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Cycloadditions of Nitrile Oxides and Nitrones to 4,4-Methylene-1-methylpiperidine**: Studies in Regio- and Stereoselectivity

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Summary. A series of spiro-substituted isoxazole derivatives were synthesized by 1,3-dipolar cycloadditions of nitrile oxides and nitrones to 4,4-methylene-1-methylpiperidine. Since nmr studies confirmed that only one regioisomer was formed selectively, semi-empirical quantum mechanical methods (AM1) were used to rationalize this regiochemical preference via calculation and inspection of HOMO-LUMO-energy and coefficients. X-ray structure analysis carried out for one of these products showed the occurrence of only one stereoisomer, explicable by comparing AM1-calculated ΔH_f-values of all possible cycloadducts.

Keywords. 1,3-Dipolar cycloaddition; Nitrile oxide; Nitrone; 4,4-Methylene-1-methylpiperidine; AM1 calculations.

Cycloadditionen von Nitriloxiden und Nitronen an 4,4-Methylen-1-methylpiperidin: Untersuchungen zur Regio- und Stereoselektivität

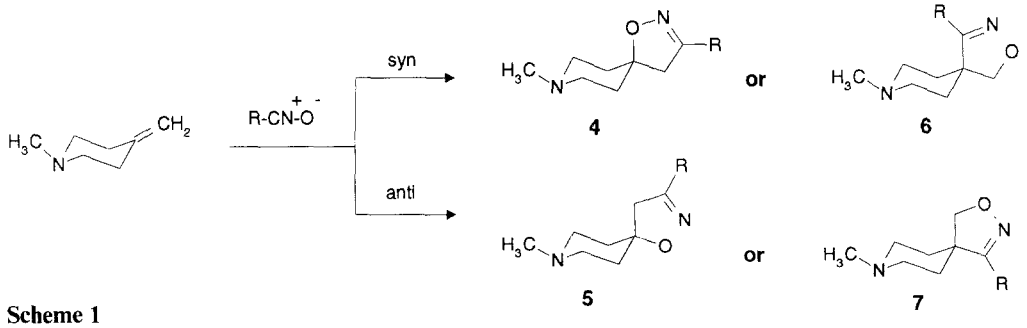
Zusammenfassung. Eine Reihe von spiro-substituierten Isoxazolderivaten wurden durch 1,3-dipolare Cycloadditon von Nitriloxiden und Nitronen an 4,4-Methylen-1-methylpiperidin erhalten. Da NMR-Studien ergaben, daß dabei nur eine der beiden denkbaren regioisomeren Strukturen entsteht, wurde versucht, diese regiochemische Preferenz durch Berechnung und Vergleich von aus halbempirischen quantenmechanischen Methoden (AM1) ermittelten HOMO-LUMO-Energien und Koeffizienten zu erklären. Zusätzlich wurde an einem dieser Produkte dessen Stereochemie mittels Röntgenstrukturanalyse als einheitlich festgestellt, interpretierbar durch Vergleich der AM1-ermittelten ΔH_f-Werte der in Frage kommenden Cycloaddukte.

Introduction

The present work is linking long-term studies on 1,3-dipolar cycloadditions [1, 13–15], carried out at the STU Bratislava [3–5], with a second long-term project

** Part XXXI in the series 1,3-Dipolar Cycloaddition on Heterocycles. Part XXX [Ref. 5]

dealing with the synthesis of spiro-heterocycles at the TU Vienna [6–9] to a joint effort to approach spiro-substituted isoxazole derivatives by reacting nitrile oxides and nitrones [2] with 4,4-methylene-1-methylpiperidine **1** [16]. This was the more desirable as some substances already known in the literature and structurally related to our compounds exhibit interesting pharmacological features [10–12] (Scheme 1).



Scheme 1

Taking into account that in all cases two regioisomeric products are conceivable a major part of the work is not only dealing with the synthesis itself but also

(i) with structure elucidations of the products thus obtained (carried out by nmr studies), and, after having established empirically that only one regioisomer is obtained selectively,

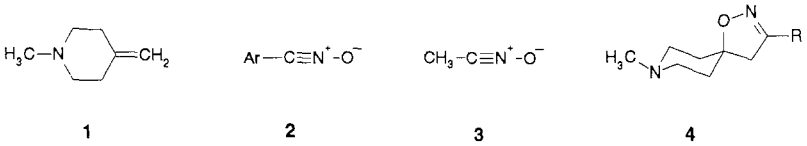
(ii) with efforts to rationalize the regiochemical preference via semi-empirical quantum mechanical calculations (carried out by the AM1 method [21]).

