Chemical transformations of 3-aminopyrrolidin-2-ones of the norbornane and cyclopropane series*

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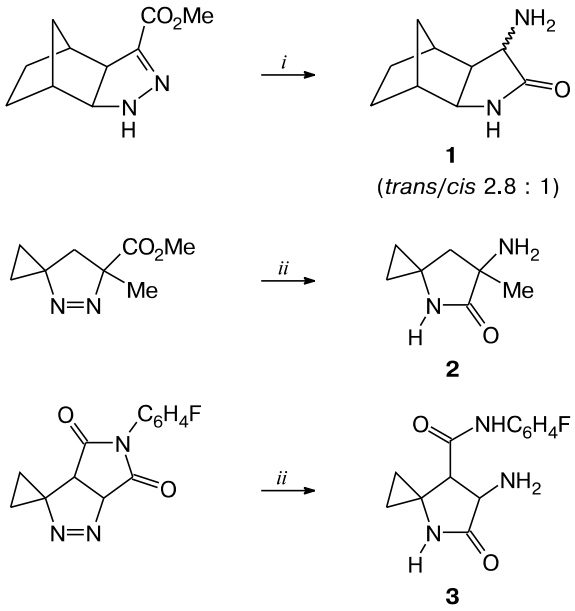
3-Aminopyrrolidin-2-ones containing a fused norbornane or spirocyclopropane fragment react with benzaldehyde to give azomethines, which can be transformed into N-substituted 3-aminopyrrolidin-2-ones by reduction with sodium borohydride. Diazotization of aminopyrrolidinones with $NaNO_2$ in acetic acid results in the elimination of molecular nitrogen and in the formation of acetoxy or unsaturated derivatives (through stabilization of intermediate carbocations). 6-Methylidene-4-azaspiro[2.4]heptan-5-one obtained by diazotization of 6-amino-6-methyl-4-azaspiro[2.4]heptan-5-one easily reacts with diazomethane, diazocyclopropane, and benzonitrile oxide to yield heterocyclic spiranes by means of 1,3-dipolar cycloaddition.

Key words: 3-aminopyrrolidin-2-ones, spirocyclopropane-containing azaheterocycles, azomethines, diazotization, 1,3-dipolar addition.

In the last few years, active interest has been shown in substituted 3-aminopyrrolidin-2-ones as promising biologically active compounds or synthons for target modification of this heterocyclic fragment.[1—5] For instance, 5-amino-*exo*-3-azatricyclo[5.2.1.$0^{2,6}$]decan-4-one (**1**) containing a 3-aminopyrrolidin-2-one fragment (obtained by catalytic hydrogenation of a methyl diazoacetate—norbornene adduct with Raney nickel[2]) has high antiarrhythmic and antifibrillatory effects on simulated arrhythmias of different types. Along with aminopyrrolidin-2-ones, their 5-spirocyclopropane-containing analogs have also been tested for biological activity.[6,7]

Recently, we developed a method for the synthesis of pyrrolidin-2-ones containing the amino group and the spirocyclopropane fragment in positions 3 and 5.[8] A general route to these compounds, in particular, 2-oxospiro[pyrrolidine-5,1′-cyclopropanes] **2** and **3** (Scheme 1), involves catalytic hydrogenation of spiro[1-pyrazoline-5,1′-cyclopropane]-3-carboxylates or the corresponding amides (Raney Ni, H_2, 80—90 bar, 60—70 °C). As with the formation of compound **1**, the reaction occurs by

Scheme 1



Reagents and conditions: *i*. H_2, Ni—Ra, 110 bar, 25—40 °C; *ii*. H_2, Ni—Ra, 80—90 bar, 60—70 °C.

† Deceased.

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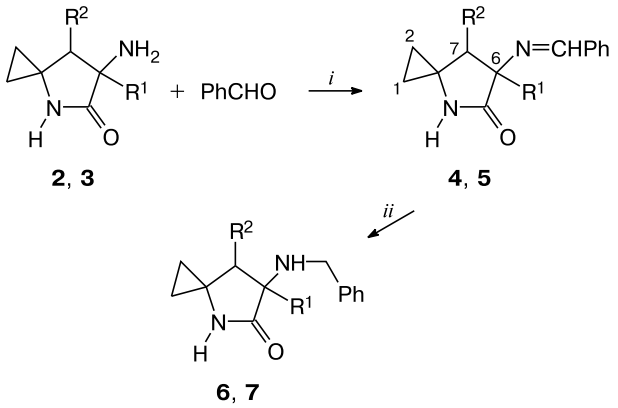
complete reduction of the pyrazolines to diamines followed by intramolecular cyclocondensation of the ester or amide fragment at the distant amino group.

In the present work, we studied some chemical transformations of 3-aminopyrrolidin-2-ones **1**—**3** mainly occurring at the amino group and obtained new spiro structures with the retained cyclopropane fragment.

Results and Discussion

First of all, we tried to obtain azomethines under mild conditions and reduce them to substituted amines. A similar approach has been employed earlier[1] for the synthesis of substituted 3-aminopyrrolidin-2-ones acting as farnesyltransferase inhibitors. We found that condensation of 3-aminopyrrolidin-2-one **2** or **3** with benzaldehyde in boiling CH_2Cl_2 in the presence of anhydrous $MgSO_4$ easily leads to azomethine **4** or **5**, respectively, in 78—85% yields (Scheme 2). These azomethines can be smoothly reduced with $NaBH_4$ in methanol to substituted 3-aminopyrrolidin-2-ones **6** and **7** in high yields, the other functional groups being intact.

Scheme 2



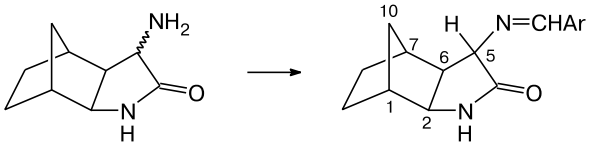
Reagents: *i*. $MgSO_4$, CH_2Cl_2; *ii*. $NaBH_4$, MeOH

2, **4**, **6:** R^1 = Me, R^2 = H
3, **5**, **7:** R^1 = H, R^2 = $CONHC_6H_4F$

The ^1H and ^{13}C NMR spectra of azomethines **4** and **5** show signals at δ_H 8.3—8.4 and δ_C 158—164 (N=CH). Instead, the ^1H NMR spectra of reduction products **6** and **7** contain two doublets at δ_H 3.8—4.0 (geminal coupling constant J = 12—13 Hz) and a broadened singlet at δ_H 2.0—2.5 and their ^{13}C NMR spectra exhibit a signal at δ_C 48—51 ($NH—CH_2$). The NOESY experiment for compound **5** revealed a sufficiently strong coupling between the H(7) proton and either a cyclopropane proton or the amide proton of the aliphatic fragment, a coupling between the H(6) proton and the N=CH proton, and a very weak coupling between the vicinal H(6) and H(7) protons, which suggests the transoid arrangement of the substituents in pyrrolidinone **5** and, consequently, in the starting and substituted amines **3** and **7**.

