

Electroreduction of 5-Nitroindoles in Acidic, Neutral and Basic Hydro-organic Media: Electrosynthesis of 4-Substituted 5-Aminoindoles

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Dedicated to Professor Henning Lund on the occasion of his 70th birthday.

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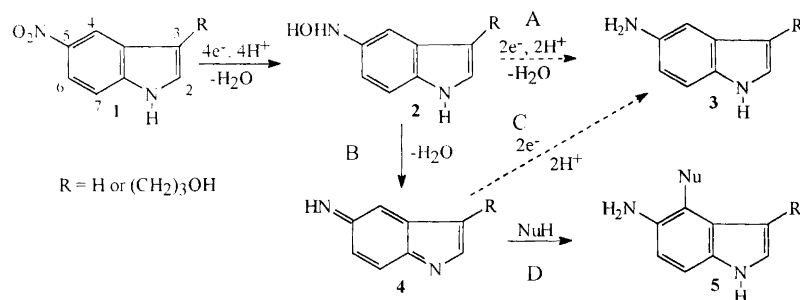
The electrochemical behavior of 5-nitroindoles (**1**) at Hg in acidic, neutral and basic methanol–water solutions has been studied by polarography and cyclic voltammetry and compared with that of nitrobenzene. Preparative electrolyses of 5-nitroindoles (**1**) in acidic and basic methanol solutions gave 4-substituted 5-aminoindoles (**5**) resulting from the regiospecific addition, to a diiminoquinone intermediate **4** (protonated in acidic medium), of methanol or methanolate ion and/or of any other good nucleophile present in the electrolytic solution. A protonated form of **4** was trapped in a cycloaddition reaction with cyclopentadiene in an electrolysis performed in acidic medium. The regiochemistry of nucleophilic addition to **4** and its two conjugate acids is discussed in the light of the results of AM1 calculations (heats of formation, coefficients of the LUMO, Mulliken charges).

Aminoindoles and their derivatives have many uses in the pharmaceutical and cosmetic field.^{1,2} A patent² reported that the zinc reduction of 3-(3-hydroxypropyl)-5-nitroindole [**1**, R=(CH₂)₃OH] in DMF containing ammonium chloride as a proton source and ethanethiol in excess (10 equiv.) gave 20% of 3-(3-hydroxypropyl)-4-ethylthio-5-aminoindole [**5**, Nu=EtS, R=(CH₂)₃OH] and 55% of 3-(3-hydroxypropyl)-5-aminoindole [**3**, R=(CH₂)₃OH] (Scheme 1). In order to see whether 5-substituted aminoindoles (**5**) could be synthesized by electrochemical reduction of 5-nitroindoles (**1**) and to learn more on the mechanism and regiochemistry of formation of **5**, we studied the polarographic and cyclic voltammetric behavior of 5-nitroindole (**1**, R=H) and the preparative electroreduction of 5-nitroindole (**1**, R=H) and of 3-(3-hydroxypropyl)-5-nitroindole [**1**, R=(CH₂)₃OH] at a Hg cathode in acidic (pH=0.3), neutral (pH=6.5) and basic (pH=13.5) aqueous methanolic solutions (MeOH–H₂O 93:7 w/w). The results are reported in this paper together with theoretical calculations (heats of formation, coefficients of the LUMO, Mulliken charges) on the electrogenerated diimino-

quinone intermediate **4** and its conjugate acids **4H⁺a** and **4H⁺b** (Scheme 3).

Voltammetric behavior. To our knowledge, only two papers have been published on the electroreduction of nitroindoles.^{3,4} Person *et al.*³ reported on the polarographic and coulometric behavior of 3-, 5-, 6- and 7-nitroindoles in aqueous media as a function of pH (no electrolyte composition given in the paper). In acidic medium (pH < 5), the polarogram of nitroindoles showed one wave corresponding to a six-electron reduction to the corresponding aminoindole. In neutral media (5 ≤ pH < 8), two waves were observed, the first one corresponding to a four-electron reduction to the corresponding hydroxylaminoindole. The second wave, corresponding to the transfer of two electrons at pH 5, decreased when the pH was increased and disappeared at pH 8. In basic media (pH ≥ 8), only one four-electron wave was observed. Microcoulometric measurements at controlled potential did not fully agree with values determined by polarography. In acidic media (pH < 5), exhaustive reduction of nitroindoles consumed 4–4.5 F of electricity per mole of substrate (F mol⁻¹) instead of 6 F mol⁻¹ in polarography. In neutral media

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Scheme 1.

($5 \leq \text{pH} < 8$), coulometric measurements indicated 4 F mol^{-1} as observed in polarography. Finally, in basic media ($\text{pH} \geq 8$), 5 F mol^{-1} of substrate were consumed as opposed to 4 F mol^{-1} in polarography. No explanation of the observed discrepancies was suggested and no results of preparative electrolyses were reported. More recently, Kokkinidis *et al.*⁴ found no such discrepancies since they reported that the same number of electrons was transferred in d.c. polarographic and coulometric (Hg pool) reductions of 4- and 5-nitroindoles in aqueous buffered electrolytes (HClO_4 0.2 M for $\text{pH} \approx 1$, Britton–Robinson buffers for $1.8 \leq \text{pH} \leq 11.7$, NaOH 0.1 M for $\text{pH} \approx 13$): a six-electron reduction in acidic media ($\text{pH} < 6.8$) and a four-electron reduction in neutral and basic media ($\text{pH} \geq 6.8$). However, as in Person's paper, no preparative electrolyses were performed.

