PREPARATIONS OF 1-HYDROXYINDOLE DERIVATIVES AND THEIR POTENT INHIBITORY ACTIVITIES ON PLATELET AGGREGATION[1]

Masanori Somei,* Koji Yamada, Masakazu Hasegawa, Mutsuko Tabata, Yoshiyuki Nagahama, Harunobu Morikawa, and Fumio Yamada

Faculty of Pharmaceutical Sciences, Kanazawa University,

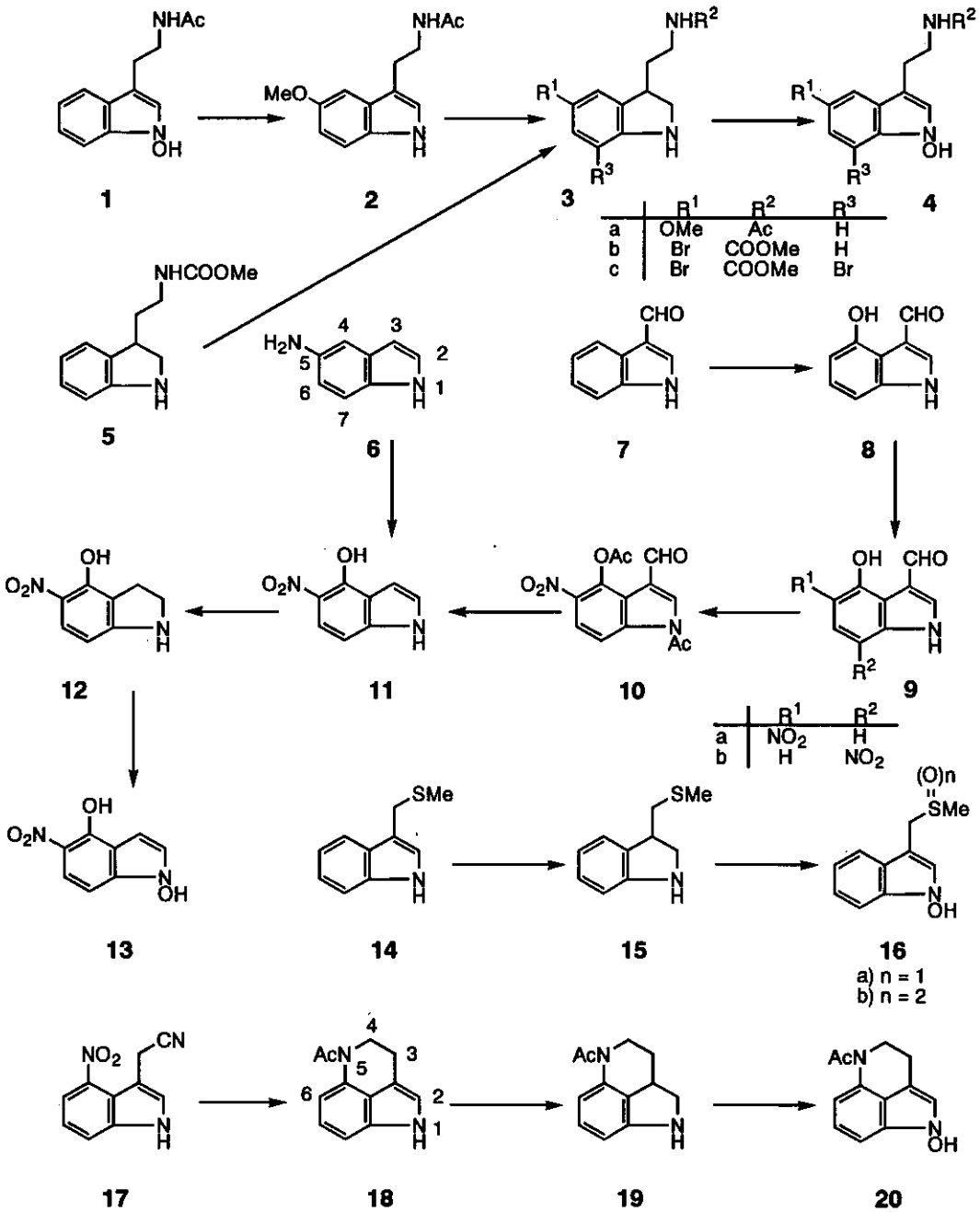
13-1 Takara-machi, Kanazawa 920, Japan

Abstract —— 1-Hydroxymelatonin, 5-bromo- and 5,7-dibromo-1-hydroxytryptamine derivatives, 1,4-dihydroxy-5-nitroindole, 1-hydroxy-3-methylsulfinylmethylindole, and 5-acetyl-1,3,4,5-tetrahydro-1-hydroxypyrrolo[4,3,2-*de*]quinoline were synthesized for the first time. 1-Hydroxyindoles revealed potent inhibitory activities on platelet aggregation.

We have established simple synthesis method[2a] for 1-hydroxyindole derivatives. Stabilities of 1-hydroxyindoles depend on their structures.[2b] In order to determine factors governing their stabilities and to develop new biologically active lead compounds, we have attempted preparations of 1-hydroxyindoles having either a substituent in the benzene ring or a sulfur containing side chain at the 3-position.

Melatonin (**2**, *Scheme* 1) *has recently attracted much attention because of their remarkable biological activities.*[3] We therefore aimed at the synthesis of 1-hydroxymelatonin (**4a**) and bromine containing 1-hydroxytryptamines expecting them to be lead compounds as well as building blocks for various derivatives. As for melatonin synthesis,[4] we have now endeavored in raising its yield up to 80% by reacting *N*b-acetyl-1-hydroxytryptamine[2] (**1**) with BF_3-MeOH