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CONDENSED ISOQUINOLINES 22*. SYNTHESIS AND PROPERTIES OF 6,11-DIHYDRO-13H-ISOQUINO-[3,2-*b*]QUINAZOLIN-13-ONES

L. M. Potikha

The reaction of 3-haloanthranilic acids with o-bromomethylphenylacetonitrile gave 2-(2-carboxy-6-halophenyl)-1,4-dihydro-3(2H)-isoquinolinium bromides. 2-Chlorophenylisoquinolinium bromides are readily converted into 4-R-6,11-dihydro-13H-isoquino[3,2-b]quinazolin-13-ones by heating >145°C, but 2,4-dibromophenylisoquinolinium bromide only on fusing with anthranilic acid. The effect of the nature and position of substituents in the quinazoline fragment of 7,12-dihydro-5H-isoquino[2,3-a]quinazolin-5-ones on the rate of the rearrangement into 6,11-dihydro-13H-isoquino[3,2-b]quinazol-13-ones has been studied. The oxidation and borohydride reduction of 6,11-dihydro-13H-isoquino[3,2-b]quinazol-13-ones has been studied.

Keywords: anthranilic acid, *o*-bromomethylphenylacetonitrile, 6,11-dihydro-13H-isoquino[3,2-*b*]-quinazol-13-one, rearrangement.

Derivatives of the isoquino[3,2-*b*]quinazoline series are relatively inaccessible and consequently have been little studied. Currently the syntheses of just two derivatives of this heterosystem have been described – 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-6-one [2] and 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (**1**) [3, 4]. Antifungal activity of the latter has been observed [3]. A relatively simple method for the synthesis of derivatives of isoquino[3,2-*b*]quinazolin-13-one **1** consists of the thermal rearrangement of the isomeric derivatives of 7,12-dihydro-5H-isoquino-[2,3-*a*]quinazolin-5-one (**2**) [4, 5]. We have previously studied [1] the reaction of *o*-bromomethylphenylacetonitrile (*o*-BMPA) with anthranilic acids and their esters, by which a series of Ar-substituted isoquino[2,3-*a*]quinazolines were obtained. These, in their turn, opened a route to Ar-substituted isoquino[3,2-*b*]quinazolines, which are difficult to obtain by other methods. In this paper we have studied the characteristics of this reaction, determined by the structure of the substituted anthranilic acids **3a-f**.

As has been shown earlier [6, 7], the reaction of *o*-BMPA with anthranilic acids and their functional derivatives is a multistep process including the formation of 2-aryl-1,4-dihydro-3(2H)-isoquinolinium bromides **4.** In the case of esters of anthranilic acids, isolation of the intermediates was difficult because of their high reactivity which led directly to the cyclic product **2a**. In the case of the acids **3a-c,** formation of the isoquinolinimines **4a-c** was not successfully recorded [1].

* For part 21 see [1].

Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: potiha_l@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, 899-909, June, 2007. Original article submitted March 28, 2006

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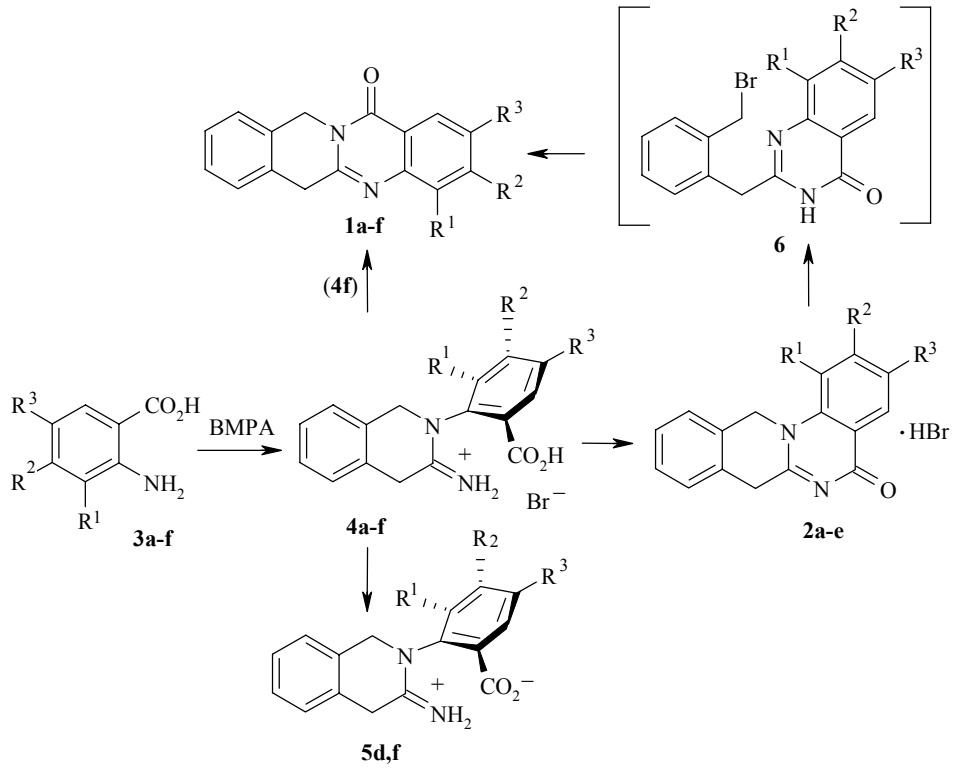
Scheme 1



