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Synthesis and Some Transformations of Ethyl 5-Alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates

T. V. Kochikyan, M. A. Samvelyan, V. S. Arutyunyan, and A. A. Avetisyan

Erevan State University, ul. Aleka Manukyana 1, Erevan, 375049 Armenia

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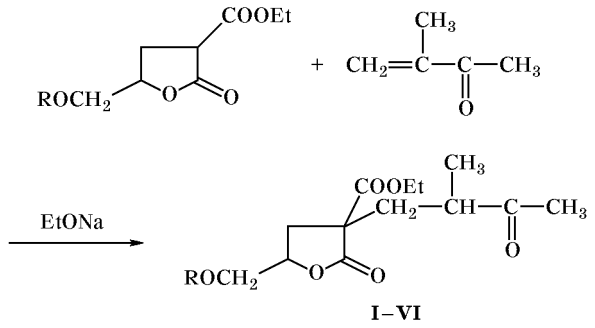
Abstract—Michael reaction of ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates with 3-methyl-3-buten-2-one gave ethyl 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates. Alkaline hydrolysis of the latter, followed by decarboxylation afforded 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)tetrahydrofuran-2-ones. The bromination of ethyl 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates provides a convenient method for the preparation of 3-acetyl-8-alkoxymethyl-3-methyl- and 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones in high yields.

On the basis of 3-acetyl-5-alkoxymethyltetrahydrofuran-2-ones we previously developed [1–3] convenient methods for the preparation of 4-butanolide derivatives which are key intermediate products in the synthesis of compounds interesting from the biological viewpoint [4, 5]. In continuation of these studies, we examined the Michael reaction of ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates with 3-methyl-3-buten-2-one (Scheme 1).

Scheme 1.

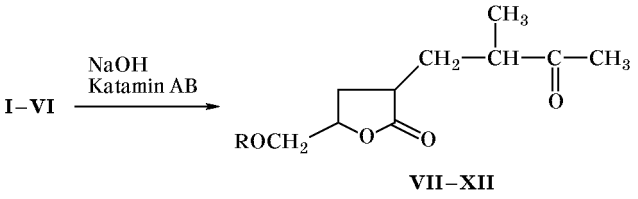


I–VI

I, R = *i*-Pr; **II**, R = Pr; **III**, R = *i*-Bu; **IV**, R = Bu; **V**, R = *iso*-C_5H_{11}; **VI**, R = C_5H_{11}.

Optimal conditions were found, which ensure high yields of the target products, ethyl 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates **I**–**VI**. The best results (yield 85–91%) were obtained when the condensation was carried out in the presence of a catalytic amount of sodium ethoxide at 55–60°C (reaction time 3 h). Alkaline hydrolysis of compounds **I**–**VI** and subsequent decarboxylation under conditions of phase-transfer catalysis afforded 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)tetrahydrofuran-2-ones **VII**–**XII** (Scheme 2).

Scheme 2.



VII–XII

VII, R = *i*-Pr; **VIII**, R = Pr; **IX**, R = *i*-Bu; **X**, R = Bu; **XI**, R = *iso*-C_5H_{11}; **XII**, R = C_5H_{11}.

The best results (yield 80–83%) were achieved with the use of Katamin AB as catalyst. Compounds **I**–**XII** give a positive test with iodoform, which is characteristic of methyl ketones.

Spiro lactones occupy a specific place among the lactone series due to their diverse biological activity. Some spiro lactones, e.g., Spironolactone (or Verospiron), are used in medicine as potassium-saving diuretics [6–8]. Lactones can be fused through a spiro junction with various carbocycles, both saturated and unsaturated [9], and heterocycles [10]. In the series of spiro lactones, spirodilactones, specifically poorly studied α-spirodilactones, attract certain interest [11, 12]. With the goal of developing a procedure for

