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# A CONVENIENT OXIDATION METHOD OF THE BENZYLIC 10-POSITION IN 4,5-EPOXYMORPHINAN

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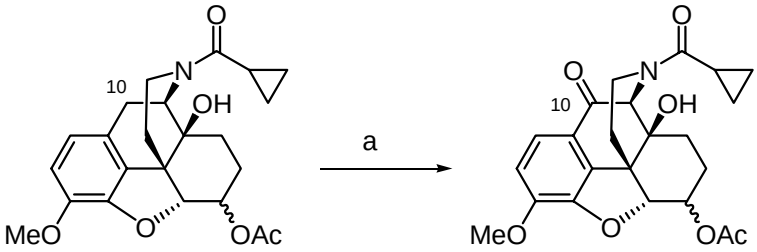
**Abstract** – A convenient oxidation method of the benzylic 10-position in 4,5-epoxymorphinan to obtain its 10-oxo derivatives is described. The reaction by using potassium permanganate proceeds in good yield and can be performed in large scale.

Three types of opioid receptors (μ, δ, κ) are now well established by not only pharmacological studies but also molecular biological studies.[1-3] Especially, the κ-opioid receptor has been of interest because its activation produces analgesia with minimum physical dependence and respiratory depression.[4] Thus, a highly selective κ-opioid agonist may provide a useful analgesic free from abuse potential and the adverse effects of a μ-agonist like morphine.[4,5] Oxo derivatives at the benzylic position of 4,5-epoxymorphinan and benzomorphan were described to possess more κ–receptor selectivity than the corresponding parent compounds, respectively.[6-8] In our research program searching for opioid receptor-type selective compounds, we focused on the 10-oxo derivatives of 4,5-epoxymorphinan compounds. In the field of opioid chemistry, several oxidation methods at the benzylic position are well known using various oxidants and reaction conditions such as chromic acid,[9-19] selenium dioxide,[8,20] oxygen,[21] electrochemical oxidation,[22] and photo-oxidation.[23] It is interesting to note that the benzylic oxidation using a common oxidant, chromic acid, affords the oxo derivative at the benzylic position in morphinan[13-15] or benzomorphan[16,17] series in good yields, but the same oxidant affords 10-hydroxylated derivative in 4,5-epoxymorphinan series concomitant with a trace amount of its 10-oxo derivative.[9-12, 18, 19] Selenium dioxide is the only oxidant which can directly convert 4,5-epoxymorphinan into its 10-oxo derivative. In our 4,5-epoxymorphinan substrate, the oxidation proceeds in moderate yield by using selenium dioxide (Figure 1). However, in general, the reaction requires drastic conditions (sealed tube at 180 ˚C) so that it is difficult to apply to large-scale synthesis. Herein, we wish to report a more convenient oxidation method of 4,5-epoxymorpinans by using potassium permanganate which can easily be scaled up and

afford 10-oxo derivatives in good yields.

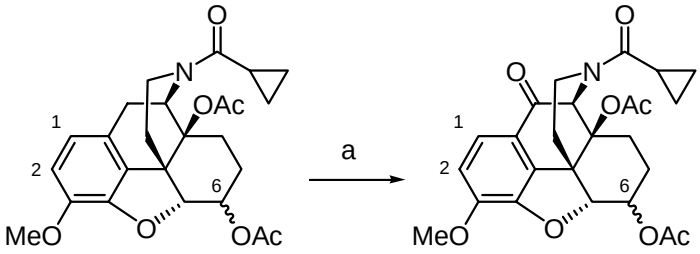



**1** **2**

a) $SeO_2$ (3 eq.), 1,4-dioxane, 180 ˚C (sealed tube), 24 h (60-70%)

Figure 1. $SeO_2$ oxidation of compound (**1**)

It is well known that potassium permanganate is one of the strongest oxidants and that it is difficult to control the oxidation stage of products.[24] On the other hand, 10-oxo derivatives of 4,5-epoxymorphinan could not enolize so that we considered further oxidation at the 10-position of 10-oxo derivatives would not proceed. On the basis of this hypothesis, we attempted to apply potassium permanganate for oxidation at the 10-benzylic position of 4,5-epoxymorphinans to obtain their 10-oxo derivatives. To the best of our knowlege, this is the first example of application of potassium permanganate to the 10-position oxidation in 4,5-epoxymorphinan.




