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SYNTHESIS AND SOME TRANSFORMATIONS OF DERIVATIVES OF PYRIDO-[3,2-*b*]INDOLE (δ-CARBOLINE)

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

The reactions of 2-dimethyliminomethyl-3-(p-nitrophenyl)aminoindole chloride with compounds with an active methylene center have been studied. A series of derivatives of δ-carboline have been synthesized. By the reaction of 3-ethoxycarbonyl-2-methyl-1-p-nitrophenylpyrido[3,2-b]indolinium chloride with the diethyl acetal of DMF the corresponding 2-dimethylaminovinyl derivative was synthesized which was converted into 5-p-nitrophenyl-1-oxo-1,10-dihydropyrano[3',4':5,6]pyrido[3,2-b]indol-5-ium chloride in the presence of acid.

Keywords: indole, carboline, pyranopyridoindole, pyridoindolinium, pyridoindole.

Previously we have synthesized the corresponding 2-formyl derivative (**2**) by Wilsmeier formylation of 3-(*p*-nitrophenyl)aminoindole (**1**). Compound **2** is a suitable starting material for the synthesis of various substituted δ-carbolines [2, 4]. It is known [5] that the basic intermediate in the synthesis of aldehydes by the Wilsmeier reaction is an immonium salt of type **3**. We did not isolate **3** but it was established that, in contrast to aldehyde **2**, it is capable of cyclizing to give derivatives of indolo[3,2-*b*]quinoline [1]. In other words the immonium salt, because of the positive charge, is a more reactive synthon in reactions with electron-excess centers than the corresponding formyl derivative. From this it appeared interesting to study the reactions of immonium salt **3** with a series of carbanions and to compare the results with data previously obtained about the reactions of aldehyde **2** with the same active methylene compounds. Salt **3** was isolated from the reaction mixture and, without special purification*, was used in reactions with compounds containing active methylene units in the presence of triethylamine. It appeared that reactions of salt **3** with malonodinitrile (**4a**), cyanacetamide (**4b**), and ethyl cyanoacetate (**4c**) occurred considerably more readily than the reactions of aldehyde **2** with the same compounds. Reactions with the immonium salt occurred even at room temperature and did not require prolonged heating as in the case of aldehyde **2**. Derivatives of indolylacrylic acid **5a-c** were isolated in high yield from condensation of salt **3** with compounds **4a-c**.

* As was to be expected, salt **3** is readily hydrolyzed with water to give aldehyde **2**. On the chromatogram on Silufol a small spot of aldehyde **2** was observed in addition to a spot of the salt at the starting point. The FAB mass spectrum has *m/z* 309 $[M+H]^+$; the compound does not have a melting point and, unlike aldehyde **2** which has mp 237-238°C, decomposes at >200°C.

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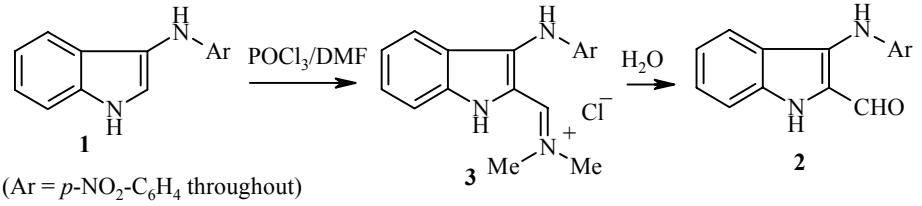
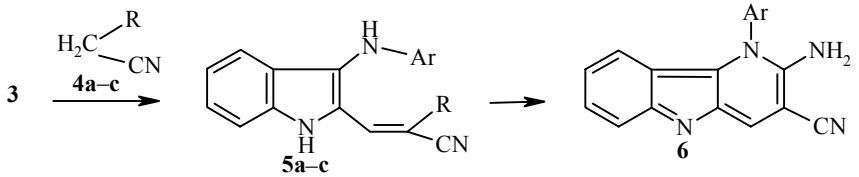


(Ar = *p*-NO_2-C_6H_4 throughout)