Subsequently, the stereochemistry of one of these (regiochemically well defined) products had to be determined by X-ray structure analysis.

Results and Discussion

Reactions with Nitrile Oxides

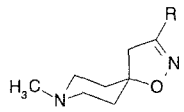
4,4-Methylene-1-methylpiperidine (**1**) was prepared by applying a Wittig reaction to 1-methyl-4-piperidone with phosphorus ylide [16]. Ar-substituted benzenenitrile oxides **2** (where Ar is phenyl-, 4-Cl-phenyl- and 3-NO_2-phenyl) were generated from the corresponding benzaldoximes, N-chlorosuccinimide and triethylamine [17] in chloroform in the presence of methylenepiperidine **1**. The formation of the cycloadducts **4a–c** (R = Ar) was accompanied by 3,4-diarylfuroxan – the nitrile oxide dimer [18] – as a by-product (Scheme 2).



1 2 3 4

Scheme 2

Cycloaddition of **1** with acetonitrile oxide (**3**) proceeded analogously to give a cycloadduct **4d** (R = CH_3). Stereoisomer **5** and regioisomers **6** and **7** have not been detected in the crude reaction mixture by NMR spectroscopy (Scheme 3).



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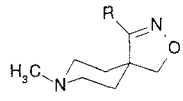

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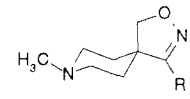

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Scheme 3

The assignment of the regiochemistry in isoxazolines **4a–d** was unequivocally made on the basis of diagnostic ^{1}H- and ^{13}C-NMR data of the isoxazoline ring moiety.

Their C-5 resonances lie at lower fields ($\delta = 82.28$–84.87 ppm) and are roughly 50 ppm higher than those of the other possible regioisomers **6** or **7** [5]. On the other hand, C-4 resonances ($\delta = 44.40$–48.57 ppm) attest to the shielding effect of a spiro-fused piperidine ring. Moreover, the ^{1}H-NMR spectrum showed the isoxazoline ring H_2-4 protons in the regions $\delta = 3.05$–3.62 ppm, which is completely consistent with an isoxazoline unsubstituted at the 4-position. If the spiro atom were at the 4-position of the isoxazoline ring (the possible regioisomers **6** and **7**), protons at the 5-position would appear at lower fields [19].

We have shown that the ^{1}H and ^{13}C NMR spectra indicate the regiochemistry of the [3 + 2] cycloadducts **4a–d** which are formed by the attack of the carbon of the nitrile oxide at the CH_2 terminus of the exocyclic double bond.

A similar regioselectivity was observed in the cycloaddition of nitrile oxides to methylenecycloalkanes [3–5] as well as in the cycloaddition of bromonitrile oxide to the N-benzyloxycarbonyl-protected form of 4-methylenepiperidine [20]. A methylene moiety certainly exhibits lower steric requirement than a piperidine system; moreover, it should be emphasized that mono- and 1,1-dialkylethylenes react with nitrile oxides to give the 5-substituted isoxazolines exclusively [18]. Frontier molecular orbital considerations of the reacting systems also favour formation of the regioisomer **4**. The frontier orbital energies calculated by AM1 method [21] are given in Table 1.

Inspection of energy levels shows that the cycloaddition is governed by the $LUMO_{DIPOLE}$. The LUMO orbital of benzenenitrile oxide **2** and π-orbital of the C=C exocyclic double bond of **1** are shown in Figs. 1 and 2. The HOMO of **1** is

Table 1. HOMO and LUMO energies of **1**, benzenenitrile oxide (**2**) and acetonitrile oxide (**3**) calculated by AM1 [21]

