Cyclization of (1,2,4,5-tetrazin-3-yl)hydrazones to 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines*

*S. G. Tolshchina, A. G. Vyakhireva, N. K. Ignatenko, R. I. Ishmetova, I. N. Ganebnykh, P. A. Slepukhin, and G. L. Rusinov**

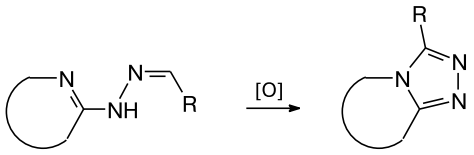
I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22/20 ul. S. Kovalevskoi, 620041 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 1189. E-mail: rusinov@ios.uran.ru

The intramolecular cyclization of (6-R-1,2,4,5-tetrazin-3-yl)hydrazones of ketones (R is 3,5-dimethylpyrazol-1-yl, 4-methylimidazol-1-yl, or 2-alkylidenehydrazino) giving rise to the previously unknown 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines, including spiro compounds, was studied. The reactivity and the yields of the reaction products depend on the structure of the alkylidene fragment and the nature of the substituent in the tetrazine ring.

Key words: 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines, 3,6-disubstituted 1,2,4,5-tetrazines, hydrazones, cyclization, ring-chain isomerism, nucleophilic substitution, alkylation.

The cyclization of hydrazones has found wide use for the construction of various heterocyclic systems.[1,2] In particular, hetarylhydrazones of aldehydes, including 1,2,4,5-tetrazinylhydrazones, are oxidized to give triazole-annulated azines[3—7] (Scheme 1). Attempts to isolate dihydrotriazoloazines failed.

Scheme 1



In the present study, we showed that 6-substituted (1,2,4,5-tetrazin-3-yl)hydrazones of ketones prepared from hydrazine **1** can undergo the isomerization upon heating to give the previously unknown 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines. To study the reactivity depending on the structure of the compounds, we considered a series of tetrazinylhydrazones **2a—n** containing alkyl, aryl, or hetaryl fragments (Scheme 2).

[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazones **2a—n** were synthesized according to the procedure described previously[8] starting from 3-hydrazino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine and ketones (see Scheme 2, Table 1).

* Dedicated to Academician O. N. Chupakhin on the occasion of his 75th birthday.

The IR spectra of the hydrazones show absorption bands at 1560—1543 cm^{-1} (an intense band) and 1481—1374 cm^{-1} (a broad band with several maxima) characteristic of the pyrazole moiety, as well as stretching bands of the tetrazine ring at 1088—1076, 1040—1036, 1023—987, and 976—950 cm^{-1}. The electronic absorption spectra of compounds **2a—f** contain two peaks with maxima at 443—457 and 510—536 nm in the visible region.

The heating of hydrazones **2a—f** containing aliphatic substituents in acetonitrile affords isomeric 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines **3a—f**, including spiro compounds **3a—d**, in 70—85% yields (see Scheme 2). Cyclization products **3a—f** are stable crystalline compounds with m.p. > 100 °C. In the ^1H NMR spectra of triazolotetrazines **3**, the signals for all protons are slightly (by 0.15—0.20 ppm) shifted upfield with respect to those of the starting hydrazones (Table 2). The chemical shift of the carbon atom of the hydrazone group in the ^{13}C NMR spectra of cyclic isomers **3a—f** is shifted from 167 to 104—114 ppm (Table 3). The IR spectra of triazolotetrazines are characterized by the appearance of two intense absorption bands at 1680—1640 cm^{-1}. The electronic absorption spectra of compounds **3a—f** show one band with a maximum at 435—480 nm.

The elemental analysis and LC-mass spectrometric data confirmed that the cyclization is not accompanied by changes in the elemental composition of the molecules. The mass spectra of hydrazones and triazolotetrazines (APCI, atmospheric pressure chemical ionization) have molecular ion peaks $[MH]^+$ or $[M]^+$ in the case of triazolotetrazines. However, in the spectra of the cyclic

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Scheme 2

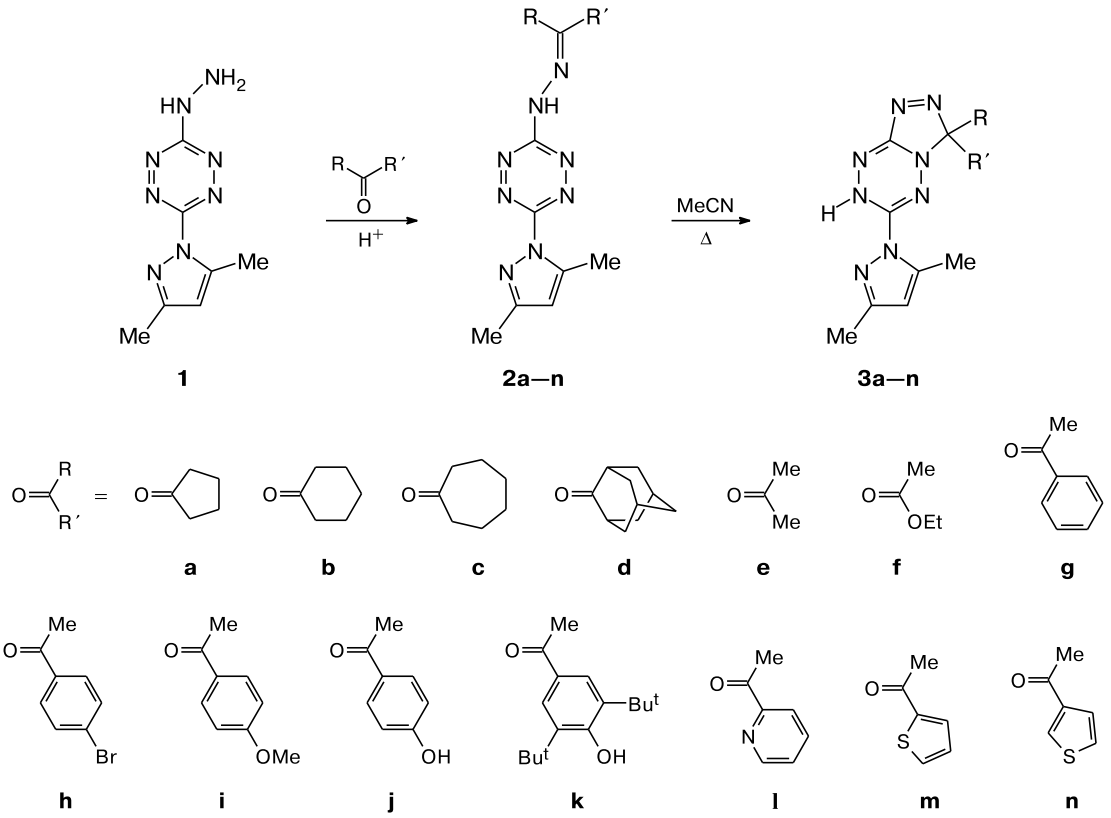


Table 1. Reaction times and yields of compounds **2a—n**, **3a—n**, **9a,b**, **10a,b**, **12a—c**, and **13a—c**

Compound	τ* /h	Yield (%)	Compound	τ* /h	Yield (%)
2a	0.5	92	**3a**	5	82
2b	0.25	85	**3b**	1	84
2c	0.25	91	**3c**	3	74
2d	0.5	74	**3d**	1.5	85
2e	1	92	**3e**	4	77
2f	1	84	**3f**	5	76
2g	2	78	**3g**	10	16
2h	2	79	**3h**	10	5
2i	2	84	**3i**	10	23
2j	8	80	**3j**	10	22
2k	8	86	**3k**	10	21
2l	8	75	**3l**	10	18
2m	8	93	**3m**	10	Traces
2n	8	94	**3n**	10	Traces
9a	1	76	**10a**	1	86
9b	1	79	**10b**	4	42
12a	0.5	59	**13a**	4	57
12b	—	—	**13b**	2	63
12c	0.5	88	**13c**	4	52

* The reaction time.

isomers, the molecular ion peak $[MH - N_2]^+$ is, as a rule, more intense. In the reversed-phase column chromatography, hydrazones **2a—f** are retained more weakly than the corresponding triazolotetrazines.

