

Preparations of melatonin and
1-hydroxymelatonin, and its novel nucleophilic
dimerization to (\pm
)-3a,3a'-bispyrrolo[2,3-b]indoles

著者	Somei Masanori, Oshikiri Naoki, Hasegawa Masakazu, Yamada Fumio
journal or publication title	Heterocycles
volume	51
number	6
page range	1237-1242
year	1999-06-01
URL	http://hdl.handle.net/2297/4353

PREPARATIONS OF MELATONIN AND 1-HYDROXYMELATONIN,
AND ITS NOVEL NUCLEOPHILIC DIMERIZATION TO (\pm)-3a,3a'-BIS-
PYRROLO[2,3-*b*]INDOLES¹

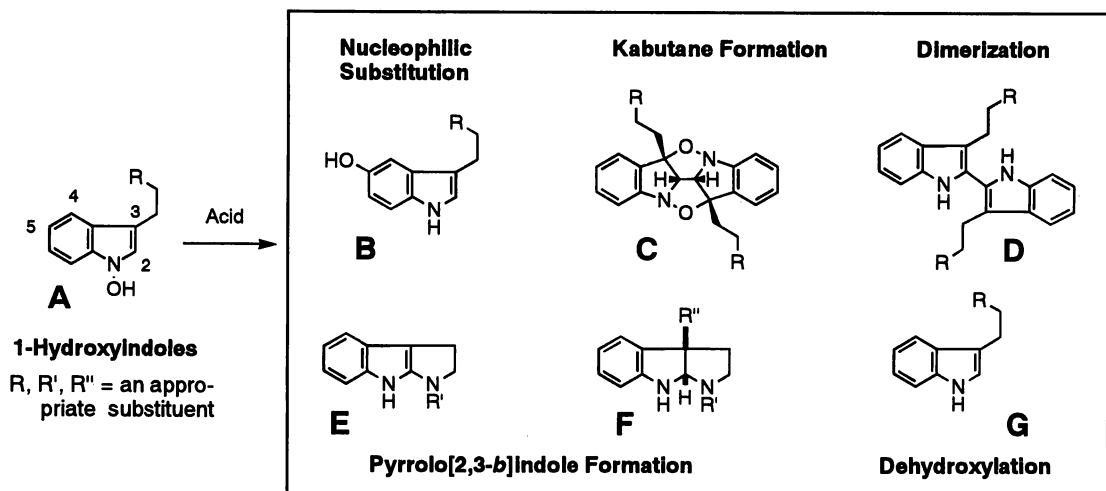
Masanori Somei,* Naoki Oshikiri, Masakazu Hasegawa, and Fumio Yamada
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract ——— A unique synthetic method for melatonin was established through biologically promising synthetic intermediates. 1-Hydroxymelatonin was prepared as crystals for the first time. It reacted with 85% formic acid to give (\pm)-3a,3a'-bispyrrolo[2,3-*b*]indole compound, whose structure was unequivocally determined by X-Ray crystallographic analysis.

