2-(Methylpyridyl)-X-azolo[4,5-*b*]pyridines: Bases, Salts and Polymethine Dyes [1]

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A series of heterocyclic bases containing 2-(methyl-3-pyridyl)-X-azolo[4,5-*b*]pyridine was synthesized and the obtained bases were then quaternized. The structures of the salts were assessed by nmr and uv spectroscopy. From quaternary salts, styryl dyes were prepared and similarly characterized. The physical and spectroscopic data of the compounds were compared with those of other isomers, previously described, and of the corresponding benzo-X-azole derivatives.

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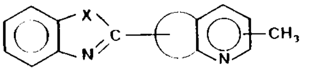
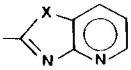
In the course of our researches on synthesis and properties of assembled heterocyclic systems having the general structure **I**, we extensively studied a great number of pyridyl and quinolyl benz-X-azoles [2-7]. Special attention was devoted to elucidate the relationships between the site of quaternization (azine or azole nitrogen) and the relative linkage of the two systems. Recently we extended our interest to the replacement of benzo-X-azole moiety with X-azolo[4,5-*b*]pyridine **II**, with the view of determining the scope of the effects of an additional azine nitrogen on the reactivity towards quaternizing agents [8].



I

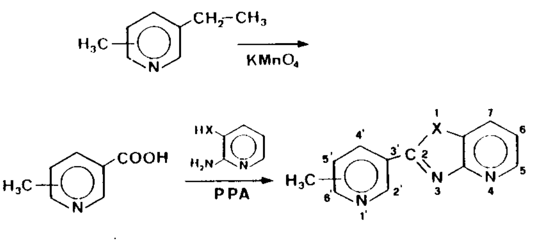
X = O, S, NH



II, X = O, NH

Results and Discussion.

The bases have been synthesized following the indicated pathway below. In Table 1 the data of the bases are reported and compared with those of the corresponding "benzo" derivatives, **5-8**, and of other position isomers, **9-12**.

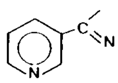


X = O, NH; CH3 4' or 6'

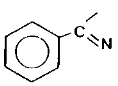
A regular trend is observed for the melting points in the three series. Imidazo derivatives are high-melting compared with oxazoles, according to their tendency to form hydrogen bonds. Substitution of a CH with an N (compounds **1-4** *vs* **5-8**) similarly increases the melting points in agreement with the increased polarity and with the enhanced tendency to form hydrogen bonds.

The opposite behaviour is shown if R_f values are considered. The polar substrate strongly interacts with the more polar (and high melting) substances which result in greater retention. Thus, lower R_f values characterize imidazo derivatives *vs* oxazo ones and pyrido derivatives, **1-4**, *vs* "benzo" ones, **5-8**.

The electronic absorption spectra of compounds **1-4** show an intense absorption band in the range 298-311 nm, probably due to a pyrilideneimino chromogen **III**, closely related to the benzylideneimino **IV** of 2-phenylbenz-X-azoles [9-11]. In Figure 1 the sample spectrum of compound **1** is reported.



III



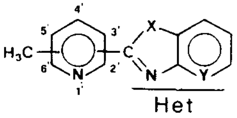
IV

The positions and the intensities of the maxima can be formed into three groups: "benzo" (**5, 6, 7, 8**), "3'-pyrido" (**1, 2, 3, 4**), "2'-pyrido" (**9, 10, 11, 12**). Following the above sequence, batho-hyperchromic effects are observed for the corresponding compounds. Furthermore, other things being equal, the same effects are shown by the 4'-methyl isomers compared with their 6'-methyl counterparts.

