Ryanoids and related compounds — Chemoselective electrocatalytic hydrogenation of alkyl α-pyrrole carboxylates: Selective hydrogenation of ryanodine

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Abstract: A study of the electrocatalytic hydrogenation (ECH) process of pyrrole and different alkyl pyrrole-2-carboxylates is presented. Once hydrogenated, the alkyl pyrrole-2-carboxylate becomes an ester of proline, an important natural amino acid. The process is chemoselective to the pyrrole ring. Ryanodine is a natural ryanoid known to be biologically active. The tetrahydroryanodine derivative thus obtained may now represent a molecule of high biological interest. The hydrogenation of ryanodine is possible with electrocatalytic and catalytic processes. In both cases the reaction is not diastereoselective.

Key words: electrocatalytic hydrogenation, proline esters, ryanodine, tetrahydroryanodine.

Résumé : Une étude sur l'hydrogénation électrocatalytique (HEC) du pyrrole et de quelques esters de l'acide pyrrole-2-carboxylique est présentée. Une fois hydrogéné, le pyrrole-2-carboxylate d'alkyle devient un ester de la proline, un acide aminé naturel important. Le procédé est chimiosélectif au cycle pyrrole. La ryanodine est un ryanoïde connu pour son activité biologique. Le dérivé tétrahydroryanodine ainsi obtenu peut maintenant présenter un grand intérêt biologique. L'hydrogénation de la ryanodine est possible par le procédé électrocatalytique et catalytique. Dans les deux cas, la réaction n'est pas diastéréosélective.

Mots clés: hydrogénation électrocatalytique, esters de proline, ryanodine, tétrahydroryanodine.

Introduction

Ryanodine (Fig. 1) is a natural ryanoid extracted from the plant *Ryania speciosa*. This molecule is known to be a potent modulator of the sarcoplasmic reticulum calcium release channel (1). The interesting functional group of ryanodine in the present study is the aromatic pyrrole ring attached to the main polycyclic structure (ryanodol) by an ester function. Once hydrogenated, this heterocycle becomes an ester of proline, a natural amino acid. This tetrahydroryanodine derivative may now represent a molecule of high biological interest. Theoretically, removal of the pyrrole moiety and then esterification of the free hydroxyl group in position 3 with proline could lead to the desired compound, but in fact it has been shown that specific esterification at this endo hydroxyl group is not possible (1*c* and references therein).

We began the present study with simple molecules like pyrrole (**1**), pyrrole-2-carboxylic acid (**3A**), and its methyl (**3B**), ethyl (**3C**), and isopropyl (**3D**) esters (Fig. 1). All these molecules have a pyrrole ring and, except for pyrrole and pyrrole-2-carboxylic acid, an ester group, as seen in ryanodine. With these simple molecules we determined the best conditions (electrocatalyst and electrolyte) for the electrocatalytic hydrogenation (ECH) process of ryanodine.

The ECH process is achieved at room temperature and atmospheric pressure, unlike most of the classical catalytic hydrogenation methods. The classical process often requires a high pressure of hydrogen to reduce an aromatic pyrrole ring (2, 3). Recently, a pressure of 20 bar (1 bar = 10^5 Pa) was used to hydrogenate a compound with a pyrrole ring (4). Previous works in our laboratory used the ECH of phenol, cyclohexanone, and 2-cyclohexen-1-one to develop new electrocatalysts (5–7). The ECH of alkyl pyrrole-2-carboxylate molecules proceeds in acidic medium to prevent the poisoning of the catalyst by pyrrole or its derivatives (8, 9)

The ECH mechanism can be explained by the equations presented in Fig. 2. The electrocatalysts used in an ECH are constituted of a metallic part (M) and an adsorbent part (A). In the first step there is an electroadsorption of hydrogen atoms on the metallic part resulting from the reduction of water (eq. [1]). The alkyl pyrrole-2-carboxylate compound is adsorbed by the adsorbent of the electrocatalyst (eq. [2]). The hydrogenation is possible when the site of adsorption of the molecule is near to the electroadsorbed hydrogen (eq. [3]); this site is called the "triple point" (5). After saturation of the ring, the hydrogenated molecule is liberated by

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Fig. 1. Simple alkyl pyrrole-2-carboxylates and their hydrogenated products, ryanodine and anhydroryanodine.

