Chemistry of Heterocyclic Compounds, Vol. 38, No. 10, 2002

CONDENSED ISOQUINOLINES. 15*. SYNTHESIS OF 5,10-DIHYDRO[1,2,4]TRIAZOLO[1,5-*b*]-ISOQUINOLINES AND RELATED SPIRANES

V. M. Kisel [1], E. O. Kostyrko [1], O. V. Shishkin [2], S. V. Shishkina [2], and V. A. Kovtunenko[1]

Condensation of o-bromomethylphenylacetonitrile with arylcarbohydrazides gave, depending on the reaction conditions, 2-arylcarboxamido-1,4-dihydroisoquinoline-3(2H)-imine hydrobromides or 2-aryl-5,10-dihydro[1,2,4]triazolo[1,5-b]isoquinolines. Analogous condensation of 4-(2-bromomethylphenyl)tetrahydro-2H-pyran-4-carbonitrile and 1-(2-bromomethylphenyl)-1-cyclopentanecarbonitrile with arylcarbohydrazides gave respectively 2-aryl-2,3,5,6-tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-b]isoquinolines and 2-arylspiro[1,2,4]triazolo[1,5,b]isoquinoline-10(5'H)-1'-cyclopentanes, derivatives of new spirane heterocycles. The reaction with condensing agents of 3-imino-2,2',3,3'5',6'-hexahydrospiro[isoquinoline-4(1H),4'-4H-pyran]-2-amine and 3-imino-2,3-dihydrospiro-[isoquinoline-4(1H),1'-cyclopentane]-2-amine hydrobromides, synthesized from the corresponding bromo nitriles and hydrazine, may serve as an alternative route for the synthesis of these compounds. The structure of obtained triazoloisoquinolines was established from IR, ^{1}H and ^{13}C NMR spectra. An X-ray crystallographic study of 2-phenylspiro[1,2,4]triazolo[1,5-b]isoquinoline-10(5H),1'-cyclopentane was carried out.

Keywords: condensed isoquinolines, condensed triazoles, spirocyclic compounds.

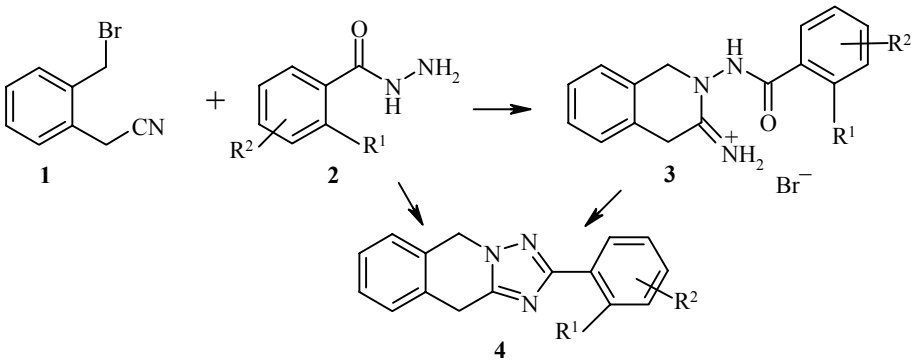
Condensed 1,2,4-triazoles are of interest as potential biologically active compounds [2, 3]. Some of them have found use in medicine and veterinary practice as tranquilizers, anti-inflammatories, and antiallergic medicines [4]. In particular, derivatives of [1,2,4]triazolo[1,5-*b*]isoquinolines have been patented as inotropes [5-7]. Since the development of synthetic methods for the previously undescribed [1,2,4]triazolo[1,5-*b*]-isoquinolines has considerable promise, we have studied in the present work the interaction of *o*-bromomethylphenylacetonitrile **1** and its cycloalkylated analogs with hydrazine and with carboxylic acid hydrazides.

It was found that condensation of bromo nitrile **1** with a series of benzoic acid hydrazides by heating equimolar quantities of the starting materials in dioxane gave 2-arylcarboxamido-1,4-dihydroquinolin-3(2H)-imine hydrobromides **3** in high yields. The absence from their IR spectra of C≡N stretching frequencies, the presence of C=O stretching frequencies and also those of the symmetric and asymmetric N^{+}–H stretches characteristic of the protonated salts of 1,4-dihydroisoquinolin-3(2H)-amines gave evidence of the above-

* For part 14 see [1].

[1] Taras Shevchenko Kiev National University, Kiev 01033, Ukraine; e-mail: kysil@sbet.com, e-mail: v-kysil@mail.univ.kiev.ua. [2] Institute of Monocrystals, Ukraine National Academy of Sciences, Kharkov 610001; e-mail: shishkin@isc.kharkov.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1421-1431, October 2002. Article submitted June 6, 2001.

mentioned structure (Table 1). Intense absorption band with several maxima in the 1600-1700 cm^{-1} region was interpreted as superposition of the C=O stretch of the amide group [9] and of the exocyclic $C=N^{+-}$ bond [8]. The ^1H NMR spectra of the condensation products were characterized by three broad singlets which exchanged with D_2O protons, two of which were ascribed to resonance of the protons of the iminium groups (the reason for their nonequivalence is analogous to that discussed previously [8]), and the third to a proton of an amide N–H group.



