Dyes and Pigments **12** (1990) 27–34

Synthesis and Spectra of Pyrazolo(4,5-*b*)pyrido-(2,3-*c*)pyrazine Dimethine Cyanine Dyes

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(Received 30 September 1988; accepted 16 November 1988)

ABSTRACT

New asymmetrical dimethine cyanines and their bases incorporating pyrazolo(4,5-b)pyrido(2,3-c)pyrazine or its ethiodide have been prepared and their spectral behaviour was studied.

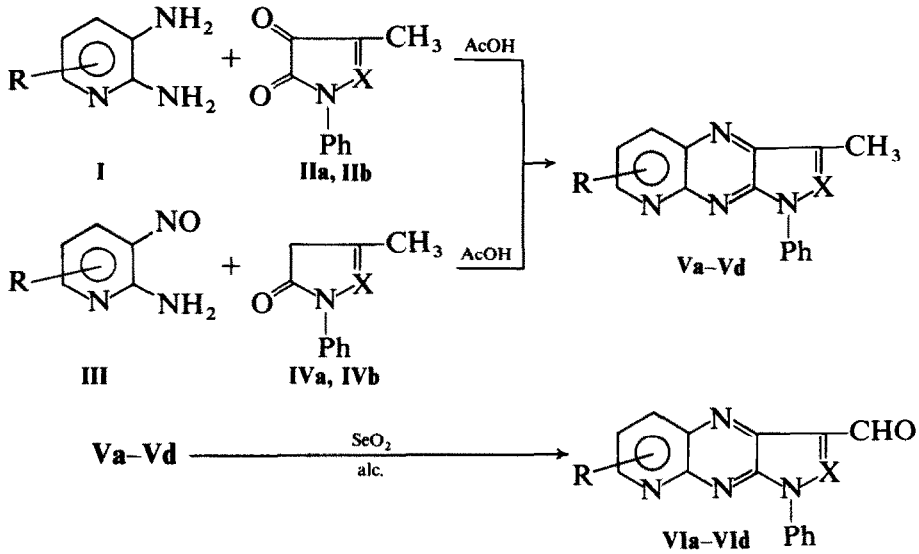
1 INTRODUCTION

As an extension to our earlier work[1] on the synthesis of dimethine cyanines incorporating the pyrazole residue in conjunction with other heterocyclic residues, and in view of the applicability of such compounds as photosensitisers,[2] textile dyes[3] and bactericidal agents,[4] some new pyrazolo(4,5-*b*)pyrido(2,3-*c*)pyrazines were prepared for use in the synthesis of dimethine cyanine dyes. It was anticipated that these new dyes might exhibit a strong photosensitisation effect.

