Tandem transformations of 10-substituted tetrahydrobenzo[*b*][1,6]naphthyridines resulted from the Michael addition of the nitrogen atom of the tetrahydropyridine fragment to the triple bond of activated alkynes

L. G. Voskressensky, T. N. Borisova, I. V. Vorob´ev, N. M. Postika, E. A. Sorokina, and A. V. Varlamov*

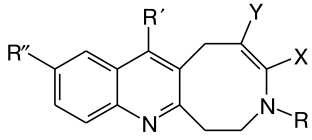
Peoples' Friendship University of Russia,
6 ul. Miklukho-Maklaya, 117198 Moscow, Russian Federation.
Fax: +7 (495) 955 0779. E-mail: lvoskressensky@sci.pfu.edu.ru

A reaction of 10-R-substituted tetrahydrobenzo[*b*][1,6]naphthyridines (R = CN, $CONH_2$, Me) with dimethyl acetylenedicarboxylate, methyl and ethyl propiolates, and acetylacetylene has been studied. It was found that 1-acryloyl-10-cyanotetrahydrobenzo[*b*][1,6]naphthyridines are the major products of the reaction of alkyl propiolates with 10-cyano-substituted naphthyridines, whereas the reaction with 10-carbamoyl-substituted naphthyridines gives a mixture of 1-acryloyl-substituted naphthyridines and hexahydrobenzo[*b*]pyrido[3,4,5-*d*,*e*][1,6]naphthyridines. The latter are the only products in the reaction of 10-carbamoyl-substituted naphthyridines with acetylacetylene.

Key words: alkynes, the Michael reaction, benzo[*b*][1,6]naphthyridines, benzo[*b*]pyrido-[3,4,5-*d*,*e*][1,6]naphthyridines.

Quinoline derivatives display a wide range of biological activity, some of them are used in medical practice.[1] Quinolines are widely spread in the nature being a structural fragment of the quinoline alkaloids family.[2] For a long time, quinolines served as the basis for the search of synthetic anti-malaria drugs. Therefore, the synthesis of new quinoline derivatives or fused heterocyclic systems containing quinoline fragment is an important synthetic and practical problem. Recently, we developed two approaches to the synthesis of pyrroloazocines and azocinoindoles from tetrahydropyrrolo[3,2-*c*]pyridines and tetrahydro-γ- and -β-carbolines upon action of activated alkynes. The first of them consists in the expansion of the tetrahydropyridine ring in the indicated above heterocycles upon action of dimethyl acetylenedicarboxylate (DMAD) or alkyl propiolates in aprotic solvents.[3—5] This method gives rather low yield of fused azocines and is limited in the type of substituents in the hydrogenated ring; in addition, when methyl substituents are present in the piperidine fragment, the process is complicated by the formation of the Hofmann degradation products.[6] The second approach is more general and promising and consists in the tandem opening of the tetrahydropyridine ring of the pyrrolopyridines and tetrahydrocarbolines with alkynes in MeOH and cyclization of the thus formed α-methoxyalkyl-β-alkoxycarbonylvinylaminoethyl-substituted pyrroles and indoles upon action of the Lewis acids into pyrroloazocines and azocinoindoles.[7] It was found that the latter are able to efficiently inhibit acetyl- and butyrylcholinesterases.[8]

It seemed reasonable to broaden this method to 10-substituted tetrahydrobenzo[*b*][1,6]naphthyridines, in which the tetrahydropyridine fragment is annulated with the electron-withdrawing quinoline. Reactions of compounds of such a type with activated alkynes have not been studied. It would have been interesting to examine the influence of electronic effects of substituents on the reaction course and to obtain new heterocyclic system, *viz.*, tetrahydroazocinoquinoline one.



However, the first experiments showed that tetrahydrobenzo[*b*][1,6]naphthyridines react with alkynes without opening and expansion of the tetrahydropyridine ring.[9,10] We conducted systematic research on the reaction of 10-substituted tetrahydronaphthyridines **1—18** with DMAD, methyl and ethyl propiolates, and acetylacetylene, the results of which are reported in the present work.

Results and Discussion

10-Carbamoyl-substituted naphthyridines **1—9** were obtained by the Pfitzinger reaction from isatins and

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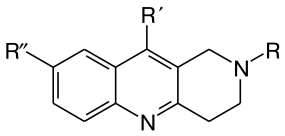
γ-piperidones in the presence of gaseous ammonia.[11] Naphthyridines **1—7** upon action of $POCl_3$ were converted into 10-cyano-substituted naphthyridines **10—16**. 10-Methyl-substituted naphthyridines **17** and **18** were synthesized from 2-aminoacetophenone and γ-piperidones according to the known procedure.[12]



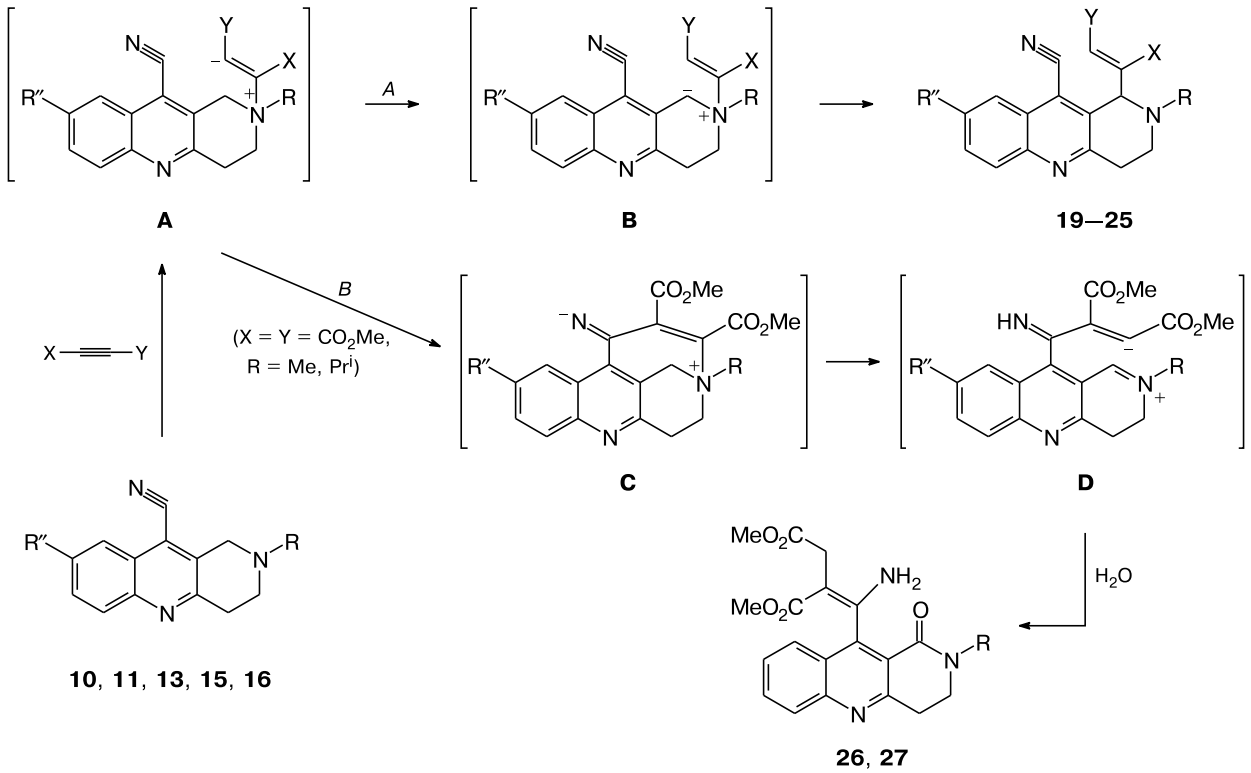
1—18

Compound	R	R′	R″	Compound	R	R′	R″
1	Me	$CONH_2$	H	**10**	Me	CN	H
2	Pr^i	$CONH_2$	H	**11**	Pr^i	CN	H
3	Bn	$CONH_2$	H	**12**	Bn	CN	H
4	Me	$CONH_2$	Br	**13**	Me	CN	Br
5	Pr^i	$CONH_2$	Br	**14**	Pr^i	CN	Br
6	Me	$CONH_2$	F	**15**	Me	CN	F
7	Pr^i	$CONH_2$	F	**16**	Pr^i	CN	F
8	Me	$CONH_2$	NO_2	**17**	Me	Me	H
9	Pr^i	$CONH_2$	NO_2	**18**	Pr^i	Me	H

