SYNTHETIC STUDIES OF 1, 2, 3, 4-TETRAHYDRO-1, 3, 4-TRIOXO-β-CARBOLINE ALKALOIDS I[1]

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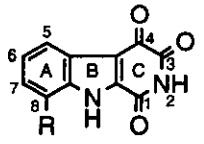
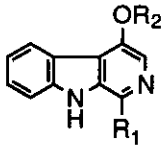
Abstract - A simple and efficient total synthesis of 1, 2, 3, 4-tetrahydro-1, 3, 4-trioxo-β-carboline (**1**) was accomplished *via* C_3-selective acylation of indole-2-carboxylate (**5**). On the course of this study, we found that the cyclization of *N*-(2-indolecarbonyl)glycine (**8a**) with PPA gave only an *N*-cyclized 6-membered ring (**10a**), whereas *N*-(2-indolecarbonyl)-β-alanine (**8b**) gave a C_3-cyclized 7-membered ring (**9b**) as a main product.

Recently 1, 2, 3, 4-tetrahydro-1, 3, 4-trioxo-β-carbolines (β-carboline-triones) (**1**, **2**) were isolated from the *Simaroubaceae* plant as minor alkaloids[2a] along with 4-oxygenated β-carbolines[2b](**3**). These have a highly oxygenated C-ring which is a novel skeleton in natural β-carbolines, and are expected to have some biological activity, as some of **3** have shown biological activities. However, the activities have not been examined, because of their minor productions from nature. One of these (**1**) has been known compound derived from natural brevicolline (**4**) by CrO_3-oxidation during the structural determination.[3]



1: R = H

2: R = OMe
(Picrasidine-V)



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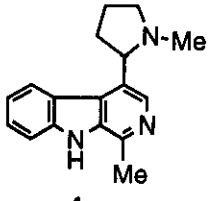

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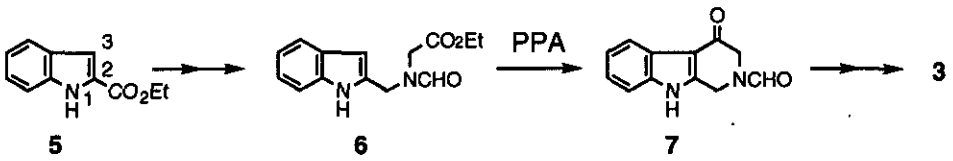
Scheme I

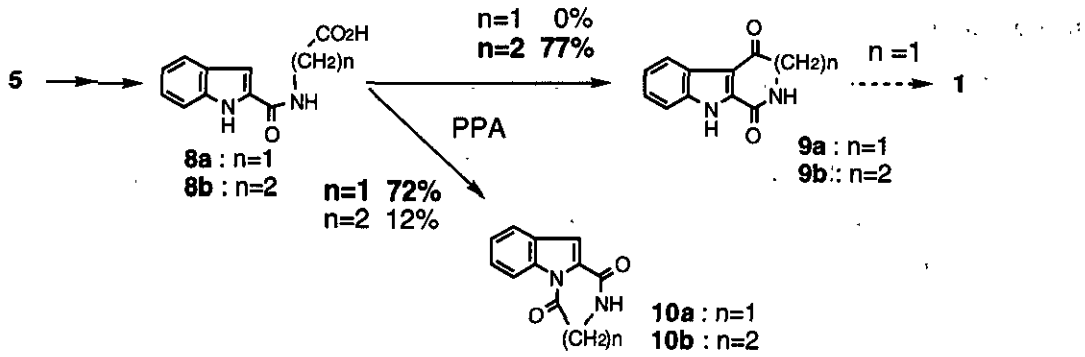
† Dedicated to the memory of late Prof. Yoshio Ban.

In this paper we report the total synthesis of **1** starting from ethyl indole-2-carboxylate (**5**). We have already succeeded[4] in the synthesis of 4-methoxy-β-carbolines (**3**, $R_2 = CH_3$) starting from **5** *via* elongation of C_2-substituent to **6** and cyclization toward the C_3-position to **7**.

