H-D EXCHANGE OF PSILOCIN AND ITS ANALOGS

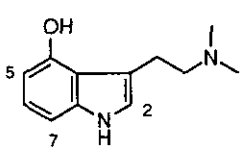
Kazuyo Sogawa, Kimiko Hashimoto, and Haruhisa Shirahama*

School of Science, Kwansei Gakuin University, Uegahara Nishinomiya, 662-8501, Japan

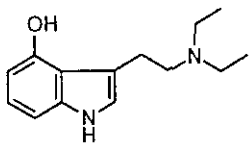
Abstract - H-D exchange experiments were performed on psilocin (**1**) and its analogs in MeOH-d_4. The various exchange rates depending on their C3-substituents were observed. The exchange of bufotenine (**5**) and 5-hydroxyindole (**7**) is much slower than psilocin (**1**) and its analogs (**2** ~ **4**).

Psilocin (**1**) is a hallucinogenic principle isolated from the poisonous mushroom, *Psilocybe mexicana*,[1] and it was recently detected in other *Psilocybe* species and also other genera, such as *Paneolus*, *Pluteus*, and *Conocybe*.[2] The white fruiting body of this fungi turns blue upon exposure to air, which was probably caused by the air oxidation of psilocin to produce blue pigments.[3] During the study of the structure of the blue materials, we synthesized some psilocin derivatives and found that they show various H-D exchange rates.[4] Bufotenine (**5**) also underwent H-D exchange but its rate was much slower than psilocin. The exchange must have occurred through the keto-enol and imine-enemine tautomerisms of the phenolic and anilinic protons.

Psilocin (**1**) and its analogs (**2** ~ **4**) were synthesized from 4-hydroxyindole using the oxalyl chloride-method;[5] acylation of the indole with oxalyl chloride at the C3 position followed by aminolysis of the resulting acid chloride in one pot and then reduction of the α-keto amide with $LiAlH_4$ produced **1** (Figure 1). The H-D exchange experiments on **1** ~ **8** were performed under the following conditions. The sample was dissolved in MeOH-d_4 (40 mM), which was allowed to stand at ambient temperature for 2 weeks. To some samples, Et_3N (1.0 equiv.) was also added. The product was analyzed by ^{1}HNMR spectroscopy. The results of the H-D exchange experiments are summarized in Table 1.



psilocin (**1**)



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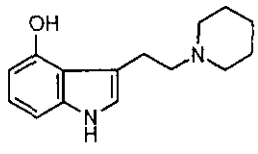

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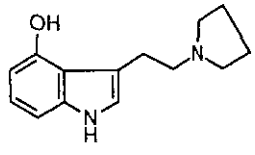

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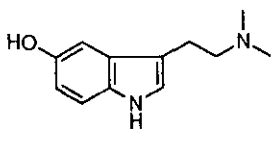
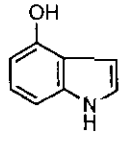


bufotenine (**5**)



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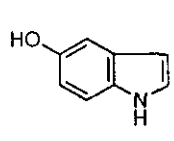

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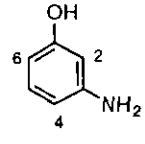

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Figure 1

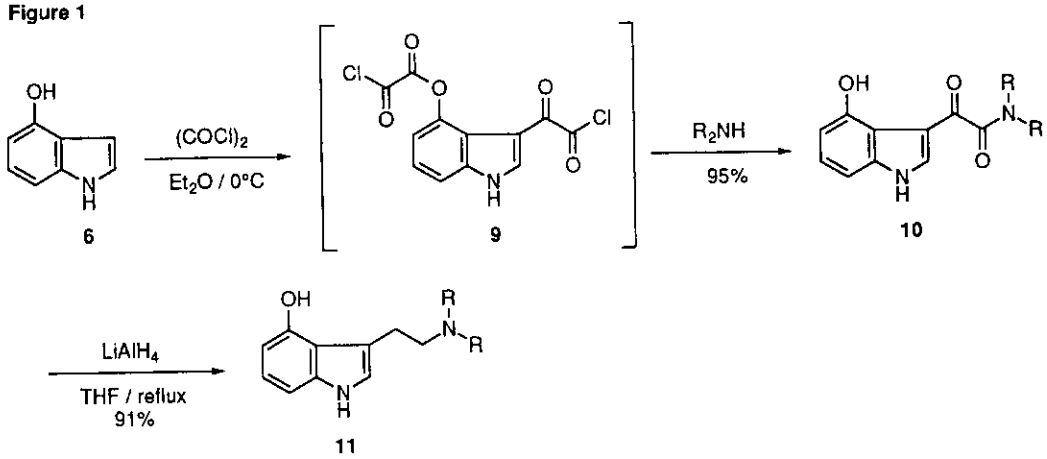
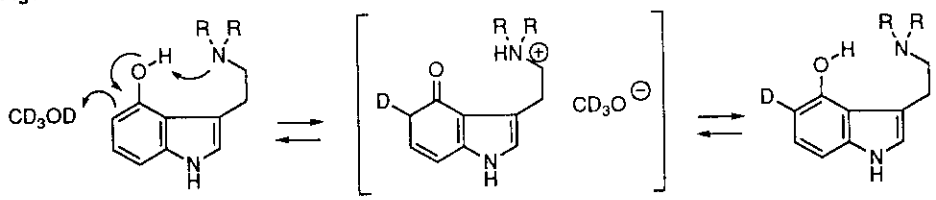


