Synthesis of derivatives of a new heterocyclic system, indolo[2,3-*f*][1,7]naphthyridine

*N. A. Rastorgueva, S. Yu. Ryabova, E. A. Lisitsa, L. M. Alekseeva, and V. G. Granik**

Federal State Unitary Enterprise State Scientific Center "Scientific Research Institute of Organic Intermediates and Dyes", 1, building 4 ul. Bolshaya Sadovaya, 123995 Moscow, Russian Federation. Fax: +7 (095) 254 6574. E-mail: vggranik@mail.ru

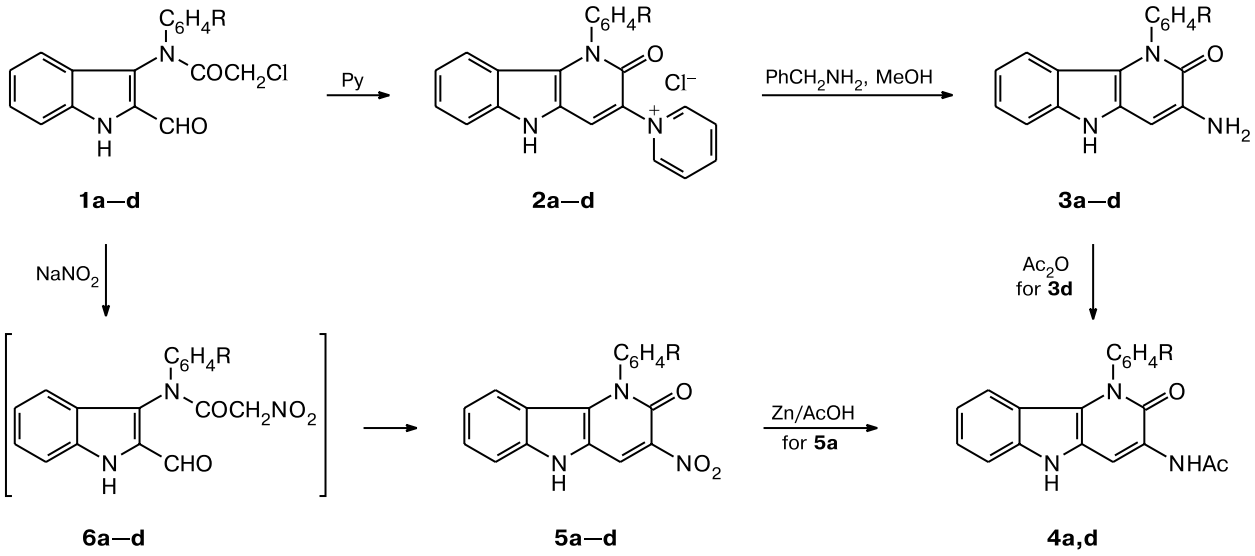
3-(*N*′-Aryl-*N*′-chloroacetyl)amino-2-formylindoles were converted into 3-amino-1-aryl-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles, which were used to synthesize derivatives of a new heterocyclic system, namely, indolo[2,3-*f*][1,7]naphthyridine. The structures of the resulting compounds were proved by IR and ^{1}H NMR spectroscopy and mass spectrometry.

Key words: 3-(*N*′-aryl-*N*′-chloroacetyl)amino-2-formylindoles, pyrido[3,2-*b*]indoles, indolo[2,3-*f*][1,7]naphthyridines, functionalization.

Known highly efficient drugs include a group of compounds that belong to the β- and γ-carboline series (incazan, carbidine, dimebon, diazoline).[1] However, the chemistry and biology of substituted pyrido[3,2-*b*]indoles has not been adequately studied. Recently,[2] we developed a new approach to the synthesis of previously inaccessible 3-amino derivative of pyrido[3,2-*b*]indole. The present study was focused on extending this approach to the synthesis of other 3-amino-1-arylpyrido[3,2-*b*]indoles and using the resulting compounds for the preparation of annelated heterocycles.

3-(*N*′-Aryl-*N*′-chloroacetyl)amino-2-formylindoles **1a—d** were used as the key compounds.[3,4] It was found that irrespective of the substituent in the aryl fragment, these compounds react with pyridine with cyclization leading smoothly not only to known[2] compound **2a** but also to other (1-aryl-2-oxo-1,2-dihydropyrido[3,2-*b*]indol-3-yl)pyridinium chlorides **2b—d** (Scheme 1). Without further purification, chlorides **2a—d** were treated with benzylamine in methanol at reflux. This resulted in opening of the pyridinium ring followed by complete degradation of the azapolyene fragment (these processes were

Scheme 1



R = H (**a**), 4-Cl (**b**), 4-OEt (**c**), 4-NO_2 (**d**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2036—2042, October, 2003.

