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CONDENSED ISOQUINOLINES. 21*. CONDENSATION OF *o*-BROMOMETHYLPHENYLACETONITRILE WITH SUBSTITUTED ANTHRANILIC ACIDS

L. M. Potikha, V. A. Kovtunenko, and V. M. Kisil

The reaction of substituted anthranilic acids and esters with o-bromomethylphenylacetonitrile give 2,3-R,R^1-7,12-dihydro-5H-isoquino[2,3-a]quinazolin-5-one hydrobromides. It was found that 7,12-dihydro-5H-isoquino[2,3-a]quinazolin-5-ones can exist in the two tautomeric imine and enamine forms. The tautomeric equilibrium position depends on the nature and position of the substituent in the quinazoline fragment. The borohydride reduction, oxidation, and reaction of 2,3-R,R^1-7,12-dihydro-5H-isoquino[2,3-a]quinazolin-5-ones with electrophilic reagents has been studied.

Keywords: anthranilic acid, *o*-bromomethylphenylacetonitrile, 7,12-dihydro-5H-isoquino[2,3-*a*]-quinazolin-5-one, enamine.

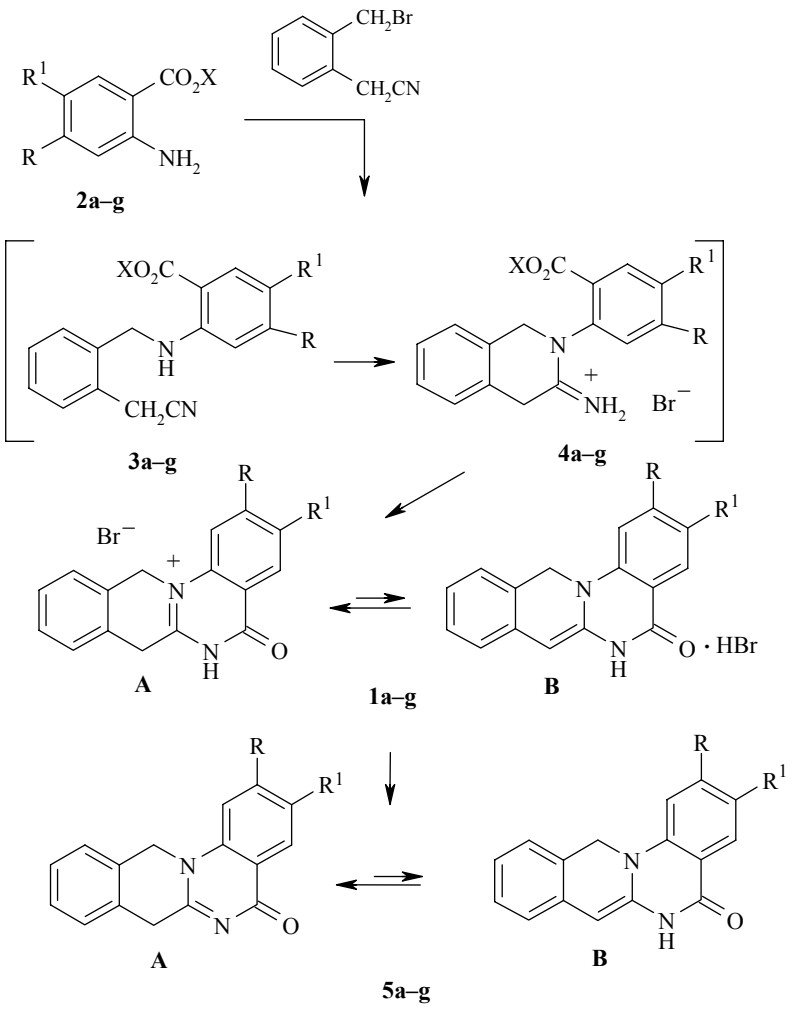
We have previously developed a relatively simple procedure for the synthesis of isoquino[2,3-*a*]quinazoline system derivatives *via* the reaction of *o*-bromomethylphenylacetonitrile (*o*-BMPA) with the ester and nitrile of anthranilic acid. The properties of 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**1**) prepared by this method have been studied in a series of publications [1, 4-10]. Isoquinoquinazoline **1** shows high reactivity towards electrophilic reagents [4-8] being readily reduced by $NaBH_4$ to 6,6a,7,12-tetrahydro derivatives [4, 9] and also readily oxidized to give aromatic derivatives [1, 5, 10]. All of these reactions affecting principally the $N_{(6)}$–$C_{(6a)}$–$C_{(7)}$ triad permitted preparation of a series of isoquino[2,3-*a*]quinazolines substituted at positions 6 and 7. We made attempts to carry out classical aromatic electrophilic substitution reactions. However, because of the high tendency of compound **1** to oxidize not depending on reaction conditions, these experiments led to tarring or to formation of a complex mixture of unidentified products. The only solution to this problem was the use of substituted starting reagents in the synthesis of the isoquinoquinazolines **1**. With this in mind we have studied the interaction of *o*-BMPA with substituted anthranilic acids and their esters.

