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SYNTHESES BASED ON 8-SUBSTITUTED 3-BROMOACETYL-3,8-DIMETHYL-2,7-DIOXASPIRO[4,4]NONANE-1,6-DIONES

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By reaction of 8-substituted 3-bromoacetyl-3,8-dimethyl-2,7-dioxaspiro[4,4]nonane-1,6-diones with thiourea and substituted thioureas under Hansch reaction conditions, we have obtained the novel heterocycles 3-[2'-amino(arylamino)thiazol-4-yl]-3,8-dimethyl-2,7-dioxaspiro[4,4]nonane-1,6-diones. By reacting the above-indicated bromoacetyl spirodilactones with 5-aryl-3-mercapto-1,2,4-triazoles, we obtained 8-substituted 3-(aryl-3,8-dimethyl-1',2',4'-triazol-3'-yl)thioacetyl-2,7-dioxaspiro[4,4]nonane-1,6-diones.

Keywords: aminothiazoles, bromoacetyl lactones, spirodibutanolides, triazoles.

In recent years, there has been vigorous development of the chemistry of heterocycles containing a butanolide moiety because of the broad spectrum of biological action for compounds in this class. In particular, thiazolyl, benzimidazolyl, and triazolyl derivatives of 4-butanolides exhibit anti-inflammatory, antitumor, cardiovascular activity and a muscle relaxant effect [1]. Especially interesting heterocyclic compounds are those which contain a spiro-linked butanolide moiety and which are a structural unit for various natural substances [2-4], since individual representatives of this class are used in medicine for edema, ascites, and nephrotic syndrome [5, 6]. From the above we see the importance of studies in the field of spiro-linked heterocyclic butanolides.

Earlier [7] we reported on a method for obtaining 8-substituted 3-bromoacetyl-3,8-dimethyl-2,7-dioxaspiro[4,4]nonane-1,6-diones **1**, **2**, containing an active bromoacetyl group, which makes it possible to go on to various heterocyclic compounds of unusual structure. With this aim, we have studied the reaction of compounds **1, 2** with thiourea and arylthioureas under Hansch reaction conditions. We have shown that bromoacetyl spirolactones **1, 2** react readily with thioureas to form 8-substituted 3-[2'-amino(or arylamino)thiazol-4'-yl]-3,8-dimethyl-2,7-dioxaspiro[4,4]nonane-1,6-dione hydrobromides, which when treated with aqueous ammonia lead to the corresponding free bases in quantitative yield. The reaction was carried out in an absolute acetone medium for 30 min.

