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CONDENSED ISOQUINOLINES 25*. ALKYLATION OF 6,11-DIHYDRO-13H-ISOQUINO[3,2-*b*]QUINAZOLIN-13-ONE

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Interaction of 6,11-dihydro-13H-isoquino[2,3-b]quinazolin-13-one with alkylating agents occurs at two positions depending on their nature and the reaction conditions – at $C_{(6)}$ or $N_{(5)}$. Fusion with methyl tosylate leads to 5-methyl-13-oxo-6,13-dihydro-11H-isoquino[3,2-b]quinazolin-5-ium salts, while interaction with benzyl halides in the presence of i-PrONa gave 6-benzyl- and 6,6-dibenzyl-6,11-dihydro-13H-isoquino[3,2-b]quinazolin-13-ones. Alkylation with olefins led to two types of products. In the case of maleinimides and maleic acid anhydride Michael adducts at $C_{(6)}$ were formed and in the case of cyanocinnamic acid esters the reaction was accompanied by intramolecular acylation at $N_{(5)}$ to give 1-aryl-3,9-dioxo-3H,9H,11H-benzo[5,6][1,8]naphthyridino[1,8-ab]quinazoline-2-carbonitrile.

Keywords: 3,9-dioxo-3H,9H,11H-benzo[5,6][1,8]naphthyridino[1,8-*ab*]quinazoline-2-carbonitrile, isoquino[3,2-*b*]quinazoline, spiro[6,11-dihydro-13H-isoquino[3,2-*b*]quinazoline-6,2'-indan]-13-one, alkylation.

We have previously studied alkylation, one of the characteristic reactions of enamines, using benzimidazo[1,2-*b*]isoquinolin-11(5H)-one [2, 3] and 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one [4, 5] as examples. It seemed of interest to investigate the characteristics of this reaction for the linear isomer – 6,11-dihydro-13H-isoquino[3,2-*b*]quinaxolin-13-one (**1**) which had been shown previously [1] to be ambident as nucleophilic agent with the example of reactions with carbonyls. We had previously [4] obtained the hydrobromides of 6-benzyl-substituted derivatives of compound **1** by rearrangement of the corresponding compounds with an angular structure. However, under the reaction conditions (170-180°C) the process was accompanied by oxidation of both the starting materials and the final reaction products [6]. Thus this method of rearrangement was not suitable for the preparation of the 5-substituted or disubstituted derivatives of isoquino[3,2-*b*]quinazoline.

In the present work we have carried out the direct alkylation of the isoquinoquinazoline **1** by heating it with 1 equiv. of benzyl halides in 2-propanol solution in the presence of *i*-PrONa. The yields of compounds **2** reached 70-80%. Use of a two-fold excess of a benzyl halide gave the formation of the disubstituted compound **3** under these conditions (Tables 1-3).

* For Communication 24 see [1].

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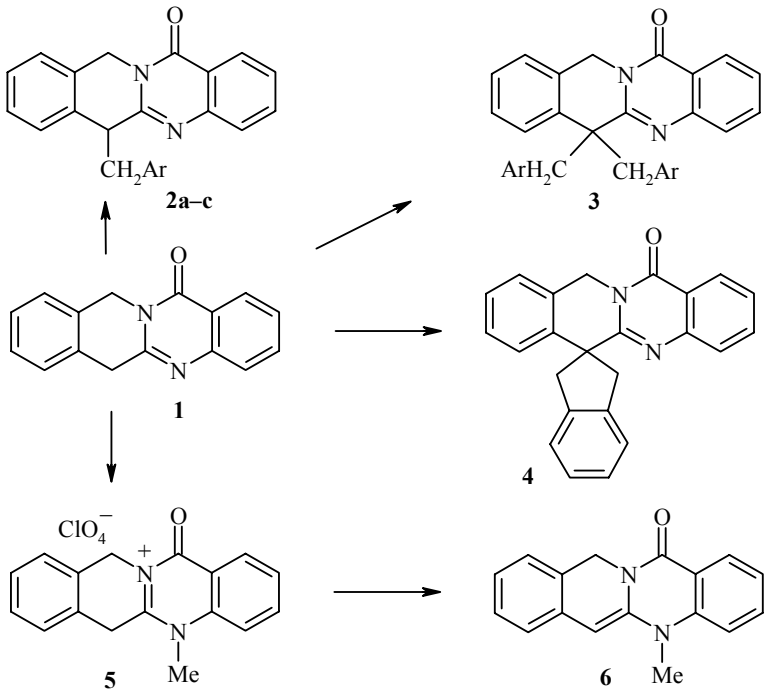


2 a Ar = Ph, **b** Ar = 2-MeC_6H_4, **c** Ar = 3-$O_2NC_6H_4$; **3** Ar = Ph

Attempts to synthesize benzyl derivatives of isoquino[3,2-*b*]quinazoline by other methods – fusing a mixture of the reagents and heating in polar solvents (acetonitrile and DMF) in the presence or absence of bases – led to resinification or the formation of multicomponent mixtures of oxidation products.