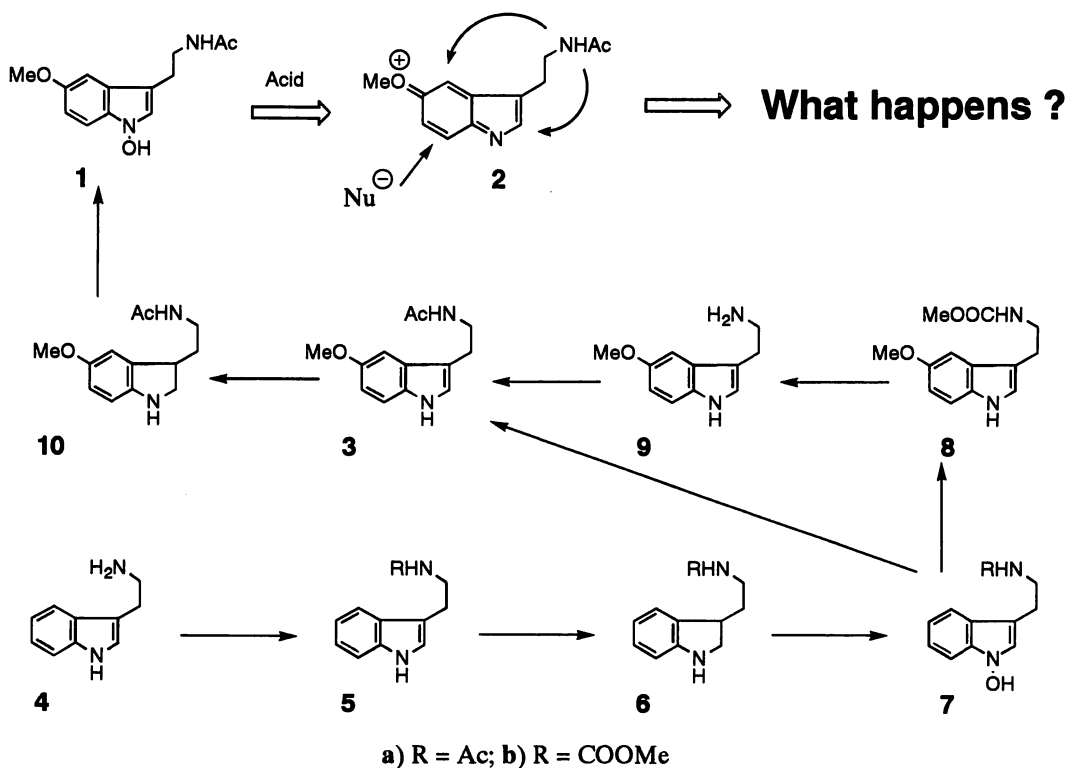
We have disclosed that in an acidic conditions 1-hydroxyindoles² (**A**) undergo five types of reactions, as shown in Scheme 1, such as 1) regioselective nucleophilic substitution to give 5-substituted indoles (**B**),³ 2) formation of kabutanes (**C**),^{3e} 3) dimerization to afford 2,2'-bisindole derivatives (**D**),^{4b} 4) formation of pyrrolo[2,3-*b*]indoles (**E** and **F**),^{3a} and 5) dehydroxylation to give indoles (**G**),³ depending on acids and the structure of 1-hydroxyindoles. In our continuing research on verifying 1-hydroxyindole hypotheses,⁴ we have now reached to the stage to clarify the reactivity of 1-hydroxymelatonin (**1**). When it reacts with acid, departure of its 1-hydroxy group as a water would form a stable cation (**2**) (Scheme 2). Then, what happens? We have expected to discover a new type of nucleophilic substitution reaction through **2**.

To answer the above question, we needed biologically important melatonin⁵ (**3**) as a starting material. Although we have reported four-step melatonin synthesis⁶ from tryptamine (**4**) as shown in Scheme 2 through *N*b-acetyltryptamine (**5a**), **6a**, and **7a**, both nucleophilic substitution and dehydroxylation took place in the fourth step of the treatment of **7a** with BF₃•MeOH culminating in the formation of about 20:1 mixture of **3** and **5a** in 85% yield. The problem is that R_f values of them are close and their separations are not easy particularly in large scale production. Therefore, we tried to find another improved synthesis for **3**

Scheme 1



Scheme 2



by changing *Nb*-substituent of **7a** from acetyl to methoxycarbonyl group.

1-Hydroxy-*Nb*-methoxycarbonyltryptamine (**7b**) was prepared according to our previous method⁶ through **5b** and **6b** in 59% overall yield from **4** in g scale. It should be noted that the reaction rate of **7b** with $\text{BF}_3 \cdot \text{MeOH}$ in refluxing MeOH was enhanced dramatically and reaction time was shortened to 10 min contrasting to 40 min of that of **7a**. As a result, **7b** produced **8** in 85% yield without any contamination of **5b**. Subsequent hydrolysis of **8** and acetylation of the resultant 5-methoxytryptamine⁷ (**9**) with Ac_2O -pyridine afforded **3** in 92% overall yield.

