

SIMPLE SYNTHESSES OF LESPEDAMINE AND 5-BROMO-*N,N*-DIMETHYLTRYPTAMINE BASED ON 1-HYDROXYINDOLE CHEMISTRY¹

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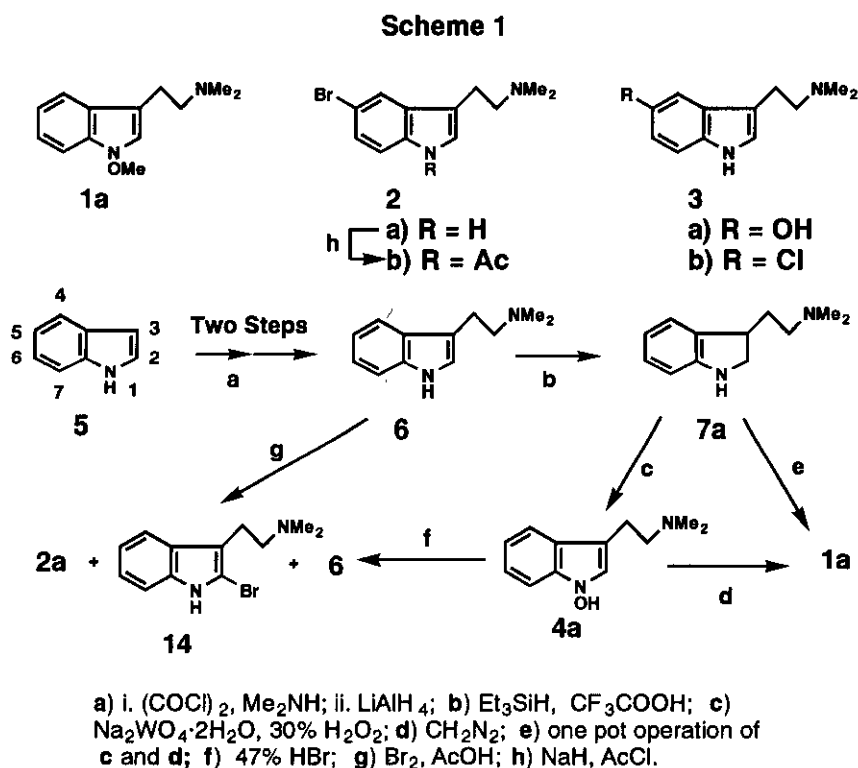
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Abstract----- Various types of 1-hydroxyindoles were prepared for the first time. Through methylation or acid catalyzed nucleophilic bromination of *N,N*-dimethyl-1-hydroxytryptamine, simple syntheses of lespedamine and 5-bromo-*N,N*-dimethyltryptamine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

Lespedamine² (**1 a**, Scheme 1) was isolated from *Lespedeza bicolor* var. *japonica* Nakai and 5-bromo-*N,N*-dimethyltryptamine³ (**2 a**) from marine sponge *Smenospongia aurea*. 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**.

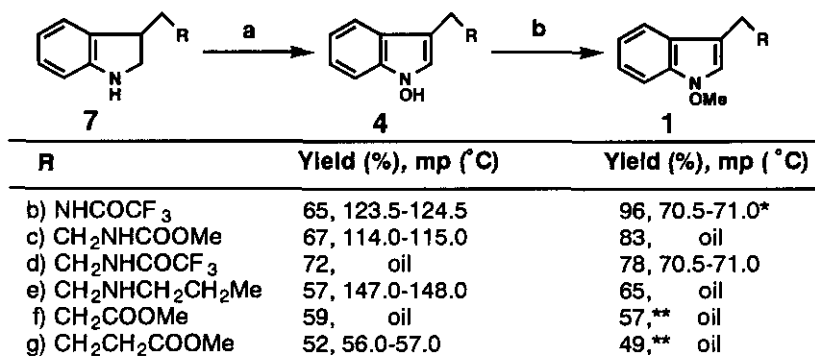
We have succeeded for the first time in the syntheses⁶ of various 1-hydroxyindoles. Initially, *N,N*-dimethyltryptamine (**6**) was prepared from indole (**5**) according to either the known two step sequence⁷ (87% yield) of *N,N*-dimethylindole-3-glyoxylamide formation and treatment with LiAlH₄ or direct dimethylation of tryptamine⁸ (70% yield). Reduction of **6** with triethylsilane⁹ in CF₃COOH afforded 2,3-dihydro-*N,N*-dimethyltryptamine (**7 a**) in 92% yield. Oxidation of **7 a** with Na₂WO₄·2H₂O and 30% H₂O₂^{5,6} in MeOH-H₂O 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, successively. Thus, the shortest synthetic route among so far reported for **1 a** was established.

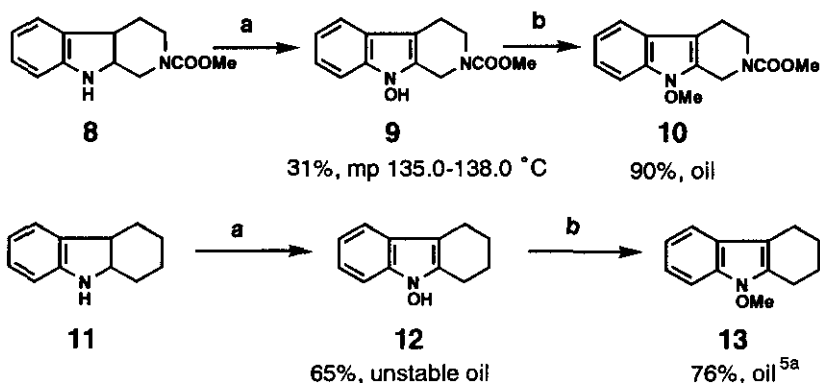


Similar oxidation of indolines (**7b-g**), 1,2,3,4,4a,9a-hexahydro-2-methoxycarbonyl- β -carboline (**8**), and 1,2,3,4,4a,9a-hexahydrocarbazole (**11**) produced the corresponding 1-hydroxyindoles (**4b-g**) and 9-hydroxy compounds (**9** and **12**) in good yields and the results are summarized in Scheme 2. Surprisingly, these 1-hydroxy and 9-hydroxy compounds were stable except for **12** and they were converted to the corresponding more stable 1-methoxy (**1b-g**) and 9-methoxy compounds (**10** and **13**) by methylation either with diazomethane or dimethyl sulfate. Next, based on the nucleophilic substitution reactions on indole nucleus,⁵ **4a** was treated with 47% aqueous HBr at room temperature for 1 h to produce expectedly the 5-bromo- (**2a**), 2-bromo-*N,N*-dimethyltryptamine (**14**) and **6** in 25, 2, and 11% yields, respectively (Scheme 1).

Scheme 2



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



a: Na₂WO₄·2H₂O, 30% H₂O₂, MeOH-H₂O; b: CH₂N₂ or Me₂SO₄, K₂CO₃.

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 ¹H-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 Br₂ in AcOH to afford exclusively 2-bromo-*N,N*-dimethyltryptamine (**14**) 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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Received, 13th April, 1994