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CONDENSED ISOQUINOLINES 30.* ACYLATION AND ALKYLATION OF 5,13-DIHYDRO-11H-ISOQUINO-[3,2-*b*]QUINAZOLIN-11-ONE

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It was shown that 6-acyl-5,13-dihydro-11H-isoquino[3,2-b]quinazolin-11-ones are formed when 5,13-dihydro-11H-isoquino[3,2-b]quinazolin-11-one is heated with the chlorides and anhydrides of carboxylic acids in the presence of bases (pyridine, NaOAc) while 5-acyl-5,13-dihydro-11H-isoquino[3,2-b]quinazolin-11-ones are formed in the presence of NaH. In the presence of NaH 6-acyl-5,13-dihydro-11H-isoquino[3,2-b]quinazolin-11-ones form the products from acylation and alkylation at position 5. The action of heat on 5,13-dihydro-11H-isoquino[3,2-b]quinazolin-11-one in oxalyl chloride leads to 7H,8H-2a,7a-diazacyclopenta[fg]naphthacene-1,2,8-trione.

Keywords: 2a,7a-diazacyclopenta[fg]naphthacene, enamines, isoquino[3,2-b]quinazoline, acylation, alkylation.

Investigations in the region of the chemistry of isocarbostyril derivatives are extremely promising from the pharmacological standpoint. According to the MDDR database [2], the isoquinol-1-one structural fragment is present in three medical products on the pharmaceutical market: *Draquinolol*, *Tilisolol*, and *Palonosetron*. Derivatives of 3-aminoisoquinol-1-one have also been patented: A non-narcotic analgesic [3] and an inhibitor of poly(ADP-riboso)synthetase [4].

Data on the properties of derivatives of the isoquino[3,2-*b*]quinazoline series first appeared in the middle of the last century: The cyanoethylation and oxidation of 5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**1**) were mentioned in [5], and high antifungal and antibacterial activity was discovered in the case of 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one [6]. The presence of a secondary enamine fragment in the molecule of isoquino[3,2-*b*]quinazolin-11-one **1** is promising in respect of further modification of the structure, and this makes it possible to expect that the high activity and chemical selectivity of this group will appear in reactions with electrophilic reagents.

In the present work we studied the most characteristic reactions of enamines – acylation and alkylation.

* For Communication 29 see [1].

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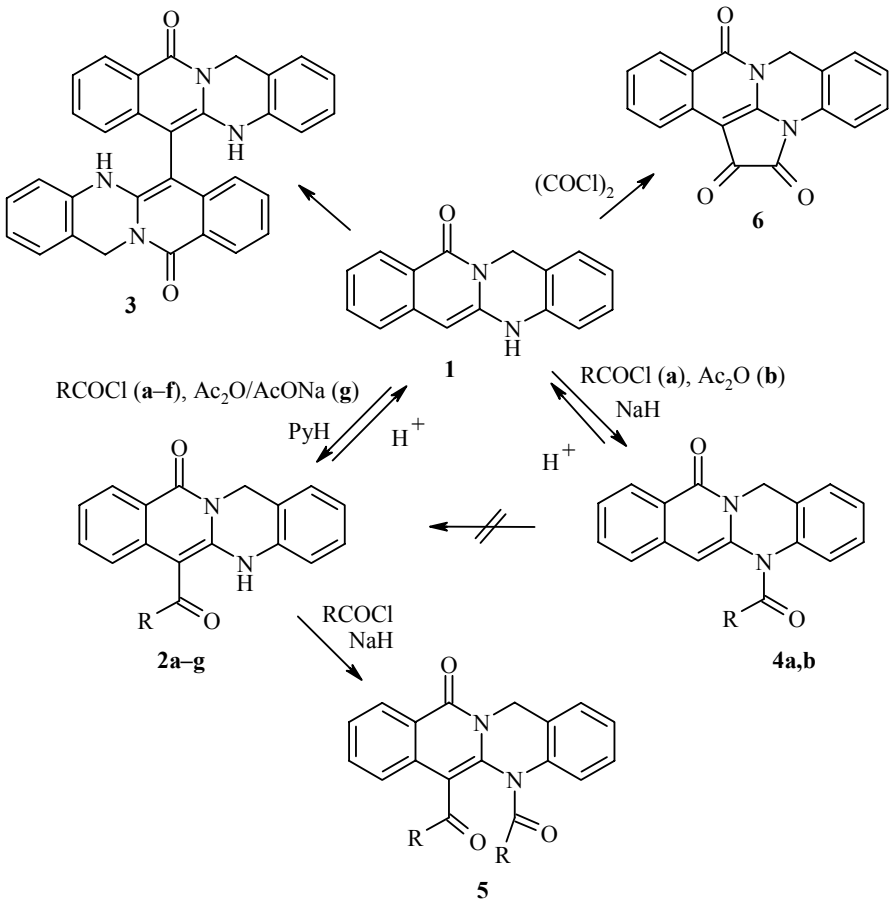