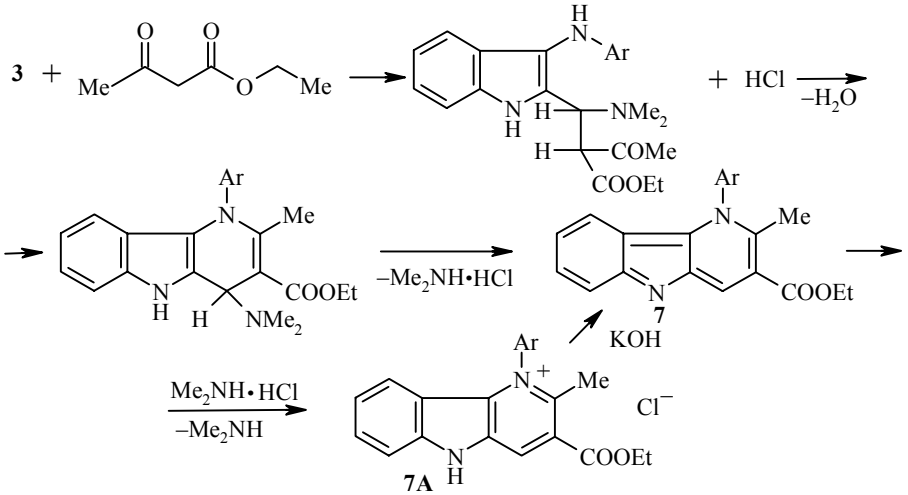
With cyanacetamide **4b** and ethyl cyanoacetate **4c** the same products are obtained at higher temperature, but with malonodinitrile **4a** under these conditions only a derivative of δ-carboline – 1H-2-amino-3-cyano-1-*p*-nitrophenylpyrido[3,2-*b*]indole (**6**) – was obtained.



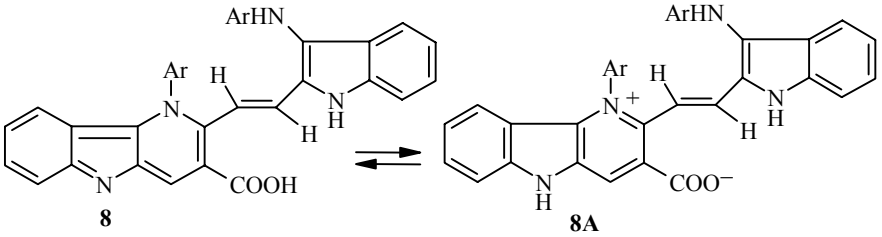
4, 5 a R = CN, **b** R = $CONH_2$, **c** R = COOEt

Compound **5a**, which is undoubtedly formed initially, cyclizes on heating so rapidly that it could not be isolated. It is probable that the different reactivity of compounds **5a-c** with respect to cyclization is a result of steric factors. The bulky substituents in **5b,c** lead to a partial deflection of the vinyl fragment from the indole ring plane which inhibits cyclization, whereas the two "rod-like" cyano groups in compound **5a** make possible a configuration favorable for closing the pyridine ring.

The next step in this work was the reaction of ethyl acetoacetate with the immonium salt **3** and the aldehyde **2**. Two substances were formed when **3** was boiled in propanol-2 with ethyl acetoacetate. The principal product was 3-ethoxycarbonyl-2-methyl-1-*p*-nitrophenyl-5H-pyrido[3,2-*b*]indolinium chloride (**7A**) in a yield of 39% (dimethylamine evolved during the reaction). The formation of the tricycle **7A** evidently occurs as follows:



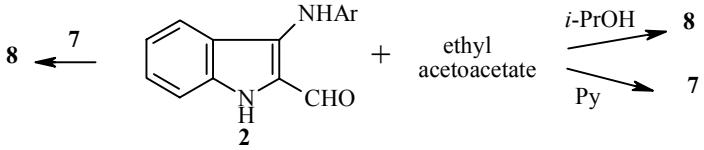
In other words, stabilization of **7A** as a result of aromatization is so great that the tricycle **7** is a stronger base than dimethylamine. Only treatment of salt **7A** with alkali makes possible the formation of the base **7**. The minor product, isolated from this reaction in 7% yield, was 3-carboxy-1-[3-(*p*-nitrophenyl)aminoindolyl-2]-2-[1-*p*-nitrophenyl)pyrido[3,2-*b*]indolyl-2]ethylene (**8**).