Results of polarographic measurements of 5-nitroindole **1** ($\text{R} = \text{H}$) and nitrobenzene in acidic, neutral and basic aqueous methanolic solutions are reported in Table 1. At pH 0.3, with HCl or H_2SO_4 as the supporting electrolyte, polarograms of nitrobenzene showed a four-electron reduction wave followed by a two-electron wave in HCl ($E_{1/2} = -0.95 \text{ V}$, entry 2, Table 1) or a continuously increasing limiting current in H_2SO_4 (entry 4, Table 1) as previously described.⁵ In H_2SO_4 , the polarogram of 5-nitroindole (**1**, $\text{R} = \text{H}$) was identical with that of nitrobenzene in the same medium, a four-electron reduction wave ($E_{1/2} = -0.28 \text{ V}$) corresponding to reduc-

tion of **1** ($\text{R} = \text{H}$) to 5-hydroxylaminoindole **2** ($\text{R} = \text{H}$) (Scheme 1) followed by the slow reduction to the corresponding amine, but differed from those reported by Person³ and Kokkinidis⁴ in aqueous acidic medium (a single six-electron reduction wave). In HCl, the polarogram of **1** ($\text{R} = \text{H}$) differs from that of nitrobenzene in showing a single four-electron reduction wave. The transfer of four electrons was confirmed by microcoulometric measurements (see also the results of preparative electrolysis in Table 3, entry 2). The transfer of only four electrons in HCl can be explained by Scheme 1 and will be discussed below. In neutral medium, the polarogram of nitrobenzene ($E_{1/2} = -0.63 \text{ V}$, entry 6, Table 1) showed a four-electron reduction wave as expected⁵ since phenylhydroxylamine is not reducible under neutral conditions. On the other hand, in the same medium, the polarogram of 5-nitroindole (**1**, $\text{R} = \text{H}$) showed a second reduction wave ($E_{1/2} = -1.21 \text{ V}$, entry 5, Table 1) as reported by Person.³ This second wave was not observed by Kokkinidis⁴ and could correspond to the two-electron reduction of 5-hydroxylaminoindole (**2**, $\text{R} = \text{H}$) to 5-aminoindole (**3**, $\text{R} = \text{H}$), in contrast to phenylhydroxylamine which is not reducible in neutral media.⁵ Finally, in basic media, the polarographic behavior of 5-nitroindole (**1**, $\text{R} = \text{H}$) ($E_{1/2} = -1.11 \text{ V}$, entry 7, Table 1) was similar to that of nitrobenzene ($E_{1/2} = -0.92 \text{ V}$, entry 8, Table 1): only a four-electron reduction wave is observed. This result is in agreement with previously reported

Table 1. Polarographic behavior of 5-nitroindole (**1**, $\text{R} = \text{H}$) in methanol–water (93:7 v/v).^a

Entry	Electrolyte ^b	pH	Substrate ^c	$(E_{1/2})_1/\text{V}$	$(i_d)_1/\mu\text{A}$	$(E_{1/2})_2/\text{V}$	$(i_d)_2/\mu\text{A}$
1	HCl ^d	0.3	1	-0.24	-3.80		
2			PhNO ₂	-0.28	-4.70	-0.95	-2.20
3	H ₂ SO ₄	0.3	1	-0.28	-4.00 ^e		
4			PhNO ₂	-0.30	-4.05 ^f		
5	AcOH–AcONa	6.5	1	-0.70	-3.20	-1.21	-1.55
6			PhNO ₂	-0.63	-4.15		
7	KOH	13.5	1	-1.11	-3.15		
8			PhNO ₂	-0.92	-4.25		

^a $T = 25 \pm 2^\circ \text{C}$; glassy carbon as auxiliary electrode; SCE as reference electrode; $t = 2 \text{ s}$; $v = 2 \text{ mV s}^{-1}$. ^b Electrolytes: HCl 0.15 M; AcOH 0.54 M–AcONa 0.37 M; KOH 0.15 M. ^c Substrate concentration: $2.5 \times 10^{-4} \text{ M}$. ^d Similar potential and current intensities were obtained using HBr instead of HCl. ^e The limiting current increases continuously with a slope equal to $2.50 \mu\text{A V}^{-1}$ from the beginning of the plateau ($E = -0.35 \text{ V}$). ^f The limiting current increases continuously with a slope equal to $4.28 \mu\text{A V}^{-1}$ from $E = -0.7 \text{ V}$.

Table 2. Cyclic voltammetry of 5-nitroindole (**1**, R=H) at Hg in methanol-water (93:7 v/v).^a

Entry	Electrolyte ^b	pH	Substrate ^c	(E _{pc}) ₁ /V	(i _{pc}) ₁ /μA	(E _{pc}) ₂ /V	(i _{pc}) _t ^d /μA	E _{pa} /V	i _{pa} /μA	(E _{pc}) ₃ /V	(i _{pc}) ₃ /μA
1	HCl ^d	0.3	1	-0.35	-7.80						
2			PhNO ₂	-0.43	-6.38						
3	H ₂ SO ₄	0.3	1	-0.35	-6.95						
4			PhNO ₂	-0.46	-4.62						
5	AcOH-AcONa	6.5	1	-0.74	-4.73			-0.13	1.32	-0.18	-0.89
6			PhNO ₂	-0.68	-5.23			-0.04	1.13	-0.09	-0.73
7	KOH	13.5	1	-1.06	-2.70	-1.28	-5.07	-0.58	0.41	-0.61	-0.17
8			PhNO ₂	-1.03	-5.21			-0.47	1.26	-0.51	-0.76

^a T = 25 ± 2 °C; glassy carbon as auxiliary electrode; Ag/AgCl/(Cl⁻)_{dil.} as reference electrode; v = 100 mV s⁻¹. ^b Electrolytes: see footnote b of Table 1. ^c Substrate concentration: 2.5 × 10⁻⁴ M. ^d i_t represents the sum i₁ + i₂ where i₁ is the current of the first peak and i₂ the current corresponding to the second peak.

measurements performed by Person³ and Kokkinidis⁴ in basic media.

