Radical Cations. Part 3.[1] Chemical and Electrochemical Oxidation of 3,3′-Bisindolizines

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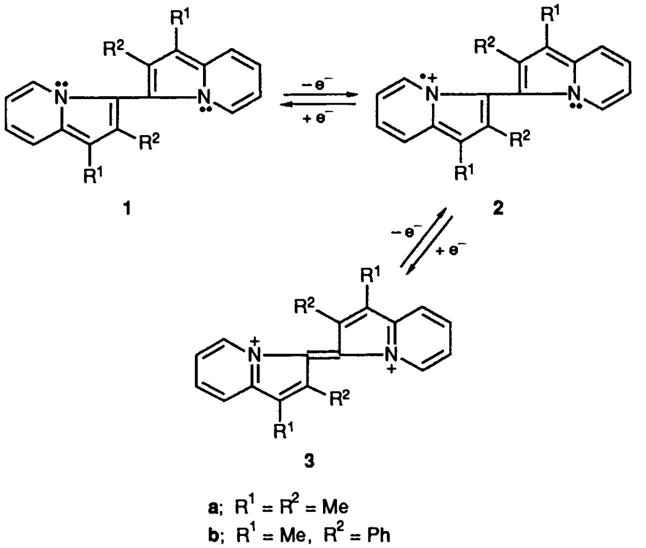
Indolizine dimers **1a–c** are oxidized by chemical and electrochemical methods. Anodic oxidation shows that the title compounds are oxidized in two different steps, and cyclic voltammetry demonstrated their reversibility. The radical cations **2a–c** and the dications **3a–c** are characterized by an EPR study and by comproportionation reactions, respectively. The dimers **1a–c**, treated with diazonium ions, undergo retrogression reactions, forming the arylazoindolizines **7a** and **7b**. Formation of the radical cation **2b** in the reaction of compound **1b** with diazonium salts has been explained through the homolytic evolution of the intermediate σ-complex by means of an indolic aminoxyl as radical scavenger.

Years ago one of us studied the chemical and electrochemical oxidation of azobisindolizines[2] and azobisindoles.[3] The chemical oxidation of these compounds, performed with Gomberg's reagent (I_2–$AgClO_4$), was found to occur in two well separated steps, the first of which led to the corresponding radical cation and the second to the dication. Since the radical cation was formed by mixing equimolar quantities of the free base and dication, it was possible to assert that the system composed of the free base (RED), the radical cation (SEM) and the dication (OX)[4] gives rise to a reversible redox system as shown in eqn. (1).

For all radical cations studied the EPR signal was represented by only one broadened line.

$$\mathrm{RED} \underset{+e}{\overset{-e}{\rightleftharpoons}} \mathrm{SEM} \underset{+e}{\overset{-e}{\rightleftharpoons}} \mathrm{OX} \qquad (1)$$

In the present paper we describe the reversible redox system obtained from 3,3′-bisindolizines **1a–c**, for which the reversibility was demonstrated by voltammetric measurements, and EPR studies of the radical cations **2a–c**.

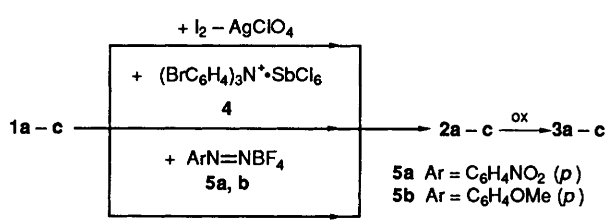


a; $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = Ph$
c; $R^1 = Me$, $R^2 = C_6H_4Me$ - *p*

