Functionalization of benzo[*b*][1,6]naphthyridine derivatives

*A. S. Ivanov, N. Z. Tugusheva, L. M. Alekseeva, and V. G. Granik**

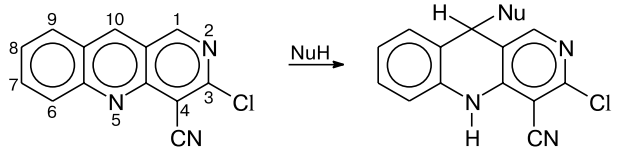
The State Scientific Center of the Russian Federation
"Scientific Research Institute of Organic Intermediates and Dyes" (NIOPIK),
1/4 ul. B. Sadovaya, 123995 Moscow, Russian Federation.
Fax: +7 (095) 254 6574. E-mail: aivanov@email.ru

Two routes to consecutive functionalization of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**1a**) at positions 3 and 10 were developed. Oxidation of compound **1a** with *m*-chloroperbenzoic acid in acetone leads to 3-chloro-4-cyano-10-oxobenzo[*b*][1,6]naphthyridine, while in acetic acid, the reaction gives 3-chloro-4-cyano-10-(3-chlorobenzoyloxy)-5-hydroxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine. The reactions of **1a** with some C-nucleophiles give σ-adducts at position 10. The reactions of *N*,*N*-dimethylamide acetals with chloride **1a** leads to 4-cyano-3-dimethylaminobenzo[*b*][1,6]naphthyridine.

Key words: benzo[*b*][1,6]naphthyridines, nucleophilic addition to π-deficient azines, oxidation, Thorpe—Ziegler cyclization, hetarylation of amide acetals.

Previously, it was shown[1] that 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**1a**) reacts with various S-, C-, and N-nucleophiles to give σ-adducts **2** at position 10 (Scheme 1).

Scheme 1

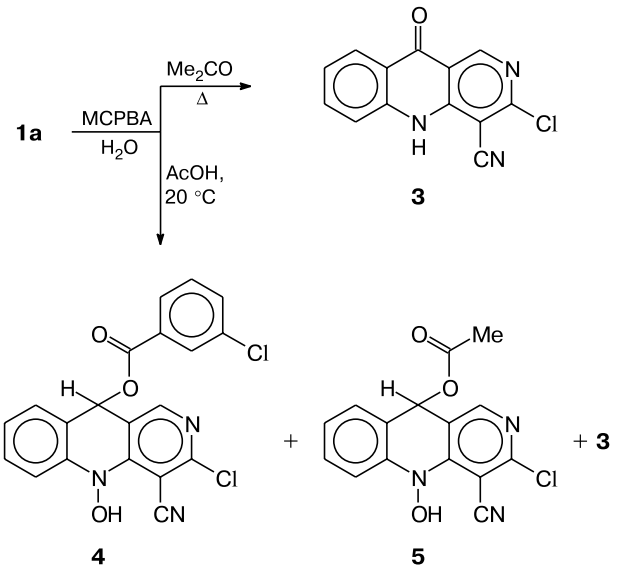


1a **2**

It is known[2] that σ-adducts formed by nucleophiles with noncharged azines are unstable and, as a rule, they can be detected only by physical methods at low temperatures. However, σ-adducts **2** prove to be rather stable and can be isolated and identified. This indicates that their formation is not very unfavorable from the energy standpoint, and the addition at position 10 of the tricyclic system **1a** may underlie a convenient synthetic strategy for further functionalization of this system. The purpose of this study is to explore the possibility of the synthesis of 3,10-disubstituted 4-cyanobenzo[*b*][1,6]naphthyridines with different substituents in these positions of the rings.

The oxidation of compound **1a** with *m*-chloroperbenzoic acid (MCPBA) on refluxing in acetone was studied. This reaction gave 10-oxo derivative **3** in a good yield (previously,[1] we described the preparation of this compound in a 0.4% yield by oxidation of **1a** with H_2O_2 in AcOH). When oxidation with MCPBA was carried out at ~20 °C in AcOH, compound **4** was isolated in a moderate yield. In addition, as shown by ^{1}H NMR spectroscopy, the mother liquor contained 10-acetoxy-3-chloro-4-cyano-5-hydroxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (**5**), which we described previously,[1] and tricyclic derivative **3** (Scheme 2).

Scheme 2



To elucidate the reasons of this crucial dependence of the oxidation route of compound **1a** on the properties of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 1120—1126, May, 2003.