In Table 1 the ^{1}H nmr chemical shifts of methyl groups are reported. $\Delta\delta$ values, obtained as differences with the corresponding unsubstituted picolines evidence the effects

Table 1

Characterization Data of Bases



Compound number	CH$_3$ position	Structure Hetaryl position	X	Y	Crystallization solvent	Yield %	Mp °C	R$_f$	Electronic absorption spectra [a] λ max nm (log ε)	NMR (δ) δ-CH$_3$	NMR (δ) Δδ [b]	Empirical formula	Elemental Analyses Calcd./Found C	H	N
1	4′	3′	NH	N	Acetonitrile	98	242-243	0.59	298 (4.30)	2.70	0.38	$C_{12}H_{10}N_4$	68.56 68.43	4.79 4.88	26.65 26.72
2	4′	3′	O	N	Water	54	150-151	0.69	306 (4.39)	2.80	0.48	$C_{12}H_9N_3O$	68.23 68.11	4.29 4.29	19.89 19.77
3	6′	3′	NH	N	Water	98	306-307	0.63	311 (4.47)	2.60	0.12	$C_{12}H_{10}N_4$	68.56 68.58	4.79 4.67	26.65 26.49
4	6′	3′	O	N	Ligroine	96	170-172	0.66	309 (4.51)	2.63	0.16	$C_{12}H_9N_3O$	68.23 68.36	4.29 4.39	19.89 19.78
5 [c]	4′	3′	NH	CH			197-198	0.67	290 (4.20)	2.67	0.35				
6 [c]	4′	3′	O	CH			118-119	0.86	299 (4.28)	2.75	0.44				
7 [c]	6′	3′	NH	CH			265-266	0.83	307 (4.38)	2.55	0.10				
8 [c]	6′	3′	O	CH			111-112	0.81	302 (4.39)	2.59	0.11				
9 [d]	4′	2′	NH	N			268-269	0.25	311 (4.49)	2.43	0.11				
10 [d]	4′	2′	O	N			194-196	0.52	306 (4.47)	2.50	0.18				
11 [d]	6′	2′	NH	N			198-199	0.35	313 (4.49)	2.63	0.16				
12 [d]	6′	2′	O	N			166-168	0.59	310 (4.48)	2.62	0.15				

[a] The main absorptions above 250 nm are indicated. [b] $\Delta\delta = \delta\text{-CH}_{3\,\text{present compounds}} - \delta\text{-CH}_{3\,\text{picoline}}$. [c] Data taken from ref [4]. [d] Data taken from ref [8].

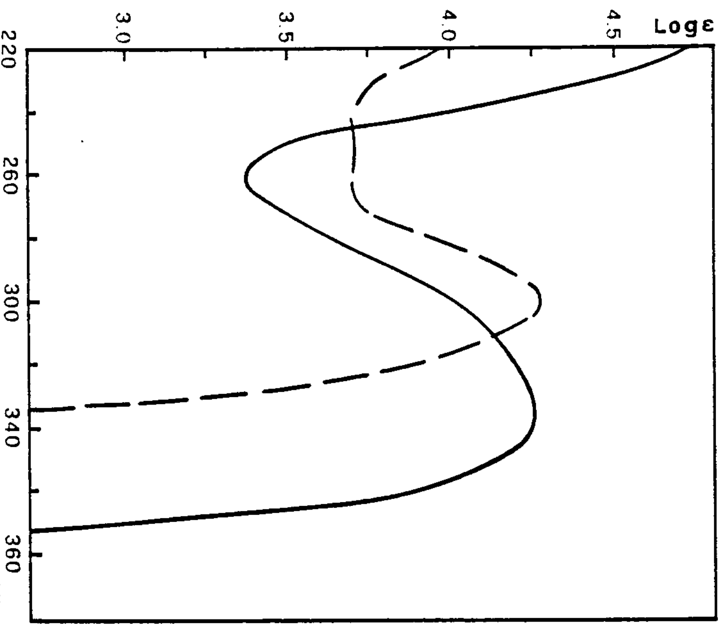


Figure 1. Electronic absorption spectrum of compound **1**.