1–5 a $R^1 = R^2 = R^3 = H$, **b** $R^1 = R^2 = H$, $R^3 = Br$, **c** $R^1 = R^3 = H$, $R^2 = Cl$, **d** $R^1 = Cl$, $R^2 = R^3 = H$, **e** $R^1 = R^3 = Cl$, $R^2 = H$, **f** $R^1 = R^3 = Br$, $R^2 = H$

However it appeared that when *o*-BMPA reacted with the 3-halo-substituted anthranilic acids **3d-f** the reaction stopped at the stage of formation of 2-aryl-1,4-dihydro-3(2H)-isoquinolinium bromides **4d-f**. The salts **4d-f** were formed on fusing an equimolar mixture of the components at 120-140°C or on prolonged (~10 h) boiling in 2-propanol. The yields of compounds **4e** and **4f** from the reaction in solution were lower, but they did not require further purification. Isoquinolinimine hydrobromide **4d** appears to be less stable than salts **4e** and **4f** and all attempts to prepare **4d** in a pure form by recrystallization led to further conversion. Nevertheless, we succeeded in confirming the structure of the product of the reaction of *o*-BMPA with 3-chloroanthranilic acid as 2-(2-carboxy-6-chlorphenyl)-1,4-dihydro-3(2H)-isoquinoliniminium bromide **4d**. 3-Chloro-2-[3-imino-3,4-dihydro-2(1H)-isoquinolinyl]benzoate **5d** was obtained by recrystallization of the reaction mixture from morpholine. The internal salt of structure **5f** was readily obtained by interaction of 4,6-dibromophenylizoquinolinium bromide **4f** with morpholine.

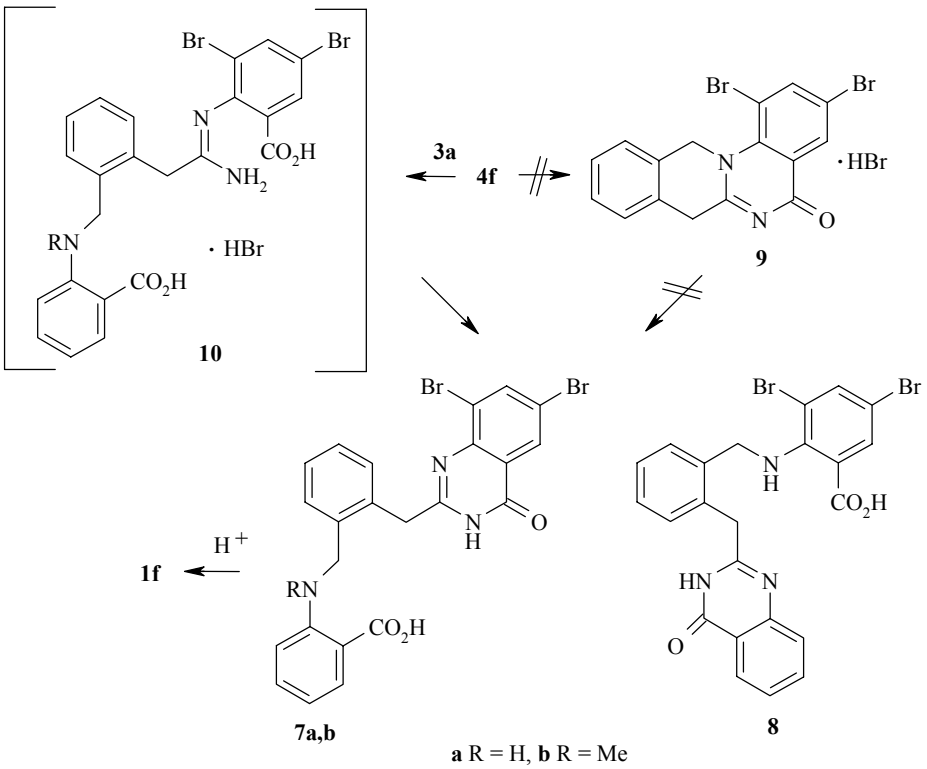
The spectral characteristics of the isoquinolinimines **4e,f** and **5d,f** agreed completely with those of the 2-aryl derivatives prepared previously [6, 7]. Protons of the imonium group are non-equivalent and in the ^{1}H NMR spectra of salts **4e,f** they appear as two sharp singlets at 10.0 and 8.9 ppm and in the spectra of the benzoates **5a,b** as strongly broadened multiplets. The presence of the bulky *o*-substituents in the 2-aryl fragment leads to considerable decrease in rotation about the $N_{(2)}$–Ar bond and consequently to asymmetry of the molecule and nonequivalence of the protons of the methylene groups $C_{(1)}H_2$ and $C_{(4)}H_2$, observed as AB-spin systems with ^2J =15.2 ($C_{(1)}H_2$) and ^2J = 18.4 Hz ($C_{(4)}H_2$). The difference in the chemical shifts for the salts **4e,f** is $\Delta\delta$ ~0.18 ppm, but for the benzoates **5a,b** for the pair of protons $C_{(1)}H_2$ $\Delta\delta$ is greater (~0.3-0.6 ppm) than for the pair $C_{(4)}H_2$ (~0.1 ppm). The latter is explained by the interaction between the polar groups $=NH_2^+$ and $-CO_2^-$ which leads to increased fixation of the 2-aryl substituent. IR spectra of the bromides **4e,f** and the benzoates **5a,b** are

different in the positions of the carbonyl stretching vibrations $\nu_{(C=O)}$ (1700-1712 for **4e,f** and 1600 cm^{-1} for **5a,b**) and also in the spectrum of the latter strong bands in the 1350-1360 cm^{-1} region characteristic for the carboxylate anion.

