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CHEMICAL AND ELECTROCHEMICAL SYNTHESIS OF QUINONEIMINE N-OXIDES FROM INDOLINONE-3-ARYLIMINO NITROXIDE RADICALS

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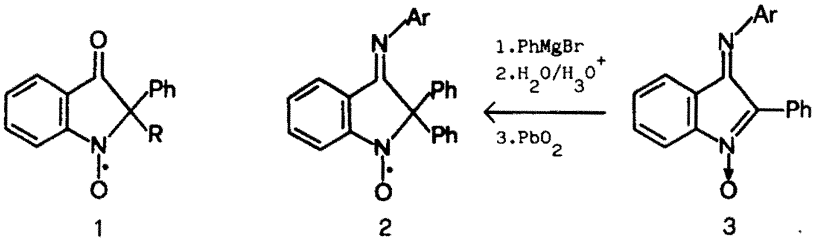
Abstract: 2,2-Diphenyl-3-arylimino-indoline-1-oxyls are efficiently converted to the corresponding isomeric 5- and 7-quinoneimine N-oxides either by chemical (cerium ammonium nitrate) or electrochemical oxidation in aqueous acetonitrile. The electrochemical studies indicate that mono-electronic oxidation of the starting compounds leads to the corresponding oxoammonium ions. These are stable in anhydrous acetonitrile, as indicated by cyclic voltammetry, but in non-anhydrous conditions undergo rapid nucleophilic attack by water molecule followed by further oxidation to the final products. The relative economic and practical advantages of the electrochemical vs the chemical process are discussed. The ESR parameters for the new nitroxide radicals involved in the present investigation are also reported.

2,2-Disubstituted-3-oxo-indoline-1-oxyls 1 (indolinone nitroxides) have been extensively studied in different contexts. They undergo homolytic substitution in the indolic ring with electrophilic paramagnetic species such as aroyloxyl,[1] tert-butoxyl,[2a] and aminyl radicals,[3] or coupling to the nitroxide free valence with nucleophilic methyl[2a] and benzyl[2b] radicals. Nitroxides 1 also undergo nucleophilic substitution when oxidized in the presence of halogen and carboxy anions,[4] water[5] and methanol.[6]



a: Ar = C_6H_5
b: Ar = $C_6H_4OMe(p)$
c: Ar = $C_6H_4Me(p)$
d: Ar = $C_6H_4Cl(p)$
e: Ar = $C_6H_4Br(p)$

Scheme 1

Nitroxides in general undergo a mono-electronic oxidation[7,8] leading to the formation of oxoammonium ions. These species behave as oxidants in the mediated chemical[9] and electrochemical[10] oxidation when formed from tetra-methylpiperidino- and pyrrolidino-1-oxyls, but as strong electrophiles when the oxoammonium function is in a conjugated position with a benzene ring. This is actually the case of nitroxides **1** and **2** where the N-O function, and consequently the oxoammonium function originated by mono-electronic oxidation, is conjugated to the benzene ring of the indole nucleus. The present paper deals with chemical and electrochemical oxidation of nitroxides **2a–e** in the presence of water. The study has been carried out in order to verify whether substitution of an arylimino group for the carbonyl oxygen at C-3 induces any significant variation in the behaviour of the nitroxides and in the reactivity of the involved oxoammonium ions **4a–e**, which were detected and investigated by voltammetric techniques. The controlled-potential macroscale electrolysis of nitroxides **2a–e** represents a new convenient synthetic route to quinoneimine N-oxides **7a–e** and **8a–e**, particularly if compared to the chemical method, which requires a substantial amount of oxidizing agent.

RESULTS AND DISCUSSION

Chemical or electrochemical oxidation of nitroxides **2a–e** in MeCN in the presence of water affords quinoneimine N-oxides **7a–e** and **8a–e**. The higher yields of the former compounds can be reasonably imputed to the lower steric hindrance which characterizes position 5 with respect to position 7 in the intermediate oxoammonium ion. The finding that overall yields of the chemical and anodic oxidations are practically the same, provides indication that both processes involve the same intermediate species, i.e. the oxoammonium ions. We therefore propose the reaction sequence shown in Scheme 2 to explain the formation of quinoneimine N-oxides, irrespective of the nature of the oxidizing process.