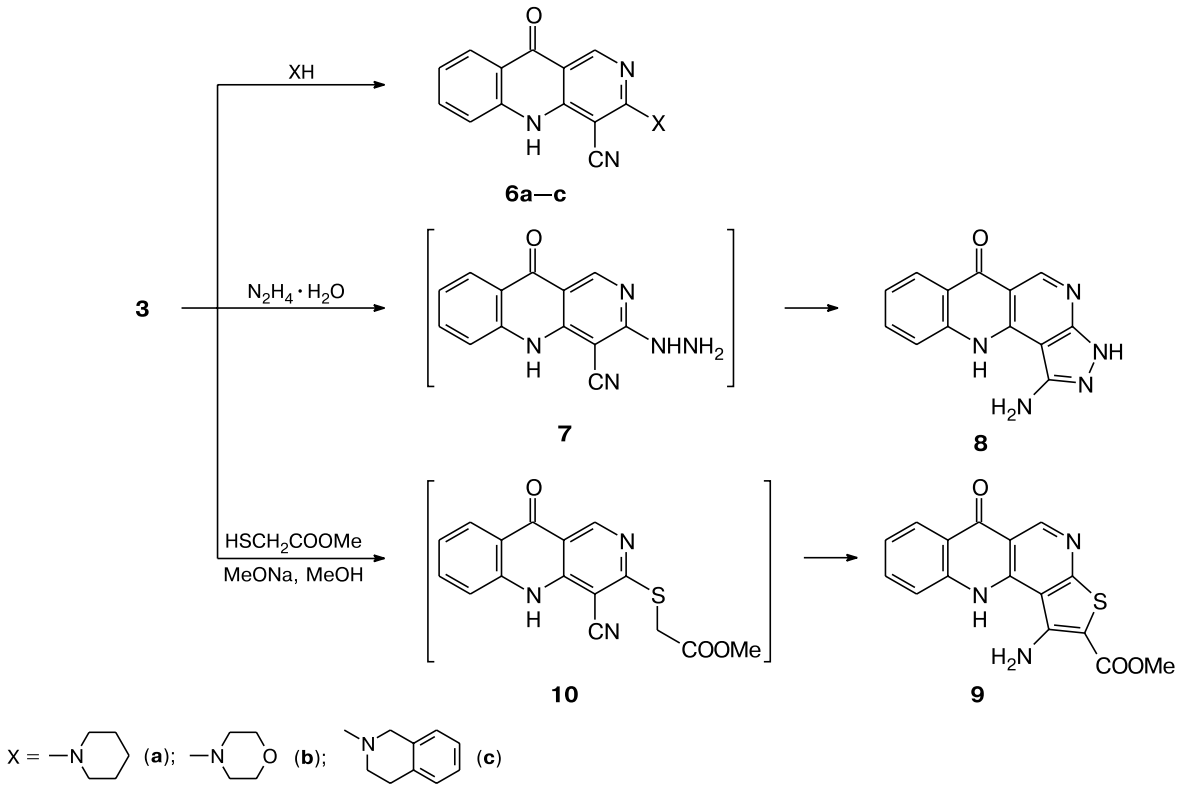
the medium, a special investigation is required, which is planned for the future.

The structure of compound **3** shows that it can react with nucleophiles at position 3, while position 10 would remain intact. Subsequently, position 10 can be activated, for example, by transforming the obtained compounds into 10-chloro derivatives, which could provide a pathway to 3,10-disubstituted derivatives of the system under study. At the first stage, it was shown that the Cl atom in position 3 of compound **3** can be smoothly replaced by amino groups to give 3-amino derivatives **6a—c** (Scheme 3). On refluxing with hydrazine hydrate, the Cl atom is replaced by the hydrazine residue, which is followed by cyclization of the intermediate hydrazine **7** involving the nitrile group and giving rise to 1-amino-6-oxo-3,11-dihydro-6*H*-benzo[*b*]pyrazolo[3,4-*h*][1,6]naphthyridine (**8**). 1-Amino-2-ethoxycarbonyl-6-oxo-6,11-dihydrobenzo[*b*]thieno[2,3-*h*][1,6]naphthyridine (**9**) was prepared by refluxing compound **3** with methyl mercaptoacetate in the presence of MeONa as a basic catalyst. By analogy with the synthesis of 2-substituted 1-aminobenzo[*b*]thieno[2,3-*h*][1,6]naphthyridines,[1] it can be assumed that the thiolate anion attacks position 3 to yield 3-methoxycarbonylmethylthio derivative **10**, which subsequently undergoes the Thorpe—Ziegler cyclization[3] to give tetracyclic product **9**.

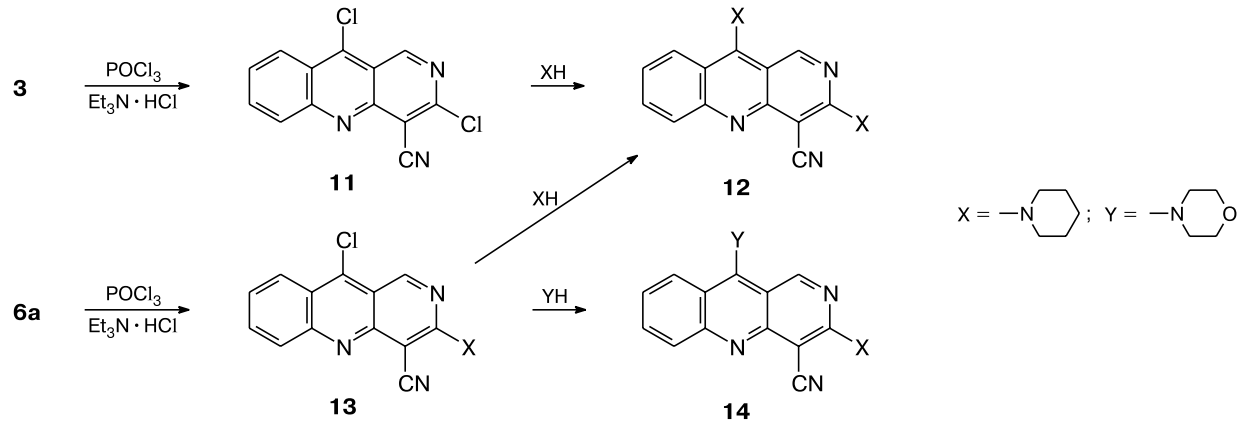
On refluxing in $POCl_3$ in the presence of $Et_3N \cdot HCl$, the oxo group in compound **3** was replaced by a Cl atom, which afforded 3,10-dichloro-4-cyanobenzo[*b*][1,6]naphthyridine (**11**) (Scheme 4). It is noteworthy that recording the ^1H NMR spectrum in DMSO-d_6 containing a small amount of water resulted in hydrolysis of compound **11** to the initial tricyclic structure **3**. This indicates that the Cl atom in position 10 possesses a higher mobility than the 3-Cl atom. Due to the low solubility of compounds **3** and **11** in other solvents ($CDCl_3$, CD_2Cl_2, C_6D_6), low-polar solvents cannot be used for recording the spectra. Therefore, the purity of product **11** was established relying on TLC, IR spectroscopy, and mass spectrometry. In the resulting dichloro-substituted compound **11**, both Cl atoms are readily substituted by piperidine residues, which gives rise to bis-amino derivative **12** with identical substituents in positions 3 and 10 (see Scheme 4).