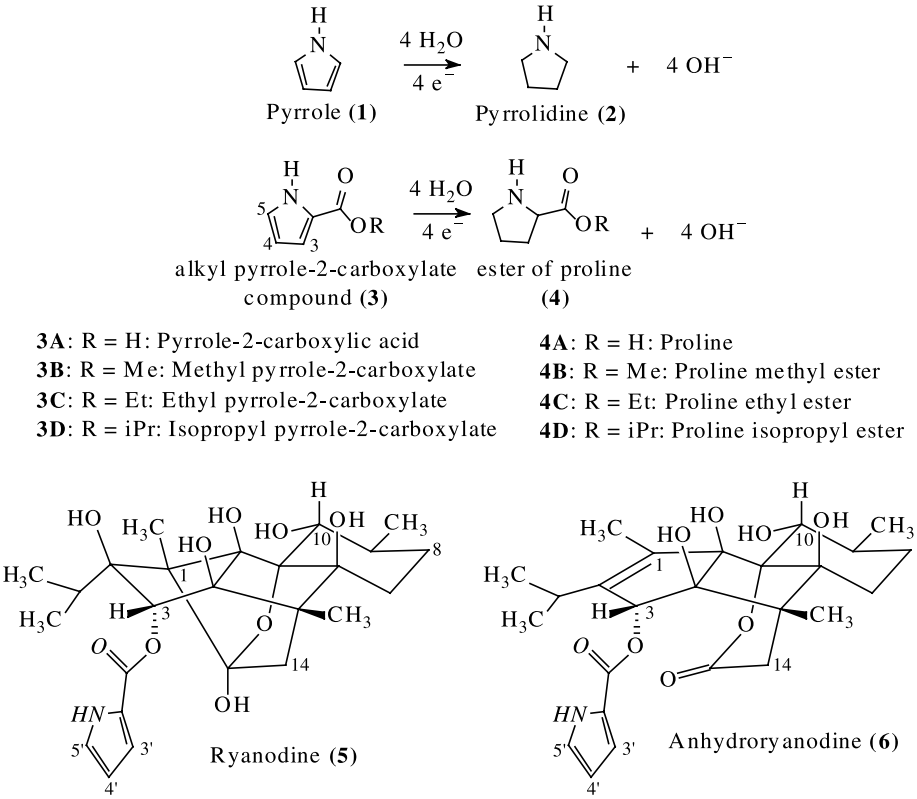
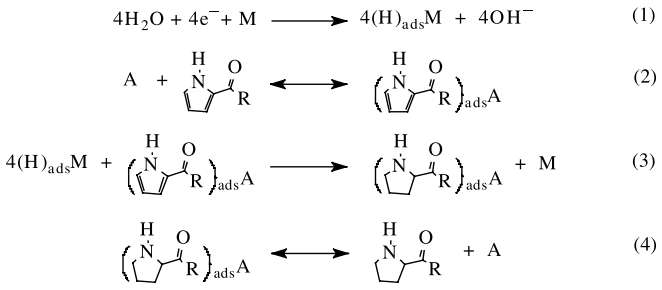


Fig. 2. The electrocatalytic hydrogenation (ECH) mechanism of alkyl pyrrole-2-carboxylate compound.



the adsorbent (eq. [4]). These equations represent the global hydrogenation process of the alkyl pyrrole-2-carboxylate compounds.

Experimental section

Melting points were recorded on a Melter Toledo FP62 hot stage apparatus and are uncorrected. Mass spectra (MS) and peak matching (HR-MS) data were determined at 70 eV on a VG Micromass ZAB-1F spectrometer. The ^{1}H (300 MHz) NMR spectra were recorded on a Bruker AC-300 instrument with CD_2HOD as internal standard centered at 3.30. The usual standard abbreviations have been used to indicate the multiplicity of the proton signals. Column chromatography (flash) was performed with Merck silica gel (200–400 mesh). All the electrocatalysts (5% Pd/Al_2O_3, 5% Pt/Al_2O_3, 5% Rh/Al_2O_3, and 5% Rh/C) were purchased from Sigma-Aldrich. The solvents used for chromatography were HPLC grade. The electrolyte solutions were made with deionized water.

