SYNTHESES OF 1-HYDROXYTRYPTAMINES AND SEROTONINS HAVING FATTYACYL OR (*E*)-3-PHENYLPROPENOYL DERIVATIVES AS A *Nb*-SUBSTITUENT, AND A NOVEL HOMOLOGATION ON THE 3-SUBSTITUENT OF THE 1-HYDROXYTRYPTAMINES UPON TREATMENT WITH DIAZOMETHANE[1]

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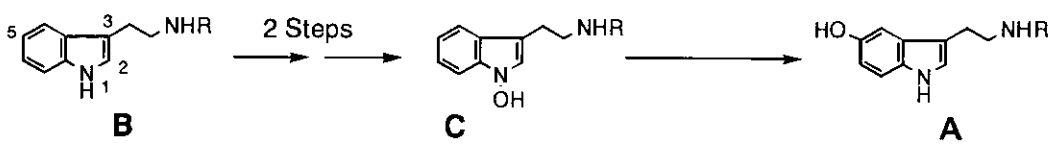
Abstract——— 1-Hydroxytryptamines (**6a-f**) having (*E*)-3-phenyl-, (*E*)-3-(4-hydroxyphenyl)-, (*E*)-3-(4-hydroxy-3-methoxyphenyl)propenoyl, octanoyl, hexadecanoyl, and docosanoyl group as a *Nb*-substituent are prepared for the first time. Preparations of serotonins (**2a-c**, **e**) from the corresponding 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.

Serotonins (**A**) and tryptamines (**B**) are biologically important amines.[2] As shown in Scheme 1, we have chemically correlated[2d] **A** with **B** through 1-hydroxytryptamines[2] (**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]

Scheme 1

R = CH_3, $COOCH_3$, $COCH_3$, and indol-3-ylmethyl



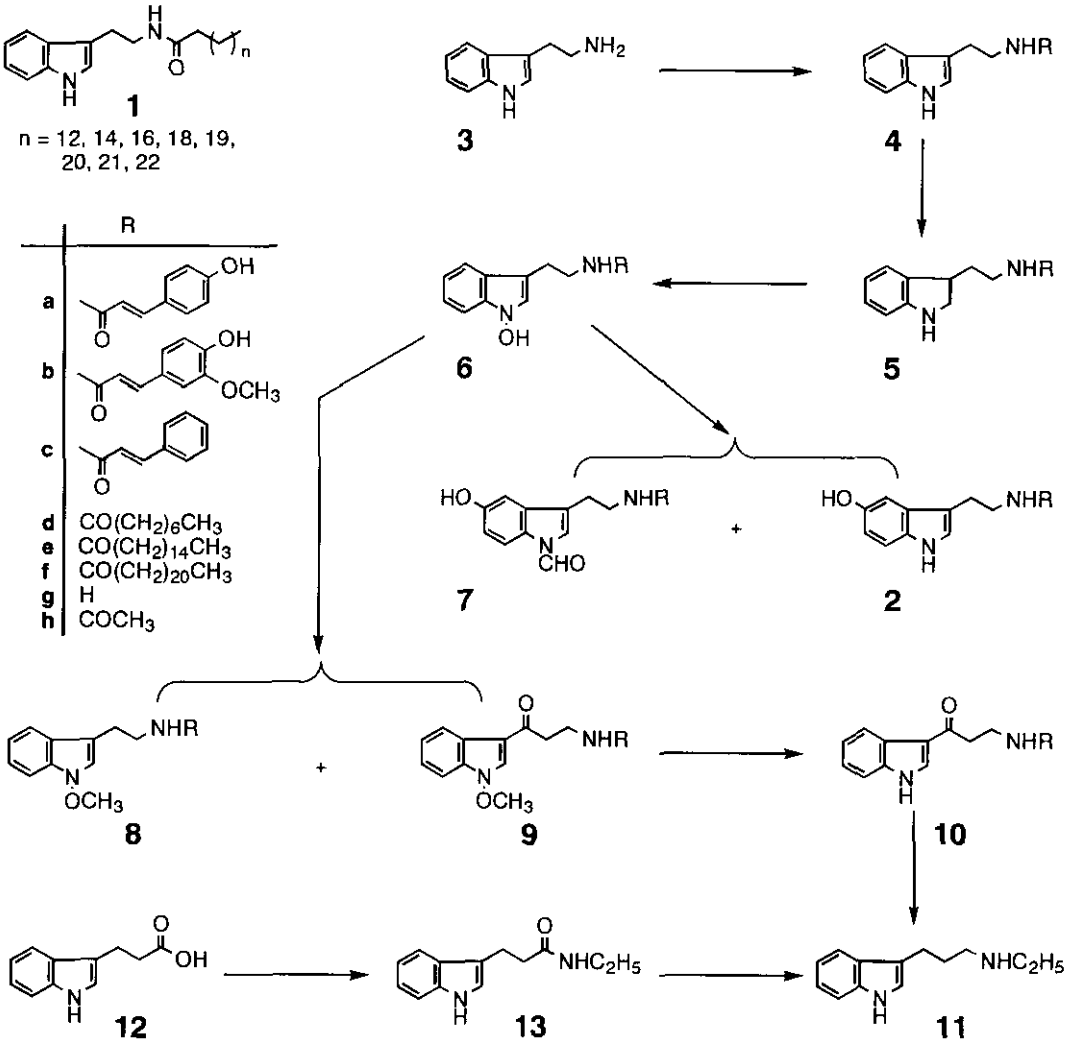
On the other hand, *Nb*-fattyacyltryptamine derivatives (**1**, Scheme 2) were isolated from the seeds of *Annona reticulata* by Maeda and co-workers.[4] Sakakibara and co-workers reported serotonin derivatives (**2a**,**b**) as antioxidants from sufflower (*Carthamus tinctorius L.*) oil cake.[5] These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

mines (**6a-f**) and serotonins (**2a-c, e**) having fattyacyl or (*E*)-3-phenylpropenoyl derivatives as a *Nb*-substituent in order to develop a new inhibitor of blood platelet aggregation. Furthermore, an interesting theme is to determine whether the above synthetic methodology shown in Scheme 1 is applicable for their preparations without forming kabutanes and dimers.[2c]

Now, we wish to report syntheses of the target compounds and also describe a new homologation on the side chain at the 3-position upon treatment with CH_2N_2 which is characteristic to 1-hydroxyindole structure.

The reaction of tryptamine (**3**) with octanoic chloride, hexadecanoic chloride, and docosanoic anhydride afforded the corresponding amides (**4d-f**) in 48, 95, and 92% yields, respectively. Reduction of **4d-f** with Et_3SiH[6] in tri-

Scheme 2



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 $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2[2,7] were successfully realized by changing the original solvent system[2,7] (*MeOH-H*$_2$*O*) to *CHCl*$_3$-*MeOH-H*$_2$*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-phenylpropenoyltryptamine (**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 $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 in MeOH-H_2O 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 sofar 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 serotonins 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.
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