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N-Demethylation of *N*-methyl alkaloids with ferrocene

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ABSTRACT

Under Polonovski-type conditions, ferrocene has been found to be a convenient and efficient catalyst for the N-demethylation of a number of *N*-methyl alkaloids such as opiates and tropanes. By judicious choice of solvent, good yields have been obtained for dextromethorphan, codeine methyl ether, and thebaine. The current methodology is also successful for the N-demethylation of morphine, oripavine, and tropane alkaloids, producing the corresponding *N*-nor compounds in reasonable yields. Key pharmaceutical intermediates such oxycodone and oxymorphone are also readily N-demethylated using this approach.

N-Demethylation of opiate alkaloids is a key step in the semi-synthesis of a number of medicinally important opiate derivatives.[1] For example, the mixed agonist antagonists, nalorphine (**1**) and buprenorphine (**2**) as well as the potent antagonists, naloxone (**3**) and naltrexone (**4**) (Fig. 1), are obtained from the corresponding *N*-nor opiates.[2–5] These *N*-nor opiates are, in turn, derived from naturally occurring *N*-methyl opiates such as morphine, codeine, thebaine and oripavine.[6]

N-Demethylation of alkaloids generally, and opiates in particular, has been a long-standing challenge to synthetic chemists.[1] A wide variety of methods have been developed that attempt to accommodate the often competing requirements of reagent costs, toxicity, substrate specificity, yield, ease of operation and amenability to scale up. More traditional methods include the use of reagents such as cyanogen bromide (von Braun reaction),[7] chloroformates,[8] and dialkyl azodicarboxylates.[9] Less generally applicable methods include those that involve photochemical[10] and biochemical[11] processes.

There is considerable scope for the further development of alternative methods for the N-demethylation of opiate derivatives. We have previously reported that, under Polonovski-type conditions, iron(II) reagents such as $FeSO_4{\cdot}7H_2O$[12] and the ferrous porphyrin, tetrasodium 5,10,15,20-tetra(4-sulfophenyl)porphyrinatoiron(II)[13] are effective for N-demethylation of a number of opiate and tropane alkaloids. Thus, the tertiary *N*-methylamine is first converted into the corresponding *N*-oxide hydrochloride which, following subsequent treatment with the ferrous reagent, has provided the *N*-nor compound in moderate to good yields. In most cases, the only by-product obtained is the parent tertiary amine. This result is consistent with a reaction pathway which involves a number of intermediates. A plausible mechanism for the reaction which implicates a Fe(II)/Fe(III) redox couple, as shown in Scheme 1, has previously been proposed.[14]

We now report a simple and mild two-step process employing ferrocene to N-demethylated opiate and tropane alkaloids: formation and isolation of the corresponding *N*-methylamine *N*-oxide hydrochloride, and subsequent reaction with ferrocene (Scheme 2).

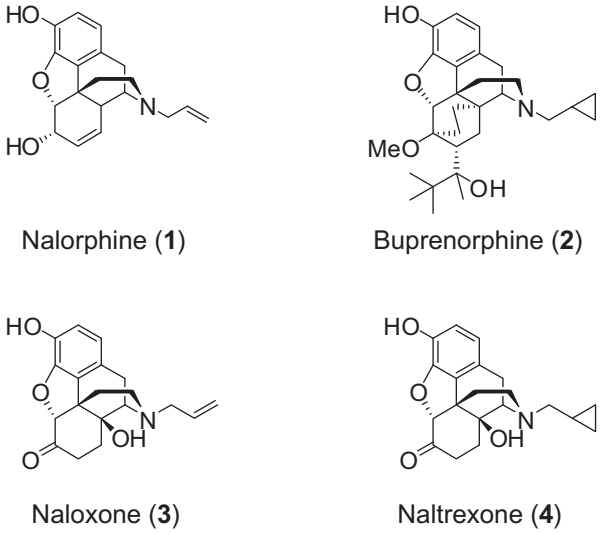

Figure 1. Examples of semi-synthetic opiates.

