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Reaction of Methyl 1-Bromocyclohexanecarboxylate with Zinc and 3-Aryl-2-cyanopropenoic Acids Amides

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Abstract—Methyl 1-bromocyclohexanecarboxylate reacts with zinc and amides or methylamides of 3-aryl-2-cyanopropenoic acids to give 5-aryl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitriles or 5-aryl-2-methyl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitriles.

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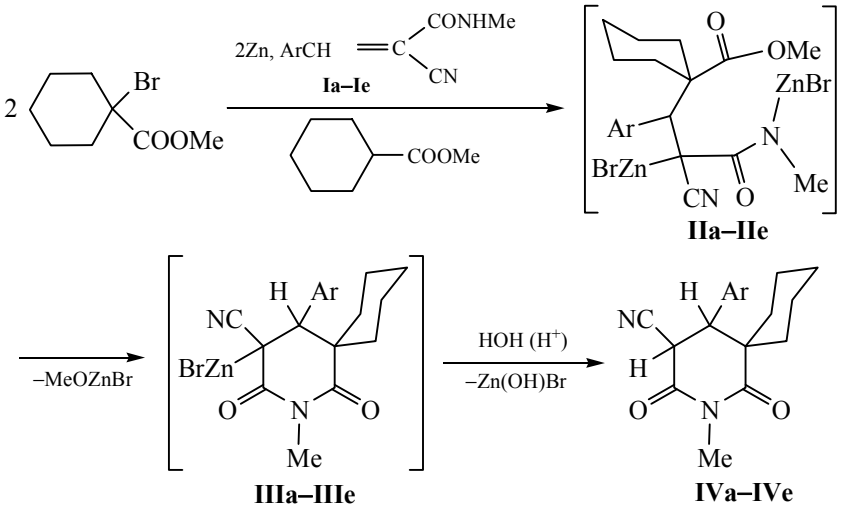
The Reformatsky reagents have been found to attach to the double bond of 3-aryl-2-cyanopropenoic acids amides followed by the intermediates cyclization to form the substituted piperidine-2,6-diones [1–3]. In order to obtain the similar compounds involving the spiro-carbon atom we studied the reaction of the Reformatsky reagent derived from methyl 1-bromocyclohexanecarboxylate and zinc with amides and methylamides of 3-aryl-2-cyanopropenoic acid.

According to our research, at the heating in a benzene–ethyl acetate–HMPA mixture, the double bond of methylamides **Ia**–**Ie** attaches the Reformatsky reagent to yield the intermediates **IIa**–**IIe**. The latter are cyclized into the intermediate compounds **IIIa**–**IIIe** by the nucleophilic attack of the amide nitrogen atom on the carbonyl carbon atom of the ester group. After the reaction mixture decomposing, we isolated the substituted spiropiperidin-2,6-diones, namely 5-aryl-2-methyl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitriles **IVa**–**IVe**.

The composition and structure of compounds **IVa**–**IVe** were confirmed by the elemental analysis, IR and ^{1}H NMR spectroscopy. In the IR spectra of compounds **IVa**–**IVe** there are the absorption bands in the ranges



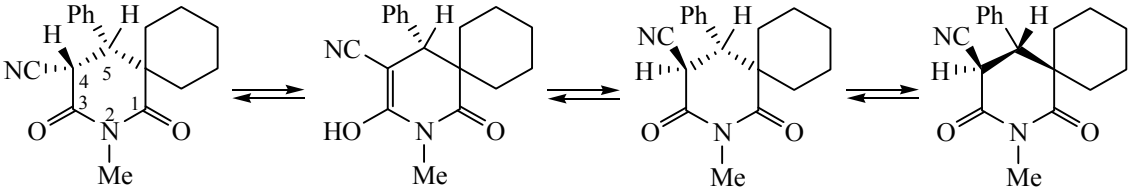
I–IV, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 3,4-$(MeO)_2C_6H_3$ (**e**).

of 1660–1680 and 1710–1725 cm^{-1}, belonging to the carbonyl groups of the imide fragment. Occurrence of only one set of signals in the ^1H NMR spectra ($CDCl_3$) indicates that the compounds **IVa**–**IVe** are isolated as one diastereomer. The most characteristic signals in the ^1H NMR spectra are the doublets of the protons at the $C^{4,5}$ atoms in the regions of the 3.54–3.64 and 4.16–4.52 ppm (J 5.7 Hz). It is noteworthy that the proton signals of the $C^{2,6}$ atoms of aromatic ring are broadened, probably due to the hindered internal rotation around the C–Ar bond. In the ^1H NMR spectrum of compound **IVc** recorded at 50°C this broad signal is converted into a doublet. However, at this temperature a second set of signals manifests the presence of a second isomer appearing probably owing to the piperidine ring inversion.