The isoquinoliniminium bromides **4e,f** are stable compounds which do not undergo change on prolonged boiling in acetic acid or DMF, conditions in which 2-[2-(2-methoxycarbonyl)phenyl]-1,4-dihydro-3(H)-isoquinoliniminium bromides are readily converted into the cyclic products **2** [1, 6]. This is explained in the first place by steric hindrance by the *o*-substituent for optimal positions of the reacting groups, and also the decrease in the carbonyl activity of the acid. We attempted to decrease the effect of the latter by using methyl 3,5-dihaloanthranilic acids in the reaction. However in the reaction conditions (see above) hydrolysis occurred readily to give the salts **4e,f**. Products of the cyclization of bromides **4d,e** were obtained by fusing *o*-BMPA with the acids **3d,e** at temperature greater than 145°C. However the compounds we isolated appeared to be not the isoquinoxinazolines with the angular structure **2d,e**, but the products of their rearrangement – 2,4- R^1,R^2-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones **1d,e**.

Attempts to carry out a similar conversion of 2,6-dibromoisoquinolinimine **4f** into **1f** by this method was unsuccessful. Raising the fusion temperature (>150°C) or carrying out the reaction in higher boiling solvents lead to resin formation. Previously [4] we proposed a mechanism including an intermediate with the structure 2-[2-(bromomethyl)benzyl]-4(3H)-quinazolinone (**6**) to explain rearrangement of isoquino[2,3-*a*]quinazolines **2** into isoquino[3,2-*b*]quinazolines **1**. We attempted to reduce the temperature of fusion by introduction of an additives, which in view of their basic nature might take part in the formation of the product **6**. With this in mind we tested various amines and their hydrohalides and, unexpectedly, achieved success on fusing salt **4f** with N-methylanthranilic acid. Fusing salt **4f** with anthranilic acid **3a,** depending on the reaction time gave compound **1f** in low yield (3 h, 15%) or a mixture (1.5 h) containing isoquinazoline **1f** and 2-({2-[(6,7-dibromo-4-oxo-3,4-dihydro-2-quinazolinyl)methyl]benzyl}amino)benzoic acid (**7a**) (Scheme 2).

Scheme 2



a R = H, **b** R = Me

Table 1. Spectral Characteristics of Isoquino[3,2-*b*]quinazolines **1b-f, 11e**, **12d,f, 14a,b**

Com-pound*	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm ($\varepsilon\times10^3$)	^{1}H NMR spectrum, δ, ppm. (*J*, Hz)			
			ArH	$C_{(11)}H_2$	$C_{(6)}H_2$	other signals
1	2	3	4	5	6	7
1b	1690 (C=O), 1605 (C=N), 1480, 835, 745	275 (68.4), 315*[2] (29.7), 328 (26.8), 355*[2] (16.3)	8.22 (1H, br.s, H-1); 7.84 (1H, br. d, ^oJ = 8.2, H-3); 7.51 (1H, d, ^oJ = 8.2, H-4), 7.45 (1H, d, ^oJ = 7.2, H-10); 7.39 (1H, d, ^oJ = 7.2, H-7); 7.32-7.25 (2H, m, H-8,9)	5.23 (2H, s)	4.15 (2H, s)	—
1c	1672 (C=O), 1601 (C=N), 1582, 777, 745	270*[2] (19.2), 277 (20.2), 305 (9.6), 318 (8.6)	8.10 (1H, d, ^oJ = 8.2, H-1); 7.54 (1H, br. s, H-4); 7.44-7.37 (3H, m, H-3,7,10); 7.29 (2H, m, H-8,9)	5.19 (2H, s)	4.13 (2H, s)	—
1d	1670 (C=O), 1601 (C=N), 1440, 755	273 (33.2), 280*[2] (32.6), 312 (14.7), 325 (12.0)	8.10 (1H, d, ^oJ = 8.0, H-1); 7.84 (1H, d, ^oJ = 6.8, H-3); 7.48-7.39 (3H, m, H-2,7,10), 7.31 (2H, m, H-8,9)	5.24 (2H, s)	4.24 (2H, s)	—
1e	1677 (C=O), 1590 (C=N), 1453, 748	280 (9.1), 322 (3.5), 335 (2.0)	8.03 (1H, d, ^mJ = 2.4, H-1), 7.86 (1H, d, ^mJ = 2.4, H-3), 7.46 (1H, d, ^oJ = 7.2, H-10), 7.43 (1H, d, ^oJ = 6.8, H-7), 7.31 (2H, m, H-8,9)	5.23 (2H, s)	4.2 (2H, s)	—
1f	1680 (C=O), 1595 (C=N), 1450, 740	282 (8.6), 325 (4.2), 340 (2.9)	8.23 (1H, d, ^mJ = 2.0, H-1); 8.16 (1H, d, ^mJ = 2.0, H-3); 7.48 (1H, d, ^oJ = 6.8, H-10); 7.45 (1H, d, ^oJ = 7.0, H-7); 7.32 (2H, m, H-8,9)	5.24 (2H, s)	4.23 (2H, s)	—

