Further insight into the reaction of electrogenerated *o*-quinone with amino-alcohols and amines. Products and mechanism

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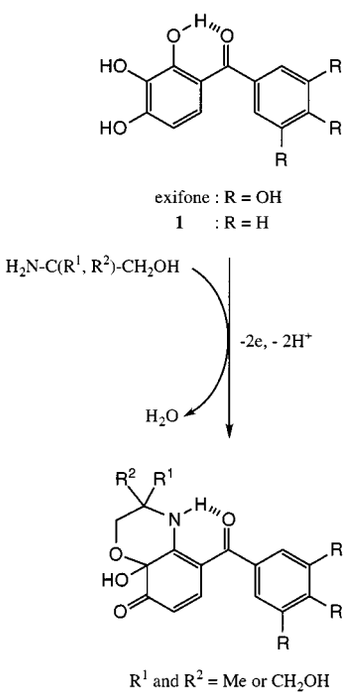
Using 2,3,4-trihydroxybenzophenone as the starting material, the reaction of the electrogenerated 3,4-quinone with amino-alcohols and amines $HC(R^1,R^2)–NH_2$ is suggested to proceed *via* an ionic mechanism that would involve a C(3) aminated carbinolamine intermediate and would afford, after dehydration, a 3,4-iminoquinone species. The subsequent step would consist either of a transamination reaction, or of the formation of a spiro aminoketal species (when using amino-alcohols as the substrate), or of a redox cycling reaction allowing the isolation of 3,4-alkylaminophenol derivatives.

In a preceding paper, we reported the results of a study[1] devoted to the oxidation chemistry of exifone [*Adlone*^{R}, Scheme 1], a drug which was launched in France[2] for the treatment of



Scheme 1

cognitive disorders in the elderly,[3,4] but which was withdrawn rapidly from the market because of its hepatotoxic effects.

Mainly based on previous results concerning the possible role of highly electrophilic oxidation products (quinone or iminoquinone) in the toxicological effects of drugs,[5–7] we hypothesized that a potential toxic metabolite of exifone could be the transient reactive *o*-quinone species, that would bind irreversibly to the NH_2 and SH residues of cellular proteins to form conjugates.[8–11] Our objective was then to scavenge the transient reactive *o*-quinone by the formation of an adduct blocking the electrophilic sites generally attacked by membrane nucleophiles, and consequently to prevent toxicity. Using electrochemical techniques to oxidize exifone and its model compound **1**, we have found that the attachment of an amino-alcohol residue resulted in the trapping of the transient unstable electrogenerated 3,4-quinone and provided a convenient route to novel 1,4-benzoxazin-8-one derivatives (Scheme 1). These compounds were identified as significantly more active and about twenty fold less toxic than the parent exifone.[12]

By varying the nature of the condensed amino-alcohol, we established that neither R^1 nor R^2 could be a hydrogen atom. This condition appeared to constitute a prerequisite to the formation of 1,4-benzoxazin-8-one derivatives. Nevertheless, in the presence of amino-alcohols derived from natural amino-acids, $H_2N–CH(R)–CH_2OH$, a competing reaction arose implying a nucleophilic attack of the transient electrogenerated 3,4-quinone species at the 3-position rather than at the 2-position. Recently, we focused our attention on this competing reaction for three reasons. First, from the viewpoint of organic chemistry, this reaction constituted a key step in a simple one-pot electrochemical procedure that permitted a rapid access to novel 3,4-alkylaminophenol derivatives[13] (Table 1). Second, from a pharmacological viewpoint, this reaction could be regarded as another way to scavenge the transient unstable 3,4-quinone, and consequently to prevent toxicity. Third, from a mechanistic viewpoint, this reaction that involves the C(3) reactivity of the electrogenerated transient 3,4-quinone with amino-alcohols, and more generally with amines, very closely reproduced the behaviour of PQQ, TTQ, TPQ, model cofactors of amine dehydrogenases or amine oxidases. Consequently, we thought that an electrochemical investigation of such reactions could be worthwhile to provide additional information about the reaction mechanisms.[14–19]

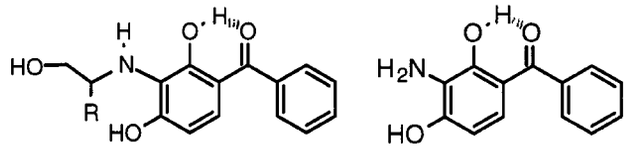
In this paper, we would like to report the results of our study concerning the electrochemical oxidation of compound **1**, in methanol, in the presence of various amino-alcohols $H_2N–CH(R)–CH_2OH$ and aliphatic amines. Particular attention has been paid to the elucidation of competing reaction pathways that led to the 3,4-alkylaminophenol derivatives.

Results and discussion

Electrochemical oxidation of compound 1 in the presence of amino-alcohols or aliphatic amines

Reaction of the *o*-quinone proximate oxidative product with amino-alcohols, $H_2N–CH(R)–CH_2OH$. The cyclic voltammogram of compound **1**, in methanol containing lithium

Table 1 Products and yields of controlled potential electrolyses of **1** in methanol containing an excess of amino-alcohol $CH_2OH–CH(R)–NH_2$



$CH_2OH–CH(R)–NH_2$

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R	Product	Yield (%)	Yield (%)
Bu^t	**2**	65	—
Pr^i	**3**	57	8
Me	**4**	60	5
CH_2OH	**5**	55	10
Bzl	**6**	55	10

Abbreviations: *tert*-butyl (Bu^t), isopropyl (Pr^i), benzyl (Bzl).