Scheme 1

Results and Discussion

(a) *Chemical Oxidation.*—3,3′-Bisindolizines **1a–c** were oxidized in MeCN with I_2–$AgClO_4$ (2 mol equiv.) to the corresponding dications **3a–c**, isolated in the solid state as perchlorates. The oxidation of substrates **1a–c** with only one mol equiv. of I_2–$AgClO_4$ reagent led to the radical cations **2a–c**. All attempts to purify compounds **2a–c** and **3a–c** for elemental analysis were unsuccessful. However, the EPR signals of the radical cations **2a–c** were easily recorded and could be observed for hours in MeCN solution. Compounds **2b** and **2c** gave similar EPR spectra (Fig. 1), which was computer simulated on the basis of the following hyperfine splitting constants (hfsc): *a*(N) 3.52 (2 N); *a*(H) 3.08 (6 H); *a*(H) 1.2 (2 H); *a*(H) 0.85 (2 H); *a*(H) 0.42 (2 H); *a*(H) 0.35 (2 H) G.† The assigned hfsc values, though not reproducing exactly the experimental spectrum owing to the large number of nuclei and the low intensity of the wing lines, agree with the spin-density distribution calculated for the indolizine radical cation (Table 1). The EPR spectrum of radical cation **2a** was not completely resolved and showed only eleven lines, which could possibly be due to the two nitrogens and two methyl groups bonded at C-1, with hfscs: *a*(N) 3.5 (2 N); *a*(H) 3.2 (6 H) G. Radical cations **2a**, **2b**, and **2c** have the same *g*-factor [2.002 5(5)].



The oxidation of dimers **1a–c** might be achieved by other oxidants such as tris-(*p*-bromophenyl)amino radical cation hexachloroantimonate **4** and diazonium salts, namely *p*-nitro-**5a** and *p*-methoxy-benzenediazonium tetrafluoroborates **5b**. The oxidative power of the amino radical cation **4** is well known,[5] so that the reaction of compounds **1a–c** with **4** may be considered completely shifted to the right, in particular because

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† 1 G = 10^{-4} T.

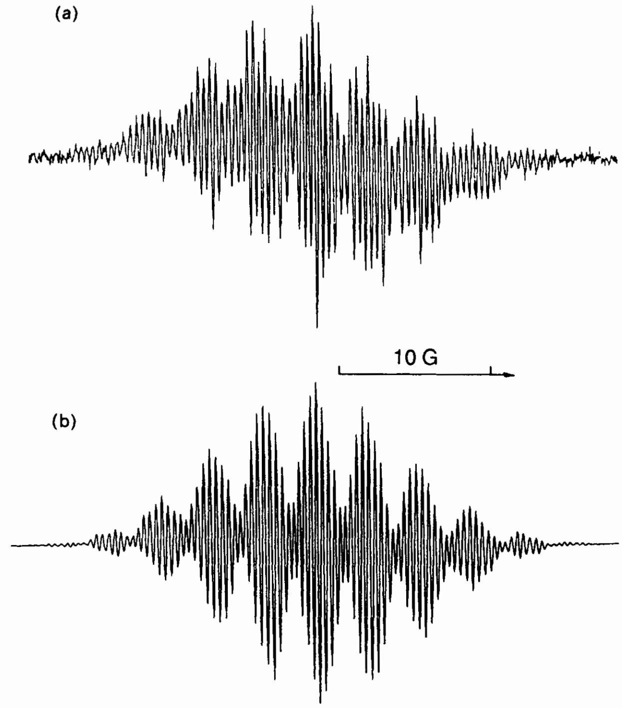
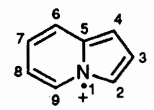


Fig. 1 EPR spectrum of radical cation **2b** recorded at room temperature: (a) experimental, (b) computer-simulated with a linewidth of 0.15 G

Table 1 Spin Density Distributions



Position	McLachlan spin density
1	−0.0188
2	0.3415
3	−0.0845
4	0.2960
5	0.0464
6	0.0861
7	0.1355
8	0.0017
9	0.1961

of the extremely low oxidation potentials of the dimers **1a–c** (Table 2). In addition, the solutions obtained by mixing solutions of compounds **1a–c** with **4** in 1:2 molar ratio showed a deep green colour due to the dications **3a–c** (Fig. 2) which did not give EPR signals. When solutions of substrates **1a–c** and **4** were mixed in 1:1 molar ratio, a deep green colour was again obtained and the solution showed the UV spectrum reported in Fig. 2 for **2b** and a strong EPR signal similar to that reported in Fig. 1. The radical cations **2a–c** were also prepared by mixing equal volumes of equimolar solutions of species **1a–c** and **3a–c**,[2–4] in agreement with the comproportionation reaction reported in eqn. (2) which, in general, gives rise to an equilibrium.

