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Spiroheterocyclic Compounds Based on 2-Bromobutanolides

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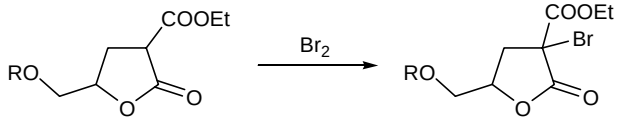
Abstract—Bromination of ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates afforded ethyl 5-alkoxymethyl-3-bromo-2-oxotetrahydrofuran-3-carboxylates which reacted with thiourea, substituted thioureas, benzimidazole-2-thiol, and benzothiazole-2-thiol to give new heterocyclic compounds.

We previously showed that ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates as CH acids successfully undergo condensation with conjugated unsaturated compounds according to the Michael reaction pattern [1, 2] and alkylation with halogen derivatives [3]. In continuation of studies in this line, the present communication reports on the bromination of ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates **I**–**III**, which was performed with a view to extend the series of synthons containing a lactone fragment.

Compounds **I**–**III** were readily brominated with molecular bromine in inert solvents at room temperature. The best results were obtained by treatment of **I**–**III** with an equimolar amount of bromine in dry carbon tetrachloride. The corresponding ethyl 5-alkoxymethyl-3-bromo-2-oxotetrahydrofuran-3-carboxylates **IV**–**VI** were thus obtained in high yields (87–91%; Scheme 1).

Scheme 1.

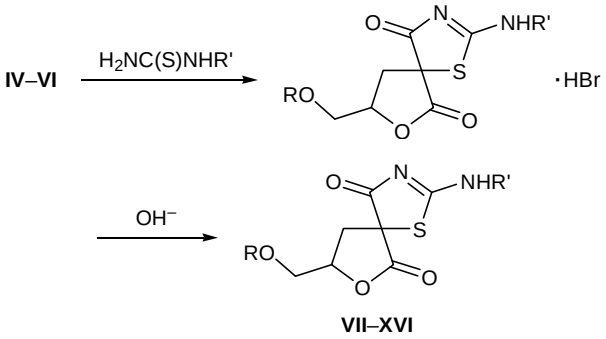


I–**III** **IV**–**VI**

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

Halogen-substituted butanolides are used in the synthesis of various compounds [4–6]. In order to obtain new heterocyclic derivatives of 4-butanolides, specifically those in which the heteroring is spirofused to the butanolide ring (they are analogs of natural compounds [7, 8]), bromo derivatives **IV**–**VI** were brought into reactions with thiourea and substituted thioureas. These reactions included initial replacement of the bromine atom and subsequent heterocyclization to previously unknown 8-alkoxymethyl-2-amino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione hydrobromides. Treatment of the latter with aqueous ammonia gave the corresponding free bases **VII**–**XVI** in good yields (Scheme 2). It is advisable to carry out the reaction with equimolar amounts of the reactants in anhydrous acetone (reaction time 2 h).

Scheme 2.



VII–**XVI**

VII, R = *i*-Pr, R' = Ph; **VIII**, R = *i*-Pr, R' = *p*-MeC_6H_4; **IX**, R = *i*-Pr, R' = *m*-MeC_6H_4; **X**, R = *i*-Bu, R' = H; **XI**, R = *i*-Bu, R' = Ph; **XII**, R = *i*-Bu, R' = *p*-MeC_6H_4; **XIII**, R = *i*-Bu, R' = *o*-MeC_6H_4; **XIV**, R = C_5H_{11}, R' = H; **XV**, R = C_5H_{11}, R' = Ph; **XVI**, R = C_5H_{11}, R' = *p*-MeC_6H_4.

Under analogous conditions, compound **IV** readily reacted with benzimidazole-2-thiol and benzothiazole-2-thiol to afford ethyl 3-(2-benzimidazolylsulfanyl)- and 3-(2-benzothiazolylsulfanyl)-5-isopropoxymethyl-2-oxotetrahydrofuran-3-carboxylates **XVII** and **XVIII**, respectively, in high yields (Scheme 3).

The newly synthesized compounds were characterized by the spectral (IR and ^1H NMR) and analytical data, and their purity was checked by thin-layer chromatography (see table).

