

Electrochemical reduction of 4'-demycarosyl-10-hydro-11-dehydro-11-hydroxyimino-9-carbonyl-9-nor-8a,9*seco*-8a-aza-8a-homorelomyacin, the novel *seco* compound from the class of tylosin

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Abstract

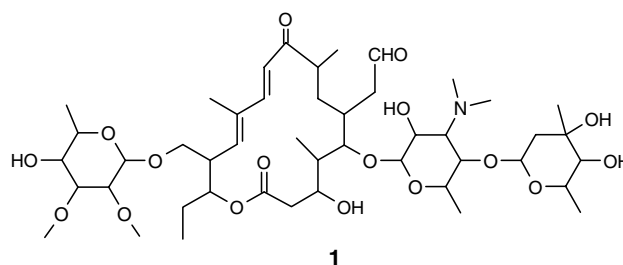
The electrochemical reduction of 4'-demycarosyl-10-hydro-11-dehydro-11-hydroxyimino-9-carbonyl-9-nor-8a,9*seco*-8a-aza-8a-homorelomyacin was investigated by cyclic voltammetry and preparative scale electrolysis. It has been found that oxime group is reduced by ECEC mechanism in a four-electron process. The resulting products of the reduction consisted of the corresponding α,β -unsaturated amine and α,β -saturated ketone. The rate determining step was identified to be the cleavage of N–O bond. In the acidic media the actual leaving group is water and in neutral and moderate basic media hydroxyde ion.

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1. Introduction

Tylosin, **1**, is a representative of the very important family of 16-membered macrolide antibiotics. Its broad microbial spectrum includes Gram-positive bacteria and *Mycoplasma* species what enables its widespread use in veterinary medicine for the treatment and prevention of serious respiratory illness among farm animals. Owing to their highly functionalized and stereochemically complex structure, these compounds have elicited intense interest, and a huge number of novel derivatives have been synthesized.



Recently, we have found that by oximation of 8a-aza derivatives of tylosin, the ring opening takes place resulting in the novel *seco* compounds [1]. These compounds are valuable intermediates for the preparation of novel azalide antibiotics via backward macrocyclization strategy.

Electrochemical methods have proven very useful in the synthesis of the valuable organic intermediates [2]. They have already been applied to the number of electrochemical modifications of tylosin [3–5] and azalide

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antibiotics [6]. Presently, our interest is focused on the electrochemical reduction of 4'-demecarosyl-10-hydro-11-dehydro-11-hydroxyimino-9-carbonyl-9-nor-8a,9*seco*-8a-aza-8a-homorelomyacin, **2**, at mercury electrode. The studies have been carried out in order to investigate the mechanism of electroreduction of **2**, and to identify the resulting products.

It is known that oximes readily undergo the four electronic reduction affording corresponding amines [7–12]. The summary of the work was generalized in the recent review by Leibzon [13]. The reduction generally proceeds via imine species and voltammetric behavior depends on the experimental conditions and the nature of the rest of the molecule. However, a separate two-electron wave corresponding to the imine formation stage was observed only for some oximes in acidic media [7]. In some cases the imine is hydrolysed to the ketone and ammonia before the second electron transfer takes place. In some cases, it has been demonstrated that oximes can be electroreduced to hydroxylamine derivatives without cleaving off the hydroxyl group [8]. α,β -unsaturated oximes that are not coupled with the phenyl ring and contain no electron-acceptor substituents are shown to be reducible only in the protonated form [7].

2. Experimental

2.1. Cyclic voltammetry

Cyclic voltammetry experiments were carried out using standard three electrode setup using PAR M283 potentiostat and PAR 303A HMDE system. Mercury drop of approximate surface area of 0.015 cm² was used. The counter electrode was platinum wire, and the reference electrode was an Ag/AgCl electrode. The experiments were performed in Britton–Robinson buffer solutions at wide range of scan rates and in the pH range of 2–10. The concentration of **2** in the experiments ranged between 0.1 and 1.0 mM. The HMDE cell solutions were deoxygenated by purging nitrogen through the solutions prior to the experiments and above the solutions while the runs were being carried out. All experiments were carried out at room temperature.

