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Synthesis of Spiro-substituted 1,3-Oxazines by a New Sequence Leading to Spiroheterocycles

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Summary. The target compounds, i.e. 1,3-oxazines which are spiro-substituted in position 6 by a piperidine moiety, are derived from 1-oxa-3,9-diaza-spiro[5.5]undecane, a novel heterocyclic parent system. They were all approached by the following three-step sequence: 1,3-dipolar cycloadditions of nitrile oxides and nitrones to piperidines bearing an exocyclic methylene group gave the corresponding spiro-substituted oxazole derivatives **3**. In a consecutive step these were cleaved by hydrogenolysis to γ-amino-alcohols **4**, which in a final step were recyclized by insertions of a C_1-unit to yield the target structures **5**–**10**: thus a *de facto* ring-extension of spiro-oxazoles to spiro-oxazines was accomplished.

Keywords. Spiroheterocyles; Reductive cleavage of isoxazolines; Amino-alcohols; Spiropiperidines.

Synthese von spirosubstituierten 1,3-Oxazinen mittels einer neuen zu Spiroheterocyclen führenden Synthesefolge

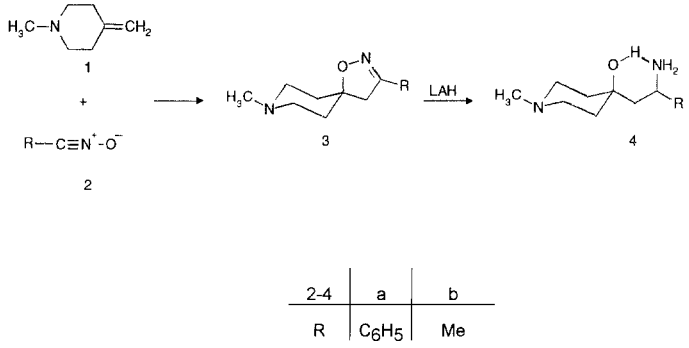
Zusammenfassung. Die Zielverbindungen, d.h. 1,3-Oxazine mit einem Piperidinring als Spiro-Substituenten in 6-Stellung, leiten sich von 1-Oxa-3,9-diaza-spiro[5.5]undecan, einem neuen heterocyclischen Grundkörper, ab. Sie wurden alle mit Hilfe der folgenden dreistufigen Synthesefolge zugänglich gemacht: 1,3-dipolare Cycloadditionen von Nitriloxiden und Nitronen an Piperidinderivate mit einer exocylischen Methylengruppe gaben die entsprechenden spiro-substituierten Oxazolderivate **3**. Diese wurden anschließend hydrogenolytisch zu den γ-Aminoalkoholen **4** gespalten, welche schließlich wieder unter Einschub von einem C-Atom zu den Zielstrukturen **5**–**10** cyclisiert wurden: dadurch wurde eine *de facto*-Ringerweiterung von Spiro-Oxazolen zu Spiro-Oxazinen erreicht.

Introduction

The chemistry of spirocyclic compounds was stimulated recently by an increasing interest in a variety of spiro-structures of pronounced biological importance, such as pheromones, antibiotics, alkaloids [1], antineoplastics [2, 3], herbicides with low toxicity to microorganisms [4], etc.

Since general routes leading to spirocyclic systems other than spiro-ketals or -acetals are very limited, the present work describes a synthetic strategy permitting the approach of the target structures using isoxazoline intermediates (known to be

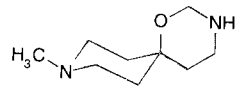
versatile synthetic equivalents of ß-hydroxy ketones [6], γ-amino-alcohols [7], enamino-aldehydes [8] and other related structures [9]) according to the three-step sequence shown in Scheme 1.



2-4	a	b
R	C_6H_5	Me

Scheme 1

As the first step (i.e. the 1,3-dipolar cycloaddition leading to spiro-substituted isoxazolines **3**) was already described in a previous paper [5], we are now dealing with the reductive cleavage of these spiroisoxazolines **3** and with various cyclizations of the γ-amino-alcohols **4** thus obtained to yield the target structures **5**–**10**, all of them being derivatives of 1-oxa-3,9-diaza-spiro[5.5]undecane, a novel spiroheterocyclic parent system:



