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Full Paper

Efficient Iron-Catalyzed N-Demethylation of Tertiary Amine-*N*-oxides under Oxidative Conditions

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An investigation into the influence of oxidative conditions on the efficiency of opiate N-demethylation using iron powder has been carried out under non-classical Polonovski conditions. This approach involves a two-step process of N-oxidation and subsequent treatment of the intermediate *N*-oxide hydrochloride with the redox catalyst. Significant improvements in rate and yield have been realized for these reactions in the presence of molecular oxygen. In this context, further rate enhancement was achieved by the judicious addition of small amounts of ferric ions, leading to a concomitant reduction in the amount of the zero-valent iron primary catalyst that is required. This has led to a generalized improved methodology for the N-demethylation of oripavine, codeine, morphine, and thebaine. This protocol can also be carried out in one-pot without the need to isolate the intermediate *N*-oxide.

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Introduction

Morphine (**1a**) and codeine (**2a**, Fig. 1) are the two most abundant opiate alkaloids present in traditional strains of the opium poppy, *Papaver somniferum*. In addition to their own well known therapeutic applications, they have also proven to be useful raw materials for the production of semi-synthetic opiate pharmaceuticals, such as naltrexone (**3**), naloxone (**4**), and buprenorphine (**5**).[1] These compounds are used in the therapy of opiate and alcohol dependence and buprenorphine is also used in pain management.[2] More recently, new strains of *Papaver somniferum* have been developed which have a higher content of the Δ^6,Δ^8-morphine alkaloids, oripavine (**6a**) and thebaine (**7a**). These compounds are even more attractive substrates for the preparation of buprenorphine and 'nal salts' such as naltrexone and naloxone. Both thebaine and oripavine possess a diene moiety in their C ring which provides a useful handle for further transformations, such as a Diels-Alder reaction used in the synthesis of buprenorphine or the introduction of 14-hydroxy functionality present in the nal salts. Another important modification present in many semi-synthetic opiate pharmaceuticals, is the replacement of the naturally occurring *N*-methyl group with other alkyl substituents such as allyl and cyclopropylmethyl. This necessitates the inclusion of an N-demethylation and N-alkylation step(s) in the syntheses of compounds of this type. Whilst the latter step is a relatively simple operation, removal of the *N*-methyl group still presents a challenge to the synthetic chemist,[3] particularly for large scale operations.

There are several general methods for removal of the *N*-methyl group described in the literature.[3] For many years, the von Braun reaction[4] using cyanogen bromide and the use of chloroformate esters[5] have been two of the most frequently used methods. From an industrial perspective, the von Braun reaction is undesirable due to the toxicity of the reagent whilst chloroformate esters, though generally high-yielding, are expensive reagents. A range of other methods have also been employed including the use of dialkyl azodicarboxylates,[6] as well as photochemical,[7] and biochemical transformations.[8] Our own efforts in this area have primarily focussed on Polonovski-type[9] N-demethylation on opiate and tropane alkaloids. Thus, the tertiary *N*-methylamine is first converted into the *N*-oxide, which is then treated with an activating agent, generating the secondary amine. In most cases, the only significant byproduct of the reaction is the parent *N*-methylamine. Several Fe(II)-based reagents including $FeSO_4 \cdot 7H_2O$,[10] Fe(II)TPPS,[11] and ferrocene[12] have been shown to be effective activating agents. However, depending upon the quantity of the Fe(II)-based reagent used, emulsions due to iron hydroxides and related iron compounds have been found to be an operational issue especially for large scale reactions. There is therefore a need for the development of improved processes for the N-demethylation of opiates, particularly direct processes from the corresponding naturally occurring *N*-methyl morphinanes.

Recently, under inert conditions, we reported the use of zero-valent iron in Polonovski-type N-demethylation of several opiates, including morphine, codeine methyl ether, thebaine, and oripavine as well as the 14-hydroxy derivatives, oxycodeinone, oxycodone, oxymorphinone, and oxymorphone.[13] Whilst the yields of *N*-norcodeine methyl ether and *N*-northebaine were excellent (>80 %), the N-demethylation of the other opiate substrates proceeded in modest yield (<60 %) and were accompanied by the formation of significant amounts of the corresponding *N*-methyl byproduct (up to ~40 %). Subsequently, under a wide range of reaction conditions, employing oripavine

