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Two-Step Iron(0)-Mediated N-Demethylation of *N*-Methyl Alkaloids

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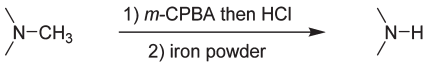

A mild and simple two-step Fe(0)-mediated N-demethylation of a number of tertiary *N*-methyl alkaloids is described. The tertiary *N*-methylamine is first oxidized to the corresponding *N*-oxide, which is isolated as the hydrochloride salt. Subsequent treatment of the *N*-oxide hydrochloride with iron powder readily provides the N-demethylated amine. Representative substrates include a number of opiate and tropane alkaloids. Key intermediates in the synthesis of semisynthetic 14-hydroxy pharmaceutical opiates such as oxycodone and oxymorphone are also readily N-demethylated using this method.

Introduction

Many tertiary *N*-methylamines have profound pharmacological properties. These include alkaloids from the opiate family, such as the powerful analgesics morphine (**1**) and codeine (**2**), as well as tropanes such as cocaine (**3**) and the potent CNS stimulant atropine (**4**) (Figure 1). Dextromethorphan (**5**) is a potent NMDA antagonist that is used in a range of cough and cold formulations.

N-Demethylation is a chemical transformation important to the pharmaceutical industry. Besides being tools for both pharmacological and metabolic studies, N-demethylated compounds themselves may have intrinsic biological activity. For example, *N*-nortropane (**6**) has been shown to have increased potency and selectivity over the corresponding *N*-methyl analogue as a serotonin transporter ligand.[1] N-Demethylated compounds also serve as key synthetic precursors to other important pharmaceuticals. For example, a number of semisynthetic pharmaceutical opiates such as naloxone (**7**) and naltrexone (**8**) are derived from the corresponding *N*-nor opiates, which in turn are synthesized from naturally occurring *N*-methyl opiates.

A number of general methods for N-demethylation of tertiary amines have been reported in the literature.[2] Most notably, these methods include the use of cyanogen bromide (von Braun reaction),[3] chloroformate esters,[4] and dialkyl azodicarboxylates.[5] Many of these methods have drawbacks such as the employment of toxic reagents, use of less readily available and expensive reagents, or vigorous reaction conditions. Photochemical[6] and biochemical[7] methods for N-demethylation have also been reported, but these are generally relatively low yielding. More recently, Hudlicky and co-workers have found that hydrocodone and a few tropane-type alkaloids were N-demethylated/N-acylated using palladium(II).[8]

The Polonovski reaction is a two-step process for the N-demethylation of tertiary amines (Scheme 1).[9] The tertiary amine is first converted into the *N*-oxide, which is then reacted with an activating agent to afford the N-demethylated product. The classical Polonovski reaction employs acylating agents such as acid chlorides, acid anhydrides, or chloroformate esters as the activating agent. However,

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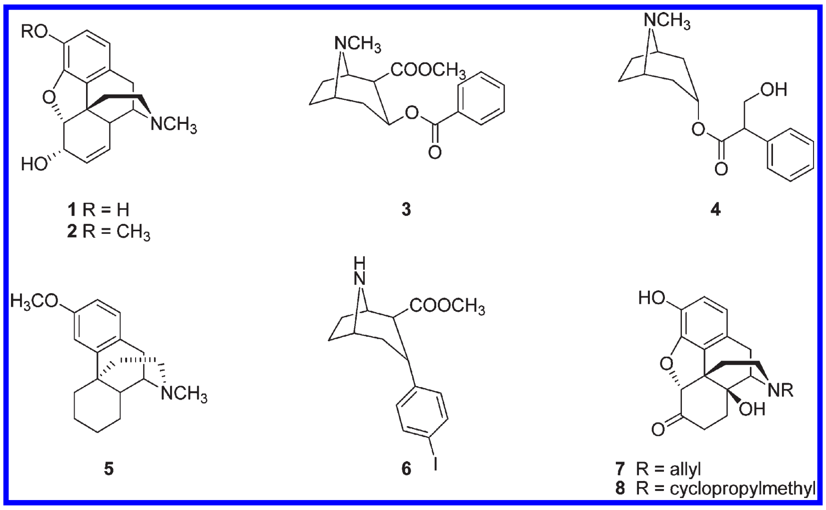
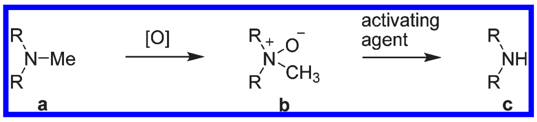


FIGURE 1. Some examples of natural and semisynthetic opiate and tropane alkaloids.