Results and Discussion

Reductive Cleavage of the Spiroisoxazolines **3**

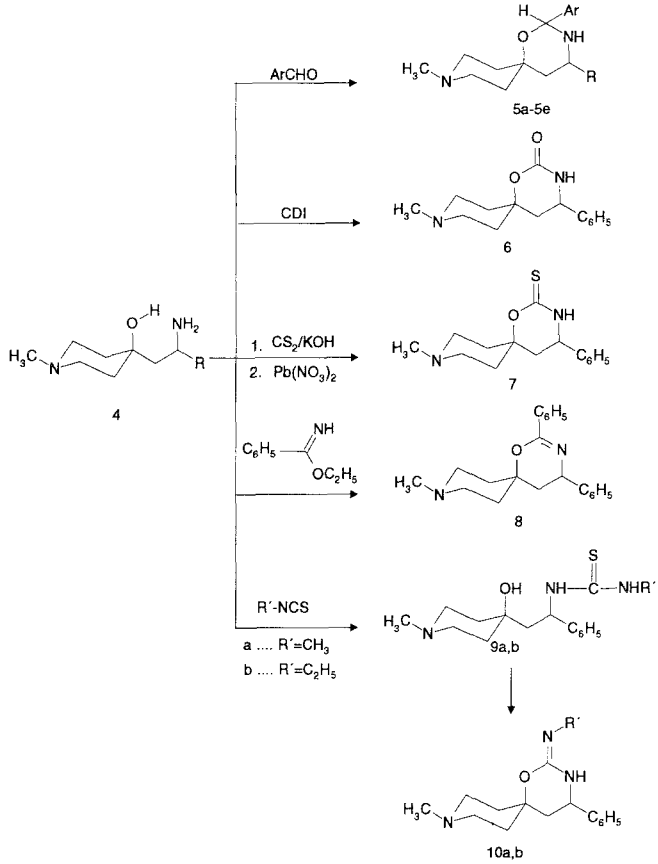
In accordance with the literature dealing with hydrogenolysis of isoxazolines in general [10–12] the reductive cleavage was successfully effected (40–75%) by $LiAlH_4$ (= LAH) in ether, preferentially by applying an excess of 4 moles LAH. The structures of the γ-amino-alcohols **4** thus obtained were confirmed by their spectral data, based on the observation [10–12] that a chair-conformation is favoured in solution by intramolecular hydrogen bonds, and via comparison with X-ray data determined for compound **3a** [5]. According to the latter, in **3a** the isoxazoline oxygen is in an axial, whilst the methylene group is in an equatorial position. Provided that the configuration was retained in the course of the reduction it can be assumed that the hydroxyl group in the amino-alcohols **4** might also be in the axial position.

Cyclization of the γ-Amino-Alcohols **4** *to Spiro-1,3-oxazines* **5**–**8** *and* **10**

Various ring closure reactions of γ-amino-alcohols in general, mainly leading to tetrahydro-1,3-oxazines, are described in the literature, e.g. with acetone [13], benzaldehydes [12, 14], ethyl benzimidate [15, 16] and ethyl chloroformate [12, 17]. For the particular case of compounds **4**, bearing the future spiro substituent,

it turned out that some of these reactions were not directly applicable: although published cyclizations using acetone proceeded with high yields, our γ-amino-alcohols **4** failed to react at all.

Nevertheless, various ring closure reactions to the 6-membered target ring structures were approached according to Scheme 2. While the cyclization of **4a** to **6** gave only very poor yields when attempted with ethyl chloroformate and subsequent treatment with MeONa, the same reaction proceeded with carbonyl-diimidazole (CDI) in 34% yield.

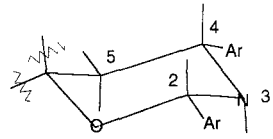


5	a	b	c	d	e
R	C_6H_5	C_6H_5	C_6H_5	C_6H_5	CH_3
Ar	4-$NO_2C_6H_5$	3-$NO_2C_6H_5$	2-$NO_2C_6H_5$	4-ClC_6H_5	4-$NO_2C_6H_5$

Scheme 2

The corresponding thiones **7** were obtained by lead(II) nitrate-oxidation of dithiocarbamates, prepared from **4** by treatment with carbon disulphide [16]. Reacting **4a** with ethyl benzimidate yielded the spiro-dihydro-1,3-oxazine **8**, while reactions with methyl- and ethyl-isothiocyanate (in ether at ambient temperature) furnished only the corresponding thioureas **9a** and **9b** which had to be cyclized to **10a** and **10b** in an ensuing step via an intermediate S-methylation (MeI/KOH) [18]. Reactions with various substituted benzaldehydes (2-nitro-, 3-nitro-, 4-nitro- and

4-chloro-benzaldehyde) proceeded smoothly with formation of spiro-1,3-oxazines **5a–d**, which are derivatives of a new spiro-heterocyclic parent system. It turned out that only one out of two possible diastereoisomers – the one with both of the aryl-substituents in equatorial positions – was obtained. These findings were proved by analyzing the vic-J_{HH}-couplings of the protons at positions 2 and 4 as shown for **5a** in the structural formula below:



In the ^{1}H-NMR spectrum H–2 appears at 5.60 ppm as a doublet with $J_{2,3} = 12.6$ Hz (collapses to a singlet after D_2O-exchange): therefore H-2 and N–H are assumed to be in axial positions. H–4 exhibits at 4.30 ppm a doublet of triplet due to $J_{4,3} = J_{4,5a} = 10.8$ Hz and $J_{4,5e} = 1$ Hz ($J_{4,3}$ was also proved by a D_2O-exchange experiment).

