Monatshefte für Chemie 125, 301–312 (1994)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Regioselectivity in the 1,3-Dipolar Cycloaddition of Nitrile Oxides to N-(3,5-Dichlorophenyl)itaconimide**

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Summary. The regioselectivity of the nitrile oxide cycloaddition with 3,3-methylene-1-(3,5-dichlorophenyl)-2,5-pyrrolidindione (**1**) is discussed. Arylnitrile oxides add regioselectively to the carbon-carbon double bond of **1**, giving exclusively spiro-isoxazolines **3a–k**, whereas acetonitrile oxide gives both adducts **3l** and **4l**. AM1 calculations of the reactants and cycloadducts were performed, the regiochemistry of the cycloaddition seems to be controlled by steric effects. Reduction of **3a** with $NaBH_4$ in the presence of magnesium perchlorate at $-20\,°C$ was regio- and stereoselective to yield the hydroxylactams **9a** and **10a**, whereas hydroxymethylisoxazoline **14a** was obtained in the absence of $Mg(ClO_4)_2$.

Keywords. 1,3-Dipolar cycloaddition of nitrile oxides; N-(3,5-Dichlorophenyl)itaconimide; AM1 calculations; Regio- and stereoselective $NaBH_4$ reductions; Hydroxylactams.

Regioselektivität bei der 1,3-dipolaren Cycloaddition von Nitriloxiden mit N-(3,5-Dichlorphenyl)itaconimid

Zusammenfassung. Es wird die Regioselektivität der Cycloaddition von Nitriloxiden mit 3,3-Methylen-1-(3,5-Dichlorphenyl)-2,5-pyrrolidinon (**1**) diskutiert. Arylnitriloxide addieren regioselektiv an die Kohlenstoff-Kohlenstoff-Doppelbindung von **1** unter ausschließlicher Bildung der Spiro-isoxazoline **3a–k**, währenddessen Acetonitriloxid beide Addukte **3l** und **4l** ergibt. AM1-Rechnungen der Reaktanden und der Cycloaddukte sprechen dafür, daß der regiochemische Verlauf der Cycloaddition durch sterische Effekte bewirkt wird. Reduktion von **3a** mit $NaBH_4$ in Gegenwart von Magnesiumperchlorat bei $-20\,°C$ ergab in einer regio- und stereoselektiven Reaktion die Hydroxylaktame **9a** und **10a**, in Abwesenheit von $Mg(ClO_4)_2$ wurde Hydroxymethylisoxazolin **14a** erhalten.

Introduction

Some compounds of dicarboximide type are reported to reveal effective systemic activity against *Botrytis cinerea*, *Cochliobolus miyabeanus* and *Pellicularia sasaci* [1].

** Part XXX in the series 1,3-Dipolar Cycloaddition on Heterocycles. Part XXIX [27]

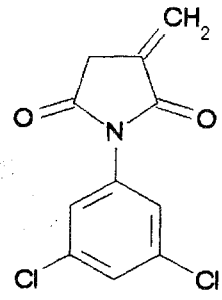
In addition, 3,3-methylene-1-aryl-2,5-pyrrolidindiones (N-arylitaconimides) inhibit mould growth on young plants and can be used as soil and foliage fungicides [2, 3]. The recent observation of the strong herbicidal activity of spiro-cyclic lactams (coupled with the absence of toxicity to microorganisms [4]), the preparation of some spiroimides as potential anticonvulsant agents [5], and also the antimicrobial activity of some natural spiroisoxazolines [6, 8] have stimulated our interest in the synthesis of other spirocyclic derivatives.

The most developed methodology of the synthesis of spiro-cyclic systems, other than the spiroketals, are cycloaddition to exocyclic double bonds [9–12]. In continuation of our project to utilize products of 1,3-dipolar cycloaddition to heterocyclic compounds we have chosen N-(3,5-dichlorophenyl)itaconimide (**1**) as a model system, since a characteristic feature of some commercial agrochemicals is the N-(3,5-dichlorophenyl)-building block [1]. We report now on the regiochemical features associated with the cycloaddition of several nitrile oxides to **1** and reductions of so prepared products **3** with $NaBH_4$, together with quantum mechanical calculations using the AM1 method.

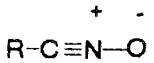
Results and Discussion

The cycloadditions of X-substituted benzenenitrile oxides **2** (where X is 4-CH_3, 2-Cl, 4-Cl, 2,4-diCl, 2,6-diCl, 2-F, 2-Br, 2-NO_2, 3-NO_2, 4-NO_2, 2-CF_3) with 3,3-methylene-1-(3,5-dichlorophenyl)-2,5-pyrrolidindione (**1**, N-(3,5-dichlorophenyl)itaconimide) proceeded smoothly at 0 °C to afford exclusively cycloadducts **3a–k** in high yields (62–95%). The nitrile oxides **2** were generated from the corresponding benzohydroxyamoyl chlorides and triethylamine in diethyl ether. The carbon-carbon double bond of **1** seems to be a excellent reactive dipolarophile; since unstable nitrile oxides, such as *p*- and *m*-substituted benzenenitrile oxides gave only small amounts of the dimers. In all cases only one regioisomer **3** was isolated. The second possible regioisomer **4** has not been detected in the crude reaction mixture by NMR spectroscopy.

