Synthesis and thermal transformations of pyrazolines obtained by 1,3-dipolar addition of diazocyclopropane to maleimides

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1-Pyrazolines, obtained by 1,3-dipolar cycloaddition of diazocyclopropane to *N*-phenyl- and *N*-cyclohexylmaleimides, undergo complete dediazoniation at 175 °C for 10—16 h with the formation of spiro[3-azabicyclo[3.1.0]hexane-6,1′-cyclopropane]-2,4-diones **3** (80—89%) and isomeric 3-cyclopropyl-1*H*-pyrrole-2,5-diones **4**. On the example of 3-cyclopropyl-1-phenyl-1*H*-pyrrole-2,5-dione, it was shown that compounds **4** are able again to enter into 1,3-dipolar cycloaddition with diazomethane or diazocyclopropane with the reaction in the case of diazocyclopropane being nonselective and leading to two regioisomeric pyrazolines in the ratio ~1.7 : 1, thermolysis of which, conversely, proceeds with high selectivity and exclusively affords a spiropentane derivative. An action of the aqueous methanol solution of sodium hydroxide on the spiropentanes fused with succinimide fragment and subsequent acidification of the salts obtained lead to stable *cis*-amidoacids of spiropentane series.

Key words: spiro[1-pyrazoline-3,1′-cyclopropanes], spiropentanosuccinimides, spiropentane-1,2-dicarboxylic acid monoamides, diazo compounds, 1,3-dipolar cycloaddition, thermolysis.

Earlier, it was shown that 1,3-dipolar cycloaddition of the *in situ* generated diazocyclopropane to unsaturated compounds[1—5] is a convenient general method for the preparation of 1- or 2-pyrazolines containing spiro-jointed cyclopropane fragment. This process occurs the most readily for sterically unhindered C=C bonds, which contain electron-withdrawing substituents or which are a part of strained fragments. In its turn, thermal dediazoniation of spirocyclopropane-containing 1-pyrazolines allows one to obtain spiropentane derivatives,[3—6] though, desired selectivity is not always achievable in such processes. In a number of cases, the formation of spiropentanes is accompanied by side reactions, which lead to isomeric unsaturated compounds.[5,6]

In the present work, a synthesis of spirocyclopropane-containing pyrazolines fused with a succinimide fragment has been accomplished and their thermal dediazoniation has been studied in order to prepare spiropentane-1,2-dicarboxylic acid derivatives. The latter, similarly to the cyclopropanedicarboxylic acid derivatives, can be of interest as synthons for the synthesis of new biologycally active compounds. Thus, for example, a modification of 4-benzyl-2*H*-phthalazin-1-one, which is a powerful inhibitor of poly(adenazindiphosphateribose)polymerase, by introduction of 2-amidocyclopropanecarboxylic acid fragment and cyclization into imide leads to an increase in metabolic activity of enzyme PARP-1 (see Ref. 7). The fragment of 2-amidocyclopropanecarboxylic acid was used in the development of *pseudo*-tri- and pentapeptides to make their conformational mobility limited,[8,9] as well as in the synthesis of bicyclic monothioimides, which are of interest as chiral synthons.[10]

Results and Discussion

Earlier, we have shown[2] that *N*-(4-methyl)- or *N*-(4-bromophenyl)maleimides are suitable substrates for the synthesis of spirocyclopropane-containing pyrazolines fused with a succinimide fragment. Similar process also occurs on 1,3-dipolar cycloaddition of the *in situ* generated diazocyclopropane to *N*-phenyl- and *N*-cyclohexylmaleimides (**1a,b**). The use of 1.5-fold molar excess of *N*-cyclopropyl-*N*-nitrosourea as the source diazocyclopropane and potassium or cesium carbonates as the bases leads to spirocyclopropane-containing heterocycles **2a,b** in 70 and 62% yield, respectively (Scheme 1). In this case, the use of Cs_2CO_3 instead of K_2CO_3 decreases the reaction time by 5—6 times, having virtually no effect on the yields of the corresponding heterocycles **2a,b**. In our view, the somewhat lower yield of adduct **2b** has a reason: the presence of the cyclohexyl substituent instead of the aryl one, apparently, decreases polarizability of the

† Deceased.

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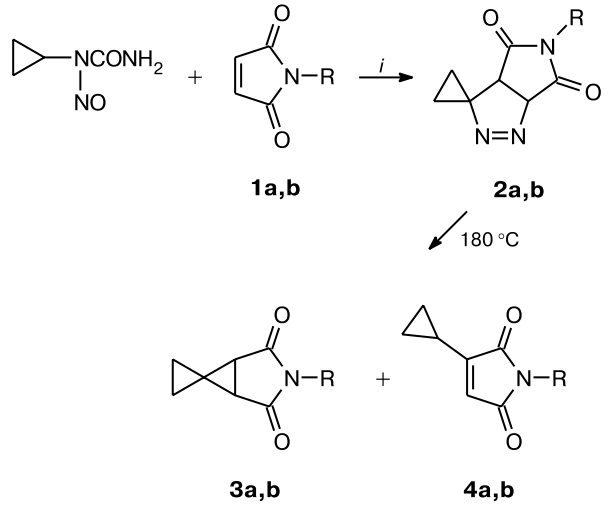
molecule in the transition state and makes the reaction of 1,3-dipolar cycloaddition less efficient.

