ADVANCES IN *N*- and *O*-DEMETHYLATION OF OPIATES

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Abstract. *This chapter provides an overview of various methods for N- and O-demethylations of morphinans and opiate-derived pharmaceuticals thereof. The review is divided into three main sections: N-demethylation, O-demethylation, and biological methods. The sections dealing with chemical methods are further subdivided according to the type of transformations or reagents used, i.e., electrophilic, nucleophilic, oxidative, and acid- or transition metal-mediated processes. The section on biological methods provides recent developments in enzymatic demethylations.*

Contents

1. Introduction

The cleavage of carbon-heteroatom bonds is one of the most fundamental transformations in organic chemistry. This review covers the development of *N*- and *O*-demethylation methods focusing primarily on procedures applied to various morphine alkaloids and opiate-derived agents.[1] The methods described are of practical synthetic value and also represent an instructive insight into the non-trivial problems with *N*- and *O*-demethylations. In the area of semisynthesis of various morphinan-derived agents such as buprenorphine or morphinan antagonists, such as naltrexone or naloxone, the exchange of a *N*-methyl functionality for another alkyl group frequently demands several steps.

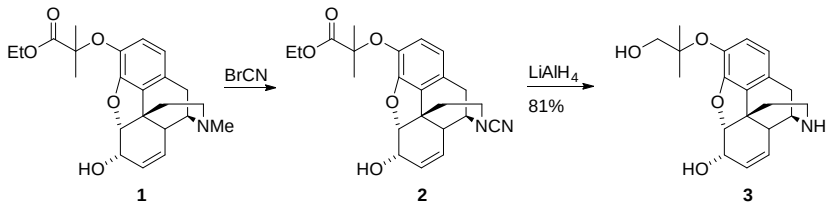
2. *N*-Demethylations

N-Demethylation represents a crucial step in the semi-synthesis of various morphinans. The replacement of naturally occurring *N*-methyl moiety with some other alkyl substituent is desired as the opioid activity of drugs derived from morphine alkaloids is very sensitive to the nature of nitrogen substituents. The *N*-demethylation is carried out using a variety of reagents and conditions. The secondary amines then serve as important intermediates for the preparation of pharmaceutical agents such as buprenorphine,[2] naltrexone,[3] naloxone,[4] nalbuphine,[5] noroxymorphone,[6] and others. The following sections provide a survey of reagents and conditions used for the common cases of *N*-demethylation.

2.1. *N*-Demethylations with hard electrophiles

Without doubt morphine is one the most well-known opioids. This compound has been subjected to countless methods of *N*-demethylation and therefore it represents a good starting point for describing the development in this field.

One of the oldest methods for removing methyl moiety is the von Braun reaction.[7] The protection of the phenol moiety prior to *N*-demethylation is necessary;[8,9] the reaction of cyanogen bromide with unprotected morphine has never been reported. However, there are examples where the protection step of C-6 hydroxyl was not performed and the product was still obtained in good yield (Scheme 1). Reaction of the tertiary amine **1** with cyanogen bromide led to the formation of cyanamide **2**.[10] This intermediate is then submitted to a subsequent reaction (hydrolysis or reduction) in order to obtain the desired secondary amine **3**. Complex hydrides (e.g. $LiAlH_4$) are frequently used as long as the opiate does not contain any other reducible moieties.

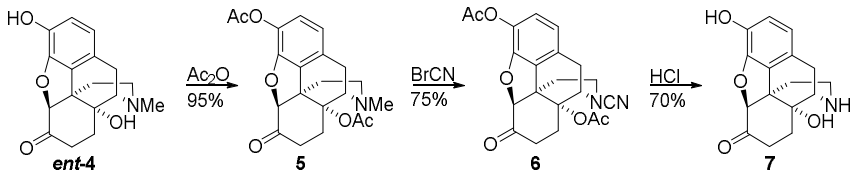


1 **2** **3**

Scheme 1

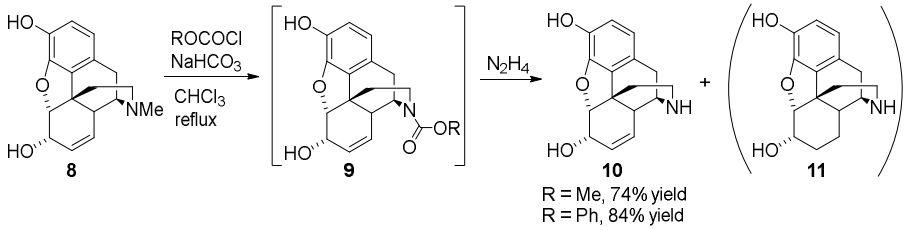
The synthesis of *ent*-noroxymorphone (**7**) is an example where reduction with complex hydrides is not viable because such a transformation would lead to the reduction of C-6 oxy functionality (Scheme 2). The synthesis disclosed by Rice[11] started with (-)-sinomenin, which was converted into *ent*-oxymorphone (***ent*-4**). Its diacetylation with acetic anhydride afforded **5** and subsequent treatment with cyanogen bromide furnished cyanamide **6**. Treatment of the cyanamide with aqueous hydrochloric acid at reflux led to the formation of the desired nor-compound **7**. Similar sequence is carried out during manufacturing of noroxymorphone (enantiomeric compound). This compound is the key precursor to naloxone, naltrexone and nalbuphone (aka Nal-drugs). The industrial process differs from the sequence depicted in Scheme 2 in that it uses the less corrosive sulfuric acid for the hydrolysis of cyanamide.

The reaction of tertiary amines with chloroformates was first reported in 1911.[12] The simplest chloroformate, methyl chloroformate, is regularly used for *N*-demethylation of morphinans.



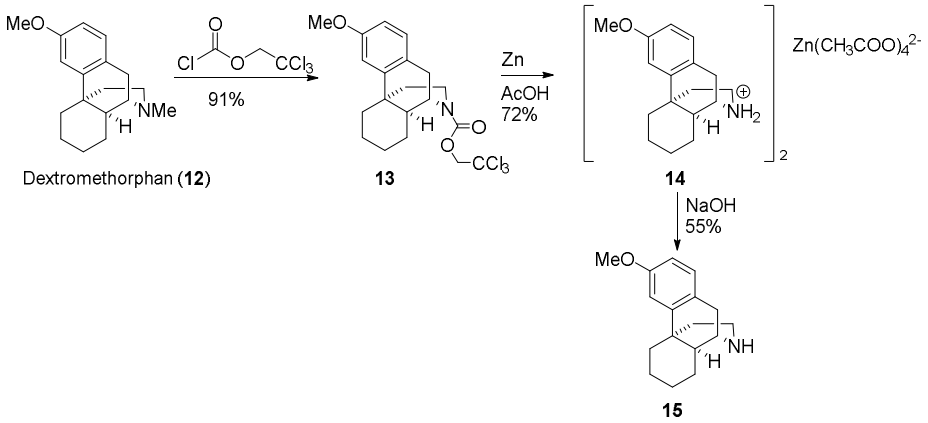
Scheme 2

Brine[13] prepared normorphine (**10**) using this reagent in 2009 (Scheme 3) and therefore also had the occasion to apply the best procedure for the cleavage of the carbamate that was available at that time. The best procedure utilized hydrazine instead of potassium hydroxide. In 1972 Abdel-Monem and Portoghese[14] were actually the first who reported reaction of morphine (**8**) with other chloroformates. The treatment of morphine with phenyl chloroformate in the presence of bicarbonate followed by chromatography, crystallization, and basic hydrolysis in caustic soda afforded normorphine (**10**) in an overall yield of 43%. Later, in 1975, Rice[15] published an improved procedure for preparation of normorphine (**10**) that was based on the treatment of morphine with phenyl chloroformate and subsequent hydrazinolysis of the carbamate moiety in **9**. In terms of yield this method is far superior to the first reported method that used potassium hydroxide but suffered from the generation of dihydronormorphine (**11**; 5-10% yield). The authors suggested that byproduct **11** is formed by reduction of 7,8-double bond by the action of diimide (generated from hydrazine). A follow up paper[16] reported on further improvement of this *N*-demethylation method. Shortening of reaction times (of acylation and hydrazinolysis), use of a steady stream of inert gas passed through the reaction mixture, and the use of allyl alcohol as a co-solvent (diimide interceptor) led to diminished yields of dihydronormorphine (**11**).



