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PREPARATIONS OF TRYPTAMINE-4,5-DIONES, AND THEIR DIELS-ALDER AND NUCLEOPHILIC ADDITION REACTIONS¹

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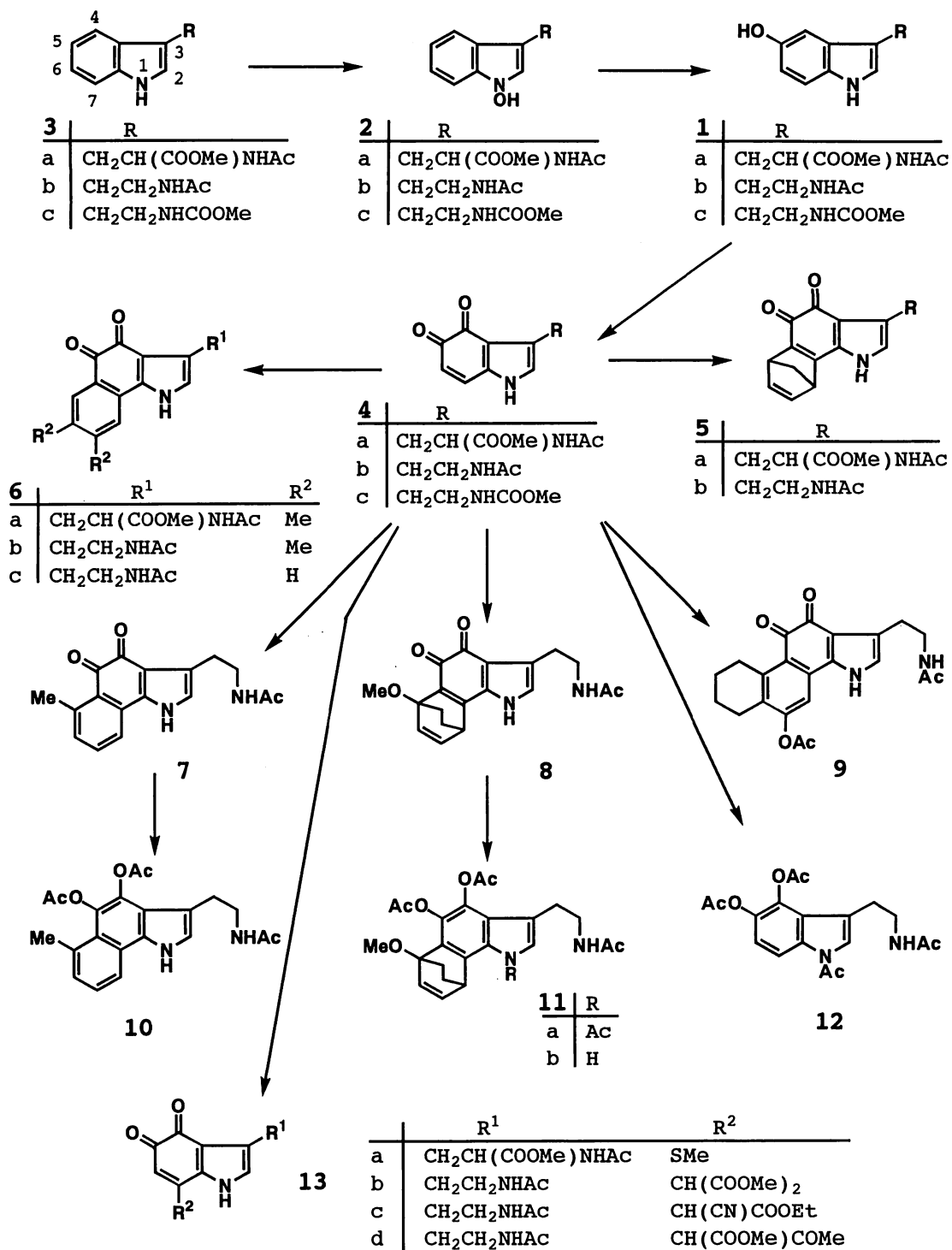
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Abstract — Syntheses of *Nb*-acetyltryptamine-4,5-dione and (±)-*Nb*-acetyltryptophan-4,5-dione methyl ester are reported. They were excellent dienophiles as well as good electrophiles, and produced 6,7-disubstituted indoles in Diels-Alder reaction and various 7-substituted indoles with nucleophiles.