$$\text{RED} + \text{OX} \rightleftharpoons 2\text{SEM} \qquad (2)$$

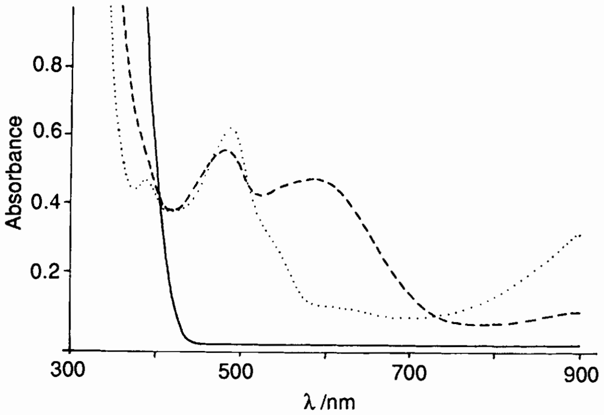


Fig. 2 UV spectra of species **1b** (solid line), **2b** (dashed line), and **3b** (dotted line) recorded for 10^{-3} mol dm^{-3} MeCN solutions.

The equilibrium constant may be calculated from eqn. (3), where E_2 and E_1 are the oxidation potentials in the

$$E_2 - E_1 = \frac{RT}{F} \ln K_{\text{comp}} \qquad (3)$$

formation of cation (OX) and radical cation (SEM), respectively.[6] The comproportionation constants, in our case, are *ca.* 10^4 (Table 2) and this means that the equilibrium is completely shifted towards formation of the SEM form.

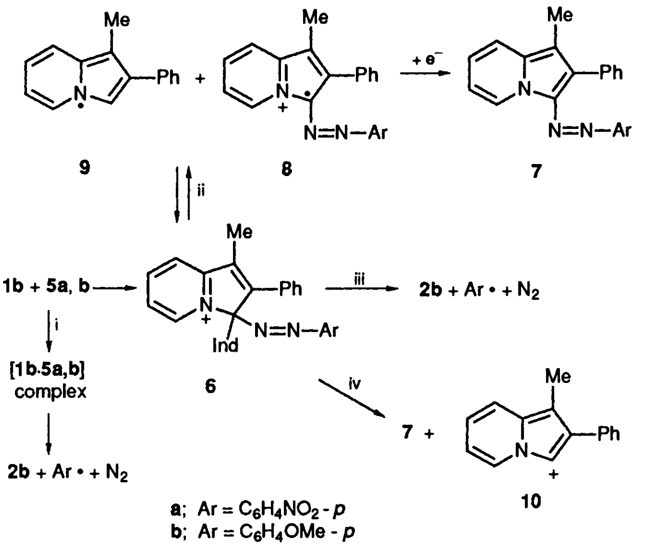
The oxidation with diazonium salts deserves explanation. The *p*-nitro- and the *p*-methoxy-benzenediazonium ions show reduction potentials of +0.45 V and +0.25 V *vs* SCE in sulpholane, respectively.[7] On the basis of these reduction values, the *p*-nitro derivative may be considered able to oxidize the dimers **1a–c**, while doubts about the oxidative power of *p*-methoxybenzenediazonium salt remain. However, in both cases, the oxidation carried out directly in the EPR spectrometer cavity, by mixing of 10^{-2} mol dm^{-3} deoxygenated solutions of the reactants gave a new solution from which a strong EPR signal was recorded. These results could be interpreted either by a single-electron transfer (SET) between a substrate **1a–c** and the diazonium ions **5a** or **5b** or through a homolytic retrogression of the σ-complex[8] formed by electrophilic attack on one of the two indolizine nuclei as shown in Scheme 2. The hypothesis of σ-complex formation was supported by the fact that compounds **7a** and **7b** are the main reaction products.

