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SYNTHESIS OF N_b -ACYLTRYPTAMINES AND THEIR 1-HYDROXY-TRYPTAMINE DERIVATIVES AS NEW α_2 -BLOCKERS^{1,#}

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Abstract – N_b -Acyl- and N_b -acyl-1-hydroxytryptamines are found to be novel and structurally simple α_2 -blocker for the treatment of erectile dysfunction.

Nowadays, a lot of people need a drug for the treatment of erectile dysfunction (ED). Sildenafil citrate (**1**, Figure 1) has been used as a promising drug, but it has some side-effects² to be improved. Although yohimbine³ (**2**) is a folk medicine and widely used among people as a α_2 -blocker to treat ED, it is a powerful medicine and dangerous unless we are careful about quantity to take. Therefore, when the safer drug is found, it would not only bring happiness to a human being, but also be applied for raising the breeding rate of animals.^{4,5} Cows and pigs could lay a lot of calves and child pigs, respectively and offer meat to us solving the significant problem of food shortage in the world.

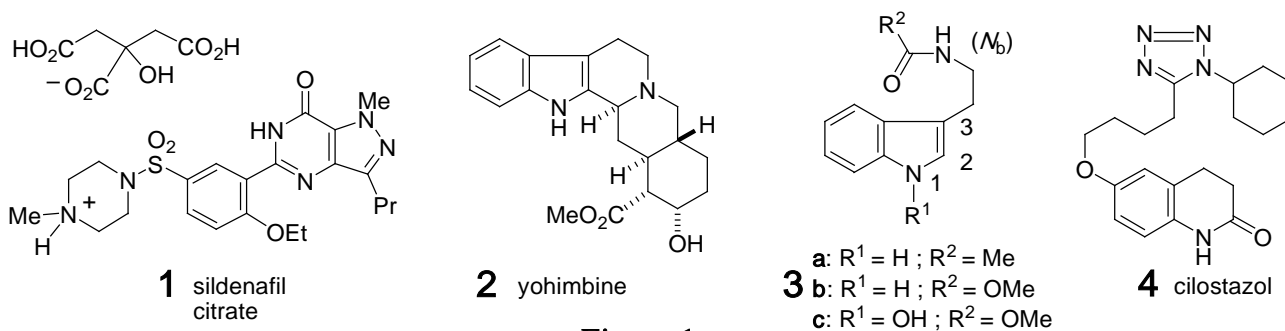


Figure 1

Dedicated to the memory of Dr. John Daly

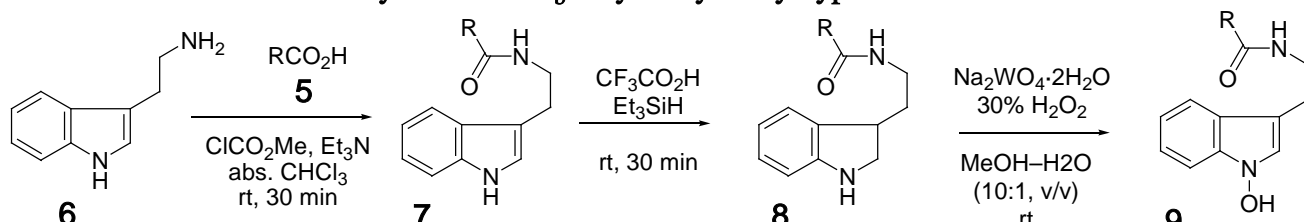
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


In our project for developing a novel and potent α_2 -blocker, structurally simpler than **1** and **2**, we discovered that N_6 -acetyl- (**3a**) and N_6 -methoxycarbonyltryptamines (**3b**) have weak but reliable activity as a α_2 -blocker.⁴ On the other hand, we succeeded in the establishment of 1-hydroxyindole chemistry.⁵ As a result, we found that 1-hydroxy- N_6 -methoxycarbonyltryptamine (**3c**: IC₅₀ 0.32 μ M) is one of the best leads and ten times more potent than cilostazol (**4**: IC₅₀ 3.10 μ M) in the inhibition test on arachidonic acid induced platelet aggregation in rabbit PRP.⁶ It is expected to be a possible lead for cerebral and myocardial infarction.⁷

We attempted therefore to pursue the study of structure-activity relationship of N_6 -acyltryptamines and their 1-hydroxytryptamine derivatives hoping to develop a potent lead for ED and cerebral infarction.

For the preparation of N_6 -acyltryptamines, a conventional mixed anhydride method was applied. Appropriate carboxylic acids (**5**, Table 1) were treated with methyl chloroformate. The resultant anhydrides were then reacted with tryptamine (**6**) to afford the desired compounds (**7**) and the results are summarized in Table 1. Employing propanoic (**5a**), pentanoic (**5b**), heptanoic (**5c**), and nonanoic acids (**5d**), the corresponding N_6 -propanoyl- (**7a**), N_6 -pentanoyl- (**7b**), N_6 -heptanoyl- (**7c**), and N_6 -nonanoyltryptamines (**7d**) were produced in 94, 91, 95, and 93% yields, respectively. Cyclopropane- (**5e**), cyclohexane- (**5f**), and 2-furancarboxylic acids (**5g**) provided N_6 -cyclopropanecarbonyl- (**7e**), N_6 -cyclohexanecarbonyl- (**7f**), and N_6 -2-furancarboxyltryptamine (**7g**) in the respective yields of 85, 61, and 62%.

