Chemistry of Heterocyclic Compounds, Vol. 36, No. 3, 2000

1H-PYRIDO[3,2-*b*]INDOLES. SYNTHESIS AND INVESTIGATION OF SOME THEIR SPECTROSCOPIC AND CHEMICAL PROPERTIES

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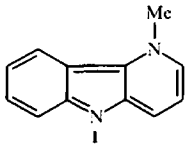
At boiling in trifluoroacetic acid derivatives of 3-cyanovinyl-3-p-nitrophenylaminoindole are cyclized into the corresponding pyrido[3,2-b]indoles as a result of activation of the CN group. Thermal cyclization of ethyl indolylacrylate occurs with participation of the more reactive ethoxycarbonyl group to give 3-cyanopyrido[3,2-b]indole.

Keywords: indole, indolineacrylic acid, carboline, malononitrile, pyridoindole, cyanoacetontrile.

Although pyrido[3,2-*b*]indoles (δ-carbolines) have been studied less extensively than the α-, β-, and γ-carbolines, there are literature data on the beneficial properties of this class, in particular on the biological activity of 1-unsubstituted derivatives of this heterocyclic system [1, 2]. There is only one paper concerned with the synthesis and properties of 1H-pyrido[3,2-*b*]indoles [3]. It describes a multistep and experimentally complicated synthesis of 1-methyl-1H-pyrido[3,2-*b*]indole (**1**) and some chemical properties of this compound and its basicity in comparison with isomeric carbolines were studied.



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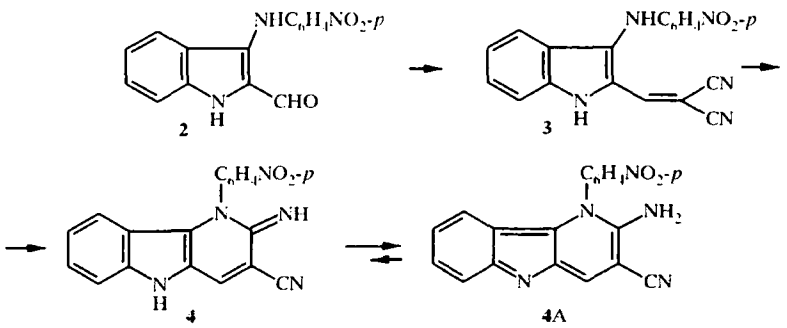
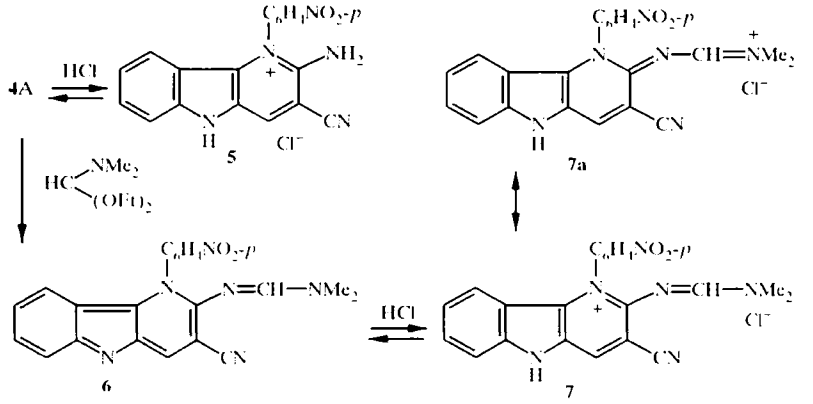
We have established that 2-formyl-3-*p*-nitrophenylaminoindole (**2**) reacts with malononitrile to give the dicyanovinyl derivative **3** which is transformed into the corresponding 2-iminodihydropyrido[3,2-*b*]indole (**4**) on heating. To judge from the ^1H and ^{13}C NMR spectra, compound **4** is in equilibrium with 1-*p*-nitrophenyl-2-amino-3-cyano-1H-pyrido[3,2-*b*]indole **4A** [4, 5].



