Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2014, **16**, 1399

Studies on the oxidative N-demethylation of atropine, thebaine and oxycodone using a Fe^{III}-TAML catalyst†

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Received 20th September 2013,
Accepted 26th November 2013

DOI: 10.1039/c3gc41972j

www.rsc.org/greenchem

The reaction pathway and selectivity of the oxidative N-demethylation of the alkaloid atropine with H_2O_2 using a Fe^{III}-TAML catalyst has been investigated. The conversion of atropine in ethanol with aqueous H_2O_2 produces noratropine as the main product and *N*-formyl-noratropine and other atropine derivatives involving carbon-hydroxylated tropane species as minor by-products. Comparative reactivity studies with noratropine, *N*-formyl-noratropine and atropine *N*-oxide demonstrated that the Fe^{III}-TAML catalyses the N-demethylation of atropine by a biomimetic oxidation pathway involving the formation and then decomposition of a *N*-hydroxymethylnoratropine intermediate. The reaction selectivity for atropine N-demethylation *versus* *N*-methyl oxidation to *N*-formyl-noratropine was found to be sensitive to the structure of the alcohol co-solvent, the rate of H_2O_2 addition and the concentration of water, whereas temperature mainly affected the atropine conversion efficiency. The use of *tert*-butyl or cumene hydroperoxide as oxidants shifted the reaction selectivity toward *N*-methyl oxidation compared to aqueous H_2O_2. Various inorganic oxidants were found to be ineffective. The Fe^{III}-TAML also catalysed the N-demethylation of the opiate alkaloids thebaine and oxycodone with aqueous H_2O_2 in higher conversion efficiencies compared to atropine but with lower selectivity. These investigations thus document key mechanistic features of the Fe^{III}-TAML-catalysed N-demethylation of these alkaloids and provide insight into how this benign catalytic system could find broader utilisation for N-demethylation in general.

Introduction

The naturally occurring alkaloids atropine (**1**), scopolamine (**2**) and cocaine (**3**) along with the opiate morphine (**4**) all contain a tertiary *N*-methylamine group (Fig. 1) and have been used for many centuries by humans as medicinal and psychoactive agents. Modification of the *N*-methylamine group alters the pharmacological properties of these alkaloids and provides an avenue to many important pharmaceutical compounds. For example, N-demethylation of **1** to noratropine (**13**) (Scheme 1) followed by N-alkylation with isopropyl bromide and then with methyl bromide provides the bronchodilator ipratropium bromide (**6**), containing axial and equatorial *N*-isopropyl and *N*-methyl substituents, respectively.[1] A similar transformation of **2** provides the bronchodilator oxitropium bromide (**7**) with axial and equatorial *N*-ethyl and *N*-methyl substituents, respectively.[1b] In contrast, N-alkylation of **1** installs the alkyl group in both axial and equatorial positions,[1a] while for **2** the alkyl group is located in the equatorial position.[2]

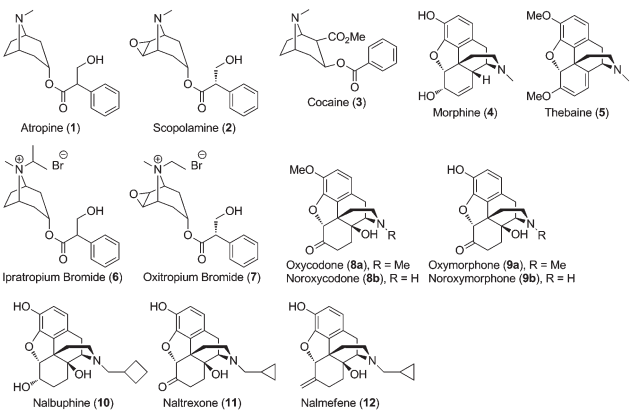

Fig. 1 Structures of various naturally occurring tertiary *N*-methyl alkaloids (**1–5**) and their synthetic derivatives (**6–12**).

Amongst the opiate family, thebaine (**5**) serves as a synthetic precursor for the analgesic oxycodone (**8a**) and the intermediate oxymorphone (**9a**).[3] The latter compound is used to prepare the *N*-methylcyclobutyl-based analgesic nalbuphine (**10**) and the *N*-methylcyclopropyl-based opioid antagonists naltrexone (**11**) and nalmefene (**12**) (Fig. 1) used in the treatment

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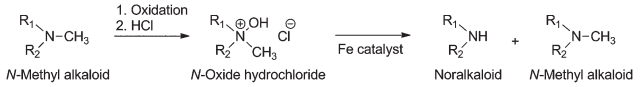
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3gc41972j



Scheme 1 Modified Polonovski reaction for *N*-demethylating tertiary *N*-methyl alkaloids using iron-based catalysts.

of alcohol or opiate dependence and for rapid opiate detoxification. Transformation of **9a** to **10–12** incorporates a N-demethylation step, leading to noroxymorphone (**9b**), whereby the nascent secondary nitrogen atom can be alkylated directly with an alkyl halide or indirectly *via* reductive acylation.[3] N-demethylation of tropane and opiate alkaloids to their noralkaloid derivatives is thus a key step in the synthesis of multiple pharmaceuticals.

A number of procedures have been developed to *N*-demethylate **1** or **2** to nortropane derivatives, *e.g.* phosgene,[1b] 2,2,2-tri-chloroethylchloroformate[4] or α-chloroethylchloroformate,[5] oxidative N-demethylation with $KMnO_4$ [1b,5,6] or photochemical oxidative N-demethylation.[7] Although these methods can provide nortropane derivatives in mid to high yields (*e.g.* 35–90%), they employ toxic reagents and solvents and generate hazardous waste by-products. N-demethylation of oxymorphone (**9a**) to noroxymorphone (**9b**) in the commercial syntheses of **10–12** uses the highly toxic cyanogen bromide (BrCN) as demethylating reagent and generates stoichiometric waste by-products.[3] Moreover, this von Braun reaction requires O-protection and O-deprotection steps which reduce the overall synthetic efficiency and create additional solvent waste.

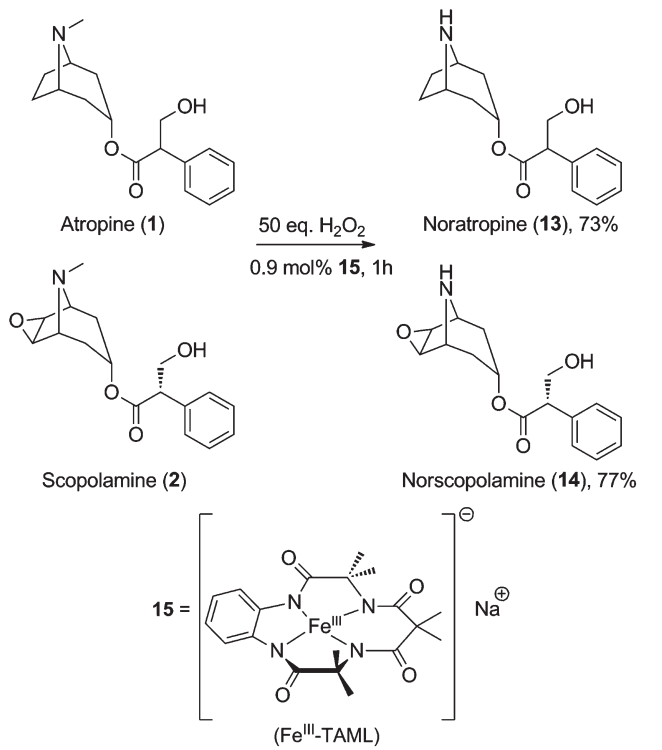
During the last ten years, modifications of the Polonovski reaction have been used to N-demethylate tropane and opiate alkaloids *via* their *N*-oxides using Fe(II)SO_4,[8] tetrasodium 5,10,15,20-tetra(4-sulfophenyl)porphyrinato-Fe(II),[9] ferrocene and its derivatives,[10] iron powder[11] or stainless steel[11b] as catalysts (Scheme 1). These processes typically employ a two-step process with oxidation of the alkaloid using *m*-chloroperbenzoic acid (*m*CPBA) to the corresponding *N*-oxide which is isolated as a hydrochloride salt and then heated with an iron catalyst.

m-Chloroperbenzoic acid has also been used as the oxidant followed by addition of aqueous HCl and a mixture of iron powder (13 mol%) and $FeCl_3 \cdot 6H_2O$ (2 mol%) in a one-pot procedure.[12] Although satisfactory yields of specific noralkaloids were achieved with this method, a limitation was the significant regeneration of the starting *N*-methyl alkaloid due to a competing reduction of an intermediate aminium radical cation by the iron catalyst. Thus, the product noralkaloid has to be purified from the starting material by chromatography and these additional unit operations are undesirable in a commercial production setting due to the yield reduction, additional solvent use and excessive waste disposal. Further, the use of *m*CPBA as an oxidant on a large scale presents its own hazard and waste disposal issues.