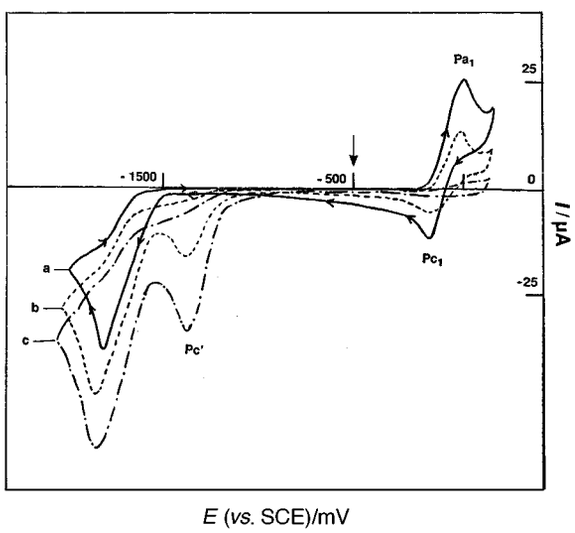


Fig. 1 Progress of the cyclic voltammogram in the course of anodic controlled potential electrolysis of **1** ($c = 2$ mmol dm^{-3}), at a mercury working electrode ($E = +50$ mV *vs.* SCE), in methanol containing 0.02 mol dm^{-3} lithium perchlorate and 0.02 mol dm^{-3} *S-tert*-leucinol. Curve a (—), before electrolysis; curve b (- - -), after consumption of 1 Faraday per mole of substrate; curve c (– · –), after exhaustive anodic electrolysis (2 Faraday per mole of **1**). Arrowheads indicate the direction of the potential sweep; $v = 0.5$ V s^{-1}. The vertical arrow indicates the initial potential point.

perchlorate as the supporting electrolyte and an excess of *S-tert*-leucinol (R = Bu^t), at a dropping mercury electrode, showed an oxidation peak Pa_1 due to a diffusion-controlled two-electron process, at 0.0 mV *vs.* SCE, the sweep rate being 0.5 V s^{-1}. As can be seen in Fig. 1 (curve a), a cathodic peak Pc_1 appeared on the reverse sweep, at − 100 mV *vs.* SCE, illustrating the partial reversibility of the two-electron transfer that could be assigned to the 3,4-quinol/3,4-quinone redox couple. However, the redox potential $E^{\circ\prime}$ could not be easily evaluated under our experimental conditions as the system (Pa_1, Pc_1) did not fulfil all the diagnostic criteria required for a reversible process, at least when v was ≤ 500 V s^{-1}: the ratio of the height of Pa_1 over that of Pc_1 never reached unity ($i_{Pc_1} / i_{Pa_1} \approx 0.8$) and the value of $E_{Pa_1} - E_{Pc_1}$ (E being the peak potential) was found to be higher than 30 mVp

Furthermore, in the reverse sweep, a second reduction peak was recorded at a more negative potential (−1800 mV *vs.* SCE), due to the irreversible two-electron reduction of the carbonyl group of the benzophenone skeleton (Fig. 1, curve a), as previously reported.[1]

When the controlled potential of the mercury pool (E) was fixed at +50 mV *vs.* SCE, *i.e.* at a potential immediately following the peak Pa_1, a coulometric value of 2.0 ± 0.1 was found for the number of electrons (n) involved in the oxidation of one molecule of **1**. As the electrolysis proceeded, a decrease in the Pa_1 and Pc_1 intensities was observed simultaneously. The lack of peak Pc_1 in the voltammogram of the exhaustively oxidized solution clearly indicated that the electrochemical oxidation of **1** was followed by a chemical reaction involving the produced 3,4-quinone. This was converted into an unstable product which probably decomposed, either under our electrolysis experimental conditions, or in the course of the isolation procedure, since no defined product could be isolated after exhaustive electrochemical oxidation, except of 27% of the recovered quinol **1**.

The progress of the electrolysis was simultaneously followed by monitoring the UV–VIS absorption spectrum; after applying the potential E, a decrease in the UV–VIS absorption band shown by the monoanionic form of the starting material **1** at 348 nm (ε/dm^3 mol^{-1} cm^{-1} = 16 900) was observed, while new bands at 326 and 428 nm developed, the height of the absorption band at 326 nm being roughly two fold higher than the absorption band at 428 nm. Spectral changes showed three isosbestic points at 240, 340 and 393 nm, which disappeared when the degree of conversion of the starting material exceeded 75%. This result indicated that the unstable oxidation product essentially decomposed during the isolation procedure.

Interestingly, the voltammogram of the exhaustively oxidized solution exhibited a well defined cathodic peak Pc′ at −1400 mV *vs.* SCE (Fig. 1). We hypothesized that Pc′ probably corresponded to the reduction of the overall oxidation product. Consequently, we thought that the latter could be stabilized through a reduction step, provided that the potential of the mercury cathode was fixed immediately after the cathodic peak Pc′ ($E = -1500$ mV *vs.* SCE). Therefore, after exhaustive anodic electrolysis, the resulting oxidized solution was electrochemically reduced. As the cathodic electrolysis proceeded, a decrease in the cathodic peak Pc′ was observed, while a new system of peaks (Pa_2, Pc_2) developed in the same potential region as the system of peaks (Pa_1, Pc_1), but shifted 100 mV towards more positive potentials. The exhaustively reduced solution (2 F mol^{-1}) no longer exhibited the peak Pc′ and showed an absorption band at 350 nm, very close to that exhibited by the monoanionic form of the starting quinol **1**, indicating a similarity in their chromophoric groups.

Preparative scale electrolyses allowed the isolation of 3,4-alkylaminophenol **2** in 65% yield (Table 1). The structure of product **2** justified, in the cyclic voltammogram of the exhaustively reduced solution, the presence of the system of peaks (Pa_2, Pc_2) that could be assigned to the oxidation/reduction of the 3,4-alkylaminophenol/3,4-alkyliminoquinone redox couple. This structure was also consistent with the analogy existing between the UV–VIS absorption spectrum of the exhaustively reduced solution (which essentially contained 3,4-alkylaminophenol **2**), and that of the starting quinol **1**. Variously

Table 2 Products and yields of controlled potential electrolyses of **1** in methanol containing an excess of benzhydrylamine

Product Yield (%)	Procedure **a**	**b**
3,4-Aminophenol **7**	72	23[a]
3,4-Alkylaminophenol **8**	—	37
Benzophenone	54	20
$Ph_2C{=}NCHPh_2$	20	15

[a] Yield of 3,4-aminophenol **7** was probably higher than indicated because significant amounts could be lost upon column chromatography due to its instability.

substituted amino-alcohols behaved similarly, except for the production of 3,4-aminophenol **7** in low yield (Table 1).