We also attempted to obtain benzo[*b*][1,6]naphthyridine derivatives containing different substituents in positions 3 and 10. To this end, the oxo group in position 10 of compound **6a** was replaced by chlorine on refluxing the starting compound in $POCl_3$ in the presence of $Et_3N \cdot HCl$ with subsequent evaporation of $POCl_3$ *in vacuo* and treatment of the resulting chloroxide complex[4] with a sodium carbonate solution. As expected, the product isolated in this way was 10-chloro-3-piperidino-4-cyanoben-

Scheme 3



Scheme 4

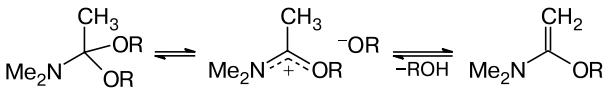


zo[*b*][1,6]naphthyridine (**13**). In this compound, as in **11**, the Cl atom in position 10 is rather active and susceptible for hydrolysis, which affords the starting tricyclic compound **6a**. The reaction of compound **13** with morpholine yielded 10-morpholino derivative **14**. In addition, product **13** was converted into bis(piperidine) derivative **12** by an alternative synthetic route (see Scheme 4).

Another approach to the synthesis of 3,10-disubstituted benzo[*b*][1,6]naphthyridines was also studied. Now the goal was to introduce a heteronucleophile (*e.g.*, amino or mercapto group) in position 3 and a C-nucleophile in position 10. As previously,[1] the synthetic strategy was based on the possibility of formation of σ-complexes at position 10 of the benzonaphthyridine molecule, but C-nucleophiles were employed as the reagents.

The first nucleophiles chosen were dimethyl and diethyl acetals of *N*,*N*-dimethylacetamide (**15a,b**), which are known[5] to behave as enamines in various reactions due to the ternary equilibrium (Scheme 5).

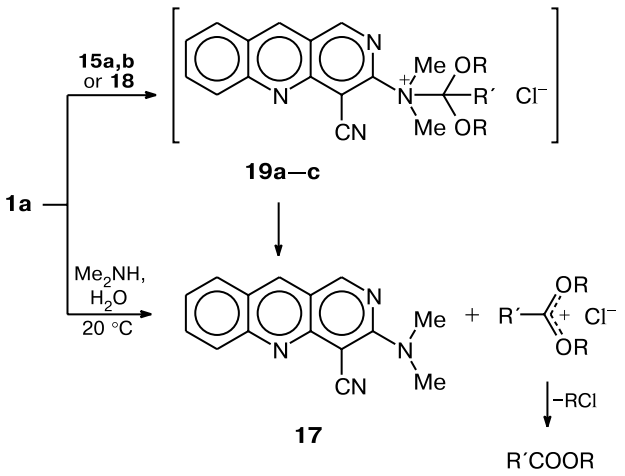
Scheme 5



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

However, the reaction between acetals **15a,b** and tricyclic compound **1a** gave an unexpected result. 3-Dimethylamino derivative **17** was formed as the only product. In order to verify whether α-alkoxyenamine **16** participates in this unusual transformation, a similar reaction was carried out with DMF diethyl acetal (**18**). In this case, too, compound **17** was isolated in a high yield. For confirming the structure, this compound was also prepared by an alternative protocol, *i.e.*, by the reaction of chloro derivative **1a** with dimethylamine (Scheme 6).

Scheme 6

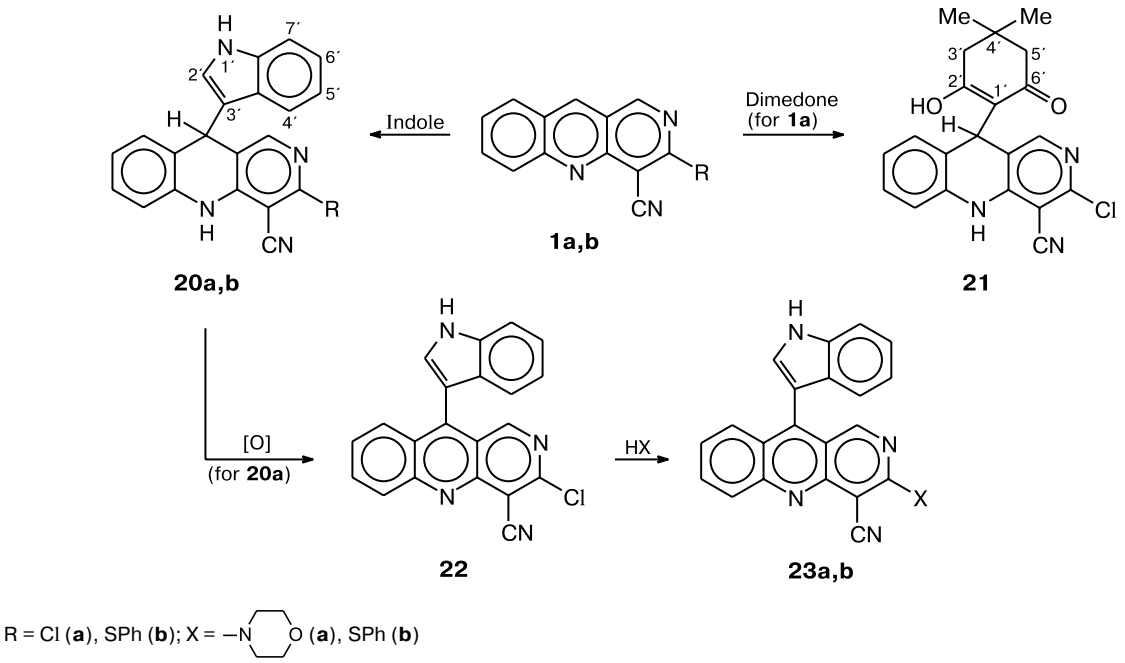


R = Me (**a**), Et (**b**, **c**); R′ = Me (**a**, **b**), H (**c**)

The alkylation of amide acetals is known[6] to involve the N atom. Since the Cl atom in compound **1a** is quite mobile due to the presence of the electron-withdrawing cyano group and the fused quinoline ring, one can assume that arylation of amide acetals by chloro derivative **1a** would also follow this route giving intermediates **19a—c**. The reaction of chloride **1a** and acetal **15b** proceeding according to this pattern should be accompanied by ethyl acetate evolution; this was really established by GLC (see Scheme 6).