In the ^1H NMR spectra of the synthesized compounds dissolved in DMSO-d_6 there are two sets of signals, explainable by the appearance of the second isomer characterized by the coupling of the protons at the C^4 and C^5 atoms (doublets) with the constant equal to 12.9 Hz.

In order to explain these results, we calculated *ab initio* the geometric characteristics and the total energies (E_{tot}, a.u.) of various forms of compound **IVa** using the SCF MO LCAO method in the 6-31G(d) basis. As can be seen from a comparison of the calculated total energies, there is the most stable **A** form of the compound, in which the chiral centers, the C^4 and C^5 atoms, are *S*/*R*- and *R*/*S*-configured, respectively. The piperidine ring is a flattened *chair*, and the C^5–H bond has an equatorial orientation. The calculated dihedral angle HC^4C^5H equals to 52.6°. The $J_{HC^4C^5H}$ coupling constant value was evaluated by us according to the Karplus equation involving the Bothner–By parameters [4]. The estimated value was 5.1 Hz, which is quite satisfactory agree with the experiment.

We assumed that in DMSO-d_6 the most stable form of **A** converts via the enol form **B** into the **C** form with the *S*/*S*- or *R*/*R*-configured chiral centers. Due to the inversion of piperidine ring the form **C** transforms into the form **D** with transoid orientation of the H–C^4 and H–C^5 bonds.

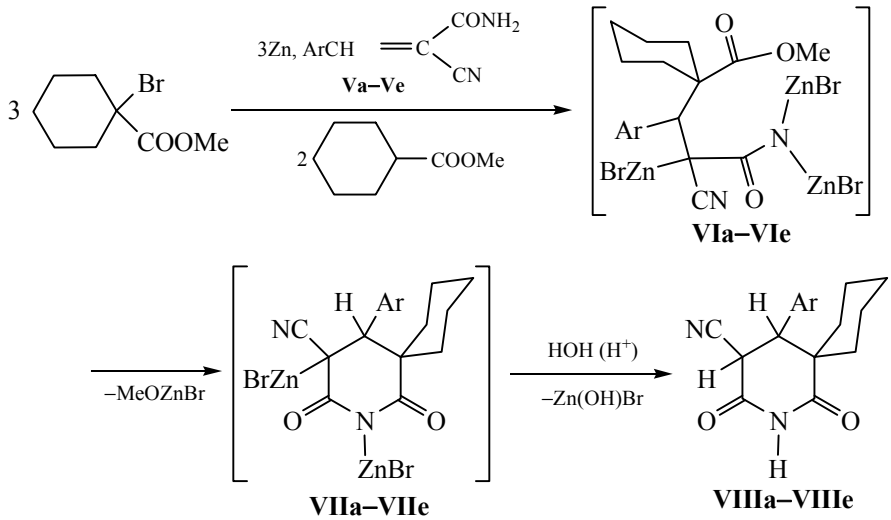


E_{tot} –951.9343 au E_{tot} –951.9119 au E_{tot} –951.9340 au E_{tot} –951.9271 au

In the form **C** the calculated dihedral angle HC^4C^5H is 89.3° that corresponds to the coupling constants equal to 2.00 Hz, which contradict the experimental data. In the form **D** the H–C^5 bond is axial; the calculated dihedral HC^4C^5H angle is 174.4°. The similarly calculated coupling constant was equal to 12.9 Hz, which coincides with the experimental value. Despite the fact that the calculated energy of the form **C** is lower than that of the form **D**, the first form was not found in a DMSO-d_6 solution. Perhaps the form **D** is more efficiently solvated compared with the form **C**, and the equilibrium **C** $\rightleftarrows$ **D** is shifted to the right. However, the form **A** is more stable than **D**. Therefore it is dominant in a DMSO-d_6 solution.

