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CONDENSED ISOQUINOLINES 24*. REACTION OF 6,11-DIHYDRO-13H-ISOQUINO[3,2-*b*]QUINAZOLIN-13-ONE WITH CARBONYL COMPOUNDS

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The reaction of 6,11-dihydro-13H-isoquino[3,2-b]quinazolin-13-one with carbonyl compounds occurs at the $C_{(6)}$ and/or $N_{(5)}$ atoms depending on the nature of the reagent and the conditions. Condensation with aldehydes gives 6-arylidene-6,11-dihydro-13H-isoquino[3,2-b]quinazolin-13-ones. Acylation using acid anhydrides or acid chlorides gave 5-acyl-, 6-acyl-, and 5,6-diacyl-5,11-dihydro-13H-isoquino[3,2-b]quinazolin-13-ones depending again on the reaction conditions. Acylation using chloroacetyl chloride is accompanied by an intramolecular alkylation to give 7H,8H-2a,7a-diaza-cyclopenta[f,g]naphthacene-1,7(2H)-dione. Phenyl isocyanate gave the derivative containing a CONHPh group at position 6.

Keywords: 7H,8H-2a,7a-diazacyclopenta[*f*,*g*]naphthacene-1,7(2H)-dione, isoquino[3,2-*b*]quinazoline, acylation.

The first report of the synthesis of isoquino[3,2-*b*]quinazolines appeared as long ago as the end of the 1960's [2]. However, their properties have not been systematically studied to the present time because of the poor availability of the compounds. In the study [2] only the cyanoethylation and oxidation of isoquino[3,2-*b*]quinazolin-11-one were reported. The high fungicidal and antimicrobial activity discovered for 6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (**1a**) [3] pointed to a promising study of the properties of related materials.

We have previously developed a relatively simple method for preparing derivatives of compound **1a** based on the rearrangement of the corresponding isomers of the angularly structured 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones. Examination of the features of this reaction showed an increased tendency of dihydro-13H-isoquinoquinazoline **1a** towards oxidation by atmospheric oxygen to give 6-oxo derivatives and dimerization products [1, 6, 7]. We have also studied deuterium exchange in compound **1a** which points to the activation of the 6-methylene group of the tetracycle towards electrophilic agents [4].

In the current work we have investigated the reaction of dihydro-13-isoquinoquinazolines **1a,b** with the aromatic aldehydes **2a-f** with the aim of preparing a series of 6-arylidene-6,11-dihydro-13H-isoquino[3,2-*b*]-quinazolin-13-ones **3a-f** (Tables 1-3). Three methods of synthesis of compounds of type **3** were studied: A – refluxing the indicated reagents in acetic anhydride; B – refluxing the base hydrobromides of **1a,b** with the

* For Communication 23 see [1].

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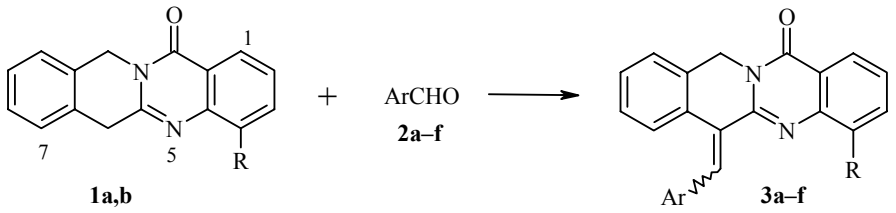


1a • HBr + 4-$O_2NC_6H_4CHO$ ⟶ **3g** • HBr

1 a R = H, **b** R = Cl; **2 a** Ar = 4-$Me_2NC_6H_4$, **b** Ar = Ph, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 4-BrC_6H_4, **e** Ar = 4-ClC_6H_4, **f** Ar = 4-$O_2NC_6H_4$; **3 a** R = H, Ar = 4-$Me_2NC_6H_4$; **b** R = Cl, Ar = 4-$Me_2NC_6H_4$; **c–g** R = H, **c** Ar = Ph, **d** Ar = 4-$MeOC_6H_4$, **e** Ar = 4-BrC_6H_4, **f** Ar = 4-ClC_6H_4, **g** Ar = 4-$O_2NC_6H_4$

aldehydes under the same conditions; C – refluxing the indicated reagents in 2-propanol in the presence of base. Method A proved successful only when using the *p*-(dimethylamino)benzaldehyde; products **3a** and **3b** being obtained in 50 and 65% yields respectively. The use of aldehydes **2b-f** under these conditions led to the formation of only trace amounts of the target substances **3**. The reaction occurred faster under method B conditions but was accompanied by the formation of significant amounts of side products. Only in the case of the hydrobromide **1a**·HBr and *p*-nitrobenzaldehyde **2f** was it possible to prepare the corresponding product **3g**·HBr (45% yield). Using the method **C** allowed the synthesis of the products **3c-f** from the base **1a** and aldehydes **2b-e** in moderate yields (30-37%) with prolonged (3-10 h) refluxing of the reagents in 2-propanol and in the presence of the base *t*-BuOK. It has previously been shown [8, 9] that the **1a** isomer 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**4**) reacts readily with substituted benzaldehydes over 30 min to give the arylidene derivatives in about 60% yields when the process is carried out in 2-propanol in the presence of morpholine or piperidine. The results we obtained are likely connected with the decreased activity of the linear isomer **1a** (when compared with the angular **4**) and also by its tendency to form oxidation products. Attempts to prepare the condensation products of 4-chlorodihydroisoquinoquinazolinone **1b** with the aldehydes **2b,d** under method **C** conditions were unsuccessful because of the readier oxidation of the halo substituted dihydro-13H-isoquino[3,2-*b*]quinazolinones than the unsubstituted **1a**.