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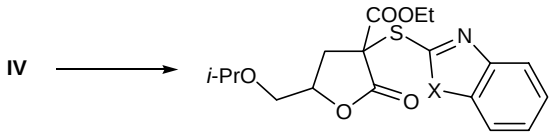
Scheme 3.



XVII, **XVIII**

XVII, X = NH; **XVIII**, X = S.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet FTIR Nexus instrument from samples prepared as thin films (**IV**–**VI**) or dispersed in mineral oil (**VII**–**XVIII**). The ^{1}H NMR spectra were measured from solutions in chloroform-*d* on a Varian Mercury-300 spectrometer (300 MHz). Silufol UV-254 plates were used for thin-layer chromatography (eluent ethanol–benzene, 1:5; development with iodine vapor). The melting points were determined on a Boetius melting point apparatus. Initial ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates **I**–**III** were synthesized by the procedure reported in [9].

Ethyl 3-bromo-5-isopropoxymethyl-2-oxotetrahydrofuran-3-carboxylate (IV). A solution of 16 g (0.1 mol) of bromine in 30 ml of dry carbon tetrachloride was added dropwise to a mixture of 23 g (0.1 mol) of compound **I** and 70 ml of dry carbon tetrachloride. The rate of bromine addition was controlled judging by decoloration of the solution. When the addition was complete, the mixture was stirred for 15 min, hydrogen bromide was removed under reduced pressure (14–20 mm) on cooling, and the solvent was then removed under reduced pressure on heating. The residue was subjected to vacuum distillation at 121–122°C (1 mm). Yield 27.5 g (89%), n_D^{20} = 1.4750, d_4^{20} = 1.3676, R_f 0.67. Found, %: C 42.85; H 5.35; Br 25.95. $C_{11}H_{17}BrO_5$. Calculated, %: C 42.72; H 5.50; Br 25.89.

Ethyl 3-bromo-5-isobutoxymethyl-2-oxotetrahydrofuran-3-carboxylate (V) was synthesized in a similar way from 18.3 g (0.075 mol) compound **II** and 12 g (0.075 mol) of bromine in 25 ml of dry carbon tetrachloride. Yield 22 g (91%), bp 135°C (1 mm), n_D^{20} = 1.4720, d_4^{20} = 1.3138, R_f = 0.58. Found, %: C 44.45; H 5.95; Br 24.90. $C_{12}H_{19}BrO_5$. Calculated, %: C 44.58; H 5.75; Br 24.77.

Ethyl 3-bromo-5-pentyloxymethyl-2-oxotetrahydrofuran-3-carboxylate (VI) was synthesized in a similar way from 12.9 g (0.05 mol) of compound **III** and 8 g (0.05 mol) of bromine in 20 ml of dry carbon tetrachloride. Yield 13.8 g (82%), bp 159°C (2 mm), n_D^{20} = 1.4705, d_4^{20} = 1.2767, R_f 0.65. Found, %: C 46.35; H 6.15; Br 23.90. $C_{13}H_{21}BrO_5$. Calculated, %: C 46.29; H 6.23; Br 23.74.

IR spectra of compounds **IV**–**VI**, ν, cm^{-1}: 1780 (C=O, lactone); 1725 (C=O, ester); 1275, 1170, 1125 (C–O–C); 945 (C–Br).

2-Amino-8-isopropoxymethyl-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione hydrobromide. A mixture of 1.1 g (0.005 mol) of compound **IV** and 1.5 g (0.005 mol) of thiourea in 5 ml of anhydrous acetone was stirred for 1 h at room temperature and for 1 h on heating in such a way that the mixture slightly boiled. The precipitate was filtered off, washed with anhydrous diethyl ether, and dried. Yield 1.5 g (89%), mp 149–151°C. IR spectrum, ν, cm^{-1}: 1783 (C=O, lactone); 1697 (C=O, amide); 1125, 1170 (C–O–C);

Yields, melting points, R_f values, and elemental analyses of 3-alkyl(aryl)amino-8-alkoxymethyl-7-oxa-4-thia-2-azaspiro[4.4]-non-2-ene-1,6-diones **VII**–**XVI**

