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A Ring Opening Rearrangement Reaction of 6β-Hydroxytropinone

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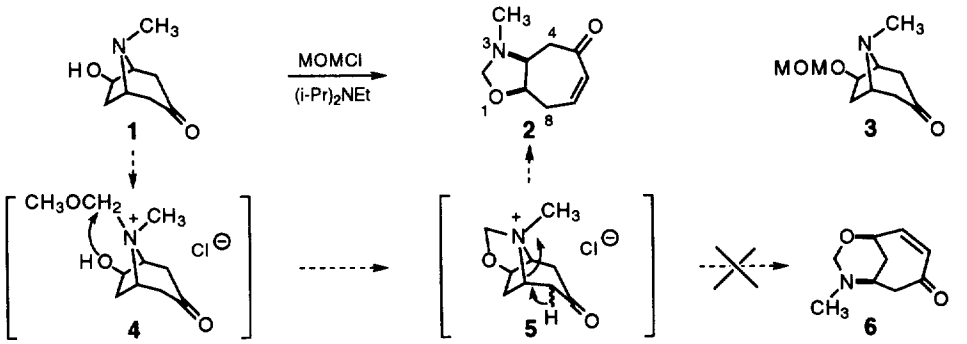
Abstract: *A ring opening rearrangement reaction of 6β-hydroxytropinone resulted in the novel bicyclic oxazolidine* **2**. *Hydrolysis of* **2** *with hydrochloric acid in methanol provided 6β-hydroxytropinone and 6α-hydroxytropinone.* © 1997 Elsevier Science Ltd.

Nucleophilic ring opening reactions of the bicyclo[3.n.1] system provide important routes to cyclic and acyclic compounds with multiple stereocenters.[1,2] For example, asymmetric cleavage of 8-azabicyclo-[3.2.1]octan-3-one and 9-azabicyclo[3.3.1]octan-3-one at the keto position gives *cis*-2,5-disubstituted pyrrolidine and *cis*-2,6-disubstituted piperidine derivatives which have been utilized in the total synthesis of the indolizidine alkaloids monomorine I and indolizidine 223AB.[3] Stereoselective deprotonation of tropinone with a chiral lithium amide and ring opening with chloroformates has also been employed in the asymmetric synthesis of the tropane alkaloids physoperuvine and dihydroxytropanes.[4]

During our synthesis of 6- or 7-hydroxy-2-carbomethoxy-3-aryltropanes as dopamine transporter inhibitors,[5] we discovered a novel ring opening reaction of 6β-hydroxytropinone. We had planned to use the methoxymethyl (MOM) protected hydroxytropinone **3** as a synthetic intermediate and attempted to obtain it by treatment of tropinone **1**[6] with chloromethyl methyl ether in the presence of the base diisopropylethylamine.[7] However, the product of this reaction was not the anticipated tropinone **3** (Scheme 1), but rather the ring opened bicyclic oxazolidine **2** obtained in 93% yield.[8]

Scheme 1

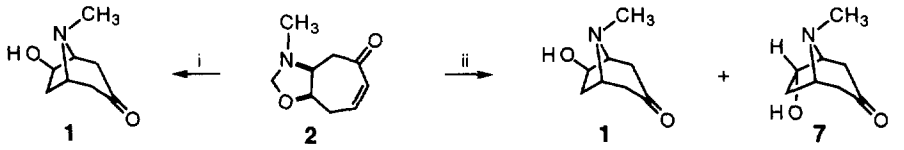


A proposed mechanism for this unprecedented ring opening rearrangement is shown in Scheme 1. First, the tropinone is quaternized by MOMCl at the preferred equatorial position to provide **4**.[9] The hydroxy group may then attack the proximate acetal group to form the intermediate oxazolidinium **5**, which could undergo ring

opening upon deprotonation at C-4 to furnish the oxazolidine **2**. Diisopropylethylamine is crucial to this ring opening reaction. In a side by side comparison reaction without the base, no oxazolidine **2** was obtained; only the starting material was recovered along with a trace amount of **3**. It is also interesting that the formation of a 5-membered oxazolidine ring is preferred since none of the alternative 6-membered oxazine **6** was detected.

It is well known that oxazolidines are labile towards hydrolysis.[10] A pure sample of **2** was found to convert back to 6β-hydroxytropinone **1** after a period of 4 months (Scheme 2). More interestingly, when **2** was treated with hydrochloric acid in methanol, a moderate yield (40%) of 6β- and 6α-hydroxytropinones **1** and **7** was obtained in a 2 to 1 ratio (GC). Compounds **1** and **7** are separated by preparative TLC and they could be easily differentiated by the ^{1}H NMR multiplicity of their 6-hydrogens.[6b,8] This route provides access to 6α-hydroxytropinone. To our knowledge, no direct method for the synthesis of the 6α-hydroxytropinone (**7**) has been reported.[6] Further study of the hydrolysis reaction mechanism and the use of oxazolidine **2** as an intermediate for the stereospecific synthesis of aminohydroxycycloheptane derivatives is currently under investigation.

Scheme 2



Reagents and Conditions: i) air, r.t.; ii) HCl (Con.), Methanol, r.t.

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References and Notes

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8. Selected analytical data:

   Oxazolidine (**2**). ^{1}H NMR (100 MHz, $CDCl_3$), δ 6.67 (ddd, J = 13.2, 7.5, 5.7 Hz, 1H, H_7), 6.17 (d, J = 13.0 Hz, 1H, H_6), 4.60 (d, J = 3.2 Hz, 1H, H_{2A}), 4.38 (ddd, J = 12.2, 7.4, 4.1 Hz, 1H, H_{8a}), 3.87 (d, J = 3.1 Hz, 1H, H_{2B}), 2.89 - 2.60 (m, 5H, H_{3a}, H_4 & H_8), 2.34 (s, 3H, *NMe*).

   ^{13}C NMR (25 MHz, $CDCl_3$), δ 198.4, 142.7, 134.3, 87.1, 78.8, 61.4, 44.0, 36.3, 31.2.
   Elemental analysis ($C_9H_{13}NO_2$). Calc.: C: 64.63, H: 7.84, N: 8.38; Found: C: 64.50, H: 7.88, N: 8.38.

   6α-Hydroxytropinone (**7**). ^{1}H NMR (100 MHz, $CDCl_3$), δ 4.63 (ddd, J = 10.4, 6.2, 3.9 Hz, 1H, H_6), 3.50 (m, 2H), 2.59 (s, 3H, *NMe*), 3-2 (m, 6H).

   ^{13}C NMR data (25 MHz, $CDCl_3$), δ 209.1, 72.2, 63.6, 58.6, 44.5, 39.3, 38.4, 35.9.
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