The structures of the hydrazones and dihydrotriazolotetrazines were confirmed by the X-ray diffraction data for compounds **2b** and **3b** (Figs 1 and 2, respectively).

The geometry of the pyrazolyltetrazine moiety in hydrazone **2b** is substantially distorted. The deviation of the C(1) and C(2) atoms from the mean plane of the tetrazine ring is 0.09 Å. Nevertheless, the bond conjugation in the ring is retained; the bond lengths are equalized

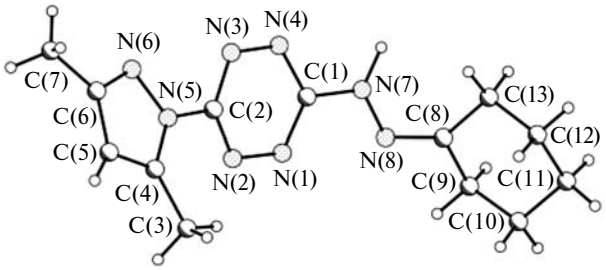


Fig. 1. Molecular structure of **2b** in the crystal structure.

Table 2. ^{1}H NMR spectra ($CDCl_3$) of compounds **2a—n**, **3a—n**, **4a,b**, **5**, **7a,b**, **8a,b**, **9a,b**, **10a,b**, **12a,c**, and **13a—c**

Compound	δ (*J*/Hz)
2a	1.83—1.90, 1.95—2.02, 2.44—2.47, 2.62—2.66 (all m, 2 H each, 4 CH_2); 2.37 (s, 3 H, C(3)Me); 2.59 (s, 3 H, (5)Me); 6.12 (s, 1 H, H(4)); 8.41 (br.s, 1 H, NH)
2b	1.70—1.82 (m, 6 H, 3 CH_2); 2.37 (s, 3 H, C(3)Me); 2.46—2.59 (m, 4 H, 2 CH_2); 2.59 (s, 3 H, C(5)Me); 6.12 (s, 1 H, H(4)); 8.66 (br.s, 1 H, NH)
2c	1.65 (m, 4 H, 2 CH_2); 1.73, 1.85, 2.58, 2.69 (all m, 2 H each, 4 CH_2); 2.37 (s, 3 H, C(3)Me); 2.59 (s, 3 H, C(5)Me); 6.12 (s, 1 H, H(4)); 8.61 (br.s, 1 H, NH)
2d	1.86—2.10 (m, 12 H, 2 CH, 5 CH_2); 2.37 (s, 3 H, C(3)Me); 2.59 (s, 3 H, C(5)Me); 2.92, 3.25 (both br.s, 1 H each, 2 CH); 6.12 (s, 1 H, H(4)); 8.72 (br.s, 1 H, NH)
2e	2.09, 2.21 (both s, 3 H each, 2 Me); 2.37 (s, 3 H, C(3)Me); 2.60 (s, 3 H, C(5)Me); 6.12 (s, 1 H, H(4)); 8.57 (br.s, 1 H, NH)
2f	1.21 (t, 3H, $CH_2\underline{Me}$, J = 7.5); 2.06 (s, 3 H, Me); 2.37 (s, 3 H, C(3)Me); 2.50 (q, 2 H, $\underline{CH_2}Me$, J = 7.5); 2.60 (s, 3 H, C(5)Me); 6.12 (s, 1 H, H(4)); 8.52 (br.s, 1 H, NH)
2g	2.37 (s, 3 H, C(3)Me); 2.46 (s, 3 H, Me); 2.62 (s, 3 H, C(5)Me); 6.13 (s, 1 H, H(4)); 7.50 (m, 5 H, Ph); 8.97 (br.s, 1 H, NH)
2h	2.38 (s, 3 H, C(3)Me); 2.40 (s, 3 H, Me); 2.63 (s, 3 H, C(5)Me); 6.14 (s, 1 H, H(4)); 7.54, 7.76 (both m, 2 H each, Ar); 8.97 (br.s, 1 H, NH)
2i	2.38 (s, 3 H, C(3)Me); 2.42 (s, 3 H, Me); 2.63 (s, 3 H, C(5)Me); 3.86 (s, 3 H, OMe); 6.14 (s, 1 H, H(4)); 6.94, 7.85 (both m, 2 H each, Ar); 8.83 (br.s, 1 H, NH)
2j*	2.25 (s, 3 H, C(3)Me); 2.41 (s, 3 H, Me); 2.46 (s, 3 H, C(5)Me); 6.23 (s, 1 H, H(4)); 6.82, 7.75 (both m, 2 H each, Ar); 9.79 (s, 1 H, OH); 11.45 (br.s, 1 H, NH)
2k	1.47 (m, 18 H, 2 Bu^t); 2.38 (s, 3 H, C(3)Me); 2.43 (s, 3 H, Me); 2.63 (s, 3 H, C(5)Me); 5.46 (br.s, 1 H, OH); 6.13 (s, 1 H, H(4)); 7.69 (s, 2 H, Ar); 8.78 (br.s, 1 H, NH)
2l	2.39 (s, 3 H, C(3)Me); 2.60 (s, 3 H, Me); 2.65 (s, 3 H, C(5)Me); 6.15 (s, 1 H, H(4)); 7.29, 7.75, 8.32, 8.63 (all m, 1 H each, py); 8.99 (br.s, 1 H, NH)
2m	2.38 (s, 3 H, C(3)Me); 2.47 (s, 3 H, Me); 2.63 (s, 3 H, C(5)Me); 6.14 (s, 1 H, H(4)); 7.07, 7.40 (both m, 1 H и 2 H, 2-thienyl); 8.81 (br.s, 1 H, NH)
2n	2.38 (s, 3 H, C(3)Me); 2.43 (s, 3 H, Me); 2.63 (s, 3 H, C(5)Me); 6.14 (s, 1 H, H(4)); 7.34, 7.62, 7.73 (all m, 1 H each, 3-thienyl); 8.79 (br.s, 1 H, NH)
3a	1.94—2.08, 2.17—2.20 (both m, 4 H each, 4 CH_2); 2.23 (s, 3 H, C(3)Me); 2.45 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.44 (br.s, 1 H, NH)
3b	1.58, 2.01 (both m, 2 H each, 2 CH_2); 1.76—1.89 (m, 6 H, 3 CH_2); 2.23 (s, 3 H, C(3)Me); 2.45 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.46 (br.s, 1 H, NH)
3c	1.72—2.04 (m, 12 H, 6 CH_2); 2.23 (s, 3 H, C(3)Me); 2.46 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.41 (br.s, 1 H, NH)
3d	1.77—1.80, 2.47—2.50, 2.80—2.83 (all m, 2 H each, 3 CH_2); 1.87 (m, 6 H, 2 CH, 2 CH_2); 2.01, 2.20 (both br.s, 1 H each, 2 CH); 2.23 (s, 3 H, C(3)Me); 2.44 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.55 (br.s, 1 H, NH)
3e	1.62 (s, 6 H, 2 Me); 2.23 (s, 3 H, C(3)Me); 2.45 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.47 (br.s, 1 H, NH)
3f	0.95 (t, 3 H, $CH_2\underline{Me}$, J = 7.5); 1.54 (s, 3 H, Me); 2.09 (q, 2 H, $\underline{CH_2}Me$, J = 7.5); 2.23 (s, 3 H, C(3)Me); 2.44 (s, 3 H, C(5)Me); 5.99 (s, 1 H, H(4)); 8.41 (br.s, 1 H, NH)
3g	1.84 (s, 3 H, Me); 2.24 (s, 3 H, C(3)Me); 2.43 (s, 3 H, C(5)Me); 6.00 (s, 1 H, H(4)); 7.36—7.46 (m, 3 H, Ph); 7.66 (m, 2 H, Ph); 8.55 (br.s, 1 H, NH)
3h	1.81 (s, 3 H, Me); 2.24 (s, 3 H, C(3)Me); 2.43 (s, 3 H, C(5)Me); 6.01 (s, 1 H, H(4)); 7.55 (m, 4 H, Ar); 8.59 (br.s, 1 H, NH)
3i	1.82 (s, 3 H, Me); 2.24 (s, 3 H, C(3)Me); 2.42 (s, 3 H, C(5)Me); 3.82 (s, 3 H, OMe); 5.99 (s, 1 H, H(4)); 6.95, 7.55 (both m, 2 H each, Ar); 8.53 (br.s, 1 H, NH)
3j	1.81 (s, 3 H, Me); 2.24 (s, 3 H, C(3)Me); 2.42 (s, 3 H, C(5)Me); 5.37 (s, 1 H, OH); 5.99 (s, 1 H, H(4)); 6.88, 7.50 (both m, 2 H each, Ar); 8.53 (br.s, 1 H, NH)
3k	1.45 (m, 18 H, 2 Bu^t); 1.81 (s, 3 H, Me); 2.24 (s, 3 H, C(3)Me); 2.43 (s, 3 H, C(5)Me); 5.31 (br.s, 1 H, OH); 6.00 (s, 1 H, H(4)); 7.44 (s, 2 H, Ar); 8.49 (br.s, 1 H, NH)
3l	2.00 (s, 3 H, Me); 2.23 (s, 3 H, C(3)Me); 2.35 (s, 3 H, C(5)Me); 5.97 (s, 1 H, H(4)); 7.30, 7.50, 7.73, 8.73 (all m, 1 H each, py); 8.58 (br.s, 1 H, NH)
3m	1.92 (s, 3 H, Me); 2.23 (s, 3 H, C(3)Me); 2.42 (s, 3 H, C(5)Me); 5.98 (s, 1 H, H(4)); 7.14, 7.61 (both m, 1 H and 2 H, 2-thienyl); 8.23 (br.s, 1H, NH)
3n	1.86 (s, 3 H, Me); 2.23 (s, 3 H, C(3)Me); 2.40 (s, 3 H, C(5)Me); 5.98 (s, 1 H, H(4)); 7.22, 7.38, 7.45 (all m, 1 H each, 3-thienyl); 8.59 (br.s, 1 H, NH)