The results of molecular mechanics calculations [20] also support these suggestions. The following torsion angles φ have been obtained from energy minimization (**MM+** force field): φ(H-5a, H-4a) = 179.3° φ(H-5e, H-4a) = 64.1°, φ(H-4a, H-3a) = 177.6° and φ(H-3a, H-2a) = 174.0°. They are in good agreement with the coupling constants observed.

The second possible diastereoisomer was not detected in the crude product by ^{1}H- and ^{13}C-nmr spectroscopy.

Independently the suggested constitution and conformation of **5a** was proved by X-ray crystal structure determination. Technical details of this work on compound **5a** are given in the experimental part. Atomic coordinates and selected bond distances and angles are presented in Tables 1 and 2.

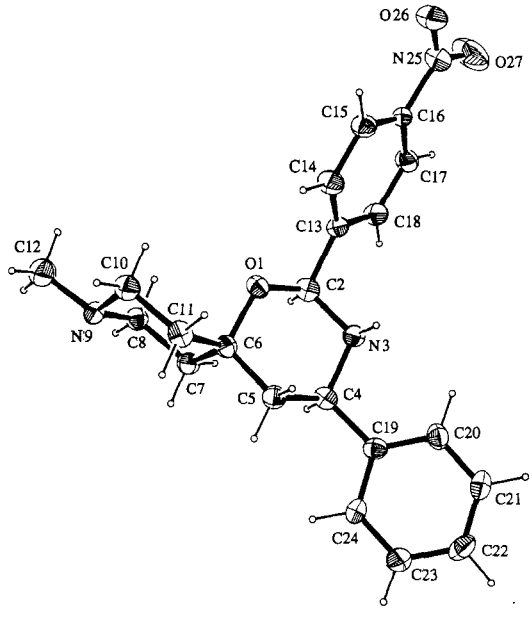


Fig. 1

Table 1. Crystal structure of **5a**: non-hydrogen atom positional and equivalent isotropic thermal displacement parameters

	x/a	y/b	z/c	U_{eq}[Å^2]
O(1)	0.2495(2)	0.4589(4)	0.5039(2)	0.042(1)
C(2)	0.3308(3)	0.4663(7)	0.4945(3)	0.044(2)
N(3)	0.3769(2)	0.6340(6)	0.5261(2)	0.042(2)
C(4)	0.3813(3)	0.6715(7)	0.6171(3)	0.044(2)
C(5)	0.2933(3)	0.6707(7)	0.6248(3)	0.046(3)
C(6)	0.2474(3)	0.4936(7)	0.5914(3)	0.040(2)
C(7)	0.2822(3)	0.3316(7)	0.6513(3)	0.045(2)
C(8)	0.2301(3)	0.1606(7)	0.6242(3)	0.044(2)
N(9)	0.1430(2)	0.1947(6)	0.6191(2)	0.042(2)
C(10)	0.1057(3)	0.3341(7)	0.5540(3)	0.050(2)
C(11)	0.1543(3)	0.5117(7)	0.5790(3)	0.045(2)
C(12)	0.0938(3)	0.0256(7)	0.5994(3)	0.065(3)
C(13)	0.3197(3)	0.4471(7)	0.3989(3)	0.041(2)
C(14)	0.2434(3)	0.4763(7)	0.3351(3)	0.052(2)
C(15)	0.2355(3)	0.4738(7)	0.2478(3)	0.049(2)
C(16)	0.3054(3)	0.4387(7)	0.2245(3)	0.043(2)
C(17)	0.3819(3)	0.4010(7)	0.2867(3)	0.049(2)
C(18)	0.3884(3)	0.4078(7)	0.3730(3)	0.048(2)
C(19)	0.4280(3)	0.8487(7)	0.6502(3)	0.042(2)
C(20)	0.4557(3)	0.9671(8)	0.5993(3)	0.049(2)
C(21)	0.5008(3)	1.1210(8)	0.6349(4)	0.055(3)
C(22)	0.5187(3)	1.1622(8)	0.7216(4)	0.059(3)
C(23)	0.4904(3)	1.0461(8)	0.7729(3)	0.061(3)
C(24)	0.4456(3)	0.8927(7)	0.7380(3)	0.051(3)
N(25)	0.2990(4)	0.4396(7)	0.1315(3)	0.065(2)
O(26)	0.2300(3)	0.4687(6)	0.0780(2)	0.079(2)
O(27)	0.3619(3)	0.4105(8)	0.1130(3)	0.115(3)

A view of the molecule **5a** is shown in Figure 1. The two six-membered rings of the 1-oxa-3,9-diazaspiro[5.5]undecane moiety adopt usual chair-like conformations and exhibit normal bond lengths and angles (Table 2). All substituents of this moiety – the methyl group C(12)H_3, the phenyl residue C(19) through C(24), and the 4-nitrophenyl residue – are in equatorial positions to the six-rings. The 4-nitrophenyl residue is essentially flat with respect to its carbon atoms [C(13) through C(18)]. However, the nitro-group and C(2) are by 0.05 to 0.13 Å off from the least-squares plane through the six benzene carbon atoms C(13) through C(18). One remarkable feature of the molecule is that the N(3)-bonded hydrogen H(3) is not equatorial with respect to the six-ring O(1) through C(6), as one might expect. It is in fact in an axial position and forms an almost straight hydrogen bond to the nitro-oxygen O(26) of a neighbouring molecule and with a H-bond distance of N(3)···O(26) = 3.186 Å. The second oxygen of the nitro group, O(27), lacks such an interaction, and possibly, therefore, exhibits relatively strong thermal motions perpendicular to the 4-nitrophenyl residue.