Polycyclic amine **1**, in which the *anti*-isomer is dominant (3.2 : 1), reacts with benzaldehyde or 2,4-dimethoxybenzaldehyde in a similar way. Although both isomers are involved in the reaction, double recrystallization from benzene—ethyl acetate (1 : 2) gives the individual *anti*-isomers of azomethines **8a,b** in 62—68% yields (Scheme 3). In the ^1H NMR spectra of compounds **8a,b**, the signal for the methine H(5) proton is shifted downfield by ~0.5 ppm compared to the analogous signal for *anti*-**1** but the coupling constant ($J_{5,6} \approx 3.5$ Hz) has the same order of magnitude,[2] which suggests the identical arrangement of the substituents in these compounds.

Scheme 3



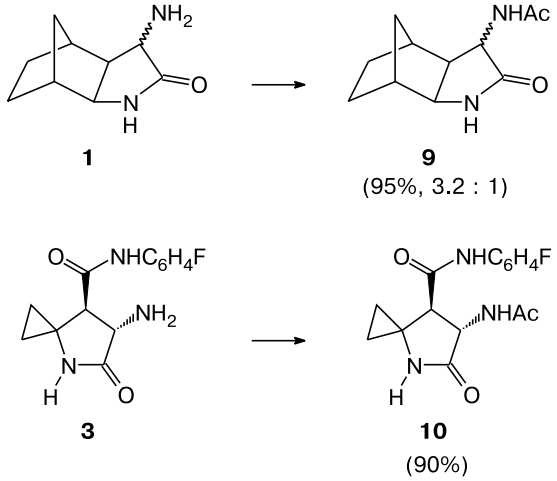
(*anti*/*syn* 3.2 : 1)

Reagents and conditions: ArCHO, $MgSO_4$, CH_2Cl_2, 40 °C, 3 h.

Ar = Ph (**a**), 2,4-$C_6H_3(OMe)_2$ (**b**)

Acylation of pyrrolidinones **1** and **3** with acetyl chloride in triethylamine involves only the amino group, giving the corresponding *N*-acetyl derivatives **9** and **10** in good yields (Scheme 4). As expected, the ratio of the

Scheme 4

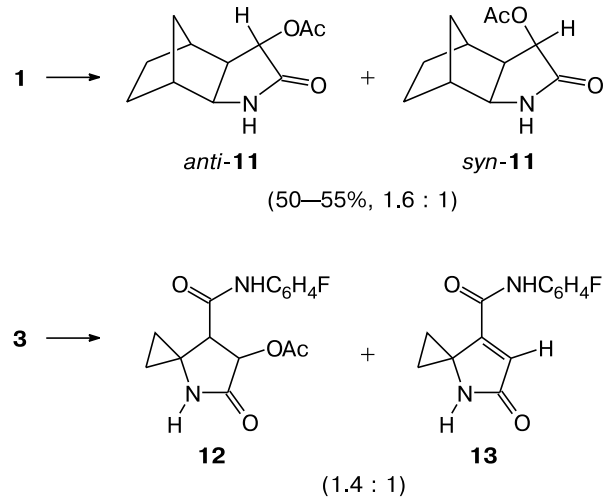


Reagents and conditions: AcCl, Et_3N, CH_2Cl_2, 10 °C.

anti- and *syn*-isomers of product **9** is the same as in the starting pyrrolidinone **1** (~3.2 : 1). The major, *anti*-isomer was isolated in the individual state by preparative TLC; in its ^{1}H NMR spectrum, the coupling constant for the vicinal H(5) and H(6) protons has the same order of magnitude as in the starting *anti*-**1** (J = 4.4 Hz).

We studied transformations of compounds **1**—**3** under nitrosation conditions. It is known[9] that 3-aminopyrrolin-2-ones, which contain a double bond in the heterocycle, can be diazotized with $NaNO_2$ in acetic acid to give 3-diazo-4-pyrrolin-2-ones as stable crystalline compounds. However, our attempted synthesis of diazo compounds from aminopyrrolidinones **1**—**3** failed under analogous conditions. It turned out that diazonium ions generated in the diazotization of compounds **1**—**3** with $NaNO_2$ in acetic acid at 10 °C tend to lose a nitrogen molecule, giving the corresponding carbocations rather than cyclic diazo amides. Further stabilization of these carbocations depends on the structure of the starting aminopyrrolidinone, mainly proceeding through their deprotonation or addition of an acetate anion. For instance, diazotization of amine **1** gives a mixture of products, isomeric *anti*- and *syn*-3-acetoxypyrrolidinones **11** being dominant. Their total yield is 50—55%. According to the ^{1}H NMR data, the ratio of the *anti*- and *syn*-isomers of compound **11** is ~1.6 : 1 (for the starting aminopyrrolidinone **1**, 3.2 : 1), which agrees with the carbocationic reaction mechanism (Scheme 5). Using preparative TLC, we isolated a fraction containing *anti*- and *syn*-**11** in a ratio of ~6 : 1 and a fraction with a somewhat lower R_f value. The latter fraction contains *syn*-**11** and probably a number of unsaturated compounds resulting from carbocationic rearrangements (the presence of four signals with different intensities at δ 5.6—6.2 in the ^{1}H NMR spectrum); their structures were not determined. The ratio of the total integral intensity of the signals at δ 5.6—6.2 to the intensity of the signal at δ 5.30 for the single H(5) proton in the isomer *syn*-**11** is ~2.6 : 1.

Scheme 5

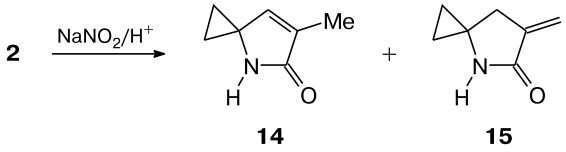


Reagents and conditions: AcOH, $NaNO_2$, 10 °C.

Diazotization of aminopyrrolidinone **3** under similar conditions gives acetoxy derivative **12** and dihydropyrrolone **13** as major products in a total yield of 70—73% (Scheme 5). Compounds **12** and **13** were identified from the ^{1}H and ^{13}C NMR spectra of the reaction mixture. The only isomer obtained of compound **12** seems to be a *trans*-isomer since the coupling constants for the protons of the heterocycle ($J_{6,7}$ = 7.3 Hz) are close to those for compound **10** ($J_{6,7}$ = 8.4 Hz).

