# Study of the reactions of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine with nucleophilic reagents

*A. S. Ivanov,[a] N. Z. Tugusheva,[a] N. P. Solov´eva,[b] and V. G. Granik[a]★*

[a]*State Scientific Center of the Russian Federation "Organic Intermediate Products and Dyes Institute" (NIOPIK), 1/4 ul. Bol´shaya Sadovaya, 103787 Moscow, Russian Federation. Fax: +7 (095) 254 6574. E-mail: aivanov@email.ru*

[b]*Center of Drug Chemistry, All-Russian Research Chemical Pharmaceutical Institute, 7 Zubovskaya pl., 119815 Moscow, Russian Federation. Fax: +7 (095) 246 7805*

The reactions of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**4**) with S-, C-, and N-nucleophiles afford stable σ-adducts at position 10. In the base-catalyzed reactions of compound **4** with thiols, the resulting σ-complexes are rearranged into sulfides **14a**—**c**. Sulfides **14b,c** undergo the Thorpe—Ziegler cyclization to give 1-aminobenzo[*b*]thieno[2,3-*h*][1,6]naphthyridine derivatives **15a,b**. The reaction of naphthyridine **4** with aniline affords a mixture of σ-adducts of the C—N and C—C types, while those with aliphatic amines yield 3-amino derivatives **17a**—**c**. In the presence of $H_2O_2$, benzonaphthyridine **4** adds peroxycarboxylic acids to give compounds **8a,b**. In alkaline medium, adduct **8a** is rearranged into 4-aminopyridine-3-carbaldehyde derivative **10**.

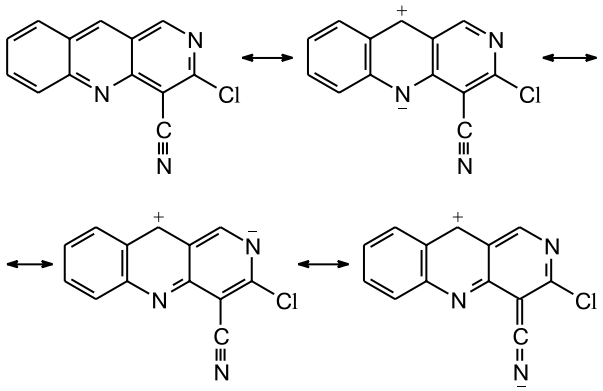
**Key words:** benzo[*b*][1,6]naphthyridine, 2-chloro-3-cyano-5-formyl-4-(2-hydroxyanilino)pyridine, benzo[*b*]thieno[2,3-*h*][1,6]naphthyridine, Thorpe—Ziegler cyclization.

Earlier, it was shown that hydrolytic opening of 5-cyano-6-(2-dimethylaminovinyl)-1-phenylpyrimidin-4-one (**1**) is followed by recyclization, which gives 4-anilino-3-cyanopyridin-2-one (**2**) in alkaline medium[1] and 4-anilino-3-cyano-5-formylpyridin-2-one (**3**) in acidic media.[2] It was also found[2] that heating of formylpyridone **3** in $POCl_3$ in the presence of $Et_3N \cdot HCl$ smoothly affords 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**4**) (Scheme 1).

In the present study, we found that the recyclization of pyrimidinone **1** in aqueous AcOH yields both pyridones **2** and **3** in the ratio ~1 : 2, while the major recyclization product in glacial AcOH is 4-cyano-3-oxobenzo[*b*][1,6]naphthyridine (**5**). In the latter case, intermediate *N*-formyl amide **6** undergoes cyclization into 3-oxobenzonaphthyridine **5**, which is convertible by reaction with $POCl_3$ into the known[2] 3-chloro derivative **4**.

One can believe that a partial positive charge in tricyclic compound **4** is localized at position 10.

Hence, this position can be attacked by various nucleophiles. Reactions of this type, which afford corresponding σ-complexes,[3] are well studied for azines. In a relevant review,[3] neutral azine derivatives were mentioned among possible substrates for these reactions. However, corresponding azinium cations or *N*-oxides are certainly more reactive in such transformations. Because of this, the goal of this work was to study the reactions of nucleophiles with both compound **4** proper and its *N*-oxide.

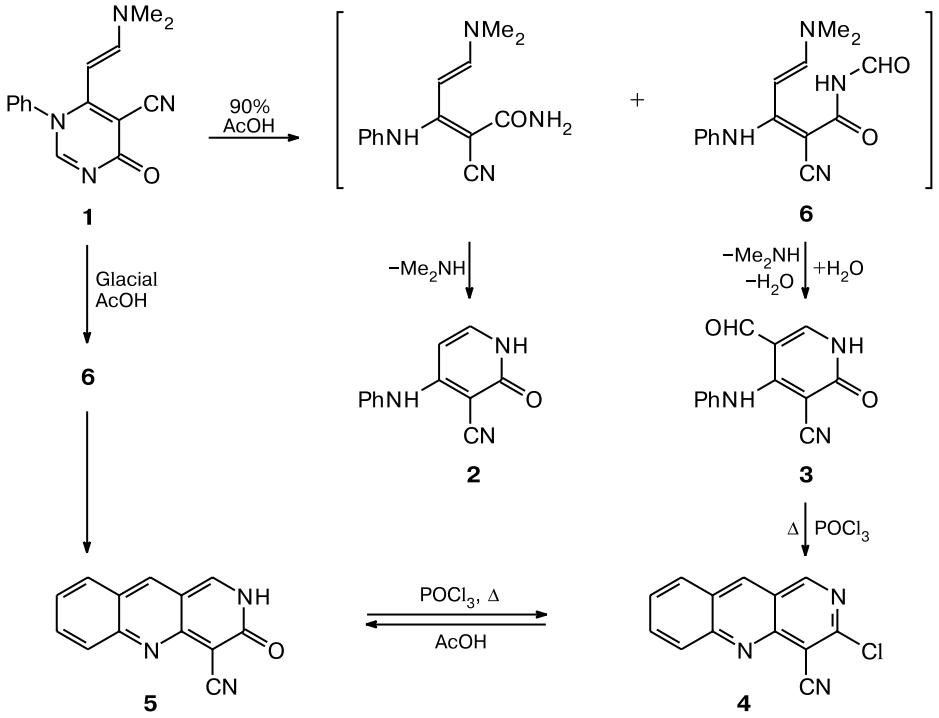


However, oxidation of compound **4** with $H_2O_2$ in hot AcOH gave 10-acetyloxy-3-chloro-4-cyano-5-hydroxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (**8a**) rather than the expected 5-*N*-oxide; *i.e.*, the acetate anion is added at position 10 (Scheme 2). An analogous reaction in propionic acid afforded corresponding 10-propionyloxy derivative **8b**. 3-Chloro-4-cyano-10-oxo-5,10-dihydrobenzo[*b*][1,6]naphthyridine (**9**) was isolated as a by-product in these reactions.

