Voltammetric Behaviour of Heterocyclic Systems. Pyridyl-substituted Benzimidazoles, Benzoxazoles and Benzothiazoles [1].

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The voltammetric properties, measured at a dropping mercury electrode, have been studied for a series of **18** pyridyl-substituted heterocyclic bases [benzimidazoles, benzoxazoles and benzothiazoles]. The corresponding quarternary salts, obtained by reaction with methyl iodide, were also studied. The reduction potential was found to be dependent on the nature of the benzimidazole, benzoxazole or benzothiazole moiety and on its position on the pyridine ring as well as on the presence of a positive charge. The reversibility of the voltammetric waves was found to be function of the system structure. The effects of proton donors on the voltammetric behaviour of the bases was also investigated.

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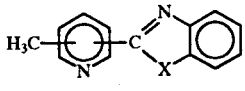
The synthesis and properties of a series of compounds with the general formula **I** and their quarternary salts, obtained by reaction with methyl iodide, were reported in previous publications [2-9].



I, X = O, S, NH

The present communication reports the redox properties of systems **I** (X = O, S, NH) and their quarternary salts by cyclic voltammetry. Our attention was focused on: (i) form and number of signals, (ii) voltammetric wave reversibility, (iii) effect of different proton donors, (iv) effect of the structure on the potential of the voltammetric wave.

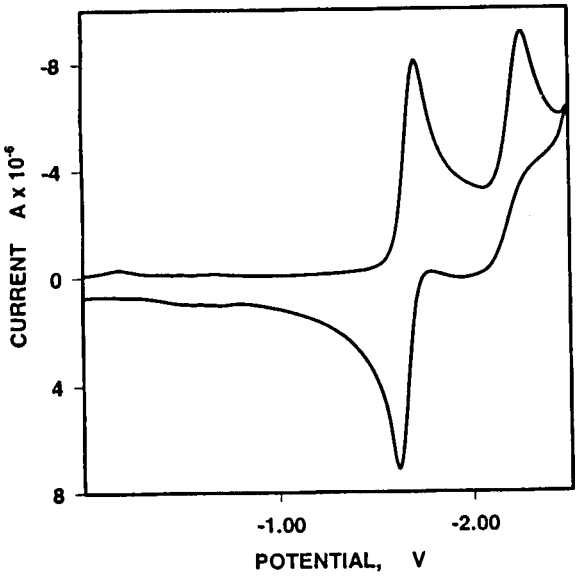


Figure 1. Cyclic voltammogram of compound **5**, inversion potential -2.50V, scan rate 1 V/s.

The bases **1-10**, containing the benzoxazole or benzothiazole rings show a common voltammetric behaviour as illustrated in Figures 1 and 2.

In Figure 1 the voltammetric curve of **5**, exhibits two cathodic reduction peaks at -1.68 V and -2.23 V respectively. The first wave is accompanied by the corresponding oxidation wave at -1.59 V. With regard to the second wave, the oxidation signal was not detected during the scanning towards anodic potentials. A further oxidation wave is present however at approximately -0.7 V. This is absent if the inversion potential is less cathodic than the second wave (Figure 2). It follows that the peak is due to

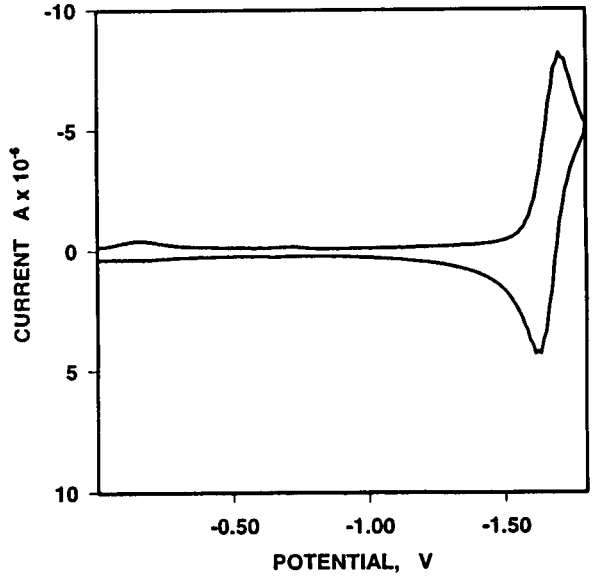


Figure 2. Cyclic voltammogram of compound **5**, inversion potential -1.80 V, scan rate 1 V/s.

the oxidation of the product formed by the irreversible reduction process at the level of the second wave. In agreement with a reversible reduction mechanism, controlled by diffusion processes, the potential of the first

wave does not change with the scan rate and the plot of i_p against the square root of the scan rate is linear, as shown in Figures 3a and 3b.