The reactions were carried out by the previously reported method [2] of melting an equimolar mixture of reagents at 130-150ºC or by heating their solutions in 2-propanol. The use of the unsubstituted anthranilic acid **2c** gives the 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one hydrobromide (**1c**) which was identical in constants and spectroscopic properties with that obtained before. The reaction in this case needed a longer heating time or higher melting temperature and the yield of the target product proved a little lower (by 15-20%) than when using the ester and this is fully consistent with the lowered reactivity when compared with the ester.

* For Communication 20 see [1]

Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: potikha_l@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 562-573, April, 2007. Original article submitted December 1, 2005.

Reaction of *o*-BMPA with substituted anthranilic acids and their esters also gave the target isoquino[2,3-*a*]quinazolines **1b-g** in good yields (50-60%). When the reaction was carried out in 2-propanol the yield of the salts **1b-g** was a little lower but the reaction products did not generally need further purification.



1–5 a R = R^1 = OMe; **b** R = H, R^1 = Me; **c** R = R^1 = H; **d** R = Cl, R^1 = H; **e** R = H, R^1 = Cl; **f** R = H, R^1 = Br; **g** R = CO_2Me, R^1 = H; **a, g** X = OMe, **b–f** X = OH

The nature of the substituents in the anthranilic acids and esters proves to have a marked effect on the yield and structure of the products. It was previously shown that formation of isoquino[2,3-*a*]quinazolines is a multistage process including the formation of the alkylation products **3** and 2-aryl-1,4-dihydro-3(2H)-isoquinoline iminium bromides **4**.

In the case of the anthranilic acid ester the separation of the intermediate structure products **3** and **4** was difficult due to their high reactivity which immediately led to the cyclic product **1c**. For the reaction of *o*-BMPA with other amines it was found [11] that the determining effect on the yield of the isoquinoline imine **4** was the basicity of the amino group, the yield of compound **4** being lower with increased basicity. In turn the likelihood of the cyclization of **4** to **1** is determined by the reactivity of the carboxyl group and this depends on the electronic effects of the substituent. As a consequence of these factors our reaction led to a mixture of methyl

TABLE 1. Spectroscopic Characteristics of the Isoquino[2,3-*a*]quinazolin-5-ones **1a-g, 5a-g, 7a-c, 8a,b, 9a-d**

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz)				
		NH	ArH	$C_{(12)}H_2$, 2H, s	$C_{(7)}H_2$, 2H, s	others signals
1	2	3	4	5	6	7
1a-A	3450 (NH), 1720 (C=O), 1640 (C=N), 1295 (C–O)	—	7.68 (1H, s, H-1), 7.61 (2H, m, H-4,11), 7.43 (3H, m, H-8,9,10)	5.69	4.45	4.16 (3H, s, 2-OCH_3), 3.98 (3H, s, 3-OCH_3)
1b-A	3390 (NH), 1720 (C=O), 1620 (C=N)	—	8.34 (1H, d, ^oJ = 9.2, H-1), 8.11 (1H, br. s, H-4), 7.99 (1H, br. d, ^oJ = 9.2, H-2), 7.61 (1H, m, H-11), 7.42 (3H, m, H-8,9,10)	5.69	4.53	2.57 (3H, s, CH_3)
1c-A	—*	—	8.46 (1H, d, ^oJ = 8.0, H-1), 8.32 (1H, d, ^oJ = 7.8, H-4), 8.17 (1H, t, ^oJ = 7.8, H-3), 7.84 (1H, t, ^oJ = 7.8, H-2), 7.63 (1H, m, H-11), 7.43 (3H, m, H-8,9,10)	5.74	4.56	—
1d-A	3420 (NH), 1715 (C=O), 1610 (C=N)	—	8.52 (1H, br. s, H-1), 8.31 (1H, d, ^oJ = 8.2, H-4), 7.82 (1H, br. d, ^oJ = 8.2, H-3), 7.57 (1H, m, H-11), 7.43 (3H, m, H-8,9,10)	5.67	4.52	—
1d-B (22%)		9.60 br.	7.78 (1H, d, ^oJ = 8.4, H-4), 7.31 (1H, s, H-1), 7.17 (1H, m, H-11), 6.97 (1H, d, *J* = 8.4, H-3), 6.92 (2H, m, H-9,10), 6.61 (1H, m, H-8)	5.19 (3H, br. s)		—
1e-A	(NH), 1730 (C=O), 1640 (C=N)	—	8.52 (1H, d, ^oJ = 9.0, H-1), 8.23 (1H, d, ^mJ = 2.0, H-4), 8.17 (1H, dd, ^oJ = 9.0, ^mJ = 2.0, H-2), 7.61 (1H, m, H-11), 7.42 (3H, m, H-8,9,10)	5.72	4.55	—
1e-B (33%)		9.65 br	7.73 (1H, d, ^mJ = 2.0, H-4), 7.57 (1H, dd, ^oJ = 9.0, ^mJ = 2.0, H-2), 7.30 (1H, d, ^oJ = 9.0, H-1), 7.14 (1H, m, H-11), 6.92 (2H, m, H-9,10), 6.61 (1H, d, ^oJ = 6.4, H-8)	5.20 (3H, br. s)		—
1f-A	3420 (NH), 1700 (C=O), 1625 (C=N)	—	8.42 (1H, d, ^oJ = 9.0, H-1), 8.38 (1H, d, ^mJ = 2.0, H-4), 8.29 (1H, dd, ^oJ = 9.0, ^mJ = 2.0, H-2), 7.62 (1H, m, H-11), 7.43 (3H, m, H-8,9,10)	5.70	4.53	—
1f-B (34%)		9.66 br.	7.89 (1H, d, ^mJ = 2.5, H-4), 7.70 (1H, dd, ^oJ = 8.8, ^mJ = 2.5, H-2), 7.30 (1H, d, ^oJ = 8.8, H-1), 7.15 (1H, m, H-11), 6.93 (2H, m, H-9,10), 6.63 (1H, m, H-8)	5.20 (3H, br. s)		—
1g-A	3400 (NH), 1710 (br., C=O, C=N), 1290 (C–O)	—	8.77 (1H, br. s, H-1), 8.42 (1H, d, ^oJ = 8.0, H-4), 8.29 (1H, br. d, ^oJ = 8.0, H-3), 7.67 (1H, m, H-11), 7.42 (3H, m, H-8,9,10)	5.77	4.58	4.02 (3H, s, OCH_3)
1g-B (40%)		9.72 br.	7.89 (1H, d, ^oJ = 7.6, H-4), 7.68 (1H, s, H-1), 7.54 (1H, d, ^oJ = 7.6, H-3), 7.23 (1H, d, ^oJ = 6.4, H-11), 6.93 (2H, m, H-9,10), 6.64 (1H, d, ^oJ = 7.6, H-8)	5.24 (3H, br. s)		3.94 (3H, s, OCH_3)
5a-A	1600 (br., C=O, C=N), 1500, 1250 (C–O)	—	7.53 (1H, dd, ^oJ = 7.2, ^mJ = 2.0, H-11), 7.47 (1H, s, H-4), 7.41 (1H, dd, ^oJ = 7.2, ^mJ = 2.0, H-8), 7.37–7.33 (3H, m, H-1,9,10)	5.41	4.13	4.05 (3H, s, 2-OCH_3), 3.90 (3H, s, 3-OCH_3)

