New synthesis of benzo[*b*][1,6]naphthyridines and pyrido[4,3-*b*]benz[*f*]azepines from lactim ethers of 3,4-dihydrocarbostyril and 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one

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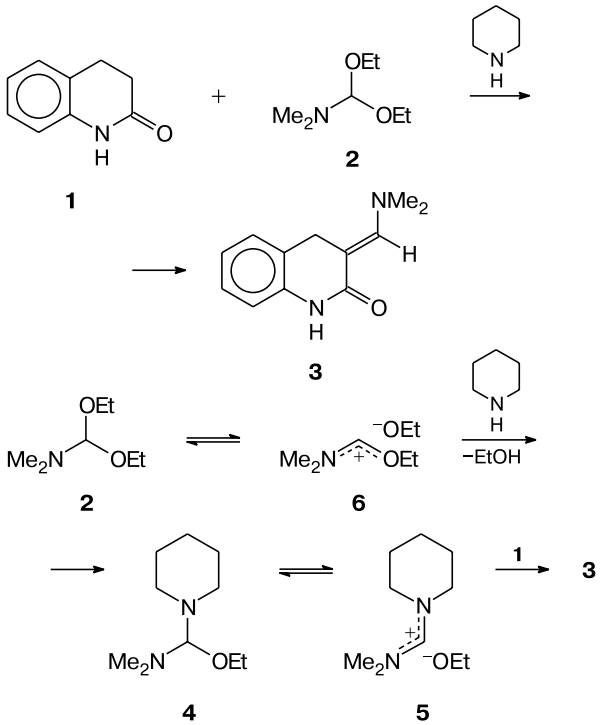
Condensation of lactim ethers of 3,4-dihydrocarbostyril and 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one with malonodinitrile, cyanoacetamide, and ethyl cyanoacetate gave the corresponding 2-methylidene derivatives. Their reactions with dimethylformamide diethyl acetal followed by cyclization into benzo[*b*][1,6]naphthyridines and pyrido[4,3-*b*]benz[*f*]azepines were studied.

Key words: 3,4-dihydrocarbostyril, 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one, dimethylformamide diethyl acetal, cyanoacetic acid derivatives, benzo[*b*][1,6]naphthyridines, pyrido[4,3-*b*]benz[*f*]azepines.

Proceeding further in our investigations into the synthesis of heterocyclic oxindole-based systems,[1] we used in the present work the homologous benzolactams 3,4-dihydrocarbostyril (**1**) and 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one as the starting reagents. In oxindole, the 3-methylene fragment is activated by both the carbonyl group and the annulated benzene ring, while the corresponding activation in the above lactams is only due to the lactam CO group. Because of this, condensation at the 3-CH_2 group could be expected to be substantially more difficult. Indeed, compound **1** does not react with dimethylformamide diethyl acetal (**2**) either in boiling ethanol, benzene, or toluene (oxindole reacts with acetal **2** at room temperature) or with $AlCl_3$ as a catalyst.[2] Only when refluxing lactam **1** in excess acetal **2** for 5 h in the presence of catalytic amounts of piperidine, we obtained 3-dimethylaminomethylidene derivative **3** in low yield (22%) (Scheme 1). The catalytic effect of piperidine is associated with the formation of intermediate *N*,*O*-acetal **4**. This acetal is much more reactive than amide acetals of the type **2** because of the substantially better stabilization of amidinium cation **5** compared to imino ether cation **6** (its stabilization determines the electrophilic properties of amide acetals).

Scheme 1



According to the ^{1}H NMR spectrum, compound **3** in DMSO-d_6 exists as one geometric isomer. In terms of molecular models, one can assume the formation of the *E*-isomer, in which the H(3´) proton and the CO group are close to each other. Enamino amide **3** was subjected to transamination, which is the most representative reac-

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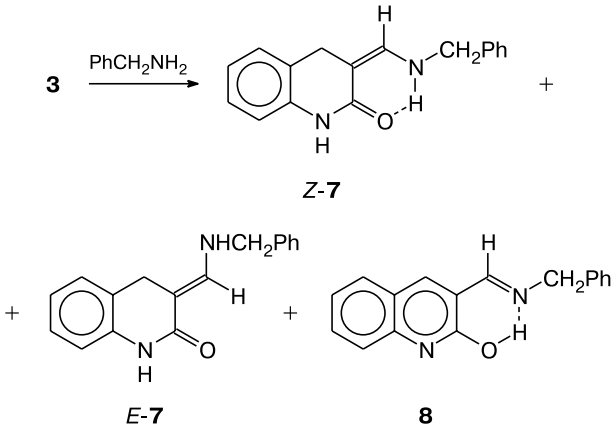
tion of enamines. A reaction with benzylamine gave a multicomponent mixture. Its mass spectrum shows two molecular ion peaks with *m/z* 264 and 262 due to the expected 3-benzylaminomethylidene-1,2,3,4-tetrahydroquinolin-2-one **7** and its dehydrogenation product **8**. The ^{1}H NMR spectrum of this mixture contains signals for two geometric isomers (*E*-**7** and *Z*-**7**) in the ratio 4 : 1 (the presence of the *Z*-isomer is due to its stabilization by intramolecular hydrogen bonding) and signals for dehydrogenated derivative **8**, which exists in DMSO-d_6 in the enol form (Scheme 2).

Scheme 2

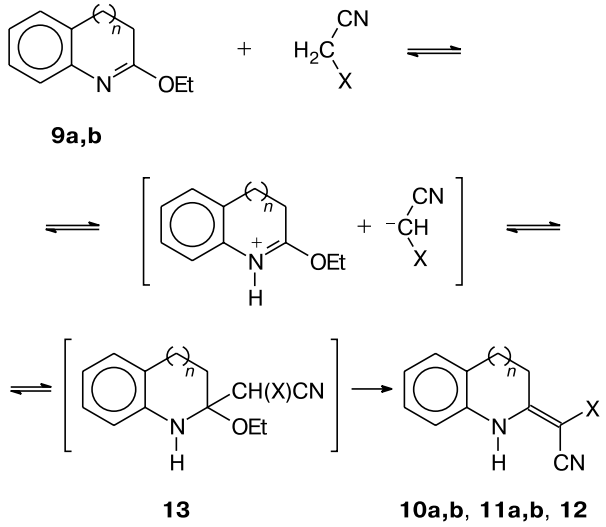


Since the aforementioned synthesis of compound **3** is unsuitable for preparative purposes, we followed an alternative route involving condensation of lactim ethers **9a,b** with cyanoacetic acid derivatives. We could expect that introduction of a methylene fragment with two strong electron-withdrawing β-substituents into position 2 of tetrahydroquinoline and 1*H*-2,3,4,5-tetrahydrobenzazepine would greatly activate the 3-CH_2 group and allow their reactions with amide acetal.