RF State Scientific Center "NIOPIK", Moscow 103787, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 362-367, March, 2000. Original article submitted November 17, 1998.

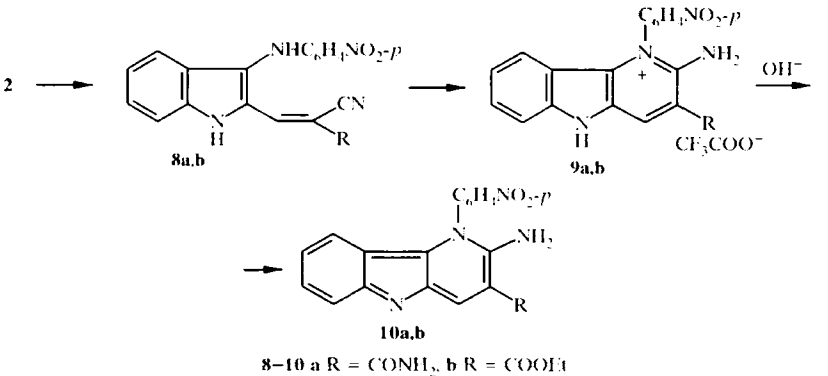
0009-3122/00/3603-0301$25.00©2000 KluwerAcademic/Plenum Publishers

The high basicity of compound **1** (pK_a 10.77) [3] leaves no doubt that it is protonated at the nitrogen atom of the five-membered ring. To establish that protonation at the same site is retained in the presence of the 2-amino group in compound **4A**, the chloride of this tricyclic compound **5** was prepared and the ^{1}H NMR spectra of protonated **5** and non-protonated **4A** were compared. The most characteristic difference is the presence in the ^{1}H NMR spectrum of **4A** of a broad signal at 6.17 ppm (2H, br. s, NH_2) and its conversion in the chloride into signals at 8.48 (2H, br. s, NH_2) and 12.78 ppm (1H, br. s, NH indole). Naturally all proton signals in the chloride **5** are shifted downfield (see Experimental), but the biggest shift of 0.88 ppm is observed for the signal of 4-H, which indicates that the positive charge is predominantly localized on the endocyclic nitrogen atom of the pyridine ring. The presence of a primary amino group in **4A** is confirmed by the reaction of this compound with dimethylformamide diacetal to give the corresponding amidine **6**. Analogously to chloride **5**, chloride **7** was obtained from the amidine **6** and the ^{1}H NMR spectra of compounds **6** and **7** were compared.



In this case also on going from **6** to **7** the biggest shift downfield is for the proton at position 4, but the difference of 0.42 ppm is noticeably smaller than for the pair **4** → **6**, which is probably connected with some delocalization of the positive charge onto the amide unit (resonance **7** → **7A**).

The possibility of synthesizing 1H-δ-carbolines is not limited to the cyclization of the dicyanovinyl derivative **3**. Reaction of the aldehyde **2** with cyanoacetamide and ethyl cyanoacetate gave the amide **8a** and the ester **8b** of β-indolineacrylic acid. These compounds did not cyclize in the conditions for the cyclization **3** → **4** (heating in a methanol-DMF mixture [4, 5]).*



