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Synthesis of Dispirotetrahydropyran-2,4-diones Containing Six- and Seven-Membered Rings

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Abstract—Methyl 1-(1-bromocyclohexylcarbonyl)cycloheptane- and 1-(1-bromocycloheptylcarbonyl)cyclohexanecarboxylates react with zinc and aromatic aldehydes yielding 17-aryl-16-oxadispiro[5.1.6.3]heptadecane-7,15-diones and 15-aryl-16-oxadispiro[5.1.6.3]heptadecane-7,17-diones respectively.

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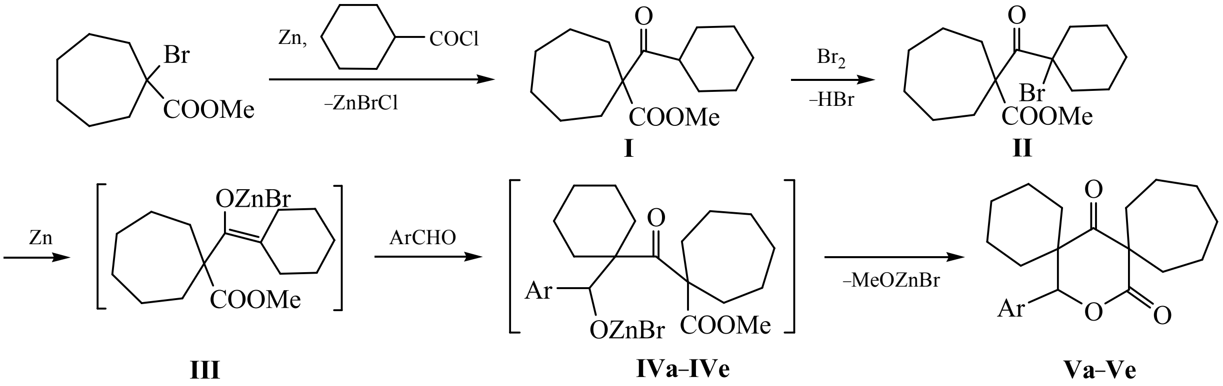
Dispirotetrahydropyran-2,4-diones involving four-, five- and six-membered rings were earlier obtained by the Reformatorskii’s reaction [1-3]. We synthesized dispirotetrahydropyran-2,4-diones containing six- and seven-membered rings simultaneously. Reaction of methyl 1-bromocycloheptanecarboxylate with zinc and cyclohexanecarboxylic acid chloride gives rise to methyl 1-cyclohexylcarbonylcycloheptanecarboxylate **I**. Methyl 1-(1-bromocyclohexylcarbonyl)cycloheptanecarboxylate **II** was produced, when compound **I** was brominated in acetic acid. Reaction of **II** with zinc yields bromozinc-enolate **III**, which was added to the carbonyl group of aromatic aldehydes to give bromozinc-alcoholates **IVa–IVe**. In the course of the reaction the latter suffered a spontaneous ring closure liberating bromozinc methylate and forming the substituted dispirotetrahydropyran-2,4-diones containing six- and seven-membered rings, namely, 17-aryl-16-oxadispiro[5.1.6.3]heptadecane-7,15-diones **Va–Ve** (Scheme 1).

Similarly the reaction of methyl 1-bromocyclohexanecarboxylate with zinc and the cycloheptanecarboxylic acid chloride produces methyl 1-cycloheptylcarbonylcyclohexanecarboxylate **VI**, the bromination of which yields methyl 1-(1-bromo-cycloheptylcarbonyl)cyclohexanecarboxylate **VII**. The latter reacts with zinc to form bromozinc-enolate **VIII**, which was added to the carbonyl group of aromatic aldehydes yielding bromozincalcoholates **IXa–IXd**. Their cyclization results in 15-aryl-16-oxadispiro-[5.1.6.3]heptadecane-7,17-diones **Xa–Xd** (Scheme 2).

