Chemistry of Heterocyclic Compounds, Vol. 48, No. 3, June, 2012 (Russian Original Vol. 48, No. 3, March, 2012)

NEW HETEROCYCLIC SYSTEMS BASED ON 1-HYDRAZINO-5,6,7,8-TETRAHYDRO[2,7]NAPHTHYRIDINE: 7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[3,4-*a*]- AND 7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[5,1-*a*][2,7]NAPHTHYRIDINES

S. N. Sirakanyan[1]*, N. G. Avetisyan[1], and A. S. Noravyan[1]

Methods have been developed for the synthesis of new substituted 7,8,9,10-tetrahydro[1,2,4]triazolo-[3,4-a][2,7]naphthyridines from 3-chloro-1-hydrazino-7-methyl-5,6,7,8-tetrahydro-[2,7]naphthyridine-4-carbonitrile. It was shown that on heating in an amine (ethanolamine, pyrrolidine, 2-hydroxypropylamine), they undergo a Dimroth rearrangement at the triazole fragment, being converted into 7,8,9,10-tetrahydro[1,2,4]triazolo[5,1-a][2,7]naphthyridine derivatives.

Keywords: 5,6,7,8-tetrahydro[2,7]naphthyridines, 7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*][2,7]naphthyridines, 7,8,9,10-tetrahydro[1,2,4]triazolo[5,1-*a*][2,7]naphthyridines, nucleophilic substitution, Dimroth rearrangement.

The enhanced interest towards 1,2,4-triazoles and 2,7-naphthyridines is caused by a wide spectrum of their biological activity [1-3]. In the present work, the synthesis of compounds combining said heterocycles as their structural fragments, is described. The desired products were obtained from the 1,3-dichloro-7-methyl-5,6,7,8-tetrahydro[2,7]naphthyridine-4-carbonitrile (**1**) synthesized by us previously [4]. The difference in reactivity of the chlorine atoms at 0-25°C in dichloro compound **1** enabled to obtain 1-hydrazino-substituted compound **2** in 82% yield upon treating compound **1** with hydrazine. The interaction of compound **2** with triethyl orthoformate led to product **3** which is a representative of a new heterocyclic system of 7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine. Compound **3** on refluxing in methanol for 2 h with amines **4a-p** was converted into the corresponding amino derivatives **5a-p** (with 75-93% yield). Mention must be made of the significant increase in reactivity of the second chlorine atom in cyclization product **3** in comparison with its reactivity in 3-chloro-5,6,7,8-tetrahydro[2,7]naphthyridines (including also compound **2**), in which substitution by amine occurs only on extended (no less than 10 h) refluxing in butanol [4].

Attempts to rearrange compound 3 with recyclization of the piperidine ring, similarly to the rearrangement of 1,3-diamino-5,6,7,8-tetrahydro[2,7]naphthyridines carried out by us previously [4], were not successful, but it was discovered that under the conditions described in place of the f ormation of compounds **7a,b**,

