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CONDENSED ISOQUINOLINES 27*. SYNTHESIS AND OXIDATION REACTIONS OF 5,13-DIHYDRO-11H-ISOQUINO[3,2-*b*]QUINAZOLIN-11-ONE

L. M. Potikha, R. M. Gutsul, A. V. Turov, and V. A. Kovtunenko

Condensation of 2-(cyanomethyl)benzoic acid with 2-aminobenzylamine gave 6,11-dihydro-13H-isoquino[3,2-b]quinazolin-11-one. Its oxidation in nitrobenzene led to the formation of 5,13,5',13'-hexahydro[6,6']bi[isoquino[3,2-b]quinazoline]-11,11'-dione, but in dichlorobenzene in the presence of elemental sulfur and iodine it gave the rearrangement product 6H-dibenzo[b,f][1,8]naphthyridin-5-one.

Keywords: 2-aminobenzylamine, [6,6′]bi[isoquino[3,2-*b*]quinazoline], dibenzo[*b,f*][1,8]naphthyridine, isoquino[3,2-*b*]quinazoline, 2-(cyanomethyl)benzoic acid, oxidation, rearrangement.

2-(Cyanomethyl)benzoic acid (**1**) on condensation with benzylamine [2], aniline [3], and substituted anilines [4] behaves as 1,5-dielectrophilic synthon and gives derivatives of 3-aminoisocarbostyrene. On interaction with anthranilic acid or its esters acid **1** behaves as a monofunctional compound to give derivatives of 2-[(3,4-dihydro-4-oxo-2-quinazolinyl)methyl]benzoic acid [5].

In the present work we have investigated the condensation of acid **1** with 2-aminobenzylamine (**2**). This reaction was studied previously [6, 7], but the structure of the condensation product – 5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**3**) was not shown conclusively.

We have found that compound **3** can be obtained in higher yield (82%) by boiling the reagents in butanol for 5 h than by carrying out the reaction in anyl (6 h, 68% yield [6, 7]. Prolongation the reaction is considerably decreased by using DMF (2 h) as the solvent and the reaction product does not require further purification. However, as a result of unexpected oxidation, the yield of compound **3** in the last case was considerably reduced (<50%).

The reaction of 2-(cyanomethyl)benzoic acid with 2-aminobenzylamine may lead to condensation products with either an angular structure – 5,6-dihydro-12H-isoquino[2,3-*a*]quinazolin-12-one (**4**) or a linear structure –5,13-dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (**3**). It is not possible using IR and ^{1}H NMR spectra to determine unequivocally the structures of **3** and **4**, it can only be said that an enamine structure is present: ν_{NH} 3250 cm^{-1}, δ_{NH} 9.72 (s) and $\delta_{=CH}$ 5.85 ppm (s). In addition the absence of coupling between the protons of the amino and methylene groups (5.06 ppm, 2H, s) indicates the formation of compound **3**.

* For Communication 26 see [1].

