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Synthesis and Stereochemistry of Some New Spiro-1,3-perhydrooxazines

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Summary. The synthesis and the stereochemistry of new spiro-1,3-perhydrooxazines are reported. The stereoisomerism of these compounds is discussed considering the data of conformational analysis, the helical chirality of the spiro[5.5]undecane skeleton, and the triligand virtual chiral center belonging to the 1,3-perhydrooxazine ring.

Keywords. Conformational analysis; Molecular chirality; 1,3-Perhydrooxazine derivatives; Spiro compounds.

Introduction

The stereochemistry of 1,3-perhydrooxazine derivatives has been investigated in a limited number of studies [1–13], mainly due to the relatively high chemical instability of the majority of the compounds and to the complexity of the problem involving conformational as well as complex configurational aspects concerning the chirality of the six-membered ring and nitrogen atom inversion. No data have been reported on the stereochemistry of spiro-1,3-perhydrooxazines.

The chirality of the 1,3-perhydrooxazine ring (similar to that observed for the 1,3-oxathiane ring [14]) has been recently discussed [15] considering the formal derivation of the heterocycle by the desymmetrization of adamantane. The presence of a virtual triligand chiral center has been predicted (Scheme 1). The flipping of the heterocycle is combined with an enantiomeric inversion $\mathbf{G} \rightleftharpoons \mathbf{H}$ (*R* configuration of the virtual chiral center $C^* \rightleftharpoons S$ configuration of the virtual chiral center C^*).

The dissymmetry of spiro compounds containing six-membered rings has been discussed in the terms of axial and helical chirality [15–18]. The parent spiro skeleton of this type (spiro[5.5]undecane) shows helical chirality, the flipping of the cyclohexane rings representing an enantiomeric inversion (Scheme 2).

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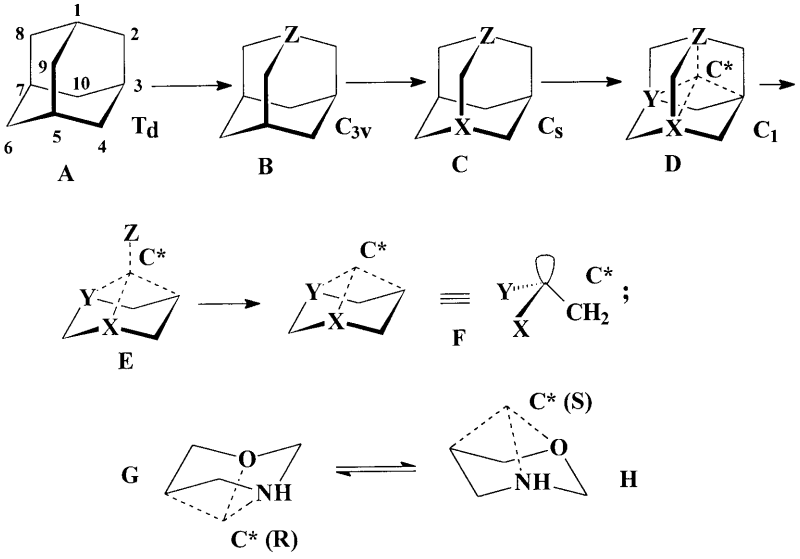
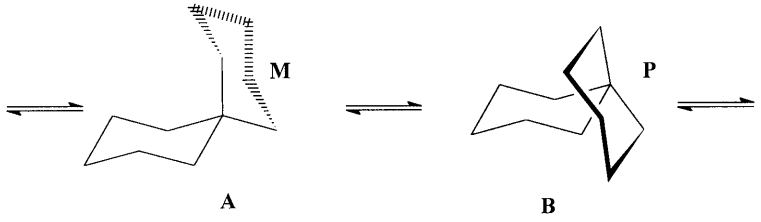


Scheme 1



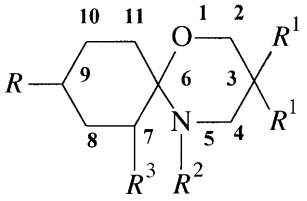
Scheme 2

Investigations on the stereochemistry of spiro-1,3-perhydrooxazines seem promising due to their relatively high chemical stability and the interesting combination of configurational and conformational problems.