In contrast to amines **1** and **3**, nitrosation of amine **2** with $NaNO_2$ in acetic acid was more efficient, being accompanied only by deprotonation of the intermediate carbocation leading to a difficult-to-separate mixture of unsaturated compounds **14** and **15** (Scheme 6). The ratio of these isomers varies widely with the solvent and the acidity of the medium; however, compound **14** containing the endocyclic double bond is always dominant (Table 1).

Scheme 6



Methylidenepyrrolidinone **15** is of interest for the synthesis of heterocyclic spiranes (*e.g.*, by analogy with 1,3-dipolar cycloaddition to 1-substituted 5,5-dimethyl-3-methylidenepyrrolidin-2-one[10,11]). Its highest yield (up to 20%, ^{1}H NMR data) was achieved in a nonpolar solvent (CCl_4) at 30 °C (see Table 1). Because isomers **14** and **15** are difficult to separate, their further transformations were studied without separation of their reaction mixture.

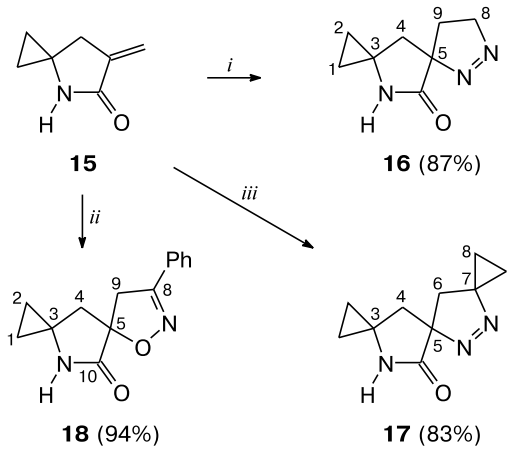
It turned out that the action of diazomethane or diazocyclopropane (generated by decomposition of *N*-cyclo-

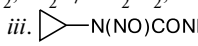
Table 1. Yields and ratios of compounds **14** and **15** for different solvents and reaction conditions

Reagents and solvents	T/°C	Total yield (%)	Ratio of **14** and **15**
$NaNO_2$/AcOH	5	80	8 : 1
$NaNO_2$/$(CO_2H)_2$/Me_2CO—H_2O	5	75	10 : 1
$NaNO_2$/AcOH/CCl_4	30	88	3.5 : 1
BuONO/CH_2Cl_2/Me_3COOH	5	73	6 : 1
N_2O_3/$CHCl_3$	15	48	>50 : 1

propyl-*N*-nitrosourea in the presence of Cs_2CO_3) on a mixture of compounds **14** and **15** (3.5 : 1) results in 1,3-dipolar cycloaddition involving only isomer **15**. In both cases, the reaction proceeds regioselectively to give di- and trispyro adducts **16** and **17** in high yields, the conversion of 3-methylidenepyrrolidin-2-one (**15**) being complete (Scheme 7). Products **16** and **17** can be easily separated from the unreacted dihydropyrrolone **14** by preparative TLC.

Scheme 7



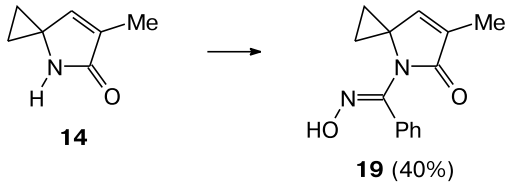
Reagents and conditions: *i*. CH_2N_2, Et_2O/CH_2Cl_2; *ii*. PhCCl=NOH, NEt_3, CH_2Cl_2; *iii*.  , Cs_2CO_3, CH_2Cl_2, 5 °C.

In the ^{13}C NMR spectra, the signals at δ 37.4 and 97.3 are due to the C(3) and C(5) spiro atoms in compound **16** and the signals at δ 37.3, 95.9, and 70.3 are due to the C(3), C(5), and C(7) spiro atoms in compound **17**, respectively.

Nitrile oxide generated from benzohydroximoyl chloride and triethylamine in a mixture of compounds **14** and **15** also reacts only with the latter to give cycloadduct **18** in high yield (Scheme 7). As expected, the only one isomer was obtained, which agrees with the literature data on 1,3-dipolar cycloaddition of benzonitrile oxide to structurally similar 5,5-dimethyl-3-methylidenepyrrolidin-2-one.[10] The resulting dispirane **18** can easily be isolated by precipitation from methanol at −15 °C. In the ^{13}C NMR spectrum of this compound, the signals at δ 35.3 and 87.9 are due to the C(3) and C(5) spiro atoms.

Dihydropyrrol-2-one **14**, which was isolated in the individual state from its mixtures with pyrazolines **16** and **17** by preparative TLC also reacts with benzohydroximoyl chloride in the presence of triethylamine in boiling benzene for 12 h. However, the reaction occurs by acylation of the N—H bond of dihydropyrrolone **14** rather than by 1,3-dipolar cycloaddition of benzonitrile oxide to the endocyclic double bond. With an equimolar ratio of the reagents, the conversion of compound **14** is ~50% and the yield of product **19** is ~40% (Scheme 8). According to the NOESY data, the hydroxy and phenyl groups in oxime **19** are on the same side of the double bond.

Scheme 8



Reagents and conditions: PhCCl=NOH/NEt_3, C_6H_6, 80 °C.

Thus, we demonstrated that 3-aminopyrrolidin-2-ones containing a polycyclic or spirocyclopropane fragment can be used as new structural units for the targeted synthesis of their *N*-substituted derivatives and heterocyclic di- and trispyrans containing a cyclopropane fragment, which are of interest as potential biologically active compounds and as structural fragments of more complicated polycyclic systems.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II 300 spectrometer (300 and 75.5 MHz, respectively) for solutions in $CDCl_3$, $(CD_3)_2CO$, or $(CD_3)_2SO$ with 0.05% Me_4Si as the internal standard. Mass spectra were measured on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct inlet probe). Elemental analysis was carried out on a Perkin—Elmer Series II, 2400 C,H,N-analyzer. *N*-Cyclopropyl-*N*-nitrosourea,[12] *N*-(4-fluorophenyl)maleimide,[13] 5-amino-*exo*-3-azatricyclo[5.2.1.$0^{2,6}$]decan-4-one (**1**),[2] 6-amino-6-methyl-4-azaspiro[2.4]heptan-5-one (**2**),[8] and benzohydroximoyl chloride[14] were prepared as described earlier. Compound **1** was additionally recrystallized from ethyl acetate; the ratio of its *anti*- and *syn*-isomers was 3.2 : 1. Thin-layer chromatography was carried out on Silica gel 60 plates (Merck); spots were visualized with the iodine vapor. For preparative separation, Silica gel 60 plates (0.040—0.063 mm, Merck) with a layer thickness of 1.5—1.8 mm were employed. Reagent-grade solvents (>99.6%) were used without additional purification.