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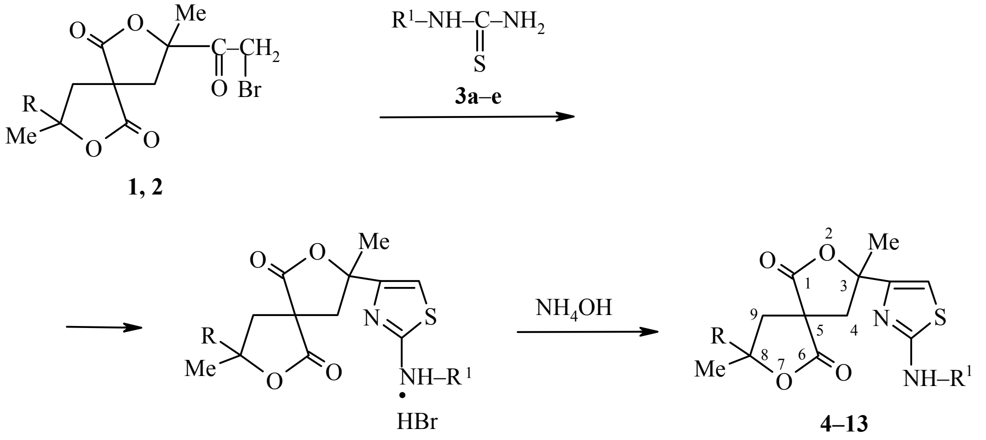
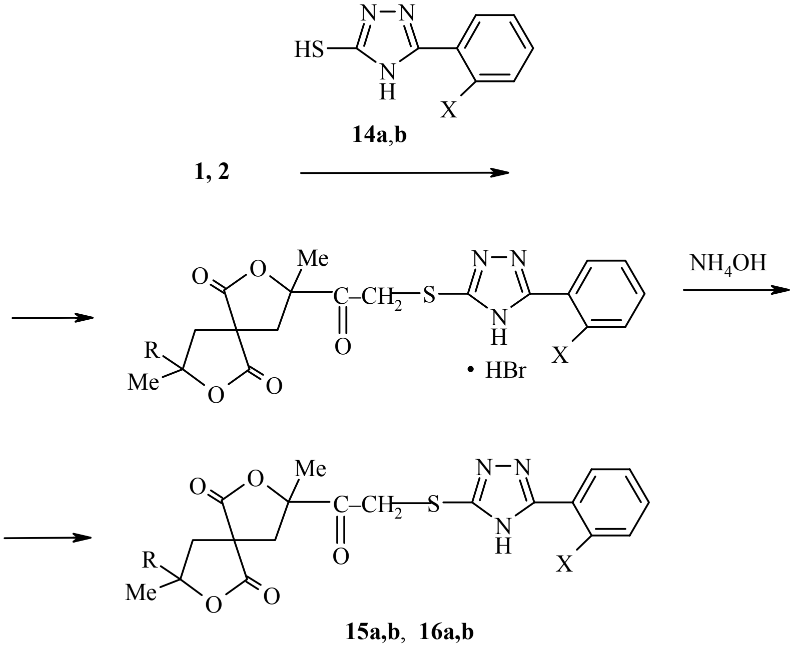


1, **4**, **6**, **8**, **10**, **11** R = H; **2**, **5**, **7**, **9**, **12**, **13** R = Me; **3a**, **4**, **5** R^1 = H;
3b, **6**, **7** R^1 = Ph; **3c**, **8**, **9** R^1 = 2-ClC$_6$H$_4$; **3d**, **10**, **13** R^1 = 2-MeC$_6$H$_4$;
3e, **11**, **12** R^1 = 4-MeC$_6$H$_4$

With the aim of expanding the range of application of spirolactones **1, 2** and also obtaining heterocyclic compounds with a novel structure, we studied the reaction of the starting bromoacetyl lactones **1** and **2** with 5-aryl-3-mercapto-1,2,4-triazoles **14a,b**, a reaction which occurs with formation of the coupling products: 3,8-dimethyl-8-R-3-(aryl-1',2',4'-triazol-3'-yl)thioacetyl-2,7-dioxaspiro[4,4]nonane-1,6-diones **15a,b, 16a,b** in high yields (92-98%).



15 a, **b** R = H; **16** R = Me; **15**, **16 a** X = Cl, **b** X = Br

The structure of compounds **15, 16** was proven by an alternate synthesis: reaction of the starting bromoacetyl spirobutanolides with the sodium salts of the corresponding triazoles.

The synthesized compounds were characterized by determining their physicochemical constants and analytical data, and their structure was proven by IR and ^{1}H NMR spectral data. The purity was checked by TLC.