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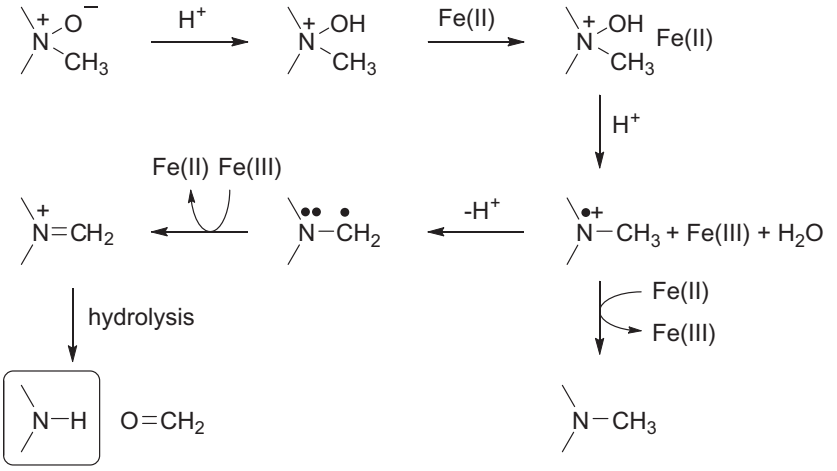
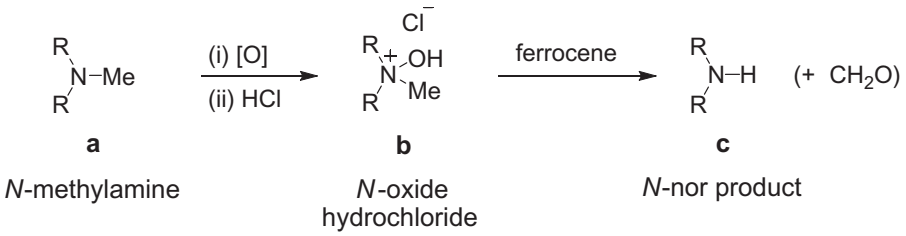


Scheme 1. Proposed mechanism[14] for the non-classical Polonovski reaction.



Scheme 2. N-Demethylation with ferrocene.

Structural effects have been studied using a range of opiates and tropanes and, for a number of these substrates, the effects of solvent on the reaction outcome have been investigated.

Our initial efforts began with an examination of the conditions that were effective for the N-demethylation of dextromethorphan (**5a**) as a representative opiate substrate, and the optimized conditions were subsequently applied to a larger test set of opiate alkaloids (Fig. 2). As the ferrocene/ferrocenium redox couple has been extensively studied and found to be solvent dependent,[15] we were interested in exploring the effects that different solvents have on N-demethylation. Hence, experiments were conducted in a range of solvents: $CHCl_3$, CH_2Cl_2, MeCN, MeOH, and *i*-PrOH. The solvents were used as supplied and degassed with nitrogen prior to use.

Employing *m*-CPBA as oxidant, **5a** was readily converted into the corresponding *N*-oxide, which was isolated as the hydrochloride salt **5b**. In a typical experiment,[16] the *N*-oxide **5b** and ferrocene were degassed prior to the addition of solvent. The resulting solution was then stirred at the specified temperature until the consumption of starting material **5b** was complete (by TLC analysis) or for the specified length of time. After standard workup, the desired *N*-nor product **5c** was isolated from a small amount of the starting tertiary *N*-methylamine **5a** via column chromatog-

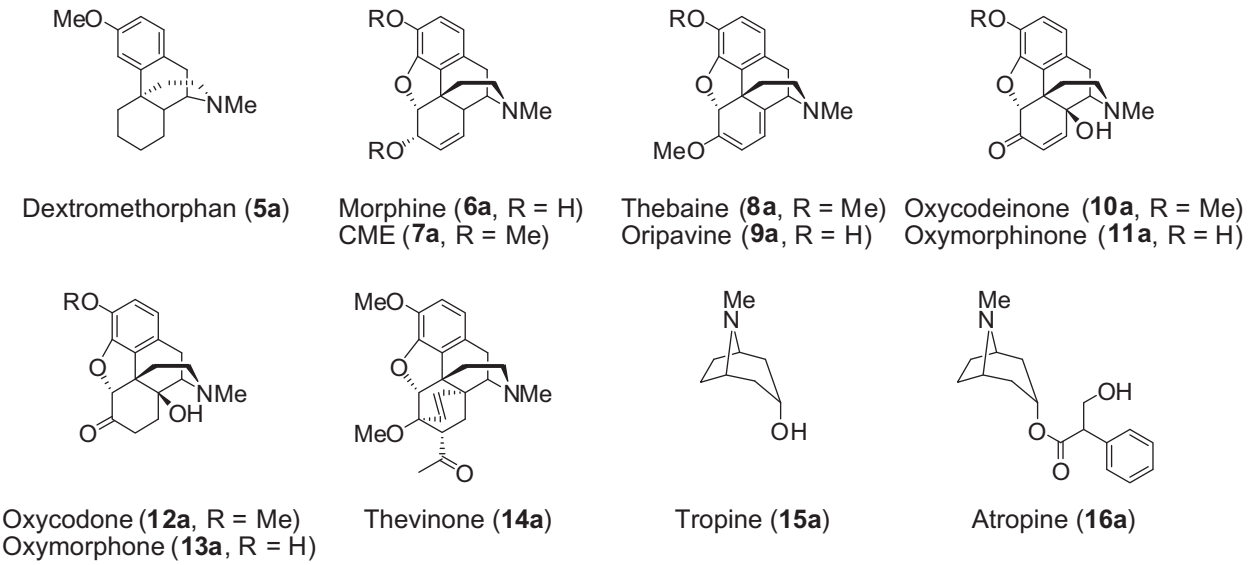


Figure 2. Alkaloid test set.