Finally, electrochemical oxidation of **1** in the presence of substituted amino-alcohols $CH_2OH–CH(R)–NH_2$, followed by electrochemical reduction of the two-electron oxidation intermediate species, constituted an easy method of synthesizing 3,4-alkylaminophenol derivatives **2**–**6** (see Experimental section).

In order to explore further the scope of this electrochemical procedure with respect to synthetic applications, we investigated the behaviour of **1** in the presence of amines.

Reaction of the electrogenerated 3,4-quinone with benzhydrylamine. As expected, the cyclic voltammogram of compound **1**, in methanol containing lithium perchlorate as the supporting electrolyte and an excess of benzhydrylamine, at a dropping mercury electrode, was identical to that previously described in the presence of *S*-*tert*-leucinol (curve a in Fig. 1).

When E was fixed at +50 mV *vs.* SCE, *i.e.* at a potential immediately following the peak Pa_1, a coulometric value of 2.0 ± 0.1 was found for n. As the electrolysis proceeded, a decrease in both the Pa_1 and Pc_1 intensities was observed, while a new system of peaks (Pa_2, Pc_2) developed at a slightly more positive potential. Nevertheless, in the cyclic voltammogram of the exhaustively oxidized solution, the height of Pa_2 was found to be three fold lower than that of Pa_1. Moreover, a cathodic peak Pc′ appeared at −1150 mV *vs.* SCE. Note that the UV–VIS absorption spectrum shown by the exhaustively oxidized solution was very different from that observed in the presence of amino-alcohols as a sole absorption band at 310 nm was recorded.

In the procedure **a**, the products were isolated just after exhaustive anodic electrolysis. In the procedure **b**, the products were isolated after the subsequent electrochemical reduction of the exhaustively oxidized solution, conducted at a potential fixed at −1300 mV *vs.* SCE, *i.e.* at a potential immediately following the peak Pc′ (see Experimental section). As the electrolysis proceeded, a decrease in the peak Pc′ was observed and the voltammogram of the exhaustively reduced solution exhibited the system of peaks (Pa_2, Pc_2). The UV–VIS absorption spectrum shown by the exhaustively reduced solution was nearly identical with that of the monoanionic form of the starting quinol **1**. The results of these experiments are summarized in Table 2.

Reaction of the electrogenerated 3,4-quinone with aliphatic amines $HC(R^1,R^2)–NH_2$. The cyclic voltammogram of compound **1**, in methanol containing lithium perchlorate as the supporting electrolyte and an excess of isopropylamine, at a dropping mercury electrode, very closely resembled that recorded above using amino-alcohols (Fig. 2, curve a).

When E was fixed at −50 mV *vs.* SCE, *i.e.* at a potential immediately following the anodic peak Pa_1, a coulometric value of 1.3 ± 0.1 was found for n. As the electrolysis proceeded, a decrease in the Pa_1 and Pc_1 intensities was observed simultaneously, while a new system of peaks (Pa_2, Pc_2) developed at a 100 mV more positive potential, due to a partially reversible two-electron transfer. It could be noted that, contrary to the cases of amino-alcohols and benzhydrylamine reported above, the voltammogram given by the exhaustively oxidized solution no longer exhibited the cathodic peak around −1400 mV *vs.* SCE. Moreover, the height of Pa_2 was found to be identical to that of the initial peak Pa_1 (Fig. 2). Interestingly enough, the UV–VIS absorption spectrum shown by the exhaustively oxidized solution was nearly identical with that of the monoanionic form of the starting quinol **1**, indicating a similarity in their chromophoric groups.

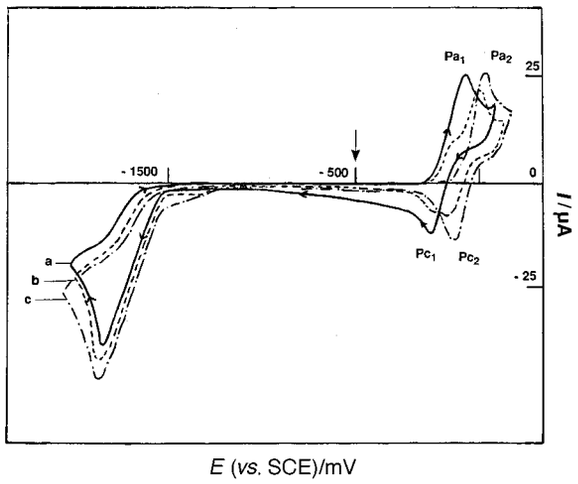


Fig. 2 Progress of the cyclic voltammogram in the course of anodic controlled potential electrolysis of **1** (c = 2 mmol dm^{-3}), at a mercury working electrode (E = +50 mV *vs.* SCE), in methanol containing 0.02 mol dm^{-3} lithium perchlorate and 0.02 mol dm^{-3} isopropylamine. Curve a (—), before electrolysis; curve b (- - -), after consumption of 1 Faraday per mole of substrate; curve c (–·–), after exhaustive anodic electrolysis (1.3 Faraday per mole of **1**). Arrowheads indicate the direction of the potential sweep; v = 0.5 V s^{-1}. The vertical arrow indicates the initial potential point.

Thus, preparative scale anodic electrolysis allowed the isolation of 3,4-alkylaminophenol **9** (45% yield) as the major product, as well as 3,4-aminophenol **7** (5% yield) as the minor one (see Experimental section), without proceeding to subsequent cathodic electrolysis. Accordingly, a system of peaks (Pa_2, Pc_2) was recorded in the cyclic voltammogram of the exhaustively oxidized solution that could be assigned to the two-electron oxidation/reduction of the 3,4-alkylaminophenol/3,4-alkyliminoquinone redox couple.

