

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-HYDROXYTRYPTAMINE¹

Masanori Somei,* Fumio Yamada, and Harunobu Morikawa

Faculty of Pharmaceutical Sciences, Kanazawa University,

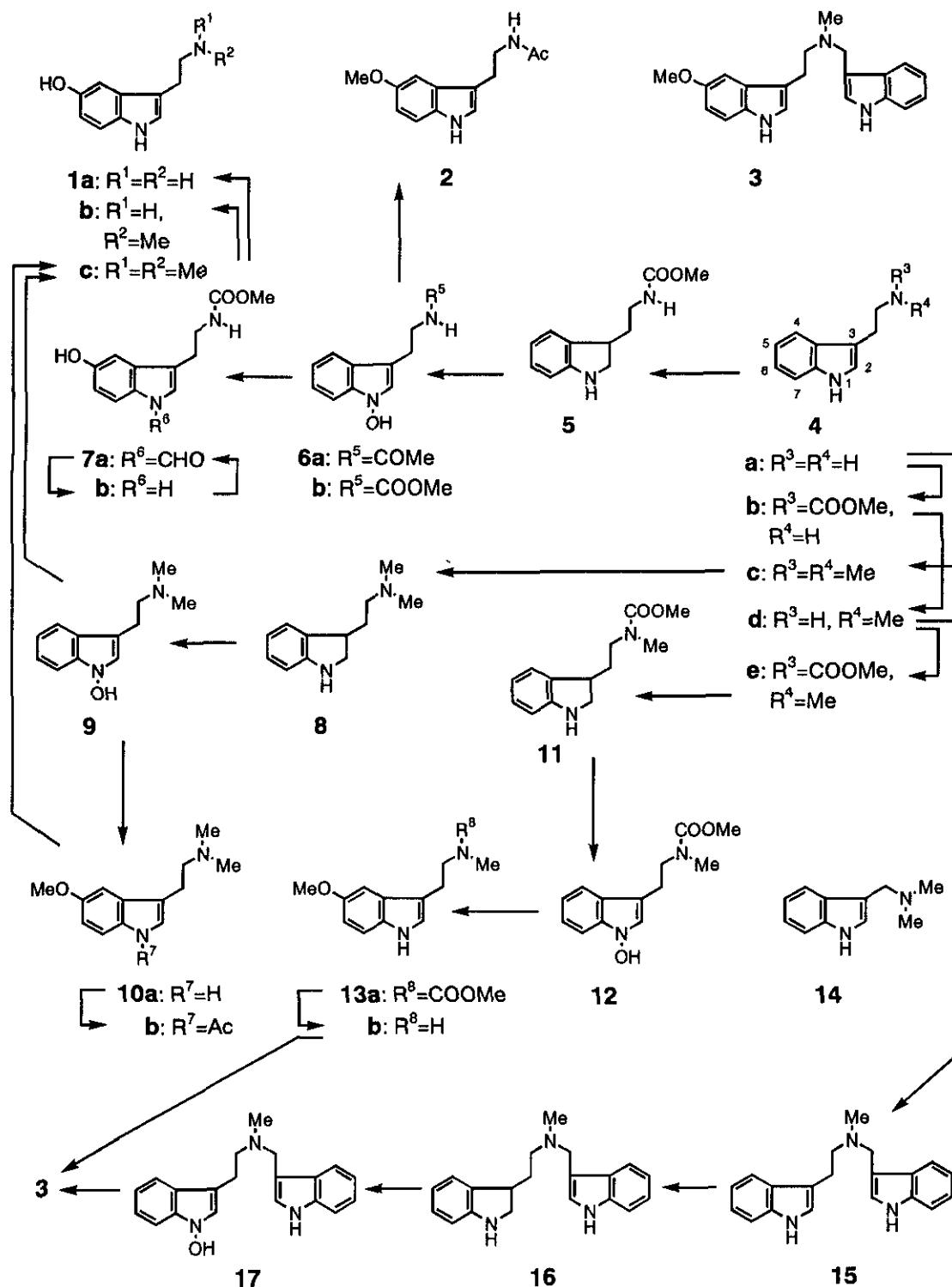
13-1 Takara-machi, Kanazawa 920, Japan

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 hypotheses⁷ 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 triethylsilane⁸ in CF₃COOH (Et₃SiH-TFA). Oxidation of **5** with Na₂WO₄·2H₂O and 30% H₂O₂^{7,9} (Na₂WO₄-H₂O₂) 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



48 h afforded **7a** (69%), while its alkaline hydrolysis with 2N-NaOH in MeOH gave **7b** (76%). Further treatment of **7b** with LiAlH₄ in refluxing Et₂O-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% H₂SO₄-H₂O 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 ¹H-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 BBr₃ in CH₂Cl₂-toluene also gave **1c**^{4c} (63%).

Total synthesis of **3**⁶ was carried out by the following two routes. The conventional LiAlH₄ reduction of **4b** to **4d**, followed by the treatment with ClCOOMe-Et₃N, afforded **4e** (94% overall yield). Further reduction of **4e** with Et₃SiH-TFA afforded **11** (95%). Subsequent oxidation of **11** with Na₂WO₄-H₂O₂ gave *N*-methoxycarbonyl-*N*-methyl-1-hydroxytryptamine (**12**, 77%). Treatment of **12** with 5% H₂SO₄ in refluxing MeOH produced **13a** (39%). Hydrolysis of **13a** with 40% NaOH in refluxing MeOH afforded **13b**¹⁰ (93%). Then our Bu₃P¹¹ 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 NaBH₃CN¹³ in AcOH-TFA (3:1, v/v) resulting in the formation of **16** (71%). Subsequent oxidation of **16** with Na₂WO₄-H₂O₂ gave **17** (51%). Treatment of **17** with BF₃·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 ¹H-NMR data differ slightly from the reported ones,⁶ we found that proton signals shift markedly depending on the deuterated solvent. The data of ¹³C-NMR are completely identical with the reported ones.⁶ ¹H-NMR (5% CD₃OD in CDCl₃) 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). ¹³C-NMR (CDCl₃) 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 (CHCl₃): 3450, 2780, 1621, 1585, 1483, 1451 cm⁻¹. High Resolution MS *m/z*: Calcd for C₂₁H₂₃N₃O: 333.1841. Found: 333.1852.
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 14. Optimum reaction conditions have not been made yet.

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