Reduction of 2-amino-1-(4-nitrophenyl)-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile by sodium borohydride and sodium cyanoborohydride

S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik*

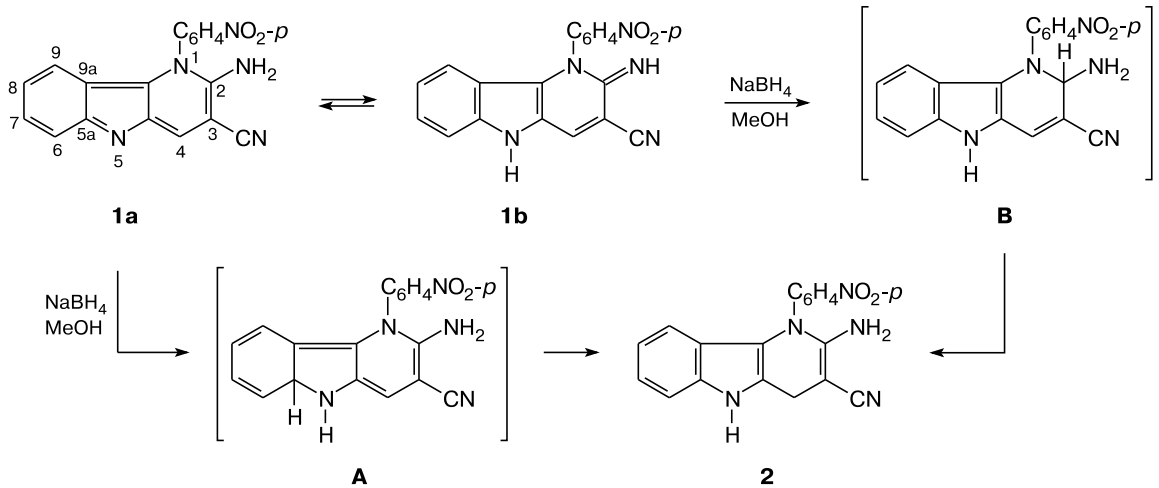
State Scientific Center on Antibiotics,
3a Nagatinskaya ul., 117003 Moscow, Russian Federation.
Fax: +7 (499) 611 1548. E-mail: syuryabova@yandex.ru

The reduction of pyridoindole derivative **1** by sodium borohydride in methanol gives 4,5-dihydropyridoindole **2.** On treatment of 5*H*-pyrido[3,2-*b*]indolium chloride **3** with sodium cyanoborohydride in methanol in the presence of hydrogen chloride, reduction of the pyridine ring is accompanied by reduction of the CN group, resulting in the formation of tetrahydropyridoindole **4.** Compound **4** reacts with DMF dimethyl acetal to yield amidine **6**, and refluxing of **4** with acetic anhydride results in tetrahydropyridine ring cleavage yielding indolylacrylonitrile **9**. The hydrochloride and chloride of compounds **4** and **6** were obtained

Key words: dihydropyridoindole, tetrahydropyridoindole, reduction, amidine, acetylation, indolylacrylonitrile.

Previously, we developed approaches to the synthesis of diverse 1-aryl-substituted pyrido[3,2-*b*]indoles (δ-carbolines) from 3-arylaminoindoles and studied some properties of the obtained compounds, in particular, a method was found for converting 2-imino-2,5-dihydropyridoindole to 2-dimethylamino-4,5-dihydropyridoindole derivatives.[1,2] Many indole derivatives are pharmaceutical agents used in medical practice,[3,4] and 1,4-dihydropyridine derivatives exhibit biological activities.[5,6] Therefore, combination of these fragments in one molecule may prove to be of interest as regards the search of compounds with new biological properties in the 4,5-dihydropyrido[3,2-*b*]indole series. However, no data on the synthesis of 4,5-dihydropyrido[3,2-*b*]indoles by the reduction of pyrido[3,2-*b*]indoles have been reported. Our work deals with the reduction of 1-aryl-δ-carboline derivatives exemplified by the reduction of 2-amino-1-(4-nitrophenyl)-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile (**1a**), which is a 2-imino-2,5-dihydropyrido[3,2-*b*]indole **1b** derivative in a tautomeric form (see Refs 1, 2, 7), with sodium borohydride and sodium cyanoborohydride. These reducing agents do not tend[8,9] to reduce nitro and cyano groups in the absence of catalysts, although some exceptions still have been reported. Thus it was shown, for

