Chemistry of Heterocyclic Compounds, Vol. 39, No. 5, 2003

UNEXPECTED RECYCLIZATION OF 1H-δ-CARBOLINES TO PYRROLO[1,2-*a*]INDOLES

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*When 1H-2-methyl-1-p-nitrophenyl-3-ethoxycarbonylpyrido[3,2-b]indole (**1**) is heated in alcoholic solutions of ammonia, we observe a previously unknown recyclization leading to formation of 2-alkoxycarbonyl-3-methyl-9-p-nitrophenylimino-9H-pyrrolo[1,2-a]indoles (**3,6**).*

Keywords: δ-carboline, pyrido[3,2-*b*]indole, pyrrolo[1,2-*a*]indole, hydrolysis, transesterification, recyclization.

As a continuation of research on synthesis and properties of pyrido[3,2-*b*]indole derivatives obtained on the basis of 1-acetylindoxyl, in this work we have studied the reaction of 1H-2-methyl-1-*p*-nitrophenyl-3-ethoxycarbonylpyrido[3,2-*b*]indole (**1**) [1] with ammonia, with the aim of obtaining the corresponding carbamide **2**. However, we found that when compound **1** is heated in an ethanolic solution of ammonia at 100°C in an autoclave for 8 h, the process occurs in a different direction and unexpectedly leads to formation of 2-ethoxycarbonyl-3-methyl-9-*p*-nitrophenylimino-9H-pyrrolo[1,2-*a*]indole (**3**) in 75% yield. Considering that derivatives of 2-amino-δ-carboline can add nucleophilic reagents at the 4 position [2,3], we can give the scheme for this unusual reaction (Scheme 1).

In the first step, addition of ammonia occurs to form the 4-amino-1,4-dihydro-δ-carboline derivative **A**. This process is possible due to rearrangement of the double bonds to form the aromatic indole ring. The 1,4-dihydropyridine moiety, which is a cyclic enamine, can open up when treated with nucleophilic reagents (in this case, opening occurs during a transamination reaction [4]), to form an enamine of the indole series **B**, which then undergoes ring closure to form the pyrrolo[1,2-*a*]indole derivative **C** and then is converted to the end product **3.**

We should note that opening of 1,4-dihydropyridines when treated with acids is described in the literature [5].

As we see from the suggested scheme, as a result of this unusual recyclization, the pyridine moiety of compound **1** is converted to a pyrrole with formation of the isomeric pyrrolo[1,2-*a*]indole **3**. Evidence for the occurrence of such isomerization comes from the fact that the molecular weights of the starting compound and the compound obtained are identical (mass spectra: $[M]^{+\cdot}$ 375), although fragmentation by electron impact gives different results. The structure of compound **3** unambiguously follows from comparison of its ^{1}H NMR

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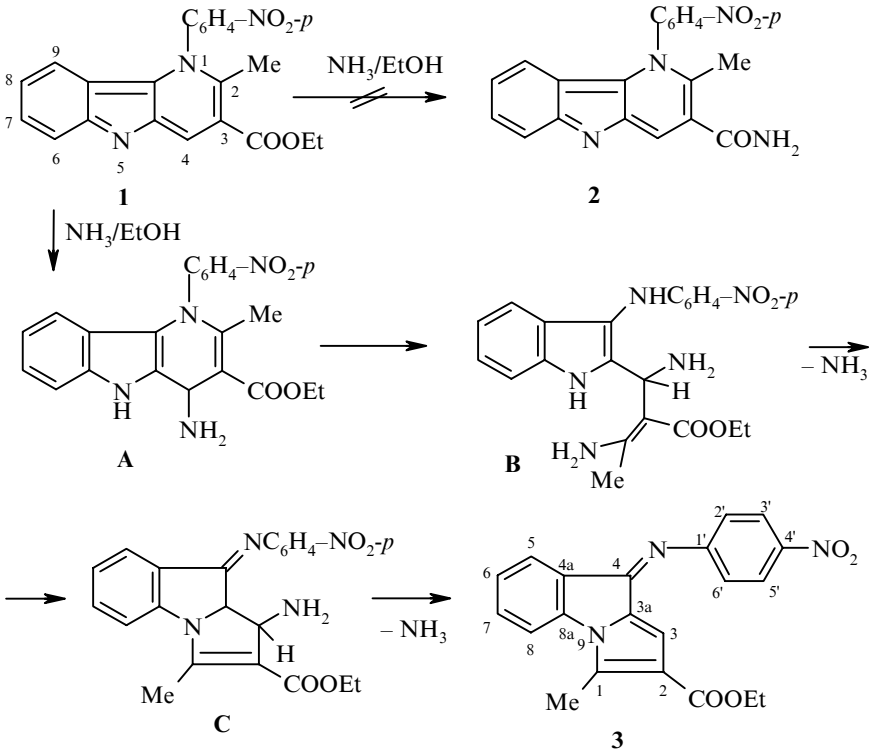
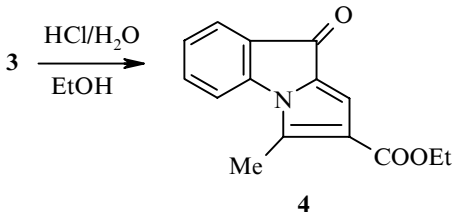
 0009-3122/03/3905-0654$25.00