Compound	E_{HOMO} [eV]	E_{LUMO} [eV]
1	−9.76[a]	1.26
2	−9.38	−0.51
3	−10.12	0.94

[a] HOMO-1 orbital, HOMO of 1 is the non-bonding orbital on nitrogen

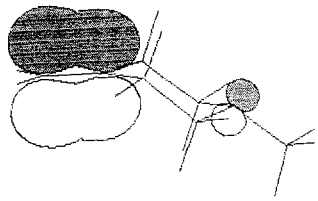


Fig. 1. HOMO orbital of **1** (AM1 [21])

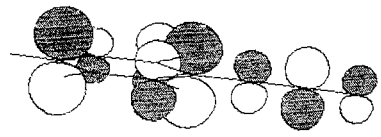
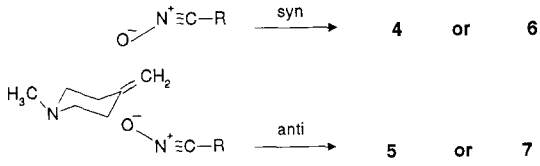


Fig. 2. LUMO orbital of **2** (AM1 [21])

the p_z orbital of nitrogen, the (HOMO-1) being 0.7 eV lower than that of HOMO of **1**. In the (HOMO-1) of **1** the methylene-carbon has a large orbital coefficient (0.66 versus 0.57); thus it would be expected to interact with the carbon terminus of the nitrile oxide, since in nitrile oxides the LUMO have larger coefficients at the carbon atom as compared with at the oxygen atom (0.23 versus 0.21 for **2** and 0.65 versus 0.37 for **3**).

The cycloadducts **4a–d** were formed in lower yields – due to incomplete conversion of starting material – as compared with those observed in the cycloaddition of nitrile oxides to methylenecycloalkanes possessing a (3–5)-membered ring [3–5, 13, 14], which can be explained by the well known fact that angular strain in a dipolarophile can effect its reactivity [22]: it has been observed that a decrease in strain by converting educts into adducts induces an increase in reaction rate. Therefore, it is not surprising that the reactivity of methylenepiperidine is lower.

There are four possible adducts between **1** and nitrile oxides: two regioisomers **4** and **6** resulting from *syn* approach of the 1,3-dipole to the N-methyl group, and two corresponding isomers **5** and **7** from *anti* attack (Scheme 4).



Scheme 4

The assignment of isolated adducts **4a–d** to the stereoisomer possessing an oxygen atom in axial position was based on an X-ray crystal structure determination of **4**. Technical details of this work on compound **4** are given in the experimental part. Atomic coordinates and selected bond distances and angles are presented in Tables 4 and 5.

Figure 3 shows molecule **4a** as encountered in the crystalline state. The molecule consists of an essentially flat part formed by the benzene and the isoxazoline ring.

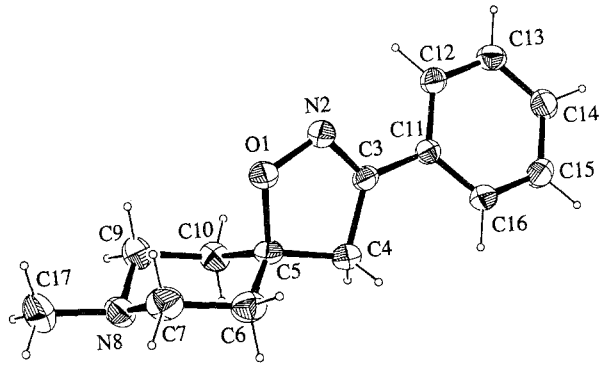
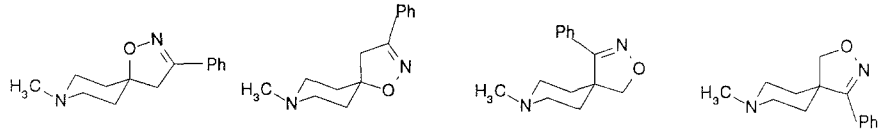


Fig. 3. ORTEP-plot (30% ellipsoids) of compound **4a**

The isoxazoline ring is moderately puckered with O(1), N(2), C(3) and C(4) forming an almost exactly planar arrangement, while the spiro-atom C(5) is 0.325(3) Å off from this plane. The twist angle between the planar part of the isoxazoline ring and the benzene ring is 17.0(1)°. The spiro-piperidine ring moiety is oriented approximately perpendicular to the isoxazoline ring and shows the usual chair conformation.