Table 1. (continued)

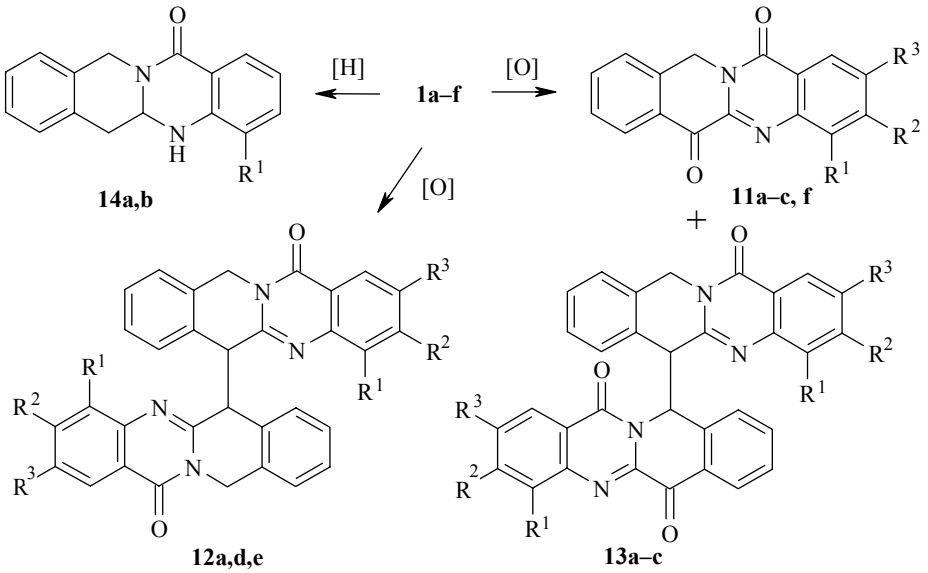
1	2	3	4	5	6	7
11f (85)	—	—	8.35 (1H, d, ^{m}J = 2.0, H-1), 8.20 (1H, d, ^{m}J = 2.0, H-3); 8.14 (1H, d, ^{o}J = 8.0, H-7), 7.80 (1H, t, ^{o}J = 8.0, H-9); 7.72 (1H, d, ^{o}J = 8.0, H-10), 7.59 (1H, t, ^{o}J = 8.0, H-8)	5.36 (2H, s)	—	—
12d (75)	—	—	8.16 (1H, dd, ^{o}J = 8.0, ^{m}J = 1.2, H-1); 7.92 (1H, dd, ^{o}J = 8.0, ^{m}J = 1.2, H-3); 7.53 (1H, t, ^{o}J = 8.0, H-2); 7.44 (2H, m, H-8,9), 7.75 (1H, m, H-10); 7.60 (1H, m, H-7)	5.86, d; 4.72, d; ^{2}J = 16.8	6.70 (1H)	—
12e (80)	—	—	8.09 (1H, d, ^{m}J = 2.0, H-1); 7.97 (1H, d, ^{m}J = 2.0, H-3); 7.74 (1H, m, H-10); 7.59 (1H, m, H-7), 7.44 (2H, m, H-8,9)	5.84, d; 4.72, d; ^{2}J = 17.2	6.69 (1H)	—
14a	3390 (NH), 1605 (C=O), 1480, 1455, 1415, 753	—	7.63 (1H, d, ^{o}J = 8.0, H-1); 7.23-7.17 (5H, m, H-2–H-4, H-8,9); 6.69 (2H, m, H-7,9)	4.97, d; 4.58, d; ^{2}J = 16.5	3.20 (1H, dd, ^{2}J = 15.5, ^{3}J = 10.0); 3.00 (1H, dd, ^{2}J = 15.5, ^{3}J = 4.5)	6.85(1H, s, $N_{(5)}H$); 5.04 (1H, dd, ^{3}J = 4.5, ^{3}J = 10.0, H-5a)
14b	3280 (NH), 1630 (C=O), 1590, 1490, 1440, 1415, 740	—	7.64 (1H, d, ^{o}J = 8.0, H-1); 7.35 (1H, dd, ^{o}J = 8.0, ^{m}J = 1.2, H-3); 7.24-7.13 (4H, m, H-2,7,8,10); 6.68 (1H, t, ^{o}J = 8.0, H-9)	5.14 *[3], m; 4.49, d; ^{2}J = 16.5	3.19 (1H, dd, ^{2}J = 15.2, ^{3}J = 9.6); 3.12 (1H, dd, ^{2}J = 15.2, ^{3}J = 4.4)	6.70 (1H, s, $N_{(5)}H$); 5.14 *[3] (1H, m, H-5a)

* The figures in brackets for compounds **11f** and **12d** are the contents in the mixtures.

*[2] Inflection points are given.

*[3] The signals of H_A-11 and H-5a overlap.

