

STERESELECTIVE INTERMOLECULAR HYDRIDE SHIFT MECHANISM OF THE NEW REDUCTION OF BENZYLIC ALCOHOLS WITH ACID

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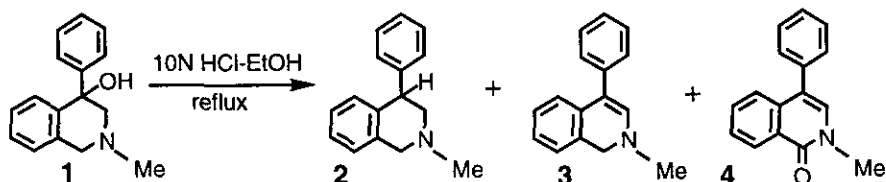
Abstract- A stereoselective intermolecular hydride shift mechanism of the new reduction reaction of the benzylic hydroxy group of 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**) to the corresponding alkane (**2**) with acid was proved by reaction of the deuterated derivatives (**5** and **6**) of **1**.

In the course of our study¹ on the synthesis of anti-breast cancer agents, we found a novel reduction of a tetrahydroisoquinoline derivative (**1**)² having a benzylic hydroxy group with boiling 10N HCl-EtOH to an alkane (**2**) with a dehydrated compound (**3**) and an amide (**4**) (Scheme 1). This reaction and the mechanism are very interesting since the reduction occurred without using a reducing agent³ under acidic conditions. We now report the mechanism of the reduction of **1** with acid.

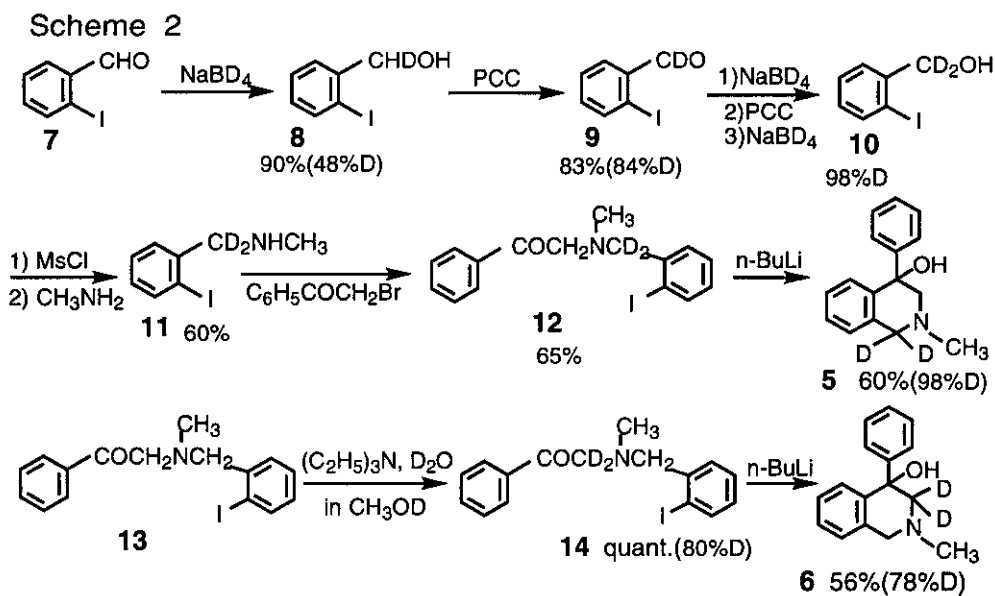
The reaction of the benzyl alcohol (**1**) to the reduced product (**2**) was suggested to proceed through **3** as an intermediate by the following facts. TLC behavior of the reaction mixture of **1** and 10N HCl-EtOH at room temperature for 30 min showed a presence of the olefin (**3**) as a sole product. This mixture was successively refluxed for 3 h to give **2** in 33% yield, indicating the intermediate from **1** to **2** to be **3**.

