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Synthesis and Some Transformations of Bicyclic γ-Lactones with a Fused Cyclopropane Ring

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Abstract—Reductive cyclization of 4-hydroxymethyl-5,5-dimethyl(or pentamethylene)-2,5-dihydrofuran-2-ones by the action of sodium tetrahydridoborate gave bicyclic compounds in which the lactone ring is fused to a cyclopropane ring. Hydrolysis of the products with aqueous sodium hydroxide resulted in the formation of the corresponding disodium cyclopropane-1,1-dicarboxylates, which reacted with alkyl halides to produce the diesters. Acid hydrolysis of the fused systems was accompanied by opening of the cyclopropane ring with formation of 4-chloromethyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylic acid.

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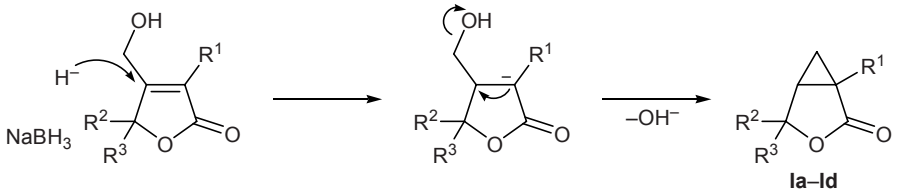
Functionally substituted cyclopropane derivatives, as well as derivatives of saturated γ-lactones, are widespread in nature, and they often exhibit pronounced biological activity. Apart from monocyclic cyclopropane derivatives, fused bicyclic terpenes containing a cyclopropane ring, derivatives of carane and carene [1], thujane and thujene [2], etc., are encountered in nature. Therefore, synthesis of systems including both γ-lactone and cyclopropane ring is important.

We previously patented a procedure for the synthesis of bicyclic lactones containing a cyclopropane ring via reductive cyclization of 5,5-dialkyl(or polymethylene)-4-bromomethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acids or their esters by the action of sodium tetrahydridoborate [3]. While studying selective hydrogenation of the endocyclic double bond in 5,5-dialkyl-(or pentamethylene)-4-hydroxymethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acids or their esters [4] with $NaBH_4$ in tetrahydrofuran we found that the products were ethyl 4,4-dimethyl(or pentamethylene)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylates **Ia** and **Ib** or the corresponding carboxylic acids **Ic** and **Id** rather than expected saturated γ-butyrolactones (Scheme 1). The product structure was determined on the basis of their IR, ^{1}H and ^{13}C NMR, and mass spectra, which unambiguously showed that the lactone ring in **Ia**–**Id** is fused to a cyclopropane ring, i.e., the reaction was similar to that observed for the corresponding 4-bromomethyl derivatives. Presumably, initial attack by hydride ion at the activated (electrophilic) β-carbon atom in 4-hydroxymethyl derivatives gives intermediate carbanion with localization of the negative charge on the α-carbon atom (with respect to the carbonyl group), and the intermediate is stabilized by intramolecular nucleophilic cyclization.

Thus we were the first to obtain bicyclic systems consisting of cyclopropane and γ-lactone rings by reductive cyclization of hydroxymethyl-substituted butenolides. The products may be used as initial compounds for the synthesis of functionally substituted

Scheme 1.

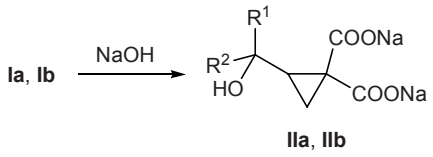


Ia–Id

R^1 = EtOCO (**a**, **b**), HOCO (**c**, **d**); $R^2 = R^3$ = Me (**a**, **c**), $R^2R^3 = (CH_2)_5$ (**b**, **d**).

cyclopropane derivatives. Taking into account that γ-lactone ring is unstable in alkaline medium, compounds **Ia** and **Ib** were subjected to alkaline hydrolysis by heating in aqueous sodium hydroxide; as a result, the corresponding disodium cyclopropane-1,1-dicarboxylates **IIa** and **IIb** were formed (Scheme 2).

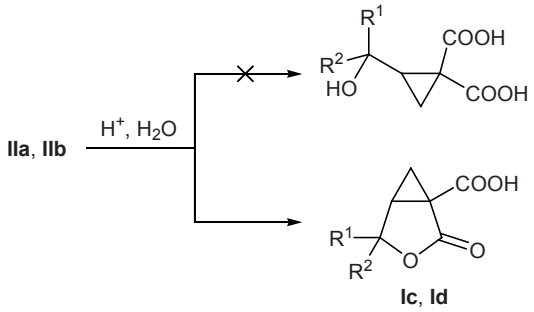
Scheme 2.



