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An Improved Process for the N-Demethylation of Opiate Alkaloids using an Iron(II) Catalyst in Acetate Buffer

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Abstract: An improved process to N-demethylate opiate alkaloids utilising a solution of the ferrous porphyrin, tetrasodium 5,10,15,20-tetra(4-sulfophenyl)porphyrinatoiron(II) [=Fe(II)-TPPS (**8**)], in acetate buffer is described. This method provided the corresponding N-demethylated opiates in good yield with high reproducibility.

Keywords: alkaloids; amine *N*-oxides; iron(II) porphyrins; N-demethylation; Polonovski reaction

Naturally occurring opiates such as morphine and codeine possess an *N*-methyl group. Varying this substituent produces profound pharmacological effects and there are a number of clinically relevant, semi-synthetic opiates in which the *N*-methyl group has been replaced by other alkyl moieties. Substituents such as allyl, cyclopropylmethyl and cyclobutylmethyl typically endow antagonist properties, although agonist activity is restored with longer alkyl groups such as phenethyl. For example, nalorphine (**1**) (Figure 1), which has an *N*-allyl group, has mixed agonist and antagonist activity, while *N*-phenethylnormorphine (**2**) acts as a (μ) agonist with 10-fold greater potency than morphine itself.[1] The combination of an *N*-allyl or *N*-cyclopropylmethyl group and some additional C-ring modifications (6-keto and 14-hydroxy functionality) affords the potent antagonists, naloxone (**3**) and naltrexone (**4**), respectively. Accordingly, N-demethylation of natural opiates is a key chemical transformation in the synthesis of semi-synthetic opiates.

N-Demethylation of natural opiates has been achieved in many ways including the use of reagents such as cyanogen bromide (von Braun reaction),[2] chloroformates[3] and diethyl azodicarboxylate,[4] as well as procedures utilising photochemistry,[5] electrochemistry[6] and microorganisms.[7] Our own laboratory has shown that the $FeSO_4 \cdot 7H_2O$-mediated non-classical Polonovski reaction is also effective in the N-demethylation of several opiate alkaloids.[8] These and other methods for the N-demethylation of alkaloids have been the subject of a recent review.[9]

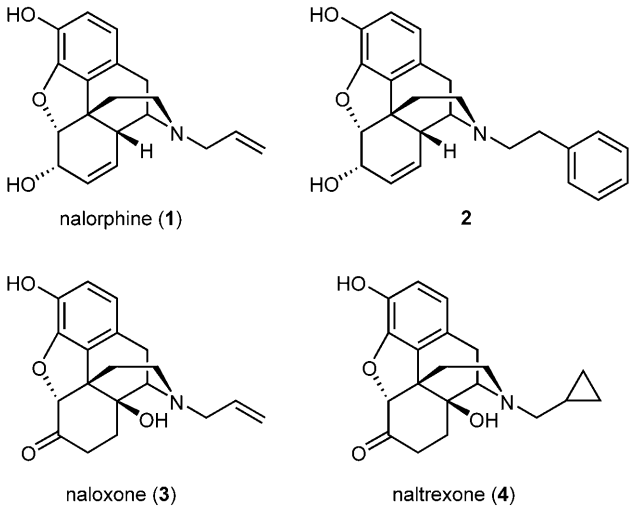
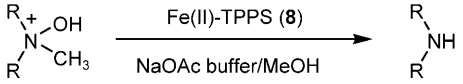
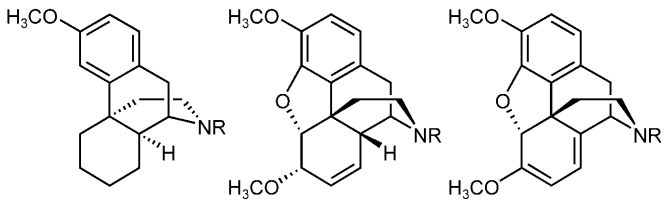


Figure 1. Semi-synthetic opiates.

We recently reported,[10] as summarised in Scheme 1, a new chemical process utilising a Fe(II) porphyrin-based complex for the N-demethylation of several opiate alkaloids such as dextromethorphan (**5a**), codeine methyl ether (CME) (**6a**), and thebaine (**7a**) (Figure 2). Thus, 0.3 molar equivalents of tetrasodium 5,10,15,20-tetra(4-sulfophenyl)porphyrinatoiron(II) [Fe(II)-TPPS (**8**)] in MeOH readily effected



Scheme 1. Fe(II)-TPPS-mediated N-demethylation.