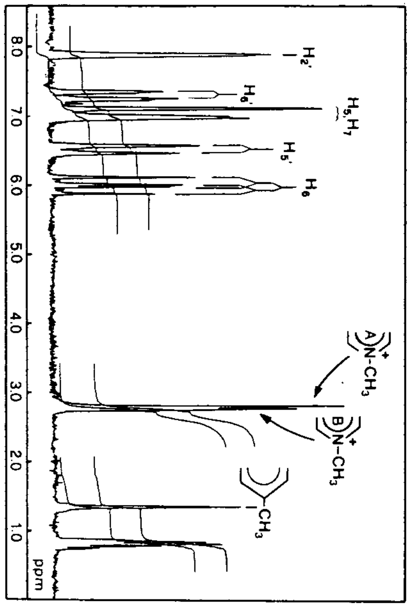
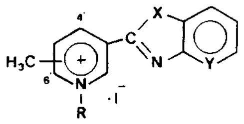


Figure 2. ^{1}H nmr spectrum of compound **13**.

Table 2

Characterization Data of Quaternary Salts



Compound number	CH_3 position	X	Structure Y	R	Crystallization solvent	Yield %	Mp °C	R_f	Electronic absorption spectra [a] λ max nm (log ε)	Δλ max nm [b] (Δ log ε) [b]	Empirical formula	Elemental Analyses Calcd./Found C	H	N
13	4'	NH	$\overset{+}{N}$-CH_3	CH_3	Ethanol	91	148-150	0.01	334 (4.31)	36 (0.01)	$C_{14}H_{16}I_2N_4$	34.03 34.22	3.26 3.35	11.34 11.41
14	4'	O	N	CH_3	Absolute ethanol	81	205-207	0.03	311 (4.27)	4 (-0.12)	$C_{13}H_{12}IN_3O$	44.21 44.36	3.42 3.57	11.90 11.80
15	6'	NH	$\overset{+}{N}$-CH_3	CH_3	Ethanol	52	273-275	0.00	339 (4.41)	28 (-0.03)	$C_{14}H_{16}I_2N_4$	34.03 33.97	3.26 3.31	11.34 11.38
16	6'	O	N	CH_3	Acetonitrile	33	242-243	0.02	312 (4.35)	3 (-0.16)	$C_{13}H_{12}IN_3O$	44.21 44.27	3.42 3.52	11.90 11.99
17	4'	NH	$\overset{+}{N}$-$C_{16}H_{33}$	$C_{16}H_{33}$	Methanol	29	188-189	0.29	334 (4.30)	36 (0.00)	$C_{44}H_{46}I_2N_4$	57.76 57.60	8.37 8.48	6.12 6.21
18	4'	NH	$\overset{+}{N}$-$C_{12}H_{25}$	$C_{12}H_{25}$	Isopentanol	30	186-188	0.28	334 (4.31)	36 (0.01)	$C_{36}H_{60}I_2N_4$	53.87 53.98	7.53 7.39	6.98 6.88
19	4'	NH	$\overset{+}{N}$-C_8H_{17}	C_8H_{17}	Isopentanol	24	162-163	0.27	334 (4.30)	36 (0.00)	$C_{28}H_{44}I_2N_4$	48.70 48.59	6.42 6.54	8.11 8.20

[a] The main absorptions above 250 nm are indicated. [b] Δ = values for salts - values for bases.

of the heteroaryl moieties on methyl groups. According to their electron-withdrawing character, the X-azolyls show a neat deshielding effect (0.10÷0.48 ppm), oxazolyl being more efficient than imidazolyl [12]. The highest $\Delta\delta$ values occur when the methyl group is *ortho* to heteroaryls (**1**, **2**, **5**, **6**) in agreement with the prevalence of inductive effects.