$R^1 = R^2 = Me$ (**a**), $R^1R^2 = (CH_2)_5$ (**b**).

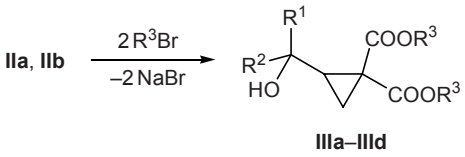
However, our attempt to convert salts **IIa** and **IIb** into the diacids resulted in closure of cyclopropane ring with formation of initial bicyclic systems **Ic** and **Id** (Scheme 3).

Scheme 3.



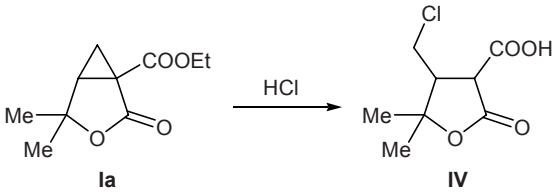
Disodium salts **IIa** and **IIb** were converted into diethyl and dipropyl esters **IIIa**–**IIId** by treatment with 2 equiv of ethyl or propyl bromide (Scheme 4). Acid

Scheme 4.



$R^1 = R^2 = Me$ (**a**, **c**), $R^1R^2 = (CH_2)_5$ (**b**, **d**);
$R^3 = Et$ (**a**, **b**), Pr (**c**, **d**).

Scheme 5.



hydrolysis of compound **Ia** in the presence of hydrochloric acid was accompanied by opening of the cyclopropane ring with formation of 4-chloromethyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylic acid (**IV**) (Scheme 5).

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Varian Mercury 300 instrument (300 MHz for ^1H) relative to tetramethylsilane as internal reference using DMSO-d_6–CCl_4 (1:3) as solvent. The mass spectrum of compound **Ia** (electron impact, 50–70 eV) was obtained on an MKh-1321A instrument with direct sample admission into the ion source. The purity of the products was checked by TLC on Silufol UV-254 plates using acetone–benzene (1:2) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

Ethyl 4,4-dimethyl(or pentamethylene)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylates Ia and Ib and 4,4-dimethyl(or pentamethylene)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acids Ic and Id (*general procedure***).** Sodium tetrahydridoborate, 0.19 g (5 mmol), was added in small portions to a solution of 3 mmol of the corresponding hydroxymethyl-substituted γ-butyrolactone in a mixture of 5 ml of tetrahydrofuran and 1 ml of water. The mixture was stirred for 3 h at room temperature, acidified to pH 3 with dilute (1:1) hydrochloric acid, and extracted with chloroform. The extract was dried over magnesium sulfate, and the solvent was distilled off to isolate compound **Ia**–**Id** as a crystalline substance.

Ethyl 4,4-dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate (Ia). Yield 0.5 g (84%), mp 78°C (from hexane), R_f 0.56. IR spectrum, ν, cm^{-1}: 1740 (C=O, ester), 1780 (C=O, lactone). ^1H NMR spectrum, δ, ppm: 1.31 t (3H, CH_2CH_3, J = 7.1 Hz), 1.39 s and 1.50 s (3H each, CH_3), 1.44 d and 1.46 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.9 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 4.27 q (2H, OCH_2, J = 7.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.63 (CH_3), 23.22 and 28.62 (CH_3), 18.14 (CH_2), 36.24 (CH), 39.79 (C), 60.61 (OCH_2), 79.81 (C^4), 165.58 and 16.793 (C=O). Mass spectrum, m/z (I_{rel}, %): 198 (10), 184 (11), 183 (100), 155 (13), 139 (11), 81 (10), 43 (44). Found, %: C 60.54; H 7.00. $C_{10}H_{14}O_4$. Calculated, %: C 60.60; H 7.07.

Ethyl 4-oxo-3-oxaspiro[bicyclo[3.1.0]hexane-2,1′-cyclohexane]-5-carboxylate (Ib). Yield 0.54 g (75%), mp 79°C (from hexane), R_f 0.54. IR spectrum, ν, cm^{-1}: 1740 (C=O, ester), 1780 (C=O, lactone). ^1H NMR spectrum, δ, ppm: 1.3 t (3H, CH_2CH_3, J = 7.1 Hz), 1.43 d and 1.45 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.6–1.9 m (10H, CH_2), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.9 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 4.2 q (2H, OCH_2, J = 7.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.34 and 28.69 (CH_3), 18.08 (CH_2), 36.25 (CH), 39.78 (C), 79.64 (C_{spiro}), 167.28 and 168.63 (C=O). Found, %: C 65.51; H 7.53. $C_{13}H_{18}O_4$. Calculated, %: C 65.55; H 7.56.