**3** **4**

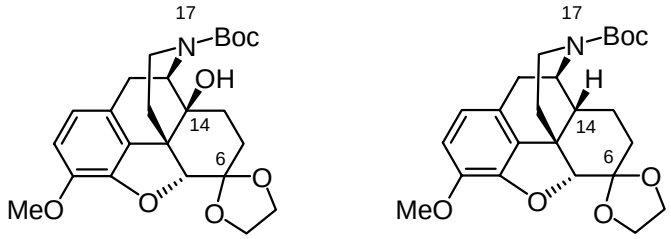
a) $KMnO_4$ (1+2 eq.), $MgSO_4$, aq. NaOH, *t*-BuOH, rt (74%) (6α/6β = 1/1)

Figure 2. $KMnO_4$ oxidation of compound (**3**)

First, compound (**3**) was subjected to potassium permanganate oxidation to investigate whether the 10-oxo derivative could be obtained or the 10-hydroxy derivative could be obtained (Figure 2). Thus, potassium permanganate (1 eq.) was added to a solution of compound (**3**) in *t*-BuOH under basic conditions (2.5 M aq. NaOH) at room temperature and stirring was continued for 12 h. At this point, the reaction mixture was worked up and the resulting residue was checked by $^1$H-NMR spectrum to show that the residue was constructed of *ca.* 1:1 mixture of the starting material (**3**) and 10-oxo derivative (**4**). Further oxidation of the crude mixture with potassium permanganate (2 eq.) under the same conditions

was carried out for 15.5 h. After work-up and chromatographic separation, the desired 10-oxo derivative (**4**) was obtained in 74% yield without any 10-hydroxy compound.[25] The above results suggest that potassium permanganate could be a useful oxidant to directly obtain 10-oxo-4,5-epoxymorphinans.

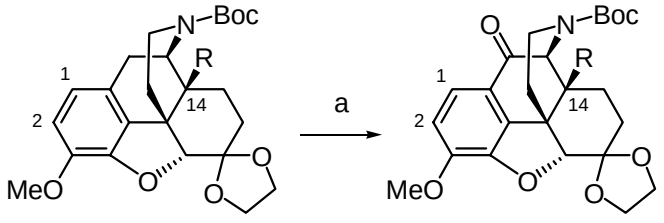
Next, suitably protected 4,5-epoxymorphinans (**5**) and (**6**) as shown in Figure 3 were used as the starting materials for potassium permanganate oxidation. Oxidation of these substrates having 6-ketal and 17-*N*-*tert*-butoxycarbonyl groups could afford 10-oxo derivatives favorable for further derivatization to κ-selective opioid ligands.




**5** **6**

Figure 3. Protected 4,5-epoxymorphinan as oxidation substrates

In this benzylic oxidation, 5 equivalents or more of potassium permanganate were used to complete the oxidation reaction. As the results, the oxidation of compound (**5**) proceeded completely to give the corresponding 10-oxo derivative (**7**)[26] in 96% isolated yield after chromatographic separation. Similarly, the oxidation of compound (**6**) also gave the corresponding 10-oxo derivative (**8**)[27] in 74% isolated yield (Figure 4).




**5**: R = OH
**6**: R = H

**7**: R = OH (96%)
**8**: R = H (74%)

a) $KMnO_4$ (5.2 eq. for **5**, 7.4 eq. for **6**), $MgSO_4$, aq. NaOH, *t*-BuOH/Py (10/1), rt

Figure 4. $KMnO_4$ oxidation of compounds (**5**) and (**6**)

In these reactions, *t*-BuOH and pyridine (10/1 v/v) were used as co-solvents because compound (**5**) and (**6**) were hardly dissolved only in *t*-BuOH. When only pyridine was used as solvent[28], the oxidation resulted in poor yield (35%) in the case of substrate (**5**). The solvent ratio (*t*-BuOH/pyridine = 10/1) was an important factor to attain good yield in this reaction system.[29]

The structures of 10-oxo derivatives (**4**, **7**, **8**) were confirmed mainly by $^1$H-NMR spectral analyses. It is known that the chemical shifts of protons of the 1- and 2-positions in 10-oxo derivatives shift to more down-field[20] than those of their parent compounds (**3**, **5**, **6**). The chemical shift values of the 1- and 2-positions are in good agreement with those of literature.[20]

As the results described above, potassium permanganate is a useful reagent to oxidize 4,5-epoxymorphinans having a hydrogen, hydroxy or acetoxy group on angular 14-position. The oxidation of compound (**5**) was carried out in 15 g scale under the same reaction conditions and its 10-oxo derivative (**7**) was obtained in high yield again (92%).