Figure 2



Psilocin (**1**) underwent exchange of the C5 and C7 hydrogens for deuterium, the former hydrogen was more labile than the latter upon exposure to the above conditions. The psilocin analogs (**2** ~ **4**) also exchange C5 and C7 hydrogens for deuterium, whose rates seemed to depend on the bulkiness of the amine groups attached to the C3-chain in MeOH-d_4. The order of the exchange rate is **4**>**1**>**2**=**3**. The pKa values of the amine groups also probably played a role. The amino group of psilocin must function as an intramolecular proton acceptor and accelerate the proton exchange at the C5 and C7 positions in a manner as depicted in Figure 2. Also, the smaller amine was more effective. Compounds (**6** ~ **8**), which have no alkylamine side chain in their molecules, showed exchange only in the presence of Et_3N, and exchange rate of psilocin (**1**) was not affected by addition of Et_3N. From these facts, the added Et_3N also works as a proton acceptor but the intramolecular action is more effective. The H-D exchange rate of bufotenine (**5**) and 5-hydroxyindole (**7**) is notably slower than those of psilocin (**1**) and its analogs (**2** ~ **4**). The faster exchanges of the 4-hydroxyindole derivatives are reasonable since the C5 position is doubly activated by the OH and NH groups. Besides, in the bufotenine molecule (**5**), the intramolecular assistance of the side group like those of **1** is impossible and the added Et_3N accelerates the exchange.

5-Hydroxyindole (**7**) exchanges the C4 hydrogen, which is similar to **5**, and also exchanges the C3 hydrogen more slowly. Aminophenol (**8**) has three exchangeable hydrogens, among these, the C6 hydrogen is more labile than the other two hydrogens (C2 and C4 protons). The integral of these two protons in the ^{1}HNMR decreased by about half the rate of the C6 proton, but they have the same chemical shift, so whether both or one exchange is not clear. The difference in the exchange rate between the C4 and C6 hydrogens should be attributable to the energy difference between the imine-enamine and keto-enol

tautomerism energy differences.

The position of these H-D exchanges should be an indication of the electron density of each atom.[6] From the fact that psilocin (**1**) exchanges the C5 hydrogen, whose oxidation should be initiated from the oxidation at the C5 position, it produces the blue pigments.[7]

Table 1

Compound	H-D Exchange Position	Conversion yield (%) 1 (day)	2 (days)	1 (week)	2 (weeks)
1	5	77	98	100	100
	7	20	31	56	73
1*	5	80	100	100	100
	7	16	33	56	79
2	5	31	49	89	100
	7	5	17	25	31
3	5	29	50	92	100
	7	0	3	26	39
4	5	85	100	100	100
	7	21	57	73	88
5	4	0	4	22	39
5*	4	10	22	41	65
6*	5	87	100	100	100
	7	4	11	24	39
7*	4	0	7	17	32
	3	0	0	7	13
8*	6 †	31	59	99	100
	2 (4)	15	25	54	68

* Triethylamine (1.0 equiv.) was added . The compounds (**6**,**7**,**8**) showed no exchange in the absence of Et_3N.

† Two protons appear at the same chemical shift, so it is not clear that both or one of two protons are exchanged.

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