2,5-DIMETHYLINDOLO[3,2-b]PYRIDINES AND POLYMETHINE DYES BASED ON THEM

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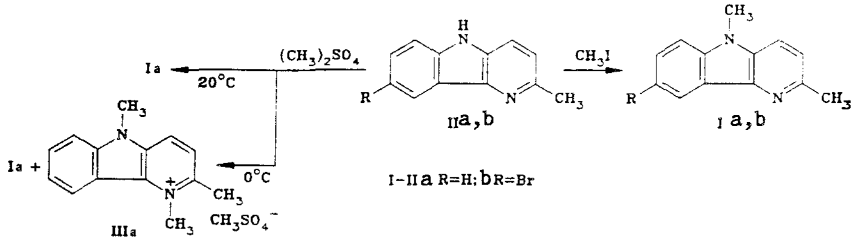
Alkylation at the nitrogen atom of the pyrrole ring of 2-methylindolo[3,2-b]-pyridine was studied, and new 2,5-dimethyl-8-R-indolo[3,2-b]pyridines (R = H, Br) were synthesized. The ethiodides of these compounds and their 2-β-acetanilinovinyl derivatives, in the condensation of which in DMSO in the presence of potassium tert-butoxide symmetrical carbocyanines were synthesized, were obtained.

The effect of the nature of nitrogen-containing heterocyclic residues on the sensitizing action of polymethine dyes of various classes has been established [1-7]. A number of extremely effective orthochromatic sensitizers have been discovered in series of symmetrical highly basic imidocarbocyanines, and a relationship between the overall effect of spectral sensitization and their basicities has been established [8-10].

In this connection, in order to search for new effective panchromatic sensitizers in series of carbocyanines it seemed expedient to synthesize the highly basic 2,5-dimethylindolo-[3,2-b]pyridine (2,5-dimethyl-δ-carboline, Ia) the electron-donor character of which according to calculated data (Φ_0) is 81°, while $pK_a = 7.0$ for the symmetrical carbocyanine obtained from it [11].

The starting compound for the synthesis of this new heterocyclic base is 2-methylindolo-[3,2-b]pyridine (2-methyl-δ-carboline, IIa). The most convenient method for obtaining δ-carbolines is a recently proposed method of synthesis [12, 13] that consists in the addition of methyl vinyl ketone to N-acetyl-indoxyl [12] and subsequent cyclization of the resulting 1,5-dicarbonyl compound with hydrazine hydrate. The mechanism of the formation of 2-methyl-δ-carboline (IIa) was discussed in detail in [13].

We carried out the methylation of carboline IIa with dimethyl sulfate in acetone in the presence of a 50% aqueous solution of NaOH. The reaction proceeds in different ways, depending on the reaction temperature: at 20°C 2,5-dimethyl-δ-carboline (Ia) is formed; at 0-5°C primarily 1,2,5-trimethylindolo[3,2-b]pyridinium methylsulfate (IIIa) is formed.



The alkylation of δ-carboline IIa with methyl iodide under interphase-catalysis conditions proceeds more smoothly and makes it possible to obtain 2,5-dimethyl-δ-carboline (Ia) in high yield.

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TABLE 1. PMR Spectra of δ-Carbolines Ia,b and Their Ethiodides IVa,b

Compound	Solvent	Chemical shift, δ, ppm								SSCC, J, Hz					
		3-H, d	4-H, d	6-H, d	7-H	8-H, m	9-H	2-CH₃, s	5-CH₃, s	3,4	6,7	6,8	7,8	7,9	8,9
Ia	d_6-DMSO	7,30	7,88	7,61	7,53 m	7,24	8,18 br.s	2,64	3,85	8,40	8,00	1,2	6,80	1,20	7,80
	$CDCl_3$	7,20	7,53	7,37	7,51 m	7,27	8,38 dt	2,74	3,78	8,40	8,20	1,07	6,80	1,20	7,90
Ib	d_6-DMSO	7,34	7,92	7,65	7,60 d	—	8,24 br.s	2,63	3,84	—	—	—	—	—	—
	$CDCl_3$	7,22	7,54	7,22	7,56 dd	—	8,48 d	2,72	3,76	8,40	8,60	—	—	1,98	—
IVa*	d_6-DMSO	8,07	8,86	7,99	7,88 m	7,55	8,50 br.d	3,03	4,10	8,50	8,50	1,50	7,00	1,00	8,40
IVb*	d_6-DMSO	8,11	8,89	7,97	7,92 d	—	8,59 br.s	3,04	4,08	8,40	—	—	—	—	—