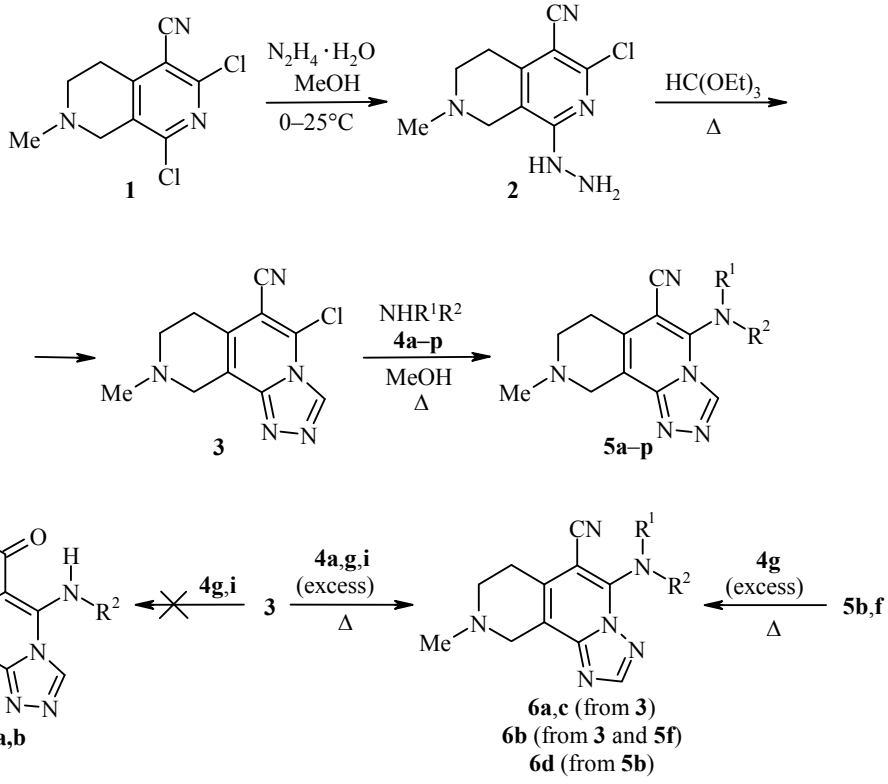
*To whom correspondence should be addressed, e-mail: shnnr@mail.ru.

[1]The Scientific Technological Center of Organic and Pharmaceutical Chemistry of National Academy of Sciences of the Republic of Armenia, A. L. Mnjoyan Institute of Fine Organic Chemistry, 26 Azatutyan Ave., Yerevan 0014, Armenia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 500-505, March, 2012. Original article submitted February 13, 2011. Revision submitted June 5, 2011.

 0009-3122/12/4803-0470©2012 Springer Science+Business Media, Inc.

a Dimroth rearrangement of the triazole ring occurred, which is highly characteristic for such compounds [5]. Thus, refluxing the tetrahydrotriazolo[3,4-*a*][2,7]naphthyridine **3** in an excess of amine **4a,g,i** led to the formation of the corresponding products **6a-c**, representing a new heterocyclic system, the 7,8,9,10-tetrahydro[1,2,4]-tria-zolo[5,1-*a*][2,7]naphthyridines.



4, 5 a $R^1 + R^2 = –(CH_2)_4–$, **b** $R^1 + R^2 = –(CH_2)_5–$, **c** $R^1 + R^2 = –(CH_2)_2CH(CH_2Ph)(CH_2)_2–$, **d** $R^1 + R^2 = –(CH_2)_2N(CH_2CH_2OH)(CH_2)_2–$, **e** $R^1 + R^2 = –(CH_2)_2O(CH_2)_2–$, **f–p** R^1 = H; **f** $R^2 = CH_2CH_2CHMe_2$, **g** $R^2 = CH_2CH_2OH$, **h** R^2 = 2-methoxyethyl, **i** $R^2 = CH_2CH(OH)Me$, **j** $R^2 = CH_2Ph$, **k** R^2 = 4-4-pyridylmethyl, **l** R^2 = 2-furylmethyl, **m** R^2 = 2-morpholinoethyl, **n** $R^2 = (CH_2)_3OH$, **o** $R^2 = CH_2CH_2Ph$, **p** $R^2 = CH_2CH_2(3,4\text{-}(MeO)_2C_6H_3)$; **6 a** $R^1 + R^2 = –(CH_2)_4–$, **b,c** R^1 = H, **d** $R^1 + R^2 = –(CH_2)_5–$; **6b**, **7a** $R^2 = CH_2CH_2OH$, **6c, 7b** $R^2 = CH_2CH(OH)Me$

An analogous rearrangement also took place on refluxing amino derivatives **5b,f** in ethanolamine (**4g**), but in the case of the (isopentyl)amino-substituted carbonitrile **5f** reamination also occurred involving the solvent, and the sole product **6b** in 77% yield was formed.

