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CONDENSED ISOQUINOLINES. 36*. CYCLIZATION OF N-ALKYL-3-(2-BENZOYLBENZYL)AZOLIUM SALTS. A NOVEL METHOD OF PREPARING AZOLO[*b*]ISOQUINOLINES

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A novel method is proposed for the preparation of azolo[b]isoquinolines based on the alkylation of N-alkyl-1,3-diazoles or 1,3-thiazole derivatives using [2-(bromomethyl)phenyl](phenyl)methanone with subsequent cyclization of the quaternary azolium salts in the presence of base. The 10(11)-hydroxy derivatives of the 5,10-dihydro-1H-imidazo[1,2-b]isoquinolinium, 6,11-dihydro-5H-benzimidazo-[1,2-b]isoquinolinium, 5,10-dihydro-1H-[1,2,4]triazolo[4,3-b]isoquinolinium, or 5,10-dihydro[1,3]-thiazolo[3,2-b]isoquinolinium bromides obtained in this way readily lose a molecule of water upon heating with HBr or Ac_2O to give the corresponding quasi-aromatic azolo[b]isoquinolinium salts.

Keywords: benzimidazo[1,2-*b*]isoquinoline, benzophenone, imidazo[1,2-*b*]isoquinoline, [1,3]thiazolo-[3,2-*b*]isoquinoline, [1,2,4]triazolo[4,3-*b*]isoquinoline.

Treatment of amines with 1,5-dielectrophile synthon equivalents is one of the routes in the design of isoquinoline type structures. This kind of heterocyclization has been demonstrated by us before for *o*-bromomethylphenylacetonitrile [2] and *o*-cyanomethylbenzoic acid [3].

In this work we propose the use of [2-(bromomethyl)phenyl](phenyl)methanone (*o*-bromomethylbenzophenone) derivatives **1a**,**b** as novel equivalents of 1,4-dielectrophile synthons in the preparation of the condensed isoquinolines. Their structure as vinylogs [4] of α-bromoacetophenone [5] allows one to proporse possibility to combine the carbonyl and bromomethyl functions in cyclizations. Their counterparts have been known for a long time but, in view of their inaccessibility, have had limited use.

We have found that the reaction of the *o*-bromomethylbenzophenones **1a**,**b** with 1-alkyl-1H-imidazoles **2a**,**e**, 1-methyl-1H-benzomidazole (**2b**), 1-methyl-1H-1,2,4-triazole (**2c**), and 4-methyl-1,3-thiazole (**2d**) in benzene at room temperature gives high yields (61-89%) of the N-(2-benzoylbenzyl)azolium bromides **3a-d**, **4a-e**.

The rate of the formation of the quaternary salts **3**, **4** and their yield are principally determined by the basicity of the azole. With its decrease the reaction time increases (from 1-2 days for the imidazoles to 30 days for thiazole) and the yield is decreased (from 85-89% for the imidazoles to 61% for the thiazole).

* For Communication 35, see [1].

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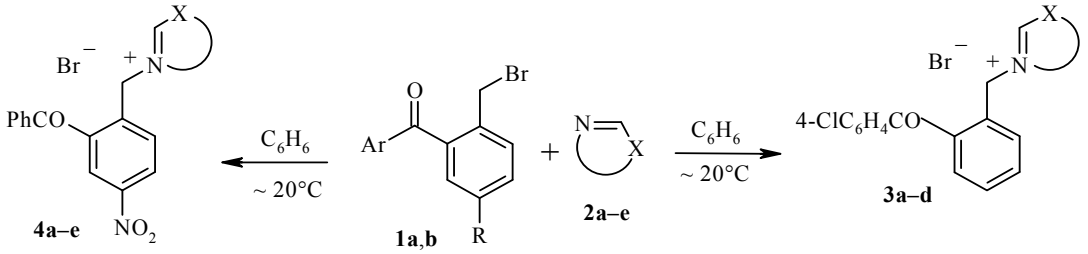
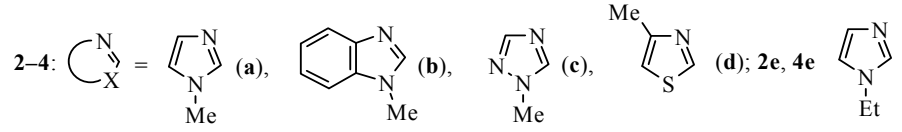
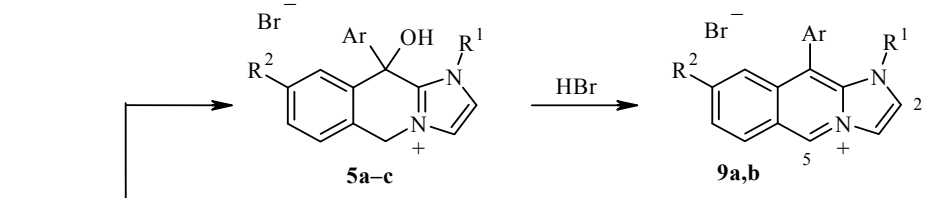
The result of the reaction depends on the structure of the starting benzophenone **1**. In the case of compound **1a** it was not possible to prepare the corresponding bromides **3c** and **3d** in the pure state and a mixture of quaternary salts and the starting azole hydrobromide was obtained. Attempts to increase the yield of the quaternary salts **3** and **4** by heating or increasing the time of holding the mixture of reagents at room temperature gave a reaction mixture of cyclization products, initiated by the starting azole base. A similar result



