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Electrochemical Deacetoxylation: Synthesis of 11-Ketotigogenin

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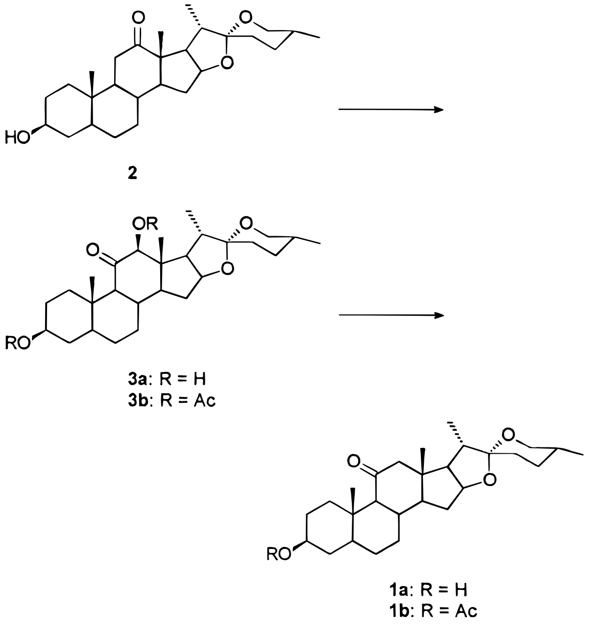
Introduction

11-Ketotigogenin ($(3\beta,5\alpha,25R)$-3-hydroxyspirostan-11-one, **1a**) is a useful potential intermediate for the synthesis of corticosteroids and related compounds. It has traditionally been prepared from naturally-occurring hecogenin (**2**), with a variety of synthetic schemes[1,2] being used to establish the desired functionality at C-11. The best results have been obtained by reduction of readily available[3] 11-ketorockogenin diacetate (**3b**) with calcium in liquid ammonia.[2] Although the calcium/ammonia reduction proceeds in good yield, it has features which might make it unattractive for large-scale production. These include the capital investment associated with the necessary equipment for low-temperature reactions, as well as safety and environmental factors associated with the handling and recovery of liquid ammonia and the disposal of residual calcium. For these reasons, an alternative route from **3b** to **1a** was sought. An electrochemical approach seemed particularly attractive from safety and environmental standpoints. In addition to the advantage of providing mild, easily scalable reaction conditions, the electrochemical approach could conceivably offer improved chemical selectivity.



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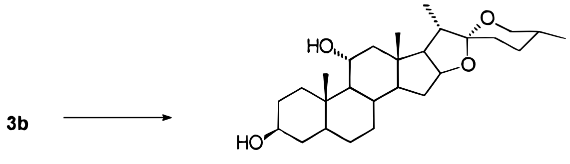
3a: R = H
3b: R = Ac

1a: R = H
1b: R = Ac

A polarographic study[4] of a number of steroidal α-ketols indicated two separate and distinct reduction waves at −2.0 and −2.45 V (vs a saturated calomel electrode); these were ascribed to the cleavage of the hydroxyl (or acetoxyl) group and the reduction of the carbonyl group, respectively. On the basis of this result, a number of preparative electrolyses were attempted[5] using a mercury pool cathode in a divided cell, with aqueous ethanol as solvent. However, in most of the cases studied, cleavage of the α-substituent could not be accomplished without concomitant reduction of the ketone carbonyl group; compound **3b** gave diol **4** as the only isolated product, in a yield of over 90%.



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Dissolving metal reductions of steroidal α-ketols have been observed[2,6] to be profoundly sensitive to reaction conditions, particularly to the nature of the proton source used. It was hypothesized that similar considerations might apply to the electrochemical reaction and that the desired selectivity of reduction might be achieved in a different electrolysis medium, using high hydrogen overpotential electrodes such as lead or carbon-based materials such as vitreous carbon or high surface area graphite.[7] Use of these electrode materials in place of mercury would also be desirable from an environmental standpoint.