Conclusion

The reaction sequence presented above, i.e. applying 1,3-dipolar cycloaddition to heterocycles with an exocyclic double bond, followed by reduction and subsequent

Table 2. Crystal structure of **5a**: bond distances (Å) and angles (°)

O(1)-C(2)	1.427(7)	C(2)-O(1)-C(6)	115.2(3)
O(1)-C(6)	1.451(6)	O(1)-C(2)-N(3)	114.5(4)
C(2)-N(3)	1.457(6)	O(1)-C(2)-C(13)	107.6(3)
C(2)-C(13)	1.504(7)	N(3)-C(2)-C(13)	108.3(4)
N(3)-C(4)	1.477(6)	C(2)-N(3)-C(4)	110.9(4)
C(4)-C(5)	1.527(8)	N(3)-C(4)-C(5)	110.2(3)
C(4)-C(19)	1.525(7)	N(3)-C(4)-C(19)	111.3(4)
C(5)-C(6)	1.520(7)	C(5)-C(4)-C(19)	112.2(4)
C(6)-C(7)	1.526(7)	C(4)-C(5)-C(6)	111.7(4)
C(6)-C(11)	1.521(7)	O(1)-C(6)-C(5)	109.1(4)
C(7)-C(8)	1.513(7)	O(1)-C(6)-C(7)	110.9(4)
C(8)-N(9)	1.464(6)	O(1)-C(6)-C(11)	103.7(3)
N(9)-C(10)	1.457(6)	C(5)-C(6)-C(7)	113.2(3)
N(9)-C(12)	1.469(6)	C(5)-C(6)-C(11)	110.9(4)
C(10)-C(11)	1.523(7)	C(7)-C(6)-C(11)	108.6(4)
C(13)-C(14)	1.380(6)	C(6)-C(7)-C(8)	113.3(3)
C(13)-C(18)	1.383(8)	C(7)-C(8)-N(9)	110.5(4)
C(14)-C(15)	1.376(7)	C(8)-N(9)-C(10)	110.5(4)
C(15)-C(16)	1.372(8)	C(8)-N(9)-C(12)	110.6(4)
C(16)-C(17)	1.382(6)	C(10)-N(9)-C(12)	110.9(3)
C(16)-N(25)	1.474(7)	N(9)-C(10)-C(11)	109.9(3)
C(17)-C(18)	1.366(7)	C(6)-C(11)-C(10)	113.7(4)
C(19)-C(20)	1.379(8)	C(2)-C(13)-C(14)	122.0(5)
C(19)-C(24)	1.392(7)	C(2)-C(13)-C(18)	119.6(4)
C(20)-C(21)	1.379(8)	C(14)-C(13)-C(18)	118.3(5)
C(21)-C(22)	1.370(9)	C(13)-C(14)-C(15)	121.5(5)
C(22)-C(23)	1.378(9)	C(14)-C(15)-C(16)	118.6(4)
C(23)-C(24)	1.371(7)	C(15)-C(16)-C(17)	121.2(5)
N(25)-O(26)	1.222(7)	C(15)-C(16)-N(25)	119.7(4)
N(25)-O(27)	1.210(9)	C(17)-C(16)-N(25)	119.1(5)
		C(16)-C(17)-C(18)	119.0(5)
		C(13)-C(18)-C(17)	121.3(4)
		C(4)-C(19)-C(20)	124.3(4)
		C(4)-C(19)-C(24)	118.1(5)
		C(20)-C(19)-C(24)	117.5(5)
		C(19)-C(20)-C(21)	120.9(5)
		C(20)-C(21)-C(22)	121.1(6)
		C(21)-C(22)-C(23)	118.4(5)
		C(22)-C(23)-C(24)	120.8(5)
		C(19)-C(24)-C(23)	121.2(5)
		C(16)-N(25)-O(26)	117.5(6)
		C(16)-N(25)-O(27)	118.2(5)
		O(26)-N(25)-O(27)	124.3(5)

recyclization with ring expansion constitutes a new route to spiro-heterocyclic derivatives.

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). TLC analyses were performed on Merck DC- silica gel sheets. All reagents were purified and dried if necessary prior to use.

Data for compounds **4**–**10** are summarised in Table 3.

3-Phenyl- and 3-methyl-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-enes (**3a, b**) were prepared according to Ref. [5] by 1,3-dipolar cycloaddition of nitrile oxides **2** to 4,4-methylene-1-methylpiperidine **1**.