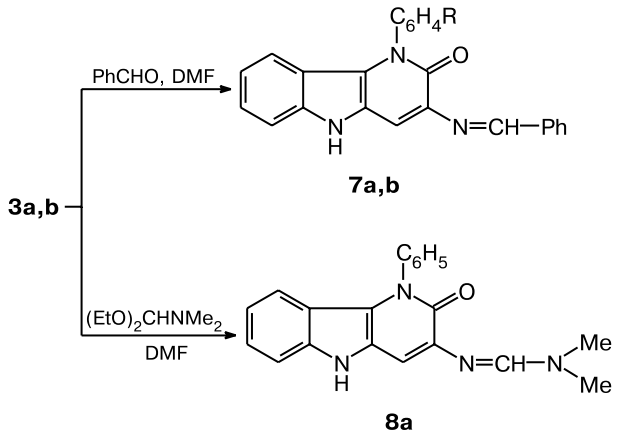
1066-5285/03/5210-2149 $25.00

described in detail for another system, 1-(3-cyano-5-nitropyridin-2-yl)pyridinium chloride[5]) giving rise to amino derivatives **3a** [2] and **3b—d**. Compounds **3a,d** were also characterized as acetyl derivatives **4a,d**.

An alternative approach developed to synthesize 3-aminopyrido[3,2-*b*]indole derivatives involves the reaction of chloroacyl derivatives **1a—d** with sodium nitrite to yield 1-aryl-3-nitro-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles (**5a—d**), which are subsequently subjected to reduction. As in the case of reaction with pyridine, the intermediate ω-nitro-substituted compounds **6a—d** cyclize as early as during the reaction to afford pyrido[3,2-*b*]indoles **5a—d**. It is noteworthy that the presence of the electron-withdrawing nitro group in the pyridone ring induces a substantial downfield shift of the H(4) signal in the ^{1}H NMR spectrum (the positions of this signal for the nitro and amino derivatives differ by $\Delta\delta \approx 2$). The reduction of nitro derivative **5a** with zinc in acetic acid was shown to lead smoothly to the previously described acylamine **4a**.[2]

The amino group in pyrido[3,2-*b*]indoles **3a—d** occupies position 3 of the pyridine ring and, hence, it participates rather easily in reactions with electrophilic reagents. Indeed, treatment of compounds **3a,b** with benzaldehyde yields Schiff´s bases **7a,b**, while condensation of **3a** with dimethylformamide diethyl acetal results in amidine **8a** (Scheme 2).

Scheme 2

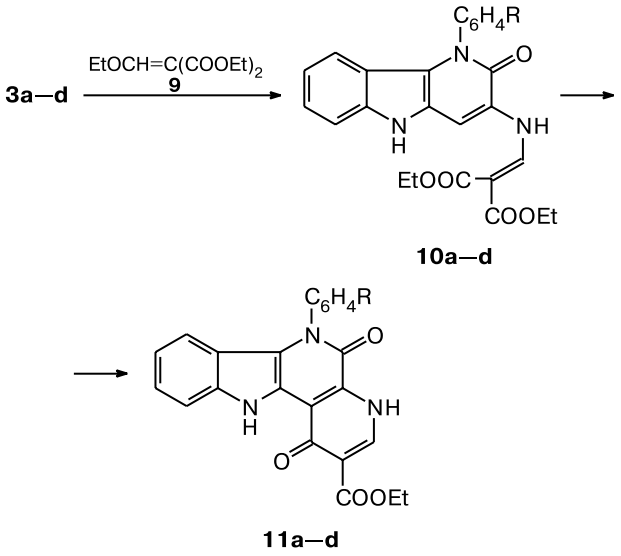


R = H (**a**), 4-Cl (**b**)

In order to prepare angular polyannelated heterocycles, the synthesized aminopyrido[3,2-*b*]indoles were introduced in the condensation reaction with diethyl ethoxymethylenemalonate (**9**). It is known that the reaction of aromatic or heteroaromatic amine with this reagent is the first stage in the synthesis of a vast group of medical preparations, namely, quinolonecarboxylic acids exhibiting a high antibacterial activity, for example, oxolinic and nalidixic acids and numerous fluoroquinolonecarboxylic acids.[6,7]

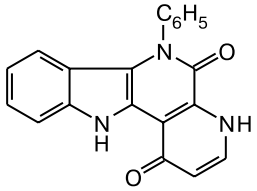
The reaction of 3-aminopyrido[3,2-*b*]indoles **3a—d** with ester **9** smoothly afforded the corresponding enamines **10a—d** in good yields. The intramolecular cyclization of compounds of this type requires fairly drastic conditions (heating in diphenyl at 270 °C)[7,8] (Scheme 3). Under similar conditions, we synthesized derivatives of a new heterocyclic system, namely ethyl 6-aryl-1,5-dioxo-4,5,6,11-tetrahydro-1*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylates (**11a—d**).

Scheme 3



R = H (**a**), 4-Cl (**b**), 4-OEt (**c**), 4-NO_2 (**d**)

It is worth noting that cyclization of enamine **10a** is accompanied by partial decarbethoxylation of the resulting ester **11a**, apparently, through the attack of the ester carbonyl by the alcohol molecule liberated upon cyclization. This yields target tetracyclic ester **11a** with an admixture of 1,5-dioxo-6-phenyl-4,5,6,11-tetrahydro-1*H*-indolo[2,3-*f*][1,7]naphthyridine (**12**) (minor product). The composition of the mixture was derived from examination of the ^{1}H NMR spectrum of the crude product. The spectrum (DMSO-d_6) exhibits signals for **11a** (δ): 1.35 (t, 3 H, $COOCH_2\underline{CH_3}$); 4.30 (q, 2 H, $COO\underline{CH_2}CH_3$, J = 7.0 Hz); 5.93 (d, 1 H, H(7), $J_{7,8}$ = 8.2 Hz); 6.74 (t, 1 H, H(8), $J_{8,7} = J_{8,9}$ = 8.2 Hz); 7.17 (t, 1 H, H(9), $J_{9,8} = J_{9,10}$ = 8.2 Hz); 7.57—8.43 (m, 6 H, H(10), Ph); 8.43 (s, 1 H, H(3)); 11.97 (br.s, 1 H, N(4)H); 12.53 (br.s, 1 H, N(11)H); and **12**: 6.45 (d, 1 H, H(2), $J_{2,3}$ = 8.2 Hz); 11.75 (br.s, 1 H, N(4)H); 12.10 (br.s, 1 H, N(11)H). The other proton signals of compound **12** coincide with those of compound **11a**, while the signal for the