Considering that the higher oxidative power of species **2a** compared with that of **2b** is accompanied by its stronger electrophilic character, it can be assumed that both the diazonium ions form the σ-complex. The evolution of this intermediate (paths ii and iii) could explain, as well as the SET (path i), the development of nitrogen, and the formation of the monomer radical cation and the diazo derivatives **7a** and **7b**. We have no evidence to support the transformation reported in path iv. In order to justify the mechanistic proposals reported in Scheme 2, the dimer **1b** was treated with species **2b** in the presence of the aminoxyl **11**, it having been demonstrated that this radical does not significantly react either with the dimer **1b** or with the diazonium ion **2b** during one hour. Since aminoxyl **11** reacts with aryl radicals we would expect the formation of compounds such as **12**, **13** and **14** as experimental proof of this.[9] From this reaction, together with traces of azo compound **7b** products **12** and **13** were also isolated. The yellow compound **12** was identified by comparison with an authentic sample,[10] and the yellow compound **13** was identified by its elemental analysis, and NMR and mass spectra. The two methyl groups at δ_H 1.78

Table 2 Voltammetric data for the oxidation of compounds **1a–c** in MeCN at a platinum electrode

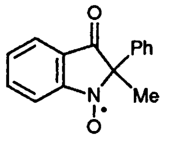
Compound	$E'_{\frac{1}{2}}$/V	(i'/c)/μA dm^3 mmol^{-1}	$E''_{\frac{1}{2}}$/V	(i''/c)/μA dm^3 mmol^{-1}	$10^{-4}\,K$[a]
1a R = Me	0.034	14.1	0.268	14.1	0.9
1b R = Ph	0.088	14.8	0.325	14.8	1.0
1c R = p-MeC$_6$H$_4$	0.080	14.2	0.315	14.1	0.9

[a] Calculated by equation (3) at T 298 K.



a; Ar = C$_6$H$_4$NO$_2$-p
b; Ar = C$_6$H$_4$OMe-p
Ind = 1-methyl-2-indolizin-3-yl

Scheme 2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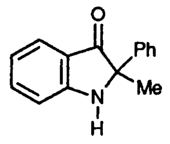
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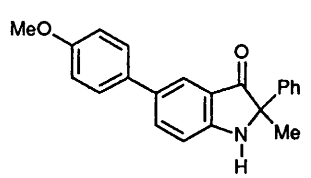
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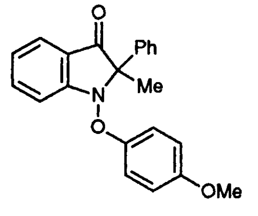
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and 3.87 are typical for the methyl at C-2 in the indoxyl moiety * and for the methyl of the p-methoxyphenyl group; the fragmentation observed in the mass spectrum is also consistent with the assigned structure. It would have been very interesting to capture the indolizyl radical **9** by the aminoxyl **11**, but we were unable to isolate such a coupling product. We did, however, succeed in the isolation of another yellow compound, which slowly decomposed to form the aminoxyl **11**. Since the yellow compound did not correspond to the hydroxylamine related to radical **11**, we have assigned structure **14** to it, considering the behaviour of alkylated and arylated hydroxylamines.[11,†]

(b) *Electrochemical Oxidation*.—In the range of concentration used (~ 10^{-4} mol dm^{-3}) the 3,3-bisindolizines **1a–c** in MeCN, with Et$_4$NClO$_4$ as supporting electrolyte, exhibited, at a pulsed vitreous carbon electrode,[12] two well defined oxidation steps of the same height (Table 2). A comparison of the i/c-values reported in Table 2 with the corresponding values determined under the same experimental conditions used for the reversible one-electron oxidation of 2,2-disubstituted 3-oxoindolin-1-oxyls[13] allowed us to conclude that the number of electrons involved in both oxidation steps of the electrochemical oxidation of indolizines **1a–c** is *ca.* 1 (n 1).