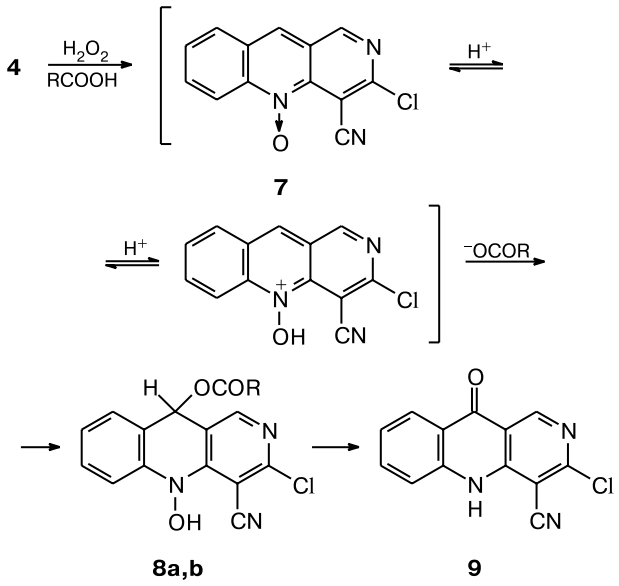
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1966—1973, November, 2002.

1066-5285/02/5111-2121 $27.00 

**Scheme 1**



**Scheme 2**



**8:** R = Me (**a**), Et (**b**)

Apparently, intermediate *N*-oxide **7**, in which position 10 is activated for nucleophilic attack, is initially protonated at the O atom. This is followed by addition of an acyloxy anion at position 10 to give compound **8a,b**. The structures of the latter were unambiguously determined from their $^1$H and $^{13}$C NMR spectra. In the $^1$H NMR spectra of the compounds obtained, signals for all aromatic protons are significantly shifted upfield compared to those for the starting benzonaphthyridine **4** *; in addition, they show narrow singlets at δ ~7.00 for the methine protons ($^1J_{^{13}C,H}$ = 175 Hz), signals for the protons of the acyloxy groups, and broadened singlets at δ ~9.40 for the N—OH protons (Table 1). The NOE experiment for *N*-hydroxynaphthyridine **8a** revealed a 20% intensification of the singlet at δ 8.38 for the H(1) proton upon irradiation of the signal at δ 7.00. When the singlet at δ 8.38 was irradiated, the signal at δ 7.00 becomes, in turn, more intense by 12%. These data indicate a spatial vicinity of the H(1) and H(10) protons, which correlates with the proposed structure **8a**. Analogously, irradiation of the broadened singlet at δ 9.41 intensifies the signal at δ 7.52 for the H(6) atom by 10%, thus confirming the presence of the N(5)—OH fragment in the molecule. The structure of compound **8a** was unambiguously proved by $^{13}$C NMR data (see Experimental). The $^{13}$C NMR spectrum contains a signal δ 93.5 for the C(10) atom (dd, $^1J_{C,H}$ = 175 Hz, $^3J_{H(1),C(10)}$ = 4.6 Hz). The signals for C(4a) and C(4) were found to be sensitive to deuteration of the N(5)—OH fragment. Addition of a $D_2O$—water mixture (four to five drops) to the solution under study caused these signals to shift by 0.11 and 0.06 ppm, respec-

* Naphthyridine **4**: $^1$H NMR (DMSO-$d_6$), δ: 7.85, 8.17 (both t, 1 H each, H(7), H(8)); 8.31, 8.40 (both d, 1 H each, H(6), H(9)); 9.68 (br.s, 1 H, H(10), $^1J_{C,H}$ = 169.3 Hz); 9.83 (s, 1 H, H(1), $^1J_{C,H}$ = 189.1 Hz).

**Table 1.** $^1$H NMR spectra of compounds **8a,b**, **9**, **13a—c**, **16**, and **18**

| Compound | δ (*J*/Hz) | | | | |
|---|---|---|---|---|---|
| | H(1) (s, 1 H) | H(10) (s, 1 H) | H arom. (1 H each, H(6), H(7), H(8), H(9)) | Substituent at the C(10) atom | N(O)—H(5) (s, 1 H) |
| **8a** | 8.38 ($^1J_{C,H}$ = 185.0) | 7.00 ($^1J_{C,H}$ = 175.0) | 6.90, 7.52 (both d, $J_o$ = 8.0); 7.06, 7.16 (both t, $J_o$ = 8.0) | 1.94 (s, 3 H, Me) | 9.41 [a] |
| **8b** | 8.38 ($^1J_{C,H}$ = 185.0) | 7.04 ($^1J_{C,H}$ = 175.6) | 6.90, 7.52 (both d, $J_o$ = 8.0); 7.05, 7.16 (both t, $J_o$ = 8.0) | 0.84 (t, 3 H, $CH_2\underline{Me}$, $J_o$ = 7.6); 2.20 (sym.m, 2 H, $C\underline{H}_2Me$, $J_o$ = 7.6) | 9.43 [a] |
| **9** | 9.18 | — | 7.44, 7.85 (both t, $J_o$ = 8.4); 8.00, 8.20 (both d, $J_o$ = 8.4) | — | 12.13 [a] |
| **13a** | 7.78 ($^1J_{C,H}$ = 184.0) | 5.93 ($^1J_{C,H}$ = 153.6) | 7.07, 7.25 (both t, $J_o$ = 8.0); 7.34 (d, $J_o$ = 8.0)[b] | 7.04 (d, 2 H, H(2′), H(6′), $J_o$ = 7.2); 7.27 (t, 2 H, H(3′), H(5′), $J_o$ = 7.2); 7.38 (t, 1 H, H(4′), $J_o$ = 7.2) | 10.17 |
| **13b** | 8.26 ($^1J_{C,H}$ = 183.8) | 5.64 ($^1J_{C,H}$ = 151.0) | 7.10, 7.30 (both t, $J_o$ = 7.6); 7.34, 7.44 (both d, $J_o$ = 7.6) | 1.14 (t, 3 H, $CH_2\underline{Me}$, $J_o$ = 7.2); 3.20 (q, 2 H, $SCH_{AB}$, $^2J_{H_A,H_B}$ = 15.8); 3.94 (q, 2 H, $C\underline{H}_2Me$, $J_o$ = 7.2) | 10.40 |
| **13c** | 8.32 ($^1J_{C,H}$ = 184.7) | 5.71 ($^1J_{C,H}$ = 152.0) | 7.10, 7.28 (both t, $J_o$ = 7.8); 7.39, 7.44 (both d, $J_o$ = 7.8) | 3.18 (q, 2 H, $SCH_{AB}$, $^2J_{H_A,H_B}$ = 14.6); 7.04 (t, 1 H, H(4′)); 7.28 (t, 2 H, H(3′), H(5′)); 7.49 (d, 2 H, H(2′), H(6′)); 9.99 (s, 1 H, CONH) | 10.37 |
| **16** | 8.38 ($^1J_{C,H}$ = 181.6) | 5.19 [c] ($^1J_{C,H}$ = 148.2) | 7.19, 7.39 (both t, $J_o$ = 7.2); 7.47, 7.51 (both d, $J_o$ = 7.2) | 5.09 (d, 1 H, $HC(CN)_2$, $^3J_{H(10),H}$ = 5.3) | 10.49 |
| **18** | 8.03 ($^1J_{C,H}$ = 181.4) | 5.22 ($^1J_{C,H}$ = 134.0) | 6.96, 7.16 (both t, $J_o$ = 7.4); 7.06, 7.40 (both d, $J_o$ = 7.4) | 4.98 (br.s, 2 H, $NH_2$); 6.41 (d, 2 H, Ph, H(3′), H(5′), $J_o$ = 8.8); 6.75 (d, 2 H, Ph, H(2′), H(6′), $J_o$ = 8.8) | 10.01 |