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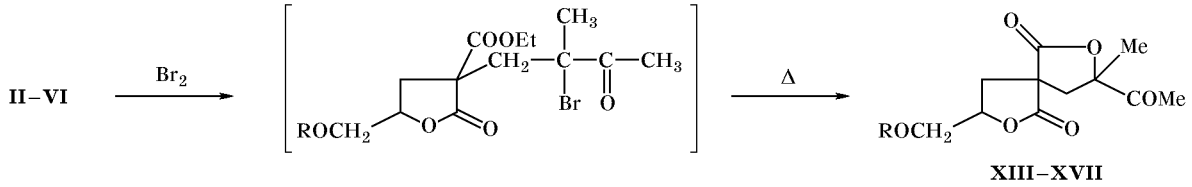
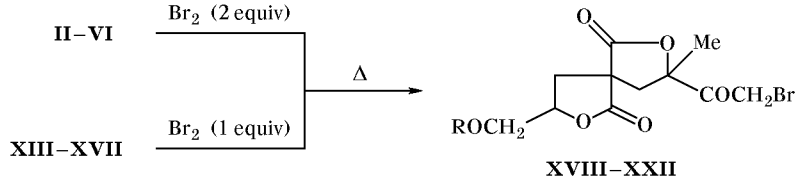
Scheme 3.



XIII–XVII

XIII, R = Pr; **XIV**, R = *i*-Bu; **XV**, R = Bu; **XVI**, R = *iso*-C_5H_{11}; **XVII**, R = C_5H_{11}.

Scheme 4.



XVIII–XXII

XVIII, R = Pr; **XIX**, R = *i*-Bu; **XX**, R = Bu; **XXI**, R = *iso*-C_5H_{11}; **XXII**, R = C_5H_{11}.

the preparation of functionally substituted α-spirodilactones and studying chemical properties of lactones **I**–**VI**, the latter were subjected to bromination. We also found optimal conditions ensuring the process to occur in a selective fashion. The bromination of lactones **II**–**VI** with an equimolar amount of bromine in carbon tetrachloride at room temperature afforded ethyl 5-alkoxymethyl-3-(2-bromo-2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates which readily underwent thermal cyclization to 3-acetyl-8-alkoxymethyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones in 91–94% yield (Scheme 3). When the bromination of **II**–**VI** was performed using 2 equiv of bromine, other conditions being equal, the products were 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **XVIII**–**XXII** (yield 70–75%); the same products were obtained by bromination of acetyl derivatives **XIII**–**XVII** with an equimolar amount of bromine (Scheme 4).

Thus, using ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates as starting compounds, we have developed a simple and convenient procedure for the preparation of α-spirodilactones of new generation, 3-acetyl-8-alkoxymethyl-3-methyl- and 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]-nonane-1,6-diones, which possess a great synthetic potential.

EXPERIMENTAL

The IR spectra of compounds **I**–**XVII** (as liquid films) and **XVIII**–**XXII** (as mulls in mineral oil) were recorded on UR-20 and Nicolet FTIR NEXUS instruments. GLC was performed on a Varian Model 3600 chromatograph, equipped with a flame-ionization detector; DB-5 column (15 m × 0.25 mm × 0.25 μm); detector temperature 300°C; oven temperature 180–250°C; carrier gas helium, flow rate 18.9 ml/s. The ^{1}H NMR spectra of solutions in DMSO-d_6 were obtained on a Varian Model Mercury-300 spectrometer (300 MHz). Silufol UV-254 plates were used for thin-layer chromatography; eluent ethanol–benzene–hexane, 2:3:7 (A) or 3:3:10 (B); development with iodine vapor. The melting points of crystalline products were determined on a Boetius device.

Initial ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates were synthesized as described in [13].

Ethyl 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates I–VI. A mixture of 0.25 mol of the corresponding ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylate and 21.8 g (0.26 mol) of 3-methyl-3-buten-2-one (stabilized with hydroquinone) was heated to 45°C with protection from atmospheric moisture, and a solution of sodium ethoxide (prepared by dissolution of 0.5 g of metallic sodium in 25 ml of anhydrous ethanol) was added dropwise at such a rate that the temperature did not exceed 50°C. When the addition was complete, the mixture was stirred for 2 h, heated for 1 h at 55–60°C on a water bath, cooled, and acidified to pH 2–3 with dilute hydrochloric acid. The product was extracted into diethyl ether, the extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated, and the residue was distilled under reduced pressure (Table 1). The IR spectra of compounds **I**–**VI** contained the following bands, ν, cm^{-1}:

Table 1. Yields, physical constants, and elemental analyses of ethyl 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)-2-oxotetrahydrofuran-3-carboxylates **I**–**VI** and 5-alkoxymethyl-3-(2-methyl-3-oxobutyl)tetrahydrofuran-2-ones **VII**–**XII**

