

# Synthesis of 6-Aryltetrahydropyran-2,4-diones Containing a Hexamethylene Substituent in Positions 3 or 5 of Heterocycle

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**Abstract**— Methyl 3-(1-bromocycloheptyl)-2,2-dimethyl-3-oxopropanoate and methyl 1-(2-bromo-2-methylpropanoyl)cycloheptanecarboxylates react with zinc and arylaldehydes yielding 5-aryl-2,2-dimethyl-4-oxaspiro[5.6]dodecan-1.3-diones and 3-aryl-4,4-dimethyl-2-oxaspiro[5.6]dodecan-1.5-diones respectively.

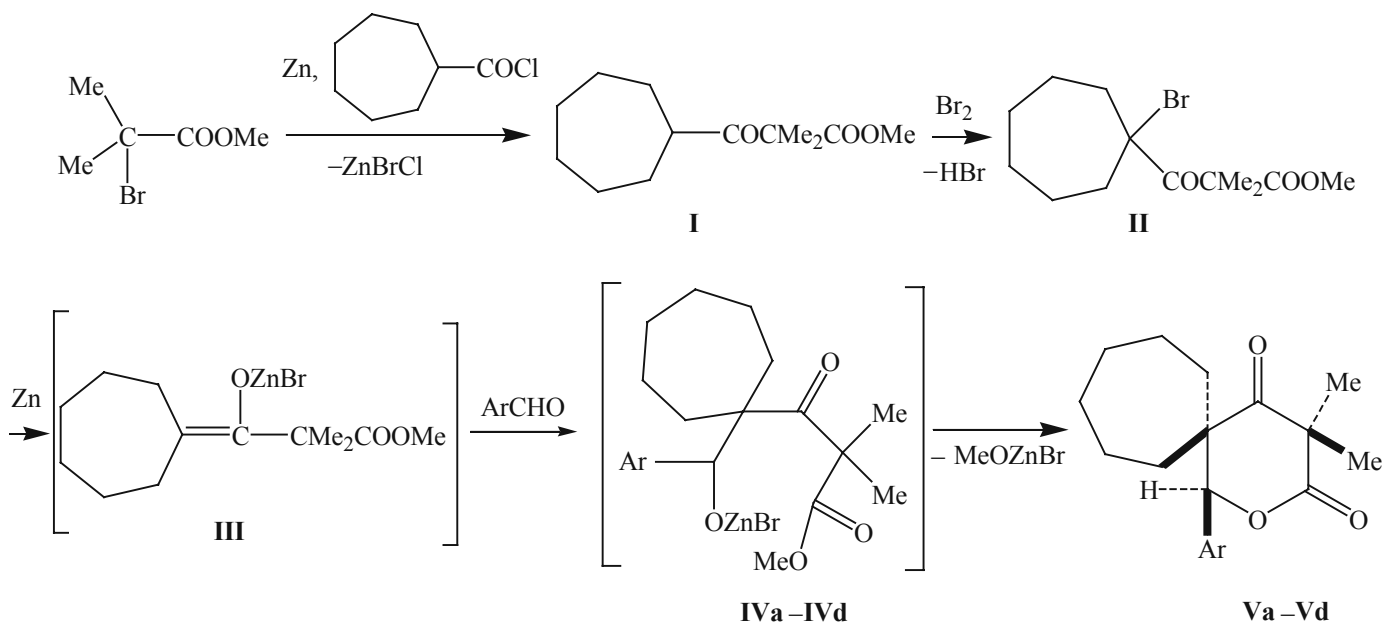
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In extension of previous research on preparation of substituted tetrahydropyran-2,4-diones possessing in positions 3 or 5 of the heterocycle a spiro carbon atom included into a five- or six-membered ring [1–3] we synthesized analogous compounds containing in these positions a hexamethylene substituent.