Since the attempt of using acetals **15a,b** as enamines has not met with success, we used indole as the C-nucleophile. This compound is known to exhibit properties of an enamine in many respects.[7] It was found that refluxing compound **1a** with indole in Pr^{i}OH fur-

Scheme 7



nishes the σ-adduct whose structure is described as 3-chloro-4-cyano-10-(1*H*-indol-3-yl)-5,10-dihydrobenzo[*b*][1,6]naphthyridine (**20a**) (Scheme 7). 4- Cyano-3-phenylthiobenzo[*b*][1,6]naphthyridine (**1b**), reported in our previous publication,[1] does not react with indole under these conditions; however, when the conditions are made more drastic (refluxing in Bu^nOH), σ-adduct **20b** appears. In compounds **20a,b**, position 3 of indole molecule is linked to position 10 of the initial compounds **1a,b** (see Scheme 7), which was proved by ^1H NMR spectroscopy. The spectra exhibit a doublet corresponding to the indole fragment, which can be assigned to the H(2′) atom relying on the chemical shifts (δ 7.20 and 7.16) and spin-spin coupling constant (J = 2.4—2.7 Hz).[8] The reaction of compound **1a** with dimedone (refluxing in Pr^iOH) was also studied. This reaction results in the corresponding σ-adduct having the structure of 3-chloro-4-cyano-10-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexenyl)-5,10-dihydrobenzo[*b*][1,6]naphthyridine (**21**) (see Scheme 7).

In order to prepare a fully aromatic compound containing an indole residue in position 10, σ-adduct **20a** had to be oxidized. For this purpose, the adduct was refluxed with $K_3[Fe(CN)_6]$ in aqueous Pr^iOH, which gave 3-chloro-4-cyano-10-(1*H*-indol-3-yl)benzo[*b*][1,6]naphthyridine (**22**), in which the active Cl atom in position 3 is retained (see Scheme 7). The use of $[Ag(Py)_2]MnO_4$ as a mild oxidant in this reaction[7,9] also led to product **22**.

Compound **22** reacts with nucleophilic reagents; this was used to prepare derivatives having other 3-substituents. The reaction with morpholine gave 4-cyano-10-(1*H*-indol-3-yl)-3-morpholinobenzo[*b*][1,6]naphthyridine (**23a**), while the reaction with benzenethiol in the presence of AcONa gave rise to 4-cyano-10-(1*H*-indol-3-yl)-3-phenylthiobenzo[*b*][1,6]naphthyridine (**23b**) (see Scheme 7).

Thus, new approaches to the synthesis of 3,10-functionally substituted benzo[*b*][1,6]naphthyridines with either identical or different substituents in positions 3 and 10 have been developed on the basis of nucleophilic addition to the electron-deficient C atom in a π-deficient aromatic system.

Experimental

IR spectra were recorded on a Perkin—Elmer 457 instrument in mineral oil, mass spectra (EI) were run on a Finnigan SSQ-710 mass spectrometer with direct sample injection into the ion source. The ^1H NMR spectra were measured on a Varian Unity 400 and Bruker AC-200 spectrometers in DMSO-d_6. The reactions were monitored and the purity of the compounds was checked by TLC on Silufol UV-254 plates (using AcOEt for elution and UV light for visualization). Melting points were determined on a Electrothermal 9100 instrument (UK). Physicochemical characteristics and the data of elemental analysis for the synthesized compounds are listed in Table 1 and the ^1H NMR spectra are in Table 2. In the synthesis of compounds **3** and **4**, 50—55% MCPBA (Lancaster) was used containing 10% of *m*-chlorobenzoic acid and water.

3-Chloro-4-cyano-10-oxo-5,10-dihydrobenzo[*b*][1,6]naphthyridine (3). 50% MCPBA (15 g) was added in portions over a period of 18 h to a suspension of compound **1a** (6 g, 25.1 mmol) in 200 mL of acetone stirred at reflux. Then the mixture was refluxed for additional 5 h. Acetone was evaporated to 2/3 its

Table 1. Melting points and elemental analysis data for compounds **4**, **6a—c, 8**, **9**, **11**, **12**, **14**, **17**, **20—23**

Compound	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
		C	H	N	S (Cl)*	
4	242—243.5 (benzene)	58.36 / 58.27	2.76 / 2.69	10.21 / 10.20	16.89 / 17.20	$C_{20}H_{11}Cl_2N_3O_3$
6a	270—271.5 (BuOH)	71.28 / 71.03	5.39 / 5.30	18.29 / 18.41	—	$C_{18}H_{16}N_4O$
6b	281—282.5 (Pr^iOH)	66.60 / 66.65	4.60 / 4.61	18.26 / 18.29	—	$C_{17}H_{14}N_4O_2$
6c	288.5—289.5 (DMF)	75.26 / 74.98	4.67 / 4.58	15.96 / 15.90	—	$C_{22}H_{16}N_4O$
8	>400 (DMF)	61.80 / 62.14	3.62 / 3.61	27.46 / 27.88	—	$C_{13}H_9N_5O$
9	278.5—279.5 (AcOH)	59.38 / 59.07	3.36 / 3.41	12.57 / 12.92	9.78 / 9.85	$C_{16}H_{11}N_3O_3S$
11	257—260 (acetone)	57.21 / 56.96	1.77 / 1.84	15.21 / 15.33	25.72 / 25.87	$C_{13}H_5Cl_2N_3$
12	215.5—216.5 (Pr^iOH)	74.78 / 74.36	6.73 / 6.78	19.00 / 18.86	—	$C_{23}H_{25}N_5$
14	269—270 (Pr^iOH)	70.57 / 70.76	6.46 / 6.21	18.78 / 18.75	—	$C_{22}H_{23}N_5O$
17	210.5—212 (CH_2Cl_2—AcOEt)	73.11 / 72.56	4.83 / 4.87	22.46 / 22.57	—	$C_{15}H_{12}N_4$
20a	251—251.5 (Pr^iOH)	70.25 / 70.69	3.82 / 3.67	15.83 / 15.70	9.87 / 9.94	$C_{21}H_{13}ClN_4$
20b	218.5—219.5 (Pr^iOH)	75.61 / 75.33	4.13 / 4.21	13.12 / 13.01	7.68 / 7.45	$C_{27}H_{18}N_4S$
21	263—265 (DMF)	66.51 / 66.40	4.86 / 4.78	11.01 / 11.06	9.18 / 9.33	$C_{21}H_{18}ClN_3O_2$
22	383.5—384.5 (DMF)	71.23 / 71.09	3.13 / 3.13	15.82 / 15.79	9.93 / 9.99	$C_{21}H_{11}ClN_4$
23a	281—282.5 (Pr^iOH)	73.75 / 74.05	4.72 / 4.72	17.15 / 17.28	—	$C_{25}H_{19}N_5O$
23b	320—323 (Pr^iOH)	75.70 / 75.68	3.67 / 3.76	12.99 / 13.08	7.43 / 7.48	$C_{27}H_{16}N_4S$

