

# Synthesis of 6-Arylspiro[tetrahydropyran-3,1'-cyclobutane]-2,4-diones

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**Abstract**—Methyl 1-(2-bromo-2-methyl-1-oxopropyl)-, 1-(1-bromocyclopentylcarbonyl)-, and 1-(1-bromocyclohexylcarbonyl)cyclobutanecarboxylates reacted with zinc and aromatic aldehydes to give, respectively, 7-aryl-2,2-dimethyl-6-oxaspiro[3.5]nonane-5,9-diones, 11-aryl-12-oxadispiro[3.1.4.3]tridecane-5,13-diones, and 12-aryl-13-oxadispiro[3.1.5.3]tetradecane-5,14-diones.

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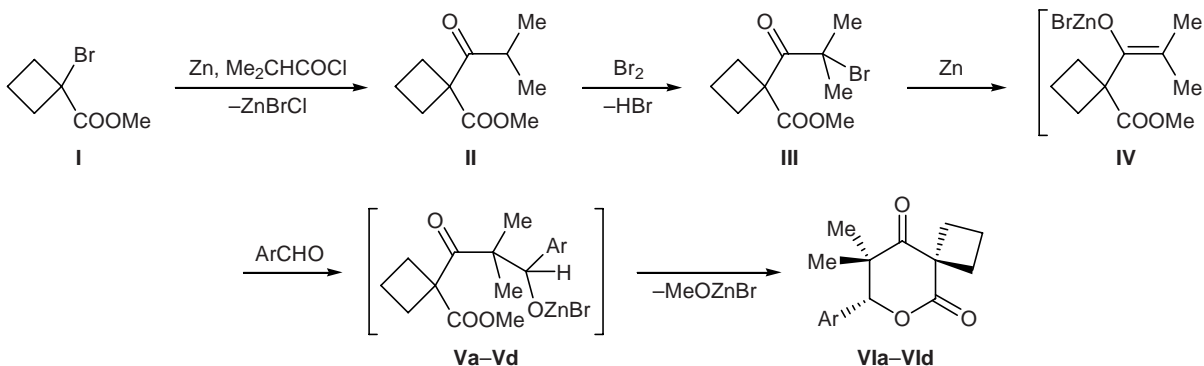
In continuation of our previous studies on the synthesis of substituted tetrahydropyran-2,4-diones having spiro carbon atoms in positions 3 and 5 of the heteroring [1–3], we now report on the preparation of analogous compounds in which the C<sup>3</sup> atom is shared with cyclobutane ring. By the Reformatsky reaction of methyl 1-bromocyclobutanecarboxylate (**I**) with zinc and isobutyryl chloride we obtained methyl 1-(2-methyl-1-oxo-propyl)cyclobutanecarboxylate (**II**) whose bromination gave methyl 1-(2-bromo-2-methyl-1-oxo-propyl)cyclobutanecarboxylate (**III**) as the key intermediate product. The reaction of bromo derivative **III** with zinc and aromatic aldehydes involved addition of zinc enolate **IV** at the carbonyl group of the aldehyde, followed by spontaneous cyclization of intermediate **V** into tetrahydropyran-2,4-dione spiro-fused with cyclobutane ring at the 3-position. We thus isolated 7-aryl-

8,8-dimethyl-6-oxaspiro[3.5]nonane-5,9-diones **Vla–VId** (Scheme 1).

Likewise, from bromocyclobutane **I**, zinc, and cyclopentanecarbonyl chloride we obtained methyl 1-(cyclopentylcarbonyl)cyclobutanecarboxylate (**VII**), bromination of the latter gave methyl 1-(1-bromocyclopentylcarbonyl)cyclobutanecarboxylate (**VIII**), and compound **VIII** was brought into reaction with zinc and aromatic aldehydes. As a result, we isolated tetrahydropyran-2,4-dione derivatives with two spiro carbon atoms in positions 3 and 5 of the heteroring, 11-aryl-12-oxadispiro[3.1.4.3]tridecane-5,13-diones **IXa–IXc** (Scheme 2).

