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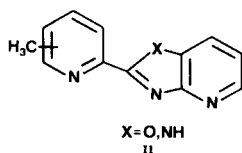
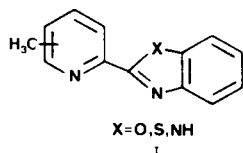
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If picoline and X-azolo[4,5-*b*]pyridine are linked, an assembled system arises which has a particular behaviour towards various quaternizing agents. As soon as picolinium salts could be obtained, the corresponding styryl dyes were prepared. The structures of bases, salts and dyes were clarified and their physical and spectroscopic data were correlated and compared with those of similar systems previously studied.

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Assembled heterocycles of the general formula **I**, containing benz-X-azole and pyridine, their quaternary salts and the related polymethine dyes have been described in a



series of papers in this journal [2-8]. The present study deals with the synthesis and characterization of analogous systems **II**, containing a X-azolo[4,5-*b*]pyridine moiety. A comparison between the two series ('benzo' and 'pyrido') is not superfluous considering the important role of a further pyridine nitrogen atom in heterocyclic bases which can give rise to quaternization.

Scheme I shows the general pathway followed in the synthesis of bases **1-4**. Table 1 reports the physical constants and spectroscopic data of the above compounds and

Scheme I

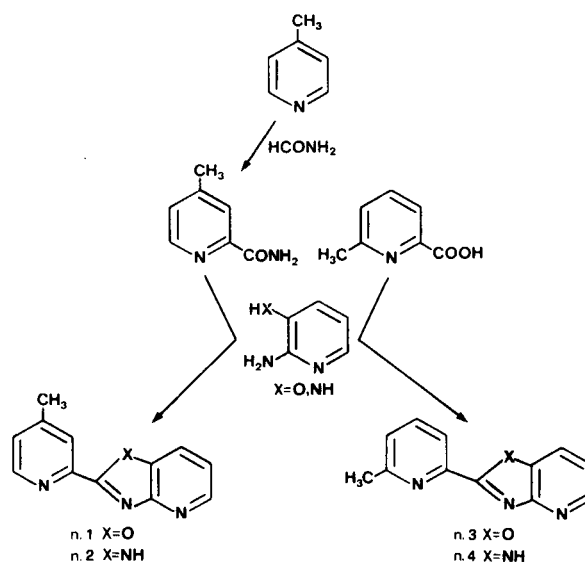


Table 1

Physical Constants and Spectroscopic Data of Bases

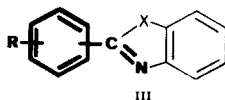
Compound number	CH ₃ position	X =	Y =	Mp °C	R _f	Electronic absorption spectra		NMR (δ) ≥ C-CH ₃
						λ max nm [a]	log ε	
1	4'	O	N	194-196	0.52	306	4.47	2.50
2	4'	NH	N	268-269	0.25	311	4.49	2.43
3	6'	O	N	166-168	0.59	310	4.48	2.62
4	6'	NH	N	198-199	0.35	313	4.49	2.63
—	4'	O	CH	124-125	0.67	303	4.36	2.43
—	4'	NH	CH	225-226	0.45	308	4.40	2.40
—	6'	O	CH	124-125	0.78	305	4.40	2.60
—	6'	NH	CH	224-225	0.48	312	4.42	2.60

[a] The λ max and log ε values correspond to the most intense peak of the long-wavelength band.

of their 'benzo' counterparts (taken from reference [2]) for a direct comparison.

Melting points and R_f (on silica gel, eluent B.A.W.) show the general trend, previously observed in similar cases, connected with the higher polarity and with the ability of imidazole derivatives to give hydrogen bonds, *i.e.* higher melting points and lower R_f values than their oxazole analogues. A further feature has now been observed, linked to the presence or not of a second pyridine nitrogen: probably for the same reasons, compounds of the general formula **II**, have higher melting points and lower R_f than their counterparts of formula **I**.