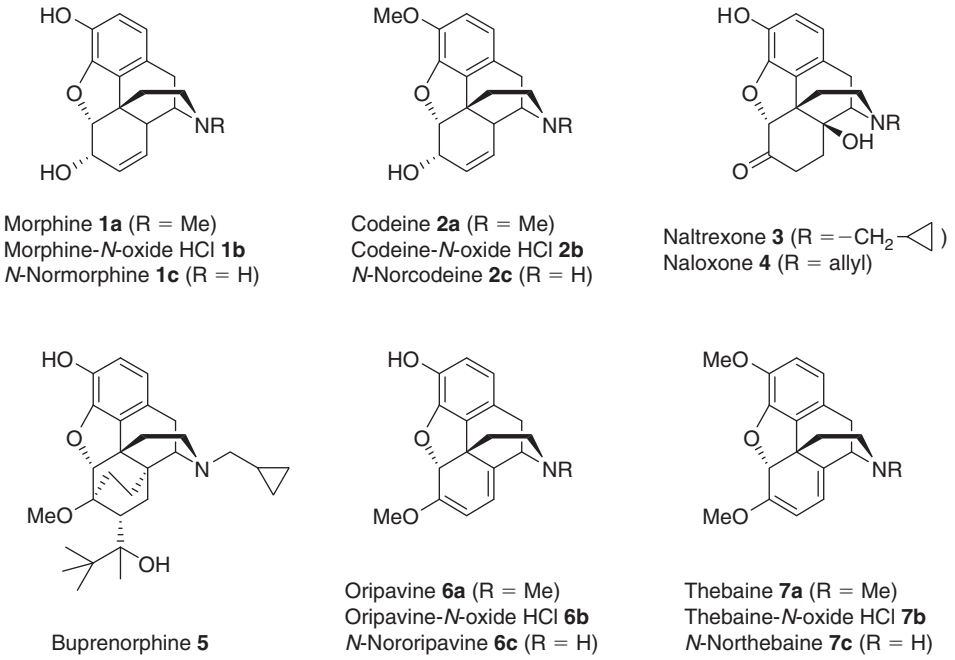
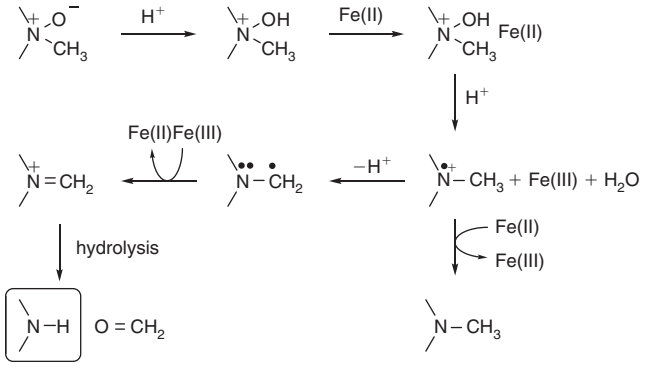


Fig. 1. Examples of opiate raw materials and semi-synthetic opiate pharmaceuticals.



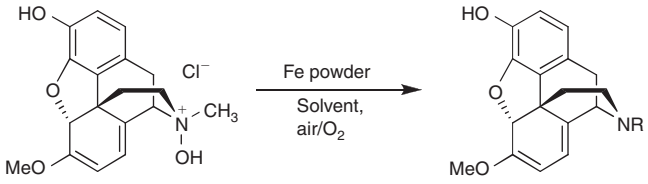
Scheme 1. Proposed mechanism of the Fe^{2+}/Fe^{3+}-mediated non-classical Polonovski reaction.

as a model substrate,[14] we found that the yield of *N*-nororipavine improved when stainless steel 303-L powder was substituted for iron powder as catalyst. However, the reactions took a considerably longer time to reach completion.