We have established simple synthesis method² for (±)-*Nb*-acetyl-5-hydroxytryptophan methyl ester ((±)-**1 a**) and 5-hydroxytryptamines (**1 b**, **c**) through the corresponding 1-hydroxyindoles³ (**2 a**, **b**, **c**) starting from (±)-*Nb*-acetyltryptophan methyl ester ((±)-**3 a**) and tryptamines (**3 b**, **c**), respectively. We have also disclosed² that (±)-**1 a** was readily oxidized to (±)-*Nb*-acetyltryptophan-4,5-dione methyl ester ((±)-**4 a**). In this communication, we wish to report that indole-4,5-diones⁴ work as dienophiles and electrophiles as predicted in our hypothesis.²

First we examined the oxidation of **1 b** to *Nb*-acetyltryptamine-4,5-dione⁵ (**4 b**) with various reagents, such as ceric ammonium nitrate (CAN), FeCl₃, K₃Fe(CN)₆, and Fenton reagent, but no isolable products were formed except for tars. Utilizing iodosylbenzene, the desired **4 b** was obtained in 38% yield, and finally we found that Fremy's salt (4 mol eq.) could produce **4 b** in 99% yield under special conditions such as in MeOH-H₂O at 0°C for 30 min. Whereas, the oxidation of (±)-**1 a** with Fremy's salt gave tars and would not afford (±)-**4 a** under various examined reaction conditions. Other oxidizing reagents (CAN, K₃Fe(CN)₆, Na₂WO₄-H₂O₂, etc.) were also extensively examined, but we could not improve the yield of (±)-**4 a** more than 39% yield, which was attained previously² by the oxidation with iodosylbenzene. Indole-4,5-diones ((±)-**4 a** and **4 b**) were excellent dienophiles and produced Diels-Alder adducts, which were highly sensitive to air and oxidized during work-up to 6,7-disubstituted indole-4,5-dione derivatives, contrary to the results by Cai and co-workers⁴ reporting the isolation of Diels-Alder adduct in a similar reaction of *Nb*-methoxycarbonyltryptamine-4,5-dione (**4 c**). Thus, **4 b** reacted with cyclopentadiene to produce **5 b** in 81% yield, while (±)-**4 a** (generated *in situ* by the reaction of (±)-**1 a** with iodosylbenzene and used without purification) afforded (±)-**5 a** (2:1

Scheme 1



mixture of diastereomers) in 35% overall yield from (\pm)-**1 a**. In the reaction with 2,3-dimethylbutadiene, **4 b** afforded a quantitative yield of **6 b**, while (\pm)-**4 a** (generated *in situ* as described above) afforded (\pm)-**6 a** in 33% overall yield from (\pm)-**1 a**. Interestingly, the reaction of **4 b** with 1-acetoxybutadiene afforded 40% yield of **6 c**. Similarly, **4 b** underwent Diels-Alder reaction with 1,3-pentadiene, 1-methoxy-1,3-cyclohexadiene, and 1-(1-acetoxyvinyl)cyclohexene to give the expected **7**, **8**, and **9** in 22, 41, and 39% yields, respectively.