4a–e **1a**,**b** **2a–e** **3a–d**

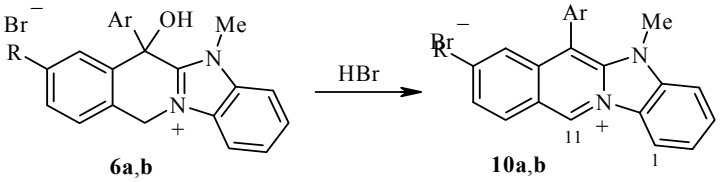
1 a R = H, Ar = 4-ClC_6H_4; **b** R = NO_2, Ar = Ph;





5a–c **9a,b**

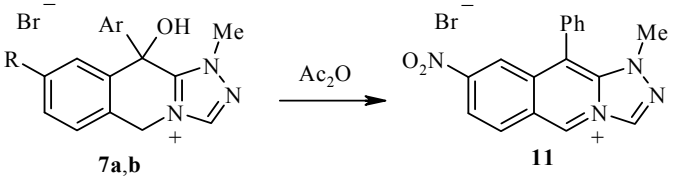
a R^1 = Me, R^2 = H, Ar = 4-ClC_6H_4; **b** R^1 = Me, R^2 = NO_2, Ar = Ph;
c R^1 = Et, R^2 = NO_2, Ar = Ph



6a,**b** **10a**,**b**

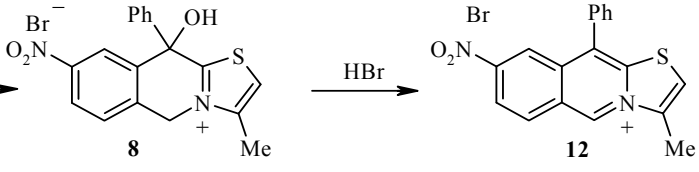
a R = H, Ar = 4-ClC_6H_4; **b** R = NO_2, Ar = Ph

3a–c, **4a–e** B: / Δ



7a,**b** **11**

a R = H, Ar = 4-ClC_6H_4; **b** R = NO_2, Ar = Ph



8 **12**

TABLE 1. Spectral Characteristics for Compounds **3**, **4**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)			
		H-2, (1H, s)	Aromatic protons	CH_2, (2H, s)	Other signals
3a	3064, 1650 (C=O), 1586, 1569, 1267, 1163, 1082, 929, 738, 632	9.18	7.74-7.65 (7H, m, H Ar); 7.57-7.52 (3H, m, H Ar)	5.53	3.83 (3H, s, NCH_3)
3b	3042, 2975, 1656 (C=O), 1583, 1566, 1272, 1091, 923, 761, 752	9.68	7.98 (1H, d, ^3J = 8.0, H-4); 7.82 (1H, d, ^3J = 8.0, H-7); 7.69-7.57 (9H, m, H Ar); 7.50 (1H, d, ^3J = 8.0, H-3')	5.88	4.05 (3H, s, NCH_3)
4a	3137, 3048, 1653 (C=O), 1527 (NO_2), 1345 (NO_2), 1320, 1155, 719	9.18	8.48 (1H, d, ^3J = 8.0, H-4'); 8.28 (1H, s, H-6'); 7.82-7.72 (6H, m, H Ar); 7.61 (2H, t, ^3J = 8.0, H-3",5")	5.66	3.82 (3H, s, NCH_3)
4b	3081, 2992, 1656 (C=O), 1532 (NO_2), 1449, 1351 (NO_2), 1273, 747, 730	9.71	8.44 (1H, d, ^3J = 8.0, H-4'); 8.33 (1H, s, H-6'); 7.97 (1H, d, ^3J = 8.0, H-4); 7.79 (1H, d, ^3J = 8.0, H-7); 7.73-7.62 (6H, m, H Ar); 7.54 (2H, t, ^3J = 8.0, H-3",5")	6.02	4.03 (3H, s, NCH_3)
4c	3008, 2969, 1664 (C=O), 1524 (NO_2), 1354 (NO_2), 1320, 1267, 1147, 722, 691	10.15*	9.25 (1H, s, H-3); 8.52 (1H, d, ^3J = 8.0, H-4'); 8.31 (1H, d, ^3J = 8.0, H-6'); 7.91-7.82 (4H, m, H Ar); 7.63 (2H, t, ^3J = 8.0, H-3",5")	5.74	4.07 (3H, s, NCH_3)
4d	3052, 2980, 1659 (C=O), 1575, 1522 (NO_2), 1449, 1348 (NO_2), 1309, 1273, 957, 797, 744, 694, 646	10.13	8.48 (1H, d, ^3J = 8.0, H-4'); 8.33 (1H, d, ^3J = 8.0, H-6'); 8.09 (1H, s, H-5); 7.83 (2H, d, ^3J = 8.0, H-2",6"); 7.79 (1H, t, ^3J = 8.0, H-4"); 7.62 (2H, t, ^3J = 8.0, H-3",5"); 7.47 (1H, d, ^3J = 8.0, H-3')	6.02	2.36 (3H, s, 4-CH_3)