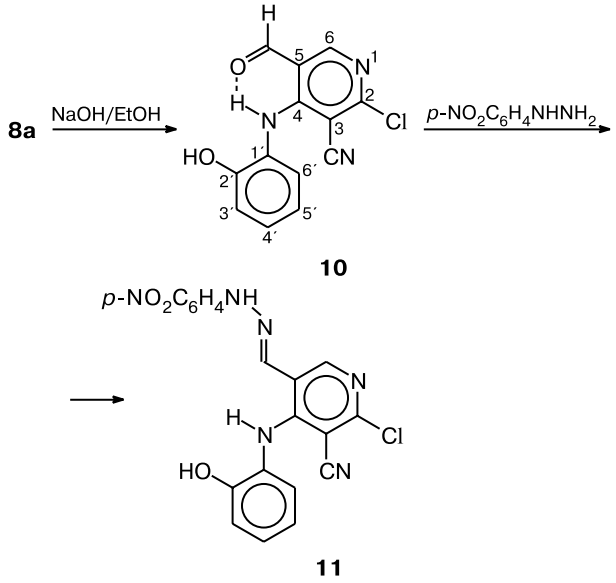
[a] Br.s.
[b] 2 H (H(6), H(9)).
[c] Doublet.

tively. The signals for the C(5a), C(6), C(9), and C(10) atoms are less sensitive to the deuteration, simply becoming noticeably broader. Thus, this effect is mainly confined to the atoms in the vicinity of the N—OH group.

Alkaline hydrolysis of compound **8a** occurs in a rather unusual way (Scheme 3). Cleavage of the C(9a)—C(10) and N—OH bonds is followed by migration of the OH group to the *ortho*-position of the benzene ring to give 2-chloro-3-cyano-5-formyl-4-(2-hydroxyanilino)pyridine (**10**) ($^1$H and $^{13}$C NMR data).

The $^1$H NMR spectrum of compound **10** contains two narrow singlets at δ 8.72 (1 H, $^1J_{C,H}$ = 184.7 Hz) and δ 10.02 (1 H, $^1J_{C,H}$ = 185.4 Hz), two broadened singlets at δ 10.32 (1 H) and δ 10.55 (1 H), and multiplets for four aromatic protons at δ 6.80 and 7.18 (both t, 1 H each, H(4′), H(5′), $J_o$ = 7.2 Hz) and δ 6.97 and 7.27 (both d, 1 H each, H(3′), H(6′), $J_o$ = 7.2 Hz). The signal at δ 10.32 becomes even broader at 60 °C and is shifted to δ 10.20, while the position of the lower-field signal (δ 10.55) remains unchanged. Based on these data, we assigned the singlet at δ 10.02 to the aldehyde proton, the signal at δ 10.32 to the OH proton, and the broadened signal at δ 10.55 to the NH proton involved in intramolecular hydrogen bonding. Selective decoupling experiment enabled us to assign signals in the $^{13}$C NMR spectrum. The lowest-field doublet at δ 194.3 ($^1J_{^{13}C,H}$ = 185.4 Hz) belongs to the $\underline{C}$H=O group. Its components are additionally split because of spin-spin coupling

**Scheme 3**



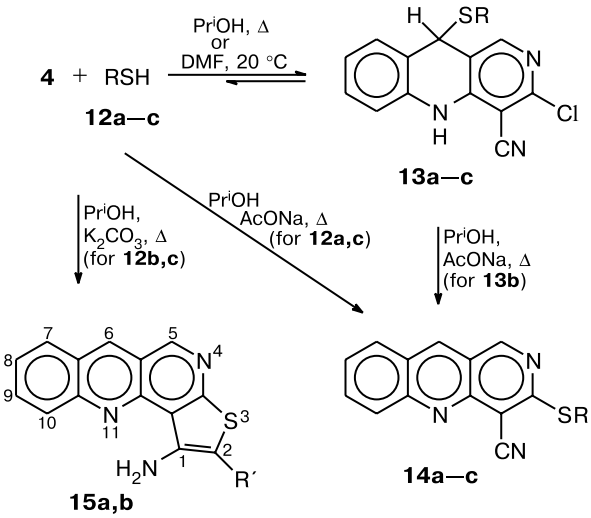

with the C(6)H proton (δ 159.7, $^{1}J_{^{13}C,H}$ = 184.7 Hz, $^{3}J_{(C=O),H(6)}$ = 5.4 Hz). A high geminal heteroconstant ($\delta_{^{13}C}$ 115.8 (C(5)), $^{2}J_{C(5),CHO}$ = 22.9 Hz) is characteristic of an aldehyde fragment.[4] The CN fragment gives a singlet at δ 113.0, while the signal for the C(3) atom appears at δ 93.6 ($^{3}J_{C(3),NH}$ = 7.7 Hz). Signals at δ 159.2 (d, $^{3}J_{C(2),H(6)}$ = 14.5 Hz) and δ 154.5 (t, $^{3}J_{C(4),HOC} \approx {}^{3}J_{C(4),H(6)} \approx 6$ Hz) were unambiguously assigned to the C(2) and C(4) atoms, respectively. Signals at δ 116.1, 119.3, 128.3, and 129.7 correspond to the benzene CH groups. The two remaining signals at δ 123.2 (m) and 153.4 (t, $^{\Sigma}J_{C,HC}$ = 17 Hz) can be assigned to the C(1′) and C(2′) atoms of the 2′-hydroxyphenyl substituent. The last signal assignment was verified against the chemical shifts for the C(1′) and C(2′) atoms in a model compound **3** ($\delta_{C(2')}$ 126.0, $\delta_{C(1')}$ 136.1). In addition, the expected $\delta_{^{13}C}$ values for the C(1′) and C(2′) atoms in the *ortho*-hydroxyphenyl fragment (δ 124.1 and 153.0, respectively), which were calculated with the use of increments for an OH group in the benzene series,[4] proved to be very close to the experimental data (δ 123.2 and 153.4). The presence of the formyl group in compound **10** was also confirmed by the synthesis of *p*-nitrophenylhydrazone **11** (see Scheme 3).