Thermolysis of spiro[pyrazolinecyclopropanes] **2a,b** obtained was carried out by reflux of their solutions in *o*-dichlorobenzene for 10—16 h until evolution of nitrogen was stopped. According to the TLC and ^{1}H NMR spectral data, the complete conversion of starting pyrazolines and the formation in every case of two isomeric compounds, *viz.*, fused spiropentanes **3a,b** and 3-cyclopropyl-1*H*-pyrrole-2,5-diones **4a,b**, are observed. The nature of substituent in the succinimide ring has considerable influence on the ratio of the compounds formed: thus, in the case of cyclohexyl substituent the selectivity of the process with respect to the forming spiropentane **3b** is somewhat higher than in the case of phenyl substituent (Scheme 1).

Scheme 1



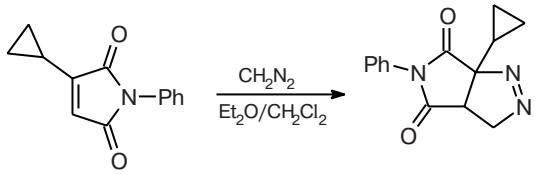
R = Ph (**a**), C_6H_{11} (**b**). **3a** : **4a** ~ 4 : 1; **3b** : **4b** ~ 8 : 1.
Reagents and conditions: *i*, K_2CO_3 (Cs_2CO_3), CH_2Cl_2, 5—7 °C.

The observed dediazoniation of pyrazolines **2a,b**, despite the side formation of cyclopropyl-1*H*-pyrrole-2,5-diones **4**, turned out to be more selective in comparison, for example, with the earlier described[11] thermolysis of 1-pyrazoline, obtained by addition of diazomethane to *N*-phenylmaleimide, which resulted, along with cyclopropane derivative, in isomeric unsaturated compounds, *viz.*, 3-methyl-1-phenyl-3-pyrroline-2,5-dione and 3-methylene-1-phenylpyrrolidine-2,5-dione, as well as 2-pyrazoline, the product of isomerization of starting 1-pyrazoline, in the ratio 5 : 6 : 1.5 : 1, respectively.

The spiropentane derivative of succinimide **3a** was successfully isolated in the individual state by partial crystallization of the reaction mixture from benzene—light petroleum (1 : 2) with the yield of the target product being 52%. According to the ^{1}H NMR spectrum, the filtrate was a mixture of compounds **3a** and **4a** in the ratio 1.4 : 1. Similarly, from the ethereal solution of the reaction mixture obtained on the thermolysis of pyrazoline **2b**, spiropentane **3b** was isolated in 44% yield by cooling down to −20 °C, whereas the mother liquor was a mixture of compounds **3b** and **4b** in the ratio ~4 : 1. The structures of the compounds obtained were established on the basis of the ^{1}H and ^{13}C NMR spectra of individual spiropentanes **3a** and **3b** and their mixtures with the corresponding cyclopropyl-1*H*-pyrrole-2,5-diones **4a** and **4b**. Spiropentanes **3a** and **3b** are characterized by the presence of two muliplets in the region 0.9—1.2 ppm and a singlet at 2.89 or 2.66 ppm, whereas cyclopropyl-1*H*-pyrrole-2,5-diones **4a** and **4b**, by the presence of the signals of equal intensities at 2.0 (CH) and 6.1 ppm (=CH).

Further, we studied the reactivity of 1-phenyl-1*H*-pyrrole-2,5-dione **4a** in the reaction of 1,3-dipolar cycloaddition with diazomethane and diazocyclopropane. The action of ethereal solution of diazomethane (15 °C, 3 days) on the mixture of compounds **3a** and **4a** obtained (ratio 1.4 : 1) leads to a complete transformation of 1*H*-pyrrole-2,5-dione **4a** into 2,3,7-triazabicyclo[3.3.0]-octene-6,8-dione **5** (Scheme 2). In this case, the succinimide fused with the spiropentane fragment remains intact. The addition of CH_2N_2 to the double bond of 1*H*-pyrrole-2,5-dione **4a** proceeds with high selectivity with the cyclopropyl substituent being placed in position 1 of the bicyclic system, which is indicated by the presence of the three-spin system CH_2CH in the ^{1}H NMR spectrum and by position of the quaternary C atom at 103.2 ppm in the ^{13}C NMR spectrum.

