Electrochemical N-Demethylation of 14-Hydroxy Morphinans – Sustainable Access towards Opioid Antagonists

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The growing demand for opioid antagonists necessitates the development of more efficient and affordable synthetic routes. The most challenging step in the preparation of these essential medicines is the selective N-demethylation of a 14-hydroxy opioid precursor to the corresponding nor-opioid, which is followed by N-alkylation of the resulting secondary amine. This process is carried out on large scales using stoichiometric amounts of hazardous chemicals like cyanogen bromide or chloroformates. We have developed a mild, reagent- and catalyst-free procedure for the N-demethylation step, based on the anodic oxidation of the tertiary amine. The ensuing iminium cation rapidly undergoes cyclization with the 14-hydroxy group, or acyl transfer from its acetylated derivative, resulting in intermediates that can be readily hydrolyzed to the target nor-opioids. The electrochemical method provides excellent yields and has successfully been transferred to a flow electrolysis cell, thus enabling the potential scale-up of this synthetic strategy.

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Abstract: The growing demand for opioid antagonists necessitates the development of more efficient and affordable synthetic routes. The most challenging step in the preparation of these essential medicines is the selective N-demethylation of a 14-hydroxy opioid precursor to the corresponding nor-opioid, which is followed by N-alkylation of the resulting secondary amine. This process is carried out on large scales using stoichiometric amounts of hazardous chemicals like cyanogen bromide or chloroformates. We have developed a mild, reagent- and catalyst-free procedure for the N-demethylation step, based on the anodic oxidation of the tertiary amine. The ensuing iminium cation rapidly undergoes cyclization with the 14-hydroxy group, or acyl transfer from its acylated derivative, resulting in intermediates that can be readily hydrolyzed to the target nor-opioids. The electrochemical method provides excellent yields and has successfully been transferred to a flow electrolysis cell, thus enabling the potential scale-up of this synthetic strategy.

The ongoing opioids crisis, which is causing nearly a thousand overdose-related deaths per week in the US, has dramatically increased the demand for opioid antagonists like naloxone or naltrexone. The need of these lifesaving antidotes for drug overdose treatment has, unfortunately, also led to a significant rise in their price, which reduces their availability to less favored communities. Decreasing the cost of production for opioid antagonists via more efficient synthetic routes is therefore highly desired and a very active field of research. The most challenging step in the preparation of these 14-hydroxy morphinans is the selective removal of the N-methyl group from the relatively complex morphine precursor (Figure 1A). The resulting nor-derivative (i.e., the ensuing secondary amine) is a key intermediate from which a range of essential medicines, including naloxone or naltrexone, can be synthetized by simple re-alkylation with the corresponding alkyl bromide. The N-demethylation process is currently carried out using excess amounts of harmful electrophilic reagents like cyanogen bromide (via the von Braun reaction) or chloroalkyl formates. The combination of stoichiometric amounts of peroxides and acylating agents (classical Polonovsky reaction) or metal reductants (non-classical Polonovsky reaction) has also been applied. Not surprisingly, more benign alternatives have been actively investigated during the past two decades, including palladium catalyzed and photochemical aerobic oxidations as well as chemoenzymatic procedures. However, these methods have not been adopted by industry.

Notably, all N-demethylation reactions mentioned above entail either an oxidation of the N-CH₃ group or withdrawal of the nitrogen electron pair by an electrophilic reagent to initiate the demethylation process. Indeed, iminium cation intermediates have been invoked for the palladium catalyzed and photochemical routes as well as for the non-classical Polonovsky reaction. We hypothesized that, under suitable electrochemical conditions, the N-methyl group could be anodically oxidized to the corresponding iminium cation in a 2-electron process. Trapping of the iminium radical by the 14-hydroxy group or acyl transfer from the same position would generate intermediates that can be readily hydrolyzed to the target nor-derivative (Figure 1C). This electrochemical strategy would not require any external oxidant and, ideally, could be carried out in benign solvents under mild conditions, delivering a highly convenient, sustainable and inexpensive N-demethylation methodology.

Supporting Information for this article is available online.

Figure 1. Importance and strategies for the N-demethylation of 14-hydroxy opioids for the preparation of overdose antidotes.
aromatic ring can cause undesired oxidations leading to the formation of biaryl dimers.\(^{14}\) Analogous voltammograms were obtained for both compounds. The oxidation of the amine was observed at ca. \(E_{\text{pa}} = 1.1\) V vs SCE, following the typical irreversible pattern for tertiary amines.\(^{15}\) The second oxidation peak, corresponding to the oxidation of the aromatic ring, appeared at \(E_{\text{pa}} = 1.6\) V vs SCE. In this case, reversibility of the electron transfer could be observed by increasing the scan rate (Figure S1), indicating a relatively slow degradation (i.e., dimerization) of the oxidized species at the low concentrations utilized for the recording of the voltammograms. Most notably, the difference in oxidation potentials between the two moieties (ca. 0.5 V) pointed to a selective reaction, probably even under galvanostatic conditions.

An initial screening of the reaction conditions was carried out using as model the electrolysis of oxycodone (1a), which was expected to provide oxazolidine 2a upon formation of an iminium cation (Figure 2B).\(^{16}\) All reactions were performed in an undivided cell at room temperature. To our delight, the first attempt using graphite as the anode and stainless steel as the cathode material in acetonitrile, using LiClO\(_4\) as the supporting electrolyte, provided 29% conversion to 2a and very good selectivity (Figure 2B, entry 1). The main side products observed were the expected biaryl dimers (see Figure S3).\(^{14}\) Dimerization can take place both for the starting oxycodone (1a) and the oxazolidine electrolysis product (2a), and thus generation of small amounts of dimers at a late stage of the reaction was expected. A screen of several solvent systems and supporting electrolytes (entries 2-8) revealed that utilization of quaternary ammonium salts had a significant beneficial influence on the reaction (entries 2-3). The poorer performance of the lithium salt could be ascribed to the formation of a complex with the tertiary amine.\(^{17}\) As expected, addition of protic solvents had a positive effect, providing a source of protons for the concurrent cathodic reduction. Utilization of pure methanol as solvent resulted in a lower conversion (entry 5), a 4:1 combination of aprotic solvents being the best solvent system (entry 8). Several electrode materials were also evaluated (see Table S1 in the Supporting Information). None of the electrode combinations provided significant improvements with respect to graphite/stainless steel, and therefore the initial electrode materials were selected due to their lower cost. Indeed, utilization of platinum as anode material, for example, resulted in lower conversion under otherwise identical conditions (entry 8 vs 9).