Cyclic voltammetric experiments at a stationary vitreous carbon electrode showed two well defined anodic peaks with the corresponding cathodic peaks. Also, upon using a lower scan rate (50 mV s^{-1}) the anodic–cathodic peak-potential widths are close to the theoretical value[14] for a reversible one-electron transfer.

Experimental

M.p.s were measured on an electrothermal melting point apparatus and are uncorrected. UV spectra were recorded on a Perkin-Elmer 554 spectrophotometer; EPR spectra were recorded on a Varian E4 spectrometer. ^{1}H NMR spectra were recorded on a Varian XL 100 with SiMe$_4$ as internal standard. Liquid chromatography was performed on a Perkin-Elmer series 2 HPLC. IR spectra were performed on a Nicolet 20-SX spectrophotometer equipped with a Spectra Tech. DRIFT collector.

Compounds **1a–c**,[5a] *tris*-(p-bromophenyl)ammonium hexachloroantimonate **4**,[5a] aminoxyl **11**, and the corresponding hydroxylamine[15] were prepared as described in the literature. p-Nitro- **5a** and p-methoxy-benzenediazonium **5b** ions were Aldrich commercial products.

Synthesis of the Radical Monocations **2a–c**.—A solution of iodine (63 mg, 0.5 mmol) and AgClO$_4$ (206 mg, 1 mmol) in MeCN (10 cm^3) was added to a stirred solution of compound **1b** (412 mg, 1 mmol) in MeCN (10 cm^3) at room temperature. After 10 min the deep green solution was filtered from the precipitated AgI. Dried Et$_2$O (10 cm^3) was added to the filtrate, promoting the precipitation of the radical monocation **2b**, which was filtered off (98 mg, 70%), m.p. > 300 °C. Radical cations **2a** and **2c** were obtained in the same way in 65 and 75% yield: m.p. > 300 °C for both compounds.

Synthesis of Dications **3a–c**.—A solution of iodine (126 mg, 1 mmol) and AgClO$_4$ (412 mg, 2 mmol) in MeCN (10 cm^3) was

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* As to the formation of compounds **12** and **13** from the corresponding aminoxyls, we are unable to suggest a mechanism; however, it may be affirmed that when aryl radicals are formed in the presence of aminoxyls such as **11**, indoxyls **12** and **13** were always isolated (P. Carloni, L Greci and P. Stipa, unpublished results).

† Though we have no quantitative data, experimental evidence suggests that arylated hydroxylamines are not stable: in fact, all attempts to force a reaction between aryl radicals with nitroxides, in order to synthesize arylated hydroxylamines, failed.

added to a solution of a substrate **1a–c** (1 mmol) in MeCN (10 cm^3) and the mixture was worked up as described above; the dications **3a–c** were isolated in *ca.* 75% yield; all isolated products had m.p. > 300 °C.

Radical Monocations **2b** *and Dications* **3b** *by Oxidation of Compound* **1b** *with Aminium Radical* **4**.—Equimolar volumes of 10^{-5} mol dm^{-3} solutions of compounds **1b** and **4** were mixed at room temperature. The resulting green solution gave the UV spectrum reported in Fig. 2 corresponding to the radical cation **2b**. This spectrum was identical with that recorded for species **2b** prepared as described above. A deoxygenated part of this solution gave an intense EPR signal identical with that reported in Fig. 1. In the same way, solutions containing species **3b** were obtained by mixing of one volume of a 10^{-3} mol dm^{-3} solution of **1b** and two volumes of 10^{-3} mol dm^{-3} solutions of species **1b** and **4**. The UV spectrum, reported in Fig. 2, corresponds to that obtained from species **3b**, prepared by oxidation of compound **1b** with the Gomberg reagent.