Results of voltammetric measurements of 5-nitroindole (**1**, R=H) and nitrobenzene in acidic, neutral and basic aqueous methanolic solutions are gathered in Table 2. An increase of the scan rate from 100 to 500 mV s⁻¹ caused the expected increase of current (diffusion controlled processes), shift of potential (globally irreversible system), but there was no variation of the number of electrons exchanged. In acidic media, the cyclic voltammograms of 5-nitroindole (**1**, R=H) (entries 1 and 3) and nitrobenzene (entries 2 and 4) were identical and showed only one peak corresponding to the six-electron reduction to the corresponding amine. In the particular case of 5-nitroindole (**1**, R=H) in MeOH-H₂O-HCl 0.15 M, the current peak corresponded to a six-electron transfer, contrary to what was observed by polarography (four-electron wave). The discrepancy between the number of electrons exchanged in cyclic voltammetry and in polarography will be discussed in the next section. In neutral and basic media, the voltammetric behavior of 5-nitroindole (**1**, R=H) and nitrobenzene is similar to the well-known electrochemical behavior of aromatic nitro com-

pounds⁵ showing (i) a four-electron reduction peak sometimes split into two peaks owing to the reversible mono-electronic reduction to the radical anion followed by its further reduction to the hydroxylamine and (ii) the presence, at less negative potential, of the hydroxylamine/nitroso reversible redox couple.

Preparative electrolyses of 5-nitroindole (**1**, R=H).

Results of the preparative electroreduction of 5-nitroindole (**1**, R=H), at Hg, in MeOH-H₂O solutions are presented in Table 3. In HBr and HCl media, the electroreduction of 5-nitroindole consumed 4.2–4.3 F mol⁻¹ and led to the corresponding 4-halo-5-aminoindole **5** (R=H, Nu=X) as the major product (71–86% for Nu=Br and 82% for Nu=Cl). In both cases, trace amounts of 5-aminoindole (**3**, R=H) were detected by vapor phase chromatography (VPC). On the basis of the well-known mechanism of electroreduction of nitroaryl compounds in the type of medium used in this study,⁵ **1** (R=H) would be reduced first to hydroxylamine **2** (R=H) through four successive electron and proton transfers (see Scheme 1). In acidic medium (pH 0.3), there would be a competition between path A,

Table 3. Electroreduction of 5-nitroindole (**1**, R=H) (6 × 10⁻³ M) at Hg in MeOH-H₂O (93:7 w/w).

Entry	Supporting electrolyte ^a	Added nucleophile ^b	E/V ^c	Charge/F mol ⁻¹	Yield (%) of products ^d	
					3	5
1	HBr	—	-0.61	4.3	Traces ^e	71–86 (Nu=Br)
2	HCl	—	-0.62	4.2	Traces ^e	82 (Nu=Cl)
3	H ₂ SO ₄	—	-0.77	5.0	12 ^e	14 ^e (Nu=MeO)
4	H ₂ SO ₄	PhSH	-0.77	4.3	—	16–29 (Nu=PhS) 2 (Nu=MeO) ^f
5	AcOH-AcONa	—	-0.94	5.1	16	—
6	KOH	—	-1.31	5.6	30–34	43–47 (Nu=MeO)
7	KOH	EtSH	-1.31	4.7	15	70 (Nu=EtS)
8	KOH	PhSH	-1.31	4.7	—	59 (Nu=PhS)

^a Supporting electrolyte concentration: see footnote b of Table 1. ^b Added nucleophile concentration: 4.8 × 10⁻² M for EtSH, 1.2 × 10⁻² M for PhSH. ^c Working potential vs. SCE. ^d Yield of product isolated by flash chromatography on silica gel (unless stated otherwise) and based on two to three electrolyses (range given when variations were larger than ±4%); see Scheme 1 for the structures of **3** and **5**. ^e Determined by vapor phase chromatography. ^f 3-Thiophenoxy-5-aminoindole was also isolated in a 14% yield.

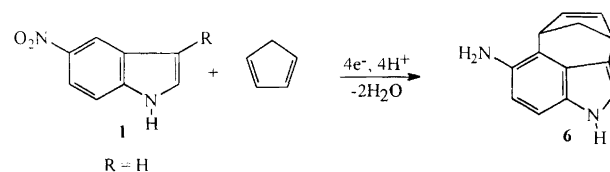
the two-electron reduction of protonated **2** ($R=H$) ($2H^+$) to aminoindole **3** ($R=H$) and path B, acid-catalyzed elimination of water from $2H^+$ to give the diiminoquinone intermediate **4**, most probably protonated ($4H^+$) at pH 0.3 (Scheme 1). The latter could be reduced to aminoindole **3** ($R=H$) in a two-electron process (path C). The 4-substituted-5-aminoindole **5** ($R=H$) would result from the addition of a nucleophile to diiminoquinone **4** ($R=H$) (path D) which would compete with its reduction (path C). The fact that only $4 F mol^{-1}$ were consumed in the media containing HBr or HCl (entries 1 and 2, Table 3) agrees with **5** ($R=H$, Nu=Br or Cl) being the only product isolated and shows that the dehydration of $2H^+$ (path B) would be much faster than reduction to **3** (path A) and that the addition of Br^- or Cl^- to $4H^+$ (path D) would be much faster than reduction of $2H^+$ to **3** ($R=H$). The mechanism of Scheme 1 could account for the discrepancy of the number of electrons exchanged in polarography (four electrons) and in cyclic voltammetry (six electrons) in MeOH–H₂O HCl. In polarography, at a scan rate of $2 mV s^{-1}$, the protonated hydroxylaminoindole $2H^+$ (four-electron reduction) would leave the diffusion layer before the electrode reached the reduction potential of $2H^+$ to **3** ($R=H$). In cyclic voltammetry, at a scan rate of $100 mV s^{-1}$, the hydroxylaminoindole $2H^+$ would not have time to leave the diffusion layer before the electrode reached its reduction potential and would be reduced to **3** ($R=H$) (six-electron reduction).