* See the molecular formula.

initial volume and the precipitate was filtered off, washed with acetone and benzene, and dried to give product **3** as fine light-yellow needles. Yield 4.86 g (76%). The melting point of a mixed sample with the compound prepared by a previously described procedure[1] was undepressed. The IR spectra of both samples were identical.

3-Chloro-10-(3-chlorobenzoyloxy)-4-cyano-5-hydroxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (4). A solution of compound **1a** (0.25 g, 1.044 mmol) and 50% aqueous MCPBA (0.72 g) in 10 mL of AcOH was stirred for 2 h at ~20 °C, and the precipitate was filtered off, washed with EtOH, and dried to give 0.12 g (28%) of benzonaphthyridine **4**. ^{1}H NMR, δ: 6.92 (d, 1 H, H(9), J_o = 7.2 Hz); 6.97 (t, 1 H, H(8), J_o = 7.2 Hz); 7.15 (t, 1 H, H(7), J_o = 7.2 Hz); 7.33 (s, 1 H, H(10), $^1J_{C,H}$ = 178 Hz); 7.48 (t, 1 H, H(5′), J_o = 8.0 Hz); 7.57 (d, 1 H, H(6), J_o = 7.2 Hz); 7.57 (s, 1 H, H(2′)); 7.68 (d, 2 H, H(4′), H(6′), J_o = 8.0 Hz); 8.48 (s, 1 H, H(1), $^1J_{C,H}$ = 186.1 Hz); 9.42 (br.s, 1 H, NOH). MS, *m*/*z* (I_{rel} (%)): 412 $[M]^+$ (7), 255 $[M - m\text{-Cl-}C_6H_4CO_2H]^+$ (97), 239 $[M - m\text{-Cl-}C_6H_4CO_3H]^+$ (71), 220 (55), 156 $[m\text{-Cl-}C_6H_4\text{-}CO_2]^+$ (55).

Synthesis of compounds 6a—c (general procedure). Compound **3** (1 mmol) and the corresponding amine (2 mmol) in 4 mL of DMF were stirred for 4 h at 40 °C, 10 mL of water was added, and the precipitate was filtered off, washed with water and ether, and dried.

4-Cyano-10-oxo-3-piperidino-5,10-dihydrobenzo[*b*][1,6]naphthyridine (6a). Yield 83%. IR, ν/cm^{-1}: 3271 (NH), 2200 (CN), 1627 (CO). MS, *m*/*z* (I_{rel} (%)): 304 $[M]^+$ (100), 275 $[M - C_2H_5]^+$ (96), 262 $[M - (CH_2)_3]^+$ (90), 249 (73), 236 (28), 221 $[M$ – piperidine + 2 H$]^+$ (94).

4-Cyano-3-morpholino-10-oxo-5,10-dihydrobenzo[*b*][1,6]naphthyridine (6b). Yield 92%. MS, *m*/*z* (I_{rel} (%)): 306 $[M]^+$ (90), 275 (80), 261 (80), 249 $[M - C_3H_5O]^+$ (100), 221 $[M$ – morpholine + 2 H$]^+$ (85).

Table 2. ^{1}H NMR spectra of compounds **6a**, **12**, **14**, **20—22**, and **23b**

