JOC*Note*

Efficient N-Demethylation of Opiate Alkaloids Using a Modified Nonclassical Polonovski Reaction

Kristy McCamley,[†] Justin A. Ripper,[‡] Robert D. Singer,[§] and Peter J. Scammells*,[†]

Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia, School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria 3217, Australia, and Department of Chemistry, Saint Mary's University, Halifax, Nova Scotia, B3H 3C3, Canada

peter.scammells@vcp.monash.edu.au

Received August 25, 2003

Abstract: A modified Polonovski reaction has been employed to N-demethylate several opiate alkaloids in moderate to high yield. This method provides an alternative to traditional N-demethylation procedures which utilize toxic reagents such as cyanogen bromide or expensive reagents such as vinyl chloroformate. The current synthesis involves *N*-oxide formation, isolation of the corresponding *N*-oxide hydrochloride, and an $FeSO_4 \cdot 7H_2O$ mediated Polonovski reaction to afford the desired secondary amine.

The opium poppy, *Papaver somniferum*, is the primary source of the analgesic opiate alkaloids morphine and codeine. A number of synthetic opiate derivatives have also been approved for therapeutic use. In many of these synthetic, pharmaceutically useful opiates, the naturally occurring *N*-methyl group has been replaced by other alkyl groups to give, for example, the antagonists nalorphine (**1**) and naltrexone (**2**) and the mixed agonist−antagonist buprenorphine (**3**) (Chart 1).[1] The N-demethylation of naturally occurring opiates has been achieved in numerous ways. Certain chloroformates[2] are effective reagents for N-demethylation; however, usage on a large scale is limited by their expense. The von Braun reaction[3] is another alternative, though large scale application is restricted because of poor yields and the toxicity of cyanogen bromide. Other reagents such as azocarboxylic esters,[4] nitrous acid,[5] and thiolates[6] have also been employed in the demethylation of tertiary *N*-methylamines. Additionally, procedures utilizing photochemistry,[7] electrochemistry,[8] and microorganisms[9] have been investigated.

The Polonovski reaction has also proven to be effective for the demethylation of tertiary *N*-methylamines.[10,11] This approach initially involves conversion of the amine to the corresponding *N*-oxide using an appropriate peroxide or peracid. The amine *N*-oxide is then reacted with an "activating agent" which induces an elimination and ultimately affords an iminium ion intermediate that reacts further to yield the N-demethylated product and formaldehyde.[11] There are three main categories of activating agents, namely, acylating agents (acid anhydrides and chlorides), iron salts, and sulfur dioxide. To date, the Polonovski reaction has been unsuccessful in the N-demethylation of opiate alkaloids.[12,13] Morphine *N*-oxide has been reported to react with acetic anhydride to give predominantly 3,6-diacetylmorphine (heroin), with only trace amounts 3,6,17-triacetylnormorphine detected.[12] In contrast, treatment with acetyl chloride gave a 50−70% yield of $\Delta^{16,17}$-dehydroheronium acetate.[13]

Because iron salts were successfully used to N-demethylate galanthamine-*N*-oxide,[14] the application of this nonclassical variant of the Polonovski reaction for the N-demethylation of opiate alkaloids was explored. The mechanism of this process is believed to involve two successive one-electron steps involving Fe(II)/Fe(III) redox reactions (Scheme 1).[11] In this mechanism, the iron(II) coordinates to the protonated *N*-oxide which subsequently undergoes a one-electron reduction resulting in cleavage of the N−O bond and formation of an aminium radical cation. The radical cation loses an α-proton and undergoes an electron reorganization to form a carbon-centered radical which is oxidized by iron(III) to form an iminium ion. Hydrolysis of this iminium ion affords the secondary amine. The major byproduct from such reactions is generally the parent tertiary *N*-methylamine which results from iron(II) reduction of the intermediate aminium radical cation.

Our initial studies were performed on codeine (**4**), codeine methyl ether (CME) (**5**), thebaine (**6**), the 14-hydroxy opiates **7**−**9**, and thevinone (**10**) (Chart 2).