Excellent results were achieved by applying a 20% excess of electricity (2.4 F/mol) under a current of 5 mA in MeCN/MeOH with Et\(_4\)NBF\(_4\) as the supporting electrolyte (entry 10).

With the optimal conditions in hand, several key 14-hydroxy and 14-acytetyl opioid precursors were electrolyzed, leading to cyclization to oxazolidines or O,N-acyl transfer, respectively (Figure 3A). The optimal reaction parameters were directly utilized without further re-optimization. The very good conversions and selectivities obtained for all cases enabled a simple work-up procedure entailing evaporation of solvent followed by purification by short-path column chromatography over neutral alumina. In addition to oxycodone (1a) and O-acytetyl oxycodone (1b), O-acytetyl codeine (1c) was also successfully subjected to the electrochemical oxidation, resulting in a highly selective O,N-acyl transfer (vide infra).\(^{10e}\)

Opioid antagonists such as naloxone or naltrexone generally feature a 3-hydroxy group (cf. Figure 1), which is generated by O-demethylation of the naturally occurring 3-methoxy opiates, either at an early\(^{18}\) or late\(^{18}\) stage of the synthetic route. The presence of phenols is particularly problematic during anodic oxidations due to their relatively low oxidation potentials.\(^{15}\) Indeed, cyclic voltammograms of 3,14-dihydroxy opioids typically shows product degradation starting at ca. 0.6 V vs SCE.\(^{20}\) Gratifyingly, selective electrochemical N-demethylation of 14-hydroxymorphinone was enabled by first generating its 3,14-O-diacytetyl derivative (1d) (Figure 3A). Cyclic voltammograms of the opioid precursor and the diacytetyl derivative showed a clear differentiation between the amine and aryl oxidation peaks upon protection, pointing to a selective electrochemical reaction (see Figure S2). Indeed, electrochemical N-demethylationt acyl transfer under the optimal conditions resulted in 2d in 78% isolated yield. Notably, this compound can be easily transformed to noroxymorphone by acidic workup.\(^{10e}\)
In order to improve the scalability of our electrochemical protocol, the reaction was transferred to a flow electrolysis cell, using as model the electrolysis of oxycodone (1a) (Figure 3B). The flow cell consisted of a parallel plate arrangement, with the two electrodes separated by a 0.3 mm chemically resistant Mylar film incorporating a reaction channel (the flow electrolysis cell is described in detail in the Supporting Information). The contact surface area between the electrodes and the solution was 6.4 cm². The reaction mixture was pumped through the cell using a syringe pump and recirculated at a flow rate of 2 mL/min until the desired amount of charge had been passed. Using an identical reaction mixture as in batch mode, and a current of 10 mA, the outcome of the reaction was analogous. Nearly identical conversion and selectivity to the oxazolidine intermediate as in batch was obtained. It is worth noting that direct treatment of the crude electrolysis reaction mixture with HCl delivered the target nor-derivative 3a in 75% overall isolated yield. Furthermore, it should be mentioned that no inert atmosphere or anhydrous solvents were required to perform this transformation. This N-demethylation, that generally is executed using rather hazardous reagents in stoichiometric quantities (cf. Figure 1B), here is driven simply by electricity via inexpensive electrode materials and producing hydrogen as byproduct.

The proposed mechanism for the reaction (Figure 4A) starts with a 2-electron oxidation of the tertiary amine with release of one proton, generating the key iminium cation intermediate. In the case of the 14-hydroxy opioids, rapid intramolecular 1,5-cyclization, with release of a second proton, generates the oxazolidine intermediate. The two protons released during the process are reduced at the cathode, producing hydrogen gas. Thus, no net amount of base is generated during the electrolysis, which may have a negative influence on selectivity. In the case of the O-acetyl protected derivatives, with no hydroxy group available for an intramolecular cyclization, the iminium cation intermediate is trapped by the methanol present as co-solvent. The resulting N,O-acetal intermediate reacts with a second molecule of methanol, releasing the N-methyl carbonate via a cyclic intermediate. Alternatively, release of dimethoxymethane may directly provide the free secondary amine, which then undergoes rapid O,N-acyl transfer. This acyl transfer mechanism is analogous to the pathway proposed by Hudlicky for palladium-promoted acyl transfer reactions.10c
To gain further insights into the reaction mechanism, several experiments were performed. The kinetic isotope effect (KIE) was evaluated using oxycodone-D₃ (1a-d₃), in a parallel single-component experiment (Figure 4B). A modest KIE (k_H/k_D = 1.5) was observed. This observation suggests that the second oxidation event, with the release of a proton, is the rate-determining step of the reaction. This KIE value is in agreement with a proton-coupled electron transfer (PCET) in which the proton donor is close to the acceptor (the solvent in this case). Moreover, the intermediacy of the iminium cation could be confirmed by its trapping with cyanide and diphenylamine (Figure 4C). This was achieved by generating the iminium ion in a "cation pool" at -45 °C using a divided cell (lower temperatures could not be reached in acetonitrile as the solvent) and adding the nucleophile after the electricity had been turned off (see Supporting Information for details). The trapping products were obtained in low amounts, indicating that the temperature was not sufficiently low to permit accumulation of the cation for an extended period of time. To ensure that the observed products were the result of trapping of the iminium cation and not of ring-opening of the oxazolidine, the latter was treated with excess amounts of the nucleophilic reagents. No reaction was observed. Finally, direct observation of the iminium ion by infrared spectroscopy was also attempted, again using the "cation pool" methodology (Figure 4D). In this case an FTIR probe was immersed in the anodic chamber of the divided cell. Oxycodone derivative 6-oxydol (1e), with the ketone group reduced to an alcohol, was used as substrate to eliminate interference of the carbonyl signal from the IR. Gratifyingly, under electrolysis, a weak peak appeared at ca. 1657 cm⁻¹ which could be ascribed to the C=N stretch of the intermediate. The weak signal observed supported the hypothesis that the iminium cation is not sufficiently stable at -45 °C.

