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# Synthesis of a Stable Iminium Salt and Propellane Derivatives

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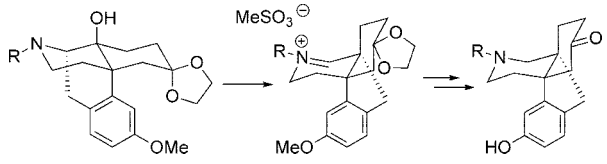
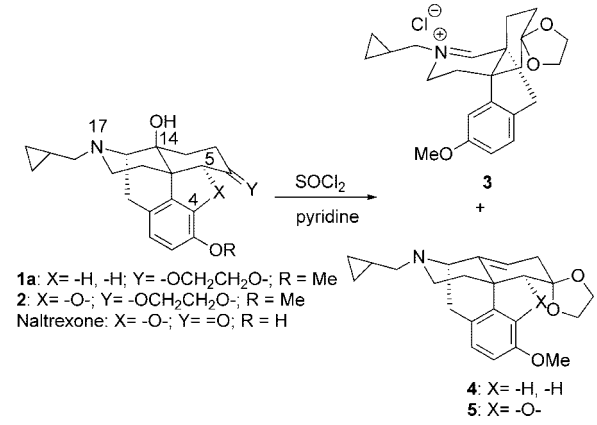



The treatment of morphinan **1** with NaH and MsCl provided very stable iminium salt **7** possessing propellane skeleton. One of the synthesized iminium salts **7**, isobutyl derivative **7b**, was crystallized and its structure was determined by X-ray crystallography. The natural bond orbital analysis suggested that the stability of the iminium should result from the stereoelectronic effect (hyperconjugation) attributed to their own structures.

Naturally occurring morphine and semisynthetic naltrexone are representative opioid ligands and are used as potent analgesics and a therapeutic agent for alcohol addiction or opioid dependence, respectively.[1] A common structure of these ligands, the 4,5-epoxymorphinan skeleton, is believed to influence the intrinsic activity of the opioid receptor,[2] and has been considered to contribute to three points of association between the drug molecule and the receptor site, namely an ionic interaction of the 17-nitrogen, a $\pi-\pi$ interaction of the phenol ring, and a hydrogen bond between the phenol hydroxyl and the opioid receptor.[3] However, the role of the 14-hydroxyl group for the receptor binding has not yet been clarified. We attempted to remove the 14-hydroxyl group in order to compare the pharmacological profiles of the 14-hydroxy derivatives and the 14-hydrogen variants. In the course of these investigations, we obtained iminium salt **3**, which has a propellane skeleton. Surprisingly, the iminium salt **3** was stable and could be purified by silica gel column chromatography. Herein, we report the synthesis of this stable iminium ion bearing a propellane skeleton and discuss its stability.

**SCHEME 1. Dehydration of Morphinan 1a and 4,5-Epoxymorphinan 2**




Morphinan derivative **1a**, which was synthesized from naltrexone,[4] was dehydrated with $SOCl_2$ in pyridine to afford dehydrated product **4** and abnormal rearrangement product **3** (iminium salt) (Scheme 1). Silica gel column chromatography of the reaction mixture with $CHCl_3$/MeOH as eluent successfully afforded pure iminium ion **3** in 28% yield along with the dehydrated product **4** in 71% yield. In $^1$H NMR, a vinyl proton of iminium chloride **3** was observed at 10.13 ppm, suggesting that **3** was an iminium compound and not an α-chloroamine. In contrast to morphinan **1a**, the reaction of 4,5-epoxymorphinan **2** under the same reaction conditions afforded only dehydrated product **5** (Scheme 1).[5] We became interested in the abnormal stability of the iminium salt and attempted to improve its yield.