Scheme 2

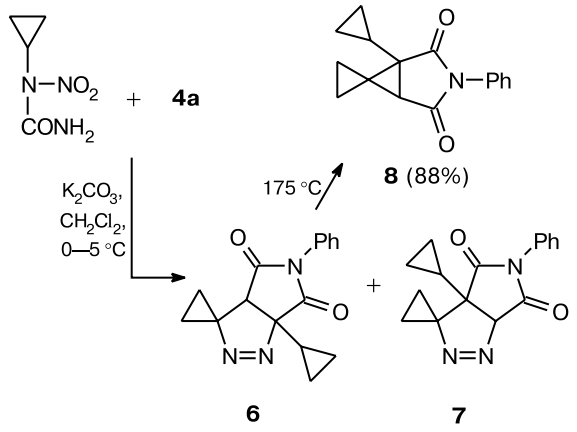


4a **5** (~100%)

In contrast to diazomethane, 1,3-dipolar cycloaddition of diazocyclopropane to the double bond of 1*H*-pyrrole-2,5-dione **4a** proceeds unselectively and leads to a mixture of spiro{2,3,7-triazabicyclo[3.3.0]octene-4,1′-cyclopropanes} **6** and **7** containing the cyclopropyl substituent in positions 1 or 5 of the bicyclic system (Scheme 3). The lack of selectivity of the addition of diazocyclopropane to the unsymmetrically substituted cyclic double bond was observed earlier, for example, during its interaction with 1-methylcyclopropene-3-carboxylate.[12] We used approximately three-fold molar excess of *N*-cyclopropyl-*N*-nitrosourea for the generation of diazocyclopropane and complete conversion of 1*H*-pyrrole-2,5-dione **4a** into adducts **6** and **7**.

Isomer **6** was isolated from the reaction mixture by crystallization from ether, whereas isomer **7** by preparative TLC of the residue left after evaporation of ether.

Scheme 3



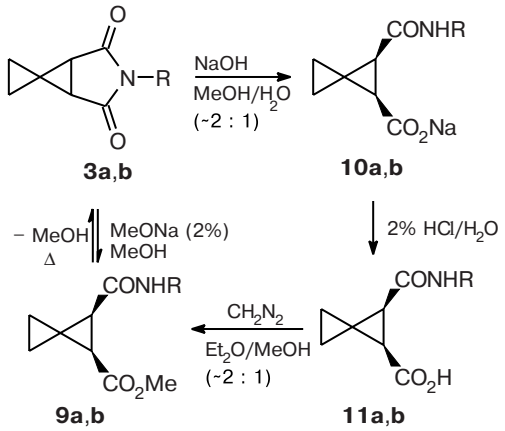
6 : **7** = 1.7 : 1

According to the ^{1}H and ^{13}C NMR spectra, the signals of the angular fragment H—C in isomer **6** have chemical shifts of δ_H 2.48 and δ_C 72.9, whereas in isomer **7**, δ_H 5.40 and δ_C 94.0, that indicates the bonding of this fragment with the C or N atoms of the pyrazoline ring.

In contrast to pyrazoline **2a**, thermal dediazoniation of pyrazoline **6** proceeds with high selectivity and leads to spiropentane **8** (Scheme 3), that is indicated by the only set of signals in the ^{1}H and ^{13}C NMR spectra.

It is known[13] that the fused succinimide ring can be easily opened by the action of bases. Earlier, we have shown[2] that the action of even catalytic amount of NaOH in ethanol on the fused succinimidopyrazolines leads to the succinimide ring opening with the formation of *N*-aryl-6-ethoxycarbonyl-4,5-diazaspiro[2.4]hept-5-ene-7-carboxamides. However, in contrast to succinimidopyrazolines, succinimides with the fused spiropentane fragment turned out to be rather resistant to the action of bases. Thus, the action of sodium methoxide (~2 mol. %) in methanol on compounds **3a** and **3b** at room temperature for 120 h leads to amidoesters of spiropentane-1,2-dicarboxylic acid **9** with conversion of 50% in the case of compound **3a** and ~10% in the case of compound **3b**. Moreover, a reflux of the mixture of compounds **3a** and **9a** formed with evaporation of ethanol leads to a reverse cyclization of amidoester **9a** formed back into the starting spiropentanosuccinimide **3a**. However, the action of NaOH in aq. methanol on succinimides **3** affords the corresponding salts of spiropentanecarboxylic acids **10**, which on acidification with 2% aq. hydrochloric acid are converted into stable amidoacids **11** in 84—87% yield (Scheme 4). The latter upon treatment with ethereal solution of diazomethane are converted into methyl esters **9a** and **9b**, which can partially cyclize into the corresponding succinimides **3a** or **3b**. According to the ^{1}H NMR spectra of the reaction mixtures, the ratio of amidoesters to the corresponding succinimides was ~4 : 1 in the case of phenyl substituent and ~3.3 : 1 in the case of cyclohexyl one.