The condensation of salt **3** with ethyl acetoacetate in the presence of triethylamine occurs more unambiguously. In this case the only product isolated was the chloride of **7A**, while the product of its further condensation (**8** ⇄ **8A**) was observed in only trace amounts by TLC. In other words, the presence of large amounts of base (without triethylamine the process is catalyzed only as a result of the diethylamine formed, which produces a very small rate of condensation in the initial reaction) leads to considerable acceleration of the formation of the tricycle **7**, complete consumption of the starting material **3**, and a sharply deceleration of the secondary condensation to the bisheterylethylene derivative **8**.

The structure of compound **8** follows from the ^{1}H NMR spectrum (see Experimental) in which there is a strongly broadened COOH signal at 12 ppm. The chemical shifts of the protons of the benzene ring of the tricyclic part of the molecule are found between the signals observed in the ^{1}H NMR spectra of compounds **7A** and **7** (salt and base) which supports the proposal that the equilibrium **8** ⇄ **8A** occurs in solution. At the same time the absence of COOH absorption in the IR spectrum of this compound suggests that in the solid state it exists primarily as the zwitterion **8A.** Compound **8** is evidently formed by reaction of the tricycle **7** with the initial immonium salt **3** or with the aldehyde **2** formed in the reaction mixture as a result of hydrolysis of **3** with water in the solvent. Hydrolysis of ethoxycarbonyl groups occurs very easily because of water formed during the condensation reaction. The driving force for such easy saponification is probably also stabilization achieved by the aromatic indole ring (**8A**). The structure of **8** ⇄ **8A** was confirmed by an independent synthesis – condensation of aldehyde **2** with tricycle **7** gave this compound in 92% yield.

It is interesting that the condensation of aldehyde **2** with ethyl acetoacetate depends on the solvent used. The sole product on boiling in propanol-2 was the disubstituted ethylene **8**, while the δ-carboline **7** was isolated in 40% yield on boiling in pyridine.



When the reaction of immonium salt **3** with ethyl acetoacetate was carried out at room temperature in the presence of triethylamine, a mixture of **7** and **7A** was formed, from which compound **7** was isolated in 30% yield (see Experimental). Under these condensation conditions, an intermediate vinyl containing compound with M^+ 393 occurred as an impurity in **7** (for **7** M^+ = 375). Considering the low yield of compound **7** (30%) the mother liquor after removal of the precipitate was kept at 20°C for 1 week; stepwise formation of a yellowish compound was observed which was ascribed structure **9**.