2-4 a, **b** R^1 = H; **c**, **d** R^1 = OH; **a**, **c** R^2 = H, **b** R^2 = 3-Br, **d** R^2 = 5-Br; **3e** R^1 = OAc, R^2 = H

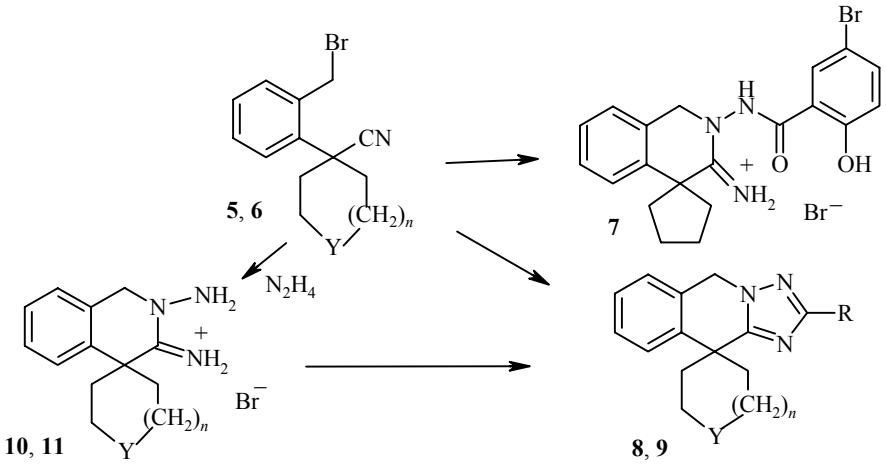
Taking into account the known tendency (see [2, 3] and the literature cited there) of the 1,2,4-triazole ring to annelate with azaheterocycles, we studied the behavior of isoquinoline **3c** on interaction with various condensing agents. Apparently boiling this compound with acetic anhydride led only to acetylation of the phenolic hydroxyl group to give 2-(2-acetoxyphenyl)carboxamido-1,4-dihydroisoquinolin-3(2H)-imine hydrobromide (**3e**). The expected 2-(2-hydroxyphenyl)-5,10-dihydro[1,2,4]triazolo[1,5-*b*]isoquinoline (**4c**) was only obtained in low yield on treatment of imine **3c** with phosphorus oxychloride. The best results were obtained by prolonged heating (15 h) of isoquinolinimine **3c** in DMF in the presence of sodium acetate, which gave the required product **4c** in 50% yield. The other 2-aryl-5,10-[1,2,4]triazolo[1,5-*b*]isoquinolines (**4**) were synthesized under the same conditions. The optimal method for their preparation appeared to be the direct condensation of bromonitrile **1** with benzhydrazides **2** in the presence of sodium acetate.

Absorption bands for C=O and N–H stretching vibrations were absent from the IR spectra of the synthesized triazoloisoquinolines. In the case of compounds **4c** and **4d** absorption of the phenolic hydroxyl groups was observed as strongly broadened diffuse bands with several maxima, which has ben explained [9] by participation of the OH group in intramolecular hydrogen bonding with nitrogen atoms of the triazole ring. The absorption bands of the latter appeared in the IR spectra of compounds **4a** and **4b** in the 1485-1495 cm^{-1} region which is characteristic of conjugation of the C=N group within the ring [10]. In contrast, in the IR spectra of phenols **4c** and **4d** these bands underwent a low frequency shift to 1450 cm^{-1} as a result of nitrogen atoms of the triazole ring participating in the formation of hydrogen bonds with hydroxy groups in compounds **4c** and **4d**. The signals of the methylene group protons in the ^1H NMR spectra of triazoloisoquinolines **4** appear as triplets with homoallylic coupling constant J = 2.5 Hz [11].

It might be expected that in condensation with hydrazides **2** the cycloalkylated analogs of bromo nitrile **1**: 4-(2-bromomethylphenyl)tetrahydro-2H-pyran-4-carbonitrile (**5**) and 1-(2-bromomethylphenyl)-1-cyclopentanecarbonitrile (**6**) would behave in analogous way. However, it was difficult to stop the reaction at the stage of formation of the corresponding isoquinolin-3-imines. 2-(5-Bromo-2-hydroxyphenyl)-carboxamidospiro[isoquinoline-4(1H),1'-cyclopentan]-3(2H)-imine (**7**) was formed only in the case of condensation of bromo nitrile **6** with 5-bromosalicylic acid hydrazide in dioxane at boiling for 6 h. In the remaining cases mixtures of salt-like compounds were produced which we did not investigate further. The reaction with sodium acetate behaved completely differently. 2-Aryl-2,3,5,6-tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-*b*]isoquinolines] (**8**) were obtained from bromo nitrile **5** in good yields. Analogous conversion of bromo nitrile **6** gave 2-arylspiro[[1,2,4]triazolo[1,5-*b*]isoquinoline-10(5H),1'-cyclopentanes] (**9**).