Table 1
N-Demethylation of dextromethorphan-*N*-oxide hydrochloride (**5b**)[a] with ferrocene

Entry	Ferrocene (equiv)	Solvent	Temperature (°C)	Time (h)	% Isolated yield[b]	
					5c	**5a**
1	0.25	$CHCl_3$	40	72	92	8
2	0.25	$CHCl_3$	60	16	92	7
3	0.05	$CHCl_3$	60	22	89	10
4	0.25	CH_2Cl_2[c]	Reflux	16	82	16
5	0.25	MeCN	40	96	37	47
6	0.25	MeOH	40	96	13	0[d]
7	1.00	MeOH	Reflux	336	64	23[e]
8	0.25	*i*-PrOH	40	40	70	26
9[f]	0.25	*i*-PrOH	40	68	71	26

[a] Unless otherwise indicated, concentration: 5 mL solvent per 100 mg (0.309 mmol) of substrate **5b**.
[b] Isolated yield after column chromatography.
[c] Concentration: 10 mL solvent per 100 mg of substrate **5b**.
[d] No dextromethorphan was isolated; however, 86% of *N*-oxide was recovered.
[e] 12% of *N*-oxide was also recovered.
[f] Reaction conducted in air.

raphy on silica gel, using a $CHCl_3$/MeOH/NH_4OH gradient. Most of the ferrocene, if desired, could readily be recovered either via extraction with hexane at an appropriate stage of the workup, or via column chromatography. For example, in the reaction using CH_2Cl_2 as solvent, a 97% recovery of ferrocene was obtained via column chromatography; in the case of MeCN, the recovery was approximately 90%.

Table 1 compiles the key results for the N-demethylation of dextromethorphan-*N*-oxide under a variety of conditions. The reaction in $CHCl_3$ proceeded efficiently and provided *N*-nordextromethorphan (**5c**) in high isolated yields of ~90% (entries 1 and 2). Although catalyst loadings as low as 5 mol % were effective (entry 3), 25 mol % of ferrocene was typically used for subsequent experiments to minimize the reaction time. Dichloromethane also proved to be a reasonable solvent, returning an 82% yield of *N*-nordextromethorphan (entry 4). However, with higher coordinating solvents such MeCN the reaction produced relatively more tertiary amine **5a** (47%, entry 5). The total percentage recovery of product was also lower (84%). In MeOH, only a small amount of the *N*-nor product **5c** was produced after 96 h at 40 °C, with most of the *N*-oxide being recovered unchanged (entry 6). We found that the reaction was still incomplete even when the amount of ferrocene employed was increased fourfold (entry 7) and the reaction conducted at a higher temperature (refluxing MeOH) for a prolonged period (336 h).

The results using either MeCN or MeOH as solvent suggest that the ferrocene/ferrocenium one-electron oxidation reduction process may be quasi-reversible in these solvents. Indeed, previous studies on the electrochemical oxidation of ferrocene have suggested that there is a very slow decomposition reaction of the oxidized species in certain media such as MeCN, MeOH, and EtOH.[17] The reaction conducted in *i*-PrOH proceeded to completion after 40 h at 40 °C, producing the *N*-nor product **5c** in a modest yield of 70% (entry 8). Finally, N-demethylation of dextromethorphan-*N*-oxide with ferrocene using *i*-PrOH as solvent at 40 °C was repeated with the whole operation being conducted in air (entry 9). These conditions afforded effectively the same isolated yield of *N*-nordextromethorphan (**5c**), although the reaction took longer time to reach completion (68 h compared to 40 h).