Table 1. Synthesis of N_6 -Acyl-1-hydroxytryptamine Derivatives



Carboxylic Acid 5	R	Compound 7	Yield (%)	Compound 8	Yield (%)	Compound 9	Reaction Time (min)	Yield (%)
5a	—CH ₂ Me	7a	94	8a	98	9a	15	67
5b	—(CH ₂) ₃ Me	7b	91	8b	86	9b	15	61
5c	—(CH ₂) ₅ Me	7c	95	8c	87	9c	30	68
5d	—(CH ₂) ₇ Me	7d	93	8d	78	9d	30	61
5e		7e	85	8e	84	9e	30	69
5f		7f	61	8f	73	9f	30	62
5g		7g	62	8g	97* ¹	9g	30	64

*1: reacted at around 60 °C for 1 h.

According to the first step of our 1-hydroxyindole synthetic method,⁵ N_6 -acyltryptamines (**7**) were

converted to N_6 -acyl-2,3-dihydrotryptamines (**8**) by the reduction with Et_3SiH in trifluoroacetic acid at rt for 30 min. Thus, **7a**, **7b**, **7c**, and **7d** afforded 2,3-dihydro- N_6 -propanoyl- (**8a**), - N_6 -pentanoyl- (**8b**), - N_6 -heptanoyl- (**8c**), and - N_6 -nonanoyltryptamines (**8d**) in 98, 86, 87, and 78% yields, respectively. Similarly, **7e** and **7f** provided 2,3-dihydro- N_6 -cyclopropanecarbonyl- (**8e**) and - N_6 -cyclohexanecarbonyltryptamine (**8f**) in the respective yields of 84 and 73%. In the case of **7g**, the reduction was slow and heating at around 60 °C for 1 h was necessary to produce 2,3-dihydro- N_6 -2-furancarboxyltryptamine (**8g**) in 97% yield.

In the second step, 2,3-dihydro- N_6 -acyltryptamines (**8**) were led to the desired new N_6 -acyl-1-hydroxytryptamines (**9**) by the oxidation with $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ and 30% aqueous H_2O_2 in $\text{MeOH-H}_2\text{O}$. For example, **8a**, **8b**, **8c**, and **8d** produced 1-hydroxy- N_6 -propanoyl- (**9a**), - N_6 -pentanoyl- (**9b**), N_6 -heptanoyl-1-hydroxy- (**9c**), and 1-hydroxy- N_6 -nonanoyltryptamines (**9d**) in 67, 61, 68, and 61% yields, respectively. In the cases of **8e**, **8f**, and **8g**, N_6 -cyclopropanecarbonyl- (**9e**), N_6 -cyclohexanecarbonyl- (**9f**), and N_6 -2-furancarboxyl-1-hydroxytryptamines (**9g**) were obtained in 69, 62, and 64% yields, respectively.

Table 2. The Extent of Vascular Relaxation

Yohimbine: 100%			
9b	25.6 ± 6.0%	9d	79.0 ± 13%
7b	26.9 ± 11.4%	7d	80.7 ± 2.5%
9c	66.2 ± 13.9%	9e	15.7 ± 6.8%
7c	70.0 ± 6.9%	7e	21.4%

With the desired compounds in hand, we next evaluated the relaxant potencies of **7b-e** and **9b-e** as a preliminary test. The extent of the vascular relaxation produced in the muscle contracted with clonidine is summarized in Figure 1, making the activity of yohimbine as a standard for 100. It is interesting to

note that the activity increases depending on the length of N_6 -acyl side chain.^{5e,8} In addition, differences in activities are small between N(1)-H (**7b-e**) and N(1)-OH compounds (**9b-e**). These results strongly suggest that these simple tryptamine derivatives possess at least the antagonistic effect on vascular smooth muscle α_2 -AR.⁸ The potencies of **7d** and **9d** reached to about 80% of that of yohimbine. Furthermore, LD_{50} of **7d** was determined to be more than 80 mg/kg on ddy male mouse, showing its safety. The details will be reported elsewhere in due course.