Compounds **7a–e** and **8a–e** were identified by using a variety of spectroscopic techniques, including IR, UV, NMR and mass spectrometry; in the case of the 5-substituted derivatives **7a–e**, identification was further supported by correct elemental analysis. The distinction between compounds **7a–e** and the corresponding 7-substituted compounds **8a–e** was mainly based on their ^1H NMR and UV spectra. Indeed the proton NMR spectra of **7** and **8** (independent of the nature of the arylimino group) have very characteristic features that provide a useful means of identification.

Table 1 - Percent yields of 5- (**7a–e**) and 7- (**8a–e**) quinoneimine N-oxides isolated in the electrochemical oxidation (at 0.90 V) of **2a–e** in MeCN-H_2O.

Compound	Ar	Product (% yields)	
2a	C_6H_5	**7a** (86%)	**8a** (11%)
2b	C_6H_4-OMe(p)	**7b** (78%)	**8b** (15%)
2c	C_6H_4-Me(p)	**7c** (85%)	**8c** (13%)
2d	C_6H_4-Cl(p)	**7d** (90%)	**8d** (7%)
2e	C_6H_4-Br(p)	**7e** (82%)	**8e** (15%)

Table 2 - Analytical and spectroscopic data of compounds **7a–e** and **8a–e**.

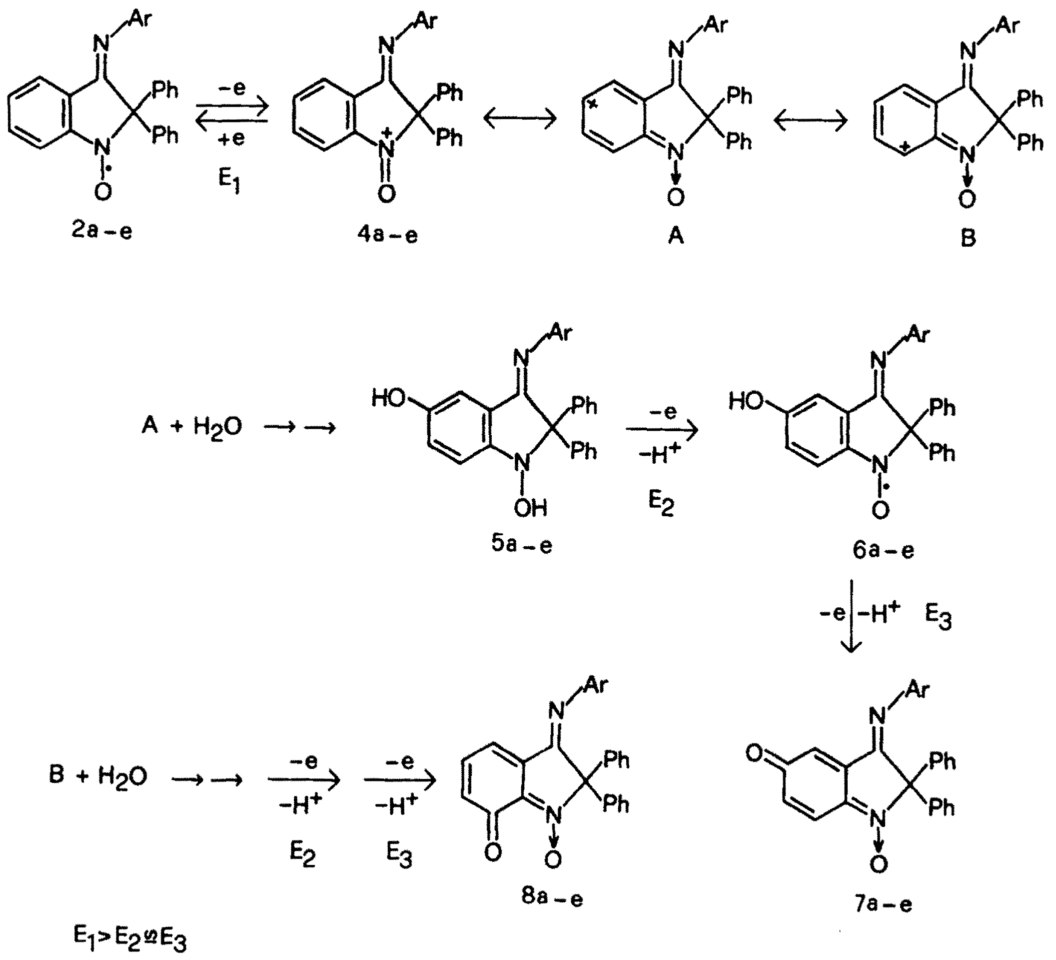
Compound[a]	M.p. °C	Formula	Found (%) Calc. %			IR νmax cm^{-1}	UV λmax nm (ε)[d]
7a	173-4[b]	$C_{26}H_{18}N_2O_2$	C 80.05 (79.98)	H 4.55 (4.64)	N 7.08 (7.19)	1670-1610 1548	216 (29,560) 379 (22,059)
7b	81-2[b]	$C_{27}H_{20}N_2O_3$	C 77.23 (77.12)	H 4.83 (4.79)	N 6.46 (6.66)	1665-1610 1550	
7c	105-6[b]	$C_{27}H_{20}N_2O_2$	C 79.95 (80.18)	H 4.87 (4.98)	N 6.95 (6.92)	1660-1610 1550	
7d	81[b]	$C_{26}H_{17}N_2O_2Cl$	C 73.54 (73.49)	H 4.15 (4.03)	N 6.52 (6.59)	1670-1610 1547	
7e	167[b]	$C_{26}H_{17}N_2O_2Br$	C 66.62 (66.53)	H 3.71 (3.65)	N 5.93 (5.97)	1673-1610 1548	
8a	192-4[c]	$C_{26}H_{18}N_2O_2$				1655-1628 1600	214 (36,579) 334 (9,186) 468 (3,652)
8b	180-2[c]	$C_{27}H_{20}N_2O_3$				1650-1630 1598	
8c	200-2[c]	$C_{27}H_{20}N_2O_2$				1660-1630 1600	
8d	204-6[c]	$C_{26}H_{17}N_2O_2Cl$				1672-1630 1602	
8e	214-6[c]	$C_{26}H_{17}N_2O_2Br$				1675-1632 1604	