Since the quantum-chemical calculations describe the behavior of the isolated molecules in a gas phase, we undertook a study of a single crystal of compound **IVa** by the X-ray analysis. According to the X-ray data, two crystallographically independent molecules crystallize in the centrosymmetric space group of the monoclinic system. General view and adopted in the structural experiment numbering of the atoms of one crystallographically independent molecule are shown in the figure. The numbers of atoms of the second molecule carry an additional index "A." The geometrical parameters of the molecules (bond length and bond angles) are close to each other and close to the standard values. The torsion angle HC^4C^5H (the $H^{2A}C^2C^3H^{3A}$ and $H^{2AA}C^{2A}C^{3A}H^{3AA}$ groups in the struc-tural experiment) equals to –51.2 and –52.0° for the first and the second molecule, respectively, which agrees well with the calculated data for a major diastereomeric form **A**.

Similarly, the reaction of the Reformatsky reagent derived from methyl 1-bromocyclohexanecarboxylate and zinc with amides of 3-aryl-2-cyanopropenoic acids **Va**–**Ve** results in 5-aryl-1,3-oxo-2-azaspiro[5.5] undecane-4-carbonitriles **VIIIa**–**VIIIe** via the intermediates **VIa**–**VIe** and **VIIa**–**VIIe**.



V–VIII: Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 2.4-$Cl_2C_6H_3$ (**e**).

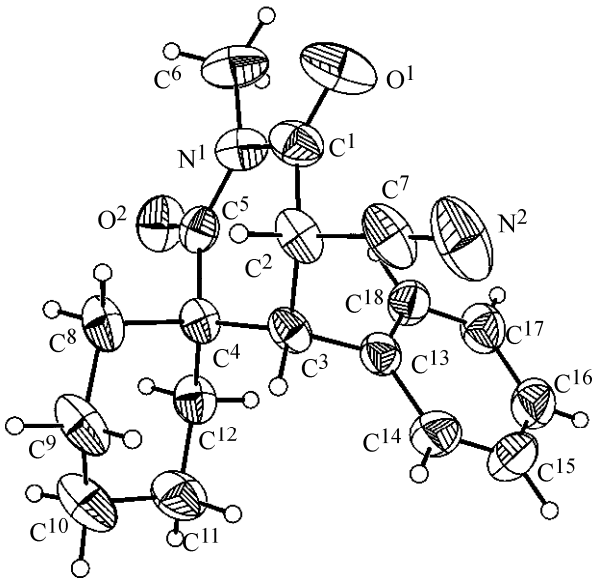
Existence of only one set of the signals in the ^1H NMR spectra of compounds **VIIIa**, **VIIIc** and **VIIId** (solvent $CDCl_3$) shows that these compounds are isolated as single diastereomer. Since the compounds **VIIIb** and **VIIIe** are practically insoluble in $CDCl_3$ their ^1H NMR spectra were obtained for the solutions in DMSO-d_6 and therefore contain the signals of two isomers.

EXPERIMENTAL

The IR spectra of compounds **IV** and **VIII** were obtained on a Specord-75IR spectrophotometer for the samples in vaseline oil. The NMR spectra of these compounds in $CDCl_3$ and DMSO-d_6 were recorded on a Mercury Plus-300 spectrometer (300 MHz) relative to internal TMS.

The quantum-chemical calculations of various forms of compound **IVa** was performed using a Firefly (PC GAMESS, version 7.1.G) software package [5].