The N-demethylation of morphine-*N*-oxide (**6b**), CME-*N*-oxide (**7b**), thebaine-*N*-oxide (**8b**), and oripavine-*N*-oxide (**9b**) were next investigated and the results are summarized in Table 2. Both $CHCl_3$ and *i*-PrOH were evaluated as solvents for these reactions. Chloroform was chosen as it gave the best results for the N-demethylation of dextromethorphan, while isopropanol was included as a less toxic, non-halogenated solvent that may be more suitable for industrial applications. *N*-NorCME and *N*-northebaine were obtained in good yield (92% and 84%, respectively) when $CHCl_3$ was used as the reaction solvent. With oripavine-*N*-oxide (**9b**), using a catalyst loading of 0.5 molar equiv, no reaction was observed after 24 h in $CHCl_3$ at 50 °C, and it was thought that solubility may be the limiting factor. Likewise, N-demethylation was not ob-

Table 2
N-Demethylation of other opiate and tropane alkaloid *N*-oxides

Entry	Substrate[a] (*N*-oxide)	Ferrocene (equiv)	Solvent	Temp (°C)	Time (h)	Isolation method[b]	% Isolated yield	
							#c	**#a**
1	Morphine (**6b**)	0.2	*i*-PrOH	40	120	B	63	35
2	CME (**7b**)	0.25	$CHCl_3$	50	22	A	92	8
3	CME (**7b**)	0.25	*i*-PrOH	50	48	A	75	13
4	Thebaine (**8b**)[c]	0.5	$CHCl_3$	50	48	A	84	7
5	Thebaine (**8b**)[c]	0.5	*i*-PrOH	50	48	A	83	11
6	Oripavine (**9b**)	2.0	*i*-PrOH	70	20	D	38	29
7	Oxycodeinone (**10b**)	0.5	$CHCl_3$	40	5	C	50	40
8	Oxycodeinone (**10b**)	0.5	*i*-PrOH	40	18	B	45	32[d]
9	Oxycodeinone (**10b**)	0.2	*i*-PrOH	40	16	C	51	30
10	Oxymorphinone (**11b**)	0.2	*i*-PrOH	40	17	B	34	32
11	Oxycodone (**12b**)	0.2	$CHCl_3$	40	20	A	32	23
12	Oxycodone (**12b**)	0.2	*i*-PrOH	40	20	B	47	22
13	Oxycodone (**12b**)	0.2	*i*-PrOH	40	20	C	58	23
14	Oxymorphone (**13b**)	0.2	*i*-PrOH	40	48	B	59	32
15	Thevinone (**14b**)	0.25	$CHCl_3$	35	24	A	37	62
16	Thevinone (**14b**)	0.25	*i*-PrOH	60	3	A	16	83
17	Tropine (**15b**)	0.25	$CHCl_3$	Reflux	24	A	74	8
18	Tropine (**15b**)	0.25	*i*-PrOH	80	24	A	50	46
19	Atropine (**16b**)	0.1	$CHCl_3$	Reflux	24	A	55	6
20	Atropine (**16b**)	0.1	*i*-PrOH	80	24	A	59	21

[a] Unless otherwise specified, concentration: 10 mL solvent per 100 mg of substrate.
[b] *Method A*: column chromatography on SiO_2, eluting with a gradient of $CHCl_3$/MeOH/NH_4OH (90:10:1–85:15:1) or ethyl acetate/MeOH/NH_4OH (70:30:1–60:40:1). *Method B*: extraction of an aqueous solution of the crude at pH 2–10 with a suitable solvent. *Method C*: 10% aqueous HCl was added to the crude and the solution was heated at 50 °C for 1–48 h. The pH of the resultant solution was adjusted to 2–10 before extractions with a suitable solvent/solvent system. *Method D*: column chromatography on SiO_2, eluting with a gradient of $CHCl_3$/MeOH (97:1–9:1).
[c] Concentration: 20 mL solvent per 100 mg of substrate.
[d] Tertiary amine was approximately 90% pure by ^1H NMR.

served for morphine-*N*-oxide (**6b**) using 0.2 molar equiv of catalyst in refluxing $CHCl_3$ for 48 h. However, when these reactions were conducted in *i*-PrOH, modest amounts of *N*-nororipavine (38%) and *N*-normorphine (63%) were obtained (Table 2).