***N*-(4-Fluorophenyl)-6-amino-5-oxo-4-azaspiro[2.4]heptane-7-carboxamide (3).** A 100-cm^3 steel autoclave was charged with 7-(4-fluorophenyl)spiro{cyclopropane-1,4′-2,3,7-triazabicyclo-[3.3.0]oct-2-ene-6,8-dione} (0.52 g, 2 mmol) (prepared from diazocyclopropane and *N*-(4-fluorophenyl)maleimide by analogy with the synthesis of the corresponding 4-bromophenyl derivative),[8] ethanol (50 mL), and Raney nickel (0.05 g). Hydrogenation was carried out at 60 °C and a hydrogen pressure of 80 bar for 4 h. Then the reaction mixture was filtered and concen-

trated, the residue was treated with ethyl acetate, and the precipitate that formed was filtered off and dried *in vacuo*. The yield of compound **3** was 0.21 g (40%), colorless crystals, m.p. 256—258 °C. Found (%): C, 59.04; H, 5.55; N, 15.80. $C_{13}H_{14}FN_3O_2$. Calculated (%): C, 59.31; H 5.36; N, 15.96. Partial MS, *m/z* (I_{rel} (%)): 263 (3) $[M]^+$, 246 (2), 207 (5), 153 (12), 126 (42), 125 (67), 111 (100), 109 (97). ^{1}H NMR ($(CD_3)_2SO$), δ: 0.52, 0.81 (both m, 2 H each, CH_2CH_2); 2.00 (br.s, 2 H, NH_2); 3.11 (d, 1 H, H(7)), J = 8.8 Hz); 3.83 (d, 1 H, H(6)), J = 8.8 Hz); 7.12, 7.60 (both m, 2 H each, C_6H_4); 7.81, 10.3 (both br.s, 1 H each, 2 NH). ^{13}C NMR ($(CD_3)_2SO$), δ: 7.9, 8.7 (CH_2CH_2); 37.2 (C(3)); 54.8, 55.4 (C(6), C(7)); 114.8 (d, C_m, $J_{C,F}$ = 22.0 Hz); 128.6 (d, C_o, $J_{C,F}$ = 7.8 Hz); 134.6 (d, C_{ipso}, $J_{C,F}$ = 2.3 Hz); 157.7 (d, C_p, $J_{C,F}$ = 239 Hz); 167.8, 175.2 (2 CO).

Synthesis of azomethines (general procedure). A suspension of 3-aminopyrrolidin-2-ones **1**—**3** (0.38 mmol), benzaldehyde (0.4 mmol), and anhydrous $MgSO_4$ (0.7 mmol) in CH_2Cl_2 (5 mL) was stirred at 40 °C for 3—4 h. The reaction mixture was filtered and concentrated. The product was extracted from the residue with ethyl acetate and recrystallized from benzene—AcOEt (1 : 2) to give azomethines **4**, **5**, and *trans*-**8a,b**.

6-Benzylideneamino-6-methyl-4-azaspiro[2.4]heptan-5-one (4), 85% yield, m.p. 174—176 °C. Found (%): C, 73.31; H, 7.35; N, 12.08. $C_{14}H_{16}N_2O$. Calculated (%): C, 73.66; H 7.06; N, 12.27. MS, *m/z* (I_{rel} (%)): 228 (2) $[M]^+$, 199 (5), 158 (17), 130 (26), 125 (100). ^{1}H NMR ($(CD_3)_2SO$), δ: 0.56—0.77 (m, 4 H, CH_2CH_2); 1.42 (s, 3 H, Me); 2.19, 2.49 (both d, 1 H each, $H_2C(7)$, ^2J = 12.9 Hz); 7.43, 7.72 (both m, 3+2 H, Ph); 7.98 (br.s, 1 H, NH); 8.41 (s, HC=N). ^{13}C NMR ($(CD_3)_2SO$), δ: 9.0, 9.3 (CH_2CH_2); 22.3 (Me); 35.1 (C(3)); 44.7 (C(7)); 67.1 (C(6)); 127.4 (C_m); 128.2 (C_o); 130.3 (C_p); 135.8 (C_{ipso}); 158.6 (C=N), 175.1 (CO).

***N*-(4-Fluorophenyl)-*trans*-6-benzylideneamino-5-oxo-4-azaspiro[2.4]heptane-7-carboxamide (5)**, 78% yield, m.p. 222—224 °C. Partial MS, *m/z* (I_{rel} (%)): 351 (2) $[M]^+$, 213 (17), 137 (10), 106 (100). ^{1}H NMR ($(CD_3)_2SO$), δ: 0.56, 0.70, 0.90 (all m, 1+1+2 H, CH_2CH_2); 3.68 (d, 1 H, H(7), ^3J = 7.4 Hz); 4.52 (d, 1 H, H(6), ^3J = 7.4 Hz); 7.11, 7.56 (both m, 2 H each, C_6H_4); 7.43, 7.74 (both m, 3+2 H, Ph); 8.18, 10.2 (both br.s, 1 H each, 2 NH); 8.40 (s, HC=N). ^{13}C NMR ($(CD_3)_2SO$), δ: 8.4, 8.7 (CH_2CH_2); 33.4 (C(3)); 52.9 (C(7)); 71.9 (C(6)); 114.8 (d, C_m, $J_{C,F}$ = 21.7 Hz); 120.8 (d, C_o, $J_{C,F}$ = 8.0 Hz); 127.7, 128.3 (C_o, C_m); 130.7 (C_p); 134.5 (d, C_{ipso}, $J_{C,F}$ = 2.2 Hz); 135.0 (C_{ipso}); 157.5 (d, C_p, $J_{C,F}$ = 238 Hz); 164.1 (C=N); 167.6, 171.0 (2 CO).

***anti*-5-Benzylideneamino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one (8a)**, 62% yield, m.p. 168—170 °C. Partial MS, *m/z* (I_{rel} (%)): 254 (1) $[M]^+$, 151 (100), 122 (47), 110 (23), 104 (12). ^{1}H NMR ($CDCl_3$), δ: 1.19 (m, 3 H, H_{endo}(8), H_{endo}(9), H_{anti}(10)); 1.51 (m, 3 H, H_{exo}(8 and 9), H_{syn}(10)); 2.21 (m, 2 H, H(1), H(7)); 2.48 (ddd, 1 H, H(6), $J_{2,6}$ = 7.2 Hz, $J_{5,6}$ = 3.5 Hz, J = 1.5 Hz); 3.65 (br.d, 1 H, H(5), $J_{5,6}$ = 3.5 Hz); 3.67 (br.d, 1 H, H(2), $J_{2,6}$ = 7.2 Hz); 7.08 (br.s, 1 H, NH); 7.40, 7.79 (both m, 3+2 H, Ph); 8.37 (s, HC=N). ^{13}C NMR ($CDCl_3$), δ: 25.3, 28.2 (C(8), C(9)); 32.2 (C(10)); 40.8, 41.2 (C(1), C(7)); 49.9 (C(6)); 60.8 (C(2)); 75.3 (C(5)); 128.5 (C_o, C_m); 131.0 (C_p); 135.8 (C_{ipso}); 163.4 (C=N), 176.3 (CO).

