

SYNTHESES OF 1-HYDROXYTRYPTAMINES AND SEROTONINS HAVING FATTYAC-
YL OR (*E*)-3-PHENYLPROPENOYL DERIVATIVES AS A *Nb*-SUBSTITUENT, AND A
NOVEL HOMOLOGATION ON THE 3-SUBSTITUENT OF THE 1-HYDROXYTRYPTA-
MINES UPON TREATMENT WITH DIAZOMETHANE¹

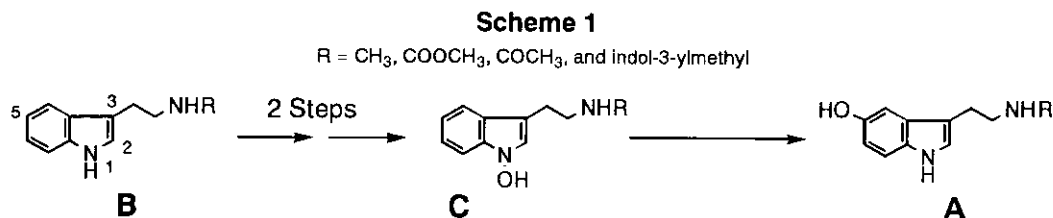
Masanori Somei, * Harunobu Morikawa, Koji Yamada, and Fumio Yamada

Faculty of Pharmaceutical Sciences, Kanazawa University,

13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract——— 1-Hydroxytryptamines (**6a-f**) having (*E*)-3-phenyl-, (*E*)-3-(4-hydroxyphenyl)-, (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoyl, octanoyl, hexadecanoyl, and docosanoyl group as a *Nb*-substituent are prepared for the first time. Preparations of serotoninins (**2a-c, e**) from the corresponding 1-hydroxytryptamines (**6a-c, e**) are also reported. A novel homologation on the 3-substituent of 1-hydroxytryptamines is discovered upon treatment with diazomethane in chloroform or dichloromethane.

Serotoninins (**A**) and tryptamines (**B**) are biologically important amines.² As shown in Scheme 1, we have chemically correlated^{2d} **A** with **B** through 1-hydroxytryptamines² (**C**) as the intermediates which undergo nucleophilic substitution reactions selectively at the 5-position.² Whether the reaction pathway is operating *in vivo* still remains to be investigated.^{2a,b} We have also discovered that 1-hydroxyindoles have potent anti-blood platelet aggregation activity.³



On the other hand, *Nb*-fattyacyltryptamine derivatives (**1**, Scheme 2) were isolated from the seeds of *Annona reticulata* by Maeda and co-workers.⁴ Sakakibara and co-workers reported serotonin derivatives (**2a,b**) as antioxidants from sunflower (*Carthamus tinctorius* L.) oil cake.⁵ These facts prompted us to design both 1-hydroxytrypta-

fluoroacetic acid (TFA) afforded 2,3-dihydroindoles (**5d-f**) in 96, 98 and 91% yields, respectively. Subsequent 1-hydroxyindole syntheses from **5d-f** by the reaction with $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ and 30% H_2O_2 ^{2,7} were successfully realized by changing the original solvent system^{2,7} ($\text{MeOH-H}_2\text{O}$) to $\text{CHCl}_3\text{-MeOH-H}_2\text{O}$ resulting in the formation of **6d-f** in 77, 62, and 79% yields, respectively. Similarly, (*E*)-*Nb*-3-(4-hydroxyphenyl)- (**4a**), (*E*)-3-(4-hydroxy-3-methoxyphenyl)- (**4b**), and (*E*)-3-phenylpropenyltryptamine (**4c**) were produced in 71, 73, and 97% yields, respectively. Although their reduction with Et_3SiH in TFA gave poor results, NaBH_3CN ⁸ in AcOH was the reagent of choice to produce **5a-c** in 85, 82, and 83% yields, respectively. In the cases of **5a-c**, application of 1-hydroxyindole syntheses with $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ and 30% H_2O_2 in $\text{MeOH-H}_2\text{O}$ was successful giving **6a-c** in 57, 44, and 63% yields, respectively.

The expected regioselective nucleophilic substitution took place in the reaction of **6e** with 85% HCOOH ^{2,7} at room temperature to afford *Nb*-hexadecanoylserotonin (**2e**) and its 1-formyl derivative (**7e**) in 42 and 22% yields, respectively. Similar reaction of **6c** produced **2c** and **7c** in the respective yields of 33 and 8%. Syntheses of natural products (**2a** and **2b**) were attained in 5 and 16% yields, respectively, by the treatment of **6a** and **6b** with 85% HCOOH , though the optimum reaction conditions are not made yet.

The structures of **2a** and **2b** were proved unequivocally by direct comparison with the authentic samples which were obtained in 79 and 99% yields, respectively, by reacting authentic serotonin (**2g**), prepared according to our procedure,^{2d} with (*E*)-3-(4-hydroxyphenyl)- and (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoic acid in the presence of DCC and 1-hydroxybenzotriazole.