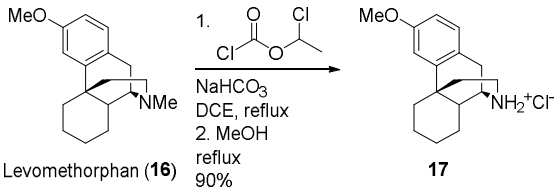
Scheme 3

Another reagent, 2,2,2-trichloroethyl chloroformate, has also been found to smoothly afford carbamate intermediates.[17] These intermediates could be cleaved under relatively mild conditions with zinc in acetic acid or in methanol. *N*-Demethylation of dextromethorphan (**12**) was accomplished by such a sequence starting with this chloroformate (Scheme 4).[18,19] The carbamate intermediate **13** was treated with a suspension of zinc in acetic acid resulting in material, which was characterized and assigned as the zinc tetraacetate salt **14**. The material was finally partitioned between aqueous hydroxide and diethyl ether to afford the corresponding secondary amine **15**.



Scheme 4

1-Chloroethyl chloroformate (ACE-Cl) is used to *N*-demethylate various morphinans, including 14-hydroxymorphinones and 6,14-ethano-bridged congeners, in reasonable yields.[20] With the use of this reagent the isolation and purification of the intermediate carbamate is unnecessary. After the disappearance of starting material the entire reaction mixture is filtered, the filtrate is evaporated, and the residue is subjected to methanolysis. Thus, this general procedure leads directly to hydrochlorides of the secondary amines. Scheme 5 illustrates the simplicity and superiority of the procedure employing ACE-Cl, in contrast to the tedious procedure with 2,2,2-trichloroethyl chloroformate (see Scheme 4 for the enantiomer of **16**).[21]

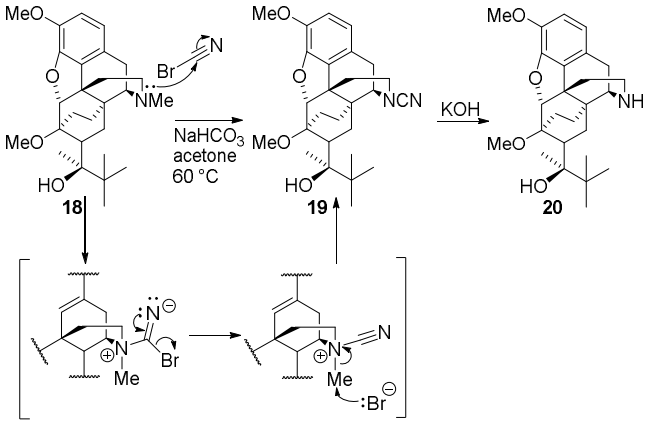


Scheme 5

Other chloroformates, for example ethyl or vinyl derivatives, are also used for *N*-demethylation but to a smaller extent. Ethyl chloroformate[22] is inexpensive and the formation of the corresponding carbamate is high yielding but its hydrolysis requires harsh conditions. Vinyl chloroformate (VOC-Cl) is exactly the opposite; the reagent is expensive but the hydrolysis of the carbamate is effortless (hydrolysis is performed with dilute hydrochloric acid).[23,24]

The mechanisms of all the above mentioned procedures are based on the nucleophilic addition of the *N*-methyl moiety like **18** to chloroformate (or to cyanogen bromide, as shown in Scheme 6). Subsequent elimination furnishes the quaternary ammonium species and the halide, which immediately attacks the methyl group in an S_N2 process, providing the volatile methyl halide and the neutral carbamate (or carbamide **19**, in the case of von Braun procedures). The intermediate is then isolated or is directly subjected to hydrolysis providing the corresponding nor-derivative **20**. The industrial process for the production of

buprenorphine is good example of such a transformation. This multi-ton process utilizes a solution of cyanogen bromide in dichloromethane and sodium bicarbonate, whose role is unclear but effectively leads to the suppression of formation of by-products. The solvent of choice is, surprisingly, acetone since reactions in acetone do not suffer from incomplete conversion contrary to the use of other solvents, such as dichloromethane or chloroform. Plausible intermediates in the von Braun reaction are depicted in Scheme 6.

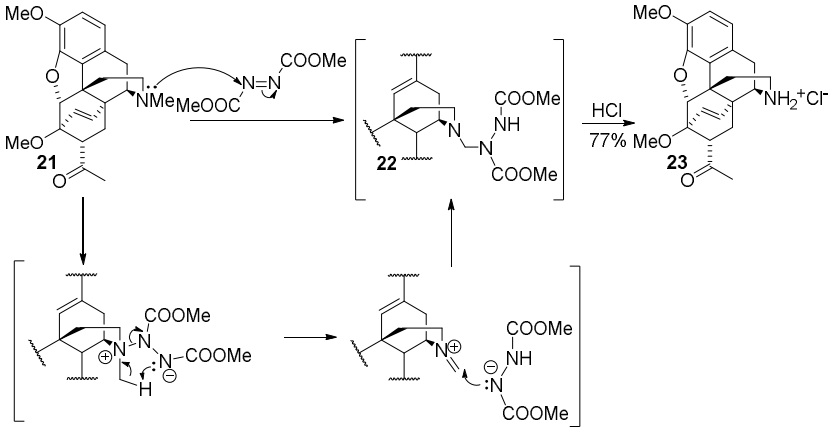


Scheme 6

2.2. *N*-Demethylations with dialkyl azodicarboxylates

The approaches described below utilize an oxidation step followed by hydrolysis of iminium species (or intermediates in the same oxidation state as that of iminium).

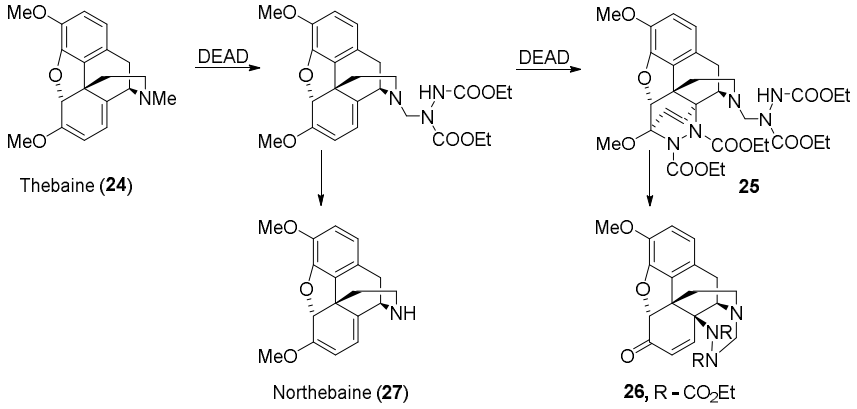
The use of dialkyl azodicarboxylates as a demethylation agent has been reported since the 1960s.[25,26] Tertiary amines react with azodicarboxylates to yield a compound such as **22**, corresponding to the addition of one molecule of the amine to one molecule of azodicarboxylate. On acidic hydrolysis the corresponding secondary amine **23** is obtained with a molecule of formaldehyde (Scheme 7).



Scheme 7

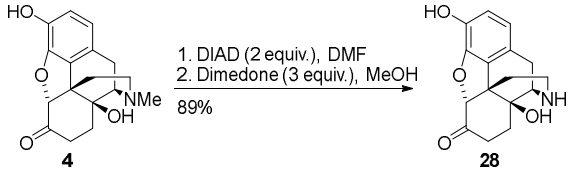
The *N*-demethylation of thevinone (**21**) illustrates the course of such a reaction. Formation of product involves initial nucleophilic addition of basic nitrogen atom to the electrophilic azo moiety followed by the rearrangement of zwitterionic species. Some evidence in support of such a mechanism were provided by Stedman[27] and Jakob.[28]

This methodology was used by Bentley and others for the *N*-demethylation of thebaine (**24**) and 6,14-*endo*-ethano-tetrahydrooripavine derivatives.[29] Surprisingly, after addition of diethyl azodicarboxylate (DEAD) to the solution of thebaine the *N*-methyl moiety reacts faster than the methoxydiene, which, if DEAD is used in excess, subsequently undergoes a [4+2] cycloaddition with the second molecule of DEAD.[30,31] The intermediate **25** that is formed in this process then undergoes an unusual rearrangement affording **26** (Scheme 8). Careful addition of one equivalent of azodicarboxylate leads to preparation of northebaine (**27**).