2 a R = 4-$EtOC_6H_4$, **b** R = 4- $O_2NC_6H_4$, **c** R = 2-MeC_6H_4, **d** R = 3,5-$(O_2N)_2C_6H_3$,
e R = 2-furyl, **f** R = 2-thienyl, **g** R = Me; **4 a** R = 4-$EtOC_6H_4$, **b** R = Me; **5** R = 4-$EtOC_6H_4$

The limited solubility of the quinazolinone **1** in a series of solvents (nonpolar and low-boiling polar solvents) and also its tendency to oxidize that we had previously observed [7] predetermined the choice of conditions for acylation to a significant degree. It was found that 6-acyl-5,13-dihydro-11H-isoquino-[3,2-*b*]quinazolin-11-ones **2a-f** are formed with high yields (64-83%) when compound **1** is heated with carboxylic acid chlorides in anhydrous pyridine. The use of 4-nitro- and 3,5-dinitrobenzoyl chlorides in this reaction leads to a mixture of products from acylation **2b**,**d** and oxidation (the dimer 5,13,5',13'-tetrahydro[6,6']bi[isoquino[3,2-*b*]quinazoline]-11,11'-dione (**3**) [7]); the latter is easily separated during recrystallization of the reaction products from DMF. The boiling of isoquino[3,2-*b*]quinazolin-11-one (**1**) in acetic anhydride in the presence of an excess of anhydrous sodium acetate leads to the formation of 6-acetyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**2g**).

The structure of the obtained acyl-substituted isoquino[3,2-*b*]quinazolin-11-ones was established on the basis of their spectral characteristics (see Table 1). The retention of the signal for the N(5)H group (ν_{NH} 3450 cm^{-1} and δ_{NH} in the region of 13.02-10.19 ppm respectively) in the IR and ^1H NMR spectra and the absence of resonance from the H-6 proton in the ^1H NMR spectra indicate the formation of C(6)-substitution products. Attention is drawn to the position of the signal for the H-7 proton in the ^1H NMR spectra of the products **2a-g**. In the case of the 6-acetyl derivative **2g**, as expected, its resonance is observed in a more downfield region (7.81 ppm) compared with the initial compound **1** (7.36 ppm) [7], while in the 6-aroyl and 6-hetaroyl

TABLE 1. The Spectral Characteristics of the Products from Acylation and Alkylation of Isoquino[3,2-*b*]quinazolin-11-one **1**