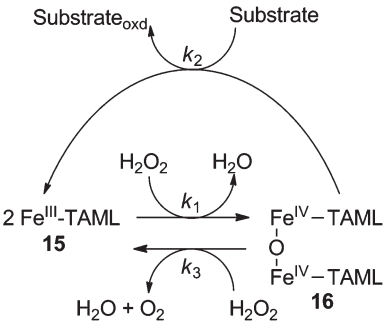
Palladium-based catalytic methods under an oxygen atmosphere have also been used for N-demethylation/N-acylation of **1** and opiate alkaloids using 2–20 mol% catalyst, depending on the substrate.[13] However, in the case of **1**, due to dehydration of the primary alcohol group, the Pd-catalysed N-demethylation/N-acylation lacked chemoselectivity.[13a] Although Pd-catalysed N-demethylation/N-acylations have been applied in the syntheses of the opiate drugs buprenorphine[13b] and naltrexone,[13c] use of Pd catalysts in the commercial production of active pharmaceutical ingredients (APIs) leads to the problematic issues of cost and Pd contamination where levels well below 10 ppm are mandated.[14]

Collectively, there is thus a need to develop efficient and more benign catalytic methods for the N-demethylation of *N*-methyl alkaloids to overcome these constraints. We have recently reported an efficient and convenient method for *N*-demethylating the tropane alkaloids **1** and **2** in high yield and product purity using aqueous H_2O_2 and the iron(III) tetraamido macrocyclic complex Fe^{III}-TAML (**15**) as a catalyst in various organic co-solvents (Scheme 2).[15] The potential offered by **15** for selective N-demethylation of other compounds has also been documented in a study on the catalytic oxidative decomposition of the environmentally persistent antidepressant drug sertraline in water.[16] Sertraline contains a secondary *N*-methylamine group and **15** was found to catalyse its N-demethylation to the primary amine as part of the decomposition pathway.

The Fe^{III}-TAML complex **15** was originally developed by the Collins group as an environmentally benign catalyst for oxidative remediation of persistent organic pollutants using aqueous H_2O_2.[17] Its catalytic properties have subsequently



Scheme 2 N-Demethylation of atropine (**1**) and scopolamine (**2**) using aqueous H_2O_2 and Fe^{III}-TAML catalyst (**15**) in 96% EtOH co-solvent.



Scheme 3 Catalytic pathways for the oxidation of substrate with the Fe^{III}-TAML catalyst **15** in an aqueous solution of H_2O_2.

been studied in pulp and paper processing,[18] aluminium refining[19] and fuel desulfurization.[20] A general pathway for the **15**-catalyzed oxidation of organic substrates with H_2O_2 in water involves a pH-dependant oxidation of **15** by H_2O_2 to a Fe(IV) μ-oxo dimer (**16**) which is then reduced by the substrate (Scheme 3).[17a] The **15**-catalysed decomposition of H_2O_2 to H_2O and O_2 [21] or solvent oxidation represent competing reactions.

Although **15** has been investigated extensively as a catalyst for the destruction of water pollutants, its full potential in organic synthesis is less well documented. Here, we report further studies designed to delineate the reaction pathway of the **15**-catalysed N-demethylation of **1** and the impact of various parameters on the reaction selectivity and conversion efficiency. The reactivity of the opiate alkaloids thebaine (**5**) and oxycodone (**8a**) with the **15**/H_2O_2 system has also been documented, demonstrating that N-demethylation also occurs with these compounds, but with a reduced level of selectivity under the same conditions optimised for the tropane alkaloids.

Experimental section

General analytical procedures

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz with a Bruker DRX400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard (δ 0.00 ppm). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz on a Bruker DRX400 spectrometer in $CDCl_3$. Low resolution electrospray ionization (ESI) mass spectra were recorded on a Micromass Platform II API QMS Electrospray mass spectrometer with cone voltage at 20 V or 35 V as solutions in MeOH containing formic acid. High resolution ESI mass spectra were recorded on a Brucker BioApex 47e Fourier Transform mass spectrometer. Principle ion peaks (*m*/*z*) are reported and M denotes the molecular ion.

High performance liquid chromatography-mass spectrometry (HPLC-MS) analyses were performed using a 1100 Series microflow HPLC coupled to an Agilent LC/MSD Trap electrospray ionization ion trap mass spectrometer. A Zorbax 300SB-C18 (150 × 0.3 mm, 3.5 μm sorbent) reverse phase column was used and the solvent systems were 0.2% acetic acid in H_2O (A) and 0.2% acetic acid in acetonitrile (B). Samples were chromatographed using a gradient of 0–2 min 5% B and then 2–30 min 5% B to 65% B at a flow rate of 4 μL min^{-1} and a sample (0.1 μL, 20 μg mL^{-1}) injected in 5% B. Temperature measurements were made using a HI-93530 K-thermocouple thermometer from Hanna Instruments, Keysborough, Australia. Controlled addition of aqueous H_2O_2 to reaction mixtures was performed with a Model 100 Series syringe pump from KD Scientific.

Reagents

Aqueous hydrogen peroxide (30%) was purchased from Merck, Kilsyth, Australia. Atropine, 70% aq. *tert*-butyl hydroperoxide, 5.0–6.0 M *tert*-butyl hydroperoxide in decane, 80% cumene hydroperoxide, potassium peroxymonosulfate, potassium persulfate and MnO_2 were purchased from Sigma-Aldrich, Castle Hill, Australia. Chlorine-based household bleach (4%) was used as a source of NaOCl. Thebaine was a gift from Tasmanian Alkaloids (Launceston, Australia). The Fe^{III}-TAML catalyst **15** (CAS: 895567-73-4) was purchased from GreenOx Catalysts Inc., Pittsburgh, USA. The composition of **15** was specified by the manufacturer to be 70% w/w **15**, 20–30% w/w isopropanol, 3–5 wt% NaCl and 5% w/w metal-free tetraamido macrocycle.

Synthesis of *N*-formyl-noratropine (17)

To a stirred solution of formic acid (115 mg, 2.51 mmol) in dichloromethane (5 mL) on an ice bath was added solid *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydro-chloride (240 mg, 1.25 mmol) and the mixture stirred to give a solution. After 15 min, a solution of noratropine (345 mg, 1.25 mmol) and *N*-methylmorpholine (126 mg, 1.25 mmol) in dichloromethane (10 mL) at 0 °C was added. The mixture was then removed from the ice bath and stirred for 1 day, and then washed successively with 1 M HCl (2 × 15 mL), sat. $NaHCO_3$ (15 mL) and sat. NaCl (15 mL). The solution was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a 1 : 1 mixture of **17** *N*-formyl isomers as an oil (204 mg, 54%). ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 0.5H, N**H**CO), 8.04 (s, 0.5H, N**H**CO), 7.45–7.20 (m, 5H, Ph**H**), 5.17 (t, J = 4.0 Hz, 1H, C**H**–O–), 4.54 (m, 0.5H, C**H**–NCHO), 4.42 (m, 0.5H, C**H**–NCHO), 4.20 (dd, J = 9.6 Hz, 1H, **H**CH–OH), 3.99 (m, 0.5H, C**H**–NCHO), 3.85–3.79 (m, 2.5H, C**H**–NCHO, HC**H**–OH, Ph–C**H**–), 2.39 (broad s, 1H, O**H**), 2.17–1.54 (m, 7H, C**H**$_2$), 1.33–1.24 (m, 1H, tropane –**H**CH–); ^{13}C NMR ($CDCl_3$) 172.03 (O**C**=O), 172.02 (O**C**=O), 157.38 (**C**H=O), 135.57 (**C**), 135.50 (**C**), 128.95 (**C**H), 128.94 (**C**H), 128.08 (**C**H), 128.06 (**C**H), 127.86 (**C**H), 127.84 (**C**H), 68.09 (H**C**–O), 63.97 (**C**H$_2$–OH), 63.95 (**C**H$_2$–OH), 54.46 (**C**H), 54.45 (**C**H), 53.39 (**C**H), 53.31 (**C**H), 48.56 (**C**H), 48.47 (**C**H), 38.43 (**C**H$_2$), 38.12 (**C**H$_2$), 35.79 (**C**H$_2$), 35.54 (**C**H$_2$), 27.84 (**C**H$_2$), 27.41 (**C**H$_2$), 27.09 (**C**H$_2$), 26.70 (**C**H$_2$); Calcd for $[C_{17}H_{22}NO_4 + H]^+$: 304.1549, obsvd: 304.1545.

