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

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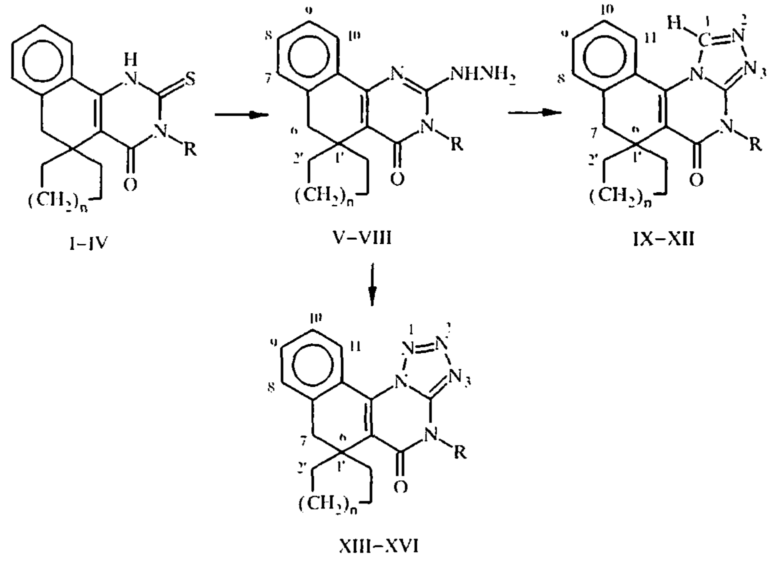
3-p-Tolyl- and 3-cyclohexyl-4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1'-cycloalkanes) react with hydrazine hydrate to give 2-hydrazino-3-substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1'-cycloalkanes), from which the corresponding triazoles and tetrazoles were subsequently obtained

In previous works [1, 2], we reported the syntheses of triazoles and tetrazoles condensed at positions *a*, *b*, and *c* with benzo[*h*]quinazolines. We have shown that benzo[*h*]quinazolines spirofused with cycloalkane rings possess antitumor activity [3].



I, V, IX, XIII n = 1, R = cyclohexyl; II, VI, X, XIV n = 1, R = *p*-tolyl;
III, VII, XI, XV n = 2, R = cyclohexyl; IV, VIII, XII, XVI n = 2, R = *p*-tolyl

Condensation of 2-thioxo-3-substituted 4-oxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) [4, 5] I–IV with hydrazine hydrate gave the corresponding 2-hydrazino-3-substituted 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) V–VII. Then, reaction with triethyl orthoformate gave 4-substituted 5-oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]triazolo[4,3-*a*]quinazoline-6,1'-cycloalkanes) IX–XII, while reaction with sodium nitrite in acid media gave 5-oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]tetrazolo[5,4-*a*]quinazoline-6,1'-cycloalkanes) XIII–XVI.

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TABLE 1. Characteristics for Benzo[*h*]quinazolines IX–XVI