TABLE 1. (continued)

1	2	3	4	5	6	7
5b-A	3420, 1630 (C=O), 1600 (C=N), 1520, 1470	—	7.91 (1H, s, H-4), 7.82 (1H, d, ^{o}J = 8.0, H-1), 7.63–7.31 (5H**, m, H-2, H-8–H-11), 6.82 (1H, m, H-10), 6.71 (1H, m, H-8)	5.34	4.12	2.47 (3H, s, CH_3)
5b-B (24%)		10.74	7.63-7.31 (2H*[2], m, H-1, H-4), 7.03 (3H, m, H-2,9,11), 6.82 (1H, m, H-10), 6.71 (1H, m, H-8)	4.91	4.89 (1H, s)	2.32 (3H, s, CH3)
5c-A	—*	—	8.10 (1H, d, ^{o}J = 7.6, H-4), 7.97 (1H, d, ^{o}J = 8.0, H-1), 7.86 (1H, t, ^{o}J = 8.0, H-2), 7.52-7.31 (5H, m, H-3, H-8–H-11)	5.39	4.15	—
5c-B (31%)		10.83	7.80 (1H, d, ^{o}J = 7.2, H-4), 7.58 (1H, t, ^{o}J = 8.0, H-2), 7.20 (1H, d, ^{o}J = 8.0, H-1), 7.08-7.00 (3H, m, H-3,9,11), 6.88 (1H, t, ^{o}J = 6.8, H-10), 6.76 (1H, d, ^{o}J = 7.2, H-8)	5.03	4.93 (1H, s)	—
5d-A	3440 (NH), 1635 (C=O), 1585 (C=N), 1510, 1440, 745	—	8.09 (2H, m, H-1, H-4), 7.51-7.45 (2H, m, H-3,11), 7.39 (1H, d, ^{o}J = 7.6, H-8), 7.32 (2H, m, H-9,10)	5.37	4.15	—
5d-B (54%)		10.91	7.73 (1H, d, ^{o}J = 8.2, H-4), 7.21 (1H, s, H-1), 7.06 (1H, d, ^{o}J = 8.0, H-11), 7.02 (1H, t, ^{o}J = 8.0, H-9), 6.94 (1H, d, ^{o}J = 8.0, H-3), 6.87 (1H, t, ^{o}J = 8.0, H-10), 6.75 (1H, d, ^{o}J = 7.6, H-8)	5.01	4.95 (1H, s)	—
5e-A	1645 (C=O), 1610 (C=N), 1510, 1475, 1345, 760	—	8.02 (1H, d, ^{m}J = 2.8, H-4), 7.80 (1H, dd, ^{o}J = 8.8, ^{m}J = 2.8, H-2), 7.49 (1H, d, ^{o}J = 8.8, H-1), 7.39-7.27 (4H, m, H-8–H-11)	5.37	4.14	—
5e-B (35%)		10.96	8.02 (1H, d, ^{o}J = 8.2, H-2), 7.49 (1H, d, ^{m}J = 2.8, H-4), 7.17 (1H, d, ^{o}J = 8.2, H-1), 7.02 (2H, m, H-9,11), 6.86 (1H, t, ^{o}J = 7.6, H-10), 6.74 (1H, d, ^{o}J = 7.6, H-8)	4.99	4.94 (1H, s)	—
5f-A	1623 (C=O), 1585 (C=N), 1510, 1485, 1460, 745	—	8.15 (1H, s, H-4), 7.92 (2H, m, H-1,2), 7.47 (1H, d, ^{o}J = 6.4, H-11), 7.38 (1H, d, ^{o}J = 6.8, H-8), 7.31 (2H, m, H-9,10)	5.35	4.12	—
5f-B (38%)		10.95	7.82 (1H, d, ^{m}J = 2.0, H-4), 7.62 (1H, dd, ^{o}J = 8.8, ^{m}J = 2.0, H-2), 7.10 (1H, d, ^{o}J = 8.8, H-1), 7.01 (2H, m, H-9,11), 6.85 (1H, t, ^{o}J = 7.2, H-10), 6.73 (1H, d, ^{o}J = 6.8, H-8)	4.98	4.93 (1H, s)	—
5g-A	3420 (NH), 1720 (C=O), 1630 (C=O), 1590 (C=N), 1245 (C–O), 755	—	8.44 (1H, s, H-1), 8.19 (1H, d, ^{o}J = 7.6, H-4), 7.87 (1H, d, ^{o}J = 7.6, H-3), 7.57 (1H*[2], m, H-11), 7.39-7.30 (3H, m, H-8,9,10)	5.43	4.16	3.98 (3H, s, OCH_3)
5g-B (46%)		11.01	7.99 (1H, d, ^{o}J = 7.2, H-4), 7.57 (1H*[2], m, H-1), 7.51 (1H, d, ^{o}J = 7.2, H-3), 7.12 (1H, d, ^{o}J = 6.0, H-11), 7.02 (1H, m, H-9), 6.87 (1H, m, H-10), 6.75 (1H, d, ^{o}J = = 6.4, H-8)	5.04	4.94 (1H, s)	3.92 (3H, s, OCH_3)