Reactions of lactim ethers **9a,b** with malonodinitrile with removal of ethanol during the condensation gave the corresponding β-dicyanomethylidene derivatives **10a,b** (Scheme 3). The removal of ethanol began at 95—100 °C for six-membered lactim ether **9a** and at 120—125 °C for seven-membered ether **9b**. Condensation with cyanoacetamide occurred at a higher temperature (165—175 °C) to give β-carbamoyl-β-cyanomethylidene derivatives **11a,b**. A still higher temperature (225—230 °C) was required for reactions with ethyl cyanoacetate: in this case, only compound **12** was isolated in the individual state.

One can see that condensation with active methylene compounds occurs for lactim ether **9a** containing the six-membered ring more easily than for seven-membered ether **9b**. For quantitative estimation of the tendency of ethers **9a,b** toward condensation of this type, a mixture of lactim ethers **9a,b** (5 mmol each) and malonodinitrile

Scheme 3

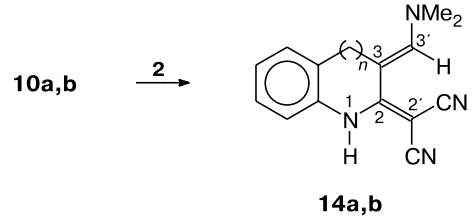


X = CN (**10a,b**), $CONH_2$ (**11a,b**), COOEt (**12**);
n = 1 (**9a**—**11a**, **12**), 2 (**9b**—**11b**)

(1.25 mmol) was heated at 120—125 °C until ethanol was completely removed. According to the ^{1}H NMR spectrum, the resulting mixture contained compounds **9a**, **9b**, **10a**, **10b**, and 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one in the ratio 41 : 46 : 10 : 2 : 1; *i.e.*, the condensation rate of the six-membered lactim ether is ~5 times higher than that of the seven-membered ether. The ratio of the components in the reaction mixture was assessed from the integral intensities of the signals for the ring methylene protons and the methyl protons in the lactim ethers. This reaction outcome can be explained by a reaction mechanism in which addition of the CH acid anion to position 2 of the lactim ethers is a rate-limiting step. The formation of intermediate **13** (see Scheme 3) involves a transformation of the sp^2-hybridized C(2) atom into the sp^3-hybridized state, which is thermodynamically much more favorable for a six-membered ring than for a seven-membered one.[3]

As expected, condensation of compounds **10a,b** with acetal **2** proceeded smoothly enough to yield diene diamines **14a,b** (Scheme 4).

Scheme 4



n = 1 (**a**), 2 (**b**)

The ^{1}H NMR spectra of compounds **3**, **7**, **8**, **10a,b**, **11a,b**, **12**, and **14a,b** are given in Tables 1 and 2.

The characteristic features of the ^{13}C NMR spectrum of compound **14a** (see Experimental) include a broadened signal at δ 120.1 (CN) and a high-field signal for the quaternary sp^2-hybridized C(2′) atom (δ 38.6), which is due to the strong electron-donating effects of the endocyclic NH group and the NMe_2 fragment. The ^{1}H NMR

Table 1. ^{1}H NMR spectra of compounds **3**, **7**, **8**, and **14a,b** in DMSO-d_6

Compound	δ (*J*/Hz)				
	CH_2	H(3′)	H arom. (m)	N(1)H (br.s, 1 H)	Other protons
3	3.96 (s, 2 H, H(4))	7.21 (t, 1 H, $^4J_{H(3'),H(4)} = 1.5$)	6.70—7.07 (4 H, H(5)—H(8))	9.25	3.04 (s, 6 H, NMe_2)
E-**7**[a]	3.55 (s, 2 H, H(4))	7.30 (dt, 1 H, $^3J_{H(3'),NH} = 12.2$, $^4J_{H(3'),H(4)} = 2.0$)	6.75—7.10 (4 H, H(5)—H(8))	9.25	6.95 (dt, 1 H, N<u>H</u>CH_2Ph, $^3J_{NH,CH_2} = 5.2$); 4.36 (d, 2 H, NHC<u>H_2</u>Ph); 6.75—7.36 (m, 5 H, Ph)
Z-**7**[a]	3.52 (s, 2 H, H(4))	—[b]	6.75—7.10 (H(5)—H(8))	9.28	4.32 (d, 2 H, NHC<u>H_2</u>Ph, $^3J_{NH,CH_2} = 6.4$)[c]; 6.75—7.36 (m, 5 H, Ph)
8	—	8.70 (t, 1 H, $^4J_{H(3'),CH_2} = 1.5$)	7.15—7.82 (4 H, H(5)—H(8))	—	4.80 (d, 2 H, C<u>H_2</u>Ph); 6.75—7.36 (m, 5 H, Ph); 8.49 (s, 1 H, H(4)); 12.05 (br.s, 1 H, OH)
14a	3.63 (br.s, 2 H, H(4))	7.41 (s, 1 H)	6.95—7.15 (4 H, H(5)—H(8))	10.03	3.16 (s, 6 H, NMe_2)
E-**14b**[d]	2.36 (m, 2 H, H(4)); 2.78 (m, 2 H, H(5))	5.54 (s, 1 H)	6.70—7.16 (H(6)—H(9))	7.30	~3.20 (br.s, 6 H, NMe_2)
Z-**14b**[d]	2.70 (m, 2 H, H(4)); 2.86 (m, 2 H, H(5))	6.37 (s, 1 H)	6.70—7.16 (H(6)—H(9))	9.60	3.13, 3.24 (both s, 3 H each, NMe_2)

[a] The relative contents of the *E*- and *Z*-isomers are 80 and 20%, respectively.
[b] The signals are masked by a multiplet for the aromatic protons in the components of the mixture under analysis.
[c] The signal for N<u>H</u>CH_2Ph overlaps with a multiplet for the aromatic protons.
[d] The relative contents of the *Z*- and *E*-isomers are 60 and 40%, respectively.

