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SYNTHESIS OF TRIAZOLES AND TETRAZOLES CONDENSED WITH SPIRO(BENZO[*h*]QUINAZOLINE-5,1'-CYCLOHEXANE)

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Condensation of 3-R-4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1'-cyclohexanes) with 2-ethanolamine, 3-propanolamine, and hydrazine hydrate gives the corresponding 2-ethanolamino, 2-propanolamino, and 2-hydrazino derivatives. Triazoles and tetrazoles, a- or b-condensed with benzo[h]quinazolines were obtained from 2-hydrazinobenzo[h]quinazolines depending on the presence of a substituent at position 3.

Keywords: benzo[*h*]quinazolines, hydrazines, triazole, tetrazole, condensation.

We have recently reported the synthesis of triazoles and tetrazoles condensed with benzo[*h*]quinazolines at the *c* bond and their anxiolytic properties [1]. Other benzo[*h*]quinazolines which are spiro-joined with cyclohexane ring show antitumor activity [2]. In continuation of this work we now report data for the synthesis of triazoles and tetrazoles which are *a*- or *b*-condensed with benzo[*h*]quinazolines.

Refluxing 3-R-4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) (**1a-c**) with excess of β-ethanolamine or γ-propanolamine gives 2-(β-hydroxyethylamino)- and 2-(γ-hydroxypropylamino)-3-R-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) **2a-d** and **3a-d** respectively.

Reaction of compounds **1a-d** with hydrazine hydrate gave their 2-hydrazino derivatives **4a-d**.

2-Hydrazino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) condenses with orthoformic ester to give 6-oxo-1H-7,8-dihydrospiro(benzo[*h*]triazolo[3,4-*b*]quinazoline-7,1'-cyclopentane) [3]. The analog with spiro-linked cyclohexane ring **4a** reacts similarly with orthoformic ester or with sodium nitrite in acidic medium to give 6-oxo-1H-7,8-dihydrospiro(benzo[*h*]triazolo[3,4-*b*]quinazoline-7,1'-cyclohexane) (**5**) or 6-oxo-1H-7,8-dihydrospiro(benzo[*h*]tetrazolo[5,4-*b*]quinazoline-7,1'-cyclohexane (**6**) respectively. For compounds **4b-d**, which contain a substituent in the 3 position, the products were 4-substituted 5-oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]triazolo[4,3-*a*]quinazoline-6,1'-cyclohexanones) **7a-d** and 4-substituted 5-oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]tetrazolo[4,5-*a*]quinazoline-6,1'-cyclohexanones) **8a-c**, in which the azoles are condensed at the *a* bond with the benzo[*h*]quinazoline ring.

