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Synthesis of Substituted Methyl 5,5-Polymethylene-2,4-dioxotetrahydropyran-3-carboxylates

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Abstract—Dimethyl 2-(1-bromocyclohexylcarbonyl)-, 2-(1-bromocyclopentylcarbonyl)-, and 2-(1-bromocyclobutylcarbonyl)-2-methylmalonates reacted with zinc and aromatic aldehydes to give the corresponding methyl 1-aryl-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-, 6-aryl-9-methyl-8,10-dioxo-7-oxaspiro[4.5]-decane-9-, and 5-aryl-8-methyl-7,9-dioxo-6-oxaspiro[3.5]nonane-8-carboxylates.

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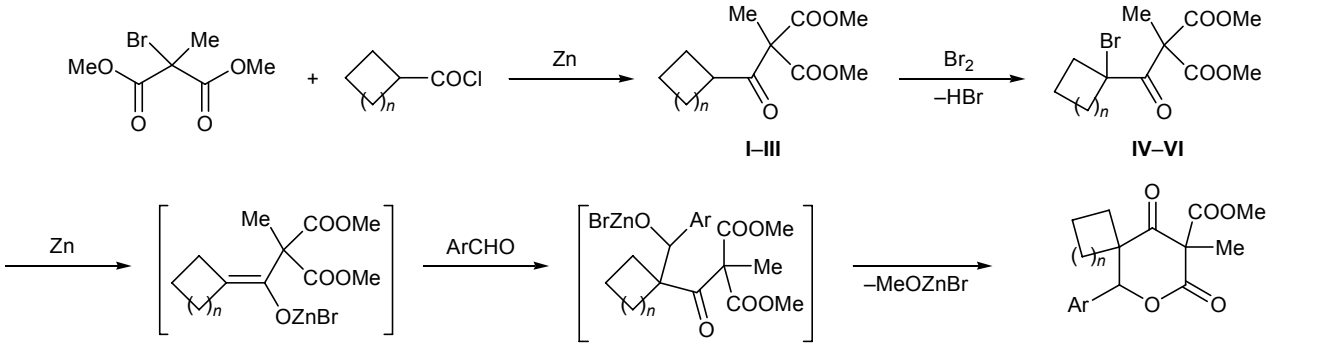
We found previously [1] that dialkyl 2-(2-bromoisobutyryl)malonates react with zinc and aldehydes to give the corresponding alkyl 2,4-dioxotetrahydropyran-3-carboxylates [1]. In the present communication we report on the synthesis of analogous compounds having a spiro carbon atom. The reactions of dimethyl 2-bromo-2-methylmalonate with zinc and cyclohexane-, cyclopentane-, and cyclobutanecarbonyl chlorides gave dimethyl 2-cycloalkylcarbonyl-2-methylmalonates **I**–**III** which were subjected to bromination with molecular bromine to obtain bromo derivatives **IV**–**VI**. The latter reacted with zinc yielding zinc enolates **VII**–**IX** which added at the carbonyl group of aromatic aldehydes with formation of alkoxides **X**–**XII**. Intramolecular cyclization of **X**–**XII** with elimination of MeOBrZn resulted in the formation of methyl 1-aryl-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-carboxylates **XIIIa**–**XIIId**, methyl 6-aryl-9-methyl-8,10-dioxo-7-oxaspiro[4.5]decane-9-carboxylates **XIVa** and **XIVb**, and 5-aryl-8-methyl-7,9-dioxo-6-oxaspiro[3.5]nonane-8-carboxylates **XVa** and **XVb** (Scheme 1).

The structure of the isolated compounds was confirmed by their elemental compositions and IR and ^{1}H NMR spectra. In the IR spectra of **XIII**–**XV**, absorption bands belonging to stretching vibrations of

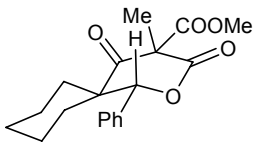
Scheme 1.