In conclusion, potassium permanganate is proved to be an efficient and more convenient oxidant than selenium dioxide for oxidation of the benzylic 10-position of 4,5-epoxymorphinan and this procedure can easily be scaled up. After oxidizing the 10-position, the obtained compounds (**7**) and (**8**) which possess convertible functional groups at the 6-, 10-, and 17-positions would be appropriate starting materials for a variety of new opioid ligands especially those having κ-receptor selectivity.

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25. The analytical and spectral data of compound (**4**): White powder, mp 190 ˚C; $^1$H-NMR (300 MHz, $CDCl_3$) δ: 0.86-1.00 (4H, m), 1.40-1.93 (5H, m), 1.95 (1.5H, s), 2.11 (1.5H, s), 2.25 (1.5H, s), 2.26 (1.5H, s), 2.40-2.80 (3H, m), 3.99 (1.5H, s), 4.01 (1.5H, s), 4.45-4.55 (1H, m), 4.70-4.80 (1H, m), 4.91 (0.5H, d, *J* = 4.8 Hz), 5.30-5.40 (0.5H, m), 5.46-5.48 (1H, m), 6.94 (0.5H, d, *J* = 8.4 Hz), 6.95 (0.5H, d, *J* = 8.4 Hz), 7.47 (0.5H, d, *J* = 8.4 Hz), 7.50 (0.5H, d, *J* = 8.4 Hz); IR (KBr) cm$^{-1}$: 1737, 1687, 1617, 1509. HRMS (EI) *m/z* Calcd for $C_{25}H_{27}NO_8$: 469.1737 ($M^+$). Found: 469.1711.
26. The analytical and spectral data of compound (**7**): Amorphous solid, $^1$H-NMR (300 MHz $CDCl_3$) δ: 1.39-1.80 (5H, m), 1.50 (9H, s), 2.03-2.12 (1H, m), 2.47 (1H, m), 2.71 (1H, m), 3.12 (1H, m), 3.76-3.89 (1H, m), 3.91-4.06 (2H, m), 3.97 (3H, s), 4.13-4.17 (1H, m), 4.56 (1H, s), 6.92 (1H, d, *J* = 8.4 Hz), 7.45 (1H, d, *J* = 8.4 Hz). IR (KBr) cm$^{-1}$: 3444, 1691, 1619, 1507, 1286. HRMS (EI) *m/z* Calcd for $C_{24}H_{29}NO_8$: 459.1893 ($M^+$). Found: 459.1913.
27. The analytical and spectral data of compound (**8**): Amorphous solid, $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.22-1.30 (3H, m), 1.45-1.62 (2H, m), 1.50 (9H, s), 1.66-1.80 (2H, m), 2.24-2.30 (1H, m), 2.75-2.95 (1H, m), 3.79-3.93 (2H, m), 3.95-4.04 (1H, m), 3.97 (3H, s), 4.15-4.20 (1H, m), 4.52 (1H, s), 4.60-4.85 (1H, m), 6.90 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 8.4 Hz). IR (KBr) cm$^{-1}$: 1691, 1620, 1506. HRMS (EI) *m/z* Calcd for $C_{24}H_{29}NO_7$: 443.1944 ($M^+$). Found: 443.1928.
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29. The general procedure for potassium permanganate oxidation of compound (**5**): To a stirred solution of compound (**5**) (3.33 g, 7.47 mmol) in 120 mL of *t*-BuOH and 12 mL of pyridine was added $MgSO_4$ (20.9 g, 173 mmol) at rt. To this suspension, a solution of $KMnO_4$ (6.18 g, 39.1 mmol) in a 2.5M aq. NaOH solution (30 mL, 75 mmol) and 120 mL of water was added, and the mixture was stirred at rt. After stirring for 12 h, 10% sodium thiosulfate solution was added to the suspension, and the mixture

was filtered through hyflo super-cell® and washed with $CHCl_3$ followed by water. The organic layer was separated and the water layer was extracted with $CHCl_3$. The combined organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo* to give 3.31 g of crude products. This was chromatographed on silica gel (86 g). Elution with *n*-hexane/EtOAc (1/1) gave 3.30 g (96%) of desired compound (**7**) as an amorphous solid.