A plausible mechanism for the rearrangement reaction to yield the iminium chloride **3** is shown in Scheme 2. Lone pair electrons of the 17-nitrogen could play a crucial role for facilitating the rearrangement. We hypothesized that a proton acquired during the reaction would protonate the 17-nitrogen to interrupt the rearrangement reaction. We postulated that reaction conditions in the absence of protons could facilitate the rearrangement to afford the iminium salt **3**. After extensive investigation based on our working hypothesis, the reaction of morphinan **1a** with MsCl and NaH provided the objective

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(4) (a) Sawa, Y. K.; Toda, H. *Tetrahedron Lett.* **1968**, *24*, 6185. (b) Nemoto, T.; Fujii, H.; Nagase, H. *Tetrahedron Lett.* **2007**, *48*, 7413. (c) Nemoto, T.; Fujii, H.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 4304.
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**SCHEME 2. Plausible Mechanism of the Rearrangement**

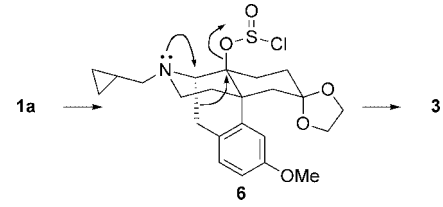
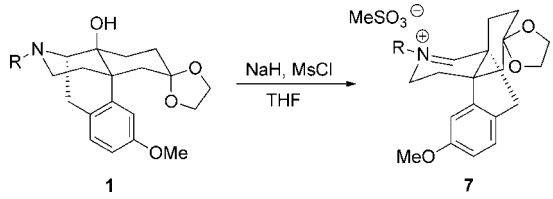



**TABLE 1. Substituent Effect on Rearrangement Reaction**




| entry | morphinan | product | R | yield (%) | reaction time (h) |
|---|---|---|---|---|---|
| 1 | **1a** | **7a** | CPM | 93 | 1 |
| 2 | **1b** | **7b** | *i*-Bu | 39 | 2 |
| 3 | **1c** | **7c** | Me | 95[a] | 1.25 |
| 4 | **1d** | **7d** | Et | 93 | 1.25 |
| 5 | **1e** | **7e** | allyl | 92 | 3.5 |
| 6 | **1f** | **7f** | $CF_3$ | 0[b] | 31.5 |

[a] Including some amount of inseparable impurities. [b] Only the morphinan **1f** was recovered.

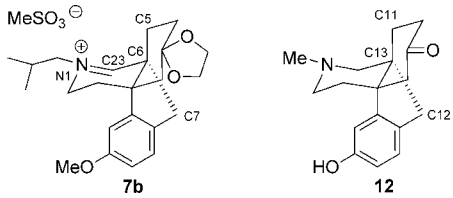



**FIGURE 1.** Structures of compounds **7b** and **12** (see the Supporting Information for CIF files and ORTEP plots of compounds **7b** and **12**).

iminium **7a** in 93% yield without dehydrated product **4** (Table 1, entry 1). The rearrangement reactions of morphinans **1a**−**e** with some 17-substituents proceeded in moderate to excellent yields, but iminium **7f** was not obtained from morphinan **1f** with the strong electron-withdrawing $CF_3$ group[6] at the 17-position and only the starting material **1f** was recovered (entry 6). These results suggested that the 14-hydroxy group may not be directly mesylated. If the lone pair electrons on the 17-nitrogen initially attacked the sulfene prepared in situ, followed by migration of the Ms group from the 17-nitrogen to the 14-hydroxy group, the results shown in Table 1 could be reasonably explained.[7] The strong electron-withdrawing $CF_3$ group[6] would drastically reduce the electron density on the 17-nitrogen and decrease its nucleophilicity, resulting in recovery of the starting material **1f**. Purifications of all the synthesized iminium **7** compounds (Figure 1) by silica gel column chromatography were effected. In $^1$H NMR, a vinyl proton was observed at around 9.5 ppm for each iminium mesylate **7**. Among them, compound **7b** with a 17-*i*-Bu group was isolated