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TABLE 1. Characteristics for 2-(β-Hydroxyethylamino)- and 2-(γ-Hydroxypropylamino)-3-R-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) **2a-d*** and **3a-d**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm	^{1}H NMR spectrum ($CDCl_3$), δ, ppm, spin-spin coupling (*J*, Hz)	Yield, %
		C	H	N				
2a	$C_{19}H_{23}N_3O_2$	70.33 / 70.13	7.26 / 7.12	13.10 / 12.91	246-248	1600 (C=C_{arom}), 1660 (C=O), 3200-3420 (NH, OH)	10.40 (1H, br. s, NH); 7.30-8.15 (4H, m, C_6H_4); 6.25 (1H, m, NH); 4.68 (1H, m, OH); 3.35-3.55 (4H, m, NCH_2CH_2); 2.96 (2H, s, 6-CH_2); 1.10–2.60 (10H, m, 2'-,3'-,4'-,5'-,6'-CH_2)	76
2b	$C_{20}H_{25}N_3O_2$	70.75 / 70.78	7.57 / 7.42	12.55 / 12.38	182-184	1610 (C=C_{arom}), 1655 (C=O), 3200-3350 (NH, OH)	7.40–8.06 (4H, m, C_6H_4); 6.90 (1H, t, *J* = 7, NH); 4.58 (1H, t, *J* = 7, OH); 3.65 (2H, t, *J* = 7, OCH_2); 3.55 (2H, t, *J* = 7, NCH_2); 3.30 (3H, s, NCH_3); 2.95 (2H, s, 6-CH_2); 1.10-2.55 (10H, m, 2'-,3'-,4'-,5'-,6'-CH_2)	82
2c	$C_{26}H_{27}N_3O_2$	74.22 / 74.01	6.79 / 6.99	10.60 / 10.79	247-250	1610 (C=C_{arom}), 1660 (C=O), 3250-3420 (NH, OH)	7.25-8.15 (9H, m, C_6H_4, C_6H_5); 5.40 (1H, m, NH); 4.50 (1H, m, OH); 3.40-3.60 (4H, m, NCH_2CH_2); 3.00 (2H, s, 6-CH_2); 1.00-2.60 (10H, m, 2'-,3'-,4'-,5'-,6'-CH_2)	62
2d	$C_{26}H_{29}N_3O_2$	74.60 / 74.41	7.11 / 7.24	10.27 / 10.41	175-177	1600 (C=C_{arom}), 1660 (C=O), 3200-3430 (NH, OH)	7.40–8.20 (9H, m, C_6H_4, C_6H_5); 6.68 (1H, m, NH); 5.23 (2H, s, $CH_2C_6H_5$); 4.49 (1H, m, OH); 3.45-3.65 (4H, m, NCH_2CH_2); 3.00 (2H, s, 6-CH_2); 1.20-2.65 (10H, m, 2'-,3'-,4'-,5'-,6'-CH_2)	96
3a	$C_{20}H_{25}N_3O_2$	70.89 / 70.78	7.56 / 7.42	12.22 / 12.38	190-192	1605 (C=C_{arom}), 1650 (C=O), 3200-3430 (NH, OH)	7.20-8.10 (4H, m, C_6H_4); 6.89 (1H, t, *J* = 6, NH); 4.43 (1H, t, *J* = 6, OH); 3.45-3.60 (4H, m, NCH_2, OCH_2); 2.95 (2H, s, 6-CH_2); 1.10-2.60 (12H, m, 2'-,3'-,4'-,5'-,6'-CH_2, NCH_2CH_2)	87
3b	$C_{21}H_{27}N_3O_2$	71.24 / 71.36	7.88 / 7.70	11.98 / 11.89	194-195	1600 (C=C_{arom}), 1650 (C=O), 3200-3400 (NH, OH)	7.03-8.23 (4H, m, C_6H_3); 5.37 (1H, m, NH); 3.40-3.90 (4H, m, NCH_2OCH_2); 3.27 (3H, s, NCH_3); 2.90 (2H, s, 6-CH_2); 1.00-2.73 (12H, m, 2'-,3'-,4'-,5'-6'-CH_2, NCH_2CH_2)	88
3c	$C_{26}H_{29}N_3O_2$	74.20 / 74.01	6.89 / 6.99	10.59 / 10.79	264-266	1600 (C=C_{arom}), 1655 (C=O), 3250-3450 (NH, OH)	7.10-8.20 (9H, m, C_6H_4, C_6H_5); 5.47 (1H, t, *J* = 6, NH); 4.27 (1H, t, *J* = 6, OH); 3.40-3.64 (4H, m, NCH_2, OCH_2); 2.93 (2H, s, 6-CH_2); 1.00-2.70 (12H, m, 2'-,3'-,4'-,5'-,6'-CH_2, NCH_2CH_2)	71
3d	$C_{27}H_{31}N_3O_2$	74.98 / 74.79	7.30 / 7.48	9.85 / 10.06	138-140	1605 (C=C_{arom}), 1650 (C=O), 3180-3330 (NH, OH)	7.20-8.20 (9H, m, C_6H_4, C_6H_5); 5.20 (2H, s, $CH_2C_6H_5$); 5,03 (1H, t, *J* = 6, NH); 3.66 (2H, t, *J* = 6, OCH_2), 3.50 (2H, t, *J* = 6, NCH_2); 3.03 (2H, s, 6-CH_2); 1.10-2.83 (12H, m, 2'-,3'-,4'-,5'-,6'-CH_2, NCH_2CH_2)	94