Figure 4. (A) Proposed mechanism for the electrochemical oxazolidination and demethylative O,N-acyl transfer of opioids and (B, C, D) experiments carried out to gain mechanistic insights.

In summary, we have designed a catalyst and reagent free electrochemical methodology for the N-demethylation of 14-hydroxy opioids, the crucial step in the synthesis of important opioid antagonists such as naloxone or naltrexone. The synthetic strategy is based on the 2-electron anodic oxidation of the tertiary amine, generating an iminium ion that rapidly undergoes intramolecular oxazolidination or demethylative O,N-acyl transfer. The procedure has been evaluated for several important opioid API precursors including oxycodone and 3,14-diacetylmorphinone. The protocol has been transferred to a flow electrolysis cell enabling its scale-up. Notably, the key nor-derivatives could be prepared in one-pot by simply adding hydrochloric acid to the crude electrolysis reaction mixture. This strategy avoids the use of stoichiometric amounts of hazardous electrophilic reagents and provides the target compounds in good yields.

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Keywords: opioid antagonists • N-demethylation • electrochemistry • iminium cations • sustainable chemistry
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Supporting Information

Electrochemical N-Demethylation of 14-Hydroxy Morphinans – Sustainable Access towards Opioid Antagonists

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General Information

$^1$H NMR spectra were recorded on a 300 MHz instrument. $^{13}$C NMR and $^{19}$F NMR spectra were recorded on the same instrument at 75 MHz and 282 MHz, respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 x 4.6 mm, particle size 5 mm) at 37 °C by using mobile phases A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 3% B to 100% B within 10 min. Tetrabutylammonium tetrafluoroborate (Code: 217964, Lot: BCBV1430), tetraethylammonium tetrafluoroborate (Code: 242144, Lot: BCBV4670) and lithium perchlorate (Code: 634565, Lot: 0000011388) were purchased from Aldrich. All other chemicals and solvents were obtained from standard commercial vendors and were used without any further purification. Batch electrochemical reactions were carried out in IKA ElectraSyn 2.0 vials utilizing standard Electrasyn electrodes.

HPLC Analysis – Sample Preparation

Many of the opioid starting materials and products in this work did not separate adequately in a C18 column (particularly the non-protected derivatives). Thus, a previously established$^{[51]}$ derivatization procedure was applied to aliquots of the reaction mixture for analysis: 50 µL of the crude reaction mixture and Ac$_2$O (200 µL) were added to a HPLC vial containing a saturated aqueous solution (1 mL) of NaHCO$_3$. The vial was capped, the septum perforated with a needle, and the mixture stirred vigorously at room temperature for 20 min. The content of the vial was then directly analyzed by HPLC–UV/Vis with the method described above in the General Information section. Peak area integration was carried out at 205 nm.
Preparation of Opioid Precursors

1. Synthesis of Oxycodone

14-Hydroxycodeinone. This compound was prepared according to a modified literature procedure.\textsuperscript{[S2]} In a 30 mL microwave vial equipped with a magnetic stir bar, thebaine (3.11 g, 10 mmol) was dissolved in 10 mL of formic acid under stirring. When the solid was fully dissolved (5-10 min stirring), the mixture was cooled to 5 °C using an ice/water bath. Then, 1.05 mL of 30% w/w H\textsubscript{2}O\textsubscript{2} (1.02 equiv) was added under stirring and the mixture was heated in a microwave reactor at 100°C for 7 min. The reaction mixture was cooled to room temperature using compressed air and then the solvent was evaporated under reduced pressure. The solid residue (which could be directly used for the next step) was dissolved in the minimum possible amount of saturated aqueous NaHCO\textsubscript{3} and extracted with CHCl\textsubscript{3} (3x 50 mL). The combined organic layers were dried over MgSO\textsubscript{4} and evaporated under reduced pressure, yielding the title compound as brown crystals (83%). M.p. 275 °C decomp. (lit.\textsuperscript{[S3]} 278 °C decomp).

\textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) \( \delta \) 6.89 (d, \( J = 10.1 \) Hz, 1H), 6.73 (d, \( J = 8.2 \) Hz, 1H), 6.64 (d, \( J = 8.2 \) Hz, 1H), 6.06 (d, \( J = 10.0 \) Hz, 1H), 5.34 (s, 1H), 4.71 (s, 1H), 3.72 (s, 3H), 3.23 – 3.03 (m, 2H), 2.43 (dt, \( J = 17.2, 5.5 \) Hz, 3H), 2.35 (s, 3H), 2.09 (td, \( J = 11.0, 10.3, 3.6 \) Hz, 1H), 1.43 (dd, \( J = 12.0, 3.0 \) Hz, 1H). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) \( \delta \) 194.4, 150.6, 143.7, 141.75, 132.7, 130.9, 125.9, 119.5, 114.2, 86.7, 67.5, 62.6, 56.0, 46.2, 44.9, 42.2, 28.7, 21.9. MS (ESI+) m/z: 314 (M + H\textsuperscript{+}). These data are in agreement with those reported previously in the literature.\textsuperscript{[S3]}