* 1H, s, H-5.

(mixture of quaternary salt **4a** and the product of subsequent cyclization) was also obtained in the reaction of the benzophenone **1b** with 2-ethyl-1H-imidazole **2e**. The structure of salts **3**, **4** was determined by IR and ^{1}H NMR spectroscopic methods (Table 1).

When heated in the presence of morpholine or triethylamine bases, the quaternary azolium salts cyclized in high yield (62-93%) to the 1-alkyl-10-aryl-10-hydroxy-5,10-dihydro-1H-imidazo[1,2-*b*]isoquinolin-4-ium **5a-c**, 6-aryl-6-hydroxy-5-methyl-6,11-dihydro-5H-benzimidazo[1,2-*b*]isoquinolin-12-ium **6a**,**b**, 10-aryl-10-hydroxy-1-methyl-5,10-dihydro-1H-[1,2,4]triazolo[4,3-*b*]isoquinolin-4-ium **7a**,**b**, or 10-hydroxy-3-methyl-8-nitro-10-phenyl-5,10-dihydro[1,3]thiazolo[3,2-*b*]isoquinolin-4-ium (**8**) bromides. Carrying out the reaction in acetone in the presence of morpholine leads to reaction products **5-8** in high purity and virtually without the need for further purification. With the use of triethylamine as base (in acetone) or ethanol as solvent (morpholine or triethylamine as base) up to 30% of dehydration products are formed (according to their ^{1}H NMR spectra).

The structure of the hydroxy derivatives of the 1,4-dihydroisoquinoline was suggested by the presence of signals for OH groups in the IR spectra of compounds **5-8** (Table 2) which showed a broad band for ν_{OH} at 3171-3064 cm^{-1} and a medium intensity ν_{C-O} at 1043-1049 cm^{-1} in a region characteristic of the C–O stretching vibrations of tertiary alcohols. The ^{1}H NMR spectra showed a singlet for the OH group (which exchanged with D_2O) in the region 7.9-8.3 ppm and a signal for a methylene group at 5.6-6.4 ppm as two doublets of an AB spin system with ^2J = 16.5-19.0 Hz.

In order to prove the structure of salts **5-8** and to make a full assignment of signals in the NMR spectra there were measured the ^{13}C NMR, COSY, and NOESY spectra of **5b** together with the use of HMBC and HMQC 2D heteronuclear correlation spectroscopic methods. The results for the 2D NOESY spectra are given in Figure, 1*a* and led to a secure assignment of signals in the proton spectrum of compound **5b**. The position of the hydroxyl group proton signal at 8.11 ppm follows from the presence of its negative correlation with the water signal present in the solvent. This correlation points to the presence of proton exchange. The structure of the carbon skeleton was confirmed from the basic heteronuclear correlations (Figure, 1*b*).

It is known [6] that 1(4)-hydroxy 1,4-dihydroisoquinolines readily aromatize in the presence of strong acids. In our case, heating the hydroxy derivatives of the azolo[*b*]isoquinolinium bromides **5a**,**b**, **6a**,**b**, **8** in the presence of hydrobromic acid led to dehydration and gave the 10-aryl-1-methyl-1H-imidazo[1,2-*b*]isoquinolin-4-ium **9a**,**b**, 6-aryl-5-methyl-5H-benzimidazo[1,2-*b*]isoquinolin-12-ium **10a**,**b**, or 3-methyl-8-nitro-10-phenyl-[1,3]thiazolo[3,2-*b*]isoquinolin-4-ium (**12**) bromides. In the case of the [1,2,4]triazolo[4,3-*b*]isoquinolinium bromide **7b** an efficient conversion to the 1-methyl-8-nitro-10-phenyl-1H-[1,2,4]triazolo[4,3-*b*]isoquinolin-4-ium bromide (**11**) could only be achieved by heating salt **7b** in acetic anhydride. Heating it in the presence of HBr led to only slow dehydration and was accompanied by the formation of side products.