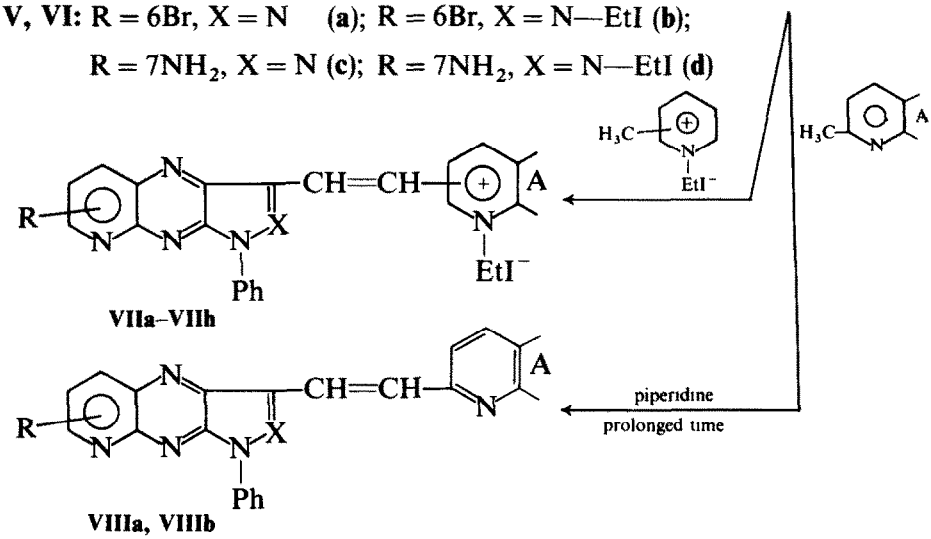
2 RESULTS AND DISCUSSION

Two types of condensation reaction were carried out to afford the desired pyrazolo(4,5-*b*)pyrido(2,3-*c*)pyrazine and its ethiodide derivatives incorporating either bromine or amino substituents in the pyrido nucleus (**Va–Vd**). The first involved reaction of 5-bromo-2,3-diaminopyridine[5] (**I**) with 3-methyl-4,5-dioxo-1-phenyl-2-pyrazoline and its pyrazolinium-2-yl salt

Dyes and Pigments 0143-7208/89/$03·50



V, VI: R = 6Br, X = N **(a)**; R = 6Br, X = N—EtI **(b)**;
R = 7NH_2, X = N **(c)**; R = 7NH_2, X = N—EtI **(d)**



VII: X(R) = N(7-NH_2), A(yl) = H(2) **(a)**;
X(R) = N(7-NH_2), A(yl) = C_4H_4(2) **(b)**;
X(R) = N(7-NH_2), A(yl) = H(4) **(c)**;
X(R) = N(6-Br), A(yl) = C_4H_4(2) **(d)**;
X(R) = N—EtI(7-NH_2), A(yl) = H(2) **(e)**;
X(R) = N—EtI(7-NH_2), A(yl) = C_4H_4(2) **(f)**;
X(R) = N—EtI(7-NH_2), A(yl) = H(4) **(g)**;
X(R) = N—EtI(6-Br), A(yl) = C_4H_4(2) **(h)**.
(yl): Linkage position of heterocyclic quaternary salts.

VIII: X(R) = N(7-NH_2), A = H **(a)**; X(R) = N(7-NH_2), A = C_4H_4 **(b)**.

Scheme 1

(**IIa, IIb**)[6] to give **Va** and **Vb**. The second involved interaction of 3-nitroso-2,6-diaminopyridine (**III**)[7] with 3-methyl-1-phenyl-2-pyrazolin-5-one and its pyrazolinium-2-yl salt (**IVa** and **IVb**)[8] to give **Vc** and **Vd**.

The desired asymmetrical dimethine cyanine dyes (**VIIa–VIIh**) were obtained by selective oxidation of **Va–Vd** with SeO_2[9] in ethanol to give the 3-formyl derivatives **VIa–VId**. Reaction of **VIa–VId** with methyl quaternary salts then gave the corresponding asymmetrical dimethine cyanine dyes **VIIa–VIIh** (Tables 1 and 2). The structures of these compounds were established by elemental analysis and by IR and NMR data (Table 3).

The dimethine cyanines **VIIa–VIIh** were highly coloured reddish-brown to violet compounds, fairly soluble in polar organic solvents and in conc. H_2SO_4 liberating iodine vapour on heating. Their ethanolic solutions gave a violet colour in alkaline medium which disappeared on acidification. The visible absorption spectra in 95% ethanol exhibited bands which became more intense and with a strong red shift on increasing the conjugation of the quaternary heterocyclic residue (A). For example, **VIIa** (X = N, A = 1-ethylpyridinium-2-yl salt) had absorption maxima at 410 nm (ε_{max} 5200 $mol^{-1} cm^2$), but on replacing the pyridyl residue by quinoline (compound **VIIb**), there appeared two absorption bands at 510 and 585 nm (ε_{max} 4500 and 6000 $mol^{-1} cm^2$ respectively). Additionally, changing the linkage position of the heterocyclic quaternary residue from 2-yl to 4-yl resulted in a slight blue shift of 5 nm (compound **VIIc**, X = N, A = 1-ethylpyridinium-4-yl salt, λ_{max} 405 nm (ε_{max} 4200 $mol^{-1} cm^2$). Similar behaviour was also noticed in the asymmetrical dimethine cyanines (**VIIe–VIIh**), X = N—EtI^- (Table 2). Comparison of the absorption spectra of **VIIb** and **VIIf** shows that quaternisation not only results in a bathochromic shift of 35 nm, but also enhances the band intensity (Table 2).