EPR Spectra.—The EPR spectra of the radical cations **2a–c**, obtained from compounds **1a–c** by I_2–$AgClO_4$ oxidation, were recorded for 10^{-3} mol dm^{-3} MeCN deoxygenated solutions. Good EPR spectra were also obtained by mixing of 10^{-3} mol dm^{-3} MeCN solutions of **1a–c** and the aminium radical **4**, and of 10^{-2} mol dm^{-3} MeCN solutions of **1a–c** and the diazonium salts **5a** and **5b**, using an inverted U-cell.[16]

MacLachlan Spin Density Distribution.—The spin density distribution was calculated by a computer program[17] using the following values: h_N 1.85; $K_{C(1)-C(2)} = K_{C(1)-C(5)} = K_{C(1)-C(9)} =$ 0.9; K_{CC} 1.0; λ 1.2.[18]

Synthesis of Compound **7a**.—A solution of the fluoroborate **5a** (472 mg, 2 mmol) in water (30 cm^3) was added to a mixture of 1-methyl-2-phenylindolizine (414 mg, 2 mmol), dissolved in ethanol (100 cm^3), and sodium hydrogen carbonate (840 mg, 10 mmol). The deep red-brown mixture was stirred for 30 min, then filtered, and the dark green precipitate **7a** was washed several times with water and crystallized from chloroform (75%), m.p. 270–272 °C; ν_{max}(DRIFT) 1580, 1505 and 1375 cm^{-1}; δ_H($CDCl_3$) 2.61 (3 H, s, Me), 7.20–8.0 (H, m, ArH), 8.11 (4 H, pseudo-q, A_2B_2, *J* 6 Hz, ArH) and 10.45 (1 H, d, *J* 4 Hz, arom); *m/z* 356 (44%) (Calc. for $C_{21}H_{16}N_4O_2$: M, 356.38), 206 (57), 122 (33) and 77 (100). (Found: C, 70.65; H, 4.6; N, 15.9. Calc. for $C_{21}H_{16}N_4O_2$: C, 70.79; H, 4.49; N, 15.73%).

Synthesis of Compound **7b**.—A solution of the fluoroborate **5b** (442 mg, 2 mmol), in water (10 cm^3) was added to a mixture of 1-methyl-2-phenylindolizine (414 mg, 2 mmol), dissolved in ethanol (50 cm^3) and sodium hydrogen carbonate (840 mg, 10 mmol). The red-brown solution was stirred for 30 min, extracted with diethyl ether (4 × 25 cm^3), and the extract was dried over sodium sulphate, filtered and evaporated to give the red coloured adduct **7b**, which was crystallized from hexane (80%), (m.p. 100–102 °C); ν_{max}(DRIFT) 1588 and 1573 cm^{-1}; δ_H($CDCl_3$) 2.43 (3 H, s, Me), 3.86 (3 H, s, OMe), 7.41 (4 H, pseudo-q, A_2B_2, *J* 6.4 Hz, ArH), 6.62–8.01 (8 H, m, ArH) and 10.54 (1 H, d, *J* 4 Hz, ArH); *m/z* 341 (37%) (Calc. for $C_{22}H_{19}N_3O$: M, 341.30), 206 (49), 107 (29) and 107 (100) (Found: C, 77.6; H, 5.5; N, 12.4. Calc. for $C_{22}H_{19}N_3O$: C, 77.42; H, 5.57; N, 12.32%).