Scheme 8

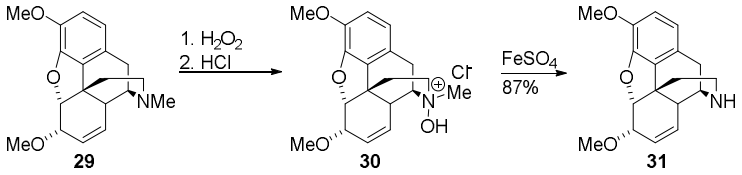
Recently, the *N*-demethylation with azodicarboxylates was improved by Lauterbach[32] who filed a patent claiming a very high yielding *N*-demethylation of unprotected oxymorphone (**4**; Scheme 9). Lauterbach set the bar for his competitors from the field of opiate manufacturing very high indeed as noroxymorphone (**28**) is provided in *one pot* fashion and in very good purity. The initial adduct of the substrate with diisopropyl azodicarboxylate (DIAD) is subjected to mild methanolysis in the following step. The molecule of formaldehyde released during this process is intercepted with dimedone and therefore cannot lead to the formation of any by-products with noroxymorphone.



Scheme 9

2.3. *N*-Demethylations through *N*-oxides

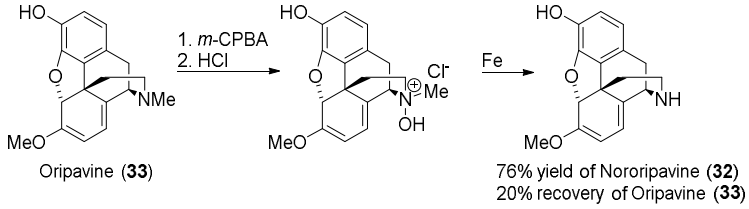
The formation of *N*-oxides and their application as key intermediates in *N*-demethylations represents a completely different strategy in the preparation of nor-derivatives. In 2003 Scammells, inspired with Monkovič's work,[33] reported a protocol for *N*-demethylation of opiates that employed a modified iron salt-mediated Polonovski reaction.[34] His approach involved the conversion of substrate to its *N*-oxide followed by treatment with iron (II) sulfate. The major drawback of this method was the formation of (deoxygenated) parent opiate along with the corresponding nor-opiate (desired product). Later, he reported that hydrochloride salts of *N*-oxides are better substrate for such non-classical Polonovski reaction.[35,36] Good example of this procedure is the transformation of codeine methyl ether **29** to the corresponding nor-analogue **31** through *N*-oxide **30** that proceeded in 87% yield over two steps (Scheme 10).



Scheme 10

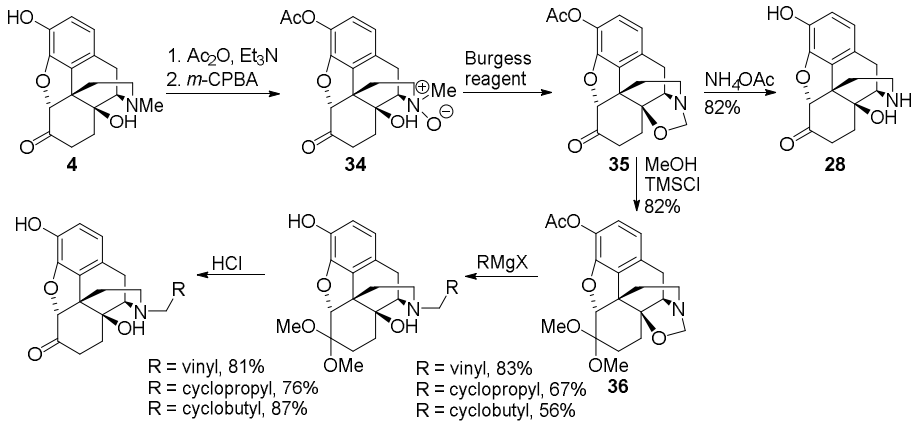
Another limitation of the aforementioned method is encountered in difficulties in separating the products from the iron salts. In a follow up paper Scammells disclosed the use of *meso*-tetra(4-sulfonatophenyl)porphyrine or ethylenediamineteraacetic acid (EDTA) employed for the removal of iron salts and for simplifying work-up procedures.[37] The same group conducted a systematic investigation of this non-classical Polovonski reaction that finally resulted in the use of stainless steel as a redox catalyst.[38]

Since northebaine (**27**) and nororipavine (**32**) are perfect starting materials for the production of Nal-drugs Scammells also reported the *N*-demethylation of thebaine (**24**) and oripavine (**33**). To this end he developed a procedure for preparation of the corresponding *N*-oxide hydrochloride salts (oxidation of amine functionality in the presence of electron rich methoxydiene moiety), which were then converted into northebaine (**27**) and nororipavine (**32**) by the action of Fe(0) in 86% and 40% yield, respectively (Scheme 11).[38] Further optimization of this method using iron revealed that the *N*-demethylation of oripavine is particularly sensitive to subtle changes in experimental conditions (including stoichiometry, temperature, the nature of 'iron' in the steel reactor, and solvents). Under the best conditions nororipavine (**32**) was prepared in 76% yield along with 20% yield of recovered oripavine.



Scheme 11

The scope of *N*-demethylations using *N*-oxides was significantly expanded by Hudlicky and coworkers who investigated the ability of various dehydration agents, for example Burgess reagent, to cause formation of iminium species from *N*-oxides. They reported that the treatment of *N*-oxide of *O*-acetyloxymorphone (**34**) with Burgess reagent provided the corresponding oxazolidine **35** in one-pot sequence and in excellent yield (Scheme 12).[39] Since the iminium species so generated has in its proximity C-14 hydroxy functionality the relatively stable 5-membered heterocycle is consequently obtained. This intermediate was hydrolyzed in a buffer system to furnish the desired noroxymorphone (**28**). In a follow-up paper Hudlicky[40] reported a different strategy for the utilization of oxazolidine **35**. After protection of the C-6 ketone the resulting dimethoxy-ketal **36** was reacted with several Grignard reagents to provide directly *N*-allyl, *N*-cyclopropylmethyl, and *N*-cyclobutylmethyl derivatives that were converted into naloxone, naltrexone and nalbuphone, respectively, in high yields. The authors reasoned that the oxazolidine is in equilibrium with its opened iminium form and therefore it can undergo the addition of Grignard reagents. Compared to the classical approaches used in the synthesis of *N*-alkyl opiates this strategy is very innovative as the original carbon of the methyl group remains in the product. In this manner all commercially relevant Nal-drugs can be prepared.

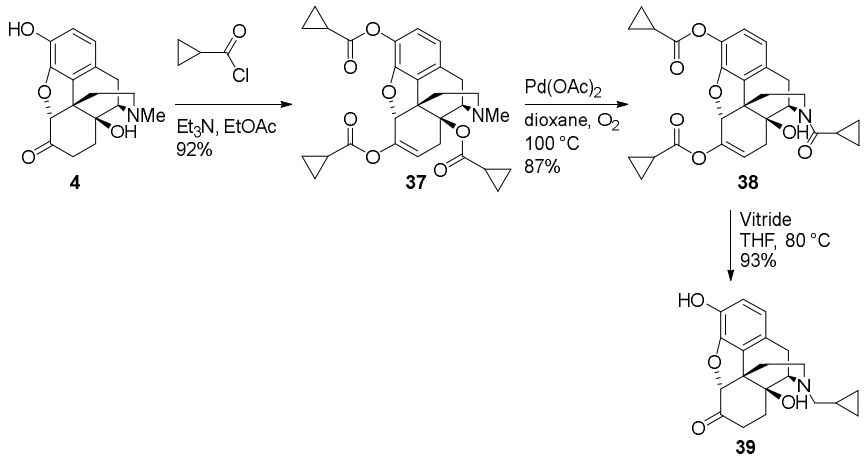


Scheme 12

2.4. Oxidative *N*-demethylations mediated by palladium catalysts

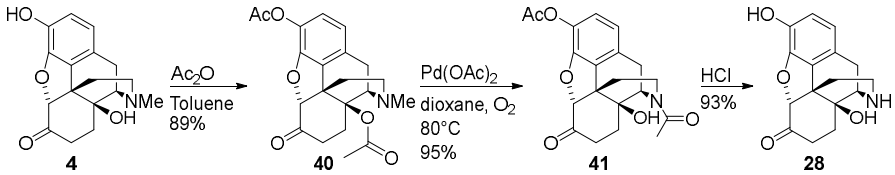
In 2012 Hudlicky[41,42] reported a very efficient *N*-demethylation of opiates based on the palladium-catalyzed oxidation of tertiary amines. The exposure of peracylated oxymorphone **37** to oxygen in the presence of 5 mol% of palladium acetate in refluxing dioxane provided the corresponding amide **38** in excellent yield (Scheme 13). The formation of the amide is caused by the intramolecular acyl transfer from *O*-14 to *N*-17. The intramolecular nature of the acyl migration was investigated and proved by cross-over experiments. It is important to note that the formation of palladium black at the beginning of the experiment was the sign of a successful reaction. This observation could shed more light on the mechanism of the reaction that the authors proposed several options for in their publication. Another unique feature of this approach is the use of Pd on charcoal. This heterogeneous catalyst furnished *N*-demethylated product in similar yields as those from the reactions mediated by palladium acetate. The subsequent reduction of amide