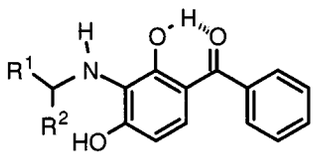
The results obtained with a series of aliphatic amines which behaved similarly are collected in Table 3.

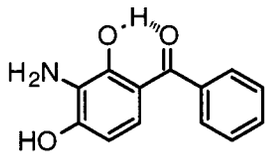
Mechanistic deductions

On the basis of the results mentioned above, we can formulate the following assumptions about the mechanistic pattern of the aminophenol derivatives formation. As already reported,[1] the formation of the transient 3,4-quinone would result from a two-electron oxidation of the monoanionic species of **1** [eqn. (1), Scheme 2]. Once formed, the transient 3,4-quinone is converted into a C(3) aminated carbinolamine intermediate [eqn. (2)], that loses water to form a 3,4-iminoquinone species [eqn. (3)]. Then, the latter is engaged in three competing reaction pathways **A**, **B** and **C**, depending on the nature of the condensed amine.

Path A. For the most part of the studied amines, and in a process of minor importance with amino-alcohols, the 3,4-iminoquinone intermediate tautomerizes to a Schiff base [eqn. (4)], the driving force of the hydrogen atom migration being the tendency to restore aromaticity within the 3,4-iminoquinone

Table 3 Products and yields of controlled potential electrolyses of **1** in methanol containing an excess of aliphatic amines $HC(R^1,R^2)–NH_2$





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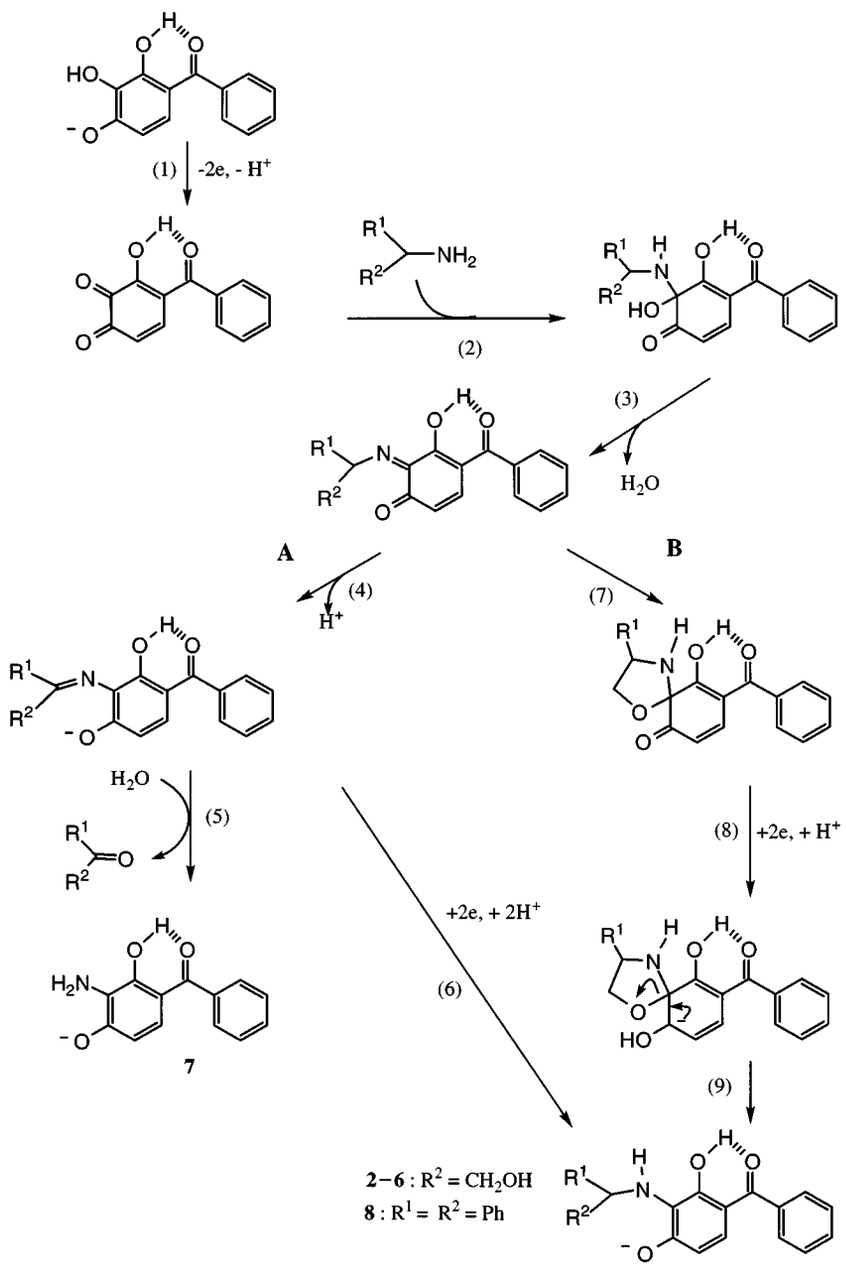
Entry	R^1	R^2	Product	Yield (%)	Yield (%)
1	Me	Me	**9**	45	5
2	Me	Pr^i	**10**	31	40
3	Pr^i	Pr^i	**11**	15	55
4	CH_2OMe	Me	**12**	37	23



Scheme 2

ring. Release of the ketone product then can occur by hydrolysis of the imine function of the Schiff base to produce 3,4-aminophenol **7** [eqn. (5)]. Accordingly, when benzhydrylamine was used as the substrate, besides 3,4-aminophenol **7** isolated in 72% yield, benzophenone was obtained in roughly 54% yield, as well as the imine derivative $Ph_2C{=}N–CHPh_2$, isolated in 20% yield. As could be demonstrated, the latter arose from the spontaneous condensation of benzophenone with the

excess of benzhydrylamine. Note that the Schiff base was stable enough through the anodic electrolysis procedure, enabling its subsequent cathodic reduction to afford 3,4-alkylaminophenol derivative **8** in 37% yield [eqn. (6)]. A likely explanation is that the imine group would be conjugated with the two phenyl rings. However, the Schiff base could be partially hydrolysed in the course of the anodic process, since 3,4-aminophenol **7** was isolated in 23% yield, along with benzophenone (20% yield) and *N*-benzhydryldiphenylmethanimine (15% yield) as shown in Table 2. It is the reason why a system of peaks (Pa_2, Pc_2), due to the 3,4-aminophenol/3,4-iminoquinone redox couple, was recorded in the voltammogram of the exhaustively oxidized solution.