complex in refluxing MeOH. Then **2** was reduced to 2,3-dihydroindole (**3a**) with triethylsilane (Et_3SiH) and trifluoroacetic acid (TFA) in 86% yield. Subsequent oxidation[2a] of **3a** with sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) and 30% hydrogen peroxide (H_2O_2) afforded the desired **4a** in 28% yield. While, bromination of 2,3-dihydro-*N*b-methoxycarbonyltryptamine (**5**) with bromine in acetic acid (AcOH) generated monobromo (**3b**) and dibromo (**3c**) compounds in 61 and 30% yields, respectively. Oxidation of **3b** and **3c** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 produced the corresponding 1-hydroxytryptamines (**4b**) and (**4c**), in 57 and 51% yields, respectively.

Scheme 1

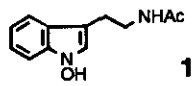
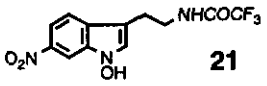
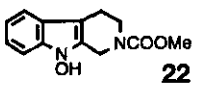
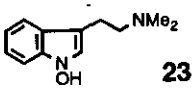
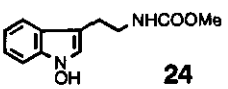
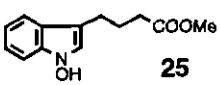
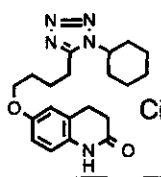


For the preparation of 1,4-dihydroxy-5-nitroindole (**13**), 4-hydroxy-5-nitroindole[5] (**11**) was required as a starting material. Although we reported its formation[5] by the oxidation of 5-aminoindole (**6**) with *m*-chloroperbenzoic acid (MCPBA) in acetone, the yield was miserable (4%). We have thus far examined *in vain* various oxidative reagents and reaction conditions to increase the yield. Therefore, we tried to develop an alternative synthesis method for **11**. First, we have improved the reaction[6] for obtaining 4-hydroxyindole-3-carboxaldehyde (**8**) from indole-3-