5a R = CH_3 **6a** R = CH_3 **7a** R = CH_3
5b R = H **6b** R = H **7b** R = H

Figure 2. Dextromethorphan, codeine methyl ether and thebaine.

the N-demethylation of these *N*-methyl alkaloids, *via* the corresponding *N*-oxide hydrochloride, in moderate to high yields.

Using literature methodology,[10,11] Fe(II)-TPPS (**8**) was prepared *via* a two-step process: preparation of the porphyrin TPPS and the subsequent incorporation of ferrous ion into the porphyrin. Employing microwave-assisted irradiation at 200 °C for 15 min, pyrrole reacted with benzaldehyde to afford 5,10,15,20-tetraphenylporphyrin (TPP) in 25% yield. Subsequent sulfonation of TPP with concentrated sulfuric acid, followed by work-up with sodium hydroxide (pH 8–10) and lyophilisation, gave a quantitative yield of TPPS. TPPS was then treated with $FeSO_4 \cdot 7H_2O$ in a 1 M acetate buffer (pH 4) under refluxing conditions for 3.5 h. The reaction mixture was cooled and filtered. The filtrate was poured into acetone and the resulting precipitate isolated *via* centrifugation. The co-precipitation of the solution with acetone and the centrifugation processes were repeated. This provided a total isolated yield of 92% Fe(II)-TPPS (**8**).

In the earlier study,[10] a number of Fe(III)-porphyrins were evaluated as catalysts for N-demethylation. Using the *N*-oxide of CME (**6a**) as a substrate, stoichiometric or substoichiometric amounts of Fe(III)-TPPSCl failed to yield any of the desired N-demethylated product. Therefore, in the preparation and isolation of **8**, much care was taken to minimise exposure of the catalyst to air oxidation. Degassed buffer and solvents were employed and all operations were conducted under an inert atmosphere. Despite these measures we have subsequently observed variable efficiency from different batches of catalyst. Clearly a simpler and more consistent operation would enhance the synthetic utility of this catalyst.

Recently, Huszánk and Horváth reported that Fe(II)-TPPS (**8**) was stable in an acetate buffer, even after saturation with air or oxygen.[12] It was found that when a solution of **8** in acetate buffer was exposed to air, the ferrous species was stable even over weeks, with no conversion to the ferric form. These authors postulated that the acetate was able to trap traces of Fe(III), responsible for conversion of Fe(II)-porphyrins to the corresponding Fe(III) species. These findings prompted us to explore the use of **8** as a solution in acetate buffer in N-demethylations.

We report herein an improved process which utilises a solution of **8** in 1 M acetate pH 4 buffer for the N-demethylation of opiate alkaloids. A stock solution of a 0.025 M solution of **8** in 1 M sodium acetate pH 4 buffer was prepared by heating $FeSO_4 \cdot 7H_2O$ and TPPS in buffer under reflux for 3.5 h, as described above. The deep red-brown solution of Fe(II)-TPPS (**8**) in buffer was then cooled and used in N-demethylations without further purification.

The method was first illustrated with dextromethorphan (**5a**). Thus, oxidation of **5a** with *m*-CPBA in $CHCl_3$ and treatment with HCl provided the corresponding *N*-oxide hydrochloride in near quantitative yield. The solution of Fe(II)-TPPS (**8**) in buffer was then added to a stirred solution of the opiate *N*-oxide hydrochloride in MeOH. Using 20 mol% of catalyst, the reaction was found to proceed effectively at room temperature and was complete, as monitored by TLC analysis, after 144 h. Since only a substoichiometric amount of **7** was employed, when the reaction was complete, the bulk of the catalyst was readily removed *via* precipitation after the addition of Et_2O. The volatile organics were then removed and the crude product re-dissolved in $CHCl_3$. This was followed by a simple extractive work up and purification *via* column chromatography to remove a small amount of dextromethorphan (**5a**) (~5% by ^{1}H NMR). This provided an 87% yield of *N*-nordextromethorphan (**5b**) (Table 1, entry 1), which is comparable to that obtained in the case where isolated catalyst was employed.[10]

A number of experiments were then conducted to evaluate the scope of the reaction, varying the substrate to catalyst loading ratio, the reaction time and the temperature. Reactions were slow at room temperature, but proceeded at synthetically useful rates at 50–100 °C (Table 1). At these temperatures the reactions could be conducted with catalyst loadings as low as 2 mol% (entry 6).

