A NOVEL SYNTHESIS OF THEBAINE FROM CODEINE

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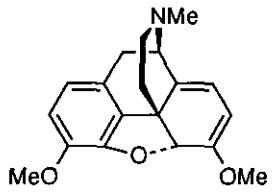
Abstract - Codeine was converted into thebaine through methylation of the enolate of codeinone.

The minor opium alkaloid thebaine (**1**) occupies a unique position as the key intermediate in the synthesis of many medically important opioids.[1,2] Oxidation of the diene system to give 14-hydroxycodeinone (**2**)[3] leads to the opioid antagonists, important medications for the treatment of opiate abuse, [4] opiate overdose,[5] and alcohol addiction.[6] Diels-Alder reaction to give thevinone,[7] leads to the orvinols such as buprenorphine (**3**) a potent clinical analgesic that has found use as a treatment for opiate addition.[8] Recent findings that the orvinol, dihydroetorphine (**4**), appears to possess a low physical dependence potential[9] further underscores the clinical importance of thebaine derived opioids.



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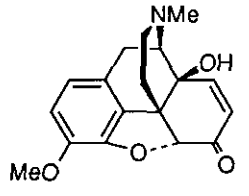

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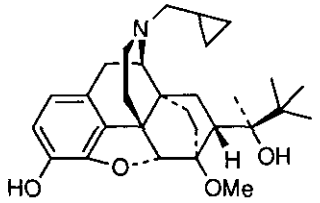

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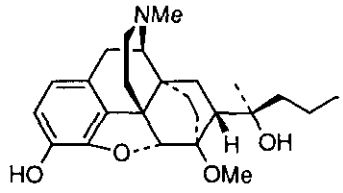

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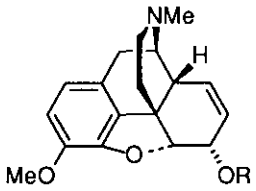
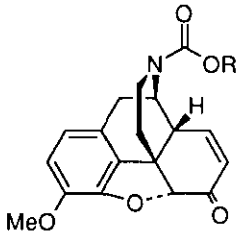
The increasingly huge demand for these medicinal opioids, coupled with the low natural abundance of thebaine in opium,[10] has led to the need for a practical synthesis of **1** from the more available opium alkaloid codeine (**5**). At present the most efficient synthesis of **1** from **5** (67% yield) was described by Rapoport. Codeine-6-methyl ether (**6**), prepared by methylation of **5**, was oxidized directly

to **1** with MnO_2.[11] Although efficient, the large quantities of MnO_2 that would be required for industrial scales limits its practicality.

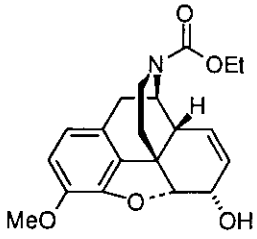


5 R=H
6 R=Me

Subsequently, it was shown by Schwartz that the *N*-protected codeinone (**7a**), prepared by MnO_2 oxidation of **8**, can be smoothly converted into the corresponding dienol acetate (**9**) , a close analog of thebaine.[12] Oxidation by singlet oxygen allowed access to the opiate antagonists, however this approach is limited by the lack of a 6-methoxyl group which is required for the Diels-Alder derived orvinols. Obviously, direct methyl dienol ether formation from codeinone (**10**) or the non-basic derivatives (**7**) would have great advantages over these methods, especially considering that MnO_2 could be eliminated through the use of Oppenhauer oxidation for the conversion of **5** to **10**.[13]



7a R=Et
7b R=Me



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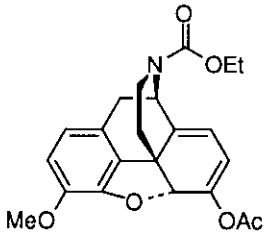

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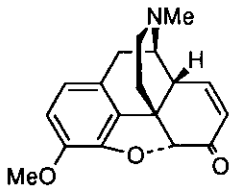
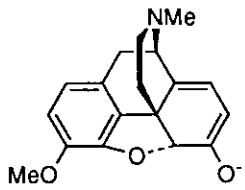
However, it has been shown that acid catalyzed dienol ether formation from **10**[11,14,15] and its 1-iodo analog[16] gives low yields of thebaine and 1-iodothebaine due to competing Michael addition of methanol to the α,β-unsaturated system, and that treatment with base leads to dimerized product (**11**).[17] After further

study of this reaction, we concluded that under the thermodynamic basic conditions employed, any enolate (**12**) formed reacts rapidly with non-enolized codeinone to give the dimer. We envisaged that under non-reversible conditions, where all the of codeinone existed as **12**, no dimerization would occur and the enolate could be *O*-methylated to give thebaine.



10



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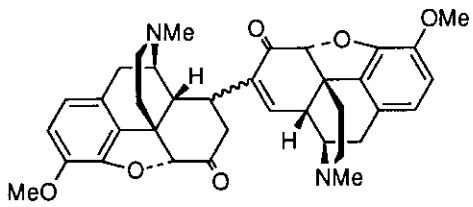
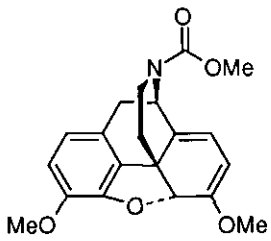


11

We initially considered the use of metallic hydrides to form the desired enolate (**12**), however treatment of **10** with either NaH/15-crown-5 or KH/18-crown-6 followed by Me_2SO_4, under a wide range of conditions, failed to yield more than a trace of desired product. We therefore turned our attention to other bases and found that the use of *t*-BuOK as base in the presence of 18-crown-6 at 0°C gave rise to a 54% yield of thebaine, a comparable yield to Rapoport and a vast improvement over the reported acid catalyzed enol ether formation.

With the methodology in place we turned our attention to the carbamate of thebaine (**13**). Morphine antagonists possess *N*-substitution other than methyl and, as all synthetically useful natural opiates are *N*-methyl substituted, an *N*-demethylation step is required at some stage in their synthesis.[1]



13

Such steps are usually performed *via* conversion to the carbamates, which can be cleaved under a variety of conditions to give the *N*-norcompounds.[18] Direct formation of carbamates, such as **13**, from

thebaine has not been achieved and we considered that our dienol ether formation methodology may allow a convenient synthesis of this potentially useful intermediate. The carbamate of codeinone (**7b**) was prepared *via* a modification of the method of Schultz.[19] It was found that unlike the basic analog, the use of NaH as base followed by Me_2SO_4, gave a 57% yield of **13** and that the use of *t*-BuOK as base gave a 72% yield.[20]

In summary we have shown that the enolate of codeinone can be successfully methylated, and allows a practical synthesis of thebaine from codeine in two simple steps. In addition, we have shown that the methyl carbamate of thebaine can be prepared in excellent yield from the corresponding carbamate of codeinone and offers a practical synthesis of this potentially useful intermediate for opioid synthesis.

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20. The spectra of **13** were identical to those previously reported for the racemate. See M. A. Schwartz and P. T. K. Pham, *J. Org. Chem.*, 1988, **53**, 2318. The identity of **13** was confirmed by treatment with $LiAlH_4$. The thebaine obtained was identical to an authentic sample.

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