The 6-benzoisoquino[3,2-*b*]quinazolines **2a-c** were identical to those we had prepared previously [4]. In the ^{1}H NMR spectrum of 6,6-dibenzylisoquino[3,2-*b*]quinazoline **3** (Table 2) the protons of the methylene groups of the benzyl groups were nonequivalent and were observed as an AB spin system with ^2J = 13.5 Hz. This results, as in the case of the isomeric 7,7-dibenzyl-7,12-dihydro-5H-isoquino(2,3-*a*)quinazolin-5-ones [4], from spatially restricted rotation of the bulky substituents around the $C_{(6)}$–$C_{(\alpha')}$ and $C_{(6)}$–$C_{(\alpha'')}$ bonds.

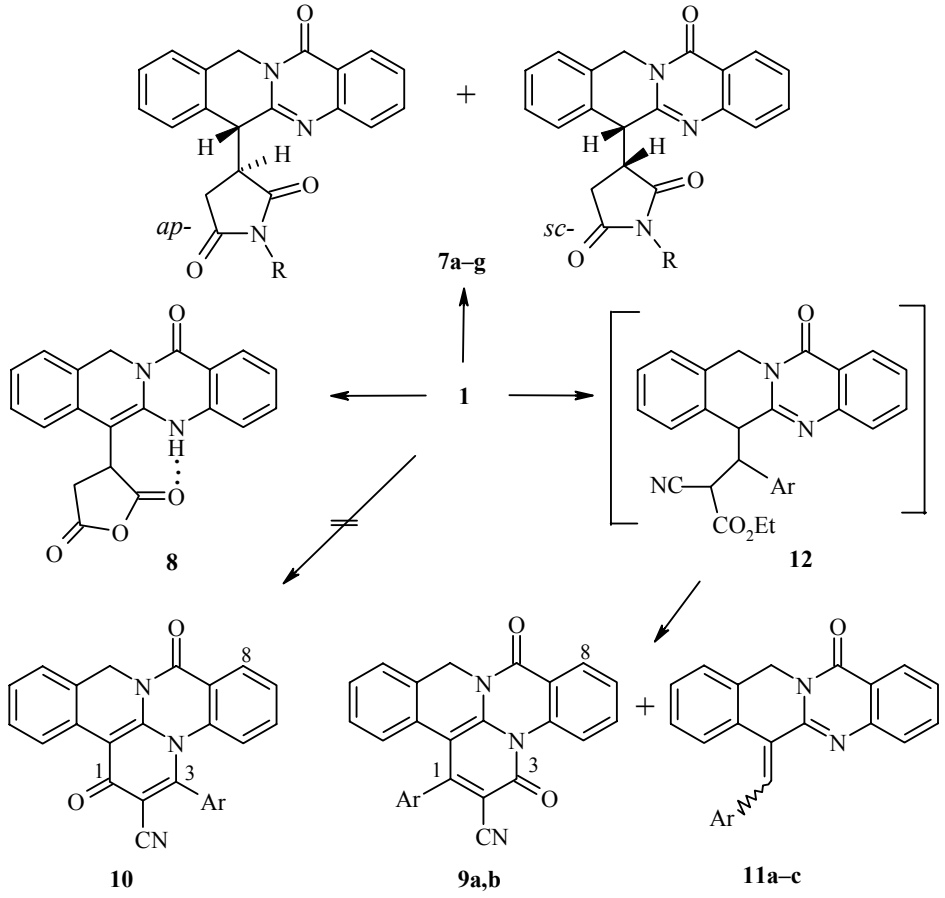
The necessity to use bases for the synthesis of the benzyl derivatives **2** and **3** is explained by the nature of isoquino[3,2-*b*]quinazoline **1** is an activated "imine". In the presence of a strong base it is converted into a deprotonated form – a carbanion. However the tautomeric conversion of compound **1** into an "enamine" in polar solvents or at high temperature is not excluded. The alkylation of compound **1** with *o*-xylylene dibromide may serve as an indirect test of this hypothesis. On fusing (160-170°C) an equimolar mixture of the reagents we obtained a small yield (30%) of spiro[6,11-dihydro-13H-isoquino[3,2-*b*]quinazoline-6,2'-9-indan]-13-one (**4**). This compound is formed considerably more readily and with higher yield (63%) on carrying out the reaction in 2-propanol in the presence of *i*-PrONa. As in the case of the isomeric spiro[7,12-dihydro-5H-isoquino[2,3-*a*]-quinazoline-7,2′-indan]-5-one [4], in the ^{1}H NMR spectrum of the spiroindane **4** the protons of the methylene groups $C_{(2')}H_2$ and $C_{(6')}H_2$ are observed as AB spin systems with ^2J = 11.0 Hz and $\Delta\delta$ = 0.82 ppm.

