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Unexpected Hydroxylation of Galanthamine During the Course of a Polonovski-Potier Reaction

Dolor Renko, Aude Mary, Catherine Guillou, Pierre Potier and Claude Thal

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex (France)

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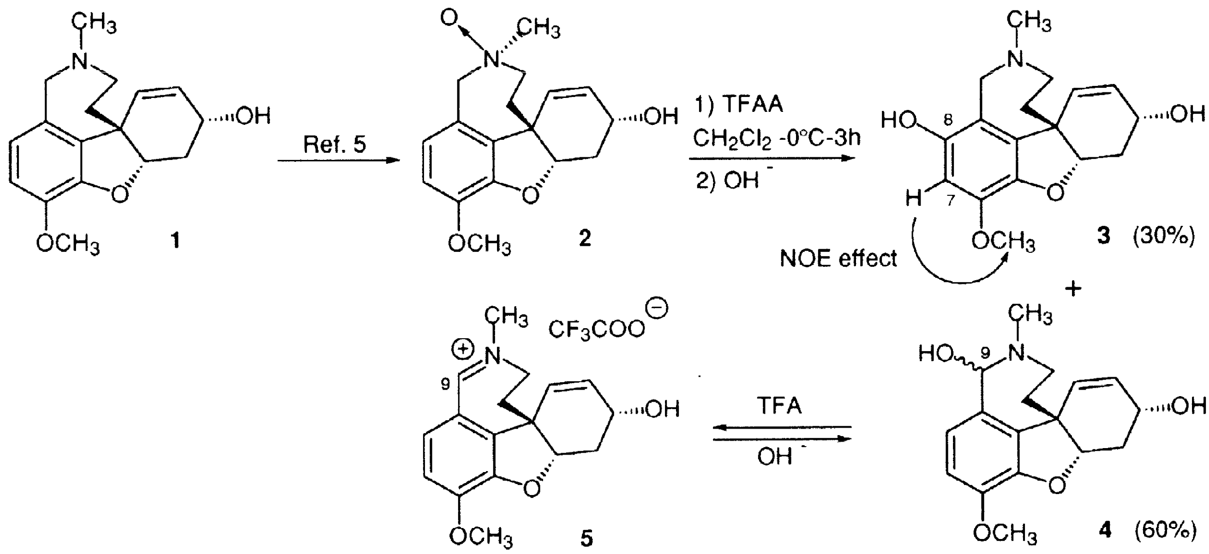
Abstract : *Galanthamine N-oxide 2 undergoes a Polonovski-Potier reaction to give the iminium salt 5 and the unexpected 8-hydroxygalanthamine 3. An intramolecular oxygen transfer is proposed to explain hydroxylation of the aromatic nucleus.*

Galanthamine **1**, an alkaloid of the *Amaryllidaceae* family, is an acetylcholinesterase (AChE) inhibitor proposed as a possible agent in the treatment of Alzheimer's disease[1,2]. In the course of our research on new galanthamine derivatives, we used the modified Polonovski reaction[3] to prepare the iminium salt **5** that was found to be more potent than galanthamine in inhibiting AChE (Scheme 1)[4]. We discuss here an unexpected hydroxylation reaction on the galanthamine aromatic nucleus during the course of this reaction. Thus, addition of excess trifluoroacetic anhydride (TFAA) to galanthamine N-oxide **2** (obtained as a single stereomer as described by Kobayashi *et al.*)[5] in dichloromethane at 0 °C afforded, after alkaline treatment, phenol **3**[6] and carbinolamine **4** as a mixture of α/β isomers. The latter mixture was completely deshydrated, on reaction with trifluoroacetic acid (TFA), into the endocyclic iminium salt **5**[7].



Scheme 1

The position of the hydroxyl group of phenol **3** was confirmed by an NOE effect observed between the H7 proton and the methoxyl group.