Comp. no.	Yield, %	mp, °C	R_f	Found, %				Formula	Calculated, %			
				C	H	N	S		C	H	N	S
VII	60	230–231	0.43	57.30	4.85	8.50	9.45	$C_{16}H_{18}N_2O_4S$	57.49	4.79	8.38	9.58
VIII	75	255–257	0.47	58.80	5.65	8.15	9.05	$C_{17}H_{20}N_2O_4S$	58.62	5.75	8.05	9.20
IX	81	217–219	0.57	58.51	5.83	8.12	9.32	$C_{17}H_{20}N_2O_4S$	58.62	5.75	8.05	9.20
X	80	188–191	0.41	48.40	6.00	10.40	11.60	$C_{11}H_{16}N_2O_4S$	48.53	5.88	10.29	11.76
XI	90	204–205	0.67	58.75	5.70	8.15	9.05	$C_{17}H_{20}N_2O_4S$	58.62	5.75	8.05	9.19
XII	97	249	0.62	59.55	6.15	7.85	9.10	$C_{18}H_{22}N_2O_4S$	59.67	6.08	7.73	8.84
XIII	92	176–177	0.64	59.85	5.95	7.90	8.70	$C_{18}H_{22}N_2O_4S$	59.67	6.08	7.73	8.84
XIV	70	146–147	0.41	50.25	6.40	9.90	11.05	$C_{12}H_{18}N_2O_4S$	50.35	6.29	9.79	11.19
XV	85	192–193	0.56	59.75	5.95	7.85	8.75	$C_{18}H_{22}N_2O_4S$	59.67	6.08	7.73	8.84
XVI	88	211–212	0.53	60.55	6.45	7.55	8.40	$C_{19}H_{24}N_2O_4S$	60.64	6.38	7.45	8.51

1610 (C=C_{arom}); 1528 (C=N); 2700 (HN^+); 3130, 3300 (NH_2). Found, %: C 35.50; H 4.55; Br 23.75; N 8.35; S 9.30. $C_{10}H_{15}BrN_2O_4S$. Calculated, %: C 35.40; H 4.42; Br 23.60; N 8.26; S 9.44.

8-Isobutoxymethyl-2-*p*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione hydrobromide was synthesized in a similar way from 2.4 g (0.005 mol) of compound **II** and 0.8 g (0.005 mol) of *N*-(*p*-tolyl)thiourea in 5 ml of anhydrous acetone. Yield 2.1 g (95%), mp 244–245°C. IR spectrum, ν, cm^{-1}: 3300, 3130 (NH); 3080 (C–H_{arom}); 2710 (HN^+); 1783 (C=O, lactone); 1697 (C=O, amide); 1610 (C=C_{arom}); 1528 (C=N); 1170, 1125 (C–O–C). Found, %: C 48.55; H 5.05; Br 17.95; N 7.35; S 7.40. $C_{18}H_{23}BrN_2O_4S$. Calculated, %: C 48.76; H 5.19; Br 18.06; N 6.32; S 7.22.

8-Isobutoxymethyl-2-*p*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XII). *a*. The procedure was the same as in the preceding experiment. After removal of acetone, the residue was cooled, water was added, and the mixture was treated with aqueous ammonia to pH 9–10. The precipitate was filtered off, washed with water, and dried. Yield 1.8 g (97%), mp 249°C, R_f 0.62. ^{1}H NMR spectrum, δ, ppm: 0.92 t [1H, C**H**$(CH_3)_2$], 1.93 d.d [1H, C**H**$(CH_3)_2$], 2.35 s (3H, C**H**$_3C_6H_4$), 2.55 d and 3.15 d (2H, CH_2, ring), 3.43 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.90 m (1H, CH, ring), 7.15 m (3H, H_{arom}), 7.60 m (1H, H_{arom}), 11.20 s (1H, NH). Found, %: C 59.75; H 6.20; N 7.85; S 8.75. $C_{18}H_{22}O_4N_2S$. Calculated, %: C 59.67; H 6.08; N 7.73; S 8.84.

b. Water, 50 ml, was added to 1.8 g (0.005 mol) of 8-isobutoxymethyl-3-*p*-tolylamino-7-oxa-4-thia-2-azaspiro[4.4]non-2-ene-1,6-dione hydrobromide, and aqueous ammonia was added to the mixture under stirring until pH 9–10. The mixture was left to stand for 2 h, and the precipitate was filtered off, washed with water until neutral washings, and dried. Yield quantitative, mp 249°C, R_f 0.62. Sampes of **XII** prepared as described in *a* and *b* showed no depression of the melting point on mixing.