On the other hand, the colour of these dyes was also influenced by the nature of the substituent R attached to the fused pyridine heterocyclic system. Thus, the presence of a 6-bromo substituent in the heterocyclic ring increases its electron-accepting ability. This results in a more difficult charge transfer from the hetero nitrogen atom to the quinolinium-2-yl cation, causing the blue shift of 50 nm (compound **VIId**, λ_{max} 535 nm, ε_{max} 14 800 $mol^{-1} cm^2$; Table 2).

The reaction of **VIc** with non-quaternised 2-methyl heterocyclic compounds for prolonged periods in the presence of piperidine as catalyst gave the corresponding dimethine bases (**VIIIa** and **VIIIb**). The structure of these was established by elemental analysis and IR spectra, which indicated the absence of the CHO function and presence of absorption bands at 1600 cm^{-1} (νC=C).[10]

Comparison of the absorption spectra of the dimethine dye incorporating the quaternary quinoline nucleus (**VIIb**) with its dimethine base (**VIIIb**)

TABLE 1

Characterisation Data for 3-Methyl(formyl)-1-phenylpyrazolino(pyrazolinium-2-yl salt)-(4,5-*b*)-6(7)-bromo(amino)-pyrido(2,3-*c*)pyrazine (**Va–Vd, VIa–VId**)

Compd no.	*Mp* (°C)	*Yield* (%)	*Molecular formula* (*M. wt*)	*Colour of product*	*Elemental analysis* (%)					
					Calculated			*Found*		
					C	*H*	*N*	*C*	*H*	*N*
Va	140	65	$C_{15}H_{10}N_5Br$ (340)	Yellowish-brown	52·9	2·9	20·6	53·0	2·9	20·65
Vb	230	70	$C_{17}H_{15}N_5BrI$ (496)	Yellow	41·1	3·0	14·1	41·3	3·0	14·5
Vc	280	65	$C_{15}H_{12}N_6$ (276)	Intense green	47·2	4·35	30·4	47·2	4·35	30·3
Vd	245	68	$C_{17}H_{17}N_6I$ (432)	Intense bluish-green	47·2	3·9	19·4	47·2	3·9	19·4
VIa	100	45	$C_{15}H_8N_5OBr$ (354)	Red	50·85	2·3	19·8	51·0	2·3	20·1
VIb	105	40	$C_{17}H_{13}N_5OBrI$ (510)	Intense brown	40·0	2·55	13·7	39·8	2·5	13·9
VIc	300	60	$C_{15}H_{10}N_6O$ (290)	Intense brown	62·1	3·45	29·0	62·0	3·4	28·9
VId	155	58	$C_{17}H_{15}N_6OI$ (446)	Deep brown	45·7	3·4	18·8	45·6	3·3	18·6

TABLE 2

Characterisation Data for Pyrazolo(4,5-*b*)-6(7)-bromo(amino)pyrido(2,3-*c*)pyrazine-3[2(4)]-dimethine Cyanines (**VIIa–VIIh**) and Their Bases (**VIIIa, VIIIb**)