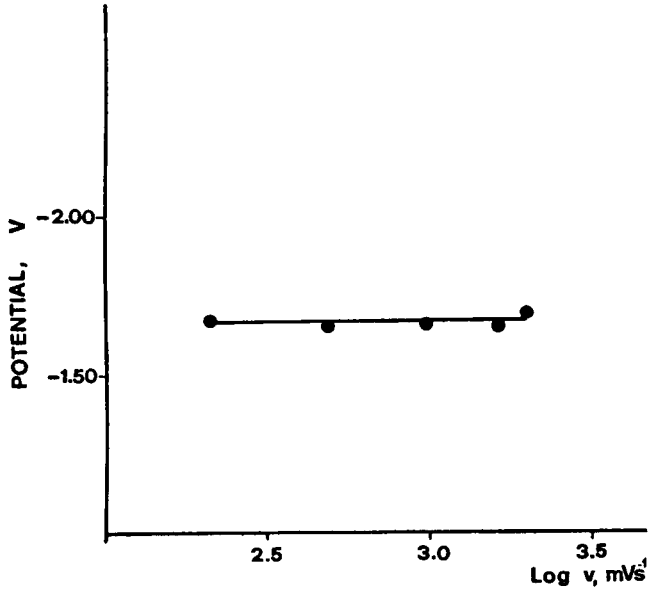


Figure 3a. Dependence of cathodic peak potential (first wave) on scan rate for compound 5.

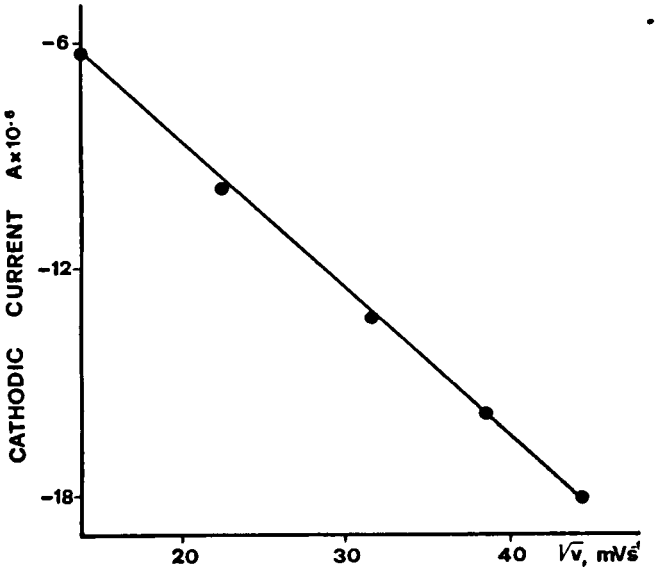


Figure 3b. Dependence of cathodic peak current (first wave) on scan rate for compound 5.

The intensity of the first wave is of the same order of magnitude of the corresponding reference (anthracene), thus confirming for compound 5 that the first wave is generated by an one-electron exchange [10]. The reduction product is therefore a radical anion. The position of the first voltammetric wave and its reversibility are in agreement with the structures of the substituted heterocyclic systems; the unsubstituted rings, *i.e.* picoline and benzimidazole, benzoxazole, benzothiazole, show more negative reduction potentials. As an example, 4-picoline, shows a single cathodic wave at -2.86 V [11]. The easier reduction and the corresponding appearance of anodic signals relative to the first wave are to be associated with the greater resonance stabilization of the radical mono anion in the substituted systems. The second wave, corresponds to a further mono-

