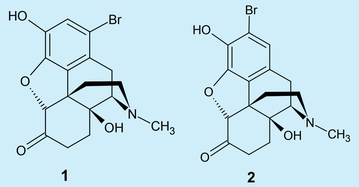
Brominated Oxymorphone Impurities: Regioselective Synthesis and Characterization of 1-Bromo- and 2-Bromooxymorphone

Authors Elizabeth B. Marek PhD, Gregory J. Kirkovits PhD, Huahua Jian PhD, Uma Sreenivasan PhD

Abstract

The use of synthetic opiate impurities as reference materials has become vital to the pharmaceutical industry. To this end, brominated oxymorphone impurities 1-bromooxymorphone (1) and 2-bromooxymorphone (2) were synthesized using desirable short, direct, and regioselective methods. Using a combination of ^{1}H, ^{13}C and 2-D NMR spectra, unequivocal evidence for the electrophilic aromatic substitution of bromine at the 1- and 2-positions of the aromatic ring of oxymorphone has been demonstrated.



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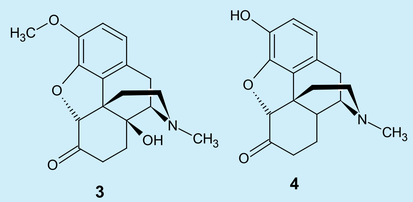
Introduction

Impurities in drugs and drug substances (APIs) are a major concern for the pharmaceutical industry. These impurities can be unreacted starting materials, intermediates, or by-products from the manufacturing process and can affect the safety and efficacy of the drug. Identification and monitoring of these impurities is critical to this industry. Therefore there is a growing need for these impurities as high purity reference materials, applicable to process development and validation of compounds as APIs or routine impurity analysis in the pharmaceutical industry.

Opiates are an extremely important class of compounds for use in pain management. Chlorinated and brominated opiates, substituted on the aromatic ring, have been reported in the literature as manufacturing impurities and degradants in opiates used as active pharmaceutical ingredients.[1] Interestingly, whereas the regioselective bromination of related opiates such as oxycodone (3)[2,3] and hydromorphone (4)[3] have been studied; to date no details of the bromination of oxymorphone can be found in the literature. As a consequence, we sought to synthesize the mono-brominated species, 1-bromooxymorphone (1) and 2-bromooxymorphone (2). Utilizing divergent methods we were able to regioselectively synthesize and isolate both products in high purity.



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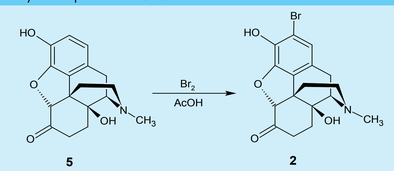
Synthesis of 1- and 2-bromooxymorphone

- Based on literature precedence for similar compounds[2,3], it was expected that electrophilic aromatic substitution could be used to install a bromine at the 1 position of oxymorphone. Synthesis of 1-bromooxymorphone (1) was therefore initially attempted by direct bromination of oxymorphone using bromine under acidic conditions. However, to our surprise, we isolated exclusively 2-bromooxymorphone (2) in 6% yield and 97% chromatographic purity, along with overbromination impurities. Unfortunately, this was not discovered for several months and was not evident from the ^{1}H NMR, thus requiring extensive 2D NMR for structural confirmation.
- Alternate methods were therefore sought to synthesize the corresponding 1-bromo derivative. Direct bromination of oxymorphone via NBS resulted in a complex mixture of unreacted starting material and degradation products. It was found that only by first brominating oxycodone followed by O-demethylation could 1-bromooxymorphone (1) be successfully synthesized in 16% yield and 98% chromatographic purity.
- HPLC, HPLC/MS and ^{1}H, ^{13}C, HMBC, COSY, and HSQC NMR techniques were used to determine the purity and to confirm the identity of 1- and 2-bromooxymorphone.

Synthesis of 2-bromooxymorphone (2)



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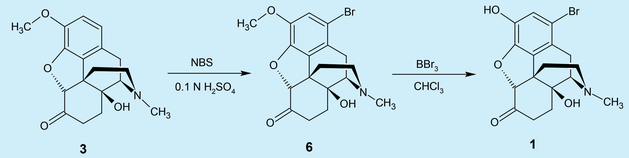
Treatment of oxymorphone (5) with bromine in acetic acid gives exclusively 2-bromooxymorphone (2) in 6% yield and 97% chromatographic purity.

Synthesis of 1-bromooxymorphone (1)



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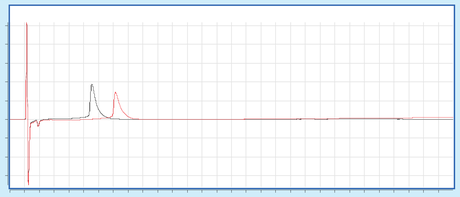
- Treatment of oxycodone (3) with NBS in sulfuric acid gives exclusively 1-bromooxycodone (6) in 68% yield and 97% purity. The structure was confirmed by comparison of the ^{1}H NMR to the literature.[2] For comparison, 2-bromooxymorphone was derivatized using diazomethane to give 2-bromooxycodone. ^{1}H NMR and HPLC for this compound were found to be different than that of 1-bromooxycodone (6) synthesized above, indicating both of the desired compounds had been synthesized by their respective methods.
- 1-Bromooxycodone (6) can then be deprotected using BBr_3 to give the desired 1-bromooxymorphone (1) in 24% yield and 98% chromatographic purity.