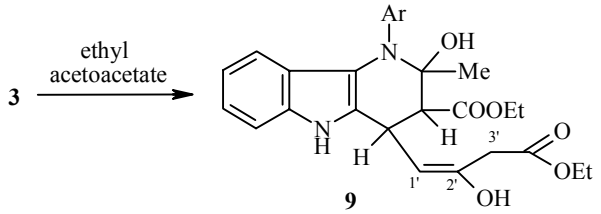


TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Mass spectrum, *m/z*	Found, % / Calculated, %				IR spectrum, ν, cm^{-1}	mp, °C, recrystallization solvent	Yield, % (method)
			C	H	N	Cl			
7A	$C_{21}H_{18}ClN_3O_4$	375	61.64 / 61.24	4.59 / 4.41	10.20 / 10.20	8.40 / 8.61	3420, 2700-2500, 1720, 1630, 1610, 1590	252-254 dec. *i*-PrOH–MeOH, 2 : 1	39 (A) 67 (B)
7	$C_{21}H_{17}N_3O_4$	375	66.94 / 67.19	4.50 / 4.57	11.05 / 11.20		1710, 1695, 1610, 1590	236-270 dec.	53 (A) 40 (B) 30 (C)
8	$C_{34}H_{22}N_6O_6 \cdot H_2O$	610	64.44 / 64.96	4.04 / 3.85	12.98 / 13.37		3640-3600, 3460, 3380, 1620, 1590	248 dec.	92 (A) 92 (B) 7 (C)
9	$C_{27}H_{29}N_3O_8$	523	61.89 / 61.94	5.78 / 5.58	7.90 / 8.03		3460, 3350, 3300, 1730, 1710, 1595, 1580	220-221 MeOH	32
10	$C_{24}H_{22}N_4O_4$	430	66.88 / 66.97	5.06 / 5.15	12.7 / 13.02		1710, 1620	200-220 dec. *i*-PrOH	59
10A	$C_{24}H_{23}ClN_4O_4$	430	61.79 / 61.74	4.86 / 4.97	11.96 / 12.00	7.68 / 7.59	2700-2620, 1715, 1620	>200 dec. *i*-PrOH	13
11	$C_{20}H_{12}ClN_3O_4 \cdot H_2O$	357	58.50 / 58.33	3.25 / 3.64	10.23 / 10.21		3360, 3600, 3420-3300, 1740, 1635, 1600	>350 MeOH	55

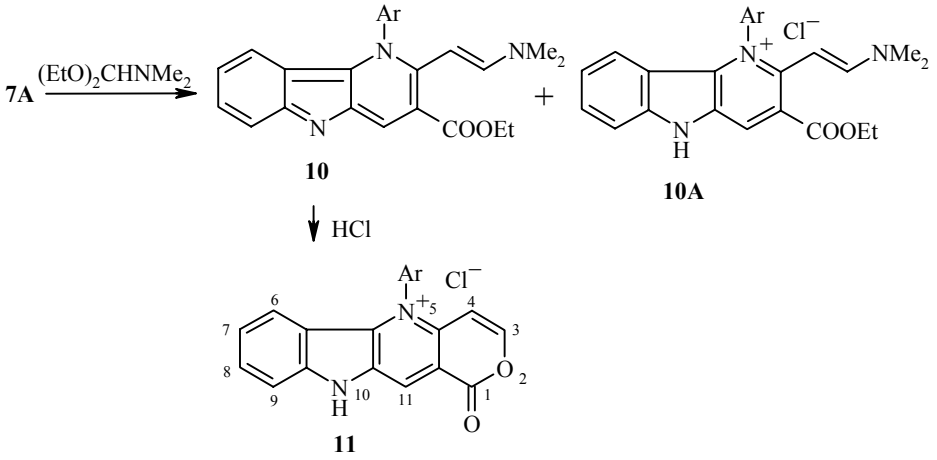
TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized, δ, ppm, *J* (Hz)

Com-pound	4-H s	6-H m	7-H m	8-H m	9-H m	C_6H_4–NO_2 A_2B_2-system	2-CH_3 s	3-$COOC_2H_5$ *J* = 7.2		Other signals
								t	q	
7A	9.2	7.9	7.7	7.1	6.1	8.2; 8.8	2.75	1.42	4.5	13.6 (br. s, 5-NH)
7	8.91	7.63	7.35	6.7	6.08	8.1; 8.7	2.7	1.41	4.4	
8	8.61	7.73	7.58	7.16	5.97	8.10; 7.51				7.14, 7.32 (two d, vinyl protons, *J* = 16.4); 9.03 (br. s, NH–$C_6H_4NO_2$); 11.65 (br. s, NH-indole); 12.00 (br. s, COOH); 6.5, 7.94 (A_2B_2-system, $C_6H_4NO_2$); 6.94-7.33 (m, arom., protons of the benzene ring of indole)
10	8.57	7.48	7.2	6.61	6.0	7.96; 8.64		1.32	4.34	2.72 (s, $N(CH_3)_2$); 4.59, 6.62 (two d, vinyl protons, *J* = 12.4)
10A	8.79	7.71	7.54	7.00	6.00	8.10; 8.70		1.34	4.39	2.82 (s, $N(CH_3)_2$); 4.59, 7.00 (two d, vinyl protons); 12.9 (br. s, 5-NH, *J* = 12.4)
	11-H	9-H	8-H	7-H	6-H	$C_6H_4NO_2$	3-H	4-H		
11	9.52	7.94	7.85	7.19	6.38	8.2; 8.8	8.07 *J* = 6.5	6.68 *J* = 6.5		13.65 (br. s, 10-NH)