Reduction of 3-R-8-Methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-enes (**3a, b**) *with Lithium Aluminium Hydride. General Procedue*

To the suspension of $LiAlH_4$ (8.4 mmol) in 20 ml of dry ether a solution of the isoxazoline **3a** (R = Phenyl) or **3b** (R = Methyl) (1.82 mmol) in 5 ml of dry ether was added dropwise. The reaction

Table 3. Data for compounds **4–10**

Compound	m.p. (° C)	Yield (%)	Formula[a]	M.W.
4a	52–54	75	$C_{14}H_{22}N_2O$	234.34
4b	30–32	40	$C_9H_{20}N_2O$	172.27
5a	170–180	87	$C_{21}H_{25}N_3O_3$	367.45
5b	30–32	81	$C_{21}H_{25}N_3O_3$	367.45
5c	66–68	58	$C_{21}H_{25}N_3O_3$	367.45
5d	110–112	29	$C_{21}H_{25}ClN_2O$	358.88
5e	78–80	79	$C_{16}H_{23}N_3O_3$	305.38
6	224–226	34	$C_{15}H_{20}N_2O_2$	261.75
7	227–229	60	$C_{15}H_{20}N_2OS$	276.40
8	105–107	52	$C_{21}H_{24}N_2O$	320.44
9a	115–117	47	$C_{16}H_{25}N_3OS$	307.46
9b	28–30	99	$C_{17}H_{27}N_3O$	321.49
10a	oil	25	$C_{16}H_{23}N_3O$	273.38
10b	oil	22	$C_{17}H_{25}N_3O$	287.41

[a] Satisfactory microanalyses obtained: C+/−0.28, H+/−0.30, N+/−0.20

mixture was then refluxed for 18 h and subsequently the excess of hydride was destroyed by addition of 20 ml water and 20 ml of 20% NaOH to the stirred reaction mixture until the precipitate bleached white. The precipitate was then filtered off and washed with 2 × 20 ml of ether. Then the aqueous layer was extracted with ether and the combined organic filtrates were concentrated in vacuo.

1-Methyl-4-hydroxy-4-(2'-phenyl-2'-aminoethyl)-piperidine (**4a**)

^{1}H-NMR: 1.50–2.05 (m, 7H), 2.25–2.70 (m, H, H_2-2, H_2-6), 2.30 (s, 3H, N–CH_3), 4.19 (dd, 1H, H-2'), 7.20–7.46 (m, 5H, aromat. H). ^{13}C-NMR: 36.08 and 39.47 (t, t, C-3 and C-5), 46.09 (q, N–CH_3), 47.91 (t, C-1'), 51.06 and 51.55 (t, t, C-2 and C-6), 52.56 (d, C-2'), 68.23 (s, C-4), 125.21, 126.98, 128.67, 146.83 (aromat. C).

1-Methyl-4-hydroxy-4-(2'-methyl-2'-aminoethyl)-piperidine (**4b**)

^{1}H-NMR: 1.10 (d, 3H, CH_3, $J = 6.3$), 1.20–1.90 (m, 7H), 2.23–2.80 (m, 4H, H_2-2, H_2-6), 2.25 (s, 3H, CH_3), 3.20 (m, 1H, H-2'). ^{13}C-NMR: 27.66 (q, CH_3), 36.03 and 39.34 (t, t, C-3 and C-5), 43.72 (d, C-2'), 45.94 (q, N–CH_3), 47.90 (t, C-1'), 50.99 and 51.46 (t, t, C-2 and C-6), 68.04 (s, C-4).

2-Ar-4-R-Disubstituted-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecanes (**5a–5e**)

To the solution of γ-amino-alcohol **4** (2.14 mmol, R = Phenyl, Methyl) in 20 ml of dry chloroform a solution of the corresponding benzaldehyde (2.45 mmol, Ar = 4-NO_2-phenyl, 3-NO_2-phenyl, 2-NO_2-phenyl, 4-Cl-phenyl) in 10 ml of dry chloroform was added, followed by the addition of *p*-toluenesufonic acid (48 mg dissolved in 5 ml of dry chloroform). Finally 1.35 g of molecular sieve (4Å) were added, the reaction mixture was refluxed (4 days), then filtered through a short column filled with sodium carbonate and washed with dry chloroform. The filtrate was then concentrated in vacuo, chromatographed on an aluminium oxide column and crystallized from ether (aluminium oxide proved to be essential, the products were unstable on silica gel).

2-(4-Nitrophenyl)-4-phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane (**5a**)

^{1}H-NMR: 1.30–2.05 (m, 7H, NH, H_2-5, H_2-7, H_2-11), 2.34 (s, 3H, CH_3), 2.38–2.83 (m, 4H, H_2-8, H_2-10), 4.30 (ddd, 1H, H-4, $J_{4,5a} = J_{4,3} = 10.8$, $J_{4,5e} = 1$), 5.60 (d, 1H, H-2, $J_{2,3} = 12.6$), 7.25–8.20 (m, 9H, aromat. H). ^{13}C-NMR: 30.07 and 40.10 (t, t, C-7 and C-11), 42.76 (t, C-5), 46.11 (q, N–CH_3), 50.82 and 50.87 (t, t, C-8 and C-10), 53.96 (d, C-4), 70.99 (s, C-6), 80.19 (d, C-2), 123.22, 126.08, 127.16, 127.44, 128.56, 142.34, 147.50, 147.82 (aromat. C).