In the ^{1}H NMR spectra of products **6a-d**, the signal of the CH proton of the triazole ring was shifted towards high field by 0.7-1.2 ppm in comparison with the analogous signal of the isomeric compounds **5a,g,i,b** while the remaining signals differed insignificantly. This confirmed the formation of a 7,8,9,10-tetrahydro-[1,2,4]triazolo[5,1-*a*][2,7]naphthyridine system. In the case of formation of structure **7** the differences in the spectra of these compounds would be more substantial by far.

Thus, in the course of investigations, derivatives have been obtained of two new heterocyclic systems containing in their structure 1,2,4-triazole and 2,7-naphthyridine rings as fragments, that opens new possibilities in the synthesis of heterocyclic compounds. In addition, the broad spectrum of biological activity of analogous derivatives predetermines the expediency of investigating this promising class of condensed compounds for the creation of new pharmacologically active substances.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2**, **3, 5a-p, 6a-d**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
2	$C_{10}H_{12}ClN_5$	50.41 / 50.53	5.14 / 5.09	29.35 / 29.46	233-235	82
3	$C_{11}H_{10}ClN_5$	53.42 / 53.34	4.15 / 4.07	28.35 / 28.28	230-232	85
5a	$C_{15}H_{18}N_6$	63.84 / 63.81	6.31 / 6.43	29.68 / 29.76	210-212	78
5b	$C_{16}H_{20}N_6$	64.75 / 64.84	6.71 / 6.80	28.42 / 28.36	225-227	81
5c	$C_{23}H_{26}N_6$	71.62 / 71.48	6.71 / 6.78	21.68 / 21.74	212-214	75
5d	$C_{17}H_{23}N_7O$	59.75 / 59.81	6.73 / 6.79	28.65 / 28.72	224-226	82
5e	$C_{15}H_{18}N_6O$	60.27 / 60.39	6.11 / 6.08	28.22 / 28.17	246-248	84
5f	$C_{16}H_{22}N_6$	64.29 / 64.40	7.35 / 7.43	28.24 / 28.16	159-161	87
5g	$C_{13}H_{16}N_6O$	57.28 / 57.34	5.85 / 5.92	30.75 / 30.86	207-209	85
5h	$C_{14}H_{18}N_6O$	58.68 / 58.73	6.27 / 6.34	29.29 / 29.35	147-149	80
5i	$C_{14}H_{18}N_6O$	58.68 / 58.73	6.26 / 6.34	29.26 / 29.35	175-178	87
5j	$C_{18}H_{18}N_6$	67.85 / 67.91	5.58 / 5.70	26.34 / 26.40	244-247	85
5k	$C_{17}H_{17}N_7$	63.86 / 63.93	5.28 / 5.37	30.64 / 30.70	230-232	75
5l	$C_{16}H_{16}N_6O$	62.25 / 62.33	5.14 / 5.23	27.21 / 27.26	221-223	84
5m	$C_{17}H_{23}N_7O$	59.69 / 59.81	6.75 / 6.79	28.68 / 28.72	208-210	91
5n	$C_{14}H_{18}N_6O$	58.65 / 58.73	6.29 / 6.34	29.28 / 29.35	166-168	84
5o	$C_{19}H_{20}N_6$	68.60 / 68.65	6.13 / 6.06	25.22 / 25.28	242-244	93
5p	$C_{21}H_{24}N_6O_2$	64.15 / 64.27	6.20 / 6.16	21.35 / 21.41	218-220	89
6a	$C_{15}H_{18}N_6$	63.78 / 63.81	6.32 / 6.43	29.64 / 29.76	202-204	81
6b	$C_{13}H_{16}N_6O$	57.28 / 57.34	5.85 / 5.92	30.75 / 30.86	197-199	85
6c	$C_{14}H_{18}N_6O$	58.66 / 58.73	6.28 / 6.34	29.29 / 29.35	165-167	77
6d	$C_{16}H_{20}N_6$	64.72 / 64.84	6.75 / 6.80	28.33 / 28.36	221-223	74

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in nujol. The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury-300 VX instrument (at 300 MHz) in DMSO-d_6, internal standard was TMS. A check on the progress of reactions and the purity of the obtained compounds was performed by TLC on Silufol UV-254 plates. Physicochemical characteristics of the synthesized compounds are shown in Table 1 and ^{1}H NMR spectral data are given in Table 2.