Results and Discussion

Initial experiments on the electroreduction of **3b** were carried out in a divided glass H-cell equipped with a Nafion 417 cation exchange membrane, using tetraalkylammonium salts as supporting electrolytes. The cathode materials examined included lead, vitreous carbon, and high surface area graphite felt. In protic media such as methanol or aqueous acetonitrile, compound **3b** was rapidly and efficiently hydrolyzed to **3a**, which was relatively inert to further reaction under the conditions used. This hydrolysis is believed to be caused by electrogenerated base and could be completely suppressed by using a pH 5 tetraethylammonium acetate/acetic acid buffer as the electrolyte; in experiments involving a buffered catholyte, no reaction of **3b** was observed.

In contrast to the above results, it was found that **3b** was readily reduced in aprotic media with a lead or graphite felt cathode. Electrolyses were typically carried out in *N*-methyl-2-pyrrolidinone (NMP) or NMP/THF mixtures,[8] with tetrabutylammonium tetrafluoroborate

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(1) Djerassi, C.; Ringold, H. J.; Rosenkranz, G. *J. Am. Chem. Soc.* **1954**, *76*, 5533.

(2) Chapman, J. H.; Elks, J.; Phillipps, G. H.; Wyman, L. J. *J. Chem. Soc.* **1956**, 4344.

(3) Djerassi, C.; Ringold, H. J.; Rosenkranz, G. *J. Am. Chem. Soc.* **1951**, *73*, 5513.

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(5) Kabasakalian, P.; McGlotten, J.; Basch, A.; Yudis, M. D. *J. Org. Chem.* **1961**, *26*, 1738.

(6) Rothman, E. S.; Wall, M. E. *J. Am. Chem. Soc.* **1957**, *79*, 3228.

(7) Tilak, B. V.; Sarangapani, S.; Weinberg, N. L. In *Technique of Electroorganic Synthesis*: Weinberg, N. L., Tilak, B. V., Eds.; John Wiley & Sons: New York, 1982; Vol. III, Chapter IV.

(8) The lack of solubility of the starting material in solvents such as DMF or acetonitrile was a limiting factor, but the material is quite soluble in THF, and the use of this cosolvent gave the best overall results.

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or acetate as the electrolyte. Under these conditions, complete consumption of the starting material was observed after passage of 2−4 F/mol of starting material added; at this point the catholyte contained primarily a mixture of the desired product **1a** and its corresponding acetate **1b**, along with a small amount (5−10%) of the deacetylated material **3a**. Although **1b** was slowly converted to **1a** upon continued electrolysis,[9] it proved more convenient to stop the electrolysis as soon as the starting material was consumed and hydrolyze the acetate *in situ* by addition of a catalytic amount of potassium hydroxide in methanol to the catholyte. After neutralization of the mixture, the steroidal materials were separated from residual solvent/electrolyte by removing the majority of the volatile solvents under reduced pressure and diluting the residue with several volumes of water. In this way, 74−97% yields of crude product assaying at 65−80% by HPLC were typically obtained.

The nonaqueous electrolysis process was initially carried out in a divided glass cell and was also successfully scaled up to a small (10 cm^2 electrode area) filter-press type electrochemical flow cell with no loss of current efficiency. In the course of these experiments it was observed that a polymeric coating was gradually formed on the surface of the anode, except when an easily oxidizable species such as acetate ion was present in the anode compartment; the polymerization problem was most easily avoided by use of tetrabutylammonium acetate as the electrolyte. This observation also suggested the possibility of carrying out the reaction in an undivided cell. The anodic oxidation of acetate can take place in a variety of ways, depending on the conditions;[10] two possible anodic processes are shown below.

$$2\mathrm{AcO}^- \rightarrow 2\mathrm{CO}_2 + \mathrm{CH}_3\mathrm{CH}_3 + 2\mathrm{e}^-$$

$$2\mathrm{AcO}^- \rightarrow \mathrm{CO}_2 + \mathrm{CH}_3\mathrm{OAc} + 2\mathrm{e}^-$$

The cathodic transformation of **3b** to **1b** produces an equimolar amount of acetate in a two-electron process, and would thus help to minimize loss of acetate. On a larger scale, replenishment of acetate could be accomplished by pH-controlled addition of acetic acid. The transformation of **3b** to **1b** (and ultimately to **1a**) in an undivided cell using tetrabutylammonium acetate as the electrolyte was successfully carried out, with no evidence of anodic degradation of the products. No anode fouling or increase in cell voltage was observed over the course of the run.