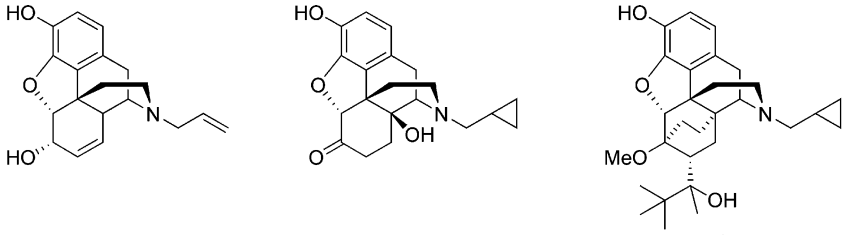
Oxidation by *m*-CPBA or H_2O_2 produced the corresponding *N*-oxides of **4**−**7** in quantitative yields, whereas the oxidation of **8**−**10** was less efficient (Table 1). Although the oxidation of thebaine (**6**) under acidic

[†] Monash University.
[‡] Deakin University.
[§] Saint Mary's University.

(1) Nogrady, T. In *Medicinal Chemistry—A Biochemical Approach*, 2nd ed.; Oxford University Press: Oxford, U.K., 1988.
(2) (a) Cooley, J. H.; Evian, E. J. *Synthesis* **1989**, 1. (b) Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850. (c) Rice, K. C.; May, E. L. *J. Heterocycl. Chem.* **1977**, *14*, 665.
(3) Von Braun, J. *Chem. Ber.* **1909**, *42*, 2035.
(4) Merz, H.; Pook, K. H. *Tetrahedron* **1970**, *26*, 1727.
(5) Hosztafi, S.; Makleit, S.; Bognar, R. *Acta Chim. Acad. Sci. Hung.* **1980**, *103*, 371.
(6) (a) Manoharan, T. S.; Madyastha, K. M. *Synthesis* **1983**, 809. (b) Anastasia, L.; Cighetti, G.; Allevi, P. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2398.
(7) Ripper, J. A.; Tiekink, E. R. T.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 443.
(8) (a) Smith, P. J.; Mann, C. K. *J. Org. Chem.* **1969**, *34*, 1821. (b) Barry, J. E.; Finkelstein, M.; Mayeda, E. A.; Ross, S. D. *J. Org. Chem.* **1974**, *39*, 2695. (c) Portis, L. C.; Klug, J. T.; Mann, C. K. *J. Org. Chem.* **1974**, *39*, 3488.
(9) (a) Madyastha, K. M. *Proc. Indian Acad. Sci.* **1994**, *106*, 1203. (b) Vijay Bhasker Reddy, G.; Madyastha, K. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 911.
(10) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190.
(11) Grierson, D. *Org. React.* **1990**, *39*, 85−295.
(12) Klein, M. In *Mass Spectrometry in Drug Metabolism*; Frigerio, A., Ghisalberti, E. L., Eds.; Plenium Press: New York, 1977, p 449.
(13) Allen, A. C.; Moore, J. M.; Cooper, A. C. *J. Org. Chem.* **1983**, *48*, 3951.
(14) Mary, A.; Renko, D. Z.; Guillou, C.; Thal, C. *Tetrahedron Lett.* **1997**, *38*, 5151.

10.1021/jo035243z CCC: $25.00
Published on Web 11/12/2003

CHART 1



1 **2** **3**

SCHEME 1. Proposed Mechanism of the Polonovski Reaction[11]

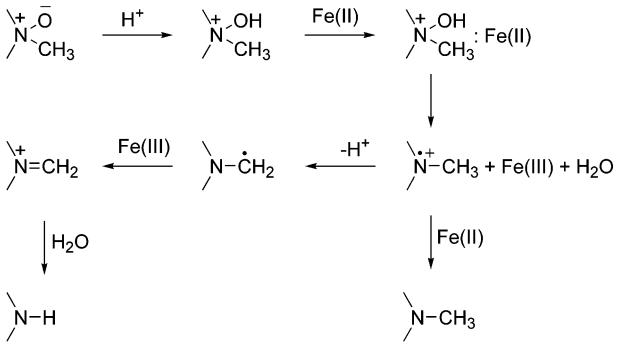
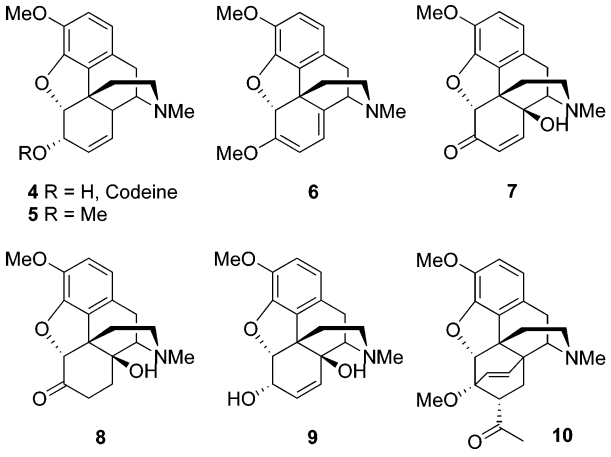