a, all compounds gave the expected molecular ion peak in their mass spectra; b, yellow crystals from EtOH; c, red crystals from ethylacetate solution by spontaneous evaporation to dryness; d, from MeOH solutions.

Table 3 - Voltammetric data for the oxidation at a pulsed platinum electrode of nitroxide radicals **2a–e** in dried acetonitrile(a).

Compound	Conc. (mM)	$E_{1/2}$ (V)	i_e (μA)	slope (mV)
2a	1.29	0.68	6.64	60
2b	1.08	0.66	5.60	65
2c	0.96	0.62	4.88	65
2d	1.12	0.69	5.76	60
2e	1.03	0.69	5.40	60

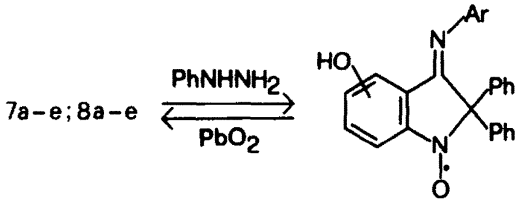
(a) Solutions containing 0.1M Et_4NClO_4; electrode pulsing time, t_p = 2s; T = 22°C; the voltammograms were recorded by dc-sampled technique; the potentials are referred to Ag/AgClO$_4$ 0.1M in MeCN solution; the slope was calculated using $E_{3/4}-E_{1/4}$.