Oxycodone (1a). This compound was prepared according to a modified literature procedure.\textsuperscript{[S2]} 14-Hydroxycodeinone (10 mmol) was dissolved in 50 mL of HPLC grade methanol. 10% Pd/C (106 mg, 1 mol%) was added, and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm, room temperature). The reaction progress was monitored by HPLC. Additional fresh 10% Pd/C was added if the reaction stopped before full conversion had been achieved. Upon completion, the crude reaction mixture was filtered through a plug of celite. The celite was washed with chloroform and the combined solutions were evaporated under reduced pressure to dryness. The residue was dissolved in chloroform (50 mL) and washed with saturated aqueous NaHCO\textsubscript{3}. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and evaporated to dryness. The resulting brown solid was recrystallized from ethanol/ethyl acetate 1:1, yielding oxycodone 1a as colorless needles (1984 mg, 63% over two steps). M.p. 218-220 °C (lit.\textsuperscript{[S4]} 225-226 °C). \textsuperscript{1}H NMR (300 MHz, Chloroform-d) \( \delta \) 6.76 – 6.55 (m, 2H), 4.64 (s, 1H), 3.87 (s, 3H), 3.13 (d, \( J = 18.6 \) Hz, 1H), 3.00 (td, \( J = 14.4, 5.1 \) Hz, 1H), 2.84 (d, \( J = 5.9 \) Hz, 1H), 2.59 – 2.39 (m, 3H), 2.38 (s, 3H), 2.29 (t, \( J = 3.1 \) Hz, 1H), 2.24 (t, \( J = 3.2 \) Hz, 1H), 2.18 – 2.08 (m, 1H), 1.84 (ddd, \( J = 13.3, 5.0, 3.0 \) Hz, 1H), 1.66 – 1.49 (m, 2H). \textsuperscript{13}C
NMR (75 MHz, Chloroform-d) δ 208.6, 145.0, 142.9, 129.4, 125.0, 119.5, 114.8, 90.4, 70.4, 64.6, 56.8, 50.3, 45.8, 42.8, 36.2, 31.4, 30.5, 21.9. MS (ESI+) m/z: 316 (M + H'). These data are in agreement with those reported previously in the literature.\textsuperscript{[S4]}

2. Preparation of 14-Acetyloxycodone (1b)

This compound was prepared according to a modified literature procedure.\textsuperscript{[S5]} Oxycodone 1a (630 mg, 2 mmol) was placed in a round bottom flask and dissolved in 1.89 mL of acetic anhydride (20 mmol, 10 equiv) under gentle heating. The solution was then heated under reflux for ca. 2 minutes and left cooling to ambient temperature. The title compound crystallized after standing overnight at 6 °C (if the product does not crystallize, a small amount of diethyl ether can be added). The resulting crystals were collected by filtration and washed with cold diethyl ether to afford 636 mg (89%) of 1b as white needles. M.p. 214-215 °C (lit.\textsuperscript{[S5]} 184-186 °C). \textsuperscript{1}H NMR (300 MHz, Chloroform-d) δ 6.74 – 6.59 (m, 2H), 4.66 (s, 1H), 4.17 (d, J = 5.5 Hz, 1H), 3.88 (s, 3H), 3.19 (d, J = 18.6 Hz, 1H), 2.78 (ddd, J = 14.3, 5.1, 2.8 Hz, 1H), 2.70 – 2.40 (m, 4H), 2.31 (s, 3H), 2.17 (s, 3H), 1.62 (td, J = 14.4, 3.7 Hz, 1H), 1.51 (dd, J = 11.0, 3.3 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, Chloroform-d) δ 207.5, 170.4, 145.0, 143.0, 128.5, 125.9, 119.7, 115.0, 90.1, 82.6, 57.9, 56.9, 50.6, 45.7, 42.8, 35.8, 30.1, 27.1, 22.4. MS (ESI+) m/z: 358 (M + H'). These data are in agreement with those reported previously in the literature.\textsuperscript{[S5]}

3. Preparation of 14-Hydroxycodeinone O-acetyl ester (1c)

This compound was prepared according to a modified literature procedure.\textsuperscript{[S6]} 14-Hydroxycodeinone (626 mg, 2 mmol) was placed in a round bottom flask and dissolved in 1.89 mL of acetic anhydride (20 mmol, 10 equiv) under gently heating. The solution was then heated under reflux for ca. 2 minutes and left cooling to ambient temperature. The title compound crystallized after standing overnight at 6 °C. The resulting crystals were collected by filtration and washed with cold diethyl ether to afford 646 mg (91% yield) of 1c as colorless crystals. M.p. 157-160 °C. \textsuperscript{1}H NMR (300 MHz, Chloroform-d) δ 7.08 (d, J = 10.1 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.65 (d, J =
8.2 Hz, 1H), 6.13 (d, J = 10.1 Hz, 1H), 4.76 (s, 1H), 4.07 (d, J = 5.3 Hz, 1H), 3.30 (d, J = 18.9 Hz, 1H), 2.58 – 2.40 (m, 3H), 2.37 (s, 3H), 2.34 – 2.27 (m, 1H), 2.25 (s, 3H), 2.07 (s, 3H), 1.81 – 1.61 (m, 1H). ^13^C NMR (75 MHz, Chloroform-d) δ 192.6, 170.1, 168.3, 147.5, 146.4, 134.2, 132.3, 131.4, 130.7, 123.1, 119.7, 87.8, 76.7, 58.1, 46.9, 45.3, 42.8, 29.0, 22.8, 21.6, 20.7. MS (ESI+) m/z: 386 (M + H^+). These data are in agreement with those reported previously in the literature.^[66]

