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journal or publication title	Heterocycles
volume	41
number	10
page range	2157-2160
year	1995-01-01
URL	http://hdl.handle.net/2297/4336

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

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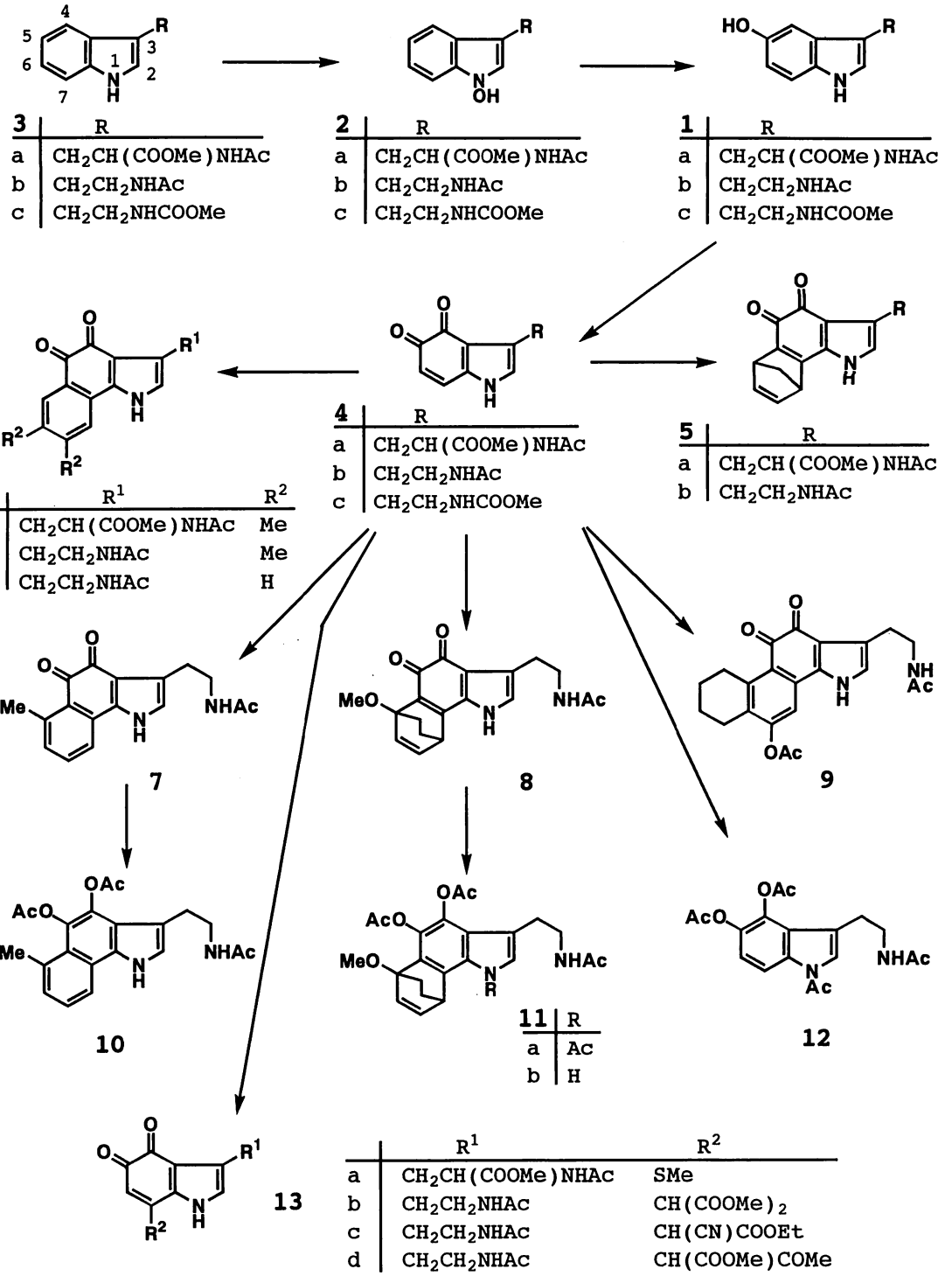
Abstract —— Syntheses of *N*b-acetyltryptamine-4,5-dione and (±)-*N*b-acetyltryptophan-4,5-dione methyl ester are reported. They were excellent dienophiles as well as good electrophiles, and produced 6,7-disubstituted indoles in Diels-Alder reaction and various 7-substituted indoles with nucleophiles.