Comp. no.	Yield, %	bp, °C (*p*, mm)	n_D^{20}	d_4^{20}	Found, %		Formula	Calculated, %		R_f (A)
					C	H		C	H	
I	86	149–150 (1)	1.4590	1.0916	61.24	8.33	$C_{16}H_{26}O_6$	61.15	8.28	0.63
II	85	155–157 (2)	1.4605	1.0902	61.31	8.38	$C_{16}H_{26}O_6$	61.15	8.28	0.61
III	90	168 (2)	1.4590	1.0709	62.28	8.55	$C_{17}H_{28}O_6$	62.20	8.54	0.48
IV	89	157–158 (1)	1.4590	1.0743	62.32	8.58	$C_{17}H_{28}O_6$	62.20	8.54	0.45
V	91	176–177 (2)	1.4595	1.0635	63.05	8.70	$C_{18}H_{30}O_6$	63.16	8.77	0.46
VI	92	167–168 (1)	1.4610	1.0628	63.02	8.72	$C_{18}H_{30}O_6$	63.16	8.77	0.44
VII	81	136 (1)	1.4575	1.0368	66.37	9.00	$C_{13}H_{22}O_4$	66.44	9.09	0.51
VIII	80	140–141 (2)	1.4595	1.0427	66.48	9.10	$C_{13}H_{22}O_4$	66.44	9.09	0.49
IX	83	153 (2)	1.4560	1.0225	65.40	9.43	$C_{14}H_{24}O_4$	65.63	9.38	0.45
X	83	156 (2)	1.4578	1.0291	65.46	9.51	$C_{14}H_{24}O_4$	65.63	9.38	0.43
XI	83	151–152 (1)	1.4582	1.0155	66.55	9.62	$C_{15}H_{26}O_4$	66.67	9.63	0.47
XII	82	152–153 (1)	1.4600	1.0153	66.64	9.65	$C_{15}H_{26}O_4$	66.67	9.63	0.44

1770 (C=O, lactone); 1740 (C=O, ester); 1720 (C=O, ketone); 1110, 1190, 1230 (C–O–C).

5-Alkoxymethyl-3-(2-methyl-3-oxobutyl)tetrahydrofuran-2-ones VII–XII. A 30% aqueous solution of sodium hydroxide (4.4 g, 0.11 mol) was added dropwise with stirring to a mixture of 0.05 mol of compound **I**–**VI** and 0.5 ml of 50% Katamin AB. After 0.5 h, the mixture was heated for 1.5 h on a water bath, cooled, acidified to pH 1–2 with hydrochloric acid, and extracted with ether. The extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was heated at 250–300°C under reduced pressure (water-jet pump, 15–20 mm) and was then distilled in a vacuum (Table 1). The IR spectra of the products contained the following bands, ν, cm^{-1}: 1760 (C=O, lactone); 1710 (C=O, ketone); 1120, 1140 (C–O–C); no ester carbonyl absorption was present.

3-Acetyl-8-alkoxymethyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones XIII–XVII. A solution of 24 g (0.15 mol) of bromine in 50 ml of dry carbon tetrachloride was added dropwise to a mixture of 0.15 mol of compound **I**–**VI** and 100 ml of dry carbon tetrachloride. The rate of addition was controlled by decoloration of the solution. The mixture was then stirred for 15 min and kept under reduced pressure (water-jet pump) first in the cold to remove hydrogen bromide and then on heating to remove the solvent. The residue was heated at 250–300°C under reduced pressure (15–20 mm) and was then distilled in a vacuum (Table 2). The IR spectra of the products contained the following bands, ν, cm^{-1}: 1770, 1780 (C=O, lactone); 1740 (C=O, ketone); 1110, 1190, 1240 (C–O–C).