Fusion of isoquinoquinazoline **1** with methyl tosylate also gave a product of alkylation (55% yield) which was isolated from the reaction mixture as 5-methyl-13-oxo-6,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-5-ium perchlorate (**5**). Reaction of morpholine with this salt gave deprotonation at position 6 to give 5-methyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-13-one (**6**). Formation of the product of N-alkylation in the reaction with methyl tosylate is completely natural as in the "imine" form for isoquinoquinazoline **1** or the "enamine" form (according to the HSAB principle). The structures of compounds **5** and **6** were confirmed spectroscopically. It should be noted that deprotonation of salt **5** occurs readily even with such weak bases as

Table 1. IR Spectra of Derivatives of Isoquino[3,2-*b*]quinazolines **3-8**

Compound	IR spectrum, ν, cm^{-1}	Compound	IR spectrum, ν, cm^{-1}
3	1663 (br., C=O), 1600 (C=N), 1580, 1560, 1470, 1445, 778, 750, 720, 690	**7c**	1705 (C=O), 1687 (C=O), 1603 (C=N), 1400, 1250 (C–O), 1163, 1030, 730
4	1670 (C=O), 1590 (C=N), 1455, 1387, 1170, 755	**7d**	1713 (C=O), 1684 (C=O), 1600 (C=N), 1385, 1165, 770
5	1715 (C=O), 1620 (C=N), 1090, 755	**7e**	1710 (C=O), 1670 (C=O), 1590 (C=N), 1380, 1155, 760
6	1620 (C=N), 1565, 1490, 1455, 1380, 740	**7f**	1723 (C=O), 1687 (C=O), 1605 (C=N), 1382, 1345 (NO_2), 1170
7a	3220 (NH), 1705 (C=O), 1670 (C=O), 1600 (C=N), 1190, 1165, 765	**7g**	1713 (C=O), 1680 (C=O), 1608 (C=N), 1405, 1197, 1166, 780
7b	1710 (C=O), 1670 (C=O), 1590 (C=N), 1380, 1190, 1155, 760	**8**	3420 (NH), 1725 (C=O), 1685 (C=O), 1590, 1520, 1495, 1475, 1500, 1370 (C–O), 847

polar solvents. Thus the ^{1}H NMR spectrum of salt **5** in DMSO-d_6 appears as the spectrum of a mixture of two compounds – the salt **5** and the anhydro base **6** – as indicated by the presence of signals of the aliphatic and aromatic protons of the protonated and deprotonated forms (Table 2).



7 **a** R = H, **b** R = CH_2Ph, **c** R = 4-$MeOC_6H_4$, **d** R = 4-MeC_6H_4, **e** R = Ph, **f** R = 4-$O_2NC_6H_4$, **g** R = α-naphthyl; **9**, **11** **a** Ar = 4-$MeOC_6H_4$, **b** Ar = 4-ClC_6H_4, **c** Ar = 4-$Me_2NC_6H_4$

TABLE 2. ^{1}H NMR Spectra of Derivatives of Isoquino[3,2-*b*]quinazolines **3–8**

Com-pound	Chemical shifts (DMSO-d_6); δ, ppm (*J*, Hz)			
	ArH	(2H, $C_{(11)}H_2$)	(1H, H-6)	Other signals
1	2	3	4	5
3	8.12 (1H, d, ^oJ = 7.6, H-1); 7.86 (1H, t, ^oJ = 8.0, H-3); 7.82 (2H, m, H-4,10); 7.52 (1H, t, ^oJ = 7.8, H-2); 7.42 (1H, t, ^oJ = 8.0, H-8); 7.25 (1H, t, ^oJ = 8.0, H-9); 7.05 (1H, d, ^oJ = 8.0, H-7); 6.96 (2H, t, ^oJ = 7.6, H-4'); 6.86 (4H, t, ^oJ = 7.6, H-3',5'); 6.52 (4H, d, ^oJ =7.6, H-2',6')	4.02 (s)	—	4.08 (2H, d, ^2J = 13.5, PhC$\underline{H}_A$H$_B$); 3.52 (2H, d, ^2J = 13.5, PhCH$_A\underline{H}_B$)
4	8.17 (1H, dd, ^mJ = 1.6, ^oJ = 8.0, H-1); 7.74 (1H, td, ^mJ = 1.6, ^oJ = 8.0, H-3); 7.59 (1H, d, ^oJ = 8.0, H-4); 7.46 (2H, m, H-2,7); 7.24 (3H, m, H-8–10); 7.19-7.12 (4H, m, H-3'–6')	5.38 (s)	—	4.20 (2H, d, ^2J = 11.0, $\underline{H}_A$-1', $\underline{H}_A$-3'); 3.38 (2H, d, ^2J = 11.0, $\underline{H}_B$-1', $\underline{H}_B$-3')
5	[8.60 (1H, dd, ^mJ = 1.2, ^oJ = 8.0, H-1); 8.21 (1H, td, ^mJ = 1.2, ^oJ = 8.0, H-3); 8.05 (1H, d, ^oJ = 8.5, H-4); 7.93 (1H, t, ^oJ = 8.0, H-2); 7.52 (4H, m, H-7–10)]*	[5.59 (s)]*	[4.83 (2H, s)]*	[4.44 (3H, s, CH_3)]*
	8.39 (1H, d, ^oJ = 7.6, H-1); 8.17 (2H, m, H-3,4); 7.86 (1H, t, ^oJ = 7.6, H-2); 7.56 (2H, m, H-7,10); 7.42 (2H, m, H-8,9)	5.39 (s)	4.83 (2H, s)	4.24 (3H, s, CH_3)
6	7.84 (1H, d, ^oJ = 7.6, H-1); 7.48 (1H, t, ^oJ = 8.0, H-3); 7.06 (3H, m, H-2,4,7); 6.91 (3H, m, H-8–10)	5.08 (s)	5.19 (s)	3.32 (3H, s, CH_3)
7a	8.14 (1H, dd, ^mJ = 1.2, ^oJ = 8.0, H-1); 7.76 (1H, td, ^mJ = 1.2, *J* = 8.0, H-3); 7.52 (1H, d, ^oJ = 7.2, H-10); 7.48-7.33 (5H, m, H-2,4,7–9)	5.86, 4.72 (dd, ^2J = 15.6)	4.78 (d, ^3J = 0.8)	11.24 (1H, s, NH); 3.95 (1H, m, H-3'); 3.05 (1H, dd, ^3J = 8.0, ^2J = 17.6, H$_A$-4'); 2.56 (1H, dd, ^2J = 17.6, ^3J = 4.4, H$_B$-4')
7b	8.07 (1H, d, ^oJ = 7.6, H-1); 7.51-7.45 (5H, m, H-3,7,10,2'',6''); 7.41-7.30 (6H, m, H-2,8,9,3''–5''); 6.56 (1H, d, ^oJ = 8.0, H-4)	5.85, 4.67 (dd, ^2J = 15.8)	4.86 (d, ^3J = 0.8)	4.82 (1H, d, ^2J = 14.4, C$\underline{H}_A$H$_B$Ph); 4.70 (1H, d, ^2J = 14.4, CH$_A\underline{H}_B$Ph); 4.07 (1H, m, H-3'); 3.15 (1H, dd, ^3J = 9.0, ^2J = 17.6, H$_A$-4'); 2.62 (1H, dd, ^2J = 17.6, ^3J = 4.8, H$_B$-4')

