Electrochemical behavior of benzo[*b*][1,6]naphthyridine derivatives

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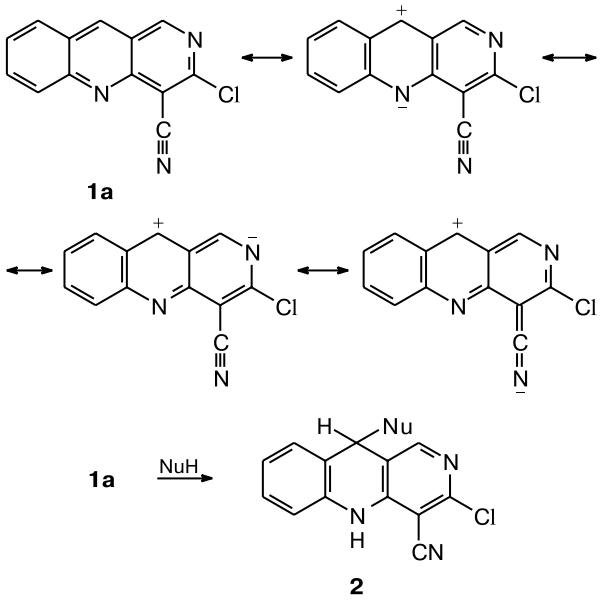
The electroreduction of benzo[*b*][1,6]naphthyridine derivatives in anhydrous media by the polarographic method was studied. It is found that the first step of the process is the transfer of an electron to position 10 of the molecule, which is consistent with the addition of nucleophilic reagents to this particular position of the tricyclic system in question.

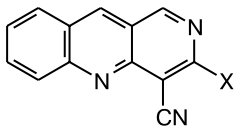
Key words: benzo[*b*][1,6]naphthyridines, σ-adducts, polarography.

We have shown recently[1,2] that 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**1a**) smoothly reacts with N-, C- and O-nucleophiles (NuH) to give so-called σ-adducts **2** at position 10 of the molecule. The ease of these reactions is apparently determined by the presence of a significant partial positive charge in this position of the tricyclic system caused by the electron-withdrawing influence of the cyano-substituted annelated pyridine ring (Scheme 1).

Scheme 1



This stimulated us to study the addition of an electron to 3-substituted 4-cyanobenzo[*b*][1,6]naphtyridines **1a**—**i** in aprotic solvents as a model reaction. We intended to compare the reactivity of compounds of this type containing different substituents in position 3 and to evaluate the possible transformation pathways for the intermediates formed.



1a—i

X = Cl (**a**), NHBu^n (**b**), NHCH(Et)CH_2OH (**c**), $N(C_5H_{11})_2$ (**d**), $N(CH_2)_6$ (**e**), *p*-NHC_6H_4Me (**f**), *p*-NHC_6H_4OMe (**g**), SPh (**h**), $SCH_2CONHPh$ (**i**)

Polarography was chosen as the investigation method. The polarographic behavior of the tricyclic compound under study has not been described in the literature. The closest possible analogy is that with the electrochemical behavior of acridine and its derivatives.[3—5] These compounds are known to be reduced in nonaqueous solvents in two successive irreversible single-electron steps. Transition of the first electron yields a radical anion (RA) capable of dimerization.

The polarograms of compounds **1a—i** in anhydrous DMF in the presence of Bu_4NClO_4 show two or three waves, whose irreversibility is determined by the slope of the plot of $\log(i/i_d - i)$ (i is the current on the rise of the wave, i_d is the maximum diffusion current) *vs.* the potential E (the slopes are 120—140 mV) and by the peak width at half-height ($E_{1/2}$) on a differential pulse polarogram.[6] The number of transferred electrons was calculated using the Ilkovic equation by comparing the peak current of the waves with that for a compound having a similar size of molecules and, hence, a similar diffusion coefficient. In this study, acridine was chosen as the reference. The results are presented in Table 1.

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Table 1. Polarographic data for compounds **1a—i**

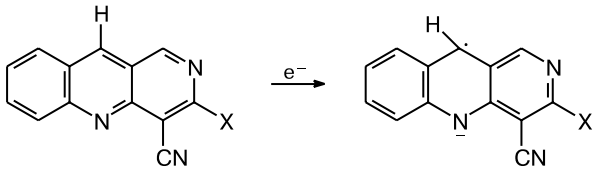
Compound	First wave		Intermediate wave	Second wave	
	$-E_{1/2}$/V	$K^a \cdot 10^3$	$-E_{1/2}$/V	$-E_{1/2}$/V	$K^{a,b} \cdot 10^3$
1a	0.81	2.11	—[c]	—[d]	—[d]
1b	1.22	1.41	—[c]	2.13	3.03
1c	1.21	1.57	—[c]	1.98	3.07
1d	1.24	1.45	2.06	2.60	2.68
1e	1.24	1.43	—	2.06	2.86
1f	1.15	0.78	1.70 (0.39)[e]	2.05	2.66
1g	1.16	0.84	1.69 (0.54)[e]	2.03	2.73
1h	0.92	2.27	1.75	—[d]	—[d]
1i	0.91	1.43	1.47	2.48	2.95
Acridine	1.62	2.10	—	2.35	3.65

[a] K/μA L mol^{-1} is the proportionality coefficient in the Ilkovic equation.
[b] For the sum of two waves.
[c] Poorly pronounced.
[d] Merges with the background.
[e] The K values are given in parentheses.