In conclusion, we have succeeded in finding new leads for the treatment of ED. We named them SST-VED-I type compounds. In order to discover more potent α_2 -blocker, we are preparing tryptamines having various N_6 -side chain. The biological evaluation concerning cerebral infarction is now in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Shimadzu IR-420 and proton nuclear magnetic resonance

(¹H-NMR) spectra with a JEOL GSX-500 or JEOL JMS-AX5 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-SX102A instruments. Column chromatography was performed on silica gel (SiO₂, 100-200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

N₆-Propanoyltryptamine (7a) from Tryptamine (6) - General Procedure: Et₃N (1.89 mL, 13.6 mmol) and ClCO₂Me (1.05 mL, 1.36 mmol) were added to a solution of propanoic acid (912.7 mg, 12.3 mmol) in anhydrous CHCl₃ (30 mL), and the mixture was stirred at 0 °C for 30 min. To the resulting mixture, **6** (2.17 g, 13.6 mmol) was added and the mixture was stirred at rt for 30 min. After addition of H₂O the whole was extracted with CHCl₃-MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO₂ with EtOAc-hexane (1:1, v/v) to give **7a** (2.51 g, 94%). **7a**: mp 88-89 °C (colorless fine needles, recrystallized from Et₂O). IR (KBr): 3377, 1635, 1563, 1453, 1368, 1250 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.11 (3H, t, *J*=7.6 Hz), 2.14 (2H, q, *J*=7.6 Hz), 2.98 (2H, dt, *J*=6.6, 0.7 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.50 (1H, br s), 7.04 (1H, d, *J*=2.2 Hz), 7.13 (1H, ddd, *J*=7.8, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=7.8, 7.1, 1.2 Hz), 7.37 (1H, dt, *J*=7.8, 1.0 Hz), 7.61 (1H, ddd, *J*=7.8, 1.2, 0.7 Hz), 8.09 (1H, br s). *Anal.* Calcd for C₁₃H₁₆N₂O·1/8H₂O: C, 71.45; H, 7.50; N, 12.82. Found: C, 71.77; H, 7.34; N, 12.52.

N₆-Pentanoyltryptamine (7b) from 6 - In the general procedure for the synthesis of **7a**, Et₃N (1.57 mL, 11.3 mmol), ClCO₂Me (0.87 mL, 11.3 mmol), pentanoic acid (1.05 g, 10.3 mmol), anhydrous CHCl₃ (30 mL), and **6** (1.81 g, 11.3 mmol) were used. After the work-up and column-chromatography with EtOAc-hexane (2:3, v/v), **7b** (2.29 g, 91%) was obtained. **7b**: mp 93-94 °C (colorless powder, recrystallized from EtOAc-hexane). IR (KBr): 3377, 3237, 2927, 1630, 1561, 1450 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.26-1.34 (2H, m), 1.53-1.60 (2H, m), 2.11 (2H, t, *J*=7.5 Hz), 2.98 (2H, t, *J*=6.6 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.56 (1H, br s), 7.04 (1H, s), 7.13 (1H, ddd, *J*=7.9, 7.0, 0.9 Hz), 7.22 (1H, ddd, *J*=7.9, 7.0, 0.9 Hz), 7.38 (1H, dt, *J*=7.9, 0.9 Hz), 7.61 (1H, d, *J*=7.9 Hz), 8.09 (1H, br s). *Anal.* Calcd for C₁₅H₂₀N₂O: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.48; H, 8.23; N, 11.42.

N₆-Heptanoyltryptamine (7c) from 6 - In the general procedure for the synthesis of **7a**, Et₃N (1.19 mL, 8.58 mmol), ClCO₂Me (0.66 mL, 8.58 mmol), heptanoic acid (1.01 g, 7.80 mmol), anhydrous CHCl₃ (30 mL), and **6** (1.37 g, 8.58 mmol) were used. After the work-up and column-chromatography with CHCl₃ **7c** (2.02 g, 95%) was obtained. **7c**: mp 97-98 °C (colorless powder, recrystallized from EtOAc-hexane). IR (KBr): 3410, 1632, 1565, 1457, 1425 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.87 (3H, t, *J*=7.3 Hz), 1.21-1.31 (6H, m), 1.57 (2H, quint, *J*=7.5 Hz), 2.10 (2H, t, *J*=7.5 Hz), 2.98 (2H, t, *J*=6.6 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.52 (1H, br s), 7.04 (1H, d, *J*=2.2 Hz), 7.13 (1H, ddd, *J*=8.1, 7.0, 1.0 Hz), 7.22 (1H, ddd, *J*=8.1, 7.0, 1.0 Hz), 7.38 (1H, dt, *J*=8.1, 1.0 Hz), 7.61 (1H, d, *J*=8.1 Hz), 8.08 (1H, br s). *Anal.* Calcd for C₁₇H₂₄N₂O: C,

74.96; H, 8.88; N, 10.29. Found: C, 74.80; H, 8.92; N, 10.26.

N₆-Nonanoyltryptamine (7d) from 6 - In the general procedure for the synthesis of **7a**, Et₃N (0.99 mL, 7.09 mmol), ClCO₂Me (0.55 mL, 7.09 mmol), nonanoic acid (1.02 g, 6.45 mmol), anhydrous CHCl₃ (30 mL), and **6** (1.14 g, 7.09 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7d** (1.78 g, 93%) was obtained. **7d**: mp 101-102 °C (colorless fine needles, recrystallized from CHCl₃–hexane). IR (CHCl₃): 2950, 1652, 1506, 1165 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.87 (3H, t, *J*=7.0 Hz), 1.22-1.31 (10H, m), 1.57 (2H, br quint, *J*=7.0 Hz), 2.10 (2H, t, *J*=7.6 Hz), 2.98 (2H, t, *J*=6.7 Hz), 3.61 (2H, q, *J*=6.7 Hz, collapsed to t, *J*=6.7 Hz, on addition of D₂O), 5.52 (1H, br s, disappeared on addition of D₂O), 7.04 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.38 (1H, d, *J*=8.1 Hz), 7.61 (1H, d, *J*=8.1 Hz), 8.09 (1H, br s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₉H₂₈N₂O: C, 75.96; H, 9.39; N, 9.33. Found: C, 75.66; H, 9.49; N, 9.24.