Starting materials

Pyrrole-2-carboxylic acid and pyrrole were purchased from Sigma-Aldrich. Commercial pyrrole was distilled before use. Compounds **3B**, **3C**, and **3D** were synthesized by the following procedure: a solution of *N*,*N*′-dicyclohexylcarbodiimide (4 g, 19 mmol) in distilled CH_2Cl_2 (10 mL) was transferred (cannula) to a solution of pyrrole-2-carboxylic acid (1.9 g, 17 mmol) dissolved in 25 mL of the corresponding alcohol used as solvent (methanol for **3B**, ethanol for **3C**, and isopropanol for **3D**). After the addition of 100 mg of 4-dimethylaminopyridine, the mixture was stirred for 12 h at ambient temperature and under an inert atmosphere. The mixture was filtered on silica gel (40% EtOAc – 60% hexane) before purification by flash chromatography to give esters **3B**, **3C**, and **3D** in 90% yield.

Methyl pyrrole-2-carboxylate (3B)

White crystalline solid; mp 71°C (lit. (10) value mp 72–73°C). ^{1}H NMR (CD_3OD) (ppm): 6.95 (m, 1H, HC5), 6.84 (m, 1H, HC3), 6.18 (m, 1H, HC4), 3.80 (s, 3H, O-CH_3). MS *m/e*: 125 ([M]$^+$). HR-MS calcd. for $C_6H_7NO_2$: 125.0477; found: 125.0474.

Ethyl pyrrole-2-carboxylate (3C)

Beige solid; mp 38°C (lit. (11) value mp 40–42°C). ^{1}H NMR (CD_3OD) (ppm): 6.94 (m, 1H, HC5), 6.84 (m, 1H, HC3), 6.17 (m, 1H, HC4), 4.27 (q, 7.1 Hz, 2H, O-CH_2-CH_3), 1.33

(t, 7.1 Hz, 3H, O-CH_2-CH_3). MS *m/e*: 139 ($[M]^+$). HR-MS calcd. for $C_7H_9NO_2$: 139.0633; found: 139.0627.

Isopropyl pyrrole-2-carboxylate (3D)

White solid; mp 41°C. ^{1}H NMR (CD_3OD) (ppm): 6.93 (m, 1H, HC5), 6.82 (m, 1H, HC3), 6.16 (m, 1H, HC4), 5.12 (h, 6.3 Hz, 1H, O-CH-$(CH_3)_2$), 1.31 (d, 6.3 Hz, 6H, O-CH-$(CH_3)_2$). MS *m/e*: 153 ($[M]^+$). HR-MS calcd. for $C_8H_{11}NO_2$: 153.0790; found: 153.0793.

Ryanodine used in the study was purified by a known procedure (1).

Hydrogenated products

All the products obtained by ECH were characterized by ^{1}H NMR and a comparison with authentic samples was done. Pyrrolidine, proline, and proline methyl ester hydrochloride (**4B**) were purchased from Sigma-Aldrich.

Proline ethyl ester hydrochloride (4C)

This material was prepared by a very slow addition of $SOCl_2$ (300 µL, 3.6 mmol) to a solution of proline (244 mg, 2.1 mmol) in ethanol (6 mL) following a known method (12). The mixture was kept at 0°C during the addition. After 5 h, the solvent was evaporated to leave a pure product, an amorphous beige solid (mp 55°C) (99%). ^{1}H NMR (CD_3OD) (ppm): 4.42 (m, 1H, HC2), 4.30 (q, 7.1 Hz, 2H, O-CH_2-CH_3), 3.38 (m, 2H, H_2C5), 2.42 (m, 1H, H_AC3), 2.12 (m, 3H, H_BC3, H_2C4), 1.32 (t, 3H, O-CH_2-CH_3). MS *m/e*: 143 ($[M]^+$). HR-MS calcd. for $C_7H_{13}NO_2$: 143.0946; found: 143.0950.

Proline isopropyl ester hydrochloride (4D)

Synthesis of proline isopropyl ester hydrochloride (4D) was prepared by the previous procedure using isopropanol (99%). The product obtained was a yellowish oil. ^{1}H NMR (CD_3OD) (ppm): 5.12 (h, 6.2 Hz, 1H, O-CH-$(CH_3)_2$), 4.35 (m, 1H, HC2), 3.35 (m, 2H, H_2C5), 2.40 (m, 1H, H_AC3), 2.05 (m, 3H, H_BC3, H_2C4), 1.30 and 1.31 (two d, 6.3 Hz, 6H, O-CH-$(CH_3)_2$). MS *m/e*: 157 ($[M]^+$). HR-MS calcd. for $C_8H_{15}NO_2$: 157.1103; found: 157.1098.