Compound **7a** was isolated from the reaction mixture in pure form and its structure was shown by spectral methods. In the ^{1}H NMR spectrum of acid **7a** three proton signals were observed which underwent exchange with D_2O – a sharp singlet -NHCO (12.79 ppm) and two broad proton signals –CO_2H (12.35) and –CH_2NHAr (8.18 ppm), and in the IR spectrum there were stretching vibrations corresponding to this groups in the 3380-3180 cm^{-1} region. A two-proton singlet in the aliphatic region of the ^{1}H NMR spectrum was assigned to the resonance of the protons of the methylene group. However, it should be noted that these data may correspond also to a compound with the isomeric structure **8**, the formation of which is theoretically possible under conditions when the reactive center for reaction with anthranilic acid is the imino group of salt **4f**. From a comparative analysis of the positions of the aromatic protons of the acid **7a**, the anthranilic acids **3a,f**, and 2-alkylquinazolines [8] corresponding signals were found in strong field at 6.68 (1H, d) and 6.52 (1H, t) for the aromatic protons H-3 and H-5 of the anthranilic acid **3a**, which is the evidence of the formation of the structure **7a**. It was established in a separate experiment that heating compound **7a** in N-methylpyrrolidone-2 in the presence of hydrogen bromide gave isoquinoquinazoline **1f**.



11–13 a $R^1 = R^2 = R^3 = H$, **b** $R^1 = R^2 = H$, $R^3 = Br$, **c** $R^1 = R^3 = H$, $R^2 = Cl$, **d** $R^1 = Cl$, $R^2 = R^3 = H$, **e** $R^1 = R^3 = Cl$, $R^2 = H$, **f** $R^1 = R^3 = Br$, $R^2 = H$; **14 a** $R^1 = H$, **b** $R^1 = Cl$

Formation of isoquinoquinazoline with a linear structure and the acid **7a** on reaction with anthranilic acid – a nucleophile with spatial parameters with decreased probability attack at position 12, which is screened by a bulky bromine atom (1-Br), in the intermediate isoquino[2,3-*a*]quinazoline **9**, we explained by the change in the sequence of the stages of the cyclization and cleavage of the isoquinoline ring during formation of isoquino[3,2-*b*]quinazoline. Cleavage at the initial stage with formation of the intermediate product **10** removes the steric hindrance to cyclization into quinazoline **7** and further formation of **1f**.

The protonic salts of 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one **2a** easily rearrange to **1a** on heating in N-methylpyrrolidone-2 [4]. We have used these conditions to rearrange the previously obtained [1] Ar-substituted isoquino[2,3-*a*]quinazolines. Prolonged boiling of the hydrobromides of isoquino[2,3-*a*]-quinazolines, containing electron-donor substituents (3-Me, 2,3-$(OMe)_2$) led only to a mixture of products of their oxidation. But in the presence of electron-acceptor groups rearrangement occurs considerably faster than in unsubstituted **2a**. The reaction is accompanied by formation of side products of oxidation, such as isoquino[2,3-*a*]quinazoline, and product of its rearrangement. In the case of 3-bromo- and 2-chloro-

izoquino[2,3-*a*]quinazolines **2b,c** products of their rearrangement, 2-bromo- and 3-chloro-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones (**1b** and **1c**) were obtained in pure form on heating in N-methylpyrrolidone-2 for 2-5 min. An increase in the time of heating led to an increase in the amount of products of the oxidation of compounds **1b** and **1c** in the reaction mixture.

The linear structure of compounds **1b-f** was indicated by their spectral characteristics (Table 1) which corresponded to criteria established earlier [4] for distinquishing isomers with linear and angular structures. The carbonyl stretching vibrations, $\nu_{C=O}$, are observed in a higher frequency region (1670-1690 cm^{-1}), while the resonance of protons of methylene groups in the ^1H NMR spectrum occurs at stronger field than for the angular isomers [1, 4]. Comparative analysis of the electronic spectra of isoquinoquinazoline **1a** and the compounds prepared also confirms the correctness of these conclusions. It should be noted that isoquinoquinazolines with angular structures **2a-f** with electron-acceptor substituents in the quinazoline fragment may exist in polar solvents in two isomeric forms, "imine" and "enamine" [1]. Only the "imine" form exists in the linear isomers under these conditions.

We reported earlier [9] that 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one **1a** was relatively easily oxidized by aerial oxygen to 11H-isoquino[3,2-*b*]quinazoline-6,13-dione (**11a**) and the dimers 6,11,6',11'-tetrahydro[6,6']bi[isoquino[3,2-*b*]quinazolinyl]-13,13'-dione (**12a**) and 6,11-dihydro-11'H-[6,11']bi[isoquino-[3,2-*b*]quinazolinyl]-13,6',13'-trione (**13a**). In the case of halo-substituted isoquino[3,2-*b*]quinazolines compounds with the structures **11-13** are formed under milder conditions. For example on fusing *o*-BMPA with