2.2. Preparative scale electrolysis

Preparative scale electrolyses have been carried out at constant potential with 100 mg of **2** in 30 ml 0.1 mol dm³ Britton–Robinson buffer. A conventional H-type electrolysis cell was used with compartments separated by a glass frit. Mercury pool and graphite rod have been employed as cathode and anode, respectively. Reference Ag/AgCl electrode has been positioned in the catholyte as close as possible to the cathode. During the electrolysis, the solution was stirred with magnetic stirrer and

solution is purged with nitrogen. All electrolyses were carried out at room temperature.

2.3. Isolation and identification of products

The products have been isolated from the reaction mixture by means of gradient extraction with chloroform at pH 5.5 and 9.5 (adjusted with NaOH). The combined chloroform extracts were dried (K₂CO₃) and evaporated under reduced pressure. The products were separated by column chromatography. Identification of products has been carried out by MS and NMR.

2.4. 4'-Demecarosyl-10-hydro-11-dehydro-11-hydroxyimino-9-carbonyl-9-nor-8a, 9*seco*-8a-aza-8a-homorelomyacin (**2**)

M.p. 83–87 °C. TLC: CH₂Cl₂–CH₃OH – conc. NH₄OH (90:20:2) system A R_f 0.214.

¹H NMR (CDCl₃) δ ppm: 5.70 (H-13), 4.56 (H-1''), 4.41 (H-1'), 3.90 (Ha-20), 3.58 (Hb-20), 3.61 (3''-(OCH₃)), 3.48 (2''-(OCH₃)), 3.09 (H-8), 2.49 (3'-N(CH₃)₂), 1.99 (H-10), 1.82 (H-22), 1.17 (H-21).

¹³C NMR (CDCl₃) δ ppm: 173.3 (C-1), 157.5 (C-11), 135.9 (C-12), 129.3 (C-13), 106.6 (C-1'), 101.0 (C-1''), 61.7 (3''-(OCH₃)), 60.3 (C-20), 59.5 (2''-(OCH₃)), 44.9 (C-8), 41.7 (3'-N(CH₃)₂), 41.7 (C-7), 35.6 (C-6), 24.1 (C-21), 13.6 (C-22), 10.5 (C-10).

FAB (MH⁺) 794.

2.5. 4'-Demecarosyl-10-hydro-11-dehydro-11-amino-9-carbonyl-9-nor-8a, 9*seco*-8a-aza-8a-homorelomyacin (**3**)

M.p. 64–68 °C.

¹H NMR (CDCl₃) δ ppm: 5.28 (H-13), 4.55 (H-1''), 4.36 (H-1'), 3.62 (3''-(OCH₃)), 3.51 (2''-(OCH₃)), 3.01 (H-

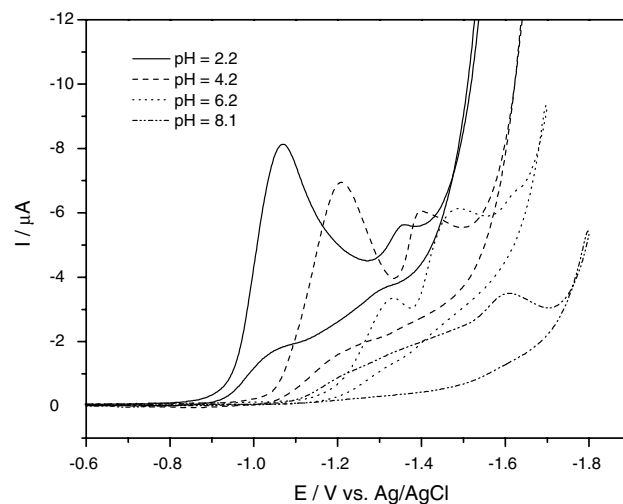


Fig. 1. Cyclic voltammograms of 1×10^{-3} mol dm⁻³ of **2** at different pH, $\nu = 100$ mV/s.

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