was a much better hydrogen atom donor than *cis*-**1H**. While this is simple to rationalize in terms of differences in steric hindrance of the benzylic hydrogen atoms, it prevented even an estimation of k_r for *cis*-**1**$^{\bullet}$ → **2**$^{\bullet}$. Unfortunately, all our attempts to separate pure *cis*-**1H** were unsuccessful.

Experimental Section

1-Benzyl-*trans*-2-phenylcyclopropane (1H). Following a literature procedure,[26] 95% ethanol (70 mL), KOH (10 g), and phenylacetaldehyde (20 g) were refluxed for 4 h and the resultant solution was then washed with brine, followed by extraction with ether, water washing, and drying over Na_2SO_4. Removal of the ether and purification by column chromatography (silica gel, hexane eluent) gave 6.5 g (40% yield) of a clear oil, *trans*-1,3-diphenylpropene, 99% pure by GC-MS, *m/z* (relative abundance): 194 (M^+, 99), 193 (60), 179 (50), 178 (42), 115 (100).

Again following a literature procedure,[27] a mixture of zinc dust (10.5 g, 0.15 mol) and cuprous chloride (1.59 g, 0.016 mol) in ether (30 mL) was stirred and refluxed under N_2 for 1 h, after which diiodomethane (6.47 mL, 0.080 mol) was added and refluxing was continued for 15 min. The diphenylpropene (6.0 g, 0.080 mol) was added and refluxing was continued for 5 days, it being necessary to add more of the Zn/Cu couple after 2 days in order to force the reaction to completion (as determined by GC-MS). Filtration through Celite, followed by removal of the ether and chromatographic purification (silica gel/hexane) gave 5.0 g (78% yield) of **1H** as a clear oil, 98% pure by GC-MS. ^{1}H NMR: δ 0.85–1.10 (m, 2 H, cyclopropyl CH_2), 1.21–1.48 (m, 1 H, CH_2CHCH_2), 1.67–1.87 (m, 1 H, C_6H_5-*CH*), 2.55–2.82 (m, 2 H, $C_6H_5CH_2$), 6.85–7.30 (m, 10 H, aromatic H's). ^{13}C NMR: δ 16.10 (cyclopropyl CH_2), 22.96 (CH_2CHCH_2), 24.71 (C_6H_5CH), 39.99 ($C_6H_5CH_2$). GC-MS: *m/z* (relative abundance) 208 (M^+, 7), 178 (13), 117 (100), 115 (30), 104 (31).

1-Benzyl-*cis*-2-phenylcyclopropane (*cis*-1H). Since this compound was not prepared in a pure and "useful" form, only the general procedure, following literature precedents,[27-29] is given: (1) $C_6H_5C{\equiv}CH$ ($+CH_3CH_2MgBr + CuCl + C_6H_5CH_2Br$)[28] → $C_6H_5C{\equiv}CCH_2C_6H_5$ (68% yield, 99% purity by GC-MS). (2) $C_6H_5C{\equiv}CCH_2C_6H_5$ (+5% $Pd/BaSO_4$/quinoline + H_2(gas))[29] → $C_6H_5CH{=}CHCH_2C_6H_5$(81% cis, 5% trans, and 14% $(C_6H_5C-H_2)_2CH_2$ by GC-MS). (3) $C_6H_5CH{=}CHCH_2C_6H_5$ (+Zn + CuCl + CH_2I_2)[27] → $C_6H_5\overline{CHCH_2CHCH_2}C_6H_5$ (69% *cis*-**1H**, 16% *trans*-**1H**, 15% $(C_6H_5CH_2)_2CH_2$ by GC-MS and ^{13}C NMR).