Compd no.	*M.p.* (°C)	*Yield* (%)	*Molecular formula* (*Mol. wt*)	*Colour of product*	*Analysis* (%)						*Absorption spectra in 95% ethanol* λ_{max} (*nm*) (ε_{max}(*mol*$^{-1}$ *cm*^{2}))
					Calcd			*Found*			
					C	*H*	*N*	*C*	*H*	*N*	
VIIa	300	39	$C_{23}H_{20}N_7I$ (525)	Brownish-violet	53·0	3·8	18·8	53·0	3·8	18·9	410 (5 200)
VIIb	230	35	$C_{27}H_{22}N_7I$ (575)	Violet	56·7	3·85	17·2	56·8	3·8	17·2	510 (4 500) 585 (6 000)
VIIc	300	33·4	$C_{23}H_{20}N_7I$ (525)	Brownish-violet	52·9	3·8	18·8	52·9	3·9	18·9	405 (4 200)
VIId	120	48	$C_{27}H_{20}N_6BrI$	Violet	51·0	3·15	13·2	51·3	3·2	13·7	390 (19 600) 535 (14 800)
VIIe	280–285	53	$C_{25}H_{25}N_7I_2$ (685)	Reddish-violet	44·5	3·7	14·5	44·5	3·6	14·7	350 (10 000) 415 (7 000)
VIIf	230	55·2	$C_{29}H_{27}N_7I_2$ (735)	Deep violet	47·9	3·7	13·5	47·9	3·7	13·7	545 (8 000) 587 (12 000)
VIIg	310	55·3	$C_{25}H_{25}N_7I_2$ (685)	Reddish violet	44·3	3·7	14·5	44·7	3·8	14·8	355 (6 000) 410 (5 000)
VIIh	250	37	$C_{29}H_{25}N_6BrI_2$ (791)	Deep violet	44·0	3·2	10·6	43·7	3·0	10·2	585 (30 000), 545 (44 000), 665 (10 000), 510 (38 000)
VIIIa	290	6·62	$C_{21}H_{15}N_7$ (365)	Pale brown	69·0	4·1	26·85	70·0	4·2	27·0	400 (3 300)
VIIIb	215	6·61	$C_{25}H_{17}N_7$ (415)	Deep brown	72·3	4·1	23·6	72·6	4·2	23·9	410 (5 550)

TABLE 3
IR and ^{1}H-NMR Spectral Data of Selected Pyrazolo(4,5-*b*)pyrido(2,3-*c*)pyrazine and Their Cyanine Derivatives

Comp no.	*IR* (ν_{max}^{KBr} (cm^{-1}))	^{1}*H-NMR* ($CDCl_3$), δ (*ppm*)[a]
Va	1 660 (νC=N) 750 700 (ν aromatic substitution) 3 090 (ν CH_3 stretching)	6·3–7 (m, aromatic and heterocyclic) 1·9–2·3 (s, 3H, CH_3) 3·2 (s, 1H, CH—Br)
Vb	1 660 (ν C=N) 2 940 (ν ethiodide of heterocyclic system) 750 700 (ν arom. substitution) 3 070 (ν CH_3 stretching)	6·3–7 (m, arom., heter.) 0·68 (s, 3H, CH_3) 2·0–3·1 (t, 3H, CH_3I) 3·5 (q, 2H, NCH_2)
VIa	1 730 (ν CHO) 1 660 (ν C=N) 750 700 (ν arom. substitution)	6·5–7 (m, arom. heter.) 9·9 (s, 1H, aldehydic)
VIb	1 730 (ν CHO) 1 670 (ν C=N) 750 700 (ν arom. subst.) 2 945 (ν ethiodide of heterocyclic system)	6·5–7 (m, arom. heter.) 2·5–3·1 (t, 3H, CH_3I) 3·7 (q, 2H, NCH_2) 9·85 (s, 1H, aldehydic)
VIIb	1 600 (ν C=C) 2 950 (ν ethiodide system) 1 660 (ν C=N) 750 700 (ν arom. subst.)	7·3–7·8 (m, arom., heter.) 2·3 (d, 2H, olefinic) 1·2 (q, 2H, $N(CH_2)$) 0·6 (t, 3H, CH_3I)
VIIIb	1 600 (ν C=C) 1 670 (ν C=N) 750 700 (ν arom. subst.)	7·3–7·6 (m, arom., heter.) 2·0–2·3 (d, 2H, olefinic)

[a] Abbreviations: s, singlet; m, multiplet; q, quartet; t, triplet; d, doublet.

shows that quaternisation at the quinoline residue causes a strong red shift of 100 nm with increase in intensity of the absorption band (Table 2).

Ethanolic solutions of the asymmetrical dimethine cyanine dye **VIIb** were violet in basic medium and turned yellow or were discharged on acidification. This prompted us to study the effect of variation of pH on the electronic spectra of this dye, as a representative example of these cyanines, in order to optimise the pH in the application of the dyes as photosensitisers. The spectra of dye **VIIb** in aqueous solutions of varying pH showed a bathochromic shift in alkaline media, this shift being mainly due to increase in the negative charge on hetero nitrogen atom of the pyrazolo-(4,5-*b*)pyrido(2,3-*c*)pyrazine nucleus. On the other hand, the band was hypsochromically shifted in acid media of low pH and this can be interpreted on the basis that the hetero nitrogen atom becomes protonated, thus making CT interaction difficult.