Cyano-substituted naphthyridines **10**, **11**, **13**, **15**, and **16** readily react with DMAD and methyl propiolate in MeOH, as well as with ethyl propiolate in ethanol for 5—6 h at 20 °C. Acryloyl-substituted naphthyridines **19—25** are the major products of the reaction (Scheme 1). The reaction of naphthyridines **10** and **11** with DMAD, in addition to compounds **19** and **20**, gives also (1-oxonaphthyridin-10-yl)methylenesuccinates **26** and **27**.[9]

We assume that the reaction begins with the Michael addition of the tertiary amine in benzonaphthyridines **10**, **11**, **13**, **15**, and **16** to the triple bond of the alkyne. The intermediate zwitterion **A** is further transformed by two pathways, *A* and *B*. Pathway *A* is conditioned by the acidic character of the $C(1)H_2$ group and leads to ylide **B**, which by the Stevens rearrangement characteristic of ylides is transformed into acryloyl-substituted naphthyridines **19—25**. The implementation of pathway *B* is caused by the nucleophilic attack of the zwitterion at the nitrile group. The intermediate **C** that formed through imine **D** is converted into succinates **26** and **27** (see Scheme 1).

Scheme 1



A **B** **19—25** **C** **D**

10, **11**, **13**, **15**, **16**

26, **27**

Compound	R	R″	X	Y
19	Me	H	CO_2Me	CO_2Me
20	Pr^i	H	CO_2Me	CO_2Me
21	Me	H	H	CO_2Et
22	Pr^i	H	H	CO_2Et

Compound	R	R″	X	Y
23	Me	Br	H	CO_2Et
24	Pr^i	Br	H	CO_2Et
25	Pr^i	F	H	CO_2Me

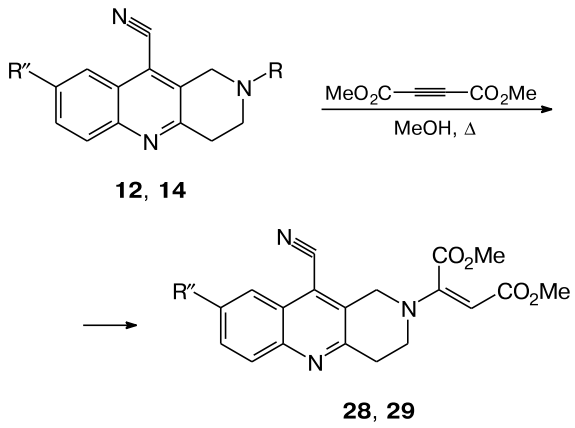
R = Me (**26**), Pr^i (**27**)

The structures of compounds **25** and **26** unambiguously were confirmed by the X-ray data.[9]

It should be noted that in all the experiments, in addition to compounds **19—25**, colored crystalline compounds were isolated by chromatography in 2—5% yield, the structures of which will be described in separate publication.

Naphthyridines **12** (R = Bn, R″ = H) and **14** (R = Pr^i, R″ = Br) do not react with DMAD in methanol at room temperature. A reflux leads to elimination of benzyl or isopropyl substituents and to formation of *N*-di(methoxycarbonyl)vinyl-substituted derivatives **28** and **29** (Scheme 2). Such an unusual behavior of compounds **12** and **14** requires additional studies.

Scheme 2



R″ = H (**28**), Br (**29**)

The *E*-configuration of the double bond in butenoates **19**, **20**, **28**, and **29** is ascribed on the basis of the literature data.[13]

The carbamoyl group in position 10 of the naphthyridines causes new directions in their tandem transformations upon action of alkynes to appear. 10-Carbamoylnaphthyridines **1—9** are insoluble in methanol, therefore, their reactions with activated alkynes were studied in a DMF—methanol mixture (5 : 1, v/v) at 50 °C. Naphthyridines **1—9** turned out to be inactive in the reaction with DMAD. After prolonged heating, only small amounts of the tar-like products were formed, while compounds **1—9** were recovered from the reaction mainly unchanged. Conversely, the terminal alkynes such as alkyl propiolates and acetylacetylene readily reacted with naphthyridines **1—9** under the conditions indicated above (Scheme 3). Naphthyridines **1**, **2**, **5**, and **9** upon action of ethyl and methyl propiolates for 1 h produce a mixture of *cis*-hexahydrobenzo[*b*]pyrido[3,4,5-*d*,*e*]-[1,6]naphthyridines *cis*-**30—33** (see Ref. 10), and *trans*-acryloylnaphthyridines *trans*-**38—40** and *trans*-**43**. Naphthyridines **4** and **7** afforded only acrylates **41** and **42**, respectively. In the case of naphthyridine **2**, *N*-ethoxycarbonylvinyl-substituted benzonaphthyridine **44**, the product of further vinylation of benzopyridonaphthyridine **31**, was also isolated in small amount (6%). Hexahydrobenzo[*b*]pyrido[3,4,5-*d*,*e*][1,6]naphthyridines **34—37**, which (excluding compound **37**) are mixtures of *cis*- and *trans*-isomers with respect to the position of protons H(3a) and H(3), were only isolated from the reaction mixtures obtained in the reactions of naphthyridines **1**, **6**, **7**, and **9** with acetylacetylene. In the case of naphthyridine **6**, in addition to product **35**, the product of its further vinylation, *viz*, benzopyridonaphthyridine **45**, was isolated in 12% yield.

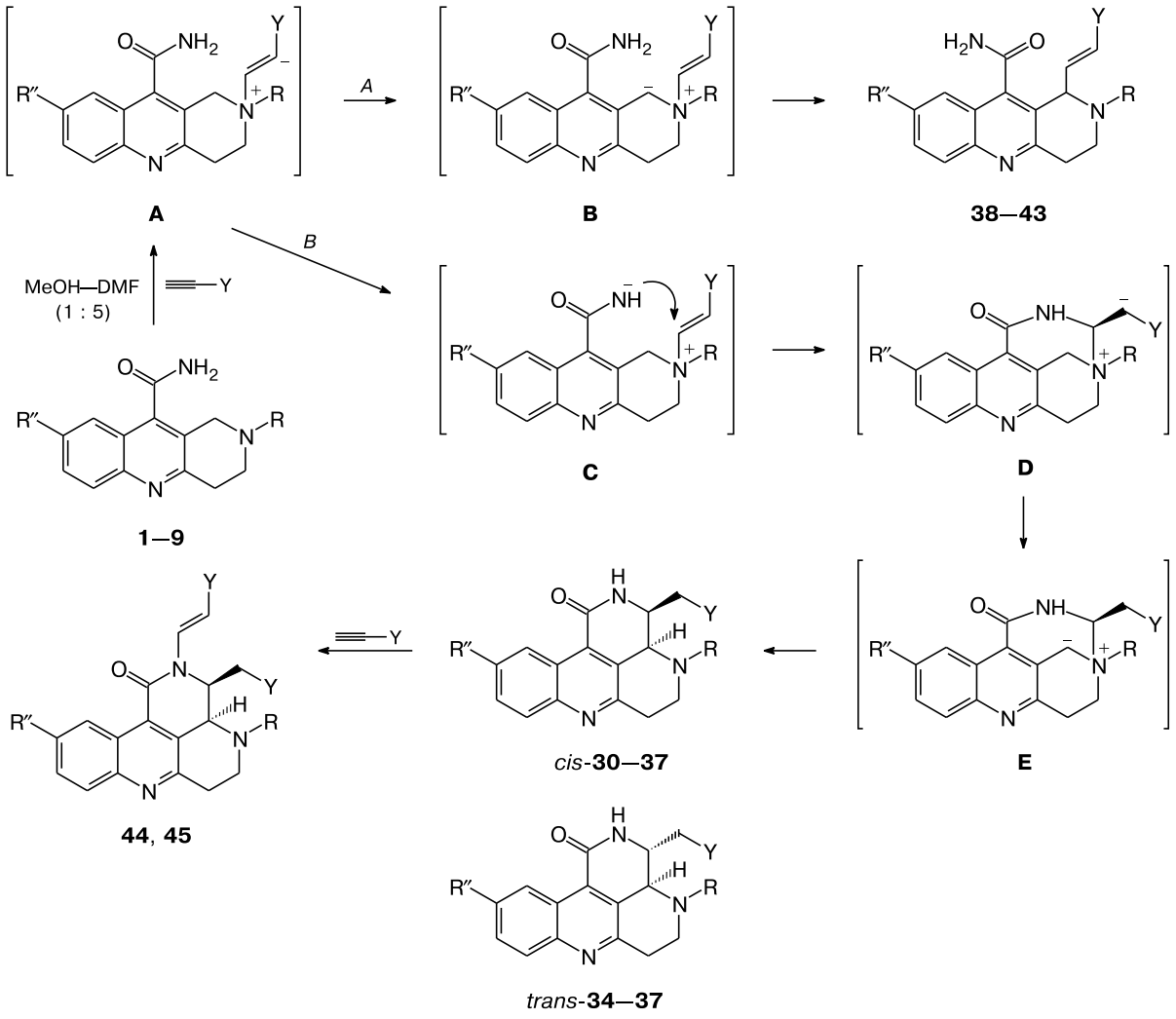
The formation of mixtures of diastereomers **34—36**, apparently, is defined by the higher electronegativity of the acetyl group (in comparison with ester group), which leads to the more planar anionic center in the original zwitterion **A** and causes formation by protonation of intermediate **C** with the *trans*- and *cis*-configuration of the acrylate fragment.