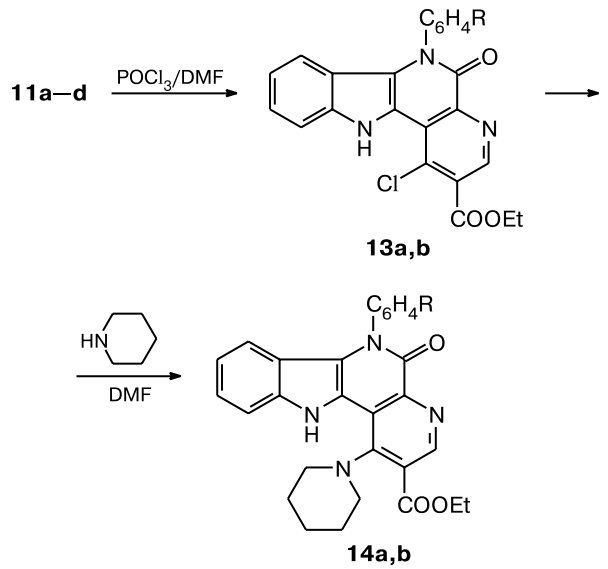


12

H(3) proton of compound **12** falls in the region containing the signals from the aromatic protons of the benzene ring (δ 7.57—8.43). The ratio of compounds in the mixture (5 : 1) was determined from the intensity of the N(11)H signals.

A similar cyclization of compounds **10b—d** can be carried out with retention of the ethoxycarbonyl group in position 2; in this case, the reaction furnishes tetracyclic esters **11b—d**, which are individual compounds according to spectral characteristics. It is difficult to purify these products by recrystallization, and only compounds **11c,d** have been obtained in an analytically pure state (Tables 2—4, Experimental). Therefore, further evidence for the structure of indolonaphthyridines **11a,b** was gained from their subsequent transformations. The corresponding 1-chloro derivatives were prepared by the reactions of **11a,b** with the Vilsmeier reagent;[9] this gave rise to ethyl 6-aryl-1-chloro-5-oxo-5,6-dihydro-11*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylates (**13a,b**) (Scheme 4). The structure of these compounds can be unambiguously deduced from the data of ^{1}H NMR and IR spectroscopy and mass spectrometry (see Experimental), although we were unable to prepare them as analytically pure products. The chlorine atom in compounds **13a,b** is rather active, which creates conditions for the synthesis and biological study of functionally substituted indolonaphthyridines. For example, treatment of compounds **13a,b** with piperidine in DMF furnished ethyl 6-aryl-5-oxo-1-piperidino-5,6-dihydro-11*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylates (**14a,b**), which were characterized by spectral data and elemental analysis.

Scheme 4



R = H (**a**), 4-Cl (**b**), 4-OEt (**c**), 4-NO_2 (**d**)

Thus, this study presents the synthesis of previously inaccessible 1-aryl-3-amino- and 3-nitropyrido[3,2-*b*]indoles. We synthesized representatives of a new heterocyclic system, indolo[2,3-*f*][1,7]naphthyridine, and created the grounds for preparing its functionally substituted derivatives that present interest for synthetic, physicochemical, and biological research.

Experimental

The IR spectra of compounds were measured on a Perkin-Elmer 457 instrument in mineral oil. Mass spectra were recorded on a JSQ-900 mass spectrometer with direct sample injection into the ion source. ^{1}H NMR spectra were run on a Bruker AC-200 spectrometer in DMSO-d_6. The reactions were monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates using a 10 : 1 chloroform—methanol (for compounds **2b—d**, **3b—d**, **4d**, **5a—d**, **8a**, **10a—d**, **11a,b**, **13a,b**, and **14a,b**), a 5 : 3 : 1 ethyl acetate—propan-2-ol—ammonia system (for compound **7a,b**, **11c**), and chloroform (for compound **11d**) as eluents. The ^{1}H NMR spectra of compounds **2d**, **3b—d**, **4d**, **5a—d**, **7a,b**, **8a**, and **10a—d** are presented in Table 1, those of compounds **11b—d**, **13a,b**, and **14a,b** are listed in Table 2. The physicochemical characteristics and the yields of compounds **3b—d**, **4d**, **5a—d**, **7a,b**, **8a**, **10a—d**, **11c,d**, and **14a,b** are presented in Table 3 and the spectral characteristics of these compounds are in Table 4. Compounds **1a,b**,[3,4] **1c,d**,[4] **2a**, **3a**, and **4a** [2] were described in our previous study.