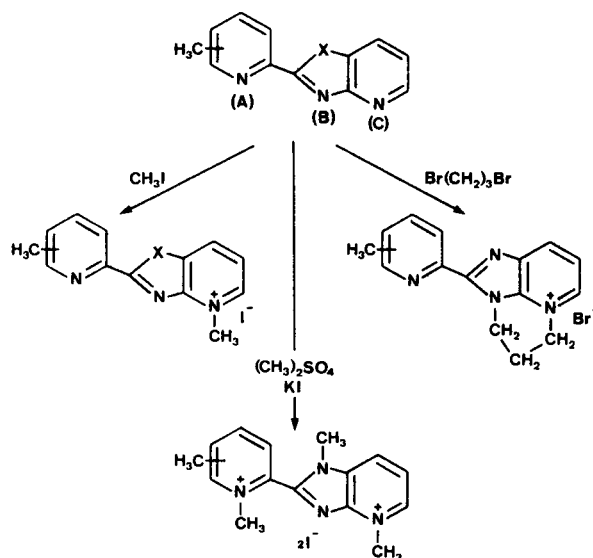
The chromogen responsible for the most intense absorption in the electronic spectra of phenylbenz-X-azoles **III**,



has been identified with the benzylidene-imino moiety [10-12] outlined in bold type. As the general patterns of compounds **I** and **II** are closely similar to those of compounds **III**, it is reasonable to identify for the first a 'pyridylidene-imino' chromogen. The perturbations caused by the extrachromophoric portions are different and compounds **II** show a systematic batho-hyperchromic effect when compared with compounds **I**. The nmr spectra also reveal, as expected, similar differences owing to the fact that the methyl protons of series **II** are slightly deshielded when compared with series **I**.

The presence in compounds **1-4** of one azole and two pyridine nitrogen atoms and, in the imidazole derivatives, of a NH group capable of *N*-alkylation, makes these bases very interesting substrates for quaternizations. Scheme II shows the quaternizations performed which lead to obtain mono and bis quaternary salts, bridged and not.

Scheme II



(A) = 'picoline' nitrogen; (B) = 'azole' nitrogen; (C) = 'pyridine' nitrogen.

By reaction with methyl iodide the bases added one mole of reagent giving monomethiodides **5-8** (formulas in Table 2). Evidently the pyridine nitrogen displays higher basicity and accessibility towards the attacking group. Chemical evidence for the structure of the salts is given by the unreactivity of the methyl groups in the picoline ring towards α,β -unsaturated carbonyl compounds and by the instability of the oxazole derivatives towards water (hydrolysis of the salts easily occurred if the solvents used for the crystallization were not accurately dried). More convincing evidence is given by spectroscopic analysis.

Table 2

Physical Constants and Spectroscopic Data of Monomethiodides

Compound number	CH ₃ position	X =	Mp °C	R_f	Electronic Absorption Spectra				NMR (δ)		
					λ max [a] nm	$\Delta\lambda$ max [b] nm	log ϵ	Δ log ϵ [b]	\geq C-CH ₃	$\Delta \geq$ C-CH ₃ [b]	\geq N-CH ₃
5	4'	O	209-211	0.25	322	16	4.07	-0.40	2.53	0.03	4.56
6	4'	NH	289-290	0.16	339	28	4.49	0.00	2.53	0.10	4.53
7	6'	O	239-241	0.23	322	12	3.98	-0.50	2.70	0.08	4.58
8	6'	NH	265-267	0.23	343	30	4.51	0.02	2.70	0.07	4.53

[a] The λ max and log ϵ values correspond to the most intense peak of the long-wavelength band. [b] Δ indicates the difference between the values of the salts and of the bases.

Table 2 reports the physical constants and spectroscopic data salts **5-8**. Quaternization keeps the picoline nitrogen unchanged, as shown by the low values of $\Delta\delta \geq \text{C-CH}_3$ (0.03-0.10 ppm) if compared with the corresponding value of 2-picoline (0.29 ppm) and 4-picoline (0.30 ppm). The imidazole ring also remains unchanged because, if reaction with methyl iodide occurred, a *N*-methylation followed by quaternization would be observed and the presence of two methyl groups would be revealed by integration and elemental analysis. The ^1H nmr spectra are fortunately simple, even as aromatic protons are concerned. Figure 1 shows, as example, the spectrum of compound **6** and Table 3 summarizes the data for the whole series. Changing from