SCHEME 1. N-Demethylation via the Polonovski Reaction



N-demethylation of opiate alkaloids has not been successful under "classical Polonovski" conditions.[10,11]

In recent years, other variants of the original activating agent have successfully been employed to N-demethylate tertiary amine alkaloids, including opiates and tropanes. Our previous efforts have primarily focused on Fe(II)-mediated Polonovski-type N-demethylations on a range of opiate and tropane alkaloids. We have found that a number of Fe(II)-based reagents including $FeSO_4 \cdot 7H_2O$[12,13] and the ferrous porphyrin, Fe(II)TPPS,[14,15] are effective catalysts. Sipos and co-workers have also successfully employed $FeSO_4$ for the one-pot N-demethylation of apomorphine *N*-oxide as well as the acid-catalyzed rearrangement of morphinan *N*-oxides into noraporphine derivatives.[16] Thus, a process involving *N*-oxide formation, isolation of the corresponding *N*-oxide hydrochloride, and treatment with the iron(II) reagent has afforded the desired N-demethylated product, in most cases with the only byproduct being the parent tertiary amine. This reaction outcome can be rationalized from a consideration of the proposed reaction mechanism[9] which involves two successive one-electron steps in a Fe(II)/Fe(III) redox system. Further examination of the different Fe(0)/Fe(II)/Fe(III) redox potentials suggests that a redox couple involving iron in the zero oxidation state may prove viable as an alternate electron source in these Polonovski-type reactions. Iron is one of the most abundant metals on earth and is consequently inexpensive.[17] Furthermore, iron is an essential metal for living organisms and is typically very environmentally friendly. As a result of these features, it has been identified as an attractive catalyst for large-scale applications, such as those conducted by the pharmaceutical industry.[18]

Herein we describe a mild and simple two-step Polonovski-type process for N-demethylation involving the formation and isolation of the *N*-oxide hydrochloride and subsequent reaction with iron powder.

Results and Discussion

N-Demethylation using iron(0) was initially investigated using the commercially available substrate dextromethorphan (**5a**). Oxidation of **5a** with *m*-CPBA according to published procedures[12−15] provided the *N*-oxide **5b**, which was isolated as the corresponding hydrochloride salt. The *N*-oxide hydrochloride in an appropriate solvent was treated with a stoichiometric amount of iron powder, and the resulting mixture was stirred at room temperature until starting material was consumed, as monitored by TLC analysis. A standard workup followed by purification via column chromatography employing a $CHCl_3$/MeOH/NH_4OH gradient was used to isolate the desired *N*-nor product **5c** from the corresponding tertiary *N*-methylamine **5a**. The N-demethylation step was initially performed using methanol as the solvent. However, a number of commonly used solvents (EtOH, *i*-PrOH, MeCN, EtOAc, $CHCl_3$, and CH_2Cl_2) were subsequently evaluated. As the results in Table 1 show, solvent also plays a critical role in product outcome in these zerovalent iron-mediated reactions. Of the three alcoholic solvents studied (entries 1−3), the reaction was fastest in MeOH with the reaction complete in 3 h while the reaction in *i*-PrOH (21 h) delivered the best outcome with respect to the yield of the desired *N*-nor product **5c** (89%). In MeCN, all substrate *N*-oxide was consumed within 1.5 h (via TLC analysis), with the reaction delivering a modest yield of **5c**

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TABLE 1. Solvent Effects on N-Demethylation of Dextromethorphan *N*-Oxide Hydrochloride with Iron Powder[a]

entry	solvent	time (h)	% yield[b] 5c	% yield[b] 5a
1	MeOH	3	59	24
2	EtOH	8	62	23
3	*i*-PrOH	21	89	5
4	MeCN	1.5	75	21
5	EtOAc	2 (40 °C)	72	16
6	$CHCl_3$	1	97	*c*
7	CH_2Cl_2	1.5	86	10

[a] Unless otherwise indicated, reactions employed 1 equiv of iron and were conducted at room temperature (concentration: 5 mL of solvent per 100 mg of substrate). [b] Yields following column chromatography. [c] Although a trace amount of **5a** was observed by TLC, it was not recovered in the isolation process.

TABLE 2. Effects of Stoichiometry and Temperature on the N-Demethylation of Dextromethorphan *N*-Oxide Hydrochloride with Iron Powder[a]

entry	solvent	iron powder (equiv)	temp (°C)	time (h)	% yield[b] 5c	% yield[b] 5a
1	*i*-PrOH	1	rt	21	89	5
2	*i*-PrOH	0.25	rt	24	88	8
3	*i*-PrOH	0.25	60	3	89	7
4	$CHCl_3$	1	rt	1	97	
5	$CHCl_3$	0.1	rt	20	97	2

[a] Concentration: 5 mL of solvent per 100 mg of substrate. [b] Isolated via column chromatography.

of 75%. Although there was no apparent product formation after 3 h at room temperature in ethyl acetate, the reaction was complete in only 2 h when the temperature was increased to 40 °C. Chloroform and dichloromethane were found to be efficient solvents with all starting material being consumed within 1−1.5 h, delivering the *N*-nor product **5c** in high yields (Table 1, entries 6 and 7).

The effects of stoichiometry and temperature were explored to further optimize the reaction conditions for the N-demethylation of dextromethorphan *N*-oxide (Table 2). These experiments were conducted in both 2-propanol and chloroform. Employing 2-propanol as solvent at room temperature and lowering the catalyst loading from 1 to 0.25 equiv (entries 1 and 2) did not significantly alter the reaction time (21−24 h) or product yield ratio (**5c**:**5a**). By increasing the temperature to 60 °C (entry 3), the reaction took only 3 h to complete, without compromising the product yield ratio. Likewise, in $CHCl_3$, lowering the catalyst loading to 0.1 molar equiv increased the completion time for the reaction (20 h) without any consequence on the yield of **5c** (97%) and with only a small amount of the parent amine **5a** isolated (2%).