Scheme 1



spectrum with the spectrum of the starting δ-carboline **1** and with the spectrum of 4-ethoxycarbonyl-1-methyl-4-oxo-4H-pyrrolo[1,2-*a*]indole (**4**) described previously in the literature [6] and isolated as a result of hydrolysis of the tricyclic derivative **3** in acid medium.



In the ^{1}H NMR spectrum of compound **3**, we observe the following signals (DMSO-d_6), δ, ppm: 1.17 (3H, t, 2-COOCH$_2$<u>CH$_3$</u>); 4.08 (2H, q, 2-COO<u>CH$_2$</u>CH$_3$); 2.74 (3H, s, 1-CH$_3$); 7.06, 8.20 (4H, A_2B_2-system, 1-*p*-nitrophenyl); 7.20 (1H, t, 6-H); 7.40 (1H, d, 8-H); 7.42 (1H, t, 7-H); 7.75 (1H, d, 5-H) and 5.93 (1H, s, 3-H). In comparing this spectrum with the spectrum of the starting δ-carboline **1** [1], it is established that both spectra have the same set of signals which however have markedly different chemical shifts. This is especially so for the chemical shifts of the 3-H and 4-H protons and the 5-H and 9-H protons in compounds **3** and **1** respectively. The signal from the proton in the 3 position (~5.93 ppm) of tricycle **3** is upfield from the signal from the proton in the 4 position (~8.9 ppm) of δ-carboline **1** for two reasons: first of all, because the 3-H proton in compound **3** belongs to the electron-rich pyrrole ring (in contrast to the 4-H proton in compound **1**, which is found on the electron-poor pyridine ring), and secondly because of the shielding effect of the *p*-nitrophenyl substituent on the proton in the 3 position (in pyrroloindole **3**). The latter circumstance explains why the 3-H signal in compound **3** is found upfield not only from the 4-H signal in δ-carboline **1** but also from signals from analogous protons in

other pyrrolo[1,2-*a*]indole derivatives (~7.0-7.5 ppm) that do not have such a substituent in the 4 position [7, 8]. Of course such an effect of the *p*-nitrophenylimine substituent on the proton in the 3 position can occur only if the *p*-nitrophenyl substituent is turned toward the pyrrole (rather than the benzene) moiety of the molecule. In fact, the NOE difference spectrum supports such a configuration: when the proton in the 3 position is presaturated, we observe a response from the protons of the *p*-nitrophenyl substituent (7.06 ppm and 8.20 ppm) indicating their spatial proximity. At the same time, in the ^{1}H NMR spectrum of tricycle **3**, the signal from the proton in the 3 position is shifted upfield, the signal from the aromatic 5-H proton is shifted downfield compared with the signal from the 9-H proton in compound **2**, which is also consistent with the structural changes on going from δ-carboline to pyrroloindole. In the latter compound, the 5-H proton (in contrast to 9-H in δ-carboline) does not experience an anisotropic effect from the *p*-nitrophenyl substituent and probably is in the deshielding region of the double bond.

If we compare the ^{1}H NMR spectra of tricycle **3** and its hydrolysis product **4** (the full spectrum is given in the experimental section), we see that the chemical shifts of the aromatic protons and also the protons of the $COOCH_2CH_3$ and CH_3 groups as we go from **3** to **4** do not undergo any substantial changes, while the signal from the proton in the 1 position in compound **4**, which not does experience the shielding effect of the *p*-nitrophenyl substituent, is shifted downfield and is observed at 7.02 ppm (which is typical for pyrroloindole compounds with such a structure [7, 8]).

Additional support for compound **1** undergoing significant structural changes come from NOE difference spectral data: when the protons of the methyl group in compound **3** are presaturated, we observe a response from the proton in the 8 position which confirms the steric proximity of the 1-CH_3 group and the 8-H proton and is evidence in favor of an angular structure for tricycle **3**.

