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SYNTHESIS AND STRUCTURE OF 2-METHYL-6-OXO-7,8-DIHYDROSPIRO(BENZO[*h*]-TRIAZOLO[3,4-*b*]QUINAZOLINE-7,1'-CYCLOPENTANE)

A. I. Markosyan[1], R. A. Kuroyan[1], S. V. Dilanyan[1], M. S. Aleksanyan[2], A. A. Karapetyan[2], and Yu. T. Struchkov[2]

The reaction of 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) with benzoyl isothiocyanate led to the corresponding 4-(N'-benzoylthioureido) derivative, the cyclization of which gave 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1'-cyclopentane). Condensation of the latter with hydrazine hydrate gave 2-hydrazino-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1'-cyclopentane), which formed 6-oxo-1H-7,8-dihydrospiro(benzo[h]triazolo[3,4-b]quinazoline-7,1'-cyclopentane) in reaction with orthoformic ester. Methylation of the product with methyl iodide led to its 2-methyl derivative.

Keywords: benzo[*h*]quinazolines, triazole, condensation, methylation, cyclization.

Earlier we reported on the synthesis and anxiolytic characteristics of 3-substituted 7,8-dihydrospiro(benzo[*h*]triazolo[4,3-*c*]quinazoline-7,1'-cyclopentanes) [1]. In a continuation of these researches in the present work the corresponding N'-benzoylthioureido derivative **2** was synthesized by the reaction of the familiar 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (**1**) [2] with benzoyl isothiocyanate. Treatment of **2** with a solution of potassium hydroxide in alcohol led to 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (**3**), which was converted by the action of hydrazine hydrate in butanol into the hydrazine derivative **4**. The reaction of compound **4** with orthoformic ester could be expected theoretically to form 5-oxo-4H-6,7-dihydrospiro(benzo[*h*]triazolo[4,3-*a*]quinazoline-6,1'-cyclopentane) (**5**), 6-oxo-1H-7,8-dihydrospiro(benzo[*h*]triazolo[3,4-*b*]quinazoline-7,1'-cyclopentane) (**6**), or their mixture.

Since we were unable to obtain crystals of the synthesized product suitable for X-ray crystallographic analysis, the product was methylated by methyl iodide in isobutanol. The data from X-ray crystallographic analysis of the methyl derivative correspond to structure **7**, which in turn indicates that compound **6** is formed from the hydrazine **4**.

The coordinates of the hydrogen atoms and the equivalent isotropic temperature parameters for the methylation product **7** are given in Table 1. The bond lengths and bond angles are given in Tables 2 and 3. The molecular structure of compound **7** and the numbering of the atoms are shown in Fig. 1.

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* Communication 1, see ref. [1].

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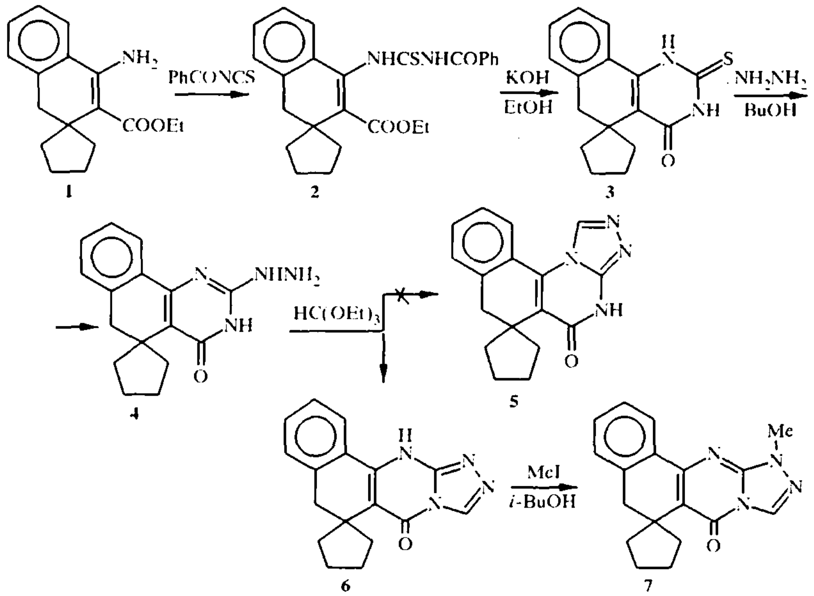
[1] A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan 375014. [2] Center for the Study of Molecular Structure, National Academy of Science of the Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 658-662, May, 2000. Original article submitted October 8, 1998; revision submitted March 3, 1999.