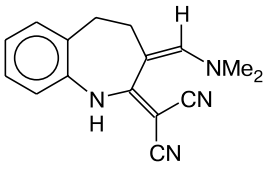
Table 2. ^{1}H NMR spectra of compounds **10a,b**, **11a,b**, **12**, and **15** in DMSO-d_6

Compound	δ (*J*/Hz)			
	CH_2	H arom. (m)	N(1)H	Other protons
10a	2.84 (m, 4 H, H(3), H(4))	7.00—7.35 (4 H, H(5)—H(8))	11.06 (br.s, 1 H)	—
10b	2.18 (quint, 2 H, H(4), $^3J_{H(3),H(4)} = {}^3J_{H(4),H(5)} = 7.2$); 2.38 (t, 2 H, H(3), $^3J_{H(3),H(4)} = 7.2$); 2.65 (t, 2 H, H(5), $^3J_{H(4),H(5)} = 7.2$)	7.20—7.32 (4 H, H(6)—H(9))	10.79 (br.s, 1 H)	—
11a	2.85 (m, 4 H, H(3), H(4))	6.95—7.20 (6 H, H(5)—H(8), NH_2)*	12.55 (s, 1 H)	—
11b	2.20 (quint, 2 H, H(4), $^3J_{H(3),H(4)} = {}^3J_{H(4),H(5)} = 7.2$); 2.40 (t, 2 H, H(3), $^3J_{H(3),H(4)} = 7.2$); 2.70 (t, 2 H, H(5), $^3J_{H(4),H(5)} = 7.2$)	7.15—7.30 (6 H, H(6)—H(9), NH_2)*	12.26 (s, 1 H)	~7.20*
12	2.80—2.95 (m, 4 H, H(3), H(4))	7.05—7.23 (4 H, H(5)—H(8))	11.41 (s, 1 H)	1.25 (t, 3 H, Me, $^3J = 7.2$); 4.16 (q, 2 H, CH_2, $^3J = 7.2$)
15	2.87 (m, 4 H, H(3), H(4))	7.00—7.20 (4 H, H(5)—H(8))	12.93 (br.s, 1 H)	8.50 (s, 1 H, N=CH); 3.08, 3.18 (both s, 3 H each, NMe_2)

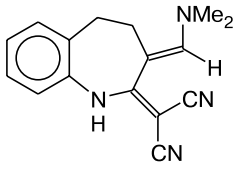
* The protons of the $CONH_2$ fragment are manifested by two strongly broadened signals that overlap with a multiplet for the aromatic protons, making its integral intensity equal to 6 H.

spectrum of this compound contains one set of signals (see Table 1). To determine the configuration of this compound, we carried out a nuclear Overhauser effect (NOE) experiment. Irradiation at the frequency of the signal for the Me_2N group (δ 3.16) increased the intensity of the narrow singlet for the vinylic proton (δ 7.41, NOE 28%) and slightly (but distinctly) increased the intensity of the singlet for the methylene protons (δ 3.63, NOE 3%). Such an insignificant effect for the 4-CH_2 group is probably associated with the inversion of the tetrahydropyridine ring that causes broadening of this singlet. Irradiation at the frequency of the singlet for the 4-CH_2 protons increased the intensity of the doublet for the H(5) proton (δ 7.10, NOE 9%). Thus, the NOE experiment revealed that compound **14a** have spatially close Me_2N and 4-CH_2 groups and hence exists (like compound **3**) in the *E*-configuration.

The ^{1}H NMR spectrum of compound **14b** in DMSO-d_6 (see Table 1) shows a double set of signals indicating the presence of a mixture of geometric isomers in solution. The largest difference between the chemical shifts relates to the vinylic protons (δ 6.37 for *Z*-isomer (60%) and δ 5.54 for *E*-isomer (40%); $\Delta\delta = 0.83$ ppm). In CD_3OD, the equilibrium shift to the major isomer (76%) is more pronounced. The correctness of our assignment of the signals to the *E*- and *Z*-isomers is evident from a good agreement between the chemical shifts of the methylene protons in the seven-membered ring in the major *Z*-isomer of compound **14b** (δ 2.70 (H(4)) and 2.86 (H(5))) and in compound **16b** (δ 2.74 and 2.92; see below), as well as from an appreciable difference between these values and the chemical shifts of the methylene protons of the seven-membered ring in the minor *E*-isomer (δ 2.36 and 2.78).



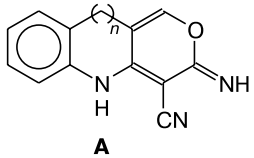
Z-**14b**



E-**14b**

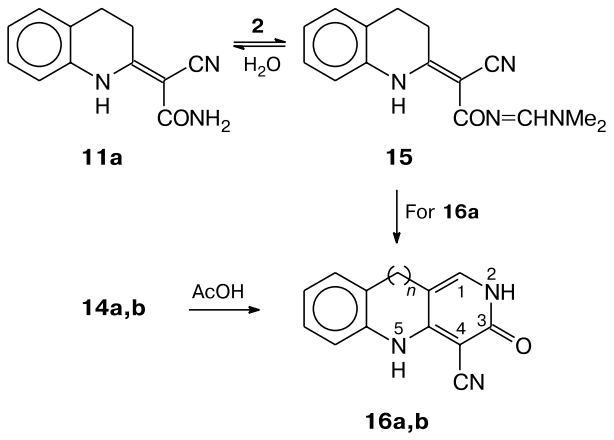
Note that the reaction of acetal **2** with enamino amide **11a** occurs at the carbamoyl NH_2 group rather than the 3-CH_2 fragment. The resulting enamino acylamidine **15** easily undergoes hydrolysis in boiling water to give the starting compound **11a** (Scheme 5).

Then we studied heterocyclization of diene diamines **14a,b**. Heating of the latter in acetic acid yielded tricyclic products **16a,b** (see Scheme 5). The ^{1}H NMR spectra of compounds **16a,b** (Table 3) do not contradict structure **A** as well.



A

Scheme 5



n = 1 (**a**), 2 (**b**)

A NOE experiment (Table 4) *via* irradiation at the frequency of the signal for the N(2)H group caused an increase in the intensity of the signal for the H(1) proton (by 17.5%) in the spectrum of compound **16a**. Therefore, we can assign to this compound a pyridone rather than iminopyran structure. Unambiguous chemical proof of the structure of tricyclic product **16a** was obtained by high-temperature cyclization of enamino acylamidine **15** from which no iminopyran can form. According to the ^{1}H NMR spectra, the final reaction mixture contains compound **16a** and resinification products (see Scheme 5).