I, **IV**, **VII**, **X**, **XIII**, n = 3; **II**, **V**, **VIII**, **XI**, **XIV**, n = 2; **III**, **VI**, **IX**, **XII**, **XV**, n = 1; **X**–**XV**, Ar = 4-BrC_6H_4 (**a**), 4-ClC_6H_4 (**b**); **X**, **XIII**, Ar = Ph (**c**), 4-$MeOC_6H_4$ (**d**).

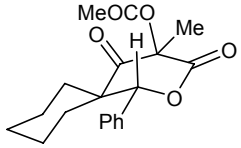
ketone (1695–1710 cm^{-1}), ester (1720–1730 cm^{-1}), and lactone carbonyl groups (1730–1760 cm^{-1}) were present. The ^1H NMR spectra of **XIII**–**XV** contained only one set of signals, the most characteristic signal being that of the ArC**H** proton (δ 5.82–5.93 ppm).

Theoretically, compounds **XIII**–**XV** may exist as four diastereoisomers differing by configuration of substituents on C^3 and C^6 in the pyran ring. Structures of diastereoisomers **A**–**D** of compound **XIIIc** are shown below; the corresponding total energies are also given. With a view to determine which of the above diastereoisomers is the most stable, their structures were analyzed by nonempirical quantum-chemical calculations usng 6-31(*d*) basis set with full geometry optimization. The results showed that isomers **C** and **D** are the least stable, so that their formation is likely to be improbable. Diastereoisomers **A** and **B** are characterized by similar energies; therefore, their stabilities should be comparable, though structure **A** is formally more stable. The C^6–Ph bond in stereoisomer **A** is equatorial, the 6-H proton and protons in the 3-CH_3 group appear spatially close, and the calculated distance 6-H···H–CH_2–C^3 is 2.271 Å. The corresponding fragments in stereoisomer **B** are distant from each other. The tetrahydropyran ring in isomer **A** has a flattened *chair* conformation: the C^6, O^1, C^2, and C^3 atoms lie almost in one plane, while the C^4 and C^5 atoms deviate from that plane by 0.678 and 1.048 Å, respectively. The cyclohexane ring has a *chair* conformation, and the C^5–C^4 bond in the tetrahydropyran ring occupies equatorial position in the cyclohexane ring. The steric structure of compound **XIIIc** was studied in detail by ^1H and ^{13}C NMR spectroscopy, including two-dimensional experiments (^1H–^1H COSY, ^1H–^1H NOESY, ^1H–^{13}C HSQC, ^1H–^1H ROESY, ^1H–^{13}C HMBC). Signals from carbon atoms were assigned on the basis of the DEPT, HMBC, and HSQC data. The results of ROESY and NOESY experiments indicated coupling of the ArC**H** proton with protons in the methyl group, and the HMBC data revealed interaction of the same proton with the methyl carbon atom. These findings suggest that the methyl group and ArC**H** hydrogen atom in molecule **XIIIc** are located at the same side of the tetrahydropyran ring (structure **A**).



A

–2913889.94 kJ/mol



B

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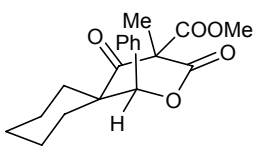
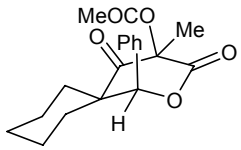


C

–2913882.83 kJ/mol



D

–2913878.09 kJ/mol

EXPERIMENTAL

The IR spectra of compounds **I**–**VI** and **XIII**–**XV** were recorded on a Specord 75IR spectrophotometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Varian Mercury Plus-300 instrument (300 MHz) using tetramethylsilane as internal reference and $CDCl_3$ (**I**–**VI**, **XVb**) or DMSO-d_6 as solvent (**XIIIa**–**XIIId**, **XIVa**, **XIVb**, **XVa**). Quantum-chemical calculations were performed using Gaussian-03w software package [2].

