2-(Methylpyridyl or quinolyl)benz-X-azoles, Salts and Polymethine Dyes (1)

Ermanno Barni and Piero Savarino

Istituto di Chimica Organica Industriale, Università di Torino, C.so M. D'Azeglio 48, 10125 Torino, Italy

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2-(Methylpyridyl or quinolyl)benz-X-azoles were synthesized by the general reaction between carboxylic acids and *o*-bifunctional compounds. By reaction of the bases with methyl iodide, a series of salts were recovered which were identified and when possible transformed into the corresponding polymethine dyes. The main spectroscopic features of these compounds are briefly discussed.

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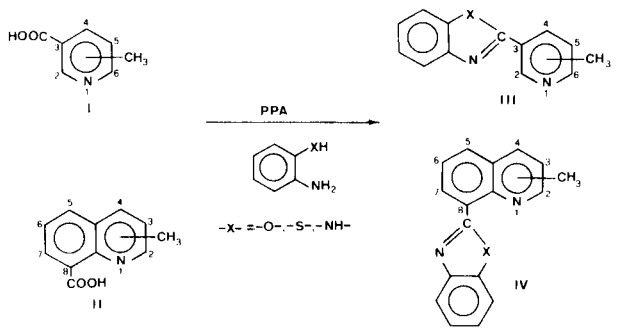
The reaction of methylpyridine or quinoline carboxylic acids with *o*-bifunctional compounds (2) is a useful way to obtain various 2-(methylpyridyl or quinolyl)benz-X-azoles (3). We report now details on the synthesis of new compounds of this family. Several bases of general structure III and IV have been obtained from the corresponding acids I and II. The analytical and spectroscopic data for these compounds are reported in Table I.



The melting points of the benzimidazole derivatives are higher than those of the benzoxazole and benzothiazole series, as previously observed (3). Quinoline derivatives (**7-12**, in which the benz-X-azolyl is linked on the 8 position) melt, except in one case, at a lower temperature than the corresponding bases (3).

Electronic absorption spectra of the bases show an intense broad band in the region 260-350 nm with a maxima in the range of 287-345 nm. The patterns of the quinoline derivatives and of the pyridine derivatives are very similar as previously observed for the corresponding 4-hetaryl quinolines (3). Nmr spectra are consistent with the expected structures.

The reaction of the bases (**1-12**) with methyl iodide gives rise to the corresponding salts (imidazole derivatives corresponding to bases **3,6,9** and **12** are described elsewhere (4)). Previous investigations on isomeric compounds (5) showed the formation of methiodides at the azine or at the azole nitrogen atoms depending on the nature of the hetaryl moiety and on the relative positions of the rings. The pyridine derivatives show a similar behaviour, where compounds **1,2,4** and **5** give rise to *N*-methylpyridinium iodides and compounds **8** and **11** give *N*-methylbenzothiazolium iodides, respectively. On the other hand, the benzoxazolyl derivatives (**7-10**) surprisingly give rise to hydroiodides instead of the expected *N*-methyliodides. The data for these salts are reported in Table II. The structures of the salts are proposed on the basis of chemical and spectroscopic evidence as is discussed later.

Pyridine Derivatives.

The relative positions of the azine and azole nitrogen atoms in compounds of the general structure III allow quaternisation at the pyridine nitrogen, as previously observed (4,5).

The main evidence for the assigned structures arises from analysis of the nmr spectra, and in particular from the $\Delta\delta$ values (see Table II), which lie between 14.0-21.0 Hz when compared with the $\Delta\delta$ values of the reference *N*-methylpicolinium salts (**17-18**). It is interesting to evaluate the effect of the hetaryls on the chemical shifts of the $\overset{\diagdown}{\underset{//}{C}}\text{-}CH_3$ and $+\overset{\diagdown}{\underset{//}{N}}\text{-}CH_3$ protons; suitable data are reported in Table III.

