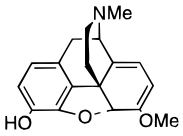
Direct and Simple O-Demethylation of Thebaine to Oripavine

Andrew Coop, John W. Lewis,† and Kenner C. Rice*

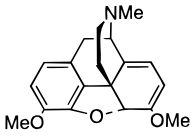
Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, Building 8, Room B1-23, Bethesda, Maryland 20892-0815, and School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

Received August 2, 1996

Oripavine (**1**) is a potentially valuable starting material for opioid synthesis, yet, despite many efforts since its discovery[1] more than 60 years ago no simple method for obtaining it has been described. The corresponding methyl ether, thebaine (**2**), a relatively abundant opium



1

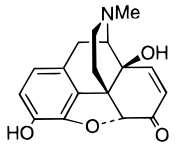


2

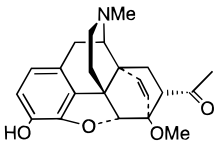
alkaloid and obvious starting material for **1**, is widely used as a raw material for the synthesis of many medically important opioids.[2,3] Since the vast majority of these thebaine derivatives are 3-phenols like oripavine, a frequently troublesome demethylation step is required that could be avoided if oripavine were available as a starting material. Oripavine occurs in extremely minor quantities in opium, and the only available synthesis requires four steps from morphine.[4] A one step O-demethylation of thebaine to oripavine has thus been an important goal in the chemistry of the opium alkaloids. Previous attempts[5−7] at this conversion have been unsuccessful, due to the sensitivity of the allylic and dienol ether functions to acids, bases, and nucleophiles.[8,9] We now wish to disclose that this transformation can be accomplished conveniently by the use of L-Selectride (Aldrich).

L-Selectride has recently been reported as an efficient O-demethylating agent for simple systems.[10,11] We envisaged that this reagent may allow 3-O-demethylation of **2**, while the steric bulk would prevent close approach to C-5 and hence cleavage of the labile ether bridge. We found that this was indeed the case, with the greatest yields (23%) of oripavine being obtained with 1 M L-Selectride in THF at reflux for 30 min. Longer reaction times gave rise to products of further reaction, notably those due to 6-O-demethylation. Although the yield was low, 31% of unreacted thebaine could be recovered. Further study of the reaction conditions led to the discovery that prolonged stirring (14 days) at room temperature gave a 35% yield of oripavine but lower recovery (5%) of thebaine.[12]

The ease of this transformation allowed investigation of the chemistry of oripavine for the first time.[8] In order to demonstrate its potential use in opioid synthesis, it was necessary to compare the chemistry with that of thebaine. The two most important reactions of thebaine are the oxidation to 14-hydroxycodeinone, leading to the opiate antagonists, and the Diels−Alder reactions leading to the orvinols, a class of very potent and important opioid drugs.[2] As expected, it was found that the chemistry of oripavine is very similar to that of thebaine. Unoptimized oxidation of the oripavine dienol ether system to give 14-hydroxymorphinone (**3**) proceeded in 62% yield with *m*-chloroperbenzoic acid under modified conditions to those described for thebaine,[13,14] and Diels−Alder reaction with 1-buten-3-one gave the orvinone (**4**) (82%).[7,15]



3



4

In summary, we have demonstrated that L-Selectride allows a practical O-demethylation of thebaine to oripavine in reasonable yield without chromatography and that oripavine has the potential to be a useful intermediate in the synthesis of novel opioids. The general application of this 3-O-demethylation procedure to opium alkaloids and their derivatives will be the subject of a future paper.

Supporting Information Available: Experimental procedures and characterization data (2 pages).

JO961473K

† University of Bristol.

(1) Konowalowa, R.; Yunussoff, S.; Orechoff, A. *Ber.* **1935**, *68*, 2158.
(2) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics*; Plenum Press: New York and London, 1986.
(3) Casy, A. F. *The Steric Factor in Medicinal Chemistry*; Plenum Press: New York and London, **1993**; pp 429−465.
(4) Barber, R. B.; Rapoport, H. *J. Med. Chem.* **1975**, *18*, 1074.
(5) Andre, J. D.; Dormoy, J. R.; Heymes, A. *Synth. Commun.* **1992**, *22*, 2313.
(6) Lawson, J. A.; Degraw, J. I. *J. Med. Chem.* **1977**, *20*, 165.
(7) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, E.; Iwamura, T.; Nozaki, M.; Niwa, M.; Fujimura, H. *Chem. Pharm. Bull.* **1984,** *32*, 1268.
(8) Bentley, K. W. *The Chemistry of the Morphine Alkaloids*; Clarendon Press: Oxford, England, 1954.
(9) Bentley, K. W. *J. Am. Chem. Soc.* **1967**, *89*, 2464.
(10) Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727.
(11) Mathis, C. A.; Mahmood, K.; Huang, Y.; Simpson, N. R.; Gerdes, J. M.; Price, J. C. *Med. Chem. Res.* **1996**, *6*, 1.
(12) Oripavine was isolated as the oxalate salt from methanol. Thebaine was isolated as the (+)-tartaric acid salt from methanol.
(13) Hauser, F. H.; Chen, T.-K.; Carroll, F. I. *J. Med. Chem.* **1974**, *17*, 1117.
(14) It was found that oxidation of the dienol ether system with *m*-CPBA proceeded smoothly in water at room temperature in the presence of 1 equiv of sulfuric acid. Under these conditions thebaine gave 14-hydroxycodeinone in 87% yield.
(15) Brown, J. J.; Hardy, R. A.; Roth, C. N. US Patent 3562279, 1971.

S0022-3263(96)01473-9 CCC: $12.00