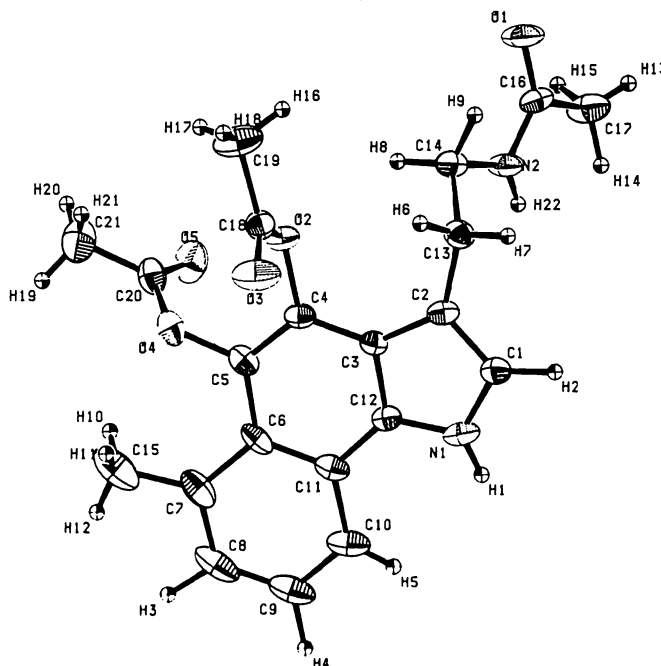
Concerning the structures of **7**, **8**, and **9**, the other regioisomers are possible candidates. To determine their structures, our finding that the reductive acetylation⁴ of **4 b** with Zn in Ac₂O and Et₃N at 100°C for 20 min cleanly generated **12** in 77% yield, was applied to **8** under similar reaction conditions to produce **11 a** and **11 b** in 37 and 25% yields, respectively. However, **11 a** was not suitable crystals for X-ray analysis and **11 b** was an oil. Fortunately, X-ray single crystallographic analysis of the compound **10**, obtained in 81% yield from **7** by the reductive acetylation as mentioned above,

could be carried out successfully. The results obtained in Figure 1 proved not only its structure but also regiochemistries of the related compounds (**8** and **9**).

On the other hand, (\pm)-**4 a** and **4 b** underwent nucleophilic addition and spontaneous oxidation resulting in the formation of 7-substituted tryptamine-4,5-diones. Thus, (\pm)-**4 a** reacted with methyl mercaptan in MeOH at room temperature to afford (\pm)-**13 a** in 69% overall yield from (\pm)-**1 a**. Similarly, **4 b** reacted with methyl malonate, ethyl cyanoacetate, and methyl acetoacetate in the presence of KO^tBu, to afford **13 b**, **13 c**, and **13 d** in 83, 88, and 71% yields, respectively.

In the central nervous system, 5-hydroxyindole derivatives play important roles.⁶ The present study suggests if those 5-hydroxyindoles were oxidized by chance with dioxygen or reactive oxygen species (hydrogen peroxide, superoxide, etc.) to indole-4,5-diones *in vivo*, they should react as electrophiles and dienophiles with nearby proteins, alkadienoic

Figure 1
ORTEP Drawing of **10**



acids, leucotrienes, and so on, resulting in the malfunction of nerves and neurodegenerative diseases.^{2,7} Along these lines, the reactions of (\pm)-**4 a** and **4 b** with proteins and nucleic acids are currently in progress.

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5. **4 b**: mp 185-186°C (decomp., dark purple powder, recrystallized from MeOH). ¹H-Nmr (CD₃OD) δ : 1.89 (3H, s), 2.84 (2H, t, $J=7.0$ Hz), 3.40 (2H, t, $J=7.0$ Hz), 5.93 (1H, d, $J=9.9$ Hz), 6.73 (1H, s), 7.25 (1H, d, $J=9.9$ Hz). Ir (KBr): 3190, 1630, 1505, 1460, 1370, 1320, 780 cm⁻¹. Ms m/z : 232 (M⁺), 234 (M⁺+2). Uv λ_{max}^{MeOH} nm (log ϵ): 233 (4.37), 352 (3.50), 520 (3.31). Anal. Calcd for C₁₂H₁₂N₂O₃·1/4H₂O: C, 60.88; H, 5.32; N, 11.83. Found: C, 61.08; H, 5.30; N, 11.84.
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