On the whole the bond lengths found in the investigated molecule have the expected values and are comparable within the limits of 3σ with the standard values [3], but a detailed discussion of the individual values seems inappropriate on account of the low accuracy of the obtained data. However, the problems of establishing an objective structure for the compound and determining the mutual arrangement of the fragments were solved conclusively.

Apart from the $C_{(17)}\cdots C_{(20)}$ atoms of the cyclopentane fragment, the other atoms in the molecule lie in a layer 1.25 Å thick. (The largest individual deviations from the mean-square plane are 0.77 Å for $C_{(15)}$ and 0.48 Å for $O_{(1)}$, although the individual rings of the condensed system are nonplanar.) In the investigated structure the triazole and benzene rings are in fact planar. (The largest individual deviation of the atoms forming them from the

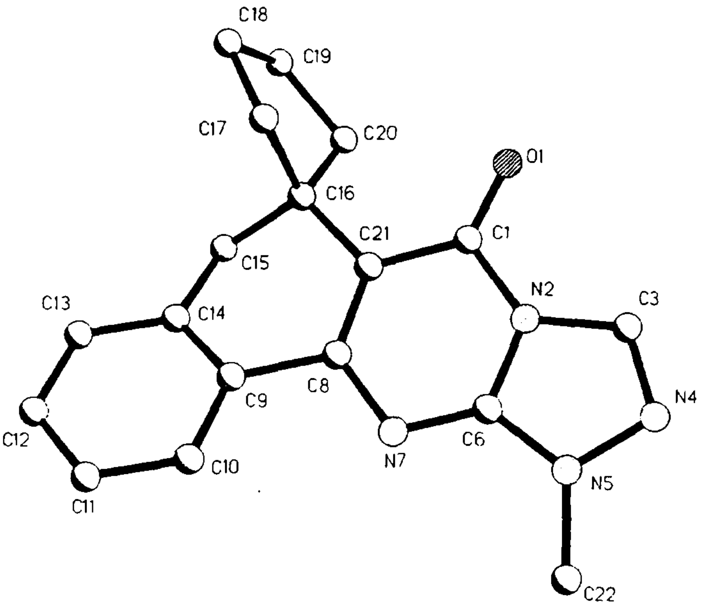


Fig. 1. The structure of the molecule of compound 7 in the crystal.

TABLE 1. The Coordinates of the Non-hydrogen Atoms ($\times 10^4$) and their Isotropic Equivalent Temperature Parameters in the Molecule of Compound 7

Atom	x/a	y/b	z/c	B_{iso}
O	3312(2)	-1160(4)	-1560(2)	4.0(1)
$C_{(1)}$	3244(3)	-403(5)	-865(2)	2.8(1)
$N_{(2)}$	3839(2)	-1119(4)	-137(2)	2.8(1)
$C_{(3)}$	4439(3)	-2750(6)	-48(3)	3.4(1)
$N_{(4)}$	4836(2)	-2945(4)	730(2)	3.6(1)
$N_{(5)}$	4503(2)	-1392(4)	1173(2)	3.1(1)
$C_{(6)}$	3899(2)	-274(5)	652(2)	2.6(1)
$N_{(7)}$	3449(2)	1331(4)	840(2)	2.7(1)
$C_{(8)}$	2833(2)	2025(5)	162(2)	2.4(1)
$C_{(9)}$	2364(2)	3910(5)	350(2)	2.4(1)
$C_{(10)}$	2718(3)	5047(5)	1051(2)	2.8(1)
$C_{(11)}$	2282(3)	6845(5)	1190(3)	3.1(1)
$C_{(12)}$	1514(3)	7466(5)	631(3)	3.4(1)
$C_{(13)}$	148(3)	6335(5)	-56(3)	3.1(1)
$C_{(14)}$	1564(2)	4516(5)	-194(2)	2.5(1)
$C_{(15)}$	1141(3)	3151(6)	-880(2)	3.0(1)
$C_{(16)}$	1897(3)	2067(5)	-1329(2)	2.5(1)
$C_{(17)}$	2329(3)	3414(5)	-1962(2)	3.1(1)
$C_{(18)}$	1554(3)	3608(6)	-2728(3)	3.8(1)
$C_{(19)}$	895(3)	1798(6)	-2705(3)	4.0(1)
$C_{(20)}$	1342(3)	573(6)	-1945(2)	3.4(1)
$C_{(21)}$	2651(2)	1204(5)	-644(2)	2.4(1)
$C_{(22)}$	4723(3)	-1214(6)	2087(3)	4.2(1)

