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Novel cleavage reaction of the C16–N17 bond in naltrexone derivatives

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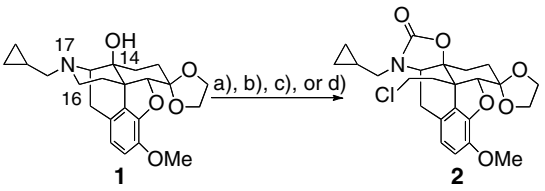
ABSTRACT

A dealkylation reaction of tertiary amines using chloroformate was a useful method for synthesizing morphinan derivatives without 17-substituents; however, the reaction has been applied to only the 14-hydromorphinans. In the course of the investigation of the 17-dealkylation reaction in 14-hydroxymorphinan, the novel cleavage reaction of the C16–N17 bond in the naltrexone derivative was found. A plausible reaction mechanism based on the stereoelectronic effect is presented. The examinations of dealkylation reactions in general tertiary amines ranked the tendency of cleavage as follows: benzyl > cyclopropylmethyl (CPM) ≈ allyl > methyl, ethyl. The preferable cleavage of the CPM group may be explained by the polarization of CPM–N17 bond due to a postulation of extreme stability of the cyclopropylcarbinyl cation.

Most therapeutically valuable opioids have a common structure, the morphinan scaffold. These morphinans include powerful pain relieving agents such as naturally occurring alkaloids (e.g., morphine, codeine), semisynthetic derivatives (e.g., oxymorphone, buprenorphine), and synthetic analogs (e.g., levorphanol, butorphanol). The 17-substituent of morphinans is believed to influence the agonistic or antagonistic character for the opioid receptor. For example, 17-methyl morphinans, morphine and oxymorphone are agonists. On the other hand, 17-allyl and 17-cyclopropylmethyl (CPM) morphinans, naloxone and naltrexone are antagonists.[1] Therefore, a dealkylation, especially demethylation, reaction of 17-substituents has been widely used to synthesize morphinan derivatives possessing various 17-substituents.[2–8] However, the reaction with chloroformates has been applied for only 14-hydromorphinans. To the best of our knowledge, the application of the reaction to 14-hydroxymorphinan has not been reported. Therefore, we were interested in the 17-dealkylation reaction in 14-hydroxymorphinans such as naltrexone. In the course of the study, we found a novel cleavage reaction of the C16–N17 bond in naltrexone derivative **1** that afforded oxazolidinone **2**. This novel cleavage reaction is interesting from the viewpoint not only of organic chemistry but also of medicinal chemistry, because the reaction could open the door for the synthesis of the morphinan derivatives without piperidine ring, which may be utilized to lead a μ opioid receptor partial agonist morphine[9] to full agonistic derivatives. We also observed a preferential cleavage of the CPM group in general tertiary amine **9** under the dealkylation conditions with 2,2,2-trichloroethyl chloroformate (Troc-Cl). Herein, we report the novel cleavage reaction of the C16–N17 bond in naltrexone derivative **1** to afford oxazolidinone derivative **2** and the scission reaction that favors the CPM group over the methyl and ethyl groups in compound **9**.

Although we attempted to dealkylate the CPM group in naltrexone using 1-chloroethyl chloroformate (ACE-Cl) under the original reaction conditions,[8] the reaction hardly proceeded. After extensive investigations, we found that the piperidine ring of naltrexone derivative **1** was cleaved with ACE-Cl (9 equiv) in pyridine to give, surprisingly, oxazolidinone **2**[10] in 60% yield concomitantly with starting material **1**, but the objective carbamate derivative **3** was not obtained (Scheme 1, condition (a), structure of compound **3** as shown in Fig. 1). We focused on the abnormal cleavage reaction of the C16–N17 bond which afforded oxazolidinone **2**, and attempted to improve the yield of the compound **2** and also to examine the reaction mechanism.