8–10 a R = $CONH_2$, b R = COOEt

* After heating in this way amide **8a** was isolated as a DMF solvate which was stable under normal conditions and only decomposed when heated to 150°C.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Mass spectrum, *m/z*	Found, % / Calculated, % C	H	N	IR spectrum, cm^{-1}	mp, °C (*)	Yield, %
5	$C_{18}H_{12}ClN_5O_2 \cdot 0.5\ H_2O$	329	57.57 / 57.68	3.69 / 3.50	18.74 / 18.69	3500-3300, 3200-3000, 2220, 1650, 1620	>390 (H_2O)	100
6	$C_{21}H_{16}N_6O_2$	384	65.96 / 65.62	4.30 / 4.20	21.92 / 21.86	2220, 1630, 1615	>300 dec. ($CHCl_3$)	93
7	$C_{21}H_{17}ClN_6O_2 \cdot H_2O$	384	55.85 / 55.20	4.23 / 4.63	18.74 / 18.40	3460, 3390, 2210, 1630, 1610	>300 dec. (H_2O)	64
8a	$C_{18}H_{13}N_5O_3$	347	62.27 / 62.24	3.95 / 3.77	19.93 / 20.17	3400, 3300-3260, 3180, 2220, 1675, 1610, 1590	*(DMF–MeOH, 1 : 1)	84
8b	$C_{20}H_{16}N_4O_4$	376	63.79 / 63.82	4.26 / 4.29	14.82 / 14.89	3340, 2210, 1720, 1665, 1600, 1575	*(DMF–MeOH, 1 : 1)	97
9a	$C_{20}H_{14}F_3N_5O_5$		52.18 / 52.07	3.05 / 3.06	15.39 / 15.18	3420 (sh), 3360 (sh), 3280, 3140-3020, 1670, 1640, 1625	240-243 (MeOH)	86
9b	$C_{22}H_{17}F_3N_4O_6$		53.72 / 53.88	3.56 / 3.49	11.43 / 11.43	3300, 1695, 1665, 1615, 1590	239-240 (*i*-PrOH–MeOH)	92
10a	$C_{18}H_{13}N_5O_3$	347	62.45 / 62.24	3.87 / 3.77	20.23 / 20.17	3330-3100, 1650	241-242 (DMF–MeOH)	66
10b	$C_{20}H_{16}N_4O_4$	376	63.56 / 63.82	4.29 / 4.29	14.69 / 14.89	3370, 3130-3040, 1700, 1680, 1620	239-240 (DMF–acetone)	80
11	$C_{18}H_{10}N_4O_3$	330	65.33 / 65.45	3.35 / 3.05	16.87 / 16.96	3300-3100, 2210, 1625	392-394 (DMF–H_2O, 3 : 1)	78

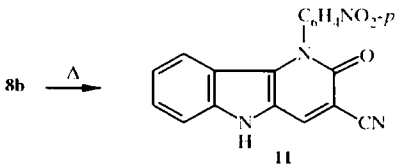
* Determination of the mp was unsuccessful, probably due to thermal cyclization of the compound.

TABLE 2. ^{1}H NMR Spectra of the Synthesized δ-Carbolines (DMSO-d_6)

Compound	Chemical shifts, δ, ppm								
	4-H, s	6-H, d	7-H, t	8-H, t	9-H, d	$C_6H_4NO_2$, A_2B_2-system	NH, br. s	NH_2, br. s	other signals
4	8.25	7.42	7.23	6.74	5.91	7.88; 8.55		6.17	
5	9.13	7.67	7.52	6.95	5.96	8.13; 8.72	12.78	8.48	
6	8.83	7.54	7.22	6.6	6.05	7.90; 8.60			8.2 (1H, s, CH); 2.69; 3.1 (6H, two s, $N(CH_3)_2$)
7	9.25	7.75	7.6	7.1	6.2	8.0; 8.62	13		8.4 (1H, s, CH); 2.75; 3.2 (6H, two s, $N(CH_3)_2$)
9b	9.08	8	7.53	6.98	5.99	8.16; 8.75	12.4	8.48	1.42 (3H, m, $COOCH_2\underline{CH_3}$); 4.47 (2H, q, $COO\underline{CH_2}CH_3$)
10b	8.41	7.43	7.22	6.71	5.93	7.81; 8.51		*	1.35 (3H, m, $COOCH_2\underline{CH_3}$); 4.31 (2H, q, $COO\underline{CH_2}CH_3$)
11	8.68	7.52	7.32	6.82	6.11	7.88; 8.54	12		

* Signals of the NH_2 group were not observed (masked by the signals of the water solvent).

