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New Heterocyclic Derivatives of α-Spirodilactones

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Abstract—8-Alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones react with thiourea, substituted thioureas, and 5-aryl-1,2,4-triazole-3-thiols to give new heterocyclic compounds containing an α-spirobutanolide fragment.

γ-Lactone ring is known to constitute a structural fragment of many natural molecules, some of which, e.g., vitamin C, Clavicin, Pilocarpine, Veroshpiron, and Gigoxin, are used in medical practice. Numerous synthetic γ-lactone derivatives also exhibit a broad spectrum of biological activity. In particular, indolyllactones show cardiovascular activity [1, 2], thiazolyl derivatives are antiphlogistic agents [3], ketolactone thiosemicarbazones possess antimutagenic properties [4], triazolyllactones exhibit hypotensive activity [5], etc. γ-Lactones spiro-fused to various rings attract specific interest, for analogous structural fragments were found in many natural compounds possessing valuable physiological properties [6–8].

We previously [9] described a procedure for the preparation of new 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **I**–**III** as compounds with a high synthetic potential. With a view to obtain heterocyclic derivatives of spirodibutanolides we examined reactions of compounds **I**–**III** with thiourea and substituted thioureas under conditions of the Hantzsch reaction. These reactions smoothly occurred in dry acetone in 0.5 h to afford the corresponding 3-methyl-3-(2-ammoniothiazolyl- or 2-arylammoniothiazol-4-yl)-8-alkoxymethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione hydrobromides which were treated with aqueous ammonia to obtain free bases **IV**–**XIII** (Scheme 1).

We also studied reactions of compounds **I**–**III** with 5-aryl-1,2,4-triazole-3-thiols under analogous conditions. As a result, we isolated 3-methyl-3-(5-aryl-1,2,4-triazol-3-ylsulfanylacetyl)-8-alkoxymethyl-2,7-dioxaspiro[4.4]-nonane-1,6-diones **XIV**–**XVII** (Scheme 2).

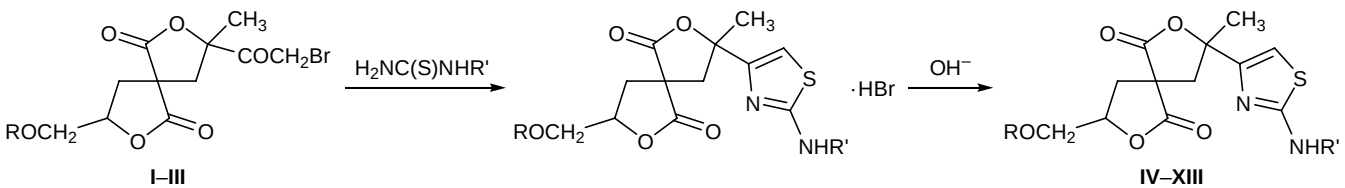
The isolated compounds were characterized by physical constants and analytical data, and their structure was proved by the IR and ^{1}H NMR spectra.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet FTIR Nexus instrument from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-300 spectrometer (300 MHz) from solutions in $CDCl_3$. The purity of the products was checked by TLC on Silufol UV-254 plates using ethanol–benzene (1:5) as eluent (development with iodine vapor). The melting points were determined using a Boëtius melting point apparatus.

Initial 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones were synthesized by the procedure described in [9].

Scheme 1.



I, **IV**–**VII**, R = C_4H_9; **IV**, R' = H; **V**, R' = C_6H_5; **VI**, R' = *o*-ClC_6H_4; **VII**, R' = *p*-$CH_3C_6H_4$; **II**, **VIII**–**X**, R = *iso*-C_4H_9; **VIII**, R' = CH_2=$CHCH_2$; **IX**, R' = *o*-$CH_3C_6H_4$; **X**, R' = *o*-ClC_6H_4; **III**, **XI**–**XIII**, R = *iso*-C_5H_{11}; **XI**, R' = CH_2=$CHCH_2$; **XII**, R' = *o*-$CH_3C_6H_4$; **XIII**, R' = *o*-ClC_6H_4.