Our current methodology is also applicable to the N-demethylation of the *N*-oxides of various 14-hydroxy semi-synthetic opiates: oxycodeinone-*N*-oxide (**10b**), oxymorphinone-*N*-oxide (**11b**), oxycodone-*N*-oxide (**12b**), and oxymorphone-*N*-oxide (**13b**). For **10b** and **12b**, reactions were conducted in both $CHCl_3$ and *i*-PrOH. However, due to solubility issues, reactions for **11b** and **13b** were performed only in *i*-PrOH. Results are summarized in Table 2. In the product isolation process, we have found that the α,β-unsaturated ketones such as oxycodeinone and oxymorphinone are not stable to chromatography over silica gel. After some experimentation, we have found that the desired *N*-nor products **10c** and **11c** could be isolated from the respective tertiary *N*-methylamine **10a** and **11a** via simple extractions with a suitable solvent or solvent mixture. The extractive workup protocol was also successful in the separation of oxycodone (**12a**) from *N*-noroxycodone (**12c**), and oxymorphone (**13a**) from *N*-noroxymorphone (**13c**). N-Demethylation of thevinone-*N*-oxide (**14b**) was also investigated using both $CHCl_3$ and *i*-PrOH. Interestingly, for this substrate, relatively more of the tertiary *N*-methylamine **14a** was produced compared to the N-demethylated product **14c** (entries 15 and 16).

Finally, N-demethylation of the *N*-oxides of tropane alkaloids (**15b** and **16b**) was also investigated. Experiments were conducted in both $CHCl_3$ and *i*-PrOH. For **15b**, the reaction in $CHCl_3$ delivered a better outcome; for **16b**, comparable yields of *N*-nor product **16c** were obtained for both solvents (Table 2).

In summary, a number of opiate and tropane alkaloids, including key pharmaceutical intermediates such as oxycodone and oxymorphone, are readily N-demethylated in a two-step Polonovski-type process using a sub-stoichiometric amount of ferrocene. To the best of our knowledge, this is the first time ferrocene has been shown to effect a Polonovski reaction. This method offers a number of advantages with the ferrocene catalyst being inexpensive and readily available, as well as being air and thermally stable. If desired, most of the catalyst could readily be recovered from the reaction via a simple extraction with hexane or column chromatography. The reaction is mild and, as demonstrated for substrates such as oripavine, morphine, and oxymorphone, does not require protection of functional groups such as hydroxyl. As ferrocene is both stable and soluble in most organic solvents, we have been able to demonstrate that the reaction medium greatly influences the outcome of Fe(II)-mediated N-demethylation of opiate and tropane alkaloids, both with respect to completion time as well as to the product yield ratio of starting tertiary amine and *N*-nor product.

In general, the N-demethylation of tertiary amine-*N*-oxides with ferrocene proceeds in a comparable or superior yield to the previously reported Polonovski reactions that employed $FeSO_4{\cdot}7H_2O$[12] or Fe(II)TPPS [tetrasodium 5,10,15,20-tetra(4-sulfophenyl)porphyrinatoiron(II)][13] in cases where a direct comparison can be made. Furthermore, ferrocene is required in amounts as low as 0.05 molar equiv, whereas the best results with $FeSO_4{\cdot}7H_2O$ required an excess of the Fe(II) species (typically 2 molar equiv). The use of ferrocene also has a number of advantages over Fe(II)TPPS, as the latter is not commercially available and only gave the best results when it was retained in an acetate buffer to prevent decomposition.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.031.

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16. *General procedure for N-demethylation of the tertiary N-methylamine N-oxide hydrochlorides with ferrocene*: A solution or slurry of the tertiary *N*-methylamine *N*-oxide hydrochloride (approx. 0.27 mmol), ferrocene (0.05–2.0 molar equiv) and $CHCl_3$, CH_2Cl_2, MeCN, MeOH or *i*-PrOH (10 mL) was stirred at 40–80 °C until reaction was complete or for the specified length of time. The reaction mixture was concentrated to dryness to give a crude mixture of the hydrochloride salt of the *N*-nor compound and the starting tertiary *N*-methylamine. Pure *N*-nor compound was isolated via one of the following methods: *Method A*: The crude mixture was dissolved in $CHCl_3$ or $CHCl_3$/*i*-PrOH (3:1) and the resulting solution was washed with 10% aqueous NaOH, dried (Na_2SO_4), filtered and concentrated. The remaining residue was subjected to column chromatography on SiO_2, eluting with a gradient of $CHCl_3$/MeOH/NH_4OH (90:10:1–85:15:1) or, in the case of **15a**/**15c**, using ethyl acetate/MeOH/NH_4OH (70:30:1–60:40:1), which provided first the starting tertiary amine followed by the *N*-nor product. *Method B*: extraction of an aqueous solution of the crude at pH 2–10 (adjusted with concd NH_4OH) with a suitable solvent or solvent system. *Method C*: 10% aqueous HCl was added and the solution was heated at 50 °C for 1–48 h. The pH of the resultant solution was adjusted to 2–10 (concd NH_4OH) before extractions with a suitable solvent or solvent system. *Method D*: as per Method A, with column chromatography using a $CHCl_3$/MeOH gradient (97:3–9:1).
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