Compound	IK spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)				
		$N_{(5)}H$ (1H, s)	ArH	H-6 (1H, s)	H-13 (2H, s)	Other signals
1	2	3	4	5	6	7
2a	3450 (NH), 1672 (C=O), 1606, 1591, 1564, 1323, 1255 (C–O), 1163, 785	10.81	8.12 (1H, d, ^3J = 7.5, H-10); 7.59 (2H, d, ^3J = 9.0, H-2',6'); 7.35 (1H, d, ^3J = 7.5, H-1); 7.31 (1H, t, ^3J = 7.5, H-8); 7.21 (1H, t, ^3J = 7.5, H-3); 7.17 (1H, t, ^3J = 7.5, H-9); 7.02 (2H, m, H-2,4); 6.94 (3H, m, H-7,3',5')	—	5.22	4.07 (2H, q, ^3J = 7.0, OCH_2); 1.32 (3H, t, ^3J = 7.0, CH_3)
2b	3450 (NH), 1676 (C=O), 1585, 1558 (NO_2), 1524, 1358, 1319 (NO_2), 1236, 750	11.91	8.23 (2H, d, ^3J = 8.5, H-3',5'); 8.11 (1H, d, ^3J = 8.0, H-10); 7.78 (2H, d, ^3J = 8.5, H-2',6'); 7.38 (1H, d, ^3J = 7.5, H-1); 7.26 (2H, m, H-3,8); 7.19 (1H, t, ^3J = 7.5, H-9); 7.09 (1H, t, ^3J = 7.5, H-2); 7.04 (1H, d, ^3J = 8.0, H-4); 6.84 (1H, d, ^3J = 8.0, H-7)	—	5.25	—
2c	3450 (NH), 1672 (C=O), 1583, 1558, 1321, 760	13.02	8.08 (1H, d, ^3J = 7.5, H-10); 7.38 (1H, d, ^3J = 7.5, H-1); 7.35 (1H, m, H-4'); 7.31 (1H, d, ^3J = 7.5, H-6'); 7.29 (1H, t, ^3J = 7.5, H-8); 7.16-7.08 (5H, m, H-2,3,4,3',5'); 6.66 (1H, d, ^3J = 8.0, H-7)	—	5.25	2.29 (3H, s, CH_3)
2d	3450 (NH), 1674 (C=O), 1597, 1564 (NO_2), 1543, 1340 (NO_2), 750, 705	11.80	8.93 (1H, s, H-4'); 8.68 (2H, s, H-2',6'); 8.18 (1H, d, ^3J = 8.0, H-10); 7.40 (1H, d, ^3J = 7.5, H-1); 7.31-7.22 (3H, m, H-3,8,9); 7.11 (1H, t, ^3J = 7.5, H-2); 7.05 (1H, d, ^3J = 8.0, H-4); 6.98 (1H, d, ^3J = 8.0, H-7)	—	5.28	—
2e	3450 (NH), 1666 (C=O), 1591, 1560, 1323	10.60	8.12 (1H, d, ^3J = 7.5, H-10); 7.88 (1H, s, H-3'); 7.45 (1H, t, ^3J = 7.5, H-8); 7.34 (1H, d, ^3J = 7.5, H-1); 7.21 (2H, m, H-3,9); 7.16 (1H, d, ^3J = 4.0, H-5'); 7.06 (1H, d, ^3J = 8.0, H-7); 7.02 (1H, t, ^3J = 8.0, H-2); 6.99 (1H, d, ^3J = 8.0, H-4); 6.66 (1H, dd, ^3J = 1.5, ^3J = 4.0, H-4')	—	5.19	—
2f	3450 (NH), 1664 (C=O), 1591, 1560, 1487, 1319, 1240	10.19	8.12 (1H, d, ^3J = 8.0, H-10); 7.97 (1H, br. s, H-3'); 7.42 (2H, m, H-8,5'); 7.34 (1H, d, ^3J = 7.5, H-1); 7.25 (1H, d, ^3J = 7.5, H-7); 7.20 (2H, m, H-3,9); 7.07 (1H, m, H-4'); 7.00 (1H, t, ^3J = 8.0, H-2); 6.96 (1H, d, ^3J = 7.5, H-4)	—	5.20	—
2g	3450 (NH), 1674 (C=O), 1583, 1560, 1500, 1317, 770	12.92	8.15 (1H, d, ^3J = 7.5, H-10); 7.81 (1H, d, ^3J = 8.0, H-7); 7.66 (1H, t, ^3J = 7.5, H-8); 7.35 (1H, d, ^3J = 7.5, H-1); 7.31 (1H, t, ^3J = 7.5, H-9); 7.26 (1H, t, ^3J = 7.5, H-3); 7.07 (2H, m, H-2,4)	—	5.19	2.52 (3H, s, CH_3)
4a	1672 (C=O), 1630 (C=O), 1605, 1317, 1257 (C–O), 1176, 770, 750	—	8.19 (1H, d, ^3J = 8.0, H-10); 7.61 (3H, m, H-1,4,8); 7.46 (3H, m, H-7,2',6'); 7.43 (1H, t, ^3J = 7.5, H-9); 7.33 (1H, t, ^3J = 7.5, H-3); 7.28 (1H, t, ^3J = 7.5, H-2); 6.82 (2H, d, ^3J = 8.5, H-3',5')	6.68	5.42	3.97 (2H, q, ^3J = 6.5, OCH_2); 1.25 (3H, t, ^3J = 6.5, CH_3)

TABLE 1 (continued)

