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SYNTHESIS OF 2,3-DISUBSTITUTED 4-OXO-3,4,5,6-TETRAHYDROSPIRO-(BENZO[*h*]QUINAZOLINE-5,1'-CYCLOPENTANES)

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3-Substituted 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1'-cyclopentanes) were obtained by the reaction of 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) with methyl, phenyl, and benzyl isothiocyanates and cyclization of the obtained thioureas. Condensation of the products with various halides gave 2,3-substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1'-cyclopentanes). The reaction of 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1'-cyclopentane) with 1,2-dibromoethane and 1,3-dibromopropane led to 6-oxo-7,8-dihydrospiro-(benzo[h]thiazolidino[2,3-b]quinazoline-7,1'-cyclopentane) and 7-oxo-8,9-dihydrospiro(benzo[h]-perhydrothiazino[2,3-b]quinazoline-8,1'-cyclopentane) respectively.

Keywords: spirocyclopentane, substitution, benzo[*h*]quinazolines, condensation, cyclization.

2,3-Disubstituted benzo[*h*]quinazolines spirocoupled with a cyclohexane ring are low-toxicity compounds and exhibit antitumor activity [1]. We also established that 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (**1**) reacts with benzoyl isothiocyanate with the formation of 4-(N'-benzoylthioureido)-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (**2a**), which readily undergoes cyclization to 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (**3a**) [2].

In a continuation of research into this region in the present work we studied the reaction of the amino ester **1** with methyl, phenyl, and benzyl isothiocyanates in ethanol. It was shown that at room temperature, as also during boiling, the initially formed thioureido derivatives **2b-d** undergo partial cyclization to the quinazolines **3b-d**, leading to a mixture of products **2** and **3**. For this reason the thioureas were subjected to cyclization without isolation from the reaction mixture by the addition of aqueous potassium hydroxide, and this secured the production of the quinazolines **3b-d** in the pure form. Condensation of the latter with alkyl, allyl, and benzyl halides and also with diethyl ether of chloroacetic acid in the presence of potassium hydroxide gave 2,3-disubstituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentanes) **4a-o**. It was shown by X-ray crystallographic analysis that the reaction of 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]-quinazoline-5,1'-cyclopentane) with 1,2-dibromoethane and 1,3-dibromopropane leads to the formation of the thiazoline and perhydrothiazine rings respectively through the sulfur atom and the $N_{(3)}$ atom of the quinazoline ring [3]. The reaction of the quinazoline **3a** not substituted at position 3 with 1,2-dibromoethane takes place similarly and leads to 6-oxo-7,8-dihydrospiro(benzo[*h*]thiazolidino[2,3-*b*]quinazoline-7,1'-cyclopentane) (**5**) and 7-oxo-8,9-dihydrospiro(benzo[*h*]perhydrothiazino[2,3-*h*]quinazoline-8,1'-cyclopentane) (**6**) respectively (see the scheme).

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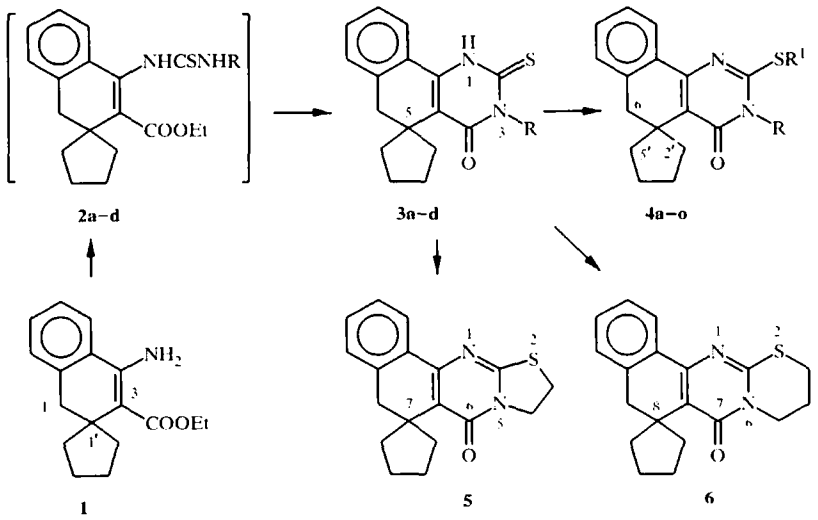
TABLE 1. The Characteristics of the 2,3-Disubstituted 4-Oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentanes) **4a-o**