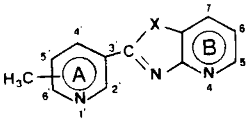
The bases **1-4**, reacting with methyl iodide, gave quaternary salts **13-16**; compound **1** was also quaternized with long-chain iodides giving salts **17-19**. Table 2 reports the data for the obtained compounds. The structure of the bases markedly influences the reaction pattern. The yields are about duplicated if the methyl is in 4′ instead of 6′, and the observed steric effect led us to choose compound **1** for experiments with long-chain iodides. Oxazole derivatives gave monoquaternary salts, whereas imidazoles led to bisquaternary salts. *N*-alkylation of imidazoles, previously reported for similar compounds [8], was not observed.

The conversion of bases into quaternary salts leads to the following changes: (1) R_f values are practically nil because of the introduction of a neat positive charge, except for long-chain terms in which the hydrophobic contribution promotes migration; (ii) melting points of oxazoles increase (55 to 72°), while those of imidazoles decrease (92 to 33°); (iii) the main absorption band (Figure 1) is shifted towards longer wavelengths more markedly for imidazoles (28 to 36 nm) than for oxazoles (3 to 4 nm).

Complete data for the ^{1}H nmr spectra of bases **1-4** and of related salts **13-16** are reported in Table 3. Figure 2 shows the sample spectrum of salt **13**.

Table 3

^{1}H NMR Data of Bases and Salts [a]



Compound number	Position 2′	4′	5′	6′	4′-CH$_3$	6′-CH$_3$	1′-$\overset{+}{\mathrm{N}}$-CH$_3$	4-$\overset{+}{\mathrm{N}}$-CH$_3$	5	6	7
1	9.00		7.47	8.57	2.70				8.42	7.32	8.10
			(5)	(5)					(5)	(5)(8)	(8)
2	9.29		7.57	8.70	2.80				8.63	7.53	8.32
			(5)	(5)					(5)	(5)(8)	(8)
3	9.35	8.47	7.50			2.59			8.42	7.30	8.08
		(8)	(8)						(5)	(5)(8)	(8)
4	9.29	8.48	7.57			2.63			8.63	7.50	8.28
		(8)	(8)						(5)	(5)(8)	(8)
13	9.57		8.22	8.98	3.03		4.50 [b]	4.47 [b]	8.78	7.68	8.76
			(6)	(6)					(6)	(6)(8)	(8)
14	9.82		8.32	9.12	3.10		4.50 [b]		8.72	7.66	8.43
			(6)	(6)					(5)	(5)(8)	(8)
15	9.85	9.18	8.38			2.94	4.56 [b]	4.45 [b]	8.95	7.87	8.88
		(8)	(8)						(6)	(6)(8)	(8)
16	9.95	9.18	8.32			2.96	4.45 [b]		8.68	7.62	8.40
		(8)	(8)						(5)	(5)(8)	(8)

[a] In the upper line chemical shifts, δ (ppm); in the lower J values (Hz). [b] Integration corresponding to three protons.

Table 4

Effect of Quaternization on Chemical Shift Values ($\Delta\delta$) [a] [b]

Salt number	Position 2′	4′	5′	6′	4′-CH$_3$	6′-CH$_3$	5	6	7
13	0.57		0.75	0.41	0.33		0.36	0.36	0.66
14	0.53		0.75	0.42	0.30		0.09	0.13	0.11
15	0.50	0.71	0.88			0.36	0.53	0.57	0.80
16	0.66	0.70	0.75			0.32	0.05	0.12	0.12

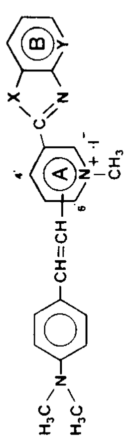
[a] Formulas given in Table 3. [b] $\Delta\delta = \delta_{salt} - \delta_{base}$.

The problem of the assignment of signals to individual protons has been settled by combining various observations, obviously including integration data: (i) when methyl is shifted from the 4′ to the 6′ position only pyridine protons in ring A are substantially affected; (ii) the nature of X heteroatom more markedly influences pyridine protons in ring B, *i.e.* 5, 6, 7; (iii) protons 2′ and 6 are easily identified by the multiplicity of their first order signals; (iiii) α protons in pyridine rings lie downfield to the γ and β protons.