3-Amino-1-aryl-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles 3b—d (general procedure). A mixture of aldehyde **1b—d** (8 mmol) and pyridine (19 mL) was stirred at a temperature of 20 °C (see Ref. 2) to give (1-aryl-2-oxo-1,2-dihydropyrido[3,2-*b*]indol-3-yl)pyridinium chlorides **2b—d**: 3.19 g (98%) of salt **2b**, m.p. 252—254 °C; 2.85 g (84%) of salt **2c,** m.p. ~300 °C; or 3.06 g (90%) of salt **2d**, m.p. ~300 °C. IR, ν/cm^{-1}: 1638 (CO), 3562, 3112, 3068 (NH).

Then benzylamine (1.25 mL, 6 mmol) was added to a solution of 2 mmol of the corresponding salt **2b—d** in 30 mL of methanol and the mixture was refluxed for 3 h and cooled. The precipitate was filtered off and washed with methanol to give 0.62 g of compound **3b**, 0.86 g of compound **3c,** and 0.53 g of compound **3d**.

3-Acetylamino-2-oxo-1-phenyl-1,2-dihydropyrido[3,2-*b*]indole (4a). A suspension of compound **5a** (0.23 g, 0.75 mmol) in 7 mL of AcOH was heated to boiling with stirring, zinc dust (0.24 g, 3.8 mmol) was added in portions, and the mixture was refluxed for 2 h and cooled. The precipitate was filtered off, washed with water, and dried to give 0.21 g (74%) of monoacetyl derivative **4a**, m.p. 356—358 °C (Ref. 2: m.p. 358—360 °C). IR, ν/cm^{-1}: 1675 (CO), 3273, 3223 (NH).

3-Acetylamino-1-(4-nitrophenyl)-2-oxo-1,2-dihydropyrido[3,2-*b*]indole (4d). A suspension (0.1 g, 0.3 mmol) of 3-amino derivatives **3d** in 2 mL of Ac_2O was stirred for 18 h at 20 °C. The precipitate was filtered off and washed with Ac_2O and ether to give 0.1 g of compound **4d**.

1-Aryl-3-nitro-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles 5a—d (general procedure). Sodium nitrite (0.12 g, 1.7 mmol), potassium iodide (0.17 g, 1 mmol), and 3 drops of triethylamine were added to a solution of aldehyde **1a—d** in 6 mL of ethyl acetate.

Table 1. ^{1}H NMR spectra of 3-substituted 1-aryl-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles **3b—d**, **4d**, **5a—d**, **7a,b**, **8a**, and **10a—d**

Compound	δ, *J*/Hz							
	H(4), s	N(5)H, br.s	H(6), d, $J_{6,7}$ = 8.2	H(7), t, $J_{7,6}$ = $J_{7,8}$ = 8.2	H(8), t, $J_{8,7}$ = $J_{8,9}$ = 8.2	H(9), d, $J_{9,8}$ = 8.2	C_6H_4—R	Other signals
3b	6.96	10.91	7.29	6.96	6.67	6.02	7.44, 7.65 (both m, 4 H, C_6H_4Cl)	5.22 (br.s, 2 H, NH_2)
3c	7.00	11.02	7.36	7.04	6.73	6.02	1.46 (t, 3 H, OCH_2Me, *J* = 7.0); 4.21 (d, 2 H, OCH_2Me, *J* = 7.0); 7.19, 7.36 (both m, 4 H, C_6H_4OEt)	5.41 (br.s, 2 H, NH_2)
3d	6.98	11.13	7.34	7.00	6.70	6.00	7.79, 8.49 (both m, 4 H, $C_6H_4NO_2$)	5.48 (br.s, 2 H, NH_2)
4d	8.85	11.51	7.45	7.17	6.77	6.10	7.86, 8.52 (both m, 4 H, $C_6H_4NO_2$)	2.20 (s, 3 H, NHCOMe); 9.36 (br.s, 1 H, NHCOMe)
5a	8.87	11.84	*	7.36	6.81	5.97	7.50—7.70 (both m, 6 H, H(6), Ph)	—
5b	8.96	11.85	7.58	7.41	6.91	6.12	7.62, 7.80 (both m, 4 H, C_6H_4Cl)	—
5c	8.87	11.80	7.55	7.38	6.87	6.10	7.20, 7.55 (both m, 4 H, C_6H_4OEt)	—
5d	8.95	11.90	7.58	7.41	6.87	6.13	7.91, 8.55 (both m, 4 H, $C_6H_4NO_2$)	—
7a	7.85	11.52	7.47	7.20	6.75	5.96	7.53, 7.70 (both m, 5 H, Ph)	7.53, 7.92 (m, 5 H, N=CHPh); 9.40 (s, 1 H, N=CH Ph)
7b	7.84	11.47	*	7.22	6.83	6.14	7.56, 7.74 (both m, 4 H, C_6H_4Cl)	7.53, 7.92 (m, 5 H, N=CHPh); 9.39 (s, 1 H, N=CH Ph)
8a	7.27	11.17	7.37	7.07	6.67	5.89	7.42, 7.64 (both m, 5 H, Ph)	2.96 (s, 6 H, $N=CHN(Me)_2$); 8.50 (s, 1 H, $N=CHN(Me)_2$)
10a	8.02	11.46	7.46	7.17	6.75	5.95	7.49, 7.68 (both m, 5 H, Ph)	1.26, 1.29 (both t, 3 H each, $(COOCH_2Me)_2$, *J* = 7.0); 4.19 (m, 4 H, $(COOCH_2Me)_2$); 8.58 (d, 1 H, CH=, *J* = 11.2); 11.04 (d, 1 H, NH)
10b	8.03	11.51	7.48	7.20	6.83	6.10	7.58 (m, 2 H, H(3′)H(5′)); 7.76 (m, 2 H, H(2′), H(6′))	1.26, 1.29 (both t, 3 H each, $(COOCH_2Me)_2$, *J* = 7.0); 4.20 (m, 4 H, $(COOCH_2Me)_2$); 8.59 (d, 1 H, CH=, *J* = 11.2); 11.04 (d, 1 H, NH)
10c	8.01	11.45	7.47	7.19	6.80	6.10	1.42 (t, 3 H, OCH_2Me),** 7.19 (m, 2 H, H(3′)H(5′)); 7.40 (m, 2 H, H(2′), H(6′))	1.26, 1.29 (both t, 3 H each, $(COOCH_2Me)_2$, *J* = 7.0); 4.19 (m, 4 H, $(COOCH_2Me)_2$); 8.59 (d, 1 H, CH=, *J* = 11.2); 11.05 (d, 1 H, NH)
10d	8.06	11.56	7.50	7.21	6.81	6.12	7.88 (m, 2 H, H(3′)H(5′)); 8.53 (m, 2 H, H(2′), H(6′))	1.27, 1.29 (both t, 3 H each, $(COOCH_2Me)_2$, *J* = 7.0); 4.22 (m, 4 H, $(COOCH_2Me)_2$); 8.60 (d, 1 H, CH=, *J* = 11.2); 11.03 (d, 1 H, NH)

