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Synthesis of *N*-isobutylnoroxymorphone from naltrexone by a selective cyclopropane ring opening reaction

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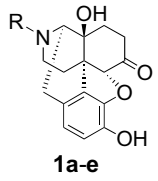
ABSTRACT

Selective ring opening reaction of the *N*-cyclopropylmethyl group in naltrexone (**1d**) was effected in the presence of platinum (IV) oxide and hydrobromic acid under a hydrogen atmosphere at rt to selectively afford *N*-isobutyl derivative **10**. The binding affinity of *N*-*i*-Bu derivative **10** for opioid receptors was 11–17 times less than that of the corresponding *N*-CPM compound, naltrexone (**1d**). However, compound **10** showed dose-dependent analgesic effects. Contrary to expectations based on previous structure–activity relationship studies for a series of *N*-substituted naltrexone derivatives that compound **10** would be an opioid antagonist, **10** showed dose-dependent analgesia in the mouse acetic acid writhing test (ED_{50}: 5.05 mg/kg, sc), indicating it was an opioid agonist. This finding may have a great influence on the drug design of opioid agonists.

Morphine is a representative opioid and is used even now as a potent analgesic. Since the determination of the structure of morphine, numerous derivatives of its core structure have been synthesized and evaluated their pharmacological effects. Nitrogen substituents have been widely recognized to affect the opioid activities. The *N*-substituents of 4,5-epoxymorphinan derivatives significantly influence the μ opioid receptor activities, that is, agonist or antagonist. For example, *N*-methyl derivative **1a** and *N*-phenethyl derivative **1b** are agonists, while *N*-allyl derivative **1c**, *N*-cyclopropylmethyl (CPM) derivative **1d**, and *N*-cyclobutylmethyl (CBM) derivative **1e** exhibit antagonist activities (Fig. 1).[1]

When selective reduction of 17-CPM-5,6-didehydromorphinan-6-carbaldehyde derivative **2** (Fig. 2) was investigated,[2] hydrogenation with platinum (IV) oxide gave a 17-isobutyl (*i*-Bu) derivative as a minor product. This result prompted us to investigate the transformation of the *N*-CPM to the *N*-*i*-Bu group for three reasons. First, the pharmacological effects of *N*-*i*-Bu-4,5-epoxymorphinan derivatives are interesting as the 17-substituent can influence both agonist and antagonist opioid activities.[3] Second, the reductive ring cleavage reaction is a facile one-step transformation of *N*-CPM derivatives into *N*-*i*-Bu derivatives. Generally, the transformation of *N*-substituents requires multiple steps using cyanogen bromide (von Braun reaction)[4] or chloroformate.[5] Furthermore, the 17-substitution reaction hardly proceeds in naltrexone derivatives having 14-hydroxyl group[6] because of an intramolecular hydrogen bond



1a-e

Agonist	Antagonist
1a: R=Me (Oxymorphone)	**1c**: R=allyl (Naloxone)
1b: R=phenethyl	**1d**: R=CPM (Naltrexone)
	1e: R=CBM

Figure 1. *N*-Substituted 4,5-epoxymorphinan derivatives and their pharmacological properties.

formed between the lone pair electrons of 17-nitrogen and the 14-hydroxyl group.[7] Third, hydrogenolysis of general cyclopropane rings is exceedingly slow, tending not to proceed. Although the cyclopropane ring activated by some conjugated substituents such as aromatic ring, acyl group, and vinyl group was cleaved under mild reaction conditions, hydrogenolysis of the unactivated rings required harsher reaction conditions such as high pressure and/or high temperature.[8] Here, we report the selective ring opening reaction of the cyclopropane ring in *N*-CPM-4,5-epoxymorphinan-6-one derivatives to give *i*-Bu derivatives, and we describe the pharmacological effects of the resulting *N*-*i*-Bu-noroxymorphone (**10**).

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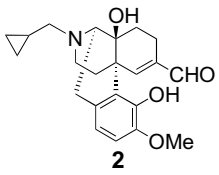


Figure 2. Structure of compound **2**.