The structure of products **3a-f, 3g**·HBr was confirmed from their ^{1}H NMR spectroscopic data (Table 3) which show characteristic C-11 methylene group signals in the region 5.1-5.2 ppm and for =C<u>H</u>Ar at 7.8-7.9 ppm as well as the signals for the substituent R, Ar protons and the aromatic protons of the tetracyclic system.

We have also studied the acylation of dihydro-13H-isoquinoquinazolinone **1a** with carboxylic acid chlorides and anhydrides. We and other authors have previously reported the acylation of compound **4** [8] and benzimidazo[1,2-*b*]isoquinolin-11(5H)-one (**5**) [10]. It was found that compound **4** exists in DMSO in the tautomeric imine and enamine forms but compound **5** only in the enamine form.

This difference affects their reactivity and the results of the acylation. A higher activity and the appearance of ambident properties is observed only for enamine **5** in reactions with substituted benzaldehydes. The dihydro-13H-isoquinoquinazolinone **1a** studied in our work has been established by spectroscopic methods to be in the imine form [6] and it proved to have significantly lower reactivity in the acylation reaction than both compound **4** and **5**.

It was found that, in contrast to the favored acylation of the dihydro-5H-isoquino[2,3-*a*]quinazolinone **4** (occurring after 15 min [8]), prolonged refluxing (4 h) of its linear isomer **1a** with acid chlorides in anhydrous pyridine gave products whose structure depends on the nature of the acylating reagent. The ratio of reagents also affects the result of the reaction markedly. With the use of an equimolar amount of compound **1a** and the acyl chloride the acylation does not fully occur and ^{1}H NMR data for the reaction mixture shows the presence of a considerable amount of the starting imine **1a**. The use of a two fold excess of acylating reagent leads to

TABLE 1. Characteristics for the Compounds Synthesized

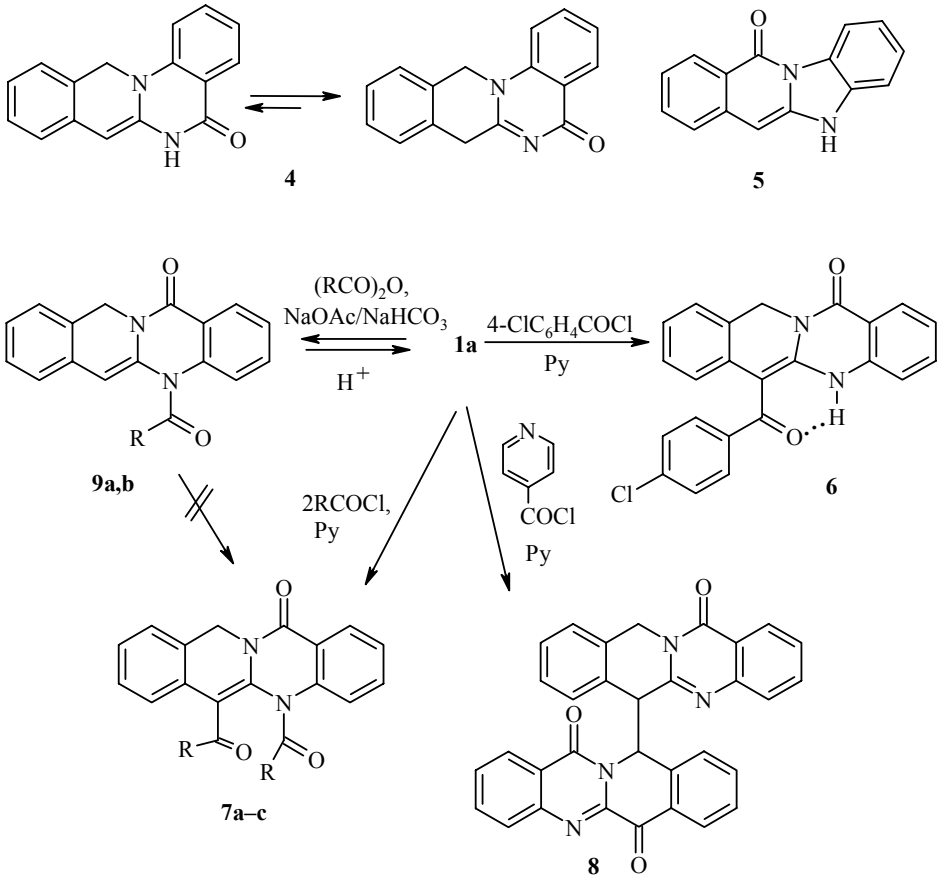
Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	Hal	N		
3a	$C_{25}H_{21}N_3O$	79.00 / 79.13	5.50 / 5.58	—	11.12 / 11.07	233-235	50
3b	$C_{25}H_{20}ClN_3O$	72.49 / 72.55	4.80 / 4.87	8.57 / 8.57	10.19 / 10.15	222-224	65
3c	$C_{23}H_{16}N_2O$	82.08 / 82.12	4.72 / 4.79	—	8.37 / 8.33	200-203	37
3d	$C_{24}H_{18}N_2O_2$	78.59 / 78.67	4.89 / 4.95	—	7.70 / 7.65	210-213	35
3e	$C_{23}H_{15}BrN_2O$	66.48 / 66.52	3.60 / 3.64	19.26 / 19.24	6.76 / 6.75	222-225	35
3f	$C_{23}H_{15}ClN_2O$	74.42 / 74.49	4.00 / 4.08	9.55 / 9.56	7.55 / 7.55	225-228	30
3g•HBr	$C_{23}H_{16}BrN_3O_3$	59.69 / 59.76	3.43 / 3.49	17.29 / 17.28	9.11 / 9.09	233-235	45
6	$C_{23}H_{15}ClN_2O_2$	71.37 / 71.41	3.87 / 3.91	9.15 / 9.16	7.28 / 7.24	196-199	65
7a	$C_{20}H_{16}N_2O_3$	72.20 / 72.28	4.80 / 4.85	—	8.45 / 8.43	193-195	70
7b	$C_{30}H_{20}N_2O_3$	78.89 / 78.93	4.40 / 4.42	—	6.16 / 6.14	233-235	65
7c	$C_{32}H_{24}N_2O_3$	79.28 / 79.32	4.92 / 4.99	—	5.80 / 5.78	268-270	67
9a	$C_{18}H_{14}N_2O_2$	74.40 / 74.47	4.81 / 4.86	—	9.66 / 9.65	221-223	47
9b	$C_{19}H_{16}N_2O_2$	74.90 / 74.98	5.27 / 5.30	—	9.23 / 9.20	187-190	35
10	$C_{18}H_{12}N_2O_2$	74.91 / 74.99	4.18 / 4.20	—	9.74 / 9.72	293-294	45
13	$C_{23}H_{17}N_3O_2$	75.12 / 75.19	4.60 / 4.66	—	11.45 / 11.44	> 300	25