mean-square planes amounts to 0.004 Å for the former and 0.016 Å for the latter.) The pyrimidine and cyclohexadiene fragments are on the whole nonplanar. The individual deviations from the mean-square plane, calculated for the atoms of the pyrimidine ring and the $O_{(1)}$ atom, appreciably exceed 3σ, and the largest deviation amounts to 0.09 Å for the $C_{(21)}$ atom. The cyclohexadiene fragment has a distorted half-chair conformation with the $C_{(15)}$ atoms projecting 0.47 and 0.18 Å respectively from the mean-square plane of the other atoms of the ring.

The cyclopentane ring has the expected envelope conformation. The projection of the $C_{(16)}$ atom from the mean-square plane of the other four atoms of the ring amounts to 0.616 Å.

TABLE 2. The Bond Lengths in the Molecule of Compound 7

Bond	d, Å	Bond	d, A
$C_{(1)}$–$O_{(1)}$	1.223(4)	$C_{(9)}$–$C_{(14)}$	1.384(5)
$C_{(1)}$–$N_{(2)}$	1.415(5)	$C_{(10)}$–$C_{(11)}$	1.406(5)
$C_{(1)}$–$C_{(21)}$	1.448(5)	$C_{(11)}$–$C_{(12)}$	1.367(6)
$N_{(2)}$–$C_{(3)}$	1.395(5)	$C_{(12)}$–$C_{(13)}$	1.376(6)
$N_{(2)}$–$C_{(6)}$	1.362(5)	$C_{(13)}$–$C_{(14)}$	1.405(5)
$C_{(3)}$–$N_{(4)}$	1.285(5)	$C_{(14)}$–$C_{(15)}$	1.492(5)
$N_{(4)}$–$N_{(5)}$	1.386(4)	$C_{(15)}$–$C_{(16)}$	1.534(5)
$N_{(5)}$–$C_{(6)}$	1.342(5)	$C_{(16)}$–$C_{(17)}$	1.536(5)
$N_{(5)}$–$C_{(22)}$	1.437(5)	$C_{(16)}$–$C_{(20)}$	1.550(5)
$C_{(6)}$–$N_{(7)}$	1.319(5)	$C_{(16)}$–$C_{(21)}$	1.528(5)
$N_{(7)}$–$C_{(8)}$	1.369(5)	$C_{(17)}$–$C_{(18)}$	1.521(6)
$C_{(8)}$–$C_{(9)}$	1.496(5)	$C_{(18)}$–$C_{(19)}$	1.549(6)
$C_{(8)}$–$C_{(21)}$	1.381(5)	$C_{(19)}$–$C_{(20)}$	1.529(6)
$C_{(9)}$–$C_{(10)}$	1.388(5)		