***anti*-5-(2,4-Dimethoxybenzylidene)amino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one (8b)**, 68% yield, m.p. 188—190 °C. Partial MS, *m/z* (I_{rel} (%)): 314 (9) $[M]^+$, 218 (5), 164 (28), 151 (100), 122 (89), 110 (43). ^{1}H NMR ($CDCl_3$), δ: 1.18 (m, 3 H, H_{endo}(8), H_{endo}(9), H_{anti}(10)); 1.52 (m, 3 H, H_{exo}(8 and 9), H_{syn}(10)); 2.20 (m, 2 H, H(6), H(7)); 2.46 (m, 1 H, H(1)); 3.62 (br.d, 1 H, H(5), $J_{5,6}$ = 3.4 Hz); 3.66 (br.d, 1 H, H(2), $J_{2,6}$ = 7.3 Hz); 3.83, 3.84 (both s, 3 H each, 2 OMe); 6.20 (br.s, 1 H, NH); 6.41 (dd, 1 H, H(3′), ^4J = 2.3 Hz, ^5J = 1.0 Hz); 6.49 (dd, 1 H, H(5′), ^3J = 8.6 Hz, ^4J = 2.3 Hz); 7.90 (dd, 1 H, H(6′), ^3J = 8.6 Hz, ^5J = 1.0 Hz); 8.65 (s, HC=N). ^{13}C NMR ($CDCl_3$), δ: 25.4, 28.2 (C(8), C(9)); 32.2 (C(10)); 40.8, 41.4 (C(1), C(7)); 50.2 (C(6)); 55.5, 55.6 (2 OMe); 60.5 (C(2)); 75.4 (C(5)); 98.0 (C(3′)); 105.4 (C(5′)); 117.7 (C(1′)); 128.9 (C(6′)); 159.0 (C=N), 160.4, 163.4 (C(2′), C(4′)); 176.5 (CO).

6-Benzylamino-6-methyl-4-azaspiro[2.4]heptan-5-one (6). Sodium borohydride (19 mg, 0.5 mmol) was added to a solution of azomethine **4** (34 mg, 0.15 mmol) in anhydrous methanol (3 mL). The reaction mixture was stirred at 20 °C for 12 h. The solvent was removed *in vacuo*, the residue was treated with water, and the product was extracted with CH_2Cl_2. The organic layer was separated, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. The yield of amine **6** was 29 mg (85%), m.p. 109—111 °C. Partial MS, *m/z* (I_{rel} (%)): 230 (1) $[M]^+$, 201 (4), 173 (5), 146 (15), 125 (22), 106 (84), 91 (100). ^{1}H NMR ($CDCl_3$), δ: 0.70, 0.87 (both m, 2 H each, CH_2CH_2); 1.46 (s, 3 H, Me); 1.88, 2.50 (both d, 1 H each, $H_2C(7)$, ^2J = 13.0 Hz); 1.95 (br.s, 1 H, NH); 3.73, 3.83 (both d, 1 H each, H_2CN, ^2J = 12.1 Hz); 6.95 (br.s, 1 H, NH); 7.20—7.40 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 9.8, 12.2 (CH_2CH_2); 24.6 (Me); 35.9 (C(3)); 41.4 (C(7)); 48.2 (NCH_2); 62.7 (C(6)); 127.1 (C_p); 128.4, 128.5 (C_o, C_m); 140.3 (C_{ipso}); 179.8 (CO).

***N*-(4-Fluorophenyl)-*trans*-6-benzylamino-5-oxo-4-azaspiro[2.4]heptane-7-carboxamide (7)** was obtained analogously by reduction of azomethine **5**. The yield was 88%, m.p. 146—148 °C. Found (%): C, 67.54; H, 5.44; N, 12.12. $C_{20}H_{20}FN_3O_2$. Calculated (%): C, 67.97; H, 5.70; N, 11.89. Partial MS, *m/z* (I_{rel} (%)): 353 (2) $[M]^+$, 262 (6), 215 (10), 125 (19), 106 (34), 91 (100). ^{1}H NMR ($(CD_3)_2SO$), δ: 0.52, 0.82, 0.96 (all m, 1+2+1 H, CH_2CH_2); 2.48 (br.s, 1 H, NH); 3.38 (d, 1 H, H(7), ^3J = 10.4 Hz); 3.93, 4.07 (both d, 1 H each, NCH_2, ^2J = 12.7 Hz); 4.04 (d, 1 H, H(6), ^3J = 10.4 Hz); 6.98, 7.41 (both m, 2 H each, C_6H_4); 7.30 (m, 5 H, Ph); 7.10, 9.3 (both br.s, 1 H each, 2 NH). ^{13}C NMR ($(CD_3)_2SO$), δ: 8.6, 9.7 (CH_2CH_2); 38.4 (C(3)); 50.7 (C(7)); 51.2 (NCH_2); 61.5 (C(6)); 115.6 (d, C_m, $J_{C,F}$ = 22.2 Hz); 121.7 (d, C_o, $J_{C,F}$ = 8.0 Hz); 127.8 (C_p); 128.5, 128.8 (C_o, C_m); 133.8 (d, C_{ipso}, $J_{C,F}$ = 2.5 Hz); 138.7 (C_{ipso}); 159.4 (d, C_p, $J_{C,F}$ = 241 Hz); 167.4, 174.6 (2 CO).

***anti*- and *syn*-5-Acetamido-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one (9).** Acetyl chloride (47 mg, 0.6 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirred solution of amine **1** (100 mg, 0.6 mmol) and triethylamine (67 mg, 0.66 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 20 °C for 10 h. Then water (3 mL) was added and the product was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The yield of compound **9** as a 3.2 : 1 mixture of *trans*- and *cis*-isomers was 116 mg (93%). The *anti*-isomer was isolated using preparative TLC on SiO_2 with benzene—AcOEt (1 : 3) as an eluent, yellowish crystals, R_f 0.30, m.p. 64—67 °C. ***anti*-Isomer of compound 9.** Found (%): C, 63.06; H, 7.89; N, 13.16. $C_{11}H_{16}N_2O_2$. Calculated (%): C, 63.44; H, 7.74; N, 13.45. Partial MS, *m/z* (I_{rel} (%)): 208 (16) $[M]^+$, 190 (5), 166 (24), 165 (70) $[M - Ac]^+$, 150 (10) $[M - NHAc]^+$, 43 (100). ^{1}H NMR ($CDCl_3$), δ: 1.19 (m, 3 H, H_{endo}(8), H_{endo}(9), H_{anti}(10));