* Recrystallization solvents: DMF (compounds **3a-f, 6, 7a-c, 9a,b, 10, 13**) and AcOH (compound **3g**·HBr).

TABLE 2. IR Spectra of the Compounds Synthesized

Compound	ν, cm^{-1}	Compound	ν, cm^{-1}
3a	1665 (C=O), 1595 (C=N), 1545, 1465, 1180, 765	**7a**	1743 (C=O), 1670 (C=O), 1655 (C=O), 1580, 1215, 1165, 775
3b	1665 (C=O), 1590 (C=N), 1510, 1425, 1180, 750	**7b**	1723 (C=O), 1660 (C=O), 1580, 1230, 1050, 760
3c	1668 (br, C=O, C=N), 1550, 1463, 770	**7c**	1730 (C=O), 1670 (C=O), 1580, 1235, 1060, 765, 745
3d	1660 (C=O), 1570 (C=N), 1550, 1450, 1248 (C–O), 770	**9a**	1640 (C=O), 1623 (C=O), 1595, 750
3e	1665 (br, C=O), 1575 (C=N), 1550, 1465, 763	**9b**	1650 (C=O), 1625 (C=O), 1600, 745
3f	1668 (br, C=O, C=N), 1550, 1465, 765	**10**	1690 (C=O), 1655 (C=O), 1590, 1540, 1480, 1275, 1140, 750
3g•HBr	1710 (C=O), 1620 (C=N), 1510 (^{as}~NO_2), 1335 (^{s}~NO_2), 765	**13**	3100 (NH), 1717 (C=O), 1680 (C=O), 1650, 1540, 1315, 745
6	3040 (NH), 1680 (br, C=O), 1613, 767, 750		

formation of the reaction products in good yields (65-70%). In the case of *p*-chlorobenzoyl chloride the monoacyl derivative **6** is obtained in 65% yield and from chlorides of acetic, benzoic, and *p*-toluic acids the diacyl derivatives **7a-c** in 65-70% yields, as shown from the results of their elemental analysis and from their ^{1}H NMR spectroscopic data.