When the hetaryl moiety is 2-benzoxazolyl, the $\Delta\delta$ values are systematically higher than those of the 2-benzothiazolyl series. This indicates, as expected (9,10), a greater electron withdrawing ability for the former heterocyclic substituent. Furthermore, the 3-hetaryl-4-CH_3 series, in which the hetaryl moieties and the methyl groups are in an *ortho* type position, show higher $\delta\Delta$ $\overset{\diagdown}{\underset{//}{C}}\text{-}CH_3$ values than the 3-hetaryl-6-CH_3 series which possess a *para* type substitution. Such an effect is absent if $\Delta\delta$ $+\overset{\diagdown}{\underset{//}{N}}\text{-}CH_3$ values are considered, as the distance between the methyl protons and the hetaryls is the same in the two series. The above data suggest an appreciable inductive effect for the hetaryls.

Electronic absorption spectra of the benzothiazolyl derivatives are reported as shown in Figure 1 (the pattern of benzoxazolyl derivatives is quite similar).

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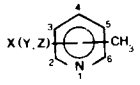
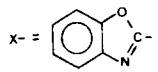
Table I

Bases

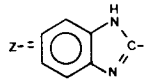
General Structure

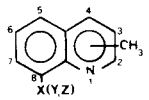
Compounds **1-6**





Compounds **7-12**



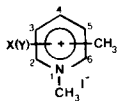


Compound Number	Structure	Yield %	M.p. °C	Crystallization Solvent	Empirical Formula	Elemental Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	Electronic Absorption Spectra λ max (log ε), nm (a)	Nmr Spectra τ-CH_3 (ppm)
1	3-X 6-CH_3	72	111-112	Ethanol/Water	$C_{13}H_{10}N_2O$	74.27	74.19	4.79	4.83	13.33	13.34	302 (4.39); 296 (4.38)	7.41
2	3-Y 6-CH_3	63	106-107	Ethanol	$C_{13}H_{10}N_2S$	69.00	69.08	4.45	4.46	12.38	12.41	301 (4.31)	7.44
3	3-Z 6-CH_3	71	265-266	Ethanol/Water	$C_{13}H_{11}N_3$	74.62	74.57	5.30	5.33	20.08	20.00	307 (4.38)	7.45
4	3-X 4-CH_3	59	118-119	Water	$C_{13}H_{10}N_2O$	74.27	74.16	4.79	4.85	13.33	13.30	299 (4.28); 290 (3.30)	7.25
5	3-Y 4-CH_3	65	70-71	Methanol	$C_{13}H_{10}N_2S$	69.00	68.89	4.45	4.50	12.38	12.50	287 (4.15)	7.33
6	3-Z 4-CH_3	58	197-198	Ethanol/Water	$C_{13}H_{11}N_3$	74.62	74.49	5.30	5.27	20.08	20.10	290 (4.20)	7.33
7	8-X 2-CH_3	74	91-92	Ligroin	$C_{17}H_{12}N_2O$	78.44	78.50	4.65	4.74	10.76	10.68	306 (4.16)	7.36
8	8-Y 2-CH_3	65	141-142	Dioxane/Water	$C_{17}H_{12}N_2S$	73.88	74.02	4.38	4.46	10.14	10.03	345 (4.24); 330 (4.26)	7.26
9	8-Z 2-CH_3	84	172-173	Dioxane/Water	$C_{17}H_{13}N_3$	78.74	78.65	5.05	5.05	16.21	16.18	342 (4.25); 329 (4.24)	7.08
10	8-X 4-CH_3	83	123-124	Ligroin	$C_{17}H_{12}N_2O$	78.44	78.48	4.65	4.72	10.76	10.69	310 (4.19)	7.25
11	8-Y 4-CH_3	66	130-131	Dioxane/Water	$C_{17}H_{12}N_2S$	73.88	73.85	4.38	4.43	10.14	10.20	338 (4.30); 330 (4.29)	7.29
12	8-Z 4-CH_3	72	195-196	Dixoane/Water	$C_{17}H_{13}N_3$	78.74	78.80	5.05	5.12	16.21	16.30	343 (4.25); 335 (4.23)	7.26

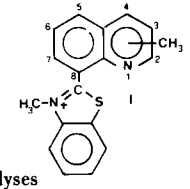
(a) The main absorption above 250 nm are indicated.