4. Preparation of oxycodone-D3 [17-(2H)methyl-derivative] (1a-d3)

Noroxycodone 2a (freshly prepared as free base from the hydrochloride, 100 mg, 0.33 mmol, see Page S16) was dissolved in 50 mL of a dry acetone/methanol 3:1 mixture. Then, 19.3 µl (0.31 mmol) of iodomethane-^d_3 and 46 mg (0.33 mmol) of potassium carbonate were added. The resulting suspension was stirred at room temperature for 24 h. The reaction mixture was added to 300 mg of neutral alumina, loaded into a short chromatography column and eluted with cyclohexane/ethyl acetate 1:3. Evaporation of the solvent provided 1a-d3 as a white solid (51 mg, 48% yield). ^1^H NMR (300 MHz, chloroform-d) δ 6.75 – 6.57 (m, 2H), 4.66 (s, 1H), 3.89 (s, 3H), 3.15 (d, J = 18.6 Hz, 1H), 3.02 (td, J = 14.4, 5.1 Hz, 1H), 2.85 (d, J = 6.0 Hz, 1H), 2.56 (dd, J = 18.6, 6.0 Hz, 1H), 2.49 – 2.34 (m, 2H), 2.30 (dt, J = 14.3, 3.1 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.87 (ddd, J = 13.3, 5.0, 3.0 Hz, 1H), 1.69 – 1.59 (m, 2H), 1.61 – 1.52 (m, 2H). ^13^C NMR (75 MHz, chloroform-d) δ 208.7, 145.1, 143.1, 129.5, 125.0, 119.5, 114.9, 90.4, 70.1, 64.6, 56.9, 50.4, 45.3, 36.2, 31.5, 30.6, 22.0. MS (ESI+) m/z: 319 (M + H^+).

5. Preparation of Bis-O-diacyethylmorphinone (1d)

This compound was prepared according to a modified literature procedure.^[83] 14-Hydroxymorphinone (594 mg, 2 mmol) was placed in a round bottom flask and dissolved in 1.89 mL of acetic anhydride (20 mmol, 10 equiv) under gentle heating. The solution was then heated under reflux for ca. 2 minutes and left cooling to ambient temperature. The title compound crystallized after standing overnight at 6 °C. The resulting crystals were collected by filtration and
washed with cold diethyl ether to afford 643 mg (84%) of 1d as colorless crystals. M.p. 240-241 °C (lit.[53] 247-250 °C). 1H NMR (300 MHz, chloroform-d) δ 7.08 (d, J = 10.1 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.13 (d, J = 10.1 Hz, 1H), 4.76 (s, 1H), 4.07 (d, J = 5.3 Hz, 1H), 3.30 (d, J = 18.9 Hz, 1H), 2.58 – 2.40 (m, 3H), 2.37 (s, 3H), 2.34 – 2.27 (m, 1H), 2.25 (s, 3H), 2.07 (s, 3H), 1.81 – 1.61 (m, 1H). 13C NMR (75 MHz, chloroform-d) δ 192.6, 170.1, 168.3, 147.5, 146.4, 134.2, 132.3, 131.4, 130.7, 123.1, 119.7, 87.8, 76.7, 58.1, 46.9, 45.3, 42.8, 29.0, 22.8, 21.6, 20.7. MS (ESI+) m/z: 384 (M + H+). These data are in agreement with those reported previously in the literature.[53]

6. Synthesis of 6-Oxycodol (1e).

This compound was prepared according to a modified literature procedure.[57] Sodium borohydride (226 mg, 6 mmol, 3 equiv) was added portionwise to a solution of oxycodone (630 mg, 2 mmol) in 30 mL of chloroform/methanol 1:1 at 10 °C. After the addition was completed, the reaction mixture was stirred at room temperature for further 30 min. Then, the reaction was quenched with a large excess of a saturated solution of ammonium chloride in water. The solution was extracted with chloroform (3 × 50 mL). The combined organic layers were combined, dried over Na2SO4 and evaporated under reduced pressure. The resulting white solid was recrystallized from toluene/cyclohexane affording 361 mg (57%) of 6-oxycodol (1e) as colorless crystals. M.p. 145-147 °C (lit.[57] 167-168 °C). The crystalline product consists of a mixture of two epimers in 80:20 ratio according to 1H NMR. Major isomer: 1H NMR (300 MHz, chloroform-d) δ 6.72 (dd, J = 8.2, 1.3 Hz, 1H), 6.61 (dd, J = 8.2, 2.5 Hz, 1H), 4.64 (d, J = 4.7 Hz, 1H), 4.19 (dt, J = 9.1, 4.4 Hz, 1H), 3.86 (s, 3H), 3.14 (d, J = 18.5 Hz, 1H), 2.77 (d, J = 6.3 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.41 (d, J = 6.9 Hz, 1H), 2.35 (s, 3H), 2.32 – 1.81 (m, 3H), 1.77 (dt, J = 13.0, 4.6 Hz, 1H), 1.69 – 1.30 (m, 3H), 1.37 – 1.09 (m, 1H). 13C NMR (75 MHz, chloroform-d) δ 146.5, 141.7, 131.5, 126.2, 125.6, 119.0, 118.7, 113.7, 95.6, 90.8, 77.3, 72.1, 70.1, 66.8, 64.7, 56.5, 46.4, 45.7, 43.1, 33.3, 31.4, 28.3, 25.1, 23.8, 22.1, 22.0. MS (ESI+) m/z: 318 (M + H+). These data are in agreement with those reported previously in the literature.[58]
Cyclic Voltammetry

Cyclic voltammograms were recorded in a glass cell with a Rodeostat open source potentiostat (IO Rodeo Inc). A glassy carbon disk (2 mm diameter rod with PTFE shroud) was used as the working electrode and a platinum wire as the counter electrode. A silver wire was utilized as quasi reference electrode, using ferrocene as reference. The electrolyte consisted of 10 mM opioid and 0.1 M Et₄NBF₄ in MeCN. Samples were degassed prior to analysis.

![Cyclic Voltammograms of oxycodone (1a) at increasing scan rates permit visualization of the reversible character of the one-electron oxidation of the aromatic ring but not of the tertiary amine.](image1)

**Figure S1.** Cyclic voltammograms of oxycodone (1a) at increasing scan rates permit visualization of the reversible character of the one-electron oxidation of the aromatic ring but not of the tertiary amine.