1.41 (dq, 1 H, $H_{syn}(10)$, ^2J = 10.2 Hz, $J \approx$ 1.8 Hz); 1.55 (m, 2 H, H_{exo}(8 and 9)); 2.00 (s, 3 H, Me); 2.18 (m, 2 H, H(6), H(7)); 2.44 (m, 1 H, H(1)); 3.54 (br.d, 1 H, H(2), $J_{2,6}$ = 7.5 Hz); 3.81 (dd, 1 H, H(5), $J_{5,6}$ = 4.4 Hz, ^3J = 6.6 Hz); 6.66 (br.d, 1 H, NHAc, ^3J = 6.6 Hz); 6.70 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 23.0 (Me); 25.4, 27.8 (C(8), C(9)); 32.0 (C(10)); 41.1, 41.3 (C(1), C(7)); 49.9 (C(6)); 56.3 (C(2)); 60.1 (C(5)); 170.8 (CO); 176.5 (C(4)). ***syn*-Isomer of compound 9** (in the mixture with the *trans*-isomer). ^{1}H NMR ($CDCl_3$), non-overlapping signals, δ: 2.07 (s, 3 H, Me); 2.59 (br.dd, 1 H, H(6), $J_{2,6}$ = 6.9 Hz, $J_{5,6}$ = 10.1 Hz); 3.59 (br.d, 1 H, H(2), $J_{2,6}$ = 6.9 Hz); 4.58 (dd, 1 H, H(5), $J_{5,6}$ = 10.1 Hz, ^3J = 6.0 Hz); 6.52 (br.d, 1 H, NHAc, ^3J = 6.0 Hz); 6.60 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 22.8 (Me);24.7, 28.5 (C(8), C(9)); 29.7 (C(10)); 36.4 (C(7)); 41.7 (C(1); 44.4 (C(6)); 52.3 (C(2)); 60.0 (C(5)); 171.0 (CO); 176.3 (C(4)).

***N*-(4-Fluorophenyl)-*trans*-6-acetamido-5-oxo-4-azaspiro[2.4]heptane-7-carboxamide (10).** Acetyl chloride (32 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirred mixture of amine **3** (105 mg, 0.4 mmol) and triethylamine (42 mg, 0.42 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at 20 °C for 12 h. Then 0.3 *M* NaOH (1.4 mL) was added and the mixture was evaporated *in vacuo* almost to dryness. The product was extracted from the residue with ethyl acetate (3×10 mL). The combined extracts were concentrated *in vacuo*. The yield of compound **10** was 110 mg (90%), colorless small crystals, m.p. 288—290 °C. Found (%): C, 58.66; H, 5.49; N, 13.37. $C_{15}H_{16}FN_3O_3$. Calculated (%): C, 59.01; H, 5.28; N, 13.76. ^{1}H NMR ($(CD_3)_2SO$), δ: 0.49, 0.59, 0.85 (all m, 1+1+2 H, CH_2CH_2); 1.82 (s, 3 H, Me); 3.52 (d, 1 H, H(7), $J_{6,7}$ = 8.4 Hz); 4.60 (dd, 1 H, H(6), $J_{6,7}$ = 8.4 Hz, ^3J = 8.1 Hz); 7.14, 7.59 (both m, 2 H each, C_6H_4); 7.99, 10.2 (both br.s, 1 H each, 2 NH); 8.44 (br.d, 1 H, NHAc, ^3J = 8.1 Hz). ^{13}C NMR ($(CD_3)_2SO$), δ: 8.7, 8.8 (CH_2CH_2); 22.1 (Me); 37.6 (C(3)); 51.2 (C(7)); 53.4 (C(6)); 114.9 (d, $C_{m,}$, $J_{C,F}$ = 22.0 Hz); 120.6 (d, C_o, $J_{C,F}$ = 8.0 Hz); 134.5 (d, C_{ipso}, $J_{C,F}$ = 2.8 Hz); 157.6 (d, C_p, $J_{C,F}$ = 240 Hz); 167.8, 169.0, 171.2 (3 CO).

***anti*- and *syn*-5-Acetoxy-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one (11).** Sodium nitrite (207 mg, 3 mmol) was added at 10 °C to a solution of aminopyrrolidinone **1** (100 mg, 0.6 mmol) in acetic acid (5 mL) containing CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 2 h. Then the acetic acid was removed *in vacuo*, water (1 mL) was added, and the product was extracted with CH_2Cl_2. The extract was concentrated *in vacuo*. According to the integral intensities of the non-overlapping signals at δ 4.82 and 5.30 in the ^{1}H NMR spectrum of the reaction mixture, the ratio of *anti*- and *syn*-**11** was ~1.6 : 1. Acetoxy derivatives **11** were isolated by preparative TLC on SiO_2 (benzene—AcOEt, 1 : 3) as a ~5 : 1 mixture of the *anti*- and *syn*-isomers (R_f 0.32). Another fraction with R_f 0.24 contained *syn*-**11** (35—40%). The total yield of compounds **11** was 50—55%. Partial MS, *m/z* (I_{rel} (%)): 209 (17) $[M]^+$, 167 (40), 166 (21) $[M - Ac]^+$, 149 (64) $[M - AcOH]^+$, 106 (84), 67 (90), 43 (100).

***anti*-Isomer of compound 11.** ^{1}H NMR ($CDCl_3$), δ: 1.15 (m, 2 H, H_{endo}(8), H_{endo}(9)); 1.22 (dq, 1 H, $H_{anti}(10)$, ^2J = 10.8 Hz, $J \approx$ 1.8 Hz); 1.36 (dq, 1 H, $H_{syn}(10)$, ^2J = 10.8 Hz, $J \approx$ 1.8 Hz); 1.55 (m, 2 H, H_{exo}(8), H_{exo}(9)); 2.07 (m, 1 H, H(6)); 2.14 (s, 3 H, Me); 2.20 (m, 1 H, H(7)); 2.48 (m, 1 H, H(1)); 3.57 (br.d, 1 H, H(2), $J_{2,6}$ = 7.0 Hz); 4.82 (d, 1 H, H(5), $J_{5,6}$ = 3.6 Hz); 6.98 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 20.9 (Me); 25.2 (C(9)); 27.9 (C(8)); 32.1 (C(10)); 40.1, 40.9 (C(1), C(7)); 49.0 (C(6)); 60.5 (C(2)); 75.4 (C(5)); 170.5 (CO); 174.3 (C(4)).