The structural assignment of the isolated spiro-isoxazolines as 3,7-diaryl-6,8-dioxo-1-oxa-2,7-diazaspiro[4, 4]non-2-enes (**3a–k**) was made on the basis of their elemental analysis and spectroscopic data (Exp. Part). Especially the isolated cycloadducts were considered as the regioisomers of type **3** instead of the possible regioisomer of type **4**. This was based on the chemical shifts of the methylenic CH_2 doublets for H_{B-9} and H_{A-9} (δ 3.21–3.38 ppm and δ 3.48–3.53 ppm), triplets of C-9 (δ 42.70–43.19 ppm) and of the adjacent spiro-C (C-5, δ 85.45–86.62 ppm) indicating a strong shielding influence of the spiroheterocyclic ring on the 5-position of the isoxazoline, together with the expected value for C-4. The chemical shift of the methylene carbon in the isoxazoline ring (δ 44.01–48.00 ppm) was assigned on the basis of their strong dependence on the substituent in the benzene ring. The ^{1}H-NMR spectrum showed the isoxazoline ring H_B-4 and H_A-4 protons in the regions δ 3.72–4.04 ppm and δ 4.08–4.25 ppm with J_{AB} = 17–18 Hz, which is completely consistent with a isoxazoline unsubstituted at the 4-position. If the spiro atom were at the 4-position of the isoxazoline ring, the protons at the 5-posision would appear at lower fields, and the coupling constant J_{AB} would be ca. 10 Hz [13].



1



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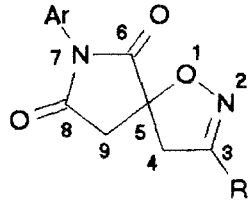

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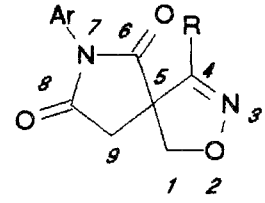

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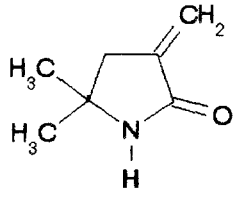

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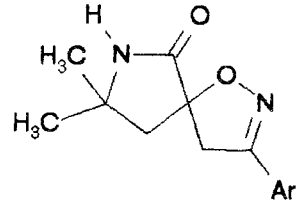

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We have shown that the ^{1}H and ^{13}C NMR spectra indicate the regiochemistry of the [3 + 2] cycloadducts **3a–k** which are formed by the attack of the carbon of the nitrile oxide at the CH_2 terminus of the α,β-unsaturated moiety. A similar regioselectivity was observed in the cycloaddition of nitrile oxides to methylene-cycloalkanes [10]. Recently, we have demonstrated that arylnitrile oxides react with 3,3-methylene-5,5-dimethyl-2-pyrrolidinone (**5**), which is isoelectronically related to **1**, to produce exclusively isoxazoline regioisomers **6** [11]. Inspection of frontier orbital energies of **2** and **5** showed that the cycloaddition of nitrile oxides is governed by the LUMO dipole and the regiochemistry of **6** is controlled by the steric effect of the methyl groups at the ring junction and by frontier orbital interactions [11]. On the other hand, it was reported that very electron deficient dipolarophiles as well as some cycloalkanes possessing an exocyclic double bond gave significant amounts of 4-substituted isoxazolines [14–16]. In order to rationalize the exclusive regioselectivity of the cycloadditions to **1** we have performed an FMO analysis of

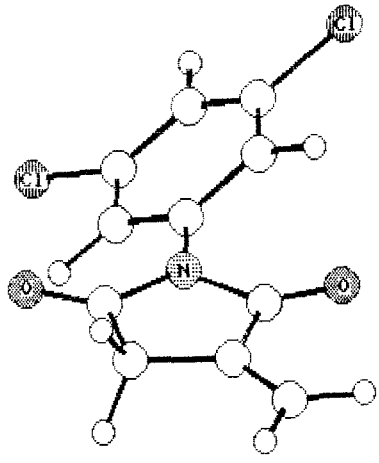


Fig. 1. Optimized geometry for N-(3,5-dichlorophenyl)itaconimide (**1**) (AM1)

the calculated (AM1) [17] frontier orbitals. An optimized geometry for **1** is shown in Fig. 1, that of benzenenitrile oxide (*BNO*) was published previously in [11]. In **1**, the 3,5-dichlorophenyl substituent on the nitrogen is out of the plane of the imide ring (31°). The itaconimide **1** is very flexible since the rotation barrier is very small, 4.1 kJ/mol. Some relevant results of calculations are summarized in Table 1. Inspection of frontier orbital energies shows that the interaction **1**–**2** is governed by the HOMO dipole. Moreover, the HOMO of **1**, located at nitrogen and therefore the p_z orbital of nitrogen is only weakly conjugated (small contributions from both α and β carbons).