The nitrile oxide cycloadditions to **1** are apparently regio- and stereospecific. We therefore tried to access the relative thermodynamic stability of the possible products **4**–**7** by semi-empirical quantum chemical calculations [21] (AM1 method). The calculated relative energies of the cycloadducts in kJ/mol are expressed as energy differences ΔH_f, the energy of the most stable isomer being the reference (the calculated heat of formation of **4a** is $H_f = 159.42$ kJ/mol) and listed in Scheme 5.



Scheme 5. Relative stabilities of **4a** (R = Pheny) calculated by AM1 [21]

AM1 calculations showed the cycloadduct **6a** to be less stable by ~17 kJ/mol than the other isomers, a fact that can mainly be accounted for on steric considerations, primarily by the presence of the van der Waals steric repulsions between the C-aryl substituent and piperidine moiety. In the case of "correct" regioisomers both diastereomers **4** and **5** are of almost equal stability, with a small preference on the isolated isomer (ca. 0.9 kJ/mol), the optimized geometry of **4a** is shown in Fig. 4. This result convincingly correlates with the X-ray structure depicted in Fig. 3.

Therefore, the high regioselectivity should be mainly determined by HOMO-LUMO interactions. Recently, it was suggested that intramolecular interactions between the nitrogen lone pair an the unsaturated bond in 4,4-methylene-1,2-dimethylpiperidine play a major role in determining the stereochemistry of hydrogenation [23]. The hydrogen addition occurred from the axial side of the molecule and the equatorially substituted products were predominant. Since the

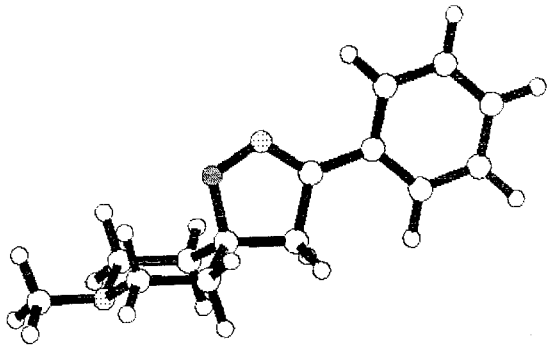


Fig. 4. Optimized geometry for **4a** (AM1)

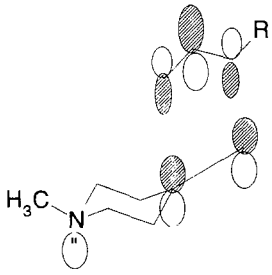
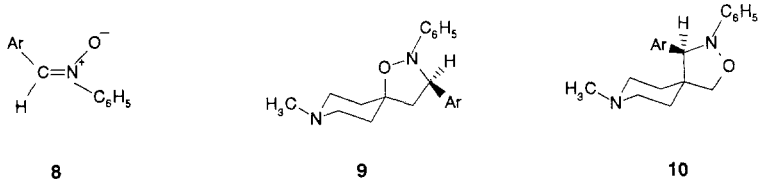


Fig. 5. Nitrile oxide cycloaddition to **1**

nitrogen lone pair in the piperidine ring must preferably occupy an axial position, the hydrogen addition occurred mainly from the side opposite of the nitrogen lone pair [22]. Similarly, the results obtained and confirmed by X-ray measurements in our case indicate that the nitrile oxide cycloaddition to **1** also occurred exclusively from the side opposite to the nitrogen lone pair in **1** (Fig. 5).

Reactions with Nitrones

1,3-Dipolar cycloadditions of C-(X-phenyl)-N-phenyl nitrones **8** (where X is H, 4-Cl and 2,4-diCl) and **1** in toluene at 110 °C afforded exclusively the spiro-isoxazolidines **9**. There are two possible adducts resulting from **1** and arylnitrones **8** (Scheme 6).



8 9 10

Scheme 6

The differentiation between these structures was made possible by analyzing spectroscopic data. In the NMR spectra of **9** an ABX system (pertaining to the two hydrogens in position 4 and to the single one in position 3 – numbering refers to the isoxazole moiety) is present. This excludes the possibility of the regioisomer **10** having been formed and proves that isolated adducts **9a–c** (with varying aryl-substituents) result from the same kind of approach between nitrone **8** and

dipolarophile **1**, i.e. that one which binds the carbon of the nitrone to the exocyclic carbon of the methylene group of **1** and the oxygen to the future spiro carbon. In the contrary, the NMR spectrum of the regioisomers **10a–c** would be expected to show a singlet for H-3 and an AB system for the two hydrogens at position 5 of the isoxazole ring.