Table 1. N-Demethylation of dextromethorphan *N*-oxide hydrochloride with Fe(II)-TPPS in acetate buffer.

Entry	Catalyst (equiv.)	Temp. [°C]	Time [h]	Yield [%] of **5b**[a]
1	0.2	20	144	87
2	0.1	20	168	nd[b]
3	0.1	50	7	88
4	0.05	50	24	86
5	0.05	100	7	86
6	0.02	50	96	83

[a] Isolated yield after column chromatography.
[b] Crude product, as analysed by ^{1}H NMR, showed incomplete conversion; *N*-oxide 16%, *N*-nordextromethorphan 81%, dextromethorphan 3%.

Table 2. N-Demethylation of CME *N*-oxide hydrochloride with Fe(II)-TPPS in acetate buffer.

Entry	Catalyst (equiv.)	Temp. [°C]	Time [h]	Yield [%] of **6b**[a]
1	0.05	20	408	61
2	0.05	50	43	90
3	0.05	80	6	84

[a] Isolated yield after column chromatography.

CME (**6a**) was also evaluated as a substrate for this reaction. Oxidation of CME with *m*-CPBA in $CHCl_3$ at 0 °C for 10 min followed by treatment with HCl provided the corresponding *N*-oxide hydrochloride in near quantitative yield. It is noteworthy that when H_2O_2 (30% w/v) was employed as the oxidant,[5,10] the reaction took longer to complete (1–2 days at room temperature).

Results for the N-demethylation of the CME *N*-oxide are summarised in Table 2. When a solution of CME *N*-oxide hydrochloride in MeOH was treated with 5 mol% of Fe(II)-TPPS (**8**) in buffer at room temperature, the reaction took approximately 17 days to complete and afforded the N-demethylated product in modest yield (Table 2, entry 1). When the reaction was conducted at 50 °C, the reaction was complete after 43 h and returned a 90% yield of the *N*-norCME (**6b**) (entry 2). A further increase in temperature reduced the reaction time to 6 h, but also gave a slightly lower yield of **6b** (entry 3).

When thebaine *N*-oxide hydrochloride was reacted with 0.1 equiv. of Fe(II)-TPPS in acetate buffer a 54% yield of *N*-northebaine was obtained. It has previously been noted that lower yields observed for the N-demethylation of thebaine may be related to the ratio and relative stability of the *N*-oxide isomers formed. Caldwell and co-workers have reported that the axial *N*-Me isomer of thebaine *N*-oxide (in the non-protonated form) completely decomposed upon standing in solution for 5 days while the equatorial *N*-Me isomer remained stable over this period.[13] As a result we investigated the ratio of *N*-oxide isomers formed by varying the oxidation conditions and the effect of this ratio on subsequent N-demethylation reactions.

Oxidation of thebaine (**7a**) with *m*-CPBA at 0 °C for 10 min provided a 65:35 mixture of two *N*-oxide isomers (Table 3, entry 1), with the *N*-oxide having the *N*-Me group equatorial being the major isomer. Isomer ratios were determined by ^{1}H NMR, according to peak assignments previously reported.[13] The ratio of isomers obtained was influenced by temperature. For example, when the oxidation was conducted at −45 °C, the ratio increased to 75:25 in favour of the equatorial isomer (*cf.* entries 1 and 3). In contrast, when a different oxidant and solvent were employed (30% H_2O_2 in MeOH),[10,13] the isomers were produced in a ratio of 35:65, with the axial isomer predominating (entry 5).

A sample of the equatorial *N*-Me isomer was isolated *via* column chromatography (silica gel column eluted with $CHCl_3$/MeOH/NH_4OH, 95:5:1–90:10:1). The hydrochloride form was also prepared by washing the free *N*-oxide in chloroform with 2 M HCl in brine. The N-demethylation of thebaine *N*-oxide was slower than the corresponding reactions with the *N*-oxides of dextromethorphan or CME. Accordingly, a higher catalyst loading and reaction temperature were required to achieve full conversion in a reasonable timeframe (0.1 equiv. of **8** at 80 °C). The pure equatorial isomer of thebaine *N*-oxide gave a significantly higher yield of the desired N-demethylated product when the protonated form of the *N*-oxide was used (Table 4, *cf.* entries 1 and 2). A similar outcome was observed when a mixture of thebaine *N*-oxide isomers was used (*cf.* entries 3 and 4).

