PREPARATIONS OF TRYPTAMINE-4,5-DIONES, AND THEIR DIELS-ALDER AND NUCLEOPHILIC ADDITION REACTIONS[1]

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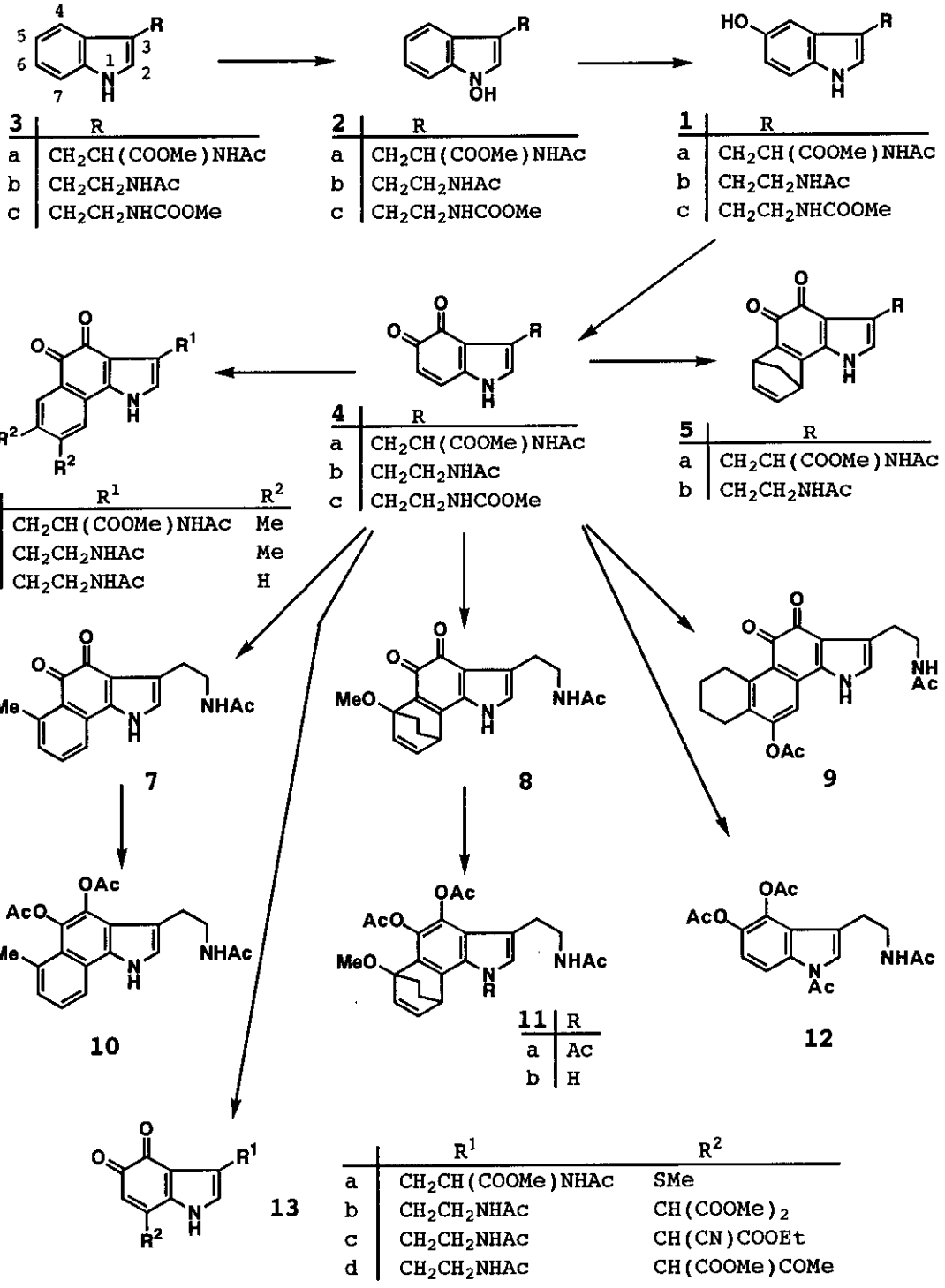
Abstract —— Syntheses of *N*b-acetyltryptamine-4,5-dione and (±)-*N*b-acetyltryptophan-4,5-dione methyl ester are reported. They were excellent dienophiles as well as good electrophiles, and produced 6,7-disubstituted indoles in Diels-Alder reaction and various 7-substituted indoles with nucleophiles.

