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Synthesis and Structure of *N*-Substituted Aryl(hetaryl)spiropyrrolidones

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Abstract—4,4'-Diaryl-3,3'-spirobi[2-pyrrolidones] were synthesized by hydrogenation of *N*-substituted 3-methoxycarbonyl-3-(2-nitro-1-arylethyl)-4-phenyl-2-pyrrolidones followed by intramolecular heterocyclization. Structure of the compounds obtained was determined by IR, ^{1}H, and COSY NMR spectroscopy.

Keywords: 2-pyrrolidone, spirobi[2-pyrrolidone], catalytic hydrogenation, heterocyclization

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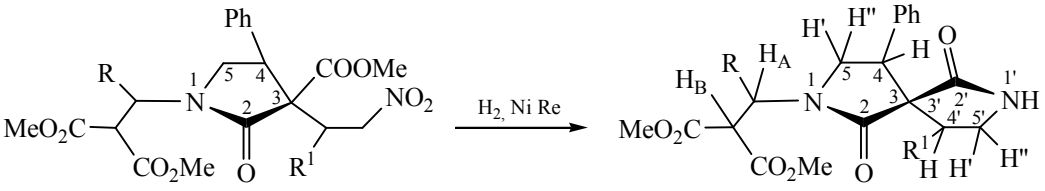
Spiro-fused heterocycles containing lactam ring are of particular interest, as many of them contain pharmacophore groups. For example, spiroheterocycles are components of antihypertensive agents (irbesartan), antihistamines, and anti-inflammatory drugs (fenspiride), antihypertensive and cardioprotective agents (spirapril), etc. [1]. 2-Pyrrolidone-containing medications are widely used [2]. They include nootropic agent *N*-carbamoylmethyl-2-pyrrolidinone (piracetam), a phenyl analog Carphedon [3, 4], which has antihypertensive and nootropic activity, and polyvinylpyrrolidones, used as blood plasma expanders (Gemodez, Enterodesum, Neogemodez) [1].

A convenient approach to the synthesis of 3,3-spiropyrrolidones is based on electrolytic reduction of nitroethylpyrrolidonecarboxylates [5].

Further developing our previous studies on the synthesis of spiropyrrolidones [5–8], we performed hydrogenation of individual diastereomers of nitroethylpyrrolidonecarboxylates **I–V** in the presence of Raney nickel catalyst at atmospheric pressure and at a temperature of 18–20°C. The starting materials **I–V** have been obtained previously by condensation of 1-[1-aryl(hetaryl)-2,2-dimethoxycarbonylethyl]-3-methoxycarbonyl-4-phenyl-2-pyrrolidones with aryl(hetaryl)nitroethenes [6, 7].

Reduction of **I–V** was accompanied by intramolecular acylation of the initially formed amino group and led to the formation of new diastereohomogeneous 4,4'-diaryl-1-[2,2-dimethoxycarbonyl-1-aryl(pyridyl-3)-ethyl]-3,3'-spirobi[2-pyrrolidones] **VI–X** in good to excellent yields (68–96%) (Scheme 1).

Scheme 1.



I–V **VI–X**

R = C_6H_5: R^1 = C_6H_5 (**I, VI**), 4-MeC_6H_4 (**II, VII**); R = 4-ClC_6H_4: R^1 = C_6H_5 (**III, VIII**), 4-ClC_6H_4 (**IV, IX**); R = pyridyl-3, R^1 = 4-MeC_6H_4 (**V, X**).