3-Chloro-1-hydrazino-7-methyl-5,6,7,8-tetrahydro[2,7]naphthyridine-4-carbonitrile (2). Hydrazine hydrate (5.00 g, 0.10 mol) was added with stirring to a solution of dichloro compound **1** (2.42 g, 0.01 mol) in abs. MeOH (100 ml) cooled to 0-5°C. The reaction mixture was stirred for 8 h, gradually increasing the

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **3**, **5a-p**, **6a-d**

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	N-methyltetrahydropyridine ring*				Triazole ring	5-N(R^1 + R^2) / NHR^2	
	NCH_3 (3H, s)	7-CH_2 (2H)	8-CH_2 (2H)	10-CH_2 (2H, t)	H-3/H-2 (1H, s)	(R^1 + R^2) / R^2	NH (1H, t)
1	2	3	4	5	6	7	8
3	2.52	2.94 (tt, ^3J = 5.7, ^5J = 2.0)	2.79 (t, ^3J = 5.7)	3.79 (^5J = 2.0)	9.33	—	—
5a	2.48	2.79 (m)	2.72 (m)	3.64 (^5J = 1.8)	9.28	2.11 (4H, m, N($CH_2C\underline{H}_2$)$_2$; 3.92 (4H, m, N(CH_2)$_2$)	—
5b	2.49	2.84 (m)	2.74 (m)	3.70 (^5J =1.8)	8.92	1.73-1.89 (6H, m, N($CH_2C\underline{H}_2$)$_2C\underline{H}_2$); 3.48 (4H, m, N(CH_2)$_2$)	—
5c	2.49	2.83 (m)	2.73 (m)	3.70 (^5J = 1.8)	8.91	1.50-1.64 and 1.81-1.94 (5H, m, CH(CH_2)$_2$); 2.65 (2H, d, ^3J = 6.9, $C\underline{H}_2C_6H_5$); 3.34 (2H, ddd, ^2J = 12.5, ^3J = 12.2, ^3J = 2.3, NCH_2); 3.60 (2H, br. d, ^2J = 12.5, NCH_2); 7.12-7.28 (5H, m, C_6H_5)	—
5d	2.49	2.84 (m)	2.74 (m)	3.70 (^5J = 1.8)	8.97	2.56 (2H, t, ^3J = 5.8, $C\underline{H}_2CH_2OH$); 2.75 (4H, m, 5-N($CH_2C\underline{H}_2$)$_2$); 3.54 (4H, m, 5-N(CH_2)$_2$); 3.57 (2H, q, ^3J = 5.8, $C\underline{H}_2OH$); 4.00 (1H, t, ^3J = 5.8, OH)	—
5e	2.50	2.85 (tt, ^3J = 5.7, ^5J = 1.8)	2.75 (t, ^3J = 5.7)	3.72 (^5J = 1.8)	9.12	3.53 (4H, m, N(CH_2)$_2$); 3.88 (4H, m, (CH_2)$_2$O)	—
5f	2.46	2.78 (m)	2.70 (m)	3.59 (^5J = 1.8)	9.32	0.99 (6H, d, ^3J = 6.6, $2CH_3$); 1.62-1.69 (2H, m, $C\underline{H}_2CH$); 1.77 (1H, nonet, ^3J = 6.6, CH); 3.78 (2H, m, NCH_2)	7.66 (^3J = 5.9)
5g	2.47	2.78 (m)	2.71 (m)	3.60 (^5J = 1.8)	9.42	3.74 (2H, m, $C\underline{H}_2OH$); 3.86 (2H, m, NCH_2); 4.74 (1H, t, ^3J = 5.7, OH)	7.78 (^3J = 5.8)
5h	2.46	2.78 (m)	2.70 (m)	3.59 (^5J = 1.8)	9.39	3.37 (3H, s, OCH_3); 3.67 (2H, t, ^3J = 5.1, CH_2O); 3.94 (2H, dt, ^3J = 6.0, ^3J = 5.1, NCH_2)	7.92 (^3J = 6.0)
5i	2.46	2.88 (tt, ^3J = 5.7, ^5J = 1.8)	2.74 (t, ^3J = 5.7)	3.57 (^5J = 1.8)	9.44	1.18 (3H, d, ^3J = 6.2, CH_3); 3.36 (1H, m, CH); 3.90-4.07 (2H, m, NCH_2); 4.82 (1H, d, ^3J = 4.5, OH)	7.83 (^3J = 6.0)