TABLE 1. Characteristics of Compounds **4-13, 15a,b, 16a,b**

Compound	Empirical formula	Found, % Calculated, %					mp, °C	R_f	Yield, %*
		C	H	N	S	Cl			
4	$C_{12}H_{14}N_2O_4S$	51.16 51.06	5.08 4.96	10.00 9.92	11.12 11.34	—	147-148	0.37	92
5	$C_{13}H_{16}N_2O_4S$	52.60 52.70	4.54 4.44	9.22 9.46	10.63 10.81	—	242-244	0.38	
6	$C_{18}H_{18}N_2O_4S$	60.30 60.34	5.13 5.03	7.64 7.82	8.72 8.94	—	166-168	0.42	
7	$C_{19}H_{20}N_2O_4S$	61.35 61.29	5.28 5.38	7.28 7.53	8.41 8.60	—	156-158	0.52	
8	$C_{18}H_{17}ClN_2O_4S$	55.20 55.03	4.50 4.33	7.00 7.13	7.96 8.15	8.87 9.04	153-155	0.69	95
9	$C_{19}H_{19}ClN_2O_4S$	56.19 56.09	4.78 4.67	6.75 6.89	7.68 7.87	8.62 8.73	141-142.5	0.66	96
10	$C_{19}H_{20}N_2O_4S$	61.39 61.29	5.50 5.38	7.38 7.52	8.42 8.60	—	146-147.5	0.56	
11	$C_{19}H_{20}N_2O_4S$	61.35 61.29	5.45 5.38	7.35 7.52	8.42 8.60	—	209-210	0.46	
12	$C_{20}H_{22}N_2O_4S$	62.30 62.18	5.78 5.70	7.32 7.25	8.00 8.29	—	165-167	0.56	
13	$C_{20}H_{22}N_2O_4S$	62.28 62.18	5.82 5.70	7.00 7.25	8.06 8.29	—	163-164.5	0.51	
15a	$C_{19}H_{18}ClN_3O_5S$	52.51 52.35	4.27 4.13	9.80 9.80	7.15 7.15	8.25 8.25	213-215	0.55	92
15b	$C_{19}H_{18}BrN_3O_5S$	47.38 47.50	3.63 3.75	8.85 8.85	6.80 6.80	—	201-203	0.51	98
16a	$C_{20}H_{20}ClN_3O_5S$	53.50 53.39	4.65 4.50	9.05 9.05	7.00 7.00	7.68 7.68	214-215.5	0.54	93
16b	$C_{20}H_{20}BrN_3O_5S$	48.71 48.58	4.05 4.05	8.65 8.65	6.35 6.35	—	207-209	0.50	96

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* Quantitative yield for compounds **5-7** and **10-13**.

EXPERIMENTAL

The IR spectra of suspensions of compounds **4-16** in nujol were obtained on a Nicolet FTIR NEXUS or UR-20. The ^1H NMR spectra were obtained on a Varian Mercury 300 spectrometer (300 MHz) in $CDCl_3$, internal standard TMS. For TLC, we used Silufol UV-254 plates, eluent 1:1 alcohol–benzene. Visualization by iodine vapor. The melting points were determined on a Boetius micro hot stage.

The starting bromoacetyl derivatives **1** and **2** were synthesized as in [7], and the substituted thioureas **3b-3e** were synthesized as in [8].

3,8-Dimethyl-3-(2'-*p*-tolylaminothiazol-4'-yl)-2,7-dioxaspiro[4,4]nonane-1,6-dione Hydrobromide (11·HBr). A mixture of 3-bromoacetyl derivative **1** (3.2 g, 0.01 mol) and *p*-tolylthiourea (**3e**) (1.7 g, 0.01 mol) in absolute acetone (15 ml) was stirred for 15 min at room temperature and for 30 min with gentle boiling of the solvent, after which the acetone was distilled off. Absolute diethyl ether (50 ml) was added to the cooled residue; then the precipitate was filtered out, washed with ether on the filter, and dried. Yield 4.4 g (97%); mp 164°C-166°C. IR spectrum, ν, cm^{-1}: 1760, 1770 (C=O lactone); 1190, 1230 (C–O–C); 1610 (C=C arom.); 1720 (C=O ketone); 1580 (C=N); 3050 (=CH); 2700 ($=N^+$); 3200-3400 (NH_2). Found, %: C 50.50; H 4.45; Br 17.42; N 6.05; S 7.00. $C_{19}H_{21}BrN_2O_4S$. Calculated, %: C 50.33; H 4.64; Br 17.66; N 6.18; S 7.06.