Synthesis of atropine *N*-oxide hydrochloride (18·HCl)

To a stirred solution of atropine (0.500 g, 1.73 mmol) in $CHCl_3$ (6 mL) at −25 °C was added solid *m*-chloroperoxybenzoic acid (77%, 409 mg, 2.94 mmol). After stirring for 2.5 h, iron(III) sulphate (4.8 mg, 12 μmol) was added to destroy excess *m*-CPBA

and the mixture was then extracted with 1 M HCl (3 × 7 mL). The aqueous extracts were combined, washed with $CHCl_3$ (2 × 20 mL) and concentrated *in vacuo*. The concentrate was then freeze-dried to obtain a 1.3 : 1 mixture of **18**·HCl equatorial and axial *N*-oxide isomers as a white solid (495 mg, 84%). ^{1}H NMR (D_2O) δ 7.49–7.40 (m, 5H, Ph**H**), 5.12–5.07 (m, 1H, C**H**–O–), 4.24 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{1,3}$ = 6.6 Hz, 1H, –**H**CH–OH), 4.13–3.93 (m, 4H, C**H**–N(CH_3)O, –HC**H**–OH, Ph–C**H**–), 3.53 (s, 1.7 H, C**H**$_3$–NO), 3.41 (s, 1.3H, C**H**$_3$–OH), 2.81 (ddd, $J_{1,2}$ = 16.4 Hz, $J_{1,3}$ = 4.0, 4.0 Hz, 0.43H, –**H**CH–), 2.74 (ddd, $J_{1,2}$ = 16.4 Hz, $J_{1,3}$ = 4.0, 4.0 Hz, 0.57H, –**H**CH–), 2.67–2.54 (m, 1H, –**H**CH–), 2.44–1.92 (m, 4.57H, –C**H**$_2$–), 1.81 (d, $J_{1,2}$ = 16.4 Hz, 0.43H, –**H**CH–), 1.68 (ddd, $J_{1,2}$ = 14.4 Hz, $J_{1,3}$ = 10.4, 4.6 Hz, 0.43H, –**H**CH–), 1.59 (ddd, $J_{1,2}$ = 12.8 Hz, $J_{1,3}$ = 9.6, 3.8 Hz, 0.57H, –**H**CH–); ^{13}C NMR (D_2O) 173.15 (**C**=O), 172.98 (**C**=O), 135.26 (**C**), 135.16 (**C**), 129.19 (**C**H), 129.10 (**C**H), 128.28 (**C**H), 128.22 (**C**H), 128.20 (**C**H), 71.71 (**C**H$_3$), 71.60 (**C**H$_3$), 70.41 (**C**H$_3$), 70.29 (**C**H$_3$), 64.71 (**C**H–OH), 63.72 (**C**H–OH), 62.09 (**C**H$_2$–OH), 53.60 (**C**H), 53.55 (**C**H), 52.36 (**C**H), 46.19 (CH), 24.64 (**C**H$_2$), 24.40 (**C**H$_2$), 22.88 (**C**H$_2$), 22.61 (**C**H$_2$); Calcd for $[C_{17}H_{23}NO_4 + H]^+$: 306.1705, obsvd: 306.1703. The ^{1}H NMR spectrum of the neutral form was measured by adding 1 equivalent of $NaHCO_3$ to the D_2O solution: 7.49–7.40 (m, 5H, Ph**H**), 5.09 (broad m, 1H, C**H**–O), 4.25 (ddd, 1H, $J_{1,2}$ = 14 Hz, $J_{1,3}$ = 7.0, 6.6 Hz, **H**CH–OH), 4.06–3.99 (m, 2H, HC**H**–OH, Ph–C**H**–), 3.89 (broad m, 0.57H, C**H**–N(CH_3)O), 3.76 (broad m, 1H, C**H**–N(CH_3)O), 3.65 (broad m, 0.43H, C**H**–N(CH_3)O), 3.39 (s, 1.7H, C**H**$_3$–NO), 3.28 (s, 1.3H, C**H**$_3$–NO), 2.78 (broad m, 1H, –**H**CH–), 2.59 (broad m, 1H, –**H**CH–), 2.36–1.87, m, 4.57H, –**H**CH–), 1.75 (d, $J_{1,2}$ = 16 Hz, 0.43H, –**H**CH–), 1.69–1.55 (m, 1H, –**H**CH–).

Synthesis of oxycodone (8a)

Oxycodone was synthesized from thebaine (6.00 g. 19.3 mmol) following the procedure of Kraβnig *et al.*,[25] with an extended hydrogenation of the 14-hydroxycodeinone intermediate. The yield of **8** from thebaine was 66%. ^{1}H NMR ($CDCl_3$) δ 6.70 (d, J = 8.0 Hz, 1H, Ph**H**), 6.64 (d, J = 8.0 Hz, 1H, Ph**H**), 5.30 (s, 1H, C**H**–O–), 3.87 (s, 3H, C**H**$_3$–O–), 3.16 (d, $J_{1,2}$ = 18.4 Hz, 1H, Ph–**H**CH–), 3.02 (ddd, $J_{1,2}$ = 14.4 Hz, $J_{1,3}$ = 14.4, 5.2 Hz, 1H, –**H**CH–C=O), 2.86 (d, J = 6.0 Hz, 1H, C**H**–N), 2.56 (dd, $J_{1,2}$ = 18.4 Hz, J_{13} = 6.0 Hz, 1H, Ph–HC**H**–), 2.49–2.35 (m, 2H, –**H**CH–N, –**H**CH–CH$_2$–N), 2.30 (ddd, $J_{1,2}$ = 14.4 Hz, $J_{1,3}$ = 3.2 Hz, 1H, HC**H**–C=O), 2.21–2.13 (m, 1H, –HC**H**–N), 1.87 (ddd, $J_{1,2}$ = 13.2 Hz, $J_{1,3}$ = 5.2, 3.2 Hz, 1H, –**H**CH–C–OH), 1.67–1.54 (m, 2H, –HC**H**–CH$_2$–N, –HC**H**–C–OH); ^{13}C NMR ($CDCl_3$) 208.44 (**C**=O), 144.87 (**C**), 142.80 (**C**) 129.34 (**C**), 124.96 (**C**), 119.39 (**C**H), 115.00 (**C**H), 90.28 (–O–**C**H), 70.25 (HO–**C**), 64.45 (*N*-**C**H), 56.74 (O–**C**H$_3$), 50.12 (**C**), 45.15 (*N*-**C**H$_2$–), 42.66 (*N*-**C**H$_3$), 36.06 (O=C–**C**H$_2$–), 31.33 (–**C**H$_2$–CH$_2$–N), 30.43 (HO–C–**C**H$_2$–), 21.83 (Ph–**C**H$_2$–); Calcd for $[C_{18}H_{21}NO_4 + H]^+$: 316.1549, obsvd: 316.1549.

General method for Fe^{III}-TAML-catalyzed N-demethylation of atropine with H_2O_2 and analysis of product fractions

To a solution of atropine (**1**) and **15** in alcohol solvent, as specified in Tables 1–5, was added the specified amount of H_2O_2 as a 30% aqueous solution. An ice bath was used for the reaction performed at 0 °C and a dry ice-acetone bath used for reactions performed at −20 and −40 °C. Reaction mixtures were left to stir for the time specified and then a catalytic amount of MnO_2 (7 mol%) was added to decompose any remaining H_2O_2. The mixture was then basified with 10% aqueous ammonia to pH 11 (indicator paper) and extracted with $CHCl_3$. Control experiments in which MnO_2 was not used to decompose H_2O_2 gave the same conversion of **1** and yields of **13** and **17** but resulted in significant bubbling and heating of the aqueous extract upon addition of 10% NH_3. The organic extract was extracted with 1 M HCl, dried (Na_2SO_4), filtered and solvent was then removed *in vacuo* to give crude *N*-formyl-noratropine (**17**), as identified by ^{1}H NMR and by comparison to the ^{1}H NMR and HPLC-MS of **17** synthesized independently from noratropine (**13**) (Fig. S3 & S4†).[22] The molecular masses of other atropine derived by-products in the sample of crude **17** were measured by HPLC-MS while the relative amount of **17** to the by-products was estimated by ^{1}H NMR integration of the NC**H**O and C**H**–O– peaks. The 1 M HCl aqueous extract above was basified with 10% aqueous ammonia and then extracted with $CHCl_3$. The organic extract was dried (Na_2SO_4), filtered and solvent was then removed *in vacuo* to give mixtures of **13** and **1**, as specified. The ratio of **13** to **1** was determined from the relative integrations of the ^{1}H NMR C**H**–OC(O) and C**H**–N signals and, along with the sample mass, used to calculate the conversions and yields of **1** and **13**, respectively.