Compounds **VII**–**XI** and **XIII**–**XVI** were synthesized as described above for **XII**, method *a* (see table). IR spectra, ν, cm^{-1}: 3300, 3130 (NH, NH_2); 3080 (C–H_{arom}); 1783 (C=O, lactone); 1697 (C=O, amide); 1610 (C=C_{arom}); 1528 (C=N); 1170, 1125 (C–O–C).

8-Isopropoxymethyl-2-phenylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (VII). ^{1}H NMR spectrum, δ, ppm: 1.15 t and 1.23 t [6H, $(CH_3)_2$CH], 1.85 d.d [1H, C**H**$(CH_3)_2$], 2.50 d and 3.10 d (2H, CH_2, ring), 3.60 d (2H, OCH_2), 4.95 m (1H, CH, ring), 7.25 m (4H, H_{arom}), 7.68 m (1H, H_{arom}), 11.25 s (1H, NH).

8-Isopropoxymethyl-2-*p*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (VIII). ^{1}H NMR spectrum, δ, ppm: 1.15 t and 1.22 t [6H, $(CH_3)_2$CH], 1.65 d.d [1H, C**H**$(CH_3)_2$], 2.25 s (3H, C**H**$_3C_6H_4$), 2.50 d and 3.15 d (2H, CH_2, ring), 3.55 d (2H, OCH_2), 4.83 m (1H, CH, ring), 7.00 m (1H, H_{arom}), 7.10 m (2H, H_{arom}), 7.20 m (1H, H_{arom}), 11.90 s (1H, NH).

8-Isopropoxymethyl-2-*m*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (IX). ^{1}H NMR spectrum, δ, ppm: 1.15 t and 1.22 t [6H, $(CH_3)_2$CH], 1.93 d.d [1H, C**H**$(CH_3)_2$], 2.25 s (3H, C**H**$_3C_6H_4$), 2.55 d and 3.10 d (2H, CH_2, ring), 3.60 d (2H, OCH_2), 4.95 m (1H, CH, ring), 7.15 m (3H, H_{arom}), 7.60 m (1H, H_{arom}), 11.20 s (1H, NH).

2-Amino-8-isobutoxymethyl-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (X). ^{1}H NMR spectrum, δ, ppm: 0.91 t [6H, $(CH_3)_2$CH], 1.90 d.d [1H, C**H**$(CH_3)_2$], 2.48 d and 3.05 d (2H, CH_2, ring), 3.25 d (2H, CH_2O), 3.58 d (2H, OCH_2), 4.93 m (1H, CH, ring), 8.95 s (2H, NH_2).

8-Isobutoxymethyl-2-phenylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XI). ^{1}H NMR spectrum, δ, ppm: 0.95 t [6H, $(CH_3)_2$CH], 1.85 d.d [1H, C**H**$(CH_3)_2$], 2.55 d and 3.10 d (2H, CH_2, ring), 3.25 d (2H, CH_2O), 3.60 d (2H, OCH_2), 4.90 m (1H, CH, ring), 7.10 m (1H, H_{arom}), 7.35 m (3H, H_{arom}), 7.75 m (1H, H_{arom}), 11.23 s (1H, NH).

8-Isobutoxymethyl-2-*o*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XIII). ^{1}H NMR spectrum, δ, ppm: 0.85 t [6H, $(CH_3)_2$CH], 1.70 d.d [1H, C**H**$(CH_3)_2$], 2.25 s (3H, C**H**$_3C_6H_4$), 2.55 d and 3.20 d (2H, CH_2, ring), 3.30 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.90 m (1H, CH, ring), 7.00 m (1H, H_{arom}), 7.25 m (3H, H_{arom}), 11.95 s (1H, NH).

2-Amino-8-pentyloxymethyl-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XIV). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, C**H**$_3CH_2$), 1.15–1.60 m [6H, $CH_3(CH_2)_3$], 2.55 d and 3.10 d (2H, CH_2, ring), 3.42 d (2H, CH_2O), 3.60 d (2H, OCH_2), 4.95 m (1H, CH, ring), 8.95 s (2H, NH_2).