3,8-Dimethyl-3-(2'-*p*-tolylaminothiazol-4'-yl)-2,7-dioxaspiro[4,4]nonane-1,6-dione (11). A. The experiment was carried out as above and with the same amounts, except that after distilling off the acetone, the residue was cooled down and then water was added and the mixture was alkalinized with aqueous ammonia to

TABLE 2. ^{1}H NMR Spectra of Compounds **4-13** and **15, 16**

Compound	Chemical shifts, δ, ppm (J, Hz)								
	$8\text{-}CH_3$	$3\text{-}CH_3$, s	$Ar\text{–}CH_3$, s	$CH_{thiaz.}$, s	4- and $9\text{-}CH_2$	NH	H-8	H_{Ar}	$S\text{-}CH_2$
1	2	3	4	5	6	7	8	9	10
4	1.60 (d, $J = 6.3$)	1.86	—	6.68	2.60 d and 3.18 d ($J = 14.3$); 2.67 (dd, $J = 13.6$, $J = 7.7$); 2.75 (d, $J = 13.5$)	11.36 (s)	4.88 (m)	—	—
5	1.49 (s) and 1.62 (s)	1.75	—	6.55	2.24 d and 2.85 d ($J = 13.3$); 2.41 d and 3.33 d ($J = 13.5$)	4.97 (s)	—	—	—
6	1.56 (d, $J = 6.3$)	1.81	—	6.65	2.43 d and 3.29 d ($J = 13.5$); 2.62 (dd, $J = 13.1$, $J = 7.9$); 2.53 (dd, $J = 13.1$, $J = 6.6$)	7.15 (br)	4.69 (dq, $J = 8.0$, $J = 6.3$)	7.08 (m) and 7.25 (m)	—
7	1.50 (s) and 1.63 (s)	1.80	—	6.65	2.27 d and 2.87 d ($J = 13.3$); 2.45 d and 3.40 d ($J = 13.5$)	7.65 (br)	—	7.09 (m) and 7.36 (m)	—
8	1.50 (d, $J = 6.3$)	1.78	—	6.71	2.40 (d, $J = 13.3$); 2.70 (dd, $J = 13.1$, $J = 6.7$); 2.57, 3.16 d, ($J = 13.5$)	9.38 (s)	4.72 (m)	6.95 (td, $J = 7.7$, $J = 1.5$); 7.25 (td, $J = 7.9$, $J = 1.5$); 7.34 (dd, $J = 7.9$, $J = 1.5$); 8.36 (dd, $J = 8.2$, $J = 1.5$)	—

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
9	1.49 (s) and 1.58 (s)	1.77	—	6.71	2.44 d and 3.29 d (*J* = 13.5); 2.56 d and 2.76 d (*J* = 13.4)	9.38 (s)	—	6.95 (td, *J* = 7.6, *J* = 1.7); 7.25 (dd. d, *J* = 8.6, *J* = 7.2, *J* = 1.6); 7.34 (dd, *J* = 7.8, *J* = 1.6); 8.36 (dd, *J* = 8.3, *J* = 1.6)	—
10	1.60 (d, *J* = 6.4)	1.79	2.35 (s)	6.58	2.23 d and 2.81 d (*J* = 13.3); 2.39 d and 3.15 d (*J* = 13.5)	7.57 (s)	4.68 (dq, *J* = 7.9, *J* = 6.3)	7.13-7.28 (m)	—
11	1.56 (d, *J* = 6.2)	1.80	2.34 (s)	6.61	2.42 d and 3.28 d. (*J* = 13.6); 2.61 (dd, *J* = 13.1, *J* = 7.7); 2.53 (dd, *J* = 13.1, *J* = 6.7)	7.07 (br)	4.68 (dq, *J* = 7.9, *J* = 6.3)	7.16 d and 7.23 d (*J* = 8.7)	—
12	1.49 (s) and 1.63 (s)	1.79	2.34 (s)	6.60	2.27 d and 2.87 d (*J* = 13.3); 2.44 d and 3.39 d (*J* = 13.5)	7.11 (br)	—	7.16 d and 7.23 d (*J* = 8.5)	—
13	1.50 and 1.63 (s)	1.79	2.33 (s)	6.61	2.26 d and 2.87 d (*J* = 13.4); 2.44 d and 3.39 d (*J* = 13.5)	6.92 (br)	—	7.09 (t, *J* = 7.3); 7.25 (t, *J* = 7.6); 7.62 (d, *J* = 8.2)	—
15a	1.56 (d, *J* = 6.3)	1.81	—	—	2.48 d and 3.29 d (*J* = 13.5); 2.53 d and 2.62 d (*J* = 13.1)	13.95 (s)	4.69 (dq, *J* = 8.0, *J* = 6.3)	7.27-7.55 (3H, m); 7.85 (1H, m)	4.35 d and 4.65 d (*J* = 18.0)
15b	1.51 (d, *J* = 6.3)	1.83	—	—	2.44 d and 3.31 d (*J* = 13.5); 2.56 d and 2.63 d (*J* = 13.1)	14.01 (s)	4.70 (dq, *J* = 8.0, *J* = 6.3)	7.29-7.59 (3H, m); 7.86 (1H, m)	4.37 d and 4.68 d (*J* = 18.0)
16a	1.47 (s), 1.56 (s)	1.63	—	—	2.27 d and 3.23 d (*J* = 13.8); 2.45 d and 2.68 d (*J* = 13.5)	14.03 (s)	—	7.30-7.53 (3H, m); 7.83 (1H, m)	4.38 d and 4.70 d (*J* = 18.0)
16b	1.49 (s), 1.59 (s)	1.65	—	—	2.25 d and 3.20 d (*J* = 13.8); 2.31 d and 2.55 d (*J* = 13.5)	14.13 (s)	—	7.33-7.57 (3H, m); 7.85 (1H, m)	4.28 d and 4.60 d (*J* = 18.0)