TABLE 1. Characteristics of Compounds **3**, **4**, and **8**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Br		
3a	$C_{16}H_{15}N_3O \cdot HBr$	55.67 / 55.51	4.72 / 4.66	12.19 / 12.14	23.06 / 23.08	257	66
3b	$C_{16}H_{14}BrN_3O \cdot HBr$	45.31 / 45.20	3.63 / 3.56	9.94 / 9.88	37.77 / 37.59	235	70
3c	$C_{16}H_{15}N_3O_2 \cdot HBr$	53.15 / 53.05	4.50 / 4.45	11.86 / 11.60	22.31 / 22.06	252	83
3d	$C_{16}H_{14}BrN_3O_2 \cdot HBr$	43.63 / 43.57	3.50 / 3.43	9.89 / 9.53	36.21 / 36.23	245	75
3e	$C_{18}H_{17}N_3O_3 \cdot HBr$	53.55 / 53.48	4.55 / 4.49	10.52 / 10.39	20.90 / 19.77	217	70
4a	$C_{16}H_{13}N_3$	77.80 / 77.71	5.42 / 5.30	17.29 / 16.99		241	45
4b	$C_{16}H_{12}BrN_3$	59.10 / 58.91	3.82 / 3.71	13.11 / 12.88	24.72 / 24.50	250	61
4c	$C_{16}H_{13}N_3O$	73.05 / 72.99	5.07 / 4.98	16.15 / 15.96		272	48
4d	$C_{16}H_{12}BrN_3O$	56.24 / 56.16	3.62 / 3.53	12.43 / 12.28	23.60 / 23.35	249	60
8a	$C_{20}H_{19}N_3O$	75.78 / 75.69	6.12 / 6.03	13.33 / 13.24		179	52
8b	$C_{20}H_{18}BrN_3O$	60.73 / 60.62	4.63 / 4.58	10.88 / 10.60	20.20 / 20.16	183	58
8c	$C_{20}H_{19}N_3O_2$	72.10 / 72.05	5.82 / 5.74	12.83 / 12.60		194	55
8d	$C_{20}H_{18}BrN_3O_2$	58.32 / 58.27	4.49 / 4.40	10.22 / 10.19	19.62 / 19.38	220	56
8e·HBr	$C_{15}H_{17}N_3O \cdot HBr$	53.65 / 53.58	5.52 / 5.40	12.28 / 12.50	23.82 / 23.76	226	50
8f	$C_{14}H_{15}N_3O$	69.77 / 69.69	6.33 / 6.27	17.60 / 17.41		244	48
9a	$C_{20}H_{19}N_3$	79.78 / 79.70	6.43 / 6.35	14.07 / 13.94		104	72
9b	$C_{20}H_{18}BrN_3$	63.23 / 63.17	4.83 / 4.77	11.30 / 11.05	21.28 / 21.01	90	70
9c	$C_{20}H_{19}N_3O$	75.78 / 75.69	6.12 / 6.03	13.41 / 13.24		128	55
9d	$C_{20}H_{18}BrN_3O$	60.73 / 60.62	4.67 / 4.58	10.70 / 10.60	20.22 / 20.16	151	73
9e·HBr	$C_{15}H_{17}N_3 \cdot HBr$	56.35 / 56.26	5.73 / 5.67	13.32 / 13.12	25.16 / 24.95	237	54



5, **8**, **10** Y = O, *n* = 1; **6**, **9**, **11** Y = CH_2, *n* = 0; **8**, **9** **a** R = Ph; **b** R = 3-BrC_6H_4; **c** R = 2-HOC_6H_4, **d** R = 2-HO-5-BrC_6H_3, **e** R = Me; **8f** R = H

The spectroscopic characteristics of the spirans obtained (Table 3), which are derivatives of new heterocyclic systems, are in accord with data for triazoloisoquinolines **4** (Table 2). We have carried out a more detailed study of the spectroscopic properties of the model compound **9a**. In the ^{13}C NMR spectrum, the ^{13}C signals of the carbon atoms of the triazole ring appear at 160.4 and 159.8 ppm, while the signal for spiro carbon atom occurs at 46.6 ppm. The structure of this compound has also been confirmed by X-ray crystallography (Fig.1, Tables 4-6). The dihydropyridine ring has the tub configuration (folding parameters [12], S = 0.15, θ 71.7, Ψ 11.7). The displacements of atoms C(5) and C(10) from the least squares plane of the remaining atoms of the ring are 0.13 and 0.07 Å respectively.

TABLE 2. Spectroscopic Characteristics of Compounds **3** and **4**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm, SSCC, J (Hz)		
		C–CH_2, 2H	N–CH_2, 2H	Other signals
3a	1675, 1650 (C=O, C=N); 3040, 3220 (NH)	4.25, s	4.9, s	7.3-8.1 (9H, m, H arom.); 9.51 (1H, br. s, N^+H); 9.94 (1H, br. s, N^+H); 11.73 (1H, br. s, CONH)
3b	1680, 1650 (C=O, C=N); 3000, 3200 (NH)	4.3, s	4.9, s	7.3-7.5 (4H, m, C(5-8)-H); 7.58 (1H, d, J_o = 8, C(5')H); 7.90 (1H, dd, J_o = 8, J_m= 2.5, C(4')H); 8.00 (1H, dd, J_o = 8, J_m = 2.5, C(6')H); 8.20 (1H, t, J_m = 2.5, C(2')H); 9.51 (1H, br. s, N^+H); 9.94 (1H, br. s, N^+H); 11.82 (1H, br. s, CONH)
3c	1630, 1660 (C=O, C=N); 3000, 3060, 3200 (NH, OH)	4.25, s	4.9, s	7.0 (1H, t, J_o = 8, C(5')H); 7.1 (1H, d, J_o = 8, C(3')H); 7.3-7.4 (4H, m, C(5-8)–H); 7.5 (1H, t. d, J_o =8, J_m = 2.5, C(4')H); 7.95 (1H, dd, J_o = 8, J_m = 2.5, C(6')H); 9.4 (1H, br. s, N^+H); 9.9 (1H, br. s, N^+H); 11.3 (2H, br. s, CONH**,** OH)
3d	1630, 1650 (C=O, C=N); 3020, 3120, 3200 (NH, OH)	4.25, s	4.9, s	7.1 (1H, d, J_o = 8, C(3')H); 7.3-7.4 (4H, m, C(5-8)–H); 7.65 (1H, dd, J_o = 8, J_m = 2.5, C(4')H); 8.05 (1H, d, J_m = 2.5, C(6')H); 9.4 (1H, br. s, N^+H); 9.95 (1H, br. s, N^+H); 11.4 (2H, br. s, CONH**,** OH)
3e	1650, 1680 (C=O, C=N); 1760 (C=O); 3040, 3220 (NH)	4.25, s	4.8, s	2.25 (3H, c, $COCH_3$); 7.25-7.5 (6H, m, C(5-8)–H, C(3')-H, C(5')-H); 7.7 (1H, t. d, J_o = 8, J_m = 2.5, C(4')H); 8.02 (1H, dd, J_o = 8, J_m = 2.5, C(6')H); 9.45 (1H, br. s, N^+H); 9.95 (1H, br. s, N^+H); 11.55 (1H, br. s, CONH)
4a	1495 (C=N)	5.3, t, J_5 = 2.5	5.5, t	7.3-7.6 (7H, m, H arom.); 8.0-8.1 (2H, m, C(2')H, C(6')H)
4b	1485 (C=N)	4.3, t	5.45, t	7.3-7.5 (5H, m, H arom.); 7.6 (1H, tt, J_o = 8, J_m = 2.5, C(4')H); 8.0 (1H, dt, J_o = 8, J_m = 2.5, C(6')H); 8.15 (1H, t, J_m = 2.5, C(2')H)
4c	1450 (C=N); 2900, 3030, 3160 (OH)	4.35, s	5.5, s	6.9-7.4 (7H, m, H arom.); 8.0 (1H, d, J_o = 8, C(3')H); 8.8 (1H, s, OH)
4d	1450 (C=N); 2880, 2900, 3010, 3100 (OH)	4.4, t	5.5, t	6.95 (1H, d, J_o = 8, C(3')H); 7.3-7.6 (5H, m, H arom); 8.05 (1H, d, J_m = 2.5, C(6')H)