Path B. In a process specific to substituted amino-alcohols, the 3,4-iminoquinone intermediate could be stabilized through an intramolecular ring-closure reaction involving the hydroxy group at the β-position of the amino-alcohol, to produce a spiro-2,4-dienone intermediate [eqn. (7)]. The subsequent step would consist of a two-electron reduction of the carbonyl group at the α position of the spiro aminoketal ring [eqn. (8)] leading, after ring-opening, to 3,4-alkylaminophenol derivatives **2**–**6** [eqn. (9) and Table 1].

Though the 3,4-iminoquinone seemed likely to rearrange into the spiro-2,4-dienone species, no direct evidence for the formation of the latter was obtained in our experiments, as it probably decomposed during the isolation procedure. However, a number of factors arguing in favour of the formation of the spiro aminoketal intermediate rather than the Schiff base could be listed:

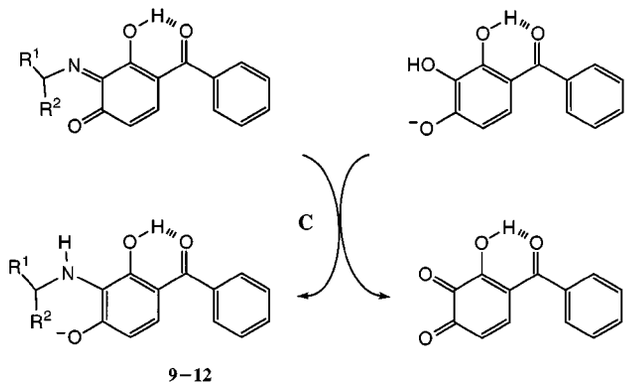
a) With *S*-*tert*-leucinol, no 3,4-aminophenol **7** was obtained at all after treatment of the exhaustively oxidized solution, while under the same experimental conditions, benzhydrylamine allowed the isolation of aminophenol **7** in 72% yield. In this case, conjugation of the imine function with the two phenyl rings would result in enhanced stability of the transient Schiff base, although its stability was not sufficient to permit its isolation under our experimental conditions. In contrast, when using *S*-*tert*-leucinol as the substrate, it is obvious that the substituents linked to the imine function could no longer exert a stabilizing effect. Consequently, the competitive step (7) could occur prior to the tautomerization reaction [step (4)].

b) The UV–VIS absorption spectrum of the exhaustively oxidized solution, which essentially would contain the spiro-2,4-dienone intermediate, very closely resembled that of the corresponding 1,4-benzoxazin-8-one derivative. The latter exhibited two absorption bands at 430 nm (ε/dm^3 mol^{-1} cm^{-1} = 5600) and 327 nm (ε/dm^3 mol^{-1} cm^{-1} = 18 500). These two structures exhibited a 2,4-dienone chromophoric group in agreement with the similarity of their UV–VIS absorption spectra.

c) The fact that 1,4-benzoxazin-8-one derivatives and the spiro aminoketal transient species are both reducible in the same potential region ($E_{Pc'}$ = −1200/−1300 mV *vs.* SCE) is in agreement with the formation of the latter in the course of the anodic electrolysis.

Finally, the specific behaviour of amino-alcohols very likely stemmed from the presence of the hydroxy group at the *β* position of the amino-alcohol. For instance, replacement of the hydroxy group at the *β* position of alaninol by a methoxy group induced noticeable changes in the product distribution, so that 2-amino-1-methoxypropane behaved as "ordinary" aliphatic amines.

Path C. In the case of amines [entries 1–4, Table 3], except for benzhydrylamine (Table 2), a redox cycling reaction in which the electrogenerated 3,4-iminoquinone species could be engaged in a bimolecular reaction with the non-reacted monoionized quinol **1** competes with the transamination reaction (path **A**, Scheme 2) . This hypothesis is in agreement with the potential values of peaks Pa_1 and Pa_2, measured on the cyclic voltammogram, since E_{Pa_2} was 100 mV higher than E_{Pa_1}. It is noteworthy that the yields of 3,4-alkylaminophenol derivatives **9**–**12** did not exceed 50%, a result in accordance with the reaction path **C** (Scheme 3).



9–**12**

Scheme 3

From the data collected in Table 3, it could be underlined that, in the aliphatic series, increasing steric crowding around the alkylamino group favours the production of aminophenol **7** (transamination path **A**) at the expense of the redox cycling reaction (path **C**). One of the possible explanations is that hydrolysis, by decreasing steric hindrance, aids the system to recover increased conformational freedom around the C*α* atom of the alkylamino group.

Finally, using electrochemical techniques to oxidize the quinol **1** in slightly basic methanolic solution, we have evidence that amino-alcohols $CH_2OH–CH(R)–NH_2$, or aliphatic amines $HC(R^1,R^2)–NH_2$, divert or block formation of melanin polymers by scavenging the electrogenerated 3,4-quinone proximate product, *via* an ionic mechanism that implies a carbinolamine adduct affording, after dehydration, the 3,4-iminoquinone intermediate. The latter would be involved in three competing reaction pathways **A**, **B** and **C**.

The transamination mechanism (path **A**) is the most popular. It has already been proposed for amine oxidases and amine dehydrogenases that contain PQQ, TPQ, TTQ as the redox cofactor.[14–19] Moreover, it is also the characteristic reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone[20,21] and phenanthrolinequinones.[22] In the studied series, a mechanism which involves an intramolecular ring-closure of the 3,4-iminoquinone species and gives a spiro aminoketal intermediate (path **B**), as well as a redox cycling reaction (path **C**), compete with transamination (path **A**). Nonetheless, all these routes yielded 3,4-aminophenol derivatives through a simple one-pot electrochemical procedure.