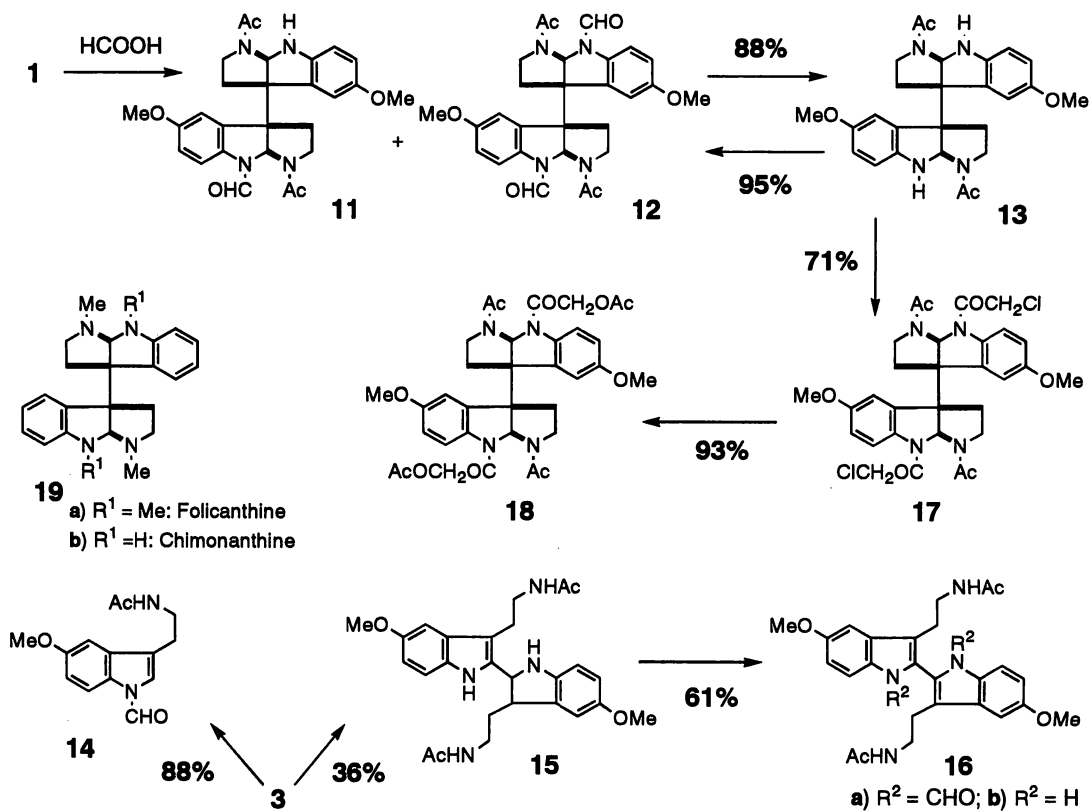
Although the route employs two more steps compared with the original one,⁶ it is a kind of our desired common synthetic method for supplying biologically active compounds, because it involves promising lead compounds, **7b** and **9**. The former is a potent inhibitor of blood platelet aggregation⁸ and the latter is known to be more potent than serotonin.⁷ Thus, an effective and economical synthetic method for melatonin⁵ (**3**) was established. With **3** in hand, it was derived to *Nb*-acetyl-2,3-dihydrotryptamine (**10**) in 83% yield by reduction with Et_3SiH in CF_3COOH . Application of our 1-hydroxyindole synthetic method,^{2,5,7} using Na_2WO_4 and 30% H_2O_2 , to **10** produced the desired 1-hydroxymelatonin (**1**) as a stable crystalline compound for the first time in 58% yield.

A new type of reaction was discovered as expected when **1** reacted with 30% HCOOH in MeOH at room temperature to produce dimeric monoformyl (**11**) and diformyl compound (**12**) in 23 and 18% yields, respectively (Scheme 3). When 85% HCOOH was employed, **1** exclusively afforded **12** in 44% yield. The reaction was proved to be characteristic to 1-hydroxyindole structure, because similar reaction of **3** with 85% HCOOH afforded 1-formylmelatonin (**14**) in 88% yield and formations of **11** and **12** were not observed at all.