Scheme 1



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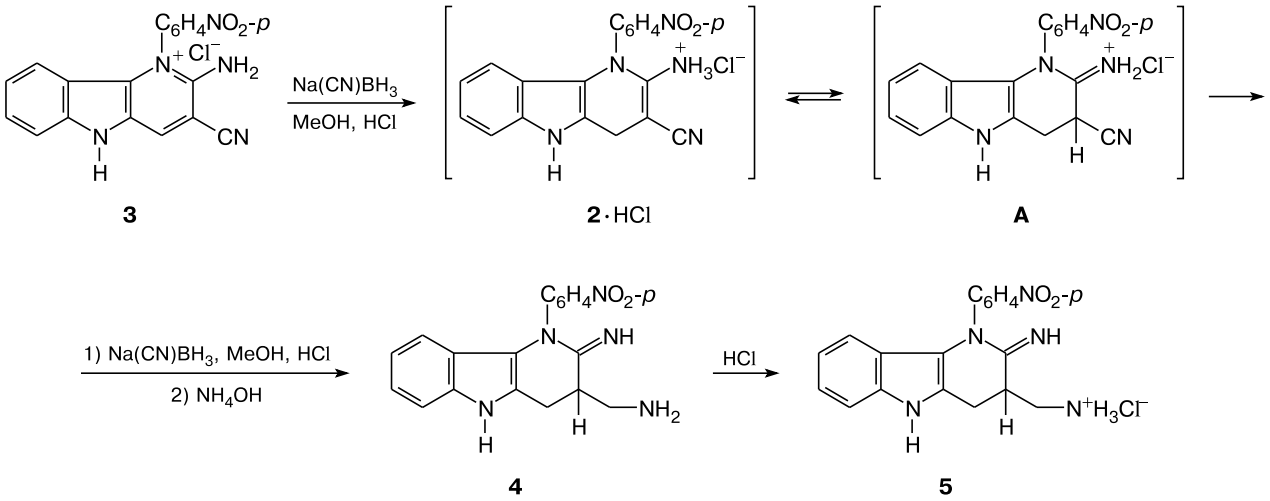
Scheme 2



example, that treatment of epoxides having two geminal cyano groups in the ring with sodium borohydride results in reduction of one cyano group to aminomethyl group.[10]

Sodium borohydride, which is used most often for the reduction of C=N bonds, reduces the N(5)=C(5a) bond in δ-carboline **1** (or the C(2)=NH bond in tautomer **1a**) to give intermediate **A** (or **B**). The subsequent proton migration yields 2-amino-1-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile (**2**) (Scheme 1). The reduction was carried out in methanol using a two-fold excess of sodium borohydride.

The structure of the reduction product as a 4,5-dihydro-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile derivative **2** was confirmed by the IR spectrum (CN absorption band at 2175 cm^{-1}) and the ^1H NMR spectrum, which exhibits, in addition to aromatic proton signals, a signal of $H_2C(4)$ (δ 3.85) and signals of the 2-NH_2 and N(5)H groups (δ 5.24 and 10.87).

Compound **2** represents dark-cherry crystals readily soluble in acetone and acetonitrile. During recrystallization of **2** from acetonitrile, impurities appeared, and a mixture of the starting compound **1** with reduction product **2** (TLC) was isolated from the mother liquor. The IR spectrum of this mixture exhibited absorption bands for both the starting and final compounds.* Thus, it was concluded that 4,5-dihydropyridoindole **2** is unstable being readily dehydrogenated to give aromatic tricyclic product **1**.

Compound **1** is actually a cyclic enediamine. It is known that enamines are readily reduced by sodium cyanoborohydride in acid medium[11] to give iminium salts.

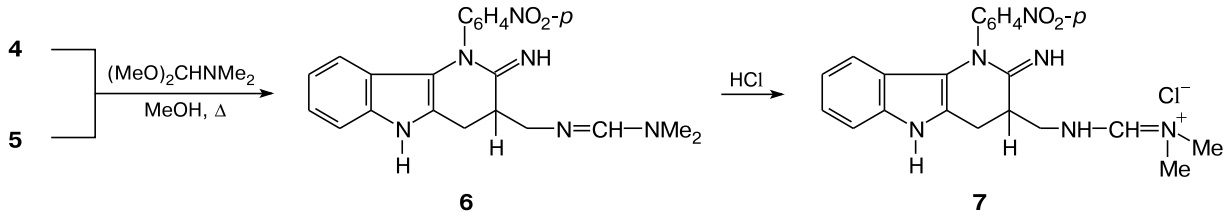
Previously we have shown that pyridoindole **1** is easily protonated in concentrated hydrochloric acid being converted into chloride **3**.[12] Therefore, it is more expedient to introduce the chloride **3** rather than the proper compound **1** into reduction by sodium cyanoborohydride in methanol in the presence of hydrogen chloride. Under these conditions, the reaction was shown to give the product of more extensive reduction than in the previous case.