* The H(6) signal falls in the region containing the signals of the aromatic protons of the benzene ring.

** The (OCH_2Me) signals fall in the region of the $(COOCH_2Me)_2$ multiplet with δ 4.19.

Table 2. ^{1}H NMR spectra of indolo[2,3-*f*][1,7]naphthyridine derivatives **11b—d**, **13a,b**, and **14a,b**

Compound	δ, *J*/Hz								
	H(3), s	N(4)H, br.s	H(7), d $J_{7,8}$ = 8.2	H(8), t $J_{8,7}$ = $J_{8,9}$ = 8.2	H(9), t $J_{9,8}$ = $J_{9,10}$ = 8.2	H(10), d $J_{10,9}$ = 8.2	N(11)H, s	C_6H_4-R	Other signals
11b	8.43	11.94	6.10	6.84	7.21	7.72	12.49	7.65, 7.79 (both m, 4 H, C_6H_4Cl)	1.35 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.30 (q, 2 H, $COO\underline{CH_2}Me$)
11c	8.43	11.88	6.12	6.81	7.19	7.70	12.45	1.43 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.0); 4.20 (q, 2 H, $O\underline{CH_2}Me$); 7.21, 7.47 (m, 4 H, C_6H_4OEt)	1.35 (t, 3 H, $COOCH_2\underline{Me}$ *J* = 7.0); 4.30 (q, 2 H, $COO\underline{CH_2}Me$)
11d	8.43	12.01	6.10	6.82	7.21	7.73	12.50	7.94, 8.56 (both m, 4 H, $C_6H_4NO_2$)	1.35 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.30 (q, 2 H, $COO\underline{CH_2}Me$)
13a	8.97	—	5.88	6.73	7.21	*	11.59	7.51—7.70 (m, 6 H, Ph, H(10))	1.42—1.48 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.50 (q, 2 H, $COO\underline{CH_2}Me$)
13b	9.02	—	6.02	6.87	7.28	*	11.62	7.61—7.80 (m, 5 H, C_6H_4Cl, H(10))	1.42—1.48 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.50 (q, 2 H, $COO\underline{CH_2}Me$)
14a	8.71	—	5.94	6.79	7.23	7.75	10.56	7.54—7.74 (m, 5 H, Ph)	1.42—1.48 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.50 (q, 2 H, $COO\underline{CH_2}Me$); 1.70, 1.96 (both br.s, 2 H and 4 H each, 2 H(4″), 2 H(3″), 2 H(5″))**
14b	8.70	—	6.08	6.87	7.25	*	10.57	7.61, 7.75 (both m, 4 H, C_6H_4Cl)	1.42—1.48 (t, 3 H, $COOCH_2\underline{Me}$, *J* = 7.0); 4.50 (q, 2 H, $COO\underline{CH_2}Me$); 1.70, 1.95 (both br.s, 2 H and 4 H each, 2 H(4″), 2 H(3″), 2 H(5″))**

* The H(10) signal falls in the region of aromatic protons of the benzene ring.
** The 2 H(2″) and 2 H(6″) signals in the spectrum recorded in DMSO-d_6 are covered by the solvent water signals. In the spectrum recorded in DMSO-d_6 + CCl_4, the 2 H(2″) and 2 H(6″) signals occur at δ 3.26.

The mixture was refluxed for 7 h. The precipitate was filtered off, washed with water and methanol, and dried to give 0.22 g of compound **5a**, 0.25 g of compound **5b**, 0.11 g of compound **5c,** or 0.2 g of compound **5d**.