Electrolysis

The electrolysis was carried out in a two-compartment jacketed glass H-cell having a Nafion-324 (E.I. Dupont de Nemours & Co.) membrane as separator. The cell temperature was fixed at 21°C during the ECH by a circulating thermostated bath (VWR 1160A). The working electrode was a reticulous vitreous carbon (RVC) foam (25 × 20 × 6 mm, 80 pores per inch (ppi; 1 inch = 25.4 mm), Electrosynthesis Co.). The electrode was mounted by inserting a glass rod (o.d. 5–6 mm, i.d. 3.5 mm) in the horizontal axis of the piece of RVC. The excess RVC was then removed and a copper wire was inserted into the RVC to be further cemented with silver epoxy (Epoxy Technology). Finally, the electrical contact zone on the RVC matrix was fixed to the glass rod with epoxy to isolate the electrical contact from the electroactive part of the electrode (5).

Both compartments were filled with the 0.1 M NaCl solution whose pH was adjusted to 1.2 with concentrated HCl. The ECH process occurred in the cathodic compartment (filled with 24 mL of the electrolyte) containing the working electrode and the electrocatalyst (200 mg). A platinum counter electrode was used in the anodic compartment. Mechanical stirring was applied during the ECH. When another electrolyte was used, the anodic compartment was filled with 2 M NaOH (5). A constant current of 5 mA was applied during the electrolysis. After passing 50 C of electricity to condition the working electrode, a solution of 0.6 M of starting material in methanol (1.0 mL) was added to the cathodic compartment.

The electrical charge passed through the system was noted in Faraday equivalents. A Faraday equivalent is the minimal amount of electrical charge needed to hydrogenate all the starting material in the cell. The equivalent charge can be calculated by the multiplication of the quantity of starting material by the number of electrons required to complete the reaction and by the Faraday constant (96 485 C per mole of electrons). Thus, 1 Faraday equivalent for 0.6 mmol of a simple alkyl pyrrole-2-carboxylate compound is 232 C, and 1 Faraday equivalent for 0.08 mmol ryanodine is 32 C.

Analysis

The hydrogenation process was tracked by monitoring the consumption of the starting material according to the Faraday equivalent. Aliquots of 500 µL were collected in the cathodic compartment during the ECH and analysed by HPLC (ZORBAX Eclipse XDB-C8 column (4.6 mm (i.d.) × 150 mm)) with an isocratic elution (40% acetonitrile – 60% water). Before the HPLC analysis, the aliquots were filtered on a 0.2 µm syringe filter. The HPLC system was an Agilent 1100 Series. A diode array detector performed the data acquisition. The wavelength was set to 265 nm for **3A**, **3B**, **3C**, and ryanodine; 280 nm for **3D**; and 207 nm for pyrrole.

Recovery of the hydrogenated products

The recovery of the hydrogenated simple alkyl pyrrole-2-carboxylate molecules, except pyrrolidine, was achieved by first evaporating water from the solution on a rotatory evaporator after filtration to remove the electrocatalyst. The product was then recovered by trituration with distilled chloroform. For pyrrolidine, the solution was saturated with K_3PO_4 to adjust the pH to 12. Pyrrolidine was extracted with ether (15 mL). The combined organic phases were dried (Na_2SO_4) and analysed by GC (HP-5890 with DB-1 column (30 m × 0.25 mm (i.d.), J&W Scientific)).

The product obtained after the hydrogenation of ryanodine was recovered with a C-18 SPE cartridge. The pH of the solution was adjusted to 8 for the elution. Distilled methanol was used to recover the product from the cartridge.

Results and discussion

Influence of the electrocatalyst

Figure 3 shows the evolution of the ECH process of **3B** (in 0.1 M NaCl at pH = 1.2 as the electrolyte (saline solution)) with the use of different electrocatalysts. The best results were obtained with the 5% Rh/Al_2O_3 electrocatalyst. The other electrocatalysts (5% Pd/Al_2O_3 and 5% Pt/Al_2O_3) allowed for only a 35% reduction of the starting material for the same Faraday equivalent. These results are consistent with the literature (2–4, 8, 9) where rhodium is the metal that is most effective in the hydrogenation of a pyrrole ring

Fig. 3. The influence of the electrocatalyst on the ECH of methyl pyrrole-2-carboxylate (**3B**) in saline solution.

