Simple syntheses of lespedamine and 5-bromo-N,N-dimethyltryptamine based on 1-hydroxyindole chemistry

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

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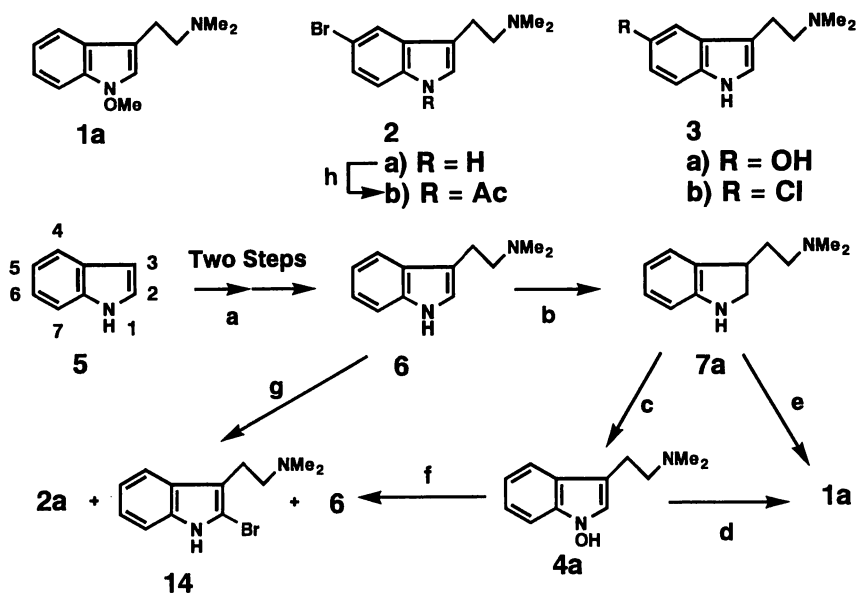
Abstract------ Various types of 1-hydroxyindoles were prepared for the first time. Through methylation or acid catalyzed nucleophilic bromination of *N,N*-dimethyl-1-hydroxytryptamine, simple syntheses of lespedamine and 5-bromo-*N,N*-dimethyltryptamine were achieved, respectively.

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

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 (**7a**) in 92% yield. Oxidation of **7a** 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 (**4a**, mp 179.5-180.0°C) as stable crystals. Subsequent methylation of **4a** with diazomethane afforded lespedamine (**1a**) in 53% yield. One pot preparation of **1a** from **7a** 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

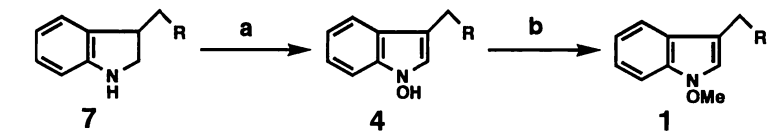


a) i. $(COCl)_2$, Me_2NH; ii. $LiAlH_4$; **b**) Et_3SiH, CF_3COOH; **c**) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2; **d**) CH_2N_2; **e**) one pot operation of **c** and **d**; **f**) 47% HBr; **g**) Br_2, AcOH; **h**) NaH, AcCl.

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 (**1b-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).

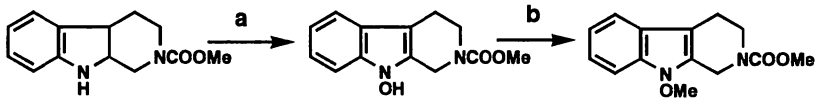
Scheme 2



7 4 1

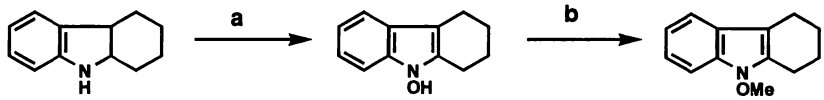
R	Yield (%), mp (°C)	Yield (%), mp (°C)
b) $NHCOCF_3$	65, 123.5-124.5	96, 70.5-71.0*
c) $CH_2NHCOOMe$	67, 114.0-115.0	83, oil
d) $CH_2NHCOCF_3$	72, oil	78, 70.5-71.0
e) $CH_2NHCH_2CH_2Me$	57, 147.0-148.0	65, oil
f) CH_2COOMe	59, oil	57,** oil
g) CH_2CH_2COOMe	52, 56.0-57.0	49,** oil

* 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

1. This paper is dedicated to Prof. R. Huisgen on his 75th birthday. a) This is Part 71 of a series entitled "The Chemistry of Indoles"; b) Part 70: M. Somei, N. Aoki, and K. Nakagawa, *Heterocycles,* 1994, **38**, 1479.
2. a) H. Morimoto and H. Oshio, *Liebigs Ann. Chem.*, 1965, **682**, 212; b) Total syntheses of **1a**: R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans.* 1, 1978, 1117; M. Somei, H. Sato, and C. Kaneko, *Heterocycles*, 1983, **20**, 1797.
3. a) P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435; b) Synthesis of **2a**: A. A. Tymiak, K. L. Rinehart, Jr., and G. J. Bakus, *Tetrahedron*, 1985, **41**, 1039.
4. T. Wieland and W. Motzel, *Ann.*, 1953, **581**, 10; V. L. Stromberg, *J. Am. Chem. Soc.*, 1954, **76**, 1707.
5. a) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221; b) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *ibid.*, 1992, **34**, 1877; c) F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *ibid.*, 1993, **35**, 99; d) M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; e) F. Yamada, D. Shinmyo, and M. Somei, *ibid.*, 1994, **38**, 273.
6. a) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; b) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205; c) M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905; d) M. Somei, K. Kobayashi, K. Shimizu, and T. Kawasaki, *Heterocycles*, 1992, **33**, 77. See also reference 5.
7. M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, 1954, **76**, 6208.
8. L. J. Street, R. Baker, J. L. Castro, M. S. Chambers, A. R. Guiblin, S. C. Hobbs, V. G. Matassa, A. J. Reeve, M. S. Beer, D. N. Middlemiss, A. J. Noble, J. A. Stanton, K. Scholey, and R. J. Hargreaves, *J. Med. Chem.*, 1993, **36**, 1529.
9. A. E. Lanzilotti, R. Littell, W. J. Fanshawe, T. C. McKenzie, and F. M. Lovell, *J. Org. Chem.*, 1979, **44**, 4809.
10. R. D. Libby, J. A. Thomas, L. W. Kaiser, and L. P. Hager, *J. Biol. Chem.*, 1982, **257**, 5030; N. Itoh, Y. Izumi, and H. Yamada, *ibid.*, 1987, **262**, 11982; E. de Boer and R. Wever, *ibid.*, 1988, **263**, 12326.

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