Naphthyridines **1**, **2**, **5—7**, and **9** afforded only benzopyridonaphthyridines **30—37** in 50—60% yield at 70 °C for 2.5 h.

The reaction of carbamoylnaphthyridines with alkynes begins also from the formation of zwitterion **A** (see Scheme 3). The formation of ylide **B** and the Stevens rearrangement lead to acryloyl-substituted naphthyridines **38—43**. The lower than in the case of 10-cyano-substituted naphthyridines CH-acidity of the C(1)H$_2$ group conditions the pathway of transformations *B*, which realizes through the formation of amide-anion **C**. The addition of the latter to the double bond of the acrylate fragment through the formation of zwitterion **D** and ylide **E** leads to the tetracyclic system of benzopyridonaphthyridines **30—37**. The *cis*-position of the protons in isomers of the type *cis*-**30—37** was confirmed by the X-ray data.[10] In the ^{1}H and ^{13}C NMR spectra of benzopyridonaphthyridines **30—33**, only one set of signals for each proton and carbon atom in the molecule is present. The signals for the protons H(3) and H(3a) are in the region δ 4.30—4.33 and overlap with the signals for other protons, which makes measuring of the spin-spin coupling constants difficult. However, in the ^{1}H NMR spectrum of compound **30**, a doublet for the proton H(3a) at δ 3.87 with $J_{3,3a}$ = 5.4 Hz can be observed.

In the mixtures of diastereomers **34—36**, apparently, the isomer with the *cis*-position of the protons H(3) and H(3a) is predominant (the ratio is (3 : 1)—(4 : 1)). We made this conclusion on the basis of the ^{1}H NMR spectrum of a mixture of diastereomers **34**, where the signals for the protons H(3) (δ 4.35 (major) and δ 4.17 (minor) and H(3a) (δ 4.03 (minor), $J_{3,3a}$ = 11.0 Hz and δ 3.79 (major), $J_{3,3a}$ = 5.4 Hz) were identified. In the spectra of naphthyridines **35** and **36**, the signals for the protons H(3) and H(3a) are observed as overlapping multiplets

Scheme 3



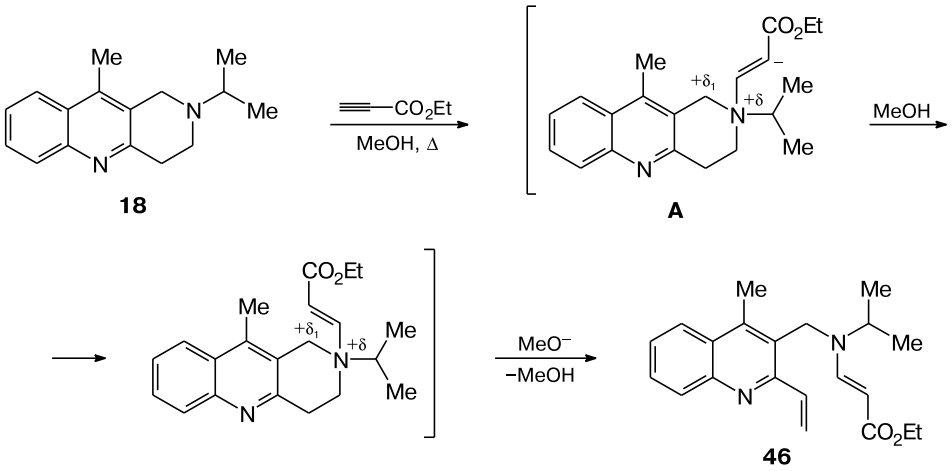
Compound	R	R″	Y	Compound	R	R″	Y	Compound	R	R″	Y
30	Me	H	CO_2Et	**36**	Pr^i	F	COMe	**42**	Pr^i	F	CO_2Me
31	Pr^i	H	CO_2Et	**37**	Pr^i	NO_2	COMe	**43**	Pr^i	NO_2	CO_2Me
32	Pr^i	Br	CO_2Et	**38**	Me	H	CO_2Et	**44**	Pr^i	H	CO_2Et
33	Pr^i	NO_2	CO_2Me	**39**	Pr^i	H	CO_2Et	**45**	Me	F	COMe
34	Me	H	COMe	**40**	Pr^i	Br	CO_2Et				
35	Me	F	COMe	**41**	Me	Br	CO_2Et				

in the region δ 4.31—4.44. According to the ^1H NMR data, the acryloyl fragment in compounds **38—43** has the *trans*-configuration, which unambiguously follows from the spin-spin coupling constant values for the olefin protons (J = 12.0—14.1 Hz).

10-Methyl-substituted tetrahydrobenzonaphthyridines **17** and **18** did not react as expected with activated alkynes even under reflux in MeOH and MeCN. Only in the case of compound **18**, the reaction with ethyl propiolate after prolonged reflux led to 2-vinylquinoline **46** in 12% yield, the product of the Hofmann degradation of the tetrahydropyridine fragment upon the action of methoxide anion (Scheme 4).

Different directions of the reactions of 10-substituted naphthyridines with alkynes, apparently, are conditioned by different acidity of the $C(1)H_2$ group (fragment $ArCH_2$—N). Calculation of charges on the C(3) atom of the 4-substituted quinolines by the Pariser—Parr—Pople method (Table 1) confirmed our suggestion. In the series of 10-CN-, 10-$CONH_2$- and 10-Me-substituted naphthyridines, CH-acidity of the methylene group in the fragment $ArCH_2$—N decreases since the electron density

Scheme 4



on the C(3) atom increases. In substituted quinolines, the introduction of electron-withdrawing substituents in position C(6) decreases the electron density on the C(3) atom.

It was shown that annulation of the tetrahydropyridine ring with electron-withdrawing heterocycle localizes a positive charge $+\delta_1$ on the C(1) atom. This causes appearance of new (as compared to the tetrahydropyridines fused with the electron-donating π-heterocycles) transformation channels, the directions of which are defined by CH-acidity of the CH_2—N group bonded to the hetaryl fragment. A considerable delocalization of the $+\delta_1$ charge decreases the reactivity of the C(1) atom with respect to nucleophiles.

Experimental

Mass spectra were recorded on a Varian MAT XL 95 mass spectrometer with direct inlet of a sample into the source of ions (70 eV). Mass spectra ESI were obtained on a Agilent 1100 Series LC/MSD Trap System VL mass spectrometer under conditions of ionization by electron cloud. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 (400 and 100 MHz) in $CDCl_3$ or DMSO with the use of solvents as the internal standards. Silufol UV-254 plates were used for thin-layer chromatography (visualization with iodine vapors). Alumina (Fluka, II degree of activity) or silica gel (Merk (230—400)) were used for column chromatography.