Following an analogous scheme, 1-(cyclohexylcarbonyl)cyclobutanecarboxylate (**X**) obtained by the Reformatsky reaction of bromo derivative **I** with zinc

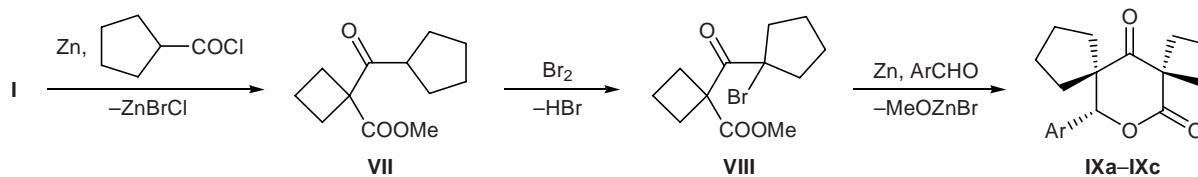
Scheme 1.



**V, VI**, Ar = 4-BrC<sub>6</sub>H<sub>4</sub> (**a**), 4-ClC<sub>6</sub>H<sub>4</sub> (**b**), 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> (**c**), 3-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> (**d**).

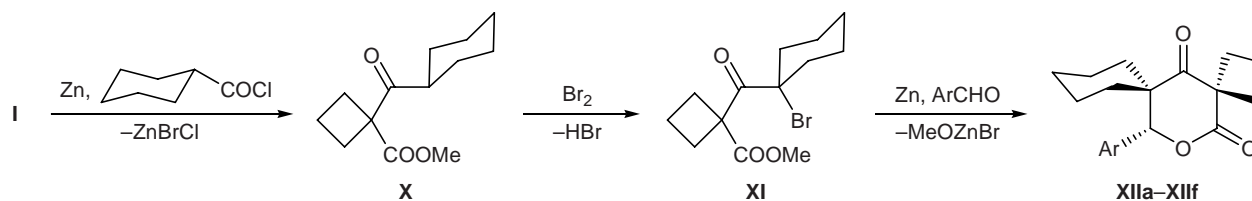
<sup>†</sup> Deceased.

Scheme 2.



IX, Ar = 4-BrC<sub>6</sub>H<sub>4</sub> (a), 4-ClC<sub>6</sub>H<sub>4</sub> (b), 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> (c).

Scheme 3.



XII, Ar = Ph (a), 4-BrC<sub>6</sub>H<sub>4</sub> (b), 4-ClC<sub>6</sub>H<sub>4</sub> (c), 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> (d), 4-MeOC<sub>6</sub>H<sub>4</sub> (e), 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> (f).

and cyclohexanecarbonyl chloride was converted into methyl 1-(1-bromocyclohexylcarbonyl)cyclobutanecarboxylate (XI). The subsequent Reformatsky reaction of bromide XI with zinc and aromatic aldehydes gave 12-aryl-13-oxadisp[3.1.5.3]tetradecane-5,14-diones XIIa–XIIif in which the tetrahydropyran ring is substituted at C<sup>3</sup> and C<sup>5</sup> by tri- and pentamethylene groups, respectively (Scheme 3).

The structure of compounds VIa–VIId, IXa–IXc, and XIIa–XIIif was proved by elemental analysis and <sup>1</sup>H NMR and IR spectroscopy. In the <sup>1</sup>H NMR spectra of these compounds, we observed a characteristic singlet at δ 5.06–5.82 ppm from the OCH proton. Their IR spectra contained absorption bands at 1705–1720 and 1720–1755 cm<sup>-1</sup> due to stretching vibrations of the ketone and lactone carbonyl groups, respectively.

## EXPERIMENTAL

The IR spectra of compounds II, III, VIa–VIId, VII, VIII, IXa–IXc, X, XI, and XIIa–XIIif were recorded on a Spesord 75IR spectrophotometer from samples dispersed in mineral oil. The <sup>1</sup>H NMR spectra were measured on a Tesla BS-576A instrument at 100 MHz in CDCl<sub>3</sub> relative to hexamethyldisiloxane as internal reference.

**Methyl 1-(2-methyl-1-oxopropyl)cyclobutanecarboxylate (II).** A solution of 0.1 mol of methyl 1-bromocyclobutanecarboxylate and 0.1 mol of isobutyryl chloride in 50 ml of anhydrous benzene was added dropwise to a mixture of 10 g of fine zinc turnings and 10 ml of anhydrous ethyl acetate. The

mixture was heated for 1 h under reflux, the liquid phase was separated by decanting and hydrolyzed with water, the organic phase was separated and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 12.0 g (65%), bp 80–82°C (4 mm),  $d_4^{20} = 1.0953$ ,  $n_D^{20} = 1.4592$ . IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1715, 1725 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.69 s (3H, OMe), 2.69 m (1H, CHCO), 1.58–2.59 m (6H, CH<sub>2</sub>), 1.05 d (6H, Me,  $J = 6.5$  Hz). Found, %: C 65.41; H 8.88. C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>. Calculated, %: C 65.19; H 8.75