Accroding to the FMO theory, regioselectivity is governed predominantly by orbital coefficients at the double bond and by those at the terminal atoms of the dipole [18]. Now, if the cycloadditions with **1** are judged by electrostatic interactions alone, the negatively charged oxygen terminus in **2** would be expected to attack the terminal carbon in **1**. The present simple FMO arguments based on calculations of electronic structure of the reactants predict the formation of the regioisomer **4**, which is in contrast to the observed regiochemistry. Therefore, the regiochemistry of **3** should be favourable for a steric reason. An examination of both transition states in these terms reveals that repulsions between the 3,5-dichlorophenyl group on nitrogen and the substituents on dipole carbon are minimized in the transition state for **3**. From Dreiding models it is obvious that the bulky aryl group on nitrogen of **1** prevents the attack to give spiro-isoxazoline **4**. Moreover, the van der Waals nonbonded interaction energies should be very large in the second regioisomer **4**

Table 1. Relevant electronic parameters of **1** and benzenenitrile oxide (*BNO*) calculated with AM1

Compound	^{E}HOMO	^{E}LUMO	HOMO		LUMO	
			Cα/O	Cβ/O	Cα/O	Cβ/O
1	−9.45	−0.60	0.03	0.05	−0.41	0.60
BNO	−9.38	−0.50	0.49	−0.37	0.21	0.23

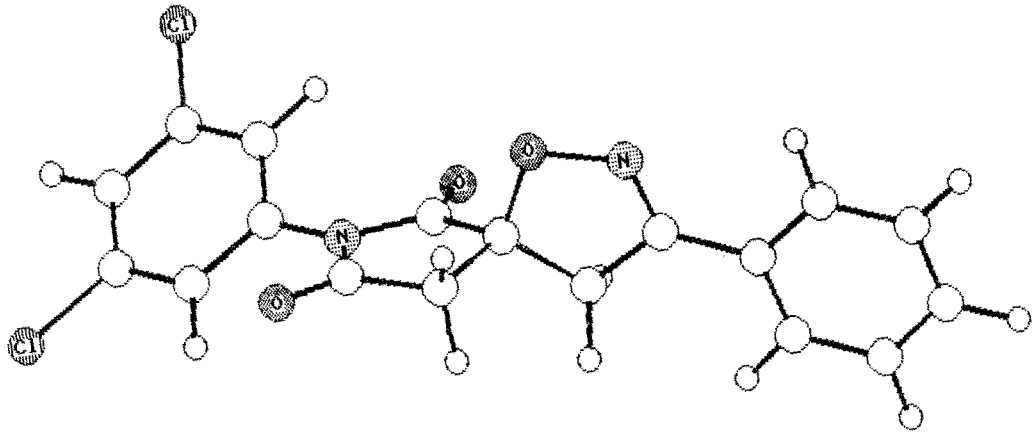


Fig. 2. Optimized geometry for cycloadduct **3** (AM1)

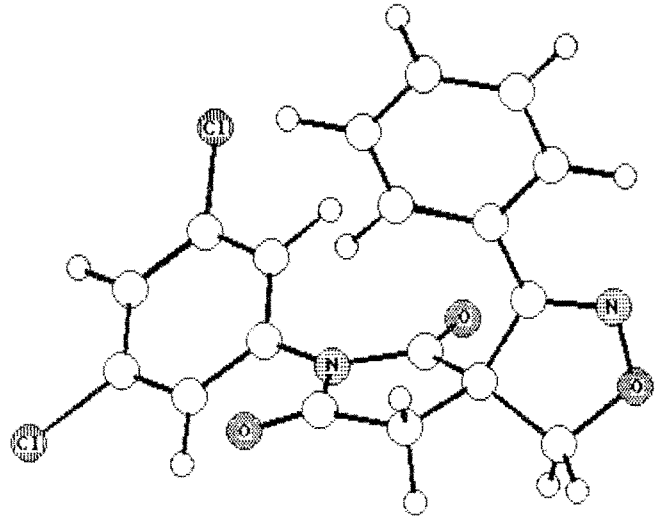
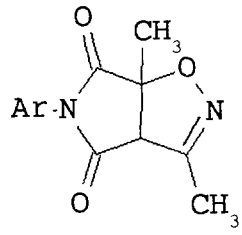


Fig. 3. Optimized geometry for cycloadduct **4** (AM1)

compared to the adduct **3**. We therefore tried to assess the relative thermodynamic stability of the possible products **3** and **4** by semi-empirical quantum chemical calculations [17] (AM1 method) and the optimised geometries are shown in Figs. 2 and 3. Subsequent AM1 calculation showed the fully unsubstituted regioisomer **4m** (R = Ar = H) to be more stable by 5.9 kJ/mol than regioisomer **3m** (R = Ar = H), which is in accord with FMO arguments. On the other hand the corresponding methyl substituted regioisomer **4n** ($R = CH_3$, Ar = H) is more stable by only 1.1 kJ/mol than **3n** and in the case of N-(3,5-dichlorophenyl) derivate structure **3a** is more stable by 7.2 kJ/mol than **4a**. Indeed, in the regioisomer **3a**, the two aryl group can be better accommodated (Fig. 2) than in the regioisomer **4a** (Fig. 3). The experimental results support this prediction, as do AM1 calculations. The regiochemistry of the cycloaddition of nitrile oxides **2** to **1** seems to be controlled by steric effects rather than by frontier orbital interactions.