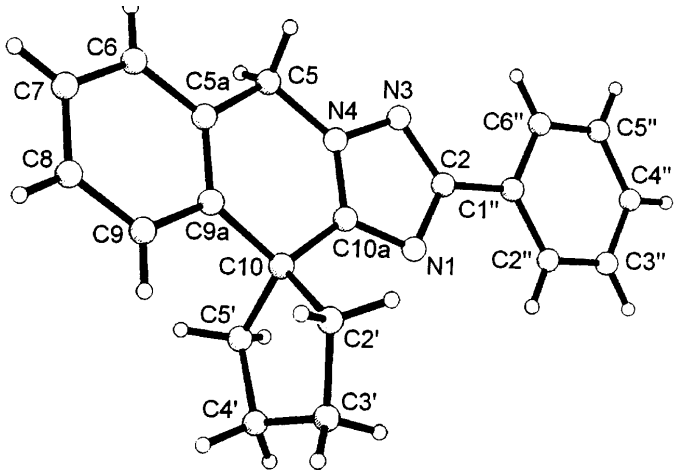


Fig. 1. Structure of the molecule of compound **9a** from X-ray crystallographic study.

The phenyl substituent is rotated somewhat relative to the plane of the triazole ring (torsion angle N(3)–C(2)–C(1")–C(6") 7.8(4)°). The cyclopentane fragment has the envelope conformation. Atom C(3') is displaced from the plane of the rest of the atoms of the ring by 0.35 Å. This spiroannelated ring is rotated somewhat relative to the mean plane of the tricyclic system so that atom C(5') is in a pseudoaxial position while atom C(2') is in a pseudoequatorial position (torsion angles N(4)–C(10a)–C10)–C(5') 113.1(3)° and N(4)–C(10a)–C(10)–C(2') -134.6(3)°. A short intramolecular contact H(2'b)···C(9) 2.69 Å (sum of the van der Waals radii 2.87 Å [13]) was observed within the molecule. In the crystal a short intermolecular contact H(5a)···C(2') 2.73 Å (2.87 Å) (1 - *x*, 2 - *y*, -*z*) was found. Molecules of compound **9a** form a mutually perpendicular stacks along the crystallographic axes (1 0 0) and (0 1 0). The distance between the π-systems of neighboring molecules in the (0 1 0) stack is about 3.5 Å which allows for stacking interactions.

TABLE 3. Spectroscopic Characteristics of Compounds **8** and **9**

Com-pound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm, SSCC, *J* (Hz)*		
	C=N	Other bands	-CH_2- of pyran (or cyclopentane) rings, m	N–CH_2 (s, 2H)	Other signals
1	2	3	4	5	6
8a	1480		1.75-2.0 (2H); 2.5-2.7 (2H); 3.8-4.0 (2H); 4.25-4.6 (2H)	5.45	7.25-7.5 (6H, m, H arom.); 7.7 (1H, dd, J_o = 8, J_m = 2.5, C(4")H); 8.1-8.2 (2H, m, C(2")H, C(6")H)
8b	1450		1.75-1.95 (2H); 2.1-2.5 (2H); 3.75-3.95 (2H); 4.25-4.55 (2H)	5.5	7.3-7.8 (6H, m, H arom.); 8.05 (1H, dt, J_o = 8, J_m = 2.5, C(6")H); 8.2 (1H, t, J_m = 2.5, C(2")H)
8c	1460	3150 (OH)	1.8-2.0 (2H); 2.15-2.5 (2H); 3.8-4.0 (2H); 4.1-4.4 (2H)	5.6	6.95 (1H, t, J_o = 8, C(5")H); 7.0 (1H, d, J_o = 8, C(3")H); 7.25-7.55 (4H, m, H arom.); 7.7-7.8 (1H, m, C(4")H); 8.0 (1H, dd, J_o = 8, J_m = 2.5, C(6")H); 10.9 (1H, s, OH)