The fact that the electrolysis of **1** ($R=H$) at pH 0.3, in the absence of HBr or HCl (entry 3, Table 3), gave a one-to-one ratio of **3** ($R=H$) and **5** ($R=H$, Nu=MeO) and consumed $5 F mol^{-1}$ of substrate can also be readily explained by the mechanism of Scheme 1. With methanol being less nucleophilic than Br^- and Cl^- in these acidic media, the reduction of $4H^+$ to **3** ($R=H$) (path C) would now compete effectively with the addition of methanol (path D), the rates of the two reactions being similar. The nearly quantitative crude material balance and the low material balance of 26% after chromatographic separation suggest that a third process must compete with paths C and D in the absence of a good nucleophile. The most probable hypothesis is polymerization and/or oligomerization of $4H^+$ since both **3** ($R=H$) and **5** ($R=H$, Nu=MeO) were found to be stable in the electrolysis medium and during the work up. These polymers and/or oligomers would be strongly adsorbed on silica gel and all attempts to isolate and characterize any polymeric material failed. In acidic media, the intermediacy of $4H^+$ was confirmed by the isolation of the tetracyclic compound **6** in 26% yield (Scheme 2) when the electrolysis of **1** ($R=H$) in acidic medium (H₂SO₄ 0.15 M) was carried out in the presence of cyclopentadiene in excess (8 equiv.). Compound **6** results from a $[\pi^4s + \pi^6s]$ cycloaddition reaction of $4H^+$. In H₂SO₄, in the presence of thiophenol, the electroreduction of 5-nitroindole (**1**, $R=H$) led to 4-thiophenoxy-5-aminoindole (**5**, $R=H$, Nu=PhS) as the major product

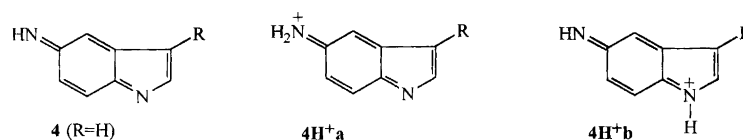
(16–29%, entry 4, Table 3), 3-thiophenoxy-5-aminoindole (14%) and to 4-methoxy-5-aminoindole (**5**, $R=H$, Nu=MeO) (2%). It is noteworthy that, in this specific case, the nucleophilic addition was not regiospecific. Experiments were performed to confirm that 3-thiophenoxy-5-aminoindole was not produced by reaction of 5-aminoindole (**3**, $R=H$) with phenyl disulfide generated by air oxidation of thiophenol during the basic work up.

In neutral medium the electroreduction of 5-nitroindole (**1**, $R=H$) gave 5-aminoindole (**3**, $R=H$) as the sole product, in a very low yield (16%, entry 5, Table 3). The low material balance indicates that competing processes gave products that could not be isolated or detected. An electrolysis performed in the presence of a large excess (50 equiv.) of a good nucleophile (Br^- from NaBr) gave 28% of **3** ($R=H$) and only 3% of 4-bromo-5-aminoindole (**5**, $R=H$, Nu=Br). The low yield of **5** strongly suggests that the dehydration of hydroxylamine **2** ($R=H$) (unprotonated in neutral medium) is a slow process and that 5-aminoindole (**3**, $R=H$) must have been formed by direct electroreduction of hydroxylamine **2** ($R=H$). It is noteworthy that electroreduction of unprotonated hydroxylamine **2** ($R=H$) occurred given the well known fact that unprotonated phenylhydroxylamine (pH > 5) is not reducible in protic media.⁵

The mechanistic hypothesis of Scheme 1 can also explain the results in basic medium (entries 6–8, Table 3), with the differences that (i) the intermediate hydroxylamine **2** ($R=H$) would not be protonated, (ii) its dehydration to diiminoquinone **4** ($R=H$) would be a base catalyzed reaction and (iii) the electrophilic intermediate **4** ($R=H$) would not be protonated. The ethanethiolate (entry 7, Table 3) and thiophenolate (entry 8, Table 3) anions are more powerful nucleophiles than the methoxide anion and hence would add more rapidly to the diiminoquinone **4** ($R=H$) (path D), which would explain the higher yields of **5** ($R=H$) (higher selectivity of the reaction) and the lower consumption of electrons in the electroreductions in the presence of thiols (compare entries 7 and 8 with entry 6). The selectivity, yield of **5** ($R=H$) and material balance after chromatographic separation in the KOH medium (absence of thiols, entry 6, Table 3) was higher than in the H₂SO₄ medium (absence of Br^- or Cl^- , entry 3), which could be explained by a larger (rate of reaction D/rate of reaction C) ratio and lesser polymerization/oligomerization in the former medium [unprotonated diiminoquinone **2** ($R=H$), CH_3O^- as nucleophile] than in the latter (protonated diiminoquinone $2H^+$, CH_3OH as nucleophile). In basic medium, the unprotonated diiminoquinone **4** ($R=H$)



Scheme 2.



Scheme 3.

was not trapped in a pericyclic reaction with 2,3-dimethyl-1,3-butadiene or 1,3-dimethoxy-1,3-butadiene because its reaction with the methoxide anion and its reduction were faster than the pericyclic reaction.