Surprisingly, this last reaction was *much* slower than the corresponding reaction with the pure trans olefin, the reaction taking 9 days instead of 5 days. We assume that under these reaction conditions there is appreciable cis to trans conversion of the olefin and that this accounts for the unexpectedly high yield of *trans*-**1H**. From this mixture of products we can extract the following analytical data about *cis*-**1H**. ^{1}H NMR: δ 0.85–1.25 (m, 2 H, cyclopropyl CH_2), 2.10–2.25 (m, 2 H, $C_6H_5CH_2CH$ and C_6H_5CH), 2.45–2.75 (m, 2 H, $C_6H_5CH_2$). ^{13}C NMR: δ 9.87 (cyclopropyl CH_2), 19.93 (CH_2CHCH_2), 21.33 (C_6H_5CH), 34.42 ($C_6H_5CH_2$).

Procedures. The nitroxide trap (Tempo or ABNO at final concentrations in the range ca. 0.4–1.9 M and ca. 0.07–0.7 M, respectively) and di-*tert*-butyl hyponitrite [at ca. 20–25% of the trap concentration for experiments run for only 1 half-life (15 h) of this compound or at half this concentration for experiments run for 10 half-lives] were dissolved in **1H** (20 μL) and cyclopentane (380 μL). The solution was degassed by several freeze–pump–thaw cycles, sealed under vacuum, and heated at 40 °C for 1 or 10 half-lives of the hyponitrite. After the reaction vessel was opened, the cyclopentane was blown off under N_2 and an equivalent volume of ethanol was added. Analysis was by LC-MS as previously described[12,13] with selective ion monitoring for **1T** and **2T** at $(M + 1)^+$. The ^{1}H and ^{13}C NMR spectra were measured on a 200-MHz Bruker instrument in $CDCl_3$ with tetramethylsilane as an internal standard.

Acknowledgment. We thank D. A. Lindsay for valuable technical assistance in the analyses of the hydroxylamine product mixtures.

Registry No. 1$^{\bullet}$, 141375-04-4; *trans*-**1H**, 14213-83-3; *cis*-**1H**, 30627-65-7; ABNO, 31785-68-9; TEMPO, 2564-83-2; $PhCH_2CHO$, 122-78-1; *trans*-$PhCH{=}CHCH_2Ph$, 3412-44-0; *cis*-$PhCH{=}CHCH_2Ph$, 1138-83-6; $PhC{\equiv}CH$, 536-74-3; $PhCH_3Br$, 100-39-0; $PhC{\equiv}CCH_2Ph$, 4980-70-5; $(PhCH_2)_2CH_2$, 1081-75-0.

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Electrochemical Reduction of 2-(Arylideneamino)furans: An Unexpected Stable Anion-Radical

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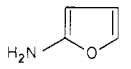
The parent 2-aminofuran ring system (1), although thermodynamically stable,[1] is not isolable.[2] In fact, 2-aminofuran itself has been only identified as a transient species.[3,4]



1

Recently, a general procedure has been developed for the synthesis of substituted 2-furanamines, by stabilizing them as Schiff bases **2** through in situ condensation with aromatic aldehydes.[5-7] Attempts to obtain the free furanamine from the Schiff base by reduction or hydrolysis failed, leading to cleavage of the furan ring.[6,8]

Given the above situation, we thought that the electrochemical reduction of the arylideneamino derivative in the presence of a proton donor could be a sensible route to furanamines **3**. However, the electrochemical reduction of compound **2a** (R = *p*-ClC_6H_4) took place in an unusual manner. In the pale yellow initial solution (DMF–H_2O/

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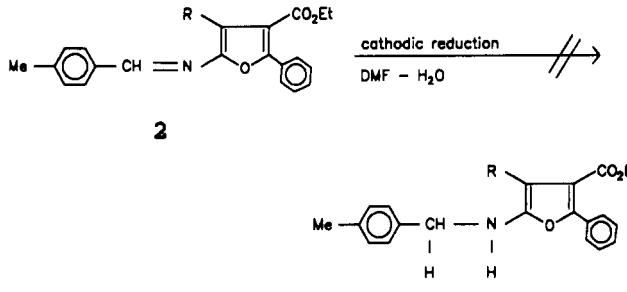


2

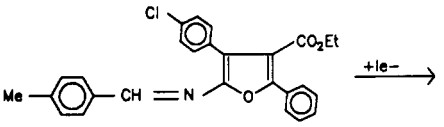
3

$NaClO_4$, open air), an intense red color immediately developed on the surface of the mercury in the cathodic compartment and diffused until the whole solution was deep red. At this point, the current dropped to zero, when one electron per molecule of substrate had been consumed. When the reaction mixture was allowed to stand for a few minutes, the contents of the cathodic compartment turned back to pale yellow and, then, the electrochemical process could be repeated again and again, with the same results.