Scheme 2

Thus, the spectra of 5-substituted derivatives show signals attributable to H_4 (doublet, $\delta = 5.74$, $J_{4,6}$ 1.75Hz), H_6 (pseudo-quartet, $\delta = 6.66$, $J_{4,6}$ 1.75Hz, $J_{6,7}$ 10Hz) and H_7 (doublet, $\delta = 7.74$, $J_{6,7}$ 10Hz), while those of the 7-substituted analogues exhibit splittings due to H_4 (doublet, $\delta = 5.86$, $J_{4,5}$ 6.25Hz), H_5 (pseudo-quartet, $\delta = 7.01$, $J_{4,5}$ 6.25 Hz, $J_{5,6}$ 10Hz), and H_6 (doublet, $\delta = 6.67$, $J_{6,7}$ 10Hz). On the other hand the UV spectra of compounds **7** and **8** differ in that those of the latter show absorption at 468 nm along with others at shorter wavelength (334, 214 nm), while those of the former do not have any absorption maximum in the visible region (379 and 216 nm). This is consistent with the greater extension of the π-system in derivatives **8a–e** (and with their red colour) if compared to that of **7a–e**, which are yellow.

Quinoneimine N-oxides **7a–e** and **8a–e** were generally contaminated by small amounts of the corresponding nitroxides, **6a–e** and **9a–e**, respectively. This was evident from the abnormally large linewidth characterizing their NMR spectra; this inconvenience was eliminated by addition of PbO_2 to the solution.



6a-e;9a-e

Conversely, addition of some phenylhydrazine to solutions of the quinoneimine N-oxides lead to the detection of strong ESR signals due to nitroxides **6** and **9**. As it is the case for the unsubstituted nitroxides **2a–e**, the spectral parameters of **6a–e** and **9a–e** proved to be independent on the nature of the arylimino group. We therefore report the data of the two monosubstituted members, *i.e.* of radical **6a**: a $(H_{4,6})$ = 0.94 G, a (N-exocyclic) = 0.94 G, a (H_7) = 3.07 G, a (N-endocyclic) = 10.17 G, *g* 2.0052_6, and **9a**: a $(H_{4,6})$ = 0.82 G, a (N-exocyclic) = 0.82 G, a (H_5) = 3.44 G, a (N-endocyclic) = 10.76 G, *g* 2.0054_2.

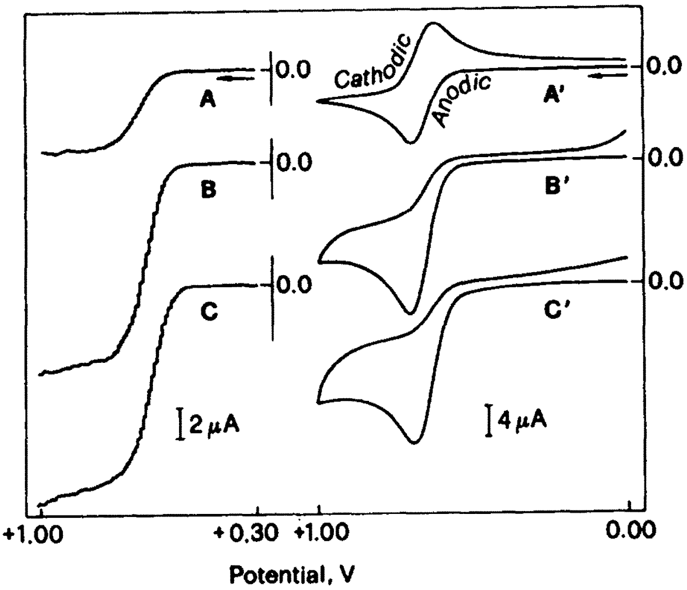


Figure 1 - Dc (curves A-C) and cyclic (curves A'-C') voltammograms of indolinone 3-p-bromophenylimino nitroxide radical **2e** at a platinum electrode. (A) $1.0x10^{-3}$ M **2e** in MeCN-0.1 M Et_4NClO_4; T = 22.0°C; electrode pulse time = 2.0 s; (A') as (A) and with the stationary platinum electrode polarized at 0.1 V s^{-1}; (B,C) or (B',C') as (A) or (A') plus H_2O: % v/v H_2O/MeCN 1.8% (B) or (B'), and 4.8% (C) or (C').

