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Synthesis of 6-Aryltetrahydropyran-2,4-diones Containing Tetra- and Pentamethylene Substituents in the 3 and 5 Positions of the Heteroring

V. V. Shchepin, N. F. Kirillov, and M. I. Vakhrin

Perm State University, Perm, Russia

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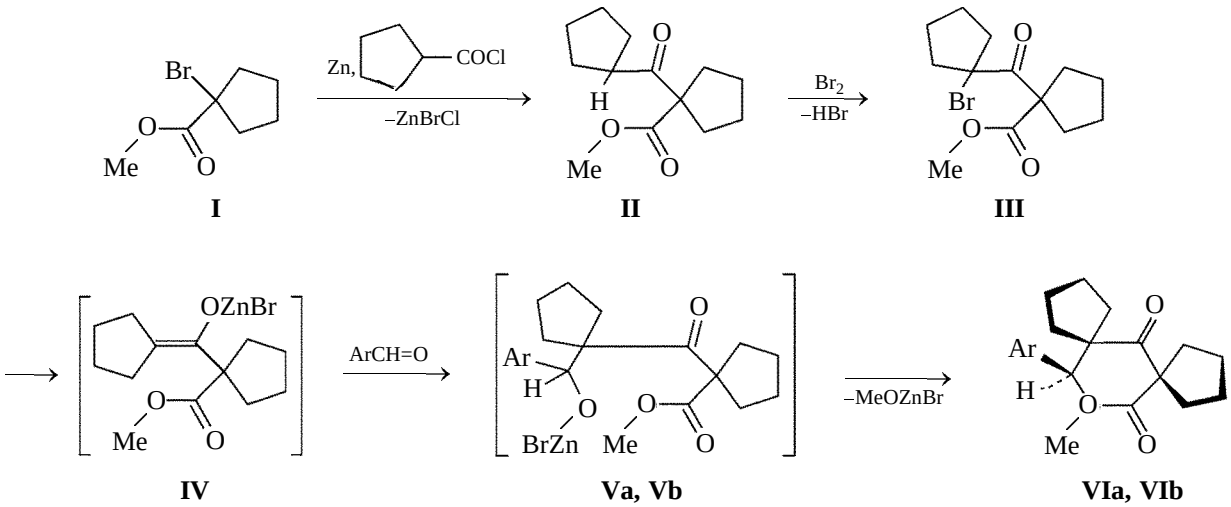
Abstract—Methyl esters of 1-(1-bromocyclopentylcarbonyl)- and 1-(1-bromocyclohexylcarbonyl)cyclopentanecarboxylic or 1-(1-bromocyclopentylcarbonyl)cyclohexanecarboxylic acids react with zinc and aromatic aldehydes to form 14-aryl-13-oxadispiro[4.1.4.3]tetradecane-6,12-diones, 13-aryl-14-oxadispiro[4.1.5.3]pentadecane-6,15-diones, and 15-aryl-14-oxadispiro[4.1.5.3]pentadecane-6,13-diones, respectively.

Proceeding with our research on the synthesis of substituted tetrahydropyran-2,4-diones with spiro carbon atoms in the 3 and 5 positions of the heteroring [1], we developed synthetic procedures for related compounds with tetra- and pentamethylene substituents in the mentioned positions. Under Reformatskii reaction conditions, starting from methyl 1-bromocyclopentanecarboxylate (**I**), zinc, and cyclopentylcarbonyl chloride, we prepared methyl 1-(cyclopentylcarbonyl)cyclopentanecarboxylate (**II**). The latter was brominated to obtain a key bromo derivative, methyl 1-(1-bromocyclopentylcarbonyl)cyclopentanecarboxylate (**III**). Bromo derivative **III** was reacted with zinc and aromatic aldehydes. The reaction involved addition of intermediate zinc enolate **IV** to the carbonyl group of the aldehyde, yielding intermediate **V** which spontaneously converted into the target pyran-2,4-diones with two tetramethylene substituents in the 3 and 5 positions of the heteroring, namely, 14-aryl-13-oxadispiro[4.1.4.3]tetradecane-6,12-diones **VIa** and **VIb**, by the following scheme.



I **II** **III**

IV **Va, Vb** **VIa, VIb**

V, VI, Ar = Ph (**a**), 4-BrC_6H_4 (**b**).