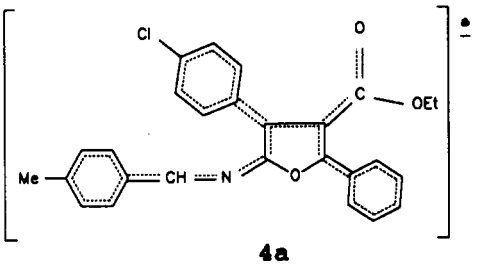
From the reversibility of the process, clearly seen in the cyclic voltamogram (E_{pc} = −1.53 V and E_{pa} = −1.47 V), it can be concluded that an anion-radical (one electron per molecule) was formed which was unable to react with water. In agreement with this, the reaction can also be carried out in the absence of water.

Therefore, the (arylidenamino)furan **2a** was subjected to chemical reduction by using a stoichiometric amount of sodium amalgam in dry THF. In this way, the red compound was isolated as a stable solid under argon (if the compound is allowed to stand in contact with air, the starting (arylideneamino)furan **2a** is regenerated).

Electron impact and chemical ionization mass spectrometry showed a molecular mass of 443, identical with the molecular mass of **2a**, in agreement with the structure **4a**. The stability of anion-radical **4a** can be accounted



2a



4a

for by the global delocalization through the totally conjugated structure. We have detected the reduced species **4a** by ESR spectroscopy, by registering the spectrum of anion-radical **4a** in the solid state with counterion Li^+. Figure 1 presents the ESR spectrum in DMSO solution. The spectrum is more complicated due to the hyperfine couplings. It consists of 14 lines with 0.04 mT line width and length over 1.11 mT. The coupling constants obtained from best-fit computer simulation in mT (0.1 mT = 1 G) are a_H = 0.54 (1:1), a_H = 0.19 (1:2:1), and a_N = 0.1 (1:1:1). We assign the doublet to the proton of the benzylic C–H, the first triplet to the ortho protons of the *p*-methylphenyl, and the second triplet to the nitrogen splitting. The spectrum's *g* factor is 2.0037. Analogously we have detected ESR signals for derivatives of **4** (**4b**, R = *p*-MePh;

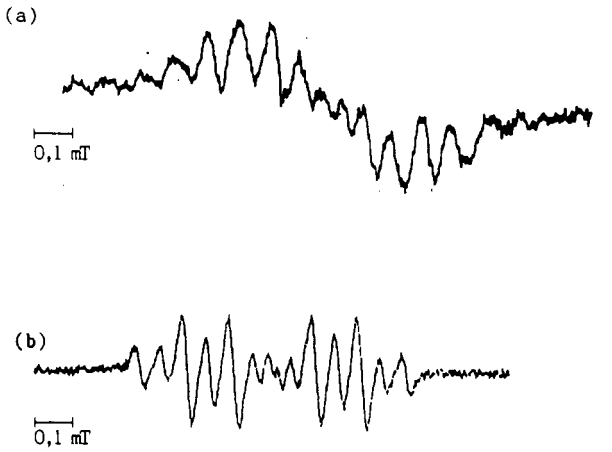
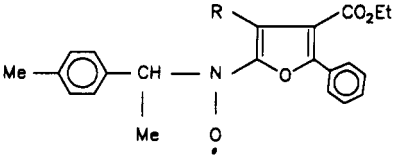


Figure 1. (a) ESR spectrum of **4a** in DMSO; modulation width 0.0125 mT; scan range 0.1 mT cm^{-1}; gain 10^4. (b) Computer simulation of (a) with 0.035 mT line width.