We developed the working hypothesis that at first a reaction intermediate, oxooxazolidinium **4** (Figs. 1 and 2), would be formed and then chloride ion would attack C16. If enough chloride ions



Scheme 1. Reagents and conditions: (a) ACE-Cl (9 equiv), pyridine, 100 °C, 6 h, 60%; (b) ACE-Cl (22 equiv), pyridine, 100 °C, 1.5 h, 80%; (c) ACE-Cl (5.6 equiv), K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, 21 h, 93%; (d) Troc-Cl (5.6 equiv), K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, 22 h, 70%.

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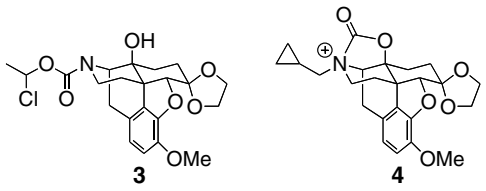
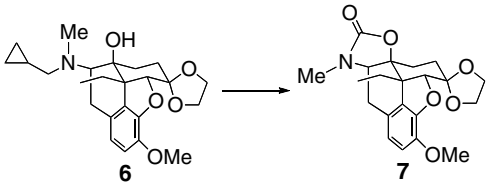


Figure 1.

would be present in the reaction system, the ion might attack C16 to easily cleave the C16–N17 bond. When sufficient free chloride ion does not exist, the cleavage reaction could not proceed rapidly enough, and the remaining intermediate **4** would be hydrolyzed to give starting material **1** during workup. Although pyridine may neutralize hydrochloric acid derived from the reaction of **1** with ACE-Cl, the resulting pyridinium chloride may not give much free chloride ion in the solution, because pyridine is a weak base and pyridinium chloride cannot dissociate effectively into free chloride ion and pyridine. On the basis of the above working hypothesis, we used a large excess of ACE-Cl (22 equiv) in pyridine to access the objective compound **2** in 80% yield (Scheme 1, condition (b)). We next tried to use potassium carbonate as a base. Reaction of potassium carbonate with hydrochloric acid gives potassium chloride and carbonic acid, which will decompose to give carbon dioxide and water. In fact, starting naltrexone derivative **1** was treated with ACE-Cl (5.6 equiv) in the presence of potassium carbonate (9 equiv) in 1,1,2,2-tetrachloroethane to give the objective oxazolidinone **2** in 93% yield (Scheme 1, condition (c)). The reaction of **1** with Troc-Cl also afforded **2** in 70% yield (Scheme 1, condition (d)).

We examined why the C16–N17 bond cleavage occurred without removal of the CPM group. Figure 2 shows respective intermediate **4** ((A) and (B)) or **5** (D) of 14-hydroxy or 14-hydromorphinan and their Newman projection formulas ((C) and (E)), and includes a postulated reaction mechanism of the bond cleavage. In Figure 2A, the carbamate moiety of the intermediate **4** was fixed by the rigid ring structure. Therefore, the σ-bond between the 17-nitrogen and the CPM group in **4** would be fixed almost orthogonally to the π-orbital of the carbonyl group in the oxazolidinone ring and, thus, may not be conjugated with the carbonyl group of oxazolidinone ring and not be activated by the carbonyl group. In contrast, the C16–N17 bond would be parallel to the π-orbital of the carbonyl group in the oxazolidinone ring (Fig. 2B). The σ-orbital of C16–N17 bond could be conjugated with the carbonyl π-orbital effectively to accelerate the cleavage reaction of the C16–N17 bond with chloride ion. As a result, the C16–N17 bond would be stereoelectronically preferred for cleavage as opposed to the bond between the 17-nitrogen and the CPM group to give oxazolidinone **2** (Fig. 2B). The Newman projection formula of intermediate **4** (C) indicated the definitive difference of the positional relationship between the carbonyl π-orbital and the CPM–N17 or the C16–N17 bond. On the other hand, in intermediate **5** of 14-hydromorphinan, the CPM group would be preferentially cleaved because the N–C bond of the carbamate moiety could rotate freely and the σ-bond between the 17-nitrogen and the CPM group could be activated (Fig. 2D).