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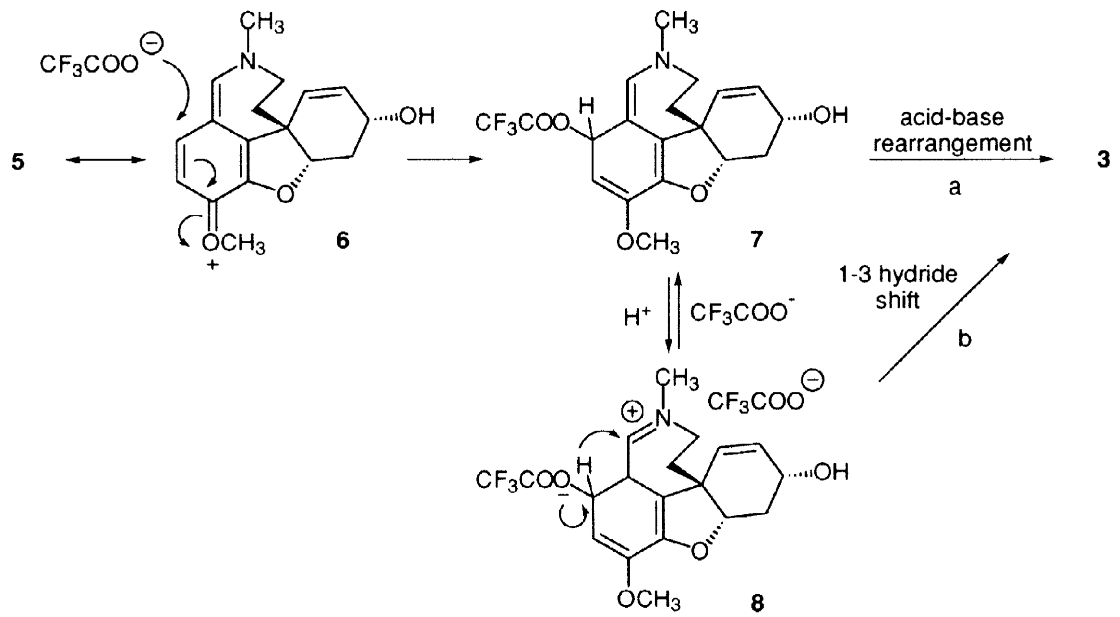
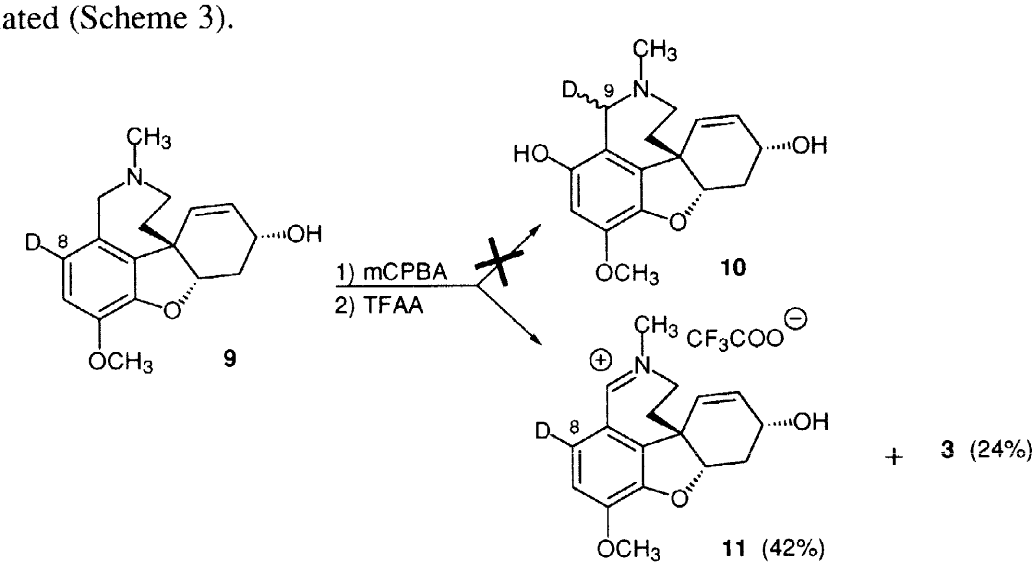
We first presumed that the hydroxylation phenomenon could be explained starting from the quinonic form **6** of the iminium salt **5** (Scheme 2). Addition of the trifluoroacetate counterion to **6** affords the intermediate **7** which undergoes an acid-base rearrangement (*pathway a*) or a 1-3 hydride shift (*pathway b*) to give phenol **3** after rearomatization and hydrolysis of the trifluoroacetate group. This latter mechanism is conceptually similar to that reported by Husson *et al.* in steroid alkaloid series[8].