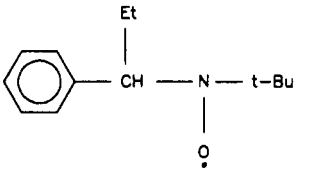
4c; R = Ph) in the solid state and in DMSO as solvent. In solution they present hyperfine structure similar to **4a**. It is difficult to discern R in these compounds owing to the poor resolution of their ESR spectra. We think that the lithium ion could be the cause of line broadening and thus lowering the attainable ESR resolution. Distortions in line width in ESR spectra of radicals due to ion pairing have been reported.[9]

Having thus proved the existence of the odd electron, the anion nature of **4** was chemically demonstrated by treating it with methyl iodide. The red color immediately and irreversibly disappeared, giving rise to a new compound. Its mass spectrum reveals the introduction of the methyl group, together with an oxygen atom. This in full



5

agreement with the known, stable, structure of alkyl adducts of nitrones used for spin-trapping, such as PBN-Et.[10]



PNB-Et

Other ethoxycarbonyl-substituted (arylideneamino)-furans (**2b**, R = *p*-MeC_6H_4; **2c**, R = C_6H_5) also show the same general behavior.

Experimental Section

Electron-impact mass spectra were obtained with a direct insertion probe and an ionizing voltage of 70 eV. Chemical ionization mass spectra were performed at 70 eV with methane. ESR spectra were recorded in the X-band provided with a 100-kHz field modulation. The *g* factor was obtained by means of a frequency-meter and gaussmeter. The hyperfine coupling constants were obtained by comparing experimental and computed-simulated

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spectra assuming a Lorentzian line shape. The radicals were detected in the solid state and also in a DMSO solution maintained in an inert atmosphere. The solution was transfered to an ESR flat quartz cell and placed inside the microwave cavity of the spectrometer.

Cyclic voltammetry was carried out at a hanging Hg drop; the cell used for electroanalytical experiments contained a working volume of 50 mL. It contained the hanging Hg drop working electrode, Pt wire secondary electrode, and SCE reference which was isolated from the electrolyte by a fine glass frit. The solution was deaerated with N_2 before analysis. Electrochemical experiments were performed with a potentiostat and an integrator.

Compounds **2** were obtained in accord with the literature.[6] Solvents were purchased from Aldrich without previous purification, except THF, which was purified following well-known standard procedures, and dried.

General Electrolysis Procedure. Electrolyses were carried out in a concentric cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The reductions were carried out in DMSO–anhydrous lithium perchlorate, 0.1 M. Approximately 60 mL and 20 mL of this solution were placed into the cathodic and the anodic compartments, respectively. A flow of dry nitrogen was bubbled through the catholyte solution, and the temperature was kept at 15 °C by external cooling. Anhydrous potassium carbonate (3 g) was placed in the anode compartment to prevent the accumulation of electrogenerated acid.

Solutions of **2** (0.2 mmol) were electrolyzed under a constant cathodic potencial of −1.6V vs SCE (**2a**) and −1.7V vs SCE (**2b**, **2c**). The electricity consumption was 1 Faraday per mole of **2**.

Chemical Reduction Procedure. **2** (0.2 mmol) was placed into a Schlenk tube with a stoichiometric amount of sodium amalgam (5 mg of Na in 2 mL of Hg) under argon and 20 mL of dry THF was added. After 3 min the reaction was complete. The red solution was transferred to another Schlenk tube through a Teflon tube. The THF was evaporated under vacuum. A crude red solid was obtained. The small amount of starting material which had not reacted was extracted with hexane and a crystalline red product was obtained.

Ethyl 3-(*p*-Chlorophenyl)-5-phenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4a): MS *m/z* (relative intensity) 445 (9, $M^+ + 2$), 443 (24, M^+), 342 (5), 208 (24), 207 (10), 189 (10), 178 (10), 146 (11), 120 (11), 105 (100), 91 (14), 77 (55).