2-(3-Nitrophenyl)-4-phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane (**5b**)

^{1}H-NMR: 1.18–1.96 (m, 7H, NH, H_2-5, H_2-7, H_2-11), 2.37 (s, 3H, CH_3), 2.30–2.72 (m, 4H, H_2-8, H_2-10), 4.30 (ddd, 1H, H-4, $J_{4,5a} = J_{4,3} = 12.2$, $J_{4,5e} = 1$), 5.58 (d, 1H, H-2, $J_{2,3} = 12.9$), 7.25–8.52 (m, 9H, aromat. H). ^{13}C-NMR: 30.05 and 40.04 (t, t, C-7 and C-11), 42.65 (t, C-5), 46.05 (q, N-CH_3), 50.76 and 50.81 (t, t, C-8 and C-10), 53.84 (d, C-4), 70.96 (s, C-6), 80.01 (d, C-2), 121.29, 122.74, 126.05, 127.32, 128.46, 128.90, 132.44, 142.32, 142.99, 148.02 (aromat. C).

2-(2-Nitrophenyl)-4-phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane (**5c**)

^{1}H-NMR: 1.52–1.96 (m, 7H, NH, H_2-5, H_2-7, H_2-11), 2.26–2.63 (m, 4H, H_2-8, H_2-10), 2.28 (s, 3H, CH_3), 4.22 (d, 1H, H-4, $J = 12.9$), 5.95 (br s, 1H, H-2), 7.25–8.02 (m, 9H, aromat. H). ^{13}C-NMR: 30.08 and 39.98 (t, t, C-7 and C-11), 42.39 (t, C-5), 45.93 (q, N–CH_3), 50.66 and 50.75 (t, t, C-8 and C-10), 53.77 (d, C-4), 71.23 (s, C-6), 78.50 (d, C-2), 123.59, 126.07, 127.92, 128.34, 128.60, 131.92, 134.21, 142.42, 149.23 (aromat. C).

2-(4-Chlorophenyl)-4-phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane (**5d**)

^{1}H-NMR: 1.33–2.00 (m, 7H, NH, H_2-5, H_2-7, H_2-11), 2.25–2.69 (m, 4H, H_2-8, H_2-10), 2.35 (s, 3H, CH_3), 4.28 (ddd, 1H, H-4, $J_{4,5a} = J_{4,3} = 12.0$, $J_{4,5e} = 1$), 5.50 (d, 1H, H-2, $J_{2,3} = 12.3$), 7.18–7.65 (m, 9H, aromat. H). ^{13}C-NMR: 30.17 and 40.13 (t, t, C-7 and C-11), 42.99 (t, C-5), 46.18 (q, N–CH_3), 50.86 and 50.92 (t, t, C-8 and C-10), 53.90 (d, C-4), 70.63 (s, C-6), 80.36 (d, C-2), 126.12, 127.30, 127.54, 128.18, 128.51, 133.61, 139.53, 142.74 (aromat. C).

2-(4-Nitrophenyl)-4,9-dimethyl-1-oxa-3,9-diazaspiro[5.5]undecane (**5e**)

^{1}H-NMR: 1.13 (d, 3H, 4-CH_3, $J = 6.3$), 1.50–1.98 (m, 7H, NH, H_2-5, H_2-7, H_2-11), 2.30 (s, 3H, N–CH_3), 2.35–2.70 (m, 4H, H_2-8, H_2-10), 3.21 (m, 1H, H-4), 5.41 (s, 1H, H-2), 7.72–8.23 (m, 4H, aromat. H), ^{13}C-NMR: 22.28 (q, 4-CH_3), 29.97 and 39.85 (t, t, C-7 and C-11), 44.18 (t, C-5), 45.82 (d, C-4), 45.94 (q, N–CH_3), 50.65 and 50.72 (t, t, C-8 and C-10), 70.48 (s, C-6), 79.73 (d, C-2), 122.95, 126.87, 147.21, 147.99 (aromat. C).

4-Phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane-2-one (**6**)

To the solution of the γ-amino-alcohol **4a** (2.13 mmol) in 20 ml dry THF CDI (6.4 mmol) was added under nitrogen and the mixture was heated for 18 h under reflux and then poured into water. After extraction with chloroform, drying (Na_2SO_4) and concentrating the combined organic layers under reduced pressure, product **6** was purified by crystallization from diisopropyl ether/isopropanol.