Table 2. Physicochemical Properties of **1b-f**, **4e,f**, **5a,b**, **14a,b**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	Hal	N		
1b	$C_{16}H_{11}BrN_2O$	58.67 58.74	3.34 3.39	24.45 24.42	8.60 8.56	178-180	28
1c	$C_{16}H_{11}ClN_2O$	67.90 67.97	3.83 3.92	12.57 12.54	9.98 9.91	151-153	35
1d	$C_{16}H_{11}ClN_2O$	67.89 67.97	3.88 3.92	12.53 12.54	9.92 9.91	166-168	70
1e	$C_{16}H_{10}Cl_2N_2O$	60.52 60.59	3.10 3.18	22.38 22.36	8.86 8.83	220-223	65
1f	$C_{16}H_{10}Br_2N_2O$	47.28 47.32	2.40 2.48	39.39 39.35	6.98 6.90	225-228	40
4e*[2]	$C_{16}H_{13}BrCl_2N_2O_2$	46.10 46.18	3.09 3.15	19.22 19.20	6.78 6.73	214-215	55
4f	$C_{16}H_{13}Br_3N_2O_2$	39.98 38.05	2.50 2.59	47.45 47.47	5.61 5.55	223-225	60
5a	$C_{16}H_{13}ClN_2O_2$	63.84 63.90	4.28 4.36	11.81 11.79	9.38 9.31	243-245	56
5b	$C_{16}H_{12}Br_2N_2O_2$	45.25 45.31	2.76 2.85	37.70 37.68	6.63 6.61	216-217	70
7a	$C_{23}H_{17}Br_2N_3O_3$	50.80 50.85	3.10 3.15	29.48 29.42	7.79 7.74	299-301	25
14a	$C_{16}H_{14}N_2O$	76.69 76.78	5.58 5.64	—	11.20 11.19	190-192	47
14b	$C_{16}H_{13}ClN_2O$	67.40 67.49	4.55 4.60	12.45 12.45	9.86 9.84	165-167	40

* Recrystallized from DMF (compounds **1b-f, 5b, 7a, 14a,b**) and AcOH (compounds **4e,f, 5a**).

*[2]Analytical date for Cl: found, %: 17.02, calculated, %: 17.04

the acids **3e** and **3f** even at temperatures >155°C mixtures were formed of isoquino[3,2-*b*]quinazolines **1e,f** with products of oxidative dimerization **12d,e**, the contents of which in the reaction mixture reached 75-80% according to ^{1}H NMR data. But heating isoquino[2,3-*a*]quinazolines **2b,c** in N-methylpyrrolidone-2 for more than 5 min gave already a mixture of oxidation products **11b, 13b** and **11c, 13c.** The most easily oxidized of the isoquino[3,2-*b*]quinazolines **1b-f** prepared is 2,4-dibromoisoquinoquinazoline **1f**. In most cases a complex mixtures containing not more than 50% of oxidation products were obtained. Only on fusing isoquinolinimine **4f** with salicylic acid (165-175°C, 2h) the contents of the product of oxidation **11f** in the mixture reach 85% (the ^{1}H NMR spectra of some of the oxidation products are cited in Table 1). Regrettably, all attempts to separate the mixtures obtained were unsuccessful.

It was established previously [1, 10] that 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones **2** were readily reduced with $NaBH_4$ in methanol to 6,6a,7,12-tetrahydro derivatives and the rate of the reaction depended on the fraction of the "imino" form in the mixture of tautomers. We established that linear isoquinoquinazolines can also be reduced with $NaBH_4$, but in this case the reaction occurred considerably more slowly and in more rigid conditions than with the corresponding angular isomers. Only in two cases (**1a** and **1d**) were 5,5a,6,11-tetrahydro-13H-isoquino[3,2-*b*]quinazolin-13-ones **14a,b** obtained when a 10-fold excess of $NaBH_4$ was used in heating acetic acid for 10-15 h. The spectral characteristics of compounds **14a,b** corresponded to those for the isomeric tetrahydroisoquino[2,3-*a*]quinazolines: the protons of the methylene groups are nonequivalent and appear in the ^{1}H NMR spectra as an AB-spin system for $C_{(11)}H_2$ with ^2J = 16.5 Hz and Δδ~0.5 ppm and as an ABX-spin system for $C_{(6)}H_2$ with ^2J = 15.5 Hz and Δδ~0.2 ppm (complete data are given in Table 1). In an attempt to produce tetrahydroderivatives of dihaloisoquino[3,2-*b*]quinazolines **1e,f** complex mixtures were obtained which contained only traces of the expected products of reduction.

EXPERIMENTAL

Melting points were determined with a Boetius type heating block and were not corrected. IR spectra of KBr disks were recorded with a Pye-Unicam SP3-300. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Varian Mercury-400 (400 MHz) instrument. The course of reactions and purity of products were controlled by TLC on Silufol-254 plates. Physicochemical characteristics and elemental analysis data are cited in Table 2.

2-Bromo-6,11-13H-isoquino[3,2-*b*]quinazolin-13-one (1b). A solution of 3-bromo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one hydrobromide (**2b)** (1 g, 2.45 mmol) was prepared by heating in N-methyl-pyrrolidin-2-one (10 ml) and then boiled for 3-4 min. The mixture was cooled and water (20 ml) was added. The precipitate was filtered off and washed with ethanol.

3-Chloro-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (1c) was obtained analogously to **1b** using 2-chloro-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**2c)** (1 g, 2.75 mmol). The solution was boiled for 2 min.