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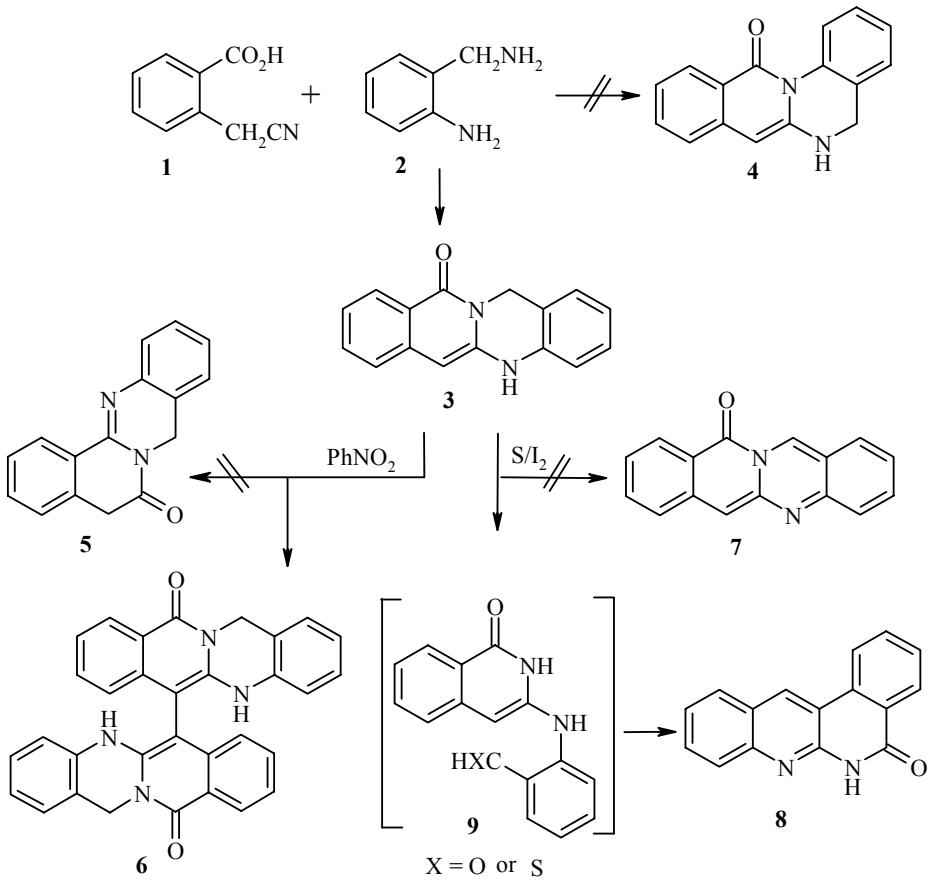
To finally elucidate this question we used ^{13}C NMR and NOESY spectra, plus homonuclear ((COSY) and heteronuclear (HMBC and HMQC) two-dimensional correlation spectroscopy. The heteronuclear correlation for compound **3** are given in the Table 1. The results obtained permit the complete assignment in the



proton and carbon spectra and provide conclusions on the structure of the compound studied. The assignments of the signals are shown in the Figure 1 and the arrows show the HMBC structural correlations. For example, in compound **3** the protons of the methylene group with chemical shift 5.06 ppm correlate with four quaternary carbon atoms, absorbing at 117.5, 137.3, 141.2, and 161.8 ppm, which are assigned to the angular atoms C-13a, C-4a, C-5a and C-11. The presence of notable value of spin-spin coupling between the protons of the CH_2 group and the carbon of the carbonyl group indicates the presence of a linear structure in compound **3**. In the alternative structure **4** the carbon of the carbonyl group C=O is more than 4 bonds from the methylene group which practically excludes the possibility of observing spin-spin interaction between them. In addition to the proton of the amino group (9.72 ppm) there are close values of the correlation with signals for the quaternary atoms C-4a and C-5a, but correlation with the protons of the CH_2 group (42.5 ppm) is absent. This is in complete agreement with the structure of isoquino[3,2-*b*]quinazolin-11-one **3**, whereas in the case of isoquino[2,3-*a*]quinazolin-12-one **4** the presence of notable spin-spin interaction would be expected between the carbon atom of the methylene group and one of the quaternary atoms C-6a, which are by 2 chemical bonds away from the proton of the NH group at.