Scheme 2

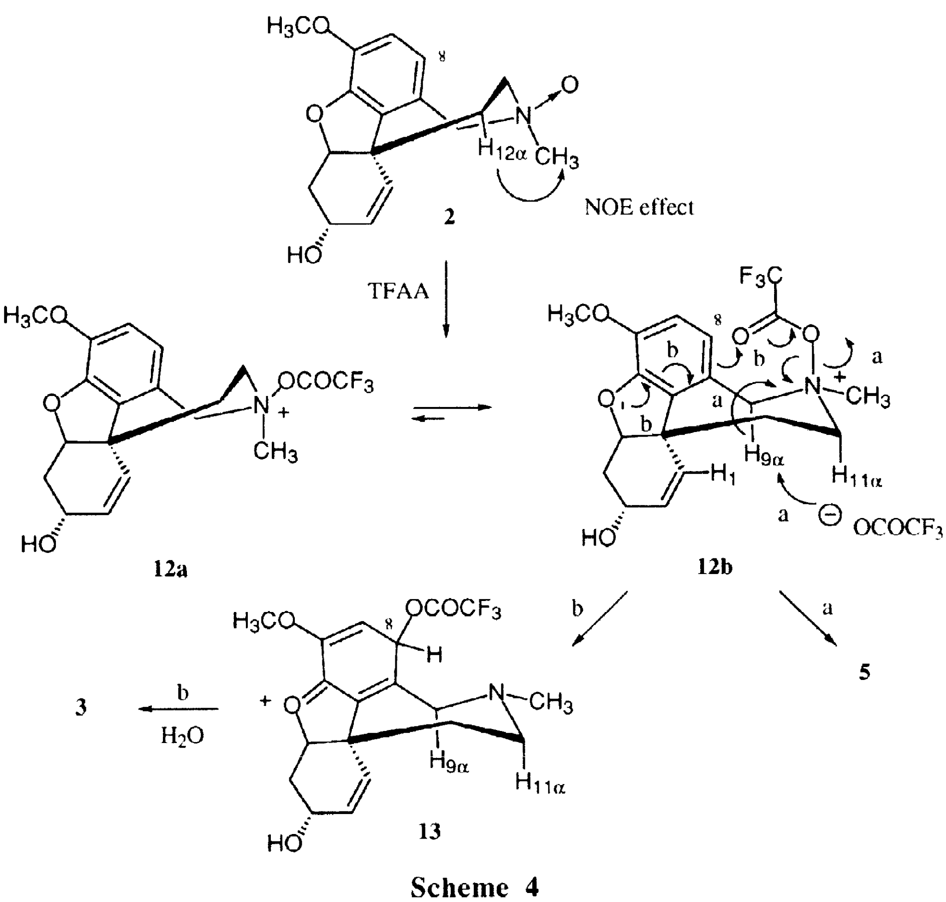
However, when the Polonovski-Potier reaction was applied to the 8-deuterated galanthamine **9**[9,10], the expected 9-deuterated phenol **10** which would have resulted from 1-3 hydride shift was not observed. Instead, the phenol **3** and the 8-deuterated iminium salt **11**[10] were isolated (Scheme 3).



Scheme 3

In order to definitively exclude the postulated role of the iminium salt **5**, it was subjected to similar Polonovski-Potier conditions as for **2**. Indeed, no formation of 8-hydroxygalanthamine **3** was observed. It is clear from these results that the iminium salt **5** is probably not the precursor of compound **3**.

We thus suggest an alternative mechanism for the formation of **3** *via* N-oxide **2** (Scheme 4). An axial position for the N-methyl group of N-oxide **2** has been previously established by NOE effects between H12α and the N-methyl proton consequently indicating a boat conformation for the seven-membered ring[5]. The first step in the Polonovski reaction is thus the formation of the trifluoroacetoxyammonium salt **12a** in the boat conformation; the latter is in equilibrium with the reactive chair form **12b** allowing the expected loss of the hydrogen atom trans-antiperiplanar to the N-O bond. In this way, the loss of the acidic benzylic hydrogen H9α provides the thermodynamically more stable iminium salt **5** (*pathway a*). However, the abstraction of the H9α proton is difficult owing to the steric hindrance on the α face of **12b**. Thus, a competitive intramolecular oxygen transfer to the aromatic nucleus can also occur (*pathway b*). The major driving force of this transfer could result from the withdrawing character of the $-CF_3$ group, the lability of the oxygen-ammonium bond and the participation of the furan oxygen lone pair. Furthermore, the close proximity of oxygen of the carbonyl group to the aromatic nucleus in the chair conformation **12b** argues in favor of this intramolecular mechanism. Subsequent rearomatization of oxonium species **13** and hydrolysis of the trifluoroacetate group then leads to the phenol **3**.



Scheme 4

In conclusion, the iminium salt **5** is the expected product of the Polonovski-Potier reaction of **2** whereas the phenol **3** results from an unusual intramolecular oxygen transfer. The transformation of **2** into **3** represents a new aspect of the modified Polonovski reaction.