TABLE 1. (continued)

1	2	3	4	5	6	7
7a	1720 (C=O), 1605 (C=N), 1515, 1290 (C–O)	—	7.93 (1H, d, ^{o}J = 8.0, H-8), 7.74 (1H, s, H-1), 7.70 (1H, d, ^{o}J = 8.0, H-11), 7.60 (1H, s, H-4), 7.50 (2H, d, ^{o}J = 8.4, H-2',6'), 7.41 (1H, t, ^{o}J = 8.0, H-10), 7.33 (1H, t, ^{o}J = 8.0, H-9), 6.62 (2H, d, ^{o}J = 8.4, H-3',5')	5.76	—	7.78 (1H, s, =CHAr), 4.20 (3H, s, 2-OCH_3), 3.99 (3H, s, 3-OCH_3), 3.07 (6H, s, $N(CH_3)_2$)
7b	1720 (C=O), 1600 (C=N), 1515, 1325	—	8.38 (1H, d, ^{o}J = 9.0, H-1), 8.17 (1H, d, ^{m}J = 2.4, H-4), 8.05 (1H, dd, ^{o}J = 9.0, ^{m}J = 2.4, H-2), 7.70 (2H, d, ^{o}J = 8.0, H-8,11), 7.51 (2H, d, ^{o}J = 8.8, H-2',6'), 7.39 (1H, t, ^{o}J = 8.0, H-10), 7.31 (1H, t, ^{o}J = 8.0, H-9), 6.64 (2H, d, ^{o}J = 8.8, H-3',5')	5.58	—	7.82 (1H, s, =CHAr), 3.07 (6H, s, $N(CH_3)_2$)
7c	1730 (C=O), 1640, 1590 (C=N), 1515, 1255 (C–O), 750	—	8.73 (1H, s, H-1), 8.37 (1H, d, ^{o}J = 8.0, H-4), 8.19 (1H, d, ^{o}J = 8.0, H-3), 7.79 (1H, d, ^{o}J = 8.0, H-8), 7.71 (1H, d, ^{o}J = 8.0, H-11), 7.53 (2H, d, ^{o}J = 8.8, H-2',6'), 7.41 (1H, t, ^{o}J = 8.0, H-10), 7.32 (1H, t, ^{o}J = 8.0, H-9), 6.65 (2H, d, ^{o}J = 8.8, H-3',5')	5.66	—	7.82 (1H, s, =CHAr), 4.03 (3H, s, OCH_3), 3.06 (6H, s, $N(CH_3)_2$)
8a	1645 (C=O), 1615 (C=O), 1595, 1550, 1260 (C–O)	14.90	7.43 (1H, s, H-4), 7.40 (1H, d, ^{o}J = 8.0, H-8), 7.33 (1H, s, H-1), 7.27 (2H, m, H-10,11), 7.09 (1H, t, ^{o}J = 8.0, H-9)	5.15	—	4.04 (3H, s, 2-OCH_3), 3.89 (3H, s, 3-OCH_3), 2.47 (3H, s, -$COCH_3$)
8b	1680 (C=O), 1595, 1550, 760	14.67	8.09 (1H, d, ^{m}J = 2.0, H-1), 8.03 (1H, d, ^{o}J = 8.0, H-4), 7.39 (1H, d, ^{o}J = 7.6, H-8), 7.32 (1H, dd, ^{o}J = 8.2, ^{m}J = 2.0, H-3), 7.27 (2H, m, H-10,11), 7.11 (1H, t, ^{o}J = 8.0, H-9)	5.14	—	2.48 (3H, s, -$COCH_3$)
9a	3220 (NH), 3100, 2940, 1675 (br., C=O), 1250 (C–O)	8.09 br.	7.24 (2H, m, H-4,11), 7.20-7.11 (3H, m, H-8,9,10), 6.55 (1H, s, H-1)	4.86 (d), 4.14 (d, ^{2}J = 16.4)	3.04 (1H, m)	4.79 (1H, m, H-6a), 3.87 (3H, s, 2-OCH_3), 3.74 (3H, s, 3-OCH_3)
9b	3220 (NH), 3100, 2940, 1675 (br., C=O), 1500	8.31 br.	7.56 (1H, br. s, H-4), 7.22-7.07 (5H, m, H-2, H-8–H-11), 6.83 (1H, d, ^{o}J = 8.0, H-1)	4.77 (d), 4.15 (d, ^{2}J = 16.8)	3.02 (1H, m)	4.81 (1H, m, H-6a), 2.26 (3H, s, CH_3)
9c	3200 (NH), 3100, 2950, 1675 (br., C=O), 1490	8.45 br.	7.80 (1H, br. s, H-4), 7.44 (1H, br. d, ^{o}J = 8.8, H-2), 7.23-7.08 (4H, m, H-8–H-11), 6.90 (1H, d, ^{o}J = 8.8, H-1)	4.80 (d), 4.23 (d, ^{2}J = 16.6)	3.03 (1H, m)	4.91 (1H, m, H-6a)
9d	3200 (NH), 3080, 2940, 1680 (br., C=O), 1605, 755	8.45 br.	7.70 (1H, d, ^{o}J = 8.4, H-4), 7.26-7.09 (4H, m, H-8–H-11), 6.96 (1H, br. s, H-1), 6.77 (1H, br. d, ^{o}J = 8.4, H-3)	4.84 (d), 4.25 (d, ^{2}J = 16.6)	3.04 (1H, m)	4.94 (1H, m, H-6a)