4-Chloro-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (1d). A mixture of *o*-bromo-methylphenylacetonitrile (2.1 g, 10 mmol) and 3-chloroanthranilic acid (**3d**) (1.72 g, 10 mmol) was heated on an oil bath at 120-130° for 2 h. The temperature of the bath was raised to 175°C when the solidified melt melted again. The mixture was then heated for a further 3.5 h until the melt had completely solidified. After cooling, the mixture was dissolved on heating in acetone (5 ml). The precipitate which formed on cooling for 2-3 h was filtred off, and washed with acetone (an additional quantity of product can be obtained after 1 d after evaporation of the acetone). The solid, which contained compound **1d** and 4,4'-dichloro-6,11,6',11'-tetrahydro[6,6']bi[isoquino[3,2-*b*]quinazolinyl]-13,13'-dione (**12d**), dissolved on heating in a mixture of Et_3N (3 ml) and 2-propanol (5 ml). The solvent was evaporated in vacuum and water (10 ml) added. The precipitate was filtered off and washed with water and 2-propanol.

2,4-Dichloro-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (1e). A mixture of *o*-bromomethylphenylacetonitrile (2.1 g, 10 mmol) and 3,5-dichloroanthranilic acid (**3e**) (2.06 g, 10 mmol) was heated on an oil bath at 125-130°C for 2 h. The temperature was increased to 145° and the mixture was heated for a further 2 h. After cooling, the solid was triturated with acetone (5 ml). The solid was filtered, washed with acetone, and dissolved on heating in a mixture of Et_3N (3 ml) and 2-propanol (5 ml). The solvent was evaporated in vacuum and water (10 ml) was added. The solid was filtered off and washed with water and acetone.

2,4-Dibromo-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (1f). A mixture of 2-(2-carboxy-4,6-dibromophenyl)-1,4-dihydro-3(2H)-isoquinoliniminium bromide (**4f)** (1 g, 1.98 mmol) and N-methylanthranilic acid (0.38 g, 2.5 mmol) was heated on an oil bath at 165-170°C for 2 h. After cooling, the melt was triturated with acetone (5 ml). The residue was filtered off and washed with acetone.

2-(2-Carboxy-4,6-R^3,R^1-phenyl)-1,4-dihydro-3(2H)-isoquinoliniminium Bromides 4e,f. A mixture of *o*-bromomethylphenylacetonitrile (2.1 g, 10 mmol) and 3,5-dihaloanthranilic acid **3e,f** (10 mmol) was heated on an oil bath at 125-135°C for 3 h. After cooling the solid was triturated with acetone (5 ml). The precipitate was filtered off and washed with acetone to give isoquinoliniminium bromides **4e,f**.

Compound 4e. IR spectrum, ν, cm^{-1}: 3190 and 3020 (NH_2), 1712 (C=O), 1670 (C=N), 1605, 1212, 766, 679. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.99 (1H, s, NH); 8.94 (1H, s, NH); 8.10 (1H, d, ^mJ = 2.0, H-6'); 8.07 (1H, d, ^mJ = 2.0, H-5'); 7.44-7.33 (4H, m, H-5–H-8); 4.88 (1H, d, ^2J = 15.2, $C_{(1)}\underline{H}_AH_B$); 4.71 (1H, d, ^2J = 15.2, $C_{(1)}H_A\underline{H}_B$); 4.25 (1H, d, ^2J = 18.4, $C_{(4)}\underline{H}_AH_B$); 4.06 (1H, d, ^2J = 18.4, $C_{(4)}H_A\underline{H}_B$).

Compound 4f. IR spectrum, ν, cm^{-1}: 3200 and 3040 (NH_2), 1715(C=O), 1665 (C=N), 1210, 730, 669. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.02 (1H, s, NH); 8.94 (1H, s, NH); 8.31 (1H, d, ^mJ = 2.0, H-6'); 8.24 (1H, d, ^mJ = 2.0, H-5'); 7.44-7.34 (4H, m, H-5–H-8); 4.88 (1H, d, ^2J = 15.2, $C_{(1)}\underline{H}_AH_B$); 4.69 (1H, d, ^2J = 15.2, $C_{(1)}H_A\underline{H}_B$); 4.26 (1H, d, ^2J = 18.4, $C_{(4)}\underline{H}_AH_B$); 4.07 (1H, d, ^2J = 18.4, $C_{(4)}H_A\underline{H}_B$).

3-Chloro-2-[3-Imino-3,4-dihydro-2(1H)-isoquinolinyl]benzoate (5a). A mixture of *o*-bromomethylphenylacetonitrile (2.1 g, 10 mmol) and 3-chloroanthranilic acid (**3d**) (1.72 g, 10 mmol) was heated on an oil bath at 120-130°C for 2 h. After cooling the melt was disolved on heating in acetone (5 ml). The precipitate formed on cooling for several hours was filtered off and washed with acetone. The solid, which contained 2-(2-carboxy-6-chlorophenyl)-1,4-dihydro-3(2H)-isoquinoliniminium bromide (**4d**) was dissolved in DMF, the insoluble impurities were filtered off, and morpholine (3 ml) was added. The precipitate, which formed on cooling, was filtered off, and washed with acetone and DMF. IR spectrum, ν, cm^{-1}: 3420 (br., NH_2), 1650 (C=N), 1579 (CO_2^-), 1553, 1362 (CO_2^-), 763, 734. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.95 (1H, d, ^oJ = 8.0, H-6); 7.76 (1H, d, *J* = 8.0, H-4); 7.57 (1H, ^oJ = 8.0, H-5); 7.36 (4H, m, H-5'–H-8'); 5.00 (1H, d, ^2J =15.2, $C_{(1')}\underline{H}_AH_B$); 4.62 (1H, d, ^2J =15.2, $C_{(1')}H_A\ \underline{H}_B$); 4.10 (1H, d, ^2J = 18.4, $C_{(4')}\underline{H}_AH_B$); 4.00 (1H, d, ^2J = 18.4, $C_{(4')}H_A\underline{H}_B$).