Although the undivided cell process utilizing tetrabutylammonium acetate is both efficient and simple to operate, it suffers from the drawback of requiring a relatively expensive electrolyte. A possible alternative to this is the use of a sacrificial anode,[11] which has been employed for a number of otherwise difficult nonaqueous electroorganic reductions; this approach requires only a minimal amount of added electrolyte. The reduction of **3b** was carried out using a magnesium rod in place of a conventional flag anode, and compound **1b** was formed smoothly. The hydrolysis of **1b** to **1a** was somewhat complicated by the presence of magnesium salts in the mixture, and a substantial excess of potassium hydroxide (2.25 equiv based on **3b**) was required to accomplish this transformation. However, this fact would not preclude the possible use of a sacrificial anode with other substrates.

The electrochemical methodology utilized in this study is straightforward, and it is felt that it could easily be extended to other α-ketol acetates and possibly also to ketones containing other α-substituents (e.g. halogen). It provides a selective method of removing the substituent under mild, neutral conditions at near ambient temperature and as such could be a potentially useful tool for organic synthesis.

Table 1. Electrochemical Deacetoxylation of 11-Ketorockogenin Diacetate (3b) to 11-Ketotigogenin (1a)

electrolyte[a]	concn of **3b** (M)	charge passed (F/mol)	yield of **1a** (%)[b]
0.2 M $\mathrm{Bu_4NBF_4}$ in NMP[c]	0.075	3.0[d]	50
0.4 M $\mathrm{Bu_4NBF_4}$ in NMP/THF (1:1)[e]	0.15	2.6[d]	79
0.3 M $\mathrm{Bu_4NOAc}$ in NMP/THF (1:1)[f]	0.2	3.25[g]	54
0.3 M $\mathrm{Bu_4NOAc}$ in NMP/THF (1:1)[h]	0.2	4.0[g]	76
0.1 M $\mathrm{Bu_4NBr}$ in NMP/THF (1:1)[i]	0.2	3.5[j]	70

[a] Graphite felt cathode. [b] Based on HPLC assay of crude isolated product. [c] Divided glass cell; catholyte as specified, anolyte 0.2 M $\mathrm{Bu_4NOAc}$ in NMP. [d] The electrolysis was continued until **1b** was completely converted to **1a**. [e] Divided glass cell; catholyte as specified, anolyte 0.4 M $\mathrm{Bu_4NOAc}$ in NMP/THF. [f] Divided flow cell. [g] The product at the end of the electrolysis was primarily **1b**, so the catholyte was treated with 0.25 equiv of KOH in methanol. [h] Undivided glass cell. [i] Undivided glass cell with Mg anode. [j] The product at the end of the electrolysis was primarily **1b**, so the catholyte was treated with 1.25 equiv of KOH in methanol.

Experimental Section

General. Melting points are uncorrected. HPLC analyses were performed using a 3.9 × 300 mm C_{18} (4 μm) column with refractive index detection. Most preparative electrolyses were carried out in either an undivided "beaker-type" glass cell of about 100 mL capacity or a divided "H-cell" having a working electrode compartment of about 100 mL capacity and a counter electrode compartment of about 50 mL capacity. The flow cell experiment was conducted in a Micro Flow Cell[12] from ElectroCell Systems AB, Sweden. The divided cell experiments utilized a Nafion 417 cation exchange membrane as a separator. A platinum flag anode was used for most glass cell experiments, and a platinum-clad niobium sheet was used as an anode in the flow cell. High surface area graphite felt electrodes were prepared from 0.6 cm thick graphitized polyacrylonitrile fiber[12] (surface area 0.5 m^2/g).

Materials. Commercial quaternary ammonium salts and reagent grade solvents were used without further purification.