The X-ray analysis of compound **IVa** was carried out on a Xcalibur-3 automatic four-circle diffractometer equipped with CCD-detector at 295(2) K, λ 0/71073 Å (MoK_α). Data collection and processing were carried out by the standard procedures [6], no correction for absorption was introduced. The crystals



General view of the molecule of **IVa** by the X-ray data with 50% probability thermal ellipsoids.

are monoclinic, space group $P2_1/c$; a 12.2673(3), b 8.6846(2), c 29.7776(6) Å; β 95.293(2)°, μ 0.082 mm^{-1}. In the range of 52.72 < θ <28.29° were collected 15 858 reflections, of which 7580 are independent (R_{int} 0.0233), 5124 with $I > 2\sigma(I)$. Completeness to θ < 28.29° is 96.7%. The structure solution and refinement were performed using a SHELX software package [7]. The refinement was carried out by a full-matrix anisotropic approximation F^2 for all non-hydrogen atoms. The hydrogen atoms were placed into the geometrically calculated positions and included into the refinement by an isotropic approximation with the dependent thermal parameters by the *rider* model. The final refinement results are: R_1 0.0480, wR_2 0.1260 [for the reflections with $I > 2\sigma(I)$], R_1 0.0685, wR_2 0.1336 (for all reflections) at S 1.001. The peaks of maximal and minimal residual electron density are 0.335 and –0.268 eÅ^{-3}, respectively. The results of the X-ray diffraction experiments were reported in the Cambridge structural data base (CCDC 863296).

5-Aryl-2-methyl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitriles (IVa–IVe). A mixture of 3 g of zinc as fine shavings, a catalytic amount of mercuric chloride, 20 ml of anhydrous ethyl acetate, 20 ml of anhydrous benzene, 1 ml of HMPA, 10 mmol of methylamides of 3-aryl-2-cyanopropene acid and 25 mmol of methyl 1-bromocyclohexanecarboxylate was refluxed for 4 h, cooled, decanted from the zinc excess and hydrolyzed with 5% acetic acid. The organic layer was separated, and the aqueous layer was washed twice with ethyl acetate. The extract was dried over anhydrous sodium sulfate and concentrated. The target compounds **IVa–IVe** were recrystallized from ethyl acetate.

2-Methyl-1,3-dioxo-5-phenyl-2-azaspiro[5.5]undecane-4-carbonitrile (IVa). Yield 2.02 g (68%), mp 146–147°C. IR spectrum, ν, cm^{-1}: 1680, 1725 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.24–1.95 m [10H, $(CH_2)_5$], 3.30 s (3H, MeN), 3.60 d (1H, CHAr, J 5.7 Hz), 4.45 d (1H, CHCN, J 5.7 Hz), 7.00 br.s, 7.31–7.36 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 20.53, 21.18, 24.95, 31.11, 34.45 [$(CH_2)_5$], 27.75 (CH_3N), 39.51 (C^5), 45.35 (C^6), 46.02 (C^4), 114.57 (CN), 128.57, 128.71, 129.41, 134.91 (Ph), 163.91 (C^3=O), 175.88 (C^1=O). Found, %: C 73.09; H 6.91, N 9.27. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

5-(4-Bromophenyl)-2-methyl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitrile (IVb). Yield 2.44 g (65%), mp 214–215°C. IR spectrum, ν, cm^{-1}: 1675, 1715 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.21–1.88 m [10H, $(CH_2)_5$], 3.29 s (3H, MeN), 3.58 d (1H, CHAr, J 5.7 Hz), 4.42 d (1H, CHCN, J 5.7 Hz), 6.89 br.s, 7.48 d (4H, 4-BrC_6H_4, J 8.7 Hz). Found, %: C 57.78; H 4.99, Br 21.52; N 7.33. $C_{18}H_{19}BrN_2O_2$. Calculated, %: C 57.61; H 5.10; Br 21.29; N 7.47.

2-Methyl-1,3-dioxo-5-(4-chlorophenyl)-2-azaspiro[5.5]undecane-4-carbonitrile (IVc). Yield 2.35 g (71%), mp 216–218°C. IR spectrum, ν, cm^{-1}: 1665, 1720 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.19–1.93 m [10H, $(CH_2)_5$], 3.32 s (3H, MeN), 3.64 d (1H, CHAr, J 5.7 Hz), 4.52 d (1H, CHCN, J 5.7 Hz), 7.03 br.s, 7.52 d (4H, 4-ClC_6H_4, J 8.7 Hz). ^{1}H NMR spectrum (50°C), δ, ppm: isomer 1, 1.19–1.93 m [$(CH_2)_5$], 3.29 s (MeN), 3.56 d (CHAr, J 5.7 Hz), 4.40 d (CHCN, J 5.7 Hz), 6.94 d, 7.32 d (4-ClC_6H_4, J 8.4 Hz); isomer 2, 1.19–1.93 m [$(CH_2)_5$], 3.27 s (MeN), 3.51 d (CHAr, J 7.5 Hz), 4.12 d (CHCN, J 7.5 Hz), 7.02 d, 7.35 d (4-ClC_6H_4, J 8.7 Hz). Found, %: C 65.22; H 5.89; Cl 10.50; N 8.61. $C_{18}H_{19}ClN_2O_2$. Calculated, %: C 65.35; H 5.79; Cl 10.72; N 8.47.