The first electron adds more easily to the benzonaphthyridines under study than to acridine (see Table 1), which is due to the electron-withdrawing influence of the cyano-substituted annelated pyridine ring. The substituents in position 3 influence the $E_{1/2}$ values for the reduction waves in the expected manner, *i.e.*, strong electron-donating groups impede the process, while for substituents with weaker electron-donating properties, this effect is less pronounced.

The first reaction step in an aprotic medium is, most likely, the addition of one electron to give the corresponding RA of type **3** (Scheme 2).

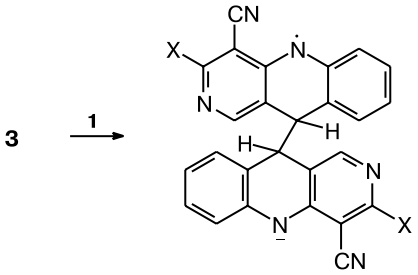
Scheme 2



1a—i **3**

The height of the first wave corresponds to the transfer of one electron for compounds **1a—e,h,i** or ~0.6 electrons for compounds **1f,g**. The total height of all waves present on the polarogram corresponds to a two-electron process. Thus, some amount of the initial depolarizer (to a degree depending on its structure) does not participate in the electrode reaction under first-wave potentials. This suggests that the reaction between RA **3** and the starting compound affords dimer **4** (Scheme 3). The anionic and radical centers in the dimeric RA **4** are located at the endocyclic N atoms of the central pyridine rings.

Scheme 3



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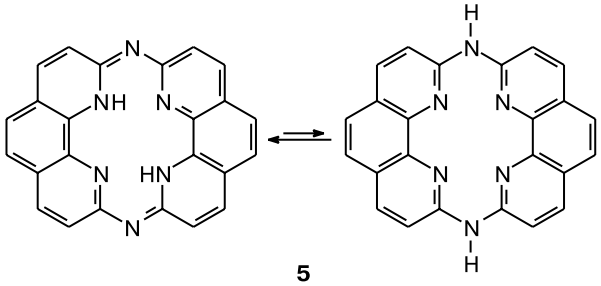
Probably, the dimers carrying integer negative charges should be reduced less easily than the initial neutral depolarizers. Indeed, the polarograms of compounds **1d,f—i** exhibit intermediate waves that complete the first wave to the single-electron level. However, only for compounds **1f,g** the height of these waves is significant, being equal, as noted above, to ~0.4 electrons, while for other compounds, these waves are small (≤10% of the first wave). It should be noted that introduction of a weak proton donor (phenol) leads in all cases to an increase in the first wave to a single-electron level accompanied by a decrease in the intermediate wave down to complete disappearance at a phenol concentration comparable to the concentration of the depolarizer.

Considering these data brings about an intricate question of what is the difference between **1f,g** and other compounds of this series and why it is these two compounds that tend to enter into dimerization involving RA **3** and the initial depolarizer. Currently, it is difficult to answer this question unambiguously. Nevertheless, we will attempt to substantiate the possible reasons for this difference.

When examining the structures of these compounds, one can note that only benzo[*b*][1,6]naphthyridines **1f,g** contain an arylamine substituent in position 3 of the tricyclic system. One the one hand, aminopyridines and