Cyclization of diene diamine **14a** under other conditions (heating with sodium methoxide in methanol) gave 3-methoxydihydrobenzonaphthyridine **17** (Scheme 6). To reliably distinguish between tricyclic structure **17** and an alternative structure (methoxymethylidene derivative **18**), we examined the ^{1}H and ^{13}C NMR spectra (see Table 3 and Experimental) and carried out a NOE experiment. Irradiation at the frequency of the signal for the C(10)H_2 protons (δ 3.97) increased the intensity of the signal for the H(1) proton (δ 7.87) by 25% and the intensity of the doublet for the H(9) proton (δ 7.09) by 20%. Based on the signal multiplicity for the C atoms in the ^{13}C NMR spectrum recorded without proton decoupling, we made an unambiguous choice for the tricyclic structure. First, in the case of bicyclic structure **18**, the components of the quartet for the methoxy C atom should be split because of a spin-spin coupling with the H(3′) proton. The actual spectrum shows a quartet ($^1J_{C,H}$ = 147.3 Hz) characteristic of structure **17**. Second, the multiplicity of the signal at δ 148.6 for the C(1) atom, which is a doublet of triplets arising from spin-spin couplings with the H(10) protons ($^1J_{C(1),H}$ = 178.5 Hz, $^3J_{C(1),H(10)}$ = 3.1 Hz) is evidence for structure **17**. In the case of structure **18**, the C(3′) atom would couple with the OMe pro-

Table 3. ^{1}H NMR spectra of compounds **16a,b**, **17**, **19**, **20a**, and **21** in DMSO-d_6

Compound	δ (*J*/Hz)					
	CH_2	H arom.	N(5)H (1 H)	N(2)H (br.s, 1 H)	H(1) (s, 1 H)	H of the substituent in position 3
16a	3.81 (s, 2 H, H(10))	6.95 (t, 1 H, ^3J = 9.3); 7.09 (d, 1 H, ^3J = 9.3); 7.15 (t, 1 H, ^3J = 9.3); 7.35 (d, 1 H, ^3J = 9.3) (H(6)—H(9))	9.60 (s)	11.40	7.36	—
16b	2.74, 2.92 (both m, 2 H each, H(10), H(11))	6.92—7.20 (m, 3 H); 7.30 (d, 1 H, ^3J = 8.3) (H(6)—H(9))	8.40 (s)	11.48	7.34	—
17	3.97 (s, 2 H, H(10))	7.09 (m, 2 H, H(9), H(7)); 6.92 (t, 1 H, H(8), ^3J = 7.7); 7.24 (d, 1 H, H(6), ^3J = 7.7)	9.48 (s)	—	7.87	3.88 (c, 3 H, OMe)
19	4.05 (s, 2 H, H(10))	6.93 (t, 1 H, H(8), ^3J = 8.0); 7.10 (m, 2 H, H(9), H(7)); 7.30 (d, 1 H, H(6), ^3J = 8.0)	9.76 (s)	—	8.03	—
20a	3.85 (s, 2 H, H(10))	6.81—7.30 (m, 10 H)*	9.14 (br.s)	—	7.74	4.55 (d, 2 H, NCH_2, $^3J_{CH_2,NH}$ = 5.7)
21	3.85 (s, 2 H, H(10))	6.88, 7.05 (both t, 1 H each, ^3J = 9.3); 7.07, 7.20 (both d, 1 H each, ^3J = 9.3) (H(6)—H(9))	9.07 (s)	—	7.71	6.37 (br.s, 2 H, NH_2)

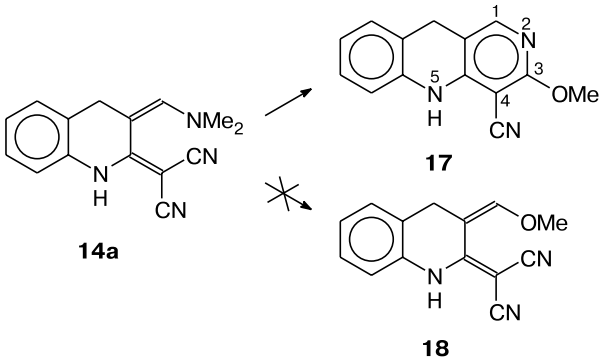
* The multiplet is due to the aromatic H(6)—H(9) protons, the protons of the Ph group, and the NH protons of the substituent in position 3.

Table 4. NOE data for compound **16a**

Signal, δ		Increase in the intensity of the observed signal (%)
irradiation	observation	
3.81 (H(10))	7.09 (H(9))	30
	7.36 (H(1))	36
7.36 (H(1))	11.40 (N(2)H)	6.5
9.60 (N(5)H)	7.35 (H(6))	16
11.40 (N(2)H)	7.36 (H(1))	17.5

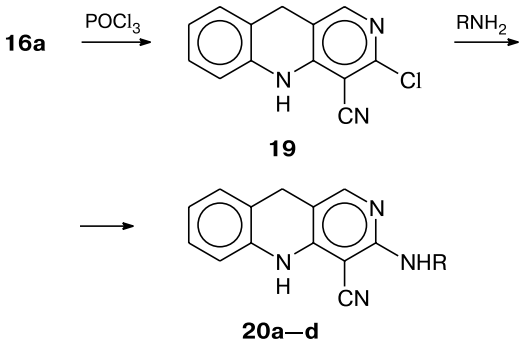
tons and the signal would appear as a doublet of multiplets.

Scheme 6



Reflux of compound **16a** with $POCl_3$ afforded chloro derivative **19**, which reacted with various amines to give amino derivatives **20a—d** (Scheme 7).

Scheme 7

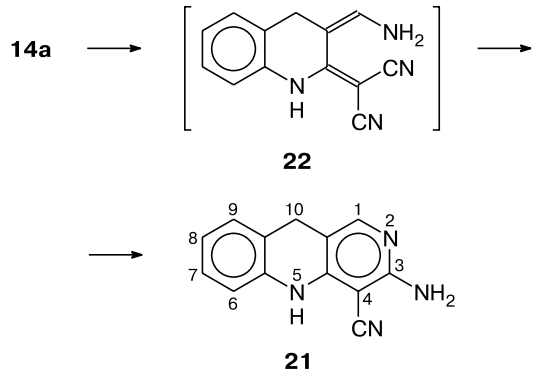


R = CH_2Ph (**a**), $(CH_2)_2C_6H_3$-3,4-$(OMe)_2$ (**b**), $(CH_2)_2NEt_2$ (**c**), Bu (**d**)

By treating compound **14a** with an ethanolic solution of ammonia, we obtained tricyclic product **21**. Apparently, the reaction proceeds *via* transamination followed by cyclization involving the amino and cyano groups (Scheme 8).