Herein, we describe significantly improved reaction outcomes – higher yields and/or shorter reaction time, by conducting the N-demethylation under oxidative conditions. Since the mechanism[9] of the non-classical Polonovski reaction is thought to proceed via a series of single electron transfers (Scheme 1), we have considered the role that molecular oxygen might play in these reactions. However, systematic control of the rate via temperature is complicated by the diverse solubility profiles of oxygen in various solvents.[15,16] For several organic solvents such as carbon tetrachloride, chlorobenzene and chlorocyclohexane, the temperature coefficient is positive, i.e. the oxygen solubility increases with temperature; and for solvents such as methanol, ethanol and propanol, the oxygen solubility as a function of temperature is quite complex.[15,16] For example, for ethanol itself, whilst oxygen solubility is essentially independent of temperature at first, it decreases markedly at temperatures above 25°C.[15] To complicate matters further, the solubility is also affected by the presence of even small amounts of water. The situation in the case of binary solvent mixtures can be even more complex.[15,16] Studies also show variable temperature dependency with respect to other relevant parameters – for example, studies conducted on the rate of iron corrosion in acid media have found[17] that the kinetics and adsorption processes at temperatures from 0 to 40°C differ markedly in character to those above 40°C. Hence some reactions conducted in air might not conform to Arrhenius kinetics. Due to such vagaries, systematic temperature dependent investigations, in an attempt to increase the reaction rates of our reactions, have not been attempted. We have also recognized that there are other complicating factors relating to the influence of dissolved oxygen in these reactions. For example, whilst it is well known that the primary reaction of Fe(0) with dissolved oxygen is oxidation to Fe^{2+}, dissolved oxygen also leads to the passivation of the Fe(0) surface by corrosion products.[18] However, in zero-valent iron processes, little is known about the kinetic chemistry of the iron oxide coatings.[18–21] On the other hand, the kinetics of the oxidation of Fe^{2+} by O_2 have been extensively studied over time.[22–25] Notably, at ordinary temperature and pressure, in both acid and neutral solutions, ferrous salts are not easily oxidized in both air and oxygen.[23–25] For example, it has been reported[24] that only 0.03 % of a 0.1 M ferrous sulfate solution was oxidized after 1 h at 25°C, with the rate doubling with a 10°C rise of temperature. The rate of Fe^{2+} oxidation has also been found to be dependent on the counterion, with the chloride salt being oxidized even slower than the sulfate.[22,26] A range of other factors such as the concentration of the ferrous salt, pH, temperature, pressure, added cations, complexing agents or ligands, and catalysts also affect the oxidation rate of the Fe^{2+} species.[27–32]

In the present study, we have found that the above problems may be addressed, in part, by doping with ferrous or ferric ions – affording more control and, indeed, addition of small amounts of ferric ions, in particular, is found to further increase the

Table 1. N-demethylation of oripavine-*N*-oxide hydrochloride with iron powder



6b

6a R = H
6c R = Me

Entry	Fe[A] [mol-%]	Conditions[B]	Atm	Time [h]	6c[C] [%]	6a[C] [%]
1	200	*i*-PrOH	Air	16	67	24
2[D]	200	*i*-PrOH	N_2	48	40	24
3	50	*i*-PrOH	Air	16	67	31
4[D]	50	*i*-PrOH	N_2	48	53	25
5	25	*i*-PrOH	Air	120	73	26
6[D]	25	*i*-PrOH	N_2	144	65	25
7	50	*i*-PrOH/$CHCl_3$ (1:1)	Air	2.5	72	25
8[D]	50	*i*-PrOH/$CHCl_3$ (1:1)	N_2	3.5	71	25
9	50	*i*-PrOH/$CHCl_3$ (1:3)	Air	2.0	74	24
10[D]	50	*i*-PrOH/$CHCl_3$ (1:3)	N_2	5.5	70	25
11	50	*i*-PrOH/$CHCl_3$ (1:9)	Air	16	60	22
12[D]	50	*i*-PrOH/$CHCl_3$ (1:9)	N_2	168	58	23

[A]Particle size distribution (sieve analysis) for 99 % of sample: 100 mesh.
[B]10 mL of solvent per 100 mg of substrate at 40°C.
[C]Isolated via column chromatography.
[D]Data from reference [14] included for comparison.

N-demethylation rate. As an overall strategy, in the first instance several experiments were conducted in air and these were then benchmarked against the results obtained for the inert atmosphere experiments. Subsequent procedural refinements in the form of added Fe(II) and Fe(III) were then conducted.

We have also found that N-demethylation reactions of this type can be conducted in one-pot without isolation of the intermediate *N*-oxide hydrochloride and the results for these one-pot procedures are also presented.

Results and Discussion

A study on the N-demethylation in air was initiated by conducting a series of experiments using oripavine (**6a**) in which the effect of iron powder loading on the reaction in isopropanol was investigated. Although consistently high yields of the *N*-oxides of such *N*-methyl alkaloids have previously been obtained via N-oxidation with the more environmentally benign hydrogen peroxide,[10a] in this study, we have employed *m*-CPBA for this purpose since it is a more effective reagent – with reactions typically taking only 10 min to complete at −5°C. Thus the *N*-oxide of oripavine, isolated as the hydrochloride salt **6b**, was obtained in near quantitative yield. A heterogenous mixture of **6b** and iron powder in isopropanol was stirred in air until complete consumption of the starting material (as analyzed by TLC). Subsequent column purification, eluting with a gradient of $CHCl_3$/MeOH (24:1–17:3) isolated the desired *N*-nor product **6c** from some tertiary *N*-methylamine **6a**.