1	2	3	4	5	6	7
4b	1674 (C=O), 1635 (C=O), 1610, 1315, 770, 755	—	8.24 (1H, d, ^3J = 8.0, H-10); 7.64 (3H, m, H-1,4,8); 7.50 (1H, d, ^3J = 7.5, H-7); 7.44 (1H, t, ^3J = 7.5, H-9); 7.40 (1H, t, ^3J = 7.5, H-3); 7.29 (1H, t, ^3J = 7.5, H-2)	6.85	5.15 (br.)	2.39 (3H, s, CH_3)
5	1675 (C=O), 1605, 1302, 1255 (C–O), 1157, 1040, 785, 760	—	8.10 (1H, d, ^3J = 8.0, H-10); 7.63 (1H, d, ^3J = 6.5, H-1); 7.59 (2H, d, ^3J = 8.5, H-2",4"); 7.53 (1H, t, ^3J = 7.5, H-8); 7.35-7.27 (3H, m, H-3,2',6'); 7.18 (2H, m, H-2,9); 7.01 (2H, m, H-3",5"); 6.93 (2H, m, H-3',5'); 6.85 (1H, d, ^3J = 8.0, H-4); 6.72 (1H, d, ^3J = 8.0, H-7)	—	5.21	4.07 (4H, m, OCH_2); 1.33 (6H, m, CH_3)
6	1686 (C=O), 1628 (C=O), 1606, 1541, 1497, 1115, 775	—	8.35 (1H, d, ^3J = 8.0, H-12); 8.19 (1H, d, ^3J = 8.0, H-3); 8.15 (1H, d, ^3J = 8.0, H-9); 7.82 (1H, t, ^3J = 8.0, H-11); 7.53 (1H, d, ^3J = 8.0, H-6); 7.45 (2H, m, H-4,10); 7.29 (1H, t, ^3J = 8.0, H-5)	—	—*	—
7a	1654 (C=O), 1617, 1592, 1551, 1474, 790, 758, 692	—	8.09 (1H, d, ^3J = 8.0, H-10); 7.56 (1H, t, ^3J = 7.0, H-8); 7.50 (1H, d, ^3J = 8.0, H-7); 7.39 (1H, d, ^3J = 7.5, H-1); 7.34 (1H, t, ^3J = 8.0, H-3); 7.22 (1H, t, ^3J = 8.0, H-9); 7.08 (1H, d, ^3J = 8.0, H-4); 7.04 (1H, t, ^3J = 7.5, H-2)	6.10	5.08	3.34 (3H, s, CH_3)
7b	1647 (C=O), 1583, 1554, 1475, 1387, 1259 (C–N), 745	—	8.07 (1H, d, ^3J = 8.0, H-10); 7.57-7.51 (2H, m, H-7,8); 7.38-7.31 (2H, m, H-1,3); 7.22 (1H, t, ^3J = 8.0, H-9); 7.14 (1H, d, ^3J = 8.0, H-4); 7.02 (1H, t, ^3J = 7.5, H-2)	6.18	5.07	4.00 (2H, q, ^3J = 6.8, OCH_2); 1.38 (3H, t, ^3J = 6.8, CH_3)
7c	1655 (C=O), 1552, 1489, 1470, 1176, 780, 750	—	8.09 (1H, d, ^3J = 8.0, H-10); 7.51 (1H, t, ^3J = 8.0, H-8); 7.43-7.32 (6H, m, H-1,7,2',3',5',6'); 7.22 (2H, m, H-3,9); 7.02 (1H, t, ^3J = 7.5, H-2); 6.84 (1H, d, ^3J = 8.0, H-4)	5.97	5.20	5.22 (2H, s, CH_2)
8	1665 (C=O), 1640, 1598, 1573, 1480, 1256 (C–O), 1170, 775	—	8.24 (1H, d, ^3J = 8.0, H-10); 7.65–7.57 (4H, m, H-1,8,2',6'); 7.45 (1H, d, ^3J = 7.5, H-4); 7.35 (1H, t, ^3J = 7.5, H-3); 7.25 (1H, t, ^3J = 8.0, H-9); 7.10 (1H, t, ^3J = 7.5, H-2); 6.86 (2H, d, ^3J = 8.5, H-3',5'); 6.40 (1H, d, ^3J = 8.0, H-7)	—	5.12 (br.)	4.05 (2H, q, ^3J = 7.0, OCH_2); 3.44 (2H, q, ^3J = 6.7, NCH_2); 1.31 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 0.95 (3H, t, ^3J = 6.7, $NCH_2C\underline{H}_3$)

* δ 5.16 (2H, s, H-7).

derivatives **2a**-**f** it is in the more upfield region (6.66-7.20 ppm). We attribute the last effect to the relative increase in the population of the synperiplanar conformation of the acylation products **2a**-**g** as a consequence of restricted rotation about the C(6)–COR bond, due to steric effects and to the formation of an intramolecular hydrogen bond between the N(5) atom and the oxygen atom of the carbonyl group in the acyl substituent.

