SIMPLE SYNTHESES OF LESPEDAMINE AND 5-BROMO-*N,N*-DIMETHYLTRYPTAMINE BASED ON 1-HYDROXYINDOLE CHEMISTRY[1]

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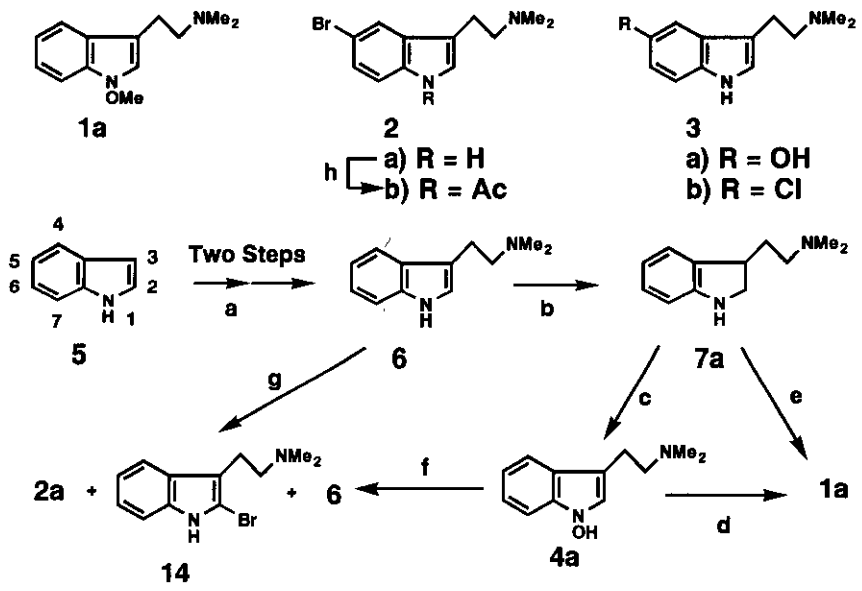
Abstract------ Various types of 1-hydroxyindoles were prepared for the first time. Through methylation or acid catalyzed nucleophilic bromination of *N,N*-dimethyl-1-hydroxytryptamine, simple syntheses of lespedamine and 5-bromo-*N,N*-dimethyltryptamine were achieved, respectively.

Lespedamine[2] (**1 a**, Scheme 1) was isolated from *Lespedeza bicolor* var. *japonica* Nakai and 5-bromo-*N,N*-dimethyltryptamine[3] (**2 a**) from marine sponge *Smenospongia aure*. Bufotenine (**3 a**),[4] **1 a**, and **2 a** seem to have no relation to each other. However, if we assume the existence of *N,N*-dimethyl-1-hydroxytryptamine (**4 a**), **1 a**, **2 a**, and **3 a** might be expected to originate from **4 a** as a common intermediate. Along this biosynthetic working hypothesis,[5] we have now achieved the simple syntheses of **1 a** and **2 a** through **4 a**.

We have succeeded for the first time in the syntheses[6] of various 1-hydroxyindoles. Initially, *N,N*-dimethyltryptamine (**6**) was prepared from indole (**5**) according to either the known two step sequence[7] (87% yield) of *N,N*-dimethylindole-3-glyoxylamide formation and treatment with $LiAlH_4$ or direct dimethylation of tryptamine[8] (70% yield). Reduction of **6** with triethylsilane[9] in CF_3COOH afforded 2,3-dihydro-*N,N*-dimethyltryptamine (**7 a**) in 92% yield. Oxidation of **7 a** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2[5,6] in MeOH-H_2O produced 55% yield of *N,N*-dimethyl-1-hydroxytryptamine (**4 a**, mp 179.5-180.0°C) as stable crystals. Subsequent methylation of **4 a** with diazomethane afforded lespedamine (**1 a**) in 53% yield. One pot preparation of **1 a** from **7 a** in

26% yield was also possible by carrying out the above two reactions, successibly. Thus, the shortest synthetic route among so far reported for **1 a** was established.