**Methyl 1-(1-bromo-2-methyl-1-oxopropyl)cyclobutanecarboxylate (III).** Compound II, 0.1 mol, was dissolved in 25 ml of acetic acid, 0.11 mol of bromine was added dropwise under stirring, and the mixture was heated for 1 h on a water bath. Excess bromine and acetic acid were distilled off, and the residue was distilled under reduced pressure. Yield 19.7 g (75%), bp 111–113°C (4 mm),  $d_4^{20} = 1.4015$ ,  $n_D^{20} = 1.4940$ . IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1715, 1735 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.68 s (3H, OMe), 1.72–2.60 m (6H, CH<sub>2</sub>), 1.86 s (6H, Me). Found, %: C 45.52; H 5.64; Br 30.51. C<sub>10</sub>H<sub>15</sub>BrO<sub>3</sub>. Calculated, %: C 45.65; H 5.75; Br 30.37.

**7-Aryl-8,8-dimethyl-6-oxaspiro[3.5]nonane-5,12-diones VIa–VIId (general procedure).** A mixture of 0.02 mol of compound III and 0.017 mol of the corresponding aldehyde in 30 ml of anhydrous ethyl acetate was added dropwise under stirring to a mixture of 3 g of fine zinc turnings and a catalytic amount of mercury(II) chloride in 30 ml of anhydrous ethyl acetate (in the synthesis of VIId, ester III was initially

heated with zinc over a period of 30 min, and 3-nitrobenzaldehyde was then added). The mixture was heated for 2 h under reflux and cooled, the liquid phase was separated by decanting and hydrolyzed with 5% hydrochloric acid, the organic phase was separated, and the aqueous phase was extracted with two portions of ethyl acetate. The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, most part of the solvent was distilled off, and the product was recrystallized from ethyl acetate.

**7-(4-Bromophenyl)-8,8-dimethyl-6-oxaspiro[3.5]nonane-5,12-dione (VIa).** Yield 5.33 g (93%), mp 163–164°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1710, 1725 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.43 d and 7.13 d (2H each, 4- $\text{BrC}_6\text{H}_4$ ,  $J = 8.3$  Hz), 5.20 s (1H, CHO), 1.92–2.84 m (6H,  $\text{CH}_2$ ), 1.10 s (3H, Me), 0.88 s (3H, Me). Found, %: C 56.77; H 5.20; Br 23.92.  $\text{C}_{16}\text{H}_{17}\text{BrO}_3$ . Calculated, %: C 56.99; H 5.08; Br 23.70.

**7-(4-Chlorophenyl)-8,8-dimethyl-6-oxaspiro[3.5]nonane-5,12-dione (VIb).** Yield 4.48 g (90%), mp 171–172°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1710, 1720 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.17–7.29 m (4H, 4- $\text{ClC}_6\text{H}_4$ ), 5.20 s (1H, CHO), 1.90–2.88 m (6H,  $\text{CH}_2$ ), 1.09 s (3H, Me), 0.87 s (3H, Me). Found, %: C 65.79; H 5.69; Cl 12.23.  $\text{C}_{16}\text{H}_{17}\text{ClO}_3$ . Calculated, %: C 65.64; H 5.85; Cl 12.11.

**7-(2,4-Dichlorophenyl)-8,8-dimethyl-6-oxaspiro[3.5]nonane-5,12-dione (VIc).** Yield 4.45 g (80%), mp 104–105°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1710, 1730 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.15–7.50 m (3H,  $\text{C}_6\text{H}_3$ ), 5.82 s (1H, CHO), 1.95–2.85 m (6H,  $\text{CH}_2$ ), 1.14 s (3H, Me), 0.97 s (3H, Me). Found, %: C 58.91; H 5.09; Cl 21.83.  $\text{C}_{16}\text{H}_{16}\text{Cl}_2\text{O}_3$ . Calculated, %: C 58.73; H 4.93; Cl 21.67.