Compound	Empirical formula	Found, % Calculated, %				R_f	mp, °C	^{1}H NMR spectrum, δ, ppm, SSCC (*J*, Hz)	Yield, %
		C	H	N	S				
1	2	3	4	5	6	7	8	9	10
4a	$C_{18}H_{20}N_2OS$	69.07 69.19	6.58 6.45	9.10 8.97	10.41 10.26	0.57	108-110	6.86-8.16 (4H, m, C_6H_4); 3.43 (3H, s, NCH_3); 2.77 (2H, s, 6-CH_2); 2.60 (3H, s, SCH_3); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	72
4b	$C_{19}H_{22}N_2OS$	69.77 69.90	6.92 6.79	8.73 8.58	9.75 9.83	0.65	115-116	6.93-8.10 (4H, m, C_6H_4); 3.40 (3H, s, NCH_3); 3.20 (2H, q, *J* = 8.0, SCH_2); 2.70 (2H, s, 6-CH_2); 1.20-2.40 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $SCH_2\underline{CH_3}$)	84
4c	$C_{20}H_{22}N_2OS$	71.11 70.97	6.72 6.55	8.39 8.28	9.66 9.47	0.63	100-101	7.00-8.20 (4H, m, C_6H_4); 5.00-6,26 (3H, m, $CH{=}CH_2$); 3.97 (2H, d, *J* = 6.5, SCH_2); 3.46 (3H, s, NCH_3); 2.76 (2H, s, 6-CH_2); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	67
4d	$C_{24}H_{24}N_2OS$	74.06 74.19	6.13 6.23	7.42 7.21	8.16 8.25	0.58	110-111	6.83-8.20 (9H, m, C_6H_4, C_6H_5); 4.50 (2H, s, C_6H_4-$\underline{CH_2}$); 3.43 (3H, s, NCH_3); 2.73 (2H, s, 6-CH_2); 1.10-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	77
4e	$C_{21}H_{24}N2O_4S$	65.78 65.60	6.44 6.29	7.15 7.29	8.27 8.34	0.37	116-118	7.00-8.20 (4H, m, C_6H_4); 4.17 (4H, q, *J* = 7.5, OCH_2); 3.97 (2H, s, SCH_2); 3.47 (3H, s, NCH_3); 2.77 (2H, s, 6-CH_2); 1.10-2.50 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $OCH_2\underline{CH_3}$)	80
4f	$C_{23}H_{22}N_2OS$	73.91 73.76	6.07 5.92	7.31 7.48	8.41. 8.56	0.56	219-221	7.00-8.30 (9H, m, C_6H_4, C_6H_3); 2.80 (2H, s, 6-CH_2); 2.43 (3H, s, SCH_3); 1.20-2.40 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	94
4g	$C_{24}H_{24}N_2OS$	74.00 74.19	6.12 6.23	7.28 7.21	8.43 8.25	0.54	194-195	6.86-8.20 (9H, m, C_6H_4, C_6H_5); 3.13 (2H, q, *J* = 7.5, SCH_2); 2.80 (2H, s, 6-CH_2); 1.20-2.50 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $SCH_2\underline{CH_3}$)	90
4h	$C_{25}H_{24}N_2OS$	75.09 74.97	5.92 6.04	7.14 6.99	8.16 8.00	0.53	177-179	6.80-8.20 (9H, m, C_6H_4, C_6H_5); 4.80-6.20 (3H, m, $CH{=}CH_2$); 3.70 (2H, d, *J* = 6.5, SCH_2); 2.73 (2H, s, 6-CH_2); 1.20-2.37 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	86