TABLE 3 (continued)

1	2	3	4	5	6
8d	1450	3070 (OH)	1.8-2.0 (2H); 2.25-2.6 (2H); 3.8-.1 (2H); 4.3-4.55 (2H)	5.45	6.9 (1H, d, J_o = 8, C(3")H); 7.3-7.55 (4H, m, H arom.); 7.7 (1H, dd, J_o = 8, J_m = 2.5, C(4")H); 8.2 (1H, d, J_m = 2.5, C(6")H); 10.85 (1H, s, OH)
8e·HBr	1585	2740 (N^+H)	2.2-2.6 (4H); 4.2-4.4 (4H)	5.6	2.75 (3H, s, CH_3); 7.5-7.8 (4H, m, H arom.)
8f	1490		1.7-1.9 (2H); 2.05-2.4 (2H); 3.7-3.9 (2H); 4.15-4.45 (2H)	5.45	7.3-7.8 (4H, m, H arom.); 8.03 (1H, s, C(2')H)
9a	1480		1.9-2.5 (8H)	5.5	7.3-7.6 (7H, m, H arom.); 8.0-8.1 (2H, m, C(2")H, C(6")H)
9b	1475		1.9-2.5 (8H)	5.45	7.3-7.5 (5H, m, H arom.); 7.55 (1H, tt, J_o = 8, J_m = 2.5, C(4")H); 8.05 (1H, dt, J_o = 8, J_m = 2.5, C(6")H); 8.15 (1H, t, J_m = 2.5, C(2")H)
9c	1460	3200 (OH)	1.9-2.5 (8H)	5.55	6.9 (1H, t, J_o= 8, C(5")H); 7.0 (1H, d, J_o = 8, C(3")H); 7.35-7.6 (5H, m, H arom.); 7.95 (1H, dd, J_o = 8, J_m = 2.5, C(6")H)
9d	1485	3150 (OH)	2.0-2.5 (8H)	5.4	6.9 (1H, d, J_o = 8, C(3")H); 7.2-7.5 (5H, m, H arom.); 8.2 (1H, d, J_m = 2.5, C(6")H); 11.25 (1H, s, OH)
9e·HBr	1580	2460 (N^+H)	2.0-2.7 (8H)	5.45	2.8 (3H, s, CH_3); 7.3-7.5 (4H, m, H arom.)

* Spectra of compounds **8a**,**d**, **9d,e** were recorded in $CDCl_3$, compound **8e** in CF_3CO_2D, the rest in DMSO-d_6.

The condensation of 1,2-diamino (or 1-amino-2-imino)azaheterocycles with carboxylic acids or their derivatives may serve as an alternative route to annelation of the triazole ring to an azaheterocycle [2]. We therefore also studied the interaction of bromonitriles **1**, **5**, and **6** with hydrazine. The reaction of bromo nitrile **1** with hydrazine hydrate occurred ambiguously to give a complex mixture of products which we did not identify. In contrast short heating of an excess of hydrazine hydrate with bromo nitriles **5** and **6** gave hydrobromides of 3-imino-2,2',3,3',5',6'-hexahydrospiro[isoquinoline-4(1H),4',4H-pyran]-2-amine (**10**) and 3-imino-2,3-dihydrospiro[isoquinoline-4(1H),1'-cyclopentane]-2-amine (**11**) respectively. The IR spectra of these compounds contain no CN absorption bands, but strong stretching frequencies of the N–H and C=N bonds are present. In the ^1H NMR spectra the protons of the NH_2 and iminium groups appear as separate two proton singlets. Acylation of hydrobromides **10** and **11** with benzoyl chloride in the presence of sodium acetate in dioxane gave spirocyclic triazoloisoquinolines **8a** and **9a**. In fact this synthetic route has no advantages when compared to that based on benzhydrazide, and what is more, substituted benzhydrazides are frequently more accessible that the corresponding acid chlorides (e.g., in the case of salicylic acids). Nevertheless, this method was completely justified for the synthesis of spirocyclic triazoloisoquinolines with alkyl substituents in position 2 or with this position open. For example, heating the salts **10** and **11** in acetic anhydride gave hydrobromides of 2-methyl-2,3,5,6-tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-*b*]isoquinoline] (**8e**·HBr) and

TABLE 4. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) of Non-hydrogen Atoms in the Structure of Spirocyclic Triazoloisoquinoline **9a**

Atom	*x*	*y*	*z*	U_{eq}
N(3)	3252(2)	9092(3)	331(1)	62(1)
N(1)	4775(2)	9040(3)	1404(1)	63(1)
N(4)	4436(2)	8271(2)	283(1)	59(1)
C(2)	3508(3)	9542(3)	1020(1)	58(1)
C(10A)	5315(3)	8247(3)	921(1)	57(1)
C(10)	6715(3)	7445(3)	1037(1)	59(1)
C(9A)	6842(3)	6499(3)	373(2)	62(1)
C(9)	7984(4)	5519(4)	399(2)	82(1)
C(8)	8183(4)	4688(4)	-189(2)	92(1)
C(7)	7255(4)	4819(4)	-836(2)	92(1)
C(6)	6135(4)	5767(4)	-876(2)	79(1)
C(5A)	5902(3)	6597(3)	-284(2)	62(1)
C(5)	4614(3)	7572(3)	-388(1)	67(1)
C(1")	2532(3)	10511(3)	1320(2)	62(1)
C(6")	1196(3)	10872(4)	921(2)	78(1)
C(5")	300(4)	11815(4)	1200(2)	92(1)
C(4")	722(4)	12462(4)	1869(2)	91(1)
C(3")	2016(4)	12125(4)	2264(2)	92(1)
C(2")	2916(4)	11155(4)	1998(2)	77(1)
C(2')	6875(3)	6551(3)	1766(2)	72(1)
C(3')	7964(4)	7367(5)	2309(2)	114(2)
C(4')	8797(5)	8244(5)	1897(2)	144(2)
C(5')	7979(3)	8566(4)	1190(2)	75(1)