2-Methyl-5-(4-methoxyphenyl)-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitrile (IVd). Yield 1.53 g (47%), mp 169–170°C. IR spectrum, ν, cm^{-1}: 1680, 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.23–1.97 m [10H, $(CH_2)_5$], 3.29 s (3H, MeN), 3.56 d (1H, CHAr, J 5.7 Hz), 3.78 s (3H, OMe), 4.16 d (1H, CHCN, J 5.7 Hz), 6.84 d, 6.90 br. d (4H, 4-$MeOC_6\underline{H}_4$, J 8.7 Hz). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (**A**:**D** = 3:1): **A**, 1.23–1.97 m [$(CH_2)_5$], 3.16 s (MeN), 3.72 d (CHAr, J 5.7 Hz), 3.75 s (OMe), 5.23 d (CHCN, J 5.7 Hz), 6.87 d, 7.22 br.s (4-$MeOC_6\underline{H}_4$, J 9.0 Hz); **D**, 1.23–1.97 m [$(CH_2)_5$], 3.09 s (MeN), 3.68 d (CHAr, J 12.9 Hz), 3.79 s (OMe), 5.29 d (CHCN, J 12.9 Hz), 6.97 d, 7.22 br.s (4-$MeOC_6\underline{H}_4$, J 8.4 Hz). Found, %: C 70.14; H 6.61; N 8.42. $C_{19}H_{22}N_2O_3$. Calculated, %: C 69.92; H 6.79; N 8.58.

5-(3,4-Dimethoxyphenyl)-2-methhyl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitrile (IVe). Yield 1.82 g (51%), mp 136–137°C. IR spectrum, ν, cm^{-1}: 1660, 1715 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.28–1.97 m [10H, $(CH_2)_5$], 3.29 s (3H, MeN), 3.54 d (1H, CHAr, J 5.7 Hz), 3.81 s (3H, OMe), 3.85 s (3H, OMe), 4.44 d (1H, CHCN, J 5.7 Hz), 6.52 br.s, 6.80 d (3H, 3,4-$(MeO)_2C_6\underline{H}_3$, J 8.7 Hz). Found, %: C 67.21; H 6.92; N 8.04. $C_{20}H_{24}N_2O_4$. Calculated, %: C 67.40; H 6.79; N 7.86.

5-Aryl-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitriles (VIIIa–VIIIe) were prepared similarly from 10 mmol of amides of 3-aryl-2-cycnopropenoic

acids and 35 mmol of methyl 1-bromocyclohexanecarboxylate.

1,3-Dioxophenyl-5-phenyl-2-azaspiro[5.5]undecane-4-carbonitrile (VIIIa). Yield 1.84 g (65%), mp 236–238°C. IR spectrum, ν, cm^{-1}: 1705, 1725 (C=O), 3200 (NH). ^{1}H NMR spectrum, δ, ppm: 1.21–2.00 m [10H, $(CH_2)_5$], 3.62 d (1H, C<u>H</u>Ph, *J* 6.0 Hz), 4.40 d (1H, CHCN, *J* 6.0 Hz), 7.10–7.41 m (5H, Ph), 8.14 s (1H, NH). Found, %: C 72.68; H 6.56; N 9.78. $C_{17}H_{18}N_2O_2$. Calculated, %: C 72.32; H 6.43; N 9.92.