The results of the above experiments are shown in Table 1. Thus, employing 200 mol-% of iron powder at 40°C, the reaction in air was complete in 16 h (entry 1). Lowering the amount of iron powder used to 50 mol-% was inconsequential, both with respect to time for completion and isolated yield of *N*-nororipavine (compare entries 1 and 3). A further reduction in the amount of catalyst to 25 mol-% significantly slowed the reaction, but the yield of *N*-nororipavine improved slightly (entry 5). In all cases, the reactions conducted in air gave superior yields of *N*-nororipavine (**6c**) compared with those performed under an atmosphere of nitrogen.[14] The difference was greatest when 200 mol-% of iron powder was used; *N*-nororipavine (**6c**) was isolated in 67 % yield when the reaction was conducted in air and in 40 % yield with an inert atmosphere of nitrogen (compare entries 1 and 2). Also, the percentage total product recovery (**6a** + **6c**), via column chromatography, for all air experiments were also found to be significantly higher than the corresponding experiments conducted under nitrogen. For example, the experiment conducted in air with 200 mol-% of iron gave a 91 % total product recovery, while the total recovery from the N_2 experiment was 64 %. Furthermore, when 50 and 200 mol-% of iron powder were used (entries 1–4), the reactions proceeded to completion three times faster in the presence of air.

Subsequently, we were interested in the effects that solvents may have on the reaction. In line with our previous inert atmosphere studies,[14] we have chosen to use a *i*-PrOH/$CHCl_3$ binary system for these experiments, varying the proportion of solvents in the mixture. These results are given in Table 1 (entries 7–12). All experiments were conducted using 50 mol-% of iron powder. Interestingly, N-demethylation was generally faster for reactions in a mixed *i*-PrOH/$CHCl_3$ solvent system than in isopropanol alone. Varying the proportion of chloroform in the mixture was also found to influence the outcome of the experiments (entries 7, 9, and 11). Of the three different *i*-PrOH/$CHCl_3$ solvent systems investigated, the reactions in 1:1 and 1:3 *i*-PrOH/$CHCl_3$ gave comparable yields of *N*-nororipavine (72 and 74 %, respectively) and both progressed to completion in a reasonable timeframe (<4 h). The reaction conducted in 1:9 *i*-PrOH/$CHCl_3$ gave a lower yield of *N*-nororipavine (60 %) and took more than four times longer to reach completion (16 h). In all three mixed *i*-PrOH/$CHCl_3$ solvent systems the isolated yields of *N*-nororipavine (**6c**) for the air experiments were comparable to the corresponding reactions performed under an atmosphere of nitrogen. However, the reactions conducted in air typically proceeded to completion in significantly less time. The difference in reaction rate was most apparent in the reactions conducted in *i*-PrOH/$CHCl_3$ (1:9) in which the reaction in air was complete in one tenth of the time required under nitrogen (compare entries 11 and 12).

We have shown that air generally accelerates N-demethylation, which broadly implies that the N-demethylation is highly dependent on the concentration of ferrous and ferric species, consistent with the proposed mechanism[9] for iron-mediated N-demethylation under Polonovski-type conditions. Using oripavine, we have therefore conducted a more systematic study on the influence of added Fe^{2+} and Fe^{3+} in such reactions. Since the rate of oxidation of ferrous ion by oxygen is dependent on the nature of the anions present,[22,26,32] and given that the hydrochloride salt of the *N*-oxide **6b** has been used as substrate, we have employed iron chlorides in these investigations. All reactions with added Fe^{2+} and Fe^{3+} were conducted at ambient temperature using 50 mol-% of the primary redox catalysts in 1:3 *i*-PrOH/$CHCl_3$.

Table 2 summarizes the results for the reactions with added Fe^{2+}. In all cases, addition of Fe^{2+} to the iron powder

experiments reduces the ratio of *N*-nororipavine relative to oripavine (**6c** : **6a**) without having a significant effect on the total product recovery (**6c** + **6a**). This finding is in accordance with the proposed mechanism of the non-classical Polonovski reaction,[2] which is believed to proceed via an intermediate aminium radical cation that is reduced by Fe^{2+} to form the corresponding parent *N*-methylamine (in this case, oripavine). In air, the time taken for the reaction to reach completion was found to be progressively shortened as the amount of added Fe^{2+} increased (compare entries 1, 2, and 4). However, this has occurred with a concomitant decrease in the amount of *N*-nororipavine produced. Notwithstanding, all reactions with added Fe^{2+} proceeded to completion in a shorter time in air than the corresponding reactions under nitrogen.