Elemental analysis data and the mass spectrum (which included a molecular ion peak at M^+ 523, which corresponds to the molecular mass of this compound) were in complete agreement with the proposed structure. Most of the signals in the ^{1}H NMR spectrum were doubled which may be connected with the presence of geometric isomers or the presence of a mixture of diastereomers. Nevertheless, the ^{1}H NMR spectrum does not disagree with the proposed structure. ^{1}H NMR spectrum of compound **9** (DMSO-d_6), δ, ppm, *J* (Hz): 0.81 and 0.87 (t, *J* = 7.2) and 3.80 (br. m) two COOEt; 1.27 (3H, s, 2-CH_3); 2.60 (2H, AB-system, J_{gem} = 14, 3'-CH_2); 3.45 (1H, d, *J* = 12, 3-H); 4.10 (1H, d, *J* = 12, 1'-H); 4.27 (1H, t, *J* = 12, 4-H); 5.1 (1H, s, 2-OH); 6.60 and 8.00 (4H, A_2B_2 system, C_6H_4-NO_2); 6.8-7.4 (4H, m, 6-H, 7-H, 8-H, 9-H); 11.2 (1H, br. s, NH). The mechanism for the formation of this compound is not completely clear and requires further study.

The presence of the *ortho*-positioned ethoxycarbonyl and methyl groups in the pyridine ring of compound **7** and the ready condensation of aldehyde **2** with the 2-methyl group suggested to us the use of the acetal of DMF in reactions to form vinyl derivatives because this compound is known [6] to condense with acid methyl and methylene groups. The reaction of the acetal of DMF with the tricycle **7A** was carried with constant monitoring by TLC. When the reagents (**7A**, acetal) were mixed formation of the basic δ-carboline **7** was observed, which dissolved in the excess of acetal on heating. After maintaining the solution for 2 h even at room temperature both the δ-carboline **7A** and compound **7** were completely absent according to TLC. After working up the reaction mixture two compounds were isolated: the 2-vinyl derivative **10** and its hydrochloride **10A** in 42 and 13% yield respectively.

So in this case we observed stabilization of the protonated form on account of aromatization of the derivative of 1H-δ-carboline **10A** despite the fact that the reaction was carried out with an excess of acetal which ought to facilitate transformation of the hydrochloride into the base.



On treating a solution of the 2-vinyl derivative of δ-carboline **10** in propanol-2 with hydrogen chloride in order to obtain the hydrochloride **10A**, closure of the pyran ring occurred to give the new tetracyclic derivative, pyrano[3',4':5,6]pyrido[3,2-*b*]indolium chloride (**11**).

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a Perkin-Elmer 457 instrument. Mass spectra were recorded by direct injection into the ion source of a Varian MAT-112 (70 eV) machine. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a UNITY plus 400 (400 MHz) spectrometer. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254

plates with 10:1 chloroform–methanol and 5:3:1 ethyl acetate–propanol-2–ammonia systems as eluents. The physicochemical properties and yields of all new compounds are presented in Table 1 and the ^{1}H NMR spectra are cited in Table 2.

2-Dimethyliminomethyl-3-(*p*-nitrophenyl)aminoindole Chloride (Immonium Salt, 3). A solution of 3-(*p*-nitrophenyl)aminoindole **1** (20.05 g, 79 mmol) in DMF (21.5 ml) was added dropwise at 15-20°C to the Wilsmeier complex prepared in the usual way from DMF (48 ml) and $POCl_3$ (21.5 ml). The mixture was kept at 20°C for 20 h. The precipitate was filtered, washed with DMF and chloroform to give the immonium salt **3** (18.3 g, 67%). $C_{17}H_{17}ClN_4O_2$; mp >200°C (dec.).