Scheme 4



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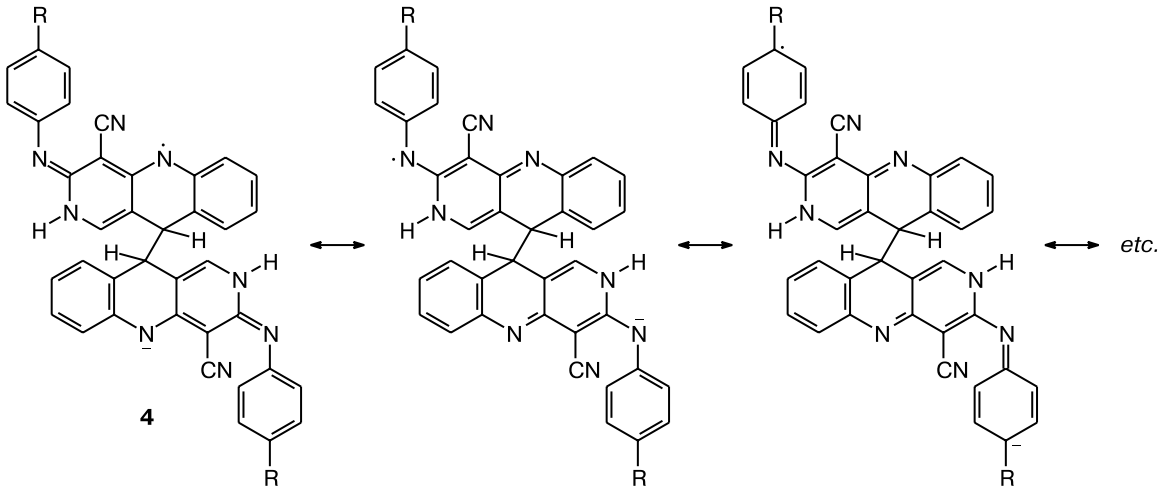
Scheme 5



R = Me, OMe

other aminoazines are known to exist mainly as amino rather than imino tautomers.[7] On the other hand, it is known[8] that in the case of 2-arylaminopyridines, the degree of predominance of the amino form over the imino form is substantially lower. Whereas for 2-aminopyridine, pK_T (the negative logarithm of the tautomeric equilibrium constant) is 6.2, in the case of 2-phenylaminopyridine, $pK_T = 4.3$. It has also been proven that for the polycyclic system **5**, the tautomeric equilibrium is shifted toward the imino form[8] (Scheme 4).

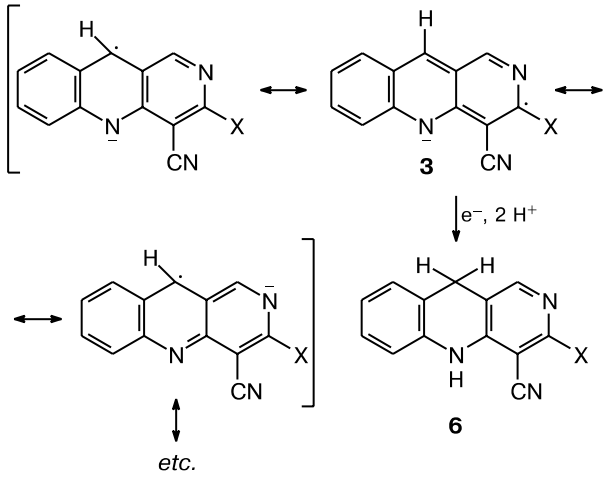
If the amine—imine tautomerism is assumed to be significant for the properties of RA **4**, then it could be responsible for the difference in kind between **1f,g** and other compounds of the given series. Indeed, analysis of the structures of the dimeric RA derived from these compounds in the imine tautomeric form reveals a high level of delocalization of the radical and anionic centers, as can be seen from the canonical structures shown in Scheme 5, and, hence, a pronounced stabilization of the dimeric RA.

Obviously, the benzene rings at the exocyclic heteroatoms involved in the mesomeric effect, which are missing from the other compounds, greatly contribute to this stabilization.

It should be noted that polarograms of compounds **1b,c,e** do not exhibit the intermediate waves and, correspondingly, the introduction of phenol virtually does not affect their polarographic behavior.

The proposed interpretation can also answer the question of what takes place in the first and intermediate polarographic waves in the presence or in the absence of a weak proton donor. Presumably, the initial tricyclic systems accept the first electron being thus transformed into RA **3**, which are fairly stable, as both the radical and anionic centers are efficiently stabilized due to conjugation with the benzene and substituted cyanopyridine rings. Type **4** dimers, which are also stabilized by resonance, are much more sterically crowded; hence, upon the addition of phenol, they accept a proton and then an electron to give the corresponding dimeric anions more easily than RA **3**. As noted above, in this case, the first wave increases to reach a single-electron level. As regards monomeric RA **3**, which needs a higher proton donor concentration, they can subsequently (at the second wave) accept the second electron and two protons giving rise to tricyclic system **6** (Scheme 6). Study of the subtle mechanistic details for the polarographic reduction of compounds **1a—i** is beyond the scope of this work, which is mainly devoted to structural issues.

Scheme 6



Thus, this publication is the first research into the electroreduction of benzo[*b*][1,6]naphthyridine derivatives in a nonaqueous medium. It was ascertained that the reduction proceeds through addition of an electron at position 10 of the molecule. The first stage of the electrode process is the formation of an RA, which is able (in the presence of certain substituents in the ring) to react with the initial depolarizer. It was shown that the possibility of this process is dictated by the degree of stabilization of the RA formed. The fact that such stabilization in the series of substituted 2-aminopyridines may depend on the position of the amine—imine tautomeric equilibrium was substantiated for the first time.