A feature of the ^{1}H NMR spectra (Table 2) of the aromatic azolo[*b*]isoquinolinium salts **9-12** is the presence of a signal for the aromatic H-5 proton (H-11 for compounds **10a**,**b**) with a chemical shift greater than 10.0 ppm. By contrast with the IR spectra of the dihydro derivatives **5-8** their IR spectra show a medium intensity absorption band at 1603-1609 cm^{-1} which is assigned to C=N stretching bands. All of the salts **9-12** are colored and their UV spectra show the presence of strong absorption maxima in the range λ 350-482 nm, which is a characteristic of azolo[*b*]isoquinolinium cations [7-9].

With the aim of evaluating the biological potential of the compounds reported here a spectrum of biological activity was calculated. The PASS (Prediction of Activity Spectra for Substances) [10-12] was used in the calculations. The selection of active compounds is made by a multilevel assessment of the closest environment of the atoms and a comparison of the calculated 3D descriptors with a set of those corresponding to the likely appearance of either high activity or its absence. The final result of the program is the potential appearance of compound activity (p_a) or inactivity (p_i) in fractional units. A spectrum of more than 3000 types of activity was calculated for each compound with activity threshold selected as $p_a > 0.75$ and $p_i < 0.2$. Amongst the activities characterizing compounds **3** and **4** should be noted the prediction of properties as CC subfamily

TABLE 2. ^{1}H NMR and IR Spectroscopic Characteristics for the Azolo[*b*]isoquinolinium Bromides **5-12**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz)		
		Aromatic signals	H-5 (H-11*)	Other signals
1	2	3	4	5
5a	3137 (OH), 1494, 1197, 1096, 1043 (C–O), 820, 769	8.03 (1H, s, H-3); 7.90 (1H, s, H-2); 7.50-7.41 (8H, m, H Ar)	5.82 (1H, d, ^2J = 18.0, H$_A$-5); 5.72 (1H, d, ^2J = 18.0, H$_B$-5)	7.86 (1H, s, OH); 3.61 (3H, s, NCH$_3$)
5b	3171 (OH), 3070, 1536 (NO$_2$), 1356 (NO$_2$), 1189, 1043 (C–O), 741, 702	8.27 (1H, d, ^3J = 8.5, H-7); 8.16 (1H, s, H-9); 8.09 (1H, s, H-3); 7.94 (1H, s, H-2); 7.83 (1H, d, ^3J = 8.5, H-6); 7.47 (2H, d, ^3J = 8.0, H-2',6'); 7.45 (2H, t, ^3J = 8.0, H-3',5'); 7.37 (1H, t, ^3J = 8.0, H-4')	6.02 (1H, d, ^2J = 18.0, H$_A$-5); 5.92 (1H, d, ^2J = 18.0, H$_B$-5)	8.11 (1H, s, OH); 3.61 (3H, s, NCH$_3$)
5c	3143 (OH), 3098, 1530 (NO$_2$), 1351 (NO$_2$), 1183, 1046 (C–O), 764, 741, 702	8.26 (1H, d, ^3J = 8.5, H-7); 8.16 (1H, s, H-9); 8.14 (1H, s, H-3); 8.07 (1H, s, H-2); 7.84 (1H, d, ^3J = 8.5, H-6); 7.49 (2H, d, ^3J = 8.0, H-2',6'); 7.45 (2H, t, ^3J = 8.0, H-3',5'); 7.38 (1H, t, ^3J = 8.0, H-4')	6.04 (1H, d, ^2J = 17.5, H$_A$-5); 5.94 (1H, d, ^2J = 17.5, H$_B$-5)	8.22 (1H, s, OH); 4.14 (2H, m, CH$_2$); 0.97 (3H, t, ^3J = 7.5, CH$_3$)
6a	3064 (OH), 1541, 1485, 1066 (C–O), 1010, 831, 758	8.22 (1H, d, ^3J = 8.0, H-1); 8.07 (1H, d, ^3J = 8.0, H-4); 7.85-7.79 (2H, m, H-2,3); 7.60-7.56 (3H, m, H Ar); 7.51-7.47 (5H, m, H Ar)	6.10 (1H, d, ^2J = 16.5, H$_A$-11); 6.04 (1H, d, ^2J = 16.5, H$_B$-11)	8.12 (1H, s, OH); 3.88 (3H, s, NCH$_3$)
6b	3109 (OH), 1546, 1533 (NO$_2$), 1351 (NO$_2$), 1049 (C–O), 755, 705	8.33 (1H, d, ^3J = 8.5, H-9); 8.23 (1H, s, H-7); 8.20 (1H, d, ^3J =8.0, H-1); 8.09 (1H, d, ^3J = 8.0, H-4); 7.90-7.80 (3H, m, H-2,3,10); 7.61 (2H, d, ^3J = 8.0, H-2',6'); 7.46 (2H, t, ^3J = 8.0, H-3',5'); 7.40 (1H, t, ^3J = 8.0, H-4')	6.32 (1H, d, ^2J = 17.0, H$_A$-11); 6.23 (1H, d, ^2J = 17.0, H$_B$-11)	8.38 (1H, s, OH); 3.89 (3H, s, NCH$_3$)
7a	3092 (OH), 1494, 1178, 1097, 1057 (C–O), 822, 772	9.53 (1H, s, H-3); 7.56 (1H, d, ^3J = 7.5, H-9); 7.50-7.44 (7H, m, H Ar)	5.87 (1H, d, ^2J = 17.0, H$_A$-5); 5.79 (1H, d, ^2J = 17.0, H$_B$-5)	8.11 (1H, s, OH); 3.89 (3H, s, NCH$_3$)
7b	3126 (OH), 3076, 1533 (NO$_2$), 1354 (NO$_2$), 1175, 1049 (C–O), 817, 741, 702, 649	9.58 (1H, s, H-3); 8.35 (1H, s, H-9); 8.32 (1H, d, ^3J = 8.5, H-7); 7.91 (1H, d, ^3J = 8.5, H-6); 7.52 (2H, d, ^3J = 8.0, H-2',6'); 7.42 (2H, t, ^3J = 8.0, H-3',5'); 7.38 (1H, t, ^3J = 8.0, H-4')	6.07 (1H, d, ^2J = 19.5, H$_A$-5); 5.97 (1H, d, ^2J = 19.5, H$_B$-5)	8.20 (1H, s, OH); 3.90 (3H, s, NCH$_3$)
8	3148 (OH), 3109, 1533 (NO$_2$), 1351 (NO$_2$), 1043 (C–O), 758, 738, 699	8.70 (1H, s, H-2); 8.40 (2H, m, H-7,9); 7.93 (1H, d, ^3J = 8.5, H-6); 7.40 (3H, m, H-3'-H-5'); 7.34 (2H, d, ^3J = 8.0, H-2',6')	6.09 (1H, d, ^2J = 19.0, H$_A$-5); 5.67 (1H, d, ^2J = 19.0, H$_B$-5)	8.17 (1H, s, OH); 2.69 (3H, s, 3-CH$_3$)