According to results in [7], a product was formed on heating isoquino[3,2-*b*]quinazolin-11-one **3** in nitrobenzene with lower solubility and a higher melting point than the starting material **3**. For this substance the authors proposed as the most likely variant the product of rearrangement – 5,8-dihydro-6H-isoquino-[1,2-*b*]quinazolin-6-one (**5**) or its isomer (formed from compound **4** – 6,13-dihydro-12H-isoquino[2,1-*a*]-

Table 1. Proton-carbon Correlations for Compounds **3** and **8**

Compound	Chemical shifts, δ, ppm of		
	protons	carbon atoms correlated by HMQC	carbon atoms correlated by HMBC
3	9.72	—	141.2, 117.5, 113.7 (s)*, 83.7(c)
	8.01	127.9	139.4, 133.1, 161.8
	7.46	133.1	139.4, 127.9
	7.36	124.7	139.4 (c), 122.8, 120.5, 83.7
	7.26	127.3	137.3, 129.1, 42.5
	7.18	129.1	137.3, 127.3
	7.10	122.8	124.7, 120.5
	6.88	121.4, 113.7	121.4, 117.5, 113.7
	5.85	83.7	141.2, 124.7, 120.5
	5.06	42.5	141.2, 137.3, 129.1 (c), 127.3, 121.4 (s), 117.5, 161.8
8	12.07	—	126.4, 115.2
	9.36	132.9	148.6, 147.4, 129.2, 133.4
	8.60	123.9	162.8 (w), 129.7, 126.4, 115.2
	8.30	128.4	162.8, 133.4, 133.9
	8.02	129.2	147.4, 132.9, 131.5, 125.7 (s)
	7.87	133.9	133.4, 128.4
	7.84	127.3	125.7, 129.2
	7.73	131.5	147.4, 129.2
	7.67	129.7	133.9, 126.4, 123.9
	7.49	125.4	131.5, 127.3, 125.7

* Weak signal.

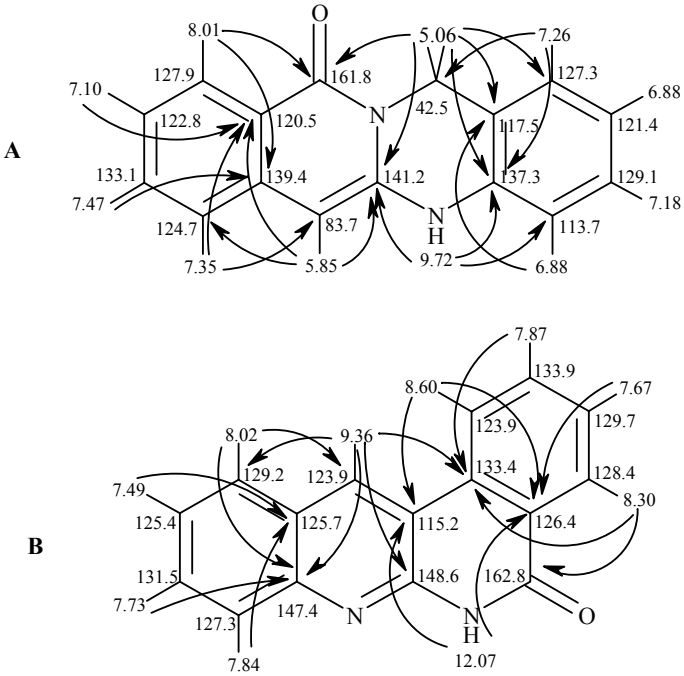


Figure 1. Structural bonding HMBC correlations for compounds **3(A)** and **8(B).**