Since the reduction process from **3** to **2** can be regarded as a formal hydrogen addition to the double bond at C-3 and C-4, it is important to clarify the hydrogen source for this reaction. We expected that the hydrogens at C-1 or C-3 of the substrate (**1**) may be a possible hydrogen source. In order to confirm this possibility, we carried out to synthesize 1- and 3-deuterated compounds (**5** and **6**) and to react them with the acid.

Scheme 1

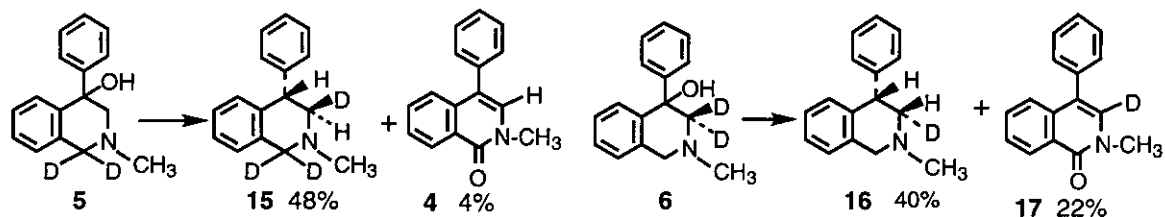


Compound (5) was prepared from the deuterated 2-iodobenzyl alcohol (10) as a key intermediate shown in Scheme 2. PCC oxidation of 8 (48%D) obtained by reduction of 2-iodobenzaldehyde (7) with NaBD₄ gave a deuterated benzaldehyde (9)(84 % D). This high deuterated ratio should be due to the isotope effect⁴ of the deuterium of 8 for the oxidation with PCC. The successive NaBD₄ reduction, PCC oxidation, and NaBD₄ reduction of 9 resulted in 98% D of 2-iodobenzyl alcohol (10). Mesylation of 10, followed by amination of the product with methylamine gave a benzylamine (11). Intramolecular Barbier reaction² of the phenacylamine (12) obtained from 11 gave the deuterated compound (5). The structure of 5 was determined by its MS spectrum and the similarity of ¹H-NMR spectrum of 5 to that of 1 except for the absence of the methylene protons at C-1. The 3-deuterated compound (6) (78% D) was prepared by intramolecular Barbier reaction of phenacylamine (14) (80% D), which was obtained by treatment of phenacylamine (13)² with Et₃N and D₂O in CH₃OD.⁵ The deuterated ratio and the structure of 6 were determined by its ¹H-NMR and MS spectra.



The reaction of compound (6) thus obtained with boiling 10N HCl-EtOH gave the reduced product (16) in 40% yield with oxygenated⁶ compound (17) having a deuterium (80% D). The molecular ion peak [m/z 224.1392(M^+); C₁₆H₁₆DN] of 16 showed that the reduced compound had one deuterium. The deuterium was found to be located at C-3 α by comparison of the ¹H-NMR spectrum with that of non-deuterated compound (2)(Table 1). These facts indicate that the reaction did not proceed by direct reduction of the hydroxy group but proceeded through a dehydrated compound as an intermediate in a stereoselective manner. On the other hand, the reaction of 1-deuterated compound (5) with boiling 10N HCl-EtOH gave reduced product (15) bearing three deuteriums[FAB-MS m/z 227.1631(M^+); C₁₆H₁₅D₃N] with non-deuterated amide (4) in 48% and 4% yields, respectively. The ¹H-NMR spectral data(Table 1) of 15 reveal that the deuteriums are at C-1 and C-3 β . The deuterated ratio at C-3 β was found to be 81%, while the

