SYNTHESES OF SEROTONIN, *N*-METHYLSEROTONIN, BUFOTENINE, AND MELATONIN, AND THE FIRST TOTAL SYNTHESIS OF *N*-(INDOL-3-YL)METHYL-*N*-METHYL-5-METHOXYTRYPTAMINE FROM TRYPTAMINE THROUGH A COMMON INTERMEDIATE, 1-HYDROXYTRYPTAMINE[1]

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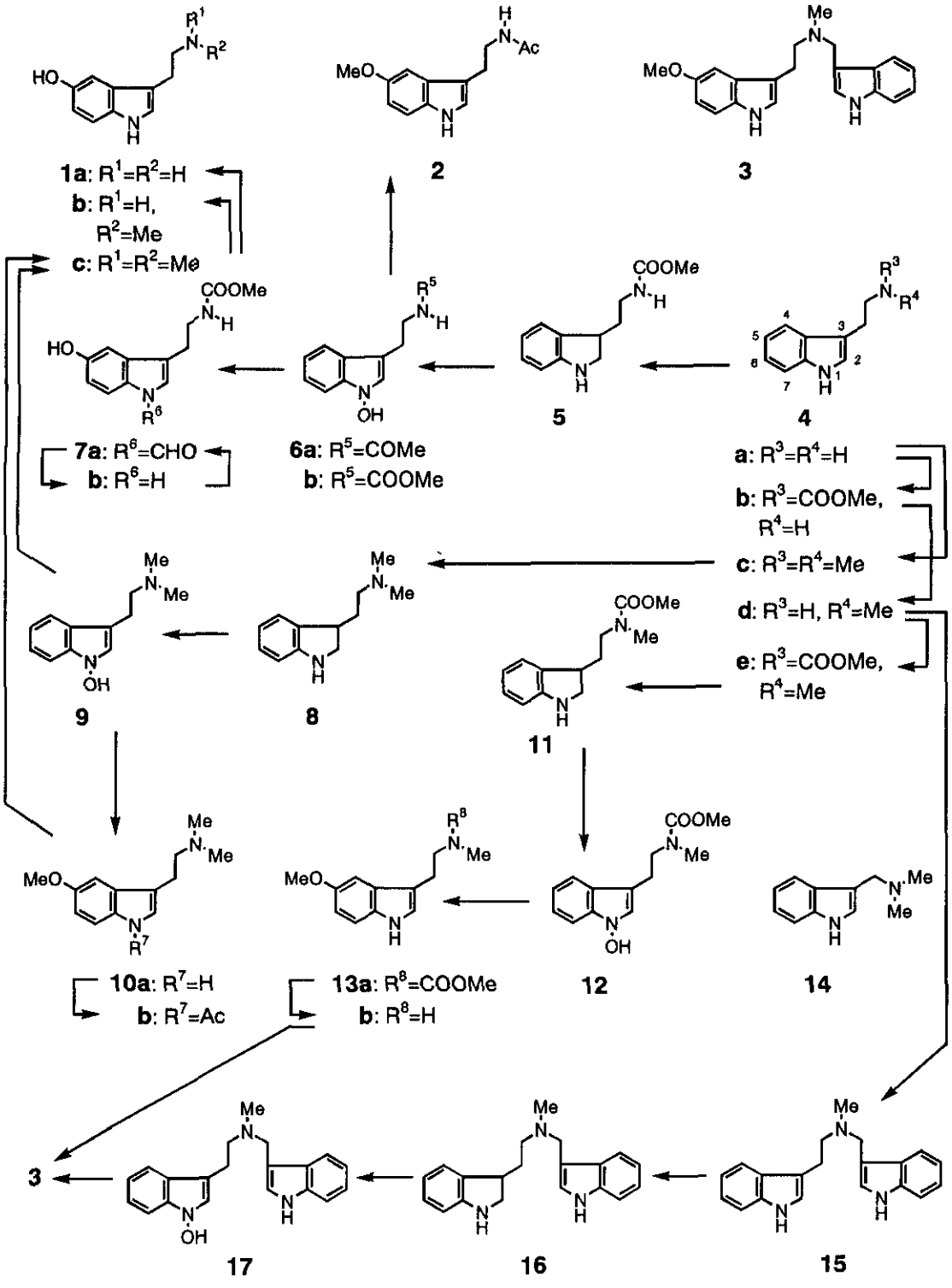
Abstract ——— Simple syntheses of serotonin (**1a**), *N*-methylserotonin (**1b**), bufotenine (**1c**), and melatonin (**2**), and the first total synthesis of *N*-(indol-3-yl)methyl-*N*-methyl-5-methoxytryptamine (**3**) from tryptamine (**4a**) are reported through acid catalyzed nucleophilic substitution reaction of 1-hydroxytryptamines.