Experiments with various amounts of added Fe^{3+} are also summarized in Table 2. The addition of 2.5 mol-% of $FeCl_3$ had no major effect on the yield of *N*-nororipavine (**6c**) or on the ratio of **6c** : **6a** (compare entries 1 and 6). However, the addition of 2.5 mol-% of $FeCl_3$ increased the reaction rate by a factor of 2–3 fold. Significantly higher loadings of $FeCl_3$ (entry 7) had a deleterious effect on both the yield of *N*-nororipavine (**6c**) and the rate of reaction. Interestingly, when 2.5 mol-% of $FeCl_3$ was added to the iron powder reaction, conducted under an atmosphere of nitrogen, almost identical outcomes in terms of the yield of **6c**, the product ratio, and the reaction time, were obtained – compared with the corresponding reaction in air (compare entries 1 and 10). This suggests that improvements observed for the reaction conducted in air relative to those under an inert atmosphere may result from the oxygen-mediated formation of Fe^{3+} in situ.

In the presence of oxygen, further reducing the amount of iron powder and $FeCl_3$ employed to 13 mol-% and 2 mol-%, respectively, N-demethylation of oripavine was complete after 6 h at ambient temperature. After standard workup followed by column chromatography, *N*-nororipavine was obtained in 82 % yield (Table 3, entry 1). Hence, the addition of only a small amount of Fe^{3+} to the reaction has significantly reduced the total amount of iron used without compromising the yield.

As entry 2 shows, the optimized conditions for oripavine also successfully N-demethylated morphine. In the case of morphine, the reaction was conducted at 40°C to enable completion within a reasonable timeframe of 48 h. After standard workup, a 77 % yield of *N*-normorphine was obtained, a significant improvement over that previously[13] reported when iron powder alone was employed as redox catalyst.

There have been at least eight previous attempts at the direct synthesis of *N*-norcodeine from codeine, with reported yields ranging from 10–80 %. To the best of our knowledge, two of the previous best reported yields of 70 and 80 % have employed toxic and/or expensive chlorofomate esters.[33,34] Gratifyingly, we have found that simply stirring the *N*-oxide hydrochloride of codeine with a combination of Fe(0) and Fe^{3+} at ambient temperature for 36 h has provided, after standard workup, *N*-norcodeine in high yield (82 %) (entry 3).

The N-demethylation of thebaine was explored using both chloroform and isopropanol (entries 4 and 5), with the reaction being greatly facilitated in chloroform. In both cases, addition of small amounts of Fe^{3+} has reduced by 10-fold the amount of iron powder used from 130 mol-%,[13] without the reaction time or the yield of the *N*-nor product **7c** being compromised. Reducing the amount of iron used in these reactions is particularly advantageous to the efficacy of workup.

Finally, it is evident that by carefully controlling the amount of oxidant in the reaction, the two-step N-oxidation and N-demethylation protocol can be reduced to a one-step process (Table 4). The one-pot process is especially advantageous for unstable or highly water soluble *N*-oxide hydrochloride intermediates.

Table 2. N-demethylation of oripavine-*N*-oxide hydrochloride with iron powder and added iron salts[A]

Entry	Catalyst [mol-%]	Iron salt, [mol-%]	Atm	Time [h]	6c[B] [%]	6a[B] [%]
1	Fe(0)(50)	–	Air	3.5	75	22
2	Fe(0)(50)	Fe^{2+}, 2.5	Air	1.5	68	21
3[C]	–	Fe^{2+}, 2.5	Air	168	42	8
4	Fe(0)(50)	Fe^{2+}, 50	Air	<1	55	43
5	–	Fe^{2+}, 50	Air	6	46	37
6	Fe(0)(50)	Fe^{3+}, 2.5	Air	1.2	77	19
7	Fe(0)(50)	Fe^{3+}, 50	Air	16	42	28
8	–	Fe^{3+}, 50	Air	168	36	11
9	Fe(0)(50)	–	N_2	5.5	70	25
10	Fe(0)(50)	Fe^{3+}, 2.5	N_2	3.5	78	20

[A]Experiments were performed with 100 mg of substrate in 10 mL of *i*-PrOH/$CHCl_3$ (1:3) at room temperature.
[B]Isolated via column chromatography.
[C]41 % of *N*-oxide hydrochloride **6b** was also recovered.