2-R-1,2,3,4-Tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamides 1—9 (general procedure). A mixture of corresponding isatin (68.0 mmol) and *N*-methyl-, *N*-isopropyl-, or *N*-benzylpiperidin-4-one (75.2 mmol) in ethylene glycol (200 mL) was heated for 2—3 h at 95—100 °C passing through the reaction mixture a flow of ammonia (TLC control). The reaction mixture was cooled and poured in water (200 mL). The crystals formed were recrystallized from ethanol. Physico-chemical constants and ^{1}H NMR spectra of naphthyridines **1**, **2**, and **5** were described earlier.[10]

2-Benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (3). The yield was 41%, white crystals, m.p. 181—183 °C. Found (%): C, 75.53; H, 6.23; N, 13.54. $C_{20}H_{19}N_3O$. Calculated (%): C, 75.69; H, 6.03; N, 13.24. MS ESI, *m/z*: 318 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.86 (t, 2 H, C(4)H_2, J = 5.7 Hz); 3.12 (t, 2 H, C(3)H_2, J = 5.7 Hz); 3.72 (s, 2 H, C(1)H_2); 3.75 (s, 2 H, CH_2Ph); 7.29—7.44 (m, 5 H, Ph); 7.53 (m, 1 H, H(8)); 7.68 (m, 1 H, H(7)); 7.74 (d, 1 H, H(6), J = 8.3 Hz); 7.91 (d, 1 H, H(9), J = 8.3 Hz); 7.95, 8.15 (both br.s, 1 H each, $CONH_2$).

8-Bromo-2-methyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (4). The yield was 50%, pale brown crystals, m.p. 228—230 °C. Found (%): C, 52.67; H, 4.12; N, 12.93. $C_{14}H_{14}BrN_3O$. Calculated (%): C, 52.50; H, 4.38; N, 13.13. MS ESI, *m/z*: 320 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.41 (s, 3 H, NMe); 2.78 (t, 2 H, C(4)H_2, J = 6.0 Hz); 3.11 (t, 2 H, C(3)H_2, J = 6.0 Hz);

Table 1. Calculation of electron density (*q*) on atoms C(2) and C(3) by the Pariser—Parr—Pople method in 4-R,6-R′-substituted quinolines

Quinoline		*q*		Quinoline		*q*	
4-R	6-R′	C(2)	C(3)	4-R	6-R′	C(2)	C(3)
H	H	0.126	−0.015	$CONH_2$	Cl	0.103	−0.023
Me	H	0.132	−0.134	$CONH_2$	NO_2	0.135	−0.020
$CONH_2$	H	0.116	−0.031	CN	Cl	0.097	+0.056
CN	H	0.121	+0.053	CN	NO_2	0.140	+0.060
NO_2	H	0.124	+0.043				

3.65 (s, 2 H, C(1)H_2); 7.81—7.88 (m, 3 H, H(6), H(7), H(9)); 8.05, 8.25 (both br.s, 1 H each, $CONH_2$).

8-Fluoro-2-methyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (6). The yield was 76%, pale brown crystals, m.p. 236—238 °C. Found (%): C, 65.00; H, 5.19; N, 16.53. $C_{14}H_{14}FN_3O$. Calculated (%): C, 64.86; H, 5.41; N, 16.22. MS, *m/z*: 259 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, NMe); 2.77 (t, 2 H, C(4)H_2, *J* = 5.9 Hz); 3.11 (t, 2 H, C(3)H_2, *J* = 5.9 Hz); 3.64 (s, 2 H, C(1)H_2); 7.38 (dt, 1 H, H(7), *J* = 2.8 Hz, *J* = 9.1 Hz); 7.63 (dd, 1 H, H(6), *J* = 2.9 Hz, *J* = 9.1 Hz); 7.98 (dd, 1 H, H(9), *J* = 5.8 Hz, *J* = 9.1 Hz); 8.06, 8.27 (both br.s, 1 H each, $CONH_2$).

8-Fluoro-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (7). The yield was 87%, pale brown crystals, m.p. 248—250 °C. Found (%): C, 66.73; H, 6.30; N, 14.70. $C_{16}H_{18}FN_3O$. Calculated (%): C, 66.90; H, 6.27; N, 14.63. MS, *m/z*: 287 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.06 (d, 6 H, 2 Me, *J* = 6.0 Hz); 2.87 (t, 2 H, C(4)H_2, *J* = 5.6 Hz); 2.94 (m, 1 H, C<u>H</u>Me_2); 3.08 (t, 2 H, C(3)H_2, *J* = 5.6 Hz); 3.79 (s, 2 H, C(1)H_2); 7.37 (dt, 1 H, H(7), *J* = 2.6 Hz, *J* = 9.0 Hz); 7.64 (dd, 1 H, H(6), *J* = 2.6 Hz, *J* = 9.0 Hz); 7.99 (dd, 1 H, H(9), *J* = 5.6 Hz, *J* = 9.0 Hz); 8.06, 8.26 (both br.s, 1 H each, $CONH_2$).

2-Methyl-8-nitro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (8). The yield was 25%, reddish yellow crystals, m.p. 239—240 °C. Found (%): C, 59.02; H, 4.87; N, 19.85. $C_{14}H_{14}N_4O_3$. Calculated (%): C, 58.74; H, 4.90; N, 19.58. MS ESI, *m/z*: 287 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.44 (s, 3 H, NMe); 2.82 (t, 2 H, C(4)H_2, *J* = 5.8 Hz); 3.19 (t, 2 H, C(3)H_2, *J* = 5.8 Hz); 3.79 (s, 2 H, C(1)H_2); 8.10 (d, 1 H, H(6), *J* = 9.2 Hz); 8.44 (dd, 1 H, H(7), *J* = 2.1 Hz, *J* = 9.2 Hz); 8.23, 8.37 (both br.s, 1 H each, $CONH_2$); 8.63 (d, 1 H, H(9), *J* = 2.1 Hz).

2-Isopropyl-8-nitro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (9). The yield was 43%, reddish yellow crystals, m.p. 221—223 °C. Found (%): C, 60.94; H, 5.97; N, 17.63. $C_{16}H_{18}N_4O_3$. Calculated (%): C, 61.15; H, 5.73; N, 17.83. MS ESI, *m/z:* 315 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.19 (d, 6 H, 2 Me, *J* = 6.5 Hz); 2.84 (t, 2 H, C(4)H_2, *J* = 5.7 Hz); 3.11 (m, 1 H, C<u>H</u>Me_2); 3.22 (t, 2 H, C(3)H_2, *J* = 5.7 Hz); 3.83 (s, 2 H, C(1)H_2); 8.15 (d, 1 H, H(6), *J* = 9.0 Hz); 8.26, 8.47 (both br.s, 1 H each, $CONH_2$); 8.54 (dd, 1 H, H(7), *J* = 2.3 Hz, *J* = 9.0 Hz); 8.77 (d, 1 H, H(9), *J* = 2.3 Hz).

10-Cyano-2-R-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines 10—16 (general procedure). A solution of carbamoyl-substituted naphthyridines **1—7** (6.5 mmol) in freshly distilled $POCl_3$ (25 mL) was heated for 2—4 h adding triethylamine (1 mL) every 1 h. The reaction course was monitored by TLC. The reaction mixture was poured in ice (100 g), neutralized with saturated aqueous soda, made basic with NaOH to pH 10, and extracted with ether (3×70 mL). The extract was dried with magnesium sulfate. The residue after evaporation of ether was crystallized from ethyl acetate.