^{1}H NMR spectra of compounds **XIII**–**XVII**, δ, ppm (*J*, Hz): **XIII**: 0.94 t (3H, CH_3, 7.4); 1.59 sext (2H, CH_2, 7.0); 1.65 s (3H, CH_3); 2.27 s (3H, $COCH_3$); 2.39 d and 2.57 d (2H, CH_2, 7.0, 8.5, 13.5); 2.43 d and 3.21 d (2H, CH_2, 13.7); 3.44 t (2H, CH_2, 6.5); 3.56–3.67 m (2H, CH_2); 4.80 m (1H, CH); **XIV**: 0.91 d (6H, $2CH_3$, 6.7); 1.51 s (3H, CH_3); 1.86 m [1H, $(CH_3)_2C\mathbf{H}$, 6.7]; 2.29 s (3H, $COCH_3$); 2.31 d and 3.16 d (2H, CH_2, 13.7); 2.38 d and 2.57 d (2H, CH_2, 7.0, 8.6, 13.4); 3.25 d (2H, CH_2O, 6.7); 3.60 d and 3.63 d (2H, CH_2, 4.2, 5.6, 11.0); 4.73 d (1H, 8-H, 6.9, 8.5); **XV**: 0.93 t (3H, CH_3, 7.3); 1.38 sext (2H, CH_2, 7.0); 1.53 m (2H, CH_2); 1.65 s (3H, CH_3); 2.28 s (3H, $COCH_3$); 2.38 d and 2.56 d (2H, CH_2, 7.1, 8.4, 13.5); 2.42 d and 3.21 d (2H, CH_2, 13.8); 3.48 t (2H, CH_2, 6.4); 3.59–3.62 m (2H, CH_2, 4.1, 5.8, 11.1); 4.75 m (1H, CH); **XVI**: 0.92 t (6H, $2CH_3$, 6.8); 1.54 m (2H, CH_2); 1.65 s (3H, CH_3); 1.85 m [1H, $(CH_3)_2C\mathbf{H}$, 6.7]; 2.29 s (3H, $COCH_3$); 2.39 d and 2.53 d (2H, CH_2, 7.0, 8.3, 13.4); 2.41 d and 3.23 d (2H, CH_2, 13.7); 3.49 t (2H, CH_2, 6.3); 3.58–3.63 m (2H, CH_2, 4.0, 5.7, 11.0); 4.75 m (1H, 8-H); **XVII**: 0.92 t (3H, CH_3, 7.0); 1.33 m (4H, $2CH_2$); 1.56 q (2H, CH_2, 6.9); 1.65 s (3H, CH_3); 2.29 s (3H, $COCH_3$); 2.38 d and 2.56 d (2H, CH_2, 7.1, 7.5); 2.42 d and 3.21 d (2H, CH_2, 13.8); 3.47 t (2H, CH_2, 6.5); 3.59 d and 3.63 d (2H, CH_2, 5.7, 11.2); 4.75 m (1H, CH, 4.2, 5.7, 7.1, 8.5).

Table 2. Yields, boiling or melting points, R_f values, and elemental analyses of 3-acetyl-8-alkoxymethyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **XIII**–**XVII** and 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **XVIII**–**XXII**

Comp. no.	Yield, %	bp, °C (*p*, mm), or mp, °C	Found, %			Formula	Calculated, %			R_f (B)
			C	H	Br		C	H	Br	
XIII[a]	91	180–182 (2)	59.40	7.00	–	$C_{14}H_{20}O_6$	59.15	7.04	–	0.57
XIV	92	183–185 (2) 93–95	60.32	7.31	–	$C_{15}H_{22}O_6$	60.40	7.38	–	0.48
XV[b]	94	170–171 (1)	60.15	7.45	–	$C_{15}H_{22}O_6$	60.40	7.38	–	0.50
XVI	94	184–186 (1) 50	61.40	7.71	–	$C_{16}H_{24}O_6$	61.53	7.69	–	0.52
XVII[c]	92	184–185 (1)	61.60	7.50	–	$C_{16}H_{24}O_6$	61.53	7.69	–	0.54
XVIII	70	113–115	46.10	5.12	22.00	$C_{14}H_{19}BrO_6$	46.28	5.23	22.03	0.59
XIX	72	124–127	47.62	5.60	21.15	$C_{15}H_{21}BrO_6$	47.74	5.57	21.22	0.55
XX	74	114–116	47.60	5.65	21.06	$C_{15}H_{21}BrO_6$	47.74	5.57	21.22	0.53
XXI	70	136–138	49.00	6.00	20.21	$C_{16}H_{23}BrO_6$	49.10	5.88	20.46	0.55
XXII	75	101–102	48.95	6.05	20.21	$C_{16}H_{23}BrO_6$	49.10	5.88	20.46	0.54

[a] n_D^{20} = 1.4720, d_4^{20} = 1.1769.
[b] n_D^{20} = 1.4725, d_4^{20} = 1.1445.
[c] n_D^{20} = 1.4730, d_4^{20} = 1.1347.