Results and Discussion

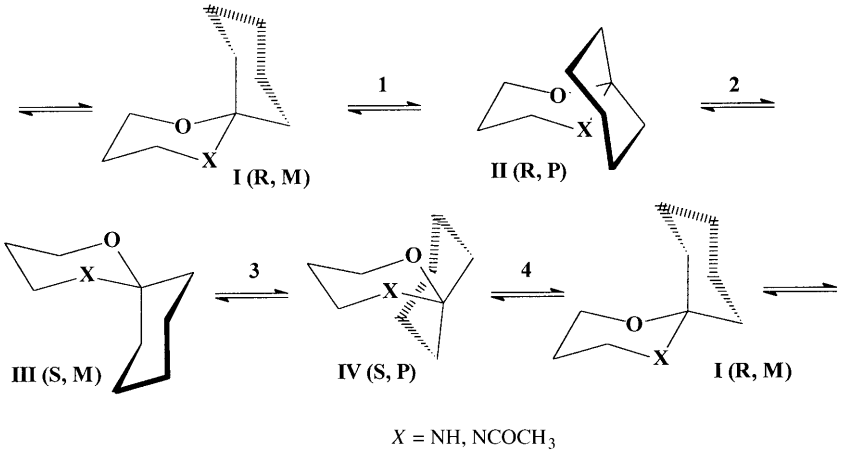
The spiro compounds **1–6** with a 1-oxa-4-azaspiro[5.5]undecane skeleton were obtained by direct condensation of some 3-amino-1-propanols with several (substituted) cyclohexanones. The reactions gave good yields (60–75%) in benzene without adding any catalyst, but removing the formed water by a *Dean-Stark* trap. Two of the previously obtained heterocyclic compounds were transformed into the corresponding amides **7** and **8** by reaction with acetyl chloride (Scheme 3).

The nitrogen atom inversion is very fast in amines as well as in amides [6]. The barrier of the process is considerably lower then the barrier of six-membered ring inversion. In all investigated compounds (**1–8**) the rapid inversion of nitrogen atom was considered, and contributions of both possible structures to the properties of the molecules were assumed. The calculated data (using PC Spartan Plus programs, *ab*



$R = R^1 = R^2 = R^3 = \mathrm{H}$	**1**
$R = t\text{-}C_4H_9$, $R^1 = R^2 = R^3 = \mathrm{H}$	**2**
$R = C_6H_5$, $R^1 = R^2 = R^3 = \mathrm{H}$	**3**
$R = R^2 = R^3 = \mathrm{H}$, $R^1 = CH_3$	**4**
$R = t\text{-}C_4H_9$, $R^1 = CH_3$, $R^2 = R^3 = \mathrm{H}$	**5**
$R = R^2 = \mathrm{H}$, $R^1 = R^3 = CH_3$	**6**
$R = R^3 = \mathrm{H}$, $R^1 = CH_3$, $R^2 = COCH_3$	**7**
$R = C_6H_5$, $R^1 = R^3 = \mathrm{H}$, $R^2 = COCH_3$	**8**

Scheme 3



Scheme 4

initio level, Table 1) show a slightly higher stability ($\Delta G^0 \approx -0.8\,\mathrm{kJ/mol}$) for the isomer with the oxygen atom in axial position (Scheme 4, structures **I** and **IV**). These data are comparable with the difference ($\Delta A = 3.09 - 2.26\,\mathrm{kJ/mol}$) between reported *A*-values for a methoxy ($A_{\mathrm{OMe}} = 2.30 - 3.13\,\mathrm{kJ/mol}$) and a methylamino group ($A_{\mathrm{NHMe}} = 5.40\,\mathrm{kJ/mol}$) on the cyclohexane ring [19]. Due to the small energy difference between the conformers with the oxygen or the nitrogen atom in equatorial positions, compounds **1**, **4**, and **7** are characterized by flexible structures, both six-membered rings being involved in a fast conformational equilibrium (Scheme 4). On the other hand, these compounds exhibit the helical chirality characteristic for spiro compounds with six-membered rings and a virtual triligand center of chirality belonging to the heterocycle. As a consequence, four structures (**I–IV**) are possible.