10-Cyano-2-methyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (10). The yield was 44%, pale yellow crystals, m.p. 153—155 °C. Found (%): C, 75.12; H, 5.95; N, 19.00. $C_{14}H_{13}N_3$. Calculated (%): C, 75.34; H, 5.83; N, 18.83. MS, *m/z*: 223 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 3 H, NMe); 2.91 (t, 2 H, C(4)H_2, *J* = 5.9 Hz); 3.19 (t, 2 H, C(3)H_2, *J* = 5.9 Hz); 3.97 (s, 2 H, C(1)H_2); 7.65 (m, 1 H, H(8)); 7.76 (m, 1 H, H(7)); 8.06 (d, 1 H, H(6), *J* = 8.9 Hz); 8.15 (d, 1 H, H(9), *J* = 8.9 Hz).

10-Cyano-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (11). The yield was 82%, colorless crystals, m.p. 110—112 °C. Found (%): C, 76.64; H, 6.53; N, 16.55. $C_{16}H_{17}N_3$. Calculated (%): C, 76.49; H, 6.77; N, 16.73. MS, *m/z*: 251 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.20 (d, 6 H, 2 Me, *J* = 6.6 Hz); 2.99 (t, 2 H, C(4)H_2, *J* = 5.9 Hz); 3.08 (m, 1 H, C<u>H</u>Me_2); 3.28 (t, 2 H, C(3)H_2, *J* = 5.9 Hz); 4.12 (s, 2 H, C(1)H_2); 7.65 (m, 1 H, H(8)); 7.77 (dd, 1 H, H(7), *J* = 9.0 Hz, *J* = 2.3 Hz); 8.06 (d, 1 H, H(6), *J* = 9.0 Hz); 8.10 (dd, 1 H, H(9), *J* = 9.0 Hz, *J* = 2.3 Hz).

2-Benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (12). The yield was 72%, yellow crystals, m.p. 130—132 °C. Found (%): C, 80.03; H, 5.43; N, 14.20. $C_{20}H_{17}N_3$. Calculated (%): C, 80.27; H, 5.69; N, 14.05. MS, *m/z*: 299 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.94 (t, 2 H, C(4)H_2, *J* = 6.2 Hz); 3.26 (t, 2 H, C(3)H_2, *J* = 6.2 Hz); 3.79 (s, 2 H, C(1)H_2); 4.10 (s, 2 H, CH_2Ph); 7.03 (ddd, 1 H, H(7), *J* = 1.6 Hz, *J* = 7.4 Hz, *J* = 8.7 Hz); 7.29—7.44 (m, 5 H, Ph); 7.65 (ddd, 1 H, H(6), *J* = 1.6 Hz, *J* = 7.4 Hz, *J* = 8.7 Hz); 8.06 (m, 2 H, H(8), H(9)).

8-Bromo-10-cyano-2-methyl-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridine (13). The yield was 32%, orange crystals, m.p. 168—170 °C. Found (%): C, 55.78; H, 3.78; N, 14.05. $C_{14}H_{12}BrN_3$. Calculated (%): C, 55.63; H, 3.97; N, 13.91. MS, *m/z*: 301 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 3 H, NMe); 2.92 (t, 2 H, C(4)H_2, *J* = 6.1 Hz); 3.26 (t, 2 H, C(3)H_2, *J* = 6.1 Hz); 3.93 (s, 2 H, C(1)H_2); 7.03 (dd, 1 H, H(7), *J* = 8.9 Hz, *J* = 1.9 Hz); 7.92 (d, 1 H, H(6), *J* = 8.9 Hz); 8.24 (d, 1 H, H(9), *J* = 1.9 Hz).

8-Bromo-10-cyano-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridine (14). The yield was 35%, pale red crystals, m.p. 96—98 °C. Found (%): C, 58.07; H, 5.01; N, 12.92. $C_{16}H_{16}BrN_3$. Calculated (%): C, 58.18; H, 4.85; N, 12.73. MS, *m/z*: 329 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.19 (d, 6 H, 2 Me, *J* = 6.6 Hz); 2.96 (t, 2 H, C(4)H_2, *J* = 6.0 Hz); 3.08 (m, 1 H, C<u>H</u>Me_2, *J* = 6.6 Hz); 3.10 (t, 2 H, C(3)H_2, *J* = 6.0 Hz); 4.10 (s, 2 H, C(1)H_2); 7.80 (dd, 1 H, H(7), *J* = 8.8 Hz, *J* = 2.0 Hz); 7.90 (d, 1 H, H(6), *J* = 8.8 Hz); 8.24 (d, 1 H, H(9), *J* = 2.0 Hz).

10-Cyano-8-fluoro-2-methyl-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridine (15). The yield was 65%, pale yellow crystals, m.p. 127—129 °C. Found (%): C, 69.78; H, 5.06; N, 17.56. $C_{14}H_{12}FN_3$. Calculated (%): C, 69.71; H, 4.98; N, 17.43. MS, *m/z*: 241 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 3 H, NMe); 2.93 (t, 2 H, C(4)H_2, *J* = 6.1 Hz); 3.29 (t, 2 H, C(3)H_2, *J* = 6.1 Hz); 3.97 (s, 2 H, C(1)H_2); 7.51 (dt, 1 H, H(7), *J* = 8.0 Hz, *J* = 2.6 Hz); 7.71 (dd, 1 H, H(6), *J* = 8.0 Hz, *J* = 2.6 Hz); 8.08 (d, 1 H, H(9), *J* = 2.6 Hz).

10-Cyano-8-fluoro-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-[1,6]naphthyridine (16). The yield was 60%, pale brown crystals, m.p. 93—95 °C. Found (%): C, 71.20; H, 6.07; N, 15.70. $C_{16}H_{16}FN_3$. Calculated (%): C, 71.38; H, 5.95; N, 15.61. MS, *m/z*: 269 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.20 (d, 6 H, 2 Me, *J* = 6.6 Hz); 2.98 (t, 2 H, C(4)H_2, *J* = 6.0 Hz); 3.06 (m, 1 H, C<u>H</u>Me_2, *J* = 6.6 Hz); 3.24 (t, 2 H, C(3)H_2, *J* = 6.0 Hz); 4.11 (s, 2 H, C(1)H_2); 7.52 (dt, 1 H, H(7), *J* = 8.0 Hz, *J* = 2.6 Hz); 7.70 (dt, 1 H, H(6), *J* = 8.0 Hz, *J* = 2.8 Hz); 8.05 (d, 1 H, H(9), *J* = 2.8 Hz).

10-Methyl-2-R-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines 17 and 18 (general procedure). A solution of *o*-aminoacetophenone (8.0 mmol) and *N*-methyl(isopropyl)piperidin-4-one (10.1 mmol) in anhydrous ethanol (50 mL) was refluxed for 4—5 h passing through it a flow of dry hydrogen chloride. The reaction course was monitored by TLC. The reaction mixture was cooled. The crystals formed were filtered off, dissolved in saturated aqueous NaOH (10 mL), extracted with dichloromethane, and dried with magnesium sulfate. The residue left after evaporation of dichloromethane was purified on a column with alumina.

2,10-Dimethyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (17). The yield was 23%, pale yellow crystals, m.p. 98—100 °C.