Chloride **3** is reduced at the $N^+(1)$=C(2) bond. TLC monitoring of the reaction mixture during reduction indicates that, first, the reaction gives dihydro derivative **2**, which exists apparently as hydrochloride **2** • HCl in the acid medium and occurs in equilibrium typical of enamines with intermediate **A** protonated at the β-position of the enediamine fragment. The presence of the protonated species in the equilibrium system of **2** • HCl and **A** facilitates electron transfer from the reducing agent to the CN group, resulting in its irreversible reduction to an aminomethyl group to afford 1-[2-imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]indol-3-yl]methanamine (**4**), which was also isolated as hydrochloride **5** (Scheme 2).

The fact that the CN group has been reduced can be proven by the IR spectra of compounds **4** and **5**, which do not exhibit absorption bands at ~2200 cm^{-1}. The ESI and EI mass spectra of base **4** are not characteristic, as they contain no molecular ion peaks, but the ESI mass spectrum of hydrochloride **5** has a peak $[M + H - HCl]^+$, which attests to addition of six hydrogen atoms to the initial molecule **3**, and this is fully consistent with the NMR data (see the spectrum of hydrochloride **5**). Note that the lack of the signal of NH_2 group in the spectrum of **4** is apparently due to the fact that basic aliphatic amines are more prone for exchange with water present in the solvent than aromatic amines, which are weaker bases. Hydrochloride **5** is protonated at the amino group giving

*IR spectrum (ν/cm^{-1}) of compound **1**: 3320, 2200, 1620, 1600, 1580. IR spectrum (ν/cm^{-1}) of compound **2**: 3466, 3443, 3385, 3366, 3292, 3194, 2175, 1620, 1600, 1580. IR spectrum (ν/cm^{-1}) of a mixture of compounds **1** and **2**: 3466, 3443, 3385, 3366, 3392, 3320, 3194, 2200, 2175, 1620, 1600, 1580.

Scheme 3



rise to a signal of N^+H_3 in the spectrum, while the signals of =NH and N(5)H are retained. This explanation was subsequently confirmed by smooth reactions of compounds **4** and **5** with DMF dimethyl acetal to give amidine **6** and its hydrochloride **7** (Scheme 3).

The reduction of 4,5-dihydropyrido[3,2-*b*]indole **2** under similar conditions followed by treatment with HCl results in hydrochloride **5** whose physicochemical characteristics are identical to those for the compound obtained from chloride **3**.

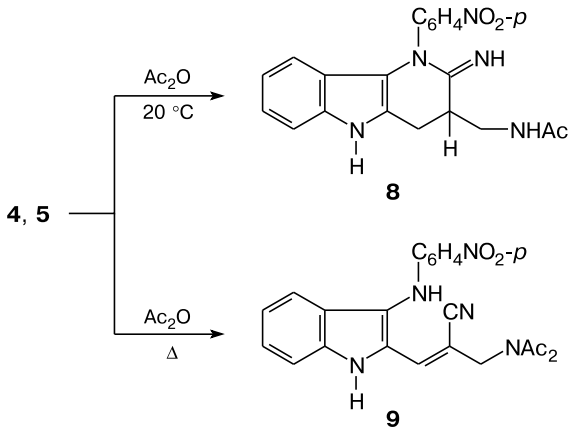
We studied some properties of compounds **4** and **5**, in particular, the reaction with DMF dimethyl acetal and acylation with acetic anhydride.

On heating with excess acetal in methanol, base **4** and hydrochloride **5** are readily converted to *N*-{[2-imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]-indol-3-yl]methylimino)methyl}-*N*-methylmethanamine (**6**), which was also isolated as chloride **7**. The structure of compounds **6** and **7** was confirmed by ^{1}H NMR data.