Scheme 1

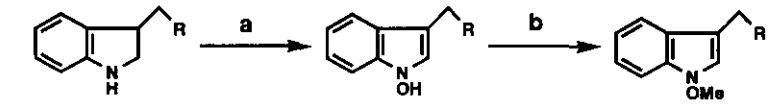


a) i. $(COCl)_2$, Me_2NH; ii. $LiAlH_4$; **b**) Et_3SiH, CF_3COOH; **c**) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2; **d**) CH_2N_2; **e**) one pot operation of **c** and **d**; **f**) 47% HBr; **g**) Br_2, AcOH; **h**) NaH, AcCl.

Similar oxidation of indolines (**7b-g**), 1,2,3,4,4a,9a-hexahydro-2-methoxycarbonyl-β-carboline (**8**), and 1,2,3,4,4a,9a-hexahydrocarbazole (**1 1**) produced the corresponding 1-hydroxyindoles (**4b-g**) and 9-hydroxy compounds (**9** and **1 2**) in good yields and the results are summarized in Scheme 2. Surprisingly, these 1-hydroxy and 9-hydroxy compounds were stable except for **1 2** and they were converted to the corresponding more stable 1-methoxy (**1 b-g**) and 9-methoxy compounds (**1 0** and **1 3**) by methylation either with diazomethane or dimethyl sulfate.

Next, based on the nucleophilic substitution reactions on indole nucleus,[5] **4 a** was treated with 47% aqueous HBr at room temperature for 1 h to produce expectedly the 5-bromo- (**2 a**), 2-bromo-*N*,*N*-dimethyltryptamine (**1 4**) and **6** in 25, 2, and 11% yields, respectively (Scheme 1).

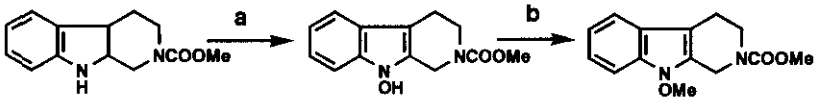
Scheme 2



7 4 1

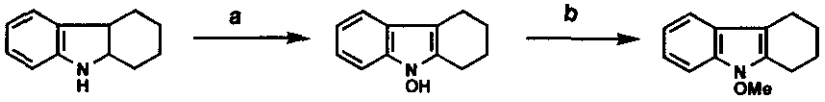
R	Yield (%), mp (°C)	Yield (%), mp (°C)
b) $NHCOCF_3$	65, 123.5-124.5	96, 70.5-71.0*
c) $CH_2NHCOOMe$	67, 114.0-115.0	83, oil
d) $CH_2NHCOCF_3$	72, oil	78, 70.5-71.0
e) $CH_2NHCH_2CH_2Me$	57, 147.0-148.0	65, oil
f) CH_2COOMe	59, oil	57,** oil
g) CH_2CH_2COOMe	52, 56.0-57.0	49,** oil

*See reference 6d, ** Overall yield from **7**.



8 **9** **10**

31%, mp 135.0-138.0 °C 90%, oil



11 **12** **13**

65%, unstable oil 76%, oil[5a]

a: $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, MeOH-H_2O; **b**: CH_2N_2 or Me_2SO_4, K_2CO_3.

Similar reaction of **4 a** with aqueous HCl proceeded cleanly and produced 55% yield of 5-chloro-*N,N*-dimethyltryptamine (**3 b**, oil). The structure of **2 a** was confirmed unequivocally by comparing its ^{1}H-nmr spectrum with that of 1-acetyl derivative (**2 b**), exhibiting that C-7 proton of **2 b** *was deshielded about 1 ppm by the anisotropy effect of* 1-acetyl *group.*

Concerning the biosynthesis of bromine containing natural products, suitable bromoperoxidases are generally believed to catalyze regioselective bromination of the substrates with electrophilic bromonium ion.[10] Therefore, electrophilic bromination of **6** was examined chemically with Br_2 in AcOH to afford exclusively 2-bromo-*N,N*-dimethyltryptamine (**1 4**) in 39% yield with no

detectable amount of **2a**. These results might suggest that acid catalyzed nucleophilic substitution reaction of 1-hydroxyindoles[5b] with halide is the other possible biosynthetic mechanism *in vivo*.

With various 1-hydroxyindoles in hand, their nucleophilic substitution reactions are in progress. Attempts to prepare bufotenine and related alkaloids are also in progress.

REFERENCES AND NOTES

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