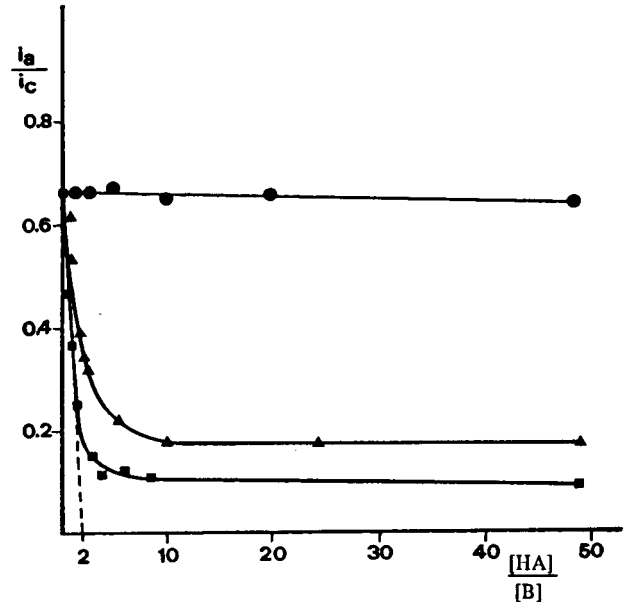


Figure 4a. Effect of [proton donors]/[compound 2] molar ratio on peak current ratio (first wave). Proton donor: ● water, ▲ phenol, ■ acetic acid.

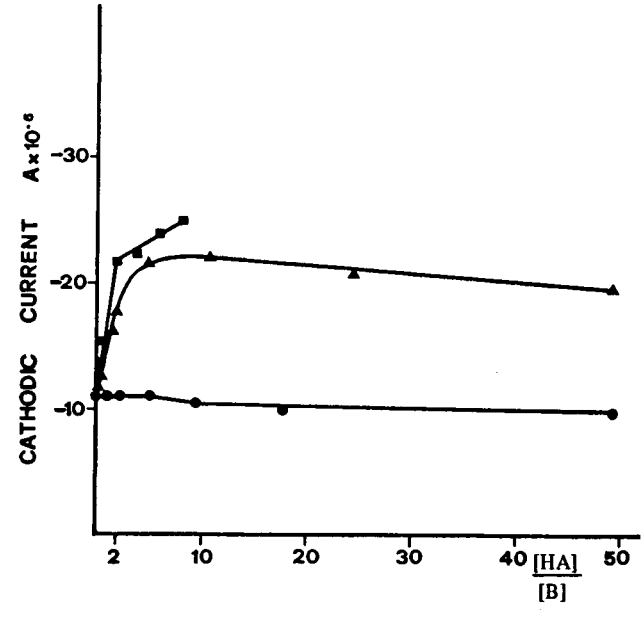


Figure 4b. Effect of [proton donors]/[compound 2] molar ratio on cathodic peak current (first wave). Proton donor: ● water, ▲ phenol, ■ acetic acid.

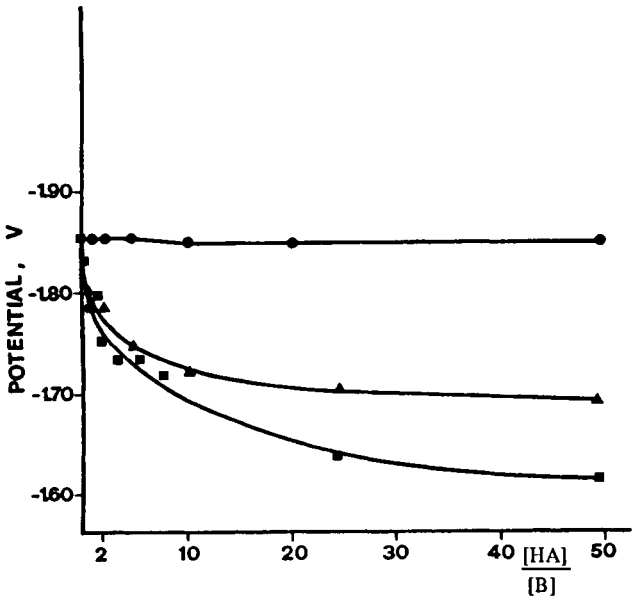


Figure 4c. Effect of [proton donors]/[compound 2] molar ratio on cathodic peak potential (first wave). Proton donor: ● water, ▲ phenol, ■ acetic acid.

electronic reduction of the radical anion with the formation of a dianion. This wave shows the typical irreversibility due to the high reactivity of the strongly basic dianion with the proton donors. Furthermore, the radical mono anion is a base and, as such, can react with proton donors. The effect of three different proton donors (water, phenol, acetic acid) on voltammetric properties of the bases was studied for compound **2**. The presence of "acids" modifies the voltammetric shape, increasing the intensity of the first cathodic wave, reducing the intensty of its anodic counterpart and anodically shifting the peak potential.

