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

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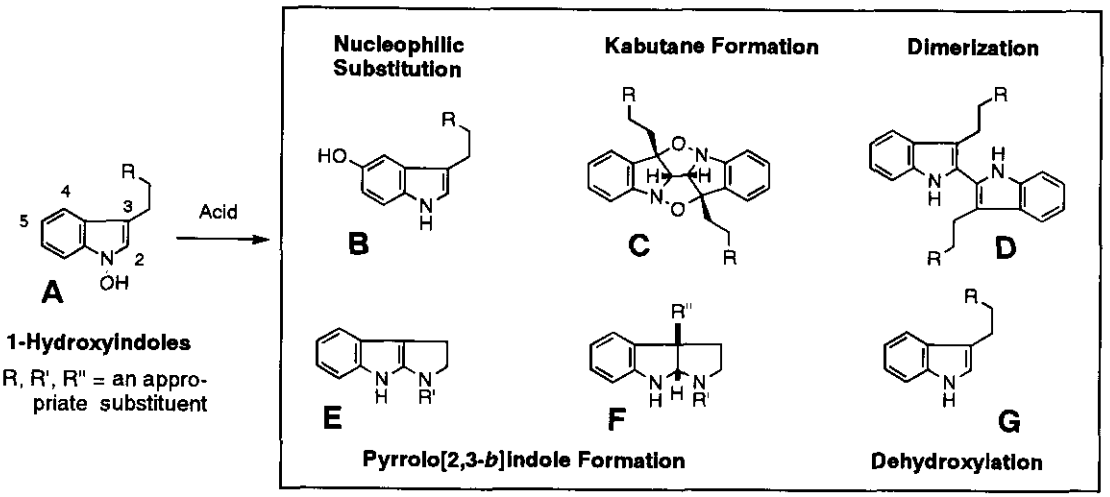
Abstract ——— A unique synthetic method for melatonin was established through biologically promising synthetic intermediates. 1-Hydroxymelatonin was prepared as crystals for the first time. It reacted with 85% formic acid to give (±)-3a,3a'-bispyrrolo[2,3-*b*]indole compound, whose structure was unequivocally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

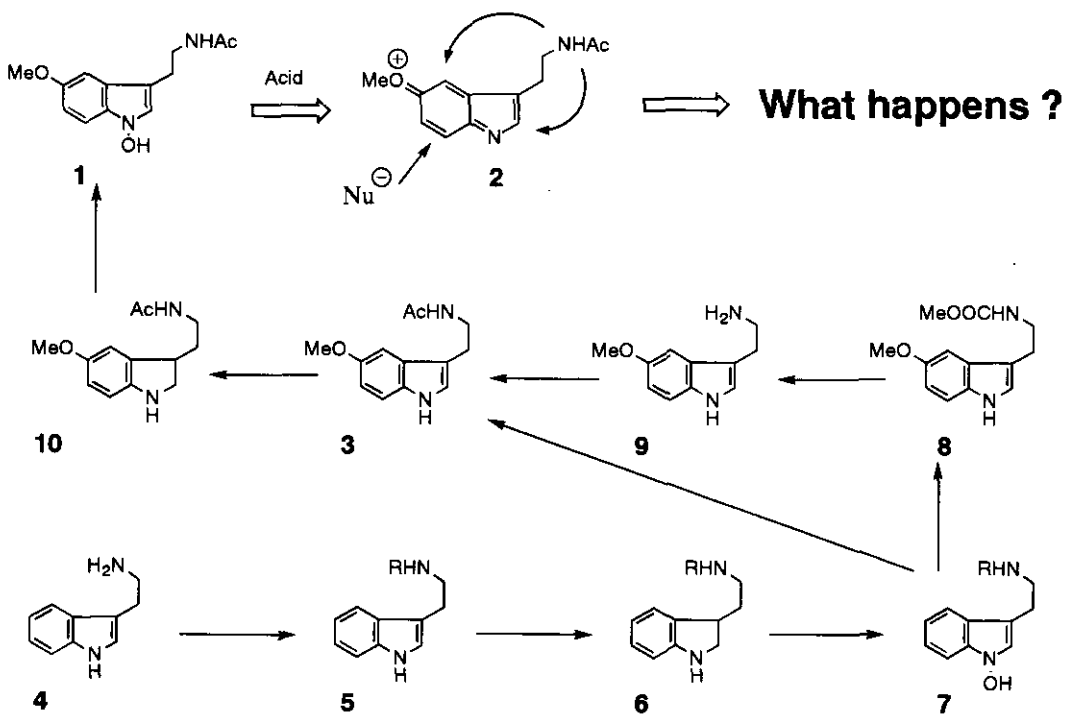
We have disclosed that in an acidic conditions 1-hydroxyindoles[2] (**A**) undergo five types of reactions, as shown in Scheme 1, such as 1) regioselective nucleophilic substitution to give 5-substituted indoles (**B**),[3] 2) formation of kabutanes (**C**),[3e] 3) dimerization to afford 2,2'-bisindole 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 melatonin[5] (**3**) as a starting material. Although we have reported four-step melatonin synthesis[6] 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 BF_3•MeOH culminating in the formation of about 20:1 mixture of **3** and **5a** in 85% yield. The problem is that Rf 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