TABLE 2. (continued)

1	2	3	4	5
7c	8.16 (1H, d, ^{o}J = 7.6, H-1); 7.70 (1H, t, ^{o}J = 7.2, H-3); 7.54 (1H, d, ^{o}J = 7.2, H-10); 7.51 (1H, d, ^{o}J = 8.0, H-7); 7.44 (2H, m, H-8,9); 7.37 (1H, t, ^{o}J = 7.6, H-2); 7.30 (3H, m, H-4,2",6"); 7.04 (2H, d, ^{o}J = 8.8, H-3",5")	5.89, 4.74 (dd, ^{2}J = 15.6)	4.95 (d, ^{3}J = 0.8)	3.83 (3H, s, OCH_3); 4.15 (1H, m, H-3'); 3.29 (1H, dd, ^{3}J = 8.8, ^{2}J = 17.6, H_A-4'); 2.72 (1H, dd, ^{2}J = 17.6, ^{3}J = 4.4, H_B-4')
7d	8.16 (1H, d, ^{o}J = 8.0, H-1); 7.69 (1H, t, ^{o}J = 8.0, H-3); 7.55 (1H, d, ^{o}J = 7.6, H-10); 7.51 (1H, d, ^{o}J = 8.0, H-7); 7.45 (2H, m, H-8,9); 7.37 (1H, t, ^{o}J = 8.0, H-2); 7.33–7.26 (5H, m, H-4,2",3",5",6")	5.90, 4.74 (dd, *J* = 15.6)	4.97 (d, ^{3}J = 0.8)	2.44 (3H, s, CH_3); 4.17 (1H, m, H-3'); 3.30 (1H, dd, ^{3}J = 7.6, ^{2}J = 17.6, H_A-4'); 2.76 (1H, dd, ^{2}J = 17.6, ^{3}J = 4.4, H_B-4')
7e	8.16 (1H, d, ^{o}J = 7.6, H-1); 7.70 (1H, t, ^{o}J = 8.0, H-3); 7.56-7.51 (4H, m, H-7,10,2",6"); 7.45 (5H, m, H-8,9,3"–5"); 7.38 (1H, t, ^{o}J = 7.6, H-2); 7.28 (1H, d, ^{o}J = 8.0, H-4)	5.90, 4.76 (dd, ^{2}J = 15.8)	4.99 (d, ^{3}J = 0.8)	4.20 (1H, m, H-3'); 3.32 (1H, dd, ^{3}J = 8.0, ^{2}J = 17.6, H_A-4'); 2.76 (1H, dd, ^{2}J = 17.6, ^{3}J = 4.4, H_B-4')
7f *ap*	8.42 (2H, dd, ^{m}J = 0.8, ^{o}J = 8.0, H-2",6"); 8.15 (1H, d, ^{o}J = 8.0, H-1); 7.78 (2H, dd, ^{m}J = 0.8, ^{o}J = 8.0, H-3",5"); 7.67 (1H, t, ^{o}J = 8.0, H-3); 7.55 (1H, d, ^{o}J = 7.6, H-10); 7.50 (1H, d, ^{o}J = 7.6, H-7); 7.45 (2H, m, H-8,9); 7.38 (1H, t, ^{o}J = 8.0, H-2); 7.17 (1H, d, ^{o}J = 8.0, H-4)	5.91, 4.75 (dd, ^{2}J = 15.8)	5.02 (d, ^{3}J = 1.0)	4.26 (1H, m, H-3'); 3.38 (1H, dd, ^{3}J = 10.0, ^{2}J = 17.6, H_A-4'); 2.74 (1H, dd, ^{2}J = 17.6, ^{3}J = 4.8, H_B-4')
7f *sc*	8.35 (2H, d, ^{o}J = 8.0, H-2",6"); 8.15 (1H, d, ^{o}J = 8.0, H-1); 7.68-7.65 (4H, m, H-3,10,3",5"); 7.49-7.38 (4H, m, H-2,7–9); 7.32 (1H, d, ^{o}J = 8.0, H-4)	5.74, 4.80 (dd, ^{2}J = 16.0)	4.73 (d, ^{3}J = 3.0)	4.33 (1H, m, H-3'); 3.25 (1H, dd, ^{3}J = 9.2, ^{2}J = 18.0, H_A-4'); 3.04 (1H, dd, ^{2}J = 18.0, ^{3}J = 5.2, H_B-4')
7g *ap*	8.22-7.11 (15H, m)	5.93, 4.78 (dd, ^{2}J = 15.6)	5.02 (d, ^{3}J = 1.0)	4.51 (1H, m, H-3'); 3.60 (1H, dd, ^{3}J = 7.2, ^{2}J = 17.6, H_A-4'); 2.87 (1H, dd, ^{2}J = 17.6, ^{3}J = 4.6, H_B-4')
7g *sc*		5.91, 4.83 (dd, ^{2}J = 16.0)	4.80 (m)	4.35 (1H, m, H-3'); 3.41 (1H, dd, ^{3}J = 9.2, ^{2}J = 17.6, H_A-4'); 3.23 (1H, dd, ^{2}J = 17.6, ^{3}J = 5.2, H_B-4')
8	8.04 (1H, dd, ^{m}J = 1.6, ^{o}J = 8.0, H-1); 7.88 (1H, d, ^{o}J = 8.0, H-7); 7.69 (1H, td, ^{m}J = 1.6, ^{o}J = 8.0, H-3); 7.26–7.14 (4H, m, H-2,4,9,10); 7.02 (1H, t, ^{o}J = 8.0, H-8)	5.22 (s)	—	4.73 (1H, t, ^{3}J = 6.5, H-3'); 2.97 (2H, d, ^{3}J = 6.5, $C_{(4')}H_2$)