The ^{1}H and ^{13}C NMR spectra of tricyclic product **21** are similar to those of compound **17** (see Table 3 and Experimental) and substantially differ from the spectra of bicyclic compounds **14** (see Table 1). This makes

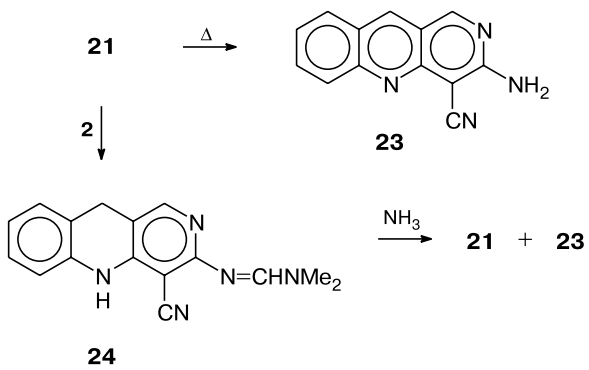
Scheme 8



structure **21** preferred to isomeric intermediate **22**. The ^{13}C NMR spectrum of compound **21** shows a characteristic doublet for the C(3) atom because of a spin-spin coupling with the aromatic H(1) proton ($^3J_{C(3),H(1)}$ = 13.4 Hz).

Compound **21** readily undergoes dehydrogenation (Scheme 9). For instance, even on heating in acetic acid (80 °C, 1.5 h), its degree of dehydrogenation was 10% (the ^1H NMR spectrum of compound **23** is given in Experimental). A mixture of compounds **23** and **21** (83 and 17%, respectively) was obtained by vacuum sublimation of compound **21** at 260—265 °C.

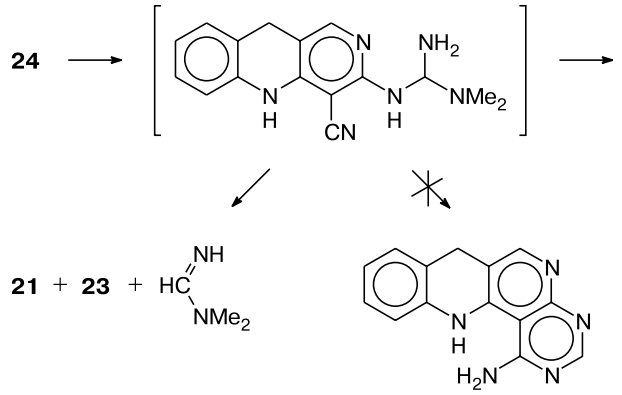
Scheme 9



A reaction of compound **21** with acetal **2** gave amidine **24** (see Scheme 9). Its attempted high-pressure cyclization by heating in a methanolic solution of ammonia failed: a 3 : 2 mixture of compounds **21** and **23** was isolated. Obviously, the reaction is accompanied by elimination of *N*,*N*-dimethylformamidine (Scheme 10).

To sum up, we found that the lactim ethers of 3,4-dihydrocarbostyril and, to a lesser degree, 1*H*-2,3,4,5-tetrahydrobenz[*b*]azepin-2-one are convenient starting reagents for various heterocyclization reactions. Based on them, we discovered a new route to benzonaphthyridines and pyridobenzazepines.

Scheme 10



Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer (400 (^1H) and 100 MHz (^{13}C)) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra (EI and CI) were recorded on a SSQ-710 Finnigan-MAT instrument (direct inlet probe, ionizing voltage 70 eV, ionization chamber temperature 150 °C). Melting points were determined on a Boetius hot stage.

The physicochemical constants and yields of the compounds obtained are summarized in Table 5; their spectroscopic characteristics are given in Tables 1—4 and 6.

Lactim ethers were prepared as described earlier.[4]

3-(*N*,*N*-Dimethylamino)methylidene-1,2,3,4-tetrahydroquinolin-2-one (3). A mixture of 1,2,3,4-tetrahydroquinolin-2-one (**1**) (0.74 g, 5 mmol), *N*,*N*-dimethylformamide diethyl acetal (**2**) (10 mL), and piperidine (0.05 mL) was refluxed for 5 h and kept at ~20 °C for 15 h. The precipitate of compound **3** that formed was filtered off.

Transamination of compound 3 with benzylamine. A mixture of compound **3** (0.4 g, 2 mmol) and benzylamine (0.32 g, 3 mmol) was refluxed in toluene (10 mL) for 3 h. The solvent was removed *in vacuo* and the residue was triturated with light petroleum and dissolved in ethyl acetate. The solution was filtered and cooled. The resulting precipitate of 3-(benzylamino)methylidene-1,2,3,4-tetrahydroquinolin-2-one (**7**) and 3-(benzylamino)methyl-2-hydroxyquinoline (**8**) was filtered off, m.p. 160—163 °C.

`2-Dicyanomethylidene-1,2,3,4-tetrahydroquinoline (10a), 2-dicyanomethylidene-1*H*-2,3,4,5-tetrahydrobenz[*b*]azepine (10b), 2-(1-carbamoyl-1-cyanomethylidene)-1,2,3,4-tetrahydroquinoline (11a), 2-(1-carbamoyl-1-cyanomethylidene)-1*H*-2,3,4,5-tetrahydrobenz[*b*]azepine (11b), and 2-(1-cyano-1-ethoxycarbonylmethylidene)-1,2,3,4-tetrahydroquinoline (12) (general procedure). A mixture of lactim ether **9a** or **9b** and an appropriate cyanoacetic acid derivative in the molar ratio 1 : 1 was heated with removal of liberated ethanol at 95—100 (for **10a**), 120—125 (**10b**), 165—170 (**11a**), 170—175 (**11b**), and 225—230 °C (**12**) until the reaction was completed (ceasing of the removal). The reaction mixture was cooled and washed with ether to give compounds **10a,b** and **11a,b**. In the case of compound **12**, the reaction mixture was cooled, the precipitate was triturated with light petroleum, and the product was extracted