It is noteworthy that the addition of nucleophiles on $4H^+$ and **4** is regiospecific (addition occurs only at position 4) given the fact that positions 2, 3, 6 and 7 are also electrophilic. In acidic media, the electrophilic diiminoquinone intermediate **4** can exist in two protonated forms, $4H^+a$ and $4H^+b$, shown in Scheme 3. According to frontier molecular orbital theory, the most important frontier orbital interaction in a reaction between an electrophile and a nucleophile^{6,7} is that between the LUMO of the electrophile and the HOMO of the nucleophile. In the case of the addition of a nucleophile to a multivalent electrophile, the reaction would be the fastest at the carbon where the coefficient of the LUMO is the largest.^{6,7} The results of theoretical calculations using the AM1 method^{8,9} on diiminoquinone **4** and its two conjugate acids $4H^+a$ and $4H^+b$ are gathered in Table 4. They show that the LUMO of unprotonated **4** has the largest coefficient at carbon 4, which agrees entirely with the experimental results: regiospecific formation of 4-substituted 5-aminoindoles (**5**) in basic medium. In addition, carbon 4 of diiminoquinone **4** also has the most positive Mulliken charge corresponding to the least repulsive electrostatic interaction with the attacking nucleophile. Calculations on the protonated forms $4H^+a$ and $4H^+b$ do not show such a perfect agreement with the experimental results observed in acidic medium, at which pH (0.3) diiminoquinone **4** is most probably protonated as already mentioned. Indeed, the most stable intermediate $4H^+a$ ($\Delta H_f = 255.4 \text{ kcal mol}^{-1}$) has the largest coefficient of its LUMO at carbon 3 and the most positive Mulliken charge at carbon 6. Neither of these carbons correspond to the position of the nucleophile in all isolated 4-substituted 5-aminoindoles **5** ($R=H$) obtained in acidic medium (see Table 3, entries 1–4) but 3-thiophenoxy-5-aminoindole, which was isolated as a minor product (14% yield) in the experiment of entry 4

(electrolysis in the presence of thiophenol). On the other hand, the least stable protonated diiminoquinone $4H^+b$ has both the largest coefficient of the LUMO and the most positive Mulliken charge on carbon 4, which would fit perfectly well with the experimental results if this less stable protonated diiminoquinone $4H^+b$ were much more reactive than its tautomer $4H^+a$. An interesting result of the AM1 calculations is the following. An attempt to protonate hydroxylamine **2** on oxygen did not lead to a stable *O*-protonated hydroxylamine $2H^+$ but led to the direct formation of diiminoquinone **4** by loss of water through progressive lengthening of the N^+-OH_2 bond. This suggests that the acid-catalyzed dehydration of hydroxylamine **2** must be a fast process.

Preparative electroreduction of 3-(3-hydroxypropyl)-5-nitroindole [1, $R=(CH_2)_3OH$]. In order to evaluate further the potential of the electrochemical reduction of 5-nitroindoles (**1**) to synthesise 4-substituted 5-aminoindoles (**5**), the electroreduction of 3-(3-hydroxypropyl)-5-nitroindole [**1**, $R=(CH_2)_3OH$] was performed at Hg and in basic medium. The results are presented in Table 5. In the absence of thiols, the electroreduction of **1** [$R=(CH_2)_3OH$] led to the 3-(3-hydroxypropyl)-4-methoxy-5-aminoindole [**5**, $R=(CH_2)_3OH$, $Nu=OMe$] in a 46–52% yield, together with 15–18% of 3-(3-hydroxypropyl)-5-aminoindole [**3**, $R=(CH_2)_3OH$]. By comparing entry 6 of Table 3 with entry 1 of Table 5, one may conclude that the presence of the hydroxypropyl substituent at position 3 of the indole nucleus had little effect on the selectivity [selectivity = $100 \times (\%5)/(\%3 + \%5)$] and the yield of the reaction. It is noteworthy that the electroreduction of 3-hydroxypropyl-5-nitroindole [**1**, $R=(CH_2)_3OH$] in the presence of an excess of EtSH (8 equiv.) in basic medium (entry 2, Table 5) gave a much higher selectivity ($\approx 100\%$) and much better yield of 3-hydroxypropyl-4-thioethoxy-5-aminoindole [**5**, $R=(CH_2)_3OH$, $Nu=EtS$] (55–72%) than its chemical reduction by Zn in DMF containing ammonium chloride (selectivity of 27% and 20% yield).²

Table 4. Heats of formation and coefficients of the LUMO and Mulliken charges of intermediates **4**, $4H^+a$ and $4H^+b$ (Scheme 3).

Intermediate	$\Delta H_f/\text{kcal mol}^{-1}$	Coefficient of the LUMO (Mulliken charge) ^a				
		C ₂	C ₃	C ₄	C ₆	C ₇
4	114.7	0.26 (−0.17)	−0.30 (−0.23)	0.44 (0.03)	0.29 (−0.25)	−0.24 (−0.11)
$4H^+a$	255.4	−0.24 (−0.90)	−0.47 (−0.05)	0.36 (0.03)	−0.46 (0.78)	−0.24 (−0.22)
$4H^+b$	257.6	−0.10 (−0.12)	0.24 (−0.15)	−0.50 (0.06)	−0.36 (−0.12)	−0.12 (−0.21)

^aC₂, C₃, etc. correspond to the numbering of carbons of nitroindoles (see **1**, Scheme 1).

Table 5. Electroreduction of 3-(3-hydroxypropyl)-5-nitroindole [**1**, R = (CH₂)₃OH] (6 × 10⁻³ M) at Hg in MeOH-H₂O (93 : 7 w/w).

Entry	Supporting electrolyte ^a	Added nucleophile ^b	E/V ^c	Charge/F mol ⁻¹	Yield (%) of products ^d	
					3 [R = (CH ₂) ₃ OH]	5 [R = (CH ₂) ₃ OH]
1	KOH	—	-1.31	5.6	15-18 ^e	46-52 ^e (Nu = MeO)
2	KOH	EtSH	-1.31	4.3	—	55-72 (Nu = EtS)
3	KOH	PhSH	-1.31	4.5	—	72-79 (Nu = PhS)

^aSupporting electrolyte concentration: see footnote *b* of Table 1. ^bAdded nucleophile concentration: 4.8 × 10⁻² M for EtSH, 1.2 × 10⁻² M for PhSH. ^cWorking potential vs. SCE. ^dYield of product isolated by flash chromatography on silica gel (unless stated otherwise) and based on two to three electrolyses (range given when variations were larger than ±4%); see Scheme 1 for the structures of **3** and **5**. ^eCompounds **3** and **5** were not isolated. The {**3** [R = (CH₂)₃OH]/**5** [R = (CH₂)₃OH, Nu = MeO]} ratio was determined by ¹H NMR analysis of the mixture and yields are based on the mass of the crude product.