The mechanism of the unusual **8a** ⟶ **10** transformation calls for further investigation.

Easy addition of a nucleophile to *N*-oxide **7** motivated us to study the reactions of tricyclic compound **4** with various nucleophilic reagents. In this case, replacement of the Cl atom and addition of a nucleophile at position 10 are both possible. Earlier,[3,5] such substrates were already used. Thus the reaction of ethylamine with 7-chloropteridine in the presence of $KMnO_4$ initially gives an adduct at position 5, while replacement of the Cl atom by the ethylamino group requires a prolonged reaction time.[5]

Compound **4** reacts with thiophenol (**12a**), ethyl thioglycolate (**12b**), and *N*-phenylthioglycolamide (**12c**) under mild conditions (DMF, 20 °C or in boiling $Pr^{i}OH$) to give adducts at position 10 (**13a—c**) in good yields (Scheme 4). Their structures were unambiguously confirmed by $^{1}H$ and $^{13}C$ NMR data. In the $^{1}H$ NMR spectra of compounds **13a—c** (as in those of **8a,b**), signals for the aromatic protons are noticeably shifted upfield compared to analogous signals for the starting benzonaphthyridine **4**. A singlet for the methine H(10) proton in compounds **13a—c** appears at δ 5.60—6.00. The presence of the asymmetric C(10) atom in the naphthyridine in question makes the S—$CH_2$ protons nonequivalent (quartets at δ 3.20 ($^{2}J_{H_A,H_B}$ = 15.8 Hz) for **13b** and δ 3.18 ($^{2}J_{H_A,H_B}$ = 14.6 Hz) for **13c**). Selective decoupling from the H(10) and H(1) protons was used to assign signals in the $^{13}C$ NMR spectrum of compound **13b** (see Experimental). In the proton-nondecoupled spectrum, a doublet for the C(10) atom at δ 41.2 ($^{1}J_{C,H}$ = 151.0 Hz) is additionally split into a triplet because of a spin-spin coupling with the $CH_2$—S protons ($^{3}J_{C(10),H_2CS} \approx 4.4$ Hz). A signal for $\underline{C}H_2$—S appears at δ 31.9 (td, $^{1}J_{C,H}$ = 138.6 Hz), its shape being due to a spin-spin coupling with the methine H(10) proton. Selective decoupling from the H(10) proton reduces the multiplicity of signals for the aromatic protons at the C(9), C(9a), C(5a), C(10a), C(4a), and C(1) atoms. It is significant that the mass spectra of σ-adducts **13a—c** contain no molecular ion peaks and correspond to the starting compound **4**.

**Scheme 4**




R = Ph (**a**), $CH_2COOEt$ (**b**), $CH_2CONHPh$ (**c**);
R′ = COOEt (**a**), CONHPh (**b**)

**Table 2.** $^1$H NMR spectra of compounds **14a—c** and **17a**

| Compound | δ (*J*/Hz) | | | |
|---|---|---|---|---|
| | H(1) (s, 1 H) | H(10) (s, 1 H) | H arom. (1 H each, H(6), H(7), H(8), H(9)) | Substituent at the C(3) atom |
| **14a** | 9.59 ($^1J_{C,H}$ = 187.1) | 9.45 ($^1J_{C,H}$ = 168.1) | 7.75, 8.03 (both t, $J_o$ = 8.4); 8.21, 8.30 (both d, $J_o$ = 8.4) | 7.48—7.53 (m, 3 H, Ph); 7.63—7.65 (m, 2 H, Ph) |
| **14b** | 9.73 ($^1J_{C,H}$ = 185.6) | 9.49 ($^1J_{C,H}$ = 168.0) | 7.73, 8.06 (both t, $J_o$ = 8.0); 8.20, 8.30 (both d, $J_o$ = 8.0) | 1.20 (t, 3 H, $CH_2\underline{Me}$, $J_o$ = 7.2); 4.14 (q, 2 H, $C\underline{H}_2Me$, $J_o$ = 7.2); 4.34 (s, 2 H, $CH_2S$, $^1J_{C,H}$ = 143.5) |
| **14c** | 9.74 ($^1J_{C,H}$ = 186.9) | 9.47 ($^1J_{C,H}$ = 168.1) | 7.73, 8.19, 8.29 (all d, $J_o$ = 8.4); 8.06 (t, $J_o$ = 8.4) | 4.45 (s, 2 H, $CH_2S$, $^1J_{C,H}$ = 142.1); 7.05 (t, 1 H, H(4′), $J_o$ = 7.6); 7.30 (t, 2 H, H(3′), H(5′), $J_o$ = 7.6); 7.59 (d, 2 H, H(2′), H(6′), $J_o$ = 7.6); 10.40 (s, 1 H, CONH) |
| **17a** | 9.42 ($^1J_{C,H}$ = 183.4) | 9.09 ($^1J_{C,H}$ = 165.2) | 7.51, 7.88 (both t, $J_o$ = 8.0); 7.97, 8.09 (both d, $J_o$ = 8.0) | 0.92 (t, 3 H, Me, $J_o$ = 7.2); 1.36 (m, 2 H, $C\underline{H}_2Me$); 1.62 (quintet, 2 H, $C\underline{H}_2Et$, $J_o$ = 7.2); 3.62 (q, 2 H, $C\underline{H}_2Pr$, $J_o$ = 7.2); 7.80 (br.s, 1 H, NH) |

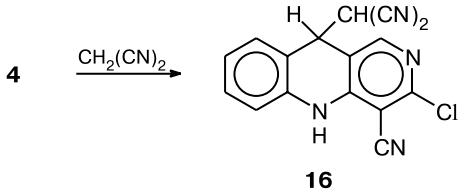
Heating of compound **4** with thiols **12a,c** (or heating of adduct **13b** without thiols) in Pr$^i$OH in the presence of AcONa afforded 3-alkyl(aryl)thio-4-cyanobenzo[*b*][1,6]naphthyridines **14a—c**. There is no doubt that the thiol is eliminated from adducts **13** under these conditions and slowly but irreversibly replaces the Cl atom.