**8,8-Dimethyl-7-(3-nitrophenyl)-6-oxaspiro[3.5]nonane-5,12-dione (VIId).** Yield 4.38 g (85%), mp 158–159°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1730 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.40–7.65 m (4H, 3- $\text{O}_2\text{NC}_6\text{H}_4$ ), 5.35 s (1H, CHO), 1.50–2.89 m (6H,  $\text{CH}_2$ ), 1.16 s (3H, Me), 0.91 s (3H, Me). Found, %: C 63.49; H 5.58; N 4.43.  $\text{C}_{16}\text{H}_{17}\text{NO}_5$ . Calculated, %: C 63.36; H 5.65; N 4.62.

**Methyl 1-(cyclopentylcarbonyl)cyclobutanecarboxylate (VII)** was synthesized as described above for compound **II** using cyclopentanecarbonyl chloride. Yield 11.6 g (55%), bp 118–120°C (7 mm),  $d_4^{25} = 1.0673$ ,  $n_D^{25} = 1.4710$ . IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1710, 1725 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.65 s (3H, OMe), 2.78 m (1H, CHCO), 1.30–2.60 m (14H,  $\text{CH}_2$ ). Found,

%: C 68.74; H 8.71.  $\text{C}_{12}\text{H}_{18}\text{O}_3$ . Calculated, %: C 68.54; H 8.63.

**Methyl 1-(1-bromocyclopentylcarbonyl)cyclobutanecarboxylate (VIII)** was synthesized by bromination of **II** according to the procedure described above for the synthesis of compound **III**. Yield 23.1 g (80%), bp 147–149°C (7 mm),  $d_4^{27} = 1.3522$ ,  $n_D^{27} = 1.5020$ . IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1725 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.69 s (3H, OMe), 1.48–2.75 m (14H,  $\text{CH}_2$ ). Found, %: C 49.70; H 6.02; Br 27.48.  $\text{C}_{12}\text{H}_{17}\text{BrO}_3$ . Calculated, %: C 49.84; H 5.93; Br 27.63.

**11-Aryl-12-oxadispiro[3.1.4.3]tridecane-5,13-diones (IXa–IXc)** were synthesized as described above for **VIa–VIId** using compound **VIII** as starting material.

**11-(4-Bromophenyl)-12-oxadispiro[3.1.4.3]tridecane-5,13-dione (IXa).** Yield 5.13 g (83%), mp 168–169°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1730 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.42 d and 7.14 d (2H each, 4- $\text{BrC}_6\text{H}_4$ ,  $J = 8.3$  Hz), 5.25 s (1H, CHO), 0.90–2.77 m (14H,  $\text{CH}_2$ ). Found, %: C 59.69; H 5.19; Br 21.88.  $\text{C}_{18}\text{H}_{19}\text{BrO}_3$ . Calculated, %: C 59.52; H 5.27; Br 22.00.

**11-(4-Chlorophenyl)-12-oxadispiro[3.1.4.3]tridecane-5,13-dione (IXb).** Yield 4.93 g (91%), mp 162–163°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1725 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.08–7.34 m (4H, 4- $\text{ClC}_6\text{H}_4$ ), 5.27 s (1H, CHO), 0.98–2.76 m (14H,  $\text{CH}_2$ ). Found, %: C 67.67; H 5.90; Cl 11.31.  $\text{C}_{18}\text{H}_{19}\text{ClO}_3$ . Calculated, %: C 67.82; H 6.01; Cl 11.12.

**11-(2,4-Dichlorophenyl)-12-oxadispiro[3.1.4.3]tridecane-5,13-dione (IXc).** Yield 4.38 g (73%), mp 107–108°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1730 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.40 d, 7.34 s, and 7.22 d (1H each,  $\text{C}_6\text{H}_3$ ,  $J = 8.0$  Hz); 5.81 s (1H, CHO); 1.08–2.78 m (14H,  $\text{CH}_2$ ). Found, %: C 61.32; H 5.29; Cl 19.89.  $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{O}_3$ . Calculated, %: C 61.20; H 5.14; Cl 20.07.

**Methyl 1-(cyclohexylcarbonyl)cyclobutanecarboxylate (X)** was synthesized from ester **I** and cyclohexanecarbonyl chloride as described above for compound **II**. Yield 14.6 g (65%), bp 122–123°C (4 mm),  $d_4^{20} = 1.0638$ ,  $n_D^{20} = 1.4760$ . IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1730, 1750 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.65 s (3H, OMe), 2.32–2.65 m (1H, CHCO), 1.05–2.27 m (16H,  $\text{CH}_2$ ). Found, %: C 69.82; H 9.09.  $\text{C}_{13}\text{H}_{20}\text{O}_3$ . Calculated, %: C 69.61; H 8.99.