2-methylspiro[[1,2,4]triazolo[1,5-*b*]isoquinoline-10(5H),1'-cyclopentane] (**9e**·HBr). 2,3,5,6-Tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-*b*]isoquinoline] (**8f**) was synthesized by condensation of hydrobromide **10** with triethyl orthoformate, followed by treatment of the raw product with N-methylmorpholine.

TABLE 5. Bond Lengths (*d*) in the Structure of Spirocyclic Triazoloisoquinoline **9a**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
N(3)–C(2)	1.349(3)	C(1")–C(2")	1.403(4)	C(10)–C(5')	1.586(4)
N(1)–C(10a)	1.343(3)	C(6")–C(5")	1.392(5)	C(9a)–C(5a)	1.409(4)
N(4)–C(10a)	1.349(3)	C(4")–C(3")	1.374(5)	C(9)–C(8)	1.390(5)
C(2)–C(1")	1.479(4)	C(2')–C(3')	1.534(5)	C(7)–C(6)	1.381(5)
C(10)–C(9a)	1.552(4)	C(4')–C(5')	1.462(4)	C(5a)–C(5)	1.518(4)
C(10)–C(2')	1.591(4)	N(3)–N(4)	1.385(3)	C(1")–C(6")	1.416(4)
C(9a)–C(9)	1.418(4)	N(1)–C(2)	1.388(3)	C(5")–C(4")	1.395(5)
C(8)–C(7)	1.391(5)	N(4)–C(5)	1.460(3)	C(3")–C(2")	1.398(4)
C(6)–C(5a)	1.406(4)	C(10a)–C(10)	1.520(4)	C(3')–C(4')	1.457(5)

TABLE 6. Bond Angles (ω) in the Molecule of Compound **9a**

Angle	ω, deg.	Angle	ω, deg.
C(2)–N(3)–N(4)	102.4(2)	C(10a)–N(1)–C(2)	103.6(2)
C(10a)–N(4)–N(3)	110.4(2)	C(10a)–N(4)–C(5)	128.3(3)
N(3)–N(4)–C(5)	121.3(2)	N(3)–C(2)–N(1)	113.7(3)
N(3)–C(2)–C(1")	122.2(2)	N(1)–C(2)–C(1")	124.1(2)
N(1)–C(10a)–N(4)	110.0(2)	N(1)–C(10a)–C(10)	127.1(2)
N(4)–C(10a)–C(10)	122.9(3)	C(10a)–C(10)–C(9a)	110.3(2)
C(10a)–C(10)–C(5')	110.1(2)	C(9a)–C(10)–C(5')	110.5(2)
C(10a)–C(10)–C(2')	109.3(2)	C(9a)–C(10)–C(2')	113.6(2)
C(5')–C(10)–C(2')	102.9(2)	C(5a)–C(9a)–C(9)	116.7(3)
C(5a)–C(9a)–C(10)	123.3(3)	C(9)–C(9a)–C(10)	119.9(3)
C(8)–C(9)–C(9a)	122.4(3)	C(9)–C(8)–C(7)	120.0(4)
C(6)–C(7)–C(8)	118.8(3)	C(7)–C(6)–C(5a)	122.1(3)
C(6)–C(5a)–C(9a)	120.1(3)	C(6)–C(5a)–C(5)	117.2(3)
C(9a)–C(5a)–C(5)	122.7(3)	N(4)–C(5)–C(5a)	111.3(2)
C(2")–C(1")–C(6")	117.4(3)	C(2")–C(1")–C(2)	121.4(3)
C(6")–C(1")–C(2)	121.1(3)	C(5")–C(6")–C(1")	120.7(3)
C(6")–C(5")–C(4")	120.6(3)	C(3")–C(4")–C(5")	119.5(4)
C(4")–C(3")–C(2")	120.7(3)	C(3")–C(2")–C(1")	121.1(3)
C(3')–C(2')–C(10)	106.2(2)	C(4')–C(3')–C(2')	106.9(3)
C(3')–C(4')–C(5')	110.0(3)	C(4')–C(5')–C(10)	108.1(3)

EXPERIMENTAL

IR spectra of the compounds in KBr disks were recorded with a Pye-Unicam SP-300 apparatus. ^{1}H and ^{13}C NMR spectra were recorded with Varian VXR-300 (300 MHz) and Bruker WP-100 SY (100 MHz) spectrometers with TMS as internal standard. Compounds **3b-e**, **4a**, **7**, **8a-c**,**e**, **9a-c**, **10**, and **11** were recrystallized from ethanol, **4c** from DMF, **3a**, **4d**, **8d**, **9c**,**d** from acetic acid, **4b** from dioxane, and **8f**, **9e** from 2-propanol.