***syn*-Isomer of compound 11.** ^{1}H NMR ($CDCl_3$), non-overlapping signals, δ: 2.02, 2.09 (both m, 1 H each, H(1), H(7)); 2.20 (s, 3 H, Me); 2.55 (m, 1 H, H(6)); 3.57 (br.d, 1 H, H(2), $J_{2,6}$ = 7.0 Hz); 5.30 (d, 1 H, H(5), $J_{5,6}$ = 10.0 Hz); 6.85 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 20.6 (Me); 24.7 (C(9)); 28.3 (C(8)); 32.3 (C(10)); 36.2 (C(7)); 41.4 (C(1)); 44.0 (C(6)); 60.0 (C(2)); 71.1 (C(5)); 170.5 (CO); 174.1 (C(4)).

***N*-(4-Fluorophenyl)-*trans*-6-acetoxy-5-oxo-4-azaspiro[2.4]heptane-7-carboxamide (12) and *N*-(4-fluorophenyl)-5-oxo-4-azaspiro[2.4]hept-6-ene-7-carboxamide (13).** Sodium nitrite (0.19 g, 2.8 mmol) was added at 10 °C to a solution of aminopyrrolidinone **3** (0.13 g, 0.5 mmol) in acetic acid (5 mL) containing CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 2 h. Then the acetic acid was removed *in vacuo*, water (1 mL) was added, and the product was extracted with ethyl acetate. The extract was concentrated *in vacuo*. A fine crystalline substance (0.10 g, 70—73%) consisting of compounds **12** and **13** (molar ratio 1.4 : 1) was isolated by preparative TLC on SiO_2 with AcOEt as an eluent, R_f 0.26—0.35.

Compound 12. ^{1}H NMR ($(CD_3)_2CO$), δ: 0.80, 0.96 (both m, CH_2CH_2); 1.96 (s, 3 H, Me); 3.53 (d, 1 H, H(7), $J_{6,7}$ = 7.3 Hz); 5.82 (d, 1 H, H(6), $J_{6,7}$ = 7.3 Hz); 7.08 and 7.63 (both m, 2 H each, C_6H_4); 7.35, 9.45 (both br.s, 1 H each, 2 NH). ^{13}C NMR ($(CD_3)_2CO$), δ: 9.0, 9.5 (CH_2CH_2); 19.8 (Me); 38.4 (C(3)); 52.6 (C(7)); 73.3 (C(6)); 115.2 (d, $C_{m,}$, $J_{C,F}$ = 22.4 Hz); 121.4 (d, C_o, $J_{C,F}$ = 8.2 Hz); 135.2 (d, C_{ipso}, $J_{C,F}$ = 2.8 Hz); 157.4 (d, C_p, $J_{C,F}$ = 240 Hz); 167.2, 169.6, 175.8 (3 CO).

Compound 13. ^{1}H NMR ($(CD_3)_2CO$), δ: 1.46, 1.91 (both m, 2 H each, CH_2CH_2); 6.71 (s, 1 H, H(6)); 7.06, 7.72 (both m, 2 H each, C_6H_4); 7.85, 9.65 (both br.s, 1 H each, 2 NH). ^{13}C NMR ($(CD_3)_2CO$), δ: 13.4 (CH_2CH_2); 37.4 (C(3)); 115.1 (d, $C_{m,}$, $J_{C,F}$ = 22.5 Hz); 122.0 (d, C_o, $J_{C,F}$ = 8.0 Hz); 126.8 (C(6)); 134.9 (d, C_{ipso}, $J_{C,F}$ = 2.8 Hz); 158.5 (d, C_p, $J_{C,F}$ = 238 Hz); 164.2, 168.1, 170.0 (C(7), 2 CO).

Nitrosation of 6-amino-6-methyl-4-azaspiro[2.4]heptan-5-one (2). Sodium nitrite (1.04 g, 15 mmol) was added at 30 °C for 30 min to an actively stirred solution of aminopyrrolidinone **2** (1.12 g, 8 mmol) in CCl_4 (14 mL) and acetic acid (6 mL). The reaction mixture was stirred for 2 h, poured into cold water, and neutralized with K_2CO_3. The product was extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was washed with a small amount of ether and dried *in vacuo*. According to ^{1}H and ^{13}C NMR data, the resulting colorless crystals (0.87 g, ~88%) consisted of 6-methyl-4-azaspiro[2.4]hept-6-en-5-one (**14**) and 6-methylidene-4-azaspiro[2.4]heptan-5-one (**15**) in a ratio of ~3.5 : 1. Compound **14** was isolated in the individual state upon treatment of the mixture of the isomers obtained with diazomethane or diazocyclopropane, because it was inert under those conditions (see below).

Compound 14. ^{1}H NMR ($CDCl_3$), δ: 1.23, 1.44 (both m, 2 H each, CH_2CH_2); 1.92 (d, 3 H, Me, J = 1.6 Hz); 6.40 (dq, 1 H, =CH, J = 1.5 Hz, J = 1.6 Hz); 8.10 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 10.8 (Me); 11.5 (CH_2CH_2); 43.3 (C(3)); 133.0 (C(6)); 144.8 (C(7)); 175.3 (C=O).

Compound 15. ^{1}H NMR ($CDCl_3$), δ: 0.71, 0.95 (both m, 2 H each, CH_2CH_2); 2.87 (t, 2 H, $H_2C(7)$, J = 2.5 Hz); 5.36, 6.02 (both m, 1 H each, $=CH_2$); 8.30 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 11.8 (CH_2CH_2); 35.1 (C(7)); 36.8 (C(3)); 115.6

(=CH_2); 140.9 (C(6)); 170.7 (C=O). The yields and ratios of compounds **14** and **15** for different solvents and reaction conditions are given in Table 1.

6,7,11-Triazadispiro[2.1.4^5.2^3]undec-6-en-10-one (16). A 0.5 *M* solution of diazomethane (0.8 mL, 0.4 mmol) in ether was added to a solution of a ~3.5 : 1 mixture (55.4 mg) of isomers **14** and **15** (this corresponds to ~0.1 mmol of compound **15**) in CH_2Cl_2 (1 mL). The reaction mixture was kept at 18 °C for two days. The solvents were removed *in vacuo* and the residue was separated by preparative TLC (SiO_2, AcOEt). The yield of dispirane **16** was 14.4 mg (87% with respect to compound **15**), colorless crystals, R_f 0.46, m.p. 156—157 °C The unreacted compound **14** (39 mg) was recovered, R_f 0.32, m.p. 123—124 °C.