TABLE 3. The Bond Angles (ω) in the Molecule of Compound 7

Angle	ω, deg	Angle	ω, deg
$O_{(1)}-C_{(1)}-N_{(2)}$	118.1(3)	$C_{(9)}-C_{(10)}-C_{(11)}$	119.9(3)
$O_{(1)}-C_{(1)}-C_{(21)}$	130.4(3)	$C_{(10)}-C_{(11)}-C_{(12)}$	119.6(3)
$N_{(2)}-C_{(1)}-C_{(21)}$	111.5(3)	$C_{(11)}-C_{(12)}-C_{(13)}$	120.9(3)
$C_{(1)}-N_{(2)}-C_{(3)}$	130.1(3)	$C_{(12)}-C_{(13)}-C_{(14)}$	120.2(3)
$C_{(1)}-N_{(2)}-C_{(6)}$	123.5(3)	$C_{(9)}-C_{(14)}-C_{(13)}$	119.2(3)
$C_{(3)}-N_{(2)}-C_{(6)}$	106.4(3)	$C_{(9)}-C_{(14)}-C_{(15)}$	118.3(3)
$N_{(2)}-C_{(3)}-N_{(4)}$	111.2(3)	$C_{(13)}-C_{(14)}-C_{(15)}$	122.3(3)
$C_{(3)}-N_{(4)}-N_{(5)}$	105.4(3)	$C_{(14)}-C_{(15)}-C_{(16)}$	113.8(3)
$N_{(4)}-N_{(5)}-C_{(6)}$	111.0(3)	$C_{(15)}-C_{(16)}-C_{(17)}$	110.8(3)
$N_{(4)}-N_{(5)}-C_{(22)}$	121.7(3)	$C_{(15)}-C_{(16)}-C_{(20)}$	106.8(3)
$C_{(6)}-N_{(5)}-C_{(22)}$	127.0(3)	$C_{(15)}-C_{(16)}-C_{(21)}$	108.5(3)
$N_{(7)}-C_{(6)}-N_{(2)}$	125.6(3)	$C_{(17)}-C_{(16)}-C_{(20)}$	101.6(3)
$N_{(7)}-C_{(6)}-N_{(5)}$	128.4(3)	$C_{(17)}-C_{(16)}-C_{(21)}$	113.5(3)
$N_{(2)}-C_{(6)}-N_{(5)}$	105.9(3)	$C_{(20)}-C_{(16)}-C_{(21)}$	115.5(3)
$C_{(6)}-N_{(7)}-C_{(8)}$	112.7(3)	$C_{(16)}-C_{(17)}-C_{(18)}$	105.5(3)
$N_{(7)}-C_{(8)}-C_{(9)}$	113.2(3)	$C_{(17)}-C_{(18)}-C_{(19)}$	106.1(3)
$N_{(7)}-C_{(8)}-C_{(21)}$	126.7(3)	$C_{(18)}-C_{(19)}-C_{(20)}$	105.9(3)
$C_{(9)}-C_{(8)}-C_{(21)}$	120.0(3)	$C_{(16)}-C_{(20)}-C_{(19)}$	104.3(3)
$C_{(8)}-C_{(9)}-C_{(10)}$	121.4(3)	$C_{(1)}-C_{(21)}-C_{(8)}$	119.1(3)
$C_{(8)}-C_{(9)}-C_{(14)}$	118.4(3)	$C_{(1)}-C_{(21)}-C_{(16)}$	119.4(3)
$C_{(10)}-C_{(9)}-C_{(14)}$	120.1(3)	$C_{(8)}-C_{(21)}-C_{(16)}$	121.3(3)

The dihedral angle between the planes of the cyclopentane and 2-methylbenzo[*h*]triazolo[3,4-*b*]-quinazoline fragments amounts to 65°.

EXPERIMENTAL*

The IR spectra were recorded on a UR-20 instrument in vaseline oil. The ^1H NMR spectra were recorded on Varian T-60 and Varian Mercury-300 spectrometers in deuterated solvents with TMS or HMDS as internal standard. The mass spectra were obtained on an MX-1321A spectrometer with direct injection into the ion source at 70 eV. The thin-layer chromatography was conducted on Silufol UV-254 plates with iodine vapor as developer.

The crystals for X-ray crystallographic analysis were obtained by slow evaporation of a chloroform solution of compound 7.

X-ray Crystallographic Analysis of Compound 7. The unit cell parameters and the intensities of the reflections were measured on a four-circle Hilger-Watts diffractometer (λMoKα, $\theta/2\theta$ scan, graphite monochromator, θ_{max} = 25°). The crystals were monoclinic: a = 13.968(7), b = 6.862(4), c = 15.718(10) Å, β = 97.18(5)°, V = 1495(1) Å^3, Z = 4, d_{calc} = 1.18 g/cm^3, space group $P2_1/c$.

The structure was interpreted by the direct method and refined by least-squares treatment in anisotropic approximation for the non-hydrogen atoms. The positions of the two hydrogen atoms of the CH_3 group were found from a difference synthesis of the electron density. The positions of the remaining hydrogen atoms were calculated by geometry and were included in F_{calc} with fixed isotropic parameters B_{iso} = 5 Å^2. All the calculations were performed by the INEXTI software on an Eclipse-S/200 computer. The final values of the divergence factors were R = 0.058 and R_w = 0.054 in 1274 reflections with $F > 5\sigma(F)$.

4-(N'-Benzoylthioureido)-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (2). To a hot solution of compound **1** (10.9 g, 0.04 mol) in ethanol (70 ml) benzoyl isothiocyanate (6.5 g, 0.04 mol) was added. The reaction mixture was kept at room temperature for 10 h. The crystals that separated were filtered off,

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* Artur Sh. Oganisyan took part in the syntheses of the compounds.

washed with ethanol, and dried in air. Yield of the product **2** 12.3 g (71%); mp 203-205°C, R_f 0.68 (1:3 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1600 (C=C arom.); 1640 (C=C); 1680 (C=O amide); 1710 (C=O); 3260 (NH). Found, %: C 69.27; H 6.26; N 6.55; S 7.23. $C_{25}H_{26}N_2O_3$. Calculated, %: C 69.09; H 6.03; N 6.45; S 7.38.