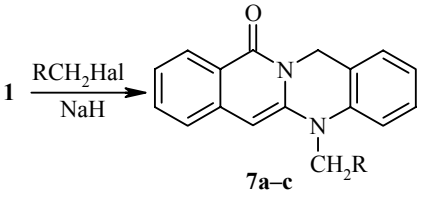
Earlier [8-10] we established that condensed derivatives of 3-aminoisoquinolin-1-one (which also have a secondary amine fragment in their structure) exhibit ambident characteristics in reactions with electrophiles. Thus, mixtures of products from C- and N-acylation, the composition of which depended on the structure of the reagents, were obtained during the acylation of 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1H)-one [8, 9] and benzimidazo[1,2-*b*]isoquinolin-11(5H)-one [10] in the presence of bases (pyridine, triethylamine). However, the formation of appreciable amounts of the isomeric acylation product was not observed (by TLC and NMR) in the case of isoquino[3,2-*b*]quinazolin-11-one (**1**). At the same time if a stronger base (sodium hydride) was used in DMF with heat the 5-acyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-ones **4a**,**b** were the only products. Acylation of the anion generated from the isoquino[3,2-*b*]quinazolin-11-one **1** by the action of the strong base obviously occurs in this case. The formation of the N(5)-acyl-substituted isoquino[3,2-*b*]quinazolin-11-ones is indicated by the absence of signals for the N(5)H group in their ^{1}H NMR and IR spectra and by the presence of signals for the methine proton in the ^{1}H NMR spectra in the region of 6.68 (**4a**) and 6.85 ppm (**4b**). The broadening of the signal for the protons of the methylene group H-13 in the spectrum of compound **4b** indicates a decrease in the conformational mobility of the isoquino[3,2-*b*]quinazoline ring as a result of the familiar effect of increase in the order of the N–CO amide bond in amides [11].

The observed changes in the chemical shifts of the aromatic protons, for the accurate assignment of which homonuclear two-dimensional correlation spectroscopy COSY was used (for the case of **2a** and **4a**), agree fully with the structure of compounds **2a**-**g** and **4a**,**b**. The assignment of the structure of the acylation products to C(6)- or N(5)-acyl-substituted isoquino[3,2-*b*]quinazolin-11-ones was also confirmed by the data from the ^{13}C NMR and UV spectra (for the case of **2a**,**g** and **4a**, see Experimental).

It is known [9, 12] that N-acyl-substituted enamines are capable of rearrangement. In the case of compounds **4a**,**b** the formation of the isomeric 6-acylisoquino[3,2-*b*]quinazolin-11-ones **2a**,**g** during prolonged heating of their solutions in high-boiling solvents (DMF, DMSO) and pyridine was not detected (according to the data from TLC). Compounds **2a**-**g** and **4a**,**b** proved unstable when heated in acetic acid and were easily hydrolyzed with the formation of isoquino[3,2-*b*]quinazolin-11-one **1**. In a basic medium (pyridine) the acyl derivatives of isoquino[3,2-*b*]quinazolin-11-one are completely stable, and they are inert to the action of acylating reagents. However, by heating compound **2a** in DMF with *p*-ethoxybenzoyl chloride in the presence of sodium hydride we were able to isolate and characterize the product from repeated acylation – 5,6-di(4-ethoxybenzoyl)-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**5**).

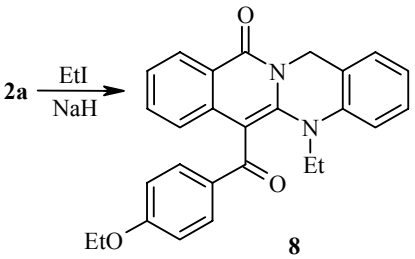
The transformation of isoquino[3,2-*b*]quinazolin-11-one **1** on heating with oxalyl chloride, leading to 7H,8H-2a,7a-diazacyclopenta[*fg*]naphthacene-1,2,8-trione (**6**), obviously takes place according to the same scheme – C-acylation followed by N-acylation. A derivative of this heterosystem (7H,8H-2a,7a-diazacyclopenta[*fg*]naphthacene-1,7(2H)-dione) was obtained earlier [13] under similar conditions by heating 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one in chloroacetyl chloride. In the case of compound **1** heating in chloroacetyl chloride leads to a complex mixture of unidentified products. The structure of the product **6** was confirmed by mass spectrometry and its IR and NMR spectra. Two strong absorption bands in the region of 1686 and 1628 cm^{-1} in the IR spectrum correspond to the stretching vibrations of the carbonyl groups of the conjugated ketones and amides respectively. In the ^{13}C NMR spectrum there are three signals for the carbon atoms of the carbonyl groups at 173.15 (C-1), 161.34 (C-8), and 158.53 ppm (C-2). The signals of the aromatic protons, observed in the downfield region, were assigned to H-12 (8.35), H-3 (8.19), and H-9 (8.16 ppm). The descreening of the H-12 and H-3 protons is due both to increase in the electron-accepting properties of the neighboring atoms (C-12b and N-2a) and to the anisotropic effect of the carbonyl groups C(1)=O and C(2)=O.