* Data given in [2].

*[2] Superimposed signals for forms **A** and **B**.

2-{[2-(cyanomethyl)benzyl]amino}-4,5-dimethoxybenzoate (**3a**) and 2-[4,5-dimethoxy-2-(carbomethoxy)-phenyl]-1,4-dihydro-3(2H)-isoquinoline iminium bromide (**4a**) when the 4,5-dimethoxyanthranilate **2a** was used in 2-propanol. The reaction of *o*-BMPA with ester **2a** occurs rapidly. After refluxing for 15 min a precipitate containing compounds **3a** and **4a** (1 : 2) is formed and further heating of the reaction mixture does not lead to a marked change in its composition. Formation of products **3a** and **4a** was established from their ^{1}H NMR spectroscopic data in which there are observed proton signals for the imonium group of compound **4a** (s, 9.51 and s, 8.27 ppm) and methylene groups $C_{(1)}H_2$ and $C_{(4)}H_2$ as AB spin systems with ^2J = 15.2 (d, 4.98 and d, 4.72 ppm) and ^2J = 18.4 Hz (d, 4.22 and 4.06 ppm) respectively. The broad signal at 6.16 ppm corresponds to the resonance of the amino group proton of the benzylaminobenzoate **3a** and the two-proton singlets at 4.54 and 4.08 ppm to the resonance of the CH_2NH and CH_2CN methylene groups. The signals for the aromatic protons at 7.57-7.26 ppm and methoxy groups at 3.92-3.55 ppm are readily assigned in both compounds. The position and multiplicity of the signals for the aliphatic protons are fully in agreement with the characteristics previously shown for related structures [11]. The target 2,3-dimethoxyisoquino[2,3-*a*]quinazoline **1a** was obtained when attempting to separate the mixture **3a, 4a** by crystallization from acetic acid or DMF.

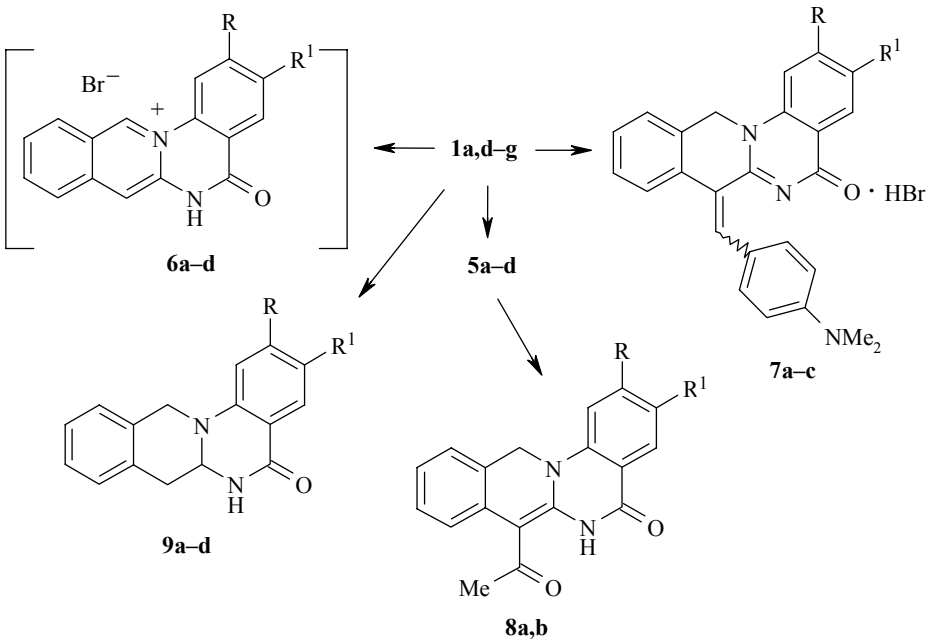
The presence of powerful electron-acceptor groups in the anthranilic acid markedly lowers the likely formation of alkylation product **3** and, correspondingly, the formation of the target isoquinoquinazoline **1**. Hence when the reaction of *o*-BMPA with 5-nitroanthranilic acid in 2-propanol was carried out even after 30 h refluxing only traces of the target 3-nitroisoquino[2,3-*a*]quinazoline were formed in the reaction mixture (according to TLC and ^{1}H NMR). Further heating led only to an increase in the amount of side products and the melting at 150ºC led to tarring.