quinazolin-12-one. It was established previously by us [8] that when the related benzimidazo[1,2-*b*]isoquinolin-11(5H)-one was heated in nitrobenzene a product of oxidative dimerization was produced – 5,5'-dihydro-[6,6']bi[benzimidazo[1,2-*b*]isoquinoline-11,11'-dione. Apparently in the case of isoquino[3,2-*b*]quinazolin-11-one **3** the reaction occurs also *via* an oxidation product – 5,13,5'13'-tetrahydro[6,6']bi[isoquino-[3,2-*b*]quinazoline]-11,11'-dione (**6**). Data from the mass spectra of the reaction product registered under chemical ionization conditions may serve as an indication of this: the most intense peaks with *m/z* 494 and 496 correspond to the ions $[M]^+$ and $[M + 2]^+$. In the IR spectrum of compound **6** there are broad absorption band of the NH group (hydrogen bonded) stretching vibrations in the 3256 region, but in the region below 1700 cm^{-1} the spectral characteristics of the oxidation product are very close to those of the starting compound. Differences are found only in the region of "specific fingerprints". Study of the structure of product **6** by NMR is difficult because of its low solubility. We have only succeeded in measuring its ^1H NMR spectrum in which signals of 11 protons were observed, one of which (a singlet at 8.43 ppm) exchanges with D_2O and corresponds to the proton of the NH group. Half of the set of signals in the spectrum reflects the high symmetry of the molecule of the "dimer" compound **6**. The difference from the spectrum of the starting compound **3** consist in the absence of the signal of H-6 and the splitting of the signal of the protons of the methylene groups which are observed as AB spin systems with J = 15.0 Hz (d, 5.28 and d, 5.14 ppm). The latter we explain as atropoisomerism, which arise as a result of sterically hindered rotation around the C(6)-C(6') bond.

According to [7], isoquino[3,2-*b*]quinazolin-11-one **3** is readily dehydrogenated on heating its solution in trichlorobenzene in the presence of elemental sulfur and iodine. In the view of the author, 11H-isoquino-[3,2-*b*]quinazolin-11-one (**7**) was formed, or its isomer 12H-isoquino[2,3-*a*]quinazolin-12-one, formed from compound **4**. We reproduced the conditions of this reaction and obtained a substance with a melting point identical with reaction product from [7]. However in the IR spectrum of the product of oxidation a broad vibration band with average intensity was observed in the 3446 cm^{-1} region, which corresponds to the streching vibrations of the bond of typeNH and OH, contrary to structure **7**. The valence band for the carbonyl group is shifted to higher frequency by 19 cm^{-1} in comparison with the starting compound **3**.

In the ^1H NMR spectrum of the oxidation product, as in the spectrum of the starting material **3**, there are two spin systems consisting of two triplets and two doublets each, which correspond to two 1,2-disubstituted phenyl units. What is more, in place of the signal of the methylene group (at 5.08 ppm), a singlet of an aromatic proton appears in the spectrum of the product at 9.36 ppm, and at 12.07 ppm a signal of an NH proton which disappears on treatment with D_2O. To elucidate the structure of the synthesized compound we measured its ^{13}C spectrum, and also carried out experiments on two-dimensional homonuclear (COSY, NOESY) and heteronuclear $^{13}C^1H$ correlation (HMQC, HMBC). The COSY experiment permits the secure assignment of hydrogen signals. The most interesting result obtained from the NOESY spectrum is that the singlet at 8.36 ppm has a correlation with a doublets placed at 8.06 and 8.02 ppm. This shows spatially close protons which correspond to these signals. These results indicate the angular structure of this molecule. Starting from these results, we propose that oxidation of isoquino[3,2-*b*]quinazolin-11-one **1** in the presence of sulfur and iodine is accompanied by rearrangement and leads to 6H-dibenzo[*b*,*f*][1,8]naphthyridin-5-one (**8**).

Further confirmation of this gave spectra of heteronuclear correlation. In the Table 1 positions of the cross-peaks for each of the ^1H signals, found in the two-dimensional HMQC and HMBC spectra. The chemical shifts of all the protonated carbon atoms were established from the HMQC spectrum correlations that, while the correlation in the HMBC spectrum made possible the assignment of the quaternary carbon atoms The assigned signals are shown on the Figure 1 and the arrows show the structural correlations HMBC. The presence of the correlation between the proton singlet at 9.36 ppm and both benzene rings carbon atoms confirmed the angular structure of the molecule, since in the alternative linear **(7)** arragment of the six-membered rings the protons giving a singlet in the spectrum is distant from one of the benzene rings by more than 3 chemical bonds and cannot give a correlation in the HMBC spectrum. The correlation between the NH signal at 12.07 ppm and the junction carbon atoms absorbing at 126.4 and 115.2 ppm, indicates that the molecule has an amide fragment.