Reaction of acyclic amine **6** with Troc-Cl afforded oxazolidinone derivative **7**[11] without CPM group in 65% yield (Scheme 2). In the case of compound **6**, the methyl group is less hindered than the CPM group and was predicted to be preferentially attacked by a



Scheme 2. Reagents and conditions: Troc-Cl (10 equiv), K_2CO_3, 1,1,2,2-tetrachloroethane, 6 h, 150 °C, 65%.

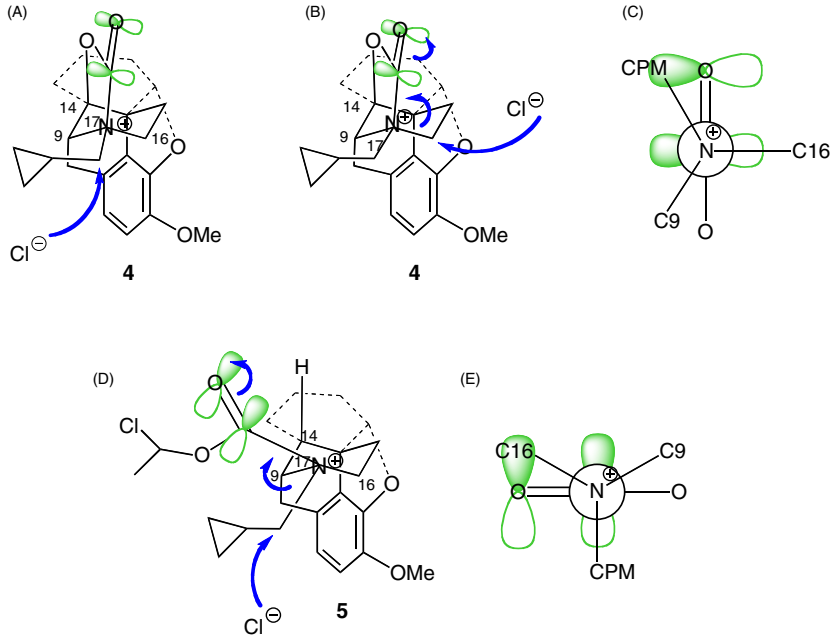


Figure 2. Respective intermediate **4** ((A), (B)) or **5** (D) of 14-hydroxy or 14-hydromorphinan and their Newman projection formulas ((C) and (E)), and postulated reaction mechanism of the bond cleavage. Dioxolane moieties were omitted for clarity. In the intermediate **4**, the CPM–N17 bond seems to be nearly orthogonal to the π-orbital (green) of the carbonyl group ((A) and (C)); however, the C16–N17 bond seems to be parallel to the π-orbital (green) ((B) and (C)). The CPM–N17 bond in intermediate **5** could be parallel to the π-orbital (green) ((D) and (E)).

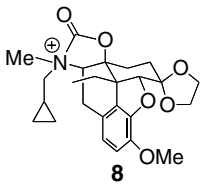


Figure 3.