38 to amine **39** elegantly utilizes the *in situ* formed C-6 enol ester, which prevents reduction of the C-6 ketone. This unusual maneuver, described in the paper,[41] is almost unprecedented. The cyclopropylmethyl alcohol can be recycled by oxidation for further use.



Scheme 13

Moreover, in order to furnish noroxymorphone (**28**), the immediate precursor of various opioid antagonists and agonists, Hudlicky patented a different procedure which involves/covers palladium catalyzed oxidative demethylation of 3,14-diacetyloxymorphone (**40**) and subsequent hydrolysis of obtained 3,17-diacetylnoroxymorphone (**41**) with 6M hydrochloric acid (Scheme 14).[43,44]

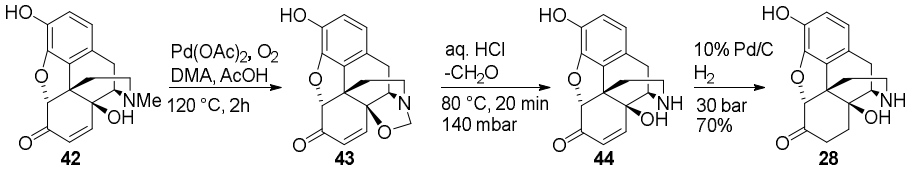


Scheme 14

In 2015 the same group has demonstrated that the *N*-demethylation/intramolecular acetyl transfer from C-14 to N-17 of **40** could also be accomplished in good yields by an $FeCl_2$-catalyzed reaction employing *t*-BuOOH as an oxidant.[45] The motivation to further improve the previous work stemmed from a need to address safety issues (potentially flammable mixture of Pd catalyst, oxygen and solvent vapors) and problems associated with Pd contamination of API precursor.

Very recently Kappe[46] reported a very similar oxidative *N*-demethylative approach for accessing noroxymorphone (**28**) under continuous flow conditions. Starting with Pd/C the *N*-demethylation under oxygen atmosphere was applied on 14-hydroxymorphinone (**42**) and 14-hydroxycodeinone yielding corresponding oxazolidines **43** (Scheme 15). This finding is a bit surprising but is in agreement with results presented in Scheme 12 (a previous report by Hudlicky Pd-catalyzed *N*-demethylation of hydrocodone stated

that oxycodone did not react. It was later determined that the oxazolidine of type **43** indeed did form from oxycodone but its presence in the reaction mixture was probably mistakenly confused with the starting material, oxycodone.[47,48] Subsequent hydrolysis of oxazolidine **43** under reduced pressure (in order to efficiently remove formaldehyde) provided nor-derivative **44**, whose hydrogenation under standard conditions led to noroxymorphone (**28**). Hence, the process consumes only oxygen and hydrogen as stoichiometric reagents and generates formaldehyde as the sole byproduct.



Scheme 15

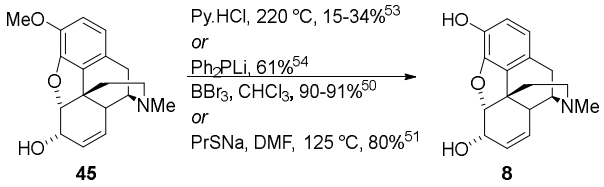
Kappe also pointed out that the oxidation proceeds through Pd(0) cycle (Pd black is the catalyst), presumably without the involvement of Pd(II) species. Faster but somewhat less selective *N*-demethylation was also observed with Pt/C.

3. *O*-Demethylation

O-Demethylation of aryl methyl ethers is a well-established strategy in synthetic chemistry for unmasking of the phenolic functionality.[49] The cleavage of aryl methyl ether functionality has been described many times and the development of new reagents is still underway, in search of even milder conditions for this transformation. Most of the high-potency opioid analgesics possess a free 3-phenolic group. On the other hand, common starting materials such as thebaine or codeine contain the 3-methoxy moiety in their structures. Thus, manufacturing or laboratory preparation of particular opiates requires *O*-demethylation of the anisole type moiety.

Two independent reports on *O*-demethylation of codeine (**45**) to morphine (**8**) were published in 1977 in the *Journal of Medicinal Chemistry* by Rice and DeGraw.[50,51] A sympathetic editor-in-chief decided to place these seminal one-page reports abreast so that the reader could appreciate and compare both of these protocols at the same time. Before these disclosures two distinctly different reagents were used for codeine *O*-demethylation (Scheme 16). The first one employed pyridinium hydrochloride but practical difficulties were encountered during the isolation and purification of product(s).[52,53] The yields of morphine obtained by this method were also unsatisfactory. The second reagent used in another previously reported protocol was lithium diphenylphosphonide.[54] The yields of morphine obtained by this method were superior to those from the pyridine hydrochloride method but the procedure lacked practicability for large-scale preparation. The disclosure of the papers by Rice and DeGraw[50,51] in *J. Med. Chem.* had a major impact on *O*-demethylations in the field of opiate chemistry. On the top of that, both reports demonstrated potential of their methods on codeine - notoriously known substrate. In the first paper Rice reported a practical procedure utilizing boron tribromide which afforded morphine in ~90% yield.[50] This finding was quite remarkable in view of the labile nature of the 4,5-oxygen bridge and the allylic alcohol functionality under strongly acidic reaction

conditions. The other paper[51] from DeGraw's group reported a convenient procedure based on work of Feutrill and Mirrington[55] who disclosed the cleavage of aryl methyl ether with alkanethiolates in aprotic solvents. Treatment of codeine with sodium propanethiolate at 125 °C consistently gave morphine in 80% yield. This finding is also somewhat remarkable since the exposure of codeine and/or morphine to strongly acidic or alkaline conditions at elevated temperatures was known to lead to substantial decomposition or skeletal rearrangements.

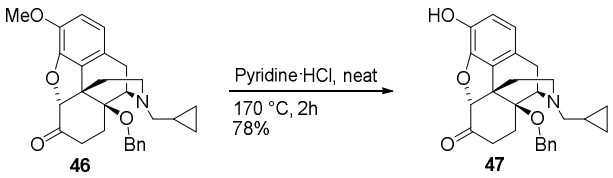


Scheme 16

The various *O*-demethylation methods will be presented here in the same order of appearance as was done in 1977 in the *J. Med. Chem.* issue to maintain the correct order from the point of view of chronology and complexity.

