

ELECTROCHEMICAL SYNTHESIS OF 2-SUBSTITUTED 5-AMINOFURANS.

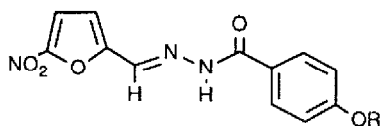
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Abstract - Electrochemical reduction of 2-substituted 5-nitrofurans in neutral hydroalcoholic media leads to the corresponding 5-aminofurans which have been isolated

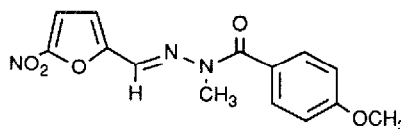
2-Substituted 5-nitrofuran derivatives are used as antimicrobial drugs¹. Some of them display mutagenic and carcinogenic activity¹ which is due to the reduction of the nitro group into active metabolites. Direct isolation and identification of metabolic intermediates have met a number of obstacles including the generally low solubility of nitrofurans in aqueous media and the extreme unstability of the intermediate products of the nitroreduction. Available information indicates a number of parallels in the mechanism of action of the carcinogenic 5-nitrofurans and that of the carcinogenic aryl nitro compounds, for which the hydroxylamine derivatives have been shown to be the proximate carcinogenic metabolites. Whereas phenylhydroxylamine is well known electrochemically², the analogous reduction product of nitrofuran has not been obtained so far. Electrochemical reduction has been shown to be a convenient method for obtaining intermediate reduced products of aromatic nitrocompounds². However, no attempt at preparative-scale electrolysis involving nitrofurans has been reported previously³.

This paper deals with the electrochemical reduction of nifuroxazide (Ercefuryl[®]) **1** and its methylated derivatives **2** and **3**⁴:



1 : R = H

2 : R = CH₃



3

The cyclic voltammogram of **1**, in roughly neutral water-methanol (5:5, v/v) media ($5.5 \leq \text{pH} \leq 8.0$), at a mercury drop electrode, showed two distinct reduction peaks recorded at -350 mV s.c.e.⁵ and -1350 mV s.c.e., the sweep rate being 0.5 V.s⁻¹. The height of the cathodic peak of the chloranilic acid⁶ in the same experimental conditions being taken as a reference, it appears that the primary irreversible electrochemical process consisted in a 4-electron reduction of the nitro group to the hydroxylamino group; at more negative potentials (-1350 mV s.c.e.), a further 4-electron reduction involving both reduction to amino group and reduction of the azomethine bond occurred.

When the controlled potential of the mercury working electrode was fixed at -500 mV s.c.e., a coulometric value of 6.0 ± 0.1 was found for the number of electrons involved in the reduction of one molecule of **1**. As the electrolysis proceeds further, a decrease in the two reduction peaks shown by **1** was observed, and the voltammogram of the exhaustively reduced solution showed a sole cathodic peak at -1350 mV s.c.e. (1.5 electron). The spectral changes which accompanied the electrochemical reduction of **1** showed a slight shift of the major absorption band from 370 to 365 nm. Finally, preparative scale electrolysis⁷ permitted isolation of the 5-aminofuran derivative **4** as the major product. Compounds **2** and **3** behave similarly, giving 5-aminofurans **6** and **8**, respectively, as indicated in the following table:

Substrate	5-Aminofuran yield %		Open-chain nitrile yield %
	Deduced from spectrometric and voltammetric data	Isolated product	Isolated product
1	70	35 ^a	5 ^b
2	60	45 ^a	5 ^b
3	65	35 ^b	10 ^b

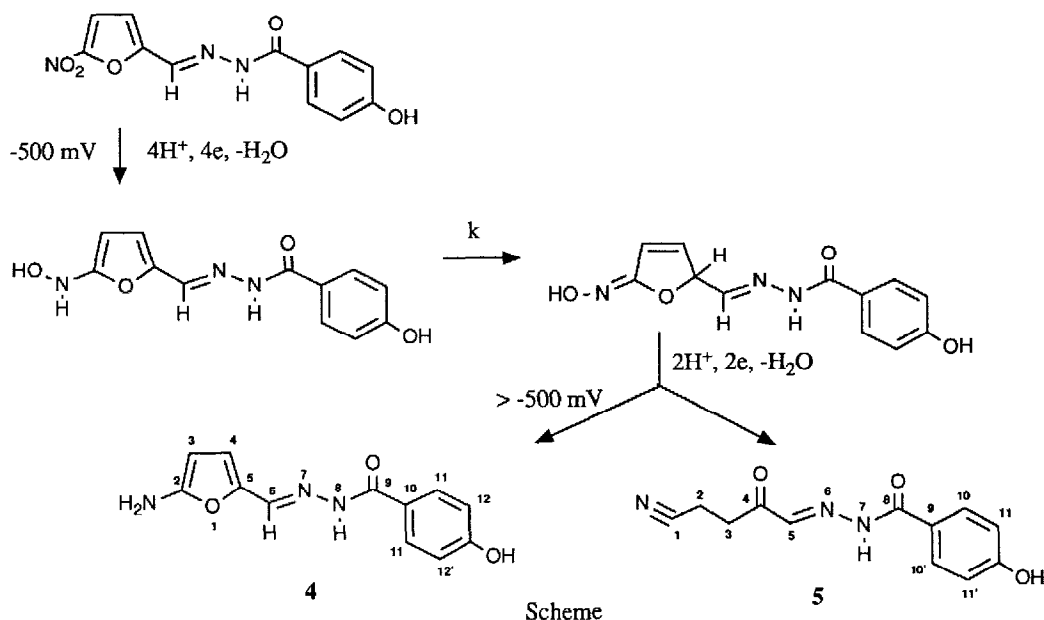
(a) isolated from methanol in which the solubility of 5-aminofuran is low