Conclusion

In this paper, we have shown that the electroreduction of 5-nitroindoles (**1**) at Hg, both in acidic and basic hydromethanolic media, leads to the regiospecific formation of 4-substituted 5-aminoindoles (**5**) in high yields and selectivities. The proposed mechanism involves first electroreduction of **1** to the corresponding hydroxylamine **2**; this is quickly dehydrated to an electrophilic diiminoquinone intermediate **4** which reacts with nucleophiles present in the medium faster than it is reduced to the corresponding 5-aminoindole (**3**). This mechanism was confirmed by unequivocal trapping of a protonated diiminoquinone intermediate **4H**⁺ (R = H), via a pericyclic reaction with cyclopentadiene, in the electrolysis of 5-nitroindole (**1**, R = H) in acidic medium. The electrochemical reduction of 5-nitroindoles (**1**) constitutes a more efficient method of synthesising 4-substituted 5-aminoindoles (**5**) than the chemical (Zn-DMF-NH₄Cl) reduction reported in a patent.³

Experimental

General information. All chemicals were commercially available (Aldrich or BDH) and all the solvents were distilled before use. Solutions for all experiments were deoxygenated by having dry argon bubbles through them for 15 min, and an argon atmosphere was maintained throughout the experiments. The polarography experiments were performed on 100 ml of 0.25 mM solutions of substrate in methanol-water (93 : 7 v/v) containing the supporting electrolyte (see Table 1). A glassy carbon rod was used as the counter electrode and Ag/AgCl/(Cl⁻)_{sat.} adjusted to the SCE potential served as the reference. The characteristics of the dropping mercury electrode were: *m* = 0.8 mg s⁻¹; *t* = 2 s; height = 38 cm. The polarograms were recorded using a PAR 174 polarographic analyzer and a PAR RE0089 X-Y recorder at a scan rate of 2 mV s⁻¹. When needed, a few drops of Triton X-100 0.2% were added. The cyclic voltammetry (CV) experiments were performed using a Princeton Applied Research (PAR) 173 potentiostat in a single compartment cell with 7 ml of the above solutions (see Table 2). No correction was applied to compensate for the solution resistance. The voltammograms were

recorded and processed using EG&G software M270. The working electrode was a mercury drop Metrohm, model E410, and the same counter and reference electrodes as in the polarography experiments were used. The controlled potential electrolyses were carried out at a mercury pool in a vertical glass cell with two compartments separated by fritted glass, using an Electrosynthesis Company (ESC) 410 potentiostat with an ESC 640 coulometer and an ammeter connected in series within the auxiliary circuit. The volume of the cathodic compartment was 45 ml, that of the anodic compartment 10 ml. The same reference electrode as above was used and a platinum grid was used as the counter electrode. The other conditions are given in Table 3.

Computational procedure. All calculations were performed at the RHF level using the AM1 method.^{8,9} The first input files for MOPAC 6.00 were created by means of SYBIL 6.01 (Tripos Associates, Inc.: 16995 Hanley Rd, Suite 303, St Louis, MO 63144-2913) for IBM RS/6000 computers. The gradients of the norm of these draft structures were then fully optimized using the Ef subroutine. The AM1 method was considered more adequate than the PM3 method for calculations on cationic species.

Typical electrolysis procedure. Electroreduction of **1** [R = (CH₂)₃OH] in basic medium in the presence of EtSH (Table 3, entry 9): argon was bubbled through the cathodic compartment containing the electrolyte for 1 h and an argon atmosphere was maintained throughout the electrolysis. A pre-electrolysis was performed at -1.31 V vs. SCE until the current was 0.1 mA or less. The circuit was opened, then **1** [R = (CH₂)₃OH] (59.8 mg, 1.27 mmol) and ethanethiol (160 μl, 2.17 mmol) were added to the catholyte. The potential was then applied and the electrolysis was stopped when the current had dropped to 0.1 mA or less. The electrolysis solution was transferred to a round-bottomed flask, the cell was washed with methanol and water, and methanol was removed on a rotatory evaporator. The pH of the resulting solution was brought to 12 with aqueous NaOH 1 M, saturated with NaCl and extracted with ether (4 × 50 ml). The organic phase was washed with brine, dried (Na₂SO₄) and the solvent removed under vacuum.

The crude material was purified by flash chromatography on silica gel (elution with hexanes–AcOEt 1:1 v/v) to give 48.6 mg of **5** [Nu=EtS, R=(CH₂)₃OH] (72% yield).

Preparation of 3-(3-Hydroxypropyl)-5-nitroindole [**1**, R=(CH₂)₃OH]. 3-(3-Hydroxypropyl)-5-nitroindole [**1**, R=(CH₂)₃OH] was prepared according to a previously described procedure² in a 64% yield: m.p. 115–117 °C (lit. 107–110 °C). IR (CHCl₃) (cm⁻¹): 3469 (NH), 3029 (NH), 1521 (NO₂), 1481 (C=C), 1326 (NO₂), 1273 (C–N). ¹H NMR (300 MHz, CDCl₃): δ 8.60 (d, *J*=2.2 Hz, 1 H, H₄), 8.32 (br, 1 H, NH), 8.12 (dd, *J*=9.0, 2.2 Hz, 1 H, H₆), 7.39 (d, *J*=9.0 Hz, 1 H, H₇), 7.17 (d, *J*=2.2 Hz, 1 H, H₂), 3.78–3.74 (m, 2 H, CH₂), 2.91 (t, *J*=7.5 Hz, 2H, CH₂), 2.05–1.96 (br, 1 H, OH). ¹³C NMR (75 MHz, MeOH-*d*₄): δ 142.1, 141.2, 116.7, 126.5, 119.2, 117.7, 112.2, 62.4, 34.3, 22.0. HRMS, *m/z*: calcd. for C₁₁H₁₂N₂O₃: 220.0848; found: 220.0864.