Parameters of IR and ^{1}H NMR spectra of compounds **VI–X**

Comp. no.	ν, cm^{-1} ($CHCl_3$)			δ, ppm							*J*, Hz
	NH	C=O	CO_2Me	Ar (Py) [Me]	$C^5H'H''$ ($C^{5'}H'H''$)	C^4H ($C^{4'}H$)	H_A	H_B	NH	Me	J_{AB}
VI	3430	1700	1750	7.03–7.41	3.05, 3.77 (3.14, 3.38)	3.11 (4.55)	5.94	4.69	5.37	3.59 3.91	12.21
VII	3430	1700	1750	7.02–7.34 [2.38]	3.00, 3.77 (3.11, 3.35)	3.11 (4.56)	5.90	4.68	5.40	3.55 3.88	12.21
VIII	3400	1695	1750	7.05–7.40	3.06, 3.80 (3.12, 3.36)	3.10 (4.54)	5.88	4.67	5.46	3.60 3.88	12.21
IX	3400	1695	1750	7.00–7.35	3.06, 3.78 (3.14, 3.34)	3.11 (4.56)	5.71	4.59	5.40	3.57 3.85	12.21
X	3445	1700	1750	7.03–7.25 (8.70, 8.84) [2.38]	3.02, 4.00 (3.39, 3.49)	3.36 (4.64)	5.71	4.63	5.46	3.60 3.77	12.21

The obtained compounds **VI–X** were stable colorless crystalline solids. Their structure was confirmed by IR and ^{1}H NMR spectroscopy methods (see the table).

In the IR spectra of 3,3'-spirobi[2-pyrrolidones] **VI–X** there are strong absorption of the ester (1750 cm^{-1}) and lactam (1695–1700 cm^{-1}) carbonyl groups (see Table). The ^{1}H NMR spectra of these compounds contain one set of the proton signals that confirms the diastereohomogeneity of the compounds obtained. For example, in the spectrum of **VI** the methine protons H_A and H_B appear as doublet signals at 5.94 and 4.69 ppm. The multiplets at 3.11 and 4.55 ppm correspond to the protons C^4H and $C^{4'}H$ of the pyrrolidone rings. The methylene protons resonate at 3.05 and 3.77 ppm (C^5H_2), 3.14 and 3.38 ppm ($C^{5'}H_2$) (Fig. 1).

The validity of the signal assignment of methine and methylene protons in the spectra of **VI–X** was confirmed by 2D NMR spectroscopy [9–11]. In the COSY spectrum (Fig. 2) of **VI** there is correlation between the protons of unsubstituted [NH (5.37 ppm) and $C^{5'}H''$ (3.38 ppm), $C^{5'}H''$ (3.38 ppm) and $C^{5'}H'$ (3.14 ppm), $C^{5'}H''$ (3.38 ppm) and $C^{4'}H$ (4.55 ppm)] and *N*-substituted [C^5H'' (3.77 ppm) and C^5H' (3.05 ppm), C^5H'' (3.77 ppm) and C^4H (3.11 ppm), C^5H' (3.05 ppm) and C^4H (3.11 ppm)] pyrrolidone rings (Scheme 2).

In summary, catalytic hydrogenation of *N*-dimethoxycarbonylethyl-3-nitroethyl-substituted pyrrolidonecarboxylates afforded new *N*-dimethoxycarbonylethyl-3,3'-spiropyrrolidones. The latter are of interest as potentially biologically active compounds, and are valuable precursors for the synthesis of new derivatives of γ-aminobutyric acid and piracetam spiroanalogs.

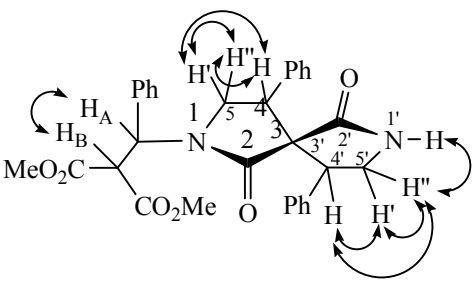
EXPERIMENTAL

The ^{1}H and ^{1}H–^{1}H COSY NMR spectra were recorded on a Jeol ECX400A spectrometer (399.78 MHz) in chloroform-d_1 relative to the residual proton signal of the solvent. The IR spectra were obtained on a Shimadzu IRPrestige-21 FTIR spectrometer in chloroform (40 mg mL^{-1}). Elemental analysis was performed on a EuroVector EA 3000 analyzer (CHN Dual mode). Melting points were determined on a PTP (M) instrument.