(b) isolated after column chromatography on silica

The new products were characterized by their ¹H NMR (300 MHz, DMSO d⁶) and mass spectroscopic data, UV-visible absorption spectra (100% methanol) and reduction potentials⁸. The only side-product is the open-chain cyano derivative **5** (**7** or **9**) which has been isolated in yields lower than 10% (see table) except when i) the electrolysis was performed with a slow stirring rate, where the yield of the side-product was 15%; ii) 2-methoxy-ethanol replaced methanol, where the yield was 25%.

Finally, these results permit the following conclusions:

a) 2-Substituted 5-nitrofuran derivatives, when reduced under well defined experimental conditions, produce the corresponding 5-aminofurans (scheme). The isolation of electrochemically prepared 5-aminofurans and their spectroscopic data have not been reported previously. Only two authors successfully carried out the catalytic reduction of 5-nitrofurans to corresponding 5-aminofurans with palladium on charcoal in anhydrous alcohols or non-hydroxylic solvent systems^{1b, 9, 10}. Our findings are consistent with the hypothesis proposed by Gavin and co workers¹¹, in which the initial product of reduction, the hydroxylamine derivative, undergoes tautomerization to yield the cis- and trans-oximes. The cis oxime is further reduced to give the amino derivatives, whereas the trans-oxime is suggested to prefer a trans elimination of water, resulting in ring opening to a nitrile.



b) The isolation of the hydroxylamine intermediate, a metabolite likely responsible for the mutagenic and carcinogenic action of the 5-nitrofurans, seems definitely impossible due to its fast tautomerization (k).

c) These aminofurans are stable in the solid state. They decompose slowly in hydroalcoholic media but they do not yield the open-chain cyano derivatives. In view of these results, we are unable to agree with the conclusion reached by Beckett and Robinson¹² that the aminofurans are so unstable that furan ring-cleavage immediately occurs to give the open chain cyano derivatives.

Acknowledgement - The authors wish to thank the Laboratoires d'études et de recherches Synthélabo (L.E.R.S.) for the financial support of this work and for providing Ercefuryl[®]. They also are very grateful to Dr. E. Kauffmann for fruitful discussions.

References and notes

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- 5 - The potentials are relative to a saturated calomel electrode (s.c.e.).
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- 7 - A typical procedure is as follows: Nifuroxazide 1 (0.1 mmol) was dissolved in methanol + 0.1 M citric or Tris buffered water (50:50 v/v), (200 ml). The resulting solution was vigorously stirred and reduced under

nitrogen, at 30°C, in a 3-compartment cell (cathode: mercury pool; anode: platinum foil). After exhaustive electrolysis, i.e. when a steady state minimum value of the current was recorded, the reduced solution was evaporated in vacuo at 35°C. The resulting solution (50 ml) was extracted with ethyl acetate (200 ml). The organic phase, dried over anhydrous sodium sulphate, was evaporated to dryness over reduced pressure at 35°C. The residue was either washed with methanol or chromatographed on silica.

8 - Amine 4: yellow powder, ^1H NMR, δ : 5.10 [d, 1H, H(3), $J(\text{H}_3\text{-H}_4) = 4$ Hz], 6.30 [s, 2H, NH_2 , D_2O exchanged], 6.70 [d, 1H, H(4), $J(\text{H}_4\text{-H}_3) = 4$ Hz], 6.85 [d, 2H, H(12) and H(12'), $J(\text{H}_{12}\text{-H}_{11}) = 9$ Hz], 7.75 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{12}) = 9$ Hz], 8.00 [s, 1H, H(6)], 10.10 [broad s, 1H, OH, D_2O exchanged], 11.10 [s, 1H, NH, D_2O exchanged]. MS (DCI): $m/z = 263$ (MNH_4^+), $m/z = 246$ (MH^+); UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$) 260 (5500), 365 (29000); reduction potential: -1350 mV s.c.e.