7 a R = Me, **b** R = Ph, **c** R = 4-MeC$_6$H$_4$; **9 a** R = Me, **b** R = Et

In the examples of the acyl-substituted compounds **4** and **5** we have previously [8, 10] determined criteria for assigning the structures of the acylation products through the presence in the ^{1}H NMR and IR spectra of characteristic signals for =CH, CH_2, and NH groups and through the trend in the shifts of the benzene ring aromatic protons annelated to the heterocyclic system. For the 6-(4-chlorobenzoyl)-5,11-dihydro-13H-isoquino-[3,2-*b*]quinazolin-13-one (**6**) its spectroscopic characteristics agreed fully with those of the C-acyl-substituted compounds of **4** and **5**. The ^{1}H NMR spectrum of compound **6** showed the absence of a signal for the protons at atom $C_{(6)}$ together with a signal for the $N_{(5)}$-H proton to low field and powerfully broadened by exchange. The fixing of the benzene substituent (through formation of an intramolecular hydrogen bond between the oxygen atom of the carbonyl group and the $N_{(5)}$ atom) leads to a shielding of the H-7 proton by the benzene ring which is positioned in a plane orthogonal to the isoquinoquinazoline fragment due to steric constraints. As a result this proton resonates at higher field (6.49 ppm) than the H-7 proton of the starting compound **1a** [7] ($\Delta\delta$ = 0.9 ppm). One broad band is observed in the IR spectrum of product **6** at 1680 cm^{-1} for the stretching vibration of the carbonyl group in the region characteristic of the stretching vibrations of amides and C=C–C=O conjugated systems.

TABLE 3. ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shifts (DMSO-d_6); δ, ppm (*J*, Hz)			
	H arom.	$C_{(11)}H_2$ (2H, s)	$C_{(6)}H$ (1H, s)	other signals
1	2	3	4	5
3a	8.14 (1H, d, ^3J = 8.0, H-1); 7.75 (1H, t, ^3J = 7.6, H-3); 7.66 (1H, d, ^3J = 7.6, H-4); 7.62 (1H, d, ^3J = 7.4, H-10); 7.51 (1H, d, ^3J = 7.6, H-7); 7.43–7.40 (3H, m, H-2,2',6'); 7.29 (1H, t, ^3J = 7.6, H-8); 7.20 (1H, t, ^3J = 7.6, H-9); 6.58 (2H, d, ^3J = 8.8, H-3',5')	5.21	—	7.79 (1H, s, =CHAr); 3.01 (6H, s, $N(CH_3)_2$)
3b	8.08 (1H, dd, ^4J = 1.4, ^3J = 8.0, H-1); 7.85 (1H, dd, ^4J = 1.4, ^3J = 8.0, H-3); 7.64 (1H, d, ^3J = 7.6, H-10); 7.52 (1H, d, ^3J = 7.6, H-7); 7.42 (2H, d, ^3J = 8.8, H-2',6'); 7.38 (1H, t, ^3J = 8.0, H-2); 7.30 (1H, t, ^3J = 7.6, H-8); 7.21 (1H, t, ^3J = 7.6, H-9); 6.60 (2H, d, ^3J = 8.8, H-3',5')	5.21	—	7.87 (1H, s, =CHAr); 3.01 (6H, s, $N(CH_3)_2$)
3c	8.17 (1H, d, ^3J = 8.0, H-1); 7.78 (1H, t, ^3J = 7.6, H-3); 7.70 (1H, d, ^3J = 7.6, H-4); 7.54 (1H, d, ^3J = 7.6, H-10); 7.47 (3H, m, H-7,2',6'); 7.34–7.30 (5H, m, H-2,8,3'–5'); 7.13 (1H, t, ^3J = 7.2, H-9)	5.27		7.89 (1H, s, =CHAr)
3d	8.17 (1H, d, ^3J = 7.6, H-1); 7.78 (1H, t, ^3J = 8.0, H-3); 7.69 (1H, d, ^3J = 8.0, H-4); 7.54 (1H, d, ^3J = 7.2, H-10); 7.45 (4H, m, H-2,7,2',6'); 7.32 (1H, t, ^3J = 7.2, H-8); 7.18 (1H, t, ^3J = 7.6, H-9); 6.85 (2H, d, ^3J = 8.8, H-3',5')	5.25	—	7.84 (1H, s, =CHAr); 3.82 (3H, s, OCH_3)
3e	8.18 (1H, d, ^3J = 7.6, H-1); 7.79 (1H, t, ^3J = 8.0, H-3); 7.70 (1H, d, ^3J = 8.0, H-4); 7.56 (1H, d, ^3J = 7.2, H-10); 7.49 (1H, d, ^3J = 7.0, H-7); 7.47 (2H, d, ^3J = 8.2, H-2',6'); 7.42 (2H, d, ^3J = 8.2, H-3',5'); 7.34 (2H, m, H-2,8); 7.17 (1H, t, ^3J = 8.0, H-9)	5.28	—	7.83 (1H, s, =CHAr)
3f	8.18 (1H, d, ^3J = 7.6, H-1); 7.79 (1H, t, ^3J = 8.0, H-3); 7.70–7.53 (3H, m, H-4,7,10); 7.49 (2H, d, ^3J = 8.2, H-2',6'); 7.40 (2H, d, ^3J = 8.2, H-3',5'); 7.37 (1H, t, ^3J = 8.0, H-2); 7.26 (2H, m, H-8,9)	5.29	—	7.86 (1H, s, =CHAr)
3g•HBr	8.18 (3H, m, H-1,3',5'); 7.82 (1H, t, ^3J = 7.6, H-3); 7.74 (3H, m, H-4,2',6'); 7.60 (1H, d, ^3J = 7.6, H-10); 7.51 (1H, t, ^3J = 7.6, H-2); 7.38 (1H, t, ^3J = 7.6, H-9); 7.23 ((1H, d, ^3J = 8.0, H-7); 7.16 (1H, t, ^3J = 8.0, H-8)	5.33	—	7.97 (1H, s, =CHAr)