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
4i	$C_{29}H_{26}N_2OS$	<u>77.50</u> 77.30	<u>5.67</u> 5.82	<u>6.16</u> 6.22	<u>7.30</u> 7.11	0.55	179-180	6.86-8.20 (14H, m, C_6H_4, $2C_6H_5$); 4.37 (2H, s, SCH_2); 2.80 (2H, s, 6-CH_2); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	80
4j	$C_{26}H_{26}N_2O_4S$	<u>70.07</u> 69.93	<u>5.71</u> 5.87	<u>6.13</u> 6.27	<u>7.03</u> 7.18	0.40	157-159	7.00-8.20 (9H, m, C_6H_4, C_6H_5); 4.10 (2H, q, J = 7.5, OCH_2); 3.77 (2H, s, SCH_2); 2.80 (2H, s, 6-CH_2); 1.03-2.50 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $OCH_2\underline{CH_3}$)	87
4k	$C_{23}H_{24}N_2OS$	<u>74.09</u> 74.19	<u>6.05</u> 6.23	<u>7.40</u> 7.21	<u>8.38</u> 8.25	0.61	164-165	7.00-8.20 (9H, m, C_6H_4, C_6H_5); 5.20 (2H, s, NCH_2); 2.77 (2H, s, 6-CH_2); 2.73 (2H, s, 6-CH_2); 2.50 (3H, s, SCH_3); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	87
4l	$C_{25}H_{26}N_2OS$	<u>74.74</u> 74.59	<u>6.56</u> 6.51	<u>7.12</u> 6.96	<u>8.10</u> 7.96	0.67	116-118	6.86-8.13 (9H, m, C_6H_4, C_6H_5); 5.23 (2H, s, NCH_2); 3.20 (2H, q, J = 7.5, SCH_2); 2.80 (2H, s, 6-CH_2); 1.20-2.57 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $SCH_2\underline{CH_3}$)	90
4m	$C_{26}H_{26}N_2OS$	<u>75.46</u> 75.33	<u>6.17</u> 6.32	<u>6.95</u> 6.76	<u>7.62</u> 7.73	0.65	112-114	6.90-8.13 (9H, m, C_6H_4, C_6H_5); 5.60-6.07 (3H, m, $CH{=}CH_2$); 3.90 (2H, d, J = 6.0, SCH_2); 2.80 (2H, s, 6-CH_2); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	78
4n	$C_{40}H_{28}N_2OS$	<u>77.44</u> 77.55	<u>6.19</u> 6.07	<u>5.91</u> 6.03	<u>7.08</u> 6.90	0.65	134-135	7.00-8.20 (14H, m, C_6H_4, $2C_6H_5$); 5.17 (2H, s, NCH_2); 4.30 (2H, s, SCH_2); 2.72 (2H, s, 6-CH_2); 1.20-2.50 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2)	75
4o	$C_{27}H_{28}N_2O_4S$	<u>70.32</u> 70.41	<u>6.28</u> 6.13	<u>6.23</u> 6.08	<u>7.14</u> 6.96	0.45	117-119	6.83-8.10 (9H, m, C_6H_4, C_6H_5); 5.20 (2H, s, NCH_2); 4.10 (2H, q, J = 7.0, OCH_2); 3.83 (2H, s, SCH_2); 2.73 (2H, s, 6-CH_2); 1.00-2.43 (11H, m, 2'-, 3'-, 4'-, 5'-CH_2, $OCH_2\underline{CH_3}$)	83

* TLC in the 2:5 ethyl acetate–hexane system.



2, **3a** R = COPh, **b** R = Me, **c** R = Ph, **d** R = CH_2Ph; **4a-e** R = Me, **f-j** R = Ph, **k-o** R = CH_2Ph; **a,f,k** R^1 = Me; **b,g,l** R^1 = Et; **c,h,m** R^1 = All; **d,i,n** R^1 = CH_2Ph; **e,j,o** R^1 = CH_2COOEt

EXPERIMENTAL

The IR spectra were recorded on an UR-20 instrument (in vaseline oil). The ^1H NMR spectra were obtained on a Varian T-60 spectrometer for solutions in deuterochloroform with TMS or HMDS as internal standard. The mass spectra were obtained on an MX-1321A spectrometer with direct injection of the sample into the ion source at 70 eV. Thin-layer chromatography was conducted on Silufol UV-254 plates with iodine vapor as developer.

3-R-(4-Oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentanes) (3b-d). A mixture of amino ester **1** (5.4 g, 0.02 mol), isothiocyanate (0.02 mol), and ethanol (30 ml) was boiled at reflux for 10 h. A solution of potassium hydroxide (2.2 g, 0.04 mol) in water (30 ml) was then added, and the mixture was boiled for 3 h. After cooling the reaction mixture was acidified with 10% hydrochloric acid to pH 3.0-3.5. The precipitate was filtered off, washed with water, and recrystallized from butanol. The products **3b-d** were obtained.