Compounds **I–V** were obtained as described in [7].

4,4'-Diphenyl-1-[2,2-dimethoxycarbonyl-1-phenylethyl]-3,3'-spirobi[2-pyrrolidone] (VI). A suspen-

Scheme 2.



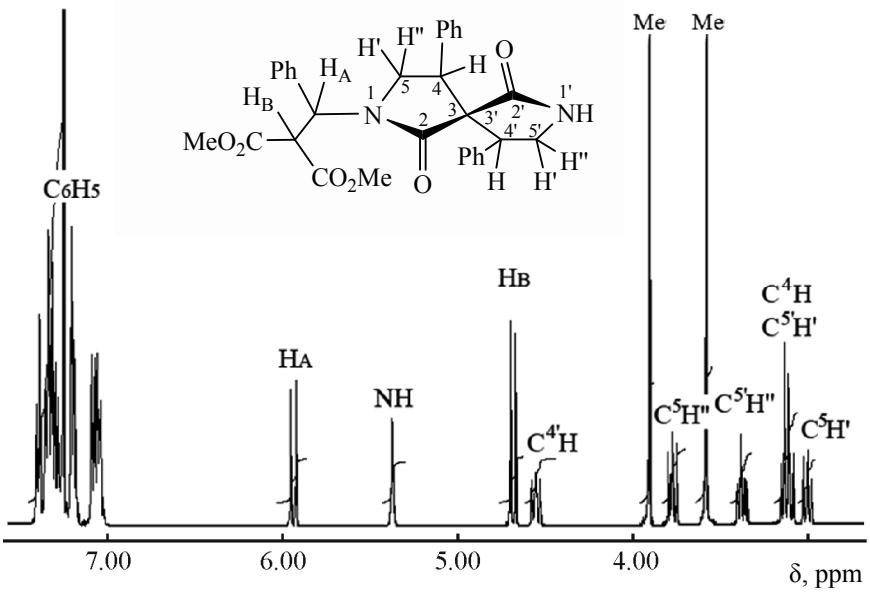


Fig. 1. ^{1}H NMR spectrum of compound **VI** in $CDCl_3$.