Compound	δ (*J*/Hz)			
	H(1) (s, 1 H)	H arom. (H(6), H(7), H(8), H(9))	C(3)-R, C(10)-R[a]	NH (br.s, 1 H)
6a	8.97 ($^1J_{C,H}$ = 181.7)	7.32, 7.72 (both t, 1 H each, J_o = 8.4); 7.92, 8.13 (both d, 1 H each, J_o = 8.4)	1.69 (br.s, 6 H, 2 H(3′), 2 H(4′), 2 H(5′)); 3.86 (br.s, 4 H, 2 H(2′), 2 H(6′))	11.20
12	9.35	7.40, 7.75 (both t, 1 H each, J_o = 8.4); 7.83, 8.16 (both d, 1 H each, J_o = 8.4)	1.71 (br.s, 6 H, 2 H(3′), 2 H(4′), 2 H(5′)); 1.83 (br.s, 6 H, 2 H(3″), 2 H(4″), 2 H(5″)); 3.80 (br.s, 4 H, 2 H(2′), 2 H(6′)); 3.96 (br.s, 4 H, 2 H(2″), 2 H(6″))	—
14	9.42	7.42, 7.80 (both t, 1 H each, J_o = 8.6); 7.88, 8.21 (both d, 1 H each, J_o = 8.6)	1.71 (br.s, 6 H, 2 H(3′), 2 H(4′), 2 H(5′)); 3.82—3.95 (m, 12 H, 2 H(2′), 2 H(6′), 2 H(2″), 2 H(3″), 2 H(5″), 2 H(6″))	—
20a	7.96 ($^1J_{C,H}$ = 182.0)	7.01, 7.14 (both t, 1 H each, J_o = 8.0); 7.06, 7.40 (both d, 1 H each, J_o = 8.0)	5.67 (s, H(10), $^1J_{C,H}$ = 132.3); 6.85, 6.89 (both t, 1 H each, J_o = 8.6); 7.27, 7.32 (both d, 1 H each, J_o = 8.6); 7.20 (d, 1 H, J_o = 2.4)	10.12 (H(5)); 10.98 (H(1′))
20b	7.91 ($^1J_{C,H}$ = 181.0)	7.02, 7.17 (both t, 1 H each, J_o = 8.0); 7.08 (d, 1 H, J_o = 8.0)[b]	5.60 (s, H(10), $^1J_{C,H}$ = 132.3); 6.87, 6.89 (both m, 1 H each); 7.30, 7.34 (both d, 1 H each, J_o = 8.4); 7.16 (d, 1 H, J_o = 2.7)[b]	9.79 (H(5)); 10.87 (H(1′))
21	7.59 ($^1J_{C,H}$ = 180.0)	6.82 (m, 2 H, H(8), H(9), J_o = 8.0); 7.02 (t, 1 H, H(7)); 7.21 (d, 1 H, H(6))	0.94 (s, 6 H, 2 Me); 2.21 (br.s, 4 H, 2 H(3′), 2 H(5′)); 5.50 (s, 1 H, H(10), $^1J_{C,H}$ = 131.5); ~11.0 (br.s, OH)	9.78
22	9.38 ($^1J_{C,H}$ = 186)	7.08, 7.27 (both t, 1 H each, J_o = 8.0); 7.23, 7.65 (both d, 1 H each, J_o = 8.0)	7.69, 8.10 (both t, 1 H each, J_o = 8.7); 8.18, 8.30 (both d, 1 H each, J_o = 8.7); 8.03 (d, 1 H, J_o = 2.4)	12.14 (H(1′))
23b	9.20	7.02, 7.23 (both t, 1 H each, J_o = 8.2); 7.16 (d, 1 H, J_o = 8.2)[b,c]	8.07, 8.21 (both d, 1 H each, J_o = 8.8); 7.97 (m, 2 H)[b]	12.04

[a] In numbering of substituents, a prime corresponds to C(3)-R and two primes, to C(10)-R.
[b] The other signals are at about δ 7.40—7.70.
[c] All m (each 1 H).

4-Cyano-3-[3,4-dihydro-2(1*H*)-isoquinolinyl]-10-oxo-5,10-dihydrobenzo[*b*][1,6]naphthyridine (6c). Yield 92%. MS, *m/z* (I_{rel} (%)): 352 $[M]^+$ (100), 338 $[M - NH]^+$ (62), 261 $[M - PhCH_2]^+$ (31), 237 (48), 236 (52), 221 [M − dihydroisoquinoline]$^+$ (82).

1-Amino-6-oxo-3,11-dihydro-6*H*-benzo[*b*]pyrazolo[3,4-*h*][1,6]naphthyridine (8). A mixture of compound **3** (0.25 g, 0.979 mmol) and 10 mL of hydrazine hydrate was refluxed for 4 h with stirring and the reaction mixture was cooled and filtered off to give 0.23 g (94%) of compound **8**. IR, ν/cm^{-1}: 3416, 3310, 3197 (NH, NH_2), 1627 (CO). ^{1}H NMR, δ: 6.05 (br.s, 2 H, NH_2); 7.40 (m, 1 H, H(8)); 7.79 (m, 2 H, H(7), H(9)); 8.22 (d, 1 H, H(10), J_o = 8.2 Hz); 9.09 (s, 1 H, H(5)); 10.91 (br.s, 1 H, NH(3)); 12.60 (br.s, 1 H, NH(11)). MS, *m/z* (I_{rel} (%)): 251 $[M]^+$ (100), 235 $[M - NH_2]^+$ (12), 209 $[M - CH_2N_2]^+$ (12).

1-Amino-2-methoxycarbonyl-6-oxo-6,11-dihydrobenzo[*b*]thieno[2,3-*h*][1,6]naphthyridine (9). Methyl mercaptoacetate (0.09 mL, 1.11 mmol) was added with stirring to a solution of MeONa (from 0.022 g of Na and 8 mL of MeOH). Then compound **3** (0.25 g, 0.979 mmol) was added, the mixture was stirred with reflux for 1.5 h and poured into 20 mL of water, and the precipitate was filtered off to give 0.30 g (94%) of compound **9**. IR, ν/cm^{-1}: 3403, 3351 (NH, NH_2), 1683 (ester C=O), 1644 (C(6)=O). ^{1}H NMR, δ: 3.81 (s, 1 H, OMe); 7.40, 7.81 (both t, each 1 H, H(8), H(9), J_o = 8.2 Hz); 7.91, 8.22 (both d, each 1 H, H(7), H(10), J_o = 8.2 Hz); 7.40 (br.s, NH + NH_2); 9.22 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 325 $[M]^+$ (87), 293 [M − S or M − MeOH]$^+$ (100), 267 [M − MeOH − CN]$^+$ (50), 220 $[M - SCH_2COOMe]^+$ (46).

3,10-Dichloro-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (11). A mixture of compound **3** (1.5 g, 5.87 mmol) and $Et_3N \cdot HCl$ (0.7 g) in 20 mL of $POCl_3$ was stirred with reflux for 18 h, $POCl_3$ was evaporated *in vacuo*, and the residue was triturated in a cooled aqueous solution of Na_2CO_3. The precipitate was filtered off, thoroughly washed with water, and dried to give 1.45 g (90%) of compound **11**. MS, *m/z* (I_{rel} (%)): 273 $[M - H]^+$ (100), 238 $[M - HCl]^+$ (26), 202 $[M - 2\ Cl]^+$ (17), 176 [M − 2 Cl − CN]$^+$ (41).