* ^{1}H NMR spectrum recorded in CF_3CO_2D.

Isoquino[3,2-*b*]quinazoline **1** also readily forms products of alkylation by interaction with activated olefins. Fusing an equimolar mixture of **1** with maleimides or maleic anhydride gave the Michael adducts – 1-R-3-(13-oxo-6,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-6-yl)-2,5-pyrrolidinediones **7a-g** and 3-(13-oxo-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-6-yl)dihydro-2,5-furandione (**8**). It should be noted that in the case of isoquino[3,2-*b*]quinazoline **1** this reaction occurs quite easily (20-40 min at 120-150°C) and with high yield (60-80%). Whereas for other condensed 3-aminoisoquinolines – benzimidazo[1,2-*b*]isoquinolin-11(5H)-one, which exists predominantly in the "enamine" form [3] and 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one, which exists as a mixture of tautomers [7] – alkylation products were not formed with these olefins. One possible reason for this is the difference in reactivity of these heterocycles as proton donors in reaction with proton acceptors – anhydride and imides of dicarboxylic acids. The structures of the pyrrolidinediones **7a-g** were established on the basis of their ^{1}H NMR spectra. In the aliphatic proton resonance region signals of 6 protons in the form of AB and ABX systems were observed. Vicinal coupling constant of H-6′ and H-3 J = 0.8-1.0 Hz is characteristic [8] for unshielded conformations with *trans* and *cis* positions of the interacting protons. The ^{1}H NMR spectrum of 1-benzyl-2,5-pyrrolidinedione **7b** permit the conclusion that an antiperiplanar conformation is predominant for compounds **7a-g**. A peculiarity of the spectrum of compound **7b** is the presence at stronger field, in comparison with signals of the other aromatic protons, of a one-proton doublet (6.56 ppm), assigned by us to the resonance of H-4' on the basis of a COSY HH experiment. Analysis of a molecular models of **7b** shows that the structure which has H-4′ extremely close to the benzyl substituent so that it falls within the region of shielding of the benzene ring, corresponds to the form **7***ap*.