pH 9-10. The crystals of base **11** that precipitated were filtered out, washed with water, and dried. Yield 3.5 g (95%); mp 209-210°C. R_f 0.46. Found, %: C 61.40; H 5.45; N 7.65; S 8.75. $C_{19}H_{20}N_2O_4S$. Calculated, %: C 61.29; H 5.38; N 7.53; S 8.60.

B. The hydrobromide **11**·HBr (2.7 g, 0.006 mol) obtained above was alkalinized with stirring in water (50 ml) with aqueous ammonia to pH 9-10. The mixture was allowed to stand for 2 h; the crystals that precipitated were filtered out, washed with water until testing neutral, and dried. Quantitative yield; mp 209-210°C, R_f 0.46.

The compounds obtained by both methods are identical, and when mixed do not result in depression of the melting points.

The rest of the compounds **4-10, 12, 13** were obtained as in method A; the data for these compounds are given in Tables 1 and 2.

The IR spectra of compounds **4-13**, ν, cm^{-1}: 1760, 1770 (C=O lactone); 1190, 1230 (C–O–C); 1610 (C=C arom.); 1580 (C=N); 3050 (=CH); 3200-3400 (NH_2). The ^{1}H NMR spectral data for compounds **4-13** are given in Table 2.

8-R-3,8-Dimethyl-3-(aryl-1',2',4'-triazol-3'-yl)thioacetyl-2,7-dioxaspiro[4,4]nonane-1,6-diones (15a,b, 16a,b). A. A mixture of compound **1** or **2** (0.1 mol) and 5-aryl-3-mercapto-1,2,4-triazole **14** (0.1 mol) in absolute acetone (15 ml) was stirred for 15 min with no heating and for 30 min in a water bath with gentle boiling of the mixture, the acetone was distilled off, and water was added to the cooled residue and it was alkalinized with aqueous ammonia to pH 9-10. The crystals formed were filtered out, washed with water, dried, and recrystallized from aqueous alcohol (Table 1).

B. The corresponding compound **14** (0.01 mol) and (after 30 min) 3-bromoacetyl-substituted **1** or **2** (0.01 mol) were added with stirring to sodium alkoxide obtained from metallic Na (0.23 g, 0.01 mol) and absolute EtOH (20 ml). Stirring was continued for 30 min while the ethanol was boiled; then the solvent was distilled off, the mixture was cooled down and water was added. The precipitate was filtered out, washed with water until it tested neutral, dried, and recrystallized.

The compounds obtained by methods A and B are identical, and when mixed do not result in depression of the melting points.

IR spectrum, ν, cm^{-1}: 1760, 1770 (C=O lactone); 1190, 1230 (C–O–C); 1610 (C=C arom.); 1580 (C=N); 1720 (C=O ketone); 3050 (C=C arom.); 3200-3400 (NH). The ^{1}H NMR spectral data for compounds **15, 16** are given in Table 2.

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