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

Masaru Kihara,* Junichi Andoh, and Chiaki Yoshida

Graduate School of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan

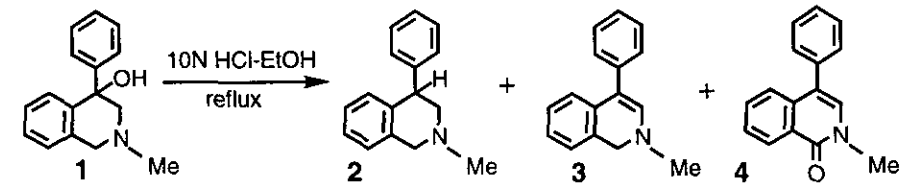
Abstract- A stereoselective intermolecular hydride shift mechanism of the new reduction reaction of the benzylic hydroxy group of 4-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**) to the corresponding alkane (**2**) with acid was proved by reaction of the deuterated derivatives (**5** and **6**)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

In the course of our study[1] 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 agent[3] 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**.

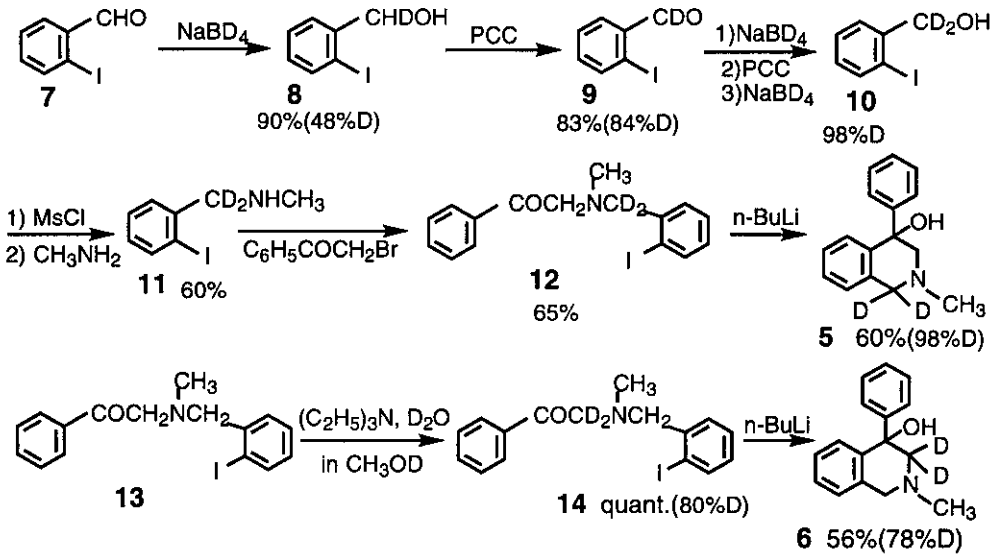
Since the reduction process from **3** to **2** can be regarded as a formal hydrogen addition to the double bond at C-3 and C-4, it is important to clarify the hydrogen source for this reaction. We expected that the hydrogens at C-1 or C-3 of the substrate (**1**) may be a possible hydrogen source. In 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 $NaBD_4$ gave a deuterated benzaldehyde (**9**)(84 % D). This high deuterated ratio should be due to the isotope effect[4] of the deuterium of **8** for the oxidation with PCC. The successive $NaBD_4$ reduction, PCC oxidation, and $NaBD_4$ 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 reaction[2] 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 ^{1}H-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 Et_3N and D_2O in CH_3OD. [5] The deuterated ratio and the structure of **6** were determined by its ^{1}H-NMR and MS spectra.

Scheme 2



The reaction of compound (**6**) thus obtained with boiling 10N HCl-EtOH gave the reduced product (**16**) in 40% yield with oxygenated[6] compound (**17**) having a deuterium (80% D). The molecular ion peak[*m/z* 224.1392(M^+); $C_{16}H_{16}DN$] of **16** showed that the reduced compound had one deuterium. The deuterium was found to be located at C-3α by comparison of the ^{1}H-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+1); $C_{16}H_{15}D_3N$] with non-deuterated amide (**4**) in 48% and 4% yields, respectively. The ^{1}H-NMR spectral data(Table 1) of **15** reveal that the deuteriums are at C-1 and C-3β. The deuterated ratio at C-3β was found to be 81%, while the