The maximum yields of 1-(4-nitrophenyl)-2,5-pyrrolidinedione **7f** and 1-(α-naphthyl)-2,5-pyrrolidinedione **7g** were obtained by fusion at higher temperatures (140-150°C) than for the remaining pyrrolidinediones. In the ^{1}H NMR spectra of these compounds double sets of aliphatic and aromatic protons were observed, with small differences in chemical shifts and similar coupling constants (Table 2). We have observed similar patterns in products of alkylation with other N-arylmaleimides **7c-e** which had not been crystallized. In the case of 1-(4-nitrophenyl)-2,5-pyrrolidinedione **7f** one of the components of the mixture ($J_{6',3}$ = 1.0 Hz) was obtained in pure form after many crystallizations of the mixture from DMF. These data show that the product of the reaction of compound **1** with maleimides is a mixture of two conformers with *cis* and *trans* positions of the interacting protons. This hypothesis was confirmed by the results of chromato-mass spectrometry studies of mixtures of isomers of compounds **7f,g** which showed the presence of a unique peak on the chromatogram, the *m/z* of which corresponds to the expected value. The vicinal coupling constant $J_{6',3}$ = 3.0 Hz of the second component of the mixture corresponds to the synclinal conformation **7***sc*. Using the modified Karplus equation [9] we determined the values of the dihedral angles H–$C_{(6)}$–$C_{(3)}$–H from the coupling constants, 173 ($J_{6',3}$ = 1.0 Hz, **7***ap*) and 49° ($J_{6',3}$ = 3.0 Hz, **7***sc*).

The observed appearance of atropoisomerism is explained by restricted rotation around the $C_{(6')}$–$C_{(3)}$ bond. Probably the transition temperature between the two forms is 130-160°C. For example, in the spectrum pyrrolidinedione **7a** (*ap*-form), which was initially heated in boiling nitrobenzene for 20 min, signals of two isomers are also observed. It should be noted that the transition between the *ap*- and *sc*-forms evidently occurs at a lower temperature in an acid medium. For example in the ^{1}H NMR spectra of compounds **7a-e** in CF_3CO_2D (**7***ap* according to the data of spectra in DMSO-d_6), signals for both forms were observed with the content of **7***sc* < 15%. The explanation for this observation was found from a study of the structure of the fusion product of compound **1** with maleic acid anhydride (furandione) **8**. In the ^{1}H NMR spectrum of compound **8** a broad signal was observed at 12.50 ppm for proton, which exchanged with D_2O, and in the IR spectrum there was a broad band in the region of 3450 cm^{-1} which indicate the presence of the $N_{(5)}H$ group in the structure. In the aliphatic proton resonance region there is a two-proton singlet of the methylene group $C_{(11)}H_2$ and signals of the protons of the furandione ring in the form of an A_2X spin system. The formation of the "enamine" form for

6-alkylisoquino[3,2-*b*]quinazoline in this case is explained by the electron-acceptor influence of the substituent. It is probable that a similar structure occurs on protonation of the pyrrolidinediones **7** as an intermediate in the conversion of the *ap*- and *sc*-forms.

Alkylation with the olefin at atom $C_{(6)}$ also occurs on reaction between isoquino[3,2-*b*]quinazoline **1** and cyanocinnamic acid esters. However, in this case the reaction does not stop at the stage of formation of the Michael product, but is accompanied by intramolecular acylation at atom $N_{(5)}$ and oxidation of the cyclic adduct which leads to the derivatives of a new heterocyclic system – 1-(4-aryl)3,9-dioxo-3H,9H,11H-benzo[5,6][1,8]-naphthyridino[1,8-*ab*]quinazoline-2-carbonitriles, **9a,b**. The cyano group remains unchanged in the reaction products: stretching bands are observed in the IR spectra in the region of 2210 cm^{-1}. The absence in the ^1H NMR spectra of proton signals of the isoquino[3,2-*b*]quinazoline unit at atoms $C_{(6)}$ and $N_{(5)}$ indicates the formation of 5,6-disubstituted derivative. In the aromatic proton resonance region we observed two doublets in weak field at 9.20 and 8.27 ppm. The latter (in the region characteristic for H-1 of the isoquinoquinazoline starting material) is assigned to the signal of a proton *peri* to a carbonyl group H-8, while the proton at weaker field is assigned to a proton falling in the region of deshielding by the carbonyl group of a pyridine ring annelated to isoquino-[3,2-*b*]quinazoline. A doublet in strong field at 6.37 ppm corresponds to the resonance of a proton screened by the benzene ring of the pyridine unit. However, the enumerated data do not allow an unambiguous conclusion on the structures of the products as products of C-alkylation or N-alkylation. Although it is known [3, 10, 11]

Table 3. Characteristics of the Compounds Synthesized

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
3	$C_{30}H_{24}N_2O$	84.00 / 84.08	5.61 / 5.65	6.56 / 6.54	156-158	66
4	$C_{24}H_{18}N_2O$	82.19 / 82.26	5.10 / 5.18	8.00 / 7.99	231-232	30*[2]
5	$C_{17}H_{15}ClN_2O_5$*[3]	56.20 / 56.29	4.12 / 4.17	7.73 / 7.72	224-226	55
6	$C_{17}H_{14}N_2O$	77.78 / 77.84	5.32 / 5.38	10.70 / 10.68	147-149	60
7a	$C_{20}H_{15}N_3O_3$	69.51 / 69.56	4.33 / 4.38	12.17 / 12.17	280-281	80
7b	$C_{27}H_{21}N_3O_3$	74.42 / 74.47	4.83 / 4.86	9.68 / 9.65	211-213	85
7c	$C_{27}H_{21}N_3O_4$	71.80 / 71.83	4.65 / 4.69	3.32 / 3.31	258-261	79
7d	$C_{27}H_{21}N_3O_3$	74.37 / 74.47	4.80 / 4.86	9.68 / 9.65	274-276	85
7e	$C_{26}H_{19}N_3O_3$	74.04 / 74.10	4.50 / 4.54	10.00 / 9.97	275-277	83
7f	$C_{26}H_{18}N_4O_5$	6.91 / 6.95	3.86 / 3.89	12.10 / 12.01	253-255	85
7g	$C_{30}H_{21}N_3O_3$	76.37 / 76.42	4.42 / 4.49	8.93 / 8.91	197-200	60
8	$C_{20}H_{14}N_2O_4$	69.30 / 69.36	4.00 / 4.07	8.10 / 8.09	175-178	75
9a	$C_{27}H_{17}N_3O_3$	75.12 / 75.16	3.91 / 3.97	9.76 / 9.74	284-287	35
9b	$C_{26}H_{14}ClN_3O_2$*[4]	71.60 / 71.65	3.19 / 3.24	9.63 / 9.64	317-320	30