In Figure 4a the effect of proton donors on the ia/ic ratio is compared. Water is practically devoid of appreciable effects, while phenol and acetic acid, added in molar ratios (proton donor:heterocyclic base) 5:1-10:1 make the wave practically irreversible. The effect of acetic acid is stronger than that of phenol. Extrapolating the curve at low molar ratios (dotted line), the X axis is intersected at 2, thus indicating a probable modification of the electrodic process. In the presence of proton donors, the new electrodic process involves a chemical step that affects two protons and two electrons.

In Figure 4b the negligible effect of water on the cathodic current is revealed, while phenol and acetic acid increase its intensity. Adding acetic acid the intensity doubles for a molar ratio 2/1. The doubling of intensity for phenol is reached with higher molar ratios. The experimental points draw a curve, whose tangents intersect at an approximate molar ratio 2/1.

In Figure 4c the effect on peak potentials of the first cathodic wave is shown. Water does not affect the potential value, while the effect is more marked in the other two cases, the maximum being for acetic acid (80 mV, 2/1 molar ratio).

It is worthwhile observing that the 0.7 V anodic oxidation wave disappears as proton donors are added, while a new one appears around 0,00 V. The second cathodic wave, starting from 1:1 proton donor/base molar ratios, shifts cathodically and increases in intensity.

Compound **2** was also studied in the presence of perchloric acid. In this case a strongly different voltammetric response was detected. A new cathodic wave, with a peak potential at -0.95 V, appears at low acid/heterocyclic base molar ratios. The intensity of this new wave increases with the amount of acid up to a ratio of 2:1. With further additions of perchloric acid, a wave appears with stronger increasing intensity .

The reported data can therefore be interpreted as follows: (i) The addition of water, even in large excess, does not cause strong variations in the electrodic process, particularly as far as the first cathodic wave is concerned. This can be due to the low acidity of water compared to the basicity of the radical mono anion. (ii) Phenol and acetic acid protonate the radical mono anion and give rise to an irreversible process at the first cathodic wave. (iii) Acetic acid and phenol do not protonate the heterocyclic base, whereas perchloric acid causes a marked protonation.

The benzimidazole derivatives **11-16** exhibit different voltammetric behaviour. As an example, in Figure 5 the

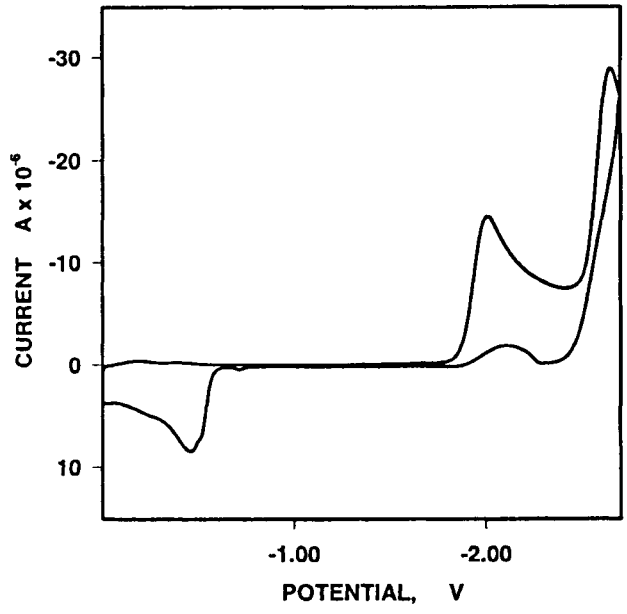


Figure 5. Cyclic voltammogram of compound **12**, scan rate 1 V/s.