In all of the other examples (**2b,d-g**) given in the Scheme the formation of intermediate products of type **3** and **4** were not registered and the difference in yields of salts **1** amounted to not more than 10%. Treatment of the salts **1a,b,d-g** with Et_3N gave the free bases **5a,b,d-g**.

The spectroscopic characteristics (IR, ^{1}H NMR spectra of solutions of the salts in CF_3CO_2D and the bases in $CDCl_3$) for the 4-substituted isoquinoquinazolines **1a,b,d-g** agreed overall with those of the unsubstituted isoquinoquinazoline **1c** [2]. We have previously reported [5-7] the presence of enamine properties for compound **1c** (ready proton/deuterium exchange at $C_{(6)}$, ability to take part in alkylation and acylation reactions at $C_{(6)}$ etc.) but a clear establishment of the enamine form was unsuccessful. A study of the ^{1}H NMR spectra of the salts **1a-g** and their free bases **5a-g** in DMSO-d_6 showed that these compounds can exist in polar aprotic solvents in the two tautomeric imine and enamine forms as indicated by a double set of signals corresponding to the predominant imine (**A**) and enamine (**B**) forms (full data is given in Table 1). Base **5** has a clearer tendency to tautomerism under these conditions. The ratio of the two **A** and **B** forms depends on the nature and position of the substituent in the quinazoline fragment, moreover the effect of the latter factor proved different for salt **1** and base **5**. These compounds are placed in order of increasing percentage of enamine form **B** content in the mixture in Table 1. The amount of form **B** correlates well with the general Hammett σ-constant values for the substituents [12] with respect to the bridging nitrogen atom $N_{(13)}$ for the bases and the $C_{(5)}$=O carbonyl group in the salts. Change in temperature also affects the ratio of these two forms. An increase in temperature leads to a small decrease in the content of form **B** in the mixture. A similar prototropic effect and corresponding temperature dependence has been observed earlier [13] for substituted 2-alkylquinazolin-4-ones but in a less clear form.

In the aromatic proton region the ^{1}H NMR spectra of the protonated salts **1** show several changes from the spectra of the bases **5** in terms of the relative position of the signals for the H-1 and H-4 protons. In the spectra of salt **1A** the H-1 signal is observed to low field of H-4 but in form **B** these are reversed. This is explained well by realization of the structure 6H-isoquino[2,3-*a*]quinazolin-5-one with protonation **1A** while the 3H form is more stable for quinazolin-4-ones [14]. Support for the 6H form of salt **1A** also comes from the observed difference in the chemical shifts of the H-11 protons (Δδ about 0.45 ppm) and of $C_{(12)}H_2$ (about 0.5 ppm) of forms **A** and **B**, which for **1A** is found to lower field than **1B**.

It turns out that the nature and position of the substituent in the quinazoline ring markedly affects the chemical properties in the isoquinoquinazolines obtained **1a-g** and **5a-g**. We have found that salts **1d-g** are unstable in DMSO solution and are readily oxidized to give mixtures of products, the main component of which (about 60-80%) is the 2-R- or 3-R-5-oxo-5H,6H-isoquino[2,3-*a*]quinazolin-13-ium bromide **6a-d**. Moreover, the rate of oxidation (from about 3 h for **1g** to about 8 h for **1d**) is fully in agreement with the dependence found for the ratio of the **A** and **B** tautomeric forms in solutions of the salts (Table 1). It was found that dehydrogenation of salt **1c** is observed under more rigid conditions (refluxing in benzonitrile) [1]. The formation of a compound of structure **6** is indicated by the presence in the ^{1}H NMR spectra of the mixture of singlet protons for H-12 (11.59, **6a**; 11.91, **6b,c**, 11.78 ppm, **6d**), H-1 (9.70 ppm), and for H-11 (d, 8.60 ppm, **6a** and 9.0-9,12 ppm, **6b-d**) and H-7 (8.3-8.5 ppm) in the region characteristic of the aromatic salts of isoquino[2,3-*a*]quinazoline [1, 10].