The influence of the isomeric ratio was further probed through a comparison of the reaction of thebaine *N*-oxide hydrochloride either as the pure equatorial *N*-Me isomer or as a 65:35 or 75:25 mixture of *N*-oxide isomers (Table 4, entries 1, 3 and 5). All of these reactions afforded comparable isolated yields of *N*-northebaine (**7b**), which suggests that the isomeric configuration of the protonated *N*-oxide does not affect the final outcome of the reaction. On the other hand, the yield of **7b** greatly diminished when a 65:35

Table 3. Oxidation of thebaine to thebaine *N*-oxide.

Entry	Oxidant	Solvent	Temp. [°C]	Time [min]	Isomers E:A[a–c]
1	*m*-CPBA	CH_2Cl_2	0	10	65:35
2	*m*-CPBA	CH_2Cl_2	−18	10	71:29
3	*m*-CPBA	CH_2Cl_2	−45	10	75:25
4	*m*-CPBA	CH_2Cl_2	−78	20	75:25
5	H_2O_2	MeOH	0	960	35:65[d]

[a] Oxidation with *m*-CPBA, in all cases, gave near quantitative yields of *N*-oxide isomers.
[b] A, axial *N*-Me isomer; E, equatorial *N*-Me isomer.
[c] Isomer ratio as analysed by ^{1}H NMR.
[d] Ref.[13]

Table 4. N-Demethylation of thebaine *N*-oxide with Fe(II)-TPPS (0.1 equiv.) in acetate buffer.

Entry	*N*-Oxide	Isomer ratio (E:A)[a]	Yield [%] of **7b** (**7a**)[b,c]
1	HCl salt	100:0	71 (28)
2	free base	100:0	49 (22)
3	HCl salt	65:35	69 (28)
4	free base	65:35	21 (44)
5	HCl salt	75.25	72 (23)

[a] A, axial *N*-Me isomer; E, equatorial *N*-Me isomer.
[b] Isolated yield after column chromatography.
[c] Reactions were conducted at 80 °C for 24 h with 0.1 equiv. of Fe(II)-TPPS.

mixture of the free *N*-oxide isomers was employed, with the major product being the tertiary amine **7a** (entry 4). These outcomes are consistent with the observed inherent instability of the free base form of the axial *N*-Me *N*-oxide isomer.[13] On the other hand, the protonated forms of both isomers were found to be stable in $CHCl_3$ for at least 10 days at room temperature.

Tropane alkaloids have also been N-demethylated using the iron sulfate-mediated Polonovski reaction, albeit in modest yield.[8b] This Fe(II)-TTPS procedure effected the *N*-demethylation of atropine in 42% isolated yield, which is slightly lower than the best yield previously obtained with iron sulfate (51%).

In conclusion, *N*-methyl alkaloids can be efficiently N-demethylated *via* conversion to the corresponding *N*-oxide and treatment with a solution of Fe(II)-TPPS in acetate buffer. This method proved to be highly reproducible and obviated the tedious processes associated with isolation of the Fe(II)-TPPS catalyst. The improved stability of the catalyst in the acetate buffer allowed significantly lower catalyst loading to be employed without any deleterious effect on the reaction yield. Furthermore, it was found that mild heating of this reaction system could also significantly reduce reaction times (from over 100 h to less than 10 h).

The N-demethylation of thebaine was also studied in greater detail. It had previously been thought that the lower yields obtained from this substrate may have resulted from the instability of the axial isomer of the *N*-oxide. However, the hydrochloride salts of both thebaine *N*-oxide isomers were found to be stable in $CHCl_3$ for at least 10 days at room temperature. Furthermore, N-demethylation of the pure equatorial isomer of thebaine *N*-oxide hydrochloride proceeded in similar yield to 65:35 and 75:25 mixtures of isomers, suggesting that the isomeric configuration of the *N*-oxide hydrochloride does not affect the final outcome of the reaction.

Experimental Section

General N-Demethylation Procedure

Dextromethorphan·HBr·H_2O (3.00 g, 8.10 mmol) was dissolved in $CHCl_3$ (60 mL) and extracted using brine/NH_4OH (pH 10), dried (Na_2SO_4), filtered and cooled to 0 °C. *m*-CPBA (2.31 g of ~73% reagent, 9.77 mmol) was added in one portion and after 10 min, the solution was successively extracted with 10% NaOH/brine (pH 10) (2×10 mL), brine (2×5 mL) and 2 M HCl/brine (pH 2). The organic phase was dried (Na_2SO_4), filtered, and concentrated to afford dextromethorphan *N*-oxide hydrochloride as a white foam; yield: 2.49 g (94%).