Table 2. Yields, melting points, elemental analysis data, and mass spectra of naphthyridines **19—46**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula	MS, m/z ($[M]^+$)
			C	H	N		
19	16	157—158	65.75 65.50	5.22 5.30	11.61 11.50	$C_{20}H_{19}N_3O_3$	365
20	13	135—137	67.35 67.18	5.90 5.85	10.75 10.69	$C_{22}H_{23}N_3O_3$	393
21	69	148—150	70.89 71.01	5.80 5.96	13.20 13.08	$C_{19}H_{19}N_3O_2$	321
22	14	111—113	73.98 73.90	4.90 5.11	12.15 12.03	$C_{21}H_{23}N_3O_2$	363
23	39	152—154	56.81 57.00	4.71 4.50	10.32 10.50	$C_{19}H_{18}BrN_3O_2$	399*
24	40	102—103	58.53 58.80	5.00 5.14	10.05 9.81	$C_{21}H_{22}BrN_3O_2$	427*
25	21	135—137	67.83 68.00	5.84 5.67	12.00 11.90	$C_{20}H_{20}FN_3O_2$	353
26	26	235—236	62.51 62.66	5.70 5.48	12.58 12.73	$C_{20}H_{21}N_3O_5$	383
27	32	205—206	64.35 64.23	5.80 6.08	10.45 10.22	$C_{22}H_{25}N_3O_5$	411
28	47	182—184	64.91 64.96	4.90 4.84	12.03 11.97	$C_{19}H_{17}N_3O_4$	351
29	24	204—206	53.18 53.02	4.89 4.72	9.81 9.77	$C_{19}H_{16}BrN_3O_4$	430*
30	33	172—173	67.41 67.26	5.95 6.19	12.53 12.39	$C_{19}H_{21}BrN_3O_3$	339
31	20	118—120	68.51 68.66	6.90 6.81	11.32 11.44	$C_{21}H_{25}N_3O_3$	367
32	19	219—220	56.28 56.50	5.54 5.38	9.35 9.42	$C_{21}H_{24}BrN_3O_3$	445*
33	23	201—203	60.51 60.30	5.36 5.53	14.21 14.07	$C_{20}H_{22}N_4O_5$	398
34	43	171—173	69.78 69.90	6.27 6.15	13.32 13.59	$C_{18}H_{19}N_3O_2$	309
35	34	167—169	65.90 66.06	5.72 5.50	12.70 12.84	$C_{18}H_{18}FN_3O_2$	327
36	28	192—194	67.35 67.60	6.38 6.20	11.67 11.83	$C_{20}H_{22}FN_3O_2$	355
37	12	224—226	62.58 62.83	5.83 5.76	14.58 14.66	$C_{20}H_{22}N_4O_4$	382
38	28	205—207	67.48 67.26	6.25 6.19	12.18 12.39	$C_{19}H_{21}N_3O_3$	339
39	32	143—145	68.50 68.66	6.90 6.81	11.57 11.44	$C_{21}H_{25}FN_3O_3$	367
40	40	103—105	56.48 56.50	5.25 5.38	9.50 9.42	$C_{21}H_{24}BrN_3O_3$	445*
41	40	121—123	54.33 54.55	5.00 4.78	9.87 10.05	$C_{19}H_{20}BrN_3O_3$	417*
42	39	152—154	62.85 62.97	5.32 5.25	12.38 12.24	$C_{18}H_{18}FN_3O_3$	343
43	22	213—215	58.53 58.38	5.00 4.86	15.23 15.12	$C_{18}H_{18}N_4O_5$	370
44	5	118—120	67.32 67.10	6.75 6.67	8.93 9.03	$C_{26}H_{31}N_3O_5$	465
45	12	189—191	66.70 66.84	5.38 5.57	10.75 10.63	$C_{22}H_{21}FN_3O_3$	395
46	12	137—139	74.32 74.56	7.51 7.69	8.32 8.28	$C_{21}H_{26}N_2O_2$	338

* For ^{79}Br.

Table 3. ^{1}H NMR spectra of substituted naphthyridines **19—29** and **38—43**

Compound	δ(*J*/Hz)											
	H(1)	N—R	$C(3)H_2$	$C(4)H_2$	H(6)	H(7)	H(8)	H(9)	CX=CHY			10-R′
			m						X	H	Y	
19	5.28 (s)	2.60 (s, Me)	3.00—3.31		8.15 (d, *J* = 8.4)	7.60 (t, *J* = 8.4)	7.73 (t, *J* = 8.4)	8.10 (d, *J* = 8.4)	3.71 (s, MeO)	5.80 (s)	3.78 (s, MeO)	—
20	5.32 (s)	1.11, 1.14 (both d, 2 Me, *J* = 6.0); 3.39 (m, CH)	2.90—3.22		8.13 (d, *J* = 8.4)	7.67 (t, *J* = 8.4)	7.80 (d, *J* = 8.4)	8.13 (d, *J* = 8.4)	3.70 (s, MeO)	5.84 (s)	3.79 (s, MeO)	—
21	4.81 (d, *J* = 8.2)	2.57 (s, Me)	3.10—3.40		8.10 (d, *J* = 8.4)	7.60 (t, *J* = 8.4)	7.70 (t, *J* = 8.4)	7.90 (d, *J* = 8.4)	7.00 (dd, 1 H, *J* = 8.2, *J* = 15.6)	6.00 (d, *J* = 15.7)	1.28 (t, Me, *J* = 7.1); 4.20 (q, CH_2O, *J* = 7.1)	—
22	5.15 (d, *J* = 7.1)	1.12, 1.14 (both d, 2 Me, *J* = 6.1); 3.15 (m, CH)	3.15—3.35		8.05 (d, *J* = 8.7)	7.65 (t, *J* = 8.7)	7.80 (t, *J* = 8.7)	8.10 (d, *J* = 8.7)	7.05 (dd, 1 H, *J* = 7.1, *J* = 15.7)	5.95 (d, *J* = 15.7)	1.25 (t, Me, *J* = 7.2); 4.25 (t, CH_2O, *J* = 7.2)	—
23	4.81 (d, *J* = 7.0)	2.56 (s , Me)	2.90—3.40		7.93 (d, *J* = 9.0)	7.86 (dd, *J* = 7.0, *J* = 1.9)	—	8.26 (d, *J* = 1.9)	6.96 (dd, 1 H, *J* = 7.0, *J* = 15.7)	5.95 (d, *J* = 15.7)	1.28 (t, Me, *J* = 7.2); 4.20 (q, CH_2O, *J* = 7.2)	—
24	5.15 (d, *J* = 7.0)	1.17, 1.18 (both d, 2 Me, *J* = 6.3); 3.04 (m, CH)	3.09—3.40		7.94 (d, *J* = 8.9)	7.85 (dd, *J* = 8.9, *J* = 1.9)	—	8.27 (d, *J* = 1.9)	7.04 (dd, 1 H, *J* = 7.0, *J* = 15.9)	5.92 (d, *J* = 15.9)	1.27 (t, Me, *J* = 7.1); 4.16 (q, CH_2O, *J* = 7.1)	—
25	5.07 (d, *J* = 7.6)	1.10, 1.09 (both d, 2 Me, *J* = 6.4); 3.06—3.20 (m, CH)	3.05—3.39		7.83 (dd, *J* = 9.0, *J* = 2.4)	7.71 (dt, *J* = 2.4, *J* = 9.0, *J* = 5.4)	—	8.87 (dd, *J* = 2.4, *J* = 5.4)	7.01 (dd, 1 H, *J* = 7.6, *J* = 15.7)	6.01 (d, *J* = 15.7)	3.65 (s, MeO)	—
26	—	3.18 (s, Me)	3.20—3.80		8.05 (d, *J* = 8.3)	7.58 (t, *J* = 8.3)	7.69 (t, *J* = 8.3)	8.15 (d, *J* = 8.3)	—	—	—	2.60, 2.78 (both d, CH_2, *J* = 17.0); 3.40, 3.78 (both s, MeO); 6.50 (br.s, NH_2)

(*to be continued*)

Table 3 (*continued*)