voltammetric curve for compound **12** is illustrated. Irreversible cathodic waves are detected. An anodic wave at approximately -0.5 V is also present. In Figure 6 the dependence of the peak potential of the first cathodic

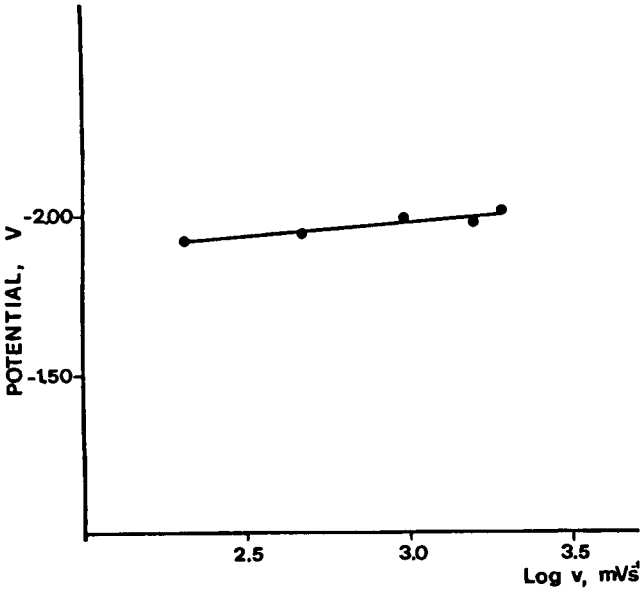


Figure 6. Dependence of cathodic peak potentials (first wave) on scan rate for compound **12**.

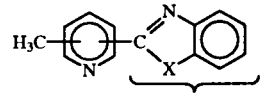
wave on the scan rate is illustrated. The potential moves cathodically by 43 mV over the speed range 0.20-2.00V/s.

The irreversible behaviour exhibited by compounds **11-16** is to be ascribed to the "acidic" (NH) hydrogen atom of the imidazole system. This behaves as an acid with a radical anion. A mechanism of self-protonation can be hypothesized. These observations are in agreement with the behaviour of compounds **17** and **18**. In these structures (*N*-alkylbenzimidazole) the hydrogen atom has been substituted by an alkyl chain. In Figure 7, compound **17**, a first reversible wave at -2.10 V is shown. Compound **18** exhibits a similar behaviour as well, as the structure only differs for the length of the alkyl chain linked to the benzimidazole nitrogen.

The voltammetric data of bases **1-18** are reported in Table 1. The substituted heterocyclic systems give cathodic reduction potentials (first wave) within the range -1.59 ÷ -2.15 V. The effect of the benzimidazole, benzoxazole and benzothiazole rings on reduction potential must be studied by comparing substituted structures with the same substitution sites. Thus, it is observed that the reduction potentials shift cathodically in the order benzothiazole < benzoxazole < benzimidazole. In turn, for one of the three ring systems above, the substitution position on the pyridine system affects the potential value. In fact, systems having the methyl group in position 6 and one of the three ring systems in question in position 3 exhibit more negative potentials, while the opposite occurs when the methyl group is in position 6 and one of the three

Table 1

Voltammetric Data of the Bases



Heteroaryl

Compound Number	Structure			$E_{1/2}$ [a] (V)	ΔE [b] (mV)	i_a/i_c [c]	E_c [d] (V)
	CH_3 position	Het	X				
1	6	2	O	-1.78	90	1.0	-2.41
2	4	2	O	-1.81	97	0.7	-2.41
3	6	3	O	-1.90	80	0.9	-2.56
4	4	3	O	-1.90	84	0.9	-2.54
5	6	4	O	-1.64	85	1.0	-2.23
6	6	2	S	-1.72	85	0.7	-2.12
7	4	2	S	-1.73	122	1.0	-2.35
8	6	3	S	-1.82	79	0.9	-2.45
9	4	3	S	-1.81	80	1.0	-2.41
10	6	4	S	-1.59	92	1.0	-2.19
11	6	2	N-H	-1.97			-2.65
12	4	2	N-H	-2.00			-2.68
13	6	3	N-H	-2.15			-2.41
14	4	3	N-H	-1.99			-2.13
15	6	4	N-H	-1.87			-1.98
16	-	2	N-H	-2.01			-2.65
17	4	2	$N-CH_3$	-2.10	108	0.6	-2.63
18	4	2	$N-C_{12}H_{25}$	-2.02	75	0.6	-2.62

[a] Half wave potential calculated as mean between cathodic and anodic peak potential (first wave), for irreversible waves for compounds **11-16**. The cathodic peak potential is reported. [b] Difference between anodic and cathodic peak potential (first wave). [c] Peak current ratio between anodic and cathodic peak current (first wave). [d] Cathodic peak potential (second wave).