Table 5. Yields, melting points, and elemental analysis data for compounds **3**, **10a,b**, **11a,b**, **12**, **14a,b**, **15**, **16a,b**, **17**, **19**, **20a—d**, **21**, and **24**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula
			C	H	N	
3	22	202—205 (AcOEt)	71.19 / 71.26	7.20 / 6.98	13.74 / 13.85	$C_{12}H_{14}N_2O$
10a	90	233—234 (Pr^iOH)	73.90 / 73.83	4.61 / 4.65	21.45 / 21.53	$C_{12}H_9N_3$
10b	91	229—230 (MeOH)	74.64 / 74.62	5.51 / 5.30	20.37 / 20.08	$C_{13}H_{11}N_3$
11a	97	217—220[a] (EtOH)	67.37 / 67.59	5.20 / 5.20	19.48 / 19.71	$C_{12}H_{11}N_3O$
11b	90	160—165 (Pr^iOH)	68.53 / 68.70	6.00 / 5.77	18.07 / 18.49	$C_{13}H_{13}N_3O$
12	23	88—92 (Et_2O)	69.50 / 69.40	6.00 / 5.83	11.32 / 11.56	$C_{14}H_{14}N_2O_2$
14a	67	226—229 (Pr^iOH)	72.00 / 71.98	5.67 / 5.64	22.44 / 22.38	$C_{15}H_{14}N_4$
14b	34	138—142 (Pr^iOH)	72.43 / 72.70	6.45 / 6.10	20.98 / 21.20	$C_{16}H_{16}N_4$
15	52	168—172 (Pr^iOH)	66.86 / 67.14	6.02 / 6.01	20.80 / 20.88	$C_{15}H_{16}N_4O$
16a[b]	83	>270 (DMF—H_2O, 1 : 1)	68.59 / 68.56	4.33 / 4.21	18.73 / 18.75	$C_{13}H_9N_3O \cdot 0.25\ H_2O$
16b	81	>270 (DMF—H_2O, 1 : 1)	70.94 / 70.87	4.77 / 4.67	17.75 / 17.71	$C_{14}H_{11}N_3O$
17	76	228—230 (MeCN)	70.86 / 70.87	4.68 / 4.67	17.64 / 17.71	$C_{14}H_{11}N_3O$
19[c]	91	245—249[a] (MeCN)	64.44 / 64.61	3.42 / 3.34	17.47 / 17.39	$C_{13}H_8ClN_3$
20a	91	216—219 (MeCN)	76.43 / 76.90	5.32 / 5.16	18.21 / 17.94	$C_{20}H_{16}N_4$
20b	65	154—156 (AcOEt)	71.62 / 71.48	5.88 / 5.74	14.00 / 14.50	$C_{23}H_{22}N_4O_2$
20c	52	108—110 (aqueous 45% Pr^iOH)	70.92 / 71.00	7.15 / 7.21	21.75 / 21.79	$C_{19}H_{23}N_5$
20d	53	126—129 (heptane)	73.26 / 73.35	6.34 / 6.52	20.02 / 20.13	$C_{17}H_{18}N_4$
21	59	260—263[a] (MeOH)	70.10 / 70.25	4.49 / 4.54	25.35 / 25.21	$C_{13}H_{10}N_4$
24	90	252—254 (MeCN)	69.27 / 69.29	5.35 / 5.45	25.00 / 25.25	$C_{16}H_{15}N_5$

[a] Decomp.
[b] Found (%): H_2O, 1.83. Calculated (%): H_2O, 1.98.
[c] Found (%): Cl, 14.72. Calculated (%): Cl, 14.67.

with ether. The resulting solution was concentrated to 1/3 of the initial volume and cooled and the precipitate of compound **12** that formed was filtered off.

2-Dicyanomethylidene-3-dimethylaminomethylidene-1,2,3,4-tetrahydroquinoline (14a). A mixture of compound **10a** (0.58 g, 3 mmol) and acetal **2** (0.53 g, 3.6 mmol) was stirred in toluene (15 mL) at 90 °C for 30 min. Then an additional portion of acetal **2** (0.3 g) was added and stirring was continued for 40 min. The reaction mixture was cooled to 0 °C and the precipitate of quinoline **14a** that formed was filtered off. ^{13}C NMR (DMSO-d_6), δ: 26.7 (C(4)); 38.6 (C(2′)); 43.8 (NMe_2); 89.6 (C(3)); 117.1, 123.9, 127.3, 127.8 (C(5)—C(8)); 120.1 (CN); 124.8 (C(4a)); 136.0 (C(8a)); 153.3 (C(3′)); 164.1 (C(2)).

2-Dicyanomethylidene-3-dimethylaminomethylidene-1*H*-2,3,4,5-tetrahydrobenz[*b*]azepine (14b). A mixture of compound **10b** (1.04 g, 5 mmol), acetal **2** (5 mL), and a catalytic amount of piperidine was heated at 80—90 °C for 30 min. The reaction mixture was concentrated, the residue was successively triturated with light petroleum and ether—ethyl acetate, and the precipitate of benzazepine **14b** was filtered off.

2-{1-Cyano-1-[(dimethylamino)methylideneaminocarbonyl]methylidene}-1,2,3,4-tetrahydroquinoline (15). A mixture of compound **11a** (2.6 g, 12.2 mmol) and acetal **2** (2.14 g, 14.6 mmol) was refluxed in methanol (30 mL) for 1 h and then with an additional portion of acetal **2** (0.5 g) for 2 h. The reaction mixture was filtered and cooled to ~15 °C. The precipitate of quinoline **15** that formed was filtered off.

Hydrolysis of compound 15. Compound **15** (0.15 g, 0.7 mmol) was refluxed in water (20 mL) for 30 min and filtered. On cooling, the precipitate of compound **11a** that formed was filtered off. Extraction from the aqueous mother liquor with chloroform gave an additional crop of compound **11a**.

4-Cyano-3-oxo-2,3,5,10-tetrahydrobenzo[*b*][1,6]naphthyridine (16a). ***A.*** A mixture of compound **14a** (9.77 g, 31.1 mmol) and glacial acetic acid (115 mL) was stirred at 85—90 °C for 4 h. On cooling, the precipitate of compound **16a** was filtered off and washed with water and isopropyl alcohol.

B. Compound **15** (0.06 g) was heated at 185—190 °C for 45 min. The reaction mixture was triturated with isopropyl alcohol and the precipitate of quinolone **16a** was filtered off.

4-Cyano-3-oxo-2*H*-3,5,10,11-tetrahydrobenzo[*f*]pyrido[4,3-*b*]azepine (16b) was obtained analogously from compound **14b** (method ***A***, 95—100 °C, 4.5 h).

4-Cyano-3-methoxy-5,10-dihydrobenzo[*b*][1,6]naphthyridine (17). Compound **14a** (0.625 g, 2.5 mmol) was refluxed for 1.5 h in a methanolic solution of sodium methoxide prepared from metallic sodium (0.06 g) and methanol (10 mL). On cooling, the precipitate of compound **17** was filtered off. ^{13}C NMR (DMSO-d_6), δ: 26.4 (split t, C(10)); 54.2 (q, OMe, $^1J_{C,H}$ = 147.3 Hz); 77.5 (s, C(4)); 110.4 (m, C(10a)); 114.5 (s, CN); 120.2 (m, C(9a)); 116.2, 123.1, 127.6, 129.8 (C(6)—C(9)); 137.0 (t, C(5a)); 148.6 (dt, C(1), $^1J_{C,H}$ = 178.5 Hz); 150.6 (d, C(4a)); 164.2 (m, C(3)).