**Methyl 1-(1-bromocyclohexylcarbonyl)cyclobutanecarboxylate (XI)** was obtained by bromination

of **X** according to the procedure described above for the synthesis of bromo ester **III**. Yield 26.1 g (86%), bp 156–158°C (4 mm), mp 49°C (from hexane). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1735, 1755 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.65 s (3H, OMe), 1.05–2.88 m (16H,  $\text{CH}_2$ ). Found, %: C 51.69; H 6.44; Br 26.53.  $\text{C}_{13}\text{H}_{19}\text{BrO}_3$ . Calculated, %: C 51.50; H 6.32; Br 26.35.

**12-Aryl-13-oxadispiro[3.1.5.3]tetradecane-5,14-diones XIIa–XIIe**. The procedures for the synthesis of compounds **XIIa–XIIe** and **XIIe** were analogous to those described above for the synthesis of **VIa–VIc** and **VIe**, respectively; compound **XI** was used as starting material.

**12-Phenyl-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIa)**. Yield 4.21 g (83%), mp 136–137°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1705, 1745 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 6.96–7.33 m (5H, Ph), 5.11 s (1H, CHO), 0.70–2.95 m (16H,  $\text{CH}_2$ ). Found, %: C 76.68; H 7.49.  $\text{C}_{19}\text{H}_{22}\text{O}_3$ . Calculated, %: C 76.48; H 7.43.

**12-(4-Bromophenyl)-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIb)**. Yield 5.96 g (83%), mp 135–136°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1750 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.40 d and 6.95 d (2H each, 4- $\text{BrC}_6\text{H}_4$ ,  $J = 8.3$  Hz), 5.06 s (1H, CHO), 0.80–2.80 m (16H,  $\text{CH}_2$ ). Found, %: C 60.69; H 5.70; Br 21.43.  $\text{C}_{19}\text{H}_{21}\text{BrO}_3$ . Calculated, %: C 60.48; H 5.61; Br 21.18.

**12-(4-Chlorophenyl)-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIc)**. Yield 4.81 g (85%), mp 127–128°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1720, 1745 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.24 d and 6.99 d (2H each, 4- $\text{ClC}_6\text{H}_4$ ,  $J = 6.5$  Hz), 5.07 s (1H, CHO), 0.80–2.79 m (16H,  $\text{CH}_2$ ). Found, %: C 68.78; H 6.49; Cl 10.42.  $\text{C}_{19}\text{H}_{21}\text{ClO}_3$ . Calculated, %: C 68.56; H 6.36; Cl 10.65.

**12-(2,4-Dichlorophenyl)-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIe)**. Yield 5.43 g (87%), mp 138–139°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1720, 1755 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.12–7.40 m (3H,  $\text{C}_6\text{H}_3$ ), 5.70 s (1H, CHO), 0.80–2.82 m (16H,  $\text{CH}_2$ ). Found, %: C 61.98; H 5.35; Cl 19.48.  $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{O}_3$ . Calculated, %: C 62.13; H 5.49; Cl 19.31.

**12-(4-Methoxyphenyl)-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIe)**. Yield 4.58 g (82%), mp 96–97°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1715, 1750 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 6.96 d and 6.77 d (2H each, 4- $\text{MeOC}_6\text{H}_4$ ,  $J = 8.4$  Hz), 5.07 s (1H, CHO), 3.76 s (3H, MeO), 0.80–2.81 m (16H,  $\text{CH}_2$ ). Found, %: C 73.02; H 7.44.  $\text{C}_{20}\text{H}_{24}\text{O}_3$ . Calculated, %: C 73.14; H 7.37.

**12-(4-Nitrophenyl)-13-oxadispiro[3.1.5.3]tetradecane-5,14-dione (XIIe)**. Yield 5.25 g (90%), mp 178–179°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1720, 1755 (C=O).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 8.13 d and 7.30 d (4H, 4- $\text{O}_2\text{NC}_6\text{H}_4$ ,  $J = 8.4$  Hz), 5.19 s (1H, CHO), 0.70–2.88 m (16H,  $\text{CH}_2$ ). Found, %: C 66.28; H 6.29; N 3.94.  $\text{C}_{19}\text{H}_{21}\text{NO}_5$ . Calculated, %: C 66.45; H 6.17; N 4.08.

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