TABLE 3. (continued)

1	2	3	4	5
6	8.08 (1H, d, ^3J = 8.4, H-1); 7.75 (1H, t, ^3J = 7.6, H-3); 7.61 (2H, d, ^3J = 8.4, H-2',6'); 7.55 (1H, d, ^3J = 7.6, H-4); 7.35 (3H, m, H-2,3',5'); 7.27 (1H, d, ^3J = 7.6, H-10); 6.97 (1H, t, ^3J = 7.2, H-8); 6.89 (1H, t, ^3J = 7.2, H-9); 6.49 (1H, d, ^3J = 7.6, H-7)	5.51	—	15.10 (1H, br. s, NH)
	[8.62 (1H, d, ^3J = 8.0, H-1); 8.15 (2H, dd, ^4J = 2.0, ^3J = 8.5, H-2',6'); 7.93 (1H, t, ^3J = 8.0, H-3); 7.62 (2H, dd, ^4J = 2.0, ^3J = 8.5, H-3',5'); 7.50 (6H, m, H-2,4,7-10)]*	6.14 (d, ^2J = 16.5); 5.27 (d, ^2J = 16.5); 5.65 br.)		—
7a	8.17 (1H, d, ^3J = 8.0, H-1); 7.77 (1H, t, ^3J = 7.6, H-3); 7.65 (1H, d, ^3J = 8.2, H-4); 7.55 (1H, d, ^3J = 7.2, H-10); 7.49 (2H, m, H-2,7); 7.37 (1H, t, ^3J = 8.0, H-8); 7.32 (1H, t, ^3J = 8.0, H-9)	5.17	—	2.46 (3H, s, 5-$COCH_3$); 2.14 (3H, s, 6-$COCH_3$)
	[8.55 (1H, d, ^3J = 8.0, H-1); 8.18 (1H, t, ^3J = 8.0, H-3); 7.99 (1H, d, ^3J = 8.0, H-4); 7.94 (1H, t, ^3J = 8.0, H-2); 7.70 (1H, d, ^3J = 7.5, H-10); 7.59 (3H, m, H-7,8,9)]*	6.16 (br. s); 4.77 (br. s)	—	—
7b	8.15 (3H, m, H-1,2',6'); 7.67 (1H, t, ^3J = 7.6, H-3); 7.58–7.49 (7H, m, H-2,4,10,4',2'',4'',6''); 7.39-7.26 (5H, m, H-7,8,9,3',5'); 7.07 (2H, m, H-3'',5'')	5.35	—	—
7c	8.15 (3H, m, H-1,2',6'); 7.97 (2H, d, ^3J = 7.2, H-2'',6''); 7.87 (1H, m, H-6'); 7.64 (1H, t, ^3J = 7.2, H-3); 7.53 (1H, d, ^3J = 7.2, H-4); 7.48–7.41 (3H, m, H-2,7,10); 7.35 (2H, d, ^3J = 8.0, H-3',5'); 7.29–7.21 (2H, m, H-8,9); 7.04 (2H, d, ^3J = 7.2, H-3'',5'')	5.33	—	2.46 (3H, s, 4'-CH_3); 2.31 (3H, s, 4''-CH_3)
9a	8.21 (1H, d, ^3J = 8.0, H-1); 7.98 (1H, d, ^3J = 8.0, H-4); 7.72 (1H, t, ^3J = 8.0, H-3); 7.36 (1H, t, ^3J = 8.0, H-2); 7.22 (1H, d, ^3J = 7.2, H-7); 7.16 (2H, m, H-9,10); 7.00 (1H, t, ^3J = 7.2, H-8)	5.30	6.43	2.76 (3H, s, CH_3)
9b	8.17 (1H, d, ^3J = 8.0, H-1); 7.89 (1H, d, ^3J = 8.0, H-4); 7.72 (1H, t, ^3J = 8.0, H-3); 7.36 (1H, t, ^3J = 8.0, H-2); 7.18 (3H, m, H-7,9,10); 7.05 (1H, t, ^3J = 7.2, H-8)	5.23	6.46	2.66 (2H, m, CH_2); 2.54 (3H, d, ^3J = 7.0, CH_3)
10	8.02 (1H, d, ^3J = 8.0, H-6); 7.91 (1H, d, ^3J = 8.0, H-12); 7.69 (1H,t, ^3J = 8.0, H-4); 7.17 (4H, m, H-3,5,9,10); 7.02 (1H, t, ^3J = 8.0, H-11)	—		5.22 (2H, s, $C_{(8)}H_2$); 4.39 (2H, s, $C_{(2)}H_2$)
13	8.53 (1H, d, ^3J = 8.0, H-7); 8.35 (1H, d, ^3J = 8.0, H-2'); 8.15 (1H, d, ^3J = 7.2, H-1); 7.73 (1H, t, ^3J = 7.6, H-3); 7.54 (2H, m, H-10,6'); 7.48 (2H, m, H-2,4); 7.37-7.32 (3H, m, H-3',4',5'); 7.28-7.22 (2H, m, H-8,9)	5.22	—	4.50 br., NH + H_2O)

* Spectrum run in CF_3CO_2D.