^{1}H-NMR: 1.63–1.92 (m, 4H, H_2-7, H_2-11), 2.00–2.18 (m, 2H, H_2-5), 2.29 (s, 3H, N–CH_3), 2.36–2.72 (m, 4H, H_2-8, H_2-10), 4.62 (d, d, 1H, H–44, $J_{4,5A} = 12.4$, $J_{4,5B} = 6.5$), 5.88 (s, 1H, NH), 7.25–7.5 (m, 5H, aromat. H). ^{13}C-NMR: 33.43 and 36.83 (t, t, C-7 and C-11), 41.14 (t, C-5), 45.70 (q, N–CH_3), 50.11 and 50.41 (t, t, C-8 and C-10), 51.91 (d, C-4), 76.30 (s, C-6), 125.94, 128.17, 128.82, 140.88 (aromat. C), 153.63 (s, C=O).

4-Phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane-2-thione (**7**)

To a solution of KOH (55 mg) in water (0.5 ml) the γ-amino-alcohol **4a** (200 mg, 0.85 mmol) was added at 0 °C, followed by the addition of 2 ml dioxane and CS_2 (65 mg). After stirring (5 min), a 5.5% solution of KOH in water (0.5 ml) and $Pb(NO_3)_2$ (262 mg in 1.5 ml of water) was added. The reaction mixture was stirred at 50 °C for 2 h, then filtered, concentrated in vacuo and again dissolved in water. After extraction with chloroform, drying (Na_2SO_4) and concentrating under reduced pressure, product **7** was purified by recrystallization from diisopropyl ether.

^{1}H-NMR: 1.79–2.20 (m. 6H, H_2-5, H_2-7, H_2-11), 2.28 (s, 3H, N–CH_3), 2.40–2.80 (m, 4H, H_2-8, H_2-10), 3.71 (s, 1H, NH), 4.60 (dd, 1H, 4-H, $J_{4,5A} = 12.9$, $J_{4,5B} = 6.5$), 7.20–7.45 (m, 5H, aromat. H). ^{13}C-NMR: 33.32 and 36.48 (t, t, C-7 and C-11), 39.56 (t, C-5), 45.66 (q, N–CH_3), 50.16 and 50.44 (t, t, C-8 and C-10), 53.34 (d, C-4), 79.51 (s, C-6), 126.22, 128.86, 129.12, 138.76 (aromat. C), 186.24 (s, C=S).

2,4-Diphenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecan-2-one (**8**)

To the γ-amino-alcohol **4a** (800 mg, 3.4 mmol) and ethyl benzimidate (507 mg, 3.4 mmol) in dry ethanol (20 ml) was added a catalytic amount of HCl and the mixture was heated under reflux for 4 h. Concentrating the solution under reduced pressure gave the corresponding spiro-product **8**, which was purified by recrystallization from diisopropyl ether.

^{1}H-NMR: 1.52–1.95 (m, 4H, H_2-7, H_2-11), 2.05–2.20 (m, 2H, H_2-5), 2.40 (s, 3H, N–CH_3), 2.28–2.80 (m, 4H, H_2-8, H_2-10), 4.75 (dd, 1H, H-4, $J_{4,5A} = 12.9$, $J_{4,5B} = 6.2$), 7.30–8.18 (m, 10H, aromat. H). ^{13}C-NMR: 34.03 and 37.35 (t, t, C-7 and C-11), 41.17 (t, C-5), 45.88 (q, N–CH_3), 50.60 and 50.91 (t, t, C-8 and C-10), 52.61 (d, C-4), 72.61 (s, C-6), 126.10, 126.26, 126.87, 127.62, 127.98, 130.06, 133.93, 144.13 (aromat. C), 154.29 (s, C=N).

Thiourea **9a**

To a stirred solution of the γ-amino-alcohol **4a** (200 mg, 0.85 mmol) in dry ether (2.5 ml) was added methyl isothiocyanate (186 mg, 3.66 mmol). The reaction mixture was stirred at room temperature for 1 h, then the precipitated thiourea **9** was filtered off and washed with dry ether (5 ml).

^{1}H-NMR: 1.60–2.00 (m, 6H, H_2-1′, H_2-3, H_2-5), 2.20–2.65 (m, 4H, H_2-2, H_2-6), 2.30 (s, 3H. N–CH_3). 2.98 (d, 3H, NH–CH_3, $J = 5.8$), 5.20 (m, 1H, H-2′), 5.98 (br. s, 1H, NH), 7.30–7.48 (m, 6H, NH and aromat. H). ^{13}C-NMR: 31.22 (q, $NHCH_3$), 35.58 and 38.34 (t, t, C-3 and C-5), 45.94 (q, NCH_3), 48.55 (t, C-1′), 51.24 and 51.38 (t, t, C-2 and C-6), 55.00 (d, C-2′), 68.97 (s, C-6), 126.06, 127.55, 128.91, 142.21 (aromat. C), 181.46 (s, C=S).

Thiourea **9b**

To the stirred solution of the γ-amino-alcohol **4a** (1.05 g, 4.49 mmol) in dry ether (15 ml) ethyl isothiocyanate (1.17 g, 13.45 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, then concentrated under reduced pressure. Product **9b** was purified by recrystallization from diisopropyl ether.