We then studied the alkylation of isoquino[3,2-*b*]quinazolin-11-one **1**. The fusion of compound **1** with alkyl halides or alkyl tosylates at 120-160°C leads to a complex mixture of products, the main component of which is the product from oxidative coupling – the dimer **3**. A similar result was obtained by heating a solution of **1** in acetonitrile with bromoacetophenone. The reaction of compound **1** with alkyl halides in the presence of bases only leads to alkylation products when the mixture of reagents is heated in DMF in the presence of sodium hydride. Under these conditions high yields of the 5-alkyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-ones **7a-c** are obtained. As in the case of the 5-acyl-substituted 4**a**,**b**, the ^{1}H NMR spectra of compounds **7a-c** are characterized by the presence of a signal for the methine proton H-6 and the absence of a signal for N(5)H (see Table 1).



7a–c

a R = H, **b** R = Me, **c** R = 4-ClC_6H_4



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The obtained 5-alkyl-substituted isoquino[3,2-*b*]quinazolin-11-ones **7a-c** are inert toward alkylating and acylating agents. At the same time 6-acylisoquino[3,2-*b*]quinazolin-11-one **2a** is readily converted into 6-(4-ethoxybenzoyl)-5-ethyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**8**) when heated with ethyl iodide in DMF in the presence of NaH. The signals in the ^{1}H NMR spectrum of compound **8** were assigned on the basis of COSY and NOESY experiments. Its ^{1}H NMR spectrum has a number of special features. The presence of bulky substituents at the *peri* positions (5 and 6) leads to restricted rotation about the N(5)–C and C(6)–C single bonds and, consequently, to the realization of restricted conformations and to increase in the asymmetry of the molecule, which shows up in the broadening of the signal for the protons of the H-13 methylene group. Another result is the upfield shift of the signals for the protons of the N(5)–C_2H_5 group compared with those for compound **7b** not having an electrophilic substituent at the C-6 atom, and this is due to the anisotropic effect of the benzoyl carbonyl group.

Analysis of the literature on the biological characteristics of 1-isoquinolone revealed an extremum in respect of transmembrane receptors in their pharmacological activity profile. In order to assess the biological potential of the substances described in the present work the biological activity spectrum was calculated. The PASS program (Prediction of Activity Spectra for Substances) was used for the calculations [14-16]. The program is based on comparison of the calculated 2D descriptors for each molecule (MNA – Multilevel Neighbourhoods of Atoms) with the set of descriptors for selection of the compounds with high activity and selection of the inactive compounds respectively. The final result is presented by the program as the probability of the appearance of activity (P_a) and inactivity (P_i) in the compounds expressed as fractions.

More than 3000 types of activities for each compound were included in the calculation, and the activity threshold was selected as $P_a > 0.75$; $P_i < 0.2$. It was found that compounds **7b** and **8** have the greatest pharmacological potential. Among the activities characteristic of most of the compounds predicted with high probability it is necessary to single out their inhibition of various types of hydrolases and hydratases and also their regulatory activity with respect to transmembrane receptors. They include muscarine acetylcholine (type M_1), GABA, and α_1-adrenoreceptors. However, whereas antagonistic activity is predicted for the first two receptors, these substances must exhibit mimetic characteristics toward the α_1-adrenoreceptor. It has also been suggested that they have the characteristics of adrenaline release inhibitors. Among the pharmacological effects predicted for compounds of such type there are the correction of sleep disturbances, coronary deficiency, and myocardial ischemia.