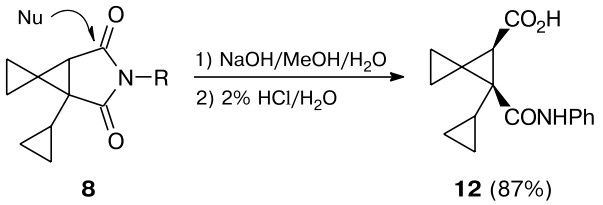
Scheme 4



R = Ph (**a**), *cyclo*-C_6H_{11} (**b**).

Interestingly, the hydrolysis of unsymmetrical spiropentanosuccinimide **8** upon action of NaOH in MeOH—H_2O (~2 : 1) proceeds strictly selectively and after acidification with 2% aq. HCl gives only one regioisomer of amidoacid **12** (Scheme 5). This assignment was made based on the literature data,[14] according to which the C-substituted succinimide ring opening with bases always proceeds by the nucleophilic attack at the sterically less hindered C=O group.

Scheme 5



Thus, the methodology suggested by us for the synthesis of spirocyclopropane-containing pyrazolines fused with a succinimide fragment and their thermal dediazoniation into the corresponding spiropentanes is rather simple and convenient method for the preparation of new polycyclopropane compounds, in particular, *N*-substituted monoamides of *cis*-spiropentane-1,2-dicarboxylic acid as new synthons for the modification of biologically active compounds.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 and 50.3 MHz) and Bruker AM-300 spectrometers (300 and 75.5 MHz, respectively) for solutions in $CDCl_3$ or $(CD_3)_2SO$

containing 0.05% Me_4Si as the internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct inlet). *N*-Cyclopropyl-*N*-nitrosourea,[15] *N*-phenyl- (**1a**)[16] and *N*-cyclohexylmaleimides (**1b**)[17] were obtained according to the described procedures. Thin-layer chromatography was performed on Silica gel 60 plates (Merck) with visualization by iodine vapors. Chromatographic plates (silica gel 60, 0.040—0.063 mm, Merck) with 1.8 mm layer were used for preparative isolations. Solvents of chemically pure grade (>99.6%) were used without additional purification.

Synthesis of 7-arylspiro[2,3,7-triazabicyclo[3.3.0]oct-2-ene-4,1′-cyclopropane]-6,8-diones (2a,b) (general procedure). Potassium carbonate (4.61 g, ~26 mmol) containing ~20% H_2O, or Cs_2CO_3 (8.47 g, ~26 mmol) was added to a mixture of maleimide **1a** (1.91 g, 11 mmol) or **1b** (1.97 g, 11 mmol) and *N*-cyclopropyl-*N*-nitrosourea (2.16 g, 16 mmol) in CH_2Cl_2 (30 mL) at 5—7 °C and this was vigorously stirred at this temperature for 160—180 or 30 min, respectively. Then the reaction mixture was filtered and washed with CH_2Cl_2, the solvent was evaporated *in vacuo* and pyrazolines **2a**,**b** were obtained by recrystallization of the residue from benzene.

Compound **2a**, the yield was 70%, m.p. 155—156 °C. Found (%): C, 64.98; H, 4.79; N, 17.21; $C_{13}H_{11}N_3O_2$. Calculated (%): C, 64.72; H, 4.60; N, 17.42. Partial MS, *m/z* (I_{rel} (%)): 241 (1) $[M]^+$, 213 (7) $[M - N_2]^+$, 185 (11), 184 (14), 94 (32), 66 (100). ^{1}H NMR ($CDCl_3$), δ: 1.44, 1.92 (both m, 1+3 H, CH_2CH_2); 3.16 (d, 1 H, H(5), ^3J = 8.4 Hz); 6.04 (d, 1 H, H(1), ^3J = 8.4 Hz); 7.23, 7.45 (both m, 2+3 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 11.3, 16.8 (CH_2CH_2); 41.6 (C(5)); 73.7 (C(4)); 91.7 (C(1)); 126.3 (*o*-C); 128.4 (*ipso*-C); 129.1 (*p*-C); 129.3 (*m*-C); 168.7 and 173.6 (2 CO).

Compound **2b**, the yield was 62%, m.p. 161—163 °C. Found (%): C, 63.43; H, 7.11; N, 16.70. $C_{13}H_{17}N_3O_2$. Calculated (%): C, 63.14; H, 6.93; N, 16.99. Partial MS, *m/z* (I_{rel} (%)): 137 (52) $[M - N_2 - C_6H_{10}]^+$, 109 (31), 94 (35), 66 (100). ^{1}H NMR ($CDCl_3$), δ: 1.15—2.20 (m, 14 H, 7 CH_2); 2.91 (d, 1 H, H(5), ^3J = 8.4 Hz); 3.89 (tt, 1 H, N(7)—CH, ^3J = 3.7 Hz, ^3J = 12.0 Hz); 5.83 (d, 1 H, H(1), ^3J = 8.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 10.9, 16.5 (C(2′), C(3′)); 24.9, 25.7, 28.6, 28.7 (1+2+1+1 CH_2); 41.1 (C(5)); 52.1 (N(7)—CH); 73.2 (C(4)); 91.4 (C(1)); 169.8, 174.5 (2 CO).