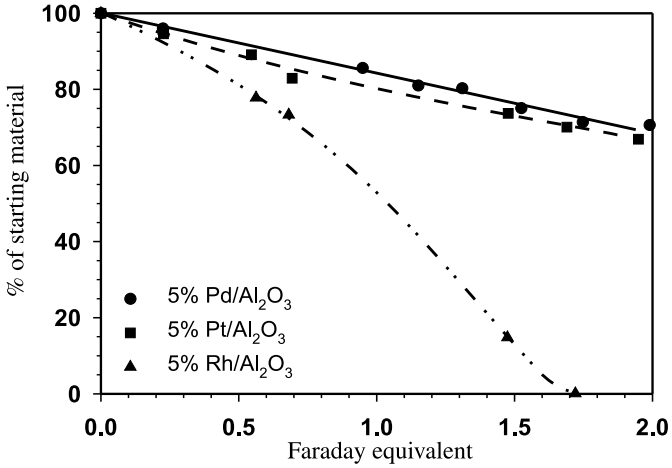


Fig. 4. The ECH process of the simple alkyl pyrrole-2-carboxylate molecules with 5% Rh/Al_2O_3 electrocatalyst and saline solution.

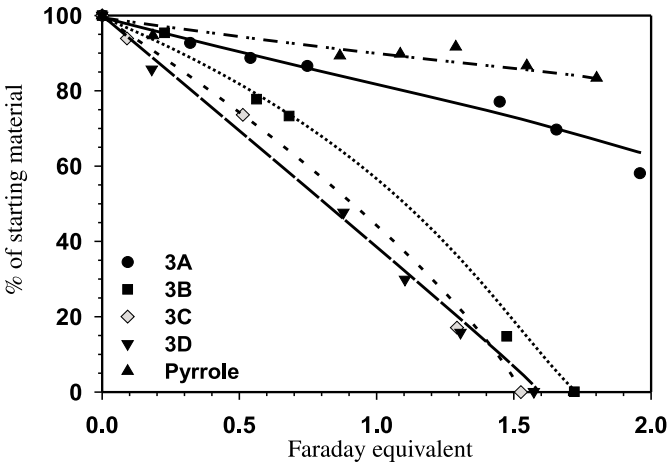


Table 1. The ECH process of ethyl pyrrole-2-carboxylate (**3C**) with 5% Rh/Al_2O_3 electrocatalyst and different electrolytes.

Electrolyte	Faraday equivalent	% of **3C**[a]
Methanol solution	1.5	69
Saline solution	1.5	0
Borate solution	1.5	0
Phosphate solution	1.5	0

[a]Percentage of ethyl pyrrole-2-carboxylate (**3C**) remaining at the indicated Faraday equivalent.

Table 2. The ECH process of pyrrole and pyrrole-2-carboxylic acid (**3A**) according the electrolyte (saline or phosphate solution) with 5% Rh/Al_2O_3 electrocatalyst.

Starting material	Electrolyte	Faraday equivalent	% of SM[a]
Pyrrole	Saline solution	2.7	81
Pyrrole	Phosphate solution	1.3	0
3A	Saline solution	2.0	58
3A	Phosphate solution	1.4	0

[a]Percentage of starting material (SM) remaining at the indicated Faraday equivalent.

compound in classical catalytic hydrogenation. The stability of the metal in the electrolyte is critical: rhodium and platinum electrocatalysts are resistant to acidic conditions but palladium was observed to dissolve in these conditions. The rhodium electrocatalyst was used for the remainder of the experiment.

Influence of the electrolyte

Several types of electrolyte were tested: phosphate solution (1 M KH_2PO_4 – 1 M NaOH; pH = 7.0), borate solution (0.1 M NaCl – 0.05 M boric acid; pH = 2.5), aqueous methanol solution (0.1 M NaCl in 5% H_2O – MeOH), and saline solution (0.1 M NaCl; pH = 1.2).

A limiting factor in the choice of the electrolyte is its pH. A high pH results in hydrolysis of the ester group of the starting material, giving the pyrrole-2-carboxylic acid and the alcohol residue (ryanodol for ryanodine). At low pH (pH < 0), ryanodine loses water through an important cleavage of the diterpenic skeleton leading to the anhydro series (anhydroryanodine (**6**)) (1).

An ECH of **3C** was performed with each electrolyte, using 5% Rh/Al_2O_3 as the electrocatalyst. The results are shown in Table 1. Aqueous methanol solution was shown to be a relatively poor electrolyte for the reaction. These results suggest a modification in quality of adsorption of the pyrrole ring onto the electrocatalyst (eq. [2]) due to the different solvents used.