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6. ***8-Hydroxygalanthamine (3).*** (amorphous). MS (EI) : 303 $(M)^{+\cdot}$; 288; 286; 272; 260. IR ($CHCl_3$) : 3555; 3276; 2935; 1670; 1629. ^1H NMR (250 MHz, $CDCl_3$) : 6.63 (br s, 1H; ArOH); 6.20 (s, 1H; H7); 6.03 (dd, 1H, J = 10; H1); 5.96 (d, 1H, J_1 = 10, J_2 = 4.5; H2); 4.55 (br s, 1H; H4a); 4.44 (d, 1H, J = 15.5; H9α); 4.15 (d, 1H, J = 4.5; H3); 3.75 (s, 3H; OCH_3); 3.69 (d, 1H, J = 15.5; H9β); 3.30 (m, 1H; H11α); 3.10 (br d, 1H, J = 14.0; H11β); 2.54 (s, 3H; NCH_3); 2.45 (dm, 1H, J = 15.5; H4α); 2.10 (ddd, 1H, J_1 = 15.5, J_2 = 5.5, J_3 = 3.0; H4β); 2.06(m, 1H; H12α); 1.75 (dm, 1H, J = 14.5; H12β). ^{13}C NMR (62.9 MHz, $CDCl_3$) : 149.5 (C8); 144.5 (C6); 139.8 (C5a); 133.7 (C8b); 128.5 (C2); 126.4 (C1); 112.5 (C8a); 102.4 (C7); 88.4 (C4a); 62.1 (C3); 56.1 (OCH_3); 54.3 (C9); 52.6 (C11); 48.3 (C4b); 43.4 (NCH_3); 34.1 (C12); 30.1 (C4). Anal. Calcd for $C_{17}H_{21}NO_4$: C 67.33; H 6.93; N 4.62, Found : C 67.21; H 6.59; N 4.79.

7. ***Iminium salt of galanthamine (5).*** (amorphous). MS (EI) : 286 $(M)^{+\cdot}$; 285 $(M-H)^+$; 284; 266. IR ($CHCl_3$) : 3561; 2932; 1662; 1622; 1589. ^1H NMR (250 MHz, $CDCl_3$ + 1 drop CF_3COOH) : 8.67 (s, 1H; H9); 7.51 (d, 1H, J = 8.5; H8); 7.05 (d, 1H, J = 8.5; H7); 6.21 (dd, 1H, J_1 = 10, J_2 = 5; H2); 5.71 (d, 1H, J = 10; H1); 4.87 (br s, 1H; H4a); 4.54 (dd, 1H, J_1 = 6, J_2 = 5; H3); 4.30-4.10 (m, 2H; H11); 4.02 (s, 3H; NCH_3); 3.88 (s, 3H; OCH_3); 2.85 (m, 1H; H4α); 2.30-2.10 (m, 3H; H4β, H12). ^{13}C NMR (62.9 MHz, $CDCl_3$ + 1 drop CF_3COOH) : 168.2 (C9); 160.3 ($\underline{C}OCF_3$); 153.7 (C6); 146.7 (C5a); 137.1 (C8b); 136.0 (C8); 129.7 (C2); 126.4 (C1); 117.6 (CF_3); 114.4 (C8a); 113.3 (C7); 88.7 (C4a); 61.5 (C3); 56.8 (OCH_3); 54.3 (C11); 52.3 (NCH_3); 46.8 (C4b); 31.2 (C12); 29.0 (C4). HRMS (EI) : Calcd 286.1394 ; Found : 286.1385.

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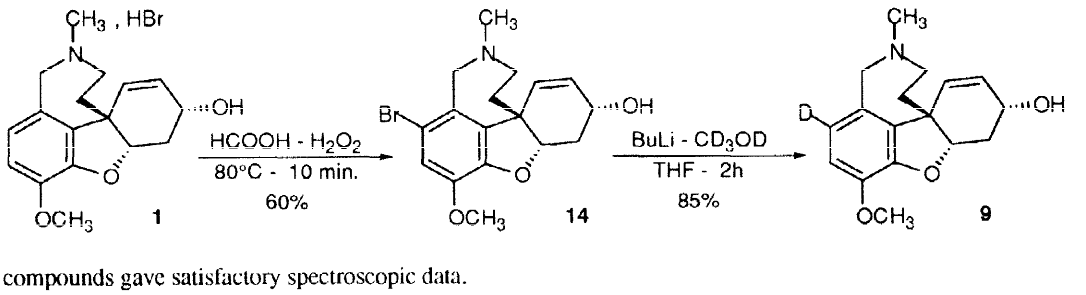
9. *Preparation of 8-deuterated galanthamine* **9** : Galanthamine hydrobromide was heated in formic acid with 30% hydrogen peroxide at 80 °C to provide bromide **14**[10] according to ref.11. Subsequent treatment of **14** with BuLi followed by CD_3OD afforded **9** in satisfactory yield.



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