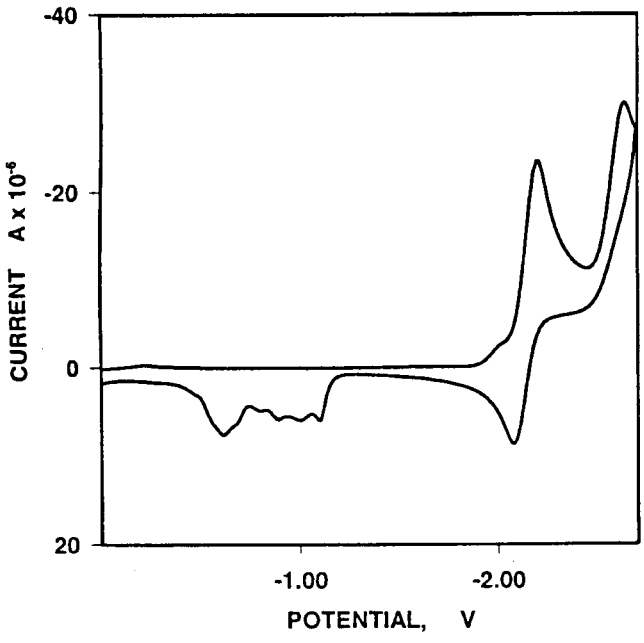


Figure 7. Cyclic voltammogram of compound **17**, scan rate 1 V/s.

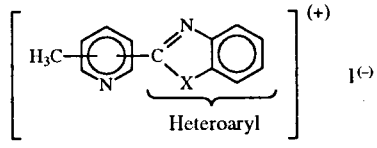
ring systems in question is in position 4. The effect of the substitution position on the reduction potentials seems to be due to resonance stabilization of the unpaired electrons in the reduction products. In the case of systems having one of the three ring systems in question in position 3, the delocalization of the unpaired electron appears to be lower if compared to the other positions and, in particular, position 4. It follows that the product of reduction is less stable and requires a more cathodic potential for being obtained.

In general, the quarternary salts exhibit reduction waves at less negative potentials than those of the corresponding bases. This is in agreement with the presence of a formal positive charge which makes easier the insertion of an electron. The voltammetric behaviour of salts **19-34** is reported in Table 2.

We have studied pyridinium salts **19-23**, benzothiazolium salts **24-25** and benzimidazolium salts **30-31.** As all the salts have an iodide ion as the counter-ion, a signal centered at around -0.20 V can be observed in the corresponding voltammetric diagrams which is due to the $I_2/2I^-$ couple and, therefore, is not reported in the table. By exchanging I^- with Cl^- the signal disappears. The potential values of the first significant wave range between -0.67 and -0.97 V for derivatives with the benzazole moiety at positions 2 or 4 of the pyridine ring, and in the range -1.02 ÷ -1.21 V when at position 3. In addition, the latter compounds always show irreversible waves. Derivatives with benzoxazole or benzothiazole in position 4 show