1-Aryl-3-(*N*′-benzylidene)amino-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles 7a,b (general procedure). Benzaldehyde (0.1 mL, 1.1 mmol) was added to a solution of amine **3a,b** (1 mmol) in 5 mL of DMF and the mixture was refluxed for 3 h and cooled. The precipitate was filtered off, washed with methanol, and dried to give 0.15 g of compound **7a** or 0.27 g of compound **7b**.

3-Amino-3-(*N*′,*N*′-dimethylaminomethylamino)-2-oxo-1-phenyl-1,2-dihydropyrido[3,2-*b*]indole (8a). Dimethylformamide diethyl acetal (0.2 mL, 1.2 mmol) was added to a solution of 3-aminopyrido[3,2-*b*]indole **3a** (0.3 g, 1 mmol) in 3 mL of DMF, and the mixture was refluxed for 3 h, cooled, and concentrated to dryness. The precipitate was triturated with acetone, filtered, and dried to give 0.16 g of amidine **8a**.

1-Aryl-3-(β,β-diethoxycarbonylethenyl)amino-2-oxo-1,2-dihydropyrido[3,2-*b*]indoles 10a—d (general procedure). A mixture of amine **3a—d** (1.6 mmol), DMF (5 mL), and ethyl ethoxymethylenemalonate (0.34 mL, 1.7 mmol) (**9**) was refluxed for 2 h and cooled. The precipitate was filtered off, washed with DMF and methanol, and dried to give 0.65 g of compound **10a**, 0.56 g of compound **10b**, 0.66 g of compound **10c**, and 0.69 g of compound **10d**.

Ethyl 6-aryl-1,5-dioxo-4,5,6,11-tetrahydro-1*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylate 11a—d (general procedure). A mixture of enamine **10a—d** (0.3 g, 0.6 mmol) and diphenyl (2 g) was heated on a Wood´s alloy bath at 270 °C for 1.5 h; during this period, boiling of the reaction mixture was observed. The mixture was cooled and diphenyl was washed out with boiling light petroleum (40—70 °C) to give 0.22 g of compound **11a** with an admixture of 1,5-dioxo-6-phenyl-4,5,6,11-tetrahydro-1*H*-indolo[2,3-*f*][1,7]naphthyridine **12**; 0.18 g (69%) of compound **11b**, which could not be purified for elemental

Table 3. Physicochemical characteristics of the synthesized compounds **3b—d**, **4d**, **5a—d**, **7a,b**, **8a**, **10a—d**, **11c,d**, and **14a,b**

Compound	Yield (%)	M.p./°C	Solvent[a]	*M*	Found / Calculated (%)				Molecular formula
					C	H	N	Cl	
3b	77	333—335	Pr^{i}OH	309	65.97 65.92	4.04 3.90	13.32 13.57	11.42 11.45	$C_{17}H_{12}N_3OCl$
3c	78	298—301	MeOH—DMF, 9 : 0.1	319	71.25 71.45	5.27 5.37	12.93 13.16	—	$C_{19}H_{17}N_3O_2$
3d	83	326—329	MeCN—DMF, 9 : 1	320	63.88 63.75	3.56 3.78	17.62 17.49	—	$C_{17}H_{12}N_4O_3$
4d	92	~400	DMF	362	63.07 62.98	3.98 3.90	15.59 15.46	—	$C_{19}H_{14}N_4O_4$
5a	47	362—364	DMF	305	67.04 66.88	3.79 3.63	13.99 13.76	—	$C_{17}H_{11}N_3O_3$
5b	53	382—384	DMF	339	59.98 60.10	2.97 2.97	12.11 12.37	10.43 10.44	$C_{17}H_{10}N_3O_3Cl$
5c	32	394—396	DMF	349	65.52 65.32	4.54 4.33	12.03 12.03		$C_{19}H_{15}N_3O_4$
5d	51	356—358	$MeCO_2$—DMF, 2 : 1	350	58.35 58.29	2.94 2.88	15.71 16.00	—	$C_{17}H_{10}N_4O_5$
7a	47	362—364	DMF	363	78.81 79.32	4.63 4.72	11.56 11.56	—	$C_{24}H_{17}N_3O$
7b	88	326—328	DMF	397	72.74 72.46	4.00 4.05	10.57 10.56	8.77 8.91	$C_{24}H_{16}N_3OCl$
8a	44	266—268	DMF	330	72.71 72.70	5.28 5.50	16.67 16.96	—	$C_{20}H_{18}N_4O$
10a	92	262—264	Pr^{i}OH	445	66.89 67.40	5.21 5.20	9.49 9.45	—	$C_{25}H_{23}N_3O_5$
10b	73	260—264	Pr^{i}OH	479	61.83 62.57	4.53 4.62	8.30 8.76	7.39 7.38	$C_{25}H_{22}N_3O_5Cl$
10c	84	269—270)	DMF—Me_2CO, 1 : 1	489	65.90 66.24	5.72 5.56	8.84 8.58	—	$C_{27}H_{27}N_3O_6$
10d	90	285—287	Pr^{i}OH—DMF, 1 : 1	490	61.23 61.22	4.42 4.52	11.34 11.42	—	$C_{25}H_{22}N_4O_7$
11c	38	366—368	DMF	443	67.91 67.71	4.87 4.77	9.33 9.48	—	$C_{25}H_{21}N_3O_5$
11d	38	362—364	DMF, AcOH[b]	444	60.73 61.44	3.84 3.73	11.98 12.20	—	$C_{23}H_{16}N_4O_6$
14a	13	158—160	toluene	466	71.87 72.08	5.77 5.62	11.35 12.01	—	$C_{28}H_{26}N_4O_3$
14b	6	252—254	DMF	500	67.20 67.13	4.99 5.03	11.12 11.18	7.07 7.08	$C_{28}H_{25}N_4O_3Cl$