So far as the salts in oxazole series are concerned (**14** and **16**), besides the picoline C-CH_3 methyl (3.10 ppm in 4′ and 2.95 ppm in 6′), a second signal characteristic of $+N\text{-}CH_3$ methyl is detected (4.50 ppm for **14** and 4.45 ppm for **16**). The latter have been assigned to quaternization of ring A at 1′, being $\Delta\delta$ values of the first closely comparable with those of 1,4-dimethyl and 1,2-dimethylpicolinium iodides respectively (Table 4); furthermore, $\Delta\delta$ values for the 2′, 4′, 5′ and 6′ protons agree with a formal positive charge on ring A.

Table 5

Characterization Data of Styryl Dyes



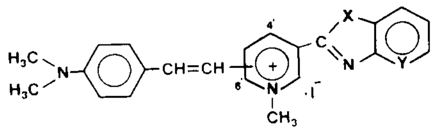
Compound number	Structure X	Structure Y	Styryl chain position	Mp °C	R_f	Empirical formula	Elemental Analyses Calcd./Found C	H	N	Electronic absorption spectra λ max nm (log ε)	NMR (δ) $N(CH_3)_2$	NMR (δ) $\overset{+}{N}\text{-}CH_3$ Ring A	NMR (δ) $\overset{+}{N}\text{-}CH_3$ Ring B
20	NH	$\overset{+}{N}\text{-}CH_3$	4′	204-205	0.04	$C_{23}H_{25}I_2N_5$	44.18 44.21	4.03 3.97	11.20 11.33	512 (4.58)	3.05	4.34	4.44
21	O	N	4′	272-273	0.13	$C_{22}H_{21}IN_4O$	54.56 54.69	4.37 4.12	11.57 11.48	548 (4.66)	3.08	4.34	
22	NH	$\overset{+}{N}\text{-}CH_3$	6′	211-212	0.06	$C_{23}H_{25}I_2N_5$	44.18 44.27	4.03 4.13	11.20 11.34	513 (4.82)	3.06	4.39	4.44
23	O	N	6′	263-264	0.11	$C_{22}H_{21}IN_4O$	54.56 54.55	4.37 4.50	11.57 11.52	541 (4.70)	3.81	4.36	

In the imidazole series a further $+N\text{-}CH_3$ signal appears, thus indicating the formation of a bisquaternary salt in agreement with elemental analysis data. One signal is easily attributed to quaternization at the A ring for the above depicted reasons (4.50 ppm for **13** and 4.56 ppm for **15**), the other (4.47 ppm for **13** and 4.45 ppm for **15**) is by force due to quaternization at the B ring for the following reasons: (i) protons 5, 6 and 7 are strongly deshielded by the proximity of a positive charge ($\Delta\delta$ 0.33 to 0.80 ppm), whereas oxazole salts show very weak effects ($\Delta\delta$ 0.05 to 0.13 ppm); (ii) formation of imidazolium salts must be excluded also on the basis of our previous experience on imidazole systems [5,13], because in such a case *N*-alkylation and quaternization should simultaneously occur, thus leading to structures containing, as a whole, four methyls (in our case integration and analysis are consistent with the presence of three methyls).

Quaternary salts **13-16** proved to be viable intermediates for the synthesis of styryl dyes, due to the enhanced reactivity of the picoline methyl groups after quaternization. By reaction with *p*-dimethylaminobenzaldehyde, dyes **20-23** were prepared, and their data are summarized in Table 5. Melting points are, as already observed for quaternary salts, higher for oxazoles and R_f values are very low for the ionic character of dyes. The chemical shifts of $+N\text{-}CH_3$ protons in ring A are upfield to those of the parent quaternary salts because the positive charge on

Table 6

Comparison of Spectra of Styryl Dyes



Styryl chain position	X	Y	Δλ [a] (nm)	Δ log ε [a]
4′	NH	$\overset{+}{N}\text{-}CH_3$	32	-0.04
4′	O	N	68	0.04
6′	NH	$\overset{+}{N}\text{-}CH_3$	53	0.25
6′	O	N	81	0.13
4′	NH	CH	35	-0.05
4′	O	CH	55	0.01
6′	NH	CH	55	0.18
6′	O	CH	71	0.25

[a] Δ = values for present dyes - values for dyes from picolines.

the nitrogen is now involved in delocalization throughout the whole chromogen.