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

First we examined the oxidation of **1 b** to *N*b-acetyltryptamine-4,5-dione[5] (**4 b**) with various reagents, such as ceric ammonium nitrate (CAN), $FeCl_3$, $K_3Fe(CN)_6$, 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-H_2O 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, $K_3Fe(CN)_6$, Na_2WO_4-H_2O_2, etc.) were also extensively examined, but we could not improve the yield of (±)-**4 a** more than 39% yield, which was attained previously[2] 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-workers[4] reporting the isolation of Diels-Alder adduct in a similar reaction of *N*b-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

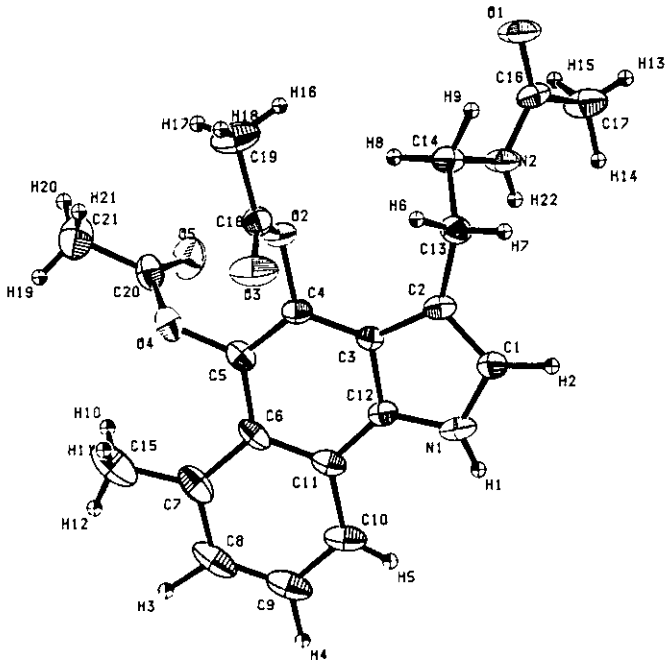
Scheme 1


3
R
a CH2CH(COOMe)NHAc
b CH2CH2NHAc
c CH2CH2NHCOOMe
2
R
a CH2CH(COOMe)NHAc
b CH2CH2NHAc
c CH2CH2NHCOOMe
1
R
a CH2CH(COOMe)NHAc
b CH2CH2NHAc
c CH2CH2NHCOOMe
4
R
a CH2CH(COOMe)NHAc
b CH2CH2NHAc
c CH2CH2NHCOOMe
5
R
a CH2CH(COOMe)NHAc
b CH2CH2NHAc
6
R1
R2
a CH2CH(COOMe)NHAc Me
b CH2CH2NHAc Me
c CH2CH2NHAc H
7
8
9
10
11
R
a Ac
b H
12
13
R1
R2
a CH2CH(COOMe)NHAc SMe
b CH2CH2NHAc CH(COOMe)2
c CH2CH2NHAc CH(CN)COOEt
d CH2CH2NHAc CH(COOMe)COMe

mixture of diastereomers) in 35% overall yield from (±)-**1 a**. In the reaction with 2,3-dimethylbutadiene, **4 b** afforded a quantitative yield of **6 b**, while (±)-**4 a** (generated *in situ* as described above) afforded (±)-**6 a** in 33% overall yield from (±)-**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 acetylation[4] of **4 b** with Zn in Ac_2O and Et_3N 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**).

Figure 1
ORTEP Drawing of 10



On the other hand, (±)-**4 a** and **4 b** underwent nucleophilic addition and spontaneous oxidation resuting in the formation of 7-substituted tryptamine-4,5-diones. Thus, (±)-**4 a** reacted with methyl mercaptan in MeOH at room temperature to afford (±)-**13 a** in 69% overall yield from (±)-**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

acids, leucotrienes, and so on, resuting in the malfunction of nerves and neurodegenerative diseases.[2,7] Along these lines, the reactions of (±)-**4 a** and **4 b** with proteins and nucleic acids are currently in progress.

REFERENCES AND NOTES

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5. **4 b**: mp 185-186°C (decomp., dark purple powder, recrystallyzed from MeOH). ^{1}H-Nmr (CD_3OD) 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 $C_{12}H_{12}N_2O_3 \cdot 1/4H_2O$: C, 60.88; H, 5.32; N, 11.83. Found: C, 61.08; H, 5.30; N, 11.84.
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