The statement that the nitrone cycloaddition is regiospecific, leading only to regioisomers with a 5-spiroisoxazolidine structure, is additionally confirmed by the chemical shift of the adjacent spiro-carbon (C-5, $\delta = 80.00–80.82$ ppm), indicating a strong shielding influence of the spiro-heterocyclic ring on the 5-position of the isoxazolidine, together with the expected value for C-4 ($\delta = 48.33–51.04$ ppm). The alternative regioisomeric structure **10** can be excluded, since **10** is not expected to exhibit signals at these chemical shift values and furthermore its formation should be sterically hindered. The same regioselectivity was also observed in several other cycloadditions [4, 15, 24]. We suppose that the spiroisoxazolidines **9** have the same stereochemistry as spiro-isoxazolines **4**, as nitrile oxides and nitrones belong to the same type of the 1,3-dipoles [2].

Conclusion

In conclusion, the regiochemistry of the nitrile oxide and nitrone cycloadditions at the exocyclic double bond of **1** seems to be controlled by frontier orbital interactions, whereas the stereochemistry of the cycloaddition is mainly dominated by the intramolecular interaction between the nitrogen lone pair and the exocyclic double bond of **1**. The scope of this principle can be extended to a number of synthetically useful transformations of **4**, on which will be reported separately.

Experimental Part

Melting points were determined on a Kofler hot plate m.p. apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H: 200.13 MHz, ^{13}C: 50.323 MHz, 5 mm dual ^{1}H/^{13}C-VT-probe head at 300 K; *TMS* as internal standard, $CDCl_3$, δ-values in ppm, J in Hz). 4,4-Methylene-1-methylpiperidine (**1**) was prepared by treatment of 1-methyl-4-piperidone with phosphorous ylide [16].

3-(X-Phenyl)- and 3-methyl-8-methyl-1-oxa-2,8-diazaspiro[4,5]dec-2-enes **4**

N-Chlorosuccinimide (9.83 mmol) was suspended under nitrogen in anhydrous chloroform. Then the corresponding benzaldoxime (7.86 mmol) and 2 drops of pyridine were added and the mixture heated to 40–50 °C for 20 min. After cooling a solution of **1** (7.86 mmol) in anhydrous chloroform (5 ml) was added dropwise during 20 min, then a solution dry triethylamine (8.33 mmol) in dry chloroform (10 ml). The reaction mixture was heated to 40–50 °C until the starting material had disappeared due to TLC and allowed to cool. After adding of water (20 ml) and extraction with diethyl ether the solvent was evaporated under reduced pressure. The solid residue thus obtained (see Table 2) was chromatographed on a silica gel column (eluent: chloroform/methanol, 10:1).

3-Phenyl-8-methyl-1-oxa-2,8-diazaspiro[4,5]dec-2-ene (**4a**)

^{1}H-NMR: 1.82–2.10 (m, 4H, H_2-6, H_2-10), 2.32 (s, 3H, CH_3), 2.41–2.70 (m, 4H, H_2-7, H_2-9), 3.10 (s, 2H, H_2-4), 7.30–7.73 (m, 5H, aromat. H). ^{13}C-NMR: 35.71 (t, C-6, C-10), 44.83 (t, C-4), 45.70 (q, CH_3), 52.25 (t, C-7, C-9), 83.68 (s, C-5), 126.20, 128.45 129.69, 129.80 (aromat. C), 155.96 (s, C-3).