It is of interest to compare the $^1$H NMR data for σ-adducts **13a—c** and benzonaphthyridines **14a—c** (see Tables 1, 2). Signals for the methylene protons in compounds **14b,c** (as opposed to **13b,c**) appear as singlets at δ 4.34 (**14b**) and 4.45 (**14c**) since their molecules contain no asymmetric centers.

When compound **4** is refluxed with methylene-active thiols **12b,c** in Pr$^i$OH in the presence of $K_2CO_3$, products **14b,c** undergo *in situ* Thorpe—Ziegler cyclization[6] to give benzo[*b*]thieno[2,3-*h*][1,6]naphthyridines **15a,b** (see Scheme 4).

We also found that the reaction of compound **4** with malononitrile affords adduct **16**, which was isolated as a mixture with the starting benzonaphthyridine **4** (~10%). The structure of the adduct was confirmed by $^1$H NMR spectra (see Table 1, Scheme 5).

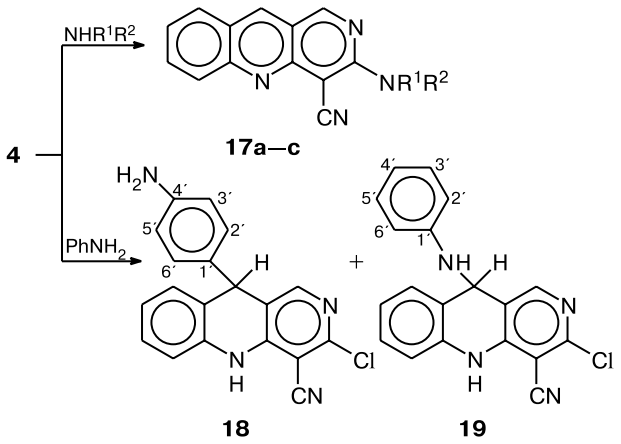
**Scheme 5**




**16**

The reactions of compound **4** with high-basic amines (β-phenylethylamine, homoveratrylamine, benzylamine, piperidine, and morpholine) are known[7] to yield 3-aminobenzo[*b*][1,6]naphthyridines. In the present work, we discovered that naphthyridine **4** reacts with butylamine, 2-aminobutanol, and hexahydroazepine to give corresponding compounds **17a—c** in high yields, as well (Scheme 6).

**Scheme 6**




$R^1$ = Bu, $R^2$ = H (**a**); $R^1$ = CH(Et)$CH_2OH$, $R^2$ = H (**b**); $R^1$, $R^2$ = $(CH_2)_6$ (**c**)

Previously, it was shown that the reactions of azines (particularly acridines as quaternary salts[3,8]) with aniline derivatives afford unstable N-adducts, which exist only at low temperatures. Above 0 °C, they change into thermodynamically stable C-adducts; the latter can be oxidized into *p*-aminophenylacridinium halides.[8]

These results motivated us to carry out a reaction of compound **4** with aniline in boiling Pr$^i$OH for a pro-

longed time. The reaction afforded 10-(4-aminophenyl)-3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**18**) in good yield. The crude product contains aniline and adduct **19** (~16%) ($^1$H NMR data). Obviously, the latter is much more stable than the aforementioned N-adducts of acridinium ions (probably, because of the electron-withdrawing groups in its pyridine ring).

## Experimental

IR spectra were recorded on a Perkin—Elmer 457 instrument (Vaseline oil). Mass spectra were obtained with a Finnigan SSQ-710 mass-spectrometer (EI, direct inlet of samples into the ion source). $^1$H and $^{13}$C NMR spectra were recorded on a Varian Unity-400 spectrometer in DMSO-$d_6$. The course of the reaction was monitored and the purity of individual compounds was checked by TLC on Silufol UV-254 plates in AcOEt (visualization under UV light). Melting points were determined on a Boetius stage. Spectral and physicochemical characteristics and elemental analysis data for the compounds obtained are given in Tables 1—3.

**4-Cyano-3-oxo-2,3-dihydrobenzo[*b*][1,6]naphthyridine (5).** ***A.*** Pyrimidinone **1** [1] (30 g, 0.11 mol) was stirred in 70 mL of glacial AcOH containing 0.5 mL of water at ~20 °C for 24 h. The precipitate that formed was filtered off, washed with distilled water and EtOH, and dried to give benzonaphthyridinone **5** (15.3 g, 61%), m.p. >350 °C.

**Table 3.** Melting points and elemental analysis data for compounds **8a,b**, **9—11**, **13a—c**, **14a—c**, **15a,b**, and **17a—c**