8-Pentyloxymethyl-2-phenylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XV). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, C**H**$_3CH_2$), 1.15–1.63 m [6H, $CH_3(CH_2)_3$], 2.58 d and 3.09 d (2H, CH_2, ring), 3.44 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.95 m (1H, CH, ring), 7.20 m (1H, H_{arom}), 7.35 m (3H, H_{arom}), 7.75 m (1H, H_{arom}), 11.23 s (1H, NH).

8-Pentoxymethyl-2-*p*-tolylamino-7-oxa-1-thia-3-azaspiro[4.4]non-2-ene-4,6-dione (XVI). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, C**H**$_3$CH$_2$), 1.15–1.60 m [6H, CH$_3$(C**H**$_2$)$_3$], 2.30 s (3H, C**H**$_3$C$_6$H$_4$), 2.55 d and 3.15 d (2H, CH$_2$, ring), 3.43 d (2H, CH$_2$O), 3.62 d (2H, OCH$_2$), 4.95 m (1H, CH, ring), 6.85 m (2H, H$_{arom}$), 7.15 m (1H, H$_{arom}$), 7.65 m (1H, H$_{arom}$), 11.25 s (1H, NH).

Ethyl 3-(2-benzimidazolylsulfanyl)-5-isopropoxymethyl-2-oxotetrahydrofuran-3-carboxylate (XVII). A mixture of 1.6 g (0.005 mol) of compound **IV** and 0.8 g (0.005 mol) of benzimidazole-2-thiol in 5 ml of anhydrous acetone was stirred for 1 h at room temperature and for 1 h on heating to maintain the mixture slightly boiling. The mixture was cooled and diluted with water, and aqueous ammonia was added to pH 9–10. The precipitate was filtered off, washed, and dried. Yield 1.4 g (75%), mp 121–123°C, R_f 0.60. IR spectrum, ν, cm^{-1}: 3080 (C–H$_{arom}$); 3130–3300 (N–H); 1770 (C=O, lactone); 1730 (C=O, ester); 1610 (C=C$_{arom}$); 1528 (C=N); 1230, 1170, 1125 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.05 t [6H, (C**H**$_3$)$_2$CH], 1.40 t (3H, OCH$_2$C**H**$_3$), 1.80 m and 2.17 m [1H, C**H**(CH$_3$)$_2$], 2.45 d.d and 2.58 d.d (2H, CH$_2$, ring), 3.80 d (2H, OCH$_2$), 4.25 d.d (2H, OC**H**$_2$CH$_3$), 4.80 m (1H, CH, ring), 7.10 m (2H, H$_{arom}$), 7.43 m (2H, H$_{arom}$), 12.45 s (1H, NH). Found, %: C 57.24; H 6.00; N 7.55; S 8.55. $C_{18}H_{22}N_2O_5S$. Calculated, %: C 57.14; H 5.82; N 7.41; S 8.47.

Ethyl 3-(2-benzothiazolylsulfanyl)-5-isopropoxymethyl-2-oxotetrahydrofuran-3-carboxylate (XVIII) was synthesized in a similar way from 1.9 g (0.006 mol) of compound **IV** and 1 g (0.006 mol) of benzothiazole-2-thiol in 5 ml of anhydrous acetone. Yield 1.7 g (71%), mp 168–170°C, R_f 0.73. IR spectrum, ν, cm^{-1}: 3080 (C–H$_{arom.}$); 1770 (C=O, lactone); 1730 (C=O, ester); 1610 (C=C$_{arom}$); 1528 (C=N); 1230, 1170, 1125 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 0.98 t [6H, (C**H**$_3$)$_2$CH], 1.43 t (3H, OCH$_2$C**H**$_3$), 1.75 m and 2.00 m [1H, C**H**(CH$_3$)$_2$], 2.35 d.d and 2.45 d.d (2H, CH$_2$, ring), 3.75 d (2H, OCH$_2$), 4.20 d.d (2H, OC**H**$_2$CH$_3$), 4.65 m (1H, CH, ring), 7.25 m (2H, H$_{arom}$), 7.55 m (2H, H$_{arom}$). Found, %: C 54.54; H 5.22; N 3.70; S 16.35. $C_{18}H_{21}NO_5S_2$. Calculated, %: C 54.68; H 5.32; N 3.54; S 16.20.

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