Table 1. Calculated energy differences between the structures with axial and equatorial nitrogen atoms; the calculations have been performed considering the hydrogen atom of the amino group in axial position (the more stable isomer)

	3	**4**	**6**	**7**
ΔG^0_{calc} kJ/mol	0.87	1.00	0.83	0.92
ΔG^0_{exp} kJ/mol	–	1.46	–	2.00

Table 2. ^{1}H NMR data (δ ppm, $CDCl_3$) of compounds **3–10**

	2-H	4-H	3-CH_3
1	3.81	2.92	–
2 *cis*	3.77	2.95	–
2 *trans*	3.86	2.88	
3 *cis*	3.88	3.03	–
3 *trans*	3.95	2.98	
4	3.39	2.60	0.85
5 *cis*	3.46	2.65	0.88
5 *trans*	3.39	2.58	0.87
6 *cis*	3.43 (*ax*), 3.23 (*eq*)	2.72 (*ax*), 2.41 (*eq*)	
6 *trans*	3.60 (*ax*), 3.23 (*eq*)	2.82 (*ax*), 2.39 (*eq*)	
7	3.26	3.02	0.92
8	3.82	3.49	–

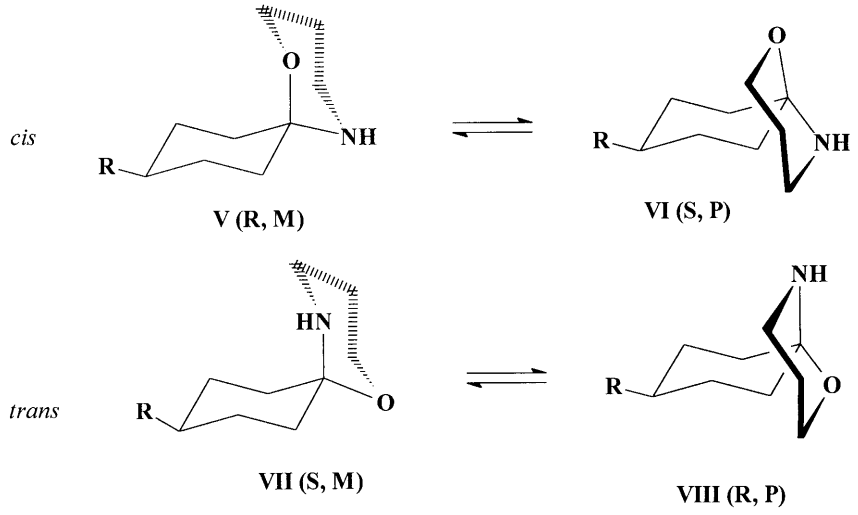
The flipping of the cyclohexane ring leads to diastereoisomers (**I** $\rightleftharpoons$ **II** and **III** $\rightleftharpoons$ **IV**), whereas the flipping of the heterocycle results in enantiomeric inversions (**II** $\rightleftharpoons$ **III** and **IV** $\rightleftharpoons$ **I**).

The flipping of the rings causes rapid equilibria of all possible stereoisomers. As a consequence, the NMR spectra (Table 2) show unique signals for the homomorphic groups, with mean values of the chemical shifts due to the specific magnetic environments belonging to the axial and equatorial positions of these groups and to their affiliation to different diastereoisomers. As an example, the ^{1}H NMR spectrum of compound **4** exhibits two singlets for the protons of the heterocycle, the more deshielded one ($\delta = 3.39$ ppm) belonging to the protons at position 2 and the another one ($\delta = 2.60$ ppm) to the protons at position 4. The spectrum shows a unique singlet ($\delta = 0.85$ ppm) for the methyl groups in position 3 (cf. Experimental).

Compounds **2**, **3**, **5**, and **8** exhibit semiflexible structures, the cyclohexane ring being anancomeric and the heterocycle flipping (Scheme 5).

Cis (**V** and **VI**) and *trans* (**VII** and **VIII**) isomers are generated by the relative position of the holding group located at C-9 (the substituent of the carbocycle) and of the oxygen atom (the substituent of highest priority connected to the spiro carbon atom).