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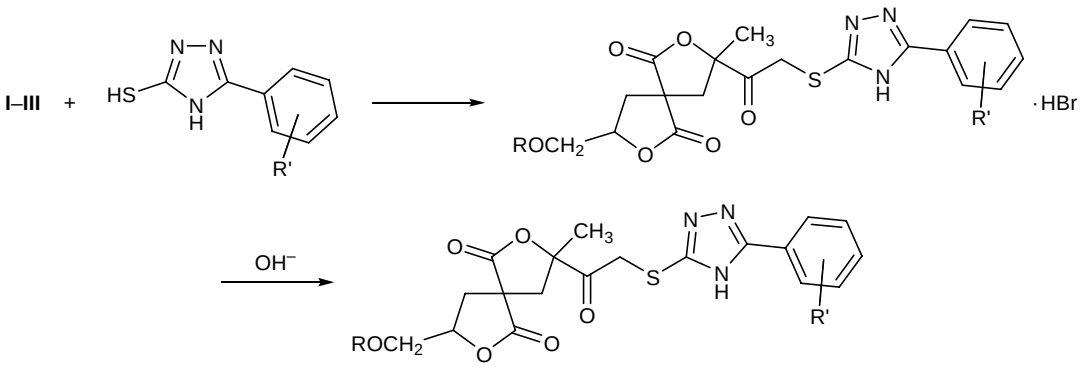
Scheme 2.



XIV–XVII

XIV, R = C_4H_9, R' = *o*-Cl; **XV**, R = C_4H_9, R' = *o*-Br; **XVI**, R = *iso*-C_4H_9, R' = *m*-NO_2; **XVII**, R = *iso*-C_5H_{11}, R' = *m*-NO_2.

8-Isopentyloxymethyl-3-methyl-3-(3-*o*-tolylammoniothiazol-4-yl)-2,7-dioxaspiro[4.4]nonane-1,6-dione hydrobromide. A mixture of 3.9 g (0.01 mol) of 3-bromoacetyl-8-isopentyloxymethyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-dione and 1.7 g (0.01 mol) of *N*-*o*-tolylthiourea in 5 ml of dry acetone was stirred for 15 min at room temperature and was then heated for 30 min to maintain it slightly boiling. The solvent was distilled off, 50 ml of dry ether was added to the residue, and the precipitate was filtered off, washed with ether, and dried. Yield 5 g (95%), mp 147–148°C. IR spectrum, ν, cm^{-1}: 3200–3400 (NH_2); 3050 (=C–H); 2700 (=N^+); 1780, 1770 (C=O, lactone); 1720 (C=O, ketone); 1610 (C=C_{arom}); 1580 (C=N); 1230, 1190, 1110 (C–O–C). Found, %: C 53.55; H 5.55; Br 15.00; N 5.25; S 6.05. $C_{24}H_{31}BrN_2O_5S$. Calculated, %: C 53.43; H 5.75; Br 14.84; N 5.19; S 5.94.

8-Isopentyloxymethyl-3-methyl-3-(3-*o*-tolylaminothiazol-4-yl)-2,7-dioxaspiro[4.4]nonane-1,6-dione (XI). *a*. Compound **XI** was synthesized following the above procedure with the difference that the residue obtained after removal of the solvent was cooled, treated with water, and made alkaline by adding aqueous ammonia to pH 9–10; the precipitate was filtered off, washed with water, and dried. Yield 3.5 g (95%), mp 132–134°C, R_f 0.50. Found, %: C 62.75; H 6.65; N 6.00; S 6.60. $C_{24}H_{30}N_2O_5S$. Calculated, %: C 62.88; H 6.55; N 6.11; S 6.98.

b. Water, 50 ml, was added to 3.2 g (0.006 mol) of 8-isopentyloxymethyl-3-methyl-3-(3-*o*-tolylammoniothiazol-4-yl)-2,7-dioxaspiro[4.4]nonane-1,6-dione, and the mixture was adjusted to pH 9–10 by adding aqueous ammonia on stirring. 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 132–134°C, R_f 0.50. Samples of **XI** prepared as described in *a* and *b* showed no depression of the melting point on mixing.