α-Cyano-α[3-(*p*-nitrophenyl)aminoindolyl-2]acrylonitrile (5a). A mixture of the immonium salt **3** (0.7 g, 2 mmol), malonodinitrile (0.22 g, 3.4 mmol), propanol-2 (20 ml), and triethylamine (0.28 ml, 2 mmol) was stirred for 1.5 h at 20°C. The precipitate was filtered off and washed with propanol-2 to give nitrile **5a** (0.66 g, 99%); mp 226-227°C. The IR and ^{1}H NMR spectra were identical with a sample obtained by method [3].

1H-2-Amino-3-cyano-1-(*p*-nitrophenyl)pyrido[3,2-*b*]indole (6). A mixture of the immonium salt **3** (0.7 g, 2 mmol), malonodinitrile (0.22 g, 3.4 mmol), propanol-2 (20 ml), and triethylamine (0.28 ml, 2 mmol) were boiled for 1 h. The mixture was cooled, the precipitate was filtered off and washed with propanol-2 to give the pyridoindole (0.57 g, 85%), the IR and ^{1}H NMR spectra of which were identical to those of the same substance prepared by method [3].

α-Cyano-β-[3-(*p*-nitrophenyl)aminoindolyl-2]acrylamide (5b). A mixture of the immonium salt **3** (0.7 g, 2 mmol), cyanacetamide (0.21 g, 2.5 mmol), propanol-2 (20 ml), and triethylamine (0.28 ml, 2 mmol) was boiled for 1 h. The mixture was cooled, the precipitate was filtered off, washed with propanol-2 to give amide **5b** (0.64 g, 92%), the IR and ^{1}H NMR spectra were identical to a sample made by method [3].

Ethyl α-Cyano-β-[3-(*p*-nitrophenyl)aminoindolyl-2]acrylate (5c). A mixture of immonium salt **3** (0.7 g, 2 mmol), ethyl cyanoacetate (0.55 ml, 7.5 mmol), propanol-2 (20 ml), and triethylamine (0.28 ml, 2 mmol) was stirred for 2 h, 20°C or boiled for 1 h (then cooled). The precipitate was filtered off and washed with propanol-2 to give ester **5c** (0.74 g, 98%), the IR and ^{1}H NMR spectra were identical to a sample made by method [3].

3-Ethoxycarbonyl-2-methyl-1-*p*-nitrophenyl-5H-pyrido[3,2-*b*]indolinium Chloride (7A). A. Ethyl acetoacetate (2.9 ml, 22.8 mmol) was added to a suspension of immonium salt **3** (2 g, 5.8 mmol) in propanol-2 (58 ml) and heated to boiling with stirring. The solution formed was boiled for 5 h. A precipitate began to form 3 h from the beginning of boiling. The reaction mixture was held at 20°C for 16 h. The precipitate was filtered off and washed with propanol-2 to give a mixture of chloride **7A** and the δ-carboline **8** (1.66 g). Water (60 ml) was added, the mixture was heated to boiling, and the insoluble deep cherry red residue was filtered off (0.26 g, disubstituted ethylene derivative **8**, Table 1, method C). The aqueous mother liquor was evaporated to dryness in vacuum to give the chloride **7A** (0.9 g).

B. Ethyl acetoacetate (2.9 ml, 22.8 mmol) and triethylamine (0.8 ml, 5.8 mmol) were added to a suspension of immonium salt **3** (2 g, 5.8 mmol) in propanol-2 (58 ml), the mixture was boiled for 5 h, and allowed to stand at 20°C for 16 h. The precipitate was filtered off and washed with propanol-2 to give chloride **7A** (1.6 g). No depression was obtained when a mixed melting point was taken with a sample made by method A.

1H-3-Ethoxycarbonyl-2-methyl-1-(*p*-nitrophenyl)pyrido[3,2-*b*]indole (7). A. The compound was made from the immonium salt **3** (2 g, 5.8 mmol) analogously to the synthesis of **7A** by method A. After separation of the disubstituted ethylene derivative **8**, the mother liquor was cooled and made basic with 1M potassium hydroxide. The precipitate was filtered off, and washed with water, propanol-2, and ether to give the δ-carboline **7** (1.15 g).