Base **4** and hydrochloride **5** are readily acetylated with acetic anhydride at room temperature (Scheme 4), the tetrahydropyridoindole structure being retained and acetylaminomethyl derivative **8** being formed as the final product.

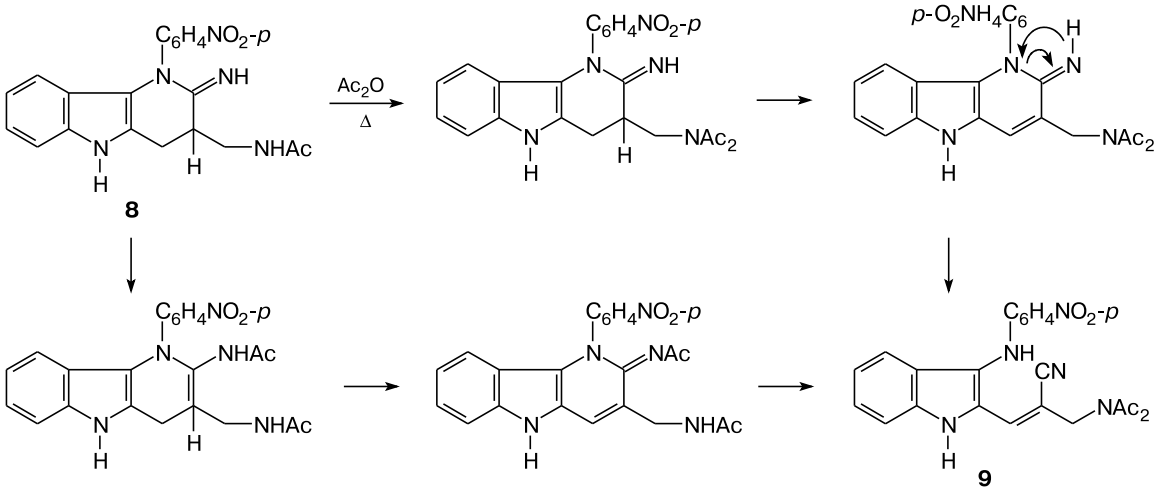
Heating of compounds **4** and **5** in acetic anhydride affords a complex mixture of compounds. 2-(Diacetylaminomethyl)-3-[3-(4-nitrophenylamino)-1*H*-indol-2-yl]acrylonitrile (**9**) resulting from tetrahydropyridine ring cleavage was the only product to be isolated from this mixture (in a low yield) and characterized (see Scheme 4).

Scheme 4



This structure of compound **9** is supported by the data of IR spectrum, in which a CN absorption band appears at 2225 cm^{-1} as compared with the spectra of initial compounds **4** and **5**. The mass spectrum exhibits a molecular

Scheme 5



ion peak corresponding to its molecular weight. The structure of compound **9** is also confirmed by the ^{1}H NMR spectrum. Additional evidence for the structure of compound **9** is the absence of high-field signals from five protons, which are present in the ^{1}H NMR spectra of tetrahydropyridoindole derivatives **4—8**.

Cleavage of the tetrahydropyridine ring induced by acetic anhydride is unusual. The isolated yield of product **9** is fairly low (19%), hence acetylation is accompanied by a series of parallel reactions, and the mechanism of formation of **9** is difficult to discuss without special investigation. However, the presence of dehydrogenation step of the same type as observed during recrystallization of dihydro derivative **2** to give δ-carboline **1** (see above) in the process scheme appears obvious.

Note that chromatographic analysis of the reaction mixture obtained on heating of compound **8** in acetic anhydride showed the presence of acrylonitrile derivative **9**.

The possible ways of ring cleavage in the acetylation of compounds **4** and **5** involving intermediate formation of tricyclic compound **8**, are shown in Scheme 5.

Acetylation may involve both the acetamide group and the amidine NH group followed by migration of the acetyl group. Certainly, other options also cannot be ruled out.

Experimental

IR spectra were recorded on an FSM-1201 instrument in mineral oil. ESI mass spectra were recorded on a Waters ZQ-2000 spectrometer; the sample was injected, bypassing the chromatographic column. ^{1}H NMR spectra were run on Bruker AC-300 and Bruker DRX-500 spectrometers. The reactions were monitored and the product purity was checked using Merck 60 F_{254} plates and chloroform—methanol, 10 : 1, and ethyl acetate—isopropyl alcohol—ammonia, 5 : 3 : 1, systems. The yields, melting points, and data of elemental analysis, mass spectra and IR spectra for the synthesized compounds are summarized in Tables 1 and 2.