(*to be continued*)

Table 2. (*continued*)

Compound	δ (*J*/Hz)
4a	1.54—1.96 (m, 10 H, 5 CH_2); 2.24 (s, 3 H, C(3)Me); 2.29 (s, 3 H, C(5)Me); 3.01 (s, 3 H, N—Me); 5.94 (s, 1 H, H(4))
4b	1.59 (s, 6H, 2 Me); 2.24 (s, 3 H, C(3)Me); 2.28 (s, 3 H, C(5)Me); 2.98 (s, 3H, NMe); 5.94 (s, 1 H, H(4))
5*	2.16 (s, 3 H, C(3)Me); 2.20 (s, 3 H, C(5)Me); 6.03 (s, 1 H, H(4))
7a	7.45, 7.68, 7.89, 8.72, 8.52 (all m, 2 H each, 2 indazolyls)
7b	2.37 (s, 6 H, 2 C(4)Me); 7.71 (s, 2 H, 2 H(5)); 8.65 (s, 2 H, 2 H(2))
8a*	4.68 (br.s, 2 H, NH_2); 7.38, 7.61, 7.96, 8.25, 8.57 (all m, 1 H each, indazolyl); 9.68 (br.s, 1 H, NH)
8b*	2.21 (s, 3 H, C(4)Me); 4.63 (br.s, 2 H, NH_2); 7.65 (s, 1 H, H(5)); 8.41 (s, 1 H, H(2)); 9.68 (br.s, 1 H, NH)
9a	1.70—1.84 (m, 6 H, 3 CH_2); 2.49—2.57 (m, 4 H, 2 CH_2); 7.38, 7.60, 7.85, 8.41, 8.56 (all m, 1 H each, indazolyl); 8.68 (br.s, 1 H, NH)
9b	1.69—1.84 (m, 6 H, 3 CH_2); 2.33 (s, 3 H, C(4)Me); 2.47—2.54 (m, 4 H, 2 CH_2); 7.62 (s, 1 H, H(5)); 8.53 (s, 1 H, H(2)); 8.71 (br.s, 1 H, NH)
10a	1.87—2.15 (m, 10 H, 5 CH_2); 7.35, 7.57, 7.78, 8.14, 8.18 (all m, 1 H each, indazolyl); 8.51 (br.s, 1 H, NH)
10b	1.55—2.03 (m, 10 H, 5 CH_2); 2.26 (s, 3 H, C(4)Me); 7.01 (s, 1 H, H(5)); 7.49 (br.s, 1 H, NH); 7.93 (s, 1 H, H(2))
12a	1.79—1.86, 1.91—1.98, 2.40, 2.60 (all m, 4 H each, 8 CH_2); 7.99 (br.s, 2 H, 2 NH)
12c	2.02, 2.17 (both s, 6 H each, 4 Me); 8.11 (br.s, 2 H, 2 NH)
13a	1.73—1.80, 1.84—1.91, 2.17, 2.40 (all m, 2 H each, 4 CH_2); 1.90—2.15 (m, 8 H, 4 CH_2); 7.12, 7.84 (both br.s, 1 H each, 2 NH)
13b	1.60—1.75 (m, 10 H, 5 CH_2); 1.83—2.06 (m, 6 H, 3 CH_2); 2.17—2.29 (m, 4 H, 2 CH_2); 7.39, 7.93 (both br.s, 1 H each, 2 NH)
13c	1.56 (s, 6 H, 2 Me); 1.81, 1.99 (both s, 3 H each, 2 Me); 7.18, 7.91 (both br.s, 1 H each, 2 NH)

* DMSO-d_6.

Table 3. ^{13}C NMR spectra ($CDCl_3$) of compounds **2a** and **3a—f**

Compound	δ							
	1, 2	3	4	5	6	7	8	R, R′
2a	13.7	152.5	110.1	142.4	158.5	160.0	167.3	24.7, 24.8, 27.7, 33.6 (4 CH_2)
3a	14.0, 13.4	150.6	110.4	142.3	141.9	162.1	114.1	25.1, 34.1 (4 CH_2)
3b	14.1, 13.5	150.6	110.4	142.3	142.0	162.3	106.5	22.7, 24.9, 33.3 (5 CH_2)
3c	14.2, 13.4	150.5	110.4	142.3	142.0	161.9	110.2	23.2, 30.5, 34.9 (6 CH_2)
3d	14.1, 13.5	150.6	110.4	142.1	142.4	162.6	110.7	26.6, 27.9, 33.4, 35.1, 37.4, 37.7 (adamantane)
3e	14.0, 13.5	150.6	110.4	142.5	142.0	162.2	104.8	22.9 (2 Me)
3f	14.0, 13.5	150.6	110.4	142.5	141.9	162.5	107.3	20.1, 30.4, 7.7 (Me, Et)

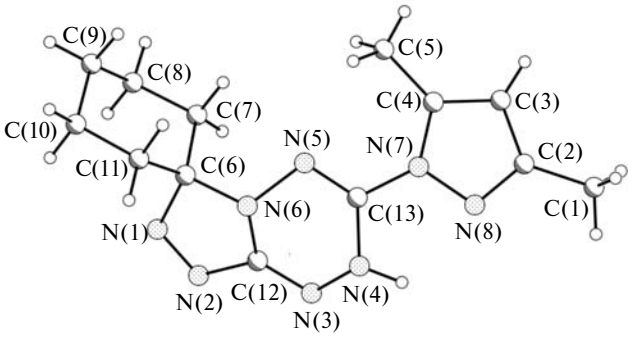
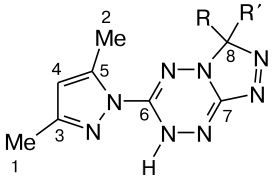


Fig. 2. Molecular structure of **3b** in the crystal structure.



3a—f

R + R′ = $(CH_2)_4$ (**a**), $(CH_2)_5$ (**b**), $(CH_2)_6$ (**c**), 2-adamantane (**d**), R = R′ = Me (**e**), R = Me, R′ = Et (**f**)

and are, on the average, 1.33(1) Å. The pyrazolyl substituent is not in the plane of the tetrazine ring (the angle between the mean planes of the rings is 24.68°) and is involved in intermolecular hydrogen bonds (Table 4).