| Compound | M.p./°C (solvent) | Found (%) / Calculated | | | | | Molecular formula |
|---|---|---|---|---|---|---|---|
| | | C | H | Cl | N | S | |
| **8a** | 109—110 | 57.07 | 3.26 | 11.22 | 13.01 | — | $C_{15}H_{10}ClN_3O_3$ |
| | ($Pr^iOH$) | 57.05 | 3.17 | 11.25 | 13.31 | | |
| **8b** | 155.5—158 | 58.15 | 3.65 | 11.09 | 12.95 | — | $C_{16}H_{12}ClN_3O_3$ |
| | ($Pr^iOH$) | 58.28 | 3.67 | 10.75 | 12.74 | | |
| **9** | —* | 60.80 | 2.24 | 12.73 | 16.58 | — | $C_{13}H_6ClN_3O$ |
| | | 61.07 | 2.37 | 13.86 | 16.44 | | |
| **10** | —* | 57.17 | 3.28 | 12.95 | 15.08 | — | $C_{13}H_8ClN_3O_2$ |
| | (EtOH) | 57.05 | 2.94 | 12.95 | 15.35 | | |
| **11**** | —* | 55.44 | 4.09 | 8.15 | 18.40 | — | $C_{19}H_{13}ClN_6O_3\cdot\cdot C_2H_5OH$ |
| | (EtOH) | 55.46 | 4.18 | 7.81 | 18.48 | | |
| **13a** | 277—278 | 65.53 | 3.39 | 10.33 | 12.26 | 9.32 | $C_{19}H_{12}ClN_3S$ |
| | (MeCN) | 65.25 | 3.43 | 10.14 | 12.01 | 9.17 | |
| **13b** | 274—276 | 57.17 | 3.85 | 10.18 | 11.62 | 8.95 | $C_{17}H_{14}ClN_3O_2S$ |
| | (MeCN) | 56.75 | 3.92 | 9.85 | 11.68 | 8.89 | |
| **13c** | 203—205 | 62.25 | 3.88 | 8.55 | 14.00 | 7.91 | $C_{21}H_{15}ClN_4OS$ |
| | (MeCN) | 61.99 | 3.72 | 8.55 | 14.00 | 7.91 | |
| **14a** | 262—267 | 72.73 | 3.46 | — | 13.86 | 10.28 | $C_{19}H_{11}N_3S$ |
| | ($Me_2CO$) | 72.82 | 3.54 | | 13.41 | 10.23 | |
| **14b** | 202—204 | — | 3.97 | — | 12.85 | 9.93 | $C_{17}H_{13}N_3O_2S$ |
| | (MeCN) | | 4.05 | | 12.99 | 9.92 | |
| **14c** | 277.5—278 | 67.88 | 3.76 | — | 15.30 | 8.51 | $C_{21}H_{14}N_4OS$ |
| | ($Pr^iOH$—DMF) | 68.09 | 3.81 | | 15.12 | 8.66 | |
| **15a** | 195.5—196 | 62.93 | 4.14 | — | 12.85 | 9.89 | $C_{17}H_{13}N_3O_2S$ |
| | ($Bu^nOH$) | 63.14 | 4.05 | | 12.99 | 9.92 | |
| **15b** | 256.5—258 | 67.98 | 3.96 | — | 14.82 | 8.52 | $C_{21}H_{14}N_4OS$ |
| | ($Bu^nOH$) | 68.09 | 3.81 | | 15.12 | 8.66 | |
| **17a** | 245.6—246 | 74.15 | 5.88 | — | 20.33 | — | $C_{17}H_{16}N_4$ |
| | ($Pr^iOH$) | 73.89 | 5.84 | | 20.27 | | |
| **17b** | 169.5—170.5 | 69.85 | 5.52 | — | 19.17 | — | $C_{17}H_{16}N_4O$ |
| | ($Pr^iOH$—$H_2O$) | 69.90 | 5.52 | | 19.15 | | |
| **17c** | 168—169 | 75.40 | 6.32 | — | 18.47 | — | $C_{19}H_{18}N_4$ |
| | ($Pr^iOH$) | 75.47 | 6.00 | | 18.53 | | |
| **18** | 247 (decomp.) | 69.09 | 3.86 | 10.56 | 16.80 | — | $C_{19}H_{13}ClN_4$ |
| | (MeCN) | 68.57 | 3.94 | 10.66 | 16.84 | | |

* No characteristic melting point.

** Solvate with EtOH (1 : 1).

***B.*** Compound **4** (0.1 g, 0.42 mmol) was refluxed in 10 mL of glacial AcOH and cooled. The precipitate that formed was filtered off, washed with water, and dried to give compound **5** (0.04 g, 43%). MS, *m/z* ($I_{rel}$ (%)): 221 $[M]^+$ (100), 193 $[M - CO]^+$ (91), 165 $[M - CO - HCN]^+$ (16), 140 (15). IR, ν/cm$^{-1}$: 2220 (CN), 1640 (CO). The melting point of a mixture with the sample obtained by method ***A*** was not depressed.

**Benzonaphthyridines 8a,b and 9 (general procedure).** An eightfold excess of 38% $H_2O_2$ was added to compound **4** in acetic (for **8a**) or propionic acid (for **8b**). The reaction mixture was stirred at 80 °C for 1.5 h and then cooled to ~20 °C. The precipitate of benzonaphthyridinone **9** was filtered off. Aqueous 25% EtOH was added to the mother liquor, and the precipitate that formed was filtered off, washed with aqueous EtOH, and dried to give benzonaphthyridines **8a,b**.

**10-Acetyloxy-3-chloro-4-cyano-5-hydroxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (8a).** The yield was 26%. MS, *m/z* ($I_{rel}$ (%)): 315 $[M]^+$ (29), 273 $[M - CH_2CO]^+$ (100), 256 $[M - CH_2CO - OH]^+$ (40). IR, ν/cm$^{-1}$: 3329 (OH), 2232 (CN), 1760 (CO). $^{13}$C NMR, δ: 20.6 (Me); 93.5 (C(10)); 95.4 (C(4)); 114.2 (CN); 118.5 (C(10a)); 122.1, 122.95, 124.8, 125.6 (C(6), C(7), C(8), C(9)); 132.8 (C(9a)); 143.6 (C(5a)); 151.1 (C(1)); 151.5 (C(4a)); 154.6 (C(3)); 168.3 (CO).

**3-Chloro-4-cyano-5-hydroxy-10-propionyloxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (8b).** The yield was 24%. MS, *m/z* ($I_{rel}$ (%)): 329 $[M]^+$ (54), 273 $[M - CH_2CH_2CO]^+$ (100), 256 $[M - CH_2CH_2CO - OH]^+$ (70), 244 (50), 220 (37). IR, ν/cm$^{-1}$: 3327 (OH), 2229 (CN), 1756 (CO).

**3-Chloro-4-cyano-10-oxo-5,10-dihydrobenzo[*b*][1,6]naphthyridine (9).** The yield was 0.4%. MS, *m/z* ($I_{rel}$ (%)): 255 $[M]^+$ (100), 220 $[M - Cl]^+$ (93), 191 $[M - Cl - CHO]^+$ (35), 165 $[M - Cl - CHO - CN]^+$ (59). IR, ν/cm$^{-1}$: 3251, 3168 (NH), 2229 (CN), 1624 (CO).

**2-Chloro-3-cyano-5-formyl-4-(2-hydroxyanilino)pyridine (10).** A solution of NaOH (0.1 g, 2.5 mmol) in 15 mL of anhydrous EtOH was slowly added to naphthyridine **8a** (0.3 g, 0.85 mmol) in 10 mL of anhydrous EtOH. The reaction mixture was stirred at 0 °C for 1.5 h and acidified with HCl. The precipitate that formed was filtered off and dried to give pyridine **10** (0.18 g, 71%). MS, *m/z* ($I_{rel}$ (%)): 273 $[M]^+$ (100), 244 $[M - CHO]^+$ (38), 232 (49), 180 $[M - C_6H_4OH]^+$ (54), 94 $[M - C_6H_4OH]^+$ (77). IR, ν/cm$^{-1}$: 3289, 3215, 3135 (OH, NH), 2220 (CN), 1659 (CO).