2-Amino-1-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrido[3,2-*b*]-indole-3-carbonitrile (2). Sodium borohydride (0.19 g, 5 mmol) (1 tablet) was added to a suspension of pyridoindole **1** (0.82 g, 2.5 mmol) in methanol (50 mL). Hydrogen evolution was accompanied by the formation of a solution and then the formation of a new precipitate. After $NaBH_4$ has been completely converted, the reaction mixture was stirred for an additional 30—40 min, and the precipitate was filtered off, washed with methanol, water, and again methanol to give 0.62 g of 4,5-dihydropyrido[3,2-*b*]indole **2**. ^{1}H NMR (DMSO-d_6), δ: 3.85 (s, 2 H, $H_2C(4)$); 5.24 (br.s, 2 H, NH_2); 5.91 (d, 1 H, H(9), J = 8.4 Hz); 6.61 (t, 1 H, H(8), J = 8.4 Hz); 6.90 (t, 1 H, H(7), J = 8.4 Hz); 7.22 (d, 1 H, H(6), J = 8.4 Hz); 7.70, 8.35 (A_2B_2, 4 H, $C_6H_4NO_2$); 10.87 (s, 1 H, NH).

1-[2-Imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido-[3,2-*b*]indol-3-yl]methaneamine (4). Method *A*. $NaBH_3(CN)$ (0.3 g, 5 mmol) was added to a suspension of 2-amino-3-cyano-1-(4-nitrophenyl)-5*H*-pyrido[3,2-*b*]indole chloride (**3**) (0.59 g, 1.6 mmol) in methanol (10 mL). Then ~2.8 mL of a saturated (7%) solution of hydrogen chloride in ethyl acetate was added dropwise with stirring over a period of 2 h. The reaction mixture was stirred for 16 h at room temperature. The inorganic precipitate was filtered off and washed with methanol. The solvent was evaporated *in vacuo*, the residue was dissolved in

Table 1. Yields, melting points,[a] and elemental analysis data[b] for synthesized compounds

Compound	Yield (%)	M.p./°C	Molecular weight	Found / Calculated (%)				Molecular formula
				C	H	N	H_2O	
2	75	275—277	331	64.75 / 64.38	3.80 / 4.05	20.63 / 20.86	—	$C_{18}H_{13}N_5O_2 \cdot 0.25\ H_2O$
4	83 (***A***) 93 (***B***)	90—92	335	64.50 / 64.53	5.34 / 5.30	19.52 / 20.23	—	$C_{18}H_{17}N_5O_2$[c]
5	70 (***A***) 84 (***B***)	190—195	371.8	55.46 / 55.90	5.17 / 5.30	17.97 / 17.80	4.62 / 3.80	$C_{18}H_{18}ClN_5O_2 \cdot H_2O$
6	86	111—113	390	63.80 / 63.86	5.34 / 5.74	20.32 / 21.28	—	$C_{21}H_{22}N_6O_2 \cdot 0.25\ H_2O$
7	64	178—190	426.9	58.60 / 58.34	5.39 / 5.50	18.87 / 19.44	1.32 / 1.25	$C_{21}H_{23}ClN_6O_2 \cdot 0.3\ H_2O$
8	84 (***A***) 99 (***B***)	140—142	377	62.33 / 62.46	4.92 / 5.18	17.58 / 18.21	2.32 / 1.87	$C_{20}H_{19}N_5O_3 \cdot 0.4\ H_2O$
9	19 (***A***) 14 (***B***)	193—194	417	63.49 / 63.30	4.45 / 4.59	16.54 / 16.77	—	$C_{22}H_{19}N_5O_4$

[a] Compounds **4—8** are amorphous and resisted recrystallization. On melting, they liquify over a broad temperature range.

[b] The results of analysis were obtained for noncrystallized substances and include water.

[c] According to ^{1}H NMR spectrum, the compound contains 0.15 mol of ethyl acetate, which was taken into account in the analysis.