We also recorded and compared the HMBC [heteronuclear multiple bond correlation] NMR spectra of compounds **3** and **4** (and also **6**, see below) (Table 1). The chemical shifts of like carbon atoms are close and have identical correlation peaks. An exception is the chemical shift of the $C_{(4)}$ atom: on going from **3** to **4**, it changes from 152.0 to 178.8 ppm. In the same region (178.1 ppm) we observe a signal from the carbonyl carbon atom $C_{(4)}$ in 2-piperidinomethylene-2H-pyrrolo[1,2-*a*]indole-1,4-dione [9].

Then we studied the reaction of δ-carboline **1** with ammonia at lower temperature. We established that the recyclization **1** → **3** does not occur at 20°C (δ-carboline **1** is isolated), while at 50°C the conversion is only 20%.

An important role is also played by the polarity of the solvent. For example, in dioxane with an 85-fold excess of ammonia and after holding for 8 h at 100°C in an autoclave, we could detect the presence of tricycle **3** in the reaction mixture only by chromatography.

Based on the reaction scheme given above, it follows that the indicated recyclization can occur not only when treated with ammonia but also when treated with other amines. When compound **1** is reacted with a 25-fold excess of piperidine under similar conditions, δ-carboline **1** is completely converted; but we could isolate pyrroloindole **3** and also its hydrolysis product **4** in slight amounts by column chromatography from the reaction mass, which is a complex mixture of compounds. The hydrolysis **3** → **4** probably occurs during prolonged heating of the reaction mass.

Under other conditions, and specifically when δ-carboline **1** is refluxed with a 25-fold excess of piperidine in alcohol, tricycle **3** is formed in 10% yield, while we recovered a mixture of compounds **3, 4** and *p*-nitroaniline from the mother liquor by column chromatography.

The reaction of δ-carboline **1** with methanol, due to the weak nucleophilicity of the latter, does not lead to formation of a dihydropyridine ring and then pyrroloindole, but transesterification occurs quite rapidly and the corresponding methyl ester **5** is formed. When compound **1** is treated with methanolic ammonia, the recyclization product **6** is formed, which contains a methoxycarbonyl group in the 2 position.

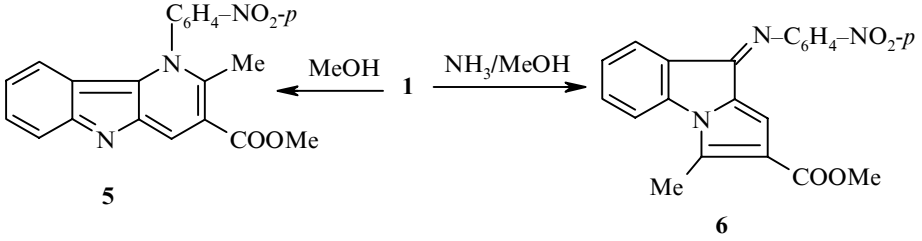
TABLE 1. ^{13}C NMR Spectra of Compounds **3, 6, 4** and Proton–Carbon Correlations in the HMBC Spectrum (^{1}H–^{13}C correlation through 2 and 3 bonds)*

Carbon atoms	^{13}C Chemical shifts, δ, ppm*[2]		
	Compound		
	3	**6**	**4**
3	114.0 (no corr.)	114.5 (no corr.)	115.0 (no corr.)
2	118.8 (1-CH_3)	118.3 (1-CH_3)	119.5 (1-CH_3)
1	135.3 (3-H, 1-CH_3)	136.2 (3-H, 1-CH_3)	138.4 (3-H, 1-CH_3)
8a	141.0 (5-, 7-H)	141.7 (5-, 7-H)	143.3 (5-, 7-H)
8	112.1 (6-H)	112.3 (6-H)	112.3 (6-H)
7	132.5 (5-H)	132.8 (5-H)	134.3 (8-, 5-H)
6	125.3 (8-H)	125.9 (8-H)	126.1 (8-H)
5	123.6 (7-H)	124.3 (7-H)	124.7 (7-H)
4a	131.5 (6-, 8-H)	132.1 (6-, 8-H)	130.7 (6-, 8-H)
4	152.3 (5-H)	153.1 (5-H)	178.8 (5-H)
4a	125.3 (3-H)	125.9 (3-H)	129.7 (3-H)
1'	157.6 (3'-, 5'-H)	158.1 (3'-, 5'-H)	—
2', 6'	119.5 (6'-, 2'-H)	119.9 (6'-, 2'-H)	—
3', 5'	124.9 (5'-, 3'-H)	125.7 (5'-, 3'-H)	—
4'	143.6 (2'-, 6'-,3'-, 5'-H)	144.5 (2'-, 6'-,3'-, 5'-H)	—
2-COOR*[3]	163.5 (O$\underline{CH_2}CH_3$)	164.5 (OCH_3)	164.0 (O$\underline{CH_2}CH_3$)
1-CH_3	11.8 (no corr.)	12.2 (no corr.)	12.4 (no corr.)