**2-Chloro-3-cyano-4-(2-hydroxyanilino)-5-[(4-nitrophenyl)hydrazono]methylpyridine (11).** *p*-Nitrophenylhydrazine (0.11 g, 0.73 mmol) and a drop of AcOH were added to aldehyde **10** (0.1 g, 0.37 mmol) in 7 mL of Pr$^i$OH. The reaction mixture was refluxed for 11 h. The precipitate that formed was filtered off, washed with Pr$^i$OH and ether, and dried to give solvate **11** · EtOH (1 : 1) (0.08 g, 53%). MS, *m/z* ($I_{rel}$ (%)): 408 $[M]^+$ (21), 406 $[M - 2H]^+$ (30), 378 $[M - NO]^+$ (7), 306 (51), 256 $[M - NHNHC_6H_4NO_2]^+$ (100). $^1$H NMR, δ: 6.84, 7.13 (both t, 1 H each, H(4′), H(5′), $J_o$ = 7.2 Hz); 6.97, 7.30 (both d, 1 H each, H(3′), H(6′), $J_o$ = 7.2 Hz); 7.13 (d, 2 H, H arom., $J$ = 9.2 Hz); 8.15 (d, 2 H, H arom., $J$ = 9.2 Hz); ~10.2, 10.53, 11.55 (all br.s, 2 NH, OH).

**Benzonaphthyridines 13a—c, 14a,c, 15a,b, 17a—c, and 18 (general procedure).** The reaction conditions are specified in Table 4. A mixture of compound **4** (0.2 g), a thiol or amine, and a catalyst (if necessary) was stirred in 15 mL of Pr$^i$OH (in 10 mL of DMF for **17c**). The precipitate that formed was filtered off, washed with Pr$^i$OH (and with water for **14a,c**, **15a,b**, **17a,c**, and **18**), and dried to give benzonaphthyridines **13a—c**, **14a,c**, **15a,b**, **17a—c**, and **18**.

**Table 4.** Reaction conditions and the yields of compounds **13a—c**, **14a,c**, **15a,b**, **17a,b**, and **18**

| Product | *t**/h | *T*/°C | Catalyst | Reagent (excess (mol.%)) | Yield (%) |
|---|---|---|---|---|---|
| **13a** | 24 | 20 | — | **12a** (20) | 96 |
| **13b** | 72 | 20 | — | **12b** (20) | 93 |
| **13c** | 5 | Refluxing | — | **12c** (10) | 59 |
| **14a** | 1.5 | The same | AcONa | **12a** (20) | 96 |
| **14c** | 5 | » | AcONa | **12c** (15) | 68 |
| **15a** | 1.5 | » | $K_2CO_3$ | **12b** (15) | 83 |
| **15b** | 2.5 | » | $K_2CO_3$ | **12c** (10) | 84 |
| **17a** | 25 | » | — | $BuNH_2$ (400) | 87 |
| **17b** | 27 | » | — | $HOCH_2CH(Et)NH_2$ (300) | 82 |
| **18** | 56 | » | — | $PhNH_2$ (400) | 78 |

* Reaction duration.

**3-Chloro-4-cyano-10-phenylthio-5,10-dihydrobenzo[*b*][1,6]naphthyridine (13a).** MS, *m/z* ($I_{rel}$ (%)): 239 $[M - PhS]^+$ (100), 204 $[M - PhS - Cl]^+$ (12), 177 $[M - PhS - Cl - HCN]^+$ (18), 110 $[PhS]^+$ (72). IR, ν/cm$^{-1}$: 3305 (NH), 2225 (CN).

**3-Chloro-4-cyano-10-ethoxycarbonylmethylthio-5,10-dihydrobenzo[*b*][1,6]naphthyridine (13b).** MS, *m/z* ($I_{rel}$ (%)): 239 $[M - SCH_2COOEt]^+$ (100), 204 $[M - SCH_2COOEt - Cl]^+$ (64), 177 $[M - SCH_2COOEt - Cl - HCN]^+$ (68). IR, ν/cm$^{-1}$: 3288 (NH), 2231 (CN), 1724 (CO). $^{13}$C NMR, δ: 14.2 (Me); 31.9 ($CH_2S$); 41.2 (C(10)); 61.3 ($\underline{C}H_2Me$); 92.2 (C(4)); 114.0 (CN); 116.0 (C(10a)); 119.9 (C(9a)); 116.9, 124.1, 129.2, 129.4 (C(6), C(7), C(8), C(9)); 136.6 (C(5a)); 149.0 (C(4a)); 151.2 (C(1)); 151.8 (C(3)); 169.8 (CO).

**10-Anilinocarbonylmethylthio-3-chloro-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (13c).** MS, *m/z* ($I_{rel}$ (%)): 239 $[M - SCH_2CONHPh]^+$ (100), 204 $[M - SCH_2CONHPh - Cl]^+$ (18), 177 $[M - SCH_2CONHPh - Cl - HCN]^+$ (19), 93 $[PhNH_2]^+$ (37). IR, ν/cm$^{-1}$: 3291, 3223, 3193, 3120 (NH), 2232 (CN), 1650 (CO).

**4-Cyano-3-(phenylthio)benzo[*b*][1,6]naphthyridine (14a).** MS, *m/z* ($I_{rel}$ (%)): 313 $[M]^+$ (95), 312 $[M - H]^+$ (100), 287 $[M - CN]^+$ (33).

**4-Cyano-3-ethoxycarbonylmethylthiobenzo[*b*][1,6]naphthyridine (14b).** Sodium acetate (0.3 g) was added to compound **13b** (0.2 g, 0.84 mmol) in 15 mL of Pr$^i$OH. The reaction mixture was refluxed with stirring for 4.5 h. The precipitate that formed was filtered off, washed with Pr$^i$OH and water, and dried to give compound **14b** (0.11 g, 61%). MS, *m/z* ($I_{rel}$ (%)): 323 $[M]^+$ (30), 250 $[M - COOEt]^+$ (100). IR, ν/cm$^{-1}$: 2218 (CN), 1728 (CO).

**3-Anilinocarbonylmethylthio-4-cyanobenzo[*b*][1,6]naphthyridine (14c).** MS, *m/z* ($I_{rel}$ (%)): 370 $[M]^+$ (23), 278 $[M - NHPh]^+$ (100), 250 $[M - CONHPh]^+$ (44). IR, ν/cm$^{-1}$: 3316 (NH), 2229 (CN), 1672 (CO).