Compounds **2**, **3**, **5**, and **8** were obtained as a mixture of diastereoisomers. The NMR spectra of these compounds exhibit two sets of signals belonging to the *cis*



Scheme 5

(main product) and *trans* isomers. The spectra display different signals for axial and equatorial protons of the cyclohexane ring, whereas for the axial and equatorial positions of the protons of the heterocycle or of the homomorphic groups located on it the spectra exhibit unique signals at averaged chemical shift values (Table 2, Fig. 1). As an example, the ^{1}H NMR spectrum of compound **5** (Fig. 1a; toluene-d_8 room temperature) exhibits two singlets for the protons at positions 2 and 4 of the *cis* isomer ($\delta_2 = 3.30, \delta_4 = 2.55$ ppm) and two singlets for the protons at the same positions ($\delta_2 = 3.44, \delta_4 = 2.45$ ppm) of the *trans* isomer. Two close singlets have been recorded for the methyl groups at C-3 ($\delta_{cis} = 0.74, \delta_{trans} = 0.76$ ppm) as well as for those of the protons of the *t*-C_4H_9 groups at C-9 ($\delta_{cis} \approx \delta_{trans} = 0.92$ ppm).

Variable temperature NMR experiments performed with compound **5** showed a dramatic change in the low temperature spectrum (Fig. 1b). Thus, instead of the two singlets recorded for the protons at positions 2 and 4 (of each isomer), in the spectrum run at 196 K two AB systems were observed for each diastereoisomer. One of the doublets of each AB system belongs to the axial protons, the other one to the equatorial ones. The freezing of the flipping of the heterocycle also causes the appearence of different signals for the axial and equatorial positions of the methyl groups at C-3. Instead of the unique singlets observed at room temperature ($\delta_{cis} = 0.74, \delta_{trans} = 0.76$ ppm), in the low temperature spectrum two sets of well separated singlets are observed $\delta_{cis} = 0.90, \delta_{trans} = 0.95$ ppm (axial methyl group) and $\delta_{cis} = 0.55, \delta_{trans} = 0.50$ ppm (equatorial methyl group) (Fig. 1b).

The ratios of *cis* and *trans* isomers were estimated using the integrals of specific signals in the ^{1}H NMR spectra and compared with calculated data (Table 1).

Compound **6** exhibits an anancomeric structure; the flipping of both rings, the cyclohexane and the 1,3-perhydrooxazine ring, are hindered. The anancomeric behaviour of the cyclohexane ring is due to the methyl group in position 7 which is a holding group and prefers an equatorial orientation, whereas the rigid behaviour of the heterocycle is due to the shifting of the characteristic conformational equilibrium towards the conformer showing the heterocycle at the opposite side

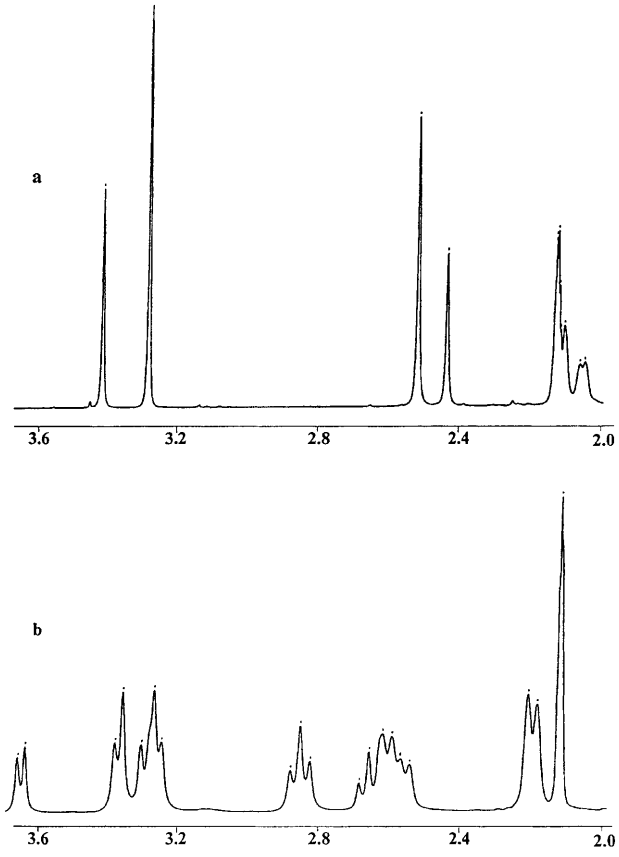
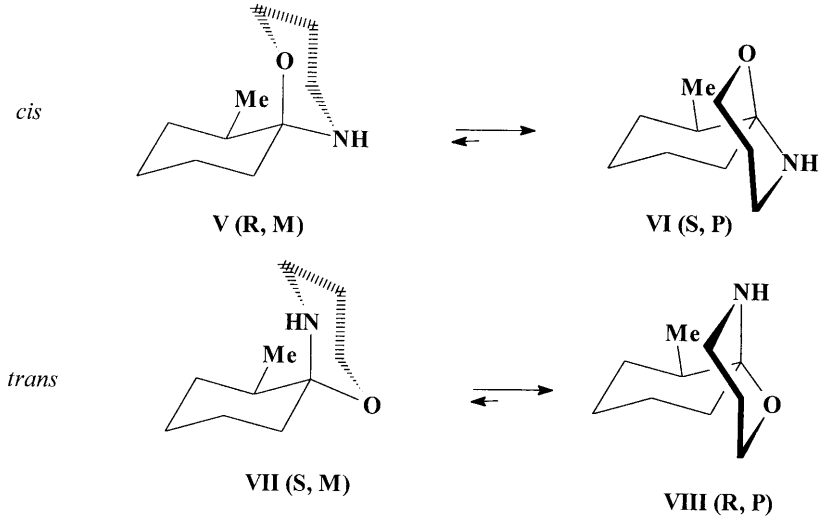