Regarding the AM1 calculations, the regiochemistry of **3** is favourable for a steric reason. Therefore, as a next model system we have chosen the 1,3-dipolar



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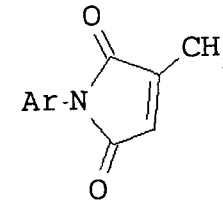

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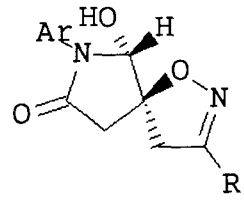
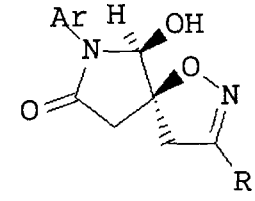
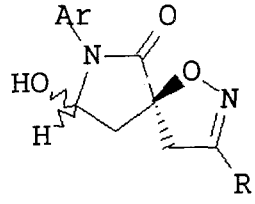


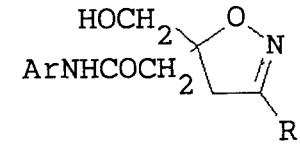
9a



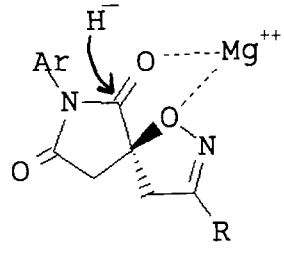
10a



11a, 12a



14a



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cycloaddition of methyl nitrile oxide with **1**, with the aim to obtain also a second regioisomer **4**. Acetonitrile oxide was prepared in situ from nitroethane and phenyl isocyanate under catalysis of triethylamine in the presence of **1** [19] Cycloaddition furnished cycloadducts **3l** (43%), **4l** (16%) and **7** (18%); compounds **3l** and **7** were obtained in pure form. The structure of the major product **3l** was determined on the

basis of the comparable chemical shifts to those of analogues **3a–k**. The second isolated product, namely 3,6a-dimethyl-5-(3,5-dichlorophenyl)-3a,4,6,6a-tetrahydropyrrolo[3,4-d]isoxazole (**7**) we have recently described by 1,3-dipolar cycloaddition of acetonitrile oxide to 1-(3,5-dichlorophenyl)-3-methylmaleimide (**8**) [20]. The origin of **7** can be explained by the isomerization **1**→**8** by the treatment of triethylamine and subsequent cycloaddition. Structural proof for the spiroisoxazoline **4l** was provided by ^{1}H and ^{13}C NMR spectra, because some relevant signals corresponding to this minor isomer **4l** were clearly observed in the crude reaction mixture and after chromatography together with **3l**, respectively. The structural assignment as 4-methyl-7-(3,5-dichlorophenyl)-6,8-dioxo-2-oxa-3,7-diazaspiro[4,4]non-3-ene (**4l**) is based on the chemical shifts of the methylenic CH_2 doublets for $H_{B\text{-}9}$ and $H_{A\text{-}9}$, (δ 2.80 ppm and δ 3.05 ppm) with $J_{AB} = 19$ Hz, the triplet of C-9 (δ 46.76 ppm), the singlet of the adjacent spiro-C (C-5, δ 31.69 ppm) and the triplet of C-1 (δ 62.47 ppm) indicating a strong shielding influence of the oxygen atom. The proton NMR spectrum showed the isoxazoline ring H-1 protons in the region δ 4.47 ppm with $J_{AB} = 11$ Hz, which is completely consistent with isoxazoline substituted at the 4-position [13]. The cycloaddition of acetonitrile oxide to **1** gave a mixture of the two regioisomers **3l** and **4l** in a ratio 72:28. The regioisomers of the type **4** were not observed in the reaction of the others itaconimides with acetonitrile oxide [21].

Recently, an increasing interest for the synthesis of hydroxylactams has emerged, because these are valuable precursors for obtaining pharmacologically active compounds [22]. Partial reductions of imides with $NaBH_4$ to the corresponding hydroxylactams are well investigated [23], but regioselectivies of the nonsymmetric imides are rarely investigated [24]. Recently, we have found that the reduction of **7** with $NaBH_4$ proceeded regio- and in the presence of magnesium perchlorate also stereoselectively [20]. Therefore, we turned our attention to the investigation of regio- and stereoselectivity of reduction of spiroimide **3a** with $NaBH_4$.

Two regioisomeric pairs of diastereomers **9a** and **10a** can originate by reduction of **3a** to the first step by reducing the C-6 carbonyl group, or derivatives **11a** and **12a** by reducing the C-8 carbonyl group; both differ in the arrangement of the hydroxyl group with respect to the isoxazoline oxygen atom. Reduction of **3a** with $NaBH_4$ in methanol in the presence of magnesium perchlorate furnished regio- and stereoisomeric hydroxylactams **9a** and **10a** at -20 °C and 0 °C, respectively. The ratio 66:34 in favour of **9a** was estimated based on NMR data. Their structures were ascribed from the chemical shift data and multiplicity of signals in the ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectra of isolated compounds possessing four doublets for H_B-9, H_A-9, H_B-4 and H_A-4 with coupling constant $J_{AB} = 17.7$ Hz. This excluded the possibility that this is a mixture of regioisomers **11a** or **12a**. The NMR spectrum of the regioisomers **11a** or **12a** would have an ABX system pertaining to the two hydrogens in position 9 and to the one in position 8 and an AB system for the two C-4 hydrogens. The *trans*-configuration of the C-6 hydroxy group in **9a** was deduced from appearance of the H-6 singlet at δ 5.60 ppm and the *cis*-configuration of the C-6 hydroxy group in **10a** from the presence of an H-6 doublet at δ 5.47 ppm and the coupling constant $J_{6\text{-}OH} = 7.5$ Hz in ^{1}H-NMR spectra. Different chemical shift values for H-6 proton in **9a** (*syn* regarding to isoxazoline oxygen atom) and **10a** (*anti* with respect to the isoxazoline oxygen atom) as well as for H_A-4 proved the suggested stereochemical arrangement.