Discussion of Synthetic Results

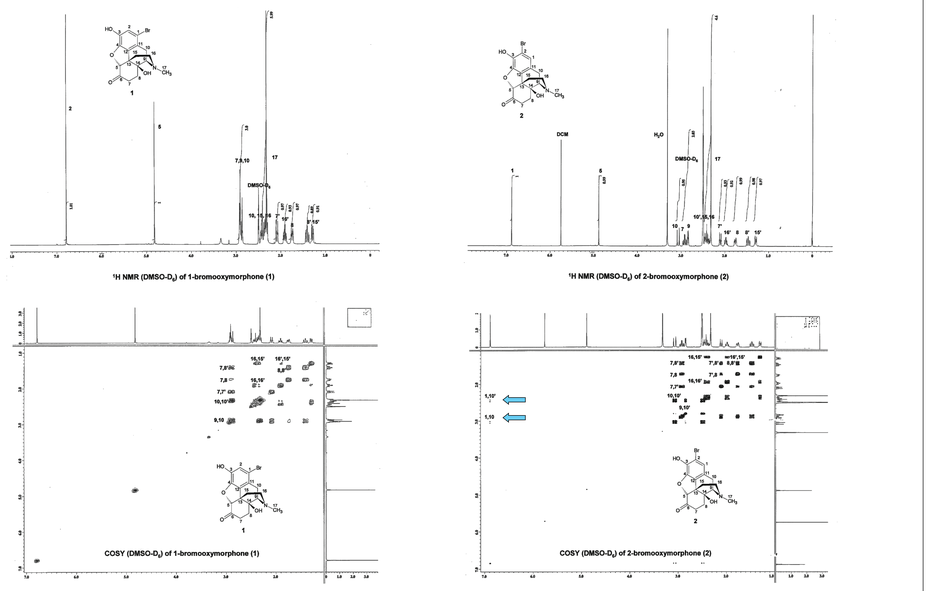
- The treatment of oxymorphone with bromine in acetic acid gives exclusively 2-bromooxymorphone (2) via electrophilic aromatic substitution. This regioselectivity can be attributed to the presence of the ortho/para directing phenol group. It is interesting to note that treating oxycodone (3) under similar conditions, results in the formation of 1-bromooxycodone (6).[3] It was this literature precedence that led us to initially incorrectly assign the position of the bromine on 2-bromooxymorphone (2).
- These results suggest that the presence of the methoxy group of oxycodone (3) sterically hinders the addition of the bulky bromine to the 2-position. Instead, substitution occurs at the 1-position, possibly further influenced by the para-directing ether at C4, resulting in the formation of 1-bromooxycodone (6).
- By manipulating this ability to control the regioselectivity of the bromine addition, we were able to synthesize both 1- and 2-bromooxymorphone in a concise manner.

Separation of 1- and 2-bromooxymorphone by HPLC

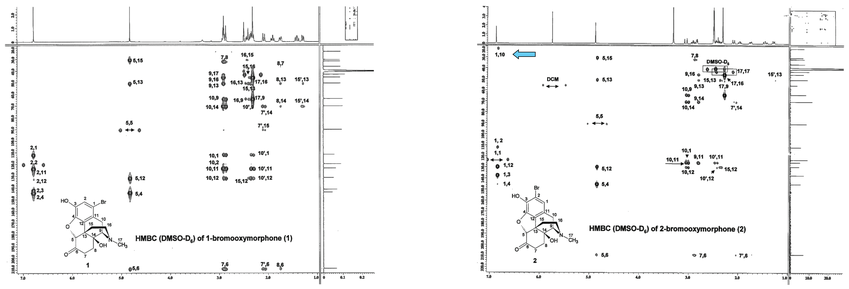


This figure presents an overlay of the HPLC-UV chromatograms (Prodigy 3m ODS, 10:90 0.1% formic acid/methanol : 0.1% formic acid/water, 0.3 mL/min, l=230 nm) of 1-bromooxymorphone (1, red) and 2-bromooxymorphone (2, black).

Characterization of 1- and 2-bromooxymorphone by NMR



The COSY spectrum for 2-bromooxymorphone (2) shows a 4 bond interaction between the proton at position 1 to that of the proton at position 10. This interaction is not seen in the COSY for 1-bromooxymorphone (1).



The 3 bond interaction between the proton at position 1 to that of the carbon at position 10 in 2-bromooxymorphone (2) is seen again in the HMBC spectrum. This interaction is not seen in the HMBC for 1-bromooxymorphone (1).

CONCLUSIONS

The syntheses of 1- and 2-bromooxymorphone in high purity have been developed and represent an example of steric vs. electronic effects controlling regioselectivity. Using a combination of ^{1}H, ^{13}C and 2-D NMR spectra, unequivocal evidence for the electrophilic aromatic substitution of bromine at the 1- and 2- positions of the aromatic ring of oxymorphone has been demonstrated. Further evidence of the formation of two unique compounds was demonstrated by derivatization of 2-bromooxymorphone (2) using diazomethane for direct comparison to 1-bromooxycodone (6). Importantly, the methods presented here would be applicable to synthesizing other brominated opiate impurities.

References
1. Walter et al Tet. Lett. 2003, 44, 7381-7384.
2. Wilson, M. L.; Carroll, P. J.; Dalton, D. R. *J. Org. Chem.* 2005, *70*, 6492-6495.
3. Görlitzer, K.; Schumann, R. *Pharm.* 1993, *48*, 30-33.

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