Dimethyl 2-(cyclohexylcarbonyl)-2-methylmalonate (I). A mixture of 0.11 mol (24.8 g) of dimethyl 2-bromo-2-methylmalonate and 0.1 mol (14.7 g) of cyclohexanecarbonyl chloride in 10 ml of ethyl acetate was added dropwise under stirring to a mixture of 15 g of fine zinc turnings, a catalytic amount of mercury(II) chloride, and 80 ml of anhydrous ethyl acetate–diethyl ether (1 : 1). The mixture was heated for 2 h under reflux and cooled, the liquid phase was separated from excess zinc by decanting and hydrolyzed with 5% acetic acid, the organic phase was separated, the aqueous phase was extracted with two portions of ethyl acetate, and the extracts were combined with the organic phase, washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was twice distilled under reduced pressure. Yield 14.1 g (55%), bp 136–138°C (3 mm), d_4^{20} = 1.1149, n_D^{20} = 1.4641. IR spectrum, ν, cm^{-1}: 1725, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.10–1.93 m (10H, CH_2), 1.63 s (3H, Me), 2.48–2.82 m (1H, CHCO), 3.74 s (6H, MeO). Found, %: C 61.11; H 7.72. $C_{13}H_{20}O_5$. Calculated, %: C 60.92; H 7.87.

Dimethyl 2-(cyclopentylcarbonyl)-2-methylmalonate (II) was synthesized in a similar way from dimethyl 2-bromo-2-methylmalonate and cyclopentanecarbonyl chloride. Yield 11.4 g (47%), bp 163–165°C (20 mm), d_4^{20} = 1.1177, n_D^{20} = 1.4556. IR spectrum, ν, cm^{-1}: 1725, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.40–1.95 m (8H, CH_2), 1.66 s (3H, Me), 3.40–3.50 m (1H, CHCO), 3.79 s (6H, MeO). Found, %: C 59.62; H 7.61. $C_{12}H_{18}O_5$. Calculated, %: C 59.49; H 7.49.

Dimethyl 2-(cyclobutylcarbonyl)-2-methylmalonate (III) was synthesized in a similar way from dimethyl 2-bromo-2-methylmalonate and cyclobutanecarbonyl chloride. Yield 15.1 g (66%), bp 154–156°C (25 mm), d_4^{20} = 1.1368, n_D^{20} = 1.4548. IR spectrum, ν, cm^{-1}: 1725, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 1.61 s (3H, Me), 1.80–2.40 m (6H, CH_2), 3.52–3.63 m (1H, CHCO), 3.78 s (6H, MeO). Found, %: C 58.02; H 6.95. $C_{11}H_{16}O_5$. Calculated, %: C 57.88; H 7.07.

Dimethyl 2-(1-bromocyclohexylcarbonyl)-2-methylmalonate (IV). Bromine, 0.055 mol (8.8 g, 2.8 ml), was added under stirring to a solution of 0.05 mol (12.8 g) of compound **I** in 30 ml of acetic acid, the mixture was heated for 1 h on a water bath, acetic acid and excess bromine were distilled off, and the product was distilled under reduced pressure. Yield 9.6 g (57%), bp 173–175°C (3 mm), mp 74–75°C (from hexane). IR spectrum, ν, cm^{-1}: 1725, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 1.50–2.30 m (10H, CH_2), 1.86 s (3H, Me), 3.74 s (6H, MeO). Found, %: C 46.73; H 5.89; Br 23.66. $C_{13}H_{19}BrO_5$. Calculated, %: C 46.58; H 5.71; Br 23.84.