Thermolysis of bicyclic pyrazoline 2a. A solution of pyrazoline **2a** (0.96 g, 4 mmol) in *o*-dichlorobenzene (5 mL) was heated at 180 °C until the gas evolution was stopped (~10 h). Then, the solvent was evaporated *in vacuo* at 0.2 Torr. According to the ^{1}H and ^{13}C NMR spectra, the residue contained two compounds: 3-phenylspiro[3-azabicyclo[3.1.0]hexane-6,1′-cyclopropane]-2.4-dione (**3a**) and 3-cyclopropyl-1-phenyl-1*H*-pyrrole-2,5-dione (**4a**) in the ratio ~4 : 1. Individual compound **3a** (0.44 g, 52%) was isolated as yellow crystals by recrystallization from benzene—light petroleum (1 : 2), m.p. 111—112 °C. Found (%): C, 73.49; H, 5.35; N, 6.50. $C_{13}H_{11}NO_2$. Calculated (%): C, 73.23; H, 5.20; N, 6.57. Partial MS (EI), *m/z* (I_{rel} (%)): 213 (78) $[M]^+$, 184 (32), 156 (33), 94 (66), 66 (100). ^{1}H NMR ($CDCl_3$), δ: 1.12, 1.21 (both m, 2 H each, CH_2CH_2); 2.89 (s, 2 H, CHCH); 7.21, 7.38, 7.46 (all m, 2+1+2 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 2.6, 6.9 (CH_2CH_2); 26.1 (2 CH); 30.2 (C(6)); 126.8 (*o*-C); 128.5 (*p*-C); 129.2 (*m*-C); 131.8 (*ipso*-C); 174.1 (2 CO). According to the ^{1}H NMR spectrum, the filtrate left after evaporation of the solvent contained a mixture of compounds **3a** and **4a** in the ratio 1.4 : 1. ^{1}H NMR ($CDCl_3$), δ: compound **4a**: 1.08 (m, 4 H, CH_2CH_2); 1.96 (m, 1 H, CH); 6.14 (s, 1 H, =CH); 7.20—7.50 (m, Ph). ^{13}C NMR ($CDCl_3$), δ: 8.4 (CH); 12.0 (CH_2CH_2); 120.7 (C(4)); 126.0 (*o*-C); 127.6 (*p*-C); 128.6 (*m*-C); 131.6 (*ipso*-C); 153.5 C(3); 169.2, 169.7 (2 CO).

Thermolysis of bicyclic pyrazoline 2b. A solution of pyrazoline **2b** (0.99 g, 4 mmol) in *o*-dichlorobenzene (5 mL) was heated at 180 °C until the gas evolution was stopped (~16 h). Then, the solvent was evaporated *in vacuo* at 0.2 Torr. According to the ^{1}H and ^{13}C NMR spectra, the residue contained two compounds: 3-cyclohexylspiro[3-azabicyclo[3.1.0]hexane-6,1′-cyclopropane]-2.4-dione (**3b**) and 1-cyclohexyl-3-cyclopropyl-1*H*-pyrrole-2,5-dione (**4b**) in the ratio ~8 : 1. Individual compound **3b** (0.39 g, 44%) was isolated as yellow crystals by recrystallization from ether upon cooling to −20 °C, m.p. 107—109 °C. Found (%): C, 71.51; H, 8.00; N, 6.31. $C_{13}H_{17}NO_2$. Calculated (%): C, 71.21; H, 7.81; N, 6.39. Partial MS (EI), *m/z* (I_{rel} (%)): 219 (12) $[M]^+$, 138 (100), 120 (3). ^{1}H NMR ($CDCl_3$), δ: 0.94, 1.14 (both m, 2 H each, CH_2CH_2); 1.2—2.1 (m, 10 H, 5 CH_2); 2.66 (s, 2 H, CHCH); 3.81 (tt, 1 H, N—CH, ^3J = 3.7 Hz, ^3J = 11.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 2.3, 7.0 (CH_2CH_2); 25.0, 25.6, 25.9 (1+2+2 CH_2); 29.1 (2 CH); 30.4 (C(6)); 51.3 (NCH); 175.3 (2 CO). According to the ^{1}H NMR spectrum, the filtrate left after evaporation of the solvent contained a mixture of compounds **3b** and **4b** in the ratio ~4 : 1. ^{1}H NMR ($CDCl_3$), δ: compound **4b**: 5.89 (s, =CH), other signals are overlapped with the signals of compound **3b**.