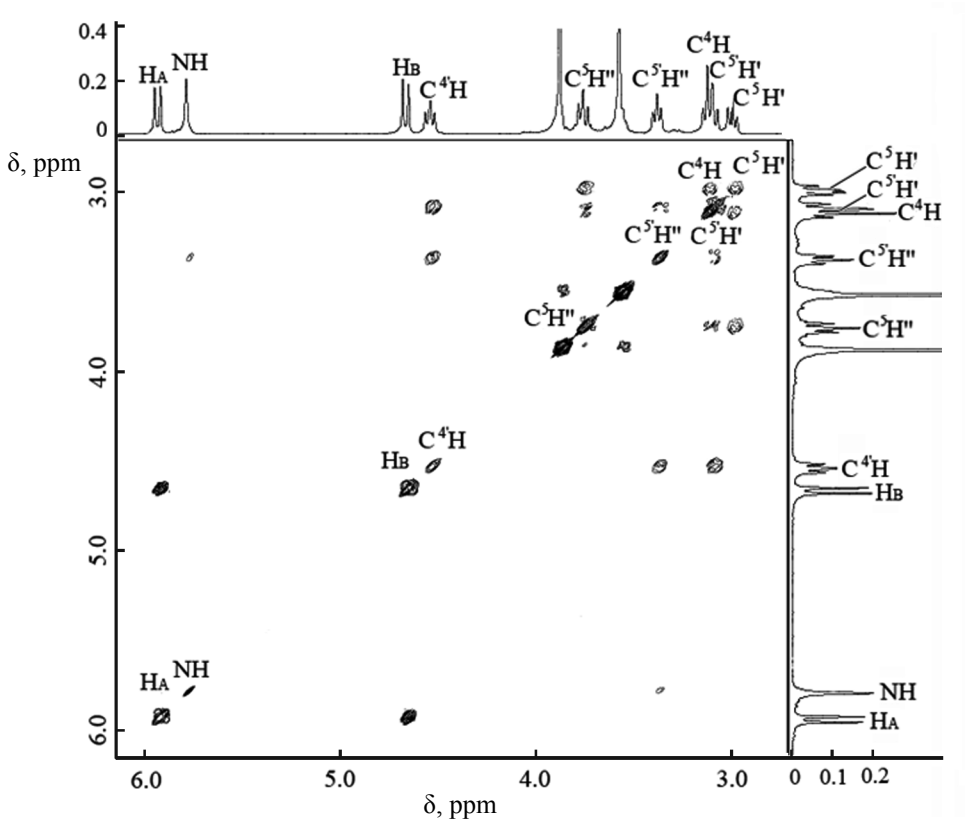


Fig. 2. Fragment of ^{1}H–^{1}H COSY NMR spectrum of compound **VI** in $CDCl_3$.

sion of 1.2 g of Raney nickel in 7 mL of methanol was saturated with electrochemically generated hydrogen. Then, to the reaction mixture was added 1.86 g (0.003 mol) of 1-(2,2-dimethoxycarbonyl-1-phenylethyl)-3-methoxycarbonyl-3-(2-nitro-1-phenylethyl)-4-phenyl-2-pyrrolidone **I** in a mixture of 50 mL of methanol and 5 mL of acetone, and the mixture was hydrogenated until the calculated amount of hydrogen was consumed

[0.202 L (0.009 mol)]. The catalyst was separated and washed on a filter with boiling ethanol (3 × 100 mL). The filtrate was evaporated under reduced pressure (15–20 mmHg) to 2/3 of the original volume. The precipitated crystalline product was filtered off. Yield 1.45 g (87%), mp 100–102°C (methanol). Found, %: C 70.21; H 5.60; N 4.98. $C_{31}H_{31}N_2O_6$. Calculated, %: C 70.59; H 5.88; N 5.31.

Compounds **VII**–**X** were prepared similarly.

4'-(4-Methylphenyl)-4-phenyl-1-[2,2-dimethoxycarbonyl-1-phenylethyl]-3,3'-spirobi[2-pyrrolidone] (VII). Yield 2.00 g (96%), mp 87–89°C (methanol). Found N, %: 4.70. $C_{32}H_{32}N_2O_6$. Calculated N, %: 5.19.

4,4'-Diphenyl-1-[2,2-dimethoxycarbonyl-1-(4-chlorophenyl)ethyl]-3,3'-spirobi[2-pyrrolidone] (VIII). Yield 0.27 g (86%), mp 105–107°C (methanol). Found N, %: 5.00. $C_{31}H_{29}N_2O_6$. Calculated N, %: 5.33.

4-Phenyl-4'-(4-chlorophenyl)-1-[2,2-dimethoxycarbonyl-1-(4-chlorophenyl)ethyl]-3,3'-spirobi[2-pyrrolidone] (IX). Yield 0.8 g (68%), mp 88–100°C (methanol). Found N, %: 4.70. $C_{31}H_{28}N_2O_6Cl_2$. Calculated N, %: 4.71.

4'-(4-Methylphenyl)-4-phenyl-1-[2,2-dimethoxycarbonyl-1-(pyridyl-3)ethyl]-3,3'-spirobi[2-pyrrolidone] (X). Yield 0.6 g (92%), mp 108–110°C (Et_2O). Found N, %: 8.05. $C_{31}H_{31}N_3O_6$. Calculated N, %: 7.76.

^{1}H NMR and IR spectra were measured at the Center for Joint Use, Herzen State Pedagogical University of Russia.

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