Reactivity studies with atropine *N*-oxide·HCl, atropine *N*-oxide, *N*-formyl-noratropine and noratropine

To a solution of substrate (50 mg) in 96% ethanol (1.5 mL) containing **15** (1 mol%), or no catalyst, was added 50 molar equivalents of H_2O_2 as a 30% aqueous solution. The mixture was stirred for 1 h and worked up as described for the N-demethylation of atropine. For the reactions of **13**, **17**, and **20**·HCl with catalyst alone, substrate (50 mg) and **15** (1 mol%) were stirred for 1 h in 96% ethanol (1.5 mL) with work up as described above. To test the reactivity of the atropine *N*-oxide, 1 equivalent of $NaHCO_3$ dissolved in the H_2O_2 solution or in water was added to **20**·HCl in 96% ethanol (1.5 mL) to generate the neutral form.

Reaction of noratropine with CH_2O, H_2O_2 and Fe^{III}-TAML

To a solution of **13** (331 mg, 1.2 mmol) and **15** (8 mg, 0.012 mmol) in 96% ethanol (10 mL) was added 40% formaldehyde (0.90 mL, 12 mmol). The mixture was stirred for 5 min and then 30% H_2O_2 (6.1 mL, 60.1 mmol) was added. The mixture was then stirred for 1 h and worked up as described for the N-demethylation of atropine. Solvent was removed from the acid-insoluble organic extract to give crude **17** (207 mg). This was chromatographed on silica gel with 19 : 1 DCM–MeOH to give **17** as a colourless oil (144 mg, 40% yield). For the reaction without **15**, the same workup and chromatography gave **17** in 10% yield. For the reactions of **13** with CH_2O and TAML alone or with CH_2O alone, the same workup gave a crude product in 6% and 10% mass recovery, respectively.

Analysis of these products by ^{1}H NMR showed they contained 10 mol% of **17** relative to the other **13**-derived products, as indicated by the relative integration values of the N**H**CO and C**H**–O– peaks.

Temperature change measurements

The thermocouple probe of the thermometer was inserted into a stirred solution **1** and **15** or **1** and **15** alone in ethanol as specified in Fig. 2. The temperature was recorded and an aqueous solution of 30% H_2O_2 was then added as specified in Fig. 2, and the temperature recorded at the times indicated.

Measurement of *n*-butanol conversion

To a stirred solution of *n*-butanol (100 mg, 1.35 mmol) in H_2O (2.0 mL) was added H_2O_2 as a 30% aqueous solution, as specified in Table 4, or an equal volume of H_2O alone. The mixture was stirred for 1 h and then extracted with $CDCl_3$ (2, 2.7 and 3.4 mL for the 1, 5 and 10 eq. H_2O_2 reactions, respectively). The $CDCl_3$ extract was dried (Na_2SO_4), filtered into a measuring cylinder and the volume recorded. Toluene (0.67 mmol) was then added as an internal standard and a portion of the solution was analysed by 1H NMR. The amount of *n*-butanol relative to toluene was then calculated from the relative integrations of the *n*-butanol and toluene ^{1}H NMR peaks. This ratio was used to derive the yield of recovered *n*-butanol. The conversions of *n*-butanol reported in Table 4 are calculated from the differences between the amount of *n*-butanol recovered from **15**/H_2O_2 reaction mixtures relative to *n*-butanol recovered from H_2O alone.

Syringe pump addition of H_2O_2

A solution of H_2O_2 as specified in Table 7 was drawn up into a 3 mL polypropylene syringe through 1 mm internal diameter (i.d.) polytetrafluoroethylene tubing. The syringe with attached tubing was then fixed to the syringe pump and the H_2O_2 solution then added to a stirred solution of **1** and **15** in 96% (v/v) ethanol.

General method for Fe^{III}-TAML-catalyzed N-demethylation of atropine with organic hydroperoxides

To a solution of **1** (50 mg, 0.173 mmol) and 1 mol% **15** in 96% EtOH or anhydrous EtOH was added hydroperoxide, as specified in Table 7. Reaction mixtures were left to stir for the time specified and then a catalytic amount of $Fe_2(SO_4)_3xH_2O$ (1 mg) was added to decompose any remaining hydroperoxide. The mixture was then worked up as described for the H_2O_2-based reactions. For the cumene hydroperoxide reactions excess cumyl alcohol was isolated with **17**. The amount of **17** relative to cumyl alcohol was estimated by ^{1}H NMR integration of the **17** NC**H**O and cumyl alcohol *ortho*-Ph**H** signals. The amount of **17** relative to other atropine by-products, as well as yield, was estimated by ^{1}H NMR and HPLC-MS, as described for **17** obtained from H_2O_2-based reactions. The conversion of **1** and yield of **13** was measured as described for mixtures from H_2O_2-based reactions.

Reactions of atropine with KO_3SOOH, $K_2O_3SOOSO_3$ or NaOCl and Fe^{III}-TAML

To a solution of **1** (50 mg, 0.173 mmol) 1 mol% **15** in 2 : 1 v/v H_2O/96% EtOH (1.5 mL) was added 1 equivalent of oxidant as a solid (for KO_3SOOH and $K_2O_3SOOSO_3$) or a solution (for NaOCl). The mixture was stirred for 1 h and worked up as described for the H_2O_2-based reactions. Neither **13** or **17** were isolated from any of these reaction mixtures.

Reaction of thebaine with H_2O_2 and Fe^{III}-TAML

To a solution of **5** (50 mg, 0.161 mmol) and 1 mol% **15** in acetone (3.0 mL) was added 0.161 or 0.483 mmol H_2O_2 as a 30% aqueous solution. The mixture was stirred for 1 h and worked up as described for the H_2O_2-based reactions with **1**. The reaction of **5** (0.161 mmol) with H_2O_2 (0.483 mmol) alone resulted in 95% recovery of **5**.

Reaction of oxycodone with H_2O_2 and Fe(III)-TAML

To a solution of **8a** (50 mg, 0.158 mmol) and 1 mol% **15** in acetone (3.0 mL) was added 0.474 mmol H_2O_2 as a 30% aqueous solution. The mixture was stirred for 1 h and worked up as described for the N-demethylation of **1**. The same reaction without **15** gave back 95% **8a**. For the reaction at −40 °C with **15**, 0.79 mmol H_2O_2 was used.

Preparative N-demethylation of oxycodone using Fe^{III}-TAML

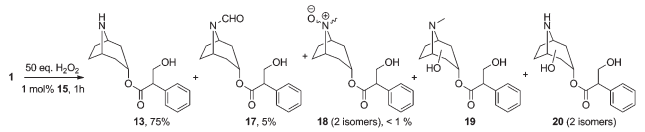
To a solution of **8a** (500 mg, 1.58 mmol) 1 mol% **15** in acetone (30 mL) at 23 °C or −40 °C was added 4.7 or 7.9 mmol H_2O_2, respectively, as a 30% aqueous solution. The mixture was stirred for 1 h and then a catalytic amount of MnO_2 (10 mg) was added to decompose excess H_2O_2. The mixture was then basified with 10% ammonia (50 mL) to pH 11 (indicator paper) and extracted with $CHCl_3$ (3 × 50 mL). The organic extract was extracted with 1 M HCl (50 mL). The aqueous extract was then basified with 10% ammonia (50 mL) to pH 11, extracted with $CHCl_3$ (3 × 100 mL), dried (Na_2SO_4), filtered and solvent removed *in vacuo* to give an oil. This was chromatographed on silica gel (99 : 1–5 : 1 v/v DCM/1.5 M methanolic ammonia) to give crude noroxycodone (**8b**) as an oil in 17% (85 mg) and 13% (66 mg) mass recoveries for the 23 °C and −40 °C reactions, respectively, as assessed by ^{1}H NMR which showed no *N*-methyl protons (Fig. S14†),[20] by high-resolution mass spectrometry which showed a predominant peak at 302.1383 *m*/*z* (calcd for $[C_{17}H_{19}NO_4 + H]^+$: 302.1392) (Fig. S16†)[22] and, for the reaction at room temperature, predominant noroxycodone signals in the ^{13}C NMR: ($CDCl_3$) 208.36 (**C**═O), 145.06 (**C**), 143.07 (**C**) 129.33 (**C**), 124.93 (**C**), 119.45 (**C**H), 115.03 (**C**H), 90.45 (–O–**C**H), 70.14 (HO–**C**), 57.38 (*N*-**C**H), 56.84 (O–CH_3), 50.93 (**C**), 37.17 (*N*-CH_2–), 36.11 (O═C–CH_2–), 32.36 (–CH_2–), 31.47 (–CH_2–), 29.74 (Ph–CH_2–) (Fig. S15†).[22]

Results and discussion

Fe^{III}-TAML-catalysed reaction of atropine with H_2O_2

The reaction of **1** with 50 equivalents of H_2O_2 in ethanol co-solvent containing 1 mol% **15** gave **13** as the main product (Fig. S1 and S2†)[22] along with *N*-formyl-noratropine (**17**) as a by-product (Scheme 4) which was separated from **13** by solvent-extraction. The identity of **17** was established by ^{1}H NMR and HPLC-MS and verified by a sample of **17** synthesized separately by N-acylation of **13** with formic acid (Fig. S3 and S4†).[22]

The effect of changes from 1 to 100 equivalents of H_2O_2 on the conversion of 1 and the production of **13** and **17** are shown in Table 1. The hydroxylated atropine by-product **19** (306.1 *m*/*z*) and two isomeric hydroxylated noratropine by-products (**20**) (*m*/*z* 292.1) were present in the aqueous extract by HPLC-MS (Scheme 4 & Fig. S5†).[22] Although **19** and atropine *N*-oxide (**18**) have the same molecular mass, they were readily distinguished by their different HPLC retention times (Fig. S5†)[22] and only trace amounts of **18** were detected in the aqueous extract. Further analysis of **19** and **20** by-products by MS/MS fragmentation led to the production of species with *m*/*z* values of 140.0 and 126.1, consistent with hydroxylated tropane and nortropane ring fragments, respectively (Fig. S4†).[22]



Scheme 4 Products from the reaction of **1** with H_2O_2 and **15**.