The fact that the reduction is regiospecific, affording only two isomers **9a** and **10a**, can be explained by the formation of chelate **13**. The chelate **13**, arising through coordination of the Mg^{2+} ion with the isoxazoline oxygen and the C-6 carbonyl group, activated this carbonyl group in reduction with $NaBH_4$ with respect to the non-chelated C-8 carbonyl group [22]. The observed stereoselectivity (66:34 in favour of **9a**) can be rationalized by application of these complexation model **13** with a preferential attack of the hydride ion from the sterically less hindered bottom side of the spiro-system.

The second-step reduction product **14a** was formed exclusively in the absence of magnesium perchlorate at $-20\,°C$ and $0\,°C$, respectively. Its structure – 5-hydroxymethylisoxazoline **14a** – was proved from the ^{13}C-NMR spectral data showing the C-4, $COCH_2$ and OCH_2 as triplets at δ 41.18 ppm, 43.02 ppm and 66.42 ppm. The formation of **14a** at $-20\,°C$ is unexpected, because it was found that the reduction chemoselectivity of imides with $NaBH_4$ is controlled by temperature. Thus, at $-20\,°C$ only hydroxylactams were produced, while at $\geqslant 50\,°C$ exclusively hydroxymethyl derivatives were obtained [22].

Experimental Part

Melting points were determined on a Kofler hot plate m.p. apparatus and are uncorrected. ^1H and ^{13}C-NMR spectra (in CD_3COCD_3) were recorded on a Varian VXR 300 (300 MHz) spectrometer. Chemical shifts are given in ppm/*TMS*. UV spectra were obtained on a M-40 (Carl Zeiss, Jena) spectrometer in methanol (nm/log ε). Chlorides of benzenehydroximic acids were prepared by chlorination of the corresponding benzaldoximes in chloroform according to [25]. N-(3,5-Dichlorophenyl) itaconimide (**1**) was prepared from 3,5-dichloraniline and itaconic anhydride according to [26].

3-(X-Phenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-enes **3**

Dry triethylamine (11 mmol) in dry ether (30 ml) was added dropwise at 0 °C to a stirred cooled solution of the corresponding benzenehydroxime acid chloride (10 mmol) and **1** (2.56 g, 10 mmol) in dry ether (30 ml) during 1 h. The product separated after stirring overnight at room temperature was filtered off and washed thoroughly with water and crystallized.

3-(4-Methylphenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3a**)

Yield: 83%, m.p. 231–232 °C. $C_{19}H_{14}Cl_2N_2O_3$ (389.23) calc.: 58.62% C, 3.62 H, 7.10 N; found: 58.79 C, 3.71 H, 7.24 N. UV: $\lambda_{max} = 257$ nm ($\log \varepsilon = 2.61$). ^1H-NMR: 2.36 (s, 3H, CH_3), 3.21 (d, 1H, H_B-9, $J = 18.4$), 3.49 (d, 1H, H_A-9), 3.79 (d, 1H, H_B-4, $J = 17.0$), 4.11 (d, 1H, H_A-4), 7.21–7.67 (m, 7H, aromat. H). ^{13}C-NMR: 21.36 (q, CH_3), 42.90 (t, C-9), 44.32 (t, C-4), 85.45 (s, C-5), 126.40, 126.86, 127.67, 129.09, 130.28, 135.44, 141.56 (aromat. C), 157.01 (s, C-3), 172.81 (s, C=O), 175.07 (s, C=O).

3-(2-Chlorophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3b**)

Yield: 92%, m.p. 193–194 °C. $C_{18}H_{11}Cl_3N_2O_3$ (409.66) calc.: 52.77% C, 2.70 H, 6.83 N; found 52.81 C, 2.77 H, 6.89 N. UV: $\lambda_{max} = 248$ nm ($\log \varepsilon = 2.53$). ^1H-NMR: 3.25 (d, 1H, H_B-9, $J = 19.6$), 3.52 (d, 1H, H_A-9), 3.90 (d, 1H, H_B-4, $J = 17.0$), 4.25 (d, 1H, H_A-4), 7.42–7.70 (m, 7H, aromat. H). ^{13}C-NMR: 42.70 (t, C-9), 46.65 (t, C-4), 86.06 (s, C-5), 126.45, 128.24, 128.96, 129.13, 131.48, 131.73, 132.41, 133.28, 135.39, 135.46 (aromat. C), 156.75 (s, C-3), 172.69 (s, C=O), 174.78 (s, C=O).

3-(4-Chlorophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3c**)

Yield: 90%, m.p. 245–248 °C. $C_{18}H_{11}Cl_3N_2O_3$ (409.66) calc.: 52.77% C, 2.70 H, 6.83 N; found: 52.70 C, 2.69 H, 6.84 N. UV: $\lambda_{max} = 258$ nm ($\log \varepsilon = 2.65$). ^{1}H-NMR: 3.33 (d, 1H, H_B-9, $J = 18.6$), 3.48 (d, 1H, H_A-9), 3.91 (d, 1H, H_B-4, $J = 17.7$), 4.13 (d, 1H, H_A-4), 7.52–7.79 (m, 7H, aromat. H). ^{13}C-NMR: 42.83 (t, C-9), 44.01 (t, C-4), 85.96 (s, C-5), 126.42, 128.48, 129.14, 129.34, 129.58, 129.84, 135.35, 136.67 (aromat. C), 156.44 (s, C-3), 172.75 (s, C=O), 174.89 (s, C=O).