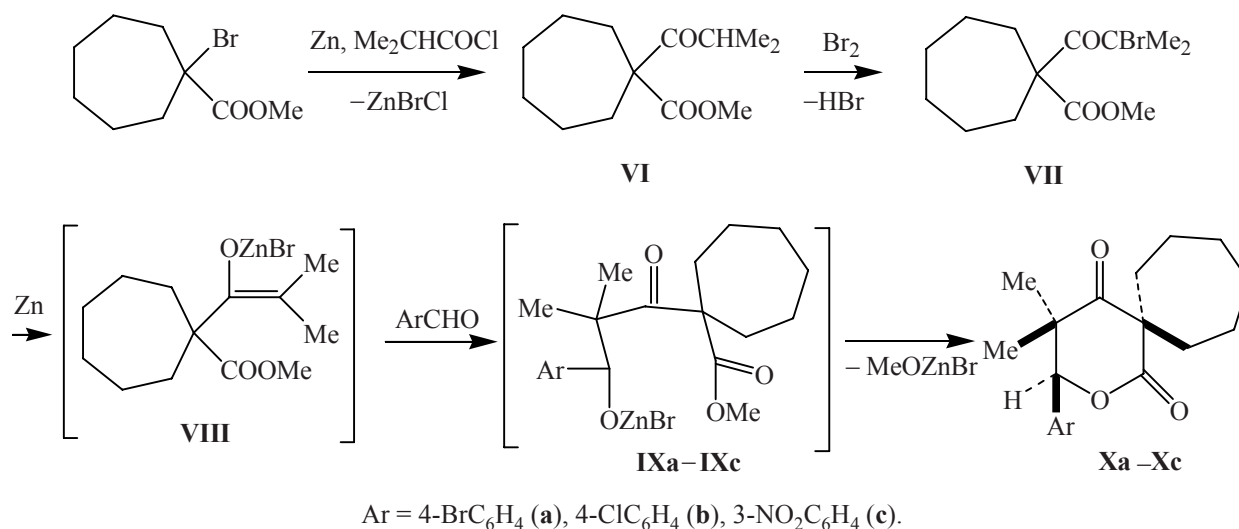
Under the conditions of Reformatsky reaction proceeding from methyl 2-bromo-2-methylpropanoate, zinc, and cycloheptanecarbonyl chloride a methyl 2,2-dimethyl-3-oxo-3-cycloheptylpropanoate (**I**) was obtained that by bromination was converted into the key bromo derivative, methyl 3-(1-bromocycloheptyl)-2,2-

dimethyl-3-oxopropanoate (**II**). Bromo derivative **II** in reaction with zinc formed a zinc enolate **III** that added to the carbonyl group of aromatic aldehydes providing intermediates **IVa–IVd**. The latter under the reaction conditions spontaneously transformed into the target tetrahydropyran-2,4-diones with a hexamethylene substituent in the position 5 of the heterocycle, namely, into 5-aryl-2,2-dimethyl-4-oxaspiro[5.6]dodecane-1,3-diones **Va–Vd**.

Similarly from the methyl 1-bromocycloheptanecarboxylate, zinc, and a 2-methylpropanoyl chloride a methyl 1-(2-methylpropanoyl)cycloheptanecarboxylate



Ar = Ph (**a**), 4- $\text{BrC}_6\text{H}_4$  (**b**), 4- $\text{ClC}_6\text{H}_4$  (**c**), 4- $\text{MeOC}_6\text{H}_4$  (**d**).



(VI) was obtained that was converted into bromo derivative VII. Further by the reaction of bromo derivative VII, zinc, and aromatic aldehydes via intermediate compounds VIII and IX we synthesized tetrahydropyran-2,4-diones with the hexamethylene substituent in the position 3 of the heterocycle, 3-aryl-4,4-dimethyl-2-oxaspiro[5.6]-dodecene-1,5-diones Xa–Xc.

The yields of reaction products attained 48–67%. The composition and structure of compounds obtained were proved by elemental analysis, IR and <sup>1</sup>H NMR spectra. In the IR spectra of aryltetrahydropyran-2,4-diones characteristic absorption bands of ketone carbonyls were present at 1705–1710 cm<sup>-1</sup>, and of lactone carbonyl groups, in the region 1730–1745 cm<sup>-1</sup>. In <sup>1</sup>H NMR spectra a characteristic singlet of the methine proton appeared in the region 5.19–5.46 ppm.

## EXPERIMENTAL

IR spectra of compounds I, II, Va–Vd, VI, VII, Xa–Xc were recorded on a spectrophotometer Specord 75IR from mulls in mineral oil. <sup>1</sup>H NMR spectra of these compounds were registered from solutions in CDCl<sub>3</sub> on a spectrometer Tesla BS-576A (100 MHz), internal reference HMDS.