N₆-Cyclopropanecarbonyltryptamine (7e) from 6 - In the general procedure for the synthesis of **7a**, Et₃N (1.81 mL, 13.0 mmol), ClCO₂Me (1.00 mL, 13.0 mmol), cyclopropanecarboxylic acid (1.12 g, 13.0 mmol), anhydrous CHCl₃ (30 mL), and **6** (1.89 g, 11.8 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7e** (2.29 g, 85%) was obtained. **7e**: mp 105.5-107 °C (colorless prisms, recrystallized from CHCl₃). IR (KBr): 3280, 1611, 1566, 1251, 1235, 1197, 754 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.69 (2H, td, *J*=7.9, 4.6 Hz), 0.97 (2H, dt, *J*=7.9, 4.6 Hz), 1.23 (1H, tt, *J*=7.9, 4.6 Hz), 2.99 (2H, t, *J*=6.8 Hz), 3.63 (2H, q, *J*=6.7 Hz, collapsed to t, *J*=6.7 Hz, on addition of D₂O), 5.69 (1H, br s, disappeared on addition of D₂O), 7.05 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz), 7.38 (1H, dt, *J*=8.1, 1.1 Hz), 7.61 (1H, br d, *J*=8.1 Hz), 8.12 (1H, br s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₄H₁₆N₂O: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.64; H, 7.09; N, 12.29.

N₆-Cyclohexanecarbonyltryptamine (7f) from 6 - In the general procedure for the synthesis of **7a**, Et₃N (1.16 mL, 8.34 mmol), ClCO₂Me (0.65 mL, 8.35 mmol), cyclohexanecarboxylic acid (1.07 g, 8.33 mmol), anhydrous CHCl₃ (25 mL), and **6** (1.21 g, 7.57 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7f** (1.25 g, 61%) was obtained. **7f**: mp 108.5-109 °C (colorless prisms, recrystallized from CHCl₃). IR (KBr): 3270, 2940, 1618, 1561, 1449, 1220, 748 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.15-1.26 (3H, m), 1.34-1.41 (2H, m), 1.65-1.81 (5H, m), 1.99 (1H, tt, *J*=11.7, 3.5 Hz), 2.97 (2H, t, *J*=6.8 Hz), 3.60 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz, on addition of D₂O), 5.52 (1H, br s, disappeared on addition of D₂O), 7.03 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.38 (1H, dt, *J*=8.1, 1.0 Hz), 7.61 (1H, br d, *J*=8.1 Hz), 8.10 (1H, br s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₇H₂₂N₂O: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.33; H, 8.26; N, 10.29.

N₆-2-Furancarboxyltryptamine (7g) from 6 - In the general procedure for the synthesis of **7a**, Et₃N

(1.30 mL, 9.34 mmol), ClCO₂Me (0.72 mL, 9.32 mmol), 2-furancarboxylic acid (1.04 g, 9.31 mmol), anhydrous CHCl₃ (30 mL), and **6** (1.21 g, 7.57 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:1, v/v), **7g** (1.33 g, 62%) was obtained. **7g**: mp 158-160 °C (colorless needles recrystallized from EtOAc). IR (KBr): 3255, 1613, 1592, 1533, 1315, 1303, 1192 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.28 (2H, t, *J*=6.8 Hz), 3.78 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz, on addition of D₂O), 6.47 (1H, br s, disappeared on addition of D₂O), 6.47 (1H, dd, *J*=3.5, 1.8 Hz), 7.08 (1H, s), 7.09 (1H, dd, *J*=3.5, 0.7 Hz), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.36 (1H, dd, *J*=1.8, 0.7 Hz), 7.38 (1H, dt, *J*=8.1, 1.0 Hz), 7.64 (1H, br d, *J*=8.1 Hz), 8.10 (1H, br s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.94; H, 5.62; N, 11.01.