1-Cyclopropyl-7-phenyl-2,3,7-triazabicyclo[3.3.0]oct-2-ene-6,8-dione (5). An ethereal solution of diazomethane (0.5 *M*, 3 mL) was added to a mixture of isomers **3a** and **4a** (0.092 g, the ratio was ~1.4 : 1, which corresponded to ~0.18 mmol of **4a**) in CH_2Cl_2 (5 mL) and this was kept for 3 days at 15 °C. The solvent was evaporated *in vacuo* and the residue was first crystallized from benzene to remove the greater portion of compound **3a** and then it was purified by preparative TLC on silica gel (eluent, ether) to obtain pyrazoline **5** (0.039 g, 85 %). Partial MS (EI), *m/z* (I_{rel} (%)): 255 (2) $[M]^+$, 227 (5), 199 (6), 91 (20), 79 (100). ^{1}H NMR ($CDCl_3$), δ: 0.46, 0.76 (both m, 2 H each, CH_2CH_2); 1.90 (m, 1 H, CH); 2.78 (dd, 1 H, J = 2.9 Hz, J = 9.9 Hz, H(5)); 4.83 (dd, 1 H, H_a(4), J = 9.9 Hz, ^2J = 19.0 Hz); 5.13 (dd, 1 H, H_b(4), J = 2.9 Hz, J_1 = 19.0 Hz); 7.23, 7.44 (both m, 2+3 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 1.4, 1.5 (CH_2CH_2); 13.0 (CH); 40.1 (C(5)); 80.9 (C(4)); 103.2 (C(1)); 126.3 (*o*-C); 129.0 (*p*-C); 129.1 (*m*-C); 130.9 (*ipso*-C); 170.9, 174.2 (2 CO).

1-Cyclopropyl- (6) and 5-cyclopropyl-7-phenylspiro[2,3,7-triazabicyclo[3.3.0]oct-2-ene-4,1′-cyclopropane]-6,8-dione (7). *N*-Cyclopropyl-*N*-nitrosourea (0.13 g, 1.0 mmol) and cesium carbonate (0.70 g, ~2 mmol) were added to a mixture of isomers **3a** and **4a** (0.21 g, the ratio was ~1.4 : 1 which corresponded to ~0.41 mmol of **4a**) in CH_2Cl_2 (10 mL) at 5—7 °C and the mixture was stirred for 40 min at this temperature. The reaction mixture was filtered and the solvent was evaporated *in vacuo*. According to the ^{1}H NMR spectrum, the residue was a mixture of starting compound **3a** and isomeric pyrazolines **6** and **7** in the molar ratio ~3.8 : 1.7 : 1, respectively. Individual pyrazoline **6** (72 mg, 60%) was isolated as colorless crystals by recrystallization from ether, m.p. 199—201 °C. Found (%): C, 68.11; H, 5.15; N, 14.71. $C_{16}H_{15}N_3O_2$. Calculated (%): C, 68.31; H, 5.37; N, 14.94. Partial MS, *m/z* (I_{rel} (%)): 253 (2) $[M - N_2]^+$, 224 (4), 119 (30), 106 (48), 91 (100), 77 (74). ^{1}H NMR ($CDCl_3$), δ: 0.49, 0.78 (both m, 2 H each, CH_2CH_2); 1.31 (m, 1 H, CH); 1.83—2.04

(m, 4 H, CH_2CH_2); 2.48 (s, 1 H, H(5)); 7.23 and 7.43 (both m, 2+3 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 1.3, 1.4 (CH_2CH_2); 11.4, 16.7 (C(2′) and C(3′)); 13.2 (CH); 44.2 (C(5)); 72.9 (C(4)); 101.9 (C(1)); 126.3 (*o*-C); 129.0 (*p*-C); 129.3 (*m*-C); 131.0 (*ipso*-C); 171.2, 173.1 (2 CO). The filtrate left after isolation of pyrazoline **6** was concentrated and the residue was separated by TLC on silica gel (eluent, ether) to obtain pyrazoline **7** (0.026 g, 22%) as yellowish fusible crystals, $R_f = 0.74$. Partial MS, *m/z* (I_{rel} (%)): 253 (2) $[M - N_2]^+$, 224 (12), 212 (9), 91 (100), 77 (56). ^{1}H NMR ($CDCl_3$), δ: 0.16, 0.57, 0.64 (all m, 1+1+2 H, CH_2CH_2); 1.09 (m, 1 H, CH); 1.67—2.01 (m, 4 H, CH_2CH_2); 5.40 (s, 1 H, H(1)); 7.24, 7.44 (both m, 2+3 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 1.0, 1.8 (CH_2CH_2); 12.3 (CH); 12.4, 13.3 (CH_2CH_2); 49.3 (C(5)); 77.3 (C(4)); 94.0 (C(1)); 126.3 (*o*-C); 129.1 (*p*-C); 129.3 (*m*-C); 131.0 (*ipso*-C); 168.0, 175.1 (2 CO).