Table II

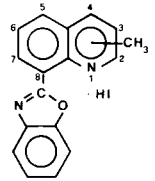
Products Obtained in the Reaction of Bases with Methyl Iodide



Compounds **13-18** (a)



Compounds **19-20**



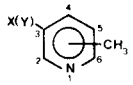
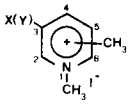
Compounds **21-22**

Compound Number	Structure	M.p. °C	Empirical Formula	Elemental Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	Electronic Absorption Spectra λ max (log ε), nm (b)	Nmr Spectra τ C-CH_3 ppm	Nmr Spectra τ N-CH_3 ppm	Δδ(c) Hz
13	3-X 6-CH_3	264-265	$C_{14}H_{13}IN_2O$	47.75	47.73	3.72	3.80	7.95	7.89	310 (4.26)	7.06	5.54	21.0
14	3-Y 6-CH_3	250-251	$C_{14}H_{13}IN_2S$	45.66	45.51	3.56	3.64	7.61	7.60	315 (4.22)	7.09	5.54	21.0
15	3-X 4-CH_3	231-233	$C_{14}H_{13}IN_2O$	47.75	47.59	3.72	3.81	7.95	8.01	309 (4.22)	6.93	5.48	19.2
16	3-Y 4-CH_3	209-211	$C_{14}H_{13}IN_2S$	45.66	45.54	3.56	3.69	7.61	7.48	304 (4.07)	7.10	5.54	14.0
17 (d)	— 2-CH_3									265 (3.78)	7.20	5.68	17.4
18 (e)	— 4-CH_3									255 (3.81)	7.40	5.63	18.0
19	2-CH_3	274-276 dec	$C_{18}H_{15}IN_2S$	51.68	51.80	3.61	3.80	6.70	6.55	318 (4.10); 307 (4.09)	7.24	5.96	1.2
20	4-CH_3	273-275 dec	$C_{18}H_{15}IN_2S$	51.68	51.71	3.61	3.77	6.70	6.56	316 (4.09); 306 (4.08)	7.18	5.82	6.6
21	2-CH_3	268-270 dec	$C_{17}H_{13}IN_2O$	52.60	52.79	3.38	3.50	7.22	7.09	308 (4.18)	6.97		23.4
22	4-CH_3	270-272 dec	$C_{17}H_{13}IN_2O$	52.60	52.76	3.38	3.53	7.22	7.39	312 (4.21)	6.92		19.8

(a) X, Y as in Table I. (b) The main absorptions above 250 nm are indicated. (c) Δδ values (Hz) are defined as follows: Δδ = δC-CH_3 (methiodide) -δC-CH_3 (base) (d) References 6 and 7. (e) References 7 and 8.

Table III

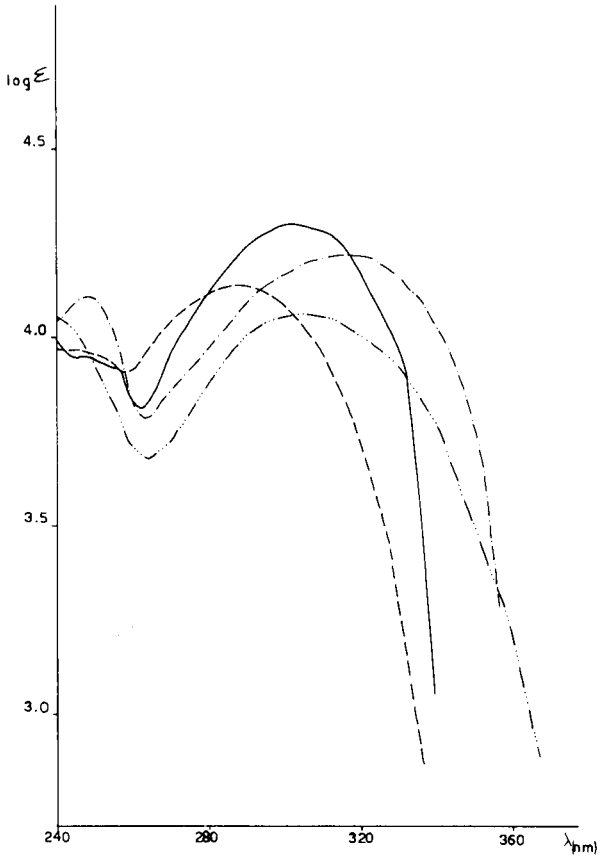
Effect of Hetaryls on Methyl Proton Chemical Shifts