CHEMICAL OXIDATION - When oxidizing nitroxides **2a–e** by chemical methods in order to obtain the quinoneimine N-oxides **7** and **8**, care must be exerted in the choice of the oxidizing agent. In the first place this must be soluble in aqueous acetonitrile, which is the reaction medium, and secondly, as the reaction proceeds *via* the oxoammonium ion (strong electrophile), it must not give rise to nucleophilic species able to overcome or to compete with water in giving nucleophilic attack of the indolinic ring. Actually, it has been previously shown that indeed the reaction of nitroxide **1** with either lead tetracetate[6] or bromine[4] leads to 5-and 7-acetoxy or

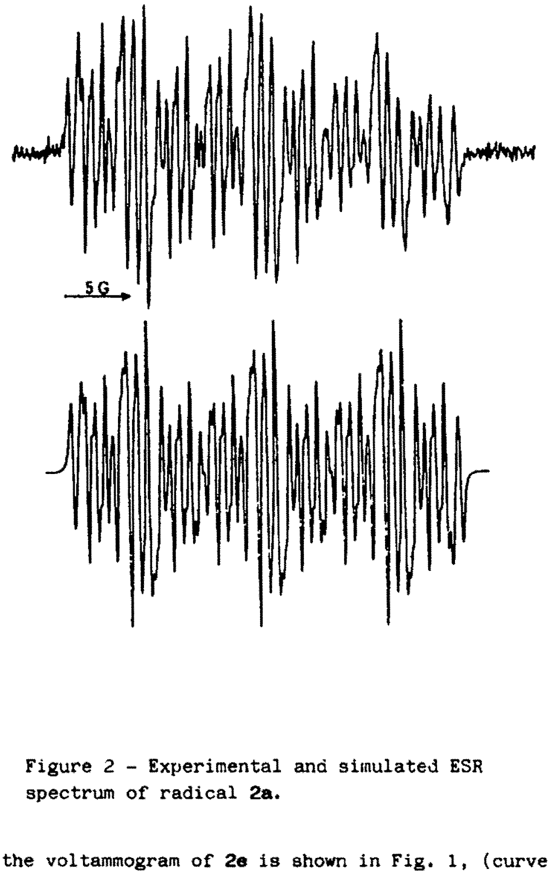


Figure 2 - Experimental and simulated ESR spectrum of radical **2a**.

bromo-substituted nitroxides.

Because of its relatively good solubility and of the low nucleophilicity of the NO_3^- anion, we have chosen cerium ammonium nitrate to carry out the chemical oxidation, although a minor drawback is given by the non insignificant cost of this chemical which must be used in substantial amount (three equivalents per equivalent of nitroxide).

ELECTROCHEMICAL OXIDATION - Because of the difficulty of finding a low cost oxidizing agent characterized by a high solubility, and able to give clean reactions, we tried the electrochemical oxidation of nitroxides **2a–e** as an alternative route to quinone-imine N-oxides.

In the range of concentration used (1.10^{-4} - 5.10^{-3}M) nitroxide radicals **2a–e** in dried MeCN (with Et_4NClO_4 as supporting electrolyte) exhibited at a pulsed platinum electrode (ppe) one oxidation step at potentials between 0.62 and 0.69 V. As example the voltammogram of **2e** is shown in Fig. 1, (curve A), whereas voltammetric data for the nitroxide radicals studied are reported in Table 3.

The oxidation process of **2a–e** turned out to be mono-electronic, reversible and diffusion-controlled as proved by the following experimental observations: i) the plot of E *vs*. log $|(i_l-i)/i|$ is a straight line, with a slope of 55-60 mV; ii) the slope of the log i_l *vs*. log t_p plot is about 0.18 and iii) the function i_l/C values are comparable with the corresponding values determined in the same experimental conditions for the reversible one-electron oxidation process of 2,2-disubstituted 3-oxoindoline-1-oxyls.[5]

At a stationary platinum electrode (spe) and in the sweep-rate range examined (v = 0.05 - 10.0 Vs^{-1}) the oxidation process of **2a–e** exhibits the following features: i) a voltage sweep from zero towards positive potentials (up to 1.0 - 1.2 V) shows an anodic peak, which corresponds to the oxidation step observed at the ppe; ii) reversal of the scan reveals the complementary cathodic peak due to the reduction of the primary oxidation product (see Fig. 1, curve A'). The parameters of this anodic-cathodic system meet the diagnostic criteria expected for a reversible one-electron process producing a species (oxammonium cations **4a–e**) which is stable during the time of the measurements, *i.e.*, i) the ratio of the anodic to the cathodic peak current (i_{p_a}/i_{p_c}) is unity; ii) the difference between anodic and cathodic peak potentials is 60-70 mV and iii) the current function $i_{p_a}/v^{1/2}$ value is constant.