Compound 16. Found (%): C, 58.46; H, 6.39; N, 25.20. $C_8H_{11}N_3O$. Calculated (%): C, 58.17; H, 6.71; N, 25.44. Partial MS (EI), *m/z* (I_{rel} (%)): 149 (4), 136 (25), 122 (100), 110 (12), 109 (24). ^{1}H NMR ($CDCl_3$), δ: 0.77, 0.96 (both m, 1+3 H, CH_2CH_2); 1.46 (ddd, 1 H, H_a(9), ^2J = 12.6 Hz, ^3J = 8.0 Hz, ^3J = 9.0 Hz); 2.28 (ddd, 1 H, H_b(9), ^2J = 12.6 Hz, ^3J = 6.4 Hz, ^3J = 8.1 Hz); 2.37, 2.53 (both d, 1 H each, H_2C(4), ^2J = 13.3 Hz); 4.66 (m, 2 H, H_2C(8)); 5.85 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 10.2, 11.7 (CH_2CH_2); 26.4 (C(9)); 37.4 (C(3)); 40.6 (C(4)); 77.6 (C(8)); 97.3 (C(5)); 173.6 (CO).

Compound 14. Partial MS (EI), *m/z* (I_{rel}(%)): 123 (100) $[M]^+$, 122 (38) $[M - H]^+$, 108 (15), 94 (27). For the ^{1}H and ^{13}C NMR spectra, see the section "Nitrosation of compound **2**").

10,11,13-Triazatrispiro[2.1.1.2^7.2^5.2^3]tridec-10-en-12-one (17). *N*-Cyclopropyl-*N*-nitrosourea (20.5 mg, 0.15 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) were added at 5—7 °C to a solution of a ~3.5 : 1 mixture (55.3 mg) of isomers **14** and **15** (this corresponds to ~0.1 mmol of compound **15**) in CH_2Cl_2 (3 mL). The reaction mixture was vigorously stirred for 30 min, filtered, and concentrated *in vacuo*. The residue was separated by preparative TLC (SiO_2, AcOEt). The unreacted compound **14** (38 mg) was recovered, R_f 0.32 (its characteristics are given above). The yield of trispyran **17** was 15.8 mg (83% with respect to compound **15**), colorless crystals, R_f 0.55, m.p. 176—177 °C. Found (%): C, 62.53; H, 6.70; N, 22.03. $C_{10}H_{13}N_3O$. Calculated (%): C, 62.81; H, 6.85; N, 21.97. Partial MS, *m/z* (I_{rel} (%)): 162 (14), 148 (27), 135 (100), 120 (29), 95 (38), 79 (90). ^{1}H NMR ($CDCl_3$), δ: 0.72, 0.93, 1.11, 1.23 (all m, 1+3+1+1 H, protons of the cyclopropane rings); 1.66, 2.44 (both d, 1 H each, H_2C(4), ^2J = 12.7 Hz); 1.81 (m, 2 H, CHCH of the cyclopropane ring next to the N=N fragment); 2.37, 2.53 (both d, 1 H each, H_2C(6), ^2J = 13.3 Hz); 6.32 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 10.2, 12.2, 14.6, 15.1 (2 CH_2CH_2); 33.6 (C(6)); 37.3 (C(3)); 41.9 (C(4)); 70.3 (C(7)); 95.9 (C(5)); 173.4 (CO).

8-Phenyl-6-oxa-7,11-diazadispiro[2.1.4^5.2^3]undec-7-en-10-one (18). Benzohydroximoyl chloride (0.16 g, 1 mmol) and triethylamine (0.11 g, 1.1 mmol) were added to a solution of a ~3.5 : 1 mixture (0.22 g) of isomers **14** and **15** (this corresponds to ~0.4 mmol of compound **15**) in CH_2Cl_2 (5 mL). The reaction mixture was kept at 18 °C for 20 h and treated with water (10 mL). The organic layer was separated and concentrated *in vacuo*. The residue was dissolved in a minimum amount of methanol at 30 °C and left at −15 °C for 12 h. The precipitate that formed was filtered off, washed with a small amount of chloroform, and dried *in vacuo*. The yield of compound **18** was 0.091 g (94%), colorless crystals, m.p. 235—236 °C. Found (%): C, 69.15; H, 5.88; N, 11.23. $C_{14}H_{14}N_2O_2$. Calculated (%): C, 69.41; H, 5.82; N, 11.56. Partial MS, *m/z* (I_{rel} (%)): 242 (3) $[M]^+$, 214 (14), 144 (36), 117 (18), 82 (40), 77 (100). ^{1}H NMR ($(CD_3)_2SO$), δ: 0.62—0.82 (m, 4 H, CH_2CH_2); 2.30, 2.46 (both d, 1 H each, H_2C(4), ^2J = 13.9 Hz); 3.52, 3.69 (both d, 1 H each, H_2C(6), ^2J = 17.2 Hz); 7.47, 7.69 (both m, 3+2 H, Ph); 8.33 (br.s, 1 H, NH). ^{13}C NMR ($(CD_3)_2SO$), δ: 8.4, 10.2 (CH_2CH_2); 35.3 (C(3)); 41.2, 41.5 (C(4), C(9)); 87.9 (C(5)); 126.2 (C_o); 128.4 (C_m); 128.5 (C_{ipso}); 129.8 (C_p); 155.5 (C(8)); 171.8 (CO).

4-[Hydroxyimino(phenyl)methyl]-6-methyl-4-azaspiro-[2.4]hept-6-en-5-one (19). A mixture of compound **14** (49 mg, 0.4 mmol), benzohydroximoyl chloride (62 mg, 0.4 mmol), and triethylamine (46 mg, 0.45 mmol) was refluxed in benzene (5 mL) for 12 h. On cooling, the precipitate that formed was filtered off, the solvent was removed *in vacuo*, and the residue was separated by preparative TLC (SiO_2, AcOEt). The yield of compound **19** was 39 mg (40%), yellow crystals, R_f 0.55, m.p. 113—115 °C. MS, *m/z* (I_{rel} (%)): 242 (52) $[M]^+$, 178 (45), 123 (100), 105 (43). ^{1}H NMR ($CDCl_3$), δ: 1.26 (m, 2 H, CH_2CH_2); 1.97 (d, 3 H, Me, ^4J = 1.5 Hz); 2.48 (m, 2 H, CH_2CH_2); 6.54 (q, 1 H, =CH, ^4J = 1.5 Hz); 7.08 (tt, 1 H, H_p, ^3J = 7.7 Hz, ^4J = 1.3 Hz); 7.31 (dd, 2 H, H_m, ^3J = 8.4 Hz, ^3J = 7.7 Hz); 7.50 (dd, 2 H, H_o, ^3J = 8.4 Hz, ^4J = 1.3 Hz); 11.0 (br.s, 1 H, NOH). ^{13}C NMR ($CDCl_3$), δ: 10.6 (Me); 11.6 (CH_2CH_2); 48.0 (C(3)); 120.4 (C_o); 124.0 (C_p); 129.0 (C_m); 129.8 (C_{ipso}); 137.5 (C(6)), 149.6 (C=N); 149.7 (C(7)); 173.7 (CO).

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