3,5-Dibromo-2-[3-imino-3,4-dihydro-2(1H)-isoquinolinyl)benzoate (5b). Compound **4f** (1 g, 2.0 mmol) was dissolved with heating in morpholine (10 ml). After cooling, water (30 ml) was added, the precipitate was filtered off and washed with water and acetone. IR spectrum, ν, cm^{-1}: 3420 (br., NH_2), 1650 (C=N), 1580 (CO_2^-), 1350 (CO_2^-), 735, 715. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.00 (H, br., NH); 8.65 (1H, br., NH); 8.07 (1H, br. d, H-6); 7.85 (1H, d, ^mJ = 2.4, H-4); 7.31 (4H, m, H-5'–H-8'); 5.13 (1H, d, ^2J =15.2, $C_{(1')}\underline{H}_AH_B$); 4.43 (1H, d, ^2J =15.2, $C_{(1')}H_A\ \underline{H}_B$); 4.15 (1H, d, ^2J = 18.4, $C_{(4')}\underline{H}_AH_B$); 3.96 (1H, d, ^2J = 18.4, $C_{(4')}H_A\underline{H}_B$).

2-({2-[(6,7-Dibromo-4-oxo-3,4-dihydro-2-quinazolinyl)methyl]benzyl}amino)benzoic Acid (7a) was made by the method described for dibromoisoquinoquinazoline **1f**, from anthranilic acid **1a** (0.34 g, 2.5 mmol). IR spectrum, ν, cm^{-1}: 3380-3180 (NH, OH), 1670 (br., C=O), 1610 (C=N), 1570, 1445, 1255 (C–O), 740. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.79 (1H, s, N$\underline{H}$CO); 12.35 (1H, br. s, OH); 8.18 (1H, br. s, $CH_2N\underline{H}$); 8.14 (1H, d, ^mJ = 2.0, H-5''); 8.10 (1H, d, ^mJ = 2.0, H-7''); 7.80 (1H, d, ^oJ = 7.6, H-6); 7.43 (1H, m, H-5'); 7.30 (1H, m, H-4'); 7.20 (3H, m, H-4,3',6'); 6.68 (1H, d, ^oJ = 8.5, H-3); 6.52 (1H, t, ^oJ = 8.0, H-5); 4.80 (2H, s, C$\underline{H}_2$NH), 4.08 (2H, s, C$\underline{H}_2$C=N).

4-R-5,5a,6,11-Tetrahydro-13H-isoquino[3,2-*b*]quinazolin-13-ones (14a,b). To a solution of isoquino-[3,2-*b*]quinazoline **1a,d** (4.02 mmol) in AcOH (15 ml), $NaBH_4$ (1.5 g) was added in portions with stirring and heating over 5 h and heating was continued for a further 5 h. The solvent was evaporated in vacuum. Water (15 ml) was added to the residue and the precipitate which formed was filtered off and washed with water, 20% aqueous soda, and acetone.

REFERENCES

1. L. M. Potikha, V. A. Kovtunenko, and V. M . Kisil, *Khim. Geterotsikl. Soeidin.,* 562 (2007). [*Chem. Heterocycl. Comp.,* **43**, 460 (2007)].
2. E. Schefczik, *Liebigs Ann. Chem.,* **729**, 83 (1969).
3. W. Wendelin, H. Keimelmayr, and M. Huber, *Sci. Pharm.,* **56**, No. 3, 437 (1973).
4. V. M. Kisel, V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, *Dokl. Akad. Nauk*, **306**, 628 (1989)
5. V. M. Kisel, L. M. Potikha, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.,* 131 (2001). [*Chem Heterocycl. Comp.,* **37**, 125 (2001)].
6. V. M. Kisel, V. A. Kovtunenko, A. K. Tyltin, and F. S. Babichev, *Ukr. Khim. Zh.,* **56**, 749 (1990).
7. F. S. Babichev, V. K. Patratii, V. A. Kovtunenko, N. G. Prodanchuk, V. G. Zinchenko, and V. M. Kisel, *Khim.-Farm. Zh.,* **24**, No.5, 32 (1990).
8. V. A. Kovtunenko, T. T. Kucherenko, O. V. Shishkin, and V. M. Kisel, *Khim. Geterotsikl. Soedin.,* 1408 (2002). [*Chem. Heterocycl. Comp*., **38**, 1242 (2002)].
9. L. M. Potikha, V. A. Kovtunenko, A. V. Tarasevich, J. G. Wolf, and Ch. Andre, *Khim. Geterotsikl. Soedin.,* 430 (2007). [*Chem. Heterocycl. Comp.,* **43**, 347 (2007)].
10. V. M. Kisel', V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.,* 389 (1991). [*Chem. Heterocycl. Comp.,* **27**, 316 (1991)].