carboxaldehyde (**7**). The yield is now increased to 70% with good reproducibility employing thallation with thallium tris(trifluoroacetate) and subsequent treatment of the resultant thallium compound with cupric sulfate pentahydrate (2 mol eq.) in *N,N*-dimethylformamide and H_2O at 120-130°C. Nitration of **8** with cupric nitrate and acetic anhydride (Ac_2O) produced 5-nitro (**9a**) and 7-nitro (**9b**) compounds in 45 and 46% yields, respectively. Since direct conversion of **9a** to **11** was unsuccessful, **9a** was transformed to diacetyl compound (**10**) in 82% yield by treatment with refluxing Ac_2O. Oxidation of 3-formyl group of **10** to carboxyl group with sodium chlorite, and subsequent treatment with 1N aqeuous sodium hydroxide caused hydrolysis and simultaneous decarboxylation to afford **11** in 90% yield. The reduction of **11** with Et_3SiH and TFA afforded **12** in 91% yield. Subsequent oxidation of **12** with MCPBA (3 mol eq.) afforded the desired **13** in 66% yield, whereas with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 only 14% yield of **13** was produced.

1-Hydroxy-3-methylsulfinylmethylindole (**16a**) was prepared as follows. 3-Methylthiomethylindole (**14**) was first prepared in 80% yield by reacting gramine with sodium methyl sulfide. Reduction of **14** with sodium cyanoborohydride ($NaBH_3CN$) in AcOH successfully generated 2,3-dihydroindole (**15**) in 55% yield.

Table 1. Effects of 1-Hydroxyindoles on Arachidonic Acid Induced Platelet Aggregation in Rabbit PRP

Compound	IC 50 (μM)	Inhibition Percent of Control Platelet Aggregation				
		10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4} (M)
 **1**	3.10	-	-	2.2	92.1	93.5
 **21**	3.31	-	-	2.3	94.0	94.7
 **22**	1.00	-	-	51.4	94.9	94.2
 **23**	2.90	-	-	11.3	95.1	95.8
 **24**	0.32	1.5	6.2	93.3	92.3	92.3
 **25**	0.32	2.9	4.4	94.1	89.7	92.6
 Cilostazol	3.10	-	-	7.1	94.3	92.9

Subsequent oxidation of **15** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 produced **16a** in 27% yield. Concomitant formation of unstable 1-hydroxy-3-methylsulfonylmethylindole (**16b**) is confirmed as a 1-methoxy derivative but its isolation is still unsuccessful.

Since 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline is a mother skeleton of biologically active marine alkaloids,[7] we have interested in the synthesis of 5-acetyl-1,3,4,5-tetrahydro-1-hydroxypyrrolo[4,3,2-*de*]quinoline (**20**). 5-Acetyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**18**) is readily available from 4-nitroindole-3-acetonitrile (**17**).[7] So, **18** was reduced with $NaBH_3CN$ in AcOH and TFA to afford 90% yield of 2,3-dihydroindole (**19**). Oxidation of **19** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 produced the desired **20** in 69% yield.

With various 1-hydroxyindoles in hand,[2,9] biological evaluations of some stable 1-hydroxytryptamines and related derivatives were carried out. As can be seen from Table 1, all of the tested compounds showed inhibition on arachidonic acid induced platelet aggregation in rabbit PRP as expected.[9] Among them, the effects of **1**, **21**, **22**, and **23** were equivalent to, while **24** and **25** showed more potent effects than that of the reference medicine, cilostazol. Biological evaluations of compounds described in the present reports are in progress.

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REFERENCES AND NOTES

1. This is Part 78 of a series entitled "The Chemistry of Indoles". Part 77: M. Somei, H. Hayashi, and S. Ohmoto, *Heterocycles*, 1997, **44**, (No. 1), in press. All new compounds gave satisfactory spectral data and elemental analyses for crystals or high resolution mass spectral data for oils. **3a**) oil; **3b**) oil; **3c**) oil; **4a**) oil; **4b**) mp 111.5-113.0°C; **4c**) mp 117.5-118.5°C; **9a**) mp 260°C (decomp.); **9b**) mp 261°C (decomp.); **10**) mp 171°C (sharp); **12**) mp 132-133°C; **13**) mp 194-200°C (decomp.); **15**) oil; **16**) mp 114.5-115.0°C; **19**) mp 179-180°C; **20**) mp 181-183°C (decomp.).

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9. Leading reference: M. Somei, Y. Fukui, and M. Hasegawa, *Heterocycles*, 1995, **41**, 2157 and references cited therein.

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