Scheme 3

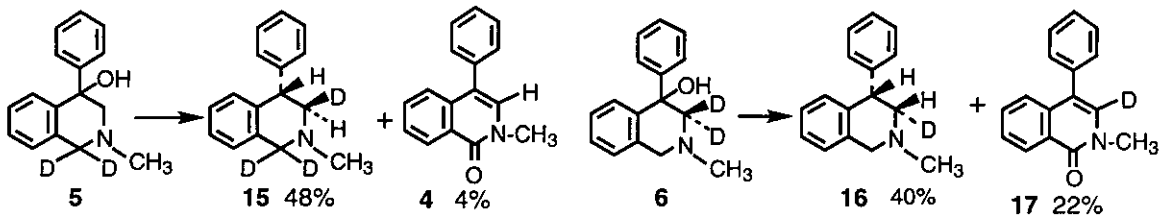


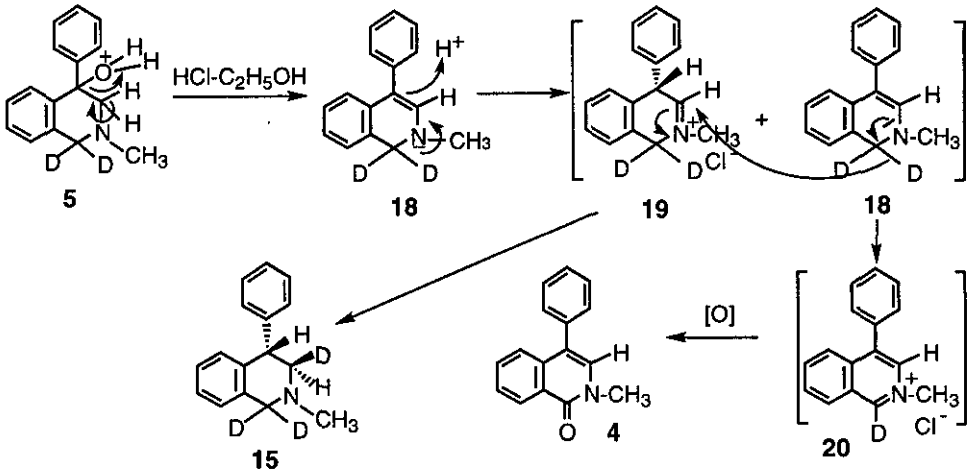
Table 1. ^{1}H-NMR Spectral Data of **2**, **15**, and **16**

	C_1		C_3		C_4
	H_β	$H\alpha$	H_β	$H\alpha$	
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-3α. 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-3β 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 stacking[7] 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 oxidized[6] 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 derivatives[8] 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 machanism with strong base is well known as Cannizzaro reaction.[9]

Scheme 4



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.

REFERENCES AND NOTES

1. M. Kihara, M. Ikeuchi, and Y. Nagao, *Drug Design and Discovery*, 1995, **12**, 259.
2. M. Kihara, M. Kashimoto, and Y. Kobayashi, *Tetrahedron*, 1992, **48**, 67.
3. G. R. Martinez, K. A. M. Walker, D. R. Hirschfeld, J. J. Bruno, D. S. Yang, and P. J. Maloney, *J. Med. Chem.*, 1992, **35**, 620.
4. a) K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713; b) F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.
5. S. Sano, Y. Nagao, M. Ochiai, and E. Fujita, *Tetrahedron*, 1990, **46**, 3211.
6. a) N. Sotomayor, E. Dominguez, and E. Lete, *Tetrahedron*, 1995, **51**, 12721; b) E. Dominguez, E. M. Marigorta, L. Carrillo, and R. Fenanas, *Tetrahderon*, 1991, **47**, 9253.
7. Y. Nagao, S. Sano, S. Nakagawa, M. Tanaka, and T. Taga, *Chem. Lett.*, 1992, 915.
8. The reaction of some derivatives subsutituted on the 4-phenyl group or the nitrogen of **1** with 10N HCl-EtOH also gave the coressponding reduced compounds in 37-45% yields. These results will be reported in the following paper.
9. T. A. Geissman, "Organic Reactions: The Cannizzaro Reaction," Vol. II, ed. by R. Adams, John Wiley & Sons, Inc., New York, 1944, pp. 94-113.

Received, 10th August, 1998