It is interesting to analyze in more detail some colour-structure relationships of the dyes. For this purpose Table 6 has been prepared, including data for simpler systems, *i.e.* $\Delta\lambda$ and $\Delta \log \epsilon$ values for the "benzo" series (Δ refers to styryl dyes from 2- and 4-picolines). Oxazole derivatives and 6′ isomers improve bathochromic shifts in both the "pyrido" and the "benzo" series. The markedly lower red-shift of bands was observed in the 4′ isomers compared to 6′ isomers, indicating that the electron-withdrawing effect of heteroaryls on the complex donor-acceptor chromogen is, to some extent, weakened by the distorsion caused by the proximity of bulky styryl and heteroaryl moieties. Even if weakened by a loss of coplanarity, oxazolyls prove to be more efficient electron-withdrawing groups than imidazolyl groups, in agreement with previous observations [12]. Finally, a direct comparison of $\Delta\lambda$ values for imidazo[4,5-*b*]pyridinium derivatives with their benzoimidazo counterparts, confirms the above exclusion of quaternization at the imidazole ring which, if present, should produce hypsochromic effects [5].

EXPERIMENTAL

6-Methyl- and 4-methylnicotinic acid were prepared by controlled oxidation of the corresponding collidines, as indicated in references [14] and [15].

Compounds **1-4** were prepared by reacting the appropriate methylnicotinic acid (0.15 mole) with equimolecular amounts of 2,3-diaminopyridine (**1,3**) or 2-amino-3-hydroxypyridine (**2,4**) in presence of polyphosphoric acid (85% phosphorus pentoxide, 200 g) for 2 hours at 210°. The reaction mixture was poured into water, neutralized, and the precipitate filtered and slurried in dilute sodium carbonate. The bases were washed with water and crystallized.

Compounds **13-16** were prepared by refluxing the bases **1-4** (0.03 mole) with methyl iodide (0.3 mole) in acetone (80 ml) for 5 hours. The cooled mixture was filtered, the precipitate washed with ether and crystallized.

Compounds **17-19** were prepared by refluxing **1** (0.005 mole) with the suitable 1-iodo-*n*-alkane (0.03 mole) in 30 ml of xylene. After cooling, the precipitate was collected, washed with ether and crystallized.

Dye **20** was obtained by reacting **13** (0.007 mole) with *p*-dimethylaminobenzaldehyde (0.07 mole) in the presence of piperidine (0.02 ml) as catalyst, at 100° for 7 minutes. After addition of ether, the precipitate was filtered, washed with ether and crystallized from water.

Dye **21** was obtained by refluxing **6** (0.007 mole) with *p*-dimethylaminobenzaldehyde (0.014 mole) in acetic anhydride (50 ml) for 20 minutes. After cooling the precipitate was collected, washed with ether, crystallized from pentanol and recrystallized from ethanol.

Dye **22**, was prepared by reacting **15** (0.007 mole) with *p*-dimethylaminobenzaldehyde (0.07 mole) and piperidine (0.007 mole), in absolute ethanol (40 ml) for 7 hours. After cooling, the precipitate was collected, washed with ether and crystallized from methanol.

Dye **23** was obtained by refluxing **16** (0.007 mole) and *p*-dimethylaminobenzaldehyde (0.014 mole) in the presence of piperidine acetate (0.05 g) in absolute ethanol (20 ml) for one hour. After cooling the precipitate was collected, washed with ether, crystallized from ethanol and recrystallized from acetonitrile.

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

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