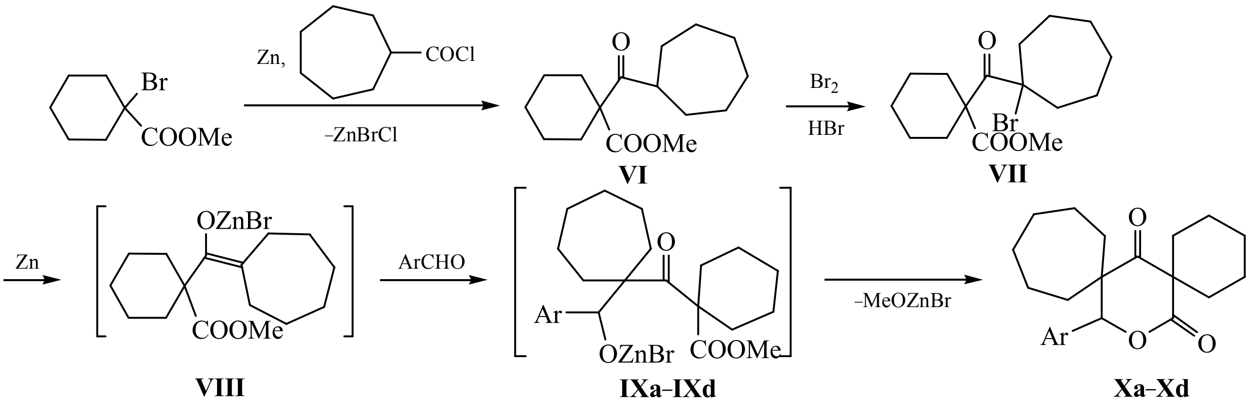
Yields of the reaction products are 63–93%. The composition and the structure of compounds **Va–Ve** and **Xa–Xd** were confirmed by the elemental analysis

Scheme 1.



IV, V: Ar = 4-BrC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**), Ph (**d**), 4-$MeOC_6H_4$ (**e**).

Scheme 2.



IX, X: Ar = 4-BrC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**), 4-FC_6H_4 (**d**).

data, IR and ^{1}H NMR spectroscopy. The IR spectra contain characteristic absorption bands of ketone carbonyls in the range of 1705–1715 cm^{-1} and of lactone carbonyl groups at 1735–1750 cm^{-1}. In the ^{1}H NMR spectra there are characteristic singlet signals of the methine protons at 5.08–5.81 ppm.

EXPERIMENTAL

The IR spectra of compounds **I**, **II**, **Va–Ve**, **VI**, **VII** and **Xa-Xd** were obtained on a Specord-75IR spectrophotometer in mineral oil. The ^{1}H NMR spectra of compounds **I**, **II**, **Vd**, **Ve**, **VI**, **VII**, **Xa–Xd** ($CDCl_3$) and **Va–Vc** (DMSO-d_6) were registered on a TESLA BS-576A spectrometer (100 MHz) relative to internal TMS.

Methyl 1-cyclohexylcarbonylcycloheptanecarboxylate (I). To a mixture of 10 g of the fine zinc turnings in 25 ml of anhydrous benzene and 10 ml of anhydrous ethyl acetate were dropwise added 0.1 mol of methyl 1-bromocycloheptanecarboxylate and 0.1 mol of chloroanhydride of cyclohexanecarbonyl chloride in 50 ml of ethyl acetate. This mixture was refluxed for 1 h, decanted from the excess zinc, and hydrolyzed with water. The organic layer was separated and dried with anhydrous sodium sulfate. Then the solvents were evaporated and the reaction product was twice distilled in a vacuum. Yield 11.2 g (42 %), mp 168–170°C (6 mm Hg), d_4^{20} 1.0523, n_D^{20} 1.4881. IR spectrum, ν, cm^{-1}: 1715, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.02–2.17 m [22H, $(CH_2)_5$, $(CH_2)_6$], 2.30–2.65 m (1H, CHCO), 3.65 s (3H, OMe). Found, %: C 72.36; H 9.68. $C_{16}H_{26}O_3$. Calculated, %: C 72.14; H 9.84.