Generally, the structure of 1-hydroxyindole is confirmed by converting it to the corresponding 1-methoxyindole by the reaction with CH_2N_2 in MeOH. Since the solubility of **6e** in MeOH was poor, it reacted in CH_2Cl_2 at room temperature. Unexpectedly, generation of an abnormal product (**9e**) was observed in 23% yield in addition to 62% yield of the normal 1-methoxyindole (**8e**). Abnormal products were similarly observed in the reactions of **6d**, **6f**, and **6h** with CH_2N_2 in CHCl_3 or CH_2Cl_2 . For example, the reaction of **6h** in CHCl_3 produced **8h**, **9h**, and two unknown products (molecular weights are 230 and 269, respectively) in the respective yields of 36, 9, 15, and 5% yields. In MeOH, however, all compounds (**6d**, **6e**, **6f**, and **6h**) afforded normal products (**8d**, **8e**, **8f**, and **8h**), exclusively.

The structures of **9d-f, h** were proved as follows. As a representative of abnormal products, **9h** was catalytically hydrogenated with 10% Pd/C to remove 1-methoxy group giving **10** in a quantitative yield. Reduction of **10** with LiAlH_4 afforded *N*-ethyl-3-(indol-3-yl)propylamine (**11**) in 64% yield. On the other hand, authentic 3-indolepropionic acid (**12**) led to the corresponding ethylamide (**13**) in 98% yield by the mixed anhydride method using methyl chloroformate and ethylamine. Subsequent reduction of **13** with LiAlH_4 produced 91% yield of the

authentic **11**, which was identical with the sample derived from **9h**.

It should be noted that the attempted reactions of both **4e** and **4h** with CH_2N_2 in CHCl_3 did not produce **10e** and **10h** even in a trace amount and unreacted starting materials were recovered quantitatively. Under similar reaction conditions, neither **8e** nor **8h** formed **9e** or **9h**, respectively, and quantitative recoveries of unreacted starting materials were observed in both cases. These facts clearly indicate that the side chain homologation is characteristic to 1-hydroxyindole structure, though the reaction mechanism is so far unknown. We are now intensely pursuing the structure determination of other two unknown products isolated in the reaction of **6h** hoping for obtaining a clue to clarify the reaction mechanism.

Biological evaluations of new 1-hydroxytryptamines and serotoninins are in progress.

REFERENCES AND NOTES

1. This report is Part 87 of a series entitled "The Chemistry of Indoles." Part 86: M. Somei, F. Yamada, and G. Yamamura, *Chem. Pharm. Bull.*, 1998, **46**, 191. All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or oils, respectively. **2a**) oil; **2b**) mp 112.0-116.5°C (CHCl_3 -MeOH); **2c**) oil; **2e**) mp 114.0-117.0°C (EtOAc); **4a**) mp 170.0-175.0°C (CHCl_3 -MeOH); **4b**) mp 166.0-167.0°C (CH_2Cl_2 -MeOH); **4c**) mp 140.0-141.0°C (CH_2Cl_2); **4d**) mp 100.0-101.0°C (CHCl_3 -hexane); **4e**) mp 115.0-116.0°C (MeOH); **4f**) mp 121.0-122.0°C (CHCl_3 -MeOH, lit.,⁴ mp 121-123°C); **5a**) oil; **5b**) mp 78.0-85.0°C (CHCl_3); **5c**) mp 132.5-133.0°C (MeOH); **5d**) oil; **5e**) mp 85.0-87.0°C (MeOH); **5f**) mp 95.0-100.0°C (CHCl_3 -MeOH); **6a**) oil; **6b**) oil; **6c**) mp 163.0-164.0°C (MeOH); **6d**) mp 96.0-97.0°C (EtOAc-hexane); **6e**) mp 77.0-78.0°C (MeOH); **6f**) mp 78.0-83.0°C (CHCl_3 -MeOH); **7c**) oil; **7e**) mp 114.0-115.0°C (EtOAc); **8c**) mp 91.0-95.0°C (CH_2Cl_2); **8d**) oil; **8e**) mp 84.0-86.5°C (CH_2Cl_2 -hexane); **8f**) mp 95.0-97.0°C (CHCl_3 -hexane); **9e**) mp 99.0-101.0°C (CH_2Cl_2 -hexane); **9h**) oil; **10e**) mp 140.0-145.0°C (MeOH); **10h**) mp 180.0-182.0°C (CHCl_3 -MeOH); **11**) mp 110.0-112.0°C (CHCl_3 -hexane); **13**) oil.
2. a) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877; b) M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; c) M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, and M. Somei, *ibid.*, 1996, **43**, 2333; d) M. Somei, F. Yamada, and H. Morikawa, *ibid.*, 1997, **46**, 91 and references cited therein.
3. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, *Heterocycles*, 1996, **43**, 1855.
4. U. Maeda, N. Hara, Y. Fujimoto, A. Srivastava, Y. K. Gupta, and M. Sahai, *Phytochemistry*, 1993, **34**, 1633.
5. H. L. Zhang, H. Kajitani, A. Nagatsu, and J. Sakakibara, Abstracts of Papers, 115th Annual Meeting of Pharmaceutical Society of Japan, Sendai, March 1995, No. 2, p. 216.
6. A. E. Lanzilotti, R. Littell, W. J. Fanshawe, T. C. McKenzie, and F. M. Lovell, *J. Org. Chem.*, 1979, **44**, 4809.
7. M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; Review: M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205 and references cited therein.
8. G. W. Gribble and J. H. Hoffman, *Synthesis*, 1977, 859; M. E. Flaugh, D. L. Mullen, R. W. Fuller, and N. R. Mason, *J. Med. Chem.*, 1988, **31**, 1746.

Received, 5th March, 1998