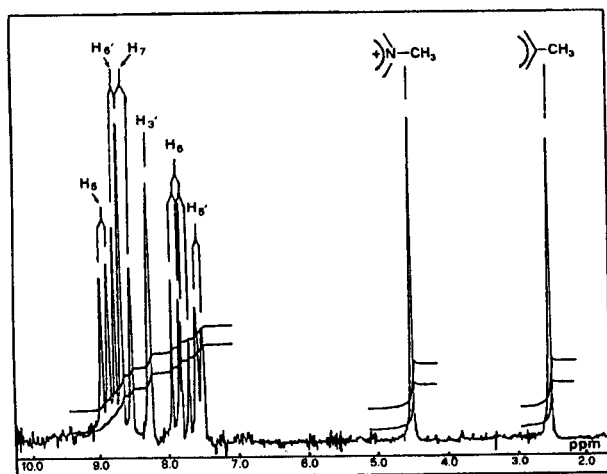


Figure 1. ^1H nmr spectrum of compound **6**

bases to salts protons 3', 4', 5', 6' are slightly deshielded (~ 0.2 ppm) whereas protons 5, 6, 7, due to proximity of the positive charge, show stronger effects (0.5-1.0 ppm). It is also interesting to note a general deshielding effect of the oxazole derivatives if compared with the imidazole ones; this effect, detectable in the picoline ring, becomes more marked for pyridine protons and attains a maximum for H-7 which is strongly affected by the proximity of oxygen.

Electronic spectra (Table 2) show that $\Delta\lambda$ values are positive and appreciable (12-30 nm). An analogous comparison with data from series **I** [2-6] indicates that alkylation and/or quaternization at the azole ring is accompanied by strong hypsochromic shifts. Finally, as already observed for melting points and R_f in Table 1, when changing from bases to salts, the enhanced polarity increases melting points and lowers R_f ; a similar trend is also observed comparing imidazole salts with their oxazole counterparts.

By reaction with a bifunctional reagent as 1,3-dibromopropane, bases **2** and **4** gave bridged monoquaternary salts **9** and **10**. Bases **1** and **3** (oxazoles) gave complex mixtures from which pure substances could not be isolated.

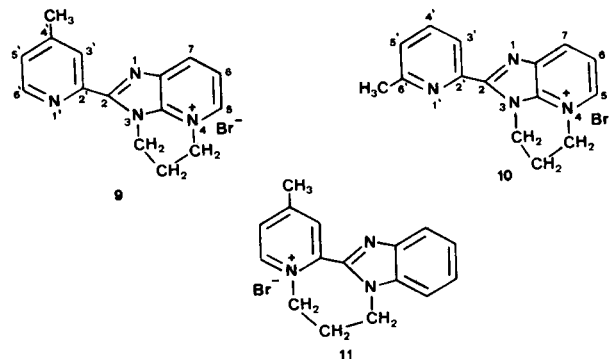
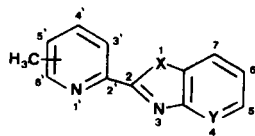


Table 3

Proton Chemical Shifts (δ , ppm) of Bases **1-4** and Salts **5-8**



Compound number	CH ₃ position	X =	Y =	Proton number							
				6'	5'	4'	3'	7	6	5	
1	4'	O	N	8.67	7.43		8.25	8.18	7.47	8.60	
2	4'	NH	N	8.55	7.33		8.23	7.97	7.17	8.38	
3	6'	O	N		7.50	7.93	8.27	8.17	7.52	8.60	
4	6'	NH	N		7.40	7.90	8.25	8.07	7.33	8.43	
5	4'	O	N-CH ₃	8.80	7.68		8.43	9.15	8.18	9.15	
6	4'	NH	N-CH ₃	8.75	7.57		8.30	8.63	7.83	8.92	
7	6'	O	N-CH ₃		7.73	8.10	8.45	9.15	8.18	9.18	
8	6'	NH	N-CH ₃			7.62	8.07	8.33	8.67	7.88	8.95

Table 4
Physical Constants and Spectroscopic Data of Salts **9**, **10**, **11**

Compound number	CH ₃ position	Mp °C	R _f	λ max nm [b]	Electronic Absorption Spectra			NMR (δ)	
					Δλmax nm [c]	log ε	Δ log ε [c]	≥ C-CH ₃	Δ ≥ C-CH ₃ [c]
9	4'	> 320	0.08	318	7	4.43	-0.06	2.50	0.07
10	6'	> 320	0.16	320	7	4.45	-0.04	2.67	0.04
11 [a]	4'	295-296	0.15	344	36	4.23	-0.17	2.72	0.27

[a] Values taken from reference [7]. [b] The λ max and log ε values correspond to the most intense peak of the long-wavelength band. [c] Δ indicates the difference between the values of the salts and of the bases.