^{1}H-NMR: 1.04 (t, 3H, CH_3, $J = 7.7$), 1.55–2.10 (m, 6H, H_2-1′, H_2-3, H_2-5), 2.22 (s, 3H, N–CH_3), 2.30–2.60 (m, 4H, H_2-2, H_2-6), 3.42 (q, 2H, CH_2), 5.15 (m, 1H, H-2′), 5.99 (br. s, 1H, NH), 7.20–7.35 (m, 5H, aromat. H), 7.65 (br. s, 1H, NH). ^{13}C-NMR: 22.65 (q, CH_3), 35.56 and 38.10 (t, t, C-3 and C-5), 39.38 (t, C-1′), 45.86 (q, N–CH_3), 48.54 (t, CH_2), 51.20 and 51.32 (t, t, C-2 and C-6), 54.85 (d, C-2′), 68.72 (s, C-6), 126.09, 127.43, 128.82, 142.35 (aromat. C), 180.23 (s, C=S).

4-Phenyl-9-methyl-1-oxa-3,9-diazaspiro[5.5]undecane-2-(N-methyl or N-ethyl) imide (**10a** or **10b**)

To a stirred solution of thiourea **9** (0.39 mmol) in methanol (1 ml) CH_3I (0.078 ml, 1.25 mmol) was added. The reaction mixture was then stirred at room temperature for 2 h, concentrated *in vacuo* and

dissolved in methanol (1.6 ml). To this solution KOH (234 mg) was added, followed by stirring at room temperature for 3 h. Concentrating the reaction mixture under reduced pressure, dissolution in water, extraction with chloroform, drying (Na_2SO_4) and evaporation of the combined organic layers afforded the product as an viscous oil.

Imide **10a**: ^{1}H-NMR: 1.50–1.90 (m, 6H, H_2-5, H_2-7, H_2-11), 2.00–2.80 (m, 4H, H_2-8, H_2-10), 2.35 (s, 3H, N–CH_3), 2.85 (s, 3H, =N–CH_3), 2.92 (br. s, 1H, NH), 4.55 (dd, 1H, H-4, $J_{4,5A} = 12.9$, $J_{4,5B} = 6.5$), 7.20–7.40 (m, 5H, aromat. H).

Imide **10b**: ^{1}H-NMR: 1.30 (t, 3H, CH_3), 1.90–2.20 (m, 6H, H_2-5, H_2-7, H_2-11), 2.20 (s, 3H, N–CH_3), 2.22–2.85 (m, 4H, H_2-8, H_2-10), 3.40 (q, 2H, CH_2), 4.75 (dd, 1H, H-4, $J_{4,5A} = 12.9$, $J_{4,5B} = 5.8$), 7.31–7.40 (m, 5H, aromat. H).

Experimental Data of X-Ray Measurement

X-ray structure determination of **5a**: Yellowish crystal ($0.07 \times 0.14 \times 0.39\,mm^3$, grown from $CHCl_3$) of 2-(4-Nitrophenyl)-4-phenyl-9-methyl-1-oxa-3,9-diaza-spiro[5.5]undecane, $C_{21}H_{25}N_3O_3$, $M_r = 364.45$ monoclinic, space group $P2_1/n$, $a = 16.844(3)$ Å, $b = 7.342(2)$ Å, $c = 16.187(3)$ Å, $\beta = 108.93(1)°$, $V = 1893.6$ Å^3, $Z = 4$, $D_x = 1.289\,g\,cm^{-3}$, $T = 22\,°C$. A Philips PW1100 four-circle diffractometer and graphite monochromatized Mo Kα radiation, $\lambda = 0.71069$ Å, were used to determine accurate cell dimensions (13 reflections, $\Theta = 15°$ to 18°) and to measure 3729 reflections by Θ-2Θ-scans in the range $\Theta = 2°$ to 25°, $h = -20$ to 18, $k = 0$ to 8, and $l = 0$ to 19. Three periodically monitored reference reflections showed only insignificant fluctuations. The data, corrected for LP but not for absorption ($\mu = 0.82\,cm^{-1}$), were merged to 3314 unique reflections ($R_{merge} = 0.040$ on F). Structure solution by direct methods. Structure refinement 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), 1748 reflections with $F_o > 4\ \sigma(F_o)$, weights $w = 1/(\sigma^2(F_o) + 0.0002 \cdot F_o^2)$, and 245 varied parameters. Final $R = 0.053$ and $wR = 0.044$. Maximum shift/σ in final least-squares cycle < 0.01. Minimum and maximum difference electron densities were -0.20 and $0.18\,e\,Å^{-3}$. The calculations were carried out with program SHELX76 [21].

Atomic parameters of non-hydrogen atoms are given in Table 1, selected bond lengths and angles are listed in Table 2. Additional details on the structure determination (anisotropic temperature factors, hydrogen atom parameters, dihedral angles, least-squares planes, structure factors) are deposited at the Fachinformationszentrum Karlsruhe, P.O. Box 2465, D-76012 Karlsruhe, under the CSD no. 57989.

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