In universal buffer solutions, the electronic spectra of **VIIb** shows increased absorbance of the CT band with increasing pH, e.g. *A* (pH) values for **VIIb** at λ_{max} 585 nm were 1·1 (2·87), 1·53 (2·72), 1·58 (6·80) and 1·62 (10·88). This variation of absorbance with pH can be utilised for the determination of the ionisation constant of compounds.[11] By plotting absorbance at λ_{max} versus pH, an S-shaped curve was obtained and from this plot, the pKa values for compound **VIIb** were found to be 7·3 and 8·06.

3 EXPERIMENTAL PROCEDURE

All melting points are uncorrected. IR spectra were recorded in KBr on a Pye–Unicam SP1100 infrared spectrophotometer. Absorption spectra were recorded on a Shimadzu UV–Vis 240 recording spectrophotometer and the ^{1}H NMR spectra on a JNM-PMX 60 NMR spectrometer (JEOL). The aqueous universal buffer solutions of pH range 1·89–11·98 were prepared[12] and checked at 25°C using an Orion pH-meter model 60/A accurate to $\pm$0·005 pH units.

3-Methyl-1-phenyl-2-pyrazolones, the 4,5-dioxo derivatives, and their ethiodide derivatives (**IIa**, **IIb**, **IVa**, **IVb**) were prepared in a similar way to that described in the literature.[6,8]

5-Bromo-2,3-diamino- and/or 3-nitroso-2,6-diaminopyridine (**I**, **III**) were prepared as previously described.[5,7]

3.1 3-Methyl-1-phenylpyrazolo(4,5-*b*)-6(7)-bromo(amino)pyrido (2,3-*c*)pyrazines and their ethiodides (Va–Vd)

Equimolar amounts of 5-bromo-2,3-diamino- or 3-nitroso-2,6-diamino-pyridine (**I** or **III**), and of 3-methyl-1-phenyl-4,5-dioxo-2-pyrazoline or 3-methyl-1-phenyl-2-pyrazoline (**IIa**, **IIb** or **IVa**, **IVb**, 0·1 mol) were dissolved in glacial acetic acid (20 ml) and the solution refluxed for 3–5 h, filtered hot, concentrated, cooled and diluted with water. The precipitated products were filtered and crystallised from aqueous ethanol to give compounds **Va–Vd**, data for which are given in Table 1.

3.2 3-Formyl-1-phenylpyrazolo(4,5-*b*)-6(7)-bromo(amino)pyrido (2,3-*c*)pyrazines and their ethiodides (VIa–VId)

A mixture of **Va–Vd** and selenium dioxide (0·01 mol) was dissolved in ethanol (20 ml) and the solution refluxed for 10–12 h. The deposited selenium was filtered and the filtrate was concentrated, cooled and the product filtered and crystallised from ethanol to give compounds **VIa–VId**, data for which are given in Table 1.

3.3 Pyrazolo(4,5-*b*)-6(7)-bromo(amino)pyrido(2,3-*c*)pyrazine-3-(dimethine cyanine)s and their 2-ethiodides (VIIa–VIIh)

Equimolar amounts of **VIa–VId** and the appropriate quaternary salt (α-picoline, γ-picoline, quinaldine (0·01 mol) were dissolved in ethanol (30 ml) and piperidine (2 ml) was added. The mixture was refluxed for 12–15 h, filtered hot, concentrated, cooled and acidified with acetic acid. The precipitated product after dilution with water was filtered and crystallised from aqueous ethanol to give compounds **VIIa–VIIh** data for which are given in Table 2.

3.4 Synthesis of dimethine bases (VIIIa, VIIIb)

An ethanolic solution (30 ml) containing **VIc**, α-picoline or quinaldine (0·01 mol) and piperidine (1 ml) was refluxed for 20–25 h. The reaction mixture was filtered hot, the filtrate concentrated, diluted with water and the product filtered and crystallised from aqueous ethanol to give **VIIIa** and **VIIIb** respectively, data for which are shown in Table 2.

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