Table 1 Percentage conversion and major/minor product yields for the Fe^{III}-TAML-catalyzed oxidative N-demethylation of atropine (**1**) with different amounts of H_2O_2

Entry	Eq. H_2O_2	**1**[h] (%)	**13**[h] (%)	**17**[i] (%)
1[a]	0	0	0	0
2[a]	1	61	36	1
3[a]	2	80	50	7
4[a]	5	94 ± 2[j]	56 ± 6[j]	6
5[b]	5	93	54	10
6[c]	5	44[k]	0	0
7[d]	5	30[k]	0	0
8[a]	10	96	70	5
9[a]	25	98	72	5
10[a]	50	97 ± 1[l]	75 ± 5[l]	5
11[e]	50	98	63	16
12[f]	50	99	46	17
13[g]	50	44	0	0
14[a]	100	99	77	4

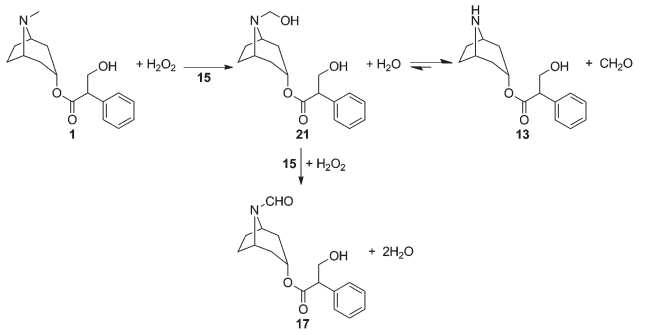
[a] 0.173 mmol **1**, 1 mol% **15**, 1.5 mL 96% EtOH, 1 h. [b] 17 h. [c] 0.5 mol% $Fe_2(SO_4)_3xH_2O$. [d] 1 mol% $FeCl_3(H_2O)_6$. [e] 0.5 M **1**. [f] 1 M **1**. [g] No catalyst. [h] Conversion of **1** and yield of **13** determined by ^{1}H NMR of the isolated product mixture. [i] Yield estimated by ^{1}H NMR and HPLC-MS of the crude acid-insoluble organic extract. [j] Mean conversion and yield from four reactions with standard deviations shown. [k] Mixtures of **1** and 5–10 mol% **18** were isolated. [l] Mean conversion and yield from six reactions with standard deviations shown.

To determine if either of the hydroxylated noratropine by-products **20** were produced by hydroxylation of **13** or by N-demethylation of a hydroxylated *N*-methyl precursor, **13** was allowed to react under the same reaction conditions as for **1** and the aqueous extract analyzed by HPLC-MS (Fig. S7†).[22] In contrast to the reaction with **1**, neither isomer of **20** was detected, suggesting that they are produced by N-demethylation of a hydroxylated *N*-methyl precursor. This result, along with the MS/MS fragmentation analysis and corresponding NMR spectral analysis, also supports the conclusion that neither of the isomers of **20** is the *N*-hydroxy-noratropine, as proposed previously,[15] but instead contain hydroxylated tropane carbon atoms.

Reaction pathway of N-demethylation

To determine if **17** or **18** were reaction intermediates or dead-end by-products of the N-demethylation reaction, their reactivity in the **15**/H_2O_2 system was investigated. Accordingly, treatment of **17**, **18**·HCl or *in situ*-neutralized **18** with 1 mol% **15** and 50 equivalents of H_2O_2 or with **15** alone or H_2O_2 alone did not produce **13**. In the case of the *N*-oxide **18**, the majority (>90%) of this compound did not react and was recovered in the aqueous phase following a standard workup, as assessed by HPLC-MS. For **17**, 80% of this material was recovered whilst again no evidence for the formation of **13** was obtained. Examination of the aqueous extract by HPLC-MS demonstrated that **17** was the predominant tropane species.

Collectively, these results confirm that **17** and **18** are not significant reaction intermediates in the **15**-catalysed N-demethylation of **1** to **13** with H_2O_2. The N-demethylation of **1** thus appears to occur *via* a biomimetic-like catalytic oxidation to *N*-hydroxymethyl-noratropine **21** which mainly decomposes to **13** and formaldehyde or, alternatively, is further oxidized to the dead-end by-product **17** (Scheme 5). Although *in vitro* or *in vivo* metabolic oxidative N-demethylation of **1** and **2** is known, the reaction pathways have not been established for these substrates nor have the putative *N*-oxide intermediates been isolated as oxidation products.[23] However, for other tertiary *N*-methyl and *N*-alkylamines, many lines of evidence suggest that metabolic N-dealkylation to secondary amine and aldehyde



Scheme 5 Reaction pathway proposed for the **15**-catalyzed oxidative N-demethylation of atropine **1** to noratropine **13** and formation of *N*-formyl-noratropine **17** *via* a *N*-hydroxymethylnoratropine intermediate **21**.

products by cytochrome p450 enzymes occurs predominantly *via* an α-hydroxy amine intermediate (*viz.* **21**) rather than *via* a *N*-oxide.[24]

In order to provide additional evidence for a role of the putative intermediate **21** in the conversion pathway, **13** was allowed to react with excess formaldehyde and 1 mol% **15**, generating an equilibrium mixture of **13** and **21**. When H_2O_2 was added this experiment led to the production of **17** in 40% yield, whereas the reaction without **15** present only gave a 10% yield. These results are consistent with the reaction pathway shown in Scheme 5 and indicate that **15** also catalyses the conversion of **21** to **17**. In contrast to the reactions carried out in the presence of H_2O_2, only trace amounts (<1%) of **17** were isolated from the reaction of **13** with formaldehyde and **15** or with formaldehyde alone.

Studies on atropine N-demethylation selectivity

The effects of various reaction parameters on atropine N-demethylation selectivity were investigated with the overall aim to find conditions giving the highest yield of **13** and reducing the need for a large excess of H_2O_2. The reaction of **1** with the **15**/H_2O_2 system is highly exothermic, as measured by the increase in temperature when H_2O_2 was added to a solution of **1** with 1 mol% **15** at room temperature (Fig. 2). In contrast, the reaction of H_2O_2 with **1** or **15** alone is much less exothermic.

These results prompted an investigation into the effect of different temperatures on the conversion of **1** and yields of **13** (Table 2) and **17**. When the reaction was carried out at 0 or 50 °C, similar conversions and product yields were obtained to those performed at room temperature (Table 2, entries 4, 5 & 6). Lowering the temperature to −20 or −40 °C gave reduced conversions and yields (Table 2, entries 1 & 2) which did not increase with an extended reaction time (Table 1, entry 3). It was noted that similar yields of **17** (3–5%) were obtained over the temperature range studied, showing that temperature only marginally influenced N-demethylation/*N*-methyl oxidation selectivity in these reactions.

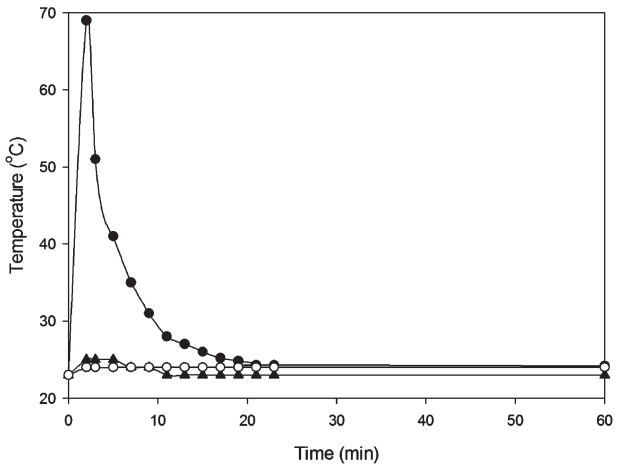


Fig. 2 Temperature *versus* time profiles for the reaction of atropine (0.173 mmol) with H_2O_2 (8.6 mmol) and 1 mol% Fe^{III}-TAML (filled circles), or with H_2O_2 alone (open circles) and for the reaction of H_2O_2 (8.6 mmol) with 1.6 μmol Fe^{III}-TAML (filled triangles). Each reaction was performed with 1.5 mL 96% ethanol co-solvent.