In a similar way, from bromo derivative **I**, zinc, and cyclohexylcarbonyl chloride we prepared methyl 1-(cyclohexylcarbonyl)cyclopentanecarboxylate (**VII**) whose subsequent bromination gave bromo derivative **VIII**. The latter was reacted with bromo derivative **VIII**, zinc, and aromatic aldehydes to obtain 13-aryl-14-oxadispiro[4.1.5.3]pentadecane-6,15-diones **IXa**–**IXc** by the following scheme.

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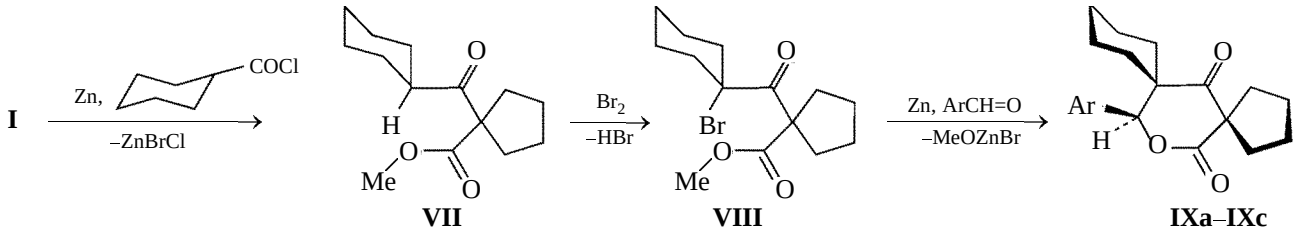
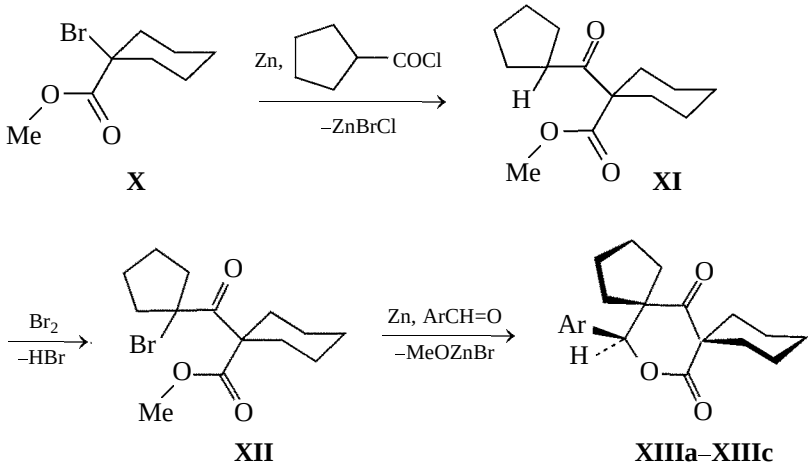


IX, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**).

In a similar way, from methyl 1-bromocyclohexanecarboxylate (**X**), zinc, and cyclopentylcarbonyl chloride we synthesized methyl 1-(cyclopentylcarbonyl)cyclohexanecarboxylate (**XI**) and brominated it to obtain compound **XII**. The Reformatskii reaction of the latter with zinc and aromatic aldehydes gave 15-aryl-14-oxadispiro[4.1.5.3]pentadecane-6,13-diones **XIIIa**–**XIIIc** by the following scheme.



XIII, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**).

The composition and structure of compounds **VIa**, **VIb**, **IXa**–**IXc**, and **XIIIa**–**XIIIc** were proved by elemental analysis and ^{1}H NMR and IR spectroscopy (see table). The ^{1}H NMR spectra of the synthesized compounds contain a methine proton signal at 5.15–5.77 ppm. The IR spectra display characteristic absorption bands at 1715–1720 and 1745–1750 cm^{-1}, belonging to the ketone and lactone carbonyl groups, respectively.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in $CDCl_3$ (**VIb**, **IXa**, **IXb**) or CCl_4 solutions (**IXc**, with DMSO-d_6 addition] on an RYa-2310 spectrometer (60 MHz), internal reference HMDS. The IR spectra were measured on a UR-20 spectrophotometer in mineral oil.