It is known [9] that the benzyl position in condensed cyclic systems is readily oxidized by various oxidants, especially if the molecule contains a methylene group of a lactam. The methylene group is predominantly oxidized to carbonyl by an oxygen-containing oxidant. Evidently, in our case a similar mechanism takes place in the conversion of isoquino[3,2-*b*]quinolin-11-one **3** under the influence of sulfur and iodine. Oxidation at the C(13)H_2 methylene group led to formation of an intermediate product – aldehyde (thioaldehyde) **9**. Further intramolecular condensation at the β-position of the enamine fragment of the molecule led to the cyclic product **8**. The previously described [10-12] methods for obtaining 6H-dibenzo-[*b*,*f*][1,8]naphthyridin-5-ones, the final stage of which is the condensation of 2-amino- or 2-nitrobenzaldehydes with 4H-isoquinoline-1,3-dione may serve to confirm our hypothesis.

Isoquino[3,2-*b*]quinazolin-11-one **3** readily dissolves in the presence of acid [7]. Heating (4 h) it in acetic acid solution in the presence of hydrochloric acid led predominantly to oxidation and the formation of the dimer **6**, but not to the opening of the isoquinoline ring at the C(11)-N(12), similarly to other condensed derivatives of 3-aminoisoquinolin-1-one [13]. Compound **3** also appears to be unstable to heating (2 h) in the presence of bases (MeONa, *i*-PrONa), which leads to its destruction.

EXPERIMENTAL

IR spectra (KBr tablets) were recorded with a Hewlett Packard UR-20 instrument. ^{1}H and ^{13}C NMR spectra of the compounds synthesized were obtained and heteronuclear correlation HMQC and HMBC experiments were carried out on a Varian Mercury-400 (400 and 100 MHz respectively) instrument with TLC internal standard. All two-dimensional experiments were carried with gradient specific signals. The mixing time in the impulse sequences corresponded to $^1J_{CH}$ = 8 Hz. The number of experiments in the HMQC spectra was 128, in the HMBC spectra was 400. In all cases the solvent was DMSO-d_6. UV spectra in methanol were recorded on a Specord M-400 spectrophotometer. Mass spectra were obtained by the HPLC-MS method with an Agilent/100 Series instrument (CI, acetonitrile, 0.05% fumaric acid) The course of reactions and the purity of the products obtained were monitored by TLC on Silufol UV-254 plates.

5,13-Dihydro-11H-isoquino[3,2-*b*]quinazolin-11-one (3). 2-Cyanomethylbenzoic acid **1** (16.1 g, 0.1 mol) was dissolved in *n*-butanol (40 ml) and 2-aminobenzylamine **2** (12.2 g, 0.1 mol) was added. The mixture was boiled for 5 h. It was cooled, the precipitate was filtered off, washed with 2-propanol, and recrystallized twice from DMF. Yield 20.3 g (81.8%); mp 308-310°C (DMF), mp 308-310°C [7]. IR spectrum, ν, cm^{-1}: 3248 (NH), 1658 (C=O), 1577, 1552, 1490, 1334, 781, 754, 691. UV spectrum (MeOH), λ_{max}, nm (ε·10^{-3}, cm^{-1}): 320 (26), 377 (5.6). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.72 (1H, s, NH); 8.01 (1H, d, ^3J =7.5, H-10); 7.47 (1H, t, ^3J = 7.5, H-8); 7.36 (1H, d, ^3J = 8.0, H-7); 7.25 (1H, d, ^3J = 7.5, H-1); 7.18 (1H, t, ^3J = 7.5, H-3); 7.10 (1H, t, ^3J = 7.5, H-9); 6.88 (2H, m, H-2,4); 5.85 (1H, s, H-6); 5.06 (2H, s, H-13). ^{13}C NMR spectrum, δ, ppm: 161.82 (C-11); 141.21 (C-5a); 139.38 (C-6a); 137.31 (C-4a); 133.13 (C-8); 129.12 (C-3); 127.90 (C-10); 127.30 (C-1); 124.70 (C-7); 122.81 (C-9); 121.35 (C-2); 120.46 (C-10a); 117.52 (C-13a); 113.68 (C-4); 83.69 (C-6); 42.48 (C-13). Mass spectrum, *m/z* ($I_{rel,}$ %): 249 [M+1]$^+$ (100). Found, %: N 11.25. $C_{16}H_{12}N_2O$. Calculated, %: N 11.28.