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

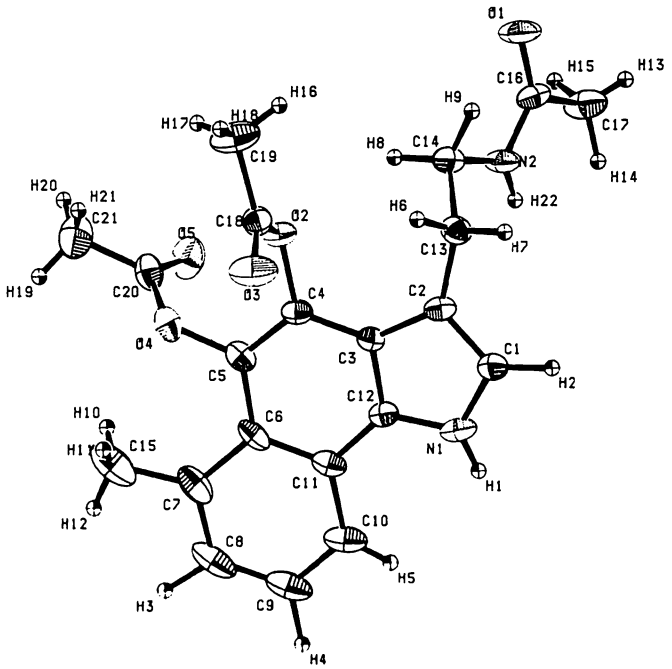
Scheme 1


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

1. This is Part 75 of a series entitled "The Chemistry of Indoles" and partly reported at the 25th Congress of Heterocyclic Chemistry, Book of Abstracts, Tokyo, October 1994, p. 93. Part 74: F. Yamada, S. Hamabuchi, A. Shimizu, and M. Somei, *Heterocycles,* 1995, in press. All new compounds gave satisfactory spectral data and elemental analyses for crystals or high resolution mass spectral data for oils. **5 b**) mp 245-256°C (decomp.); **6 a**) mp 302-310°C (decomp.); **6 b**) mp 305-307°C; **6 c**) mp 310-314°C (decomp.); **7**) mp 302-305°C (decomp.); **8**) mp 293-296°C (decomp.); **9**) mp 282-285°C (decomp.); **1 0**) mp 213-214°C; **1 1 a**) mp 192-194°C; **1 1 b**) oil ; **1 2**) mp 199-200°C; **1 3 a**) mp 253-255°C (decomp.); **1 3 b**) mp 195-197°C; **1 3 c**) mp 230-235°C (decomp.); **1 3 d**) mp 180-183°C (3:2 mixture of tautomers).
2. M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles,* 1992, **3 4**, 1877; M. Somei and Y. Fukui, *ibid.*,1993, **3 6**, 1859.
3. Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi,* 1991, **4 9**, 205 and references reported before 1991 are cited therein; M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull*, 1991, **3 9**, 1905; T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **3 2**, 221; F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *ibid.*, 1993, **3 5**, 99; F. Yamada, D. Shinmyo, and M. Somei, *ibid.*, 1994, **3 8**, 273; K. Nakagawa and M. Somei, *ibid.*, 1994, **3 9**, 31; M. Somei, K. Kobayashi, K. Tanii, T. Mochizuki, Y. Kawada, and Y. Fukui, *ibid.*, 1995, **4 0**, 119, and references cited therein.
4. P. Cai, J. K. Snyder, J. -C. Chen, R. Fine, and L. Volicer, *Tetrahedron Lett*, 1990, **3 1**, 969.
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.
6. Serotonin: R. A. Glennon, *J. Med. Chem.*, 1987, **3 0**, 1; J. R. Cooper, F. E. Bloom, and R. H. Roth, "The *Biochemical* Basis of Neuro-Pharmacology," 6th ed., Oxford University Press, 1991. Melatonin: P. J. Garratt, R. Jones, and D. A. Tocher, *J. Med. Chem.*, 1995, **3 8**, 1132 and references cited therein.
7. D. M. Bowen, S. J. Allen, J. S. Benton, M. J. Goodhardt, E. A. Haan, A. M. Palmer, N. R. Sims, C. C. T. Smith, J. A. Spillane, M. M. Esiri, D. Neary, J. S. Snowdon, G. K. Wilcock, and A. N. Davison, *J. Neurochem.*, 1983, **4 1**, 266; L. Volicer, P. J. Langlais, W. R. Matson, K. A. Mark, and P. H. Gamache, *Arch. Neurol.*, 1985, **4 2**, 1158; M. Z. Wrona, and G. Dryhurst, *J. Org. Chem.*, 1987, **5 2**, 2817; G. Dryhurst, A. Anne, M. Z. Wrona, and D. Lemordant, *J. Am. Chem. Soc.*, 1989, **1 1 1**, 719; A. K. Sinhababu and R. T. Borchardt, *ibid.*, 1989, **1 1 1**, 2230.

Received, 9th June, 1995