8-Alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones XVIII–XXII. *a.* The procedure was the same as described above for the synthesis of compounds **XIII**–**XVII** which were used as substrates; 0.05 mol of **XIII**–**XVII** was treated with 8 g (0.05 mol) of bromine in 75 ml of carbon tetrachloride. After removal of the solvent, the crystalline residue was washed with ether and dried in air (Table 2).

b. Likewise, 0.1 mol of compound **I**–**VI** was brominated with 36 g (0.2 mol) of bromine in 150 ml of carbon tetrachloride. After cyclization, the residue was cooled and treated as described above in *a*. Products **XVIII**–**XXII** obtained by the two methods (*a* and *b*) showed no depression of the melting point on mixing. Their IR spectra contained the following absorption bands, ν, cm^{-1}: 1770, 1780 (C=O, lactone); 1720 (C=O, ketone); 1110, 1190, 1240 (C–O–C); 780 (C–Br).

^{1}H NMR spectra, δ, ppm (*J*, Hz): **XVIII**: 0.94 t (3H, CH_3, 7.4); 1.59 sext (2H, CH_2, 7.0); 1.65 s (3H, CH_3); 2.39 d and 2.57 d (2H, CH_2, 7.0, 8.5, 13.5); 2.43 d and 3.21 d (2H, CH_2, 13.7); 3.44 t (2H, CH_2, 6.5); 3.56–3.67 m, 0.94 t (3H, CH_3, 7.4); 1.59 sext (2H, CH_2, 7.0); 1.65 s (3H, CH_3); 2.39 d and 2.57 d (2H, CH_2, 7.0, 8.5, 13.5); 2.43 d and 3.21 d (2H, CH_2, 13.7); 3.44 t (2H, CH_2, 6.5); 3.56–3.67 m (2H, CH_2); 4.37 d and 4.63 d (2H, CH_2Br, 14.9); 4.80 m (1H, CH); **XIX**: 0.91 d (6H, $2CH_3$, 6.7); 1.51 s and 1.65 s (3H, CH_3); 1.86 m [1H, $(CH_3)_2C\mathbf{H}$, 6.7]; 2.37 d and 2.58 d (2H, CH_2, 5.3, 8.4, 13.4); 2.42 d and 3.21 d (2H, CH_2, 13.6, 13.8); 3.25 d (2H, CH_2, 6.7); 3.59 d and 3.63 d (2H, CH_2, 4.2, 6.2, 11.2); 4.37 d and 4.63 d (2H, CH_2Br, 14.6, 14.9); 4.80 m (1H, 8-H); **XX**: 0.93 t (3H, CH_3, 7.3); 1.38 sext (2H, CH_2, 7.0); 1.53 m (2H, CH_2); 1.65 s (3H, CH_3); 2.38 d and 2.56 d (2H, CH_2, 7.1, 8.4, 13.5); 2.42 d and 3.21 d (2H, CH_2, 13.8); 3.48 t (2H, CH_2, 6.4); 3.59–3.62 m (2H, CH_2, 4.1, 5.8, 11.1); 4.37 d and 4.63 d (2H, CH_2Br, 14.9); 4.75 m (1H, CH); **XXI**: 0.91 d (6H, $2CH_3$, 6.8); 1.54 m (2H, CH_2, 6.9); 1.65 s (3H, CH_3); 1.86 m [1H, $(CH_3)_2C\mathbf{H}$, 6.7]; 2.39 d and 2.53 d (2H, CH_2, 7.0, 8.3, 13.4); 2.41 d and 3.23 d (2H, CH_2, 13.6); 3.49 t (2H, CH_2, 6.3); 3.58–3.63 m (2H, CH_2, 4.0, 5.7, 11.0); 4.37 d and 4.63 d (2H, CH_2Br, 14.9); 4.75 m (1H, 8-H); **XXII**: 0.92 t (3H, CH_3, 7.0); 1.33 m (4H, $2CH_2$); 1.56 q (2H, CH_2, 6.9); 1.65 s (3H, CH_3); 2.38 d and 2.56 d (2H, CH_2, 7.1, 7.5); 2.42 d and 3.21 d (2H, CH_2, 13.8); 3.47 t (2H, CH_2, 6.5); 3.58 d and 3.63 d (2H, CH_2, 5.7, 11.2); 4.37 d and 4.62 d (2H, CH_2Br, 14.9); 4.75 m (1H, CH, 4.2, 5.7, 7.1, 8.5).

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