3-(2,4-Dichlorophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3d**)

Yield: 81%, m.p. 187–189 °C, $C_{18}H_{10}Cl_4N_2O_3$ (444.11) calc.: 48.67% C, 2.26 H, 6.30 N; found: 48.75 C, 2.29 H, 6.35 N. UV: 252 nm ($\log \varepsilon = 2.56$). ^{1}H-NMR: 3.24 (d, 1H, H_B-9, $J = 19.2$), 3.51 (d, 1H, H_A-9), 3.91 (d, 1H, H_B-4, $J = 17.6$), 4.24 (d, 1H, H_A-4), 7.45–7.80 (m, 6H, aromat. H). ^{13}C-NMR: 42.65 (t, C-9), 46.39 (t, C-4), 86.25 (s, C-5), 126.44, 127.87, 128.54, 129.15, 131.12, 132.86, 134.24, 135.36, 135.46, 137.01 (aromat. C), 155.99 (s, C-3), 172.62 (s, C=O), 174.68 (s, C=O).

3-(2,6-Dichlorophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3e**)

Yield: 81%, m.p. 183–186 °C. $C_{18}H_{10}Cl_4N_2O_3$ (444.11) calc.: 48.67% C, 2.26 H, 6.30 N; found: 48.80 C, 2.35 H, 6.39 N. UV: 248 nm ($\log \varepsilon = 2.04$). ^{1}H-NMR: 3.38 (d, 1H, H_B-9, $J = 18.6$), 3.49 (d, 1H, H_A-9), 3.72 (d, 1H, H_B-4, $J = 18.0$), 4.10 (d, 1H, H_A-4), 7.55–7.62 (m, 6H, aromat. H). ^{13}C-NMR: 43.19 (t, C-9), 46.74 (t, C-4), 86.01 (s, C-5), 126.42, 129.15, 129.32, 133.05, 135.38, 135.46, 135.58 (aromat. C), 154.49 (s, C-3), 172.56 (s, C=O), 174.28 (s, C=O).

3-(2-Fluorophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3f**)

Yield: 62%, m.p. 191–194 °C. $C_{18}H_{11}FCl_2N_2O_3$ (393.20) calc.: 54.97% C, 2.82 H, 7.12 N; found: 54.89 C, 2.77 H, 7.05 N. UV: 252 nm ($\log \varepsilon = 2.59$). ^{1}H-NMR: 3.32 (d, 1H, H_B-9, $J = 18.6$), 3.49 (d, 1H, H_A-9), 3.92 (d, 1H, H_B-4, $J = 18.0$), 4.16 (d, 1H, H_A-4), 7.27–7.88 (m, 7H, aromat. H). ^{13}C-NMR: 42.80 (t, C-9), 48.00 (t, C-4), 85.70 (s, C-5), 117.18, 117.48, 125.63, 126.46, 129.13, 129.95, 129.99, 133.32, 133.43, 135.38, 135.44 (aromat. C), 153.70 (s, C-3), 172.76 (s, C=O), 174.95 (s, C=O).

3-(2-Bromophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3g**)

Yield: 88%, m.p. 184–187 °C. $C_{18}H_{11}BrCl_2N_2O_3$ (454.10) calc.: 47.60% C, 2.44 H, 6.17 N; found: 47.55 C, 2.46 H, 6.20 N. UV: 251 nm ($\log \varepsilon = 2.18$). ^{1}H-NMR: 3.34 (d, 1H, H_B-9, $J = 18.6$), 3.49 (d, 1H, H_A-9), 3.96 (d, 1H, H_B-4, $J = 18.0$), 4.24 (d, 1H, H_A-4), 7.46–7.80 (m, 7H, aromat. H). ^{13}C-NMR: 42.80 (t, C-9), 46.82 (t, C-4), 86.07 (s, C-5), 122.22, 126.46, 128.73, 129.13, 131.15, 132.04, 132.49, 134.65, 135.41, 135.45 (aromat. C), 157.82 (s, C-3), 172.67 (s, C=O), 174.70 (s, C=O).

3-(2-Nitrophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3h**)

Yield: 62%, m.p. 203–205 °C. $C_{18}H_{11}Cl_2N_3O_5$ (420.20) calc.: 51.44% C, 2.63 H, 10.00 N; found: 51.60 C, 2.71 H, 10.11 N. UV: 250 nm ($\log \varepsilon = 2.18$). ^{1}H-NMR: 3.34 (d, 1H, H_B-9, $J = 18.6$), 3.48 (d, 1H, H_A-9), 3.81 (d, 1H, H_B-4, $J = 17.4$), 4.08 (d, 1H, H_A-4), 7.54, 8.14 (m, 7H, aromat. H). ^{13}C-NMR: 42.92 (t, C-9), 46.23 (t, C-4), 86.22 (s, C-5), 125.40, 126.41, 129.12, 131.81, 132.21, 134.28, 135.42 (aromat. C), 155.68 (s, C-3), 172.49 (s, C=O), 174.54 (s, C=O).