Table 2. 3-(*R*)-8-methyl-1-oxa-2,8-diazaspiro[4,5]dec-2-enes **4**

Compound **4**	R	m.p. (°C)	Yield (%)	Formula	M.W.
a	C_6H_5	67–70	70	$C_{14}H_{18}N_2O$[a]	230.30
b	4-Cl-C_6H_4	108–110	17	$C_{14}H_{17}ClN_2O$	264.75
c	3-NO_2-C_6H_4	66–88	42	$C_{14}H_{17}N_3O_3$	275.30
d	CH_3	Oil	37	$C_9H_{16}N_2O$	168.26

[a] Satisfactory microanalyses obtained: max. dev. C ± 0.24, H ± 0.17, N ± 0.13

3-(4-Chlorophenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]dec-2-ene (**4b**)

^{1}H-NMR: 1.70–2.10 (m, 4H, H_2-6, H_2-10), 2.32 (s, 3H, CH_3), 2.40–2.70 (m, 4H, H_2-7, H_2-9), 3.05 (s, 2H, H_2-4), 7.38 (d, 2H, aromat. H, $J = 9.5$), 7.60 (d, 2H, aromat. H). ^{13}C-NMR: 35.95 (t, C-6, C-10), 44.71 (t, C-4), 45.92 (q, CH_3), 52.43 (t, C-7, C-9), 82.28 (s, C-5), 127.50, 128.60, 128.75. 135.60 (aromat. C), 155.03 (s, C-3).

3-(3-Nitrophenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]dec-2-ene (**4c**)

^{1}H-NMR: 1.82–2.15 (m, 4H, H_2-6, H_2-10), 2.38 (s, 3H, CH_3), 2.45–2.72 (m, 4H, H_2-7, H_2-9), 3.12 (s, 2H, H_2-4), 7.55–8.39 (m, 4H, aromat. H). ^{13}C-NMR: 35.39 (t, C6, C-10), 44.40 (t, C-4), 45.35 (q, CH_3), 51.93 (t, C-7, C-9), 84.87 (s, C-5), 121.02, 124.14, 129.62, 131.63, 131.79, 148.15 (aromat. C), 154.45 (s, C-3).

3,8-Dimethyl-1-oxa-2,8-diazaspiro[4,5]dec-2-ene (**4d**)

4d was prepared as described above, but the cycloaddition reaction was carried out at room temperature. ^{1}H-NMR: 1.60–1.92 (m, 4H, H_2-6, H_2-10), 1.93 (s, 3H, CH_3), 2.30 (s, 3H, N–CH_3), 2.32–2.60 (m, 4H, H_2-7, H_2-9), 2.62 (s, 2H, H_2-4). ^{13}C-NMR: 13.39 (q, CH_3), 35.75 (t, C-6, C-10), 45.83 (q, N–CH_3), 48.57 (t, C-4), 52.47 (t, C-7, C-9), 82.44 (s, C-5), 154.80 (s, C-3).

***2-Phenyl-3-(X-phenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]decanes* 9**

N-Phenyl-C-aryl-nitrones **8** (2.25 mmol) and 4,4-methylene-1-methylpiperidine **1** (4.5 mmol) were heated under reflux in dry toluene (10 ml) for 20 h. Concentration of the solution under reduced pressure gave corresponding cycloadducts which were purified by recrystallization from diisopropyl-ether (see Table 3).

2,3-Diphenyl-8-methyl-1-oxa-2,8-diazaspiro[4,5] decane (**9a**)

^{1}H-NMR: 1.60–2.15 (m, 4H, H_2-6, H_2-10), 2.25 (dd, 1H, H_B-4, $J_{AB} = 12.9$ Hz, $J_{3,4B} = 7.3$ Hz), 2.36 (s, 3H, CH_3), 2.40–2.65 (m, 4H, H_2-7, H_2-9), 2.70 (dd, 1H, H_A-4, $J_{AB} = 12.9$ Hz, $J_{3,4A} = 7.3$ Hz), 4.67 (dd, 1H, H-3), 6.80–7.60 (m, 10H, aromat. H). ^{13}C-NMR: 34.73, 35.49 (t, t, C-6, C-10), 46.02 (q, CH_3), 51.04 (t, C-4), 52.69, 52.91 (t, t, C-7, C-9), 68.58 (d, C-3), 80.00 (s, C-5), 114.29, 120.79, 126.25, 127.26, 128.39, 128.74, 142.00, 151.80 (aromat. C).