Methyl 1-(1-bromocyclohexylcaronyl)cycloheptanecarboxylate (II). To a solution of 0.05 mol of compound **I** in 20 ml of acetic acid was added 0.055 mol of bromine. This mixture was heated for 1 h on a water bath. Then the acetic acid and excess bromine were evaporated and the reaction product was distilled in a vacuum. Yield 12.3 g (71%), mp 48–49°C. IR spectrum, ν, cm^{-1}: 1710, 1745 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.05–2.37 m [22H, $(CH_2)_5$, $(CH_2)_6$], 3.63 s (3H, OMe). Found, %: C 55.84; H 7.17; Br 22.91. $C_{16}H_{25}BrO_3$. Calculated, %: C 55.66; H 7.30; Br 23.14.

17-Aryl-16-oxadispiro[5.1.6.3]heptadecane-7,15-diones (Va–Ve). To a mixture of 1 g of the fine zinc turnings, catalytic amount of mercury(II) chloride, and 30 ml of anhydrous ethyl acetate was dropwise added a mixture of 10 mmol of compound **II** and 9.6 mmol of the corresponding aldehyde in 15 ml of anhydrous ethyl acetate under stirring. In the preparation of compound **Vc** the 3-nitrobenzaldehyde was added after heating compound **II** with zinc for 0.5 h. The reaction mixture was refluxed for 2 h, cooled, decanted from the excess zinc and hydrolyzed with 5% hydrochloric acid. The organic layer was separated. The reaction product was twice extracted from the water layer with ethyl acetate and dried with anhydrous sodium sulfate. Then ethyl acetate was removed and the product was recrystalled from ethyl acetate.

17-(4-Bromophenyl)-16-oxadispiro[5.1.6.3]heptadecane-7,15-dione (Va). Yield 1.95 g (93%), mp 212–213°C. IR spectrum, ν, cm^{-1}: 1715, 1750 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60–2.60 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.51 s (1H, CHO), 7.26 d, 7.55 d (4H, 4-BrC_6H_4, *J* 8.3 Hz). Found, %: C 62.88; H 6.57; Br 18.83. $C_{22}H_{27}BrO_3$. Calculated, %: C 63.01; H 6.49; Br 19.05.

17-(4-Chlorphenyl)-16-oxadispiro[5.1.6.3]heptadecane-7,15-dione (Vb). Yield 1.69 g (90%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 1715, 1745 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60–2.30 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.52 s (1H, CHO), 7.30 d, 7.42 d (4H, 4-ClC_6H_4, *J* 8.4 Hz). Found, %: C 70.32; H 7.40; Cl 9.28. $C_{22}H_{27}ClO_3$. Calculated, %: C 70.48; H 7.26; Cl 9.46.

17-(3-Nitrophenyl)-16-oxadispiro[5.1.6.3]heptadecane-7,15-dione (Vc). Yield 1.60 g (83%), mp 193–194°C. IR spectrum, ν, cm^{-1}: 1715, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60–2.60 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.81 s (1H, CHO), 7.68 t, 7.72 d, 8.14 s, 8.20 d (4H, 3-$NO_2C_6H_4$, *J* 8 Hz). Found, %: C 68.42; H 7.21; N 3.44. $C_{22}H_{27}NO_5$. Calculated, %: C 68.55; H 7.06; N 3.63.

17-(Phenyl)-16-oxadispiro[5.1.6.3]heptadecane-7,15-diones (Vd). Yield 1.28 g (75%), mp 155–156°C. IR spectrum, ν, cm^{-1}: 1705, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60–2.40 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.13 s (1H, CHO), 7.27 s (5H, Ph). Found, %: C 77.39; H 8.20. $C_{22}H_{28}O_3$. Calculated, %: C 77.61; H 8.29.

17-(4-Methoxyphenyl)-16-oxadispiro[5.1.6.3]heptadecane-7,15-dione (Ve). Yield 1.33 g (72%), mp 185–186°C. IR spectrum, ν, cm^{-1}: 1705, 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.60–2.40 m [22H, $(CH_2)_5$, $(CH_2)_6$], 3.78 s (3H, MeO), 5.08 s (1H, CHO), 6.80 d, 7.15 d (4H, $MeOC_6H_4$, *J* 8.4 Hz). Found, %: C 74.69; H 8.29. $C_{23}H_{30}O_4$. Calculated, %: C 74.56; H 8.16.