3-(3-Nitrophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3i**)

Yield: 95%, m.p. 186–189 °C. $C_{18}H_{11}Cl_2N_3O_5$ (420.20) calc.: 51.44% C, 2.63 H, 10.00 N; found: 51.38 C, 2.60 H, 9.87 N. UV: 253 nm ($\log \varepsilon = 2.75$). ^{1}H-NMR: 3.37 (d, 1H, H_B-9, $J = 18.6$), 3.52 (d, 1H, H_A-9), 4.04

(d, 1H, H_B-4, $J = 17.7$), 4.24 (d, 1H, H_A-4), 7.52–8.51 (m, 7H, aromat. H). ^{13}C-NMR: 42.78 (t, C-9), 43.81 (t, C-4), 86.45 (s, C-5), 122.16, 125.65, 126.37, 129.15, 131.23, 131.28, 133.54, 135.24, 135.44, 149.33 (aromat. C), 156.16 (s, C-3), 172.64 (s, C=O), 174.69 (s, C=O).

3-(4-Nitrophenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3j**)

Yield: 71%, m.p. 203–205 °C. $C_{18}H_{11}Cl_2N_3O_5$ (420.20) calc.: 51.44% C, 2.63 H, 10.00 N; found: 51.50 C, 2.69 H, 10.10 N. UV: 268 nm ($\log \varepsilon = 2.23$) and 333 nm ($\log \varepsilon = 2.11$). ^{1}H-NMR: 3.36 (d, 1H, H_B-9, $J =$ 18.9), 3.52 (d, 1H, H_A-9), 4.01 (d, 1H, H_B-4, $J = 17.7$), 4.21 (d, 1H, H_A-4), 7.54–8.36 (m, 7H, aromat. H). ^{13}C-NMR: 42.76 (t, C-9), 43.68 (t, C-4), 86.62 (s, C-5), 124.74, 126.37, 128.81, 129.15, 135.25, 135.44, 135.60, 149.59 (aromat. C), 156.28 (s, C-3), 172.61 (s, C=O), 174.73 (s, C=O).

3-(2-Trifluoromethylphenyl)-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**3k**)

Yield: 73%, m.p. 155–156 °C. $C_{19}H_{11}F_3Cl_2N_2O_3$ (443.21) calc.: 51.48% C, 2.50 H, 6.32 N; found: 51.61 C, 2.61 H, 6.45 N. UV: 249 nm ($\log \varepsilon = 2.30$). ^{1}H-NMR: 3.25 (d, 1H, H_B-9, $J = 19.2$), 3.53 (d, 1H, H_A-9), 3.77 (d, 1H, H_B-4, $J = 17.6$), 4.15 (d, 1H, H_A-4), 7.52–7.89 (m, 7H, aromat. H). ^{13}C-NMR: 42.80 (t, C-9), 47.99 (t, C-4), 85.99 (s, C-5), 126.43, 127.57, 128.57, 129.15, 131.27, 131.79, 133.43, 135.38 (aromat. C), 156.46 (s, C-3), 172.62 (s, C=O), 174.59 (s, C=O).

3-Methyl-7-(3,5-dichlorophenyl)-6,8-dioxo-1-oxa-2,7-diazaspiro-[4,4]-non-2-ene (**3l**)

To the solution of **1** (12.8 g, 50 mmol), phenyl isocyanate (11 ml, 100 mmol), and triethylamine (0.5 ml) in 50 ml of dry ether a solution consisting of nitroethane (3.6 ml, 50 mmol), triethylamine (0.2 ml) and 50 ml of dry ether was added within 2 h. The reaction mixture was then stirred at room temperature for another 24 h, concentrated in vacuo and chromatographed on silica gel column to give cycloadduct **3l**. Yield: 43%, m.p. 201–204 °C. $C_{18}H_{10}Cl_2N_2O_3$ (313.14) calc.: 49.85% C, 3.21 H, 8.94 N; found: 49.90 C, 3.24 H, 8.97 N. ^{1}H-NMR ($CDCl_3$): 2.09 (s, 3H, CH_3), 3.01 (d, 1H, H_B-9, $J = 18.7$), 3.29 (d, 1H, H_A-9), 3.09 (d, 1H, H_B-4, $J = 17.1$), 3.66 (d, 1H, H_A-4), 7.31–7.42 (m, 3H, aromat. H). ^{13}C-NMR: 12.76 (q, CH_3), 42.29 (t, C-9), 48.80 (t, C-4), 82.99 (s, C-5), 124.82, 129.20, 129.32, 135.46 (aromat. C), 154.76 (s, C-3), 171.31 (s, C=O), 173.59 (s, C=O).

Signals corresponding to the minor regioisomer 4-methyl-7-(3,5-dichlorophenyl)-6,8-dioxo-2-oxa-3,7-diazaspiro[4,4]-non-3-ene (**4l**) were clearly observed in the one fraction together with **3l**. ^{1}H-NMR: 2.80 (d, 1H, H_B-9, $J = 19.0$ Hz), 3.05 (d, 1H, H_A-9), 4.43 (d, 1H, H_B-1, $J = 11.0$), 4.51 (d, 1H, H_A-1). ^{13}C-NMR: 12.75 (q, CH_3), 31.69 (s, C-5), 46.76 (t, C-9), 62.47 (t, C-1).

