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SYNTHESIS OF 2-ALKYLTHIO-SUBSTITUTED 4-OXO-3-*p*-TOLYL-3,4,5,6-TETRAHYDROSPIRO-(BENZO[*h*]QUINAZOLINE-5,1'-CYCLOALKANES)

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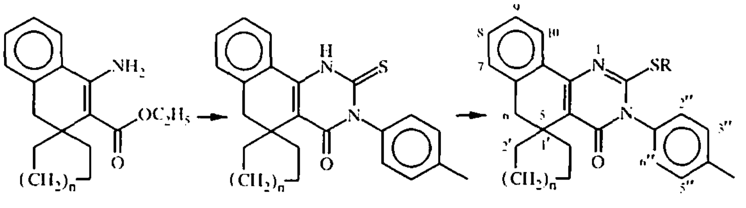
Reaction of 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1'-cycloalkanes) with p-tolylisothiocyanate gave 4-oxo-2-thioxo-3-p-tolyl-1,2,3,4,5,6-hexahydro(benzo[h]quinazoline-5,1'-cycloalkanes) which could be alkylated using various halo compounds to yield the corresponding S-alkyl derivatives.

Derivatives of benzo[*h*]quinazolines which are spiro-joined to cycloalkanes show psychotropic [1] and antitumor [2] properties. Continuing investigation in this area, we report in this communication synthetic data for benzo[*h*]quinazolines having a *p*-tolyl substituent in the 3 position. As starting materials we used 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1'-cycloalkanes) I and II [3, 4] which, upon interaction with *p*-tolylisothiocyanate and subsequent treatment of the reaction mixture with base, give the corresponding 4-oxo-2-thioxo-3-*p*-tolyl-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) III and IV. We have carried out quantum-chemical calculations [5], according to which the process of S-alkylation of the benzo[*h*]quinazoline systems is orbitally controlled (the highest fractional orbital density being localized on the sulfur atom).

By alkylation of quinazolines III and IV with halides of various structure we have shown that the single reaction route is S-alkylation and this is completely in agreement with the quantum-chemical calculations. The alkylation results in 2-alkylthio-substituted 4-oxo-3-*p*-tolyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) V-XXIV.



I, II

III, IV

V-XXIV

R = CH_3, C_2H_5, C_4H_9, $CH_2C_6H_5$, $CH_2CO_2C_2H_5$, $CH_2CH{=}CH_2$, CH_2CN, $CH_2C{\equiv}CH$, $CH_2CH_2C_6H_5$, $CH_2CO_2C_6H_4$-*p*; I, III, V-XIV n = 1; II, IV, XV-XXIV n = 2

The structure of the S-substituted benzo[*h*]quinazolines was confirmed by PMR spectroscopic data (Table 2).

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TABLE 1. 2-Alkylthio-substituted 4-Oxo-3-*p*-tolyl-3,4,5,6-tetrahydrospiro-(benzo[*h*]quinazoline-5,1'-cycloalkanes) V-XXIV