Experimental

Polarographic measurements were carried out using a PU-1 polarograph with a dropping mercury electrode. Electrode characteristics: dropping period, 3.5 s, mercury flow rate, 2.9 mg s^{-1} in a 0.1 *M* solution of KCl with an open circuit. A 0.1 *M* solution of Bu_4NClO_4 in DMF was used as the supporting electrolyte; Bu_4NClO_4 was prepared by precipitation by perchloric acid from a solution of Bu_4NOH with further crystallization from 95% EtOH. Dimethylformamide was dried over calcined K_2CO_3 and distilled *in vacuo*. The residual moisture determined by the Fisher method was 0.02%. The half-wave potentials were reduced to the scale of a saturated calomel electrode by comparing with $E_{1/2}$ for the K^+ ion (the Vlček method[9]).

Mass spectra were recorded using a Finnigan SSQ-710 mass spectrometer with direct sample injection into the ion emitter. ^{1}H NMR spectra were run using a Varian Unity-400 spectrometer in DMSO-d_6. The reactions were monitored and the compound purity was checked by TLC on Silufol UV-254 plates (AcOEt was used as the eluent, UV absorption detection). Melting points were determined using an Electrothermal 9100 device (UK). Benzo[*b*][1,6]naphthyridines **1a—c,e,h,i** were synthesized according to a known procedure.[1]

4-Cyano-3-dipentylaminobenzo[*b*][1,6]naphthyridine (1d). Compound **1a** (0.20 g, 0.835 mmol) was stirred with dipentylamine (0.45 g, 2.87 mmol) in 10 mL of DMF for 5 h at 70 °C. Water was added to the reaction mixture, and the precipitate was filtered off, washed with water and hexane, and dried to give 0.25 g (83%) of compound **1d**. To prepare an analytical grade sample, the crude product was dissolved in CH_2Cl_2, passed through a silica gel layer, and washed with CH_2Cl_2. The solvent was distilled off. M.p. 189—192 °C (from CH_2Cl_2). Found (%): C, 76.66; H, 7.89; N, 15.76. $C_{23}H_{28}N_4$. Calculated (%): C, 76.63; H, 7.83; N, 15.54. MS, *m/z* (I_{rel} (%)): 360 $[M]^+$ (156), 303 $[M - (CH_2)_3Me]^+$ (78), 289 $[M - N(CH_2)_3Me]^+$ (31), 247 $[M - (CH_2)_7Me]^+$ (79), 233 $[M - N(CH_2)_7Me]^+$ (100), 205 (35), 179 (38).

Synthesis of 3-arylamino-4-cyanobenzo[*b*][1,6]naphthyridines 1f,g (general procedure). Compound **1a** (2.00 g, 8.35 mmol) and the corresponding arylamine (16.7 mmol) were stirred at reflux in 50 mL of MeOH for 30 h. The reaction mixture was cooled to ~20 °C and the precipitate was filtered off, washed with water and 95% EtOH, and dried. To prepare an analytical grade sample, the crude product was dissolved in CH_2Cl_2, passed through a silica gel layer, and washed with CH_2Cl_2. The solvent was distilled off *in vacuo* and the dry residue was triturated and dried.

4-Cyano-3-(4-toluidino)benzo[*b*][1,6]naphthyrydine (1f). Yield 92%, m.p. 235.5—236.5 °C (from CH_2Cl_2). Found (%): C, 77.49; H, 4.66; N, 18.00. $C_{20}H_{14}N_4$. Calculated (%): C, 77.40; H, 4.55; N, 18.05. ^{1}H NMR, δ: 2.29 (s, 3 H, Me); 7.16 (d, 2 H, H(3´), H(5´), J = 8.4 Hz); 7.37 (d, 2 H, H(2´), H(6´), J = 8.4 Hz); 7.58 (t, 1 H, H(7), J = 8.0 Hz); 7.94 (t, 1 H, H(8), J = 8.0 Hz); 8.04 (d, 1 H, H(9), J = 8.0 Hz); 8.15 (d, 1 H, H(6), J = 8.0 Hz); 9.20 (br.s, 1 H, H(10), $^1J_{C,H}$ = 166.0 Hz); 9.43 (s, 1 H, H(1), $^1J_{C,H}$ = 182.0 Hz); 9.80 (br.s, 1 H, NH).

3-(4-Anisidino)-4-cyanobenzo[*b*][1,6]naphthyrydine (1g). Yield 98%, m.p. 240.5—241.5 °C (from CH_2Cl_2). Found (%): C, 73.90; H, 4.28; N, 17.14. $C_{20}H_{14}N_4O$. Calculated (%): C, 73.60; H, 4.32; N, 17.17.

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