The ^{1}H NMR spectra of the 5,6-diacyl-5,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones **7a-c** show different signals for the protons of two acyl substituents giving evidence for acylation at two positions of compound **1a**, i.e. the $C_{(6)}$ and $N_{(5)}$ atoms. The signals for the 5-NH and 6-CH_2 groups characteristic of the starting **1a** are absent. The structure of compounds **7a-c** was confirmed by their IR data. Hence the spectrum of the product **7a** showed three carbonyl group stretching bands; two amide type bands in the region 1650-1670 cm^{-1} (in the case of compounds **7b,c** one broad band) and one ketonic band in the characteristic range 1730-1740 cm^{-1}. The latter points to the absence of conjugation between the carbonyl group and the multiple $C_{(5a)}$=$C_{(6)}$ bond because of the steric hindrance which places the $N_{(5)}$ acyl substituent towards the position of the $C_{(6)}$ acyl group in the isoquinoquinazoline plane.

The tendency for oxidation of compound **1a** mentioned above became the reason for unsuccessful attempted acylated in pyridine using *p*-nitrobenzoyl chloride or isonicotinoyl chloride. In the latter example the product of oxidative dimerization 6,11-dihydro-11'H-[6,11']bis[isoquino[3,2-*b*]quinazolinyl]-13,6',13'-trione (**8**) was obtained in unexpectedly high yield (65%) and whose spectroscopic behavior and physical constants did not differ from a sample previously prepared [7].

Somewhat different results were obtained by us when studying the acylation of compound **1a** by acid anhydrides. It was found that refluxing in acetic anhydride or propionic anhydride in the presence of NaOAc (in the first case) or $NaHCO_3$ (in the second) gave the $N_{(5)}$-acyl-substituted **9a,b** in 47 and 35% yield respectively. The ^{1}H NMR spectra of these products show the absence of the signal for the 6-CH_2 group protons and the presence of a signal at 6.43-6.45 ppm which is assigned to the methine H-6 proton (Table 2). The diamagnetic shift of the H-4 proton signal by $\Delta\delta \sim 0.3$-0.4 ppm when compared with its position in the spectrum of the starting **1a** also points to the presence of an electrophilic substituent at the neighboring $N_{(5)}$ atom. The use of a stronger base (pyridine) in the case of the reaction with Ac_2O gave a mixture of the mono- and diacyl-substituted products **9a** and **7a** (5:1 according to ^{1}H NMR data).

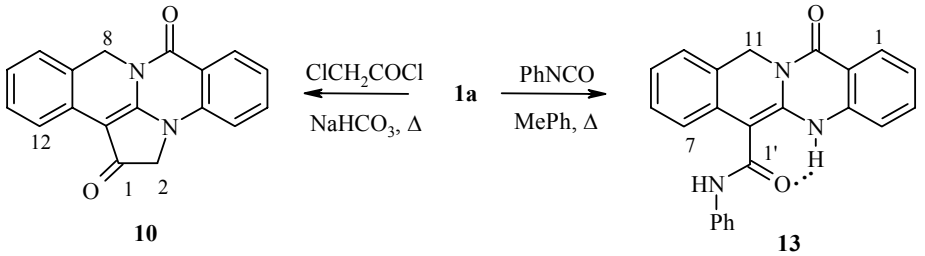
When examining the acylation of the benzimidazo[1,2-*b*]isoquinolinone **5** by acid anhydrides and chlorides in the presence of base (NaOAc and pyridine) [10] it was found that the reaction with the anhydrides gives exclusively the C-acylated compounds and in the presence of base a mixture of the C- and N-acylated products. Further, the fraction of the latter in the mixture indicated became greater with increase in the basicity of the reaction medium. According to our results the acylation of the dihydroisoquinoquinazolinone **1a** by anhydrides occurs at the imine $N_{(5)}$ nucleophilic center. The presence of the weak bases (NaOAc and $NaHCO_3$) in the reaction mixture is probably necessary for stabilization of the reaction product *via* $C_{(6)}$-deprotonation while the β–position of the N-acyl-substituted enamines formed **9** are deactivated by the N-acyl group towards subsequent acylation. The latter is confirmed by the high stability of compound **9a** which does not undergo a change even after prolonged heating with acetyl chloride in pyridine. In the conditions for generating an anion (the presence of pyridine) the acylation occurs first at the $C_{(6)}$ atom and then at $N_{(5)}$. With the presence of an electron acceptor substituent in the 6-acyl group (the chlorine atom in compound **6**) the likelihood of further acylation is markedly decreased. Hence heating compound **6** in pyridine with an excess of benzoyl chloride leads to the diacyl-substituted product **7** according to TLC data. However, this reaction is accompanied by the formation of a large amount of side products and the diacyl derivative could not be separated from the reaction mixture. We also do not exclude the possible rearrangement of the corresponding N-acyl-substituted structure **9**. However, prolonged heated of compound **9a** in pyridine or DMF does not cause a change in the structure of the latter.