Conclusion

Significantly improved reaction conditions for the N-demethylation of opiate alkaloids have been developed. We have identified reaction conditions which result in a dramatic improvement in the methodology for the N-demethylation of oripavine at ambient temperature. A scrutiny of the oxidative

Table 3. N-demethylation of various opiate-*N*-oxide hydrochlorides with iron powder and added ferric chloride hexahydrate[A]

Entry	Substrate(*N*-oxide)	Solvent	Conditions	#c[B][%]	#a[B][%]
1	Oripavine **6b**	*i*-PrOH/$CHCl_3$ (1:3)[C]	RT, 6 h	82	16
2[D]	Morphine **1b**	*i*-PrOH/$CHCl_3$ (1:3)[C]	40°C, 48 h	77	19
3	Codeine **2b**	*i*-PrOH/$CHCl_3$ (1:3)[C]	RT, 36 h	82	14
4	Thebaine **7b**	$CHCl_3$	RT, 1.5 h	85	10
5	Thebaine **7b**	*i*-PrOH	RT, 48 h	79	8

[A]100 mL of substrate in 10 mL of solvent, Fe powder (13 mol-%), $FeCl_3$ (2 mol-%).
[B]Unless otherwise indicated, products were isolated via column chromatography.
[C]*i*-PrOH/$CHCl_3$ (1:3) was used for solubility reasons.
[D]Products were isolated via extraction (Method C; see Experimental).

conditions that pertain to these reactions carried out in air, compared with those carried out under an inert atmosphere, has enabled such processes to be optimized in terms of their rate and yield. Notably, the conditions optimized for the model substrate oripavine are applicable to codeine, morphine, and thebaine. We have also found that the two-step N-oxidation and N-demethylation protocol can be reduced to a one-pot process. In this way, the rather tedious isolation process of the highly water soluble *N*-oxide hydrochloride intermediates may be avoided.

Experimental

General

Iron powder was obtained from Höganäs Sweden. *m*-Chloroperbenzoic acid, ferrous chloride tetrahydrate, and ferric chloride hexahydrate were purchased from Sigma-Aldrich (St. Louis, MO). For experiments that were conducted in air, solvents (Merck) were used as supplied. For reactions conducted under nitrogen, solvents were degassed before use: sonicated under vacuum for 10 min and then back-filled with nitrogen. Thin-layer chromatography (TLC) was performed with 0.25 μm TLC silica gel 60F aluminium plates with 254 nm fluorescent indicator and plates were visualized using both UV light and molybdate stain. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts (δ ppm) were referenced with solvent residual peaks. Coupling constants are given in hertz. High resolution mass spectra were obtained using a Waters LCT Premier XE time-of-flight mass spectrometer fitted with an electrospray (ESI) ion source and controlled with MassLynx software version 4.5. All substrate *N*-oxides, were prepared via treatment of the opiate with *m*-chloroperbenzoic acid and isolated as the corresponding hydrochloride salt, according to the literature.[14] In all cases, near quantitative yields of the *N*-oxide hydrochlorides were obtained. *N*-oxide hydrochloride **6b** isolated with ~0.5 molar equivalent of isopropanol, was employed in all experiments.

General Procedure for N-Demethylation

To a stirred solution of the *N*-oxide hydrochloride (100 mg) in solvent (10 mL) was added iron powder (varying amounts; see Table 1). The reaction mixture was then stirred at the specified temperature until complete consumption of starting material (via TLC analysis), and purified by Method A, B, or C.

Table 4. One-pot N-demethylation of various opiates with iron powder and added ferric chloride hexahydrate[A]

Entry	Substrate	Conditions[B]	#c[C] [%]	#a[C] [%]
1	Oripavine **6a**	RT/36 h	82	16
2[D]	Morphine **1a**	40°C/48 h	79	19
3	Codeine **2a**	RT/20 h	87	7
4[E]	Thebaine **7a**	RT/48 h	86	11

[A]Substrate (0.673 mmol), *m*-CPBA (0.670 mmol) then Fe powder (13 mol-%) and $FeCl_3$ (2 mol-% of $FeCl_3$) in *i*-PrOH/$CHCl_3$ (1:3) (20 mL), unless otherwise indicated.
[B]Reaction time after addition of Fe(0)/Fe^{3+}.
[C]Products were isolated via column chromatography, unless otherwise indicated.
[D]Products were isolated via extraction (see Experimental, Method C).
[E]Chloroform was the solvent used.