![Cyclic voltammograms of 14-hydroxymorphinone and its diacetyl derivative. Acetylation of the phenol hydroxyl group renders the electrochemical oxidation highly selective toward the desired N-demethylation.](image2)

**Figure S2.** Cyclic voltammograms of 14-hydroxymorphinone and its diacetyl derivative. Acetylation of the phenol hydroxyl group renders the electrochemical oxidation highly selective toward the desired N-demethylation.
Table S1. Optimization of the electrochemical oxazolidination of 1a (extended version of Figure 2B in the manuscript)

| Conditions                                | Conversion (%) | Selectivity (%) |
|-------------------------------------------|----------------|-----------------|
| MeCN, LiClO₄, (+)C/Fe(-), 5 mA, 2 F/mol   | 29             | 90              |
| MeCN, LiBF₄, (+)C/Fe(-), 5 mA, 2 F/mol    | 33             | 88              |
| MeCN, LiPF₆, (+)C/Fe(-), 5 mA, 2 F/mol    | 17             | 82              |
| MeCN, NaClO₄, (+)C/Fe(-), 5 mA, 2 F/mol   | 47             | 89              |
| MeCN, Et₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol  | 79             | 96              |
| MeCN, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 75             | 93              |
| MeCN, nBu₄NPF₆, (+)C/Fe(-), 5 mA, 2 F/mol | 76             | 96              |
| DMF, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol  | 74             | 70              |
| DMA, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol  | 80             | 31              |
| MeOH, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 66             | 92              |
| nPrOH, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 31             | 29              |
| MeOH/HFIP 4:1, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 81             | 91              |
| CHCl₃/MEOH 3:1, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 57             | 93              |
| CHCl₃/MEOH 1:1, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 49             | 94              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 88             | 94              |
| MeCN/MEOH 9:1, nBu₄NBF₄, (+)C/Fe(-), 5 mA, 2 F/mol | 78             | 90              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)Pt/Fe(-), 5 mA, 2 F/mol | 61             | 94              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)RVC/Fe(-), 5 mA, 2 F/mol | 90             | 94              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Pt(-), 5 mA, 2 F/mol | 92             | 93              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/C(-), 5 mA, 2 F/mol | 78             | 92              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Ni(-), 5 mA, 2 F/mol | 91             | 93              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Fe(-), 10 mA, 2 F/mol | 75             | 94              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Fe(-), 15 mA, 2 F/mol | 71             | 95              |
| MeCN/MEOH 4:1, nBu₄NBF₄, (+)C/Fe(-), 20 mA, 2 F/mol | 66             | 92              |
| MeCN/MEOH 4:1, Et₄NBF₄, (+)C/Fe(-), 10 mA, 2.4 F/mol | 89             | 94              |

*a General conditions: undivided cell; 0.15 mmol substrate in 3 mL solvent; 5 mL IKA Electrasyn vial.
*b Determined by HPLC peak area percent (205 nm).
*c Percent of product with respect to all peaks except the substrate (HPLC peak area percent, 205 nm).
Proposed Structures for Reaction Side Products

Identification of the side products was carried out by analyzing a crude electrolysis reaction mixture by LCMS. The sample was subjected to the standard HPLC derivatization procedure using aqueous Ac₂O (see page S2). Under the aqueous derivatization conditions, the oxazolidine moiety undergoes demethylation. The nor-derivative is subsequently acetylated resulting in the corresponding N-acetyl derivative, which could be observed in the dimer is observed (Figure S3).

Figure S3. HPLC chromatogram of a crude reaction mixture for the model electrolysis of 1a and side products observed. Identification of the side products was carried out by LCMS analysis using electrospray ionization (ESI) in positive mode.
Kinetic Isotope Effect Study

The kinetic isotope effect (KIE) was evaluated by performing two reactions in parallel under the optimal electrolysis reaction conditions (MeCN/MeOH 4:1, 0.1 M Et₄NBF₄, 5 mA constant current). One of the reaction mixtures contained oxycodone 1a and the other one its derivative with the methyl group fully deuterated (1a-d₃) (Figure S4). HPLC monitoring of the two reaction mixtures revealed a $k_{H}/k_{D} = 1.5$.

![Figure S4. HPLC monitoring of the electrolysis of oxycodone and oxycodone-D3.](image)

Chemical Trapping of the Iminium Cation with Nucleophiles

A two-compartment H-cell (1 inch MW OD x 50mm tall) divided by a 10 mm P5 frit (Adams & Chittenden Scientific Glass) was utilized for these experiments. The anode compartment was filled with a solution containing 0.3 mmol of oxycodone 1a and 6 mL of 0.1 M Et₄NBF₄ in MeCN. The cathodic chamber was filled with MeCN/MeOH 4:1 containing 0.1 M Et₄NBF₄. The cell, equipped with a standard graphite anode and a stainless steel cathode from IKA, was immersed in a cooling bath at -45 °C. Electrolysis was carried out under a constant current of 5 mA. After 1 F/mol had been passed, the electricity was turned off and the nucleophile solution (diphenylamine or tetrabuylammonium cyanide) was rapidly added to the anodic chamber. The solution was then analyzed by LC-MS analysis. The expected trapping reactions and the mass spectra obtained are shown in Figure S5 and Figure S6 for diphenylamine and the cyanide salt, respectively.
Figure S5. (a) Expected product from the trapping of the iminium cation with diphenylamine and (b) MS (ESI+) obtained from the reaction mixture featuring the corresponding M+H⁺ signal.

Figure S6. (a) Expected product from the trapping of the iminium cation with tetrabutylammonium cyanide and (b) MS (ESI+) obtained from the reaction mixture featuring the corresponding M+H⁺ signal and the complex with acetonitrile (solvent used for the LCMS).
FT-IR Detection of the Iminium Cation

The same setup as for the chemical trapping of the iminium cation was utilized (see above). In this case, oxycodone 1a was not utilized as model substrate, as the strong IR signal for the carbonyl group was expected to hinder the visualization of the C=N+ stretching vibration (expected at 1690-1640 cm⁻¹ as a medium/weak signal). For this reason, 6-oxycodol 1e was utilized as substrate instead. This compound was initially subjected to the standard reaction conditions at room temperature in a undivided cell to ensure that the reaction works properly for this particular compound.