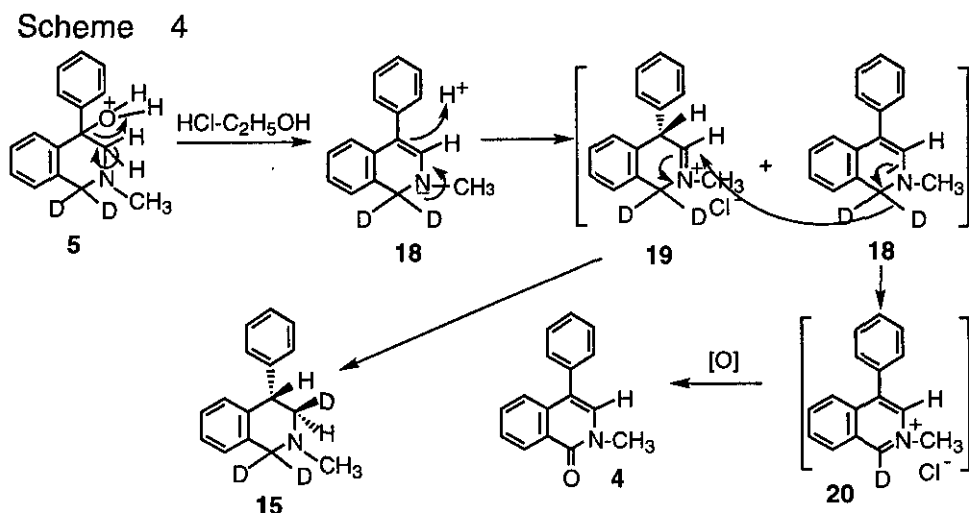
Scheme 3

Table 1. ¹H-NMR Spectral Data of **2**, **15**, and **16**

	C ₁		C ₃		C ₄
	H _β	H _α	H _β	H _α	
2	3.77 (d, J=14.7 Hz)	3.61 (d, J=14.7 Hz)	3.04 (ddd, J=11.5 5.6, 1.2 Hz)	2.56 (dd, J=11.5, 8.5 Hz)	4.29 (dd, J=8.5, 5.6 Hz)
15	-----	-----	-----	2.54 (d, J=8.5 Hz)	4.27 (d, J=8.5 Hz)
16	3.76 (d, J=14.9 Hz)	3.62 (d, J=14.9 Hz)	3.00 (d, J=5.6 Hz)	-----	4.27 (d, J=5.6 Hz)

presence of deuterium was not observed at C-3 α . Furthermore, the deuteriums (90% D) at C-1 of **15** were retained on the reaction of **5** (98% D). These findings indicate that the deuterium at C-3 β of reduced compound (**15**) is not generated from C-1 of the same molecule but from that of another molecule. Namely, this reduction includes a stereoselective and intermolecular shift of a deuterium from C-1 of one molecule to C-3 of another molecule.

On the basis of these results, the reduction of 1-deuterated compound (**5**) was concluded to proceed through a novel intermolecular deuteride(D⁻) shift mechanism as shown in Scheme 4. The benzylic alcohol (**5**) is dehydrated to give the olefin (**18**), to which acid(HCl) adds to form a quaternary iminium salt (**19**). The deuteride leaved from C-1 of another molecule of **18** attacks to C-3 of **19** from the opposite side of the 4-phenyl group because of a steric hindrance and thus produces the reduced compound (**15**) having *cis* configuration between H-4 and D-3. The reason for this stereoselective reaction is not clear but may be explained in term of intermolecular stacking⁷ between **18** and **19** in the deuteride shift process. On the other hand, the isoquinolinium salt (**20**) formed by leaving the deuteride from C-1 of **18** is oxidized⁶ to the amide (**4**). In the case of the reaction of 3-deuterated compound (**6**) with 10N HCl-EtOH, the *cis* configuration between H-3 and H-4 of the product (**16**) supports the mechanism similar to that shown in Scheme 4. In the same way, the reaction of compound (**1**) and its derivatives⁸ should also proceed through the intermolecular hydride shift mechanism depicted in Scheme 4. The reduction mechanism presented in this study is a rare example of intermolecular hydride shift under acidic conditions, although the reaction proceeded by intermolecular hydride shift mechanism with strong base is well known as Cannizzaro reaction.⁹



In conclusion, we have discovered a new reduction reaction of benzylic alcohols, 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinolines, without using a reducing agent under acidic conditions. The reaction mechanism was proved to include a novel and stereoselective intermolecular hydride shift process by the structure of the reaction products of the deuterated compounds (5 and 6) of 1 with acid.

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