1-Cyclopropyl-3-phenyl-3-azaspiro[bicyclo[3.1.0]hexane-6,1′-cyclopropane]-2,4-dione (8). A solution of pyrazoline **6** (0.034 g, 0.12 mmol) in *o*-dichlorobenzene (5 mL) was heated at 175 °C for 10 h until the gas evolution was stopped. Then, the solvent was evaporated *in vacuo* at 0.2 Torr, the residue was treated with benzene—light petroleum (1 : 1) and filtered through a short layer of silica gel. The filtrate was concentrated *in vacuo* to obtained compound **8** (0.027 g, 88%) as beige crystals, m.p. 127—129 °C. Found (%): C, 75.44; H, 5.54; N, 5.62. $C_{16}H_{15}NO_2$. Calculated (%):C, 75.87; H, 5.97; N, 5.53. Partial MS (EI), *m/z* (I_{rel} (%)): 253 (8) $[M]^+$, 225 (12), 133 (17), 91 (100). ^{1}H NMR ($CDCl_3$), δ: 0.23, 0.49, 0.69 (all m, 1+1+2 H, CH_2CH_2); 1.07, 1.20 (both m, 2 H each, CH_2CH_2); 1.45 (m, 1 H, CH); 2.41 (s, 1 H, H(5)); 7.22, 7.40 (both m, 2+3 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 2.6, 2.8 (CH_2CH_2); 3.0, 5.9 (CH_2CH_2); 28.3 (C(1)); 29.7 (C(6)); 34.2 (C(5)); 126.8 (*o*-C); 128.4 (*p*-C); 129.1 (*m*-C); 132.0 (*ipso*-C); 174.0, 175.9 (2 CO).

2-(*N*-Phenylcarbamoyl)spiropentane-1-carboxylic acid (11a). A solution of NaOH (1 *N,* 0.9 mL) was added to a solution of compound **3a** (0.192 g, 0.9 mmol) in methanol (2 mL) and this was stirred for 16 h at 20 °C. Then, methanol was evaporated, the aqueous solution was acidified with 2% aq. hydrochloric acid and extracted with chloroform (7 mL). The organic layer was dried with anhydrous Na_2SO_4, the solvent was evaporated *in vacuo* to obtained amidoacid **11a** (0.181 g, 87%) as colorless crystals, m.p. 164—166 °C. Found (%): C, 67.77; H, 5.79; N, 6.33. $C_{13}H_{13}NO_3$. Calculated (%):C, 67.52; H, 5.67; N, 6.06. Partial MS (EI), *m/z* (I_{rel} (%)): 231 (7) $[M]^+$, 186 (4) $[M - CO_2H]^+$, 93 (100). ^{1}H NMR (DMSO-d_6), δ: 0.95, 1.11 (both m, CH_2CH_2); 2.39, 2.56 (both d, 1 H each, H(1), H(2), $^3J = 8.3$ Hz); 7.03, 7.28, 7.55 (all m, 1+2+2 H, Ph); 10.05 (s, 1 H, NH); 12.25 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 3.6, 5.8 (CH_2CH_2); 20.1 (C(3)); 26.1, 27.6 (C(1) and C(2)); 118.7 (*o*-C); 122.7 (*p*-C); 127.8 (*m*-C); 138.5 (*ipso*-C); 167.2, 170.5 (2 CO).

2-(*N*-Cyclohexylcarbamoyl)spiropentane-1-carboxylic acid (11b) was synthesized similarly from compound **3b** (0.11 g, 0.5 mmol) and the NaOH solution (1 *N,* 0.5 mL). After acidification with HCl, amidoacid **11b** (0.10 g, 84%) was obtained as beige crystals, m.p. 144—146 °C. Partial MS (EI), *m/z* (I_{rel} (%)): 237 (3) $[M]^+$, 192 (10) $[M - CO_2H]^+$, 139 (15), 138 (16), 41 (100). ^{1}H NMR ($CDCl_3$), δ: 1.03—1.44 (m, 10 H, CH_2CH_2, 3 CH_2 cyclohexyl); 1.56—1.97 (m, 4 H, 2 CH_2 cyclohexyl); 2.45, 2.49 (both d, 1 H each, H(1), H(2), $^3J = 7.8$ Hz); 3.75 (m, 1 H, NCH); 7.51 (d, 1 H, NH, $J = 8.0$ Hz); 13.8 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 5.4, 8.6 (C(4) and C(5)); 23.9 (C(3)); 24.8 (2 CH_2); 25.4 (CH_2); 29.0, 30.7 (C(1) and C(2)); 32.6, 32.7 (2 CH_2); 49.7 (NCH); 172.4, 173.5 (2 CO).