This difficulty in cyclization may be connected to replacement of one of the cyano groups in compound **3** by the more bulky $CONH_2$ and COOEt groups and some displacement of the acrylic unit out of the plane of the molecule.



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Cyclization of compounds **8a** and **8b** was accomplished by heating in trifluoroacetic acid. Subsequent treatment of the intermediate trifluoroacetates **9a** and **9b** with alkali in ethanol gave the 1H-δ-carbolines **10a** and **10b**. Further study of the properties of the ester **8b** established that thermal cyclization of this compound was also possible, but the thermal cyclization followed a different route. When compound **8b** was boiled in ethylene glycol closing of the pyridine ring occurred via the 3-NH and ethoxycarbonyl groups (not the cyano group) to give 1,2-dihydro-1-*p*-nitrophenyl-3-cyanopyrido[3,2-*b*]indolone-2 (**11**).

In other words, when compound **8b** is heated in CF_3COOH the cyano group is activated, probably by protonation, while the ethoxycarbonyl group is more reactive in the thermal process.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a Perkin-Elmer 457 spectrometer. Mass spectra were recorded with a Varian MAT-112 (70 eV) with direct injection of the sample into the ion source. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on Varian Uniti Plus 400 machine. Course of

reactions and purity of products were monitored by TLC on Silufol UV-254 plates with 10:1 chloroform–methanol and 5:3:1 ethyl acetate–isopropanol–ammonia eluants. Physicochemical properties and yields are given in Table 1, and ^{1}H NMR spectra of the δ-carbolines in Table 2.

1-*p*-Nitrophenyl-2-amino-3-cyano-5H-pyrido[3,2-*b*]indolinium Chloride (5). A mixture of carboline **4** (4.5 g, 13.7 mmol) and concentrated hydrochloric acid (180 ml) were stirred for 1 h at room temperature. The precipitate was filtered off, washed with water, and dried to give chloride **5** (5.0 g).

1-*p*-Nitrophenyl-2-dimethylaminomethyleneamino-3-cyano-1H-pyrido[3,2-*b*]indole (6). A mixture of carboline **4** (3 g, 9.1 mmol) and DMF diethylacetal (30 ml) was boiled for 4 h, cooled, the precipitate filtered off, washed with ether to give amidine **6** (3.28 g).

1-*p*-Nitrophenyl-2-dimethylaminomethyleneamino-3-cyano-5H-pyrido[3,2-*b*]indolinium Chloride (7). A mixture of amidine **6** (0.4 g, 1 mmol), water (20 ml), and conc. hydrochloric acid (3 ml) was stirred for 3 h at 20°C. The yellow precipitate was filtered off, washed with water, recrystallized from water, and dried at 100°C to give chloride **7** (0.28 g).

α-Cyano-β-(3-*p*-nitrophenyl-2-aminoindolyl-2)acrylamide (8a). A mixture of 2-formylindole **2** (1.65 g, 5.9 mmol), cyanoacetamide (0.52 g, 6.2 mmol), and triethylamine (0.84 ml, 6 mmol) in isopropanol (60 ml) was stirred and boiled for 7 h. The mixture was cooled, the precipitate was filtered off and washed with isopropanol to give dark cherry colored crystals of amide **8a** (1.73 g). After crystallization from a 1:1 methanol–DMF mixture the compound became yellow and appeared as a solvate of amide **8a** with DMF. The solvate decomposed on drying at 150°C. ^{1}H NMR spectrum, δ, ppm: 7.06 (1H, m, 5-H); 7.25 (1H, m, 4-H); 7.35 (1H, m, 6-H); 7.67 (1H, m, 7-H); 6.81, 8.07 (4H, 2 m, $C_6H_4NO_2$); 8.10 (1H, s, CH); 9.45 (1H, br. s, 3-NH); 11.10 (1H, br. s, NH_{ind}); 7.86, 7.69 (2H, two br. s, $CONH_2$). Found, %: C 59.45; H 4.69; N 19.85. $C_{18}H_{13}N_5O_3 \cdot C_3H_7NO$. Calculated, %: C 59.99; H 4.80; N 19.99.