**1-Amino-2-ethoxycarbonylbenzo[*b*]thieno[2,3-*h*][1,6]naphthyridine (15a).** MS, *m/z* ($I_{rel}$ (%)): 323 $[M]^+$ (100), 295 $[M - C_2H_4]^+$ (50), 277 $[M - EtOH]^+$ (75), 250 $[M - COOEt]^+$

(80), 205 (62). IR, ν/cm$^{-1}$: 3451, 3384, 3322, 3275 ($NH_2$), 1670 (CO). $^1$H NMR, δ: 1.33 (t, 3 H, Me, $J_o$ = 7.2 Hz); 4.32 (q, 2 H, $CH_2$, $J_o$ = 7.2 Hz); 7.35, 8.65 (both br.s, 2 H, $NH_2$); 7.75 (t, 1 H, H(8), $J_o$ = 8.0 Hz); 8.03 (t, 1 H, H(9), $J_o$ = 8.0 Hz); 8.31 (d, 2 H, H(10), H(7), $J_o$ = 8.0 Hz); 9.47 (s, 1 H, H(6)); 9.53 (s, 1 H, H(5)).

**1-Amino-2-anilinocarbonylbenzo[*b*]thieno[2,3-*h*][1,6]naphthyridine (15b).** MS, $m/z$ ($I_{rel}$ (%)): 370 $[M]^+$ (40), 278 $[M - NHPh]^+$ (100). IR, ν/cm$^{-1}$: 3456, 3384, 3334 ($NH_2$, NH), 1637 (CO). $^1$H NMR, δ: 7.08 (t, 1 H, H(4′), $J_o$ = 7.6 Hz); 7.34 (t, 2 H, H(3′), H(5′), $J_o$ = 7.6 Hz); 7.74 (d, 2 H, H(2′), H(6′), $J_o$ = 7.6 Hz); 7.78 (t, 1 H, H(8), $J_o$ = 8.0 Hz); 8.07 (t, 1 H, H(9), $J_o$ = 8.0 Hz); 8.23 (br.s, 2 H, $NH_2$); 8.35, 8.36 (both d, 1 H each, H(7), H(10), $J_o$ = 8.0 Hz); 9.51 (br.s, 1 H, H(6), $^1J_{C,H}$ = 166.2 Hz); 9.56 (s, 1 H, H(5), $^1J_{C,H}$ = 184.7 Hz); 9.63 (br.s, 1 H, NH).

**3-Chloro-4-cyano-10-dicyanomethyl-5,10-dihydrobenzo[*b*][1,6]naphthyridine (16).** A mixture of compound **4** (0.2 g, 0.84 mmol) and malononitrile (0.06 g, 0.84 mmol) in 10 mL of DMF was stirred for five days and then diluted with water (20 mL). The precipitate that formed was filtered off, washed with water and ethanol, and dried to give crude adduct **16** (0.24 g, 94%). The product recrystallized from MeCN contains the starting compound **4** (~10%) ($^1$H NMR data), m.p. 285—290 °C (decomp.).

**3-Butylamino-4-cyanobenzo[*b*][1,6]naphthyridine (17a).** MS, $m/z$ ($I_{rel}$ (%)): 276 $[M]^+$ (24), 233 $[M - (CH_2)_2Me]^+$ (100).

**4-Cyano-3-[1-(hydroxymethyl)propyl]aminobenzo[*b*][1,6]naphthyridine (17b).** MS, $m/z$ ($I_{rel}$ (%)): 292 $[M]^+$ (50), 261 $[M - CH_2OH]^+$ (100).

**4-Cyano-3-(hexahydroazepino)benzo[*b*][1,6]naphthyridine (17c).** A mixture of compound **4** (0.2 g, 0.84 mmol) and hexahydroazepine (0.25 g, 2.51 mmol) in 5 mL of DMF was stirred at 40 °C for 40 min and then diluted with water (20 mL). The precipitate that formed was filtered off, washed with water and EtOH, and dried to give compound **17c** (0.20 g, 79%). MS, $m/z$ ($I_{rel}$ (%)): 302 $[M]^+$ (100), 259 $[M - (CH_2)Me]^+$ (71).

**10-(4-Aminophenyl)-3-chloro-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (18).** MS, $m/z$ ($I_{rel}$ (%)): 332 $[M]^+$ (84), 240 $[M - NHPh]^+$ (100). IR, ν/cm$^{-1}$: 3392, 3307, 3220 (NH), 2225 (CN). Compound **18** contains impurities of aniline and adduct **19** (~16%) ($^1$H NMR data). Adduct **19**: $^1$H NMR, δ: 5.10 (s, 1 H, H(10)); 6.90 (t, 1 H, H(4′), $J$ = 8.8 Hz); 6.95 (t, 1 H, H(8), $J$ = 7.4 Hz); 7.05 (d, 1 H, H(9), $J$ = 7.4 Hz); 7.12 (t, 1 H, H(7), $J$ = 7.4 Hz); 7.22 (t, 2 H, H(3′), H(5′), $J$ = 8.8 Hz); 7.36 (d, 1 H, H(6), $J$ = 7.4 Hz); 7.49 (t, 2 H, H(2′), H(6′)); 7.70 (s, 1 H, H(1)); 8.70 (s, 1 H, NHPh); 9.50 (s, 1 H, NH(5)).

## References

1. V. G. Granik and S. I. Kaimanakova, *Khim. Geterotsikl. Soedin.*, 1983, 816 [*Chem. Heterocycl. Compd.*, 1983, **19**, 714 (Engl. Transl.)].
2. N. Z. Yalysheva, N. P. Solov′eva, V. V. Chistyakov, Yu. N. Sheinker, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1986, 1118 [*Chem. Heterocycl. Compd.*, 1986, **22**, 910 (Engl. Transl.)].
3. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, *Tetrahedron*, 1988, 1.
4. G. Levy and G. Nelson, in *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience, Division of J. Wiley and Sons, Inc., New York—London—Sydney—Toronto, 1972.
5. H. Hara and H. C. van der Plas, *J. Heterocycl. Chem.*, 1982, **19**, 1527.
6. V. G. Granik, A. V. Kadushkin, and J. Liebsher, *Adv. Heterocycl. Chem.*, 1998, **72**, 79.
7. N. Z. Tugusheva, L. V. Ershov, V. G. Granik, G. Ya. Shvarts, R. D. Syubaev, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 1986, **20**, No. 7, 830 [*Pharm. Chem. J.*, 1986, **20**, No. 7, 483 (Engl. Transl.)].
8. O. N. Chupakhin and I. Ya. Postovskii, *Usp. Khim.*, 1976, **45**, 908 [*Russ. Chem. Rev.*, 1976, **45**, 454 (Engl. Transl.)].

*Received January 11, 2002;*
*in revised form March 29, 2002*