To evaluate the scope of this protocol, we have extended the study to a number of other representative opiate and tropane alkaloids, including morphine (**1a**) and atropine (**4a**). Other substrates are shown in Figure 2. Notably, these also include a number of the key pharmaceutical intermediates; namely, 14-hydroxy semisynthetic opiates **13a**−**16a**.

For CME (**9a**) and thebaine (**10a**), reactions were conducted in MeOH, $CHCl_3$, and *i*-PrOH. However, given the less favorable outcomes for **5a**, **9a**, and **10a** using MeOH as solvent, investigations on thevinone (**12a**) were performed in $CHCl_3$ and *i*-PrOH only. Due to limited solubility in $CHCl_3$, reactions on morphine (**1a**), oripavine (**11a**), and **13a**−**16a** were conducted in *i*-PrOH only. Results are summarized in Table 3.

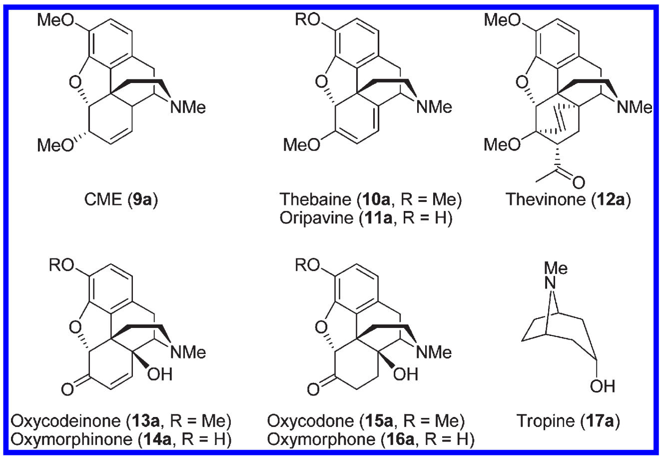

FIGURE 2. *N*-Methyl alkaloid test set.

For CME (**9a**), thebaine (**10a**), and thevinone (**12a**), solvent effects were consistent with the previous findings for dextromethorphan (**5a**), with $CHCl_3$ delivering better outcomes, both with respect to reaction time and yield of the *N*-nor product. The more polar *N*-oxides of thebaine (**10a**) and oripavine (**11a**)[19] were slower to react at lower temperatures, and subsequent heating at a higher temperature was required to complete the reactions within a reasonable time frame. After column purification on silica gel, *N*-northebaine (**10c**) and thebaine (**10a**) were isolated in 77% and 12% yield, respectively. For oripavine *N*-oxide, the respective yields of *N*-nororipavine (**11c**) and oripavine (**11a**) were 40% and 24%.

Iron powder, using *i*-PrOH as solvent, was also effective in the N-demethylation of morphine (**1a**), delivering, after column chromatography, a modest yield of the corresponding *N*-nor product **1c** of 58% (entry 1). Four semisynthetic 14-hydroxy opiates **13a**−**16a** were also readily N-demethylated (Table 3, entries 12−16). *N*-Noroxycodeinone (**13c**) and *N*-noroxymorphinone (**14c**) were found to be unstable to column chromatography using silica gel and were isolated via extraction with a suitable solvent or solvent combination. This extraction protocol was also successfully employed for the isolation of *N*-noroxymorphone (**16c**) from oxymorphone (**16a**). Noroxycodone (**15c**) was readily isolated from oxycodone (**15a**) via column chromatography on silica gel employing a $CHCl_3/MeOH/NH_4OH$ gradient.

Iron powder has also proven to be effective for the N-demethylation of tropane alkaloids (Table 3, entries 17−20). For example, atropine (**4a**) and tropine (**17a**) were readily N-demethylated to afford *N*-noratropine (**4c**) and *N*-nortropine (**17c**), respectively. Interestingly, for the tropanes, a slightly more favorable product ratio was obtained for reactions in *i*-PrOH compared to $CHCl_3$.

In summary, in cases where substrate solubility was not a limiting factor, chloroform was shown to be an effective solvent across a range of opiate substrates studied. For the tropane alkaloids **4a** and **17a**, we have found that reactions in *i*-PrOH delivered slightly better outcomes.

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(19) In $CHCl_3/MeOH/NH_4OH$ (85:15:1), the R_f values for the two thebaine *N*-oxide isomers were 0.45 and 0.53; for the two *N*-oxide isomers of oripavine, the R_f values were 0.29 and 0.36.