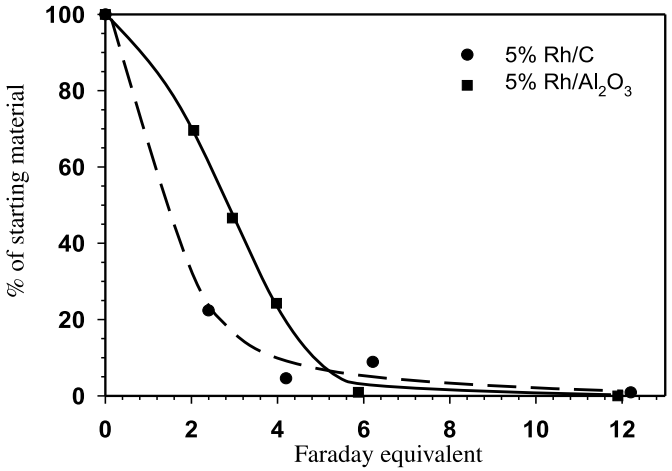
The results for the other electrolytes were approximately similar. The difference between them is the stability of the hydrogenated product and its recovery. The hydrogenated products are not stable in the phosphate solution: hydrolysis is rapid, leading to proline, not to ester. The recovery of the hydrogenated product with this electrolyte is also quite difficult owing to the presence of the phosphate salts. All the alkyl pyrrole-2-carboxylate molecules used in this study are stable in this electrolyte. We did not use boric acid (borate solution) in the case of ryanodine owing to the formation of a complex between boric acid and the numerous hydroxyl groups of the molecule (1*c*).

The best electrolyte was the saline solution, and we obtained the best recovery of hydrogenated products with this electrolyte. The ECH process of pyrrole and pyrrole-2-carboxylic acid were more effective with the phosphate solution than with the saline solution (Table 2). These results suggest that the adsorption of the molecule on the electrocatalyst is influenced by the nature and the pH of the electrolyte.

ECH process of the simple alkyl pyrrole-2-carboxylate molecules

Figure 4 shows the ECH of the different alkyl pyrrole-2-carboxylate molecules under the same conditions (5% Rh/Al_2O_3 and saline solution). We can see that the rate of hydrogenation of pyrrole and pyrrole-2-carboxylic acid is very different from that of the other molecules, as mentioned before. The complete ECH of **3B**, **3C**, and **3D** was achieved using from 1.5 to 1.7 Faraday equivalents. Thus, we can

Fig. 5. The ECH process of ryanodine with two different electrocatalysts (5% Rh/Al_2O_3 and 5% Rh/C) in saline solution.



suppose that the differences between these molecules are not large enough to have a significant influence on the ECH process.

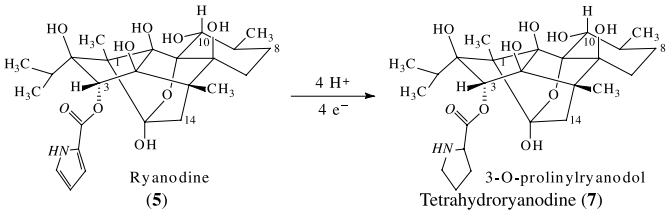
Even if the hydrogenation was shown to be complete, we did not succeed in recovering all of the hydrogenated product. With the techniques used, in the best case, we were able to recover only 59% of the hydrogenated product of **3C** (proline ethyl ester (**4C**)). We recovered 75% of the hydrogenated product of **3B** (proline methyl ester (**4B**)) and 87% of the hydrogenated product of **3D** (proline isopropyl ester (**4D**)). The recovery of the hydrogenated pyrrole-2-carboxylic acid (proline) was difficult owing to the phosphate salts (ECH with phosphate electrolyte). We recovered, in the best case, only 28% of proline. The yield of recovery of pyrrolidine is quite difficult to determine owing to its great volatility. The purity of recovered pyrrolidine was evaluated by GC to be 95%. The SPE technique cannot be used to recover the hydrogenated product of the simple alkyl pyrrole-2-carboxylate molecules.