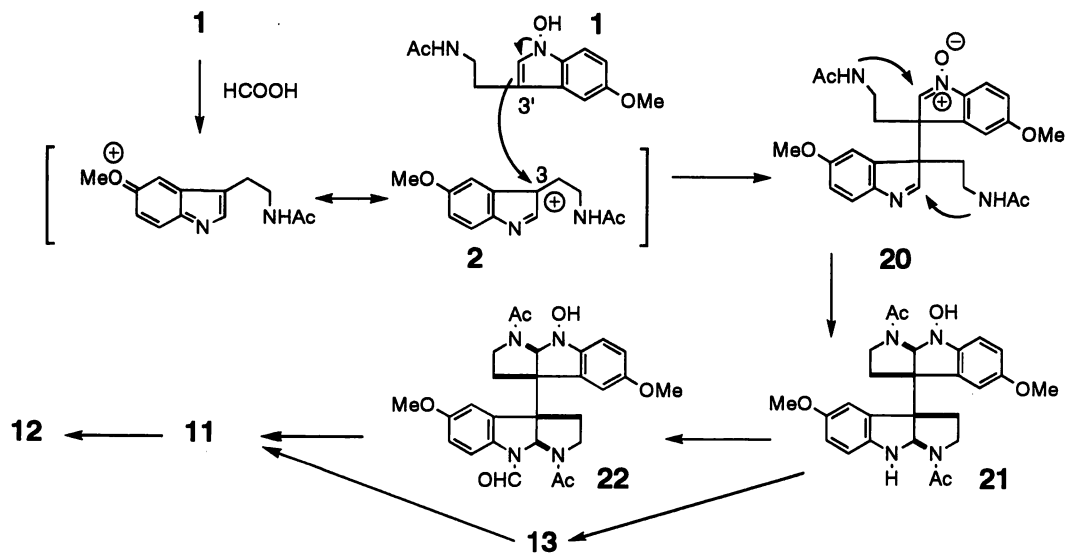
Since **16a** is another candidate for the structure of **12**, **3** was derived to 2,2'-bisindole compound (**15**) in 36% yield together with 18% yield of recovery by reaction with CF_3COOH . Oxidation of **15** with DDQ in dioxane afforded 2,2'-bismelatonin (**16b**) in 61% yield. On the other hand, alkaline hydrolysis of **12** with 8%- NaOH in refluxing MeOH removed formyl group to give 88% yield of **13**, which was reconverted to **12** in 95% yield by the reaction with 85% HCOOH . Direct comparison of **13** with **16b** proves that **13** is not the 2,2'-dimer.

Derivation of **13** was then attempted to obtain suitable crystals for X-Ray single crystallographic analysis. Treatment of **13** with NaH in DMF, followed by acylation with chloroacetyl chloride provided **17** in 71% yield. Further reaction of **17** with NaOAc in DMF at 55°C produced acetate (**18**) in 93% yield. Luckily,

Scheme 3



Scheme 4



we could perform X-Ray structural analysis with **18**. As can be seen from the results shown in Figure 1, **18** is determined to have (\pm)-3a,3a'-bispyrrolo[2,3-*b*]indole structure. Formation of *meso*-isomer was not observed in the reaction mixture of **1**.

The mechanism for the formation of **11** and **12** could be explained as shown in Scheme 4. Nucleophilic addition of carbon-3' in **1** to the initially generated cation (**2**) at the 3-position gives imine-nitrone intermediate (**20**).

Subsequent intramolecular additions of nu-

cleophiles, *Nb*- and *Nb'*-nitrogens, to the imine and nitrone carbon atoms, respectively, form 3a,3a'-bispyrrolo[2,3-*b*]indole compound (**21**). Then, formic acid functions as a reagent for both *N*-formylation and reduction of hydroxylamine to amine giving **11** and **12** through **22** and/or **13**.

In conclusion, we discovered a new and effective synthetic method for 3a,3a'-bispyrrolo[2,3-*b*]indoles. The compound (**12**) has the same skeleton with the alkaloids, folicanthine (**19a**) and chimonanthine (**19b**),⁹ and **19b** was already derived to calycanthine.⁹ Based on these facts, their total syntheses and the preparations of various derivatives bearing substituents on the benzene part of pyrrolo[2,3-*b*]indole skeleton are in progress in our structure-activity relationship project.

ACKNOWLEDGMENT

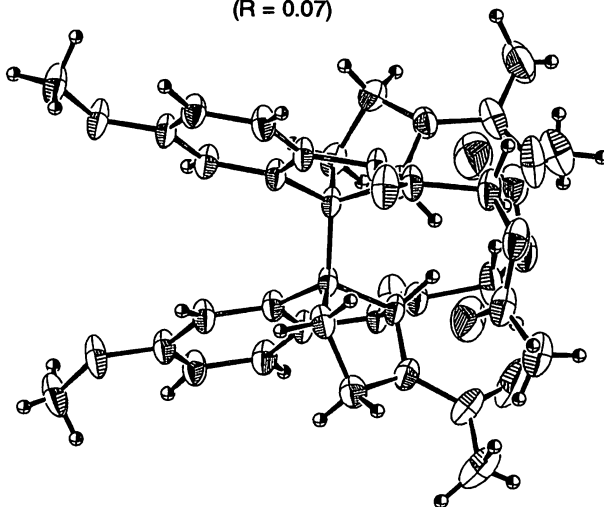
This work is supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.