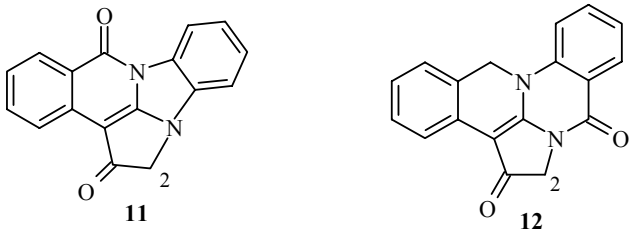
As we have noted when studying the acylation reaction of the dihydroisoquino[2,3-*a*]quinazolinone **4** (isomeric with **1a**) its 7-acyl-substituted analog is unstable in acid medium and is readily hydrolyzed to give the protonated dihydroisoquino[2,3-*a*]quinazolinium salt **4**.$HClO_4$ [8]. It was found that the C-acyl-substituted dihydroisoquino[3,2-*b*]quinazolinones **6, 7** are markedly more resistant to the action of the acid. Hence heating acetic acid solutions of compounds **6** and **7a-c** in the presence of perchloric acid gave the perchlorate **1a**.$HClO_4$ only after refluxing for 3-5 h. The N-acyl-substituted **9** was less stable and was hydrolyzed without heating over

8 h. In all cases protonation is at the $C_{(6)}$ position as indicated by the ^{1}H NMR spectroscopic data for compounds **6** and **7a** in CF_3CO_2D (Table 2). The protons at $C_{(6)}$ are seen as an AB spin system or as two signals with $\Delta\delta$ = 1.39 ppm strongly broadened as a result of conformational changes in the **7a** molecule. The spectrum of the N-acetyl-substituted **9a** in CF_3CO_2D agrees with that of a mixture of the dihydro-13H-isoquinoquinazolinone **1a** deuterated at the $C_{(6)}$ atom and acetic acid.

Heating compound **1a** with chloroacetyl chloride in the presence of $NaHCO_3$ gave us a member of the novel heterocyclic system 7H,8H-2a,7a-diazacyclopenta[*f*,*g*]napthacene-1,7(2H)-dione (**10**) which is the product of simultaneous acylation and intramolecular N-alkylation.

This reaction occurs less smoothly in pyridine and gives compound **10** but in lower yield. The ^{1}H NMR spectrum shows singlet signals for two methylene groups while the signal found at higher field (4.39 ppm) is assigned to the 2-CH_2 group from a comparative analysis of the ^{1}H NMR spectra of the related 7H-2a,6b-diazabenzo[*b*]cyclopenta[*l*,*m*]fluorene-1,7(2H)-dione (**11**, 2-CH_2 = 4.75 ppm) [11] and 7H,12H-6a,11b-diazabenzo[*e*]aceanthrylene-5,7(6H)-dione (**12**, 2-CH_2 4.26 ppm) [8] which had been prepared under similar conditions. The $H_{(12)}$ proton is observed at 7.91 ppm (at lower field than the corresponding $H_{(7)}$ signal in compound **1a** [7]) as a result of the magnetic anisotropic deshielding by the carbonyl group. The IR spectrum shows two C=O stretching absorption bands at 1690 and 1655 cm^{-1}. Compound **10** is completely stable to the action of acid, prolonged heating (8 h) in acetic acid solution in the presence of perchloric acid not giving rise to a change in structure.





Lengthy refluxing of compound **1a** with a five fold excess of phenylisocyanate in anhydrous toluene gave a modest yield (25%) of N-phenyl-13-oxo-5,13-dihydro-11H-isoquino[3,2-*b*]quinazoline-6-carboxamide (**13**). ^{1}H NMR spectroscopic data confirmed the formation of a substitution product at the $C_{(6)}$ atom, the spectrum only showing an 11-CH_2 proton group signal. Rotation around the $C_{(6)}$–CO and $C_{(1')}$–N bonds is limited due to formation of an intramolecular hydrogen bond and the high degree of conjugation at the unsaturated amide fragment. As a result the $H_{(7)}$ (8.53 ppm) and $H_{(2')}$ protons (8.37 ppm) are found in the region of carbonyl group deshielding. Because of rapid exchange with H_2O the NH group proton signals are seen as a single strongly broadened band at 4.5 ppm. Observation of the absorption bands for these groups near 3100 cm^{-1} in the IR spectrum is also hindered by the broadening due to the formation of hydrogen bonds, as in the case of compound **6**.