6 a R = CO_2Me, R^1 = H; **b** R = H, R^1 = Cl; **c** R = H, R^1 = Br; **d** R = Cl, R^1 = H;
7 a R = R^1 = OMe; **b** R = H, R^1 = Cl; **c** R = CO_2Me, R^1 = H; **8 a** R = R^1 = OMe; **b** R = Cl, R^1 = H; **9 a** R = R^1 =OMe, **b** R = H, R^1 = Me; **c** R = H, R^1 = Br; **d** R = Cl, R^1 = H

The observed dependence for the rate of reaction of salts **1d-g** is also observed for their condensation with *p*-dimethylaminobenzaldehyde in acetic anhydride. A short heating of the mixture of reagents (3 min for **1b**, 10 min for **1e**, 30 min for **1a**) leads to the formation of the dark-violet colored 7-{[4-dimethyl-amino]phenyl]methylene}-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones **7a-c**.

We have previously shown [5] that the isoquinoquinazoline **5c** readily forms the products of $C_{(7)}$-acylation when heated with carboxylic acid chlorides in anhydrous pyridine and that this reaction can come about under milder conditions. Hence the isoquinoquinazolines **5a,b** are readily acylated by acetic anhydride in the presence of AcONa to give good yields of the 7-acetyl derivatives **8a,b**. The reaction is not accompanied by the formation of side products but difference of the behavior of the bases **5a** and **5b** involves only the reaction time (greatest for **5a** and least for **5d**, see Experimental) and it correlates with the content of enamine form **B** for the starting bases **5**.

TABLE 2. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, % (method)
		C	H	Br (Cl)	N		
1a	$C_{18}H_{17}BrN_2O_3$	55.46 / 55.54	4.10 / 4.40	20.54 / 20.53	7.30 / 7.20	272-273	50 (A)
1b	$C_{17}H_{15}BrN_2O$	59.39 / 59.49	4.36 / 4.41	23.30 / 23.28	8.20 / 8.16	> 300 dec.	28 (A), 59 (B)
1d	$C_{16}H_{12}BrClN_2O$	52.74 / 52.85	3.28 / 3.33	22.00 / 21.97 (9.74) / (9.75)	7.80 / 7.70	> 300 dec.	48 (A), 67 (B)
1e	$C_{16}H_{12}BrClN_2O$	52.75 / 52.85	3.23 / 3.33	21.99 / 21.97 (9.76) / (9.75)	7.81 / 7.70	> 300 dec.	50 (A), 70 (B)
1f	$C_{16}H_{12}Br_2N_2O$	46.89 / 47.09	2.83 / 2.96	39.17 / 39.16	6.91 / 6.86	> 300 dec.	47 (A), 69 (B)
1g	$C_{18}H_{15}BrN_2O_3$	55.75 / 55.83	3.82 / 3.90	20.67 / 20.63	7.30 / 7.23	127-219	48 (A)
5a	$C_{18}H_{16}N_2O_3$	70.01 / 70.12	5.19 / 5.23	—	9.12 / 9.09	263-265	69
5b	$C_{17}H_{14}N_2O$	77.76 / 77.84	5.32 / 5.38	—	10.65 / 10.68	215-217	70
5d	$C_{16}H_{11}ClN_2O$	67.89 / 67.97	3.88 / 3.92	12.56 / 12.54	10.00 / 9.91	250-253	85
5e	$C_{16}H_{11}ClN_2O$	67.85 / 67.97	3.87 / 3.92	12.52 / 12.54	9.95 / 9.91	235-237	80
5f	$C_{16}H_{11}BrN_2O$	58.65 / 58.74	3.29 / 3.39	24.47 / 24.42	8.57 / 8.56	226-229	82
5g	$C_{18}H_{14}N_2O_3$	70.50 / 70.58	4.57 / 4.61	—	9.20 / 9.15	206-208	79
7a	$C_{27}H_{26}BrN_3O_3$	62.27 / 62.31	4.99 / 5.04	15.39 / 15.35	8.16 / 8.07	249-251	70
7b	$C_{25}H_{21}BrClN_3O$	60.62 / 60.68	4.19 / 4.28	16.16 / 16.15 (7.19) / (7.16)	8.52 / 8.49	222-225	80
7c	$C_{27}H_{24}BrN_3O_3$	62.48 / 62.56	4.60 / 4.67	15.41 / 15.41	8.12 / 8.11	255-256	75
8a	$C_{20}H_{18}N_2O_4$	68.49 / 68.56	5.10 / 5.18	—	8.10 / 8.00	237-240	65
8b	$C_{18}H_{13}ClN_2O_2$	66.50 / 66.57	3.99 / 4.03	10.96 / 10.92	8.65 / 8.63	232-233	68
9a	$C_{18}H_{18}N_2O_3$	69.60 / 69.66	5.79 / 5.85	—	9.10 / 9.03	190-193	60
9b	$C_{17}H_{16}N_2O$	77.19 / 77.25	6.09 / 6.10	—	10.62 / 10.60	191-193	49
9c	$C_{16}H_{13}BrN_2O$	58.26 / 58.38	3.89 / 3.98	24.28 / 24.27	8.60 / 8.51	202-205	40
9d	$C_{16}H_{13}ClN_2O$	67.39 / 67.49	4.56 / 4.60	12.47 / 12.45	9.89 / 9.84	238-240	42

* Solvent for recrystallization: DMF (compounds **1a, 5a,d-f, 8a,b, 9a,c,d**); AcOH (**1b,e,g**); AcOH-DMF, 3: 1 (**1d,f**); 1,4-dioxane (**5g,b**), 2-propanol (**9b**); Ac_2O (**7a**); acetone (**7b,c**).