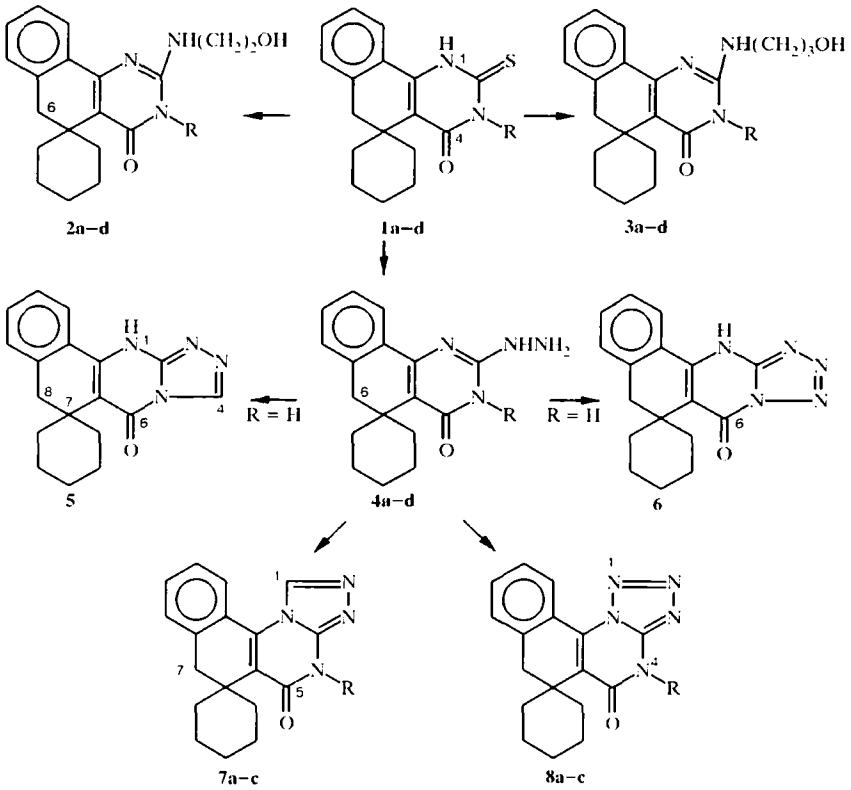
* Mass spectrum, *m/z* (*I*, %): M^+ 402 (28), 401 (100), 359 (9), 358 (35), 357 (16), 345 (12), 332 (5), 328 (5), 314 (8), 302 (6), 301 (29), 77 (12).