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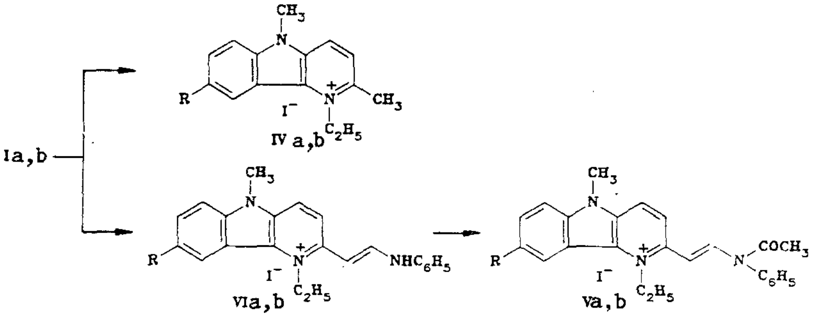
*IVa δ: 1.64 (3H, t, CH_3CH_2) 5.12 ppm (2H, q, CH_3CH_2); IVb δ: 1.61 (3H, t, CH_3CH_2) 5.08 ppm (2H, q, CH_3CH_2)

It is known that in the case of highly basic imidocarbocyanines the introduction of electronegative groups into heterocyclic residues gives rise to an increase in the sensitizing effect of these dyes [8]. In this connection we obtained the previously unknown 2,5-dimethyl-8-bromo-δ-carboline (Ib) from 5-bromo-N-acetylindoxyl via a method similar to the synthesis of base Ia.

2,5-Dimethylindole[3,2-b]pyridine ethiodides IVa,b were obtained in the reaction of the corresponding bases Ia,b with ethyl iodide.

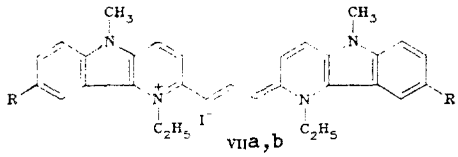
Singlets of 2- and 5-methyl groups at 2.6 and 3.8 ppm, respectively, are observed in the PMR spectra of δ-carbolines Ia,b. Signals of the 9-H proton, which in the case of recording of the spectrum of a solution in d_6-DMSO are a broad singlet for 8-bromo derivative Ib and broad doublet for base Ia, appear in the region of aromatic protons at weakest field. An appreciable shift of these signals to weaker field and distinct resolution of them to a doublet (with $J_{7,9}$ = 2 Hz) for 8-bromo derivative Ib and to a doublet of triplets for Ia, which indicates the existence of three constants of spin-spin coupling with the ortho, meta, and para protons of the benzene ring, occur when the spectra of solutions in $CDCl_3$ are recorded. The protons in the 6 and 7 positions of base Ib in d_6-DMSO have very close chemical shifts (CS) and show up in the form of characteristic signals for an AB system of strongly coupled protons. In $CDCl_3$ their CS differ to a considerably greater extent, and the signal of the 6-H proton shows up in the form of a doublet, while the signal of the 7-H proton shows up in the form of a doublet of doublets. The protons of the pyridine ring give two doublets; the doublet of the 3-H proton is found at weaker field and in the spectrum of a solution in $CDCl_3$ is superimposed precisely on the doublet of the 6-H proton. The aromatic part of the PMR spectrum of δ-carboline Ia is more complex for interpretation. The use of the double-resonance method made it possible to isolate the signals of the benzene and pyridine rings and to reliably assign each signal to a specific proton (Table 1).