Method A

The crude reaction mixture was concentrated and the remaining residue was purified via column chromatography on silica gel, eluting with a $CHCl_3$/MeOH gradient which isolated the *N*-nor product from the tertiary *N*-methylamine, both obtained as the corresponding hydrochloride salt.

Method B

The crude reaction mixture was diluted with $CHCl_3$ (30 mL) and the resulting solution was washed with 5 % aqueous NaOH (1 mL × 2), dried, filtered, and the residue purified via column chromatography on silica gel.

Method C

The crude reaction mixture was concentrated to dryness. To the residue was added H_2O (30 mL) and the pH of the mixture was adjusted to 8 (conc. NH_4OH) and subsequently extracted with *i*-PrOH/$CHCl_3$ (1:6) to remove the tertiary *N*-methylamine. The aqueous layer was concentrated to dryness and the residue was extracted with *i*-PrOH/$CHCl_3$ (1:3) to isolate the *N*-nor product. A few drops of 6N HCl were added to these extracts. Subsequent removal of the volatiles gave the *N*-nor compound as the hydrochloride salt.

The above procedure was also performed with either added $FeCl_2 \cdot 4H_2O$ or $FeCl_3 \cdot 6H_2O$ (Tables 2 and 3).

General Procedure for One-Pot N-Demethylation

To a stirred solution of the opiate (see Table 4) (0.673 mmol) in solvent (20 mL) at −5°C was added *m*-CPBA (max 77 % reagent, 0.670 mmol) portionwise over 10 min. The solution was then left to stir for 15 min and concentrated HCl (60 μL) was added dropwise. The solution was warmed to room temperature, iron powder (4.9 mg, 13 mol-%) and $FeCl_3 \cdot 6H_2O$ (4.5 mg, 2 mol-%) were added, and the mixture was left to stir until complete consumption of *N*-oxide hydrochloride (as analyzed by TLC analysis).

N-Norcodeine and *N*-northebaine were isolated from the reaction mixture according to Method B above. *N*-Nororipavine was isolated as follows: the reaction mixture was concentrated to dryness. H_2O (30 mL) was added and the resulting solution was extracted with $CHCl_3$ (10 mL × 3). The aqueous layer was concentrated to dryness and the resulting residue was purified via column chromatography according to Method A above. *N*-Normorphine was isolated according to Method C above, with the exception that the aqueous solution was extracted with $CHCl_3$ (10 mL × 3) before basification to pH 8 with concentrated ammonia.

N-Normorphine **1c** (HCl Salt)

Purified via Method C to give the hydrochloride salt of **1c** as an off-white solid. A small sample of *N*-normorphine hydrochloride was dissolved in H_2O and the pH of the solution was adjusted to 8–9 with concentrated ammonia. The precipitate was isolated via filtration to give *N*-normorphine as an off-white solid, mp 272–276°C (lit.[35] mp 275–277°C dec); $[\alpha]_D^{24}$ −54 (*c* 1.0, 10 % HOAc in H_2O); for the hydrochloride of **1c**: ^{1}H NMR (D_2O) δ 6.82 (d, J = 8.0, 1H), 6.73 (d, J = 8.0, 1H), 5.82–5.77 (m, 1H), 5.43 (ddd, J = 2.8, 2.8, and 9.6, 1H), 5.10 (dd, J = 1.2 and 6.4, 1H), 4.43–4.36 (m, 2H), 3.44–3.37 (m, 1H), 3.23–2.94 (m, 4H), 2.32 (ddd, J = 4.8, 14.0, and 14.0, 1H), 2.24–2.17 (m, 1H); ^{13}C NMR (D_2O/CF_3CO_2D)

δ 145.4, 137.8, 133.0, 129.3, 125.7, 123.4, 120.3, 117.4, 90.6, 65.5, 51.5, 42.0, 37.1, 36.7, 31.6, 25.7; MS (ESI) *m/z* 272 $[M+H]^+$; HRMS $C_{16}H_{18}NO_3$ calcd for $[M+H]^+$ 272.1281, found 272.1286.