A minor product obtained by the hydrogenation of 17-CPM-5,6-didehydromorphinan-6-carbaldehyde derivative **2** (Fig. 2) with platinum (IV) oxide in methanol[2] was identified as the *N*-*i*-Bu derivative. In the hydrogenation of naltrexone methyl ether **3**[2,9] under the same reaction conditions, *N*-*i*-Bu derivative **4** was also detected in very low yield. We developed the working hypothesis that protonation of the 17-nitrogen may evoke the activation of the cyclopropyl ring due to the tentative formation of a cyclopropylcarbinyl cation,[10] an extremely stable nonclassical carbocation,[11,12] which would facilitate the cleavage of the cyclopropane ring. We then attempted to improve the yield of the *N*-*i*-Bu derivative by hydrogenation of **3** in the presence of hydrochloric acid. As expected, the ring cleavage of CPM in the presence of hydrochloric acid proceeded effectively, but the reduction of 6-keto group occurred concomitantly (Table 1, Entry 1). Selective opening of the cyclopropane ring results in the one-step transformation of naltrexone derivatives into *N*-*i*-Bu derivatives, and retaining the intact 6-keto group. Therefore, the reduction of the compound **3** was attempted in the presence of various amounts of platinum (IV) oxide to improve the chemoselectivity of reduction between CPM and 6-keto groups, but fruitful results were not obtained. Using palladium on carbon as a catalyst instead of platinum (IV) oxide resulted in the recovery of the compound **3**. We next examined the effect of various acids (Table 1). In the presence of acetic acid or TFA, the reduction proceeded nonselectively (Entries 3, 4). Perchloric acid rather improved the chemoselectivity of the reduction in comparison to acetic acid or TFA, but the yield of *N*-*i*-Bu-6-keto compound **4** was low (Entry 6). On the other hand, camphorsulfonic acid or iodic acid mainly resulted in a recovery of starting material **3** (Entries 5, 9). Among the investigated acids, hydrobromic acid gave compound **4** predominantly (Entries 7, 8), with the concentration of hydrobromic acid having hardly any influence on the chemoselectivity (Entries 7, 8). In contrast, the concentration of hydrochloric acid had a notable effect on chemoselectivity (Entries 1, 2). These results suggested that the acidity would play an important role in both facilitation of the ring opening reaction and the chemoselectivity. The stronger the acid, the greater the amount of 17-nitrogen may be protonated to effectively activate the cyclopropane ring (Fig. 3). Additionally, a strong acid may promote intramolecular hemiacetal formation in compound **3** to afford hemiacetal **9** (Fig. 4),[13] resulting in the protection of the 6-keto group from reduction. In all cases, no *N*-*n*-Bu derivative was obtained as a product. This outcome may result from the approach of the catalyst from the less hindered side of the cyclopropane ring (Fig. 3).

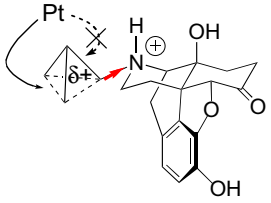


Figure 3. Diagram of Pt approaching to the activated cyclopropane ring. The σ-electrons between nitrogen and carbon in CPM group may be released to the protonated nitrogen (red arrow) because of extremely stable cyclopropylcarbinyl cation.[10] The catalyst may more easily approach the cyclopropane ring from the less hindered side (solid arrow), than from the more hindered side (dotted arrow).

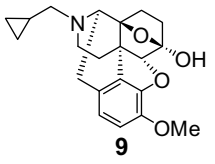
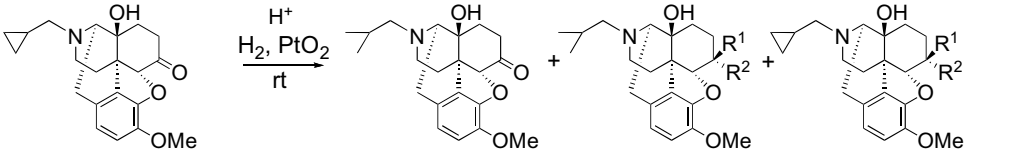


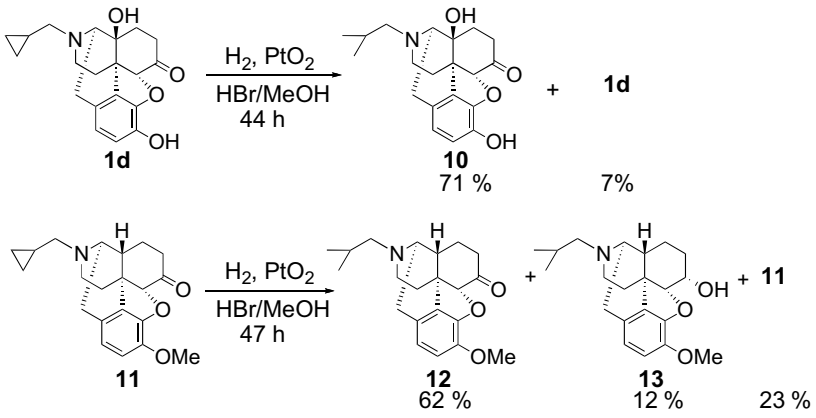
Figure 4. Structure of compound **9**.

Table 1
Reduction of naltrexone methyl ether **2** catalyzed by PtO_2



Entry	Acid[a]	Time (h)	Yield (%)					
			4	**5**	**6**	**7**	**8**	3 (recovery)
1	1*N* HCl	20	62	27	11	ND[c]	ND[c]	ND[c]
2	37% HCl	37	52	14	ND[c]	4	ND[c]	12
3	AcOH	48	4	6	ND[c]	70	12	8
4	TFA[b]	24	18	24	12	4	14	15
5	CSA	37	14	ND[c]	ND[c]	ND[c]	ND[c]	36
6	70%$HClO_4$[b]	14	20	33	47	ND[c]	ND[c]	ND[c]
7	1*N* HBr	37	61	ND[c]	ND[c]	ND[c]	ND[c]	ND[c]
8	48%HBr	37	76	2	ND[c]	ND[c]	ND[c]	ND[c]
9	57%HI	39	ND[c]	ND[c]	ND[c]	ND[c]	ND[c]	100

[a] A ratio of acid to MeOH is 1:1.2.
[b] Only acid was used as a solvent.
[c] Not detected.