For the FTIR monitoring, 6 mL of a 0.2 M solution of 1e in acetonitrile/hexafluoroisopropanol 4:1 containing 0.1 M nBu₄NBF₄ as electrolyte was prepared and placed in the anodic chamber. The FTIR probe (Mettler Toledo ReactIR, AgX Fiber Conduit with an integrated attenuated total reflectance gold-sealed silicon sensor and a mercury cadmium telluride detector) was immersed in the anodic chamber near (but not touching) the anode. The divided cell is then immersed in a cooling bath at -45 °C and the electrolysis was initiated under galvanostatic conditions and a current of 5 mA. FT-IR spectra were recorded with an average of 125 scans. Gratifyingly, a weak signal, assigned to the $\tilde{v}_{C=N^+}$ appeared after turning on the electricity (Figure 4D in the manuscript).

Figure S7. (a) Electrolysis of 6-oxycodol 1e was used to enable monitoring of the iminium ion signal. (b) Schematic view of the electrolysis setup
Description of the Flow Electrolysis Cell and Flow Setup

The flow electrolysis cell (Figure S8) followed a typical parallel plates arrangement.[S9] The two electrode plates were placed facing each other and separated by an interelectrode membrane made of 0.3 mm thick chemically resistant Mylar film, that incorporates a reaction channel. The channel provides a contact surface area of 6.4 cm² between the liquid stream and the electrodes. Graphite plate (IG-15, GTD Graphit Technologie GmbH, 50 × 50 × 3 mm) was utilized as anode. 304 stainless steel plate (50 × 50 × 1 mm) was used as cathode. To ensure that current cannot flow between the two end plates in case of electrolyte leakage, polyamide bolts were utilized to assemble the cell.

**Figure S8.** (A) Exploded view of the flow electrolysis cell and (B) picture of the cell components.
The setup for the flow electrolysis utilized a solution reservoir (A) with electrolyte recycle. The reaction mixture was pumped with a Syrris syringe pump (B) through the assembled flow cell (C), which was powered by a DC power supply (D). For details on the experimental procedure for the electrolysis, see the corresponding section on page S15.

**Figure S9.** Schematic view and picture of the flow electrolysis setup.

### Experimental Procedures for the Electrochemical Reactions

**General procedure for the electrochemical oxazolidination of 14-hydroxy opioids and the demethylicative O,N-acetyl transfer of O-acetyl protected derivatives in batch mode**

In a 5 mL IKA ElectraSyn vial equipped with a stir bar, 0.15 mmol of the corresponding opioid precursor 1 were dissolved in 3 mL of a 0.1 M solution of tetraethylammonium tetrafluoroborate (Et₄NBF₄) in acetonitrile/methanol 4:1. After assembly of the electrochemical cell, equipped with a standard IKA graphite anode and a IKA stainless steel cathode, the solution was electrolyzed under a constant current of 5 mA after 2.4 F/mol had been passed. After completion of the reaction, the reaction mixture was evaporated under reduced pressure to half of its original volume. The remaining solution was added to 500 mg of neutral alumina and filled into a short chromatography column and subsequently eluted with a suitable solvent (vide infra).

(5aR,6R,8aS,8a1S,11aR)-2-Methoxy-5,5a,9,10-tetrahydro-7H-6,8a1-ethanofuro [2′,3′,4′,5:4,5]phenanthro[9,8a-d]oxazol-11(11aH)-one (2a). Following the general electrochemical reaction procedure using oxycodon 1a (0.15 mmol, 47 mg) as the substrate and using a mixture of toluene/cyclohexane/chloroform 1:2:1 with 5% of methanol as eluent for column chromatography, 2a (41 mg, 89%) was obtained as a brown solid. ¹H NMR (300 MHz, chloroform-d) δ 6.76 (d, J = 8.3 Hz, 1H), 6.69
(d, J = 8.3 Hz, 1H), 4.81 – 4.52 (m, 3H), 3.89 (s, 3H), 3.37 – 3.14 (m, 3H), 2.94 – 2.76 (m, 3H), 2.38 (ddt, J = 12.8, 6.0, 3.5 Hz, 2H), 2.01 – 1.93 (m, 1H), 1.70 – 1.51 (m, 2H). $^{13}$C NMR (75 MHz, chloroform-d) δ 207.3, 144.8, 142.9, 129.1, 123.3, 120.1, 115.2, 91.1, 86.5, 64.1, 56.8, 52.6, 44.4, 37.2, 34.2, 30.6, 26.9. These data are in agreement with those reported previously in the literature.\[S^{10}\]

**3-Methoxy-14-hydroxy-17-acetyl-4,5alpha-epoxymorphinan-6-one (2b).** Following the general electrochemical reaction procedure using oxycodone-14-acetate (1b) (57 mg, 0.15 mmol) as the starting material and cyclohexane/ethyl acetate 1:3 with 5% methanol as eluent for column chromatography, 41 mg of the title compound, containing 5% w/w Et$_4$NBF$_4$ (NMR analysis), was isolated (75% purity-corrected yield). M.p. 240-241 °C (lit.\[S^{7}\] 254-255 °C). $^1$H NMR (300 MHz, chloroform-d) δ 6.79 – 6.60 (m, 2H), 4.68 (s, 1H), 4.51 – 4.04 (m, 1H), 3.89 (s, 3H), 3.69 – 3.23 (m, 2H), 3.14 – 2.80 (m, 4H), 2.65 – 2.52 (m, 1H), 2.30 (dd, J = 14.4, 10.1, 4.4 Hz, 1H), 2.15 (s, 3H), 1.61 (ddd, J = 32.8, 13.2, 3.1 Hz, 2H). $^{13}$C NMR (75 MHz, chloroform-d) δ 208.0, 171.1, 145.1, 143.3, 128.6, 123.9, 119.9, 115.1, 89.9, 70.7, 56.7, 53.5, 50.5, 45.1, 40.1, 35.7, 32.0, 28.9, 22.1. MS (ESI+) m/z: 344 (M + H$^+$).