On passing from bases Ia,b to ethiodides IVa,b signals of an ethyl group appear in the PMR spectra, and all of the remaining signals are shifted to weak field to a greater or lesser extent. As expected, the signals related to the protons of the pyridinium fragment undergo the most substantial shift. The proton in the 4 position has the maximum shift, viz., ∿1 ppm, while the signal of the 3-H proton is shifted 0.77 ppm and the signal of the $2\text{-}CH_3$ protons is shifted 0.4 ppm. All of the signals of the protons of the indole ring are shifted only 0.2-0.4 ppm to weak field. This difference in the changes in the CS of the protons of the indole and pyridine fragments for IVa,b additionally confirms the assignments made.

2-β-Acetanilinovinyl derivatives Va,b were synthesized by heating the ethyltosylates of 2,5-dimethylindolo[3,2-b]pyridines Ia,b with triethyl orthoformate and aniline with subsequent acylation with acetic anhydride.

The formation of dyes from ethiodides IVa,b and Va,b in absolute alcohol, DMSO, pyridine, or acetic anhydride in the presence of triethylamine or other condensing agents proceeds with great difficulty or does not occur at all; this is probably associated with the high basicities of carbolines Ia,b. Symmetrical carbocyanines VIIa,b could be synthesized only by condensation of ethiodides IVa,b with the corresponding 2-β-acetanilinovinyl derivatives Va,b in DMSO in the presence of potassium tert-butoxide.



VIIa,b

As a consequence of its high basicity, carbocyanine VIIa is an unstable compound both in solution in alcohol and in the crystalline state. Complete decolorization of its alcohol solution occurs after 8-12 h. As expected, the introduction of an electronegative bromine atom into the 8 position of the carboline ring leads to a certain increase in the stability of 8,8'-dibromo-substituted carbocyanine VIIb.

One should note the deeper color of symmetrical carbocyanines VIIa,b, which are indolo[3,2-b]pyridine derivatives (λ_{max} VIIa 678 nm, λ_{max} VIIb 686 nm), as compared with symmetrical carbocyanines that are benzothiopheno[2,3-b]pyridine (λ_{max} 648 nm) and benzofurano[2,3-b]pyridine (λ_{max} 653 nm) derivatives [14]; this constitutes evidence for greater conjugation of the π electrons of the pyrrole ring in polymethine dyes with a chromophore as compared with the π electrons of the thiophene or furan ring.

In future papers we will report the synthesis of unsymmetrical carbocyanines with an indolo[3,2-b]pyridine residue.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were monitored by TLC (Silufol UV-254) and electronic spectroscopy. The electronic spectra of solutions in ethanol were recorded with a Hitachi 557 spectrophotometer. The PMR spectra of solutions in $CDCl_3$ and d_6-DMSO were recorded with a Bruker WH-200 spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with a Varian MAT 311A spectrometer.

The results of elementary analysis for C, H, and N (Br) and the M^+ values (from mass spectrometry) were in agreement with the calculated values.

The 5-R-N-acetylindoxyls (R = H, Br) were synthesized by the methods in [15-17], 1-acetyl-2-(butan-3-on-1-yl)-5-R-indolin-3-ones were synthesized by the method in [12], and 2-methyl-δ-carboline (IIa) was obtained by a method similar to that presented in [13].

2,5-Dimethylindolo[3,2-b]pyridine (Ia, $C_{13}H_{12}N_2$). A) A solution of 0.5 g of NaOH in 0.5 ml of water and 0.55 ml (5.8 mmole) of dimethyl sulfate were added at ∿20°C to a solution of 0.47 g (2.6 mmole) of 2-methylindolo[3,2-b]pyridine (IIa) in 4 ml of acetone, after which the mixture was stirred for 1 h and then poured over ice. The aqueous mixture was extracted with chloroform (three 20-ml portions), and the organic layer was washed with water and dried with magnesium sulfate. The solvent was evaporated in vacuo, and the only residue (0.3 g) was crystallized from hexane to give 0.24 g (46%) of Ia with mp 82-83°C. UV spectrum, λ_{max} (log ε): 224 (4.58), 266 (4.38), 309 (4.24), 346 nm (3.67).

