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Selective N-Demethylation of Galanthamine to Norgalanthamine via a non classical Polonovski Reaction

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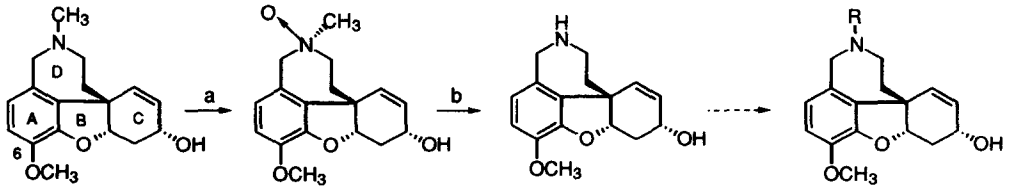
Abstract *:* The previously unknown N-demethylation of galanthamine **1** to norgalanthamine **3** was selectively accomplished by a non classical Polonovski reaction using iron salts.This transformation constitutes the first example of the application of the Polonovski reaction to an N-oxide of a seven membered cyclic amine. Norgalanthamine is a valuable intermediate in new galanthamine derivatives synthesis. © 1997 Published by Elsevier Science Ltd.

Galanthamine **1**, a tertiary *Amaryllidaceae* alkaloid, acts as a competitive acetylcholinesterase inhibitor and enhances cognitive functions of Alzheimer's patients.[1] A variety of galanthamine analogues have been previously prepared including C-ring modified,[2] 6-carbamate,[3] 6-ester[3] and ammonium[2] derivatives. In order to modify the basic amine site of galanthamine without introduction of charge, we were interested in synthesizing galanthamine derivatives **4**[4]. Such compounds could simultaneously interact with the catalytic and the peripheral sites of acetylcholinesterase.[5] Compounds **4** can be prepared from norgalanthamine **3** by N-alkylation. However, norgalanthamine **3** is present in plant in extremely low quantities[6] (lower than galanthamine) and is not commercially available. The total synthesis of (±) norgalanthamine **3** has been achieved by a biomimetic route involving an intramolecular phenolic oxidative coupling, but in low yield (0.7%).[7] Norgalanthamine **3** could ideally be obtained by selective N-demethylation of galanthamine **1**. Previous attempts at this conversion have been unsuccessful.[2] We now wish to disclose that this transformation can be selectively accomplished by a non classical Polonovski reaction using iron salts.[8]



1 : (-) Galanthamine **2** **3 : Norgalanthamine** **4**

R = straight or branched alkyl chain

a) m-CPBA 1.1eq, CH_2Cl_2, 25°C, 1.5h (96%).
b) $FeSO_4$. 7 H_2O 2 eq., MeOH, 10°C, 1.5 h (76%)

Galanthamine **1** was quantitatively converted into its N-oxide **2** by oxidation with m-chloroperbenzoic acid in dichloromethane at room temperature.[9] Subsequent treatment of **2** with hydrated ferrous sulfate in methanol at 10°C provided norgalanthamine **3** in 76% yield on a preparative scale. The spectral data are in agreement with reported values for the natural norgalanthamine.[6] It is interesting to note that no debenzylation of galanthamine was observed, whereas the classical Polonovski reaction of para-substituted N-benzylamines affords the corresponding debenzylated product (major) and the demethylated product (minor).[10] The selective demethylation of the galanthamine N-oxide **2** in the presence of iron salts can be explained by the marked preference for oxidation at the methyl center of N-methyl substituted amine oxide.[8b]

In summary, we have demonstrated that reaction of the galanthamine N-oxide **2** under non-classical Polonovski conditions affords for the first time norgalanthamine **3** in good yield. This transformation also constitutes the first example of the application of the Polonovski reaction to an N-oxide of a seven membered cyclic amine. The synthesis and the biological activities of galanthamine derivatives **4** synthesized from norgalanthamine **3** will be described in detail in a future paper.

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