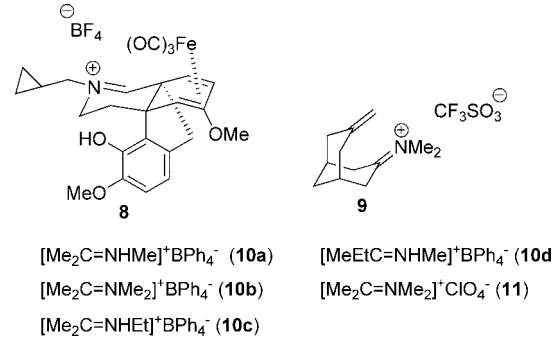



**FIGURE 2.** Iminium ions whose structures were determined by X-ray crystallography.

as a crystalline product and its structure was determined by X-ray crystallography. To the best of our knowledge, examples of X-ray crystallography of iminium ions are very rare[8] except for the case of conjugated iminium ions.[9] An example most resembling the desired iminiums **3** and **7** is $Fe(CO)_3$ complex of iminium tetrafluoroborate **8** (Figure 2).[8b,10] In the case of the iminium **8**, anchimeric participation of the double bond derived from a homoallylic system and an inert counteranion, tetrafluoroborate would stabilize the iminium ion. Moreover, the bulky $Fe(CO)_3$ group may contribute to the stability of the iminium ion **8**. The other examples of nonconjugated iminium ions **9**−**11** (Figure 2) whose structures were determined by X-ray crystallography also had inert counteranions[8] and would be stabilized by an intramolecular interaction with an olefin moiety (iminium **9**)[8c] or by intermolecular interactions with phenyl groups of a counteranion (iminium **10**).[8d] In contrast, iminium compounds **3** and **7** had neither an olefin moiety nor a $Fe(CO)_3$ group participating in stabilization of the iminium ion. Furthermore, iminium ion **3** had a reactive counteranion, the chloride ion. The X-ray crystallography indicated that the length of C5−C6 (1.545 Å) in iminium **7b**, which was parallel to the $\pi$-orbital of the N1−C23 double bond, was longer than that of the corresponding C11−C13 bond in saturated compound **12** (1.532 Å) derived from iminium **7a** (Figure 1). Parallel bonds can easily overlap each other. This observation suggested that the $\sigma$ bond C5−C6 would interact with the $\pi^*$ bond of the iminium and that the electronic interaction (hyperconjugation) may play a crucial role in stabilization of the iminium ion. To investigate hyperconjugative stabilization of the iminium, we performed natural bond orbital (NBO) analysis[11] with the ab

(6) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *Chem. Med. Chem.* **2007**, *2*, 1100.

(7) The reaction of morphinan **1a** with the CPM group seemed to proceed the most rapidly. This observation might be explained by the consideration of the very stable cyclopropylcarbinyl cation. A detailed discussion is presented in the Supporting Information.

(8) For X-ray crystallography of nonconjugated iminium salt, see: (a) Trefonas, L. M.; Flurry, R. L., Jr.; Majeste, R.; Meyers, E. A.; Copeland, R. F. *J. Am. Chem. Soc.* **1966**, *88*, 2145. (b) Birch, A. J.; Fitton, H.; McPartlin, M.; Mason, M. R. *Chem. Commun.* **1968**, 531. (c) Hollenstein, S.; Laube, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 188. (d) Knop, O.; Cameron, T. S.; Bakshi, P. K.; Kwiatkowski, W.; Choi, S. C.; Adhikesavalu, D. *Can. J. Chem.* **1993**, *71*, 1495.

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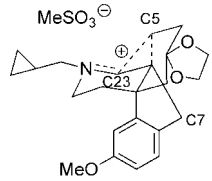
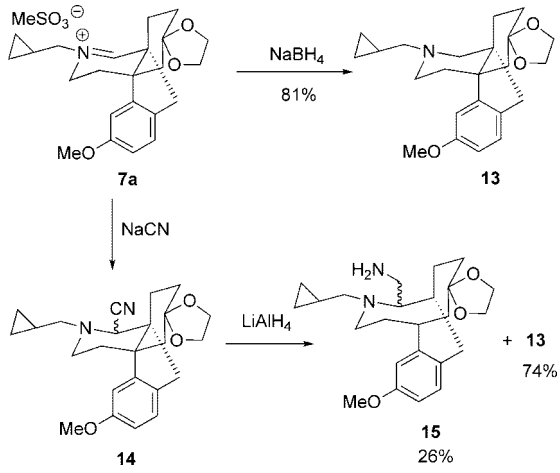



**7a**

**FIGURE 3.** Structure of iminium **7a**. The hyperconjugation was showen by dotted lines.

**SCHEME 3. Reaction of Iminium 7a**




initio molecular orbital calculation at the HF/6-31G* level. The analysis with use of the second order perturbation theory of the Fock operator with NBO basis showed substantial interaction from $\sigma$ (C5−C6) to $\pi^*$ (N1−C23) (interaction energy: 6.31 kcal/mol). The optimal bond length of C5−C6 was 0.011 Å longer than that of the corresponding bond in **12**.[12] Taken together, the stereoelectronic effect (hyperconjugation) attributed to the structure of iminiums **3** and **7a** could play an important role in the extreme stabilization of these iminiums.