a) R = Ac; b) R = COOMe

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

1-Hydroxy-*N*b-methoxycarbonyltryptamine (**7b**) was prepared according to our previous method[6] through **5b** and **6b** in 59% overall yield from **4** in g scale. It should be noted that the reaction rate of **7b** with BF_3•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-methoxytryptamine[7] (**9**) with Ac_2O-pyridine afforded **3** in 92% overall yield.

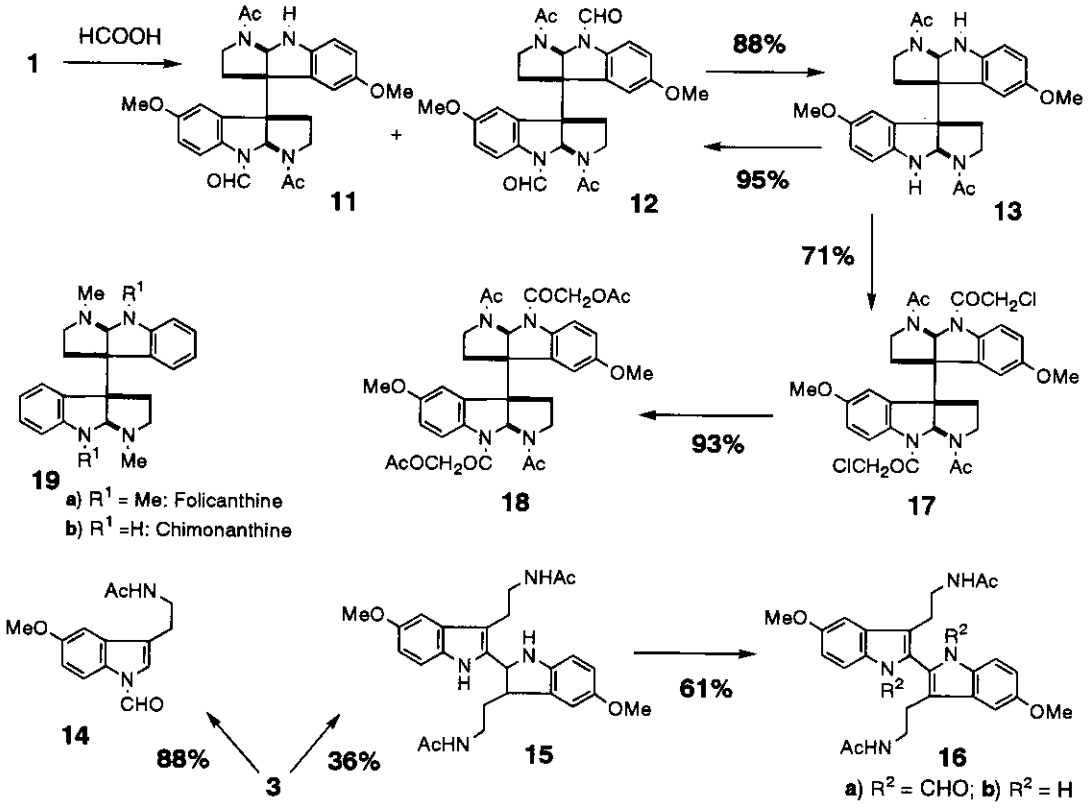
Although the route employs two more steps compared with the original one,[6] it is a kind of our desired common synthetic method for supplying biologically active compounds, because it involves promising lead compounds, **7b** and **9**. The former is a potent inhibitor of blood platelet aggregation[8] and the latter is known to be more potent than serotonin.[7] Thus, an effective and economical synthetic method for melatonin[5] (**3**) was established. With **3** in hand, it was derived to *N*b-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.