N-Norcodeine **2c**

The crude reaction mixture from N-demethylation of the *N*-oxide hydrochloride **2b** was purified via Method A using a gradient of $CHCl_3$/MeOH (40:3–8:1) to give the hydrochloride salt of **2c** as an off-white solid. The hydrochloride was dissolved in 5 % aqueous NaOH (10 mL) and the solution was extracted with $CHCl_3$ (10 mL × 3). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated to give the title compound as a white solid. Data for **2c** are consistent with the literature[10a]; mp 183–184°C (MeOH/Et_2O); [lit.[8b] mp 182–183°C]; $[\alpha]_D^{23}$ −120 (*c* 1.0, $CHCl_3$); [lit.[8b] $[\alpha]_D^{28}$ −90.9 (*c* 0.224, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 6.69 (d, *J* = 8.0, 1H), 6.59 (d, *J* = 8.0, 1H), 6.73 (dddd, *J* = 1.6, 1.6, 2.8, and 9.6, 1H), 5.28 (ddd, *J* = 2.8, 2.8, and 9.6, 1H), 4.88 (dd, *J* = 1.2 and 6.4, 1H), 4.22–4.17 (m, 1H), 3.86 (s, 3H), 3.67–3.63 (m, 1H), 3.05–2.77 (m, 4H), 2.62–2.57 (m, 1H), 1.98–1.87 (m, 2H), 1.62 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 146.5, 142.0, 133.7, 131.1, 128.1, 127.4, 119.4, 112.9, 92.2, 66.4, 56.3, 51.7, 43.8, 41.2, 38.3, 36.5, 31.1; MS (ESI) *m/z* 286 $[M+H]^+$; HRMS $C_{17}H_{20}NO_3$ calcd for $[M+H]^+$ 286.1438, found 286.1449.

N-Nororipavine **6c** (HCl Salt)

Purified via Method A using a gradient of $CHCl_3$/MeOH (24:1–17:3) to give the hydrochloride salt of **6c** as an off-white solid, mp >200°C dec; $[\alpha]_D^{24}$ −188 (*c* 1.0, 10 % HOAc in H_2O); ^1H NMR (D_2O) δ 6.78 (d, *J* = 8.0, 1H), 6.74 (d, *J* = 8.0, 1H), 5.90 (d, *J* = 6.4, 1H), 5.50 (s, 1H), 5.25 (d, *J* = 6.4, 1H), 4.61 (d, *J* = 6.0, 1H), 3.64 (s, 3H), 3.46–3.22 (m, 4H), 2.31 (ddd, *J* = 6.0, 13.3, and 13.3, 1H), 2.08–2.01 (m, 1H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 153.0, 142.8, 138.6, 132.0, 124.4, 124.2, 120.8, 117.3, 117.0, 96.1, 87.7, 55.1, 53.2, 44.6, 37.0, 33.5, 33.1; MS (ESI) *m/z* 284 $[M+H]^+$; HRMS $C_{17}H_{18}NO_3$ calcd for $[M+H]^+$ 284.1281, found 284.1287.

N-Northebaine **7c**

Purified via Method B using a gradient of $CHCl_3$/MeOH/NH_4OH (90:10:1–85:15:1) to afford **7c** as an off-white solid. Physical data for **7c** are consistent with the literature[10a]; mp 146–150°C [(lit.[36] mp 157–158°C)]; $[\alpha]_D^{24}$ −225 (*c* 0.82, 5 % MeOH in $CHCl_3$) [lit.[8b] $[\alpha]_D^{20}$ −197.9 (*c* 0.31, 5 % MeOH in $CHCl_3$)]; [lit.[37] $[\alpha]_D^{23}$ −200 (*c* 0.1, 5 % MeOH in $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 6.68 (d, *J* = 8.4, 1H), 6.62 (d, *J* = 8.4, 1H), 5.51 (d, *J* = 6.4, 1H), 5.27 (s, 1H), 5.03 (d, *J* = 6.4, 1H), 3.92 (dd, *J* = 1.6 and 6.0, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.25–3.07 (m, 3H), 2.94 (dd, *J* = 4.0 and 13.6, 1H), 2.40–2.20 (br, 1H), 2.08 (ddd, *J* = 5.2, 12.8, and 12.8, 1H), 1.85–1.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 152.4, 144.7, 142.7, 133.9, 133.3, 127.7, 119.1, 112.8, 110.0, 95.7, 89.1, 56.3, 54.8, 53.8, 46.6, 40.6, 38.4, 37.6; MS (ESI) *m/z* 298 $[M+H]^+$; HRMS $C_{18}H_{20}NO_3$ calcd for $[M+H]^+$298.1438, found 298.1432.

Accessory Publication

^1H, ^{13}C NMR, and HR-MS spectra of **1c**, **2c**, **6c**, and **7c** are available from the Journal's website.

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