TABLE 2 (continued)

1	2	3	4	5
9a	3030, 2986, 1634 (C=N), 1510, 1399, 1088, 831, 750	8.68 (1H, d, ^3J = 2.0, H-3); 8.42 (1H, d, ^3J = 2.0, H-2); 8.31 (1H, d, ^3J = 8.0, H-6); 7.77 (2H, d, ^3J = 8.0, H-2',6'); 7.74-7.69 (2H, m, H-7,8); 7.66 (2H, d, ^3J = 8.0, H-3',5'); 7.43 (1H, d, ^3J = 8.0, H-9)	10.06 (1H, s, H-5)	3.43 (3H, s, NCH_3)
9b	3025, 2992, 1620 (C=N), 1533 (NO_2), 1340 (NO_2), 1262, 1104, 405	8.88 (1H, s, H-3); 8.61 (1H, s, H-2); 8.57 (1H, d, ^3J = 9.0, H-6); 8.27 (1H, d, ^3J = 9.0, H-7); 8.22 (1H, s, H-9); 7.76 (3H, m, H-3'-H-5'); 7.70 (2H, d, ^3J = 8.0, H-2',6')	10.26 (1H, s, H-5)	3.45 (3H, s, NCH_3)
10a	3014, 2924, 1639 (C=N), 1617, 1508, 1396, 831, 738	8.90 (1H, d, ^3J = 8.0, H-1); 8.45 (1H, d, ^3J = 8.0, H-10); 8.09 (1H, d, ^3J = 8.0, H-4); 7.98 (1H, t, ^3J = 8.0, H-3); 7.92 (1H, t, ^3J = 8.0, H-2); 7.90-7.78 (4H, m, H-8,9,2',6'); 7.69 (2H, d, ^3J = 8.0, H-3',5'); 7.54 (1H, d, ^3J = 8.0, H-7)	11.03 (1H, s, H-11)	3.50 (3H, s, NCH_3)
10b	3014, 2924, 1622 (C=N), 1608, 1536, 1508 (NO_2), 1480, 1343 (NO_2), 1329, 1080, 769, 710	8.90 (1H, d, ^3J = 8.0, H-1); 8.65 (1H, d, ^3J = 8.5, H-10); 8.39 (1H, d, ^3J = 8.5, H-9); 8.30 (1H, s, H-7); 8.16 (1H, d, ^3J = 8.0, H-4); 8.07 (1H, t, ^3J = 8.0, H-3); 7.89 (1H, t, ^3J = 8.0, H-2); 7.81 (3H, m, H-3'-H-5'); 7.72 (2H, d, ^3J = 8.0, H-2',6')	11.10 (1H, s, H-11)	3.52 (3H, s, NCH_3)
11	3042, 1617 (C=N), 1533 (NO_2), 1345 (NO_2), 831, 702	10.31 (1H, s, H-3); 8.68 (1H, d, ^3J = 9.0, H-6); 8.30 (1H, d, ^3J = 9.0, H-7); 8.26 (1H, s, H-9); 7.80 (3H, m, H-3'-H-5'); 7.70 (2H, d, ^3J = 8.0, H-2',6')	10.27 (1H, s, H-5)	3.65 (3H, s, NCH_3)
12	3048, 1603 (C=N), 1527 (NO_2), 1334 (NO_2), 1314, 1228, 1077, 853, 825, 699	8.90 (1H, d, ^3J = 9.0, H-6); 8.64 (1H, d, ^3J = 9.0, H-7); 8.53 (1H, s, H-2); 8.51 (1H, s, H-9); 7.83 (3H, m, H-3'-H-5'); 7.78 (2H, d, ^3J = 8.0, H-2',6')	10.68 (1H, s, H-5)	3.34 (3H, s, 3-CH_3)