Table 2. Data of mass and IR spectra for synthesized compounds

Compound	MS m/z (I_{rel}(%))	IR, ν_{max}/cm^{-1}
2	332 $[M + H]^+$, 370 $[M + K]^+$, 683 $[2 M + H]^+$	3466 (NH, NH_2), 2175 (CN)
4	—	3350, (NH), 1633 (C=N)
5	336 $[M + H - HCl]^+$, 358 $[M - HCl + Na]^+$, 374 $[M - HCl + K]^+$, 671 $[2 M - 2 HCl + H]^+$, 693 $[2 M - 2 HCl + Na]^+$	3360 (NH, NH_2), 1600 (C=N)
6	391 $[M + H - HCl]^+$, 781 $[2 M + H - 2 HCl]^+$	3352 (NH), 1647, 1597 (C=N)
7	391 $[M + H - HCl]^+$, 781 $[2M + H - 2 HCl]^+$	3176 (NH), 1707, 1599 (C=N)
8	378 $[M + H]^+$, 400 $[M + H + Na]^+$, 416 $[M + H + K]^+$, 777 $[2 M + Na]^+$, 793 $[2 M + K]^+$	3346 (NH), 1662 (CO)
9	440 $[M + Na]^+$, 456 $[M + K]^+$, 857 $[2 M + Na]^+$	3379, 3304 (NH), 2210 (CN), 1712, 1689 (CO)

water (~30 mL) and alkalified with a concentrated ammonia solution (~0.5 mL). The precipitate was filtered off, washed with water, squeezed out on the filter, and dissolved in ethyl acetate. The solution was dried with Na_2SO_4, clarified by activated carbon, and concentrated to dryness. The residue was dried in a vacuum desiccator over P_2O_5 to give 0.45 g of tetrahydropyridoindole **4**. ^{1}H NMR (DMSO-d_6+CCl_4), δ: 2.76 (m, 2 H, $H_2C(4)$), 2.99 (d, 2 H, $\underline{CH}_2NH_2$), 3.12 (qt, 1 H, H(3)) ($^3J_{H,H}$ = 6.5—7.5 Hz); 6.63, 7.96 (A_2B_2, 4 H, $C_6H_4NO_2$); 6.96 (t, 1 H), 7.12 (m, 2 H), 7.37 (d, 1 H) (H(6)—H(9), J_o = 7.8 Hz); 8.68 (s, 1 H, =NH); 11.18 (br.s, 1 H, N(5)H).

Method B. A solution of hydrochloride **5** (0.19 g, 0.5 mmol) (see below) in water (20 mL) was alkalified by two drops of concentrated ammonia. The precipitate was filtered off, washed with water, and dried in a vacuum dessicator over KOH to give 0.16 g of base **4**. The melting point of a mixed sample with the compound obtained by method ***A*** was undepressed.

1-[2-Imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido-[3,2-*b*]indol-3-yl]methanamine hydrochloride (5). Method *A*. The product was obtained from chloride **3** (0.59 g, 1.6 mmol) as described for the synthesis of **4** by method ***A***. Drying and clarification of the ethyl acetate solution was followed (without isolation of compound **4**) by acidification with a 7% solution of hydrogen chloride in ethyl acetate (~1 mL) and stirring for 2—2.5 h at 20 °C. The precipitate was filtered off, washed with ethyl acetate, and dried in air* to give 0.33 g of hydrochloride **5**. The mother liquor was concentrated to dryness. The oily precipitate was triturated with ethyl acetate. The precipitate was filtered off and washed with ethyl acetate to give additionally 0.09 g of the same product. The total yield of hydrochloride **5** was 0.42 g. ^{1}H NMR (DMSO-d_6), δ: 3.12 (m, 4 H, $H_2C(4)$, $\underline{CH}_2N^+H_3$), 3.75 (qt, 1 H, H(3), $^3J_{H,H}$ = 6.5 Hz); 6.68, 8.00 (A_2B_2, 4 H, $C_6H_4NO_2$); 6.99 (t, 1 H), 7.13 (m, 2 H), 7.42 (d, 1 H) (H(6)—H(9), J_o = 7.8 Hz); 8.52 (br.s, 3 H, N^+H_3); 8.91 (s, 1 H, =NH); 11.43 (br.s, 1 H, N(5)H).

Method *B*. The product was obtained from dihydropyridoindole **2** (0.33 g, 1 mmol), $NaBH_3(CN)$ (0.12 g, (2 mmol), and methanol (10 mL) as described for the synthesis of **4** by method ***A*** (except that the reaction was carried out under argon). The hydrochloride was isolated as in method ***A*** to give 0.3 g of hydrochloride **5** identical to the compound obtained by method ***A***.