3-Chloro-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (19). A mixture of compound **16a** (7.2 g, 32.3 mmol), triethylamine hydrochloride (3.82 g, 27.3 mmol), and $POCl_3$ (65 mL) was refluxed for 6 h. On cooling, the precipitate of compound **19** was filtered off and washed successively with water, aqueous K_2CO_3, again water, and isopropyl alcohol.

Table 6. Selected mass spectra of the compounds obtained

Compound	MS, *m/z* (I_{rel} (%))
7 + 8[a]	264 $[M_1]^+$ (10), 263 $[M_1 - H]^+$ (11), 262 $[M_2]^+$ (12), 261 $[M_2 - H]^+$ (13), 173 $[M_1 - CH_2Ph]^+$ (20), 171 $[M_2 - CH_2Ph]^+$ (22), 159 $[PhCH_2NHCH{=}C{=}C{=}O]^+$ (25), 106 $[PhCH_2NH_2]^+$ (18), 91 $[CH_2Ph]^+$ (100), 65 $[C_5H_5]^+$ (20)
11a[b]	213 $[M]^+$ (100), 196 $[M - NH_3]^+$ (87), 195 $[M - H_2O]^+$ (42), 168 $[M - NH_3 - CO]^+$ (30), 167 $[M - NH_3 - HCO]^+$ (18), 140 $[M - NH_3 - HCO - HCN]^+$ (16), 130 $[M - CNCHCONH_2]^+$ (18), 106 $[CH_2C_6H_4NH_2]^+$ (7), 77 $[C_6H_5]^+$ (10)
11b	227 $[M]^+$ (81), 210 $[M - NH_3]^+$ (100), 181 $[M - NH_3 - HCO]^+$ (20), 154 $[M - NH_3 - HCO - HCN]^+$ (10), 144 $[M - CN - CHCONH_2]^+$ (26), 127 $[M - NH_3 - HCO - 2\ HCN]^+$ (8), 106 $[CH_2C_6H_4NH_2]^+$ (8), 91 $[C_6H_4NH]^+$ (9)
14a	250 $[M]^+$ (100), 235 $[M - CH_3]^+$ (13), 220 $[M - 2\ CH_3]^+$ (10), 207 $[M - CH_2NCH_3]^+$ (83), 206 $[M - NMe_2]^+$ (52), 193 $[M - CHNMe_2]^+$ (20), 185 $[M - CH(CN)_2]^+$ (40), 179 $[M - NMe_2 - HCN]^+$ (57), 152 $[M - NMe_2 - 2\ HCN]^+$ (10), 140 $[M - NMe_2 - C_3H_2N_2]^+$ (8), 128 $[M - NMe_2 - C_4H_2N_2]^+$ (8)
14b[c]	264 $[M]^+$ (82), 249 $[M - CH_3]^+$ (8), 236 $[M - C_2H_4]^+$ (10), 221 $[M - CH_2{=}NCH_3]^+$ (18), 220 $[M - NMe_2]^+$ (24), 207 $[M - CHNMe_2]^+$ (6), 199 $[M - CH(CN)_2]^+$ (100), 193 $[M - NMe_2 - HCN]^+$ (12), 106 $[CH_2C_6H_4NH_2]^+$ (22), 82 $[CH{\equiv}C{-}CH{=}NMe_2]^+$ (23)
15[d]	268 $[M]^+$ (96), 242 $[M - CN]^+$ (5), 224 $[M - NMe_2]^+$ (36), 197 $[M - N{=}CHNMe_2]^+$ (20), 196 $[M - NH{=}CHNMe_2]^+$ (33), 168 $[M - CONHCHNMe_2]^+$ (20), 141 $[M - CONHCHNMe_2 - HCN]^+$ (15), 140 $[M - CONHCHNMe_2 - C_2H_4]^+$ (32), 130 $[M - CNCHCONCHNMe_2]^+$ (20), 99 $[CON{=}CHNMe_2]^+$ (100), 73 $[H_2N^+{=}CHNMe_2]$ (96)
16a	223 $[M]^+$ (23), 222 $[M - H]^+$ (53), 194 $[M - H - CO]^+$ (10), 167 $[M - CONHCH]^+$ (20), 140 $[M - CONHCH - HCN]^+$ (37), 128 $[M - CHNHCOCHCN]^+$ (10), 113 $[M - CONHCH - 2\ HCN]^+$ (12), 101 $[M - CHNHCOCHCN - HCN]^+$ (11), 89 $[C_7H_5]^+$ (23), 77 $[C_6H_5]^+$ (50), 76 $[C_6H_4]^+$ (60), 66 $[O{=}C{=}C^+{-}C{\equiv}N]^+$ (47), 63 $[C_5H_3]^+$ (66), 52 $[CH{=}CH{-}CN]^+$ (100)
16b[e]	237 $[M]^+$ (100), 236 $[M - H]^+$ (62), 222 $[M - CH_3]^+$ (13), 208 $[M - H - CO]^+$ (10), 182 $[M - CO - HCN]^+$ (10), 181 $[M - H - CO - HCN]^+$ (13), 154 $[M - CH - NHCO - HCN]^+$ (8)
17	237 $[M]^+$ (56), 236 $[M - H]^+$ (100), 222 $[M - CH_3]^+$ (5), 193 $[M - H - COCH_3]^+$ (10), 181 $[M - OCH_2 - CN]^+$ (6), 140 $[M - CHNCOCH_3 - HCN]^+$ (6)
19[f]	241 $[M]^+$ (60), 240 $[M - H]^+$ (100), 204 $[M - H - HCl]^+$ (10), 177 $[M - H - HCl - HCN]^+$ (16), 153 $[M - N{\equiv}CCl - HCN]^+$ (10), 103 $[C_8H_7]^+$ (15), 89 $[C_7H_5]^+$ (12), 76 $[C_6H_4]^+$ (10)
20a	312 $[M]^+$ (100), 311 $[M - H]^+$ (85), 235 $[M - Ph]^+$ (8), 207 $[M - NH{=}CHPh]^+$ (12), 206 $[M - NHCH_2Ph]^+$ (19), 179 $[M - NHCH_2Ph - HCN]^+$ (8), 156 $[M - CN - C{\equiv}C - NHCH_2Ph]^+$ (9), 106 $[NHCH_2Ph]^+$ (48), 91 $[CH_2Ph]^+$ (45), 65 $[C_5H_5]^+$ (10)
24	277 $[M]^+$ (100), 276 $[M - H]^+$ (48), 262 $[M - CH_3]^+$ (52), 233 $[M - NMe_2]^+$ (15), 221 $[M - NC_3H_6]^+$ (40), 207 $[M - C_3H_6N_2]^+$ (21), 206 $[M - C_3H_7N_2]^+$ (20), 179 $[M - C_3H_7N_2 - HCN]^+$ (12)

[a] The mixture was obtained as the result of transamination of compound **3**. The peaks with M_1 and M_2 relate to products **7** and **8**, respectively; the other signals are shared by both compounds.