**Methyl 2,2-dimethyl-3-oxo-3-cycloheptylpropanoate (I).** To 10 g of fine zinc turnings in 25 ml of anhydrous benzene and 10 ml of anhydrous ethyl acetate was added 0.1 mol of methyl 2-bromo-2-methylpropanoate and 0.1 mol cycloheptanecarbonyl chloride in 50 ml of benzene. The mixture was boiled for 1 h, it was then decanted and hydrolyzed with water. The organic layer was separated, dried with anhydrous sodium sulfate, the

solvent was distilled off, and the reaction product was twice distilled in a vacuum. Yield 15.4 g (68%), bp 128–130°C (10 mm Hg), *d*<sub>4</sub><sup>20</sup> 1.0164, *n*<sub>D</sub><sup>20</sup> 1.4660. IR spectrum, ν, cm<sup>-1</sup>: 1705, 1725 (C=O). <sup>1</sup>H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 2.64–2.76 m (1H, CHCO), 1.36 s (6H, 2Me), 1.33–1.82 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 69.26; H 9.69. C<sub>13</sub>H<sub>22</sub>O<sub>3</sub>. Calculated, %: C 68.99; H 9.80.

**Methyl 1-(2-methylpropanoyl)cycloheptanecarboxylate (VI)** was obtained analogously to compound I. As initial compounds were used methyl 1-bromocycloheptanecarboxylate and 2-methylpropanoyl chloride. Yield 10.6 g (47%), bp 131–133°C (10 mm Hg), *d*<sub>4</sub><sup>20</sup> 1.0262, *n*<sub>D</sub><sup>20</sup> 1.4712. IR spectrum, ν, cm<sup>-1</sup>: 1710, 1725 (C=O). <sup>1</sup>H NMR spectrum, δ, ppm: 3.66 s (3H, OMe), 2.59–2.92 m (1H, CHCO), 1.42–2.15 m [12H, (CH<sub>2</sub>)<sub>6</sub>], 1.03 d (6H, 2Me, *J* 7.4 Hz). Found, %: C 69.15; H 9.89. C<sub>13</sub>H<sub>22</sub>O<sub>3</sub>. Calculated, %: C 68.99; H 9.80.

**Methyl 3-(1-bromocycloheptyl)-2,2-dimethyl-3-oxopropanoate (II).** To a solution of 0.05 mol of compound I in 20 ml of acetic acid was added 0.055 mol of bromine, the mixture was heated on a water bath for 1 h, acetic acid and excess bromine were distilled off, and the reaction product was distilled in a vacuum. Yield 11.0 g (72%), mp 56–57°C. IR spectrum, ν, cm<sup>-1</sup>: 1710, 1750 (C=O). <sup>1</sup>H NMR spectrum, δ, ppm: 3.66 s (3H, OMe), 1.50 s (6H, 2Me), 1.30–2.40 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 50.88; H 7.07; Br 25.97. C<sub>13</sub>H<sub>21</sub>BrO<sub>3</sub>. Calculated, %: C 51.16; H 6.94; Br 26.18.

**Methyl 1-(2-bromo-2-methylpropanoyl)cycloheptanecarboxylate (VII)** was similarly obtained using as initial compound ester VI. Yield 10.7 g (70%), mp 49–51°C. IR spectrum, ν, cm<sup>-1</sup>: 1715, 1735 (C=O). <sup>1</sup>H NMR spectrum, δ, ppm: 3.65 s (3H, OMe), 1.88 s (6H, 2Me),

1.41–2.32 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 50.95; H 7.11; Br 26.31. C<sub>13</sub>H<sub>21</sub>BrO<sub>3</sub>. Calculated, %: C 51.16; H 6.94; Br 26.18.

**5-Aryl-2,2-dimethyl-4-oxaspiro[5.6]dodecene-1,3-diones Va–Vd.** To a mixture of 1 g of fine zinc turnings, catalytic quantity of mercuric chloride, and 30 ml of anhydrous ethyl acetate was added dropwise at stirring a mixture of 10 mmol of compound **II** and 9.6 mmol of an appropriate aldehyde in 15 ml of anhydrous ethyl acetate. The reaction mixture was boiled for 2 h, cooled, decanted from excess zinc, and hydrolyzed with 5% hydrochloric acid. The organic layer was separated, the reaction products were twice extracted from the water layer into ethyl acetate. The combined organic solution was dried with anhydrous sodium sulfate, ethyl acetate was distilled off, and compounds **Va–Vd** were recrystallized from methanol.

**2,2-Dimethyl-5-phenyl-4-oxaspiro[5.6]dodecene-1,3-dione (Va).** Yield 1.38 g (48%), mp 162–163°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1710, 1730 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.17–7.31 m (5H, Ph), 5.24 s (1H, CHO), 1.48 s (6H, 2Me), 0.88–2.42 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 75.78; H 7.96. C<sub>19</sub>H<sub>24</sub>O<sub>3</sub>. Calculated, %: C 75.97; H 8.05.