We next examined the reactivity of the stable iminium ion **7a** (Scheme 3). When the iminium **7a** was treated with NaOAc or $NaN_3$, only the starting material was recovered. The reaction of **7a** with *n*-BuLi or lithiated dithiane afforded complex mixtures. The stronger basic nucleophiles like *n*-BuLi and lithiated dithiane may attack not only the iminium carbon (C23) but the hyperconjugated carbons (C5) to give complex mixtures (Figure 3). However, reduction of the iminium **7a** with $NaBH_4$[13] afforded saturated propellane derivative **13**. Reaction of iminium **7a** with NaCN[14] gave nitrile **14**, followed by reduction of the nitrile **14** to give amine **15** as a mixture of diastereomers along with compound **13**. Compound **13** may be obtained by reduction of the iminium derived from nitrile **14** via elimination of cyanide ion. These observations suggested that adduct **14** would be easily returned to the starting iminium ion **7a** because of its extreme stability.

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(12) The NBO analysis showed that the optimal bond length of C6−C7 was also 0.07 Å longer than that of the corresponding bond in **12**, with interaction energy between $\sigma$ (C6−C7) and $\pi^*$ (N1−C23) of 4.98 kcal/mol, although by X-ray crystallography, C6−C7 in **7b** showed the same bond length (1.551 Å) as C13−C12 in **12**. This result suggested that C5−C6 might also partially, if at all, participate in the stabilization of the iminium ion.

(13) In the case of the $Fe(CO)_3$ complex **8**, the reduction was reported to take 20 min (see ref 10b). On the other hand, the reduction of **7a** was completed within 5 min.

(14) The reaction of the $Fe(CO)_3$ complex **8** with NaCN was reported to proceed in acetone under reflux for 5 min (see ref 10a). In contrast, the reaction of **7a** was completed at rt within 5 min.

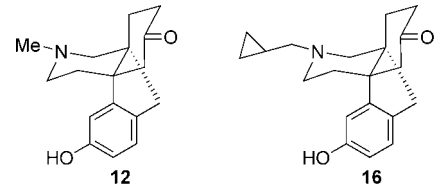


**FIGURE 4.** Structures of compounds **12** and **16**.

In a preliminary pharmacological evaluation, saturated propellane **12** and its 17-CPM derivative **16**, which were synthesized from propellane **13**,[15] selectively bound to $\mu$ ($K_i$ = 3.6 nM) and $\kappa$ opioid receptor ($K_i$ = 17.4 nM), respectively (Figure 4). The result suggests that propellane **12**, which was readily prepared from stable iminium ion **7**, could be a fundamental skeleton for opioid ligand. Birch et al. described the synthesis of a propellane derivative from a $Fe(CO)_3$ complex of an iminium ion **8** and its application for opioid ligand. Nevertheless, neither yield of the iminium ion having $Fe(CO)_3$ **8** nor the application data of the propellane derivative as an opioid ligand was shown.[10] Furthermore, their synthesis of propellane derivative required both flammable, toxic $Fe(CO)_5$ as a crucial reagent and thebaine (narcotics) as a starting material, which is not readily available. In distinct contrast, our practical synthetic route to the propellane derivative started with readily available naltrexone and required no toxic reagents.

In conclusion, the novel stable iminiums **3** and **7** were synthesized and isolated by silica gel column chromatography. Iminium compound **7b** was crystallized and its structure was determined by X-ray crystallography. The NBO analysis suggested that stability of the iminiums should result from hyperconjugation attributed to their own structures. The iminium ion is expected to be a key intermediate for synthesis of novel opioid ligands.

## Experimental Section

**Typical Procedure for the Synthesis of Iminium Salt 7.** Under an argon atmosphere, NaH (60% in oil, 480 mg, 12.0 mmol) was washed with dry hexane and suspended in THF (1 mL). MsCl (390 $\mu$L, 5.04 mmol) was added dropwise to the suspension at 0 °C and the mixture was stirred for 30 min at the same temperature. To the reaction mixture was added the solution of **1** (0.50 mmol) in THF (1.5 mL) at 0 °C with stirring at rt for several hours (see Table 1). The reaction mixture was quenched with cooled 2-butanol, followed by purification of the crude product to give iminium ion **7**.