Experimental

Materials

UV–VIS Spectra were recorded on a Varian Cary 13E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H observations. Chemical shifts (in ppm) are relative to internal tetramethylsilane. *J* values are given in Hz. The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a Nermag R 10-10 C spectrometer equipped with desorption chemical ionization (DCI) mode. Samples were introduced by means of a direct insertion probe. Ammonia was used as the reagent gas. Melting points were determined on a Köfler block and are uncorrected.

Electrochemical measurements were made with a Radiometer-Tacussel PRG 5 multipurpose polarograph that was

used only as a rapid-response potentiostat. For cyclic voltammetry, triangular waveforms were supplied by a Tacussel GSTP 4 function generator. A Radiometer-Tacussel GCMR pulse generator was used for drop-knocker control and for delay time t_1 control (t_1 being the time elapsed between the beginning of the drop life and the start of the potential sweep). Current–potential curves were recorded on a Sefram SI 8312 instrument. The cell was a Tacussel CPRA water-jacketed cell working at a temperature of 20 °C. The reference electrode was an aqueous saturated calomel electrode (SCE) (Metrohm EA 441-1). The aqueous saturated calomel was enclosed in the first compartment which was put inside the second compartment containing a 0.02 mol dm^{-3} solution of lithium perchlorate in methanol. The compartments were separated by sintered porous glass disks. The counter electrode was a platinum electrode Tacussel Pt 11. The working electrode was a Tacussel CMT 10/24 capillary. Controlled potential electrolyses were carried out using a three-compartment water-jacketed cell protected from light, whose counter and reference compartments were filled with the background solution. A Tacussel PJT 120-1 potentiostat and a Tacussel IG6-N electronic integrator were included in the circuit. The counter electrode was a platinum foil. The working electrode was a mercury pool (60 cm^2 area).

Analytical TLC was performed on Macherey-Nagel Silica Gel polygram UV_{254} (lot 805023). Column chromatography was conducted on open glass columns packed with Macherey-Nagel Silica Gel 60 (lot 815381).

The solvents used for extractions and chromatography as well as methanol (analysis purity grade) were obtained from S.D.S. Lithium perchlorate was obtained from Fluka (purum purity grade). Amino-alcohols and amines were obtained from Aldrich.

Isolation and spectroscopic data of products 2–12

[3-(2-Hydroxy-1-*tert*-butylethylamino)-2,4-dihydroxyphenyl]phenylmethanone 2. *Method.* A solution of (2,3,4-trihydroxyphenyl)phenylmethanone **1** (115 mg; 0.5 mmol), lithium perchlorate (530 mg, 5 mmol) and *S*-*tert*-leucinol (597 mg; 5 mmol) in methanol (250 cm^3) was oxidized under nitrogen, at room temperature, at a mercury pool working electrode ($E = +$ 50 mV *vs.* SCE). After exhaustive oxidation, *i.e.* when a steady-state minimum value of the current was recorded, the resulting solution was immediately reduced, after the potential of the mercury pool was switched to −1500 mV *vs.* SCE. After exhaustive cathodic electrolysis, the solution was poured into a molar acetic acid buffered aqueous solution of pH ≈ 4.5 (100 cm^3). The resulting hydroalcoholic solution was concentrated to 100 cm^3, under reduced pressure, at 40 °C, and extracted with ethyl acetate (200 cm^3). The organic phase was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure at 40 °C. Flash chromatography on silica gel with toluene–acetone (98:2) as the eluent afforded compound **2** (107 mg, 65%), mp 134–136 °C, as an amorphous yellow solid.

Spectroscopic data for product **2** have been reported earlier.[13]

[3-(2-Hydroxy-1-isopropylethylamino)-2,4-dihydroxyphenyl]phenylmethanone 3 and [3-amino-2,4-dihydroxyphenyl]phenylmethanone 7. The above described method, replacing *S*-*tert*-leucinol by *S*-2-amino-3-methylbutanol (515 mg; 5 mmol), afforded, after flash chromatography on silica gel with toluene–acetone (92:8) as the eluent, compound **3** (90 mg, 57%) as a yellow oil along with **7** (9 mg, 8%) mp 195–197 °C, as an amorphous pale yellow solid.

3 δ_H [300 MHz; $(CD_3)_2SO$] 0.92 (3H, d, *J* 6, Me), 0.96 (3H, d, *J* 6, Me), 1.90 (1H, m, *J* 6, CH, Pr^i), 3.50 (3H, m, C*H*–N and CH_2OH), 6.45 (1H, d, *J* 8, 5-H), 6.90 (1H, d, *J* 8, 6-H), 7.55 (5H, m, Ph), 12.80 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 19.4 (Me, Pr^i), 20.3 (Me, Pr^i), 30.5 (CH, Pr^i), 61.5 (CH–N), 62.7 (CH_2OH), 108.8 (C-5), 113.1 (C-1), 125.7 (C-3), 126.5 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para,* Ph), 139.2 (C_Q, Ph), 155.2 and 155.4 (C-2 and C-4), 200.1 (CO, methanone); *m*/*z* 316 (MH^+).

Spectroscopic data for product **7** have been reported earlier.[13]

[3-(2-Hydroxy-1-methylethylamino)-2,4-dihydroxyphenyl]phenylmethanone 4. The above described method, replacing *S*-*tert*-leucinol by *S*-alaninol (375 mg; 5 mmol), gave, after flash chromatography on silica gel with toluene–acetone (80:20) as the eluent, compound **4** (86 mg, 60%), mp 155–157 °C, as an amorphous pale yellow solid, along with **7** (6 mg, 5%).