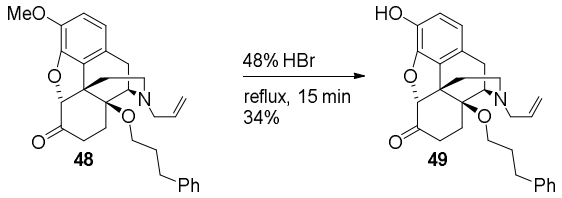
3.1. *O*-Demethylations with Brønsted acids

One of the oldest agent for *O*-demethylation commonly employed in the opiate series is pyridinium hydrochloride.[56,57] Upon heating with a substrate **46** this reagent smoothly furnishes the *O*-demethylated product **47**, as illustrated in Scheme 17.[58] The low price of the reagent along with a simple work-up represent the benefits of this procedure. The reaction typically requires high temperatures and long reaction times. Moreover, pyridinium hydrochloride is an ionic liquid with a high melting point and thus is employed in large excess as a solvent. After disappearance of the starting material the reaction mixture is allowed to cool down and then is diluted with water and extracted with diethyl ether. Yields are ranging from moderate to good. Unfortunately, the reaction mixture upon cooling solidifies and this causes problems at larger scale.[59]



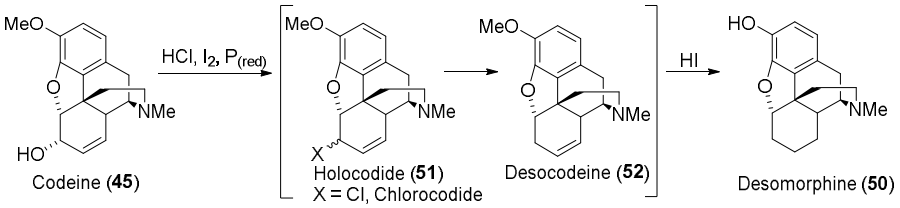
Scheme 17

Concentrated aqueous hydrobromic acid is another well-established *O*-demethylation agent. Compared with pyridinium hydrochloride it is considered to be harsher but this does not need to pose problems if the reaction time is kept as short as possible. Under careful control it is possible to accomplish *O*-demethylation even in the presence of the allylic moiety in **48**, although the yield of **49** is moderate (Scheme 18).[60]



Scheme 18

Although this focused review covers *O*-demethylation procedures used in both academia and industry we intend to describe one particular method, which has its origins in the "street" as it represents innovative chemistry and is definitively worth mentioning. "Krokodil" is the nickname for the homemade injectable drug, or rather a crude reaction mixture, containing from traces to circa 75% of desomorphine (**50**).[61,62] Its name originated either in scaly green colored ulcers on skin of users that resemble the skin of a crocodile or in a perverse mispronunciation of the intermediate, α-chlorocodide (**51**), involved in the synthetic pathway towards desomorphine (**50**). The nickname also refers to massive skin infections and ulcer formation resulting finally in rotting of the flesh and the exposure of bones (entire loss of flesh on bones). The homemade production of "krokodil" (mixtures containing desomorphine) commences with tablets of codeine (**45**), which is an over-the-counter pharmaceutical product in Russia, for example (Scheme 19). In the first step, codeine tablets or syrup are mixed with strong alkali and gasoline in a polyethylene terephthalate (PET) bottle. Shaking and separation of layers provides the free base form of codeine dissolved in gasoline. Then this extract is mixed with acidified water. Separated aqueous layer containing codeine salt is later treated with iodine, hydrochloric acid and red phosphorous. This simple one-pot reduction leads to the formation (to various extents) of desomorphine (**50**), as was reported by Kolesov.[63] Apparently, this approach relates to similar conditions used also in illicit preparation of methamphetamine from pseudoephedrine (benzylic dehydroxylation with HI/P mixture).

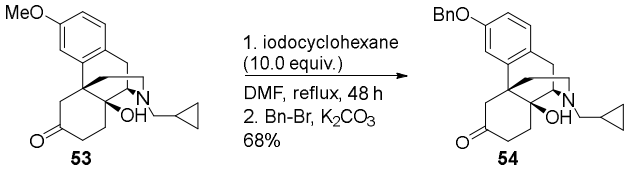


Scheme 19

It the course of this reaction sequence codeine undergoes substitution at C-6, allylic halide reduction, double bond reduction, and the subsequent cleavage of the methyl ether moiety by HI. Reduction of the 7,8-double bond perhaps proceeds through the addition of HI and deiodination. We may speculate on the actual mechanism of this transformation or discus the impurity profile of such a "shot" but some things are clear. All kinds of chemicals originating in pills (syrup), gasoline, alkali solution (household cleaners) plus traces of phosphorus and its products must be very harmful to the health of an user. Moreover, "cooking"

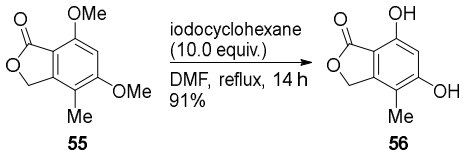
desomorphine from codeine pills is what cooks intend to do but it is not what they necessarily end up with (some analyzed samples of Krokodil contained only traces of desomorphine).

Another strategy which utilizes *in situ* formed HI was described in three independent patents.[64–66] Hydrogen iodide is generated from cyclohexyl iodide in refluxing DMF. The *O*-demethylated product **54** (reprotected with a benzyl group) was obtained in good yields from substrate **53** (Scheme 20). Unfortunately, patents did not disclose any further details of this transformation.



Scheme 20

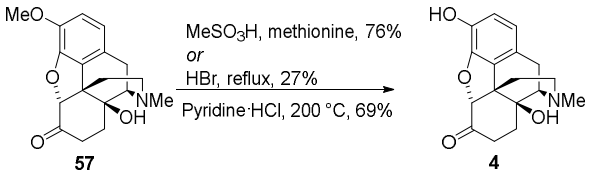
We speculate that the authors of the patents were inspired by work of Duan[67] who reported selective demethylation of 5,7-dimethoxy-4-methylphthalide (**55**) using iodocyclohexane in DMF under reflux (Scheme 21). The application of this procedure was found to be superior to the harsh conditions using HI (57% aqueous solution) with phosphorus and acetic anhydride. Slow generation of HI from iodocyclohexane via elimination provides efficient but mild reaction conditions. Screening of solvents revealed that this *O*-demethylation is highly solvent dependent. The author concluded that the basicity of the solvents plays a critical role. On one hand, the solvent needs to be basic enough to facilitate the elimination of HI from iodocyclohexane. On the other hand, the solvent basicity has to be weak to suppress a neutralization of acid since the strong HI acid is essential for the demethylation.



Scheme 21

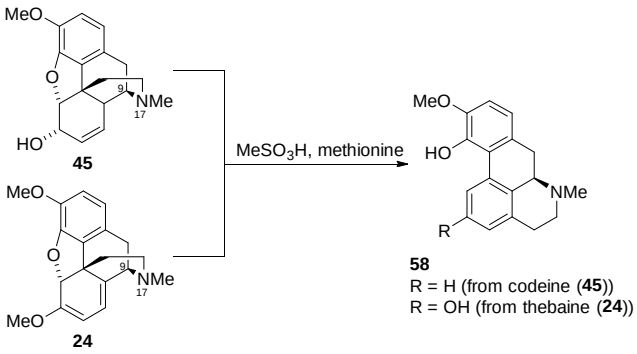
O-Demethylation with methanesulfonic acid-methionine mixture represents another practical methodology.[68] This combination of hard acid-soft nucleophile acting by “push-pull” mechanisms was originally developed by Kiso and Yajima for the deprotection of peptides.[69] A Sanofi group[68] demonstrated the utility of this Brønsted acid-nucleophile combination as an efficient demethylation system particularly for the conversion of both oxycodone to oxymorphone (**4**) and *N*-allyl noroxycodone to naloxone (Scheme 22). The reactions were run with 30 equivalents of methanesulfonic acid and 1.5 equivalents of methionine at 40 °C. The *O*-demethylation of oxycodone (**57**) afforded 76% yield of oxymorphone (**4**) and the reaction of *N*-allyl noroxycodone led to formation of naloxone in 69% yield (not shown here). The reaction time was found to be an important parameter as prolonged reaction led to much degradation, even at 40 °C. Other protic reagents like hydrobromic acid or pyridinium hydrochloride did not meet the requirements for

applications at an industrial scale. Hydrobromic acid furnished oxymorphone from oxycodone in low yield (Scheme 22) and treatment of substrate with melted pyridinium hydrochloride reagent caused notoriously reported problems (vide supra).