* For the benzimidazo[1,2-*b*]isoquinoline derivatives **6a**,**b** and **10a**,**b**.

TABLE 3. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %						mp, °C*	Yield, %
		C	H	Br	Cl	N	S		
3a	$C_{18}H_{16}BrClN_2O$	55.22 / 55.19	4.09 / 4.12	20.42 / 20.40	9.04 / 9.05	7.18 / 7.15		135-136	85
3b	$C_{22}H_{18}BrClN_2O$	59.78 / 59.82	4.13 / 4.11	18.10 / 18.09	8.05 / 8.03	6.30 / 6.34		220-221	77
4a	$C_{18}H_{16}BrN_3O_3$	53.71 / 53.75	4.06 / 4.01	19.88 / 19.86		10.44 / 10.45		160-162	89
4b	$C_{22}H_{18}BrN_3O_3$	58.40 / 58.42	3.98 / 4.01	17.65 / 17.67		9.30 / 9.29		171-172	63
4c	$C_{17}H_{15}BrN_4O_3$	50.61 / 50.64	3.77 / 3.75	19.80 / 19.82		13.86 / 13.89		184-186	67
4d	$C_{18}H_{15}BrN_2O_3S$	51.50 / 51.56	3.62 / 3.61	19.07 / 19.06		6.67 / 6.68	7.60 / 7.65	187-188	61
5a	$C_{18}H_{16}BrClN_2O$	55.21 / 55.19	4.15 / 4.12	20.41 / 20.40	9.02 / 9.05	7.18 / 7.15		> 300 (dec.)	89
5b	$C_{18}H_{16}BrN_3O_3$	53.71 / 53.75	3.99 / 4.01	19.87 / 19.86		10.40 / 10.45		280-282 (dec.)	87
5c	$C_{19}H_{18}BrN_3O_3$	54.78 / 54.82	4.31 / 4.36	19.18 / 19.20		10.12 / 10.09		229-230 (dec.)	80
6a	$C_{22}H_{18}BrClN_2O$	59.80 / 59.82	4.15 / 4.11	18.11 / 18.09	8.05 / 8.03	6.35 / 6.34		> 300 (dec.)	92
6b	$C_{22}H_{18}BrN_3O_3$	58.38 / 58.42	4.02 / 4.01		17.65 / 17.67	9.31 / 9.29		290-291 (dec.)	93
7a	$C_{17}H_{15}BrClN_3O$	51.98 / 52.00	3.80 / 3.85	20.36 / 20.35	9.05 / 9.03	10.73 / 10.70		> 300 (dec.)	87
7b	$C_{17}H_{15}BrN_4O_3$	50.62 / 50.64	3.78 / 3.75	19.80 / 19.82		13.91 / 13.89		241-243 (dec.)	88
8	$C_{18}H_{15}BrN_2O_2S$	51.57 / 51.56	3.58 / 3.61	19.09 / 19.06		6.67 / 6.68	7.62 / 7.65	264-265 (dec.)	62
9a	$C_{18}H_{14}BrClN_2$	57.83 / 57.86	3.80 / 3.78	21.40 / 21.38	9.50 / 9.49	7.52 / 7.50		> 300	82
9b	$C_{18}H_{14}BrN_3O_2$	56.25 / 56.27	3.68 / 3.67	20.78 / 20.80		10.97 / 10.94		298-300 (dec.)	90
10a	$C_{22}H_{16}BrClN_2$	62.33 / 62.36	3.78 / 3.81	18.87 / 18.86	8.35 / 8.37	6.60 / 6.61		> 300	90
10b	$C_{22}H_{16}BrN_3O_2$	60.83 / 60.84	3.67 / 3.71	18.42 / 18.40		9.70 / 9.68		> 300	93
11	$C_{17}H_{13}BrN_4O_2$	53.02 / 53.00	3.43 / 3.40	20.77 / 20.74		14.51 / 14.54		> 275 (dec.)	63
12	$C_{18}H_{13}BrN_2O_2S$	53.85 / 53.88	3.28 / 3.27	19.93 / 19.91		7.00 / 6.98	8.10 / 7.99	> 290 (dec.)	84