* Solvent, $CDCl_3$ (for **4** and **6**), $CDCl_3$ + DMSO-d_6 (for **3**).

*[2] Protons with which the correlation is observed are indicated within parentheses.

*[3] Chemical shifts, δ, ppm: **3** R = CH_2CH_3 59.3, 13.8, **6** R = CH_3 51.1, **4** R = CH_2CH_3 60.0, 14.3.



From this it follows that in conversion of δ-carboline **1** to pyrroloindole **6**, transesterification occurs in the first step followed by recyclization. It has been shown experimentally that neither transesterification nor amidation of the recyclized product **3** occur under the selected conditions.

EXPERIMENTAL

The IR spectra of the compounds were obtained on a Perkin-Elmer 457. The mass spectra were taken on a Finnigan SSQ-710 mass spectrometer with direct injection of the sample into the ion source. The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz), the two-dimensional HMBC NMR spectra were taken on a Bruker DRX-500 spectrometer using Bruker standard procedures. The reactions and purity of

TABLE 2. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C, (solvent for recrystallization)	IR spectrum (thin film), ν, cm^{-1}	Mass spectrum, *m/z*, M^+	Yield, %
		C	H	N				
3	$C_{21}H_{17}N_3O_4$	67.28 / 67.19	4.34 / 4.57	11.43 / 11.20	253-253.5	1700, 1649, 1611, 1597, 1585, 1548, 1508, 1460, 1420, 1370, 1340	375	75
4*	$C_{15}H_{13}NO_3$	70.55 / 70.58	5.38 / 5.13	5.40 / 5.49	173-173.5	1696, 1612, 1548, 1514, 1474, 1427, 1391, 1277, 1230, 1209, 1100	255	70
5	$C_{20}H_{15}N_3O_4$	66.53 / 66.48	4.17 / 4.18	11.48 / 11.63	252 dec. (methanol)	1713, 1624, 1526, 1494, 1460, 1380, 1320, 1300, 1270, 1220	361	69
6	$C_{20}H_{15}N_3O_4$	66.51 / 66.48	4.38 / 4.18	11.26 / 11.63	259-259.5 (acetone)	1700, 1649, 1611, 1598, 1585, 1548, 1508, 1460, 1420, 1370, 1340	361	44

* IR spectrum in KBr disk.

the substances were monitored on Silufol UV-254 plates in chloroform (for compounds **3, 4, 6**, visualization in UV light) and in the system ethylacetate–isopropanol–ammonia, 5:3:1 (for compounds **1** and **5**).

The physicochemical characteristics of the synthesized substances are given in Table 2.

2-Ethoxycarbonyl-1-methyl-4-*p*-nitrophenylimino-4H-pyrrolo[1,2-*a*]indole (3). A. A mixture of δ-carboline **1** (1.2 g, 3.2 mmol) and an ethanol solution of ammonia (15% solution) (60 ml) was held for 8 h at 100°C in an autoclave. This was cooled down, the precipitate was filtered out and washed with ethanol. The substance was purified by column chromatography (SiO_2, 1×40, chloroform as eluent). The yellow band was collected. Pyrroloindole **3** (0.9 g) was obtained.

B. A mixture of δ-carboline **1** (0.2 g, 0.53 mmol), absolute ethanol (15 ml), and piperidine (1.3 ml, 13 mmol) was held for 9 h at 100°C in an autoclave. The mixture was cooled and the solution was evaporated down. The oily residue was mixed with ether, the precipitate (0.15 g) was filtered out and dissolved in chloroform. The solution was applied to a SiO_2 column and eluted with chloroform. The yellow band was collected and combined with the wash ether solution and evaporated down. The residue was triturated with ethanol, the precipitate was filtered out and washed with ethanol. Obtained 0.02 g of precipitate "a", which according to TLC data is compound **3** with compound **4** as an impurity. The ethanol mother liquor was evaporated down. The residue was dissolved in chloroform and filtered through a bed of SiO_2. The chloroform was evaporated off and 0.02 g of precipitate "b" was obtained: a mixture of compounds **3** and **4** (1:1 according to TLC). Precipitate "b" was recrystallized from methanol (2 ml). Obtained 0.01 g of a substance which was added to precipitate "a". A total of 0.03 g (precipitate "a") was recrystallized from methanol (25 ml). Obtained 0.01 g (5%) of pyrroloindole **3**; there was no depression of the melting point for a mixed sample with a sample of this compound obtained by method A. The methanolic mother liquors from recrystallization of precipitates "a" and "b" were combined and evaporated down, and the precipitate (0.03 g) was recrystallized from