Fig. 1. ^{1}H NMR spectra (500 MHz, toluene-d_8, δ/ppm) of compound **5** at room temperature (a) and 196 K (b)



Scheme 6

with the equatorial methyl group located in position 7 (Scheme 6). Similar situations have been observed in the stereochemistry of some spiro 1,3-dioxanes obtained from 2-methylcyclohexanone [20].

The ^{1}H NMR spectrum (Table 2) of **6** (mixture of *cis* and *trans* isomers) is quite complex. Different signals were recorded for the protons of the two diastereoisomers and for the axial and equatorial orientation of the protons of the rings and of the homomorphic groups located in the heterocycle. The spectrum of this compound at room temperature is very similar to the spectrum obtained for compound **5** at low temperature, which proves the anancomeric character of **5** at 196 K and **6** at room temperature.

Conclusions

The stereochemistry of new spiro-1,3-perhydrooxazines was investigated by NMR spectroscopy. The flexible, semiflexible, or anancomeric behaviour of the structures has been revealed by the complexity of their NMR spectra at ambient and low temperatures. The possible stereoisomers were deduced taking into account the special chirality of the heterocycle and the spiro skeleton. In all cases, the inversion of the configuration of nitrogen was assumed very fast, and average contributions of the structures with the hydrogen atom of the amino group or the acetyl group in axial or equatorial positions were considered.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ in 5 mm tubes on a Bruker AM 400 FT NMR spectrometer equipped with a dual ^{13}C-^{1}H head operating at 400 MHz for protons and 100 MHz for carbons. Melting points were measured with an Electrothermal melting point apparatus and are uncorrected. The elemental analyses (C, H, N) for the new compounds **2–8** agreed favourable with the calculated values.

Compounds **1–6** *(general procedure)*

Stoichiometric amounts of 3-amino-1-propanol (0.1 mol) and ketone (0.1 mol) were dissolved in 200 cm^3 benzene. The mixture was refluxed, and the water resulting in the reaction was removed with a *Dean-Stark* trap. When 80% of the theoretical amount of water was separated, the benzene was removed, and the perhydro-1,3-oxazine compounds were purified by crystallisation from ethanol or by vacuum distillation (0.5–1 mm Hg). The synthesis of **1** has been reported previously [21, 22].

Compounds **7–8** *(general procedure)*

To stoichiometric amounts of spiro-1,3-perhydroxazine (0.01 mol) and triethylamine (0.01 mol) in 50 cm^3 anhydrous benzene, a solution of freshly distilled acetyl chloride (0.01 mol) in 10 cm^3 anhydrous benzene was added (0.5 h) under stirring and cooling. Stirring was continued for 3 h at room temperature. The salt of the triethylamine was filtered, the benzene was removed, and the crude product was purified by vacuum distillation.