TABLE 3. **N-Demethylation of Other Opiate and Tropane Alkaloids with Iron Powder**[a]

						% yield[b]	
entry	*N*-oxide hydrochloride of	iron (equiv)	solvent	time (h)	temp (°C)	#**c**	#**a**
1	morphine, **1b**[c]	0.5	*i*-PrOH	24	40	58	36[d]
2	CME, **9b**	1.0	MeOH	3		61	12
3	CME, **9b**	1.0	$CHCl_3$	2		97	1
4	CME, **9b**	1.0	*i*-PrOH	48		88	7
5	CME, **9b**	0.25	*i*-PrOH	48		85	11
6[c]	thebaine, **10b**	1.3	MeOH	48		30	59
7	thebaine, **10b**	1.3	$CHCl_3$	1		86	13
8	thebaine, **10b**	1.3	*i*-PrOH	48	rt−50[e]	77	12
9	oripavine, **11b**[f]	2.0	*i*-PrOH	48	40−60[g]	40	24[d]
10[e]	thevinone, **12b**[c]	1.0	$CHCl_3$	2		44	26
11	thevinone, **12b**[c]	1.0	*i*-PrOH	3	60[h]	15	76
12	oxycodeinone, **13b**	1.0	*i*-PrOH	27	40	46	26[i]
13	oxymorphinone, **14b**	0.5	*i*-PrOH	168		40	44[i]
14	oxycodone, **15b**	0.5	*i*-PrOH	120	40	59	22
15	oxycodone, **15b**	2.0	*i*-PrOH	22	60	55	26
16	oxymorphone, **16b**	0.5	*i*-PrOH	144	40	42	41[i]
17	atropine, **4b**	1.0	$CHCl_3$	2		76	15
18	atropine, **4b**[c]	1.0	*i*-PrOH	50[j]		81	17
19	tropine, **17b**	1.0	$CHCl_3$	40		66	11
20	tropine, **17b**[c]	1.0	*i*-PrOH	2		74	3

[a] Unless otherwise specified, reactions were performed at room temperature at a concentration of 5 mL per 100 mg of substrate. [b] Yield via column chromatography. [c] Concentration: 10 mL per 100 mg of substrate. [d] No NH_4OH was added during workup; accordingly, the corresponding HCl salts were isolated. [e] The reaction mixture was stirred at rt for 24 h and then at 50 °C for 24 h. [f] Concentration: 20 mL per 100 mg of substrate, [g] Reaction heated at 40 °C for 24 h and then 60 °C for 24 h. [h] No apparent reaction after 72 h at rt. [i] Isolated via extraction of an aqueous solution of the crude at pH 2−10 with a suitable solvent/solvent mixture. [j] After 48 h at rt, the reaction mixture was heated at 60 °C for 2 h.

TABLE 4. **N-Demethylation of Dextromethorphan and Thebaine with Added Salts**[a]

						% yield[c]		
entry	*N*-oxide	iron (equiv)	added salt[b]	solvent	time (h)	#**c**	#**a**	#**b**
1	**5b**	1.0		MeOH	120	58	21	9
2	**5b**	1.0[d]	$CuSO_4\cdot 5H_2O$	MeOH	6	81	12	
3	**5b**	1.0[d]	$ZnSO_4\cdot 7H_2O$	MeOH	120	81	9	9
4	**5b**	1.0	$FeSO_4\cdot 7H_2O$	MeOH	24	59	25	
5	**5b**	1.0	$CuCl_2$	MeOH	120	54	40	4
6	**5b**	1.0	$Cu(ClO_4)_2\cdot 6H_2O$	MeOH	120	47	48	4
7	**5b**	1.0	$Cu(NO_3)_2\cdot 2^1/_2H_2O$	MeOH	120	38	55	7
8	**10b**	1.3		MeOH	48	30	59	
9	**10b**	1.3	$CuSO_4\cdot 5H_2O$	MeOH	48	72	25	
10	**10b**	1.3		$CHCl_3$	1	86	13	
11	**10b**	1.3	$CuSO_4\cdot 5H_2O$	$CHCl_3$	1	86	11	

[a] Unless otherwise stated, reactions were conducted at room temperature at a concentration of 10 mL of solvent per 100 mg of substrate. [b] 0.25 equiv of salt. [c] Yield after column chromatography. [d] No reaction in the absence of Fe.

Previous studies on the iron-catalyzed dealkylation of trimethylamine oxide to a secondary amine and formaldehyde have found that the decomposition rate is dependent on the anion used.[20] These results suggest that addition of salts to the iron powder experiment may be useful. To minimize solubility as a limiting factor, subsequent experiments were conducted at higher dilution, with 0.25 equiv of added salt. Interestingly, both $CuSO_4\cdot 5H_2O$ and $ZnSO_4\cdot 7H_2O$ enhanced the product ratio in favor of the *N*-nor product **5c** (Table 4, entries 2 and 3). Additionally, while added $ZnSO_4\cdot 7H_2O$ offered no advantage with respect to reaction rate (cf. entries 1 and 3), all starting material was consumed within 6 h when $CuSO_4\cdot 5H_2O$ was added (entry 2). However, increasing the amount of $CuSO_4\cdot 5H_2O$ from 0.25 to 1 equiv offered no further advantages. Added $FeSO_4\cdot 7H_2O$ did not have a significant effect on the product ratio, but did accelerate the reaction (cf. entries 1 and 4). On the other hand, addition of $CuCl_2$, $Cu(ClO_4)_2$ and $Cu(NO_3)_2$ resulted in an increase in the proportion of dextromethorphan (**5a**) (entries 5−7).