CHART 2. Opiates Trialed in the Nonclassical Polonovski Reaction



4 R = H, Codeine
5 R = Me

6 **7** **8** **9** **10**

TABLE 1. Polonovski Reaction of Selected Opiate *N*-Oxides

opiate	oxidation conditons	*N*-oxide % yield	nor-opiate % yield[a]
4	H_2O_2 (11 equiv)	100	63
5	*m*-CPBA (1.1 equiv)	100	80
6	H_2O_2 (5 equiv)	100	38
7	*m*-CPBA (1.1 equiv)	100	
8	H_2O_2 (11 equiv)	61	
9	*m*-CPBA (1.1 equiv)	54	
10	H_2O_2 (11 equiv)	80	44

[a] Isolated yield after column chromatography.

conditions is known to produce 14-hydroxycodeinone and byproducts,[15] these compounds were not observed when thebaine was treated with hydrogen peroxide under neutral conditions. Conversion of the *N*-oxides to the N-demethylated products was attempted using a range of iron salts which included $FeSO_4 \cdot 7H_2O$, $FeCl_2 \cdot 4H_2O$, and $Fe(NH_4SO_4)_2$. Iron(II) sulfate ($FeSO_4 \cdot 7H_2O$) proved to be the most efficient reducing agent for the N-demethylation of CME-*N*-oxide and was adopted for subsequent examples. The Polonovski reaction involving CME-*N*-oxide was the most efficient overall, affording an 80% yield of the desired "nor" compound with the balance of the mass being CME. In contrast, reactions involving the 14-hydroxy compounds **7** and **8** gave multiple products and negligible yields of the desired nor-opiates. Because the iron-mediated Polonovski reaction is known to be sensitive to steric effects,[11] it was thought that the poor yields obtained for these reactions were due to the presence the proximal 14-hydroxy group. To explore this idea further, 14-hydroxycodeine (**9**) was prepared via literature methodology (aluminum isopropoxide reduction of 14-hydroxycodeinone[16] and oxidized to the corresponding *N*-oxide with hydrogen peroxide. The reaction of 14-hydroxycodeine-*N*-oxide with iron(II) sulfate also afforded a negligible yield of the N-demethylated product. This result was significantly inferior to the N-demethylation of codeine-*N*-oxide, which proceeded in 63% yield. These data support the idea that the 14-hydroxy group plays a significant role in the iron-mediated Polonovski reaction.

In all cases, the presence of iron salts complicated the reaction workup and purification of products. These difficulties were overcome by evaporating the reaction solvent and dissolving the crude product in a 0.1 M EDTA solution (basified to pH 10) prior to chloroform extraction.

Because the proposed mechanism involves protonation of the *N*-oxide, we reasoned that the addition of acid should facilitate the reaction. The addition of acid (H_2SO_4, HCl, and acetic acid) to the $FeSO_4$ catalyzed N-demethylation of CME-*N*-oxide gave variable results. A much more reliable approach involved the isolation of the chloride salt of the protonated *N*-oxide prior to treatment with iron sulfate. The optimized procedure[17] involved initial peroxide oxidation of opiates **4**−**6** and **10** (using up to 11 molar equiv of H_2O_2) in methanol at room temperature to afford the opiate *N*-oxides in quantitative yields. The hydrochloride salts of these *N*-oxides were then formed by addition of 6 M HCl (2 M HCl for thebain-*N*-oxide) and isolated via chloroform extraction. Conversion of the opiate-*N*-oxide hydrochloride salts to the desired N-demethylated products was then achieved using $FeSO_4 \cdot 7H_2O$ (2 molar equiv) in methanol at room temperature. Iron salts were removed using an EDTA−chloroform workup procedure, and the N-demethylated opiate products were purified via column chromatogra-

(15) Iijima, I.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta* **1977**, *60*, 2135.

