sensitive to the starting geometry of the propargyl residue (obtained by random search and MMFF calculations). The semiempirical calculations often end up in a local minimum.

Experimental

Synthesis

The diazabicyclononanones were synthesized according to ref. 7.

NMR measurements

All ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 300 FT NMR spectrometer operating at 299.956 MHz (^{1}H) and 75 MHz (^{13}C) with a sample temperature of 30 °C. In the case of the ^{1}H NMR spectra, a varying number of scans (depending on the experiment) with a frequency range of 2200 Hz were collected into 65000 data points, giving a digital resolution of 0.33 Hz per point. An appropriate Gaussian function was applied before Fourier transformation to enhance the spectral resolution. ^{1}H and ^{13}C NMR assignments given for each compound were confirmed by randomly running HETCOR and H,H-COSY experiments using the corresponding Varian software.

X-Ray analysis

Crystal data. $C_{26}H_{32}N_4O_5$, $M = 480.56$. Orthorhombic, space group $Pna2_1$, $Z = 4$, $a = 10.686(2)$, $b = 14.150(3)$, $c = 16.281(3)$ Å, $V = 2461.7(8)$ Å^3, μ(Mo-Kα) = 0.091 cm^{-1}, $T = 173$ K.

Data collection and processing. 11838 reflections were collected on a Stoe IPDS area diffractometer ($3.45 \leq \theta \leq 26.97°$), 5105 unique (merging $R = 0.033$), completeness of dataset 98.3%.

Structure analysis and refinement. The structure was solved by direct methods (program SHELXS-97[23] and SHELXL-97[24]) with anisotropic displacement parameters to give $wR_2 = 0.0784$ and a conventional $R = 0.0341$ for all 5105 reflections (goodness of fit on F^2 : $S = 1.034$, 320 refined parameters). No hint of a disorder could be found concerning the atom pairs N25/C21 and N35/C31. ‡

Theoretical methods

All molecules were constructed with the molecular modelling program SYBYL 6.6[25] on a Silicon Graphics Octane Workstation. Each molecule was built up using the 2D-3D conversion program CONCORD implemented in the SYBYL software or by using the corresponding X-ray structures. Afterwards they were subjected to an extensive conformational search by the SYBYL random search program. The following settings were applied: An energy cut-off of 8 kcal mol^{-1} above the energy minimum was used. The energy values during the optimisation were computed with the MMFF94[26] force field and the MMFF94 charges. Electrostatic interactions were taken into consideration by using a distance dependent relative permittivity $\varepsilon = \varepsilon_o\, r_{AB}$, where $\varepsilon_o = 4$ and r_{AB} is the interatomic distance between atoms A and B, which, to our experience, gives relevant conformations in agreement with solution conformations obtained by NMR spectroscopy. The number of maximum cycles was set to 1000 and for avoiding conformational changes during the search 'check chirality' was activated. All other default settings of the SYBYL 6.6 random search algorithm have been retained unchanged. The semiempirical calculations were carried out using the PM3[27] Hamiltonian as implemented within the MOPAC 7.0 program in SYBYL. The most stable conformations obtained from the force field calculations were optimised with PM3 using the following keyword line: PREC PM3 EF GNORM=0.1 T=3600. The AM1 calculations were correspondingly performed.

‡ CCDC reference number 152324. See http://www.rsc.org/suppdata/p2/b0/b008648g/ for crystallographic files in .cif or other electronic format.

Acknowledgements

Thanks are due to the DFG (HO 1368/3-3) and the Fonds der Chemischen Industrie for financial support.

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