X-ray crystallographic analysis of compound **9a** was carried out on Siemens P3/PC automatic diffractometer (λMoKα, graphite monochromator, θ/2θ scanning, $2\theta_{max}$ = 50°) with measurement of 2685 independent reflexions (R_{int} 0.04). Crystals of compound **9a**, $C_{20}H_{19}N_3$, were monoclinic; at 20°C: a = 9.631(4), b = 9.228(3), c = 18.910(8) Å; β = 99.86(3)°; V = 1656(1) Å^3; M_r 301.38; Z = 4; space group $P2(1)/n$; d_{calc} 1.209 g/cm^3; μ(MoKα) = 0.073 mm^{-1}; $F(000)$ = 640. The structure was solved by direct method using the SHELX97 suite of programmes [14]. Positions of the hydrogen atoms were determined from electron density difference syntheses and refined by the "rider" model with U_{iso} = 1.2 U_{equiv} of the non-hydrogen atom bonded to the hydrogen atom. The structure was refined with respect to F^2 by full-matrix least-squares method in the anisotropic approximation for all non-hydrogen atoms to wR_2 = 0.184 for 2685 reflexions (R_1 = 0.062 for 1405 reflexions with $F > 4\sigma(F)$, S = 0.91).

Hydrobromides of 2-Arylcarboxamido-1,4-dihydroisoquinolin-3(2H)-amines (3). Mixture of bromo nitrile **1** (0.63 g, 3 mmol) and arylcarbohydrazide **2** (3 mmol) in dioxane (10 ml) was boiled for 6h, cooled, the crystalline product was separated, washed with dioxane and recrystallized from the relevant solvent.

In the case of compound **3d** the raw product was filtered off and boiled in acetone (15 ml) for 8 h, the insoluble residue was filtered off, washed with acetone, and recrystallized from ethanol.

Hydrobromide of 2-(2-Acetoxyphenyl)carboxamido-1,4-dihydroisoquinolin-3(2H)-imine (3e). Hydrobromide **3c** was boiled for 0.5 h in acetic anhydride (7 ml). The precipitate which separated from the cooled reaction mixture was filtered off and recrystallized from ethanol.

2-Aryl-5,10-dihydro[1,2,4]triazolo[1,5-*b*]isoquinolines (4). Mixture of bromo nitrile **1** (0.63 g, 3 mmol), hydrazide **2** (3 mmol), and sodium acetate (0.99g, 12 mmol) in dioxane (10 ml) was boiled for 13 h, cooled, the reaction mixture was diluted twice with water, the precipitate was filtered off, washed with water, and recrystallized from the relevant solvent.

Boiling hydrobromid **3** (1.5 mmol) in DMF (7 ml) in the presence of sodium acetate (0.49 g, 6 mmol) for 6 h, followed by treatment of reaction mixture with water, and filtration of the precipitate gave compounds **4a-d** in yields of 45 (**4a**), 48 (**4b**), 50 (**4d**), and 45% (**4d**).

Compound **4d** was obtained in 20% yield by heating hydrobromide **3d** (1.5 mmol) in $POCl_3$ (2 ml) for 8 h. The cooled reaction mixture was evaporated, diluted with water and neutralized with ammonium hydroxide solution. The precipitate was filtered off , washed with water, and recrystallized from acetic acid.

Hydrobromide of 2-(5-Bromo-2-hydroxyphenyl)carboxamidospiro[isoquinoline-4(1H),1'-cyclopentan]-3(2H)-imine (7). Mixture of bromo nitrile **6** (0.79 g, 3 mmol) and 5-bromosalicylic acid hydrazide (0.69 g, 3 mmol) in dioxane (10 ml) was boiled for 6 h, cooled, the precipitated crystalline substance was filtered off, washed with dioxane, and recrystallized from ethanol. Yield 0.95 g (66%); mp 232°C (EtOH). IR spectrum, ν, cm^{-1}: 1640, shoulder 1660 (C=N, C=O); shoulder 3030, 3070, 3240 (NH, OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.7-2.5 (8H, m, –$(CH_2)_4$–); 4.9 (2H, s, CH_2N); 6.1 (1H, d, J_o = 8, C(3")H); 6.35-6.4 (4H, m, H arom); 6.65 (1H, dd, J_o = 8, J_m = 2.5, C(4")H); 7.0 (1H, d, J_m = 2.5, C(6")H); 9.28 (1H, s, N^+H); 9.35 (1H, s, N^+H); 11.42 (2H, s NH, OH). Found, %: C 48.59; H 4.35; Br 33.45; N 9.66. $C_{20}H_{20}BrN_3O_2$·HBr. Calculated, %: C 48.51; H 4.27; Br 32.27; N 8.49.

2-Aryl-2,3,5,6-tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-*b*]isoquinoline]s (8). Mixture of bromonitrile **5** (0.84 g, 3 mmol), hydrazide **2** (3 mmol) and sodium acetate (0.99g, 12 mmol) in dioxane (10 ml) was boiled for 12 h, cooled, diluted with twice as much water, the precipitate was filtered off, washed with water, and recrystallized from ethanol.

2-Arylspiro[[1,2,4]triazolo[1,5-*b*]isoquinoline-10(5H),1'-cyclopentane]s (9) were prepared analogously from bromo nitrile **6**. In addition, compounds **8a** and **9a** were obtained in 48 and 50% yields by heating a mixture respectively of compound **10** or **11** (2 mmol) and benzoyl chloride (0.26 ml, 22 mmol) in DMF (7 ml) in the presence of triethylamine (1 ml) for 2 h. The solvent was removed in vacuum, the residue was treated with water, then potassium carbonate solution, the solid substance was filtered off, washed with water, and recrystallized.