nucleophile in a bimolecular nucleophilic substitution reaction. Nevertheless, the CPM group was preferentially removed over the methyl group to afford oxazolidinone **7**. In the reaction intermediate **8** (Fig. 3), because the conformation of **8** was more flexible than that of **4**, both the nitrogen–methyl and nitrogen–CPM bonds could be oriented parallel to the carbonyl π-orbital and thus be activated. Therefore, the stereoelectronic effect could not explain the preferential cleavage of the CPM group. It may be explained by postulating the extreme stability of the cyclopropylcarbinyl cation.[12–15] Generally speaking, the CPM tosylate is solvolyzed 10^6 faster than isobutyl tosylate because the tosylate ion could be solvolitically eliminated from the CPM tosylate to afford stable cyclopropylcarbinyl cation.[14] The polarization of the CPM–N17 bond probably due to the stability of tentatively formed cyclopropylcarbinyl cation may give the carbon of the CPM group a partial positive charge,[16,17] and as a result a nucleophile could easily attack on the carbon of the CPM group. We examined the dealkylation reaction of tertiary amines **9** with Troc-Cl to confirm the preferential elimination of CPM group. A similar investigation has already been reported using the compounds shown in Figure 4.[18] However, no example of the CPM group was found. The order of removal was reported as: benzyl > allyl > methyl. So, we examined the order of reactivity among CPM, benzyl, allyl, ethyl, and methyl groups using model compounds **9** (Table 1). The stabilizing effect of a cyclopropyl group on a carbocation center was known to be larger than that of a vinyl group.[19] Although controversy exists as to a relative stabilizing effects of cyclopropyl and phenyl

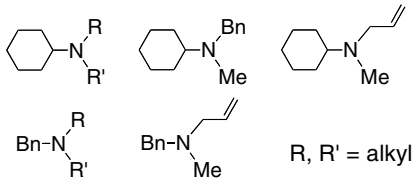
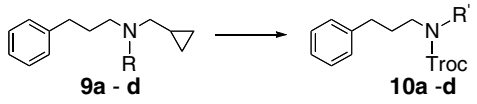


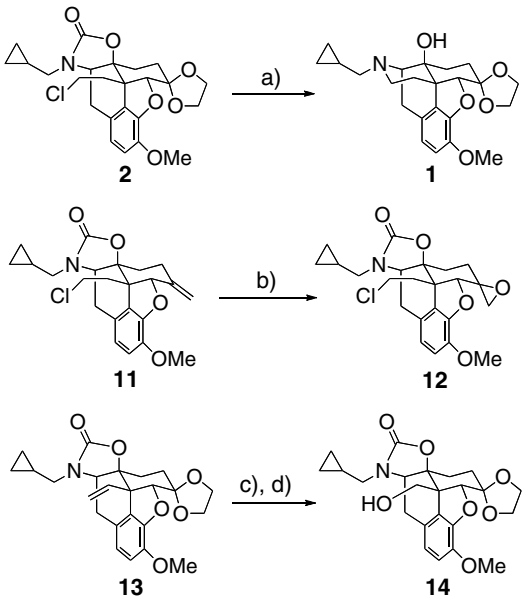
Figure 4.

Table 1
Examination of order of reactivity among cyclopropylmethyl, benzyl, allyl, ethyl, and methyl groups[a]



Entry	Substrate **9**	Product **10**	
	R	R′	Yield (%)
1	Bn (**a**)	CPM[b] (**a**)	Quant
2	allyl (**b**)	CPM[b] (**b**)	54
		allyl (**b′**)	45
3	Et (**c**)	Et (**c**)	Quant
4	Me (**d**)	Me (**d**)	Quant

[a] To the solution of **9** (0.11 mmol) in 1,2-dichloroethane were added Troc-Cl (0.22 mmol) and proton sponge (0.22 mmol), and stirred at rt for 3–4 h.
[b] CPM: cyclopropylmethyl.



Scheme 3. Reagents and conditions: (a) NaOH, DMSO, 115 °C, 50%; (b) *m*CPBA, CH_2Cl_2, rt, 67% as a mixture of α and β isomer; (c) O_3, CH_2Cl_2, −78 °C, then Me_2S, −78 °C to rt; (d) $NaBH_4$, MeOH, rt, 77% (in 2 steps).

groups,[15] it was recently reported that a high-level ab initio calculation showed the cyclopropyl group to have the largest stabilizing effect on a carbocation center among the cyclopropyl, phenyl, and vinyl groups.[20] According to this information, we expected that the CPM group would be more easily removed than the benzyl and allyl groups. However, the benzyl group was preferentially removed over the CPM group (Table 1, entry 1). The allyl and CPM groups were eliminated at almost equivalent rates (entry 2). The CPM group was removed preferentially as compared to the ethyl and methyl groups (entries 3 and 4). The order of removal of the five groups was established as: benzyl > CPM ≈ allyl > ethyl, methyl. Contrary to our expectation, the elimination rate of CPM group was not so high. This discrepancy may be attributed to steric hindrance of the CPM group and/or polarity of the reaction solvent.