Table 2 Influence of temperature on the Fe^{III}-TAML-catalysed oxidative N-demethylation of atropine

Entry[a]	*T* (°C)	*t* (h)	**1**[b] (%)	**13**[b] (%)
1	−40	1	82	65
2	−20	1	82	64
3	−20	6	80	60
4	0	1	97	73
5	23	1	98	71
6	50	1	98	78

[a] 0.173 mmol **1**, 8.65 mmol H_2O_2, 1 mol% **15**, 1.5 mL 96% EtOH, 1 h. [b] Conversion of **1** and yield of **13** determined by ^{1}H NMR of the isolated product mixture.

The use of alternative alcohol co-solvents was investigated next in order to examine the extent of competing solvent oxidation which possibly accounts, in some part, for the high excess of H_2O_2 required to achieve a good yield of **13** in high purity. In previous studies, DMSO, acetonitrile and dimethylcarbonate were all oxidized by the **15**/H_2O_2 system.[15] To estimate the relative rate of oxidation of the ethanol co-solvent, the reactivity of *n*-butanol with **15**/H_2O_2 as a model alcohol was investigated since it could be more readily extracted from the aqueous phase for measurement by ^{1}H NMR.

The results of these experiments showed that although aqueous *n*-butanol reacts more slowly with the H_2O_2/**15** system compared to **1** in ethanol (Table 3), a significant amount of the solvent is oxidized. This finding suggests that the ethanol oxidation by analogy is a significant competing reaction during the N-demethylation of **1** as it is present in a large molar excess. Moreover, the use of more sterically hindered alcohol co-solvents in the N-demethylation reaction with the **15**/H_2O_2 system may lead to improve yields because of their lower reactivity.

When compared to reactions carried out in ethanol, the **15**-catalyzed conversion of **1** with 1 equivalent of H_2O_2 was lower in isopropanol or *tert*-butanol co-solvents, and the reaction selectivity was shifted to *N*-methyl oxidation, as evident from the higher yields of **17** (Table 4, entries 1, 4 & 7). The lower conversions of **1** obtained in isopropanol and *tert*-butanol suggest that competing alcohol oxidation does not significantly limit the conversion of **1**.

Increasing the amount of H_2O_2 to 5 molar equivalents gave almost complete conversion of **1** in isopropanol and

Table 3 Reactivity of *n*-butanol with the Fe^{III}-TAML/H_2O_2 system

Entry	Eq. H_2O_2	*n*-Butanol[a] (%)	**1** (%)
1	1	0	57[b]
2	5	25	87[b]
3	10	25	96[c]

[a] 675 mM aqueous *n*-Butanol, 1 mol% **15**, 1 h. Conversion determined by ^{1}H NMR. [b] 500 mM **1** in 96% EtOH. [c] 115 mM **1** in 96% EtOH.

Table 4 Fe^{III}-TAML-catalyzed oxidative N-demethylation of atropine in different alcohol solvents

Entry[a]	Solvent	Eq. H_2O_2	**1**[b] (%)	**13**[b] (%)	**17**[c] (%)
1	EtOH	1	61	36	1
2	EtOH	5	94	56	6
3	EtOH	50	98	71	5
4	iPrOH	1	55	36	4
5	iPrOH	5	99	49	18
6	iPrOH	50	99	71	6
7	*t*BuOH	1	56	29	5
8	*t*BuOH	5	99	37	26
9	*t*BuOH	50	99	45	20
10	MeOH	5	87	53	3
11	MeOH	50	88	65	5

[a] 0.173 mmol **1**, 1 mol% **15**, 1.5 mL solvent, 1 h. [b] Conversion of **1** and yield of **13** determined by ^{1}H NMR of the isolated products. [c] Yield from the ^{1}H NMR and HPLC-MS of the crude acid-insoluble organic extract.

tert-butanol (Table 4, entries 2, 5 & 8) and higher purity **13** as assessed by ^{1}H NMR compared to the reaction in ethanol, (*cf.* Fig. S8†).[22] However, compared to the reaction with 1 equivalent of H_2O_2, there was a shift in reaction selectivity toward the production of **17**, the extent of which followed the order *tert*-butanol > isopropanol > ethanol, with lower yields of **13** being obtained with isopropanol and *tert*-butanol compared to the reaction in ethanol.

Interestingly, further increases in the amount of H_2O_2 to 50 molar equivalents in ethanol, isopropanol or *tert*-butanol led to the reaction selectivity being shifted towards N-demethylation (Table 4, entries 3, 6 & 9). In terms of conversion efficiency, methanol was a relatively poor solvent whilst the reaction selectivity was similar to that observed with ethanol (Table 4, entries 10 & 11).

Overall, these results show the conversion of **1** and selectivity of N-demethylation *vs.* *N*-methyl oxidation are influenced by both the amount of aqueous H_2O_2 and structure of the alcohol co-solvent. Competing alcohol oxidation did not appear to be significant factor in limiting the conversion of **1**. Instead, both conversion efficiency and reaction selectivity appear to be more affected by the hydrophobicity of the solvent system and substrate concentration, which presumably affect the rates of conversion of **21** to **13** and **17**, and competing alternative catalytic oxidations of **1** (*cf.* Scheme 5) and catalytic decomposition of H_2O_2.

This shift in reaction selectivity toward N-demethylation observed upon increasing H_2O_2 from 5 to 50 molar equivalents in the isopropanol or *tert*-butanol solvent systems is presumably due in part to the higher water content. To further investigate the effect of water on the reaction selectivity, reactions were performed in isopropanol containing different initial amounts of water as a co-solvent, while keeping the amount of H_2O_2 constant (Table 5). The results confirmed that increasing water content shifted the reaction selectivity of **1** toward N-demethylation over oxidation to **17** but at the expense of lower conversion. The lower conversions obtained with increasing amounts of water present is possibly a result of an increased rate of competing **15**-catalysed decomposition of H_2O_2 (Scheme 3).

Table 5 Effect of water on the reaction of atropine (**1**) with Fe^{III}-TAML and H_2O_2

Entry[a]	iPrOH (mL)	H_2O (mL)	**1**[b] (%)	**13**[b] (%)	**17**[c] (%)
1	1.25	0.25	97	64	14
2	1	0.5	94	62	9
3	0.75	0.75	84	65	5
4	0.5	1	71	49	2

[a] 0.173 mmol **1**, 0.865 mmol H_2O_2, 1 mol% **15**, 1 h. [b] Conversion of **1** and yield of **13** determined by ^{1}H NMR of the products. [c] Yield estimated by ^{1}H NMR and HPLC-MS of the crude acid-insoluble organic extract.

In order to minimize competing **15**-catalyzed decomposition of H_2O_2 during the N-demethylation reaction, the effect of reducing the H_2O_2 concentration was examined. To this end, 30% (v/v) H_2O_2 was diluted with water and added slowly to the reaction mixture using a syringe pump. Compared to the faster addition from an auto-pipette, the reaction of **1** in ethanol with H_2O_2 added as a 2.6% aqueous solution dropwise over 1 h led to almost complete conversion of **1** (99%), a lower yield but higher purity of **13** and a shift in reaction selectivity toward production of **17** (Table 5, entry 1 & *cf.* Fig. S9†[22]) and other products.

Increasing the rate of addition of H_2O_2 marginally increased the yield of **13** and gave similar reaction selectivity (Table 6, entries 1–3). The shift in reaction selectivity toward **17** resulting from the slow addition of H_2O_2 compared to faster addition from an auto-pipette may be due to the initially more hydrophobic solvent environment associated with the slower additions. To validate this hypothesis, the same slow addition of H_2O_2 experiment was carried out with a solution of **1** and **15** in 1 : 1 EtOH–H_2O, resulting in a shift in selectivity toward N-demethylation but also a lower conversion of **1** (Table 6, entries 1 & 4).