5,13,5′13′-Tetrahydro[6,6′]bi[isoquino[3,2-*b*]quinazoline]-11,11′-dione (6) was obtained by the method [7] from isoquino[3,2-*b*]quinazolin-11-one **3** (0.25 g, 1 mmol). Yield 0.15 g (59%); mp 320-322°C (DMF). IR spectrum, ν, cm^{-1}: 3256 (NH), 1656 (C=O), 1577, 1544, 1484, 750. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 8.43 (1H, s, NH); 8.19 (1H, d, ^3J = 8.0, H-10); 7.33 (1H, t, ^3J = 8.0, H-8); 7.29 (1H, d, ^3J = 8.0, H-7); 7.14 (1H, t, ^3J = 8.0, H-3); 7.04 (1H, t, ^3J = 8.0, H-9); 6.89 (1H, d, ^3J = 8.0, H-1); 6.86 (1H, t, ^3J = 8.0, H-2); 6.86 (1H, t, ^3J = 8.0, H-2); 6.80 (1H, d, ^3J = 8.0, H-4); 5.28 (1H, d, ^3J = 15.0, H_A-13); 5.14 (1H, d, ^3J = 15.0, H_B-13). Mass spectrum, *m/z* (I_{rel},*%):* 496 [M+2]$^+$ (40), 494 [M]$^+$ (100), 492 (15), 158 (30). Found, %: N 11.30. $C_{32}H_{22}N_4O_2$. Calculated, %: N 11.33.

6H-dibenzo[*b,f*][1,8]naphthyridin-5-one (8) was obtained by method [7] from isoquino-[3,2-*b*]quinazolin-11-one **3** (0.25 g, 1 mmol) with 1,2-dichlorobenzene as solvent. Yield 0.19 g (76%); mp 250-252°C (ethanol), mp 246°C [12], 257°C [11]. IR spectrum, ν, cm^{-1}: 3446 (NH); 1677 (C=O, C=N); 1567, 1332, 786, 746. ^{1}H NMR spectrum, δ ppm (*J*, Hz): 12.07 (1H, s, NH); 9.36 (1H, s, H-12); 8.60 (1H, d, ^3J = 7.5, H-1); 8.30 (1H, d, ^3J = 7.5, H-4); 8.02 (1H, d, ^3J = 8.0, H-11); 7.86 (2H, m, H-2,8); 7.73 (1H, t, ^3J = 7.5, H-9); 7.67 (1H, t, ^3J = 7.5, H-3); 7.49 (1H, t, ^3J = 8.0, H-10). ^{13}C NMR spectrum, δ, ppm : 162.82 (C-5); 148.63 (C-6a); 147.42 (C-7a); 133.86 (C-2); 133.38 (C-12b); 132.90 (C-12); 313.51 (C-9); 129.67 (C-3); 129.22 (C-11); 128.36 (C-4); 127.30 (C-8); 126.34 (C-4a); 125.68 (C-11a); 125.43 (C-10); 123.93 (C-1); 115.19 (C-12a). Mass spectrum, *m/z* (I_{rel},%): 247 $[M+1]^+$ (100). Found, %: N 11.35. $C_{16}H_{10}N_2O$. Calculated, %: N 11.38.

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