8-Alkoxymethyl-3-methyl-3-(3-aminothiazol- or 3-arylaminothiazol-4-yl)-2,7-dioxaspiro[4.4]nonane-1,6-diones **IV**–**X**, **XII**, and **XIII** were synthesized in a similar way (see table). The IR spectra of **IV**–**XIII** contained the following absorption bands, ν, cm^{-1}: 3200–3400 (NH, NH_2); 3050 (=C–H); 1780, 1770 (C=O, lactone); 1610 (C=C_{arom}); 1580 (C=N); 1230, 1190, 1110 (C–O–C).

Compound **IV**. ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, CH_3), 1.20 d and 1.53 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.70 s (3H, CCH_3), 2.52 d and 3.10 d (4H, CH_2, ring), 3.43 d (2H, CH_2O), 3.60 d (2H, OCH_2), 4.65 m (1H, CH, ring), 6.18 s (1H, CH=), 6.93 s (2H, NH_2).

Compound **V**. ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.38 d and 1.56 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.80 s (3H, CH_3), 2.58 d and 3.20 d (4H, CH_2, ring), 3.44 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.70 m (1H, CH, ring), 6.63 s (1H, CH=), 6.95 m (1H, H_{arom}), 7.22 m (2H, H_{arom}), 7.48 m (2H, H_{arom}), 10.09 s (1H, NH).

Compound **VI**. ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.38 d and 1.56 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.80 s (3H, CH_3), 2.58 d and 3.20 d (4H, CH_2, ring), 3.44 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.70 m (1H, CH, ring), 6.63 s (1H, CH=), 6.95 m (1H, H_{arom}), 7.22 m (2H, H_{arom}), 7.48 m (1H, H_{arom}), 10.09 s (1H, NH).

Compound **VII**. ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3), 1.40 d and 1.58 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.80 s (3H, CH_3), 2.30 s (3H, CH_3), 2.60 d and 3.20 d (4H, CH_2, ring), 3.48 d (2H, CH_2O), 3.63 d (2H, OCH_2), 4.70 m (1H, CH, ring), 6.60 s (1H, CH=), 7.05 m (2H, H_{arom}), 7.43 m (2H, H_{arom}), 9.98 s (1H, NH).

Yields, melting points, R_f values, and elemental analyses of 8-alkoxymethyl-3-(3-aminothiazol- or 3-arylaminothiazol-4-yl)-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **IV**–**XIII** and 8-alkoxymethyl-3-(5-aryl-1,2,4-triazol-3-ylsulfanylacetyl)-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **XIV**–**XVIII**

Comp. no.	Yield, %	mp, °C	R_f	Found, %					Formula	Calculated, %				
				C	H	N	S	Hlg		C	H	N	S	Hlg
IV	81	189–190	0.49	54.40	6.05	8.00	8.81	–	$C_{16}H_{22}N_2O_5S$	54.23	6.21	7.90	9.03	–
V	85	132–134	0.56	61.50	6.15	6.37	7.25	–	$C_{22}H_{26}N_2O_5S$	61.39	6.04	6.51	7.44	–
VI	90	139–141	0.65	56.90	5.15	6.20	7.00	7.80	$C_{22}H_{25}N_2ClO_5S$	56.83	5.38	6.02	6.88	7.64
VII	83	178–180	0.51	62.40	6.20	6.45	7.30	–	$C_{23}H_{28}N_2O_5S$	62.16	6.30	6.30	7.20	–
VIII	86	127–129	0.44	57.95	6.40	7.22	8.00	–	$C_{19}H_{26}N_2O_5S$	57.86	6.59	7.10	8.12	–
IX	91	145–146	0.47	62.25	6.40	6.18	7.02	–	$C_{23}H_{28}N_2O_5S$	62.16	6.30	6.30	7.20	–
X	82	129–130	0.67	56.70	5.50	6.00	6.84	7.42	$C_{22}H_{25}N_2ClO_5S$	56.83	5.38	6.02	6.88	7.64
XI	85	119–120	0.44	58.90	6.70	6.90	7.70	–	$C_{20}H_{28}N_2O_5S$	58.82	6.86	6.86	7.84	–
XII	87	132–134	0.50	62.75	6.65	6.00	6.60	–	$C_{24}H_{30}N_2O_5S$	62.88	6.55	6.11	6.98	–
XIII	90	128–130	0.58	52.75	5.50	5.76	6.48	7.45	$C_{23}H_{27}N_2ClO_5S$	52.66	5.64	5.85	6.68	7.41
XIV	88	148–150	0.55	54.30	5.20	8.35	6.20	7.80	$C_{23}H_{26}N_3ClO_6S$	54.38	5.12	8.27	6.30	6.99
XV	93	125–127	0.50	50.10	4.60	7.80	5.65	14.60	$C_{23}H_{26}BrN_3O_6S$	50.00	4.71	7.60	5.79	14.49
XVI	90	146–148	0.53	53.15	5.15	10.95	6.30	–	$C_{23}H_{26}N_4O_8S$	53.28	5.01	10.81	6.17	–
XVII	89	129–131	0.44	51.75	5.36	10.70	6.15	–	$C_{24}H_{28}N_3O_8S$	51.87	5.26	10.52	6.01	–