Tryptamine alkaloids such as serotonin (**1a**, Scheme 1),[2] *N*-methylserotonin (**1b**),[3] bufotenine (**1c**),[4a,b] and melatonin (**2**)[5] are biologically important amines in animals and plants. As a member of the alkaloid family, *N*-(indol-3-yl)methyl-*N*-methyl-5-methoxytryptamine (**3**)[6] was recently isolated from the roots of *Antirhea lucida* (Sw.) Hook (Rubiaceae). Our 1-hydroxyindole hypotheses[7] expect that 1-hydroxytryptamine is a common biosynthetic intermediate for these alkaloids. Attempts to verify the hypotheses have led us to disclose acid catalyzed transformations of 1-hydroxytryptamines (**6**, **9**, **12**, and **17**) into **1a-c**, **2**, and **3**.

The synthesis of **2** has already been achieved in 80% yield[7c,f] from *N*-acetyl-1-hydroxytryptamine (**6a**) utilizing acid catalyzed regioselective nucleophilic substitution at the 5-position.[7] Based on the result, simple syntheses of **1a** and **1b** from **4a** were established as follows. *N*-Methoxycarbonyltryptamine (**4b**), available from **4a** by a conventional method, was converted to **5** (83%) by the reduction with triethylsilane[8] in CF_3COOH (Et_3SiH-TFA). Oxidation of **5** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2[7,9] (Na_2WO_4-H_2O_2) produced *N*-methoxycarbonyl-1-hydroxytryptamine (**6b**, 67%). The reaction of **6b** with 85% HCOOH at room temperature for 20 min afforded **7a** (15%) and **7b** (50%). Interconversion between **7a** and **7b** was readily attained. Thus, treatment of **7b** with 85% HCOOH at room temperature for

Scheme 1


1a: R1=R2=H
b: R1=H, R2=Me
c: R1=R2=Me
2
3
4
a: R3=R4=H
b: R3=COOMe, R4=H
c: R3=R4=Me
d: R3=H, R4=Me
e: R3=COOMe, R4=Me
5
6a: R5=COMe
b: R5=COOMe
7a: R6=CHO
b: R6=H
8
9
10a: R7=H
b: R7=Ac
11
12
13a: R8=COOMe
b: R8=H
14
15
16
17
3

48 h afforded **7a** (69%), while its alkaline hydrolysis with 2N-NaOH in MeOH gave **7b** (76%). Further treatment of **7b** with $LiAlH_4$ in refluxing Et_2O-THF afforded **1b** (65%). Hydrolysis of **7b** to **1a** proceeded in 73% yield by the treatment with 10% NaOH in refluxing MeOH.