Table 5
Proton Chemical Shifts (δ, ppm) of Salts **9** and **10**

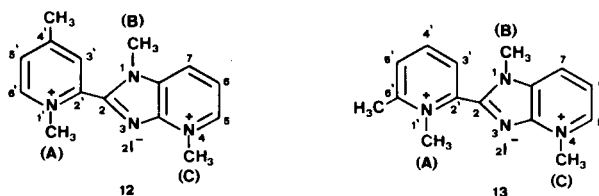
Compound number	CH ₃ position	Proton number						
		6'	5'	4'	3'	7	6	5
9	4'	8.73	7.53		8.33	8.88	7.86	9.81
10	6'		7.58	8.07	8.32	8.93	7.87	8.95

Elemental analysis (only one bromine per molecule) and the failure to give polymethine dyes give a first support to the structures proposed, but more interesting considerations arise from spectroscopic analysis. Table 4 summarizes the data, including salt **11** taken from the 'benzo' series [7], and in Table 5 the chemical shifts of aromatic protons are reported.

The low values of $\Delta\delta \geq \text{C-CH}_3$ (0.04-0.07 ppm) and the weak deshielding effect on 3', 4', 5', 6' protons lead to exclude quaternization at the picoline nitrogen, whereas the strong effect on 5, 6, 7 protons is consistent with the attack of a methylene at the pyridine nitrogen. The cyclic salts are thus formed involving *N*-alkylation of the imidazole ring.

Changing from bases to salts, monomethiodides showed appreciable bathochromic shifts whereas, as pointed out before, hypsochromic shifts accompanied alkylation and/or quaternization at the azole ring: due to the proposed structures, salts **9** and **10** should therefore exhibit a balanced effect. Indeed, the low $\Delta\lambda$ values (7 nm) agree with the above mentioned expectations. Furthermore, salt **11**, notwithstanding *N*-alkylation at the azole nitrogen, shows the greatest bathochromic effect (36 nm). The bridge in salts **9** and **10** probably allows a loss of coplanarity between the heterocyclic moieties whereas in salt **11** the constraint of the rings promotes mutual conjugation.

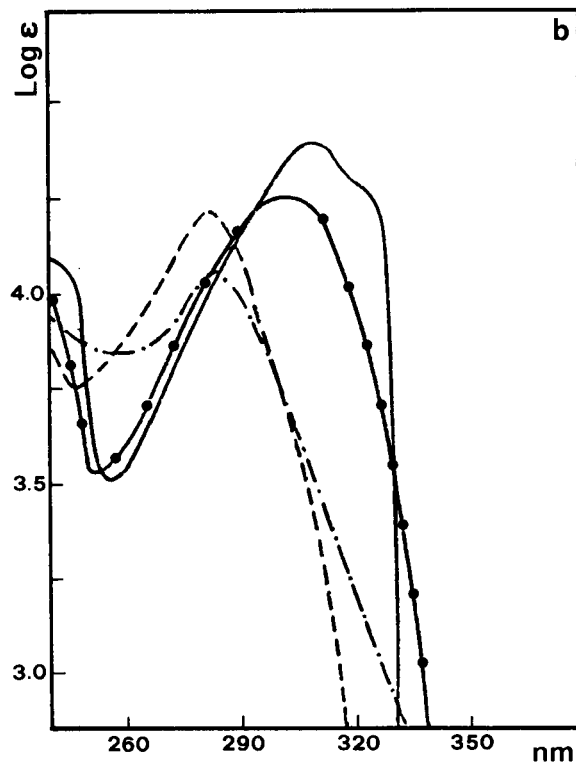
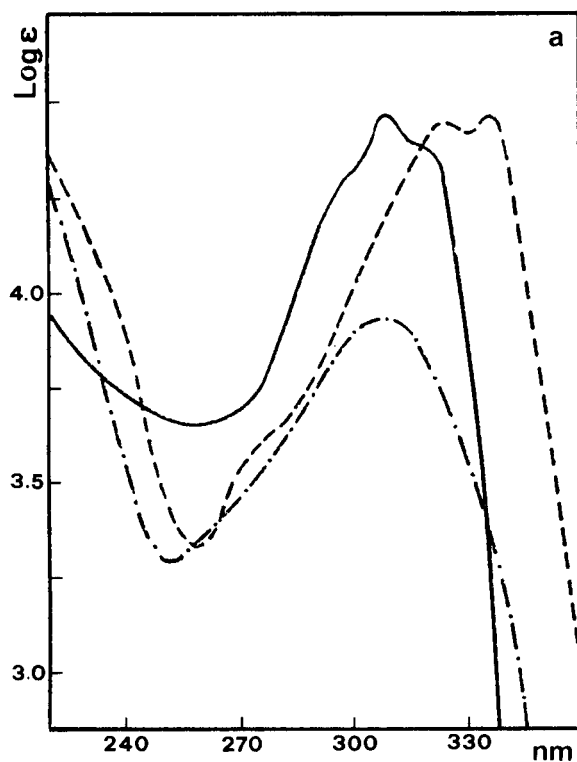
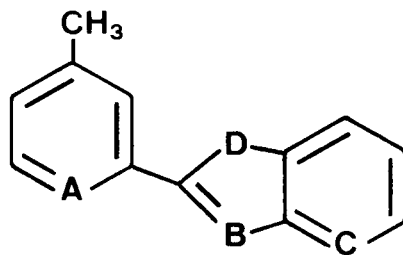
By reaction with dimethylsulphate bases **2** and **4** gave (after anion exchange with potassium iodide) bisquaternary salts **12** and **13**. Bases **1** and **3** (oxazoles) lead to monomethiodides **5** and **7**, as obtained with methyl iodide. Elemental analysis indicate the presence of three methyl groups and two iodine atoms per molecule. A series of polymethine dyes was obtained from the salts.