2,3-Dihydro-N₆-propanoyltryptamine (8a) from 7a - General Procedure: A mixture of **7a** (1.02 g, 4.74 mmol) and Et₃SiH (1.89 mL, 11.9 mmol) in TFA (20 mL) was stirred at rt for 30 min. After evaporation of the solvent, the residue was made alkaline with 8% aqueous NaOH and extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH–28% aqueous NH₃ (46:1:0.1, v/v) to give **8a** (1.01 g, 98%). **8a**: yellow viscous oil. IR (film): 3315, 2970, 1635, 1606, 1547, 1486, 1461 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.13 (3H, t, *J*=7.5 Hz), 1.78 (1H, dtd, *J*=13.6, 7.9, 6.0 Hz), 2.00 (1H, dddd, *J*=13.6, 7.9, 7.0, 5.0 Hz), 2.16 (2H, q, *J*=7.5 Hz), 2.82 (1H, br s, disappeared on addition of D₂O), 3.26-3.42 (4H, m), 3.72 (1H, t, *J*=8.8 Hz), 5.62 (1H, br s, disappeared on addition of D₂O), 6.67 (1H, d, *J*=7.3 Hz), 6.75 (1H, td, *J*=7.3, 0.9 Hz), 7.05 (1H, br t, *J*=7.3 Hz), 7.10 (1H, d, *J*=7.3 Hz). HR-MS *m/z*: Calcd for C₁₃H₁₈N₂O: 218.1419. Found: 218.1431.

2,3-Dihydro-N₆-pentanoyltryptamine (8b) from 7b - In the general procedure for the synthesis of **8a**, **7b** (102.1 mg, 0.42 mmol), Et₃SiH (0.17 mL, 1.05 mmol), and TFA (3 mL) were used. After the work-up and column chromatography with the same eluent, **8b** (88.1 mg, 86%) was obtained. **8b**: yellow viscous oil. IR (film): 3290, 2930, 1640, 1605, 1552, 1484, 1461 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.91 (3H, t, *J*=7.5 Hz), 1.33 (2H, sex, *J*=7.5 Hz), 1.59 (2H, quint, *J*=7.5 Hz), 1.73 (1H, dtd, *J*=13.6, 8.0, 6.1 Hz), 1.99 (1H, dddd, *J*=13.6, 8.0, 7.0, 5.0 Hz), 2.13 (2H, t, *J*=7.5 Hz), 2.75 (1H, br s, disappeared on addition of D₂O), 3.27-3.42 (4H, m), 3.72 (1H, t, *J*=8.6 Hz), 5.60 (1H, br s, disappeared on addition of D₂O), 6.68 (1H, d, *J*=7.3 Hz), 6.75 (1H, td, *J*=7.3, 0.9 Hz), 7.05 (1H, br t, *J*=7.3 Hz), 7.11 (1H, d, *J*=7.3 Hz). HR-MS *m/z*: Calcd for C₁₅H₂₂N₂O: 246.1732. Found: 246.1743.

N₆-Heptanoyl-2,3-dihydrotryptamine (8c) from 7c- In the general procedure for the synthesis of **8a**, **7c** (1.04 g, 3.82 mmol), Et₃SiH (1.52 mL, 9.54 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8c** (912.7 mg, 87%) was obtained. **8c**: pale brown viscous oil. IR (film): 3310, 2960, 1634, 1606, 1544, 1484, 1461 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.88

(3H, t, $J=7.5$ Hz), 1.25-1.34 (6H, m), 1.60 (2H, quint, $J=7.5$ Hz), 1.78 (1H, dtd, $J=13.6, 7.9, 5.9$ Hz), 1.99 (1H, dddd, $J=13.6, 7.9, 7.1, 5.1$ Hz), 2.12 (2H, t, $J=7.7$ Hz), 2.68 (1H, br s, disappeared on addition of D_2O), 3.27-3.42 (4H, m), 3.72 (1H, t, $J=8.6$ Hz), 5.60 (1H, br s, disappeared on addition of D_2O), 6.68 (1H, d, $J=7.5$ Hz), 6.75 (1H, td, $J=7.5, 1.1$ Hz), 7.05 (1H, br t, $J=7.5$ Hz), 7.10 (1H, d, $J=7.5$ Hz). HR-MS m/z : Calcd for $C_{17}H_{26}N_2O$: 274.2045. Found: 274.2057.

2,3-Dihydro- N_6 -nonanoyltryptamine (8d) from 7d - In the general procedure for the synthesis of **8a**, **7d** (1.10 g, 3.65 mmol), Et_3SiH (1.45 mL, 9.10 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **8d** (862.4 mg, 78%) was obtained. **8d**: mp 41-42.5 °C (colorless powder recrystallized from EtOAc–hexane). IR (KBr): 3300, 2935, 2870, 1638, 1546, 1486, 1465 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 0.84 (3H, t, $J=7.0$ Hz), 1.20-1.27 (10H, m), 1.45-1.57 (3H, m), 1.83 (1H, dtd, $J=13.2, 7.6, 5.6$ Hz), 2.04 (2H, t, $J=7.5$ Hz), 3.05 (1H, ddd, $J=9.3, 8.1, 2.2$ Hz), 3.09-3.16 (3H, m), 3.54 (1H, td, $J=8.6, 1.7$ Hz), 5.40 (1H, br s, disappeared on addition of D_2O), 6.47 (1H, d, $J=7.5$ Hz), 6.52 (1H, td, $J=7.5, 0.7$ Hz), 6.90 (1H, br t, $J=7.5$ Hz), 7.00 (1H, d, $J=7.5$ Hz), 7.80 (1H, br t, $J=6.1$ Hz, disappeared on addition of D_2O). *Anal.* Calcd for $C_{19}H_{30}N_2O$: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.25; H, 10.16; N, 9.24.