Characterization of electrolysis products. 4-Bromo-5-aminoindole (**5**, Nu=Br): m.p. 140–142 °C. IR (CHCl₃) (cm⁻¹): 3400 (NH₂), 3011–3000 (CH-arom.), 1604 (C=C), 1218 (C–N). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.0 (s, 1 H, NH), 7.22 (t, *J*=2.7 Hz, 1 H, H₂), 7.12 (d, *J*=8.4 Hz, 1 H, H₇), 6.66 (d, *J*=8.4 Hz, 1 H, H₆), 6.13 (t, *J*=2.5 Hz, 1 H, H₃), 4.68 (s, 2 H, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 138.2, 129.3, 128.7, 125.5, 112.1, 111.4, 99.9, 97.4. HRMS, *m/z*: calc. for C₈H₇BrN₂: 209.9793; found: 209.9789.

5-Aminoindole (**3**) was identified by comparison with an authentic sample (Aldrich).

4-Chloro-5-aminoindole (**5**, Nu=Cl): m.p. 154–156 °C. IR (CHCl₃) (cm⁻¹): 3480 (NH₂), 3020 (CH-arom.), 1604 (C=C), 1219 (C–N). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.0 (s, NH), 7.21 (t, *J*=2.8 Hz, 1 H, H₂), 7.11 (d, *J*=8.4 Hz, 1 H, H₇), 6.67 (d, *J*=8.6 Hz, 1 H, H₆), 6.20 (t, *J*=2.5 Hz, 1 H, H₃), 4.71 (s, 1 H, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 136.9, 129.7, 126.8, 125.5, 112.2, 110.8, 106.6, 98.1. HRMS, *m/z*: calcd. for C₈H₇ClN₂: 166.0292; found: 166.0298.

4-Methoxy-5-aminoindole (**5**, Nu=OMe): m.p. 132–133 °C. IR (CHCl₃) (cm⁻¹): 3333 (NH₂), 3010 (CH-arom.), 2943 (CH-aliph.), 1450 (C=C), 1032 (C–O). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.7 (s, 1 H, NH), 7.10 (t, *J*=2.4 Hz, 1 H, H₂), 6.86 (d, *J*=8.3 Hz, 1 H, H₇), 6.56 (d, *J*=8.0 Hz, 1 H, H₆), 6.27 (t, *J*=2.0 Hz, 1 H, H₃), 4.16 (s, NH₂), 3.80 (s, OCH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 137.1, 131.3, 128.4, 124.0, 120.8, 112.4, 106.4, 96.8, 58.5. HRMS, *m/z*: calc. for C₉H₁₀N₂O: 162.0793; found: 162.0788.

4-Thioethoxy-5-aminoindole (**5**, Nu=EtS): yellow oil. IR (CHCl₃) (cm⁻¹): 3481 (NH₂), 3005 (CH-arom.), 2980 (CH-aliph.), 1614 (NH₂), 1592 (C=C), 1479 (CH₂), 1438 (CH₃), 1189 (C–N). ¹H NMR (300 MHz, CDCl₃): δ 8.06 (s, NH), 7.19 (d, *J*=8.5 Hz, 1 H, H₇), 7.15 (d, *J*=2.8 Hz, 1 H, H₂), 6.73 (d, *J*=8.5 Hz, 1 H, H₆), 6.64 (t, *J*=2.5 Hz, 1 H, H₃), 4.29 (s, 1 H, NH₂), 2.81 (q, *J*=

7.4 Hz, 2 H, SCH₂CH₃), 1.21 (t, *J*=7.4 Hz, 3 H, SCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 142.96, 132.5, 129.8, 124.7, 112.7, 112.1, 107.0, 101.9, 28.6, 15.3. HRMS, *m/z*: calcd. for C₁₀H₁₂N₂S: 192.0724; found: 192.0721.

4-Thiophenoxy-5-aminoindole (**5**, Nu=PhS): dark oil. IR (CHCl₃) (cm⁻¹): 3191 (NH₂), 3054 (CH-arom.), 1614 (C=C), 1248 (C–N). ¹H NMR (300 MHz, acetone-*d*₆): δ 10.1 (s, 1 H, NH), 7.33 (d, *J*=8.6 Hz, 1 H, H₇), 7.19 (d, *J*=2.4 Hz, 1 H, H₂), 7.15 (d, *J*=7.2 Hz, 2 H, phenyl), 7.05 (m, 3 H, phenyl), 6.80 (d, *J*=8.8 Hz, 1 H, H₆), 6.34 (d, *J*=2.2 Hz, 1 H, H₃), 4.69 (s, 1 H, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 145.4, 138.6, 129.5, 129.3, 126.5, 126.1, 125.9, 125.7, 125.5, 115.3, 112.5, 101.3. HRMS, *m/z*: calcd. for C₁₄H₁₂N₂S: 240.0719; found: 240.0721.

Compound 6 (from the electrolysis of **5** in the presence of cyclopentadiene): oil. IR (CHCl₃) (cm⁻¹): 3480 (NH), 3010 (CH-arom.), 2958 (CH-aliph.), 1618 (NH₂), 1508 (C=C), 1443 (CH₂), 1240 (C–N). ¹H NMR (300 MHz, MeOH-*d*₄): δ 6.90 (d, *J*=8.5 Hz, 1 H, H₇), 6.78 (s, 1 H, H₂), 6.57 (d, *J*=8.4 Hz, 1 H, H₆), 5.85 (s, 2 H, H₉ and H₁₀), 3.85 (dd, *J*=2.0, 4.7 Hz, 1 H, H₈ or H₁₁), 3.63 (dd, *J*=2.0, 4.6 Hz, 1 H, H₁₁ or H₈), 2.40–2.34 (m, 1 H, H_{12b}), 1.87 (d, *J*=9.6 Hz, 1 H, H_{12a}). ¹³C NMR (75 MHz, CDCl₃): δ 132.7, 132.2, 130.8, 129.6, 124.8, 117.3, 116.5, 114.2, 109.9, 43.9, 39.1, 38.8. HRMS, *m/z*: calcd. for C₁₃H₁₂N₂: 196.1000; found: 196.1002.