Further studies on the effect of added anions were conducted using thebaine as substrate (Table 4, entries 8−11). With MeOH as solvent, the reaction of thebaine *N*-oxide hydrochloride (**10b**) with iron powder alone returned more thebaine (**10a**) than the *N*-nor product **10c** (% yield of **10c**/**10a** = 30:59) (vide supra). Interestingly, addition of 0.25 equiv of $CuSO_4\cdot 5H_2O$ reversed this outcome, delivering *N*-northebaine (**10c**) and thebaine (**10a**) in respective yields of 72% and 25%. While the reaction outcome with MeOH as solvent was positively moderated via the addition of $CuSO_4\cdot 5H_2O$, in a non-coordinating medium such as chloroform, addition of $CuSO_4\cdot 5H_2O$ offered no further advantages on the product yield ratio (entries 10 and 11).

Conclusions

In conclusion, iron powder has been shown to be an effective catalyst for the N-demethylation of a number of tertiary *N*-methylamines. To the best of our knowledge, this is the first report of iron(0) effecting a reaction of this type. In general, these reactions are very high yielding, and the product is readily separated from the iron residues. Thebaine (**10a**) is an important starting material or intermediate in the synthesis of a number of pharmaceutical opiates, including opiate antagonists such as naloxone (**7**) and naltrexone (**8**) as well the mixed agonist−antagonist buprenorphine.[21,22]

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The N-demethylation of thebaine (**10a**) was previously achieved using both $FeSO_4$- and Fe(II)TPPS-mediated Polonovski-type reactions in yields of 74% and 71%, respectively.[12,14,15] The current methodology effects this reaction in 86% yield. Where a direct comparison can be made between the three methods for the N-demethylation of codeine methyl ether (**9a**), the iron(0)-promoted method also afforded a superior yield of the desired secondary amine. Solvent was found to play a significant role in the reactivity and selectivity of the reaction, with higher coordinating solvents delivering a poorer outcome with respect to the yield of *N*-nor product. Furthermore, we also found that the coordination effect of added anions also impacts on the reaction outcome. Employing dextromethorphan and CME as substrates, it was found that the ratio of secondary to tertiary amines formed was essentially independent of the stoichiometry of the catalyst used. As iron is both inexpensive and environmentally friendly, this procedure has enormous potential for large-scale applications such as those used by the pharmaceutical industry for the preparation of semisynthetic opiates.

Experimental Section

General Methods. Iron powder (NC100.24, 99% Fe) was purchased from a commercial supplier. All solvents were degassed before use, and reactions were conducted under an atmosphere of nitrogen. All substrate *N*-oxides, isolated as the corresponding hydrochloride salt, were prepared by following the procedure previously described.[12−15] Thin-layer chromatography (TLC) was performed with 0.25 μm TLC silica gel 60F aluminum plates with 254 nm fluorescent indicator, and plates were visualized using both UV light and molybdate stain. Unless otherwise indicated, ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Chemical shifts (δ ppm) were referenced with solvent residual peaks.

General N-Demethylation Procedure Using Iron Powder. To a solution of the *N*-oxide hydrochloride (100 mg) in a solvent such as MeOH, EtOH, *i*-PrOH, MeCN, EtOAc, $CHCl_3$, or DCM (typically, 10 mL per 100 mg) was added iron powder (0.1−2.4 molar equiv). The heterogeneous mixture was allowed to stir for the specified length of time or until complete consumption of starting material and then filtered through Celite, and the filter pad was washed with a suitable solvent such as $CHCl_3$ or $CHCl_3$/*i*-PrOH (3:1) (10 mL × 2). The original filtrate and washings were combined and concentrated to dryness to give a crude mixture of the *N*-nor compound and the starting tertiary *N*-methylamine. Pure *N*-nor product was isolated from the tertiary *N*-methylamine and/or *N*-methylamine *N*-oxide via method A, B, C, or D.

Method A. To the crude product mixture was added chloroform (20 mL) or $CHCl_3$/*i*-PrOH (3:1), and the solution was washed with either concentrated ammonia in brine (5 mL) or 10% aqueous NaOH (1 mL), dried (Na_2SO_4), filtered, and concentrated. The remaining residue was purified via column chromatography on SiO_2 using a $CHCl_3/MeOH/NH_4OH$ gradient (95:5:1−85:15:1) which isolated the *N*-nor product from the tertiary *N*-methylamine.

Method B. To the crude product mixture was added 10% aqueous NaOH (1 mL), and the mixture was concentrated to dryness. The resulting residue was column purified on SiO_2 using an ethyl acetate/MeOH/NH_4OH gradient (140:60:1−70:30:1) which isolated the tertiary *N*-methylamine from the *N*-nor product.

Method C. To the crude product mixture was added 5% aqueous HCl (20 mL). The pH of the solution was then adjusted to 6−10 with concentrated ammonia before extraction with a suitable solvent or solvent system.

Method D. The crude reaction mixture 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.