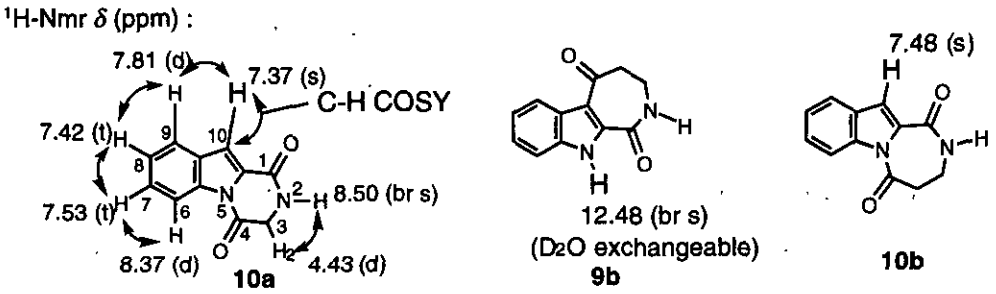


Scheme II

We planned a total synthesis of **1** *via* the oxidation of **9a** which was synthesized *via* cyclization of **8a** (Scheme III). Röder[5] had reported that the cyclization of **8a** and **8b** with polyphosphoric acid (PPA) gave only C_3-cyclized product (**9a, 9b**), respectively. When we treated **8a** with PPA according to Röder's report, we obtained a single product possessing melting point (242-245°) near to Röder's one (237°), and the nmr spectrum showed a similar signal pattern to the reported value observed at 60 MHz nmr.[6] However, we have found that the real structure of the product is *N*-cyclized one (**10a**) by the following data (measured at 500 MHz nmr in DMSO-d_6 at 50°, Scheme IV) : the C_{10}-H corresponding to usual indolic C_3-H was observed at 7.37 ppm as a sharp singlet, which was unexchangeable with D_2O, and has a NOESY to C_9-H and C-H COSY to tertiary C_{10}-carbon at 111.7 ppm. So it should be sure that they[6] took the C_6-H signal (8.37 ppm) for *N*-H one on the assignment of 60 MHz nmr spectrum. The cyclization reaction of the ethyl ester of **8a** with $MeSO_3H$ (neat, 70°, 2.5 h) increased the yield of *N*-cyclized product (**10a**, 92%).