The crude dextromethorphan *N*-oxide hydrochloride (100 mg, 0.309 mmol) was dissolved in MeOH (7 mL) and the specified equivalent of Fe(II)-TPPS from a 0.025 M stock solution in 1 M acetate pH 4 buffer was added. The total volume of buffer was then adjusted to 2.5 mL with additional buffer. The deep red-brown solution was then stirred for the specified time and temperature. When the reaction was complete, as analysed by TLC analysis, Et_2O (15 mL) was added and the precipitate was filtered over Celite. The filter pad was washed with Et_2O/MeOH (2:1, 5 mL×3) and the combined filtrate was concentrated. The resultant residue was taken up in brine (5 mL) and adjusted to pH 10 using NH_4OH. The mixture was extracted with $CHCl_3$ (3×5 mL), dried (Na_2SO_4), filtered, and evaporated. Subsequent column chromatography ($CHCl_3$/MeOH/NH_4OH; 90:10:0.5 to 85:15:1) gave *N*-nordextromethorphan as a pale yellow oil. ^{1}H NMR: δ=7.05 (1H, d, J=8.4 Hz), 6.80 (1H, d, J=2.4 Hz), 6.72 (1H, dd, J=8.4, 2.4 Hz), 3.78 (3H, s), 3.20–3.08 (2H, m), 3.00 (1H, br, NH), 2.81 (1H, d, J=18.0 Hz), 2.78–2.71 (1H, m), 2.63 (1H, ddd, J=12.6, 12.6, 3.0 Hz), 2.32 (1H, d, J=12.6 Hz), 1.82 (1H, m), 1.72–1.58 (2H, m), 1.57–1.47 (1H, m), 1.43–1.25 (5H, m), 1.07 (1H, m); HR-MS: m/z=258.1851, calcd. for $[M+H]^+$ $C_{17}H_{23}NO$: 258.1852.

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References

[1] D. S. Fries, in: *Foye's Principles of Medicinal Chemistry*, 5th edn., (Eds.: D. A. Williams, T. L. Lemke), Lippincott William & Wilkins, Philadelphia, **2002**.
[2] J. von Braun, *Ber. dtsch. chem. Ges.* **1909**, *42*, 2035.
[3] a) J. H. Cooley, E. J. Evian, *Synthesis* **1989**, 1; b) K. C. Rice, *J. Org. Chem.* **1975**, *40*, 1850; c) K. C. Rice, E. L. May, *J. Heterocycl. Chem.* **1977**, *14*, 665.
[4] a) L. S. Schwab, *J. Med. Chem.* **1980**, *23*, 698; b) H. Merz, K. H. Pook, *Tetrahedron* **1970**, *26*, 1727.
[5] J. A. Ripper, E. R. T. Tiekink, P. J. Scammells, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 443.
[6] a) P. J. Smith, C. K. Mann, *J. Org. Chem.* **1969**, *34*, 1821; b) J. E. Barry, M. Finkelstein, E. A. Mayeda, S. D. Ross, *J. Org. Chem.* **1974**, *39*, 3488.
[7] a) K. M. Madyastha, *Proc. Indian Acad. Sci.* **1994**, *106*, 1203; b) K. M. Madyastha, G. Vijay Bhasker Reddy, *J. Chem. Soc. Perkin Trans. 1* **1994**, 911.
[8] a) K. McCamley, J. A. Ripper, R. D. Singer, P. J. Scammells, *J. Org. Chem.* **2003**, *68*, 9847; b) S. Thavaneswaran, P. J. Scammells, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2868.
[9] S. Thavaneswaran, K. McCamley, P. J. Scammells, *Nat. Prod. Commun.* **2006**, *1*, 885.
[10] Z. Dong, P. J. Scammells, *J. Org. Chem.* **2007**, *72*, 9881.
[11] P. Rothemund, A. R. Menotti, *J. Am. Chem. Soc.* **1941**, *63*, 267.
[12] R. Huszánk, O. Horváth, *Chem. Commun.* **2005**, 224.
[13] G. W. Caldwell, A. D. Gauthier, J. E. Mills, *Magn. Res. Chem.* **1996**, *34*, 505.