Compound	Found, % / Calculated, % C	H	N	Mp, °C	PMR spectrum	R_f (syst.)	Yield, %
IX	73.71 / 73.76	7.05 / 7.00	15.03 / 14.96	259-261	9.00 (1H, s, 1-H); 7.93 (1H, d, 8-H); 7.60-7.40 (3H, m, 9-H, 10-H, 11-H); 5.05 (1H, m, 1''-H); 2.90 (2H, s, 7-H$_2$); 2.80-1.20 (18H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 2''-H$_2$, 3''-H$_2$, 4''-H$_2$, 5''-H$_2$, 6''-H$_2$)	0.65 (A)	78
X	75.39 / 75.36	5.86 / 5.79	14.77 / 14.65	279-281	9.00 (1H, s, 1-H); 8.00 (1H, d, 8-H); 7.60-7.30 (7H, m, 9-H, 10-H, 11-H, C_6H_4); 2.95 (2H, s, 7-H$_2$); 2.40 (3H, s, Ar-CH_3); 2.30-1.40 (8H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$)	0.66 (A)	84
XI	74.25 / 74.19	7.31 / 7.26	14.39 / 14.42	286-228	9.00 (1H, s, 1-H); 7.92 (1H, d, 8-H); 7.60-7.40 (3H, m, 9-H, 10-H, 11-H)]; 5.00 (1H, m, 1''-H); 3.10 (2H, s, 7-H$_2$); 2.70-1.20 (20H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 2''-H$_2$, 3''-H$_2$, 4''-H$_2$, 5''-H$_2$, 6''-H$_2$)	0.62 (A)	64
XII	75.69 / 75.73	6.11 / 6.10	14.10 / 14.13	284-286	9.00 (1H, s, 1-H); 7.96 (1H, d, 8-H); 7.60-7.26 (7H, m, 9-H, 10-H, 11-H, C_6H_4); 3.18 (2H, s, 7-H$_2$); 2.40 (3H, s, Ar-CH_3); 2.80-1.20 (10H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 6'-H$_2$)	0.63 (A)	78
XIII	73.05 / 70.38	6.91 / 6.71	19.35 / 18.65	214-216	8.60 (1H, d, 8-H); 7.60-7.40 (3H, m, 9-H, 10-H, 11-H); 5.00 (1H, m, 1''-H); 2.98 (2H, s, 7-H$_2$); 2.80-1.40 (18H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 2''-H$_2$, 3''-H$_2$, 4''-H$_2$, 5''-H$_2$, 6''-H$_2$)	0.63 (A)	86
XIV	71.98 / 72.04	5.53 / 5.52	18.31 / 18.26	191-193	8.65 (1H, d, 8-H); 7.60-7.20 (7H, m, 9-H, 10-H, 11-H, C_6H_4); 3.00(2H, s, 7-H$_2$); 2.40 (3H, s, Ar-CH_3); 2,38-1.40 (8H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$)	0.66 (A)	81
XV	70.98 / 70.92	7.02 / 6.99	17.95 / 17.98	237-239	8.60 (1H, d, 8-H); 7.60-7.40 (3H, m, 9-H, 10-H, 11-H); 5.00 (1H, m, 1''-H); 3.18 (2H, s, 7-H$_2$); 2.80-1.20 (20H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 6'-H$_2$, 2''-H$_2$, 3''-H$_2$, 4''-H$_2$, 5''-H$_2$, 6''-H$_2$)	0.64 (A)	90
XVI	72.55 / 72.52	6.00 / 5.83	17.66 / 17.62	212-214	8.60 (1H, d, 8-H); 7.60-7.20 (7H, m, 9-H, 10-H, 11-H, C_6H_4); 3.20 (2H, s, 7-H$_2$); 2.40 (3H, s, Ar-CH_3); 2.80-1.20 (10H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, 5'-H$_2$, 6'-H$_2$)	0.68 (A)	80

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for Vaseline mulls. The PMR spectra were recorded on a Varian Mercury 300 spectrometer using the US CRDF RESC 17–5 program and TMS as the internal standard. The nuclear Overhauser effect experiments were used to assign the aromatic ring proton signals [4]. The thin-layer chromatography was carried out on Silufol UV-254 plates using 1:3 acetone–hexane (A) or 1:7 propanol–hexane (B) as the eluent and iodine vapors as the developer.

3-Cyclohexyl-2-hydrazino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (V). Mixture of 7.3 g (0.02 mol) of benzo[*h*]quinazoline I, 30 ml of hydrazine hydrate, and 150 ml of butanol was heated at reflux for 20 h. After cooling, the precipitate formed was filtered off, washed with water and ethanol, and dried in the air to give 6 g (82%) of the compound V, mp 213-215°C. R_f 0.75 (A). IR spectrum: 1600 (C=C_{arom}), 1655 (C=O), 3250, 3480 cm^{-1} ($NHNH_2$). PMR spectrum (CD_3COCD_3): 9.80 (1H, s, NH); 7.55 (1H, d, 7-H); 7.45-7.20 (5H, m, 8-H, 9-H, 10-H, NH_2); 5.00 (1H, m, 1″-H); 2.80 (2H, s, 6$\underline{H_2}$); 2.40-1.10 ppm (18H, m, 2'-H_2 3'-H_2, 4'-H_2, 5'-H_2, 2″-H_2, 3″-H_2, 4'-H_2, 5″-H_2, 6″-H_2). Found, %: C 72.51; H 7.78; N 15.43. $C_{22}H_{28}N_4O$ Calculated, %: C 72.50; H 7.74; N, 15.37.