Hence the results discussed above for the acylation indicate that the dihydro-13H-isoquino[3,2-*b*]-quinazolinone **1a**, which has an imino form in solutions with one nucleophilic center (the nitrogen atom), shows ambident properties when acylated and forms the N- and C-acylation products depending on the reaction conditions. Such chemical behavior is typical of secondary enamines. Acylation of compound **1a** at the $C_{(6)}$ atom is associated with its conversion to a mesomeric anion under the action of base with an increase in the nucleophilicity of a carbon atom and not with the imine-enamine equilibrium.

EXPERIMENTAL

IR spectra (KBr tablets) were recorded on a Pye-Unicam SP3-300 instrument. ^{1}H NMR spectra were taken on a Varian Mercury 400 (400 MHz) instrument using TMS as internal standard. The mass spectrum of compound **10** was recorded using HPLC on an AGILENT/100-Series instrument (CI, acetonitrile, 0.05% formic acid). Melting points were taken on a Boetius heating block and not corrected. Monitoring of the course of the reactions and the purity of the compounds prepared was undertaken using TLC on Silufol UV-254 plates. Compounds **1a,b** were prepared as in the method [5].

6-{[(4-(Dimethylamino)phenyl]methylidene}-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones (3a,b). A mixture of compound **1a,b** (4.03 mmol) and aldehyde **2a** (0.60 g, 4.06 mmol) in acetic anhydride (10 ml) was refluxed for 40 min. Solvent was evaporated *in vacuo* using a rotary evaporator and the residue was treated with acetone (10 ml). The precipitated product **3a,b** was filtered, washed with acetone, and recrystallized from DMF.

6-[(4-Nitrophenyl)methylidene]-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one hydrobromide (3g·HBr**)** was prepared by the method for synthesis of compounds **3a,b** from the hydrobromide **1a·**HBr (1 g, 3.04 mmol) and aldehyde **2f** (0.53 g, 3.5 mmol), washed with acetone, and recrystallized from AcOH.

6-(Arylidene)-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones (3c-f). Morpholine (0.7 ml, 8.12 mmol) was added to a suspension of compound **1a** (1 g, 4.03 mmol) in 2-propanol (10 ml), the mixture was heated to reflux, the aldehyde **2b-e** (5.0 mmol) was added, and the reaction product was refluxed for 6 h. *t*-BuOK (0.45 g, 4.06 mmol) and the corresponding aldehyde **2b-e** (5 mmol) were added and the product was refluxed for a further 5 h. Solvent was evaporated, the residue was treated with water (10 ml), and the precipitated product **3c-f** was filtered off, washed with water and 2-propanol, and recrystallized from DMF.

6-(4-Chlorobenzoyl)-5,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (6). Compound **1a** (1 g, 4.03 mmol) was dissolved with heating in anhydrous pyridine (5 ml). *p*-Chlorobenzoyl chloride (1.02 ml, 8.0 mmol) was added to the solution and the mixture was refluxed for 4 h. The cooled reaction mixture was treated with water (20 ml) and the precipitated product **6** was filtered, carefully washed with water and 2-propanol, and recrystallized from DMF.

5,6-Dicyano-5,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones (7a-c). Using the method of synthesis for product **6** from compound **1a** and acetic, benzoic, or *p*-toluic acid chlorides to give the products **7a-c** respectively.

6,11-Dihydro-11'H-[6,11']bis[isoquino[3,2-*b*]quinazolinyl]-13,6',13'-trione (8) was prepared as for compounds **6, 7** from compound **1a** and isonicotinoyl chloride. Yield 65%; mp. 280-281ºC (DMF) (mp 279-281ºC [6]).

5-Acetyl-5,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (9a). A mixture of compound **1a** (1 g, 4.03 mmol) and anhydrous NaOAc (0.41 g, 5.1 mmol) in acetic anhydride was refluxed for 3 h, cooled, and held at room temperature for 16 h. The precipitated product **9** was filtered off, washed with acetone, and recrystallized from DMF.

5-Propionyl-5,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one (9b) was prepared by the method used for product **9a** using propionic anhydride (10 ml) in place of acetic anhydride and with $NaHCO_3$ (0.42 g, 5.1 mmol).

7H,8H-2a,7a-Diazacyclopenta[*f*,*g*]napthacene-1,7(2H)-dione (10). A mixture of compound **1a** (1 g, 4.03 mmol) and $NaHCO_3$ (0.82 g, 10.0 mmol) in chloroacetyl chloride (10 ml) was heated to formation of a clear solution and then refluxed for 10 min. Excess acid chloride was evaporated off *in vacuo* and the oily residue was washed with water (20 ml) and then with 2-propanol (10 ml). The precipitated product **10** was filtered off, washed with 2-propanol and recrystallized from DMF. Mass spectrum, *m/z* (I_{rel}, %): 288 $[M]^+$ (100).

13-Oxo-N-phenyl-5,13-dihydro-13H-isoquino[3,2-*b*]quinazoline-6-carboxamide (13). A mixture of compound **1a** (1 g, 4.03 mmol) and phenyl isocyanate (0.87 ml, 8.0 mmol) in anhydrous toluene (15 ml) was refluxed for 10 h. The precipitate of product **13** formed on cooling was filtered off, washed with toluene, and recrystallized from DMF.

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