Methyl 1-(cyclopentylcarbonyl)cyclopentanecarboxylate (II). A solution of 0.1 mol of methyl 1-bromocyclopentanecarboxylate and 0.1 mol of cyclopentylcarbonyl chloride in 50 ml of anhydrous benzene was added dropwise to 10 g of fine zinc turnings in 10 ml of anhydrous ethyl acetate. The mixture was refluxed for 1 h, decanted from excess zinc, and hydrolyzed with water. The organic layer was dried with sodium sulfate, the solvent was removed by distillation, and the reaction product was distilled in a vacuum, yield 62%, bp 137–139°C (7 mm Hg), d_4^{20} 1.0726, n_D^{20} 1.4782. IR spectrum, ν, cm^{-1}: 1720, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.62 s (3H, OCH_3), 2.50–2.95 m (1H, CHCO), 1.10–2.20 m (16H, cyclopentane ring). Found, %: C 69.48; H 9.08. $C_{13}H_{20}O_3$. Calculated, %: C 69.61; H 8.99.

Yields, melting points, IR spectra, ^{1}H NMR spectra, and elemental analyses of 6-aryltetrahydropyran-2,4-diones **IVa, IVb, IXa**–**IXc**, and **XIIIa**–**XIIIc**

Comp. no	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm			Found, %			Formula	Calculated, %		
			C=O (ketone)	C=O (lactone)	Ar	CHO	[a]	C	H	Br (N)		C	H	Br (N)
VIa	54	156–157	1715	1745	7.35 s (5H ,Ph)	5.38 s (1H)	0.70–2.35 (16H)	76.29	7.41	–	$C_{19}H_{22}O_3$	76.48	7.43	–
VIb	44	166–167	1715	1745	7.25 d, 7.55 d (4H, 4-BrC_6H_4)	5.44 s (1H)	0.65–2.45 (16H)	60.31	5.55	20.95	$C_{19}H_{21}BrO_3$	60.49	5.61	21.18
IXa	75	163–164	1715	1745	7.29 s (5H, Ph)	5.18 s (1H)	0.65–2.45 (18H)	76.73	7.59	–	$C_{20}H_{24}O_3$	76.89	7.74	–
IXb	67	172–173	1715	1745	7.14 d, 7.52 d (4H, 4-BrC_6H_4)	5.15 s (1H)	0.75–2.35 (18H)	61.45	5.84	20.36	$C_{20}H_{23}BrO_3$	61.39	5.92	20.42
IXc	48	164–166	1715	1750	7.60–7.83 m, 8.10–8.25 m (4H, 3-$NO_2C_6H_4$)	5.77 s (1H)	0.65–2.25 (18H)	67.05	6.62	(3.74)	$C_{20}H_{23}NO_5$	67.21	6.49	(3.92)
XIIIa	75	138–139	1715	1745	7.32 s (5H, Ph)	5.39 s (1H)	0.90–2.30 (18H)	76.75	7.79	–	$C_{20}H_{24}O_3$	76.89	7.74	–
XIIIb	68	172–173	1715	1745	7.32 d, 7.43 d	5.37 s 5.37 s	0.90–2.25	61.21	5.83	20.20	$C_{20}H_{23}BrO_3$	61.39	5.92	20.42
XIIIc	54	144–145	1720	1750	7.55–7.85 m, 8.05–8.25 m (4H, 3-$NO_2C_6H_4$)	5.57 s (1H)	0.75–2.40 (18H)	67.35	6.32	(3.85)	$C_{20}H_{23}NO_5$	67.21	6.49	(3.92)

[a] Cyclohexane and cyclopentane rings.

Methyl 1-(cyclohexylcarbonyl)cyclopentanecarboxylate (VII) was prepared similarly to compound **II**, starting from methyl 1-bromocyclopentanecarboxylate and cyclohexylcarbonyl chloride, yield 69%, bp 159–162°C (12 mm Hg), d_4^{20} 1.0563, n_D^{20} 1.4802. IR spectrum, ν, cm^{-1}: 1720, 1735, 1750 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 2.55–3.00 m (1H, CHCO), 1.00–2.50 m (18H, cyclopentane and cyclohexane rings). Found, %: C 70.72; H 9.25. $C_{14}H_{22}O_3$. Calculated, %: C 70.56; H 9.30.

Methyl 1-(cyclopentylcarbonyl)cyclohexanecarboxylate (XI) was prepared similarly to compound **II**, starting from methyl 1-bromocyclohexane carboxylate and cyclopentylcarbonyl chloride, yield 58%, bp 162–164°C (14 mm Hg), d_4^{20} 1.0625, n_D^{20} 1.4823. IR spectrum, ν, cm^{-1}: 1715, 1730, 1745 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 2.65–3.05 m (1H, CHCO), 1.00–2.10 m (18H, cyclopentane and cyclohexane rings). Found, %: C 70.49; H 9.23. $C_{14}H_{22}O_3$. Calculated, %: C 70.56; H 9.30.