On adding increasing amounts of a nucleophilic agent such as water (0 - 10% v/v, H_2O/MeCN) to the solutions of **2a–e** in MeCN-Et_4NClO_4, the original oxidation step increases until its height becomes

2.2 - 2.7 times higher i.e. the electrode process tends to become three-electronic, (see Fig. 1, curves B and C). The corresponding cyclic voltammetric experiments show that in MeCN-H_2O the anodic peak of **2a–e** becomes completely irreversible, kinetic in character and involves more than two electrons. In fact: i) the original anodic peak increases its height; ii) the corresponding complementary cathodic peak disappears and iii) the current function $i_{pa}/v^{1/2}$ value decreases (Fig. 1, curves B' and C').

During controlled-potential electrolysis (at 0.90V) of nitroxide radicals **2a–e** in dried MeCN-Et_4NClO_4 the current decays slowly to the background values in accordance with $2 < n_{app} < 3$.

The electrolysis followed by tlc on SiO_2 showed the increasing formation of the quinoneimine N-oxides **7** (yellow spot) and **8** (red spot).

The above results were confirmed by macroscale electrolysis of **2a–e** in MeCN-$LiClO_4$ with a large excess of water (6-8% v/v, H_2O/MeCN); actually, the current decayed rapidly to the background current with $n_{app} = 3$. The electrolysed solutions examined as reported in the Experimental Section gave quinoneimine N-oxides **7a–e** and **8a–e** with almost quantitative yields (Table 1).

The results of voltammetric and coulometric experiments by analogy with the previous studies on the oxidation of 2,2-disubstituted 3-oxo-indoline-1-oxyls[5] suggest that in MeCN-Et_4NClO_4 and in the presence of water, nitroxide radicals **2a–e** can be oxidized to the corresponding 5- (**7a–e**) and 7- (**8a–e**) quinoneimine N-oxides following Scheme 2.

Thus the anodic oxidation of nitroxide radicals **2a–e** begins with a reversible one-electron step yielding the corresponding oxammonium cations **4a–e**. These cations in dried MeCN are stable at the electrode during the time of the voltammetric measurements but during the electrolysis in aqueous acetonitrile they undergo an attack at C-5 (or at C-7) by water yielding the C-5 (or C-7) monosubstituted hydroxylamino derivatives **5a–e**. These can be further oxidized at the same potentials of **2a–e**[11] to give the corresponding C-5 (or C-7) monosubstituted nitroxide radicals **6a–e** (or **9a–e**). Eventually, oxidation of these radicals yields the 5- (or 7-) quinoneimine N-oxides **7a–e** (or **8a–e**).

When the oxidation of **2a–e** is carried out in MeCN containing a large excess of H_2O the oxammonium cations can undergo the nucleophilic attack at C-5 (or C-7) even at the electrode, therefore the anodic step tends to involve three-electrons.

EXPERIMENTAL

Chemicals - Nitroxides **2a**[12] and **2b**[12] were prepared as described in the literature starting from **3a**[13] and **3b**.[13] Cerium ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$, Merck, puriss., p.a.) and lithium perchlorate ($LiClO_4$, Fluka, purum, p.a.) were used as purchased. Acetonitrile (MeCN, Merck, spectrophotometric grade) was purified[5] with CaH_2 and P_2O_5. Tetraethylammonium perchlorate (Et_4NClO_4, Erba, RS grade for polarography) was vacuum dried at 60°C for 4 days. All other products were analytical reagent-grade.

Apparatus and equipment - ^1H NMR spectra were recorded on a Varian 90 MHz spectrometer using TMS as internal standard; IR were recorded using a Perkin-Elmer 257 spectrophotometer from nujol mulls; mass spectra were obtained with a varian MAT 112-S spectrometer; UV spectra were recorded on a Perkin-Elmer 554 spectrophotometer; ESR spectra of radicals **2a–e**, **6a–e**, and **9a–e** were recorded on a Bruker ER 200 spectrometer equipped with an NMR gaussmeter for field calibration and a frequency counter for **g-factors** determination.