Ethyl α-Cyano-β-(3-*p*-nitrophenylaminoindolyl-2)acrylate (8b). Ester **8b** (5.7 g) was obtained from a mixture of 2-formylindole **2** (4.4 g, 16 mmol), isopropanol (100 ml), ethyl cyanoacetate (4.4 ml, 60 mmol), and triethylamine (0.6 ml, 6 mmol) in the conditions used in synthesis of amide **8a**. ^{1}H NMR spectrum, δ, ppm: 7.07 (1H, m, 5-H); 7.28 (1H, m, 4-H); 7.39 (1H, m, 6-H); 7.72 (1H, m, 7-H); 8.67, 8.22 (4H, two m, $C_6H_4NO_2$); 8.22 (1H, s, CH); 9.68 (1H, br. s, 3-NH); 11.11 (1H, br. s, NH_{ind}); 1.29 (3H, t, $OCH_2\underline{CH_3}$); 4.29 (2H, q, $O\underline{CH_2}CH_3$).

1-*p*-Nitrophenyl-2-amino-3-carbamoyl-5H-pyrido[3,2-*b*]indolinium Trifluoroacetate (9a). A solution of amide **8a** (0.35 g, 1 mmol) in trifluoroacetic acid (10 ml) was boiled for 1 h and then poured into water (50 ml). The precipitate was filtered off, washed with water, 1% sodium hydrocarbonate solution, and water and then dried to give trifluoroacetate **9a** (0.4 g).

1-*p*-Nitrophenyl-2-amino-3-ethoxycarbonyl-5H-pyrido[3,2-*b*]indolinium Trifluoroacetate (9b). A solution of ester **8b** (0.1 g, 0.27 mmol) was boiled for 2 h, allowed to stand for 24 h at 20°C, and then poured into water (20 ml). The precipitate was filtered off, washed with water, 1% sodium hydrocarbonate solution, and water and then dried to give trifluoroacetate **9b** (0.12 g).

1-*p*-Nitrophenyl-2-amino-3-carbamoyl-1H-pyrido[3,2-*b*]indole (10a). 1N potassium hydroxide solution (0.5 ml) was added to a methanol solution of trifluoroacetate **9a** (0.16 g, 0.35 mmol). The mixture was heated to boiling and cooled. The precipitate was filtered off, washed with methanol and water, and dried to give the pyridoindole **10a** (0.12 g) which was suspended in methanol and heated to boiling while DMF was added dropwise until the substance dissolved. The solution was filtered and cooled. Pure pyridoindole **10a** (0.08 g) was obtained by precipitation with ether.

1-*p*-Nitrophenyl-2-amino-3-ethoxycarbonyl-1H-pyrido[3,2-*b*]indole (10b). 1N potassium hydroxide solution (7.5 ml) was added to a suspension of trifluoroacetate **9b** (2.45 g, 5 mmol) in ethanol (50 ml) and the mixture was boiled for 0.5 h, then cooled, the precipitate was filtered off, washed with ethanol and water, and dried to give pyridoindole **10b** (1.5 g).

1-*p*-Nitrophenyl-3-cyano-1,2-dihydropyrido[3,2-*b*]indolone-2 (11). Ester **8b** (3.5 g, 9 mmol) in ethyleneglycol (140 ml) was stirred and boiled for 45 min. The mixture was cooled, the precipitate was filtered off and washed with methanol to give pyridoindolone **11** (2.4 g).

This work was supported by a subvention from RFFI, grant No. 97-03-33066.

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