Compound	R	Found, % Calculated, %				mp, °C	R_f (system)	Yield, %
		C	H	N	S			
V	CH_3	74.28 74.19	6.19 6.23	7.29 7.21	8.28 8.25	179-181	0.52 (A)	75
VI	C_2H_5	74.40 74.59	6.56 6.51	7.11 6.96	8.02 7.96	188-190	0.51 (D)	72
VII	C_4H_9	75.32 75.31	6.93 7.02	6.46 6.50	7.54 7.44	118-120	0.64 (C)	66
VIII	$CH_2C_6H_5$	77.54 77.55	6.05 6.07	6.43 6.03	7.05 6.90	117-119	0.61 (C)	67
IX	$CH_2CO_2C_2H_5$	70.44 70.41	6.11 6.13	6.12 6.08	7.05 6.96	154-156	0.38 (C)	63
X	$CH_2CH{=}CH_2$	75.39 75.32	6.35 6.32	6.73 6.76	7.69 7.73	174-176	0.77 (C)	46
XI	CH_2CN	72.60 72.61	5.55 5.61	10.18 10.16	7.68 7.75	197-198	0.46 (A)	53
XII	$CH_2C{\equiv}CH$	75.65 75.69	5.72 5.86	6.91 6.79	7.73 7.77	157-159	0.64 (A)	65
XIII	$CH_2CH_2C_6H_5$	77.82 77.79	6.32 6.32	5.97 5.85	6.82 6.70	153-155	0.54 (A)	56
XIV	$CH_2COC_6H_4Cl$-*p*	70.65 70.64	5.22 5.16	5.30 5.31	6.15 6.08	244-246	0.57 (A)	71
XV	CH_3	74.58 74.59	6.55 6.51	7.13 6.96	7.88 7.96	225-227	0.51 (A)	85
XVI	C_2H_5	74.96 74.96	6.78 6.77	6.78 6.72	7.71 7.70	240-242	0.54 (D)	76
XVII	C_4H_9	75.65 75.63	7.15 7.25	6.31 6.30	7.28 7.21	140-142	0.67 (B)	75
XVIII	$CH_2C_6H_5$	77.88 77.79	6.32 6.32	5.99 5.85	6.85 6.70	170-172	0.67 (B)	89
XIX	$CH_2CO_2C_2H_5$	70.55 70.86	6.35 6.37	6.01 5.90	6.88 6.76	170-172	0.52 (A)	73
XX	$CH_2CH{=}CH_2$	75.69 75.66	6.63 6.58	6.68 6.54	7.38 7.48	231-233	0.76 (B)	78
XXI	CH_2CN	73.15 73.03	5.91 5.89	10.01 9.83	7.52 7.50	189-191	0.47 (A)	89
XXII	$CH_2C{\equiv}CH$	76.12 76.02	6.16 6.14	6.59 6.57	7.58 7.52	196-198	0.65 (A)	91
XXIII	$CH_2CH_2C_6H_5$	78.11 78.00	6.55 6.55	5.85 5.69	6.65 6.51	143-145	0.54 (A)	71
XXIV	$CH_2COC_6H_4Cl$-*p*	70.95 71.03	5.41 5.40	5.18 5.18	5.86 5.92	216-218	0.44 (C)	63

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in Vaseline oil and PMR spectra were obtained on a Varian Mercury 300 spectrometer using the US CRDF RESC 17-5 program with TMS as internal standard. Assignment of the signals for the protons of the aromatic ring of benzo[*h*]quinazolines III-XXIV was made from NOE experiments. When irradiation was at the frequency of the singlet signal for the methylene group in position 6 of the quinazolines III-XXIV, the only response was seen at the doublet signal near 8.2 ppm hence this signal was assigned to the aromatic proton at position 7. TLC was carried out on Silufol UV-254 plates in the systems propanol–hexane, 1: 7 (A), acetone–hexane, 1: 3 (B), acetone–hexane (C), or acetone–hexane, 1: 7 (D) using iodine vapor or UV visualization.

4-Oxo-2-thioxo-3-*p*-tolyl-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (III). Mixture of 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (I), (40.6 g, 0.15 mol), *p*-tolylisothiocyanate (22.3 g, 0.15 mol), and ethanol (200 ml) was refluxed for 14 h. After cooling, the precipitated crystals were filtered, solution of KOH (22.4 g, 0.4 mol) in ethanol (50%, 300 ml) was added and the product was refluxed for 5 h. After cooling again, hydrochloric acid (10%) was added dropwise to acid reaction.