N_6 -Cyclopropanecarbonyl-2,3-dihydrotryptamine (8e) from 7e - In the general procedure for the synthesis of **8a**, **7e** (137.3 mg, 0.60 mmol), Et_3SiH (0.24 mL, 1.51 mmol), and TFA (3 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8e** (116.3 mg, 84%) was obtained. **8e**: mp 41-42.5 °C (colorless powder, recrystallized from EtOAc). IR (KBr): 3310, 1621, 1605, 1543, 1490, 1258, 1240 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 0.60-0.67 (4H, m), 1.49-1.60 (2H, m), 1.86 (1H, dtd, $J=13.4, 7.6, 5.4$ Hz), 3.06 (1H, dd, $J=8.8, 7.8$ Hz), 3.12-3.17 (3H, m), 3.54 (1H, t, $J=8.8$ Hz), 5.41 (1H, br s, disappeared on addition of D_2O), 6.48 (1H, d, $J=7.6$ Hz), 6.53 (1H, td, $J=7.6, 1.0$ Hz), 6.90 (1H, br t, $J=7.6$ Hz), 7.01 (1H, d, $J=7.6$ Hz), 8.08 (1H, br t, $J=6.0$ Hz, disappeared on addition of D_2O). *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.81; H, 7.92; N, 11.88.

N_6 -Cyclohexanecarbonyl-2,3-dihydrotryptamine (8f) from 7f - In the general procedure for the synthesis of **8a**, **7f** (93.8 mg, 0.35 mmol), Et_3SiH (0.14 mL, 0.88 mmol), and TFA (1.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **8f** (68.7 mg, 73%) was obtained. **8f**: mp 109-111 °C (colorless plates, recrystallized from $CHCl_3$ –hexane). IR (KBr): 3290, 2930, 1622, 1545, 1536, 1464, 1252 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 1.16-1.29 (3H, m), 1.35-1.43 (2H, m), 1.65-1.68 (1H, m), 1.73-1.84 (4H, m), 1.95-2.05 (3H, m), 2.53 (1H, br s, disappeared on addition of D_2O), 3.26-3.41 (4H, m), 3.72 (1H, t, $J=8.5$ Hz), 5.60 (1H, br s, disappeared on addition of D_2O), 6.68 (1H, d, $J=7.3$ Hz), 6.75 (1H, td, $J=7.3, 0.9$ Hz), 7.05 (1H, br t, $J=7.3$ Hz), 7.11 (1H, d, $J=7.3$ Hz). *Anal.* Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.89; H, 8.96; N, 10.20.

N_6 -2-Furanecarbonyl-2,3-dihydrotryptamine (8g) from 7g - In the general procedure for the synthesis

of **8a**, **7g** (814.1 mg, 3.21 mmol), Et₃SiH (1.28 mL, 8.03 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8g** (794.3 mg, 97%) was obtained. **8g**: colorless viscous oil. IR (CHCl₃): 3275, 1651, 1592, 1515, 1475, 1285 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.87 (1H, dtd, *J*=13.7, 7.9, 6.0 Hz), 2.10 (1H, dtd, *J*=13.7, 7.9, 5.1 Hz), 3.33 (1H, dd, *J*=8.8, 6.3 Hz), 3.37-3.43 (1H, m), 3.47 (1H, dtd, *J*=13.7, 7.9, 6.3 Hz collapsed to dt, *J*=13.7, 7.9 Hz, on addition of D₂O), 3.57 (1H, ddt, *J*=13.7, 7.9, 6.3 Hz collapsed to ddd, *J*=13.7, 7.9, 6.3 Hz, on addition of D₂O), 3.75 (1H, t, *J*=8.8 Hz), 6.49 (1H, dd, *J*=3.5, 1.8 Hz), 6.54 (1H, br s, disappeared on addition of D₂O), 6.69 (1H, d, *J*=7.5 Hz), 6.76 (1H, td, *J*=7.5, 1.0 Hz), 7.05 (1H, br t, *J*=7.5 Hz), 7.09 (1H, dd, *J*=3.5, 0.8 Hz), 7.13 (1H, d, *J*=7.5 Hz), 7.42 (1H, dd, *J*=1.8, 0.8 Hz). HR-MS *m/z*: Calcd for C₁₅H₁₆N₂O₂: 256.1211. Found: 256.1214.