Scheme 1. Reduction of naltrexone (**1d**) and *N*-CPM-norhydrocodone (**11**).

Table 2
Binding affinity of naltrexone (**1d**) and *N*-*i*-Bu-noroxymorphone (**10**) for opioid receptors

Compound	K_i (μ)	K_i (κ)	K_i (δ)
1d	0.335 nM	0.373 nM	20.7 nM
10	5.57 nM	6.12 nM	229 nM

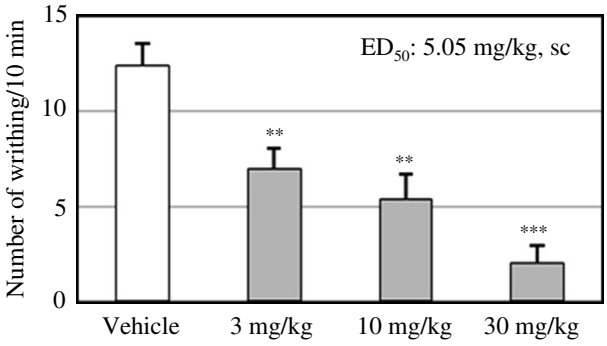


Figure 5. Antinociceptive effect of compound **10** on the mouse acetic acid writhing test.

With the selective reductive ring cleavage method of the CPM group over the 6-keto group in compound **3** in hand, we then attempted the reduction of naltrexone (**1d**) and *N*-CPM-norhydrocodone (**11**)[14] under the same reaction conditions to afford compounds **10** (71%) and **12** (62%), respectively (Scheme 1). In the case of reduction of 14-H derivative **11**, 6α-ol **13** was also obtained in 12% yield. These results suggested that intramolecular hemiacetal formation participates in protecting the 6-keto group from reduction.

We next focused on the investigation of opioid activities of *N*-*i*-Bu derivatives. In the binding assay using homogenates of guinea-pig brain (κ: cerebellum, μ and δ: forebrain), *N*-*i*-Bu-noroxymorphone (**10**) was bound to μ and κ receptors more strongly than δ receptor (Table 2). Although the binding selectivity of compound **10** resembled that of naltrexone (**1d**), the affinities of **10** for the opioid receptors were 11–17 times less than those of naltrexone (**1d**). Three important pharmacophore interactions affect the binding between the ligand and the opioid receptor: 1) the ionic interaction at 17-nitrogen; 2) the π–π interaction at the benzene ring; and 3) the hydrogen bond at the phenolic hydroxyl group.[15] Among these factors, the ionic interaction is believed to be the most significant. The larger the electron density at the 17-nitrogen of a ligand, the more strongly would the ligand bind to the receptor. The higher affinity of compound **1d** possessing the 17-CPM group (Table 2) would seem to support the proposed stronger electron-releasing property of the CPM group than a general alkyl group (Fig. 3).

Compound **10**, possessing the *N*-*i*-Bu group, was expected to be an antagonist based on structure–activity relationship studies for a series of *N*-substituted oxymorphone derivatives.[1] However, this novel derivative showed surprising analgesic effects in a dose-dependent manner in the mouse acetic acid writhing test (ED_{50}: 5.05 mg/kg, sc) (Fig. 5), indicating that compound **10** had agonistic activities.[16] Although the *N*-substituent, which was similar in size to the CPM or CBM groups, was expected to confer antagonistic activities, it elicited agonistic activities. The finding strongly indicated that the size and/or the chain length of the *N*-substituent had little influence on the opioid activities (agonist or antagonist) in a series of *N*-substituted oxymorphone derivatives. We are currently investigating the structure–activity relationship between the *N*-substituent and opioid activities in detail.

In conclusion, the platinum-catalyzed hydrogenation of *N*-CPM-4,5-epoxymorphinan-6-one derivatives in the presence of hydrobromic acid did not reduce the 6-keto group and selectively cleaved the cyclopropane ring of CPM to afford *N*-*i*-Bu-4,5-epoxymorphinan-6-one derivatives. The selective cleavage of CPM led to direct transformation of the *N*-CPM derivative into the *N*-*i*-Bu variant. The binding affinity of the *N*-*i*-Bu derivative **10** for opioid receptors was somewhat lower than that of the corresponding *N*-CPM compound, naltrexone (**1d**); however, the compound **10** showed dose-dependent analgesic effects. Contrary to the expectation that the *N*-*i*-Bu derivative would show antagonistic activities on the basis of the previous reports,[1] the *N*-*i*-Bu derivative was agonist. This finding may have a great influence on the future drug design of opioid agonists.

Acknowledgements

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