Hydrolysis of oxazolidinone **2** with sodium hydroxide in DMSO provided original morphinan **1** in 50% yield. This result means that the oxazolidinone group can protect the 17-nitrogen group from oxidation. Naltrexone derivative **1** was oxidized with *m*CPBA to give a complex mixture owing to oxidation of nitrogen. On the other hand, oxazolidinone **11** was oxidized with *m*CPBA to afford objective epoxide **12** in 67% yield as a mixture of the α and β isomers. Oxazolidinone **13** was also oxidized with ozone followed by the reduction with $NaBH_4$ to give alcohol **14** in 77% yield (Scheme 3).

In summary, we found the novel cleavage reaction of C16–N17 bond of naltrexone derivative **1** to give oxazolidinone **2**. The mechanism of the cleavage reaction was proposed. The CPM groups in tertiary amines **9c**, **d** were found to be eliminated faster than the ethyl and methyl groups, although the benzyl group in **9a** was more readily removed than the CPM group. The allyl and CPM groups in **9b** were removed at almost equivalent rates. The oxazolidinone group in compounds **11** and **13** was also shown to be useful in protecting the 17-nitrogen in naltrexone derivatives from oxidation.

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10. *Spectral data for compound* **2.** IR (KBr) cm^{-1}: 2938, 1742, 1439, 1070, 1033. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.23–0.40 (2H, m), 0.47–0.68 (2H, m), 0.94–1.09 (1H, m), 1.53–1.64 (2H,m), 1.71–1.85 (1H, m), 1.89–2.08 (2H, m), 2.37 (1H, ddd, J = 4.8, 11.7, 14.1 Hz), 2.66 (1H, ddd, J = 0.9, 9.6, 14.7 Hz), 2.86 (1H, dt, J = 5.1, 11.4 Hz), 2.97 (1H, dd, J = 7.2, 14.7 Hz), 3.21 (1H, dd, J = 6.9, 14.7 Hz), 3.52 (1H, dd, J = 7.2, 14.4 Hz), 3.58 (1H, dt, J = 5.1, 11.1 Hz), 3.80–3.90 (2H, m), 3.88 (3H, s), 3.92 (1H, dd, J = 6.6, 13.2 Hz), 4.02–4.11 (1H, m), 4.21–4.29 (1H, m), 4.76 (1H, s), 6.71 (1H, dd, J = 0.9, 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz). HRMS (FAB) calcd for $C_{24}H_{29}ClNO_6$ $[M+H]^+$: 462.1683; found 462.1675.
11. *Spectral data for compound* **7**. IR (neat) cm^{-1}: 3482, 2966, 1747, 1508, 1433, 1280, 1168, 1046. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.60 (3H, t, J = 7.5 Hz), 1.40–1.59 (2H, m), 1.66–2.02 (4H, m), 2.59 (1H, ddd, J = 0.9, 9.6, 14.4 Hz), 2.92 (3H, s), 3.12 (1H, dd, J = 7.2, 14.4 Hz), 3.55 (1H, dd, J = 7.2, 9.6 Hz), 3.79–3.93 (2H, m), 3.84 (3H, s), 4.01–4.10 (1H, m), 4.18–4.25 (1H, m), 4.67 (1H, s), 6.65 (1H, dd, J = 0.8, 8.1 Hz), 6.75 (1H, d, J = 8.1 Hz). HRMS (FAB) calcd for $C_{21}H_{26}NO_6$ $[M+H]^+$: 388.1760; found 388.1809.
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