***N*-Normorphine (1c).** Purified via method D using a gradient of $CHCl_3$/MeOH (49:1−4:1) 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 a light brown solid: mp 272−276 °C (lit.[28] mp 275−277 °C dec); $[\alpha]^{24}_D$ −54 (*c* 1, 10% HOAc); ^{1}H NMR (D_2O/CF_3CO_2D, 400 MHz) δ 6.68−6.55 (m, 2 H), 5.64 (d, J = 9.6 Hz, 1 H), 5.29 (d, J = 9.6 Hz, 1 H), 4.94 (d, J = 5.7 Hz, 1 H), 4.27−4.23 (m, 2 H), 3.32−3.22 (m, 1 H), 3.08−2.78 (m, 4 H), 2.15 (ddd, J = 4.2, 13.2 and 13.2 Hz, 1 H), 2.04 (dd, J = 3.2 and 14.0 Hz, 1 H); ^{13}C NMR (D_2O/CF_3CO_2D, 100 MHz) 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*-Noratropine (4c).** Purified via method A using a gradient of $CHCl_3/MeOH/NH_4OH$ (90:10:1−85:15:1) to afford a colorless oil; ^{1}H NMR (D_2O) δ 7.45−7.30 (m, 5 H), 4.98 (t, J = 4.2 Hz, 1 H), 4.16 (dd, J = 10.2 and 12.9 Hz, 1 H), 3.94−3.09 (m, 2 H), 3.51−3.42 (m, 1 H), 3.42−3.33 (m, 1 H), 2.10−1.51 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 172.3, 135.8, 128.8, 128.1, 127.7, 68.6, 63.9, 54.5, 53.1, 53.0, 37.0, 36.7, 28.8, 28.4; ES-MS *m/z* 276 $[M + H]^+$; HRMS $C_{16}H_{22}NO_3$ calcd for $[M + H]^+$ 276.1594, found 276.1604.

***N*-Nordextromethorphan (5c).** Purified via method A using a gradient of $CHCl_3/MeOH/NH_4OH$ (90:10:1−85:15:1) to afford a colorless oil: $[\alpha]^{24}_D$ +33 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 1 H), 6.81 (d, J = 2.6 Hz, 1 H), 6.72 (dd, J = 2.6 and 8.4 Hz, 1 H), 3.22 (s, 3 H), 3.17−3.09 (m, 2 H), 2.82−2.61 (m, 5 H), 2.32 (m, 1 H), 1.83−1.77 (m, 1 H), 1.68−1.57 (m, 2 H), 1.55−1.48 (m, 1 H), 1.44−1.25 (m, 5 H), 1.12−0.99 (m, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.8, 138.9, 129.3, 126.0, 112.0, 111.1, 55.1, 51.1, 40.7, 38.3, 37.4, 36.6, 35.4, 27.8, 25.5, 25.4, 21.5; MS (ESI) *m/z* 258 $[M + H]^+$; HRMS $C_{17}H_{24}NO$ calcd for $[M + H]^+$ 258.1852, found 258.1851.

***N*-NorCME (9c).** Purified via method A using a gradient of $CHCl_3/MeOH/NH_4OH$ (90:10:1−85:15:1) to afford an off-white solid: mp 97−101 °C (lit.[23] mp 98−100 °C); $[\alpha]^{24}_D$ −170 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.67 (d, J = 8.0 Hz, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 5.80−5.72 (m, 1 H), 5.30 (ddd, J = 2.4, 2.4, and 9.9 Hz, 1 H), 4.98 (dd, J = 1.2 and 5.7 Hz, 1 H), 3.84 (s, 3 H), 3.83−3.78 (m, 1 H), 3.73−3.67 (m, 1 H), 3.54 (s, 3 H), 3.08−2.82 (m, 4 H), 2.64−2.59 (m, 1 H), 2.00−1.90 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147. 3, 141.8, 130.6, 130.3, 128.5, 126.9, 118.5, 113.0, 89.6, 75.7, 56.9, 56.1, 51.7, 44.1, 41.4, 38.3, 36.5, 31.3; MS (ESI) *m/z* 300 $[M + H]^+$; HRMS $C_{18}H_{22}NO_3$ calcd for $[M + H]^+$ 300.1594, found 300.1586.

***N*-Northebaine (10c).** Purified via method A using a gradient of $CHCl_3/MeOH/NH_4OH$ (90:10:1−85:15:1) to afford an off-white solid: mp 146−150 °C (lit.[24] mp 157−158 °C); $[\alpha]^{24}_D$ −225 (*c* 0.82, 5% MeOH in $CHCl_3$) [lit.[7b] $[\alpha]^{20}_D$ −197.9 (*c* 0.31, 5% MeOH in $CHCl_3$); lit.[25] $[\alpha]^{23}_D$ −200 (*c* 0.1, 5% MeOH in $CHCl_3$); lit.[26] (+)-northebaine $[\alpha]^{28}_D$ +235.2 (*c* 0.108, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 6.68 (d, J = 8.1 Hz, 1 H), 6.62 (d, J = 8.1 Hz,

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1 H), 5.50 (d, J = 6.4 Hz, 1 H), 5.27 (s, 1 H), 5.03 (d, J = 6.4 Hz, 1 H), 3.92 (dd, J = 1.2 and 5.6 Hz, 1 H), 3.86 (s, 3 H), 3.61 (s, 3 H), 3.24−3.07 (m, 3 H), 2.94 (dd, J = 4.3 and 13.7 Hz, 1 H), 1.43 (br, 1 H), 2.08 (ddd, J = 5.1, 12.6, and 12.6 Hz, 1 H), 1.84 (dd, J = 2.6 and 12.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.4, 144.7, 142.7, 133.9, 133.3, 127.7, 119.1, 112.7, 110.0, 95.7, 89.1, 56.2, 54.8, 53.7, 46.6, 40.5, 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.