Methyl 1-cycloheptylcarbonylcyclohexanecarboxylate (VI) was prepared similarly to compound **I** from methyl 1-bromocyclohexanecarboxylate and cycloheptanecarbonyl chloride. Yield 12.3 g (46%), mp 171–174°C (10 mm Hg), d_4^{20} 1.0557, n_D^{20} 1.4886. IR spectrum, ν, cm^{-1}: 1710, 1725 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.10–2.25 m [22H, $(CH_2)_5$, $(CH_2)_6$], 2.60–2.90 m (1H, CHCO), 3.67 s (3H, OMe). Found, %: C 72.01; H 9.95. $C_{16}H_{26}O_3$. Calculated, %: C 72.14; H 9.84.

Methyl 1-(1-bromocycloheptylcarbonyl)cyclohexanecarboxylate (VII) was prepared similarly to compound **II** from compound **IV**. Yield 11.7 g (68%), bp 195–197°C (9 mm Hg), d_4^{20} 1.2745, n_D^{20} 1.5162. IR spectrum, ν, cm^{-1}: 1720, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.20–2.50 m [22H, $(CH_2)_5$, $(CH_2)_6$], 3.64 s (3H, OMe). Found, %: C 55.92; H 7.41; Br 23.40. $C_{16}H_{25}BrO_3$. Calculated, %: C 55.66; H 7.30; Br 23.14.

15-Aryl-16-oxadispiro[5.1.6.3]heptadecane-7,17-diones (Xa–Xd) were prepared similarly to compounds **V** using compound **VII** as the starting material.

15-(4-Bromophenyl)-16-oxadispiro[5.1.6.3]-heptadecane-7,17-dione (Xa). Yield 1.89 g (90%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 1705, 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80–2.40 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.20 s (1H, CHO), 7.20 d, 7.43 d (4H, 4-BrC_6H_4, *J* 8.3 Hz). Found, %: C 63.20; H 6.54; Br 19.28. $C_{22}H_{27}BrO_3$. Calculated, %: C 63.01; H 6.49; Br 19.05.

15-(4-Chlorophenyl)-16-oxadispiro[5.1.6.3]-heptadecane-7,17-dione (Xb). Yield 1.63 g (87%), mp 184–185°C. IR spectrum, ν, cm^{-1}: 1715, 1745 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80–2.45 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.23 s (1H, CHO), 7.32 d, 7.40 d (4H, 4-ClC_6H_4, *J* 8.4 Hz). Found, %: C 70.54; H 7.09; Cl 9.58. $C_{22}H_{27}ClO_3$. Calculated, %: C 70.48; H 7.26; Cl 9.46.

15-(3-Nitrophenyl)-16-oxadispiro[5.1.6.3]-heptadecane-7,17-dione (Xc). Yield 1.21 g (63%), mp 112–113°C. IR spectrum, ν, cm^{-1}: 1715, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80–2.50 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.37 s (1H, CHO), 7.51 t, 7.74 d, 8.17 d, 8.20 s (4H, 3-$NO_2C_6H_4$, *J* 8.3 Hz). Found, %: C 68.36; H 7.01; N 3.58. $C_{22}H_{27}NO_5$. Calculated, %: C 68.55; H 7.06; N 3.63.

15-(4-Fluorophenyl)-16-oxadispiro[5.1.6.3]-heptadecane-7,17-dione (Xd). Yield 1.34 g (75%), mp 141–142°C. IR spectrum, ν, cm^{-1}: 1705, 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80–2.44 m [22H, $(CH_2)_5$, $(CH_2)_6$], 5.23 s (1H, CHO), 6.99 t, 7.30 t (4H, 4-FC_6H_4, *J* 8.4 Hz). Found, %: C 73.86; H 7.71. $C_{22}H_{27}FO_3$. Calculated, %: C 73.72; H 7.59.

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