4-Cyano-3,10-dipiperidino-5,10-dihydrobenzo[*b*][1,6]naphthyridine (12). ***A.*** A mixture of compound **11** (0.25 g, 0.921 mmol) and piperidine (4 mL) was stirred for 5 h at ~20 °C, piperidine was evaporated *in vacuo*, the dry residue was triturated in a 1 *N* aqueous solution of KOH, and the precipitate was filtered off, washed with water and hexane, and dried to give 0.09 g (26%) of compound **12**. MS, *m/z* (I_{rel} (%)): 371 $[M]^+$ (100), 275 (88), 203 [M − (piperidinyl)$_2$]$^+$ (96).

B. A mixture of compound **13** (0.20 g, 0.620 mmol) and 1.5 mL of piperidine was stirred for 1 h at ~20 °C, piperidine was evaporated *in vacuo*, the dry residue was triturated in 1 *N* aque-

ous KOH, and the precipitate was filtered off, washed with water and hexane, and dried to give 0.13 g (56%) of compound **12**. The melting point of a mixed sample with the compound prepared by procedure ***A*** was undepressed. The IR spectra of both samples were identical.

10-Chloro-4-cyano-3-piperidino-5,10-dihydrobenzo[*b*][1,6]naphthyridine (13). A mixture of compound **6a** (0.3 g, 0.987 mmol) and $Et_3N \cdot HCl$ (0.3 g) in 24 mL of $POCl_3$ was stirred with reflux for 4 h, $POCl_3$ was evaporated *in vacuo*, and the precipitate was triturated in a solution of sodium carbonate in 10% aqueous acetone. The precipitate was filtered off, washed with water and hexane, and dried *in vacuo* over P_4O_{10} to give 0.26 g (82%) of crude product **13**, which was used subsequently without further purification. MS, m/z (I_{rel} (%)): 322 $[M]^+$ (100), 293 $[M - Et]^+$ (65), 267 $[M - C_4H_7]^+$ (40), 239 [M – piperidinyl + H]$^+$ (37).

4-Cyano-10-morpholino-3-piperidino-5,10-dihydrobenzo[*b*][1,6]naphthyridine (14). Compound **13** (0.3 g, 0.932 mmol) was stirred with morpholine (2 mL) for 1 h at ~20 °C, morpholine was evaporated *in vacuo*, the dry residue was triturated in 1 *N* aqueous KOH, and the precipitate was filtered off, washed with water and hexane, and dried to give 0.22 g (63%) of compound **14**. MS, m/z (I_{rel} (%)): 373 $[M]^+$ (100), 344 $[M - CHO]^+$ (46), 330 $[M - CHO - CH_2]^+$ (41), 317 (63), 305 (61), 290 [M – piperidinyl + H]$^+$ (59).

4-Cyano-3-dimethylaminobenzo[*b*][1,6]naphthyridine (17). ***A.*** A mixture of compound **1a** (0.2 g, 0.835 mmol) and ~70% alcohol solution (0.57 g) of *N*,*N*-dimethylformamide diethyl acetal (**18**) in 10 mL of anhydrous EtOH was stirred with reflux for 33 h, 1 mL of water was added, and the precipitate was filtered off, washed with EtOH, and dried to give 0.18 g (87%) of product **17**. An analytic grade sample was obtained by passing a solution of compound **17** through a silica gel layer (elution with CH_2Cl_2—AcOEt, 1 : 1). IR, ν/cm^{-1}: 2196 (CN). ^1H NMR, δ: 3.45 (s, 6 H, NMe_2); 7.55, 7.91 (both t, each 1 H, H(7), H(8), J_o = 8.0 Hz); 7.99, 8.12 (both d, each 1 H, H(6), H(9), J_o = 8.0 Hz); 9.12 (s, 1 H, H(10), $^1J_{C,H}$ = 165.9 Hz); 9.36 (s, 1 H, H(1), $^1J_{C,H}$ = 183.3 Hz). MS, m/z (I_{rel} (%)): 248 $[M]^+$ (100), 233 $[M - Me]^+$ (81), 219 $[M - Et]^+$ (93), 205 $[M - NMe_2]^+$ (74), 179 (48).

B. A mixture of compound **1a** (0.3 g, 0.835 mmol) and a ~70% alcohol solution (0.47 g) of *N*,*N*-dimethylacetamide dimethyl acetal (**15a**) in 12 mL of MeOH was stirred with reflux for 7 h and cooled, and the precipitate was filtered off, washed with EtOH, and dried to give 0.17 g (55%) of product **17**. Further purification was the same as in procedure ***A***. The same reaction was carried out with diethyl acetal of *N*,*N*-dimethylacetamide (**15b**) in anhydrous EtOH.

C. A mixture of compound **1a** (0.1 g, 0.418 mmol) and a 30% aqueous solution (0.28 mL) of dimethylamine was stirred for 4 h at ~20 °C, and the precipitate was filtered off, washed with water, and dried to give 0.1 g (97%) of product **17**. Further purification was the same as in procedure ***A***. A mixture of samples prepared by methods ***A***, ***B***, and ***C*** shows an undepressed melting point. The IR spectra of these samples were identical.

3-Chloro-4-cyano-10-(1*H*-indol-3-yl)-5,10-dihydrobenzo[*b*][1,6]naphthyridine (20a). A mixture of compound **1a** (0.20 g, 0.835 mmol) and indole (0.5 g, 0.919 mmol) in 15 mL of Pr^iOH was stirred with reflux for 45 min. The reaction mixture was cooled to ~20 °C and the precipitate was filtered off, washed with Pr^iOH, and dried to give 0.26 g (87%) of product **20a** as fine white crystals slowly oxidized in air. IR, ν/cm^{-1}: 3112, 3290, 3192 (2 NH), 2227 (CN). MS, m/z (I_{rel} (%)): 356 $[M]^+$ (100), 240 [M – indolyl]$^+$ (53), 204 [M – indolyl – HCl]$^+$ (27), 178 [M – indolyl – HCl – CN]$^+$ (15), 117 [indole]$^+$ (24).