* Solvents for crystallization: *i*-PrOH (compound **3**), DMF (compounds **4**, **6-9),** MeCN (compound **5**).

*[2] Yield by method B 63%.

*[3] Found, %: Cl 8.15, calculated %: Cl 8.13.

*[4] Found, %: Cl 9.78, calculated, %: Cl 9.77.

that alkylation of natural products (cyclic "imines" and "enamines") with derivatives of cyanocinnamic acid occurs predominantly at carbon atoms, it should be taken into consideration an alternate structure **10** as a product of C-alkylation and N-alkylation. The final choice of **9** resulted from a study of the structure of by-products of this reaction. We have examined different conditions – fusion or heating mixtures of reagents in polar solvents, with or without bases. In all cases a mixture of reaction products was formed, the content of **9** in which depended on the conditions used and the nature of the substituents in the benzene ring of the cyanocinnamic ester. The basically by-products of this reaction, and in the case of ethyl 2-cyano-3-(4-dimethylamino)phenyl-2-propenoate, were 6-arylidene-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones **11a-c**. These compounds were isolated from the reaction mixtures and their spectroscopic characteristics and physical constants coincided completely with compounds prepared previously [1]. The content of 6-arylidene derivatives in the reaction mixture increased with increasing electron-donor strength of the substituent in the benzene ring of the cyanocinnamic ester and also when the reaction was carried out by fusion. In solution in the presence of base and with increasing electron-acceptor strength of the substituent, the fraction of products of oxidation of isoquino[3,2-*b*]quinazoline increased. On fusing the base **1** with ethyl 3-(4-chlorophenyl)-2-cyano-2-propenoate at 150-160°C a mixture was obtained the basic components of which were compounds **9b**, **11b**, and **12** according to ^{1}H NMR data. A mixture of signals of 5 aliphatic protons, the δ values and coupling constants of which are characteristic of products of $C_{(6)}$ alkylated type of the pyrrolidinediones **7,** indicates the formation of 6-alkyl-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one **12**. The protons of the $C_{(11)}H_{(2)}$ methylene group are observed as two doublets with geminal ^2J = 17.0 Hz and Δδ = 0.63 ppm. In our view the formation of **12** in this reaction can be considered as strong evidence for structure **9** for the derivatives of benzo[5,6][1,8]naphthyri-ino[1,8-]quinazolines. The optimal yield of compound **9a** was obtained by carrying out the reaction in DMF in the presence of Et_3N, and of **9b** by fusion at 180-190°C.

EXPERIMENTAL

Melting points were determined with a Boetius block and were not corrected. IR spectra of KBr disks were recorded with a Pye-Unicam SP3-300 instrument. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Varian Mercury 400 (400 MHz) instrument. Mass spectra were recorded by the HPLC method on an Agilent/100 Series instrument (CI, acetonitrile, 0.05% formic acid). The course of reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates.

Yields, physicochemical characteristics, and elemental analysis data of the synthesized compounds are given in Table 3.

6-Arylmethyl-6,11-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-ones, 2a-c. Isoquino[3,2-*b*]quinazoline **1** (1 g, 4.03 mmol) was added to a solution of *i*-PrONa (0.33g, 4.0 mmol) in 2-propanol (15 ml). The mixture was heated with stirring while most of the solid had not dissolved. Benzyl chloride (4.0 mmol) in 2-propanol (2 ml) was then added dropwise and the mixture was heated and stirred for 30 min. The solvent was evaporated on rotary evaporator and water (10 ml) was added to the residue. The precipitate formed was filtered off, thoroughly washed with water and a small amount of 2-propanol.

Compound 2a. Yield: 1.09 g (80%); mp 146-147°C (DMF, 148°C [5]).

Compound 2b. Yield: 1.06 g (75%); mp 170-172°C (DMF, 171°C [5]).

Compound 2c. Yield: 1.07 g (69%); mp 143-145°C (DMF, 145°C [5]).

6,6-Dibenzyl-6,11-dihydro-13H-isoquino[3,2-*b*]quinazoline-13-one (3). The reaction was carried out analogously to the synthesis of compounds **2a-c** using *i*-ProNa (0.66 g, 8.1 mmol) and benzyl chloride (1 ml, 8.0 mmol).