* Compound **11** was recrystallized from 2-propanol, the remainder from MeOH–hexane (1:1).

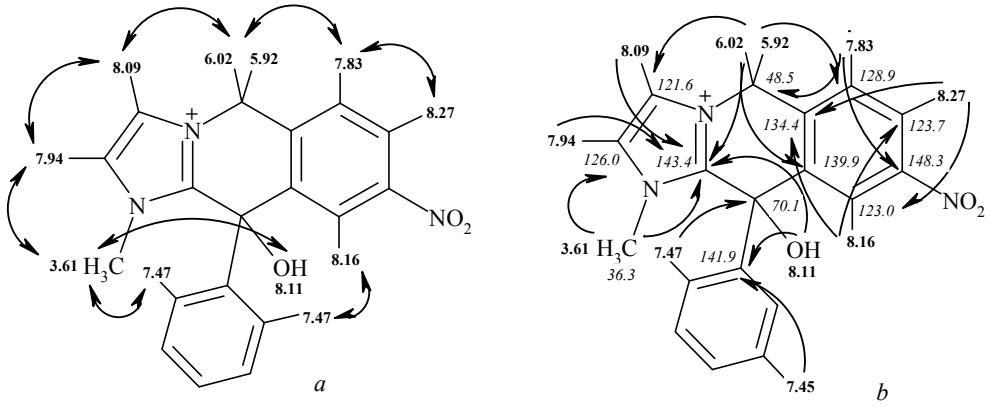


Fig. 1. Structurally significant NOESY (*a*) and HMBC (*b*) correlations for compound **5b**.

chemokin antagonists which induce the migration of monocytes from blood to tissue and their differentiation in the macrophage. The highest indicators for compounds **4a,b** are, respectively, 0.854 (p_i = 0.009) and 0.862 (p_i = 0.008). Also worthy of attention is the prediction of activity for the aromatic salts **9-12** as inhibitors of prolylamino peptidase occurring in the process of enzymatic decomposition of proteins and responsible for involved in the metabolism of regulatory peptides for different cell types: **9a** p_a = 0.821, p_i = 0.063; **10a** p_a = 0.796, p_i = 0.073.

EXPERIMENTAL

IR spectra (KBr tablets) were taken on Perkin-Elmer spectrum BX instrument. UV spectra were recorded in methanol on a Lambda 20 UV-vis spectrometer. ^{1}H NMR spectra were taken on a Bruker Avance DRX-500 (500 MHz) instrument. 2D correlation spectroscopic experiments were taken on a Varian Mercury 400 instrument (400 and 100 MHz for ^{1}H and ^{13}C respectively) with TMS used as internal standard. Melting points were recorded on a Thiele heating apparatus. Monitoring of the compound purities was carried out using HPLC–mass spectrometry on an Agilent 1100 series instrument with a selective Agilent LC/MSD SL detector (the sample was introduced in a CF_3COOH matrix, EI ionization).

The physicochemical characteristics and elemental analytical data for the synthesized compounds **3-12** are presented in Table 3.

[2-(Bromomethyl)phenyl](4-chlorophenyl)methanone (**1a**) was prepared by method [13] and [2-(bromomethyl)-5-nitrophenyl](phenyl)methanone (**1b**) as a mixture with a **1b** content of 70% using method [14].

3-(2-Benzoylbenzyl)-1-methyl-1H-imidazol-3-ium (3a, 4a), 1-(2-Benzoylbenzyl)-3-methyl-3H-benzimidazol-1-ium (3b, 4b), 4-(2-Benzoyl-4-nitrobenzyl)-1-methyl-1H-1,2,4-triazol-4-ium (4c), and 3-(2-Benzoyl-4-nitrobenzyl)-4-methyl-1,3-thiazol-3-ium (4d) Bromides (General Method). The corresponding azole **2a-d** (1.7 mmol) was added to a solution of [2-(bromomethyl)phenyl](4-chlorophenyl)methanone **1a** (0.5 g, 1.6 mmol) (or 0.73 g of a mixture containing 70% (1.6 mmol) of [2-(bromomethyl)-5-nitrophenyl]-(phenyl)methanone **1b**) in anhydrous benzene (10 ml) and held at room temperature for 1-2 days for compound **2a**, 4 days for **2b**, 10 days for **2c**, or 30 days for **2d**. The colorless precipitate was filtered off and washed with acetone.