TABLE 2. PMR Spectroscopic Data for Compounds V-XXIV

Compound	PMR spectrum, δ, ppm
V	8.20 (1H, d, 7-H); 7.40-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 2.85 (2H, s, 6-H_2); 2.55 (3H, s, SCH_3); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.25-1.2 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
VI	8.20 (1H, d, 7-H); 7.40-7.30 (4H, m, C_6H_4); 7.28-7.20 (3H, m, 8-H, 9-H, 10-H); 3.2 (2H, q, SCH_2); 2.90 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.40-1.40 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2); 1.38 (3H, t, $SCH_2\underline{CH}_3$)
VII	8.10 (1H, d, 7-H); 7.42-7.18 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 3.18 (2H, t, SCH_2); 2.78 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.30-1.30 (12H, m, $S\underline{CH}_2CH_3$, $SCH_2\underline{CH}_2CH_3$, C_6H_4, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
VIII	8.16 (1H, d, 7-H); 7.45-7.18 (12H, m, 8-H, 9-H, 10-H, C_6H_4, C_6H_5); 4.50 (2H, s, SCH_2); 2.85 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.28-1.45 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
IX	8.10 (1H, d, 7-H); 7.40-7.22 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.20–4.04 (2H, q, OCH_2); 4.00 (2H, s, SCH_2); 2.85 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.20- 1.35 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2); 1.20 (3H, t, $OCH_2\underline{CH}_3$)
X	8.15 (1H, d, 7-H); 7.40-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 6.00 (1H, m, CH_2–$\underline{CH}$=CH_2); 5.30; 5.10 (2H, dd, –$\underline{CH}$=CH_2); 3.88 (2H, d, SCH_2); 2.85 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.30-1.30 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
XI	8.30 (1H, d, 7-H); 7.45-7.25 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.20 (2H, s, SCH_2); 2.90 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.30- 1.40 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
XII	8.25 (1H, d, 7-H); 7.45-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.00 (2H, s, SCH_2); 3.15 (1H, s, $CH_2C{\equiv}C\underline{H}$); 2.87 (2H, s, 6-$H_2$); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.30-1.30 (8H, m, 2'-$H_2$, 3'-$H_2$, 4'-$H_2$, 5'-$H_2$)
XIII	8.15 (1H, d, 7-H); 7.40-7.20 (12H, m, 8-H, 9-H, 10-H, C_6H_5, C_6H_4); 3.40 (2H, t, $SCH_2\underline{CH}_2$); 3.10 (2H, t, $SCH_2\underline{CH}_2$); 2.90 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.25-1.35 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
XIV	8.10 (2H, d, 3"-H, 5"-H); 7.52 (2H, d, 2"-, 6"-H); 7.50-6.80 (8H, m, 7-H, 8-H, 9-H, 10-H, C_6H_4); 4.80 (2H, s, SCH_2); 2.80 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 2.20-1.30 (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2)
XV	8.15 (1H, d, 7-H); 7.40-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 3.05 (2H, s, 6-H_2); 2.55 (3H, s, SCH_3); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.10 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XVI	8.10 (1H, d, 7-H); 7.40-7.15 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 3.20 (2H, m, SCH_2); 3.05 (2H, c, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.30 (3H, t, $CH_2\underline{CH}_3$); 1.70-1.40; 1.25-1.10 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XVII	8.10 (1H, d, 7-H); 7.45-7.25 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 3.25 (2H, m, SCH_2); 3.05 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.10 (14H, m, $SCH_2\underline{CH}_2CH_2CH_3$, $SCH_2CH_2\underline{CH}_2CH_3$, 2'-$H_2$, 3'-$H_2$, 4'-$H_2$, 5'-$H_2$, 6'-$H_2$); 0.90 (3H, t, SCH;$CH_2CH_2\underline{CH}_3$)
XVIII	8.15 (1H, d, 7-H); 7.45-7.20 (12H, m, 8-H, 9-H, 10-H, C_6H_4, C_6H_5); 4.45 (2H, s, SCH_2); 3.05 (2H, s, 6-H_2); 2.50 (3H, s, Ar–$\underline{CH}_3$); 1.75-1.10 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XIX	8.05 (1H, d, 7-H); 7.40-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.10 (2H, q, $O\underline{CH}_2CH_3$); 4.00 (2H, s, SCH_2); 3.05 (2H, s, 6-H_2); 2.50 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.25 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2); 1.20 (3H, t, $OCH_2\underline{CH}_3$)
XX	8.15 (1H, d, 7-H); 7.45-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 5.95 (1H, m, $CH_2\underline{CH}$=CH_2); 5.30; 5.10 (2H, dd, CH_2CH=$\underline{CH}_2$); 3.90 (2H, d, SCH_2); 3.05 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.75-1.10 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XXI	8.25 (1H, d, 7-H); 7.45-7.30 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.20 (2H, s, SCH_2); 3.10 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.75-1.00 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XXII	8.20 (1H, d, 7-H); 7.45-7.20 (7H, m, 8-H, 9-H, 10-H, C_6H_4); 4.00 (2H, s, SCH_2); 3.10 (1H, s, $CH_2C{\equiv}C\underline{H}$); 3.05(2H, s, 6-$H_2$); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.10 (10H, m, 2'-H_2, 3'-H_2, 5'-H_2, 6'-H_2)
XXIII	8.15 (1H, d, 7-H); 7.45-7.15 (12H, m, 8-H, 9-H, 10-H, C_6H_4, C_6H_5); 3.40 (2H, t, $C\underline{H}_2$–C_6H_5); 3.10 (2H, s, 6-H_2); 3.00 (2H, t, SCH_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.15 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)
XXIV	8.10 (2H, d, 3"-, 5"-H); 7.65 (2H, d, 2"-, 6"-H); 7.45-7.20 (8H, m, 7-H, 8-H, 9-H, 10-H, C_6H_4); 4.80 (2H, s, SCH_2); 3.00 (2H, s, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.70-1.10 (10H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2)