isopropanol. Obtained 0.01 g (7%) of pyrroloindole **4**; there was no depression of the melting point for a mixed sample of this with a sample of this compound obtained by hydrolysis of compound **3**.

C. A mixture of δ-carboline **1** (0.3 g, 0.8 mmol), absolute ethanol (20 ml), and piperidine (0.9 ml, 9 mmol) was refluxed for 17 h, piperidine (1 ml, 10 mmol) was added and it was refluxed for another 2 h. After 16 h, the precipitate was filtered out and washed with alcohol. Obtained 0.02 g of pyrroloindole **3**. Another 1 ml of piperidine was added to the mother liquor and it was refluxed for 6 h. After 16 h, the precipitate was filtered out and washed with ethanol. An additional 0.01 g of pyrroloindole **3** was obtained. Total yield 0.03 g (10%). There was no depression of the melting point for a mixed sample of the substance with a sample of this compound obtained by method A.

2-Methoxycarbonyl-1-methyl-4-*p*-nitrophenylimino-4H-pyrrolo[1,2-*a*]indole (6). A mixture of δ-carboline **1** (0.4 g, 1.1 mmol) and methanolic ammonia (19% solution) (20 ml) was held for 5.5 h at 100°C in an autoclave. The substance was isolated and purified as for compound **3**. Obtained 0.17 g of pyrroloindole **6**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.66 (3H, s, 2-COO$\underline{CH_3}$); 2.83 (3H, s, 1-CH_3); 7.27, 8.34 (4H, A_2B_2 system, 1-*p*-nitrophenyl); 7.38 (1H, t, 6-H); 7.67 (2H, m, 7-H, 8-H); 7.87 (1H, d, 5-H), and 5.92 (1H, s, 3-H).

2-Ethoxycarbonyl-1-methyl-4-oxo-4H-pyrrolo[1,2-*a*]indole (4). 10% HCl (20 ml) was added to a suspension of imine **3** (0.4 g, 1.1 mmol) in ethanol (20 ml), heated up to 70°C; this was stirred while refluxing for 0.5 h. The solution obtained was cooled. The precipitate was filtered out and washed with 50% ethanol. The substance (0.23 g) was purified as for compound **3**. Obtained 0.19 g pyrroloindole **4**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 (3H, t, 2-COOCH$_2\underline{CH_3}$); 4.21 (2H, q, 2-COO$\underline{CH_2}$CH$_3$); 2.78 (3H, s, 1-CH_3), 7.28, 7.59 (4H, m, benzene ring protons), and 7.02 (1H, s, 3-H).

1H-3-Methoxycarbonyl-2-methyl-1-*p*-nitrophenylpyrido[3,2-*b*]indole (5). A mixture of δ-carboline **1** (0.3 g, 0.8 mmol) and methanol (10 ml) was held for 8 h at 100°C in an autoclave. This was cooled down and the solution was evaporated. The residue was stirred with methanol (1-2 ml), the precipitate was filtered out. Obtained 0.11 g of δ-carboline **5**. The methanolic mother liquor was evaporated off, the residue was suspended in water (20 ml) and a few drops of conc. HCl (pH 3) were added and it was heated to boiling. The solution of the chloride of δ-carboline **5** was filtered, cooled, and alkalinized with a 40% NaOH solution (pH 9). The precipitate was filtered out, washed with water, methanol (0.5 ml) and ether. An additional 0.09 g of δ-carboline **5** was obtained. Total yield 0.2 g. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.71 (3H, s, 2-CH_3); 3.99 (3H, s, COO$\underline{CH_3}$); 8.11, 8.70 (4H, A_2B_2 system, 1-*p*-nitrophenyl), 6.02 (1H, d, 9-H); 6.70 (1H, t, 8-H); 7.33 (1H, t, 7-H); 7.64 (1H, d, 6-H), and 8.87 (1H, s, 4-H).

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