Compound 3b. Yield 59%; mp 219-220°C. IR spectrum, cm^{-1}: 1610 (C=C arom.); 1670 (C=C); 3200 (NH). Found, %: C 68.25; H 6.14; N 9.51; S 10.88. $C_{17}H_{18}N_2OS$. Calculated, %: C 68.42; H 6.08; N 9.39; S 10.74.

Compound 3c. Yield 67%; mp 292-293°C, R_f 0.61 (1:2 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1610 (C=C arom.); 1660 (C=O); 3360 (NH). Found, %: C 73.39; H 5.40; N 7.62; S 9.05. $C_{22}H_{20}N_2OS$. Calculated, %: C 73.30; H 5.59; N 7.77; S 8.89.

Compound 3d. Mp 215-216°C, R_f 0.52 (1:3 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1600 (C=C arom); 1660 (C=O); 3200 (NH). Found, %: C 73.58; H 5.84; N 7.33; S 8.51. $C_{23}H_{22}N_2OS$. Calculated, %: C 73.76; H 5.92; N 7.48; S 8.56.

3-R-2-R^1-4-Oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentanes) (4a-o). A mixture of quinazoline (0.01 mol), potassium hydroxide (0.01 mol), and absolute ethanol (60 ml) was boiled at reflux for 30 min. A portion of halide (0.01 mol) was then added, and the mixture was boiled for 8 h and cooled. Water (10 ml) was added, and the precipitate was filtered off and recrystallized from butanol. The characteristics of the synthesized products **4a-l** are given in Table 1.

6-Oxo-3,4,7,8-tetrahydrospiro(benzo[*h*]thiazolo[2,3-*b*]quinazoline-7,1'-cyclopentane) (5). A mixture of quinazoline **3a** (5.7 g, 0.02 mol), potassium hydroxide (2.3 g, 0.041 mol), and absolute ethanol (200 ml) was boiled until dissolved. Dibromoethane (3.8 g, 0.02 mol) was added, and the mixture was boiled for 12 h. The

reaction mixture was cooled, and water (100 ml) was added. The crystals that separated were filtered off, washed with water, and recrystallized from isopropyl alcohol. Yield of the product **5** 4.2 g (68%); mp 162-164°C, R_f 0.48 (1:1 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1600 (C=C arom.), 1650 (CO). ^1H NMR spectrum: 6.90-8.10 (4H, m, 4-C_6H_4); 4.37 (2H, t, J = 7.5 Hz, 4-CH_2); 3.37 (2H, t, J = 7.5 Hz, 3-CH_2); 2.77 (2H, s, 8-CH_2); 1.1-2.43 ppm (8H, m, 4-CH_2). Found, %: C 69.67; H 5.66; N 9.21; S 10.50. $C_{18}H_{18}N_2OS$. Calculated, %: C 69.47; H 5.84; N 9.02; S 10.33.

7-Oxo-4,5,8,9-tetrahydrospiro(benzo[*h*]thiazino[2,3-*b*]quinazoline-8,1'-cyclopentane) (6). Similarly, from quinazoline **3a** (5.7 g, 0.02 mol), potassium hydroxide (2.3 g, 0.04 mol), and 1,3-dibromopropane (4 g, 0.02 mol) we obtained 4.0 g (61%) of the product **6**; mp 164-166°C, R_f 0.50 (1:1 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1600 (C=C arom.); 1650 (C=O). ^1H NMR spectrum: 7.00-8.20 (4H, m, C_6H_4); 4.03 (2H, t, J = 6.0 Hz, 5-CH_2); 3.10 (2H, t, J = 6.0 Hz, 3-CH_2); 2.73 (2H, s, 9-CH_2); 1.10-2.70 (10H, m, 4-, 2'-, 3'-, 4'-, 5'-CH_2). Found, %: C 70.16; H 6.35; N 8.54; S 10.01. $C_{19}H_{20}N_2OS$. Calculated, %: C 70.33; H 6.21; N 8.63; S 9.88.

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