The precipitated crystals were filtered, washed with water, and dried in air to give quinazoline III (42.9 g, 78%); mp 232-234°C and R_f 0.37 (C). IR spectrum: 1610 ($C{=}C_{arom}$), 1660 (C=O), 3100-3250 cm^{-1} (NH). PMR spectrum (DMSO-d_6): 10.80 (1H, s, NH); 8.0 (1H, d, 7-H); 7.50-7.30 (3H, m, 8-H, 9-H, 10-H); 7.25 (2H, d, 2"-H, 6"-H); 7.10 (2H, d, 3"-H, 5"-H); 2.85 (2H, 6-H_2); 2.40 (3H, s, Ar–$\underline{CH}_3$); 1.80-1.15 ppm (8H, m, 2'-H_2, 3'-H_2, 4'-H_2, 5'-H_2). Found, %: C 73.68; H 5.99; N 7.52; S 8.62. $C_{23}H_{22}N_2SO$. Calculated, %: C 73.75; H 5.92; N 7.48; S 8.57.

4-Oxo-2-thioxo-3-*p*-tolyl-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclohexane) (IV) was obtained similarly to compound III from 4-amino-3-carbethoxy-1,2-dihydrospiro(naphthalene-2,1'-cyclohexane) (II) (42.4 g, 0.15 mol) and *p*-tolylisothiocyanate (22.3 g, 0.15 mol). Yield 46.2 g, (81%); mp 266-268°C, R_f 0.38 (C). IR spectrum: 1610 ($C=C_{arom}$), 1660 (C=O), 3100-3250 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 10.80 (1H, s, NH); 8.00 (1H, d, 7-H); 7.60-7.40 (3H, m, 8-H, 9-H, 10-H); 7.30 ppm (2H, d, 2"-H, 6"-H). Found, %: C 74.12; H 6.21; N 7.28; S 8.21. $C_{24}H_{24}N_2SO$. Calculated, %: C 74.19; H 6.23; N 7.21; S 8.25.

2-Alkylthio-substituted 4-Oxo-3-*p*-tolyl-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) V-XXIV. Mixture of benzoquinazoline (0.01 mol), KOH (0.015 mol), and halide (0.01 mol) in ethanol (60 ml) was refluxed for 8 h. The solution was cooled, water (20 ml) was added, and the precipitated crystals were filtered and washed with water. They were recrystallized from isobutanol (Table 1).

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