[a] The solvent used for recrystallization is given in parentheses.
[b] Analysis is related to 1/4 moles of AcOH.

analysis, m.p. 254—256 °C. $C_{23}H_{16}N_3O_4Cl$. MS, m/z (I_{rel} (%)): 433 $[M]^+$ (7), 389 $[M - C_2H_4O]^+$ (9), 361 $[M - COOC_2H_5]^+$ (100), 333 $[M - COOC_2H_5 - CO]^+$ (12). IR, ν/cm^{-1}: 1716 ($COOC_2H_5$), 1643 (CO), 3313 (NH); 0.22 g of compound **11c**; or 0.29 g of compound **11d**.

Purification of compound **11c** for analysis: 0.22 g of crude **11c** was dissolved in 12 mL of boiling DMF. The mixture was cooled and the gel-like precipitate was filtered off and triturated on the filter with acetone to give 0.12 g of a substance, which was recrystallized from 8 mL of DMF. The gel-like precipitate that formed was cooled on an ice bath for 5 h with stirring. The resulting crystals were filtered off and washed with acetone to give 0.1 g of compound **11c** of analytical grade.

Purification of compound **11d** for analysis: 0.29 g of crude **11d** was dissolved in 10 mL of boiling DMF, and the solution was filtered and cooled. The resulting gel-like precipitate (which did not form crystals even after a 3-day storage in a refrigerator) was mixed with ~5 mL of water and triturated. The precipitate that formed was filtered off, washed with acetone, and then refluxed with acetone. The hot solution was filtered to give 0.2 g of a product, which was refluxed in 10 mL of AcOH. The hot suspension was filtered, washed with AcOH, water, and acetone, and dried in a Fischer apparatus at 110 °C over P_2O_5 to

Table 4. Spectral characteristics of the synthesized compounds **3b—d**, **4d**, **5a—d**, **7a,b**, **8a**, **10a—d**, **11c,d**, and **14a,b**

Compound	MS, *m/z* (I_{rel} (%))	IR, ν_{max}/cm^{-1}	
		NH (NH_2)	CO
3b	309 $[M]^+$ (100), 281 $[M - CO]^+$ (15)	3431, 3344, 3257, 3092	1633
3c	319 $[M]^+$ (100), 291 $[M - C_2H_4]^+$ (26), 262 $[M - C_2H_4 - HCO]^+$ (21), 235 $[M - C_2H_4 - HCO - HCN]^+$ (34)	3428, 3340, 3217	1637
3d	320 $[M]^+$ (98), 290 $[M - NO]^+$ (27), 274 $[M - NO_2]^+$ (100)	3432, 3361, 3306, 3171	1632
4d	362$[M]^+$(100), 320 $[M - COCH_2]^+$ (82), 274 $[M - COCH_2 - NO_2]^+$ (27)	3302, 3206	1676, 1629
5a	305 $[M]^+$ (48), 275 $[M - NO]^+$ (100), 231 $[M - CO - NO_2]^+$ (33), 170 $[M - CO - C_6H_5]^+$(57)	3175	1650
5b	339 $[M]^+$ (18), 309 $[M - NO]^+$ (100), 265 $[M - CO - NO_2]^+$ (15), 170 $[M - NO - CO - C_6H_4Cl]^+$ (33)	3172	1644
5c	349 $[M]^+$ (85), 169 $[M - C_6H_4OC_2H_5 - HCO - NO]^+$ (25)	3230	1655
5d	350 $[M]^+$ (31), 320 $[M - NO]^+$ (100), 290 $[M - 2NO]^+$ (31), 274 $[M - NO - NO_2]^+$ (42)	3338	1651
7a	363 $[M]^+$ (100), 260 $[M - C_6H_5CN]^+$ (93)	3151, 3057	1625
7b	397 $[M]^+$ (84), 294 $[M - CN - C_6H_5]^+$ (100), 266 $[M - CN - C_6H_5 - CO]^+$ (55), 231 $[M - CN - C_6H_5 - CO - Cl]^+$ (37), 155 $[M - CN - C_6H_5 - CO - C_6H_4Cl]^+$ (32)	3217	1618
8a	330 $[M]^+$ (100), 288 $[M - CO - CH_2]^+$(66)	3239, 3056	1621
10a	445 $[M]^+$ (12), 399 $[M - C_2H_5OH]^+$ (100), 353 $[M - 2C_2H_5OH]^+$ (56), 299 $[M - 2COOC_2H_5]^+$ (34)	3325	1682, 1641
10b	433 $[M - C_2H_5OH]^+$ (100), 387 $[M - 2C_2H_5OH]^+$ (41), 361 $[M - OC_2H_4 - CO]^+$ (66)	3258, 3053	1735, 1695, 1636
10c	489 $[M]^+$ (24), 443 $[M - C_2H_5OH]^+$ (100), 369 $[M - 2C_2H_5OH - CO]^+$ (90), 343 $[M - 2COOC_2H_5]^+$ (73)	3273	1715, 1638
10d	490 $[M]^+$ (89), 444 $[M - C_2H_5OH]^+$ (100), 370 $[M - 2C_2H_5OH - CO]^+$ (72), 344 $[M - 2COOC_2H_5]^+$ (77)	3528, 3378, 3270	1673, 1641
11c	443 $[M]^+$ (100), 397 $[M - C_2H_5OH]^+$ (38), 372 $[M - HCO - CH_2{=}CHNH_2]^+$ (84), 341 $[M - C_2H_5OH - 2CO]^+$ (36)	3304, 3195, 3071	1717, 1647
11d	444 $[M]^+$ (100), 398 $[M - C_2H_5OH]^+$ (39)	3529, 3370, 3181	1711, 1649
14a	466 $[M]^+$ (100), 437 $[M - HCO]^+$ (13)	3414, 3276	1723, 1656
14b	500 $[M]^+$ (100), 471 $[M - HCO]^+$ (27), 344 $[M - COOC_2H_4 - C_5H_{10}N]^+$ (11)	3414, 3325	1730, 1656