TABLE 2. Characteristics of Derivatives of Benzotriazoloquinazoline **7a-c** and Benzotetrazoloquinazoline **8a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	^{1}H NMR spectrum ($CDCl_3$)	Yield, %
		C	H	N			
7a	$C_{19}H_{20}N_4O$	71.41 / 71.23	6.37 / 6.29	17.42 / 17.49	218-220	8.83 (1H, s, 1-CH); 7.20-7.90 (4H, m, C_6H_4); 3.73 (2H, s, NCH_3); 2.83 (2H, s, 7-CH_2); 1.20-2.50 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	79
7b	$C_{24}H_{22}N_4O$	75.19 / 75.36	6.66 / 6.80	14.82 / 14.65	307-310	9.16 (1H, s, 1-CH); 7.20-7.86 (9H, m, C_6H_4, C_6H_5); 3.03 (2H, s, 7-CH_2); 1.00-2.80 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	67
7c*	$C_{25}H_{24}N_4O$	75.96 / 75.73	6.28 / 6.10	14.03 / 14.13	218-220	9.16 (1H, s, 1-CH); 7.03-7.83 (9H, m, C_6H_4, C_6H_5); 5.40 (2H, s, $CH_2C_6H_5$); 3.00 (2H, s, 7-CH_2); 1.00-2.83 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	76
8a	$C_{18}H_{19}N_5O$	67.24 / 67.27	6.08 / 5.96	21.78 / 21.89	215-217	7.20-7.70 (4H, m, C_6H_4); 3.78 (2H, s, NCH_3); 3.03 (2H, s, 7-CH_2); 1.20-2.63 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	96
8b*[2]	$C_{23}H_{21}N_5O$	72.23 / 72.04	5.39 / 5.52	18.15 / 18.26	225-228	7.60-8.55 (9H, m, C_6H_4, C_6H_5); 3.20 (2H, s, 7-CH_2); 1.13-2.60 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	81
8c	$C_{23}H_{23}N_5O$	72.70 / 72.52	5.69 / 5.83	17.51 / 17.62	172-174	7.50-8.50 (9H, m, C_6H_4, C_6H_5); 5.37 (2H, s, $CH_2C_6H_5$); 3.00 (2H, s, 7-CH_2); 1.03-2.73 (10H, m, 2'-, 3'-, 4'-, 5'-, 6'-CH_2)	83

* Mass spectrum, *m/z* (*I*, %): M^+ 397 (28), 396 (100), 395 (50), 367 (6), 354 (5), 353 (12), 340 (15), 327 (5), 305 (28), 249 (10), 85 (87).

*[2] Mass spectrum, *m/z* (*I*, %): M^+ 384 (25), 383 (100), 357 (13), 356 (11), 355 (38), 313 (12), 312 (47), 300 (14), 299 (55), 298 (45), 297 (22), 286 (19), 285 (25), 270 (10), 181 (6), 167 (6), 166 (7), 165 (6), 153 (8), 152 (6), 140 (10).



1-4 a R = H, **b** R = Me, **c** R = Ph, **d** R = CH_2Ph; **7, 8 a** R = Me, **b** R = Ph, **c** R = CH_2Ph

EXPERIMENTAL

IR spectra were taken in vaseline oil on an UR-20 instrument and ^1H NMR spectra – on Varian T-60 or Varian Mercury-300 instruments using deuterated solvents and TMS or HMDS as internal standards. Mass spectra were obtained on an MX-1321A spectrometer. TLC was performed on Silufol UV-254 plates and visualized with iodine vapor.

Characteristics for the synthesized compounds **2, 3** are given in Table 1 and **7, 8** in Table 2.

3-R-2-(β-Hydroxyethylamino)-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) (2a-d). Mixture of compound **1a-d** (0.01 mol) and ethanolamine (20 ml) was refluxed with a condenser for 25 h. The reaction mixture was cooled, water (50 ml) was added, and the precipitated crystals of the product **2a-d** were filtered off and recrystallized from ethanol.

3-R-2-(γ-Hydroxypropylamino)-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) (3a-d) were obtained similarly to **2a-d** starting from the quinazoline derivatives **1a-d** and γ-aminopropanol.

3-R-2-Hydrazino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexanes) (4a-d). Mixture of compound **1a-d** (0.02 mol), hydrazine hydrate (30 ml), and butanol (150 ml) was refluxed with a condenser for 20 h. The reaction mass was cooled and the precipitated product **4** was filtered, washed with water and then ethanol and dried in air.

Compound 4a. Yield 81%; mp 292-294°C. IR spectrum: 1605 ($C=C_{arom}$), 1655 (C=O), 3200 cm^{-1} (NH, NH_2). Found, %: C 68.70; H 6.62; N 18.89. $C_{17}H_{20}N_4O$. Calculated, %: C 68.89; H 6.80; N 18.90.