Reduction of Compound **3a** *with Sodium Hydridoborate*

Method A: Magnesium perchlorate (4.46 g, 20 mmol) was added to a stirred solution of **3a** (3.89 g, 10 mmol) in methanol–chloroform (1:1, 100 ml) at 0 °C. Stirring was continued at 0 °C for 1 h; sodium hydridoborate (0.57 g, 15 mmol) was then introduced and after the reaction had finished (TLC) the mixture was acidified with hydrochloric acid to *pH* 2 and after 10 min to *pH* 11 with aqueous sodium hydroxide. Methanol was removed under reduced pressure and the aqueous solution was stepwise extracted with chloroform (3 × 20 ml) and ethyl acetate (3 × 20 ml). The combined organic layers were dried with sodium sulfate and the distillation residue was separated on silica gel column using heptane-ethyl acetate (5:1) as eluent.

Method B: Sodium hydridoborate (4 g, 106 mmol) was added to a stirred solution of **3a** (2.76 g, 7.1 mmol) in methanol (50 ml) at −20 °C or 0 °C. A saturated aqueous ammonium chloride was introduced after a 2 h stirring which was continued for 1 h. Methanol was removed under reduced pressure and the aqueous solution was afterwards worked up as in the preceding experiment.

3-(4-Methylphenyl)-7-(3,5-dichlorophenyl)-6-trans-hydroxy-8-oxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**9a**)

Yield: 60% was obtained applying method A; m.p. 158–159 °C. $C_{19}H_{16}Cl_2N_2O_3$ (391.24) calc.: 58.32% C, 4.12 H, 7.15 N; found: 58.45 C, 4.01 H, 6.99 N. ^{1}H-NMR: 2.39 (s, 3H, CH_3), 2.84 (d, 1H, H_B-9, $J = 17.7$), 3.25 (d, 1H, H_A-9), 3.52 (d, 1H, H_B-4, $J = 17.7$), 3.95 (d, 1H, H_A-4), 5.60 (s, 1H, H-6), 7.29–7.87 (m, 7H, aromat. H). ^{13}C-NMR: 21.28 (q, CH_3), 39.01 (t, C-9), 41.46 (t, C-4), 88.87 (s, C-5), 89.04 (d, C-6), 120.11, 121.12, 125.07, 127.43, 130.16, 135.48, 141.29, 141.40 (aromat. C), 157.73 (s, C-3), 172.29 (s, C-8). IR ($CHCl_3$): 1726 cm^{-1} (C=O), 3599 cm^{-1} (OH).

3-(4-Methylphenyl)-7-(3,5-dichlorophenyl)-6-cis-hydroxy-8-oxo-1-oxa-2,7-diazaspiro[4,4]-non-2-ene (**10a**)

Yield: 31% was obtained applying method A; m.p. 171–173 °C. $C_{19}H_{16}Cl_2N_2O_3$ (391.24) calc.: 58.32% C, 4.12 H, 7.15 N; found: 58.57 C, 4.31 H, 6.89 N. ^{1}H-NMR: 2.23 (s, 3H, CH_3), 2.70 (d, 1H, H_B-9, $J = 17.7$), 3.09 (d, 1H, H_A-9), 3.36 (d, 1H, H_B-4, $J = 17.7$), 3.80 (d, 1H, H_A-4), 5.47 (d, 1H, H-6, $J_{6\text{-OH}}$-7.5), 6.23 (d, 1H, OH), 7.13–7.71 (m, 7H, aromat. H). ^{13}C-NMR: 21.31 (q, CH_3), 39.03 (t, C-9), 41.48 (t, C-4), 88.87 (s, C-5), 89.05 (d, C-6), 120.11, 121.14, 125.09, 127.44, 130.17, 135.49, 141.25 (aromat. C), 157.76 (s, C-3), 172.32 (s, C-8). IR ($CHCl_3$): 1725 cm^{-1} (C=O), 3599 cm^{-1} (OH). M^+, m/z 391.

3-(4-Methylphenyl)-5-hydroxymethyl-5-(3,5-dichlorophenylcarbamoylmethyl)-2-isoxazoline (**14a**)

Yield: 70% was obtained applying method B; m.p. 184–186 °C. $C_{19}H_{18}Cl_2N_2O_3$ (393.25) calc.: 58.02% C, 4.61 H, 7.12 N; found: 57.93 C, 4.42 H, 7.37 N. ^{1}H-NMR: 2.36 (s, 3H, CH_3), 2.88 (d, 2H, CH_2), 3.42 (d, 1H, H_B-4, $J = 17.1$ Hz), 3.63 (d, 1H, H_A-4), 3.76 (d, 2H, OCH_2, $J = 5.7$), 4.29 (t, 1H, OH), 7.16–7.71 (m, 7H, aromat. H), 9.60 (br.s., 1H, NH). ^{13}C-NMR: 21.29 (q, CH_3), 41.18, 43.02 (t, t, C-4, $COCH_2$), (t, OCH_2), 88.70 (s, C-5), 118.29, 118.38, 123.61, 127.27, 128.30, 130.07, 135.45, 140.70 (aromat. C), 157.46 (s, C-3), 169.44 (s, C=O), M^+, m/z 393.

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Received November 7, 1992. Accepted February 18, 1993