Scheme 22

In addition, the authors noted that codeine (**45**) and thebaine (**24**) undergo rearrangements to apomorphine derivatives **58** (Scheme 23) but they did not indicate the extent of *O*-demethylation of these acid-labile substrates. The presence of methoxydiene moiety in thebaine and oripavine makes these substrates susceptible to oxidation, reduction, and cycloadditions. Unfortunately, their inherent instability rules out many other reactions required for *O*- and *N*-demethylation.[70] For example, their reaction with *N*-demethylation agent (cyanogen bromide, chloroformates etc.) can lead to the cleavage of the C-9/N-17 bond.[71] As well, standard *O*-demethylation procedures that use Brønsted and Lewis acids lead to extensive degradation of substrates and thus are not suitable for use with these more functionally sensitive compounds.[51,72,73]

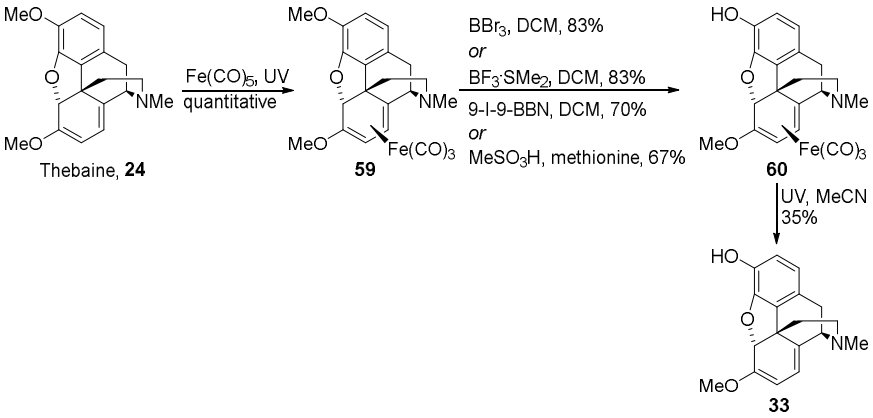


Scheme 23

3.2. *O*-Demethylations with Lewis acids

To circumvent some of the issues mentioned above, methoxydiene moiety in thebaine (**24**) has to be protected. Birch[74,75] and later Hudlicky[70,76,77] reported the protection of this diene unit with iron(0) pentacarbonyl (Scheme 24). The thebaine-iron tricarbonyl complex **59** was subjected to various *O*-demethylation methods (vide infra). The authors[76] found that both the starting material and the product are very stable under extremely acidic conditions. However, the work-up of the reaction mixture was tedious since the product has low stability in neutral or basic conditions. In addition, the oripavine complex **60** is inherently unstable as it contains a tertiary amine functionality, which is basic enough to promote

decomposition. The iron decomplexation was accomplished either by treatment with hydrogen peroxide or by irradiation in acetonitrile solution. Part of this reaction sequence was very recently utilized in a follow-up paper that disclosed a combination of *N*- and *O*-demethylations to yield nororipavine from thebaine.[70,77]



Scheme 24

Hudlicky's paper describes the utilization of four distinct *O*-demethylation agents on one substrate, namely **59**. The use of these reagents will be discussed next.

Boron tribromide is without a doubt the reagent of choice for the cleavage of aryl methyl ether moiety. It leads to high yields and exhibits selectivity under relatively mild conditions. The same is true for another Lewis acid containing a boron atom - $BF_3{\cdot}SMe_2$. However, the latter reagent is not frequently utilized in the field of opioid alkaloids. Its Lewis acidity is lower compared to boron tribromide as a result of stronger back donation of fluorine atoms compared to bromine but the capability to accomplish demethylation is not impaired. Moreover, application of 9-I-9-BBN reagents was also reported. This reagent afforded the demethylated product **60** in yields comparable to those obtained with methanesulfonic acid-methionine mixture. The price and the lower reactivity of 9-I-9-BBN to provide phenolic product could account for the relative scarcity of reports on its utilization.

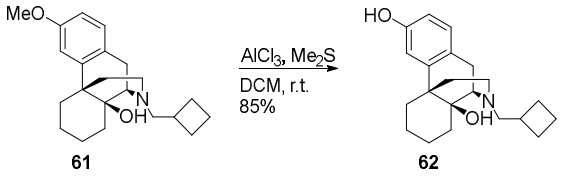
Boron tribromide could also be used for *O*-demethylation of *ent*-oxycodone (***ent*-57**) and related 14-hydroxyderivatives.[78] The reaction proceeds under mild condition and isolated yield of phenolic product ***ent*-4** is usually high. Scheme 25 shows the cleavage of the methyl ether moiety in *ent*-oxycodone (***ent*-57**). It is worth to note that boron tribromide does not promote elimination of 14-hydroxy group to 8,14-double bond as is known to occur with other reagents, such as thionyl chloride.[79]

Scheme 25

3.3. *O*-Demethylations with combination of acids and nucleophiles

Aluminum trichloride is an efficient Lewis acid that is used in various functional group transformations and in C-C bond forming reactions. To the best of our knowledge there is only one report on *O*-demethylation of a morphinan mediated by $AlCl_3$. However, this report is of a special significance as it describes industrial production of butorphanol (**62**). This drug lacks the 4,5-oxygen bridge functionality and is administered in human medicine for the management of migraines.[80] In veterinary use, butorphanol is used as a sedative and analgesic in cats, dogs, and other animals.[81]

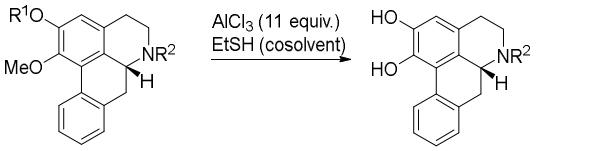
We estimate that its annual worldwide production exceeds half ton. *O*-Demethylation is the last step in the production and is carried out by treatment of *O*-methyl butorphanol (**61**) with a mixture containing four equivalent of aluminum trichloride and eight equivalents of dimethylsulfide (Scheme 26).[82] After one hour the reaction mixture is quenched with a slow addition of methanol and aqueous ammonia. The product is then thoroughly extracted with dichloromethane. Surprisingly, formation of thick suspension of aluminum salts is not observed and thus the isolation of the product is smooth.



61 **62**

Scheme 26

Very similar *O*-demethylation system, combining a hard acid and a soft nucleophile, was used on alkaloid asimilobine.[83] Although it is not an opiate it shares some features with opiates and also represents quite a remarkable example, which should be mentioned. Treatment of this pyrocatechol derivative **63** containing a tetrahydroisoquinoline subunit with $AlCl_3$-EtSH mixture failed to furnish any product (Scheme 27). Presumably aluminum trichloride coordinates with the basic secondary amine in **63** and thus forms an insoluble complex. On the other hand, its *N*,*O*-diacetyl derivative **64** smoothly afforded catechol derivative **65**. Therefore, *O*-demethylation systems based on aluminum trichloride should be applied carefully and any nucleophilic moiety in the structure of the substrate needs to be taken into account. However, butorphanol **62** looks like a good ligand for chelation of aluminum salts but problems with such salts were not encountered.



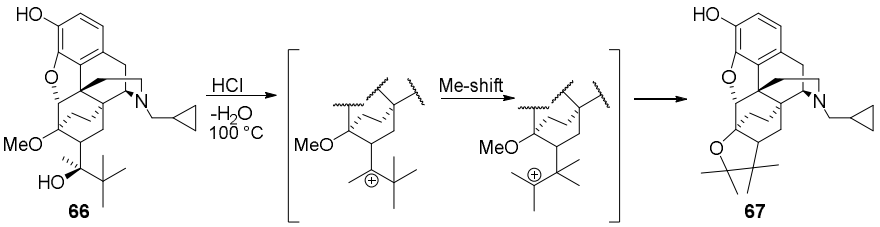
63, $R^1 = R^2 = H$
64, $R^1 = R^2 = COMe$

65, $R^1 = R^2 = COMe$, 81%
$R^1 = R^2 = H$, 0%

Scheme 27

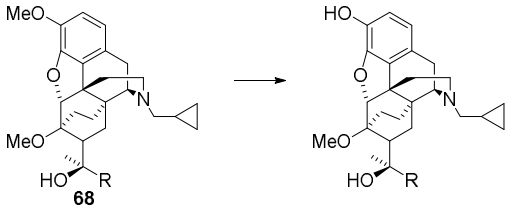
3.4. *O*-Demethylations with strongly nucleophilic reagents

O-Demethylation of 20-alkylthevinol to 20-alkylorivinols and the corresponding dihydroorivinols **66** requires non-acidic reagents otherwise the compounds rearrange with the formation of a new tetrahydrofuran ring (Scheme 28).[84] The rearrangement involves protonation, elimination of water with formation of carbocation, subsequent methyl shift and ring closure leading to the tetrahydrofuran derivative **67**. The aforementioned lability toward acids effectively rules out all protocols for *O*-demethylation based on Brønsted and Lewis acids.