Even in this case spectroscopic analysis is well worth considering. In Tables 6 and 7 physical constants and spectroscopic data of salts **12** and **13** are given. $\Delta\delta \geq \text{C-CH}_3$ (0.29-0.40 ppm) and the relevant downfield shift, for 3', 4', 5', 6' protons confirm a first quaternization at the picoline ring; the second one takes place at the pyridine nitrogen, as indicated by the deshielding effect on 5, 6, 7 protons. In the spectra a third distinct signal due to a methyl is ascribed to *N*-methylation of one azole nitrogen.

Bisquaternization involves a weak hypso-hypochromic effect probably due to hindrance to transmission of electronic effects exerted by the methyl at the azole nitrogen. Figure 2 presents a final comparison of electronic spectra. As pointed out before, the patterns are closely similar and

characterized by a broad peak in region 280-350 nm. In the 'benzo' series *N*-alkylation with a C₈ chain (—●—) causes a moderate hypsochromic shift which markedly increases in consequence of the introduction of one (---) or two (—·—) positive charges. In the pyrido series, the monomethiodides, in agreement with the different site of quaternization, show a distinct shift towards longer wavelengths (---). The presence of two positive charges is accompanied by a hypsochromic shift *vs* the corresponding bases in both the series, more evident in the 'benzo' series (—·—) than in the 'pyrido' (—·—) one.



2a	A	B	C	D	n.
—	N	N	N	NH	2
...	N	N	N-CH ₃	NH	6
...	N-CH ₃	N	N-CH ₃	N-CH ₃	12

2b	A	B	C	D
—	N	N	CH	NH [a]
●	N	N	CH	N-C ₈ H ₁₇ [a]
...	N	N-CH ₃	CH	N-C ₈ H ₁₇ [a]
...	N-CH ₃	N-CH ₃	CH	N-C ₈ H ₁₇ [a]

[a] Data taken from reference [6].

Figure 2. Comparative electronic absorption spectra.

Table 6

Physical Constants and Spectroscopic Data of Salts **12** and **13**

Compound number	CH ₃ position	Mp °C	R _f	Electronic Absorption Spectra						NMR (δ)		
				λ max nm [b]	Δλ max nm [c]	log ε	Δ log ε [c]	≥C-CH ₃	Δ ≥C-CH ₃ [c]	≥N-CH ₃ (A)	>N-CH ₃ (B)	≥N-CH ₃ (C)
12	4'	253-255	[a]	310	-1	3.97	-0.52	2.72	0.29	4.35	4.17	4.55
13	6'	256-258	0.18	309	-4	4.30	-0.19	3.03	0.40	4.18	4.13	4.57

[a] No migration occurs. [b] The λ max and log ε values correspond to the most intense peak of the long-wavelength band. [c] Δ indicates the difference between the values of the salts and of the bases.