An attempt to convert *N*,*N*-dimethyl-1-hydroxytryptamine (**9**), prepared from **4c** through **8** as reported previously,[7f] directly into bufotenine (**1c**) by the reaction with 85% HCOOH was unsuccessful. However, the treatment of **9** with more acidic 5% H_2SO_4-H_2O at reflux for 6 h produced **1c**[4c] in 47% yield together with **4c** (16%). When the solvent was changed to MeOH under similar reaction conditions, **9** afforded **10a** (57%), **1c** (7%), and **4c** (11%). The structure of **10a** was confirmed by comparing its ^{1}H-NMR spectrum with that of 1-acetyl derivative (**10b**), where the 1-acetyl group deshielded the C-7 proton (d, J= 9.0 Hz) by about 1 ppm. The cleavage of the methoxy group of **10a** using BBr_3 in CH_2Cl_2-toluene also gave **1c**[4c] (63%).

Total synthesis of **3**[6] was carried out by the following two routes. The conventional $LiAlH_4$ reduction of **4b** to **4d**, followed by the treatment with ClCOOMe-Et_3N, afforded **4e** (94% overall yield). Further reduction of **4e** with Et_3SiH-TFA afforded **11** (95%). Subsequent oxidation of **11** with Na_2WO_4-H_2O_2 gave *N*-methoxycarbonyl-*N*-methyl-1-hydroxytryptamine (**12**, 77%). Treatment of **12** with 5% H_2SO_4 in refluxing MeOH produced **13a** (39%). Hydrolysis of **13a** with 40% NaOH in refluxing MeOH afforded **13b**[10] (93%). Then our Bu_3P[11] catalyzed reaction of gramine (**14**) with nucleophiles was successfully applied to **13b** in refluxing MeCN culminating in the first total synthesis of **3**[12] in 78% yield. On the other hand, similar reaction of **14** with **4d** produced **15** (67%) together with unreacted **4d** (32%). It is interesting to note that selective reduction of tryptamine part of **15** was realized with $NaBH_3CN$[13] in AcOH-TFA (3:1, v/v) resulting in the formation of **16** (71%). Subsequent oxidation of **16** with Na_2WO_4-H_2O_2 gave **17** (51%). Treatment of **17** with BF_3·MeOH in MeOH at 65°C for 3 h accomplished an alternative route to **3** (15%)[14] together with **15** (9%) and unreacted **17** (21%).

In conclusion, we disclosed that under acidic conditions 1-hydroxytryptamines readily transform to biologically important tryptamine alkaloids (**1a-c**, **2**, and **3**). From the synthetic point of view, the reaction has a probability to produce various 5-substituted tryptamines simply by choosing suitable nucleophiles. Investigations along this line are now in progress.

REFERENCES AND NOTES

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12. Colorless oil. Although IR and ^{1}H-NMR data differ slightly from the reported ones,[6] we found that proton signals shift markedly depending on the deuterated solvent. The data of ^{13}C-NMR are completely identical with the reported ones.[6] ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ: 2.40 (3H, s), 2.81 (2H, t, *J*=8.1 Hz), 3.00 (2H, t, *J*=8.1 Hz), 3.79 (3H, s), 3.85 (2H, s), 6.82 (1H, dd, *J*=8.8 and 2.5 Hz), 6.95 (1H, s), 6.97 (1H, d, *J*=2.5 Hz), 7.11 (1H, ddd, *J*=8.1, 7.0, and 1.0 Hz), 7.17 (1H, s), 7.18 (1H, ddd, *J*=8.1, 7.0, and 1.0 Hz), 7.23 (1H, d, *J*=8.8 Hz), 7.37 (1H, dt, *J*=8.1 and 1.0 Hz), 7.69 (1H, dt, *J*=8.1 and 1.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 23.5, 42.3, 52.7, 55.9, 57.6, 100.7, 111.0, 111.8, 112.0, 113.1, 114.3, 119.4, 119.5, 121.9, 122.4, 123.6, 127.9, 131.4, 136.2 (2C), 153.8. IR ($CHCl_3$): 3450, 2780, 1621, 1585, 1483, 1451 cm^{-1}. High Resolution MS *m/z*: Calcd for $C_{21}H_{23}N_3O$: 333.1841. Found: 333.1852.
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