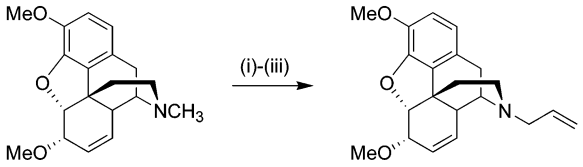
(16) Currie, A. C.; Gillion, J.; Newbold, G. T.; Spring, F. S. *J. Chem. Soc.* **1960**, 773.

TABLE 2. Polonovski Reaction of Opiate *N*-Oxide Hydrochlorides

opiate	*N*-oxide % yield	*N*-oxide HCl (%)[a]	% recovery (2°:3° amine)[b]	nor-opiate % yield[c]
4	100	100 (87:13)	82 (56:44)	49
5	100	100 (90:10)	98 (96:4)	87
6	100	100 (57:43)	98 (81:19)	74
10	80	80 (92:8)	96 (80:20)	62

[a] Ratio of isomers (axial vs equatorial) determined by CE. [b] Ratio of nor-opiate to the parent *N*-methyl compounds as determined by CE. [c] Isolated yield after column chromatography.

SCHEME 2. Synthesis of *N*-Allyl nor-CME[a]



[a] (i) H_2O_2, MeOH, and then 6 M HCl; (ii) $FeSO_4$, MeOH; (iii) allyl bromide, Na_2CO_3, EtOH.

phy. Some degradation was observed during chromatography which reduced the isolated product yields.

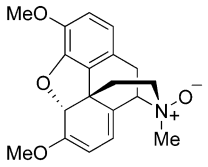
The ratios of tertiary amine to secondary amine varied between the four opiates studied (Table 2).

The N-demethylation of CME (**5**) was the most efficient. Capillary electrophoresis (CE) indicated that the ratio of nor-CME to CME was 96:4. This ratio was confirmed by ^{1}H NMR integration of the mixture. After isolation and purification, an 87% yield of nor-CME was obtained. TLC analysis of the fractions collected in this separation indicated the formation of small amounts (≤7%) of decomposition products. Alternatively, the crude reaction mixture could be treated with an alkylating agent to afford the expected *N*-alkyl product directly. *N*-Allyl nor-CME was prepared in 77% yield using this approach (Scheme 2). The oxidation and N-demethylation of thebaine (**6**) also proceeded in good yield, though CE analysis of the reaction mixture showed a comparatively lower preference for the formation of the N-demethylated product (80:20 compared with 96:4). The conversion of thevinone (**10**) to nor-thevinone proceeded in a similar fashion. The oxidation of codeine (**4**) gave quantitative yield of the *N*-oxide hydrochloride, though the subsequent reduction produced norcodeine in an isolated yield of 49%.

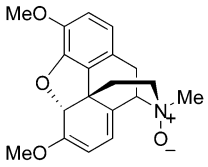
To further explore this reaction, we prepared and isolated the axial and equatorial stereoisomers of the-

(17) CME (1.0 g) was dissolved in MeOH (10 mL) and cooled on an ice−water bath. Hydrogen peroxide (30% w/v, 11 equiv) was added slowly, and the reaction mixture was stirred at room temperature for 18 h. Excess H_2O_2 was deactivated with MnO_2 and the solution was filtered and evaporated in vacuo to give CME-*N*-oxide as a pale-pink solid (100%). The crude CME-*N*-oxide was dissolved in brine (30 mL), cooled on ice, and acidified to pH 1−2 with 6 M HCl. This solution was extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and then evaporated to give CME-*N*-oxide·HCl as an off-white foam (>98%). The crude CME-*N*-oxide·HCl (1 g) was dissolved in MeOH (40 mL) and cooled in an ice−water bath. $FeSO_4·H_2O$ (2 equiv) was added, and the reaction mixture was stirred at room temperature for 1 h. Evaporation of the solvent afforded an orange solid which was dissolved in 0.1 M EDTA at pH 10 (basified by addition of NH_3) (60 mL > 2 equiv). The solution was extracted with $CHCl_3$
(3 × 20 mL), and the dried organic extracts ($MgSO_4$) were filtered and evaporated to yield a mixture of nor-CME and CME (96:4). Nor-CME was purified by column chromatography using $CHCl_3$/MeOH/NH_3 (90:10:1) as an eluent. Pure nor-CME was obtained in 87% yield from CME.