9-t-Butyl-1-oxa-5-aza-spiro[5.5]undecane (**2**; $C_{13}H_{25}NO$)

Liquid; b.p.: 86–88°C (1 mm Hg); yield: 66%; ^{1}H NMR (400 MHz, δ, $CDCl_3$, mixture of two diastereoisomers): 0.78 (18H, s, overlapped peaks, 9-C$(CH_3)_3$), 0.90–1.00 (2H, m, overlapped peaks,

9-H), 1.10–1.51 (18H, m, overlapped peaks, 3, 5, 7, 8, 10, 11-H), 2.10 (4H, m, overlapped peaks, 7, 11-H_{ax}), 2.88 (2H, t, $J = 5.7$ Hz, 4-H), 2.95 (2H, t, $J = 5.7$ Hz, 4-H), 3.86 (2H, t, $J = 5.6$ Hz, 2-H), 3.77 (2H, t, $J = 5.6$ Hz, 2-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 22.26, 23.65 (C-8, C-10), 27.93, 28.05 (C-3), 29.19 ($C(CH_3)_3$), 32.17, 32.26, 32.43 ($C(CH_3)_3$), 34.12, 35.02 (C-7, C-11), 38.23, 38.47 (C-4), 47.94, 48.38 (C-9), 59.77, 60.38 (C-2), 82.84, 84.45 (C-6) ppm.

9-Phenyl-1-oxa-5-aza-spiro[5.5]undecane (**3**; $C_{15}H_{21}NO$)

Solid; m.p.: = 75°C; yield: 75%; ^{1}H NMR (400 MHz, δ, $CDCl_3$, mixture of two diastereoisomers): 1.39–1.80 (18 H, m, overlapped peaks, 3,5,7,8,10,11-H), 2.19–2.26 (4H, m, overlapped peaks 7,11-H_{ax}); 2.54 (2H, m, overlapped peaks, 9-H), 2.98 (2H, t, $J = 5.7$ Hz, 4-H), 3.03 (2H, t, $J = 5.7$ Hz, 4-H), 3.88 (2H, t, $J = 5.5$ Hz, 2-H), 3.95 (2H, t, $J = 5.5$ Hz, 2-H), 6.70–6.87 (10H, m, overlapped peaks, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 27.26, 27.45 (C-3), 29.14, 30.34 (C-8, C-10), 34.03, 34.83 (C-7, C-11), 38.30, 38.50 (C-4), 44.18, 44.42 (C-9), 59.94, 60.48 (C-2), 82.64, 84.11 (C-6), 125.89, 126.67, 126.88, 128.23, 128.45, 146.78, 146.98 (aromatic carbon atoms) ppm.

3,3-Dimethyl-1-oxa-5-aza-spiro[5.5]undecane (**4**; $C_{11}H_{21}NO$)

Liquid; b.p.: 97°C (2 mm Hg); yield: 69%; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.85 (6H, s, 3-CH_3), 1.25–1.38 (1H, m, NH), 1.38–1.81 (10H, m, overlapped peaks, 7, 8, 9, 10, 11-H), 2.60 (2H, s, 4-H), 3.39 (2H, s, 2-H) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 22.10 (C-8, C-10), 23.50 (3-CH_3), 25.99 (C-9), 28.95(C-3), 33.79(C-7, C-11), 50.61 (C-4), 70.15 (C-2), 83.39 (C-6) ppm.

9-t-Butyl-3,3-dimethyl-1-oxa-5-aza-spirop[5.5]undecane (**5**; $C_{15}H_{29}NO$)

Solid; m.p.: = 105 − 107°C; yield: 77%; ^{1}H NMR (400 MHz, δ, $CDCl_3$, mixture of two diastereoisomers): 0.82 (18H, s, overlapped peaks, 9-$C(CH_3)_3$), 0.87 (6H, s, 3-CH_3), 0.88 (6H, s, 3-CH_3), 0.94–1.05 (2H, m, overlapped peaks, 9-H), 1.14–1.60 (12H, m, overlapped peaks, 7, 8, 10, 11-H), 2.08–2.15 (4H, m, overlapped peaks, 7, 11-H_{ax}), 2.58 (2H, s, 4-H), 2.65 (2H, s, 4-H), 3.39 (2H, s, 2-H), 3.46 (2H, s, 2-H), ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 22.43 (C-8, C-10), 23.48 (CH_3), 27.58, 27.66 ($C(CH_3)_3$), 32.00 ($C(CH_3)_3$), 29.00, 32.31 (C-7, C-11), 33.74, 34.65 (C-3), 47.94, 48.38 (C-9), 50.83 (C-4), 70.13, 70.63 (C-2), 82.72, 84.22 (C-6) ppm.