TABLE 2. The Physicochemical Characteristics and Elemental Analyses

Compound	Empirical formula	Found, % / Calculated, %			mp, °C *	Yield, %
		C	H	N		
2a	$C_{25}H_{20}N_2O_3$	75.65 / 75.74	4.98 / 5.08	7.10 / 7.07	170-172	82
2b	$C_{23}H_{15}N_3O_4$	69.42 / 69.52	3.74 / 3.80	10.60 / 10.57	226-227	85
2c	$C_{24}H_{18}N_2O_2$	78.60 / 78.67	4.88 / 4.95	7.67 / 7.65	206-208	67
2d	$C_{23}H_{14}N_4O_6$	62.37 / 62.45	3.13 / 3.19	12.67 / 12.66	288-289	83
2e	$C_{21}H_{14}N_2O_3$	73.61 / 73.68	4.04 / 4.12	8.21 / 8.18	187-188	64
2f*[2]	$C_{21}H_{14}N_2O_2S$	70.32 / 70.37	3.89 / 3.94	7.83 / 7.82	175-176	78
2g	$C_{18}H_{14}N_2O_2$	74.33 / 74.47	4.80 / 4.86	9.69 / 9.65	209-211	83
4a	$C_{25}H_{20}N_2O_3$	75.68 / 75.74	5.00 / 5.08	7.11 / 7.07	205-207	78
4b	$C_{18}H_{14}N_2O_2$	74.36 / 74.47	4.79 / 4.86	9.66 / 9.65	204-206	58
5	$C_{34}H_{28}N_2O_5$	74.85 / 74.98	5.10 / 5.18	5.15 / 5.14	152-154	53
6	$C_{18}H_{10}N_2O_3$	71.47 / 71.52	3.27 / 3.33	9.26 / 9.27	318-320	69
7a	$C_{17}H_{14}N_2O$	77.78 / 77.84	5.30 / 5.38	10.70 / 10.68	123-124	58
7b	$C_{18}H_{16}N_2O$	78.18 / 78.24	5.73 / 5.84	10.14 / 10.14	156-158	53
7c*[3]	$C_{23}H_{17}ClN_2O$	73.97 / 74.09	4.55 / 4.60	7.54 / 7.51	177-179	46
8	$C_{27}H_{24}N_2O_3$	76.33 / 76.39	5.65 / 5.70	6.61 / 6.60	148-149	75.5

* Solvent for crystallization: DMF (compounds **2a-f**, **4a**, **b** and **7a-c)** and 1:1 DMF–2-propanol (compounds **2g**, **4b**, **5**, and **8**).

*[2] Data from analysis for S: Calculated 8.95%; found 8.90%.

*[3] Data from analysis for Cl: Calculated 9.51%; found 9.55%.

EXPERIMENTAL

The IR spectra of the compounds (in tablets with potassium bromide) were recorded on a Hewlett Packard UR 20 instrument. The ^1H and ^{13}C NMR spectra of the products were obtained and the COSY homonuclear correlation experiments were preformed on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively) in DMSO-d_6 with TMS as internal standard. The UV spectra were recorded on a SHIMADZU UV-3100 UV-vis-NIR recording spectrophotometer in methanol. The mass spectra of the compounds were obtained by HPLC-MS on an AGILENT/100-Series instrument (CI, acetonitrile, 0.05% formic acid). The reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates.

6-Acyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-ones (2a-f). Isoquinoquinazoline **1** (0.25 g, 1 mmol) was dissolved by heating in anhydrous pyridine (15 ml), and aroyl (hetaroyl) chloride (1.1 mmol) was added. The mixture was boiled for 3-5 h and cooled, and of water (50 ml) was added. The precipitate was filtered off and washed with 2-propanol. The product was crystallized from DMF.

Compound 2a. ^{13}C NMR spectrum, δ, ppm: 193.37 (6-C=O); 162.28 (C-11); 161.37 (C-4"); 144.66 (C-5a); 137.03 (C-4a); 134.86 (C-1'); 133.26 (C-6a); 132.36 (C-8); 131.91 (C-2',6'); 129.01 (C-3); 127.83 (C-10); 126.97 (C-1); 125.25 (C-7); 123.66 (C-9); 123.32 (C-2); 120.47 (C-10a); 118.59 (C-13a); 115.57 (C-4); 114.58 (C-3',5'); 94.67 (C-6); 63.94 (OCH_2); 47.72 (C-13); 14.99 (CH_3). UV spectrum, λ_{max} ($\varepsilon\cdot10^{-4}$, $l\cdot mol^{-1}\cdot cm^{-1}$): 295 (2.47), 389 (1.66). Mass spectrum, *m/z* (*I,* %): 397 $[M+1]^+$ (100).

6-Acetyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (2g). A mixture of isoquinoquinazoline **1** (0.25 g, 1 mmol) and anhydrous sodium acetate (0.12 g, 1.5 mmol) in acetic anhydride (10 ml) was boiled for 2 h. The mixture was cooled, and water (30 ml) was added. The precipitate was filtered off and washed with 2-propanol. The product was crystallized from a 1:1 mixture of 2-propanol and DMF. ^{13}C NMR spectrum, δ, ppm: 197.21 (6-C=0); 161.19 (C-11); 147.11 (C-5a); 136.33 (C-4a); 133.91 (C-6a); 133.26 (C-8); 129.13 (C-3); 128.14 (C-10); 126.99 (C-1); 125.03 (C-7); 124.04 (C-2,9); 121.08 (C-10a); 118.71 (C-13a); 115.87 (C-4); 96.06 (C-6); 42.65 (C-13); 32.11 (CH_3). Mass spectrum, *m/z* (*I*, %): 291 $[M+1]^+$ (100).