5-(4-Bromophenyl)-1,3-dioxo-2-azaspiro[5.5]undecane-4-carbonitrile (VIIIb). Yield 2.28 g (63%), mp 249–250°C. IR spectrum, ν, cm^{-1}: 1710, 1725 (C=O), 3205 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (**A**:**D** = 3:1): **A**, 1.10–1.97 m [10H, $(CH_2)_5$], 3.59 d (1H, CHAr, *J* 5.7 Hz), 4.63 d (1H, CHCN, *J* 5.7 Hz), 7.08 d, 7.48 d (4H, 4-BrC_6H_4, *J* 8.4 Hz), 11.01 s (1H, NH); **D**, 1.10–1.97 m [10H, $(CH_2)_5$], 3.49 d (1H, CHAr, *J* 10.5 Hz), 4.52 d (1H, CHCN, *J* 10.5 Hz), 7.12 d, 7.52 d (4H, 4-BrC_6H_4, *J* 8.4 Hz), 10.93 s (1H, NH). Found, %: C 56.75; H 4.88; Br 22.33; N 7.70. $C_{17}H_{17}BrN_2O_2$. Calculated, %: C 56.52; H 4.74; Br 22.12; N 7.75.

1,3-Dioxo-5-(4-chlorophenyl)-2-azaspiro[5.5]undecane-4-carbonitrile (VIIIc). Yield 1.84 g (58%), mp 243–245°C. IR spectrum, ν, cm^{-1}: 1710, 1725 (C=O), 3190 (NH). ^{1}H NMR spectrum, δ, ppm: 1.16–2.02 m [10H, $(CH_2)_5$], 3.59 d (1H, CHAr, *J* 5.7 Hz), 4.37 d (1H, CHCN, *J* 5.7 Hz), 7.09 d, 7.35 d (4H, 4-ClC_6H_4, *J* 8.4 Hz), 7.99 s (1H, NH). Found, %: C 64.72; H 5.26; Cl 11.38; N 8.70. $C_{17}H_{17}ClN_2O_2$. Calculated, %: C 64.46; H 5.41; Cl 11.19; N 8.84.

5-(3,4-Dimethoxyphenyl)-1,3-dioxo-2-azaspiro-[5.5]undecane-4-carbonitrile (VIIId). Yield 1.88 g (55%), mp 184–185°C. IR spectrum, ν, cm^{-1}: 1680, 1710 (C=O), 3190 (NH). ^{1}H NMR spectrum, δ, ppm: 1.23–1.98 m [10H, $(CH_2)_5$], 3.56 d (1H, CHAr, *J* 5.7 Hz), 3.84 s (3H, OMe), 3.86 s (3H, OMe), 4.39 d (1H, CHCN, *J* 5.7 Hz), 6.63 s, 6.69 d, 6.82 d [3H, 3,4-$(MeO)_2C_6\underline{H}_3$], 8.19 s (1H, NH). Found, %: C 66.42; H 6.36; N 8.36. $C_{19}H_{22}N_2O_4$. Calculated, %: C 66.65; H 6.48; N 8.18.

5-(2,4-Dichlorophenyl)-1,3-dioxo-2-azaspiro[5.5]-undecane-4-carbonitrile (VIIIe). Yield 2.46 g (70%), mp 293–295°C. IR spectrum, ν, cm^{-1}: 1710, 1725 (C=O), 3160 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (**A**:**D** = 2:1): **A**, 1.10–2.12 m [10H, $(CH_2)_5$], 4.44 d (1H, CHAr, *J* 6.3 Hz), 4.80 d (1H, CHCN, *J* 6.3 Hz), 7.09 d, 7.26 d, 7.57 s (3H, $Cl_2C_6H_3$, *J* 8.4 Hz), 11.29 s (1H, NH); **D**, 1.10–2.12 m [10H, $(CH_2)_5$], 4.23 d (1H, CHAr, *J* 10.8 Hz), 4.70 d (1H, CHCN, *J* 10.8 Hz), 7.34 d, 7.38 d, 7.51 s (3H, $Cl_2C_6H_3$, *J* 8.4 Hz), 11.17 s (1H, NH). Found, %: C 58.39; H 4.46; Cl 19.98; N 8.11. $C_{17}H_{16}Cl_2N_2O_2$. Calculated, %: C 58.13; H 4.59; Cl 20.19; N 7.98.

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