Compound	δ (*J*/Hz)											
	H(1)	N—R	C(3)H$_2$	C(4)H$_2$	H(6)	H(7)	H(8)	H(9)	CX=CHY			10-R´
			m						X	H	Y	
27	—	1.20, 1.22 (both d, 2 Me, *J* = 6.8); 5.10 (m, CH)	3.21—3.22	3.60—3.40	8.0 (d, *J* = 8.1)	7.61 (t, *J* = 8.1)	7.80 (t, *J* = 8.1)	8.14 (d, *J* = 8.1)	—	—	—	2.60, 2.80 (both d, CH$_2$, *J* = 17.1); 3.35, 3.80 (both s, MeO); 6.60 (br.s, NH$_2$)
28	4.93 (s)	3.69, 3.95 (both s, MeO); 5.90 (s)	3.68—3.35		7.89 (d, *J* = 8.3)	7.54 (m)	7.65 (m)	8.00 (d, *J* = 8.4)	—	—	—	—
29	4.70 (s)	3.72, 4.00 (both s, MeO); 5.00 (s)	3.70	3.40	7.98 (d, *J* = 8.2)	7.90 (dd, *J* = 8.2, *J* = 2.1)	—	8.30 (d, *J* = 2.1)	—	—	—	—
38	4.93 (m)	2.72 (s, Me)	2.90—3.10		7.89 (d, *J* = 8.3)	7.54 (m)	7.65 (m)	8.00 (d, *J* = 8.3)	7.02 (dd, 1 H, *J* = 5.4, *J* = 15.1)	5.90 (dd, *J* = 15.1, *J* = 1.5)	1.17 (t, Me, *J* = 7.3); 4.12 (q, CH$_2$O, *J* = 7.3)	8.13, 8.45 (both NH)
39	5.00 (m)	1.05 (d, Me, *J* = 6.4); 3.20 (m, CH)	2.90—3.10		7.85 (d, *J* = 8.0)	7.59 (m)	7.74 (m)	7.94 (d, *J* = 8.2)	6.99 (dd, 1 H, *J* = 5.4, *J* = 15.4)	5.87 (dd, *J* = 15.4, *J* = 1.5)	1.17 (t, Me, *J* = 7.1); 4.06 (q, CH$_2$O, *J* = 7.1)	8.06, 8.32 (both NH)
40	5.07 (d, *J* = 5.4)	1.21, 1.23 (both d, Me, *J* = 5.4); 2.98 (sext, CH, *J* = 5.4)	3.09—3.29		7.85 (d, *J* = 9.4)	7.74 (dd, *J* = 9.4, *J* = 2.0)	—	8.05 (d, *J* = 2.0)	7.06 (dd, 1 H, *J* = 5.4, *J* = 15.4)	5.77 (d, *J* = 15.4)	1.24 (t, Me, *J* = 6.7); 4.12 (q, CH$_2$O, *J* = 6.7)	8.11, 8.32 (both NH)
41	5.07 (d, *J* = 5.4)	2.75 (s, Me)	2.09—3.29		7.85 (d, *J* = 9.4)	7.70 (dd, *J* = 9.4, *J* = 2.1)	—	8.07 (d, *J* = 2.1)	7.06 (dd, 1 H, *J* = 5.4, *J* = 15.4)	5.77 (d, *J* = 15.4)	1.24 (t, Me, *J* = 6.7); 4.12 (q, CH$_2$O, *J* = 6.7)	8.11, 8.32 (NH)
42	5.07 (d, *J* = 5.4)	1.09, 1.10 (both d, 2 Me, *J* = 6.4); 3.05—3.15 (m, CH)	3.30—3.39		7.71 (dd, *J* = 9.0, *J* = 2.4)	7.83 (dt, *J* = 9.0, *J* = 2.4)	—	8.87 (d, *J* = 2.0)	7.01 (dd, 1 H, *J* = 15.7, *J* = 7.6)	6.01 (d, *J* = 15.7)	3.51 (s, MeO)	8.11, 8.32 (both NH)
43	5.00 (d, *J* = 5.3)	1.19, 1.23 (both d, Me, *J* = 5.6); 3.02 (sext, CH, *J* = 5.6)	2.90—3.40		7.86 (d, *J* = 8.7)	7.93 (d, *J* = 8.7)	—	8.44 (br.s)	7.01 (dd, 1 H, *J* = 13.7, *J* = 5.3)	5.77 (d, *J* = 13.7)	3.61 (s, MeO)	8.02, 8.12 (both NH)

Table 4. ^{1}H NMR spectra of compounds **30—37**, **44**, and **45**

Compound	δ (*J*/Hz)												Ratio
	H(3)	H(3a)	CH_2Y		N(4)R	$C(5)H_2$		$C(6)H_2$	H(8)	H(9)	H(10)	H(11)	N(2)R	
			CH_2	Y										
30	4.35 (m)	3.87 (d, *J* = 5.4)	2.16 (m)	1.20 (t, $OCH_2\underline{Me}$, *J* = 7.3); 4.10 (q, $OC\underline{H}_2Me$, *J* = 7.3)	2.49 (s, Me)		3.24 (m)		8.03 (d, *J* = 8.3)	7.71 (dd, *J* = 8.3, *J* = 8.6)	7.59 (dd, *J* = 8.3, *J* = 8.6)	9.26 (d, *J* = 8.6)	6.72 (d, NH, *J* = 5.7)	—
31	4.33 (m)	4.33 (m)	2.10 (dd, *J* = 18.0, *J* = 10.9); 2.63 (m)	1.21 (t, $OCH_2\underline{Me}$, *J* = 7.2); 4.09 (q, $OC\underline{H}_2Me$, *J* = 7.2)	1.08, 1.21 (both d, Me, *J* = 6.3); 3.03—3.13 (m, $C\underline{H}Me_2$)	2.63 (m)	3.03—3.13 (m)		8.00 (d, *J* = 8.4)	7.70 (t)	7.58 (t)	9.25 (d, *J* = 8.5)	7.05 (d, NH, *J* = 4.2)	—
32	4.30—4.33 (m)		2.11 (dd, *J* = 17.6, *J* = 10.7); 2.62 (m)	1.23 (t, $OCH_2\underline{Me}$, *J* = 7.3); 4.13 (q, $OC\underline{H}_2Me$, *J* = 7.3)	1.07, 1.21 (both d, Me, *J* = 6.7); 3.16 (m, $C\underline{H}Me_2$)	2.62 (m)	3.16—3.30 (m)		7.88 (d, *J* = 8.7)	7.76 (dd, *J* = 8.7, *J* = 2.0)	—	9.48 (d, *J* = 2.0)	6.70 (d, NH, *J* = 5.4)	—
33	4.57 (m)		2.13 (dd, *J* = 17.3, *J* = 1.7); 2.68 (dd, *J* = 17.3, *J* = 2.8)	3.32 (s, CO_2Me)	1.07, 1.22 (both d, Me, *J* = 6.0); 3.17 (sext, $C\underline{H}Me_2$)	2.68 (d, *J* = 1.68)		3.11 (d, *J* = 8.8)	8.11 (d, *J* = 8.7)	8.42 (dd, *J* = 8.7, *J* = 2.7)	—	10.3 (d, *J* = 2.7)	7.11 (br.s, NH)	—
34[a]	4.35 (m)	3.79 (d, *J* = 5.4)	2.73—2.86 (m)	2.05 (s, MeCO)	2.42 (s, Me)	2.73—2.86 (m, 1 H)		3.02—3.41 (m, 3 H)	7.68 (m)	8.00 (d, *J* = 8.3)	7.56 (m)	9.27 (d, *J* = 8.6)	7.05 (br.s, NH)	4
34[b]	4.17 (m)	4.03 (d, *J* = 11.0)	2.73—2.86 (m)	2.00 (s, (MeCO)	2.28 (s, Me)	2.73—2.86 (m, 1 H)		3.02—3.41 (m, 3 H)	7.68 (m)	7.92 (d, *J* = 7.9)	7.56 (m)	9.34 (d, *J* = 9.3)	7.40 (br.s, NH)	1
35[a]	4.40 (m)	3.84 (d, *J* = 5.8)	2.34—2.40, 2.75—2.95 (both m)	2.12 (s, MeCO)	2.48 (s, Me)	2.75—2.95 (m, 1 H)		3.10—3.50 (m, 3 H)	8.05 (m)	7.52 (m)	—	9.06 (m)	6.96 (br.s, NH)	3
35[b]	4.21 (m)	4.04 (d, *J* = 12.4)	2.34—2.40, 2.75—2.95 (both m)	2.00 (s, MeCO)	2.40 (s, Me)	2.75—2.95 (m, 1 H)		3.10—3.50 (m, 3 H)	8.05 (m)	7.52 (m)	—	9.06 (m)	7.26 (br.s, NH)	1

(*to be continued*)

Table 4 (*continued*)