5-Acyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-ones 4a,b. Isoquinoquinazoline **1** (0.25 g, 1 mmol) was dissolved by heating in anhydrous DMF (25 ml). Sodium hydride (0.03 g, 1.2 mmol) was added to the cooled solution. When the release of hydrogen had stopped *p*-ethoxybenzoyl chloride or acetic anhydride (1.1 mmol) was added. The mixture was stirred at 20°C for 1.5 h, and the precipitate was filtered off. The filtrate was evaporated under vacuum, and the residue was crystallized from DMF.

Compound 4a. ^{13}C NMR spectrum, δ, ppm: 167.84 (5-C=0); 161.18 (C-11); 160.67 (C-4′); 138.12 (C-5a); 137.10 (C-4a); 136.32 (C-1′); 133.20 (C-6a,8); 131.44 (C-2',6'); 129.87 (C-3); 128.60 (C-10); 127.62 (C-1); 127.15 (C-7); 126.82 (C-4); 126.73 (C-2,9); 124.17 (C-13a); 122.98 (C-10a); 114.30 (C-3',5'); 101.21 (C-6); 63.78 (OCH_2); 42.58 (C-13); 14.91 (CH_3). UV spectrum (EtOH), λ_{max}, nm ($\varepsilon\cdot10^{-4}$, $l/mol^{-1}\cdot cm^{-1}$): 276 (1.71), 335 (0.93). Mass spectrum, *m/z* (*I*, %): 397 $[M+1]^+$ (100).

5,6-Di(4-ethoxybenzoyl)-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (5). This compound was obtained by the method described above for the synthesis of the products **4a**,**b**, using 6-(4-ethoxybenzoyl)isoquinoquinazoline **2a** (0.4 g, 1 mmol) instead of the isoquinoquinazoline **1**. The reaction mixture was heated for 7 h, and the product was purified by recrystallization from a 1:1 mixture of 2-propanol and DMF.

7H,8H-2a,7a-Diazacyclopenta[*fg*]naphthacene-1,2,8-trione (6). A mixture isoquinoquinazoline **1** (0.25 g, 1 mmol) and oxalyl chloride (10 ml) was boiled for 2 h. The excess of the oxalyl chloride was evaporated under vacuum, and the residue was recrystallized twice from DMF. ^{13}C NMR spectrum, δ, ppm: 173.15 (C-1); 161.34 (C-8); 158.53 (C-2); 157.98 (C-12c); 135.54 (C-11); 131.63 (C-2b); 129.35 (C-12a); 129.26 (C-4); 128.66 (C-9); 128.18 (C-6); 126.36 (C-12); 125.80 (C-10); 122.35 (C-5); 120.79 (C-8a); 117.81 (C-6a); 115.28 (C-3); 90.71 (C-12b); 42.87 (C-7). UV spectrum, λ_{max} ($\varepsilon\cdot10^{-4}$, $l\cdot mol^{-1}\cdot cm^{-1}$): 246 (1.74), 279 (2.11). Mass spectrum, *m/z* (*I*, %): 303 $[M+1]^+$ (100).

5-Alkyl-5,13-dihydro-11-isoquino[3,2-*b*]quinazolin-11-ones 7a-c. The compounds were obtained by the method described above for the synthesis of the products **4a**,**b**, using (1.2 mmol) of alkyl halide instead of *p*-ethoxybenzoyl chloride. The reaction mixture was heated for 3-4 h, and the product was purified by recrystallization from DMF.

6-(4-Ethoxybenzoyl)-5-ethyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (8). The compound was synthesized by the method described for the synthesis of the products **4a**,**b** using 6-(4-ethoxybenzoyl)isoquinoquinazoline **2a** (0.4 g, 1 mmol) instead of the isoquinoquinazoline **1** and ethyl iodide (0.16 g, 2 mmol) instead of *p*-ethoxybenzoyl chloride. The reaction mixture was heated for 7 h, and the product was purified by recrystallization from a 1:1 mixture of 2-propanol and DMF. Mass spectrum, *m/z* (*I*, %): 425 $[M+1]^+$ (100).

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