Compound 9a. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 26.4 (C(3')H_2, C(4')H_2); 42.1 (C(2')H_2, C(5')H_2); 46.6 (C_{spiro}); 48.6 (C(5')H_2); 125.7 (C(3")H), C(5")H); 128.6 (C(2")H, C(6")H); 126.1, 126.2, 126.5, 126.1, 128.9 (remaining C_{arom}H); 129.0, 131.2, 140.3 (carbons not bonded to H, C(1"), C(5a), C(9a)); 159.8, 160.4 (C atoms of triazole ring).

Hydrobromide of 3-Imino-2,3',3,3',5',6'-hexahydrospiro[isoquinoline-4(1H),4'-4H-pyran]-2-amine (10). 85% hydrazine hydrate (0.83 ml, 17 mmol) was added to solution of bromo nitrile **5** (0.84 g, 3 mmol) in dioxane (10 ml), the reaction mixture was boiled for 3 h, then poured on ice. The precipitate was filtered off and recrystallized from ethanol. Yield of hydrobromide **10** 0.68 g (73%); mp 312°C (EtOH). IR spectrum, ν, cm^{-1}: 1680 (C=N); 3120, 3170, 3220, 3280 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.0-2.45 (4H, m, C(CH_2)–); 3.6-4.0 (4H, m, O$(CH_2)_2$); 4.95 (2H, s, CH_2N); 5.4 (2H, br. s, N–NH_2); 7.4-7.7 (4H, m, H arom); 8.9 (2H, br. s, N^+H_2). Found, %: C 50.10; H 5.90; Br 26.06; N 13.26. $C_{13}H_{17}N_3O$·HBr. Calculated, %: C 50.01; H 5.81; Br 25.59; N 13.46.

Hydrobromide of 3-Imino-2,3-dihydrospiro[isoquinoline-4(1H),1'-cyclopentan]-2-amine 11 was obtained analogously from bromo nitrile **6** in 0.63 g (71%) yield. M.p. 268°C (EtOH). IR spectrum, ν, cm^{-1}: 1660 (C=N); 3120, 3240, 3280 (NH). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 1.75-1.95 (4H, m, C(3')H_2, C(4')H_2); 2.0-2.15 (2H, m, C(2')H, C(5')H); 2.20-2.40 (2H, m, C(2')H, C(5')H); 4.89 (2H, s, CH_2N); 5.78 (2H, s, N–NH_2); 7.34 (2H, m, H arom), 7,39 (2H, m, H arom); 8.38 (2H, s, N^+H_2). Found, %: C 52.82; H 6.20; Br 27.36; N 13.99. $C_{13}H_{17}N_3$·HBr. Calculated, %: C 52.71; H 6.12; Br 26.98; N 14.19.

Hydrobromide of 2-Methyl-2,3,5,6-tetrahydrospiro[4H-pyran-4,10'(5'H)-[1,2,4]triazolo[1,5-*b*]-isoquinoline] (8e). Mixture of hydrobromide **10** (0.62 g, 2 mmol) in acetic anhydride (7 ml) was boiled for 12 h. The precipitate was filtered off and recrystallized from propanol-2.

Hydrobromide of 2-Methylspiro[[1,2,4]-triazolo[1,5-*b*]isoquinoline-10(5H),1'-cyclopentane] (9e) was prepared analogously from hydrobromide **11**.

2,3,5,6-Tetrahydrospiro[4H-pyran-4',10(5H)-[1,2,4]triazolo[1,5-*b*]isoquinoline] (8f). Mixture of hydrobromide **10** (0.62 g, 2 mmol) and triethyl orthoformate (0.33 ml, 2 mmol) in DMF (7 ml) was boiled for 6 h, N-methylmorpholine (1 ml) was then added to the suspension and the mixture was heated for a further 1 h. The cooled reaction mixture was diluted with water, the precipitate formed was filtered off, washed with water, and propanol-2.

REFERENCES

1. V. M. Kisel, E. O. Kostyrko, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.,* 1289 (2002).
2. F. S. Babichev and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.,* 147 (1977).
3. E. M. Gizatullina and V. G. Kartsev, *Khim. Geterotsikl. Soedin.,* 1587 (1993).
4. M. Negwer, *Organic Chemical Drugs and Their Synonyms.* Akademie-Verlag, Berlin (1987).
5. P. Koeckritz, A. Folger, J. Liebscher, D. Huebler, Ger (East) DD 280.108, *Chem. Abstr.,* **114**, 102013 (1991).
6. P. Koeckritz, J. Liebscher, D. Huebler, Ger (East) DD 280.109, *Chem. Abstr.,* **114**, 102014 (1991).
7. P. Koeckritz, J. Liebscher, D. Huebler, Ger (East) DD 280.110, *Chem. Abstr.,* **114**, 81850 (1991).
8. V. M. Kisel', V. A. Kovtunenko, A. K. Tyltin, and F. S. Babichev, *Ukr. Khim. Zh.,* **56**, 749 (1990).
9. A. Gordon and R. Ford, *Handbook of Chemistry* [Russian translation], Mir, Moscow (1976), 200-234.
10. L. Bellamy, *Infrared Spectra of Complex Molecules* [Russian translation], Izd-vo. insotr. lit., Moscow (1963), 385.
11. M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).
12. N. S. Zefirov, V. A. Palyulin, and E. E. Dashevskaya, *J. Phys. Org. Chem.,* **3**, 147 (1990).
13. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.,* **58**, 713 (1989).
14. G. M. Sheldrick, *SHELX-97. PC Version. A System of Computer Programs for the Crystal Structure Solution and Refinement. Rev. 2* (1998).