10-Aryl-10-hydroxy-1-methyl-5,10-dihydro-1H-imidazo[1,2-*b*]isoquinolin-4-ium 5a,b, 6-Aryl-6-hydroxy-5-methyl-6,11-dihydro-5H-benzimidazo[1,2-*b*]isoquinolin-12-ium 6a,b, 10-Hydroxy-1-methyl-8-nitro-10-phenyl-5,10-dihydro-1H-[1,2,4]triazolo[4,3-*b*]isoquinolin-4-ium (7b), and 10-Hydroxy-3-methyl-8-nitro-10-phenyl-5,10-dihydro[1,3]thiazolo[3,2-*b*]isoquinolin-4-ium (8) Bromides (General Method). A mixture of the azolium bromide **3a-b**, **4a-d** (1.02 mmol) and morpholine (0.5 ml) in acetone (10 ml) was refluxed for 1.5 h (in the case of thiazolium bromide **4d** for 0.5 h). The product was cooled and the precipitate was filtered off and washed with acetone.

Compound 5b. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 148.3 (C-8); 143.4 (C-10a); 141.9 (C-1'); 139.9 (C-9a); 134.4 (C-5a); 130.0 (C-2',6'); 129.5 (C-4'); 128.9 (C-6); 126.0 (C-2); 125.8 (C-3',5'); 123.7 (C-7); 123.0 (C-9); 121.6 (C-3); 70.1 (C-10); 48.5 (C-5); 36.3 ($\underline{C}H_3$).

1-Ethyl-10-hydroxy-8-nitro-10-phenyl-imidazo[1,2-*b*]isoquinolin-4-ium Bromide (5c) was prepared by the method reported above for the synthesis of the azolium bromides **3, 4** (solution holding time 1 day) as a mixture containing the 3-(2-benzoyl-4-nitrobenzyl)-1-ethyl-1H-imidazol-3-ium bromide (**4a**, 82%) and the cyclization product **5c**. The mixture was treated with morpholine (0.6 ml) and benzene (10 ml) and refluxed for 1 h. The product was cooled and the precipitate was filtered off and washed with acetone.

10-(4-Chlorophenyl)-10-hydroxy-1-methyl[1,2,4]triazolo[4,3-*b*]isoquinolin-4-ium Bromide (7a) was prepared by the above method for the azolium bromides **3, 4** (solution holding time 15 days) as a mixture containing the 4-[2-(4-chlorobenzoyl)benzyl]-1-methyl-1H-1,2,4-triazol-4-ium bromide (**3c**, 65%) and the

1-methyl-1H-1,2,4-triazole hydrobromide **2c·HBr**. The mixture was treated with morpholine (0.3 ml) and acetone (10 ml) and refluxed for 1.5 h. The product was cooled and the precipitate was filtered off and washed with acetone.

10-Aryl-1-methyl-1H-imidazo[1,2-*b*]isoquinolin-4-ium 9a,b, 6-Aryl-5-methyl-5H-benzimidazo-[1,2-*b*]isoquinolin-12-ium 10a,b, and 3-Methyl-8-nitro-10-phenyl[1,3]thiazolo[3,2-*b*]isoquinolin-4-ium (12) Bromides (General Method). A mixture of salts **5a**,**b**, **6a**,**b**, **8** (0.7 mmol) and HBr solution (48%, 5 ml) was refluxed for 4 h. Solvent was evaporated *in vacuo*. The residue was treated with water (20 ml) and the solid product was filtered off and washed with water and 2-propanol.

Compound 9a. UV spectrum, λ_{max}, nm (log ε): 242 (4.55), 380 (4.22), 400 (4.21).

Compound 9b. UV spectrum, λ_{max}, nm (log ε): 262 (4.44), 418 (4.21), 430 (4.22).

Compound 10a. UV spectrum, λ_{max}, nm (log ε): 286 (4.55), 426 (3.88), 450 (3.85).

Compound 10b. UV spectrum, λ_{max}, nm (log ε): 290 (4.65), 458 (3.88), 482 (3.89).

Compound 12. UV spectrum, λ_{max}, nm (log ε): 270 (4.47), 412 (4.00), 428 (4.05).

1-Methyl-8-nitro-10-phenyl-1H-[1,2,4]triazolo[4,3-*b*]isoquinolin-4-ium Bromide (11). A mixture of compound **7b** (0.3 g, 0.75 mmol) in acetic anhydride (4 ml) was refluxed for 2 h. The product was cooled and the solid formed was filtered off and washed with 2-propanol. UV spectrum (MeOH), λ_{max}, nm (log ε): 260 (4.69), 350 (4.78), 410 (3.81).

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