**5-(4-Bromophenyl)-2,2-dimethyl-4-oxaspiro[5.6]dodecene-1,3-dione (Vb).** Yield 2.18 g (60%), mp 182–183°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1705, 1730 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.44 d, 7.21 d (4H, 4-BrC<sub>6</sub>H<sub>4</sub>, *J* 8.4 Hz), 5.19 s (1H, CHO), 1.48 s (6H, 2Me), 0.80–2.45 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 59.95; H 6.24; Br 20.84. C<sub>19</sub>H<sub>23</sub>BrO<sub>3</sub>. Calculated, %: C 60.17; H 6.11; Br 21.07.

**2,2-Dimethyl-5-(4-chlorophenyl)-4-oxaspiro[5.6]dodecene-1,3-dione (Vc).** Yield 2.15 g (67%), mp 177–178°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1710, 1740 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.17–7.28 m (4H, 4-ClC<sub>6</sub>H<sub>4</sub>), 5.21 s (1H, CHO), 1.48 s (6H, Me), 0.87–2.44 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 68.28; H 7.09; Cl 10.35. C<sub>19</sub>H<sub>23</sub>ClO<sub>3</sub>. Calculated, %: C 68.15; H 6.92; Cl 10.59.

**2,2-Dimethyl-5-(4-methoxyphenyl)-4-oxaspiro[5.6]dodecene-1,3-dione (Vd).** Yield 1.62 g (51%), mp 155–156°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1710, 1730 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.23 d, 6.82 d (4H, 4-MeOC<sub>6</sub>H<sub>4</sub>, *J* 8.4 Hz), 5.19 c (1H, CHO), 3.79 c (3H, MeO), 1.47 s (6H, 2Me), 0.90–2.44 m [12H, (CH<sub>2</sub>)<sub>6</sub>]. Found, %: C 72.52;

H 8.04. C<sub>20</sub>H<sub>26</sub>O<sub>4</sub>. Calculated, %: C 72.70; H 7.93.

**3-Aryl-4,4-dimethyl-2-oxaspiro[5.6]dodecene-1,5-diones Xa–Xc** were prepared similarly to compounds **V**. Bromooxoeester **VII** was used as initial compound. In the preparation of compound **Xc** the 3-nitrobenzaldehyde was added after heating compound **VII** with zinc for 30 min.

**3-(4-Bromophenyl)-4,4-dimethyl-2-oxaspiro[5.6]dodecene-1,5-dione (Xa).** Yield 2.26 g (62%), mp 184–185°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1705, 1745 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.44 d, 7.14 d (4H, 4-BrC<sub>6</sub>H<sub>4</sub>, *J* 7.4 Hz), 5.31 s (1H, CHO), 1.38–2.40 m [12H, (CH<sub>2</sub>)<sub>6</sub>], 0.98 s (3H, Me), 0.93 s (3H, Me). Found, %: C 60.31; H 6.28; Br 21.21. C<sub>19</sub>H<sub>23</sub>BrO<sub>3</sub>. Calculated, %: C 60.17; H 6.11; Br 21.07.

**4,4-Dimethyl-3-(4-chlorophenyl)-2-oxaspiro[5.6]dodecene-1,5-dione (Xb).** Yield 1.86 g (58%), mp 200–202°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1710, 1745 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 7.30 d, 7.18 d (4H, 4-ClC<sub>6</sub>H<sub>4</sub>, *J* 8.3 Hz), 5.32 s (1H, CHO), 1.40–2.38 m [12H, (CH<sub>2</sub>)<sub>6</sub>], 0.98 s (3H, Me), 0.92 s (3H, Me). Found, %: C 68.28; H 7.09; Cl 10.35. C<sub>19</sub>H<sub>23</sub>ClO<sub>3</sub>. Calculated, %: C 68.15; H 6.92; Cl 10.59.

**4,4-Dimethyl-3-(3-nitrophenyl)-2-oxaspiro[5.6]dodecene-1,5-dione (Xc).** Yield 1.72 g (52%), mp 157–158°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1710, 1740 (C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 8.17 d, 8.12 s, 7.65 d, 7.49 t (4H, 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *J* 8.5 Hz), 5.46 s (1H, CHO), 1.40–2.44 m [12H, (CH<sub>2</sub>)<sub>6</sub>], 1.04 s (3H, Me), 0.95 s (3H, Me). Found, %: C 65.88; H 6.93; N 3.94. C<sub>19</sub>H<sub>23</sub>NO<sub>5</sub>. Calculated, %: C 66.07; H 6.71; N 4.06.

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