As can be seen from Table 4, the H(7) atom is formally involved in intermolecular hydrogen bonds with both the N(6) atom of the pyrazole ring and the N(3) atom of the tetrazine ring. However, the geometry of the intermolecular hydrogen bonds indicates that the bond with the pyrazole nitrogen atom plays a decisive role, whereas the intermolecular hydrogen bond with the tetrazine ring

Table 4. Intermolecular hydrogen bonds in the crystal structures of compounds **2b**, **3b**, and **3i**

Compound	D—H	*d*(D—H) / Å	*d*(H..A) / Å	<DHA /deg	*d*(D...A) /Å	A [symmetry code]
2b	N(7)—H(7)	1.030	2.064	154.78	3.027	N(6) [$-x+2, y-1/2, -z+1/2$]
2b	N(7)—H(7)	1.030	2.551	132.95	3.339	N(3) [$-x+2, y-1/2, -z+1/2$]
3b	N(4)—H(4)	0.93(1)	2.24(1)	137(1)	2.996(2)	N(3) [$-x+1, -y+1, -z+1$]
3i	N(2)—H(2)	0.97(1)	2.23(1)	137(1)	3.009(2)	N(1) [$-x, -y, -z+2$]

is much closer to the usual polar contact than to the standard hydrogen bond. The presence of a system of intermolecular hydrogen bonds and the nonpolar cyclohexyl fragments determines the molecular packing. The polar parts of the molecules are linked through intermolecular hydrogen bonds to form zigzag chains, which are separated by layers formed by the cyclohexyl rings.

Unlike compound **2b**, the aromaticity of compound **3b** is disturbed. The tetrazine ring of compound **3b** adopts a *pseudo-boat* conformation with the hydrogen atom at the N(4) atom being in the equatorial orientation. The N(6) and N(4) atoms are sp^3-hybridized, as is evident from the geometry of the bonds that form a trigonal pyramid with the nitrogen atom at the vertex. The N(5)=C(13) fragment is in the plane with the pyrazolyl substituent (the N(5)C(13)N(7)N(8) torsion angle is −172.67°), which is indicative of the involvement of this fragment in the conjugation system of the pyrazole ring. In the crystals, spiro compound **3b** forms hydrogen-bonded dimers (see Table 4).

Unlike aromatic 1,2,4,5-tetrazines[8,9] and 1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines,[10] the 3,5-dimethylpyrazolyl group in dihydrotriazolotetrazines **3a—f** is not replaced by amines. According to the TLC data, triazolotetrazines **3b,e** remained intact after refluxing in acetonitrile with heptylamine or piperidine for 2 h. In DMSO, compounds **3b,e** form bright-blue salts with potassium hydroxide, and these salts give the methylation products at the nitrogen atom in position 7 (**4a,b**) in 60—65% yields (Scheme 3), which is confirmed by ^{1}H NMR spectroscopy, elemental analysis, and the X-ray diffraction study of **4b** (see Fig. 3).

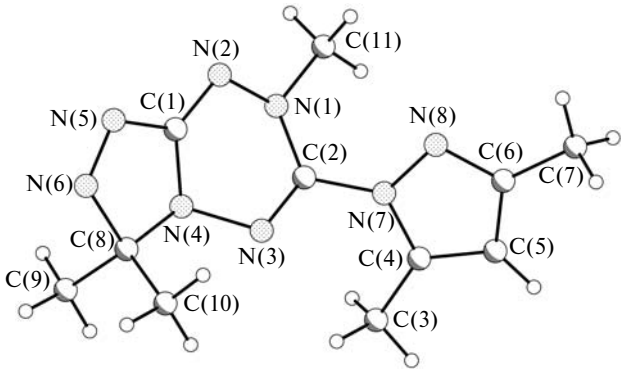
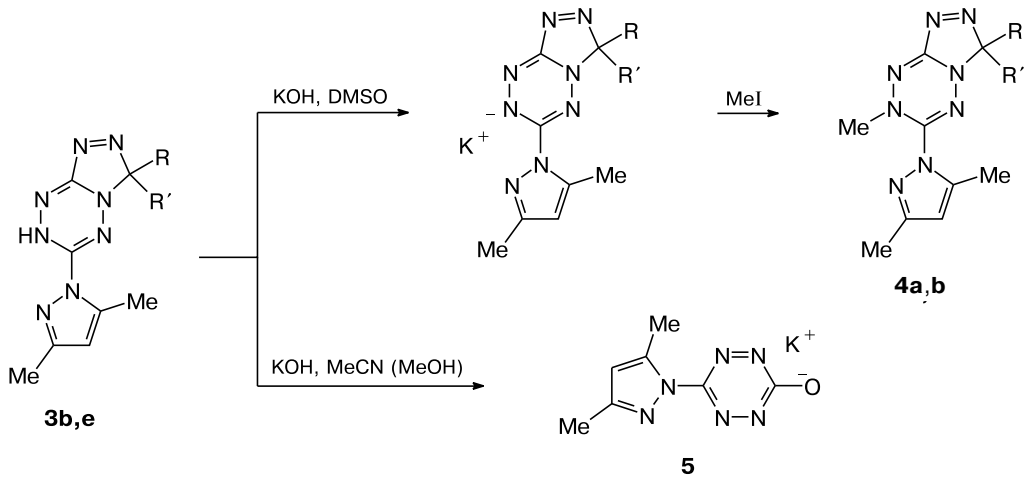


Fig. 3. Molecular structure of **4b** in the crystal structure.

According to the X-ray diffraction data, compound **4b** crystallizes in the chiral monoclinic space group $P2_1$. The geometry of **4b** is similar to that of product **3b**. The essential difference is that the pyrazolyl substituent is not conjugated to the N(3)=C(2) fragment (the N(3)C(2)-N(7)N(8) torsion angle is −119.65°) due to the steric effect of the alkyl substituent.

In acetonitrile and alcohols, triazolotetrazines are hydrolyzed under the action of KOH to give the potassium salt of 3-hydroxy-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **5** (see Scheme 3).

Scheme 3



R—R′ = $(CH_2)_5$ (**3b**, **4a**); R = R′ = Me (**3e**, **4b**)

According to the TLC, LC-mass spectrometric, and ^{1}H and ^{13}C NMR spectroscopic data in solution, the reverse transformation of cyclic isomers **3a—f** into the chain isomers was not observed. It was shown that triazolotetrazine **3b** did not give the corresponding hydrazone **2b** after refluxing in acetonitrile for 10 h.

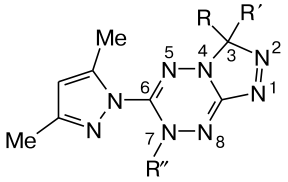
The introduction of aromatic substituents into the alkylidene fragment leads to a substantial decrease in the ability of tetrazinylhydrazones **2g—n** to form cyclic 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines (see Table 1). Thus, according to the ^{1}H NMR data, the content of cyclic isomers **3g—n** in the reaction mixture after refluxing of hydrazones **2g—n** in acetonitrile for 10 h was no higher than 45%. The yields of 3-Ar-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines **3g—l** decrease from 23 to 5% in the following series: 4-ROC_6H_4 (**i**, **j**), 4-OH-$C_6H_2(Bu^t)_2$ (**k**) > 4-C_5H_4N (**l**) > Ph (**g**) > 4-BrC_6H_4 (**h**). In the presence of thienyl substituents in the alkylidene fragment of hydrazones, cyclization products **3m,n** were formed in trace amounts (2—3% according to the ^{1}H NMR data for the reaction mixtures) and were not isolated.

Triazolotetrazines **3g—n** containing aromatic substituents can be transformed into the starting hydrazones **2g—n**. Thus, after refluxing of product **3g** in acetonitrile for 10 h, the ratio of isomers **2g** and **3g** in the reaction mixture was 1 : 3 (^{1}H NMR data). In addition, the ^{1}H NMR spectrum of the reaction mixture shows signals assigned to degradation products of triazolotetrazine **3g**, which were formed in amounts comparable to those of the ring-cleavage product.