B. Ethyl acetoacetate (0.5 ml, 4 mmol) was added to a solution of 2-formylindole **2** [1] (0.28 g, 1 mmol) in pyridine (5 ml), the mixture was boiled for 20 min, cooled, the precipitate was filtered off, and washed with pyridine, propanol-2, and ether to give δ-carboline **7** (0.15 g). A mixed melting point with a sample made by method A did not give a depression of the melting point.

C. A mixture of immonium salt **3** (0.7 g, 2 mmol), ethyl acetoacetate (1 ml, 8 mmol), propanol-2 (20 ml) and triethylamine (0.28 ml, 2 mmol) was stirred for 8 h at 20°C and then kept for 16 h at 20°C. The precipitate was filtered off and washed with propanol-2 to give a mixture of the chloride **7A** and the base **7** (0.43 g) which was heated to boiling in water (30 ml). The insoluble base was filtered off, washed with water and propanol-2 to give the δ-carboline **7** (0.13 g). The aqueous mother liquor was made basic with 1 M potassium hydroxide to give more δ-carboline **7** (0.16 g, overall yield 0.29 g). A mixed melting point with a sample made by method A did not give a depression of the melting point.

2-[3-Carboxy-1-(*p*-nitrophenyl)pyrido[3,2-*b*]indolyl-2]-1-[3-(*p*-nitrophenyl)aminoindolyl-2]ethylene (8). A. A mixture of 2-formylindole **2** [1] (1.4 g, 5 mmol), ethyl acetoacetate (2.5 ml, 19.7 mmol), and triethylamine (0.7 ml, 5 mmol) in propanol-2 (50 ml) was boiled for 4 h, then kept at 20°C for 16 h. The precipitate was filtered off and washed with propanol-2 to give the disubstituted ethylene **8** (1.4 g).

B. A mixture of δ-carboline **7** (0.2 g, 0.53 mmol), 2-formylindole **2** [1] (0.15 g, 0.53 mmol), and triethylamine (0.1 ml, 0.72 mmol) was boiled for 1.5 h. The mixture was cooled, the precipitate was filtered off and washed with propanol-2 and ether to give compound **8** (0.3 g). A mixed melting point with a sample made by method A did not give a depression of the melting point.

C. As described in the synthesis of chloride **7A.**

1H-3-Ethoxycarbonyl-2-hydroxy-4-(2-hydroxy-3-ethoxycarbonylpropen-2-yl)-2-methyl-1-(*p*-nitrophenyl)-2,3,4,5-tetrahydropyrido[3,2-*b*]indole (9). The isopropanol mother liquor after the removal of the precipitate of a mixture of the δ-carbolines **7** and **7A**, obtained by method C, was stirred for 7-8 days at 20°C. The precipitate was filtered off and washed with propanol-2 and ether to give tetrahydrocarboline **9** (0.34 g).

1H-2-β-Dimethylaminovinyl-3-ethoxycarbonyl-1-(*p*-nitrophenyl)pyrido[3,2-*b*]indole (10). A suspension of the chloride of δ-carboline **7A** (0.4 g, 1.0 mmol) and the diethyl acetal of dimethyl formamide (4 ml) was heated to solution and then stirred for 2 h at 20°C. The acetal was distilled off in vacuum. The oily residue was stirred with propanol-2 and cooled. The residue was filtered off and washed with propanol-2 and ether to give the δ-carboline **10** (0.18 g).

2-β-Dimethylaminovinyl-3-ethoxycarbonyl-1-(*p*-nitrophenyl)-5H-pyrido[3,2-*b*]indolinium Chloride (10A). The mother liquor left after separation of δ-carboline **10** was evaporated and the residue was stirred with ether containing a few drops of propanol-2 and cooled. The residue was filtered and washed with ether to give the chloride **10A** (0.06 g).

5-(*p*-Nitrophenyl)-1-oxo-1,10-dihydropyrano[3',4':5,6]pyrido[3,2-*b*]indolinium Chloride (11). A few drops of methanolic HCl were added to a solution of carboline **10** (0.5 g, 1.2 mmol) in propanol-2 to give a pH 2-3. The solution was kept at 20°C for 3 weeks. The precipitate was filtered off and washed with propanol-2 to give the tetracycle **11** (0.25 g).

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