The use of a mixture of 1 : 1 isopropanol and water as the solvent led to the higher conversion of **1** but shifted the reaction selectivity toward production of **17** (Table 5, entries 4 & 5). It is notable that the slow addition of H_2O_2 to the 1 : 1

Table 6 Fe^{III}-TAML-catalyzed oxidative N-demethylation of atropine with different rates of H_2O_2 addition

Entry[a]	Pump rate (mL h^{-1})	**1**[d] (%)	**13**[d] (%)	**17**[e] (%)
1	1	99	36	17
2	2	99	39	18
3	4	99	43	19
4[b]	1	80	36	11
5[c]	1	99	27	21

[a] 0.173 mmol **1** and 1 mol% **15** in 1.5 mL 96% EtOH. H_2O_2 (0.865 mmol, 2.6% aq., 1 mL) was delivered dropwise *via* 1 mm i.d. tubing and the reaction was stirred for 15 min after complete addition. [b] **1** and **15** in 1.5 mL 1 : 1 96% EtOH–H_2O. [c] **1** and **15** in 1.5 mL 1 : 1 iPrOH–H_2O. [d] Determined by ^{1}H NMR of the isolated mixture of **1** and **13**. [e] Yield estimated by ^{1}H NMR of the crude acid-insoluble organic extract.

isopropanol–H_2O system gave a much higher conversion and different reaction selectivity compared to the faster addition of H_2O_2 to the same solvent system (Table 6, entry 5 & Table 5, entry 3). Overall, slowing the rate of addition of H_2O_2 to the reaction milieu enabled almost complete conversion of **1** with a smaller five-fold excess of H_2O_2 and afforded **13** in better purity but in lower yield due to a shift in reaction selectivity from N-demethylation toward production of **17**.

N-Demethylation of atropine with alternative oxidants

The use of sterically hindered *tert*-butyl and cumene hydroperoxides as oxidants was anticipated to give higher conversions of **1** compared to H_2O_2 as a result of their slower catalytic decomposition by **15**, in accord with their known slow reaction with **15** to give **16** compared to H_2O_2 [17a] (Scheme 3). With aqueous *t*BuOOH, the conversion of **1** and the yield of **13** were in fact lower than that obtained with H_2O_2 while the yield of **17** was considerably higher (Table 6, entries 1–4). Similar results were obtained when a non-aqueous solution of *t*BuOOH and anhydrous ethanol was employed as the co-solvent (Table 7, entries 6–9). The reaction of **1** with *t*BuOOH alone gave a relatively low conversion (Table 7, entry 5) and produced mainly atropine *N*-oxide, as assessed by HPLC-MS.

The inorganic oxidants sodium hypochlorite, potassium peroxymonosulfate and potassium persulfate reacted with **15** to give the same yellow-to-black colour change associated with H_2O_2 or organic hydroperoxide activation. However, their use in the N-demethylation of **1** with 1 mol% **15** gave low conversions (<25%) compared to H_2O_2 with neither **13** or **17** obtained. Presumably, these differences are due to the propensity of these oxidants to destroy the catalyst and/or the competing non-catalytic solvent oxidation during substrate oxidation.

In contrast to *t*BuOOH, one equivalent of cumene hydroperoxide gave a conversion and yield of **1** and **13**, respectively, similar to that of H_2O_2 (Table 6, entry 10). Extending the reaction time with cumene hydroperoxide increased the conversion of **1** but not the yield of **13** (Table 7, entries 10 & 11). Increasing the amount of cumene hydroperoxide increased the conversion of **1**, with almost complete conversion being achieved with 3 molar equivalents (Table 7, entries 10, 12 & 13). However, compared to H_2O_2 the reaction selectivity was shifted toward production of **17** and the purity of the obtained **13** was reduced to *ca.* 87%, as assessed by ^{1}H NMR and HPLC-MS together with detected 12 mol% of atropine by-products (m/z $[M + H]^+$ 292.2, 303.2 and 350.2).

Increasing the amount of cumene hydroperoxide to five molar equivalents decreased the yield of **13** (Table 7, entries 14 & 15) and whilst **17** was not isolated from the organic extract, the presence of other *N*-formyl-containing products was evident from the ^{1}H NMR of the crude product. The identity of these products has yet to be determined.

Table 7 Fe^{III}-TAML-catalyzed oxidative N-demethylation of atropine with organic hydroperoxides

Entry[a]	ROOH	Eq.	T (h)	**1**[d] (%)	**13**[d] (%)	**17**[e] (%)
1	*t*-$Bu_{(aq)}$	1	1	47	20	12
2	*t*-$Bu_{(aq)}$	1	17	47	12	19
3	*t*-$Bu_{(aq)}$	5	1	88	30	35
4	*t*-$Bu_{(aq)}$	5	17	82	28	36
5[b]	*t*-$Bu_{(aq)}$	5	1	22	0	0
6[c]	*t*-Bu	1	1	49	16	15
7[c]	*t*-Bu	1	17	49	11	31
8[c]	*t*-Bu	5	1	100	9	24
9[c]	*t*-Bu	5	17	95	21	46
10	Cumene	1	1	57	41	3
11	Cumene	1	17	70	35	3
12	Cumene	2	1	88	70	9
13	Cumene	3	1	99	52	17
14	Cumene	5	1	100	43	0
15	Cumene	5	17	100	25	0

[a] 0.173 mmol **1**, 1 mol% **15**, 1.5 mL 96% EtOH. [b] Without **15**. [c] Anhydrous EtOH and *t*-BuOOH in decane. [d] Conversion of **1** and yield of **13** determined by ^{1}H NMR of the isolated mixture. [e] Yield estimated by ^{1}H NMR of the crude acid-insoluble organic extract.

Fe^{III}-TAML catalysed reactions of thebaine and oxycodone with H_2O_2

Based on the above results with **1**, the N-demethylation of the pharmaceutical precursor thebaine (**5**) was then investigated. For solubility reasons, it was necessary to use acetone as the water miscible organic co-solvent, a solvent system which has been shown to be suitable for the **15**-catalysed N-demethylation of atropine (**1**) in modest yield.[15] In contrast to **1**, the reaction of **5** with three equivalents of H_2O_2 and 1 mol% **15** gave complete conversion and resulted in, *inter alia*, N-demethylation and oxidation and O-demethylation of the 1-methoxycyclohexa-1,3-diene system to give a complex product mixture, as assessed by ^{1}H NMR of the crude product (*cf.* Fig. S10†).[22]

It is known that **5** reacts readily with H_2O_2 under acidic conditions to give 14-hydroxycodeinone, a reaction that is employed in the industrial synthesis of oxycodone (**8a**).[3] However, under our basic reaction conditions there was no significant reaction of **5** with H_2O_2 alone, as evident from the recovery of >95% **5** from the reaction mixture. For the crude product obtained from the reaction of **5** with one equivalent of H_2O_2 and 1 mol% **15**, the integration ratios of the diene CH to OCH_3 to *N*-CH_3 ^{1}H NMR signals indicated the rates of N-demethylation and oxidation of the diene system were similar (Fig. S10†).[22] Analysis of the crude product mixture by HPLC-MS did not detect northebaine (*cf.* Fig. S11),[22] further demonstrating that the reaction was less selective for N-demethylation.

Due to the lower reaction selectivity and complex product mixture obtained with thebaine, attention was focused on the reaction of oxycodone (**8a**) with the **15**/H_2O_2 system. Compared to **5**, complete conversion was also achieved with 3 equivalents of H_2O_2 and 1 mol% **15**, giving a complex product mixture by ^{1}H NMR (*cf.* Fig. S12†).[22] The ^{1}H NMR of the crude product showed relatively weak singlets in the *N*-CH_3 region, indicating that significant but not complete N-demethylation had occurred (*cf.* Fig. S12†).[22] The reaction of **8a** with five equivalents of H_2O_2 at −40 °C and 1 mol% **15** also resulted in complete conversion and significant N-demethylation but led to a different product mixture by HPLC-MS (Fig. S13†).[22] There was

no significant reaction of **8a** with H_2O_2 alone, as evident from the recovery of 95% of **8a** from a room temperature reaction.

The HPLC-MS chromatograms of the basic alkaloid fractions obtained from the **15**-catalyzed reactions at 23 and −40 °C showed a predominant peak due to a species with *m*/*z* 302.2, corresponding to [noroxycodone (**8b**) + H]$^+$ (*cf.* Fig. S13†).[22] For the product obtained at −40 °C, the HPLC-MS showed an additional peak of similar intensity due to a species with *m*/*z* 300.2, indicative of a dehydrogenated noroxycodone derivative (*cf.* Fig. S13†).[22] For both reactions, HPLC-MS also detected several different minor co-eluting by-products (*cf.* Fig. S13†).[22] Attempts to separate these products from both reactions by flash chromatography were unsuccessful due to similar retention times of the products, with only noroxycodone recovered in relatively low amounts, *i.e.* with ~17% overall mass recovery.