The voltammetric and coulometric measurements were performed as reported elsewhere.[5] The working electrode for the voltammetric measurements was a pulsed[14] (or stationary, in the case of cyclic voltammetry) platinum disc (Amel 492) of about 2 mm diameter. The reference electrode was Ag/0.1M $AgClO_4$-MeCN.

Synthesis of Nitroxides 2c–e - Nitroxides **2c–e** were synthetized following the method already described in the literature.[12] PhMgBr prepared from 30 mmoles of Mg and bromobenzene in the usual manner under nitrogen in 20 ml of dried THF, was added to 10 mmoles of the appropriate **3c–e** dissolved in 30 ml of dried THF. After stirring for 1h, the reaction mixture was poured in 10% aqueous NH_4Cl (100 ml), extracted with benzene, and after separation the organic layer was dried on Na_2SO_4 and filtered. The filtrate was treated with PbO_2 (1g) under stirring for 0.5 h. The inorganic solid was then filtered off and the filtrate reduced to a small volume was chromatographed on a SiO_2 column eluting with benzene. From the red fraction, nitroxides were isolated in 85-90% yields and crystallized from ethanol. All compounds showed an absorption in the IR spectrum at 1663 cm^{-1} due to the C=N group.

Nitroxides **2a–e** exhibited almost identical ESR spectra. Because of some differences between the present data and those previously reported for nitroxides **2a** and **2b**,[12] we have performed a careful computer simulation of the spectrum of **2a** recorded in benzene solution (see Fig. 2) and obtained the following parameters: a(N-endocyclic) = 9.76 G, a (N-exocyclic) = 0.75 G, a (H_4) = 1.10 G, a (H_5) = 3.26 G, a (H_6) = 1.06 G, a (H_7) = 3.15 G, a (5H phenyl) = 0.08 G, $g = 2.0053_5$. The assignement to the different positions has been made by assuming a spin density distribution similar to that unambiguously established for nitroxide **1**.[3]

2c: m.p. 163°C. Analysis. Calcd. for $C_{27}H_{21}N_2O$: C,83.26; H,5.43; N,7.19. Found: C,83.52; H,5.24; N,7.23.

2d: m.p. 158°C. Analysis. Calcd. for $C_{26}H_{18}N_2OCl$: C,76.18; H,4.42; N,6.83. Found: C,76.15; H,4.40; N,6.85.

2e: m.p. 162°C. Analysis. Calcd. for $C_{26}H_{18}N_2OBr$: C,68.73; H,3.99; N,6.17. Found: C,68.71; H,3.85; N,6.15.

ELECTROCHEMICAL OXIDATION OF 2a–e

Nitroxides **2a–e** (0.25 mmoles) were electrolysed at controlled potential (0.90 V) in 6-8% (v/v), H_2O-MeCN (30 ml)-$LiClO_4$ 0.1 M at room temperature. After the current had fallen to its background value, the solution was poured into water (50 ml) and extracted with benzene (50 ml). The separated benzene layer was washed with water (4 x 30 ml), dried on Na_2SO_4 and then chromatographed on silica preparative tlc using benzene/acetone 9:1 as an eluent. Compounds **7a–e** were isolated from the yellow spot and compounds **8a–e** from the red one. Yelds are collected in Table 1. Analytical and spectroscopic data are reported in Table 2.

CHEMICAL OXIDATION OF NITROXIDE 2a–e

$Ce(NH_4)_2(NO_3)_6$ (1,65 g, 3 mmoles in 10 ml of water) was added dropwise to a solution of nitroxides **2a–e** (1 mmole in 40 ml of MeCN) under vigorous magnetic stirring at room temperature. After 1h the reaction mixture was poured into water (50 ml) and the resulting solution extracted with benzene. The benzene layer was washed with water (2 x 20 ml), separated, dried on Na_2SO_4 and evaporated to dryness. The residue chromatographed on silica preparative tlc from benzene/acetone 9:1 gave the quinoneimine N-oxides **7a–e** and **8a–e** in 90-95% and 5-10% yields, respectively. Analytical and spectroscopic data are collected in Table 2.

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