1-Methoxycarbonyl-2-(phenylcarbamoyl)spiropentane (9a). An ethereal solution of diazomethane (0.5 *M,* 1 mL) was added dropwise to a solution of amidoacid **11a** (0.015 g, 0.06 mmol) in methanol (0.5 mL) at room temperature until persistent yellow color was present and evolution of the gas was stopped. Then, the mixture was kept for 2 h and the solvent was evaporated *in vacuo* to obtain 0.016 g of the reaction mixture, which, according to the ^{1}H NMR spectrum, contained ~80% of methyl spiropentanecarboxylate **9a** and ~20% spiropentanosuccinimide **3a**. Attempts to isolate amidoester **9a** was accompanied by its cyclization into succinimide **3a**. Partial MS (EI), *m/z* (I_{rel} (%)): 245 (52) $[M]^+$, 213 (24) $[M - MeOH]^+$, 153 (67), 93 (100). ^{1}H NMR ($CDCl_3$), δ (after the signals of compound **3a** were subtracted): 1.14, 1.28 (both m, 2 H each, CH_2CH_2); 2.50, 2.62 (both d, 1 H each, H(1) and H(2), $^3J = 8.3$ Hz); 3.73 (s, 3 H, OMe); 7.08, 7.29, 7.54 (all m, 1+2+2 H, Ph), 8.89 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 5.2, 8.3 (CH_2CH_2); 22.5 (C(3)); 27.1, 32.2 (C(1), C(2)); 52.6 (OMe); 120.0 (*o*-C); 124.1 (*p*-C); 129.0 (*m*-C); 138.1 (*ipso*-C); 167.8 (COO); 172.8 (CONH).

2-(Cyclohexylcarbamoyl)-1-methoxycarbonylspiropentane (9b) was synthesized similarly from amidoacid **11b** (0.014 g, 0.06 mmol) and an ethereal solution of diazomethane. According to the ^{1}H NMR spectrum, the reaction mixture (0.015 g) contained ~78% of methyl spiropentanecarboxylate **9b** and ~22% spiropentanosuccinimide **3b**. Partial MS (EI), *m/z* (I_{rel} (%)): 251 (7) $[M]^+$, 192 (12), 138 (100). ^{1}H NMR ($CDCl_3$), δ: 1.02—1.48 (m, 10 H, CH_2CH_2 and 3 CH_2 cyclohexyl); 1.52—1.94 (m, 4 H, 2 CH_2 cyclohexyl); 2.41, 2.49 (both d, 1 H each, H(1) and H(2), $^3J = 8.0$ Hz); 3.73 (s, 3 H, OMe); 3.75 (m, 1 H, NCH); 6.59 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 4.9, 7.9 (C(4) and C(5)); 21.4 (C(3)); 24.6, 25.6 (CH_2 cyclohexyl); 26.5, 30.9 (C(1) and C(2)); 29.1, 32.7, 33.1 (CH_2 cyclohexyl); 48.0 (NCH); 52.1 (OMe); 168.1 (COO); 172.0 (CONH).

2-(Phenylcarbamoyl)-1-cyclopropylspiropentane-1-carboxylic acid (12). A solution of NaOH (0.2 *N,* 0.3 mL) was added to a solution of compound **8** (0.015 g, 0.06 mmol) in methanol (0.3 mL) and this was kept for 16 h at 20 °C. Then, methanol was evaporated *in vacuo*, the reaction mixture was acidified with 2% aq. hydrochloric acid and extracted with chloroform (1 mL). The organic layer was dried with anhydrous Na_2SO_4, the solvent was evaporated *in vacuo*, the reaction mixture was treated with ether to obtain amidoacid **12** (0.014 g, 87%) as colorless crystals, m.p. 171—173 °C. Partial MS (EI), *m/z* (I_{rel} (%)): 271 (2) $[M]^+$, 226 (8) $[M - CO_2H]^+$, 93 (100), 77 (43). ^{1}H NMR ($CDCl_3$), δ: 0.38, 0.74, 0.89, 1.18 (all m, 1+2+1+4 H, 2 CH_2CH_2); 1.58 (m, 1 H, CH); 2.59 (s, 1 H, H(1)); 7.21, 7.38, 7.51 (all m, 1+2+2 H, Ph); 8.61 (s, 1 H, NH); 13.2 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 2.8, 4.7, 5.2, 7.7 (2 CH_2CH_2); 14.0 (CH); 27.4 (C(3)); 29.8 (C(2)); 37.3 (C(1)); 121.0 (*o*-C); 126.0 (*p*-C); 129.3 (*m*-C); 136.3 (*ipso*-C); 167.7 (COOH); 171.8 (CONH).

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