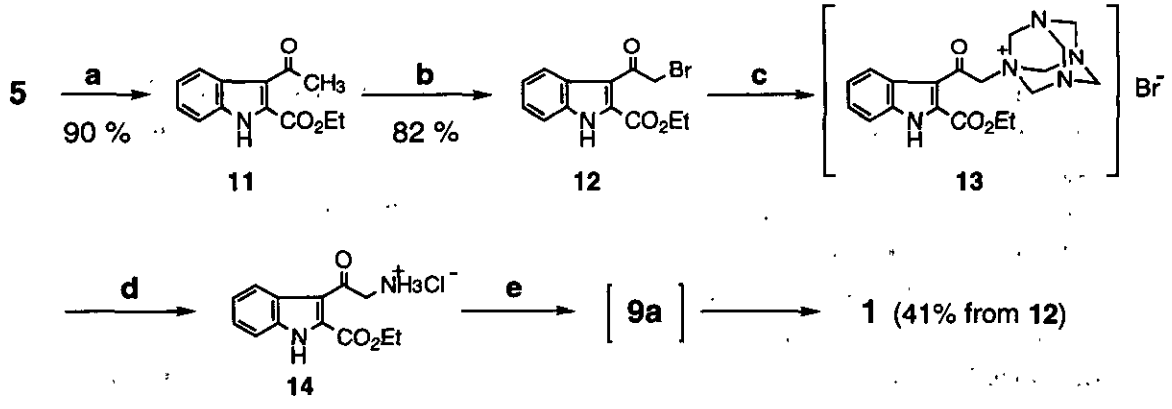
Scheme III



Scheme IV

Thus we also re-examined the cyclization of **8b**, which forms a 7-membered ring, and found that the two kinds of compounds were formed from **8b**, being different from Röder's result.[5] Surprisingly the major product (77%) was C_3-cyclized one (**9b**), while the minor product was *N*-cyclized one (12%) (**10b**), being in contrast to the cyclization of **8a**. Their structures were elucidated clearly by assigning the 7.48 ppm of indolic C_3-H (**10b**) and 12.48 ppm of *N*-H (**9b**). (Scheme IV). The reason for this interesting difference in cyclization between 6-membered ring and 7-membered ring is unknown.

Other cyclization conditions of **8a** and conversion of *N*-cyclized compound (**10a**) to C_3-cyclized product (**9a**), failed to give the desired C_3-cyclized product (**9a**). Hence we synthesized **9a** *via* a more confident route described in scheme V.



a: $(CH_3CO)_2O$, $AlCl_3$ / $ClCH_2CH_2Cl$, room temperature, 10 h **b**: $CuBr_2$ [1.8 mol(0.9 eq.)] / AcOEt, reflux, 1 h **c**: hexamethylenetetramine / $CHCl_3$, room temperature, 1 h **d**: c.HCl / EtOH, 55°, 1 h **e**: Et_3N / EtOH, room temperature, 10 h

Scheme V

The C_3-selective Friedel-Crafts acylation[7] of **5** gave the 3-acetyl product (**11**), and selective bromination of the α-carbon of the carbonyl group with $CuBr_2$ gave the bromoacetyl compound (**12**) in good yield. The reaction of **12** with hexamethylenetetramine, followed by hydrolysis with conc. HCl gave the α–aminoketone hydrochloride(**14**). The treatment of **14** with Et_3N gave unexpectedly the β–carboline-trione (**1**) without isolation of **9a**,[8] as a result of cyclization followed by spontaneous air oxidation. Consequently we accomplished a total synthesis of β–carboline-trione (**1**). Synthesized compound (**1**) was identical with the natural product (**1**).

During the pharmacological screening examination of the synthetic sample, the compound (**1**) was found to possess a weak cytotoxicity against the P-388 mouse leukemia cell (IC_{50} = 13.6 ± 0.5 μg / ml), HOC-21 human ovarian cancer cell (IC_{50} = 25.2 ± 1.3 μg / ml) and MKN-28 human cancer cell (from human stomach) (IC_{50} = 16.1 ± 1.3 μg / ml). Now we are interested in the activities of Picrasidine-V (**2**) and other analogues of **1**. The syntheses of these are now in progress.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. This paper is part XXXVII of "Synthetic Studies on Indoles and Related Compounds." Part XXXVI: Y. Yokoyama, T. Matsumoto, and Y. Murakami, *J. Org. Chem.*, 1995, **60**, 1486.
2. a) K. Koike, T. Ohmoto, and K. Ikeda, *Phytochemistry*, 1990, **29**, 3060.
   b) T. Ohmoto and K. Koike, *Chem. Pharm. Bull.*, 1983, **31**, 3198.
3. P. A. Vember, I. V. Terent'eva, and G. V. Lazur'evskii, *Khim. Prir. Soedin.*, 1967, **3**, 249 (*Chem. Abstr.*, 1967, **67**, 108816t).
4. H. Suzuki, Y. Yokoyama, C. Miyagi, and Y. Murakami, *Chem. Pharm. Bull.*, 1991, **39**, 2170.
5. J. Pigulla and E. Röder, *Liebigs Ann. Chem.*, **1978**, 1390.
6. Röder assigned the signals of 8.2 - 8.4 ppm as *N*-H's of indole and imido group.
7. Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, *Chem. Pharm. Bull.*, 1988, **36**, 2023.
8. The early stage of this reaction gave a complex mixture on tlc (presumably, **9a** was formed at first, and oxidation occurred gradually on tlc). However, the reaction mixture gave a single spot of the target compound (**1**) on tlc few hours later.

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