ECH process of ryanodine

The results of the ECH of ryanodine are presented in Fig. 5. The ECH was attempted with two electrocatalysts, 5% Rh/Al_2O_3 and 5% Rh/C (activated charcoal). With ryanodine more Faraday equivalents are needed to hydrogenate the totality of the starting material owing to the greater dilution (3.2 mM of ryanodine vs. 24 mM for a simple alkyl pyrrole-2-carboxylate molecule). The ECH process with 5% Rh/C electrocatalyst seems to be faster than with 5% Rh/Al_2O_3, but there is stronger adsorption of the hydrogenated product. With 5% Rh/C, we recovered only 7% of the hydrogenated ryanodine vs. 73% with 5% Rh/Al_2O_3 electrocatalyst.

Tetrahydroryanodine (**7**) (hydrogenated ryanodine) (Fig. 6) can be identified by ^1H NMR spectroscopy. The proton supporting the proline moiety (HC(3)) appears at a different position for each diastereomers (D or L). The ^1H NMR spectrum of hydrogenated ryanodine shows an equal amount of the two diastereomers. This reveals the equal accessibility of both sides of the pyrrole ring. These epimers are invisible

Fig. 6. Electrocatalytic hydrogenation of ryanodine.



under UV and are very close in polarity; we did not attempt to separate them.

Tetrahydroryanodine (3-O-prolinylryanodol) (7)

White solid. ^1H NMR (CD_3OD) (ppm): 5.55 and 5.58 (2 × s, 1H, HC3), 3.77 (d, 1H, 10.2 Hz, HC10), 3.73 (m, 1H, HC2′), 3.06 (m, 1H, H_AC5'), 2.86 (m, 1H, H_BC5'), 2.33 (m, 1H, H_AC14), 2.25–2.00 (m, 3H, HC3′, HC13 and $H_{ax}C7$), 2.00–1.70 (m, 5H, HC3′, H_2C4', HC9 and H_BC14), 1.59–1.49 (m, 2H, $H_{eq}C7$ and $H_{ax}C8$), 1.36 (s, 3H, CH_3(C1)), 1.30–1.25 (m, 1H, $H_{eq}C8$), 1.10 (d, 3H, CH_3(C18)), 1.02 (d, 3H, CH_3(C9)), 0.98 (d, 3H, CH_3(C5)), 0.75 (2d, 3H, CH_3(C19)). MS *m/e*: 498 ($[MH]^+$). HR-MS calcd. for $C_{25}H_{40}NO_9$: 498.2703; found: 498.2706.

Catalytic hydrogenation of ryanodine

To our knowledge, the pyrrole ring of ryanodine has never been reduced by a classical catalytic hydrogenation. In our experiments, palladium and platinum catalysts over different supports were not effective in reducing the aromatic ring at atmospheric pressure. The electrocatalytic hydrogenation gave us excellent results. The classical catalytic hydrogenation with 5% Rh/Al_2O_3 in methanol allowed for only 33% hydrogenation of ryanodine after 4 days. When the saline solution (0.1 M NaCl; pH = 1.2) and the same catalyst were used in classical hydrogenation, the reaction was completed after 6 to 12 h. These results can be explained by the difference of adsorption of ryanodine onto the catalyst according to the solvent used. The quantity of solvent, catalyst, and starting material were the same as for the ECH process. All the classical catalytic hydrogenation experiments of this study were done at atmospheric pressure.

Conclusion

The hydrogenation of an alkyl pyrrole-2-carboxylate compound is possible using an electrocatalytic hydrogenation (ECH) process. We have shown that the hydrogenation reaction is specific to the pyrrole ring of alkyl pyrrole-2-carboxylate and does not modify the ester function of the molecule. The ECH of **3B**, **3C**, and **3D** was found to be most effective with rhodium electrocatalyst (5% Rh/Al_2O_3) in saline solution (0.1 M NaCl at pH = 1.2). Pyrrole and pyrrole-2-carboxylic acid ECH gave better results in phosphate solution (1 M KH_2PO_4 – 1 M NaOH; pH = 7.0). All the simple alkyl pyrrole-2-carboxylate compounds were totally hydrogenated after the passage of 1.7 Faraday equivalents of electrical charge.

The ECH process can be used to hydrogenate a complex molecule like ryanodine. Once again, the hydrogenation was complete but there was no diastereoselection in the formation of the reduced compound because of easy access of hydrogen to both sides of the pyrrole ring. The hydrogenation of ryanodine proves that the ECH process can be used efficiently in the selective modification of complex molecules. The biological activity of the new tetrahydroryanodines is currently under study by W. Welch, University of Nevada at Reno, Nevada.

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