***N*-{[2-Imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]indol-3-yl]methyliminomethyl}-*N*-methyl methanamine (6).** A solution of tetrahydropyridoindole **4** (0.05 g, 0.15 mmol) and DMF dimethyl acetal (0.045 mL, 0.3 mmol) in methanol (1 mL) was stirred at reflux for 0.5 h. The solvent was evaporated to dryness. The residue was triturated with water. The precipitate was filtered off, washed with water, and dried in a vacuum dessicator over KOH to give 0.05 g of amidine **6**. ^{1}H NMR (DMSO-d_6+CCl_4), δ: 2.72 (s, 6 H, $N(CH_3)_2$); 3.00—3.30 (m, 5 H, $H_2C(4)$, $\underline{CH}_2NH_2$, H(3)); 6.62, 7.96 (A_2B_2, 4 H, $C_6H_4NO_2$); 6.96 (t, 1 H), 7.12 (m, 2 H), 7.37 (d, 1 H) (H(6)—H(9), J_o = 7.8 Hz); 7.34 (s, 1 H, N=CH); 8.68 (s, 1 H, =NH); 11.21 (br.s, 1 H, N(5)H).

***N*-{[2-Imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]indol-3-yl]methyliminomethyl}-*N*,*N*-dimethyl methanammonium chloride (7).** A solution of hydrochloride **5** (0.37 g, 1 mmol) and DMF dimethyl acetal (0.3 mL, 2 mmol) in methanol (6 mL) was stirred at reflux for 0.5 h. The solvent was evaporated to dryness. The oily residue was triturated with 5 mL of water with addition of 1 drop of concentrated ammonia (pH 8). Amidine **6** was filtered off, washed with water, dissolved in ethyl acetate, and dried with K_2CO_3. The solution was filtered and acidified with a 7% solution of HCl in ethyl acetate. The precipitate was filtered off, washed with ethyl acetate, and dried in air to give 0.27 g of compound **7**. For analysis, compound **7** was purified in the following way: the compound was dissolved in acetone, the solution was clarified by activated carbon and concentrated, the residue was triturated with ethyl acetate, and the precipitate was filtered off. ^{1}H NMR (DMSO-d_6), δ: 3.00, 3.13 (both s, 3 H each, $N(CH_3)_2$); 3.08 (m, 2 H, $H_2C(4)$), 3.63 (t, 2 H, $\underline{CH}_2NH_2$), 3.85 (qt, 1 H, H(3)) ($^3J_{H,H}$ = 6.0—6.5 Hz); 6.70, 7.94 (A_2B_2, 4 H, $C_6H_4NO_2$); 6.94 (т, 1 H), 7.10 (m, 2 H); 7.39 (d, 1 H) (H(6)—H(9), J_o = 7.8 Hz); 8.38 (d, 1 H, NH—C$\underline{H}$, J_{NHCH} = 12.9 Hz); 8.93 (s, 1 H, =NH); 10.03 (m, 1 H, N$\underline{H}$—CH); 11.47 (br.s, 1 H, N(5)H).

***N*-{[2-Imino-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]indol-3-yl]methyl}acetamide (8). Method *A*.** A solution of pyridoindole **4** (0.34 g, 1 mmol) in acetic anhydride (2.5 mL) was allowed to stand for 20 h at 20 °C. Acetic anhydride was evaporated to dryness, and the residue was triturated with water. The precipitate was filtered off, washed with water, and dried in air to give 0.32 g of compound **8**. For analysis, the compound was purified by column chromatography (SiO_2, elution with chloroform, chloroform—methanol, 10 : 0.25; chloroform, chloroform—methanol, 10 : 1). ^{1}H NMR (DMSO-d_6+CCl_4), δ: 1.85 (s, 3 H, $COCH_3$); 2.97 (d, 2 H, $H_2C(4)$), 3.29 (t, 2 H, $\underline{CH}_2NH_2$), 3.39 (qt, 1 H, H(3)) ($^3J_{H,H}$ = 6.0—7.5 Hz); 6.64, 7.94 (A_2B_2, 4 H, $C_6H_4NO_2$); 6.95 (t, 1 H), 7.09 (t, 1 H), 7.14 (d, 1 H), 7.36 (d, 1 H) (H(6)—H(9),

* If the hydrochloride does not precipitate, the solvent is evaporated *in vacuo*, the residue is triturated with ethyl acetate with heating, and the precipitate is filtered off.