Table 2

Voltammetric Data of the Salts



Compound Number	Structure					$E_{1/2}$ [a] (V)	ΔE [b] (mV)	i_a/i_c [c]	$E_{1/2}$ [d] (V)	ΔE [e] (mV)	i_a/i_c [f]	E_c [g] (V)
	CH_3 position	Het	X	Y	Z							
19	6	2	O	N	$N\text{-}CH_3^+$	-0.78			-1.38	80	0.5	-2.12
20	4	2	O	N	$N\text{-}CH_3^+$	-0.84	80	0.7	-1.48	100	0.4	
21	6	3	O	N	$N\text{-}CH_3^+$	-1.02						
22	4	3	O	N	$N\text{-}CH_3^+$	-1.06						-2.29
23	6	4	O	N	$N\text{-}CH_3^+$	-0.74	70	1.0	-1.45	90	0.6	
24	6	2	S	$N\text{-}CH_3^+$	N	-0.70			-1.98			-2.33
25	4	2	S	$N\text{-}CH_3^+$	N	-0.67						
26	6	3	S	N	$N\text{-}CH_3^+$	-1.06						-2.26
27	4	3	S	N	$N\text{-}CH_3^+$	-1.09						-2.27
28	6	4	S	N	$N\text{-}CH_3^+$	-0.76	70	0.9	-1.41	90	0.6	
29	-	4	S	N	$N\text{-}CH_3^+$	-0.69	70	1.0	-1.37	80	0.6	
30	6	2	$N\text{-}CH_3$	$N\text{-}CH_3^+$	N	-1.36			-1.76			
31	4	2	$N\text{-}CH_3$	$N\text{-}CH_3^+$	N	-0.79	90	0.5	-1.59			
32	6	3	N-H	N	$N\text{-}CH_3^+$	-1.16						
33	4	3	N-H	N	$N\text{-}CH_3^+$	-1.21						
34	6	4	N-H	N	$N\text{-}CH_3$	-0.97			-1.65			

[a] Half wave potentials calculated as mean between cathodic and anodic peak potential (first wave); for irreversible waves the cathodic peak potential is reported. [b] Difference between anodic and cathodic peak potential (first wave). [c] Peak current ratio (anodic/cathodic peak current) (first wave). [d] See footnote [a] (second wave). [e] See footnote [b] (second wave). [f] See footnote [c] (second wave). [g] Cathodic peak potential (third wave).

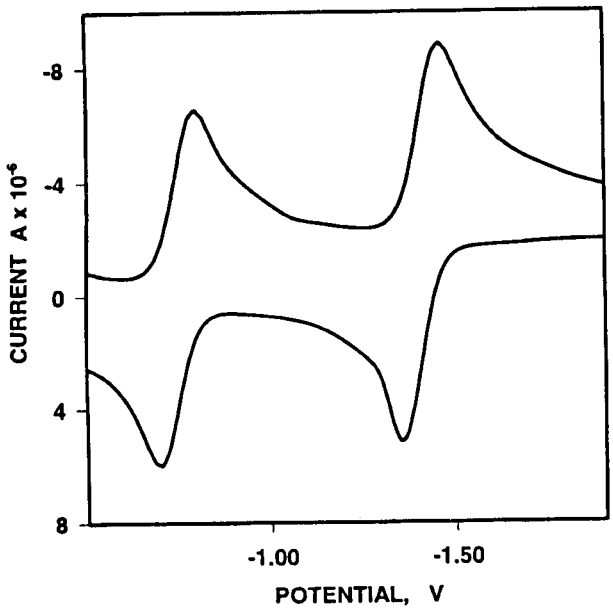


Figure 8. Cyclic voltammogram of compound **28**, scan rate 1 V/s.

reversible waves (Figure 8, compound **28**). In contrast, compound **34**, with the benzimidazole ring at position 4 shows irreversible waves, as systems having the free benzimidazolyl NH group.

If one of the three ring systems is at position 2 the behaviour depends on the position of the charge and the nature of the heterocycle. For example, compound **20**, with the benzoxazole linked to position 2 of the pyridinium ring and the methyl to position 4, a partially reversible first wave is observed. In contrast, the same wave for compound **30**, with the structure of a benzimidazolium group linked to the pyridine ring with a methyl at position 6 is totally irreversible (Figure 9).