Ethyl 3-(*p*-Methylphenyl)-5-phenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4b): MS *m/z* (relative intensity) 423 (2, M^+), 322 (3), 276 (6), 200 (8), 145 (9), 143 (9), 132 (18), 120 (34), 105 (100), 91 (23), 77 (44).

Ethyl 3,5-Diphenyl-*N*-(*p*-methylbenzylidene)-2-aminofuran-4-carboxylate anion-radical (4c): MS *m/z* (relative intensity) 409 (28, M^+), 380 (9), 333 (12), 308 (6), 208 (31), 207 (10), 193 (17), 189 (11), 178 (21), 146 (17), 132 (12), 105 (100), 91 (18), 77 (66).

Methylation of 4. Compounds **4** were generated by the electrochemical procedure (above), starting with 0.2 mmol of **2**. The electrochemical cell was then opened to air and methyl iodide (1 mmol) added to the red solution. This solution was worked up by adding 250 mL of ice–water and extracting with ethyl ether (3 × 25 mL). The organic layer was again washed with water to take the DMSO residues off. After drying over anhydrous sodium sulphate, the ether was evaporated under vacuum.

5a: MS *m/z* (relative intensity) 476 (1.4, $M^+ + 2$), 474 (3.6, M^+), 460 (3), 458 (5), 445 (2), 443 (4), 414 (3), 341 (8), 208 (7), 207 (6), 178 (9), 146 (24.5), 105 (100), 91 (7), 77 (28).

5c: MS *m/z* (relative intensity) 440 (7, M^+), 424 (3), 409 (24), 380 (6), 333 (8.5), 208 (25), 207 (9), 193 (15), 191 (11), 189 (9), 178 (16), 146 (16), 132 (11), 115 (10), 105 (100), 91 (20), 77 (65).

Acknowledgment. This study was financed by DGICYT PB88-0153.

Registry No. **2a**, 108262-51-7; **2b**, 108262-49-3; **2c**, 108262-48-2; **4a**, 141509-80-0; **4b**, 141509-81-1; **4c**, 141509-82-2; **5a**, 141526-80-9; **5c**, 141526-81-0; DMSO, 67-68-5; sodium amalgam, 11110-52-4; methyl iodide, 74-88-4.

Enzymatic Hydrolysis of Ethyl 3-Hydroxy-3-phenylpropanoate: Observations on an Enzyme Active-Site Model

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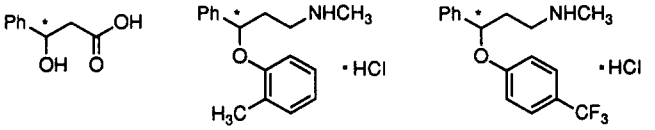
Optically active β-aryl-β-hydroxy acid derivatives are synthetically interesting, highly functionalized chiral synthons. The prototype, 3-hydroxy-3-phenylpropanoic acid (**1**), is of additional significance as a potential progenitor of optically pure tomoxetine hydrochloride (**2**) and fluoxetine hydrochloride (**3**). Both of these materials are important antidepressants,[1] with fluoxetine (Prozac, Eli Lilly Co.) exhibiting activity against such diverse conditions as anxiety, alcoholism, chronic pain, obesity, and bulimia.[1b] Preparation of these materials (or their known precursors) in optically pure form has attracted much interest,[2] although fluoxetine is currently marketed as the racemate.



1 **2** **3**

Catalytic asymmetric reduction of the corresponding β-keto ester comprises the most efficient and general synthesis of β-hydroxy acid derivatives in high optical purity.[3] However, β-aryl derivatives such as ethyl benzoylacetate require long reaction times and afford diminished (but still high) optical purities compared to the alkyl species. Alternative asymmetric syntheses of 3-hydroxy-3-phenylpropanoate exhibiting varying degrees of enantioselectivity have been reported using chemical[4] and microbiological[2d,5] reduction, aldol,[6] Reformatsky,[7] Diels–

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