4,4-Dimethyl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylic acid (Ic). Yield 0.35 g (69%), mp 105°C (from hexane), R_f 0.59. IR spectrum, ν, cm^{-1}: 1730 (C=O, acid), 1770 (C=O, lactone), 2700 (OH, assoc.). ^1H NMR spectrum, δ, ppm: 1.36 s and 1.50 s (3H each, CH_3), 1.44 d and 1.46 d (1H, CH_2, J = 5.4, 4.8 Hz), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.8 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 12.40 br (1H, COOH). Found, %: C 56.42; H 5.82. $C_8H_{10}O_4$. Calculated, %: C 56.47; H 5.88.

4-Oxo-3-oxaspiro[bicyclo[3.1.0]hexane-2,1′-cyclohexane]-5-carboxylic acid (Id). Yield 0.40 g (64%), mp 145–146°C (from petroleum ether), R_f 0.58. IR spectrum, ν, cm^{-1}: 1740 (C=O, acid), 1780 (C=O, lactone), 2700 (OH, assoc.). ^1H NMR spectrum, δ, ppm: 1.43 d and 1.45 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.6–1.9 m (10H, CH_2), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.9 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 12.40 br (1H, COOH). Found, %: C 62.52; H 6.62. $C_{11}H_{14}O_4$. Calculated, %: 62.86; H 6.67.

Disodium 2-(1-hydroxy-1-methylethyl)- and 2-(1-hydroxycyclohexyl)cyclopropane-1,1-dicarboxylates IIa and IIb (*general procedure***).** A mixture of 2.5 mmol of compound **Ia** and **Ib** and 6 ml of an aqueous solution of 0.2 g (5 mmol) of sodium hydroxide was heated for 4 h at 75°C. Water was removed from the reaction mixture under reduced pressure, and disodium salts **IIa** and **IIb** were isolated as colorless crystalline substances which were washed with cold acetone.

Disodium 2-(1-hydroxy-1-methylethyl)cyclopropane-1,1-dicarboxylate (IIa). Yield 0.45 g (77%). IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^1H NMR spectrum, δ, ppm: 1.2 d and 1.22 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.32 d and 1.34 d (1H, CH_2, J = 8.1, 4.9 Hz), 1.39 s and 1.46 s (3H each, CH_3), 1.79 d and 1.82 d (1H, CH, J = 8.1, 5.4 Hz). Found, %: C 41.52; H 4.42. $C_8H_{10}Na_2O_5$. Calculated, %: C 41.38; H 4.31.

Disodium 2-(1-hydroxycyclohexyl)cyclopropane-1,1-dicarboxylate (IIb). Yield 0.5 g (73%). IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^1H NMR spectrum, δ, ppm: 1.2 d and 1.2 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.3 d and 1.34 d (1H, CH_2, J = 8.1, 4.9 Hz), 1.62–1.9 m (10H, CH_2), 2.0 d and 2.2 d (1H, CH, J = 8.1, 5.4 Hz) Found, %: C 48.63; H 5.28. $C_{11}H_{14}Na_2O_5$. Calculated, %: C 48.52; H 5.14.

Dialkyl 2-(1-hydroxy-1-methylethyl)- and 2-(1-hydroxycyclohexyl)cyclopropane-1,1-dicarboxylates IIIa–IIId (*general procedure***).** A mixture of 0.01 mol of disodium salt **IIa** or **IIb** and 0.02 mol of ethyl or propyl bromide in 55 ml of dimethylformamide was heated for 3 h at 90–100°C. The solvent was distilled off under reduced pressure, the residue was treated with water and extracted with diethyl ether, the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

Diethyl 2-(1-hydroxy-1-methylethyl)cyclopropane-1,1-dicarboxylate (IIIa). Yield 0.35 g (56%), bp 70–72°C (5 mm), n_D^{20} = 1.4600. IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^1H NMR spectrum, δ, ppm: 1.30 t (6H, CH_2CH_3, J = 7.4 Hz), 1.44 d and 1.46 d (1H, CH, J = 5.4, 4.9 Hz), 1.38 s and 1.50 s (3H each, CH_3), 1.82 d and 1.86 d (1H, CH, J = 8.1, 4.9 Hz), 2.55 d and 2.60 d (1H, CH_2, J = 8.1, 5.4 Hz), 4.20 q (2H, OCH_2, J = 7.5 Hz). Found, %: C 59.22; H 8.11. $C_{12}H_{20}O_5$. Calculated, %: C 59.02; H 8.20.