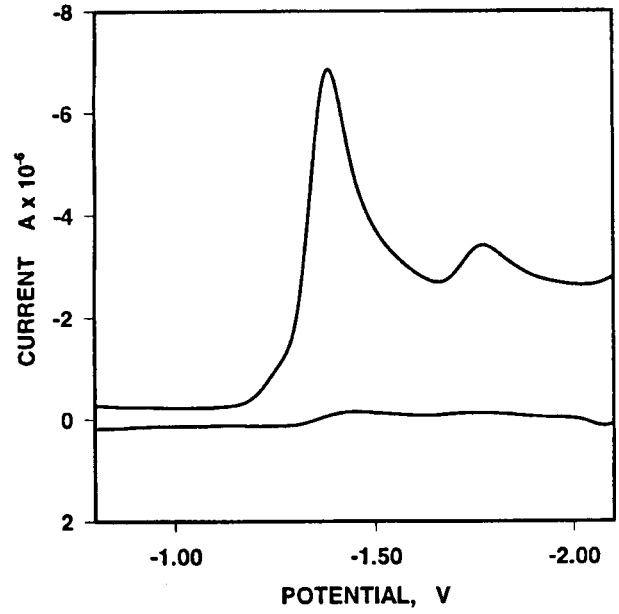


Figure 9. Cyclic voltammogram of compound 30, scan rate 1 V/s.

The effect of the structure on the reduction potential can be studied by comparing corresponding systems. The structures having one of the three ring systems at positions 3 and 4 of the picolinic ring are picolinium salts. For these systems, for a given substitution position, the reduction potentials shift cathodically in the order: benzoxazole < benzothiazole < benzimidazole. For a given substituent (benzimidazole, benzoxazole, benzothiazole), the derivatives containing the heterocycle in position 4 are more easily reduced. Similar observations cannot be made for position 2, due to the differences in the salt structure.

The cathodic reduction potentials of the substituted heterocycles have been correlated with their structures. Systems with the benzimidazole, benzoxazole or benzothiazole at positions 2 and 4 are, in general, more easily reduced than systems with the bicyclic heterocyclic ring system at position 3. The phenomenon can be explained with the greater stabilization of the product formed by reduction. Furthermore, the waves exhibit a greater reversibility as revealed by the presence of anodic signals. In turn, the nature of the bicyclic heterocycle in question influences the potential and the reversibility of the waves. The potentials for the benzimidazole derivatives are more cathodic with respect to those of the corresponding benzoxazole and benzothiazole compounds. The voltammograms do not show anodic waves in the correct position. The reduction potential is less negative in the quarternary salts, compared to the bases, the individual values being strongly influenced by the position of the positive charge, *i.e.* on the azine or azole ring.

EXPERIMENTAL

Compounds **1-16**, **18-34** were prepared as previously reported [2-9].

1-Methyl-2-(4-methyl-2-pyridyl)benzimidazole (**17**).

Compound **17** was prepared by reaction of compound **12** (10.0 g, 4.8 x 10^{-2} mole) with methyl iodide (22.7 g, 1.6 x 10^{-1} mole) and potassium *tert*-butoxide, in the presence of 18-crown-6-ether (1.3 g, 4.8 x 10^{-3} mole) using 300 ml of diethyl ether and 150 ml of *N,N*-dimethylformamide as the solvent, at a temperature of 90°. After 3 hours the mixture was poured into water and extracted with ether. The ether solution was washed with saturated sodium chloride solution. The ether layer was dried with anhydrous sodium sulfate and evaporated. The residue was crystallized from ethyl ether, mp 80-82°, yield 85%.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.26; H, 5.95; N, 18.79.

The voltammetric measurements were performed with an Amel 433 multipolarograph connected to an IBM/AT computer. All of the potentials were measured with respect to the Ag/AgCl/KCl (satu-

rated) reference electrode, with platinum wire as the counter electrode and a dropping mercury electrode. To avoid errors, all potentials were measured using anthracene as a reference, whose potential is equal to -1.92 volts (saturated calomel electrode) [10] (-1.88 volts, Ag/AgCl electrode). The measurements were carried out in *N,N*-dimethylformamide (0.1 *M* tetrabutylammonium hexafluorophosphate as the supporting electrolyte). Solvents were previously dried with activated alumina. The alumina (Merck, activity grade 1) was activated by heating for 12 hours at 350° in a vacuum, cooled and stored in a dessiccator over phosphorus pentoxide. Measurements where performed at concentration of 1×10^{-3} mole l^{-1}, at 25±0.5°, and with a scan rate in the range 0.2-2.0 V/s.

REFERENCES AND NOTES

[1] This work was supported by a contribution of National Research Council (CNR) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) of Italy.

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