TABLE 2 (continued)

1	2	3	4	5	6	7	8
5j	2.45	2.74 (m)	2.68 (m)	3.59 (^5J = 1.8)	9.41	5.00 (2H, d, ^3J = 6.2, NCH_2); 7.23-7.43 (5H, m, H Ph)	8.33 (^3J = 6.2)
5k	2.45	2.75 (m)	2.65 (m)	3.60 (^5J = 1.8)	9.39	5.01 (2H, d, ^3J = 5.1, NCH_2); 7.36 (2H, m, H-3',5' Py); 8.50 (2H, m, H-2',6' Py)	8.47 (^3J = 5.1)
5l	2.46	2.79 (m)	2.71 (m)	3.60 (^5J = 1.8)	9.38	4.98 (2H, d, ^3J = 6.1, NCH_2); 6.35 (1H, dd, ^3J = 3.3, ^3J = 1.9, H-4' Fur); 6.48 (1H, d, ^3J = 3.3, H-3' Fur); 7.46 (1H, d, ^3J = 1.9, H-5' Fur)	8.33 (^3J = 6.1)
5m	2.46	2.78 (m)	2.70 (m)	3.60 (^5J = 1.8)	9.33	2.47 (4H, m, $N(CH_2)_2$); 2.68 (2H, t, ^3J = 6.5, 5-$NCH_2C\underline{H}_2$); 3.54 (4H, m, $(CH_2)_2O$); 3.87 (2H, m, $NHC\underline{H}_2$)	7.53 (br)
5n	2.46	2.78 (m)	2.70 (m)	3.59 (^5J = 1.8)	9.33	1.91 (2H, m, $CH_2C\underline{H}_2CH_2$,); 3.58 (2H, q, ^3J = 5.6, CH_2O); 3.87 (2H, q, ^3J = 5.6, 5-NCH_2); 4.35 (1H, t, ^3J = 5.6, OH)	7.78 (^3J = 5.6)
5o	2.47	2.80 (m)	2.71 (m)	3.60 (^5J = 1.8)	9.27	3.05 (2H, m, $C\underline{H}_2$Ph); 3.99 (2H, m, NCH_2); 7.14-7.29 (5H, m, H Ph)	7.91 (^3J = 6.1)
5p	2.47	2.79 (m)	2.72 (m)	3.61 (^5J = 1.8)	9.30	2.96 (2H, m, $C\underline{H}_2$Ar); 3.75 (6H, c, $2OCH_3$); 3.96 (2H, m, NCH_2); 6.72 (2H, d, ^5J = 1.1, H-5',6' Ar); 6.86 (1H, t, ^5J = 1.1, H-2' Ar)	7.90 (^3J = 6.2)
6a	2.46	2.86 (tt, ^3J = 5.7, ^5J = 1.8)	2.71 (t, ^3J = 5.7)	3.58 (^5J = 1.8)	8.10	2.06 (4H, m, $N(CH_2C\underline{H}_2)_2$); 4.17 (4H, m, $N(CH_2)_2$)	—
6b	2.46	2.88 (tt, ^3J = 5.7, ^5J = 1.8)	2.72 (t, ^3J = 5.7)	3.58 (^5J = 1.8)	8.23	3.75 (2H, q, ^3J = 5.3, $C\underline{H}_2O$); 3.92 (2H, t, ^3J = 5.3, NCH_2); 4.78 (1H, t, ^3J = 5.3, OH)	7.36 (^3J = 5.6)
6c	2.46	2.88 (tt, ^3J = 5.7, ^5J = 1.8)	2.72 (t, ^3J = 5.7)	3.59 (^5J = 1.8)	8.23	1.22 (3H, d, ^3J = 6.2, CH_3); 3.55 (1H, m, CH); 3.92-4.04 (2H, m, $NC\underline{H}_2$); 4.84 (1H, d, ^3J = 4.8, OH)	7.28 (^3J = 5.6)
6d	2.47	2.90 (tt, ^3J = 5.7, ^5J = 1.8)	2.73 (t, ^3J = 5.7)	3.65 (^5J = 1.8)	8.20	1.72-1.87 (6H, m, $N(CH_2C\underline{H}_2)_2C\underline{H}_2$); 3.67 (4H, m, $N(CH_2)_2$)	—