Scheme 28

A number of basic reagents and procedures have been developed for the demethylation of the 6,14-bridged semisynthetic opiates such as **68** (Scheme 29). Treatment with potassium hydroxide at 200 °C used to be the most widely employed method.[85,86] In industry this method still represents the gold standard in manufacturing of buprenorphine (**69**), which is produced annually on a 4-5 ton scale worldwide. Owing to its complex structure buprenorphine is a mixed opioid agonist-antagonist and its production is not trivial. The drug is used in pain management and is also useful in the treatment of drug abuse.



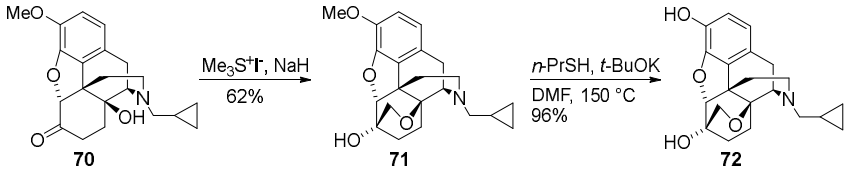
KOH, diethylene glycol, 210 °C, R = *t*-Bu, **69,** 42%
$CH_3(CH_2)_8C(CH_3)_2SNa$, DMSO, 140 °C, R = *t*-Bu, **69,** 80%
PrSNa, HMPA, 120 °C, R = various alkyls, 65-99%
DIBAL, toluene, 110 °C, R = *t*-Bu, **69,** 62%

Scheme 29

The yield of the *O*-demethylation step in the industrial manufacturing of buprenorphine (**69**) has to be significantly higher than the reported yield of 42%, which was found in the literature. The same transformation could be achieved in a very clean fashion by heating of substrate **68** with thiolates.[87–89] To the best of our knowledge recent productions of buprenorphine utilize both methods - heating either with hydroxide of with thiolates. DIBAL-H was also reported as a good *O*-demethylation agent acting on 20-alkylthevinols but this is the sole report of this kind used in chemistry of opiates.[90]

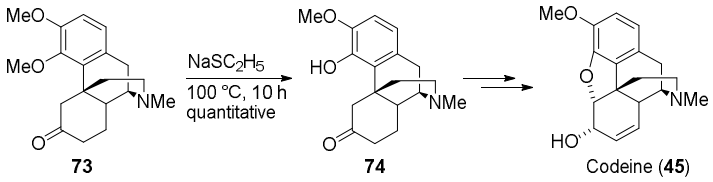
The use of thiolates is therefore an attractive alternative to the use of concentrated potassium hydroxide at temperatures exceeding 200 °C. In general thiols with longer alkyl chains (high boiling points) are preferred since the smell of ethane- and propanethiol is very unpleasant. Based on our experiences the utilization of *t*-dodecanethiol is ideal since the compound is almost odorless and the tertiary thiol center exhibits a little better selectivity with improved impurity profile compared to *n*-alkanethiols.[42] DMF and DMSO are commonly employed as solvents in these reactions. Nevertheless, when high yield is desired, HMPA is the best solvent.

In terms of the thiol counter ion, the lithium salts are usually found to be as effective as sodium salts. At least this is true for *O*-demethylation of opiates with *in situ* prepared thiolates (combination of a thiol with base). However, there is a report on observation of unsatisfactory yields in demethylation of veratrols with sodium ethanethiolate.[91] Compared to lithium ethanethiolate this reagent was not reactive enough under the same conditions. As is shown in Scheme 30, potassium alkanethiolates are also efficient demethylation agents for 14-alkoxyderivatives like **71**.[92] Substrate **71** was prepared from *O*-methyl naltrexone (**70**) by treatment with trimethylsulfonium iodide. Its subsequent *O*-demethylation afforded product **72** in 96% yield.



Scheme 30

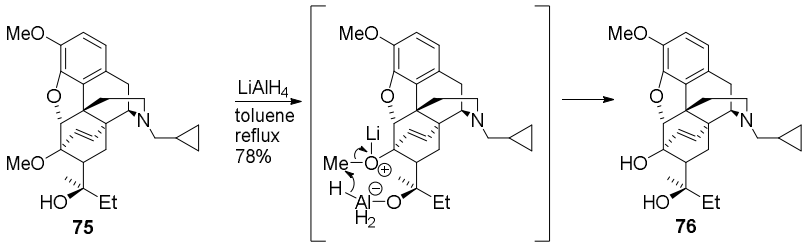
In a total synthesis of codeine Rapoport[93] employed similar condition for *O*-demethylation of dihydrothebainone methyl ether (**73**; Scheme 31). He found that the ether cleavage with ethanethiolate is specific, affording dihydrothebainone (**74**) in quantitative yield (yield of unpurified material). With regard to similar findings depicted in Scheme 34 we conclude that oxygen atom of the C-6 ketone coordinates with the sodium ion and affects/controls the site of *O*-demethylation. Surprisingly, refluxing of the same starting material, **73**, with concentrated hydrochloric acid afforded desired product **74** in very high yield (86%).



Scheme 31

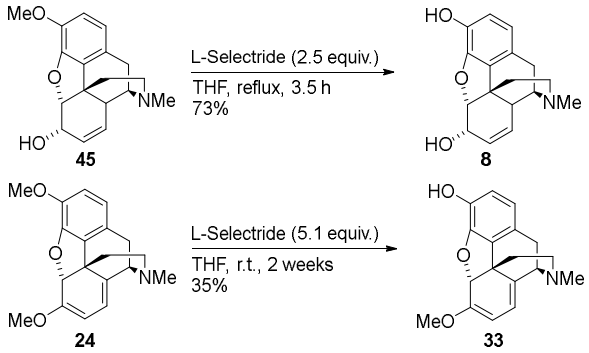
Heating of thevinols and orvinols with lithium aluminum hydride in a non-coordinating solvent such as toluene,[94] a selective 6-*O*-demethylation could be achieved with no 3-*O*-demethylation being observed.[95,96] On the other hand, refluxing of thevinols such as **75** in THF with lithium aluminum hydride has no effect on 6-OMe moiety and only 3-*O*-demethylation takes place. Apparently, toluene causes tight coordination of lithium ion with 6-MeO moiety which activates it for hydride delivery from nearby aluminum alkoxide and

thus it leads to formation of compound **76**.[97] The suggested mechanism for the 6-*O*-demethylation which proceeds *via* cyclic transition state is shown in Scheme 32.



Scheme 32

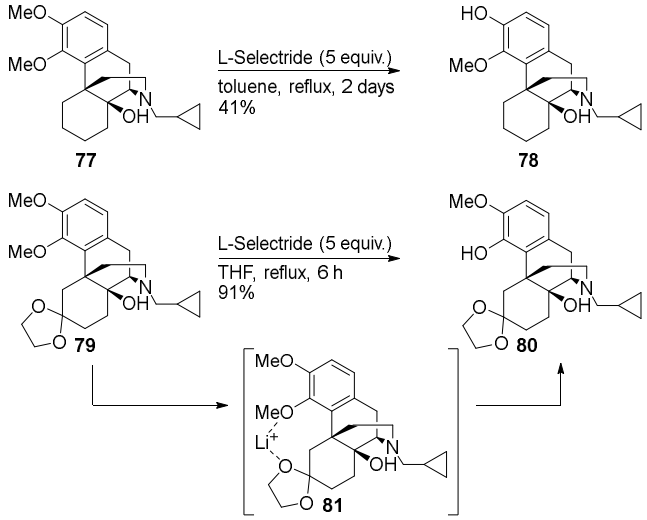
Rice[98] in 1998 reported that another complex hydride, L-Selectride, could also efficiently 3-*O*-demethylate a range of opiates (Scheme 33). Reaction of codeine with L-Selectride occurred smoothly and morphine was obtained in 73% yield. The presence of the C-6 hydroxy group in the molecule did not inhibit *O*-demethylation with excess hydride. Rice also noted that this *O*-demethylation was far more rapid (3.5 h) than was reported for simple compounds (circa 18 h). This acceleration could be explained by the presence of an *ortho* ether moiety at C-4, allowing coordination of the lithium ion. Direct 3-*O*-demethylation of thebaine (**24**) with L-Selectride furnished oripavine (**33**) in 35% yield. The reaction suffered from a low yield and unusually long reaction time. Moreover, formation of by-products was observed.