3,3,11-Trimethyl-1-oxa-5-aza-spiro[5.5]undecane (**6**; $C_{12}H_{23}NO$)

Liquid; b.p.: 74–76°C (1 mm Hg); yield: 60%; ^{1}H NMR (400 MHz, δ, $CDCl_3$, mixture of two diasereoisomers): 0.71 (6H, d, $J = 6.2$ Hz, overlapped peaks, 11-CH_3), 0.80–1.60 (32H, m, overlapped peaks, 5, 7, 8, 9, 10, 11-H, 3-CH_3), 2.39 (1H, dd, $J = 14$ Hz, $J' = 2.4$ Hz, 4-H_{eq}), 2.41 (1H, dd, $J = 14$ Hz, $J' = 2.4$ Hz, 4-H_{eq}), 2.72 (1H, d, $J = 14$ Hz, 4-H_{ax}), 2.82 (1H, d, $J = 14$ Hz, 4-H_{ax}), 3.23 (2H, dd, $J = 11.4$ Hz, $J' = 2.4$ Hz, 2-H_{eq}), 3.43 (1H, d, $J = 11.4$ Hz, 2-H_{ax}), 3.60 (1H, d, $J = 11.4$ Hz, 2-H_{ax}) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 13.66, 14.07 (11-CH_3), 21.86, 22.74 (3-CH_3), 23.01 (C-3), 24.09, 24.19 (C-8, C-10), 28.84, 29.01 (C-7), 30.49 (C-11), 50.40, 50.57 (C-4), 69.82, 70.09 (C-2), 84.55, 85.75 (C-6) ppm.

5-Acetyl-9-phenyl-1-oxa-5-aza-spiro[5.5]undecane (**7**; $C_{18}H_{26}NO_2$)

Liquid; b.p.: 174°C (1 mm Hg); yield: 36%; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 1.66–1.97 (8H, m, 3, 7, 8, 9, 10, 11-H), 2.06 (3H, s, 5-$COCH_3$), 2.67 (1H, m, 9-H), 2.83 (2H, m, overlapped peaks, 7, 11-H_{ax}), 3.49 (2H, t, $J = 5.9$ Hz, 4-H), 3.82 (2H, t, $J = 7.6$ Hz, 2-H), 7.10–7.30 (5H, m, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$): 24.61 (C-8, C-10), 24.75 ($COCH_3$), 30.30, 30.61 (C-

3, C-7, C-11), 39.86 (C-4), 42.76 (C-9), 56.39 (C-2), 89.64 (C-6), 125.84, 126.81, 128.20, 147.12 (aromatic carbons), 168.89 ($COCH_3$) ppm.

5-Acetyl-3,3-dimethyl-1-oxa-5-aza-spiro[5.5]undecane (**8**; $C_{14}H_{26}NO_2$)

Liquid; b.p.: 144°C (1 mm Hg); yield: 61%; ^{1}H NMR (400 MHz, δ, $CDCl_3$): 0.92 (6H, s, 3-CH_3), 1.10–1.74 (8H, m, 7, 8, 9, 10, 11-H), 1.96 (3H, s, 5-$COCH_3$), 2.46 (2H, m, overlapped peaks, 7, 11-H_{ax}), 3.02 (2H, s, 4-H), 3.26 (2H, s, 2-H) ppm; ^{13}C NMR (400 MHz, δ, $CDCl_3$): 22.41 (C-8, C-10), 24.61 (3-CH_3), 24.86 (C-9), 25.46 (CO*C*H_3), 29.45 (C-7, C-11), 33.60 (C-3), 52.14 (C-4), 69.08 (C-2), 90.28 (C-6), 169.67 (*C*OCH_3) ppm.

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