4-Oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (3). A mixture of thiourea **2** (8.7 g, 0.02 mol), potassium hydroxide (2.2 g, 0.04 mol), ethanol (50 ml), and water (50 ml) was boiled at reflux for 3 h. The reaction mass was cooled and acidified with a 10% solution of hydrochloric acid to pH 3-3.5. The crystals that separated were filtered off, washed with water, and recrystallized from dimethylformamide. Yield of the product **3** 5.1 g (90%); mp 292-294°C, R_f 0.47 (1:3 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1595 (C=C arom.); 1665 (C=O); 3200 (NH). ^{1}H NMR spectrum (60 MHz, pyridine-d_5), ppm: 9.03 (2H, m, 2NH); 7.03-8.07 (4H, m, C_6H_4); 2.63 (2H, s, 6-CH_2); 1.1-2.53 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2). Found, %: C 67.43; H 5.50; N 10.08; S 11.42. $C_{16}H_{16}N_2OS$. Calculated, %: C 67.58; H 5.67; N 9.85; S 11.27.

2-Hydrazino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1'-cyclopentane) (4). A mixture of compound **3** (5.7 g, 0.02 mol), hydrazine hydrate (15 ml), and butanol (60 ml) was boiled at reflux for 20 h. The precipitate separated was filtered off and washed with water and with ethanol. Yield of the product **4** 4.6 g (82%); mp 299-300°C. IR spectrum, cm^{-1}: 1600 (C=C arom.); 1660 (C=O); 3200 ($NHNH_2$). Found, %: C 67.88; H 6.69; N 19.75. $C_{16}H_{18}N_4O$. Calculated, %: C 68.06; H 6.43; N 19.84.

6-Oxo-1H-7,8-dihydrospiro(benzo[*h*]tetrazolo[3,4-*b*]quinazoline-7,1'-cyclopentane) (6). A mixture of hydrazine **4** (4.2 g, 0.015 mol) and orthoformic ester (30 ml) was boiled at reflux for 8 h. The precipitate was filtered off and recrystallized from butanol. Yield of the product **6** 4 g (91%); mp 277-279°C, R_f 0.49 (3:1 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1605 (C=C arom.); 1680 (C=O). ^{1}H NMR spectrum (pyridine-d_5), ppm: 8.93 (1H, s, CH); 7.0-8.66 (5H, m, C_6H_4 and NH); 2.80 (2H, s, 8-CH_2). Found, %: C 69.69; H 5.68; N 19.34. $C_{17}H_{16}N_4O$. Calculated, %: C 69.85; H 5.52; N 19.17.

2-Methyl-6-oxo-7,8-dihydrospiro(benzo[*h*]triazolo[3,4-*b*]quinazoline-7,1'-cyclopentane) (7). A mixture of compound **6** (1.5 g, 0.005 mol), potassium carbonate (0.7 g, 0.005 mol), and 2-butanol (10 ml) was boiled for 10 min, and a solution of methyl iodide (0.7 g, 0.05 mol) in 2-butanol (5 ml) was then added to it . The reaction mixture was boiled for 10 h and decanted. After evaporation of the solvent the product was recrystallized from 2-butanol. Yield of the product **7** 1.3 g (85%); mp 153-155°C, R_f 0.41 (1:2 ethyl acetate–hexane). IR spectrum, cm^{-1}: 1595 (C=C arom.), 1660 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm: 8.54 (1H, s, 4-CH); 8.25 (1H, m, 9-CH); 7.10-7.38 (3H, m, 10-, 11-, 12-CH); 4.00 (3H, s, NCH_3); 2.90 (2H, s, 8-CH_2); 1.52-2.40 (8H, m, 2'-, 3'-, 4'-, 5'-CH_2). Mass spectrum, m/z (I_{rel}, %): M+ 307 (95), 278 (31), 265 (100), 264 (51), 236 (5), 208 (5), 196 (5), 195 (5), 180 (6), 168 (5), 155 (6). Found, %: C 70.71; H 5.83; N 18.46. Calculated, %: C 70.57; H 5.92; N 18.29.

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