1-Hydroxy-N₆-propanoyltryptamine (9a) from 8a - General Procedure: A solution of 30% aqueous H₂O₂ (1.11 g, 9.80 mmol) in MeOH (3 mL) was added with stirring to a solution of **8a** (211.8 mg, 0.97 mmol) and Na₂WO₄·2H₂O (64.1 mg, 0.19 mmol) in MeOH (7 mL) and H₂O (1 mL) under ice cooling. Stirring was continued at rt for 15 min. After addition of H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1, v/v) to give **9a** (150.2 mg, 67%). **9a**: mp 132-133 °C (colorless fine prisms, recrystallized from CHCl₃). IR (KBr): 3290, 3100, 2935, 1598, 1566, 1352 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.99 (3H, t, *J*=7.6 Hz), 2.06 (2H, q, *J*=7.6 Hz), 2.79 (2H, t, *J*=7.3 Hz), 3.30 (2H, td, *J*=7.3, 6.1 Hz, collapsed to t, *J*=7.3 Hz, on addition of D₂O), 6.98 (1H, dd, *J*=8.0, 7.3 Hz), 7.13 (1H, dd, *J*=8.0, 7.3 Hz), 7.24 (1H, s), 7.32 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=8.0 Hz), 7.84 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.01 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.94; H, 6.95; N, 12.02.

1-Hydroxy-N₆-pentanoyltryptamine (9b) from 8b - In the general procedure for the synthesis of **9a**, 30% aqueous H₂O₂ (2.37 g, 20.9 mmol), MeOH (5 mL), **8b** (513.3 mg, 2.09 mmol), Na₂WO₄·2H₂O (138.0 mg, 0.42 mmol), MeOH (20 mL), and H₂O (2.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **9b** (331.2 mg, 61%) was obtained. **9b**: mp 114.5-115 °C (colorless powder, recrystallized from CHCl₃). IR (CHCl₃): 3125, 2922, 1649, 1513 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.86 (3H, t, *J*=7.4 Hz), 1.25 (2H, sex, *J*=7.4 Hz), 1.47 (2H, quint, *J*=7.4 Hz), 2.05 (2H, t, *J*=7.4 Hz), 2.78 (2H, t, *J*=7.4 Hz), 3.30 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of D₂O), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.23 (1H, s), 7.32 (1H, d, *J*=8.1 Hz), 7.53 (1H, d, *J*=8.1 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.00 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₅H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.17; H, 7.70; N, 10.68.

N₆-Heptanoyl-1-hydroxytryptamine (9c) from 8c - In the general procedure for the synthesis of **9a**, 30% aqueous H₂O₂ (461.4 mg, 4.07 mmol), MeOH (1 mL), **8c** (111.3 mg, 0.41 mmol), Na₂WO₄·2H₂O (27.3 mg, 0.08 mmol), MeOH (4 mL), and H₂O (0.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **9c** (79.8 mg, 68%) was obtained. **9c**: mp 83-83.5 °C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 3280, 2930, 1601, 1555, 1435, 1358, 1241 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.86 (3H, t, *J*=7.5 Hz), 1.21-1.29 (6H, m), 1.47 (2H, quint, *J*=7.5 Hz), 2.04 (2H, t, *J*=7.5 Hz), 2.78 (2H, t, *J*=7.5 Hz), 3.29 (2H, td, *J*=7.5, 6.1 Hz, collapsed to t, *J*=7.5 Hz, on addition of D₂O), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.24 (1H, s), 7.32 (1H, dt, *J*=8.1, 1.0 Hz), 7.52 (1H, dt, *J*=8.1, 1.0 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.00 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₇H₂₄N₂O₂: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.73; H, 8.40; N, 9.64.

1-Hydroxy-N₆-nonanoyltryptamine (9d) from 8d - In the general procedure for the synthesis of **9a**, 30% aqueous H₂O₂ (451.3 mg, 3.98 mmol), MeOH (1 mL), **8d** (119.3 mg, 0.40 mmol), Na₂WO₄·2H₂O (26.7 mg, 0.08 mmol), MeOH (4 mL), and H₂O (0.5 mL) were used. After the work-up and column chromatography with CHCl₃–MeOH (99:1, v/v), **9d** (75.8 mg, 61%) was obtained. **9d**: mp 82.5-83 °C (colorless powder, recrystallized from CHCl₃–hexane). IR (CHCl₃): 3155, 2915, 1648, 1510, 1457 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.86 (3H, t, *J*=7.4 Hz), 1.15-1.30 (10H, m), 1.47 (2H, quint, *J*=7.4 Hz), 2.03 (2H, t, *J*=7.4 Hz), 2.78 (2H, t, *J*=7.4 Hz), 3.30 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of D₂O), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.24 (1H, s), 7.32 (1H, d, *J*=8.1 Hz), 7.52 (1H, d, *J*=8.1 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.01 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₉H₂₈N₂O₂: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.09; H, 8.96; N, 8.85.

N₆-Cyclopropanecarbonyl-1-hydroxytryptamine (9e) from 8e - In the general procedure for the synthesis of **9a**, 30% aqueous H₂O₂ (498.0 mg, 4.39 mmol), MeOH (1 mL), **8e** (101.6 mg, 0.44 mmol), Na₂WO₄·2H₂O (29.2 mg, 0.09 mmol), MeOH (4 mL), and H₂O (0.5 mL) were used. After the work-up and column chromatography with CHCl₃–MeOH (99:1, v/v), **9e** (74.6 mg, 69%) was obtained. **9e**: mp 155-158 °C (colorless prisms, recrystallized from EtOAc). IR (KBr): 3290, 3140, 2955, 1580, 1494, 1450, 1412, 1356, 1248, 1240, 1205 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.60-0.69 (4H, m), 1.49-1.54 (1H, m), 2.80 (2H, t, *J*=7.4 Hz), 3.32 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of D₂O), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.25 (1H, s), 7.32 (1H, dt, *J*=8.1, 1.0 Hz), 7.53 (1H, dt, *J*=8.1, 1.0 Hz), 8.15 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.03 (1H, br s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₄H₁₆N₂O₂: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.84; H, 6.57; N, 11.45.