**Iminium Salt 7a:** pale yellow amorphous; IR (film) 3428, 2943, 1685, 1611, 1492, 1459, 1331, 1285, 1196, 1119, 1075, 1041, 950, 770 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.21−0.34 (m, 1H), 0.36−0.54 (m, 2H), 0.54−0.66 (m, 1H), 0.87−1.06 (m, 1H), 1.68−1.87 (m, 4H), 1.94−2.09 (m, 1H), 2.10−2.23 (m, 2H), 2.32−2.44 (m, 1H), 2.73 (s, 3H), 3.33 (d, $J$ = 16.8 Hz, 1H), 3.37 (d, $J$ = 16.8 Hz, 1H), 3.41−3.61 (m, 2H), 3.77 (s, 3H), 3.84−4.03 (m, 6H), 6.58 (d, $J$ = 2.4 Hz, 1H), 6.74 (dd, $J$ = 2.4, 8.4 Hz, 1H), 7.19 (d, $J$ = 8.4 Hz, 1H), 9.40 (s, 1H); HRMS (FAB) $[M]^+$ calcd for $C_{23}H_{30}NO_3$ 368.2226, found 368.2221.

**Reduction of Iminium Salt 7a.** To the solution of **7a** (800 mg, 1.73 mmol) in MeOH (12 mL) was added $NaBH_4$ (198 mg, 5.23 mmol) at 0 °C with stirring for 5 min. To the reaction mixture was added 50% AcOH, then saturated $NaHCO_3$ solution was added to adjust the reaction mixture to pH 9. After extraction and subsequent concentration, the residue was chromatographed to give 520 mg (82%) of **13** as a brown oil. IR (neat) 2913, 1726, 1610, 1489,

(15) See the Supporting Infromation.

1527, 1282, 1224, 1202, 1117, 1092, 1058, 1034, 949, 802, 748 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ −0.06−0.11 (m, 2H), 0.36−0.56 (m, 2H), 0.73−0.86 (m, 1H), 1.52−1.83 (m, 6H), 1.94−2.67 (m, 9H), 2.83 (br d, $J$ = 12.9 Hz, 1H), 3.67−4.03 (m, 4H), 3.78 (s, 3H), 6.60 (d, $J$ = 2.7 Hz, 1H), 6.66 (dd, $J$ = 2.7, 8.1 Hz, 1H), 7.09 (d, $J$ = 8.1 Hz, 1H). HRMS (FAB) $[M + H]^+$ calcd for $C_{23}H_{32}NO_3$ 370.2382, found 370.2388.

**Reaction of Iminium Salt 7a with NaCN.** Under an Ar atmosphere, NaCN (794 mg, 16 mmol) was added to the aqueous solution (40 mL) of **7a** (1.5 g, 3.2 mmol) with stirring at rt. Immediately white precipitate appeared. The reaction mixture was worked up by the general procedure, followed by concentration to give the crude product of **14** (1.1 g) as a white amorphous. The crude product was used for the next reaction without purification. IR (film) 2937, 2240, 1612, 1587, 1489, 1456, 1370, 1334, 1283, 1237, 1204, 1093, 1033, 948, 923, 806, 754 $cm^{-1}$.

**Reduction of Cyano Adduct 14.** Under an Ar atmosphere, the solution of crude **14** (570 mg, about 1.4 mmol) in THF (1 mL) was added to the suspension of $LiAlH_4$ (546 mg, 14 mmol) in THF (1 mL) at 0 °C with stirring for 2.5 h at rt. To the reaction mixture was added AcOEt and subsequently saturated sodium potassium tartrate solution, then the reaction mixture was stirred. The precipitate was filtered and the filtrate was concentrated. The residue was chromatographed to give 395 mg (74%) of **13** and 149 mg (26%) of **15** as a mixture of diastereomers, which could not be purified from each diastereomer. **15**: IR (film) 3376, 2938, 1611, 1489, 1371, 1330, 1275, 1196, 1096, 1035, 912, 800, 732 $cm^{-1}$. HRMS (FAB) $[M + H]^+$ calcd for $C_{24}H_{35}N_2O_3$ 399.2648, found 399.2650.

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**Supporting Information Available:** Experimental procedures and spectra for obtained new compounds; X-ray data for **7b** and **12** (CIF files and ORTEP plots). This material is available free of charge via the Internet at http://pubs.acs.org.

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