4 δ_H [300 MHz; $(CD_3)_2SO$] 1.00 (3H, d, *J* 6, Me), 3.40 (2H, m, CH_2OH), 3.80 (1H, m, *J* 6, CH–N), 6.45 (1H, d, *J* 9, 5-H), 6.95 (1H, d, *J* 9, 6-H), 7.60 (5H, m, Ph), 12.70 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 19.3 (Me), 52.4 (CH–N), 66.2 (CH_2OH), 108.8 (C-5), 113.0 (C-1), 124.7 (C-3), 127.2 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para,* Ph), 139.2 (C_Q, Ph), 156.0 and 156.2 (C-2 and C-4), 200.1 (CO, methanone); *m*/*z* 288 (MH^+).

[3-(1,3-Dihydroxyprop-2-yl)amino-2,4-dihydroxyphenyl]phenylmethanone 5. The above described method, replacing *S*-*tert*-leucinol by 2-aminopropane-1,3-diol (455 mg; 5 mmol) afforded, after chromatography on silica gel with toluene–acetone–methanol (75:20:5) as the eluent, compound **5** (84 mg, 55%) mp 123–125 °C, as an amorphous pale yellow solid, along with **7** (12 mg, 10%).

5 (Found: C, 63.24; H, 5.66; N, 4.58. $C_{16}H_{17}NO_5$ requires: C, 63.37; H, 5.61; N, 4.62%); δ_H [300 MHz; $(CD_3)_2SO$] 3.60 (5H, m, CH_2OH and C*H*–N), 6.45 (1H, d, *J* 9, 5-H), 6.95 (1H, d, *J* 9, 6-H), 7.60 (5H, m, Ph), 12.70 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 58.5 (CH–N), 61.7 (CH_2OH), 108.8 (C-5), 113.1 (C-1), 125.0 (C-3), 127.1 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.5 (CH, *para,* Ph), 139.2 (C_Q, Ph), 156.0 (C-2 and C-4), 200.0 (CO, methanone); *m*/*z* 304 (MH^+).

[3-(2-Hydroxy-1-benzylethylamino)-2,4-dihydroxyphenyl]phenylmethanone 6. The above described method, replacing *S*-*tert*-leucinol by *S*-2-amino-3-phenylpropanol (755 mg; 5 mmol), afforded, after flash chromatography on silica gel with toluene–acetone (90:10) as the eluent, compound **6** (100 mg, 55%) as a yellow oil along with **7** (12 mg, 10%).

6 δ_H [300 MHz; $(CD_3)_2SO$] 2.75 (2H, m, CH_2, bzl), 3.40 (2H, m, CH_2OH), 4.05 (1H, m, C*H*–N), 6.45 (1H, d, *J* 9, 5-H), 6.90 (1H, d, *J* 9, 6-H), 7.60 (5H, m, Ph), 12.80 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 38.5 (CH_2, bzl), 57.8 (CH–N), 62.4 (CH_2OH), 108.8 (C-5), 113.1 (C-1), 126.8 (C-6 and CH, *para*, bzl), 129.1 (CH, *meta*, bzl), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 130.3 (CH, *ortho*, bzl), 132.4 (CH, *para*, Ph), 139.3 (C_Q, Ph), 140.7 (C_Q, bzl), 155.5 and 155.6 (C-2 and C-4), 200.1 (CO, methanone); *m*/*z* 364 (MH^+).

[2,4-Dihydroxy-3-diphenylmethylaminophenyl]phenylmethanone 8 and *N*-benzhydryldiphenylmethanimine, $Ph_2C{=}NCHPh_2$. *Procedure a.* A solution of (2,3,4-trihydroxyphenyl)phenyl methanone **1** (115 mg; 0.5 mmol), lithium perchlorate (530 mg; 5 mmol) and benzhydrylamine (947 mg; 5 mmol) in methanol (250 cm^3) was oxidized, under nitrogen, at room temperature at a mercury pool working electrode ($E = +50$ mV *vs.* SCE). After exhaustive oxidation, *i.e.* when a steady-state minimum value of the current was recorded, the methanolic solution was poured into a molar acetic acid buffered aqueous solution of pH ≈ 4.5 (100 cm^3). The resulting hydroalcoholic solution was concentrated to 100 cm^3 under reduced pressure, at 40 °C, and extracted with ethyl acetate (200 cm^3). The organic phase was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure, at 40 °C. Flash chromatography on silica gel with a toluene–cyclohexane–acetone gradient (50:50:0) 50 cm^3; (100:0:0), 50 cm^3; (80:0:20), 100

cm^3 as the eluent afforded compound **7** (83 mg, 72%) along with benzophenone (50 mg, 54%) and *N*-benzhydryldiphenylmethanimine $Ph_2C{=}NCHPh_2$ (36 mg, 20%). Spectroscopic data for the latter were identical to those reported earlier.[23]

Procedure b. A solution of (2,3,4-trihydroxyphenyl)phenyl methanone **1** (115 mg; 0.5 mmol), lithium perchlorate (530 mg; 5 mmol) and benzhydrylamine (947 mg; 5 mmol) in methanol (250 cm^3), was oxidized using procedure **a**. After exhaustive oxidation, the resulting methanolic solution was immediately reduced after the potential of the mercury pool was switched to −1300 mV *vs.* SCE. After exhaustive cathodic electrolysis, the solution was poured into a molar acetic acid buffered aqueous solution of pH ≈ 4.5 (100 cm^3). The resulting hydroalcoholic solution was treated according to procedure **a** and afforded compound **8** (74 mg, 37%) mp 151–153 °C, as an amorphous pale yellow solid, along with compounds **7** (27 mg, 23%), benzophenone (18 mg, 20%) and *N*-benzhydryldiphenylmethanimine (26 mg, 15%).