Structure (a)	$\Delta\delta$ C-CH_3 (b)	$\Delta\delta$ C-CH_3 (c)	$\Delta\delta$ +N-CH_3 (c)
3-X 6-CH_3	4.8	8.4	8.4
3-Y 6-CH_3	3.0	6.6	8.4
3-X 4-CH_3	27.0	28.2	9.0
3-Y 4-CH_3	22.2	18.0	5.4

(a) X, Y as in Table I. (b) Values in Hz defined as follows: $\Delta\delta$ = [c.s. of hetarylpicolines - c.s. of unsubstituted picolines]. (c) Values in Hz defined as follows: $\Delta\delta$ = [c.s. of hetarylpicolinium - c.s. of unsubstituted picolinium iodides].

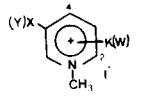
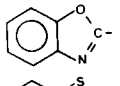
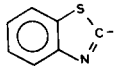
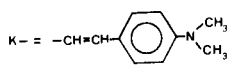
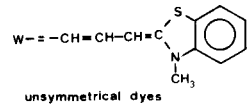
As previously observed (4,5), quaternisation at the azine nitrogen is accompanied by a bathochromic shift (a weak hypochromic effect is also detected). Both bases and salts of the 4-CH_3 series exhibit the absorption maxima at shorter wavelengths and with weaker intensity than the corresponding compounds of the 6-CH_3 series. A positive charge on the azine nitrogen (quaternisation) causes a weak bathochromic effect in the present series with respect to the former series (4,5), because of the linkage of the hetaryls to the β-position of the pyridine ring. Further evidence for the assigned structures arises from the reactivity of the C-CH_3 groups of the salts towards suitable aldehydes to give styryl and unsymmetrical dyes, the data of which are reported in Table IV.



Electronic absorption of compounds:
—·—·—·—·— methiodide **14** (_____ free base **2**)
—···—···—···— methiodide **16** (---------- free base **5**)

Table IV

Polymethine Dyes

General Formulas	Compound Number	Structure		M.p. °C	Electronic Absorption Spectra λ max, nm (log ε)
					
X- = 					
Y- = 					
K- =  styryl dyes					
W- =  unsymmetrical dyes					
	23	X	2-K	249-250	530 (4.82)
	24	Y	2-K	247-249	525 (4.78)
	25	X	2-W	255-257	587 (5.21)
	26	Y	2-W	263-265	588 (5.17)
	27	X	4-K	237-238	535 (4.63)
	28	Y	4-K	141-142	524 (4.60)
	29	X	4-W	191-193	596 (4.95)
	30	Y	4-W	186-188	590 (4.89)
	31 (a)	X, Y = H	2-K		460 (4.57)
	32 (b)	X, Y = H	2-W		536 (4.93)
	33 (a)	X, Y = H	4-K		480 (4.62)
	34 (b)	X, Y = H	4-W		557 (4.98)

(a) Reference 11. (b) Reference 12.

The spectra of the dyes show that the electron withdrawing hetaryls give rise to a bathochromic shift, which is stronger with styryl than with unsymmetrical dyes (in the range 33-71 nm), in agreement with the observed behaviour of isomeric compounds (5). The bathochromic shift increases when the polymethine chain is linked to the 2 position of the pyridine ring and, in this situation, a distinct hyperchromic effect also becomes appreciable. These data suggest that the cyanine chromogen is generally influenced by the presence of hetaryl moieties. When the relative positions of the hetaryl groups and of the polymethine chains are of a *para* type, colour effects are stronger than in the case of an *ortho* type substitution. This probably implies a steric interaction.