[b] The spectrum also contains a peak with *m/z* 143 (**1**).

[c] CIMS, *m/z*: 265 $[MH]^+$.

[d] Evaporation of the sample upon an increase in the temperature gives rise to peaks with *m/z* 223 ($[M']^+$) and 196 ($[M' - HCN]^+$); the intensity of the latter increases from 33 to 100%. Apparently, they are due to thermal transformations of compound **15** in the mass spectrometer.

[e] The spectrum also contains a peak with *m/z* 255 ($[M]^+$) due to hydrolysis of the CN group of compound **16b**.

[f] For chlorine-containing fragments, the mass numbers of ^{35}Cl-containing ions are given.

3-Benzylamino-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (20a). A mixture of compound **19** (0.6 g, 2.48 mmol) and benzylamine (1.96 g, 18.3 mmol) was heated at 115 °C for 1.5 h. The reaction mixture was diluted with water and the precipitate of compound **20a** was filtered off.

4-Cyano-3-[2-(3,4-dimethoxyphenyl)ethylamino]-5,10-dihydrobenzo[*b*][1,6]naphthyridine (20b). A mixture of compound **19** (0.5 g, 2.06 mmol) and homoveratrylamine (3 g, 16.6 mmol) was heated at 165—170 °C for 2 h. The reaction mixture was cooled and triturated with heptane and isopropyl alcohol to give compound **20b**.

4-Cyano-3-[2-(diethylamino)ethylamino]-5,10-dihydrobenzo[*b*][1,6]naphthyridine (20c). A mixture of compound **19** (0.5 g, 2.06 mmol) and β-diethylaminoethylamine (2 g, 17.2 mmol) was heated at 150 °C for 30 min. The reaction mixture was cooled and washed with water. The product was extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with light petroleum and the precipitate of compound **20c** was filtered off.

3-Butylamino-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (20d). A mixture of compound **19** (0.5 g, 2.06 mmol) and butylamine (10 mL) was heated in a closed steel vessel at

110—120 °C for 4.5 h. The reaction mixture was concentrated and washed with water. The product was extracted from the residue with chloroform. The extract was dried over Na_2SO_4 and concentrated. Recrystallization of the residue from heptane gave compound **20d**.

3-Amino-4-cyano-5,10-dihydrobenzo[*b*][1,6]naphthyridine (21). ***A.*** Compound **14a** (0.25 g, 1 mmol) and a saturated solution of ammonia in methanol (15 mL) were stirred at 20 °C for 12 h. The precipitate of compound **21** was filtered off. ^{13}C NMR (DMSO-d_6), δ: 26.4 (split t, C(10)); 73.5 (br.s, C(4)); 104.5 (m, C(10a)); 116.1 (s, CN); 120.6 (m, C(9a)); 116.2, 122.7, 127.4, 128.8 (C(6)—C(9)); 137.7 (m, C(5a)); 149.9 (m, C(4a)); 151.2 (dt, C(1), $^1J_{C,H}$ = 173.0 Hz); 160.9 (d, C(3)).

B. Compound **14a** (6 g, 24 mmol) and a saturated solution of ammonia in methanol (200 mL) were heated in a closed steel vessel 50 °C for 5.5 h. The precipitate of compound **21** was filtered off.

Dehydrogenation of compound 21. ***A.*** A mixture of compound **21** (0.25 g, 1.13 mmol) and glacial acetic acid (6 mL) was heated at 80 °C for 1.5 h. On cooling, the precipitate that formed was filtered off. According to ^1H NMR data, the precipitate contained compound **21** (90%) and 3-amino-4-cyanobenzo[*b*][1,6]naphthyridine (**23**) (10%). Compound **23**. ^1H NMR, δ: 7.52 (t, 1 H, H(8), ^3J = 8.8 Hz); 7.84 (br.s, 2 H, NH_2); 7.90 (t, 1 H, H(7), ^3J = 8.8 Hz); 8.00 (d, 1 H, H(6), ^3J = 8.8 Hz); 8.12 (d, 1 H, H(9), ^3J = 8.8 Hz); 9.20 (s, 1 H, H(10)); 9.40 (s, 1 H, H(1)).

B. Compound **21** (0.9 g, 4.05 mmol) was sublimed *in vacuo* (15 Torr) at 260—265 °C. A mixture of compounds **21** (17%) and **23** (83%) was obtained (^1H NMR).

4-Cyano-3-[(dimethylamino)methylidene]amino-5,10-dihydrobenzo[*b*][1,6]naphthyridine (24). A mixture of compound **21** (0.4 g, 1.8 mmol) and acetal **2** (0.5 g, 3.4 mmol) was refluxed in stirred toluene (15 mL) for 6 h, while adding acetal (0.5 mL) every 2 h. On cooling, the precipitate of compound **24** was filtered off.

Reaction of compound 24 with a saturated solution of ammonia in methanol. Compound **24** (0.35 g, 1.26 mmol) and a saturated solution of ammonia in methanol (35 mL) were heated in a closed steel vessel at 105—110 °C for 7 h. On cooling, the precipitate was filtered off and recrystallized from DMF (18 mL). A mixture of compounds **21** (60%) and **23** (40%) was obtained (^1H NMR). The total yield was 0.14 g.

References

1. T. V. Golovko, N. P. Solov´eva, and V. G. Granik, *Khim.-Farm. Zh.*, 1996, **30**, No. 10, 32 [*Pharm. Chem. J.*, 1996, **30**, No. 10, 637 (Engl. Transl.)].
2. V. G. Granik, N. I. Smetskaya, N. A. Mukhina, I. V. Persianova, and V. G. Klimenko, *Khim. Geterotsikl. Soedin.*, 1983, 1279 [*Chem. Heterocycl. Compd.*, 1983, **19** (Engl. Transl.)].
3. V. G. Granik, *Usp. Khim.*, 1982, **51**, 207 [*Russ. Chem. Rev.*, 1982, **51** (Engl. Transl.)].
4. R. G. Glushkov and V. G. Granik, *Adv. Heterocycl. Chem.*, 1970, **12**, 185.

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