**3-Methoxy-14-hydroxy-17-acetyl-4,5alpha-epoxy-7,8-didehydro-morphinan-6-one (2c).** Following the general electrolysis procedure using 14-acetyl codeinone 1c (57 mg, 0.15 mmol) as the substrate and cyclohexane/ethyl acetate 1:3 with 5% methanol as eluent for column chromatography, 38 mg (75%) of the title compound were isolated. M.p. 215-216 °C (lit.\[S^{7}\] 222-223 °C). $^1$H NMR (300 MHz, Chloroform-d) δ 6.88 – 6.58 (m, 3H), 6.15 (d, J = 10.1 Hz, 1H), 4.75 (s, 1H), 3.85 (s, 3H), 3.70 (d, J = 13.4 Hz, 1H), 3.57 – 3.36 (m, 1H), 3.28 – 3.11 (m, 1H), 3.06 – 2.87 (m, 2H), 2.60 (td, J = 12.7, 5.2 Hz, 1H), 2.17 (s, 3H), 1.71 (dd, J = 12.8, 2.9 Hz, 1H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 194.0, 171.5, 148.0, 144.5, 143.2, 133.9, 130.0, 124.1, 120.2, 115.5, 86.8, 68.3, 56.9, 52.8, 47.4, 40.2, 31.4, 28.1, 22.2. MS (ESI+) m/z: 342 (M + H$^+$).

**3-Acetyl-4a-hydroxy-7-oxo-2,3,4,4a,7,7a-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl Acetate (2d).** Following the general electrolysis procedure using 3,14-diacetyl morphinone 1d (57 mg, 0.15 mmol) as the substrate and ethyl acetate/cyclohexane/chloroform 6:2:1 with 5% methanol as eluent for column chromatography, 43 mg (78%) of the title compound were isolated. $^1$H NMR (300 MHz, chloroform-d) δ 6.96 – 6.80 (m, 2H), 6.69 (d, J = 8.2 Hz, 1H), 6.16 (d, J = 10.1 Hz, 1H), 4.79 (s, 1H), 4.20 (d, J = 37.4 Hz, 1H), 3.70 (dd, J = 14.0, 4.9 Hz, 1H), 3.28 – 2.86 (m, 4H), 2.61 (td, J = 12.7, 5.2 Hz, 1H), 2.28 (s, 3H), 2.16 (s, 3H). $^{13}$C NMR (75 MHz, chloroform-d) δ 193.0, 171.4, 168.2, 148.2, 147.5, 133.7, 132.6, 130.5, 129.6, 123.5, 120.0, 87.2, 67.9, 52.5,
47.3, 39.9, 31.6, 27.9, 22.0, 20.7. MS (ESI+) m/z: 370 (M + H\(^+\)). These data are in agreement with those reported previously in the literature.[S11]

**Electrolysis of Oxycodone (1a) Using a Flow Cell**

The flow electrolysis cell described in Figure S8 and the setup depicted in Figure S9 were utilized. A solution containing 1a (0.5 mmol) in 10 mL of 0.1 M Et\(_4\)NBF\(_4\) in MeCN/MeOH 4:1 was pumped through the empty cell using a syringe pump with a flow rate of 2 mL/min, while being stirred with a magnetic stir bar. The outlet of the flow cell was returned to the reaction solution container, thus recirculating the mixture. When the system was stable and all air bubbles were displaced from the flow cell, the electrical power supply of the electrolysis cell was turned on under a constant current of 10 mA. After 2.4 F/mol of current had been applied, the power supply was turned off. Then, the inlet of the pump was taken out of the reaction mixture. Air was pumped through the cell until all the remaining reaction mixture had been collected from the cell output. The reaction mixture was then evaporated under reduced pressure to one third of its original volume. The remaining solution was added to 500 mg of neutral alumina and placed into a short chromatography column and eluted with toluene/cyclohexane/chloroform 1:2:1 with 5% of methanol. Evaporation of the solvent gave 124 mg of the oxazolidine 2a (79%).

**One-pot Electrolysis/hydrolysis Sequence for the Generation of Nor-derivatives**

![Chemical diagram]

The flow electrolysis procedure described above was followed. When the electrolysis had been completed and all the solution had been collected in the solution reservoir, the crude reaction mixture was treated with 10 mL of 2 M HCl. The solution was heated under reflux overnight and then evaporated under reduced pressure. The solid residue was dissolved in water and washed with chloroform (30 mL). The aqueous phase was neutralized with saturated NaHCO\(_3\) and extracted with chloroform (3 × 50 mL). The combined organic layers were combined, dried over Na\(_2\)SO\(_4\) and evaporated under reduced pressure. The solid residue was dissolved in diethyl ether, and the solution sparged with HCl gas. Noroxycodone hydrochloride (3a•HCl) crystallized as a white powder (126 mg, 75% overall yield with respect to the initial oxycodone). M.p. 261 °C (lit.[S12] > 250 °C). \(^1\)H NMR (300 MHz, Deuterium Oxide) \(\delta\) 7.00 – 6.80 (m, 2H), 5.01 (s, 1H), 3.91 – 3.74 (m, 4H), 3.37 – 3.09 (m, 3H), 3.05 – 2.76 (m, 2H), 2.64 (td, \(J = 13.0, 4.5\) Hz, 1H), 2.39 – 2.15 (m, 1H), 2.02 (ddd, \(J = 14.3, 4.9, 2.8\) Hz, 1H), 1.67 (td, \(J = 14.6, 3.3\) Hz, 2H).\(^1\)C NMR (75 MHz, Deuterium Oxide) \(\delta\) 211.5, 144, 142.7, 127.3, 123, 121, 115.4, 89.6, 69.5, 57.4, 56.6, 49.3, 36.8, 34.5, 30.5, 27.6, 25.9. MS (ESI+) m/z: 302 (M + H\(^+\)). These data are in agreement with those reported previously in the literature.[S12]
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