Diethyl 2-(1-hydroxycyclohexyl)cyclopropane-1,1-dicarboxylate (IIIb). Yield 1.5 g (53%), bp 93–96°C (5 mm), n_D^{20} = 1.4610. IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^1H NMR spectrum, δ, ppm: 1.0 t (6H, CH_2CH_3, J = 7.1 Hz), 1.2 d and 1.22 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.30 d and 1.34 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.6–1.9 m (10H, CH_2), 2.0–2.2 d (1H, CH, J = 8.1, 5.4 Hz), 4.25 q (4H, OCH_2, J = 7.5 Hz). Found, %: C 63.45; H 8.71. $C_{15}H_{24}O_5$. Calculated, %: C 63.38; H 8.45.

Dipropyl 2-(1-hydroxy-1-methylethyl)cyclopropane-1,1-dicarboxylate (IIIc). Yield 0.4 g (55%), bp 92–95°C (5 mm), n_D^{20} = 1.4640. IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^1H NMR spectrum, δ, ppm: 0.99 t (6H, $CH_2CH_2CH_3$, J = 7.1 Hz), 1.39 s and 1.50 s (3H each, CH_3), 1.44 d and 1.46 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.9 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 1.7–1.8 m (4H, $CH_2CH_2CH_3$) 4.25 t (4H, OCH_2, J = 7.1 Hz).

Found, %: C 61.82; H 8.85. $C_{14}H_{24}O_5$. Calculated, %: C 61.76; H 8.82.

Dipropyl 2-(1-hydroxycyclohexyl)cyclopropane-1,1-dicarboxylate (IIId). Yield 1.75 g (56%), bp 180–181°C (5 mm), n_D^{20} = 1.4850. IR spectrum, ν, cm^{-1}: 1740 (C=O), 3600 (OH). ^{1}H NMR spectrum, δ, ppm: 0.99 t (6H, $CH_2CH_2CH_3$, J = 7.4 Hz), 1.43 d and 1.45 d (1H, CH_2, J = 5.4, 4.9 Hz), 1.6–1.9 m (14H, $CH_2CH_2CH_3$, CH_2), 1.83 d and 1.85 d (1H, CH_2, J = 8.1, 4.9 Hz), 2.55 d and 2.58 d (1H, CH, J = 8.1, 5.4 Hz), 4.25 t (2H, OCH_2, J = 7.4 Hz). Found, %: C 65.45; H 8.92. $C_{17}H_{28}O_5$. Calculated, %: C 65.38; H 8.97.

4-Chloromethyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylic acid (IV). A mixture of 0.49 g (2.5 mmol) of compound **Ia** and 10 ml of 10% hydrochloric acid was heated for 10 h at 70°C. Excess hydrochloric acid was distilled off under reduced pressure. Yield 0.31 g (60%), mp 145°C (from xylene). IR spectrum, ν, cm^{-1}: 1735 (C=O, acid), 1775 (C=O, lactone), 2600 (OH, assoc.). ^{1}H NMR spectrum, δ, ppm: 1.38 s and 1.58 s (3H each, CH_3), 2.98 d.t (1H, CH, J = 11.5, 7.4 Hz), 3.72 d (2H, CH_2Cl, J = 7.4 Hz), 3.76 d (1H, 3-H, J = 11.5 Hz), 12.86 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 21.599 and 28.187 (CH_3), 41.543 (CH_2), 50.255 (CH), 50.946 (CH), 83.546 (C^5), 167.956 (C=O), 168.62 (C=O). Found, %: C 56.24; H 6.41; Cl 20.50. $C_8H_{11}ClO_4$. Calculated, %: C 56.14; H 6.43; Cl 20.76.

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REFERENCES

1. Nesmeyanov, A.N. and Nesmeyanov, N.A., *Nachala organicheskoi khimii* (Basic Principles of Organic Chemistry), Moscow: Khimiya, 1970, vol. 2, p. 646.
2. *Kratkaya khimicheskaya entsiklopediya* (Brief Chemical Encyclopedia), Moscow: Sovetskaya Entsiklopediya, 1967, vol. 5, p. 294.
3. Avetisyan, A.A., Margaryan, A.Kh., Tokmadzhyan, G.G., and Piridzhanyan, R.A., Armenian Patent no. 1125, 2002; *Ofits. Byull. Promyshl. Sobst. Resp. Arm*., 2002, no. 2.
4. Avetisyan, A.A., Tokmadzhyan, G.G., and Karapetyan, L.V., *Uch. Zap. Erev. Gos. Univ*., 2003, no. 1, p. 80.