REFERENCES AND NOTES

1. This is Part 91 of a series entitled "The Chemistry of Indoles". Part 90: H. Hayashi, Y. Suzuki, and M. Somei, *Heterocycles*, in press. All new compounds gave satisfactory spectral data and elemental analyses. **1**: mp 113—114°C; **8**: mp 80—82°C; **9**: mp 124—126°C; **10**: mp 83—84°C; **11**: mp 235—236°C; **12**: mp >300°C; **13**: mp 188—189°C; **14**: colorless hard oil; **15**: colorless hard oil; **16b**: mp

Figure 1

ORTEP Drawing of **18**
(R = 0.07)



260—261°C; **17**: mp 246—247°C; **18**: mp 274—275°C.

2. M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; Review: M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205 and references cited therein.
3. a) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877; b) F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *ibid.*, 1993, **36**, 99; c) F. Yamada, D. Shinmyo, and M. Somei, *ibid.*, 1994, **38**, 273; d) M. Somei, K. Kobayashi, K. Tani, T. Mochizuki, Y. Kawada, and Y. Fukui, *ibid.*, 1995, **40**, 119; e) M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, and M. Somei, *ibid.*, 1996, **43**, 2333; M. Somei, F. Yamada, and G. Yamamura, *Chem. Pharm. Bull.*, 1998, **46**, 191 and references cited therein.
4. a) "1-Hydroxyindole Hypotheses" was first presented orally: M. Somei, Y. Karasawa, S. Tokutake, T. Shoda, F. Yamada, and C. Kaneko, Abstracts of Papers, The 13th Congress of Heterocyclic Chemistry, Shizuoka, Nov. 1980, p. 33; b) M. Somei and Y. Fukui, *Heterocycles*, 1993, **36**, 1859; c) M. Somei, Y. Fukui, and M. Hasegawa, *ibid.*, 1995, **41**, 2157; d) K. Yamada and M. Somei, *ibid.*, 1998, **48**, 2481; e) Review: M. Somei, *ibid.*, 1999, **50**, 1157.
5. W. Pierpaoli, *Aging*, 1991, **3**, 99; F. Waldhauser, B. Ehrhart, and E. Forster, *Experientia*, 1993, **49**, 671; S.-W. Ying, L.P. Niles, and C. Crocker, *Eur. J. Pharmacol. Mol. Pharmacol. Sect.*, 1993, **246**, 89; H. Schmid, *Gerontology*, 1993, **39**, 189.
6. M. Somei, F. Yamada, and H. Morikawa, *Heterocycles*, 1997, **46**, 91 and references cited therein.
7. S. Supniewski and S. Misztal, *Bull. Acad. Polon. Sci., Ser. Sci. Biol.*, 1960, **8**, 479 [*Chem. Abstr.*, 1961, **55**, 15458].
8. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, *Heterocycles*, 1996, **43**, 1855.
9. Folicanthine, chimonanthine, and calycanthine: H. F. Hodson, Sir R. Robinson, and G. F. Smith, *Proc. Chem. Soc.*, 1961, 465; T. Hino and S. Yamada, *Tetrahedron Lett.*, 1963, 1757; A. I. Scott, F. McCapra, and E. S. Hall, *J. Am. Chem. Soc.*, 1964, **86**, 302; J. B. Hendrickson, R. Göschke, and R. Rees, *Tetrahedron*, 1964, **20**, 565; E. S. Hall, F. McCapra, and A. I. Scott, *ibid.*, 1967, **23**, 4131; J. P. Springer and G. Büchi, *Tetrahedron Lett.*, 1977, 2403; M. Nakagawa, H. Sugumi, S. Kodato, and T. Hino, *ibid.*, 1981, **22**, 5323; J. T. Link and L. E. Overman, *J. Am. Chem. Soc.*, 1996, **118**, 8166.

Received, 3rd March, 1999