Conclusion

This investigation has further documented the oxidative N-demethylation of atropine (**1**) and the opioids, thebaine (**5**) and oxycodone (**8a**), using the Fe^{III}-TAML catalyst **15** and various different reaction conditions. On the basis of reactivity studies, it can be concluded that the **15**-catalysed N-demethylation of atropine (**1**) to noratropine (**13**) with H_2O_2 follows a biomimetic oxidation pathway involving formation of the *N*-hydroxymethyl-noratropine (**21**) intermediate.

Although good yields and purity of **13** can be obtained in a simple one-pot process, a relatively high 50-fold molar excess of H_2O_2 is required. Experiments using more oxidation-resistant alcohol co-solvents showed that alcohol oxidation is not a significant competing reaction that limits the conversion of **1** but that the conversion efficiency, as well as N-demethylation *versus N*-methyl oxidation selectivity, is affected by the hydrophobicity of the solvent. Slower addition of H_2O_2 to minimize the competing **15**-catalysed decomposition led to a higher conversion of **1** with a smaller excess of H_2O_2 but gave lower yields of **13** due to a shift in reaction selectivity toward the production of **17**.

Overall, these findings suggest that the more hydrophobic alcohol co-solvents stabilize the intermediate **21**, enhancing its **15**-catalyzed oxidation to **17**. In contrast, higher amounts of water in the reaction milieu favour N-demethylation by enhancing the decomposition of **21** to **13** but is also associated with reduced conversion, presumably due to increasing the rate of competing catalytic H_2O_2 decomposition. Compared to H_2O_2, a higher conversion of **1** was achieved with a smaller excess of the more sterically hindered cumene hydroperoxide but also resulted in a shift in reaction selectivity toward production of **17**. This shift in selectivity could be due to a faster non-catalytic reaction of cumene hydroperoxide with **21** compared to H_2O_2 or hydrophobic stabilisation of **21**.

When compared to the tropane alkaloid **1**, the **15**-catalysed N-demethylation of the opiate alkaloids thebaine (**5**) and oxycodone (**8a**) with H_2O_2 was less selective and gave more complex product mixtures. For **5**, both N-demethylation and oxidation of the diene system occur at similar rates and *O*-demethylation also occurs. In the case of **8a**, noroxycodone was produced from the reaction but in low yield due to poor catalyst selectivity.

It is clear from this current study that the catalytic selectivity of **15** for the N-demethylation of *N*-methylamine alkaloids is dependent on the substrate structure, with **15** providing greater N-demethylation selectivity for the tropane alkaloid class under the conditions examined. These results also highlight that further structural refinement of the Fe^{III}-TAML catalyst or related low-toxicity oxidation catalysts would be a productive line of research to enable even more efficient and selective N-demethylation reactions to be used in the industrial-scale syntheses of active pharmaceutical ingredients (APIs) and other compounds *via* one-pot processes using an environmentally benign oxidant such as H_2O_2. This objective is the focus of our on-going research.

Acknowledgements

The funding support of the Australian Research Council is gratefully acknowledged.

Notes and references

1 (*a*) I. Tsyskovskaia, M. Kandil and Y. Beaumier, *Synth. Commun.*, 2007, **37**, 439–446; (*b*) K. J. Erb, D. H. Martyres and P. Seither, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2000, vol. 3, pp. 639–675.
2 R. Glaser, D. Shiftan and M. Drouin, *J. Org. Chem.*, 1999, **64**, 9217–9224.
3 E. Friderichs, T. Christoph and H. Buschmann, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2000, vol. 3, pp. 339–386.
4 J. R. Pfister, *J. Org. Chem.*, 1978, **43**, 4373–4374.
5 F. Balssa and Y. Bonnaire, *J. Labelled Compd. Radiopharm.*, 2009, **52**, 269–272.
6 M. J. Van der Meer and H. K. L. Hundt, *J. Pharm. Pharmacol.*, 1983, **35**, 408.
7 (*a*) J. A. Ripper, E. R. T. Tiekink and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 443–445; (*b*) J. Santamaria, R. Ouchabane and J. Rigaudy, *Tetrahedron Lett.*, 1989, **30**, 3977–3980; (*c*) J. Santamaria, R. Ouchabane and J. Rigaudy, *Tetrahedron Lett.*, 1989, **30**, 2927–2928.
8 (*a*) S. Thavaneswaran and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2868–2871; (*b*) K. McCamley, J. A. Ripper, R. D. Singer and P. J. Scammells, *J. Org. Chem.*, 2003, **68**, 9847–9850.
9 (*a*) Z. Dong and P. J. Scammells, *J. Org. Chem.*, 2007, **72**, 9881–9885; (*b*) G. Kok, T. D. Ashton and P. J. Scammells, *Adv. Synth. Catal.*, 2009, **351**, 283–286.

10 (*a*) G. B. Kok and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4499–4502; (*b*) G. B. Kok and P. G. Scammells, *Synthesis*, 2012, 2587–2594.
11 (*a*) G. B. Kok, C. C. Pye, R. D. Singer and P. G. Scammells, *J. Org. Chem.*, 2010, **75**, 4806–4811; (*b*) G. B. Kok and P. G. Scammells, *Org. Biomol. Chem.*, 2011, **9**, 1008–1011.
12 G. B. Kok and P. G. Scammells, *Aust. J. Chem.*, 2011, **64**, 1515–1521.
13 (*a*) R. J. Carroll, H. Leisch, E. Scocchera, T. Hudlicky and D. P. Cox, *Adv. Synth. Catal.*, 2008, **350**, 2984–2992; (*b*) A. Machara, L. Werner, M. A. Endoma-Arias, D. P. Cox and T. Hudlicky, *Adv. Synth. Catal.*, 2012, **354**, 613–626; (*c*) A. Machara, D. P. Cox and T. Hudlicky, *Adv. Synth. Catal.*, 2012, **354**, 2713–2718.
14 C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043.
15 D. D. Do Pham, G. F. Kelso, Y. Yang and M. T. W. Hearn, *Green Chem.*, 2012, **14**, 1189–1195.
16 L. Q. Shen, E. S. Beach, Y. Xiang, D. J. Tshudy, N. Khanina, C. P. Horwitz, M. E. Bier and T. J. Collins, *Environ. Sci. Technol.*, 2011, **45**, 7882–7887.
17 (*a*) T. J. Collins, S. K. Khetan and A. D. Ryabov, in *Handbook of Green Chemistry: Green Catalysts*, ed. R. H. Crabtree, Wiley-VCH, 2009, vol. 1, pp. 39–77; (*b*) S. S. Gupta, M. Stadler, C. A. Noser, A. Ghosh, B. Steinhoff, D. Lenoir, C. P. Horwitz, K.-W. Schramm and T. J. Collins, *Science*, 2002, **296**, 326.
18 T. J. Collins, C. P. Horwitz, A. D. Ryabov, L. D. Vuocolo, S. S. Gupta, A. Ghosh, N. L. Fattaleh, Y. Hangun, B. Steinhoff, C. A. Noser, E. Beach, D. Prasuhn, T. Stuthridge, K. G. Wingate, J. Hall, L. J. Wright, I. Suckling and R. W. Allison, *ACS Symp. Ser.*, 2002, **823**, 47–60.
19 E. S. Beach, J. L. Duran, C. P. Horwitz and T. J. Collins, *Ind. Eng. Chem. Res.*, 2009, **48**, 7072–7076.
20 S. Mondal, Y. Hangun-Balkir, L. Alexandrova, D. Link, B. Howard, P. Zandhuis, A. Cugini, C. P. Horwitz and T. J. Collins, *Catal. Today*, 2006, **116**, 554–561.
21 A. Ghosh, D. A. Mitchell, A. Chanda, A. D. Ryabov, D. L. Popescu, E. C. Upham, G. J. Collins and T. J. Collins, *J. Am. Chem. Soc.*, 2008, **130**, 15116–15126.
22 ESI.†
23 J. D. Phillipson, S. S. Handa and J. W. Gorrod, *J. Pharm. Pharmacol.*, 1976, **28**, 687–691.
24 (*a*) G. C. Mueller and J. A. Miller, *J. Biol. Chem.*, 1953, **202**, 579–587; (*b*) R. E. McMahon and H. R. Sullivan, *Life Sci.*, 1964, **3**, 1167–1174; (*c*) M. M. Abdel-Monem, *J. Med. Chem.*, 1975, **18**, 427–430; (*d*) J. W. Gorrod and D. J. Temple, *Xenobiotica*, 1976, **6**, 265–274; (*e*) F. P. Guengerich and T. L. Macdonald, *Acc. Chem. Res.*, 1984, **17**, 9–16; (*f*) F. P. Guengerich, *J. Med. Chem.*, 1984, **27**, 1101–1103; (*g*) F. P. Guengerich, *Chem. Res. Toxicol.*, 2001, **14**, 611–650.
25 R. Kraβnig, C. Hederer and H. Schmidhammer, *Arch. Pharm. Pharm. Med. Chem.*, 1996, **329**, 325–326.