Compound **VIII**. ^{1}H NMR spectrum, δ, ppm: 0.90 t (6H, CH_3), 1.78 s (3H, CH_3), 2.42 d and 3.25 d (4H, CH_2, ring), 2.90 m [1H, $(CH_3)_2C\mathbf{H}$], 3.70 d (2H, CH_2O), 3.80 t.t (2H, NCH_2), 3.93 d (2H, OCH_2), 4.71 m (1H, CH, ring), 5.19 d (1H, $=CH_2$), 5.35 d (1H, $=CH_2$), 5.95 d (1H, =CH), 6.45 d (1H, SCH), 7.28 s (1H, NH).

Compound **IX**. ^{1}H NMR spectrum, δ, ppm: 0.90 t (6H, CH_3), 1.80 s (3H, CH_3), 1.90 m [1H, $(CH_3)_2C\mathbf{H}$], 2.35 s (3H, CH_3), 2.45 d and 3.23 d (4H, CH_2, ring), 3.30 d (2H, CH_2O), 3.68 d (2H, OCH_2), 4.65 m (1H, CH, ring), 6.62 s (1H, CH=), 6.90 m (1H, H_{arom}), 7.10 m (1H, H_{arom}), 7.28 m (2H, H_{arom}), 7.62 s (1H, NH).

Compound **X**. ^{1}H NMR spectrum, δ, ppm: 0.95 t (6H, CH_3), 1.80 s (3H, CH_3), 1.85 m [1H, $(CH_3)_2C\mathbf{H}$], 2.58 d and 3.18 d (4H, CH_2, ring), 3.25 d (2H, CH_2O), 3.58 d (2H, OCH_2), 4.65 m (1H, CH, ring), 6.72 s (1H, CH=), 6.93 m (1H, H_{arom}), 7.25 m (2H, H_{arom}), 7.40 m (1H, H_{arom}), 9.43 s (1H, NH).

Compound **XI**. ^{1}H NMR spectrum, δ, ppm: 0.97 t (6H, CH_3), 1.45 d and 3.42 d [4H, $(CH_3)_2CHC\mathbf{H}_2C\mathbf{H}_2$], 1.63 [1H, $(CH_3)_2C\mathbf{H}$], 1.78 s (3H, CH_3), 2.63 d and 3.22 d (4H, CH_2, ring), 3.57 d (2H, CH_2O), 3.72 d (2H, OCH_2), 3.85 t.t (2H, NCH_2), 4.65 m (1H, CH, ring), 5.16 d (1H, $=CH_2$), 5.32 d (1H, $=CH_2$), 5.91 d (1H, =CH), 6.50 d (1H, SCH), 7.28 s (1H, NH).

Compound **XII**. ^{1}H NMR spectrum, δ, ppm: 0.91 t (6H, CH_3), 1.25 d and 3.43 d [2H, $(CH_3)_2CHC\mathbf{H}_2$], 1.62 m [1H, $(CH_3)_2C\mathbf{H}$], 1.78 s (3H, CH_3), 2.78 s (3H, CH_3), 2.58 d and 3.21 d (4H, CH_2, ring), 3.48 d (2H, CH_2O), 3.65 d (2H, OCH_2), 4.75 m (1H, CH, ring), 6.73 s (1H, CH=), 6.85 m (1H, H_{arom}), 7.20 m (2H, H_{arom}), 8.35 m (1H, H_{arom}), 9.38 s (1H, NH).