In our view, a characteristic pointing to the presence of the imine structural fragment in the molecule (form **A**) is its borohydride reduction. It was found that the multiple $C_{(6a)}=N_{(6)}$ bond in the Ar-unsubstituted isoquinoquinazoline **5c** is readily reduced by $NaBH_4$ in methanol hence it was logical to propose that the rate of this reaction in the isoquinoquinazolines **5a-g** will be determined by the ratio of the two tautomeric forms **A** and

B. In fact, the time needed for the reaction of **5a,b,d,e** to the corresponding 6,6a,7,12-tetrahydro-5H-isoquino[2,3-*a*]quinazolin-5-ones **9a-d** is decreased in the case of **5a,b** (content of form **B** less or absent than in **5c**) but increased in the case of **5d,e** (form **B** content greater than in **5c**).

EXPERIMENTAL

IR spectra were recorded on a Pye Unicam SP3-300 instrument (KBr tablets). ^{1}H NMR spectra were obtained on a Varian Mercury 400 (400 MHz) instrument using DMSO-d_6 and with TMS as internal standard. UV spectra were taken on a Specord M400 instrument. The melting points of the compounds synthesized were determined on a Boetius type heating block and are not corrected. Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates.

2,3-Dimethoxy-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one Hydrobromide (1a). A solution of *o*-BMPA (2.1 g, 10 mmol) and methyl 2-amino-4,5-dimethoxybenzoate **2a** (2.11 g, 10 mmol) in 2-propanol (15 ml) was heated for 1 h. After cooling the precipitate was filtered off and washed with 2-propanol. The solid material was a mixture of methyl 2-{[2-(cyanomethyl)benzyl]amino}-4,5-dimethoxybenzoate (**3a**) and 2-[4,5-dimethoxy-2-(methoxycarbonyl)phenyl]-1,4-dihydro-3(2H)-isoquinoleniminium bromide (**4a**) in the ratio 1 : 2. The mixture of compounds **3a** and **4a** was dissolved with heating in DMF and was refluxed for 3 min. After cooling the precipitated solid was filtered off and washed with DMF and alcohol.

2,3-R,R^1-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one Hydrobromides (1b-g). A. The isoquinoquinazoline hydrobromides **1b-f** were prepared according to the method in [1] by heating a mixture of equimolar amounts of *o*-BMPA and the anthranilic acids **2b-f** in 2-propanol. The methyl 5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazoline-2-carboxylate hydrobromide (**1g**) was prepared using dimethyl 2-amino-terephthalate (**2g**).

B. A mixture of *o*-BMPA (2.1 g, 10 mmol) and the anthranilic acid **2b-f** (10 mmol) was heated on an oil bath at 130-150ºC for 4 h. After cooling, the melt was triturated in acetone (5 ml). The precipitate was filtered off and washed with acetone to give the isoquinoquinazoline hydrobromides **1b-f**.

2,3-R,R^1-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones (5a,b,d-g). Et_3N (1.5 ml) was added to a suspension of the salts **1a,b,d-g** in 2-propanol (10 ml) and refluxed for 10 min. Solvent and excess Et_3N were evaporated and water (50 ml) was added to the residue. The precipitate was filtered off and thoroughly washed with water and alcohol to give the isoquinoquinazolines **5a,b,d-g**.

7-{[4-(Dimethylamino)phenyl]methylene}-2,3-R,R^1-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one Hydrobromides (7a-c). A mixture of the isoquinoquinazoline hydrobromide **1a,e,g** (2.57 mmol) and *p*-dimethylaminobenzaldehyde (0.38 g, 2.57 mmol) in acetic anhydride (10 ml) was refluxed for 30 min (for **1a**), 10 min (for **1e**), or 3 min (for **1g**). After cooling the precipitated solid was filtered off and washed with acetone. UV spectrum (MeOH), λ_{max}, nm ($\varepsilon\times10^{-3}$): compound **7a** 204 (276.93), 232 (249.02), 265 (152.41), 328 (74.34), 415 (159.34); compound **7b** 205 (247.41), 242 (157.96), 328 (66.61), 423 (85.64); compound **7c** 250 (155.52), 320 (55.73), 423 (102.38).

7-Acetyl-2,3-R,R^1-6,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones 8a,b. A mixture of the isoquinoquinazoline **5a,d** (0.1 mmol) and anhydrous sodium acetate (0.1 g, 0.12 mmol) in acetic anhydride (10 ml) was heated for 3 h (**5a**) or for 1.5 h (**5d**). The product was cooled and left to stand overnight. The precipitate was filtered off and washed with acetone.

2,3-R,R^1-6,6a,7,12-Tetrahydro-5H-isoquino[2,3-*a*]quinazolines 9a-d. $NaBH_4$ (0.76 g, 20 mmol) was added in small portions to a suspension of the isoquinoquinazoline **1a,b,d,f** (10 mmol) in methanol (50 ml). At the end of the vigorous reaction during which the starting salt dissolved the mixture was refluxed for 15 min. Solvent was distilled off under reduced pressure and the residue was treated with NaOH solution (10%, 20 ml). The solid material was filtered off and washed with water.

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