give 0.1 g of compound **11d** of analytical grade, which contained 0.25 mol of AcOH according to ^{1}H NMR data.

Ethyl 1-chloro-5-oxo-6-phenyl-6,11-dihydro-5*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylate (13a). Crude product (**11a** + **12**) (0.3 g, 0.75 mmol) was added with stirring at 20 °C to a Vilsmeier reagent prepared from $POCl_3$ (0.7 mL, 7.5 mmol) and DMF (2.23 mL, 30 mmol), and the mixture was heated to 60 °C, stirred at this temperature for 2 h, and poured into 350 mL of an aqueous solution (pH 8) of sodium bicarbonate with ice. The resulting mixture was stirred for 40 min, and the precipitate was filtered off, washed with water, and dried to give 0.28 g (89%) of compound **13a**, m.p. 328—330 °C. $C_{23}H_{16}N_3O_3Cl$. MS, *m/z* (I_{rel} (%)): 417 $[M]^+$ (100), 389 $[M - C_2H_4]^+$ (34), 345 $[M - COOC_2H_4]^+$ (10). IR, ν/cm^{-1}: 1650, 1713, 1727 (CO), 3189, 3393 (NH).

Ethyl 1-chloro-6-(4-chlorophenyl)-5-oxo-6,11-dihydro-5*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylate (13b) was prepared similarly to compound **13a** with the difference that crude **11b** containing no impurities was used and the mixture was kept at 75 °C for 16 h. This gave 0.42 g (80%) of compound **13b**, m.p. 320—322 °C. $C_{23}H_{16}N_3O_3Cl$. MS, *m/z* (I_{rel} (%)): 417 $[M]^+$ (100), 389 $[M - C_2H_4]^+$ (34), 345 $[M - COOC_2H_4]^+$ (10). IR, ν/cm^{-1}: 1650, 1713, 1727 (CO), 3189, 3393 (NH).

Ethyl 6-aryl-5-oxo-1-piperidino-6,11-tetrahydro-5*H*-indolo[2,3-*f*][1,7]naphthyridine-2-carboxylates (14a,b) (general procedure). Piperidine (0.25 mL, 2.5 mmol) was added to chloro derivative **13a** or **13b** (1 mmol) in 15 mL of DMF and the mixture was stirred at 20 °C for 4.5 h and poured into 50 mL of water. The resulting precipitate was filtered off, washed with water, and dried. After recrystallization from toluene, compound **14a** was refluxed with 15 mL of ethyl acetate and the hot solution was filtered. This gave 0.06 g of pure compound **14a**. Recrystallization of **14b** from DMF gave 0.03 g of pure compound **14b**.

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicines*], Novaya Volna, Moscow, 2000, **I**, 72, 76, 97, 279 (in Russian).

2. N. A. Lantsetti, C. Yu. Ryabova, L. M. Alekseeva, A. S. Shashkov, and V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 470 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 506].
3. C. Yu. Ryabova, N. Z. Tugusheva, L. M. Alekseeva, and V. G. Granik, *Khim.-Farm. Zhurn.,* 1996, **30(7)**, 42 [*Pharm. Chem. J.*, 1996, **30**(7), 472 (Engl. Transl.)].
4. C. Yu. Ryabova, H. A. Rastorgueva, E. A. Lisitsa, L. M. Alekseeva, V. G. Graniq, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 1312 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1386 (Engl. Transl.)].
5. M. Yu. Yakovlev, A. V. Kadushkin, N. P. Solov´eva, O. S. Anisimova, and V. G. Granik, *Tetrahedron*, 1998, **54**, 5775.
6. V. G. Granik, *Lekarstva* [*Drugs*] Vuzovskaya kniga, Moscow, 2001, 249, 324 (in Russian).
7. E. N. Padeiskaya and V. P. Yakovlev, *Antimikrobnye preparaty gruppy ftorkhinolonov v klinicheskoi praktike* [*Antimicrobial Preparations of the Fluoroquinolone Group in Clinical Practice*] Logata, Moscow, 1998, 352 (in Russian).
8. V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Usp. Khim.*, 2000, **69**, 218 [*Russ. Chem. Rev.*, 2000, **69** (Engl. Transl.)].
9. V. P. Borovik, and O. P. Shkurko, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1974 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 2129].

Received April 28, 2003;
in revised form June 23, 2003