2-Hydrazino-4-oxo-3-*p*-tolyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (VI) was obtained analogously from 7.5 g (0.02 mol) of benzo[*h*]quinazoline II in 90% yield (6.7 g), mp 224-226°C, R_f 0.62 (A). IR spectrum: 1605 (C=C_{arom}), 1655 (C=O), 3170-3359 cm^{-1} ($NHNH_2$). PMR spectrum (DMSO): 10.00 (1H, s, NH); 8.40 (1H, d, 7-H); 7.40-7.00 (9H, m, 8-H, 9-H, 10-H, NH_2, C_6H_4); 2.80 (2H, s, 6-H_2); 2.40 (3H, s, Ar-CH_3); 1.80-1.20 ppm (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2,). Found, %: C 74.21; H 6.53; N 15.11. $C_{23}H_{24}N_4O$ Calculated: C 74.16; H 6.49; N 15.04.

3-Cyclohexyl-2-hydrazino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexane) (VII) was obtained analogously from 7.6 g (0.02 mol) of benzo[*h*]quinazoline III in 68% yield (5.1 g), mp 224-226°C, R_f 0.57 (B). IR spectrum: 1605 (C-C_{arom}), 1655 (C=O), 3100-3300 cm^{-1} ($NHNH_2$). PMR spectrum (CD_3COCD_3): 10.60 (1H, s, NH); 8.00 (1H, d, 7-H); 7.60-7.30 (5H, m, 8-H, 9-H, 10-H, NH_2); 5.60 (1H, m, 1″-H); 3.00 (2H, s, 6'-H_2,); 2.80-1.00 ppm (20H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2, 2″-H_2, 3″-H_2, 4″-H_2, 5″-H_2, 6″-H_2). Found, %: C 73.01; H 7.93; N 14.91. $C_{23}H_{30}N_4O$. Calculated, %: C 72.98; H 7.99; N 14.80.

2-Hydrazino-4-oxo-3-*p*-tolyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexane) (VIII) was obtained analogously from 7.7 g (0.02 mol) of benzo[*h*]quinazoline IV in 52% yield (4 g), mp 252–254°C, R_f 0.51 (B). IR spectrum: 1605 (C=C_{arom}), 1655 (C=O), 3150-3370 cm^{-1} ($NHNH_2$).PMR spectrum (DMSO): 9.80 (1H, s, NH); 8.40 (1H, d, 7-H); 7.40-7.05 (9H, m, 8-H, 9-H, 10-H, C_6H_4, NH_2); 3.00 (2H, s, 6-H_2); 2.40 (3H, s, Ar-C$\underline{H_3}$); 1.80–1.10 ppm (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2,). Found, %: C 74.62; H 6.75; N 14.51. $C_{24}H_{26}N_4O$ Calculated, %: C 74.58; H 6.78; N 14.50.

4-Substituted 5-Oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]triazolo[4,3-*a*]quinazoline-6,1'-cycloalkanes) IX–XII. Mixture of 0.01 mol of hydrazinoquinazoline V–VIII, 30 ml of triethyl orthoformate, and 30 ml of butanol was heated at reflux for 6 h. After cooling, the precipitate formed was filtered off and recrystallized from butanol (Table 1).

4-Substituted 5-Oxo-4,5,6,7-tetrahydrospiro(benzo[*h*]tetrazolo[5,4-*a*]quinazoline-6,1'-cycloalkanes) XIII–XVI. Sample of 0.01 mol of hydrazinoquinazoline V–VIII and 60 ml of glacial acetic acid were placed into a flask. Solution of 1 g (0.014 mol) of sodium nitrite in 10 ml of water was added dropwise under stirring. The reaction mixture was stirred at room temperature for 30 min. The precipitate formed was filtered off, washed with water, and recrystallized from butanol (Table 1).

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