4-Cyano-10-(1*H*-indol-3-yl)-3-phenylthiobenzo[*b*][1,6]naphthyridine (20b). A mixture of compound **1b** (0.2 g, 0.64 mmol) and indole (0.09 g, 0.77 mmol) in 8 mL of Bu^nOH was stirred with reflux for 6 h. The solution was cooled to ~20 °C and the precipitate was filtered off, washed with hexane, and dried to give 0.22 g (80%) of product **20b**. MS, m/z (I_{rel} (%)): 430 $[M]^+$ (88), 312 [M – indole]$^+$ (100), 117 [indole]$^+$ (83).

3-Chloro-4-cyano-10-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexenyl)-5,10-dihydrobenzo[*b*][1,6]naphthyridine (21). A mixture of compound **1a** (3 g, 12.53 mmol) and dimedone (2.28 g, 16.28 mmol) in 200 mL of Pr^iOH was stirred with reflux for 17 h and the precipitate was filtered off, washed with Pr^iOH, and dried to give 4.39 g (92%) of product **21**. MS, m/z (I_{rel} (%)): 379 $[M]^+$ (5), 344 $[M - Cl]^+$ (3), 239 [M – dimedone]$^+$ (100), 204 [M – dimedone – Cl]$^+$ (59), 177 [M – dimedone – Cl – HCN]$^+$ (57), 140 [dimedone]$^+$ (53).

3-Chloro-4-cyano-10-(1*H*-indol-3-yl)benzo[*b*][1,6]naphthyridine (22). ***A.*** A mixture of compound **20a** (0.25 g, 0.701 mmol) and $K_3[Fe(CN)_6]$ (0.5 g, 1.52 mmol) in 10 mL of 50% aqueous Pr^iOH was stirred with reflux for 60 h, the precipitate was filtered off, and extracted with boiling DMF. The extract was passed through a paper filter and the product was precipitated by 50% aqueous EtOH. The precipitate was filtered off, washed with EtOH, and dried to give 0.11 g (44%) of compound **22** as bright-red fine crystals. MS, m/z (I_{rel} (%)): 354 $[M]^+$ (100), 319 $[M - Cl]^+$ (50), 291 [M – HCl – HCN]$^+$ (13), 177 [M – indolyl – Cl – CN]$^+$ (16), 117 [indole]$^+$ (57).

B. A solution of $[Ag(Py)_2]MnO_4$ (0.32 g, 0.841 mmol) in 3 mL of pyridine was added to a solution of compound **20a** (0.2 g, 0.561 mmol) in 2 mL of pyridine and the mixture was stirred for 1 h at ~20 °C. The reaction mixture was diluted with water and left for ~12 h in a refrigerator for aggregation of the precipitate. The precipitate was filtered off, washed with EtOH, dried, and extracted with hot DMF (2×5 mL), and the extract was filtered through a paper filter. A 50% aqueous solution of EtOH (15 mL) was added to the filtrate, and the mixture was cooled. The precipitate was filtered off, washed with EtOH, and dried to give 0.11 g (55%) of compound **22**. The melting point of a mixed sample with the compound prepared by procedure ***A*** was undepressed.

4-Cyano-10-(1*H*-indol-3-yl)-3-morpholinobenzo[*b*][1,6]naphthyridine (23a). A mixture of compound **22** (0.25 g, 0.705 mmol) and morpholine (0.25 g) in 5 mL of DMF was stirred for 20 h at ~20 °C and poured in 20 mL of water. The precipitate was filtered off, washed with water, and dried to give 0.25 g (88%) of compound **23a**. MS, m/z (I_{rel} (%)): 405 $[M]^+$ (100), 348 (95) $[M - C_3H_5O]^+$, 320 [M – morpholyl]$^+$ (86), 319 [M – morpholine]$^+$ (96).

4-Cyano-10-(1*H*-indol-3-yl)-3-phenylthiobenzo[*b*][1,6]naphthyridine (23b). A mixture of compound **22** (0.25 g, 0.705 mmol), benzenethiol (0.08 mL, 0.775 mmol), and AcONa (0.1 g) in 10 mL of Pr^iOH was refluxed with stirring for 2 h, and the precipitate was filtered off, washed with water and Pr^iOH, and dried to give 0.21 g (70%) of compound **23b**. MS, m/z (I_{rel} (%)): 428 $[M]^+$ (100), 402 $[M - CN]^+$ (9), 318 [M – PhSH]$^+$ (11), 280 [M – indolyl – S]$^+$ (29).

The authors are grateful to N. P. Solov´eva for assistance in recording the NMR spectra.

References

1. A. S. Ivanov, N. Z. Tugusheva, N. P. Solov´eva, and V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1966 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 2121].
2. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, *Tetrahedron*, 1988, 1.
3. V. G. Granik, A. V. Kadushkin, and J. Liebsher, *Adv. Heterocycl. Chem.*, 1998, **72**, 79.
4. W. Kantlehner, in *Immonium Salts in Organic Chemistry*, Eds. H. Bohme and H. G. VieHe, J. Wiley and Sons, New York—London—Sydney—Toronto, 1979, Part 2, 6.
5. V. G. Granik, A. N. Zhidkova, and R. G. Glushkov, *Usp. Khim.*, 1977, **46**, 685 [*Russ. Chem. Rev.*, 1977, **46** (Engl. Transl.)].
6. H. Meerwein, W. Florian, and N. Schön, *Ann. Chem.*, 1961, **641**, 1.
7. D. V. Besedin, A. V. Gulevskaya, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 2000, 1403 [*Chem. Heterocycl. Compd.*, 2000, **36** (Engl. Transl.)].
8. J. W. Emsley, J. Feeney, and L. M. Sutcliffe, in *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford, 1965, Vol. **2**.
9. H. Firouzabadi, B. Vessal, and M. Naderi, *Tetrahedron Lett.*, 1982, **23**, 1847.

Received November 27, 2002;
in revised form January 22, 2003