J_o = 7.8 Hz); 8.29 (t, 1 H, NH, J_{NH,CH_2} = 6.4 Hz); 8.62 (s, 1 H, =NH); 11.19 (br.s, 1 H, N(5)H).

Method *B*. Acetic anhydride (0.2 mL) was added to a suspension of hydrochloride **5** (0.05 g, 0.14 mmol) in benzene (1 mL), and the mixture was stirred at reflux for 4 h. The product was isolated as in method ***A*** to give 0.05 g of acetamide **8**.

2-(Diacetylaminomethyl)-3-{3-[(4-nitrophenyl)amino]-1*H*-indol-2-yl}acrylonitrile (9). Method *A*. A solution of 3-aminomethyltetrahydropyridoindole **4** (0.35 g, 1 mmol) in acetic anhydride (5 mL) was refluxed for 6 h and kept at 20 °C for 16 h. Acetic anhydride was distilled off *in vacuo* and the residue was triturated with water. The precipitate was filtered off, washed with water, and dissolved in ethyl acetate, and the solution was clarified by activated carbon, and dried with Na_2SO_4. The solvent was evaporated *in vacuo* to dryness. The residue (0.35 g) was triturated with methanol (5 mL), and the suspension was heated to reflux. The red precipitate was filtered hot and washed with methanol and ether to give 0.06 g (14.5%) of compound **9**. Column chromatography of the mother liquor (SiO_2, elution with chloroform, chloroform—methanol, 100 : 1) gave additionally 0.02 g of the same compound. The overall yield of compound **9** was 0.08 g. For analysis, product **9** was recrystallized from DMF. ^{1}H NMR (DMSO-d_6+CCl_4), δ: 2.36 (s, 6 H, $(COCH_3)_2$); 4.68 (s, 2 H, CH_2); 6.71, 8.02 (A_2B_2, 4 H, $C_6H_4NO_2$); 7.05 (t, 1 H), 7.26 (m, 2 H), 7.59 (d, 1 H) (H(6)—H(9), J_o = 7.8 Hz); 7.21 (s, 1 H, CH=C(CN)); 9.05 (br.s, 1 H, N<u>H</u>$C_6H_4NO_2$); 11.00 (br.s, 1 H, N(5)H).

Method *B*. A solution of chloride **5** (0.19 g, 0.5 mmol) in acetic anhydride (2 mL) was refluxed for 6 h and kept at 20 °C for 16 h. The reaction mixture was poured in water (20 mL) and washed for 2 h at 20 °C. The precipitate was filtered off, washed with water, and dissolved in ethyl acetate, and the solution was clarified by activated carbon and dried with Na_2SO_4. The solvent was evaporated *in vacuo* to dryness. The residue was dissolved in chloroform and purified by column chromatography as described above to give 0.03 g of compound **9**.

References

1. S. Yu. Ryabova, L. M. Alekseeva, V. G. Granik, *Mendeleev Commun.*, 1995, № 3, 107.
2. S. Yu. Ryabova, L. M. Alekseeva, V. G. Granik, *Khim.-Farm. Zhurn.*, 1996, **30**, No. 9, 29 [*Pharm. Chem. J.* (*Engl. Transl.*), 1996, 579].
3. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicinal Agents*], issue 13, Torgsin, Kharrkov, 1997 (in Russian).
4. V. G. Granik, *Lekarstva. Farmakologicheskii, biokhimicheskii i khimicheskii aspekty* [*Drugs. Pharmocological, Biochemical, and Chemical Aspects*], Vuzovskaya kniga, Moscow, 2001, 406 pp. (in Russian).
5. A. Sausins, G. Duburs, *Heterocycles,* 1988, **27**, 269.
6. A. Sausins, G. Duburs, *Khim. Geterotsikl. Soedinen.*, **28**, 1992, 435 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1992].
7. S. Yu. Ryabova, L. M. Alekseeva, V. G. Granik, *Khimiya Geterotsikl. Soedinen.*, 2001, 1086 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2001, **37**].
8. H. C. Brown, S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567.
9. C. F. Lane, *Synthesis*, 1975, 135.
10. J. Mauger, A. Robert, *J. Chem. Soc., Chem. Commun.*, 1986, 395.
11. L. Fieser, M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1979, **7**, 377.
12. S. Yu. Ryabova, L. M. Alekseeva, V. G. Granik, *Khimiya Geterotsikl. Soedinen.*, 2000, 362 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2000, **36**, 301].

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