Table 7

Proton Chemical Shifts (δ, ppm) of Salts **12** and **13**

Compound number	CH ₃ position	Proton number						
		6'	5'	4'	3'	7	6	5
12	4'	9.33	8.35		8.55	9.20	8.15	9.21
13	6'		8.48	8.83	8.50	9.21	8.18	9.23

Table 8

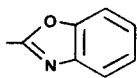
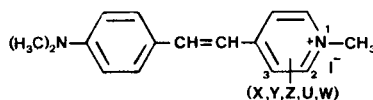
Physical Constants and Spectroscopic Data of Dyes **14** and **15**

Compound number	Styryl position	Mp °C	R _f	Electronic Absorption Spectra				NMR (δ)					
				λ max nm	Δλ max nm [a]	log ε	Δ log ε [a]	≥N-CH ₃ (A)	Δ ≥N-CH ₃ (A) [b]	>N-CH ₃ (B)	Δ >N-CH ₃ (B) [b]	≥N-CH ₃ (C)	Δ ≥N-CH ₃ (C) [b]
14	4'	258-259	0.04	539	59	4.66	0.04	4.23	-0.12	4.20	0.03	4.57	0.02
15	6'	276-277	0.05	516	56	4.61	0.04	4.13	-0.05	4.17	0.04	4.55	-0.02

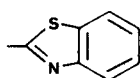
[a] Δ indicates the difference between the values of the substituted and unsubstituted dyes. [b] Δ indicates the difference between the values of the dyes and of the starting salts.

Table 9

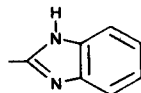
Electronic Absorption Spectra of Styryl Dyes



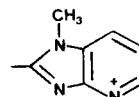
X



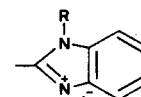
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Z



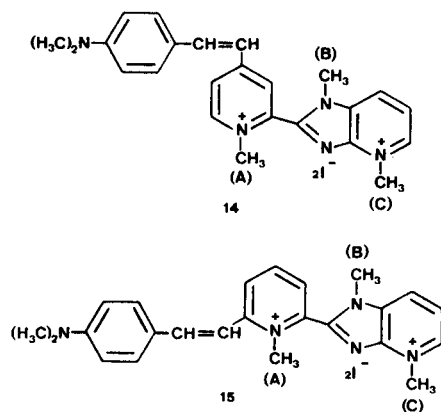
U



W

Structure	λ max	Δλ max [a]	log ε	Δ log ε [a]
H	480		4.62	
3-X	535	55	4.63	0.01
3-Y	524	44	4.60	-0.02
3-Z	525	45	4.57	-0.05
2-X	531	51	4.59	-0.03
2-U	539	59	4.66	0.04
2-W	558	78	4.58	-0.04

[a] Δ indicates the differences of the values of the substituted and unsubstituted dyes.



Salts **12** and **13** are sufficiently reactive towards *p*-dimethylaminobenzaldehyde to give styryl dyes **14** and **15**. Table 8 reports the data of dyes and $\Delta\lambda$ values related to the comparison with 'unsubstituted' dyes: these are dyes derived from **2** and **4** picoline containing a hydrogen in place of hetaryl substituent 2-*N*-methylimidazo[4,5-*b*]-*N*-methylpyridinium. The latter causes strongly bathochromic absorptions ($\Delta\lambda$ 56-59 nm) due to its high withdrawing power. $\Delta\delta$ values, related to the comparison dyes *vs* salts, point out a marked shielding of methyl 'A' probably due to a higher delocalization of the positive charge throughout the whole chromogen. A comparison of the effect of hetaryls on the absorption of styryl dyes can be made from the data in Table 9. Substituent 'U' exerts a marked shift towards long wavelengths (59 nm) and is just surpassed by 'W' (1,3-dialkylbenzimidazolium) in which the positive charge is strictly localized in the azole ring.

EXPERIMENTAL

The nmr spectra were obtained with a Varian T 60 spectrometer in DMSO-*d*₆ solution (6%) using TMS as internal standard. Electronic spectra were recorded in ethanol on a Unicam SP 8-100 spectrophotometer. The *R_f* values were determined on silica gel 60 F-254 tlc plates (Merck), using as eluent B.A.W. (butanol:acetic acid:water) 4:1:5.