Therefore, triazolotetrazines containing aromatic substituents are less stable than the products containing alkyl groups and can undergo the reverse tautomeric transformation to the corresponding hydrazones and also can be decomposed with the elimination of nitrogen, as evidenced by the mass-spectrometric data. Apparently, this is responsible for the low yields of aromatic derivatives of triazolotetrazines **3g—n**.

The different stability of the cyclization products cannot be unambiguously attributed to the structural features of the molecules. As exemplified by compound **3i** (Fig. 3, Table 5), the structural features of triazolotetrazines containing aromatic substituents are similar to the corresponding characteristics of stable molecules **3b** and **4b** containing aliphatic fragments (see Table 5). Like compound **3b**, product **3i** forms dimers in the crystals with a similar geometry of intermolecular hydrogen bonds (see Table 4). The structure of compound **3i** is characterized by an increase in the torsion angle between the planes of the pyrazolyl substituent and the C(2)N(3) fragment by 10° compared to that observed in **3b** (N(3)C(2)N(7)N(8) = = –161.33°)

The replacement of the 3,5-dimethylpyrazolyl substituent by the indazol-1-yl group in hydrazone **9a**



3b,i, 4b

R″ = H (**3**), Me (**4**), R + R′ = $(CH_2)_5$ (**3b**, **4b**), R = Me, R′ = 4-$MeOC_6H_4$ (**3i**)

Table 5. Selected bond lengths (*d*) and bond angles (ω) in molecules **3b,i** and **4b**

Parameter	**3b**	**3i**	**4b**
Bond		*d*/Å	
N(1)—N(2)	1.260(2)	1.261(2)	1.252(3)
N(2)—C(3)	1.489(2)	1.512(3)	1.494(4)
C(3)—N(4)	1.471(2)	1.472(3)	1.459(3)
N(4)—C(9)	1.378(2)	1.391(2)	1.387(3)
N(1)—C(9)	1.419(2)	1.414(3)	1.427(3)
N(4)—N(5)	1.442(2)	1.446(2)	1.440(2)
N(5)—C(6)	1.271(2)	1.276(2)	1.279(3)
C(6)—N(7)	1.383(2)	1.384(3)	1.377(3)
N(7)—N(8)	1.419(2)	1.419(2)	1.419(3)
N(8)—C(9)	1.269(2)	1.265(3)	1.261(3)
Angle		ω/deg	
N(2)—C(3)—N(4)	101.3(2)	102.0(2)	102.7(2)
C(3)—N(4)—C(9)	105.9(2)	105.5(2)	106.0(2)
N(4)—C(9)—N(1)	109.8(2)	110.6(2)	110.0(2)
C(9)—N(1)—N(2)	108.3(2)	108.8(2)	108.6(3)
N(1)—N(2)—C(3)	112.4(2)	111.8(2)	112.2(2)
N(4)—C(9)—N(8)	125.4(2)	125.6(2)	125.5(2)
C(9)—N(8)—N(7)	109.8(2)	109.8(2)	108.8(2)
C(6)—N(7)—N(8)	114.5(2)	113.7(2)	113.6(2)
N(5)—C(6)—N(7)	124.7(2)	124.8(2)	123.7(2)
N(4)—N(5)—C(6)	109.7(2)	109.7(2)	109.3(2)
C(9)—N(4)—N(5)	112.9(2)	111.6(2)	110.0(2)

(Scheme 4) does not lead to a change in the reactivity in the cyclization reaction, and the corresponding triazolotetrazine **10a** is produced in 86% yield. On the contrary, product **10b** is formed from hydrazone **9b** containing the 4-methylimidazolyl substituent more slowly and in lower

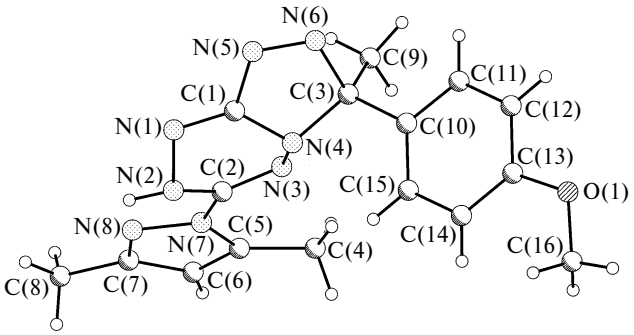
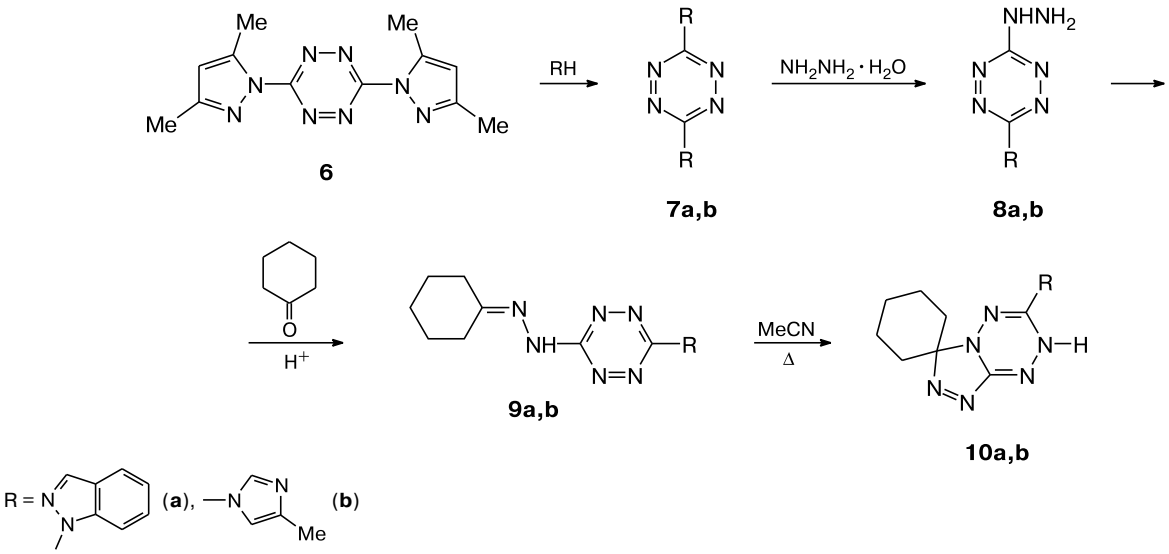
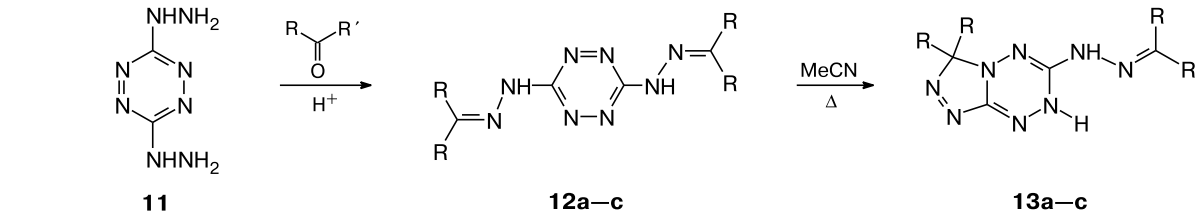


Fig. 4. Molecular structure of **3i** in the crystal structure.

Scheme 4



Scheme 5



R—R = $(CH_2)_4$ (**a**), $(CH_2)_5$ (**b**); R = Me (**c**)

yield (42%) compared to **10a**. Apparently, the cyclic form is stabilized by an intramolecular hydrogen bond with the involvement of the hydrogen atom in position 7 of triazolotetrazine and the nitrogen atom in position 2 of the substituent.

In the case of dihydrazones **12a—c** synthesized from 3,6-dihydrazino-1,2,4,5-tetrazine (**11**), only one hydrazone group was involved in the cyclization, and the tricyclic system was not formed (Scheme 5).

Attempts to isolate dihydrazone **12b** containing the cyclohexanone moiety failed because it easily undergoes cyclization to give compound **13b**.