2-Phenyl-3-(4-chlorophenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]decane (**9b**)

^{1}H-NMR: 1.60–2.10 (m, 4H, H_2-6, H_2-10), 2.20 (dd, 1H, H_B-4, $J_{AB} = 12.9$ Hz, $J_{3,4B} = 7.4$ Hz), 2.32 (s, 3H, CH_3), 2.40–2.60 (m, 4H, H_2-7, H_2-9), 2.61 (dd, 1H, H_A-4, $J_{AB} = 12.9$ Hz, $J_{3,4A} = 7.4$ Hz), 4.65 (dd,

Table 3. 2-Phenyl-3-(*X*-phenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]decanes **9**

Compound **9**	X	m.p. (°C)	Yield (%)	Formula	M.W.
a	H	69–72	77	$C_{20}H_{24}N_2O$[a]	308.43
b	4-Cl	115–117	61	$C_{20}H_{23}ClN_2O$[a]	342.87
c	2,4-di-Cl	160–162	75	$C_{20}H_{22}Cl_2N_2O$[a]	377.32

[a] Satisfactory microanalyses obtained: max. dev. C ± 0.26, H ± 0.17, N ± 0.13

1H, H-3), 6.80–7.50 (m, 9H, aromat. H). ^{13}C-NMR: 34.76, 35.51 (t, t, C-6, C-10), 46.03 (q, CH_3), 50.83 (t, C-4), 52.68, 52.89 (t, t, C-7, C-9), 67.37 (d, C-3), 80.18 (s, C-5), 114.27, 121.00, 127.64, 128.45, 132.90, 140.57, 151.50 (aromat. C).

2-Phenyl-3-(2,4-dichlorophenyl)-8-methyl-1-oxa-2,8-diazaspiro[4,5]decane (**9c**)

^{1}H-NMR: 1.60–2.20 (m, 4H, H_2-6, H_2-10), 2.02 (dd, 1H, H_B-4, J_{AB} = 12.9 Hz, $J_{3,4B}$ = 7.4 Hz), 2.32 (s, 3H, CH_3), 2.40–2.72 (m, 4H, H_2-7, H_2-9), 2.89 (dd, 1H, H_A-4, J_{AB} = 12.9 Hz, $J_{3,4A}$ = 7.4 Hz), 5.08 (dd, 1H, H-3), 6.80–7.69 (m, 8H, aromat. H). ^{13}C-NMR: 34.77, 35.45 (t, t, C-6, C-10), 46.01 (q, CH_3), 48.33 (t, C-4), 52.75, 52.88 (t, t, C-7, C-9), 64.71 (d, C-3), 80.82 (s, C-5), 113.72, 120.86, 127.74, 128.58, 128.81, 129.17, 132.31, 133.37, 138.34, 151.07 (aromat. C).

Experimental Data of X-Ray Measurement

X-ray structure determination of **4a**: Colorless crystal (0.05 × 0.31 × 0.52 mm^3), $C_{14}H_{18}N_2O$, *Mr* = 230.30, monoclinic, space group $P2_1/c$, *a* = 10.891(4) Å, *b* = 11.298(3) Å, *c* = 11.393(2) Å, β = 97.53(1)°,

Table 4. Crystal structure of **4a**: Non-hydrogen positional and isotropic displacement parameters. $U_{eq} = (1/3)\,\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* (a_i a_j)$

	x/a	*y/b*	*z/c*	U_{eq} [Å^2]
O(1)	0.2370(1)	0.4119(1)	0.6159(1)	0.051(1)
N(2)	0.3364(2)	0.4192(2)	0.7176(2)	0.048(1)
C(3)	0.4212(2)	0.3458(2)	0.6967(2)	0.042(1)
C(4)	0.3884(2)	0.2748(2)	0.5760(2)	0.057(1)
C(5)	0.2777(2)	0.3429(2)	0.5090(2)	0.046(1)
C(6)	0.1704(2)	0.2666(2)	0.4504(2)	0.061(1)
C(7)	0.0655(2)	0.3384(2)	0.3779(2)	0.067(1)
N(8)	0.1098(2)	0.4138(2)	0.2802(2)	0.057(1)
C(9)	0.2006(2)	0.4962(2)	0.3428(2)	0.056(1)
C(10)	0.3122(2)	0.4310(2)	0.4094(2)	0.054(1)
C(11)	0.5344(2)	0.3328(2)	0.7878(2)	0.040(1)
C(12)	0.5716(2)	0.4184(2)	0.8815(2)	0.048(1)
C(13)	0.6762(2)	0.4023(2)	0.9697(2)	0.055(1)
C(14)	0.7461(2)	0.3008(2)	0.9652(2)	0.057(1)
C(15)	0.7119(2)	0.2163(2)	0.8730(2)	0.056(1)
C(16)	0.6069(2)	0.2320(2)	0.7847(2)	0.048(1)
C(17)	0.0069(3)	0.4775(3)	0.2066(2)	0.087(1)