Scheme 33

In general, L-Selectride is considered a bulky reagent preferring easily accessible electrophilic sites. As far as *O*-demethylations are concerned, this reagent is supposed to cleave the least hindered methyl ether in the molecule. This may account for the observed selectivity in the former example. Moreover, it is considered that oxygen atom of the furan moiety coordinates L-Selectride and this may have an additional effect on the formation of morphine (**8**). In the same paper Rice showed that it is possible to carry out both *N*-decarboxymethylation of a carbamate (see *N*-demethylation with chloroformates) and *O*-demethylation in one pot.

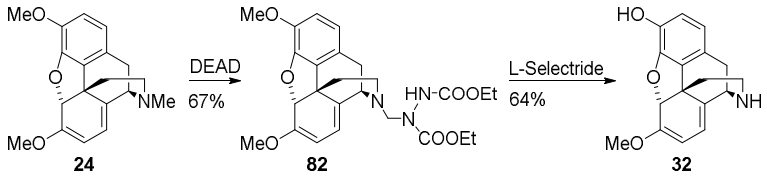
To obtain further information on this chelation effect on *O*-demethylation Rice and Coop performed various experiments on 3,4-dimethoxymorphinanes (Scheme 34).[99] Originally the authors supposed that lithium coordination to both the 3- and 4-oxygens will selectively afford products of 3-*O*-demethylation since L-Selectride is a bulky molecule and the 4-methyl ether is sterically hindered by the *ortho*–situated tertiary carbon atom. Substrate **77**, lacking the oxygen functionality at C-6, reacted according to their hypothesis but the choice of the solvent appeared to be crucial. The reaction in THF did not proceed until the solvent was changed to refluxing toluene. Product **78** was obtained in 41% yield. The slow rate of the reaction along with the moderate yield indicated that the lithium ion could not coordinate well between the 3- and 4-methoxy moieties.



Scheme 34

On the contrary, treatment of ketal **79** with L-Selectride furnished **80** as a single product in 91% yield. The structural analysis indicated that originally not-anticipated 4-*O*-demethylation took place. This result was finally confirmed by matching of the product of the hydrolyzed ketal **80** with a standard. Finally, Rice and Coop used molecular modeling to explain the observed selectivity. Modeling studies showed the coordination of lithium ion with the oxygen atom of 4-methoxy group and the oxygen atom of ketal (dioxolane). The authors concluded that the complex such as **81** is energetically favored over another complex with the lithium ion coordinated by both 3- and 4-methoxy groups. Therefore, only the 4-methoxy moiety undergoes *O*-demethylation even though it is more hindered.

In 2009 Sipos[100] reported a two-step combination of *N*- and *O*-demethylations yielding nororipavine (**32**) from thebaine (**24**; Scheme 35). In the first step, the *N*-demethylation was accomplished with DEAD and then followed by the treatment of **82** with L-Selectride in order to cleave the methyl ether and break down the hydrazinyl derivative. The yields of both steps were moderate but optimization of reaction times and reaction temperature led to a significant improvement over the *one-pot* procedure. Finally, the protocol gave rise to the desired nororipavine (**32**) in an overall yield of 64%.

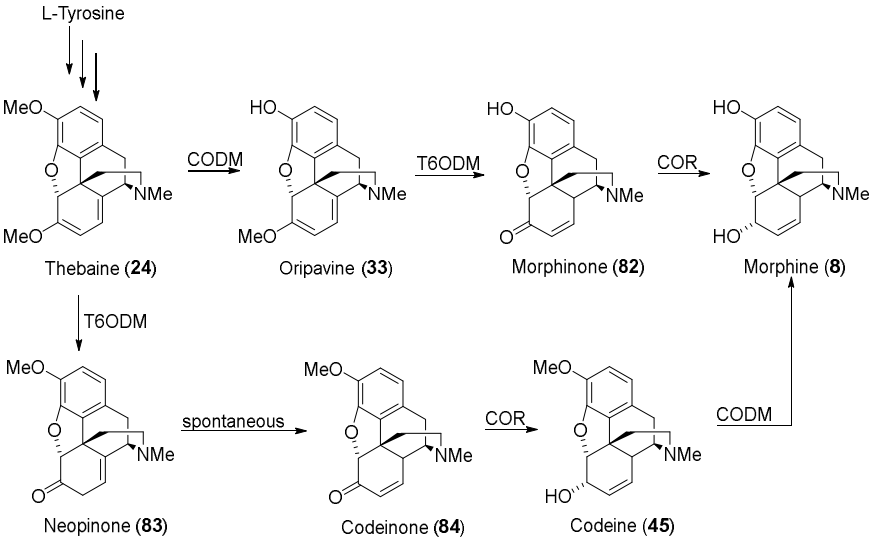


Scheme 35

This sequence serves well to conclude and summarize the topic of this focused review.

4. Biological methods

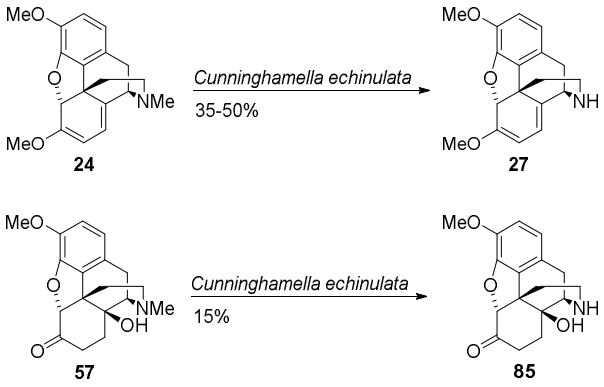
Enzymatic demethylations of morphinans are well known and have been studied primarily in connection with the biosynthesis of morphine (**8**) and congeners.[101,102] The full biogenetic pathway to morphine has been elucidated and *O*-demethylation plays a significant role. There are two major pathways to morphine (Scheme 36). In one of them thebaine (**24**) is converted to oripavine (**33**) by codeine *O*-demethylase and oripavine yields morphinone (**82**) by the further action of thebaine 6-*O*-demethylase. In the other pathway thebaine 6-*O*-demethylase yields neopinone (**83**). Neopinone rearranges to codeinone (**84**) which is converted to codeine (**45**) whose *O*-demethylation by demethylase yields morphine (**8**).[103,104]



Scheme 36

Although the enzymatic demethylations have been studied in detail from the biological perspective their applications to preparative conversion of morphinans, especially on viable industrial scale, are not yet common. *N*-Demethylation of morphinans with fungal cytochromes has been reported in whole cell biotransformations on preparative scale[105] with promising results, but scale up of fungal cultures presents problems (Scheme 37). The strain *Cunninghamella echinulata* proved to be the most efficient for *N*-

demethylation of morphine and related alkaloids. This fungal strain afforded northebaine (**27**) from thebaine in 35-50% yield. The yields of several other nor-opiates were even lower (see *N*-demethylation of oxycodone **57**).



Scheme 37

Attempts have been made to clone the expression of the fungal cytochromes into recombinant *E.coli* so that a large scale fermentation protocol could be implemented have met with limited success.[106] Future research in this area could yield practical and environmentally benign fermentation methods for large-scale manufacturing. Methods in molecular biology hold the key to providing improvements in enzymatic demethylations as well as in potential large scale synthesis of morphinans via fermentation.[107,108]

5. Conclusions and outlook

This chapter covers numerous method of *N*-/*O*-demethylation of various morphinans. All these methods are either applied in academia or in industrial manufacturing of marketed opiates. As expected, the methods used by industry are well established and very well-tuned as legal worldwide business with opioid analgesics and with other drugs possessing opiate scaffold is very profitable. Hence, a vast amount of human effort and millions of dollars have been invested in the past decades into these state-of-the-art processes. Unfortunately, it is difficult to obtain accurate information for industrial processes because patents usually do not report details that fall into the category of “trade secrets”. Thus, these very valuable bits of information are almost never publicly accessible. Therefore it is essentially impossible for a non-expert in the field to find the most recent developments and improvements in the art and craft of industrial manufacturing of opiate drugs. In this chapter we “pulled the curtain” as much as we could and we hope that the “audience” will appreciate our attempts.

Acknowledgments

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