N**-Nororipavine (11c).** Purified via method D using a gradient of $CHCl_3$/MeOH (24:1−17:3) to give the hydrochloride salt of **11c** as an off-white solid: mp > 200 °C dec; $[\alpha]^{24}_{D}$ −194 (*c* 0.83, 10% HOAc); ^{1}H NMR (D_2O/CF_3CO_2D, 400 MHz) δ 6.71−6.64 (m, 2 H), 5.76 (d, J = 6.8 Hz, 1 H), 5.38 (s, 1 H), 5.06 (d, J = 6.8 Hz, 1 H), 4.52 (d, J = 6.6 Hz, 1 H), 3.53 (s, 3 H), 3.37−3.13 (m, 4 H), 2.22 (ddd, J = 5.6, 13.4, and 13.4 Hz, 1 H), 1.91−1.85 (m, 1 H); ^{13}C NMR (D_2O/CF_3CO_2D, 100 MHz) δ 153.0, 142.8, 138.6, 132.0, 124.4, 124.2, 120.8, 117.3, 117.0, 96.0, 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**-Northevinone (12c).** Purified via method A using a gradient of $CHCl_3$/MeOH/NH_4OH (90:10:1−85:15:1) to afford a pale yellow solid: $[\alpha]^{24}_{D}$ −234 (*c* 1.25, $CHCl_3$) [lit.[27] $[\alpha]^{23}_{D}$ −240 (*c* 0.1, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 6.65 (d, J = 7.8 Hz, 1 H), 6.55 (d, J = 7.8 Hz, 1 H), 5.93 (d, J = 8.8 Hz, 1 H), 5.56 (d, J = 8.8 Hz, 1 H), 4.56 (s, 1 H), 3.82 (s, 3 H), 3.61 (s, 3 H), 3.54−3.47 (m, 1 H), 3.18−2.70 (m, 6 H), 2.16 (s, 3 H), 1.90−1.70 (m, 3 H), 1.42 (dd, J = 6.4 and 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 208.7, 147.9, 141.7, 135.7, 133.8, 128.0, 126.1, 119.2, 113.4, 95.6, 80.9, 56.4, 53.4, 52.7, 50.5, 40.1, 42.2, 37.2, 34.3, 33.0, 30.5, 29.4; MS (ESI) *m*/*z* 368 [M + H]$^+$.

N**-Noroxycodeinone (13c).** Purified via method C. Thus, 5% aqueous HCl (20 mL) was added, and the solution was adjusted to pH 7 with concentrated ammonia and extracted with CH_2Cl_2 (5 mL × 2) and $CHCl_3$ (10 mL × 4) to isolate oxycodeinone. The solution was then adjusted to pH 9 and extracted with $CHCl_3$/*i*-PrOH (3:1) to afford **13c** as an off-white solid: $[\alpha]^{24}_{D}$ −112 (*c* 1.2, 10% HOAc); ^{1}H NMR of (D_2O/CF_3CO_2D) δ 6.93 (d, J = 10.2 Hz, 1 H), 6.88−6.77 (m, 2 H), 6.14 (d, J = 10.2 Hz, 1 H), 4.94 (s, 1 H), 4.02−3.98 (m, 1 H), 3.74 (s, 3 H), 3.26−3.15 (m, 3 H), 2.90 (ddd, J = 4.0, 13.5, and 13.5 Hz, 1 H), 2.64 (ddd, J = 5.1, 13.5, and 13.5 Hz, 1 H), 1.82 (dd, J = 4.0 and 13.5 Hz, 1 H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 196.8, 147.4, 143.1, 142.2, 132.7, 128.2, 122.7, 120.8, 115.2, 85.8, 66.1, 56.2, 56.1, 45.8, 36.8, 27.1, 24.8; MS (ESI) *m*/*z* 300 [M + H]$^+$; HRMS $C_{17}H_{18}NO_4$ calcd for [M + H]$^+$ 300.1230, found 300.1240.