To sum up, we discovered for the first time the isomerization of tetrazinylhydrazones of ketones giving rise to the previously unknown 3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines. It was shown that aliphatic substituents in the alkylidene fragment promote the transformation, whereas the presence of aromatic and heteroaromatic groups leads to a decrease in the ability of hydrazones to undergo cyclization, as well as in the yields and stability of the reaction products. In addition, the cyclization of tetrazinylhydrazones is influenced by the substituent in position 6 of the tetrazine ring.

Experimental

The NMR spectra were recorded on a Bruker Avance DRX-400 instrument operating at 400 MHz with Me_4Si as the internal standard. The chemical shifts are given on the δ scale in ppm. The IR spectra were measured on a Perkin Elmer Spectrum One Fourier-transform IR spectrometer equipped with a diffuse reflectance attachment. The diffuse reflectance UV spectra were recorded on a Shimadzu UV-2401 PC spectrophotometer using an integrating sphere assembly (barium sulfate as the reference pellet). The mass spectra were obtained after the chromatographic separation on a Shimadzu LCMS-2010 LC-mass spectrometer (Supelcosil LC-18 column, 250S4.6 mm, 5 μm; MeCN—H_2O mobile phase, 65 : 35; the flow rate was 1 mL min^{-1}; the temperature of the column was 60 °C; the APCI ionization mode; the temperature of the ion source was 400 °C; the rate of the gas flow was 2.5 L min^{-1}; the other parameters of the mass spectrometer were specified according to the auto tuning procedure). The melting points were determined on a Boetius hot stage. The elemental analysis was carried out on an automated Perkin—Elmer PE-2400 analyzer. The course of the reactions was monitored and the purity of the reaction products was checked by TLC on plates with a fixed Sorbfil layer using 1 : 1 benzene—acetonitrile and 2 : 4 : 1 hexane—benzene—acetonitrile mixtures as the eluents.

Compounds **1** and **11** have been described previously.[9,11] 3-Hydrazino-6-R-1,2,4,5-tetrazines **8a,b** were synthesized analogously to compound **1**.[9] Compounds **2a—n**, **9a,b**, **12a,c**, and **13b** were synthesized for the first time according to a procedure described previously.[8]

2-Cyclopentylidene-1-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2a), m.p. 123—125 °C. Found (%): C, 52.87; H, 6.20; N, 41.16. $C_{12}H_{16}N_8$. Calculated (%): C, 52.93; H, 5.92; N, 41.15. IR, ν/cm^{-1}: 1644, 1631, 1555, 1475, 1412, 1358, 1088, 1039, 1023, 967. UV (λ_{max}/nm (A)): 446 (0.559), 510 (0.500). MS, *m/z* (*I* (%)): 273 (100) $[MH]^+$, the retention time *RT* 2.9 min.

2-Cyclohexylidene-1-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2b), m.p. 140—141 °C. Found (%): C, 54.66; H, 6.25; N, 39.00. $C_{13}H_{18}N_8$. Calculated (%): C, 54.53; H, 6.34; N, 39.13. IR, ν/cm^{-1}: 1630, 1556, 1478, 1462, 1411, 1364, 1085, 1039, 1023, 976, 965. UV (λ_{max}/nm (A)): 451 (0.339), 514 (0.321). MS, *m/z* (*I* (%)): 287 (89) $[MH]^+$, 259 (100) $[MH - N_2]^+$, *RT* 3.1 min.

2-Cycloheptylidene-1-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2c), m.p. 124—126 °C. Found (%): C, 56.23; H, 6.76; N, 37.35. $C_{14}H_{20}N_8$. Calculated (%): C, 55.98; H, 6.71; N, 37.31. IR, ν/cm^{-1}: 1624, 1569, 1536, 1466, 1450, 1420, 1408, 1378, 1365, 1342, 1063, 1039, 1022, 971, 957. UV (λ_{max}/nm (A)): 456 (0.446), 536 (0.373). MS, *m/z* (*I* (%)): 301 (96) $[MH]^+$, 273 (48) $[MH - N_2]^+$, *RT* 2.8 min.

1-Adamantanylidene-2-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2d), m.p. 176—178 °C. Found (%): C, 60.54; H, 6.80; N, 33.19. $C_{17}H_{22}N_8$. Calculated (%): C, 60.34; H, 6.55; N, 33.11. IR, ν/cm^{-1}: 1644, 1563, 1484, 1450, 1416, 1381, 1350, 1328, 1086, 1042, 1023, 967, 950. UV (λ_{max}/nm (A)): 457 (0.542), 522 (0.500). MS, *m/z* (*I* (%)): 339 (100) $[MH]^+$, *RT* 3.8 min.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-(prop-2-ylidene)hydrazine (2e), m.p. 151—153 °C. Found (%): C, 48.93; H, 5.34; N, 45.79. $C_{10}H_{14}N_8$. Calculated (%): C, 48.77; H, 5.73; N, 45.50. IR, ν/cm^{-1}: 1666, 1635, 1568, 1543, 1481, 1418, 1374, 1076, 1036, 987, 960. UV (λ_{max}/nm (A)): 443 (0.332), 528 (0.306). MS, *m/z* (*I* (%)): 247 (100) $[MH]^+$, 219 (94) $[MH - N_2]^+$, *RT* 2.7 min.

1-(But-2-ylidene)-2-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2f), m.p. 120—123 °C. Found (%): C, 50.76; H, 6.19; N, 43.04. $C_{11}H_{16}N_8$. Calculated (%): C, 50.76; H, 6.20; N, 43.05. IR, ν/cm^{-1}: 1630, 1562, 1479, 1409, 1373, 1328, 1080, 1038, 1023, 976. UV (λ_{max}/nm (A)): 445 (0.459), 510 (0.450). MS, *m/z* (*I* (%)): 261 (100) $[MH]^+$, 233 (36) $[MH - N_2]^+$, *RT* 2.9 min.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-(1-phenylethylidene)hydrazine (2g). M.p. 175—177 °C. Found (%): C, 58.61; H, 5.34; N, 36.42. $C_{15}H_{16}N_8$. Calculated (%): C, 58.43; H, 5.23; N, 36.34.

1-[1-(4-Bromophenyl)ethylidene]-2-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2h), m.p. 190—192 °C. Found (%): C, 46.45; H, 3.80; N, 28.95. $C_{15}H_{15}N_8Br$. Calculated (%): C, 46.52; H, 3.90; N, 28.94.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-[1-(4-methoxyphenyl)ethylidene]hydrazine (2i), m.p. 152—153 °C. Found (%): C, 56.66; H, 5.25; N, 32.92. $C_{16}H_{18}N_8O$. Calculated (%): C, 56.79; H, 5.36; N, 33.12.

2-[6-(3,5-Dimethylpyrazol-1-yl)-1-[1-(4-hydroxyphenyl)-ethylidene]-1,2,4,5-tetrazin-3-yl]hydrazine (2j), m.p. 212—213 °C. Found (%): C, 55.44; H, 4.88; N, 34.46. $C_{15}H_{16}N_8O$. Calculated (%): C, 55.55; H, 4.97; N, 34.55.

1-[1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)ethylidene]-2-[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (2k), m.p. 182—184 °C. Found (%): C, 63,31; H, 7.62; N, 25.82. $C_{23}H_{32}N_8O$. Calculated (%): C, 63.28; H, 7.39; N, 25.67.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-[1-(2-pyridyl)ethylidene]hydrazine (2l), m.p. 198—200 °C. Found (%): C, 54.35; H, 4.86; N, 40.93. $C_{14}H_{15}N_9$. Calculated (%): C, 54.36; H, 4.89; N, 40.75.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-[1-(2-thienyl)ethylidene]hydrazine (2m), m.p. 191—193 °C. Found (%): C, 49.24; H, 4.43; N, 35.62. $C_{13}H_{14}N_8S$. Calculated (%): C, 49.67; H, 4.49; N, 35.64.

1-[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-2-[1-(3-thienyl)ethylidene]hydrazine (2n), m.p. 173—175 °C. Found (%): C, 49.71; H, 4.43; N, 35.68. $C_{13}H_{14}N_8S$. Calculated (%): C, 49.67; H, 4.49; N, 35.64.