N₆-Cyclohexanecarbonyl-1-hydroxytryptamine (9f) from 8f - In the general procedure for the

synthesis of **9a**, 30% aqueous H₂O₂ (1.91 g, 16.8 mmol), MeOH (5 mL), **8f** (457.3 mg, 1.68 mmol), Na₂WO₄·2H₂O (112.7 mg, 0.34 mmol), MeOH (20 mL), and H₂O (2.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:3, v/v), **9f** (297.9 mg, 62%) was obtained. **9f**: mp 138.5-140 °C (colorless fine needles, recrystallized from EtOAc–hexane). IR (KBr): 2940, 1628, 1535, 1448, 1368 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 1.09-1.24 (3H, m), 1.28-1.36 (2H, m), 1.59-1.71 (5H, m), 2.06 (1H, tt, *J*=11.7, 3.4 Hz), 2.77 (2H, t, *J*=7.3 Hz), 3.28 (2H, br q, *J*=7.3 Hz, collapsed to t, *J*=7.3 Hz, on addition of D₂O), 6.98 (1H, t, *J*=8.0 Hz), 7.12 (1H, t, *J*=8.0 Hz), 7.22 (1H, s), 7.31 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=8.0 Hz), 7.77 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.01 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₇H₂₂N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.79; N, 9.75.

N₆-2-Furancarboxyl-1-hydroxytryptamine (9g) from 8g - In the general procedure for the synthesis of **9a**, 30% aqueous H₂O₂ (2.94 g, 25.9 mmol), MeOH (5 mL), **8g** (696.9 mg, 2.58 mmol), Na₂WO₄·2H₂O (171.0 mg, 0.52 mmol), MeOH (25 mL), and H₂O (3 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **9g** (467.2 mg, 64%) was obtained. **9g**: mp 167-168 °C (decomp., colorless fine needles, recrystallized from CHCl₃–hexane). IR (KBr): 3680, 3120, 2950, 1628, 1598, 1531, 1317, 1187 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.90 (2H, t, *J*=7.5 Hz), 3.49 (2H, td, *J*=7.5, 6.1 Hz, collapsed to t, *J*=7.5 Hz, on addition of D₂O), 6.60 (1H, dd, *J*=3.4, 2.0 Hz), 6.98 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.06 (1H, dd, *J*=3.4, 0.7 Hz), 7.13 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.28 (1H, s), 7.32 (1H, d, *J*=8.0 Hz), 7.57 (1H, d, *J*=8.0 Hz), 7.80 (1H, dd, *J*=2.0, 0.7 Hz), 8.45 (1H, br t, *J*=6.1 Hz, disappeared on addition of D₂O), 11.02 (1H, s, disappeared on addition of D₂O). *Anal.* Calcd for C₁₅H₁₄N₂O₃: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.63; H, 5.21; N, 10.36.

REFERENCES AND NOTES

1. This report is part 135 of a series entitled "The Chemistry of Indoles." Part 134: K. Yamada, F. Yamada, T. Shiraishi, S. Tomioka, and M. Somei, *Heterocycles*, 2009, **77**, 971.
2. J. Cartledge and I. Eardley, *Expert Opin. Pharmacother.*, 1999, **1**, 137; K. Shigenobu, *Chemistry*, 2005, **60**, 14.
3. L. E. Saxton, *The Alkaloids*, Vol. 7, ed. by R. H. F. Manske, Academic Press, USA, 1960, pp. 1-199, 1960; E. Ernst and M. H. Pittler, *J. Urol.*, 1998, **159**, 433.
4. M. Somei, T. Iwaki, F. Yamada, Y. Tanaka, K. Shigenobu, K. Koike, N. Suzuki, and A. Hattori, *Heterocycles*, 2006, **68**, 1565.
5. a) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251. b) M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205. c) M. Somei, *Heterocycles*, 1999, **50**, 1157. d) M. Somei, *Advances in Heterocyclic Chemistry*, Vol. 82, ed. by A. R. Katritzky, Elsevier Science, USA, 2002, pp. 101-155. e) M. Somei,

Topics in Heterocyclic Chemistry, Vol. 6, ed. by S. Eguchi, Springer-Verlag, Berlin, 2006, pp. 77-111. f) M. Somei, [Yakugaku Zasshi, 2008, 128, 527](#).

6. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, [Heterocycles, 1996, 43, 1855](#).
7. M. Somei, JP Patent, 3795093 (2006).
8. M. Somei, K. Shigenobu, and Y. Tanaka, JP Patent, 3964417 (2007).