*Assignment of the proton signals was confirmed by the 2D NOESY method (mixing time 1 sec).

temperature to 20-25°C. The precipitated crystals of product **2** were filtered off, washed with water, dried, and recrystallized from DMF. IR spectrum, ν, cm^{-1}: 3660, 3220 ($NHNH_2$), 2220 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3); 2.60 (2H, t, ^3J = 5.7, 6-CH_2); 2.79 (2H, tt, ^3J = 5.7, ^5J = 1.6, 5-CH_2); 3.13 (2H, t, ^5J = 1.6, 8-CH_2); 4.25 (2H, m, NH_2); 8.38 (1H, s, NH).

5-Chloro-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitrile (3). A mixture of compound **2** (2.38 g, 0.01 mol) and triethyl orthoformate (50 ml) was refluxed for 10 h, the excess of ester was distilled off to dryness, and hexane (25 ml) was added to the residue. The resulting crystals were filtered off, washed with hexane, dried, and recrystallized from $CHCl_3$. IR spectrum, ν, cm^{-1}: 2220 (CN).

5-(*R*^{1},*R*^{2}-Amino)-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitriles 5a-p (General Method). A mixture of chloro compound **3** (2.48 g, 0.010 mol) and the corresponding amine **4a-p** (0.022 mol) in abs. MeOH (50 ml) was refluxed for 2 h. The MeOH was distilled off to dryness, water (50 ml) was added to the residue, the separated crystals of product **5** were filtered off, washed with water, dried, and recrystallized from EtOH.

5-(*R*^{1},*R*^{2}-Amino)-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazolo[5,1-*a*][2,7]naphthyridine-6-carbonitriles 6a-d (General Method). A mixture of chloro compound **3** (2.48 g, 0.01 mol) or **5b,f** (0.01 mol) and the corresponding amine **4a,g,i** (0.10 mol) was refluxed for 3 h. After cooling, water (50 ml) was added, the separated crystals of product **6a-d** were filtered off, washed with water, dried, and recrystallized from EtOH. The identity of both samples of product **6b,** obtained from compounds **3** and **5f** by refluxing with amine **4g**, was demonstrated by ^1H NMR spectroscopy.

REFERENCES

1. M. Gall, R. A. Lahti, A. D. Rudzik, D. J. Duchamp, C. Chidester, and T. Scahill, *J. Med. Chem.*, **21**, 542 (1978).
2. B. S. Holla, K. N. Poojary, B. Kalluraya, and P. V. Gowda, *Farmaco*, **51**, 793 (1996).
3. T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, Y. Moritani, K. Saruta, T. Higashijima, J. Kotera, K. Fujishige, M. Tagaki, K. Kikkawa, and K. Omori, *Bioorg. Med. Chem. Lett.*, **13**, 2341 (2003).
4. S. N. Sirakanyan, V. G. Kartsev, E. G. Paronikyan, and A. S. Noravyan, in: *Nitrogen-containing Heterocycles* [in Russian], Vol. 1, ICSPF, Moscow (2006), p. 453.
5. C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan, and V. S. Bhadti, *J. Heterocycl. Chem.*, **18**, 43 (1981).