Dimethyl 2-(1-bromocyclopentylcarbonyl)-2-methylmalonate (V) was synthesized in a similar way from compound **II**. Yield 8.7 g (54%), bp 161–163°C (4 mm), d_4^{20} = 1.3830, n_D^{20} = 1.4854. IR spectrum, ν, cm^{-1}: 1735, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 1.80–2.45 m (8H, CH_2), 1.87 s (3H, Me), 3.80 s (6H, MeO). Found, %: C 45.10; H 5.48; Br 24.59. $C_{12}H_{17}BrO_5$. Calculated, %: C 44.88; H 5.34; Br 24.88.

Dimethyl 2-(1-bromocyclobutylcarbonyl)-2-methylmalonate (VI) was synthesized in a similar way from compound **III**. Yield 12.0 g (78%), bp 158–160°C (6 mm), d_4^{20} = 1.4131, n_D^{20} = 1.4845. IR spectrum, ν, cm^{-1}: 1740, 1715 (C=O). ^1H NMR spectrum, δ, ppm: 1.83 s (3H, Me), 1.85–3.12 m (6H, CH_2), 3.80 s (6H, MeO). Found, %: C 43.28; H 4.99; Br 25.84. $C_{11}H_{15}BrO_5$. Calculated, %: C 43.02; H 4.92; Br 26.02.

Methyl 1-aryl-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-carboxylates XIIIa–XIIId (*general procedure***).** A mixture of 7 mmol (2.35 g) of compound **IV** and 7 mmol of aromatic aldehyde in 15 ml of anhydrous ethyl acetate was added dropwise under stirring to a mixture of 1 g of fine zinc turnings, a catalytic amount of mercury(II) chloride, 10 ml of anhydrous diethyl ether, and 10 ml of anhydrous ethyl acetate. The mixture was heated for 2 h under reflux and cooled, the solution was separated from excess zinc by decanting and hydrolyzed with 5% acetic acid, the organic phase was separated, 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, the solvent was distilled off, and the residue was recrystallized from methanol.

Methyl 1-(4-bromophenyl)-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-carboxylate (XIIIa). Yield 1.83 g (64%), mp 184–185°C. IR spectrum, ν, cm^{-1}: 1740, 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 0.60–2.10 m (10H, CH_2), 1.74 s (3H, Me), 3.71 s (3H, MeO), 5.92 s (1H, CHO), 7.37 d and 7.67 d (2H each, C_6H_4, J = 8.4 Hz). Found, %: C 55.58; H 5.35; Br 19.77. $C_{19}H_{21}BrO_5$. Calculated, %: C 55.76; H 5.17; Br 19.52.

Methyl 1-(4-chlorophenyl)-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-carboxylate (XIIIb). Yield 1.38 g (54%), mp 171–172°C. IR spectrum, ν, cm^{-1}: 1745, 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 0.60–2.10 m (10H, CH_2), 1.74 s (3H, Me), 3.71 s (3H, MeO), 5.93 s (1H, CHO), 7.43 d and 7.53 d (2H each, ClC_6H_4, J = 8.7 Hz). Found, %: C 62.37; H 5.98; Cl 9.60. $C_{19}H_{21}ClO_5$. Calculated, %: C 62.55; H 5.80; Cl 9.72.

Methyl 4-methyl-3,5-dioxo-1-phenyl-2-oxaspiro[5.5]undecane-4-carboxylate (XIIIc). Yield 1.30 g (56%), mp 164–165°C. IR spectrum, ν, cm^{-1}: 1735, 1725, 1695 (C=O). ^1H NMR spectrum, δ, ppm: 0.60–2.10 m (10H, CH_2), 1.74 s (3H, Me), 3.71 s (3H, MeO), 5.89 s (1H, CHO), 7.38–7.50 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 20.35 (CH_3); 20.48, 21.23, 23.55, 24.70, 28.51 (C^7–C^{11}), 49.88 (C^6), 53.25 (CH_3O), 61.79 (C^4), 81.70 (C^1), 127.87 (C^m), 128.54 (C^o), 128.84 (C^p), 133.44 (C^i), 166.75 (COO), 168.89 (C^3), 205.08 (C^5). Found, %: C 68.83; H 6.89. $C_{19}H_{22}O_5$. Calculated, %: C 69.07; H 6.71.