Compound	δ (*J*/Hz)												Ratio
	H(3)	H(3a)	CH_2Y		N(4)R	$C(5)H_2$	$C(6)H_2$	H(8)	H(9)	H(10)	H(11)	N(2)R	
			CH_2	Y									
36	4.38 (m)	4.32 (m)	2.35 (dd, *J* = 10.5, *J* = 18.9); 2.75 (dd, *J* = 1.9, *J* = 18.9)	2.07 (s, MeCO)	1.03, 1.21 (both d, Me, *J* = 6.5); 3.07 (sext, C<u>H</u>Me_2, *J* = 6.5)	2.62, 3.30 (both m)	3.19 (m)	8.00 (dd, *J* = 9.3, *J* = 5.7)	7.48 (ddd, *J* = 2.9, *J* = 9.3, *J* = 7.8)	—	8.99 (dd, *J* = 2.9, *J* = 11.3)	6.67 (d, *J* = 5.4)	—
37	4.44 (m)	4.34 (m)	2.79 (dd, *J* = 18.8, *J* = 1.8); 2.98 (dd, *J* = 18.8, *J* = 10.7)	2.68 (s, MeCO)	1.01, 1.21 (both d, Me, *J* = 6.0); 3.08 (sext, C<u>H</u>Me_2, *J* = 6.0)	3.01—3.35 (m)		8.44 (dd, *J* = 9.4, *J* = 5.6)	7.51 (dd, *J* = 9.4, *J* = 2.7)	—	10.3 (dd, *J* = 2.7, *J* = 11.3)	6.74 (d, *J* = 6.0)	—
44	4.45 (m)	4.28 (s)	2.20 (m)	1.21 (t, OCH_2<u>Me</u>, *J* = 7.3); 4.15 (m, OC<u>H_2</u>Me)	1.05, 1.21 (both d, Me, *J* = 6.0); 3.10 (sext, C<u>H</u>Me_2, *J* = 6.0)	3.12—3.35 (m)		8.05 (d, *J* = 8.05)	7.75 (dd, *J* = 6.7, *J* = 8.0)	7.62 (dd, *J* = 8.0, *J* = 15.4)	9.05 (d, *J* = 8.7)	5.81, 8.71 (оба d, CH=, *J* = 14.5); 1.32 (t, OCH_2<u>Me</u>, *J* = 7.3); 4.15 (m, OC<u>H_2</u>Me)	—
45	4.42 (m)	4.31 (s)	2.78 (dd, *J* = 17.9, *J* = 1.9); 3.01 (dd, *J* = 17.9, *J* = 10.7)	2.12 (s, MeCO)	2.43 (s, Me)	3.16—3.30 (m)		8.12 (dd, *J* = 9.5, *J* = 5.7)	7.58 (ddd, *J* = 9.5, *J* = 7.8, *J* = 2.8)	—	9.01 (d, *J* = 2.8, *J* = 11.3)	5.75, 8.60 (both d, CH=, *J* = 14.8); 2.25 (s, MeCO)	—

[a] Major isomer.
[b] Minor isomer, is formed in lesser amount.

Found (%): C, 79.15; H, 7.67; N, 13.03. $C_{14}H_{16}N_2$. Calculated (%): C, 79.25; H, 7.55; N, 13.21. MS, *m/z*: 212 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.52 (s, 3 H, NMe); 2.57 (s, 3 H, 10-Me); 2.87 (t, 2 H, C(4)H_2, *J* = 5.9 Hz); 3.30 (t, 2 H, C(3)H_2, *J* = 5.9 Hz); 3.76 (s, 2 H, C(1)H_2); 7.46 (t, 1 H, H(7), *J* = 7.9 Hz); 7.68 (t, 1 H, H(8), *J* = 7.9 Hz); 7.98 (d, 2 H, H(6), H(9)).

2-Isopropyl-10-methyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (18). The yield was 50%, pale brown crystals, m.p. 100—102 °C. Found (%): C, 79.73; H, 8.20; N, 11.93. $C_{16}H_{20}N_2$. Calculated (%): C, 80.00; H, 8.33; N, 11.67. MS, *m/z*: 240 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.21 (d, 6 H, 2 Me, *J* = 6.5 Hz); 2.54 (s, 3 H, C(10)H_3); 2.91 (t, 2 H, C(4)H_2, *J* = 5.7 Hz); 3.07 (sept, 1 H, C<u>H</u>Me_2, *J* = 6.5 Hz); 3.22 (t, 2 H, C(3)H_2, *J* = 5.7 Hz); 3.92 (s, 2 H, C(1)H_2); 7.49 (t, 1 H, H(7), *J* = 8.1 Hz); 7.61 (t, 1 H, H(8), *J* = 8.1 Hz); 7.96 (d, 1 H, H(9), *J* = 8.1 Hz); 7.98 (d, 1 H, H(6)).

The reaction of 10-carbamoyl- and 10-cyanotetrahydrobenzo[*b*][1,6]naphthyridines with activated alkynes (general procedure). Methyl and ethyl propiolates or acetylacetylene (2.5 mmol) were added to a solution of 10-carbamoylnaphthyridines **1—9** (2.1 mmol) in methanol—DMF (1 : 5) (20 mL) or 10-cyanonaphthyridines **10—16** in anhydrous methanol (15 mL). The reaction mixture was stirred for 2—12 h at room temperature. The reaction course was monitored by TLC. The solvents were evaporated *in vacuo*. The residue was chromatographed on alumina. Alkyl {[3*S**,3a*R**-4-methyl(isopropyl)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]pyrido[3,4,5-*d*,*e*][1,6]naphthiridin-3-yl]}acetates **30—33** were eluted first (ethyl acetate—hexane, 1 : 10) out of products of the reaction of compounds **1—9** with alkyl propiolates, alkyl naphthiridylacrylates **38—43** were eluted second with hexane—ethyl acetate (2 : 1). In the case of reaction with acetylacetylene, *N*-methoxycarbonylvinyl-(oxopropenyl)benzopyridonaphthyridines **44** and **45** were eluted first, whereas benzopyridonaphthyridines **34—37** were eluted second.

Alkyl (2*E*)-3-[2-methyl(isopropyl)-10-cyano-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthiridin-1-yl]acrylates **21—25** were obtained from compounds **10—16**. The reaction mixture of naphthyridines **10** and **11** with DMAD, after evaporation of methanol, was chromatographed on alumina (ethyl acetate—hexane, 1 : 2) successively eluting enedioates **19** and **20** and methylenesuccinates **26** and **27**. Dimethyl 2-(1,6-naphthiridin-2-yl)but-2-enedioates **28** and **29** precipitated from the reaction mixture on cooling. The yields and physico-chemical constants of compounds synthesized are given in Table 2, ^{1}H NMR spectroscopic data in Tables 3 and 4.

Ethyl (*E*)-3-{*N*-isopropyl-*N*-[(4-methyl-2-vinylquinolin-3-yl)methyl]amino}acrylate (46). A solution of 10-methylnaphthyridine **18** (0.5 g, 0.2 mmol) and ethyl propiolate (0.29 g, 0.3 mmol) in anhydrous methanol (30 mL) was refluxed for 25 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on alumina (ethyl acetate—hexane, 1 : 10) to give acrylate **46** (40 mg, 6%). Physico-chemical constants and elemental analysis data are given in Table 2. ^{1}H NMR, δ: 1.08—1.14 (m, 9 H, <u>Me</u>CH_2, <u>Me</u>$_2$CH); 2.64 (s, 3 H, 4-Me); 3.21 (m, 1 H, C<u>H</u>Me_2); 3.97 (q, 2 H, C<u>H</u>$_2$Me); 4.57 (s, 2 H, NCH_2); 4.91 (d, 1 H, CH=, *J* = 11.8 Hz); 5.58 (dd, 1 H, CH_2=, *J* = 10.6 Hz, *J* = 2.4 Hz); 6.50 (dd, 1 H, CH_2=, *J* = 16.6 Hz, *J* = 2.4 Hz); 7.03 (dd, 1 H, CH=, *J* = 10.6 Hz, *J* = 16.6 Hz); 7.34 (d, 1 H, N—CH=, *J* = 11.8 Hz); 7.60 (dd, 1 H, H(6), *J* = 8.4 Hz, *J* = 7.3 Hz); 7.75 (dd, 1 H, H(7), *J* = 8.4 Hz, *J* = 7.3 Hz); 7.99 (d, 1 H, H(5), *J* = 8.4 Hz); 8.15 (d, 1 H, H(8), *J* = 7.3 Hz). MS, *m/z* (I_{rel} (%)): 338 $[M]^+$ (3), 323 (5), 293 (15), 265 (15), 238 (100), 223 (20), 182 (56), 167 (42).

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