B) As in method A, the reaction of 0.47 g (2.6 mmole) of IIa and 0.55 ml of dimethyl sulfate at 0-5°C for 1.5 h gave, after evaporation of the chloroform, a residue, which was dissolved in 30 ml of boiling hexane; the undissolved residue was dissolved in 20 ml of ethanol. Concentration of the hexane solution (to 5 ml) yielded 0.08 g (16%) of carboline Ia with mp 82-83°C. The addition of 20 ml of ether to the alcohol solution gave 0.33 g (40%) of 2,5-dimethylindolo[3,2-b]pyridine methylmethylsulfate (IIIa, $C_{15}H_{18}N_2SO_4$) with mp 250-252°C.

C) A solution of 20 g of NaOH in 20 ml of water, 2 ml (32 mmole) of methyl iodide, and 0.1 g of triethylbenzylammonium chloride were added to a suspension of 2.78 g (15 mmole) of base IIa in 60 ml of methylene chloride, and the reaction mixture was stirred vigorusly for 1 h at room temperature. It was then diluted with 40 ml of water, and the organic layer was washed with two 20-ml portions of water and dried with magnesium sulfate. The solvent was evapored, and the residue was chromatographed on aluminum oxide by elution with ether. The ether solution was evaporated, and the residue was crystallized from hexane to give 2.0 g (69%) of Ia.

8-Bromo-2-methylindolo[3,2-b]pyridine (IIb, $C_{12}H_9N_2Br$). A 0.5-ml (10 mmole) sample of hydrazine hydrate was added to a solution of 3.24 g (10 mmole) of 1 acetyl-2-(butan-3-on-1-yl)-5-bromo-3-indolinone in 15 ml of acetic acid, and the mixture was refluxed for 1 h. It was then cooled and poured with stirring into 100 ml of 20% aqueous KOH solution, and the mixture was allowed to stand for 12 h. It was then acidified to pH 7 with 10% HCl solution, and the precipitate was removed by filtration. Chromatography on aluminum oxide (elution with ether) gave 1.28 g (49%) of base IIb with mp 183-185°C (from benzene).

8-Bromo-2,5-dimethylindolo[3,2-b]pyridine (Ib, $C_{13}H_{11}N_2Br$). This compound was obtained as in the case of base Ia by method C by alkylation of carboline IIb with methyl iodide under interphase-catalysis conditions for 4 h. Workup gave a product with mp 127-128°C (from hexane) in 69% yield.

2,5-Dimethylindolo[3,2-b]pyridine Ethiodide (IV, $C_{15}H_{17}IN_2$). A solution of 1.0 g (5.1 mmole) of base Ia in 5 ml of dry toluene was refluxed for 20 h with 1.25 ml (15.3 mmole) of ethyl iodide, after which the precipitated light-yellow crystals were removed by filtration and washed on the filter with 10 ml of dry benzene to give 1.74 g (97%) of salt IVa with mp 243-244°C. UV spectrum, λ_{max} (log ε): 216 (4.72), 272 (4.45), 276 (4.44), 339 (4.36), 384 nm (sh) (3.54).

2,5-Dimethyl-8-bromoindolo[3,2-b]pyrdine Ethiodide (IVb, $C_{15}H_{16}BrIN_2$). This compound was obtained in the same way as ethiodide IVa from base Ib and ethyl iodide in toluene. Workup gave a product with mp 234-235°C in 62% yield.