Reaction of Compound **1b** *with the Salt* **5b** *in the Presence of Aminoxyl* **11**.—(a) A solution of compound **5b** (58 mg, 0.25 mmol) in MeCN (10 cm^3) was added to a mixture of compound **1b** [103 mg, 0.25 mmol, dissolved in MeCN (60 cm^3)] and the aminoxyl **11** [60 mg, 0.25 mmol, dissolved in MeCN (20 cm^3)] with an excess of sodium hydrogen carbonate (210 mg, 2.5 mmol). The reaction mixture was stirred for 1 h, poured into water, and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulphate, and evaporated under reduced pressure. TLC of the crude reaction mixture evidenced the presence of compounds **12** and **13** together with the starting material **1b** which were identified by HPLC [column C_{18} (10 μm); 75% MeOH–water as the eluant; flow rate 1.0 cm^3 min^{-1}; temperature 60 °C; UV detection at 254 nm]. Compounds **12** and **13** were separated by preparative TLC on silica with cyclohexane–ethyl acetate (9:1) as eluant. Compound **12** was identified with an authentic sample.[10] Compound **13** was identified on the basis of the following data: m.p. 168 °C [from light petroleum (60–80 °C)], ν_{max}(DRIFT) 1693 and 1628 cm^{-1}; δ_H($CDCl_3$) 1.78 (3 H, s, Me), 3.81 (3 H, s, OMe), 6.9–7.08 (3 H, m, ArH), 7.3–7.6 (8 H, m, ArH) and 7.7–7.82 (2 H, m, ArH); *m/z* 329 (73%) (Calc. for $C_{22}H_{19}NO_2$: M, 329.38), 300 (100), 198 (29), 104 (43) and 77 (42) (Found: C, 80.1; H, 5.9; N, 4.1. Calc. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25%). Compound **7b** was present only in trace amounts.

(b) In a second experiment, without the presence of the nitroxide radical **11** and under the above experimental conditions, the crude reaction mixture showed the presence of the azo derivative **7b** only.

Electrochemical Measurements.—A three-electrode multifunction assembly (AMEL 471) was employed for the voltammetric measurements. The working electrode was a pulsed[12] (or stationary, in the case of linear-sweep voltammetry) vitreous carbon disk of *ca.* 3 mm diameter. The reference electrode assembly was Ag/0.1 mol dm^{-3} $AgClO_4$–MeCN/sintered glass-disk/0.1 mol dm^{-3} Et_4NClO_4–MeCN/sintered glass-disk. The counter-electrode was a platinum wire. Acetonitrile (Carlo Erba, spectrophotometric grade) was purified as previously described.[13]

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References

1 Part 2, R. Andruzzi, L. Cardellini, L. Greci, P. Stipa, M. Poloni and A. Trazza, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3067.
2 M. Colonna, L. Greci, P. Bruni and G. Padovano, *Gazz. Chim. Ital.*, 1971, **101**, 396.
3 M. Colonna, L. Greci and P. Bruni, *Gazz. Chim. Ital.*, 1972, **102**, 527.
4 S. Hünig, *Pure Appl. Chem.*, 1967, **15**, 109; L. Michaelis, *Chem. Rev.*, 1935, **16**, 243.
5 (*a*) F. A. Bell, A. Ledwith and D. C. Sherrington, *J. Chem. Soc. C*, 1969, 2718; (*b*) A. Ledwith, *Acc. Chem. Res.*, 1972, **5**, 133.
6 A. L. Bard, A. Ledwith and H. J. Shine, *Adv. Phys. Org. Chem.*, 1976, **13**, 234.
7 R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, 1969, **34**, 854.
8 L. Eberson and F. Radner, *Acta Chem. Scand., Ser. B*, 1984, **38**, 861.
9 C. Berti, L. Greci and L. Marchetti, *J. Chem. Soc.. Perkin Trans. 2*, 1979, 233.
10 C. Berti, L. Greci and L. Marchetti, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1052.
11 J. Chateauneuf, J. Lusztyk and K. U. Ingold, *J. Org. Chem.*, 1988, **53**, 1629.
12 R. Andruzzi and A. Trazza, *J. Electroanal. Chem.*, 1977, **77**, 101; 1978, **90**, 389.
13 R. Andruzzi, C. Berti, L. Greci and A. Trazza, *J. Chem. Res.*, 1982, (*S*) 178; (*M*) 1840.

14 R. S. Nicholson and I. Shain, *Anal. Chem.*, 1964, **36**, 706.

15 C. Berti, M. Colonna, L. Greci and L. Marchetti, *Tetrahedron*, 1975, **31**, 1745.

16 G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, 1964, **86**, 1807.

17 A. D. MacLachlan, *Mol. Phys.*, 1960, **3**, 233.

18 A. Streitwieser, Jr., *Molecular Orbital Theory for Organic Chemists*, Wiley, New York, London 1961.

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