TABLE 3. Polonovski Reaction of Thebaine *N*-Oxide Isomers



11a



11b

entry	opiate	ionization	ratio of 2°/3°amine[a]
1	**11a**	free *N*-oxide	77:23
2	**11a**	*N*-oxide HCl	93:7
3	**11b**	free *N*-oxide	54:46
4	**11b**	*N*-oxide HCl	62:38

[a] Ratio of nor-opiate to *N*-Me as determined by CE.

baine-*N*-oxide[18] in both the protonated and the unprotonated forms. These four isomers were then treated with iron sulfate under the standard conditions, and the ratio of nor- to *N*-methyl opiate was measured by CE (Table 3). The ratio of thebaine-*N*-oxide isomers was 57:43 with the major, less polar isomer **11a** having an axial *N*-CH_3. A comparison of the results obtained for the *N*-oxide hydrochlorides with the free *N*-oxides (Table 3, entries 2 and 4 with entries 1 and 3, respectively) indicates that formation of the hydrochloride salt increases the proportion of the desired nor-opiate. Additionally, a comparison of the axial isomers (entries 1 and 2) with the equatorial isomers (entries 3 and 4) suggests that the isomeric configuration of the *N*-oxide also affects the final ratio of the N-demethylated product obtained under $FeSO_4·7H_2O$ mediated Polonovski conditions.

The effect of addition of an Fe(III) salt to increase product formation, namely, $Fe_2(SO_4)_3$, was also examined. The reduction of thebaine-*N*-oxide·HCl using (a) $FeSO_4$ (2 equiv) and $Fe_2(SO_4)_3$ (0.1 equiv) and (b) $FeSO_4$ (1.1 equiv) and $Fe_2(SO_4)_3$ (1.1 equiv) was performed. When a catalytic amount of $Fe_2(SO_4)_3$ was added, no increase in the proportion of N-demethylated product was observed. Furthermore, addition of a stoichiometric amount of $Fe_2(SO_4)_3$ actually increased the formation of thebaine.

It should also be noted that variation of the amount of $FeSO_4·7H_2O$ added (0.5, 1.0, and 2.0 equiv) did not alter the final ratio of products obtained. However, use of only 0.5 equiv failed to convert all of the *N*-oxide hydrochloride.

In conclusion, the modified Polonovski reaction conditions described in this paper demonstrate effective N-demethylation of opiates **4**, **5**, **6**, and **10** in moderate-to-high-isolated yields. This procedure utilizes much cheaper reagents[19] than other higher-yielding methods for opiate N-demethylation (such as those involving vinyl chloroformate or diethyl azodicarboxylate) which is of obvious significance for large scale processes. The wider applicability of this procedure for the N-demethylation of

(18) (a) Caldwell, G. W.; Gauthier, A. D.; Mills, J. E. *Magn. Reson. Chem.* **1996**, *34*, 505. (b) Phillipson, J. D.; Handa, S. S.; El-Dabbas, S. W. *Phytochemistry* **1976**, *15*, 1297.

(19) The Sigma-Aldrich price for $FeSO_4·7H_2O$ (98%) is $A16 per mole compared with $A4440 per mole for vinyl chloroformate (99%) and $A232 per mole for diisopropyl azodicarboxylate (95%). Prices per mole were calculated based on the price for the largest available pack size (effective August, 2003).

other *N*-methyl alkaloids is currently being evaluated and will be reported in due course.

Acknowledgment. The authors thank the Analytical Group at Deakin University for assistance running the CE and GSK for financial support.

Supporting Information Available: General experimental procedure, synthesis, and spectroscopic data for nor-opiates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035243Z