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

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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 (A) undergo five types of reactions, as
shown in Scheme 1, such as 1) regioselective nucleophilic substitution to give 5-substituted indoles (B),
2) formation of kabutanes (C), 3) dimerization to afford 2,2'-bisindole derivatives (D), 4) formation
of pyrrolo[2,3-b]indoles (E and F), and 5) dehydroxylation to give indoles (G), depending on acids
and the structure of 1-hydroxyindoles. In our continuing research on verifying 1-hydroxyindole
hypotheses, 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 (3) as a starting material.
Although we have reported four-step melatonin synthesis from tryptamine (4) as shown in Scheme 2
through Nβ-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 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

1-Hydroxyindoles

R, R', R'' = an appropriate substituent

Scheme 2

What happens?

a) R = Ac; b) R = COOMe
by changing Nb-substituent of 7a from acetyl to methoxycarbonyl group.

1-Hydroxy-Nb-methoxycarbonyltryptamine (7b) was prepared according to our previous method through 5b and 6b in 59% overall yield from 4 in g scale. It should be noted that the reaction rate of 7b with BF3⋅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 (9) with Ac2O-pyridine afforded 3 in 92% overall yield.

Although the route employs two more steps compared with the original one, 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 and the latter is known to be more potent than serotonin. Thus, an effective and economical synthetic method for melatonin (3) was established. With 3 in hand, it was derived to Nb-acetyl-2,3-dihydrotryptamine (10) in 83% yield by reduction with Et3SiH in CF3COOH. Application of our 1-hydroxyindole synthetic method, using Na2WO4 and 30% H2O2, 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 CF3COOH. 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

1. HCOOH → 11 + 12
   - 88%
   - 95%

11. MeO
12. MeO
13. MeO
14. MeO
15. MeO
16. MeO
17. MeO
18. MeO
19. MeO
20. MeO
21. MeO
22. MeO

- a) R² = CHO; b) R² = H

Scheme 4

1. HCOOH → 1
   - 88%
   - 36%

11. MeO
12. MeO
13. MeO
14. MeO
15. MeO
16. MeO
17. MeO
18. MeO
19. MeO
20. MeO
21. MeO
22. MeO

- a) R² = CHO; b) R² = H
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 nucleophiles, 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.

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


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