Table 10

Data related to the Synthesis and Analysis of Compounds 1-15

Compound number	Yield %	Crystallization solvent	Empirical formula	Elemental Analyses		
				Calcd.	Found	
				C	H	N
1	52	acetonitrile	C ₁₂ H ₉ N ₃ O	68.24	4.30	19.89
				68.29	4.27	19.78
2	81	ethanol	C ₁₂ H ₁₀ N ₄	68.56	4.79	26.65
				68.51	4.82	26.59
3	59	water	C ₁₂ H ₉ N ₃ O	68.24	4.30	19.89
				68.11	4.40	19.96
4	76	ethanol/water	C ₁₂ H ₁₀ N ₄	68.56	4.79	26.65
				68.63	4.87	26.59
5	96	[a]	C ₁₃ H ₁₂ IN ₃ O	44.21	3.42	11.90
				44.02	3.65	11.69

6	50	ethanol	C ₁₃ H ₁₃ IN ₄	44.34	3.72	15.91
				44.19	3.62	15.69
7	30	ethanol	C ₁₃ H ₁₂ IN ₃ O	44.21	3.42	11.90
				44.22	3.22	11.98
8	35	acetonitrile	C ₁₃ H ₁₃ IN ₄	44.34	3.72	15.91
				44.25	3.63	16.03
9	68	1-butanol	C ₁₅ H ₁₅ BrN ₄	54.39	4.56	16.92
				54.48	4.38	17.11
10	76	1-butanol	C ₁₅ H ₁₅ BrN ₄	54.39	4.56	16.91
				54.24	4.69	17.18
12	10	ethanol	C ₁₅ H ₁₈ I ₂ N ₄	35.46	3.57	11.03
				35.61	3.57	10.89
13	10	ethanol	C ₁₅ H ₁₈ I ₂ N ₄	35.46	3.57	11.03
				35.43	3.41	11.21
14	50	ethanol	C ₂₃ H ₂₅ I ₂ N ₅	44.18	4.03	11.20
				44.31	3.83	11.19
15	64	ethanol	C ₂₃ H ₂₅ I ₂ N ₅	44.18	4.03	11.20
				44.24	4.11	11.03

[a] Crude product (crystallization is accompanied by decomposition).

In Table 10, yields, crystallization solvents and analyses of compounds **1-15** are reported.

4-Methylpicolinamide was prepared as indicated in reference [9]. 6-Methylpicolinic acid was purchased commercially.

Bases **1-4** were prepared condensing 4-methylpicolinamide (**1** and **2**) or 6-methylpicolinic acid (**3** and **4**) (1 mole) in polyphosphoric acid (85% phosphorus pentoxide) with 2-amino-3-hydroxypyridine or 2,3-diaminopyridine (1 mole) for three hours at 220° following the general procedure indicated in reference [13]. The reaction mixture was poured into distilled water, the precipitate was collected and slurried in dilute sodium carbonate. The bases were washed with water, dried and crystallized.

Monomethiodides **5-8** were prepared by refluxing the corresponding bases with a large excess of methyl iodide for 24 hours. The reaction mixture, after cooling, was treated with a large excess of diethyl ether and crystallized.

Salts **9** and **10** were prepared refluxing equimolecular amounts (5×10^{-2} moles) of the suitable base and 1,3-dibromopropane in 40 ml of dimethylformamide for 7 hours. After cooling, the crude salts were collected, washed with diethyl ether and crystallized.

Bisquaternary salts **12** and **13** were obtained refluxing for 4 hours the corresponding bases in toluene with an excess of dimethylsulphate. The solvent was removed, the residue was slurried with diethyl ether, filtered and treated with a saturated aqueous solution of potassium iodide. The solid was collected and crystallized.

Styryl dyes **14** and **15** were prepared refluxing for one hour in absolute ethanol (piperidine acetate as catalyst) methiodides **12** and **13** with *p*-dimethylaminobenzaldehyde (molar ratio 1:2). After cooling, the crude dyes were collected, washed with diethyl ether and crystallized.

REFERENCES AND NOTES

- [1] This work was supported by Ministero della Pubblica Istruzione.
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