Preparation of 11-Ketotigogenin (1a) in an Undivided Cell. An undivided glass cell was assembled with a platinum flag anode (5 cm^2) and a graphite felt flag cathode (5 cm^2 × 0.6 cm thick). A solution of 6.33 g of tetrabutylammonium acetate and 7.43 g (14 mmol) of keto ester **3b** in 70 mL of THF/NMP (1:1 by volume) was placed in the cell. The solution was electrolyzed, with no external heating or cooling, at a constant current of 125 mA (25 mA/cm^2). Over the course of the run the temperature of the solution rose to about 40 °C. The run was continued until a total charge of 4.1 F/mol had been passed; by this time not more than a trace of starting material was noted by TLC. The electrolyte was diluted with a solution of 596 mg of potassium hydroxide in 120 mL of methanol, and the resultant

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(9) The relative amounts of **1a** and **1b** varied greatly from one experiment to another; inasmuch as the hydrolysis of **1b** to **1a** is presumably caused by cathodically-generated base, it could be strongly dependent on the amount of adventitious moisture present in the system.

(10) Torii, S.; Tanaka, H. In *Organic Electrochemistry*, 3rd ed.; Lund, H., Baizer, M. M., Eds.: Marcel Dekker: New York, 1991; Chapter 14.

(11) Chaussard, J.; Folest, J. C.; Nedelec, J. Y.; Perichon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, 369 and references cited therein.

(12) High surface area graphite felt (ESC Grade GF-S6) and ElectroCell electrochemical cells are available from the Electrosynthesis Co., Inc.

mixture was stirred at ambient temperature until all of **1b** was converted to **1a** (about 4 h). The mixture was then neutralized by addition of 2 mL of acetic acid and concentrated under reduced pressure, and the residue was added over about 15 min to 350 mL of vigorously-stirred water containing 2 mL of acetic acid. The resultant suspension was stirred overnight and filtered, and the product was washed with water and dried under vacuum at 40 °C to yield 5.87 g of a crude product mixture consisting of 78% of the desired product **1a**, together with 9% of **3a** and 3% of residual **1b**. Purification of a 2 g portion of the crude material by flash chromatography[13] gave 1.28 g (62% yield[14]) of material of 97% HPLC assay and a mp 215−219 °C (lit.[1] mp 223−226 °C), identical to authentic **1a** prepared by the literature method.[2]

Preparation of 11-Ketotigogenin (1a) Using a Sacrificial Anode. An undivided glass cell was assembled with a magnesium rod anode (1.5 cm diameter) surrounded by a ring (2.5 cm internal diameter) of graphite felt supported by a cylindrical piece of stainless steel mesh. Next, a solution of 2.90 g (9 mmol) of tetrabutylammonium bromide and 9.55 g (18 mmol) of keto ester **3b** in 80 mL of THF/NMP (1:1 by volume) was placed in the cell. The solution was electrolyzed at a constant current of 690 mA (25 mA/cm^2 cathode current density); the cell was immersed in a cold water bath in order to keep the mixture temperature below about 45 °C. After passage of 2.5 F/mol, the current was reduced to 412 mA (15 mA/cm^2), and the run was continued until another 1.0 F/mol had been passed; by this time not more than a few percent of starting material remained by TLC. The electrolyte was diluted with 90 mL of methanol and treated with 1.79 g (33 mmol) of potassium hydroxide; the mixture became somewhat viscous (presumably due to gelatinous insoluble magnesium salts). The resultant mixture was stirred at ambient temperature overnight, by which time the hydrolysis of **1b** to **1a** was complete. The mixture was neutralized by addition of 5 mL of acetic acid; upon addition of the acid most of the magnesium salts appeared to dissolve. The mixture was concentrated under reduced pressure and diluted over about 1 h with 350 mL of water. The resultant suspension was stirred for 2 h and filtered, and the product was washed with water and dried under vacuum at 40 °C to yield 7.16 g of crude material containing 70% of the desired product **1a**. The HPLC profile of this material was similar to that of the material obtained using a conventional anode. Table 1 summarizes the conditions used for electrolyses and the yields obtained for **1a**.

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(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(14) The yield has not been optimized; in particular, we believe that the amount of **3a** could very likely be reduced by more rigorous drying of the solvents and reagents.