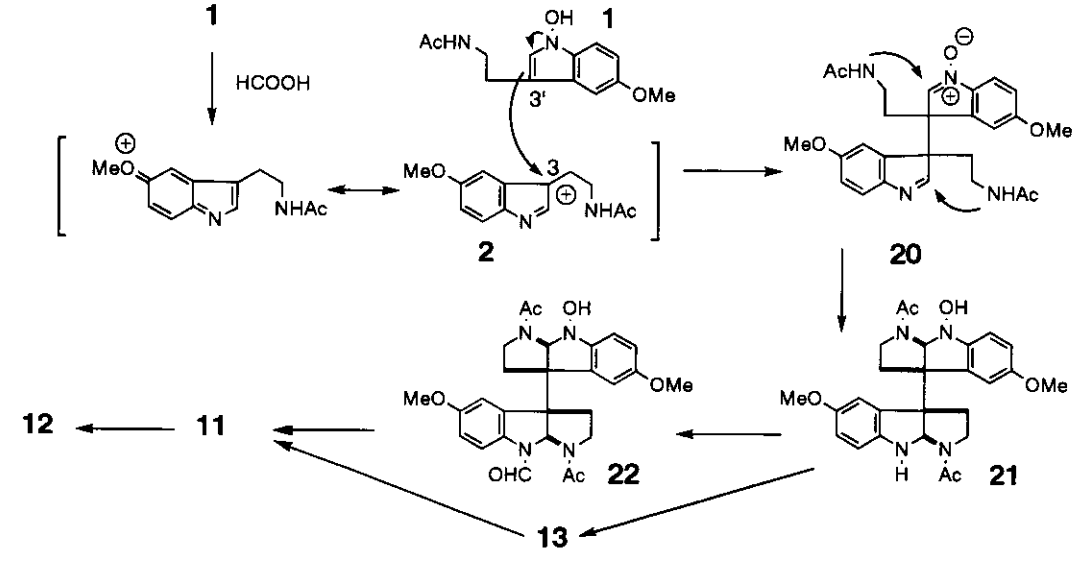
Since **16a** is another candidate for the structure of **12**, **3** was derived to 2,2'-bisindole compound (**15**) in 36% yield together with 18% yield of recovery by reaction with CF_3COOH. Oxidation of **15** with DDQ in dioxane afforded 2,2'-bismelatonin (**16b**) in 61% yield. On the other hand, 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



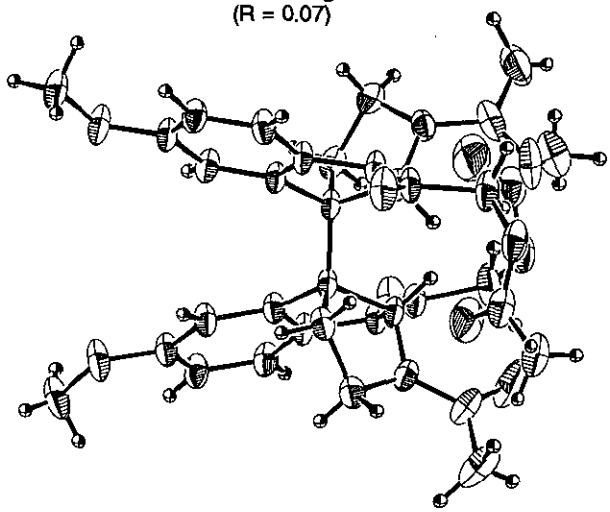
Scheme 4



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 (±)-3a,3a'-bispyrrolo[2,3-*b*]indole structure. Formation of *meso*-isomer was not observed in the reaction mixture of **1**.

Figure 1

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



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 nucleophiles, *N*b- and *N*b'-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

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

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