Synthesis of 3-R-3-R′-6-(3,5-dimethylpyrazol-1-yl)-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines 3a—l (general method). A solution of hydrazone **2a—l** (1 mmol) in acetonitrile (7 mL) was refluxed for 1—10 h. The solvent was evaporated. In the synthesis of **3a—f**, the residue was washed with ethanol and filtered off. Compounds **3g—l** were isolated by column chromatography on silica gel Lancaster 0.040—0.063 mm (230—400 mesh) using a hexane—benzene—acetonitrile mixture (2 : 4 : 1) as the eluent (R_f = 0.85).

6-(3,5-Dimethylpyrazol-1-yl)-3-spirocyclopentane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3a), m.p. 105—107 °C. Found (%): C, 52.86; H, 5.94; N, 41.21. $C_{12}H_{16}N_8$. Calculated (%): C, 52.93; H, 5.92; N, 41.15. IR, ν/cm^{-1}: 1678, 1643, 1576, 1486, 1449, 1423, 1361, 1324, 1078, 1048, 996, 975, 949, 924. UV, (λ_{max}/nm (A)): 461 (0.465). MS, *m/z* (*I* (%)): 273 (25) $[MH]^+$, 245 (100) $[MH - N_2]^+$, *RT* 6.0 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-spirocyclohexane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3b), m.p. 125—126 °C. Found (%): C, 54.21; H, 6.45; N, 38.87. $C_{13}H_{18}N_8$. Calculated (%): C, 54.53; H, 6.34; N, 39.13. IR, ν/cm^{-1}: 1672, 1648, 1578, 1489, 1451, 1423, 1384, 1364, 1070, 1045, 1031, 1010, 976, 955. UV, (λ_{max}/nm (A)): 480 (0.271). MS, *m/z* (*I* (%)): 286 (40) $[M]^+$, 259 (100) $[MH - N_2]^+$, *RT* 7.1 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-spirocycloheptane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3c), m.p. 98—99 °C. Found (%): C, 56.04; H, 6.91; N, 37.39. $C_{14}H_{20}N_8$. Calculated (%): C, 55.98; H, 6.71; N, 37.31. IR, ν/cm^{-1}: 1675, 1653, 1570, 1484, 1456, 1421, 1362, 1085, 1055, 1011, 968, 925. UV (λ_{max}/nm (A)): 435 (0.490). MS, *m/z* (*I* (%)): 301 (12) $[MH]^+$, 273 (100) $[MH - N_2]^+$, *RT* 8.8 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-spiro-2′-adamantane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3d), m.p. 161—163 °C. Found (%): C, 60.13; H, 6.79; N, 33.22. $C_{17}H_{22}N_8$. Calculated (%): C, 60.34; H, 6.55; N, 33.11. IR, ν/cm^{-1}: 1651, 1571, 1482, 1442, 1422, 1377, 1364, 1052, 1039, 1015, 996, 969. UV (λ_{max}/nm (A)): 367 (0.395); 441 (0.423). MS, *m/z* (*I* (%)): 339 (53) $[MH]^+$, 311 (80) $[MH - N_2]^+$, *RT* 13.7 min.

3,3-Dimethyl-6-(3,5-dimethylpyrazol-1-yl)-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3e), m.p. 125—127 °C. Found (%): C, 48.79; H, 5.80; N, 45.78. $C_{10}H_{14}N_8$. Calculated (%): C, 48.77; H, 5.73; N, 45.50. IR, ν/cm^{-1}: 1681, 1644, 1486, 1448, 1423, 1384, 1361, 1078, 1043, 1029, 976, 958, 927.

UV (λ_{max}/nm (A)): 464 (0.341). MS, *m/z* (*I* (%)): 246 (19) $[M]^+$, 219 (92) $[MH - N_2]^+$, 260 (100) $[MH - N_2 + CH_3CN]^+$, *RT* 4.5 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-ethyl-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3f), m.p. 120—122 °C. Found (%): C, 50.74; H, 6.22; N, 43.27. $C_{11}H_{16}N_8$. Calculated (%): C, 50.76; H, 6.20; N, 43.05. IR, ν/cm^{-1}: 1681, 1642, 1576, 1487, 1448, 1421, 1381, 1361, 1077, 1053, 1031, 1005, 975. UV (λ_{max}/nm (A)): 459 (0.347). MS, *m/z* (*I* (%)): 260 (100) $[M]^+$, 233 (88) $[MH - N_2]^+$, *RT* 5.4 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-methyl-3-phenyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3g), m.p. 118—120 °C. Found (%): C, 58.57; H, 5.24; N, 36.28. $C_{15}H_{16}N_8$. Calculated (%): C, 58.43; H, 5.23; N, 36.34.

3-(4-Bromophenyl)-6-(3,5-dimethylpyrazol-1-yl)-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3h), m.p. 158—161 °C. MS, *m/z* (*I* (%)): 387 (10) $[M]^+$, 359 (73) $[M - N_2]^+$, *RT* 10.0 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-(4-methoxyphenyl)-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3i), m.p. 154—156 °C. MS, *m/z* (*I* (%)): 339 (42) $[MH]^+$, 311 (100) $[MH - N_2]^+$, *RT* 6.2 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-(4-hydroxyphenyl)-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3j), m.p. 203—204 °C. MS, *m/z* (*I* (%)): 324 (45) $[M]^+$, 296 (67) $[M - N_2]^+$, *RT* 3.6 min.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-(3,5-dimethylpyrazol-1-yl)-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3k), m.p. 122—125 °C. MS, *m/z* (*I* (%)): 436 (33) $[M]^+$, 407 (100) $[M - H - N_2]^+$, *RT* 20.4 min.

6-(3,5-Dimethylpyrazol-1-yl)-3-methyl-3-(2-pyridyl)-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (3l), m.p. 101—104 °C. MS, *m/z* (*I* (%)): 310 (12) $[MH]^+$, 282 (100) $[MH - N_2]^+$, *RT* 4.4 min.

Synthesis of 3-R-3-R´-6-(3,5-dimethylpyrazol-1-yl)-3-methyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines 4a,b (general procedure). Dihydrotriazolotetrazine **3b,e** (1 mmol) was added with stirring to a suspension of KOH (224 mg, 4 mmol) in DMSO (15 mL). The reaction mixture was kept at room temperature for 40 min and then placed in a bath with cold water. Iodomethane (0.13 mL, 2 mmol) was added to the reaction mixture. The mixture was stirred for 1 h, extracted with Et_2O, washed with water, and dried with anhydrous $CaCl_2$. The solvent was distilled off. The residue was recrystallized from ethanol.

6-(3,5-Dimethylpyrazol-1-yl)-7-methyl-3-spirocyclohexane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (4a). The yield was 63%, m.p. 109—110 °C. Found (%): C, 56.06; H, 6.76; N, 37.73. $C_{14}H_{20}N_8$. Calculated (%): C, 55.98; H, 6.71; N, 37.31. MS, *m/z* (*I* (%)): 301 (4) $[MH]^+$, 273 (100) $[MH - N_2]^+$, *RT* 6.2 min.

6-(3,5-Dimethylpyrazol-1-yl)-3,3,7-trimethyl-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (4b). The yield was 65%, m.p. 62—64 °C. Found (%): C, 51.07; H, 6.52; N, 42.89. $C_{11}H_{16}N_8$. Calculated (%): C, 50.76; H, 6.20; N, 43.05. MS, *m/z* (*I* (%)): 261 (2) $[MH]^+$, 233 (100) $[MH - N_2]^+$, *RT* 4.1 min.

Potassium 6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-olate (5). Dihydrotriazolotetrazine **3b** (286 mg, 1 mmol) was added with stirring to a suspension of KOH (224 mg, 4 mmol) in MeCN (or MeOH) (15 mL). The reaction mixture was kept at room temperature for 30 min. The solvent was evaporated. The residue was washed with isopropanol and filtered off. The yield was 158 mg (69%), m.p. 297—299 °C. Found (%): C, 36.39; H, 3.25; N, 36.57. $C_7H_7KN_6O$. Calculated (%): C, 36.51; H, 3.06; N, 36.50.