Methyl 1-(4-methoxyphenyl)-4-methyl-3,5-dioxo-2-oxaspiro[5.5]undecane-4-carboxylate (XIIId). Yield 1.08 g (43%), mp 167–168°C. IR spectrum, ν, cm^{-1}: 1730, 1720, 1695 (C=O). ^1H NMR spectrum, δ, ppm: 0.60–2.10 m (10H, CH_2), 1.73 s (3H, Me), 3.70 s (3H, MeO), 3.79 s (3H, MeO), 5.82 s (1H, CHO), 7.01 d and 7.33 d (2H each, C_6H_4, J = 8.4 Hz). Found, %: C 66.88; H 6.56. $C_{20}H_{24}O_6$. Calculated, %: C 66.65; H 6.71.

Compounds **XIVa**, **XIVb**, **XVa**, and **XVb** were synthesized in a similar way from the corresponding diesters **V** and **VI**.

Methyl 5-(4-bromophenyl)-8-methyl-7,9-dioxo-6-oxaspiro[4.5]decane-9-carboxylate (XIVa). Yield

1.55 g (56%), mp 115–117°C. IR spectrum, ν, cm^{-1}: 1750, 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 0.77–2.18 m (8H, CH_2), 1.62 s (3H, Me), 3.80 s (3H, MeO), 5.84 s (1H, CHO), 7.50 d and 7.66 d (2H each, C_6H_4, J = 8.7 Hz). Found, %: C 54.88; H 4.93; Br 20.09. $C_{18}H_{19}BrO_5$. Calculated, %: C 54.70; H 4.85; Br 20.22.

Methyl 5-(4-chlorophenyl)-8-methyl-7,9-dioxo-6-oxaspiro[4.5]decane-9-carboxylate (XIVb). Yield 1.28 g (52%), mp 119–120°C. IR spectrum, ν, cm^{-1}: 1755, 1730, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 0.74–2.18 m (8H, CH_2), 1.62 s (3H, Me), 3.80 s (3H, MeO), 5.86 s (1H, CHO), 7.52 d and 7.57 d (2H each, C_6H_4, J = 9.0 Hz). Found, %: C 61.45; H 5.33; Cl 10.32. $C_{18}H_{19}ClO_5$. Calculated, %: C 61.63; H 5.46; Cl 10.11.

Methyl 5-(4-bromophenyl)-8-methyl-7,9-dioxo-6-oxaspiro[3.5]nonane-8-carboxylate (XVa). Yield 1.20 g (45%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 1755, 1725, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.02–2.58 m (6H, CH_2), 1.51 s (3H, Me), 3.76 s (3H, MeO), 5.89 s (1H, CHO), 7.50 d and 7.71 d (2H each, C_6H_4, J = 8.1 Hz). Found, %: C 53.78; H 4.56; Br 21.14. $C_{17}H_{17}BrO_5$. Calculated, %: C 53.56; H 4.49; Br 20.96.

Methyl 5-(4-chlorophenyl)-8-methyl-7,9-dioxo-6-oxaspiro[3.5]nonane-8-carboxylate (XVb). Yield 1.13 g (48%), mp 137–138°C. IR spectrum, ν, cm^{-1}: 1760, 1725, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 1.20–2.75 m (6H, CH_2), 1.62 s (3H, Me), 3.80 s (3H, MeO), 5.66 s (1H, CHO), 7.37 d and 7.43 d (2H each, C_6H_4, J = 8.7 Hz). Found, %: C 60.81; H 5.18; Cl 10.34. $C_{17}H_{17}ClO_5$. Calculated, %: C 60.63; H 5.09; Cl 10.53.

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