Quinoline Derivatives.

The structures of the bases (**7-12**) suggest that the hetaryls in the 8 position ("peri" type) make the quaternisation quite difficult. The behaviour of the 2-hetaryl (5) isomers supports this suggestion, as the benzothiazolyl derivatives are quaternised at the azole nitrogen atom. In the present case, some difficulties in the quaternisation of the benzothiazole series were encountered especially in the case of the 2-CH_3 derivative (**8**, see Experimental). The products (**19,20**) are benzothiazolium methiodides as evidenced by the low values of $\Delta\delta$, by the hypo and strong hypsochromic shift observed in their electronic absorption spectra when compared with the bases, and by failure to give polymethine dyes.

The bases of the benzoxazole series (**7,10**) react with an excess of methyl iodide under different experimental conditions to give salts with the hydroiodide structure. The nmr spectra show the $\overset{\diagdown}{\underset{//}{C}}$-$CH_3$ signals with the $\Delta\delta$ 23.4 and 19.8 Hz (**21,22**), while the $+\overset{\diagdown}{\underset{//}{N}}$-$CH_3$ signals are absent. Furthermore, a broad peak is observed which disappears by a rapid exchange with deuterated water and can be assigned to the $+\overset{\diagdown}{\underset{//}{N}}$-H group. The pattern of the uv spectra is substantially similar to that of the corresponding bases, showing only a feeble batho-hyperchromic effect. Remarkably, the same hydroiodides were obtained by reaction of the bases with ethyl iodide, leading to the corresponding free bases when they are treated with a solution of sodium hydroxide. Finally the $\Delta\delta$ values for $\overset{\diagdown}{\underset{//}{C}}$-$CH_3$ protons suggest that the site of protonation is the azine nitrogen atom.

EXPERIMENTAL

Nmr spectra were obtained with a Jeol C-60 HL spectrometer in DMSO-d_6 solution (6%) using TMS as internal standard. Electronic spectra were recorded in ethanol on a Unicam SP 1700 spectrophotometer.

Acids.

The starting acids of the general formulas I and II were prepared according to literature methods: 6-methyl-3-pyridinecarboxylic acid (13); 4-methyl-3-pyridinecarboxylic acid (14); 2-methyl-8-quinolinecarboxylic acid (15) and 4-methyl-8-quinolinecarboxylic acid (16).

Bases.

Compounds **1-12** were prepared by condensing a suitable carboxylic acid with *o*-aminophenol (*o*-aminothiophenol or *o*-phenylenediamine) in polyphosphoric acid (85% phosphorus pentoxide) over a period of three hours at 200°, following the general reported procedure (2). The reaction mixture was poured into water, the excess acid was neutralized (*p*H 4); the precipitate was collected and slurried in dilute sodium carbonate. The base was finally filtered, dried and crystallized.

Salts.

As a general rule the salts were prepared by refluxing the suitable free bases with a large excess of methyl iodide over a period of 3-4 hours. The crude product was collected, washed with ethyl ether and crystallized from ethanol. The quinoline derivatives (**19,20**) require a different procedure, as the quaternisation have been carried out in a sealed tube (105°, 12 hours) and the hydroiodides (**21,22**) have been obtained either in a sealed tube or by refluxing. All the crude products were washed once with ethyl ether and thrice with boiling acetone, and crystallized from ethanol.

Dyes.

The dyes were prepared by refluxing a suitable methiodide (3×10^{-3} mole) for 45 minutes in acetic anhydride (20 ml.) with *p*-dimethylaminobenzaldehyde (3.5×10^{-3} mole) (styryl dyes) or (3-methyl-2-benzothiazolynilydene) ethanal (17) (3.5×10^{-3} mole) (unsymmetrical dyes). Cyanines (**23,24**) were prepared by reaction in absolute ethanol (piperidine as a catalyst) under milder conditions (45°, 30 minutes). The crude products were collected, washed with ethyl ether, and crystallized from ethanol.

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