Compound **XIII**. ^{1}H NMR spectrum, δ, ppm: 0.93 t (6H, CH_3), 1.24 d and 3.45 d [2H, $(CH_3)_2CHC\mathbf{H}_2$], 1.65 m [1H, $(CH_3)_2C\mathbf{H}$], 1.80 s (3H, CH_3), 2.60 d and 3.18 d (4H, CH_2, ring), 3.46 d (2H, CH_2O), 3.63 d (2H, OCH_2), 4.71 m (1H, CH, ring), 6.70 s (1H, CH=), 6.98 m (1H, H_{arom}), 7.25 m (2H, H_{arom}), 7.38 m (1H, H_{arom}), 9.42 s (1H, NH).

8-Alkoxymethyl-3-(5-aryl-1,2,4-triazol-3-ylsulfanylacetyl)-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-diones XIV–XVII (*general procedure***).** A mixture of 0.1 mol of 8-alkoxymethyl-3-bromoacetyl-3-methyl-2,7-dioxaspiro[4.4]nonane-1,6-dione **I**–**III** and 0.1 mol of the corresponding 5-aryl-1,2,4-triazole-3-thiol in 15 ml of dry acetone was stirred for 15 min at room temperature and was then heated for 30 min on a water bath (to maintain in slightly boiling). The mixture was cooled, diluted with water, and adjusted to pH 9–10 by adding aqueous ammonia. The precipitate was filtered off, washed with water, dried, and recrystallized from aqueous alcohol (see table).

IR spectra of compounds **XIV**–**XVII**, ν, cm^{-1}: 3200–3400 (NH); 3050 (C–H_{arom}); 1770, 1760 (C=O, lactone); 1720 (C=O, ketone); 1610 (C=C_{arom}); 1580 (C=N); 1230, 1190 (C–O–C).

Compound **XIV**. ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, CH_3), 1.40 d and 1.53 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.63 s (3H, CH_3), 2.55 d and 3.28 d (4H, CH_2, ring), 3.45 d (2H, CH_2O), 3.60 d (2H, OCH_2), 4.25 m (1H, CH, ring), 4.70 m (2H, CH_2S), 7.42 m (3H, H_{arom}), 7.80 m (1H, H_{arom}), 14.00 s (1H, NH).

Compound **XV**. ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.42 d and 1.50 d (4H, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.60 s (3H, CH_3), 2.40 d and 3.25 d (4H, CH_2, ring), 3.40 d (2H, CH_2O), 3.63 d (2H, OCH_2), 4.37 m (1H, CH, ring), 4.75 m (2H, CH_2S), 7.38 m (3H, H_{arom}), 7.75 m (1H, H_{arom}), 14.03 s (1H, NH).

Compound **XVI**. ^{1}H NMR spectrum, δ, ppm: 0.95 t (6H, CH_3), 1.69 s (3H, CH_3), 1.85 m [1H, $(CH_3)_2C\mathbf{H}$], 2.45 d and 3.25 d (4H, CH_2, ring), 2.60 d (2H, CH_2O), 3.62 d (2H, OCH_2), 4.40 m (1H, CH, ring), 4.71 m (2H, CH_2S), 7.71 m (1H, H_{arom}), 8.33 m (2H, H_{arom}), 8.80 m (1H, H_{arom}), 14.10 s (1H, NH).

Compound **XVII**. ^{1}H NMR spectrum, δ, ppm: 0.98 t (6H, CH_3), 1.35 d and 3.40 d [2H, $(CH_3)_2CHC\mathbf{H}_2$], 1.60 m [1H, $(CH_3)_2C\mathbf{H}$], 1.75 s (3H, CH_3), 2.43 d and 3.00 d (4H, CH_2, ring), 3.48 d (2H, CH_2O), 3.65 d (2H, OCH_2), 4.45 m (1H, CH, ring), 4.70 m (2H, CH_2S), 7.70 m (1H, H_{arom}), 8.30 m (2H, H_{arom}), 8.70 m (1H, H_{arom}), 14.05 s (1H, NH).

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