Compound 4b. Yield 76%; mp 203-204°C. IR spectrum: 1600 ($C=C_{arom}$), 1660 (C=O), 3200 cm^{-1} (NH, NH_2). Found, %: C 69.80; H 7.02; N 18.89. $C_{18}H_{22}N_4O$. Calculated, %: C 69.65; H 7.14; N 19.05.

Compound 4c. Yield 72%; mp 230-233°C. R_f 0.55 (ethyl acetate–hexane, 4: 1). IR spectrum: 1605 ($C=C_{arom}$), 1660 (C=O), 3210 cm^{-1} (NH, NH_2). Found, %: C 74.11; H 6.35; N 15.23. $C_{23}H_{24}N_4O$. Calculated, %: C 74.17; H 6.49; N 15.04.

Compound 4d. Yield 95%; mp 196-197°C. R_f 0.59 (ethyl acetate–hexane, 3: 2). IR spectrum: 1600 ($C=C_{arom}$), 1655 (C=O), 3200 cm^{-1} (NH, NH_2). Found, %: C 74.71; H 6.92; N 14.69. $C_{24}H_{26}N_4O$. Calculated, %: C 74.58; H 6.78; N 14.50.

6-Oxo-1H-7,8-dihydrospiro(benzo[*h*]triazolo[3,4-b]quinazoline-7,1'-cyclohexane) (5). Mixture of compound **4a** (3 g, 0.01 mol), orthoformic ester (30 ml), and butanol (30 ml) was refluxed with a condenser for 6 h. The reaction mass was cooled and the precipitate was filtered off and recrystallized from butanol to give product **5** (2.6 g, 86%); mp 363-365°C. R_f 0.56 (chloroform–acetone, 6: 5). ^1H NMR spectrum (pyridine-d_5): 8.93 (1H, s, 4-CH); 7.30-8.53 (4H, m, C_6H_4); 3.13 (2H, s, 8-CH_2); 1.20-3.00 ppm (10H, m, 2'-, 3'-, 4'-, 5'-, 6'- CH_2). Found, %: C 70.72; H 6.07; N 18.16. $C_{18}H_{18}N_4O$. Calculated, %: C 70.57; H 5.92; N 18.29.

4-R-5-Oxo-6,7-dihydrospiro(benzo[*h*]triazolo[4,3-a]quinazoline-6,1'-cyclohexanes) (7a-c) were obtained similarly to compound **5** starting from the quinazolinones **4b-d**.

6-Oxo-1H-7,8-dihydrospiro(benzo[*h*]tetrazolo[5,4-b]quinazoline-7,1'-cyclohexane) (6). Solution of sodium nitrite (1 g, 0.014 mol) in water (10 ml) was added dropwise with stirring to mixture of compound **4a** (3 g, 0.01 mol) and glacial acetic acid (60 ml). Stirring was continued at room temperature for 30 min. The formed precipitate was filtered off, washed with water, and recrystallized from butanol to give product **6** (2 g, 65%); mp 227-229°C. R_f 0.45 (chloroform–acetone–pyridine, 6: 5: 1). ^1H NMR spectrum (pyridine-d_5): 7.00-8.40 (4H, m, C_6H_4); 3.00 (2H, s, 8-CH_2); 1.03-2.83 ppm (10H, m, 2'-, 3'-, 4'-, 5'-, 6'- CH_2). Found, %: C 66.57; H 5.68; N 22.65. $C_{17}H_{17}N_5O$. Calculated, %: C 66.43; H 5.58; N 22.79.

4-R-5-Oxo-6,7-dihydrospiro(benzo[*h*]tetrazolo[1,5-a]quinazoline-6,1'-cyclohexanes) (8a-c) were obtained similarly to compound **6** starting from the quinazolinones **4b-d** respectively.

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