3,6-Diindazol-1-yl-1,2,4,5-tetrazine (7a). A mixture of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (540 mg, 2 mmol) and indazole (500 mg, 4.24 mmol) was triturated in a crucible and then kept in the molten state at 170 °C for 40 min. The reaction mixture was cooled, successively washed with hexane and acetonitrile, and filtered off. The yield was 506 mg (81%), m.p. 274—275 °C. Found (%): C, 61.23; H, 3.14; N, 36.02. $C_{16}H_{10}N_8$. Calculated (%): C, 61.14; H, 3.21; N, 35.75.

3,6-Di(4-methylimidazol-1-yl)-1,2,4,5-tetrazine (7b). A mixture of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (1080 mg, 4 mmol) was dissolved with heating in acetonitrile (20 mL). Then 4-methylimidazole (984 mg, 12 mmol) was added. The reaction mixture was stirred at room temperature for 20 min and cooled on ice. The precipitate that formed was filtered off. The yield was 650 mg (67%), m.p. 208—209 °C. Found (%): C, 49.66; H, 4.00; N, 46.54. $C_{10}H_{10}N_8$. Calculated (%): C, 49.58; H, 4.16; N, 46.26.

3-Hydrazino-6-(indazol-1-yl)-1,2,4,5-tetrazine (8a). The yield was 75%, m.p. 169—172 °C. Found (%): C, 47.40; H, 3.34; N, 48.97. $C_9H_8N_8$. Calculated (%): C, 47.37; H, 3.53; N, 49.10.

3-Hydrazino-6-(4-methylimidazol-1-yl)-1,2,4,5-tetrazine (8b). The yield was 87%, m.p. 175—176 °C. Found (%): C, 37.27; H, 4.54; N, 57.96. $C_6H_8N_8$. Calculated (%): C, 37.50; H, 4.20; N, 58.31.

2-Cyclohexylidene-1-[6-(indazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (9a), m.p. 88—90 °C. Found (%): C, 58.59; H, 5.47; N, 36.14. $C_{15}H_{16}N_8$. Calculated (%): C, 58.43; H, 5.23; N, 36.34.

2-Cyclohexylidene-1-[6-(4-methylimidazol-1-yl)-1,2,4,5-tetrazin-3-yl]hydrazine (9b), m.p. 160—161 °C. Found (%): C, 49.84; H, 6.37; N, 38.53. $C_{12}H_{16}N_8 \cdot H_2O$. Calculated (%): C, 49.64; H, 6.25; N, 38.60.

6-(Indazol-1-yl)-3-spirocyclohexane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (10a) was synthesized analogously to compounds **3a—n**, m.p. 154—157 °C. Found (%): C, 58.09; H, 5.30; N, 35.97. $C_{15}H_{16}N_8$. Calculated (%): C, 58.43; H, 5.23; N, 36.34.

6-(4-Methylimidazol-1-yl)-3-spirocyclohexane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (10b) was synthesized analogously to compounds **3a—n**. M.p. 146—148 °C. Found (%): C, 53.07; H, 6.03; N, 39.86. $C_{12}H_{16}N_8$. Calculated (%): C, 52.93; H, 5.92; N, 41.15.

3,6-Di(2-cyclopentylidenehydrazino)-1,2,4,5-tetrazine (12a), m.p. 204—206 °C. Found (%): C, 50.95; H, 6.80; N, 39.55. $C_{12}H_{18}N_8 \cdot 0.5\,H_2O$. Calculated (%): C, 50.87; H, 6.76; N, 39.55.

3,6-Di(2-prop-2-ylidenehydrazino)-1,2,4,5-tetrazine (12C), m.p. 215—216 °C. Found (%): C, 43.13; H, 6.36; N, 50.69. $C_8H_{14}N_8$. Calculated (%): C, 43.23; H, 6.35; N, 50.42.

6-(2-Cyclopentylidenehydrazino)-3-spirocyclopentane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (13a) was synthesized analogously to compounds **3a—n**, m.p. 146—148 °C. Found (%): C, 52.43; H, 6.65; N, 40.66. $C_{12}H_{18}N_8$. Calculated (%): C, 52.54; H, 6.61; N, 40.85.

6-(2-Cyclohexylidenehydrazino)-3-spirocyclohexane-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (13b), m.p. 153—155 °C. Found (%): C, 55.78; H, 7.40; N, 36.85. $C_{14}H_{22}N_8$. Calculated (%): C, 55.61; H, 7.33; N, 37.06.

Table 6. Crystallographic parameters and the X-ray data collection and structure refinement statistics

Compound	**2b**	**3b**	**3i**	**4e**
Molecular formula	$C_{13}H_{18}N_8$	$C_{13}H_{18}N_8$	$C_{16}H_{18}N_8O$	$C_{11}H_{16}N_8$
Molecular weight	286.35	286.35	338.38	260.32
Crystal system		Monoclinic		
Space group	*P*2(1)/*c*	*P*2(1)/*c*	*P*2(1)/*c*	*P*2(1)
a/Å	12.885(4)	13.7484(5)	8.7946(8)	8.3842(10)
b/Å	7.2229(18)	9.2622(4)	16.3833(15)	8.6399(12)
c/Å	16.0562(16)	12.5604(5)	11.781(2)	9.661(3)
α/deg	90	90.00	90.00	90.00
β/deg	99.893(15)	112.529(4)	97.173(11)	97.546(15)
γ/deg	90	90.00	90.00	90.00
V/Å^3	1472.1(6)	1477.39(10)	1684.2(4)	693.7(2)
Z	4	4	4	2
d_{calc}/g cm^{-3}	1.292	1.287	1.335	1.246
μ/mm^{-1}	0.086	0.086	0.091	0.085
Scanning range	$26.39 \geq \theta \geq 3.18$	$30.52 \geq \theta \geq 2.81$	$26.37 \geq \theta \geq 2.64$	$26.39 \geq \theta \geq 3.18$
Number of measured reflections	2940	4335	3324	1511
R_{int}	0.0502	0.0275	0.0456	0.0263
Number of reflections with $I > 2\sigma(I)$	1190	2133	1447	948
Number of refined parameters	198	262	230	176
R_1 (based on reflections with $I > 2\sigma(I)$)	0.0477	0.0452	0.0443	0.0353
wR_2 (based on reflections with $I > 2\sigma(I)$)	0.0795	0.0996	0.0935	0.0754
R_1 (based on all reflections)	0.1402	0.0986	0.1283	0.0638
wR_2 (based on all reflections)	0.0873	0.0916	0.1033	0.0754

3,3-Dimethyl-6-[2-(prop-2-ylidene)hydrazino]-3,7-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (13c) was synthesized analogously to compounds **3a—n**, m.p. 153—156 °C. Found (%): C, 43.06; H, 6.33; N, 50.39. $C_8H_{14}N_8$. Calculated (%): C, 43.23; H, 6.35; N, 50.42.

X-ray diffraction study of compounds 2b, 3b, 3i, and 4b. Single crystals of compounds **2b**, **3b**, **3i**, and **4b** were grown by crystallization from MeOH, MeCN, MeOH, and hexane, respectively. The X-ray diffraction data sets were collected on a Xcalibur 3 diffractometer equipped with a CCD detector (λ(Mo-Kα) = = 0.71073, graphite monochromator, ω- and φ-scanning technique, $T = 295$ K). The structures were solved by direct methods with the use of the SHELXS97 program package and refined using the SHELXL97 program package. The positional and thermal parameters of nonhydrogen atoms were refined by the full-matrix least-squares method first isotropically and then anisotropically. The hydrogen atoms were located in difference electron density maps and refined using a riding model. The X-ray data collection and structure refinement statistics are given in Table 6. The results of the X-ray diffraction studies of compounds **2b**, **3b**, **3i**, and **4b** were deposited with the Cambridge Crystallographic Data Centre (CCDC 730344—730347 for compounds **2b**, **3b**, **3i**, and **4b**, respectively).**

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** These data can be obtained, free of charge, on application to www.ccdc.cam.ac.uk/data_request/cif.

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