Open-chain nitrile 5: beige powder, ^1H NMR, δ : 2.70 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{2,3} = 6$ Hz], 3.20 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{3,2} = 6$ Hz], 6.90 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{10}) = 9$ Hz], 7.75 [s, 1H, H(5)], 7.85 [d, 2H, H(10) and H(10'), $J(\text{H}_{10}\text{-H}_{11}) = 9$ Hz], 10.30 [broad s, 1H, OH, D_2O exchanged], 12.20 [broad s, 1H, NH, D_2O exchanged]. MS (DCI): $m/z = 263$ (MNH_4^+), $m/z = 246$ (MH^+); (EI): $m/z = 163$ ($\text{M} - \text{C}_4\text{H}_4\text{NO}^+$), $m/z = 121$ ($\text{OH-C}_6\text{H}_5\text{-C=O}^+$) (100%), $m/z = 93$ ($\text{C}_6\text{H}_4\text{OH}^+$). UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$): 225 (7200), 296 (22000); reduction potential: -770 mV s.c.e.

Amine 6: yellow powder, ^1H NMR, δ : 3.85 [s, 3H, OCH_3], 5.10 [d, 1H, H(3), $J(\text{H}_3\text{-H}_4) = 4$ Hz], 6.30 [s, 2H, NH_2 , D_2O exchanged], 6.70 [d, 1H, H(4), $J(\text{H}_4\text{-H}_3) = 4$ Hz], 7.05 [d, 2H, H(12) and H(12'), $J(\text{H}_{12}\text{-H}_{11}) = 9$ Hz], 7.85 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{12}) = 9$ Hz], 8.00 [s, 1H, H(6)], 11.25 [s, 1H, NH, D_2O exchanged]. MS (DCI): $m/z = 277$ (MNH_4^+), $m/z = 260$ (MH^+). UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$): 250 (5000), 365 (27000); reduction potential: -1260 mV s.c.e.

Open-chain nitrile 7: beige powder, ^1H NMR, δ : 2.65 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{2,3} = 6$ Hz], 3.15 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{3,2} = 6$ Hz], 3.90 [s, 3H, OCH_3], 7.10 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{10}) = 9$ Hz], 7.75 [s, 1H, H(5)], 7.95 [d, 2H, H(10) and H(10'), $J(\text{H}_{10}\text{-H}_{11}) = 9$ Hz], 12.25 [s, 1H, NH, D_2O exchanged]. MS (DCI): $m/z = 277$ (MNH_4^+), $m/z = 260$ (MH^+), (EI): $m/z = 177$ ($\text{M-C}_4\text{H}_4\text{NO}^+$), $m/z = 135$ ($\text{OCH}_3\text{-C}_6\text{H}_4\text{-C=O}^+$) (100%), $m/z = 107$ ($\text{C}_6\text{H}_4\text{OCH}_3^+$); UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$): 220 (7500), 295 (22500); reduction potential: -730 mV s.c.e.

Amine 8: yellow powder, ^1H NMR, δ : 3.25 [s, 3H, NCH_3], 3.85 [s, 3H, OCH_3], 5.05 [d, 1H, H(3), $J(\text{H}_3\text{-H}_4) = 4$ Hz], 6.15 [s, 2H, NH_2 , D_2O exchanged], 6.60 [d, 1H, H(4), $J(\text{H}_4\text{-H}_3) = 4$ Hz], 6.95 [d, 2H, H(12) and H(12'), $J(\text{H}_{12}\text{-H}_{11}) = 9$ Hz], 7.65 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{12}) = 9$ Hz], 7.75 [s, 1H, H(6)]. MS (DCI): $m/z = 274$ (MH^+); UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$): 235 (sh) (11500), 265 (11000), 350 (19500); reduction potential: -1200 mV s.c.e.

Open-chain nitrile 9: ^1H NMR, δ : 2.65 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{2,3} = 6$ Hz], 2.95 [t, 2H, $\text{CH}_2(2)$ or $\text{CH}_2(3)$, $J_{3,2} = 6$ Hz], 3.45 [s, 3H, NCH_3], 3.90 [s, 3H, OCH_3], 7.05 [d, 2H, H(11) and H(11'), $J(\text{H}_{11}\text{-H}_{10}) = 9$ Hz], 7.35 [s, 1H, H(5)], 7.70 [d, 2H, H(10) and H(10'), $J(\text{H}_{10}\text{-H}_{11}) = 9$ Hz]. MS (DCI): $m/z = 291$ (MNH_4^+), $m/z = 274$ (MH^+); (EI): $m/z = 191$ ($\text{M-C}_4\text{H}_4\text{NO}^+$), $m/z = 135$ ($\text{-C-OCH}_3\text{-C}_6\text{H}_4\text{O}^+$) (100%), $m/z = 107$ ($\text{C}_6\text{H}_4\text{OCH}_3^+$). UV-vis: λ_{nm} ($\epsilon_{\text{M}^{-1}\text{cm}^{-1}}$): 245 (14500), 275 (17500); reduction potential: -880 mV s.c.e.

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(Received in France 22 October 1990)