Spiro[6,11-dihydro-13H-isoquino[3,2-*b*]quinazoline-6,2′-indan]-13-one (4). A. A mixture of isoquinoquinazoline **1** (1 g, 4.03 mmol) and *o*-xylylene dibromide (1.06 g, 4.0 mmol) were fused on an oil bath at 160-170°C for 5 h. The melt was triturated with 2-propanol (10 ml) and the solid was filtered off and washed with 2-propanol.

B. The product was obtained by the method used for **2** using *i*-PrONa (0.66 g, 8.1 mmol) and *o*-xylylene dibromide (1.06 g, 4.0 mmol).

5-Methyl-13-oxo-6,13-dihydro-11H-isoquino[3,2-*b*]quinazolinium Perchlorate (5). A mixture of isoquinoquinazoline **1** (1 g, 4.03 mmol) and MeOTs (1.11 g, 6.0 mmol) was fused on an oil bath at 135-140°C for 2h. The melt was dissolved on heating in 2-propanol and a saturated solution of $NaClO_4$ (5 ml) was added, followed by water (10 ml). The precipitate was filtered off and washed with water and acetone.

5-Methyl-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-13-one (6). A mixture of perchlorate **5** (1 g, 2.76 mmol) and morpholine (1.5 ml) was heated until the solid had dissolved completely. The solution was cooled and water (25 ml) added. The precipitate was filtered off and washed thoroughly with water and 2-propanol.

1-R-3-(13-Oxo-6,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-6-yl)-2,5-pyrrolidinediones 7a-g. A mixture of isoquinoquinazoline **1** (1 g, 4.03 mmol) and the corresponding maleimide (5.0 mmol) was fused on an oil bath at 120-130°C (or 140-150°C for **7f,g**) for 40 min. The melt was triturated with acetone (10 ml). The solid substance was filtered off and washed with acetone.

Compound 7f. Mass spectrum, *m/z* (I_{rel}, %): 467 $[M+1]^+$ (100).

Compound 7g. Mass spectrum, *m/z* (I_{rel}, %): 472 $[M+1]^+$ (100).

3-(13-Oxo-5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-6-yl)dihydro-2,5-furandione (8) was obtained by the method described for **7** using maleic anhydride (0.49 g, 5.0 mmol) at 120-125°C (20 min).

1-(4-Methoxyphenyl)-3,9-dioxo-3H,9H,11H-benzo[5,6][1.8]naphthyridino[1,8-*ab*]quinazoline-2-carbonitrile (9a). A mixture of compound **1** (1 g, 4.03 mmol), triethylamine (3ml), and ethyl 2-cyano-3-(4-methoxyphenyl)-2-propenoate (1.27 g, 5.5 mmol) in DMF (10 ml) was boiled for 5 h. The solution was cooled and aqueous ethanol (20 ml) was added. The precipitate was filtered off and washed with ethanol. IR spectrum, ν, cm^{-1}: 2210 (CN), 1700 (C=O), 1645 (C=O), 1600, 1505, 1445, 1253 (C–O), 1170, 773, 750. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.23 (1H, d, ^oJ = 9.5, H-5); 8.27 (1H, dd, ^mJ = 1.6, ^oJ = 8.0, H-8); 7.89 (1H, td, ^mJ = 1.6, ^oJ = 8.0, H-6); 7.66 (1H, d, ^oJ = 8.0, H-7); 7.44 (2H, d, ^oJ = 8.8, H-2′,6′); 7.38 (1H, d, ^oJ = 7.6, H-12), 7.11 (1H, t, *J* = 7.6, H-14); 7.02 (2H, d, ^oJ = 8.8, H-3′,5′); 6.90 (1H, t,^oJ = 7.6, H-13); 6.37 (1H, d, *J* = 8.0, H-5); 5.24 (2H, s, $C_{(11)}H_2$); 3.88 (3H, s, OCH_3).

1-(4-Chlorophenyl)-3,9-dioxo-3H,9H,11H-benzo[5,6][1,8]naphthyridino[1,8-*ab*]quinazoline-2-carbonitrile (9b). A mixture of isoquinoquinazoline **1** (1g, 4.03 mmol) and ethyl 3-(4-chlorophenyl)-2-cyano-2-propenoate (1.18 g, 5.0 mmol) was fused on an oil bath at 180-190°C for 4 h. The melt was triturated with acetone (10 ml), the solid was filtered off and washed with acetone. IR spectrum, ν, cm^{-1}: 2210 (CN), 1695 (C=O), 1665 (C=O), 1340, 780, 758. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.20 (1H, d, ^oJ = 9.5, H-5), 8.27 (1H, dd, ^mJ = 1.6, ^oJ = 8.0, H-8), 7.91 (1H, td, ^mJ = 1.6, ^oJ = 8.0, H-6), 7.72 (1H, d, ^oJ = 8.0, H-7), 7.58 (4H, m, H-2′,3′,5′,6′), 7.43 (1H, d, ^oJ = 7.6, H-12), 7.13 (1H, t, ^oJ = 7.6, H-14), 6.97 (1H, t, ^oJ = 7.6, H-13), 6.37 (1H, d, *J* = 8.0, H-15), 5.26 (2H, s, $C_{(11)}H_2$).

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