3-(3-Hydroxypropyl)-4-methoxy-5-aminoindole [**5**, R=(CH₂)₃OH, Nu=OMe]: identified by GC–MS and ¹H NMR spectroscopy in a mixture of **3** [R=(CH₂)₃OH] and **5**: ¹H NMR (CDCl₃, 300 MHz): δ 6.95 (d, *J*=8.5 Hz, 1 H, H₇), 6.88 (d, *J*=2.3 Hz, 1 H, H₂), 6.69 (d, *J*=8.4 Hz, 1 H, H₆), 3.87 (s, 1 H, OMe), 3.64 (t, *J*=6.0 Hz, 2 H, CH₂CH₂CH₂OH), 2.95 (t, *J*=7.2 Hz, CH₂CH₂CH₂OH), 1.93 (quintet, *J*=6.5 Hz, 2 H, CH₂CH₂CH₂OH).

3-(3-Hydroxypropyl)-5-aminoindole [**5**, R=(CH₂)₃OH]: yellow oil. IR (CHCl₃) (cm⁻¹): 3472 (NH), 3023 (CH-arom.), 1629 (NH₂), 1583 (C=C), 1236 (C–N). ¹H NMR (300 MHz, CDCl₃): δ 7.76 (br, 1 H, NH), 7.16 (d, *J*=8.5 Hz, 1 H, H₇), 6.93 (d, *J*=2.2 Hz, 1 H, H₂), 6.90 (d, *J*=2.1 Hz, 1 H, H₄), 6.66 (dd, *J*=8.5, 2.2 Hz, 1 H, H₆), 5.35 (br, 1 H, NH₂), 3.72 (t, *J*=6.9 Hz, 2 H, CH₂CH₂CH₂OH), 2.78 (t, *J*=7.4 Hz, 2 H, CH₂CH₂CH₂OH), 1.93–1.84 (m, 2 H, CH₂CH₂CH₂OH). ¹³C NMR (75 MHz, MeOH-*d*₄): δ 141.5, 136.2, 132.0, 125.8, 117.8, 116.6, 115.0, 108.5, 65.3, 36.8, 25.0. HRMS, *m/z*: calcd. for C₁₁H₁₄N₂O: 190.1106; found: 190.1105.

3-(3-Hydroxypropyl)-4-thioethoxy-5-aminoindole [**5**, R=(CH₂)₃OH, Nu=EtS]: yellow oil. IR (CHCl₃) (cm⁻¹): 3478 (NH₂), 3416 (OH), 3331 (NH), 3007 (CH-arom.), 2929 (CH-aliph.), 2873 (CH-aliph.), 1593 (C=C), 1407 (C–N). ¹H RMN (300 MHz, acetone-*d*₆): δ 9.71 (br, 1 H, NH), 7.15 (d, *J*=8.6 Hz, 1 H, H₇), 7.01 (d, *J*=2.6 Hz, 1 H, H₂), 6.68 (d, *J*=8.6 Hz, 1 H, H₆), 4.70 (br, 2 H, NH₂), 3.63 (q, *J*=6.5 Hz,

2 H, CH₂CH₂CH₂OH), 3.40 (t, *J*=5.2 Hz, 1 H, OH), 3.11 (t, *J*=7.4 Hz, 2 H, CH₂CH₂CH₂OH), 2.72 (q, *J*=7.3 Hz, 2 H, SCH₂CH₃), 1.95–1.85 (m, 2 H, CH₂CH₂CH₂OH), 1.16 (t, *J*=7.3 Hz, 3 H, SCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 143.4, 131.3, 129.0, 123.4, 116.5, 113.2, 111.9, 107.4, 62.6, 34.9, 30.0, 22.8, 14.6. HRMS, *m/z*: calcd. for C₁₃H₁₈N₂OS: 250.1140; found: 250.1151.

3-(3-Hydroxypropyl)-4-thiophenoxy-5-aminoindole [**5**, *R*=(CH₂)₃OH, *Nu*=PhS]: m.p. 138–140 °C. IR (CH₂Cl₂) (cm⁻¹): 3618 (OH), 3467 (NH), 3035 (CH-arom.), 2941 (CH-aliph.), 1597 (C=C), 1477 (CH₂), 1374 (CH₃), 1046 (C–O). ¹H NMR (300 MHz, CDCl₃): δ 7.91 (s, 1 H, NH), 7.29 (d, *J*=8.5 Hz, 1 H, H₇), 7.20–7.15 (m, 2 H, phenyl), 7.08–7.01 (m, 3 H, phenyl), 6.96 (d, *J*=2.0 Hz, 1 H, H₂), 6.77 (d, *J*=8.5 Hz, 1 H, H₆), 3.62 (t, *J*=6.5, CH₂CH₂CH₂OH), 3.49 (s, OH), 2.96 (t, *J*=7.6 Hz, 2 H, CH₂CH₂CH₂OH), 1.83–1.74 (m, 2 H, CH₂CH₂CH₂OH). ¹³C NMR (75 MHz, MeOH-*d*₄): δ 144.8, 140.4, 133.6, 130.3, 129.9, 128.6, 126.4, 125.7, 125.3, 115.8, 113.3, 104.6, 62.8, 35.7, 23.7. HRMS, *m/z*: calc. for C₁₇H₁₈N₂OS: 298.1140; found: 298.1134.

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