2-β-Anilinovinyl-5-methylindolo[3,2-b]pyridine Ethiodide (VIa, $C_{22}H_{22}IN_3 \cdot H_2O$). A mixture of 0.6 g (3 mmole) of base Ia and 0.6 g (2 mmole) of ethyl p-toluenesulfonate was heated for 3 h at 120-125°C, after which 1 ml (6 mmole) of triethyl orthoformate and 0.3 ml (3.3 mmole) of aniline were added, and the mixture was heated for 3 h at 130-135°C. The excess aniline and orthoformate were removed by distillation in vacuo, and the residue was dissolved by refluxing in 10 ml of ethanol. A 4-ml sample of a 20% solution of potassium iodide was added to the solution, and the mixture was allowed to stand overnight in a refrigerator. The precipitate was removed by filtration and washed with 10 ml of water, benzene, and ether to give 1.08 g (80%) of VIa with mp 266-268°C (from alcohol). UV spectrum, λ_{max} (log ε): 218 (4.93), 305 (4.33), 352 (4.36), 422 nm (4.74). According to GLC 1 mole of VIa contained 1 mole of water.

2-β-Anilinovinyl-5-methyl-8-bromoindolo[3,2-b]pyridine Ethiodide (VIb, $C_{22}H_{21}BrIN_3 \cdot C_2H_5OH$). This compound was obtained in the same way as VIa in 78% yield and had mp 269-271°C (from alcohol). According to GLC data 1 mole of VIb contained 1 mole of alcohol.

2-β-Acentilinovinyl-5-methylindolo[3,2-b]pyridine Ethiodide (Va, $C_{24}H_{24}IN_3O \cdot 1.5H_2O$). A 1.36-g (3 mmole) sample of ethiodide VIa was heated in 6 ml of acetic anhydride for 3 h at 130-135°C, after which the mixture was cooled and treated with 20 ml of dry ether, and the mixture was allowed to stand overnight in a refrigerator. The resulting precipitate was removed by filtration and washed with 20 ml of dry ether to give 1.3 g (87%) of Va with mp 139-142°C (from alcohol). UV spectrum, λ_{max} (log ε): 216 (4.76), 284 (4.38), 262 nm (4.40). According to GLC data 1 mole of Va contained 1.5 moles of water.

2-β-Acetanilinovinyl-5-methyl-8-bromoindolo[3,2-b]pyridine Ethiodide (Vb, $C_{24}H_{23}BrIN_3O$). This compound was obtained in the same way as Va by acylation of ethiodide VIb with acetic anhydride. Workup gave a product with mp 116-118°C (from alcohol) in 61% yield.

1,1'-Diethyl-5,5'-dimethylindolo[3,2-b]pyrido-2,2'-carbocyanine Iodide (VIIa, $C_{31}H_{31}IN_4 \cdot 4H_2O$). A 3.8-ml sample of a 0.18 N (0.68 mmole) solution of potassium tert-butoxide in DMSO was added to a solution of 0.34 g (0.68 mmole) of 2-β-acetanilinovinyl derivative Va and 0.24 g (0.68 mmole) of ethiodide IVa in 2.5 ml of absolute DMSO, and the mixture was maintained at room temperature for 2.5 h. The precipitated crystals were removed by filtration and washed with 15 ml of alcohol to give 0.25 g (62%) of carbocyanine VIIa with mp 250-257°C. The carbocyanine VIIa obtained was washed with 10 20-ml portions of benzene—alcohol (2:1) and 10 2-ml portions of ethanol to give 0.12 g (31%) of dye VIIa with mp 259-261°C. Electronic spectrum, λ_{max} (log ε): 446 (3.90), 628 (4.83), and 678 nm (5.04). According to GLC data 1 mole of VIIa contained 4 moles of water.

1,1'Diethyl-5,5'-dimethyl-8,8'-dibromoindolo[3,2-b]pyrido-2,2'-carbocyanine Iodide (VIIb, $C_{31}H_{29}Br_2IN_4$). This compound was obtained in the same way as carbocyanine VIIa from ethiodides IVb and Vb. Workup gave a product with mp 264-269°C in 67% yield. Purification as in the case of VIIa gave a product with mp 269-271°C in 34% yield. Electronic spectrum, λ_{max} (log ε): 448 (4.00), 634 (4.63), 686 nm (4.83).

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