8 (Found: C, 78.90; H, 5.40; N, 3.49. $C_{26}H_{21}NO_3$ requires: C, 78.99; H, 5.32; N, 3.54%); δ_H [300 MHz; $(CD_3)_2SO$] 4.70 (1H, d, *J* 8, C*H*–N), 6.25 (1H, d, *J* 8, NH, D_2O exchanged), 6.40 (1H, d, *J* 9, 5-H), 6.90 (1H, d, *J* 9, 6-H), 7.10 to 7.30 (10H, m, benzhydryl), 7.60 (5H, m, Ph), 10.90 (1H, br s, 4-OH, D_2O exchanged), 12.90 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 62.7 (CH–N), 108.7 (C-5), 113.0 (C-1), 124.1 (C-3), 127.4 (C-6), 127.8 (CH, *para*, benzhydryl), 128.1 (CH, *meta*, benzhydryl), 129.4 (CH, *ortho*, benzhydryl and CH, *meta*, Ph), 129.4 (CH, *ortho*, benzhydryl and CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.5 (CH, *para*, Ph), 139.0 (C_Q, Ph), 145.1 (C_Q, benzhydryl) 155.4 and 155.7 (C-2 and C-4), 201.0 (CO, methanone); *m*/*z* 396 (MH^+).

[2,4-Dihydroxy-3-(isopropylamino)phenyl]phenylmethanone 9. The above described procedure **a** with $E = -50$ mV *vs.* SCE and replacing benzhydrylamine by isopropylamine (1.5 g; 25 mmol), afforded, after chromatography on silica gel with toluene–butanol (90:10) as the eluent, compound **9** (61 mg, 45%) mp 151–153 °C as an amorphous white solid along with **7** (6 mg, 5%).

9 (Found: C, 70.35; H, 6.30; N, 5.09. $C_{16}H_{17}NO_3$ requires: C, 70.85; H, 6.27; N, 5.17%); δ_H [300 MHz; $(CD_3)_2SO$] 1.05 (6H, d, *J* 6, Me), 3.95 (m, 1H, *J* 6, C*H*–N), 6.40 (1H, d, *J* 9, 5-H), 6.90 (1H, d, *J* 9, 6-H), 7.60 (5H, m, Ph), 12.80 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 24.6 (Me), 46.6 (CH–N), 108.9 (C-5), 112.8 (C-1), 124.4 (C-3), 127.4 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para*, Ph), 139.2 (C_Q, Ph), 156.3 and 156.5 (C-2 and C-4), 200.8 (CO, methanone); *m*/*z* 272 (MH^+).

{2,4-Dihydroxy-[3-(1,2-dimethylpropyl)amino]phenyl}phenylmethanone 10. The above described procedure **a** with $E = -50$ mV *vs.* SCE and replacing benzhydrylamine by 1,2-dimethylpropylamine (2.2 g, 25 mmol), afforded, after chromatography on silica gel with toluene–acetone (95:5) as the eluent, compound **10** (48 mg, 31%) as a yellow oil along with **7** (46 mg, 40%).

10 δ_H [300 MHz; $(CD_3)_2SO$] 0.85, 0.90 and 0.95 (3H, d, *J* 6, Me), 1.65 (1H, m, *J* 6, CH, Pr^i), 3.75 (1H, m, *J* 6, C*H*–N), 6.45 (1H, d, *J* 9, 5-H), 6.90 (1H, d, *J* 9, 6-H), 7.55 (5H, m, Ph), 12.80 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 17.7 (Me, Pr^i), 20.3 (Me), 33.1 (CH, Pr^i), 54.9 (CH–N), 108.7 (C-5), 113.0 (C-1), 124.8 (C-3), 126.8 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para*, Ph), 139.2 (C_Q, Ph), 155.4 and 155.7 (C-2 and C-4), 201.1 (CO, methanone); *m*/*z* 300 (MH^+).

{2,4-Dihydroxy-3-[(1-isopropyl-2-methylpropyl)amino]-phenyl}phenylmethanone 11. The above described procedure **a** with $E = -50$ mV *vs.* SCE and replacing benzhydrylamine by 2,4-dimethylpent-3-ylamine (2,87 g; 25 mmol), afforded, after chromatography on silica gel with toluene–acetone (95:5) as the eluent, compound **11** (25 mg, 15%) as a yellow oil along with **7** (63 mg, 55%).

11 δ_H [300 MHz; $(CD_3)_2SO$] 0.95 (12H, m, Me), 1.80 (2H, m, CH, Pr^i), 3.70 (1H, m, C*H*–N), 6.40 (1H, d, *J* 9, 5-H), 6.80 (1H, d, *J* 9, 6-H), 7.55 (5H, m, Ph), 12.80 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 19.0 and 21.8 (Me), 32.8 (CH, Pr^i), 63.3 (CH–N), 108.8 (C-5), 113.1 (C-1), 125.0 (C-6), 127.3 (C-3), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para*, Ph), 139.3 (C_Q, Ph), 153.4 and 153.9 (C-2 and C-4), 201.2 (CO, methanone); *m*/*z* 328 (MH^+).

{2,4-Dihydroxy-3-[(1-methoxyprop-2-yl)amino]phenyl}phenylmethanone 12. The above described procedure **a** with $E = -50$ mV *vs.* SCE and replacing benzhydrylamine by 2-amino-1-methoxypropane (445 mg; 5 mmol), afforded, after chromatography on silica gel with toluene–acetone (92:8) as the eluent, compound **12** (57 mg, 37%) as a yellow oil along with **7** (27 mg, 23%).

12 δ_H [300 MHz; $(CD_3)_2SO$] 1.00 (3H, d, *J* 6, Me), 3.20 (3H, s, OMe), 3.30 (2H, m, CH_2–OCH_3), 3.80 (1H, m, *J* 6, C*H*–N), 6.40 (1H, d, *J* 9, 5-H), 6.90 (1H, d, *J* 9, 6-H), 7.55 (5H, m, Ph), 12.60 (1H, br s, 2-OH, D_2O exchanged); δ_C [75 MHz; $(CD_3)_2SO$] 19.7 (Me), 50.3 (CH–N), 59.5 (OMe), 77.4 (CH_2–OCH_3), 108.7 (C-5), 113.0 (C-1), 124.5 (C-3), 127.3 (C-6), 129.4 (CH, *meta*, Ph), 129.7 (CH, *ortho*, Ph), 132.4 (CH, *para*, Ph), 139.2 (C_Q, Ph), 155.9 and 156.0 (C-2 and C-4), 201.0 (CO, methanone); *m*/*z* 302 (MH^+).

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