N**-Noroxymorphinone (14c).** Purified via method C. Thus, 5% aqueous HCl (20 mL) was added, and the solution was adjusted to pH 7 with concentrated ammonia and extracted with $CHCl_3$/*i*-PrOH (100:1) to isolate oxymorphinone. The solution was then adjusted to pH 9 and extracted with $CHCl_3$/*i*-PrOH (3:1) to afford **14c** as an off-white solid: mp > 230 °C dec; $[\alpha]^{24}_{D}$ −109 (*c* 1.2, 10% HOAc); ^{1}H NMR (D_2O/CF_3CO_2D) δ 6.95 (d, J = 9.9 Hz, 1 H), 6.77−6.70 (m, 2 H), 6.17 (d, J = 9.9 Hz, 1 H), 4.94 (s, 1 H), 4.05−3.98 (m, 1 H), 3.30−3.16 (m, 3 H), 2.93 (ddd, J = 3.9, 13.2, and 13.2 Hz, 1 H), 2.65 (ddd, J = 5.1, 13.2, and 13.2 Hz, 1 H), 1.86 (dd, J = 3.9 and 14.1 Hz, 1 H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 196.6, 147.5, 142.4, 138.4, 132.7, 128.6, 122.1, 120.9, 118.6, 85.8, 66.2, 56.2, 46.0, 36.9, 27.2, 24.8; MS (ESI) *m*/*z* 286 [M + H]$^+$; HRMS $C_{16}H_{16}NO_4$ calcd for [M + H]$^+$ 286.1074, found 286.1085.

N**-Noroxycodone (15c).** Purified via method A using a $CHCl_3$/MeOH/NH_4OH (90:10:1−85:15:1) gradient to afford **15c** as an off-white solid; a small sample was treated with 10% aqueous HCl to give the hydrochloride salt, mp > 250 °C. **15c**: $[\alpha]^{24}_{D}$ −123 (*c* 1.86, 10% HOAc) [lit.[7b] $[\alpha]^{20}_{D}$ −102.7 (*c* 0.875, MeOH); lit.[26] (+)-noroxycodone $[\alpha]^{25}_{D}$ +100 (*c* 0.55, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 6.74−6.61 (m, 2 H), 4.66 (s, 1 H), 3.92 (s, 3 H), 3.20−2.93 (m, 4 H), 2.75 (dd, J = 2.7 and 9.3 Hz, 1 H), 2.47−2.25 (m, 2 H), 1.89 (ddd, J = 3.0, 6.0, and 13.2 Hz, 1 H), 1.80 (br, 2 H), 1.70−1.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.5, 145.0, 143.0, 129.5, 125.2, 119.3, 114.8, 90.5, 70.2, 57.4, 56.8, 51.1, 37.2, 36.2, 32.9, 31.5, 30.1; MS (ESI) *m*/*z* 302 [M + H]$^+$; HRMS $C_{17}H_{20}NO_4$ calcd for [M + H]$^+$ 302.1387, found 302.1396.

N**-Noroxymorphone (16c).** Purified via method C. Thus, 5% aqueous HCl (20 mL) was added, and the solution was adjusted to pH 7 with concentrated ammonia and extracted with $CHCl_3$/*i*-PrOH (9:1) to isolate oxymorphone. The solution was then adjusted to pH 8−9 and extracted with $CHCl_3$/*i*-PrOH (3:1) to afford **16c** as an off-white solid: mp > 300 °C dec; $[\alpha]^{24}_{D}$ −154 (*c* 1.2, 10% HOAc); ^{1}H NMR (D_2O/CF_3CO_2D) δ 6.72−6.67 (m, 2 H), 4.90 (s, 1 H), 3.77 (dd, J = 2.1 and 4.8 Hz, 1 H), 3.15−3.10 (m, 3 H), 2.89 (ddd, J = 5.1, 14.7, and 14.7 Hz, 1 H), 2.75 (ddd, J = 3.9, 13.2, and 13.2 Hz, 1 H), 2.54 (ddd, J = 5.1, 13.2, and 13.2 Hz, 1 H), 2.25−2.15 (m, 1 H), 1.90 (ddd, J = 2.7, 4.8, and 14.1 Hz, 1 H), 1.65−1.54 (m, 2 H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 211.7, 143.0, 138.6, 127.3, 122.0, 120.9, 118.5, 89.3, 69.4, 57.4, 49.2, 36.7, 34.4, 30.3, 27.5, 25.7; MS (ESI) *m*/*z* 288 [M + H]$^+$; HRMS $C_{16}H_{18}NO_4$ calcd for [M + H]$^+$ 288.1230, found 288.1226.

N**-Nortropine (17c).** Purified via method B to give **17c** as an off-white solid: ^{1}H NMR (D_2O) δ 4.27−4.20 (m, 1 H), 4.20−4.10 (m, 1 H), 2.55−2.42 (m, 2 H), 2.36−2.30 (m, 1 H), 2.30−2.22 (m, 1 H), 2.22−2.02 (m, 4 H); ^{13}C NMR (D_2O, 150 MHz) δ 62.1, 61.9, 54.1, 54.0, 35.1, 25.5; MS (ESI) *m*/*z* 128 [M + H]$^+$; HRMS $C_7H_{13}NO$ calcd for [M + H]$^+$ 128.1070, found 128.1065. A small sample of **17c** was dissolved in H_2O, and 10% aqueous HCl was added to pH 2. The resulting solution was concentrated to dryness to give *N*-nortropine hydrochloride as a white solid, mp 281−285 °C dec (lit.[4b] mp 280−282 °C dec).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all *N*-nor compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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