Table 5. Crystal structure of **4a**: Bond distances (Å) and angles (°)

O(1)–N(2)	1.413(2)	N(2)–O(1)–C(5)	108.6(1)
O(1)–C(5)	1.472(2)	O(1)–N(2)–C(3)	109.5(2)
N(2)–C(3)	1.281(3)	N(2)–C(3)–C(4)	113.1(2)
C(3)–C(4)	1.492(3)	N(2)–C(3)–C(11)	121.4(2)
C(3)–C(11)	1.460(3)	C(4)–C(3)–C(11)	125.4(2)
C(4)–C(5)	1.520(3)	C(3)–C(4)–C(5)	101.6(2)
C(5)–C(6)	1.514(3)	O(1)–C(5)–C(4)	102.8(2)
C(5)–C(10)	1.518(3)	O(1)–C(5)–C(6)	108.2(2)
C(6)–C(7)	1.518(3)	O(1)–C(5)–C(10)	107.1(2)
C(7)–N(8)	1.455(3)	C(4)–C(5)–C(6)	114.8(2)
N(8)–C(9)	1.449(3)	C(4)–C(5)–C(10)	113.1(2)
N(8)–C(17)	1.461(4)	C(6)–C(5)–C(10)	110.2(2)
C(9)–C(10)	1.509(3)	C(5)–C(6)–C(7)	112.7(2)
C(11)–C(12)	1.394(3)	C(6)–C(7)–N(8)	111.2(2)
C(11)–C(16)	1.389(3)	C(7)–N(8)–C(9)	109.4(2)
C(12)–C(13)	1.377(3)	C(7)–N(8)–C(17)	110.6(2)
C(13)–C(14)	1.381(3)	C(9)–N(8)–C(17)	110.5(2)
C(14)–C(15)	1.369(3)	N(8)–C(9)–C(10)	110.7(2)
C(15)–C(16)	1.381(3)	C(5)–C(10)–C(9)	112.1(2)
		C(3)–C(11)–C(12)	121.8(2)
		C(3)–C(11)–C(16)	120.1(2)
		C(12)–C(11)–C(16)	118.1(2)
		C(11)–C(12)–C(13)	120.8(2)
		C(12)–C(13)–C(14)	119.9(2)
		C(13)–C(14)–C(15)	120.1(2)
		C(14)–C(15)–C(16)	120.1(2)
		C(11)–C(16)–C(15)	120.9(2)

$V = 1267.8\,Å^3$. $Z = 4$, $D_x = 1.207\,g\,cm^{-3}$, $T = 25\,°C$. A Philips PW1100 four-circle diffractometer and graphite monochromatized Mo Kα radiation, $\lambda = 0.71069$ Å, were used to measure 2352 reflections in the range $\Theta = 2°$ to 25° with $h = -12$ to 12, $k = 0$ to 13, $l = 0$ to 12. The data, corrected for LP but not for absorption ($\mu = 0.72\,cm^{-1}$), were merged to 2240 unique reflections ($R_{merge} = 0.032$ on F). Structure solution by direct methods and program SHELXS86 [25]. Structure refinement with program SHELX76 [26] using anisotropic temperature factors for non-hydrogen atoms, hydrogen atoms with isotropic temperature factors in idealized positions riding with the atom to which they are attached (C–H = 0.96 Å), 1276 reflections with $F_0 > 4\,\sigma(F_0)$, weights $w = 1/\sigma^2(F_0) + 0.0002\,(F_0^2)$, and 157 parameters converged at $R = 0.043$ and $wR = 0.037$.

Atomic parameters of non-hydrogen atoms are given in Table 4, selected bond lengths and angles are listed in Table 5. Additional details on the structure determination are deposited at the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, no. CSD-57846.

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