Methyl 1-(1-bromocyclopentylcarbonyl)cyclopentanecarboxylate (III). Bromine, 0.11 mol, was added to a stirred solution of 0.1 mol of compound **II** in 25 ml of acetic acid. The mixture was heated for

1.5 h on a water bath, excess bromine was removed by distillation, and the reaction product was distilled in a vacuum, yield 77%, bp 159–162°C (6 mm Hg), d_4^{20} 1.3508, n_D^{20} 1.5086. IR spectrum, ν, cm^{-1}: 1725, 1755 (C=O). ^1H NMR spectrum, ν, ppm: 3.60 s (3H, OCH_3), 1.10–2.35 m (16H, cyclopentane ring). Found, %: C 51.38; H 6.25; Br 26.48. $C_{13}H_{19}BrO_3$. Calculated, %: C 51.50; H 6.32; Br 26.35.

Methyl 1-(1-bromocyclohexylcarbonyl)cyclopentanecarboxylate (VIII) was prepared similarly to compound **III**, starting from compound **VII**. The reaction product was twice recrystallized from petroleum ether (bp 40–70°C), yield 61%, mp 62–63°C. IR spectrum, ν, cm^{-1}: 1715, 1730, 1755 (C=O). ^1H NMR spectrum, δ, ppm: 3.60 s (3H, OCH_3), 1.00–2.50 m (18H, cyclopentane and cyclohexane ring). Found, %: C 52.96; H 6.51; Br 25.25. $C_{14}H_{21}BrO_3$. Calculated, %: C 53.01; H 6.67; Br 25.19.

Methyl 1-(1-bromocyclopentylcarbonyl)cyclohexanecarboxylate (XII) was prepared similarly to compound **III**, starting from compound **XI**, yield 86%, bp 163–166°C (4 mm Hg), d_4^{20} 1.3369, n_D^{20} 1.5143. IR spectrum, ν, cm^{-1}: 1720, 1735, 1755 (C=O). ^1H NMR spectrum, δ, ppm: 3.61s (3H, OCH_3), 1.00–2.45 m (18H, cyclopentane and cyclohexane rings). Found, %: C 52.92; H 6.50; Br 25.01. $C_{14}H_{21}BrO_3$. Calculated, %: C 53.01; H 6.67; Br 25.19.

14-Aryl-13-oxadispiro[4.1.4.3]tetradecane-6,12-diones VIa, VIb. A solution of 0.02 mol of compound **III** and 0.017 mol of corresponding aldehyde in 30 ml of anhydrous ethyl acetate was added dropwise to a stirred mixture of 3 g of fine zinc turnings, a catalytic amount of mercuric chloride, and 30 ml of the same solvent. The reaction mixture was refluxed for 1 h, cooled, decanted from excess zinc, and hydrolyzed with 5% HCl. The organic layer was separated, and the aqueous layer was treated with two portions of ethyl acetate. The extract was dried with sodium sulfate, the solvent was removed by distillation, and compounds **VIa**, **VIb** were reacrystallized from ethyl acetate.

13-Aryl-14-oxadispiro[4.1.5.3]pentadecane-6,15-diones IXa–IXc. Compounds **IXa**, **IXb** were prepared similarly to compounds **VI**, starting from compound **VIII**. Compound **IXc** was prepared as follows. Compound **VIII**, 0.02 mol, in 15 ml of anhydrous ethyl acetate was added dropwise to a stirred mixture of 3 g of fine zinc turnings, a catalytic amount of mercuric chloride, and 30 ml of anhydrous ethyl acetate. The reaction mixture was refluxed for 0.5 h, cooled, a solution of 0.017 mol of 3-nitrobenzaldehyde in 15 ml of ethyl acetate was added, and then the reaction was performed as described for compounds **VI**.

15-Aryl-14-oxadispiro[4.1.5.3]pentadecane-6,13-diones XIIIa–XIIIc. Compounds **XIIIa**, **XIIIb** were prepared similarly to compound **VI**, and compound **XIIIc**, similarly to compound **IXc**, starting from compound **XII**.

REFERENCES

1. Kirillov, N.F. and Shchepin, V.V., *Zh. Org. Khim.*, 2001, vol. 37, no. 9, p. 1290.