

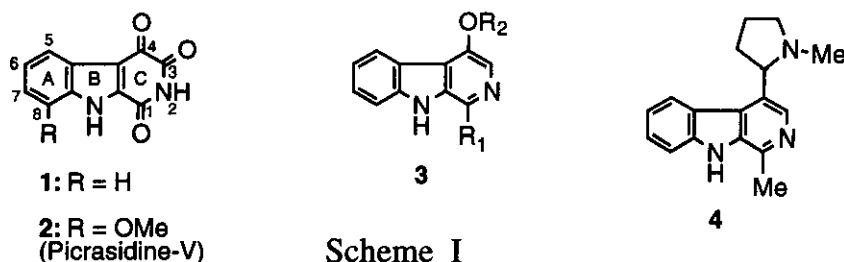
SYNTHETIC STUDIES OF 1, 2, 3, 4-TETRAHYDRO-1, 3, 4-TRIOXO- β -CARBOLINE ALKALOIDS I[†]

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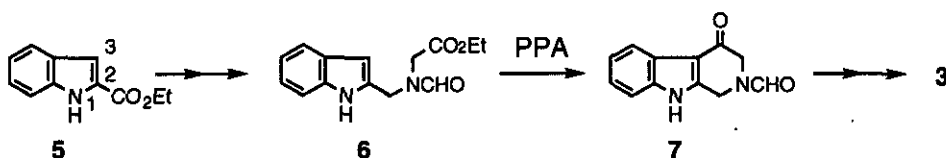
Abstract - A simple and efficient total synthesis of 1, 2, 3, 4-tetrahydro-1, 3, 4-trioxo- β -carboline (**1**) was accomplished *via* C₃-selective acylation of indole-2-carboxylate (**5**). On the course of this study, we found that the cyclization of *N*-(2-indolecarbonyl)glycine (**8a**) with PPA gave only an *N*-cyclized 6-membered ring (**10a**), whereas *N*-(2-indolecarbonyl)- β -alanine (**8b**) gave a C₃-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 CrO₃-oxidation during the structural determination.³



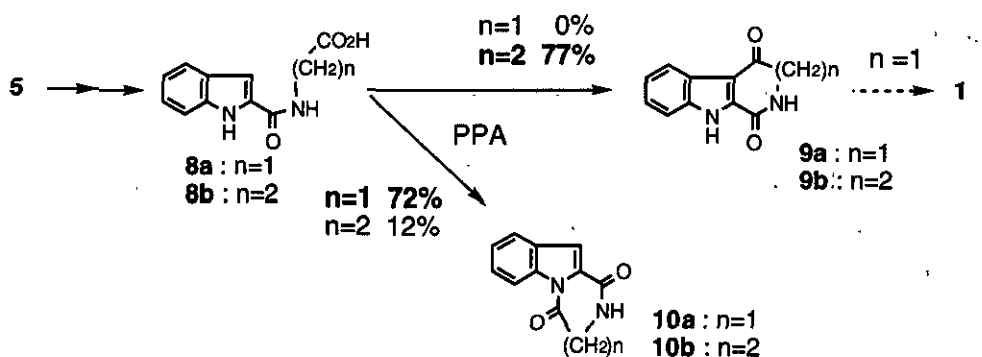
[†] Dedicated to the memory of late Prof. Yoshio Ban.

In this paper we report the total synthesis of **1** starting from ethyl indole-2-carboxylate (**5**). We have already succeeded⁴ in the synthesis of 4-methoxy- β -carboline (**3**, $R_2 = \text{CH}_3$) starting from **5** via elongation of C_2 -substituent to **6** and cyclization toward the C_3 -position to **7**.

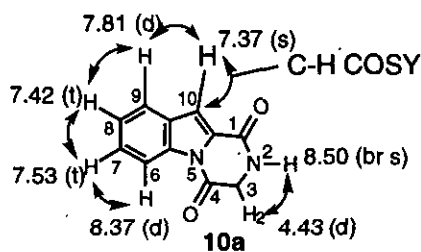


Scheme II

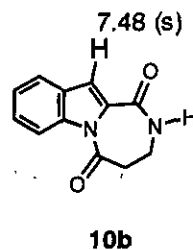
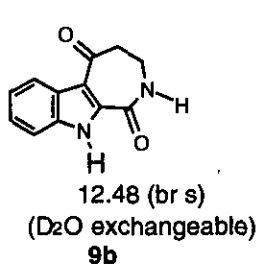
We planned a total synthesis of **1** via the oxidation of **9a** which was synthesized via cyclization of **8a** (Scheme III). Röder⁵ had reported that the cyclization of **8a** and **8b** with polyphosphoric acid (PPA) gave only C_3 -cyclized product (**9a**, **9b**), respectively. When we treated **8a** with PPA according to Röder's report, we obtained a single product possessing melting point ($242\text{--}245^\circ$) 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 $\text{C}_{10}\text{-H}$ corresponding to usual indolic $\text{C}_3\text{-H}$ was observed at 7.37 ppm as a sharp singlet, which was unexchangeable with D_2O , and has a NOESY to $\text{C}_9\text{-H}$ and C-H COSY to tertiary $\text{C}_{10}\text{-carbon}$ at 111.7 ppm. So it should be sure that they⁶ took the $\text{C}_6\text{-H}$ 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

$^1\text{H-Nmr } \delta$ (ppm) :

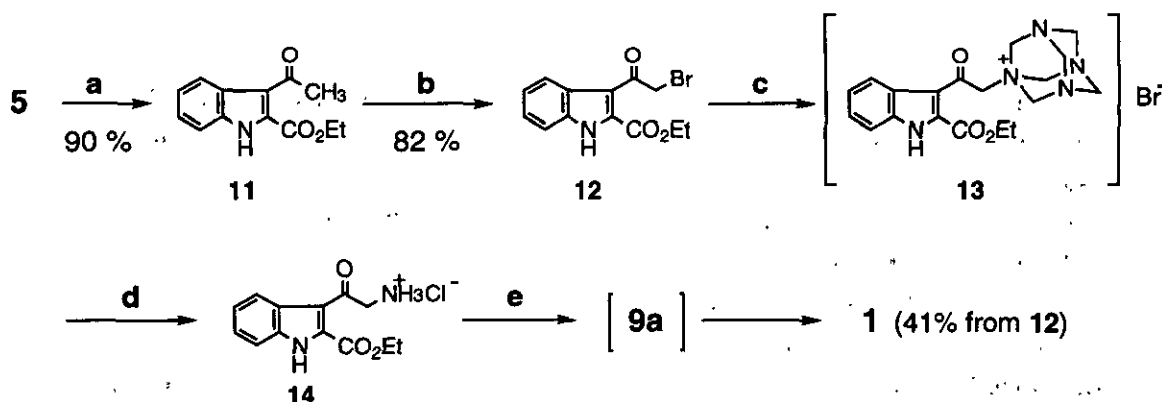
NOESY and C-H COSY observation



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 C₃-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 C₃-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 C₃-cyclized product (**9a**), failed to give the desired C₃-cyclized product (**9a**). Hence we synthesized **9a** via a more confident route described in scheme V.



a: (CH₃CO)₂O, AlCl₃ / ClCH₂CH₂Cl, room temperature, 10 h **b:** CuBr₂ [1.8 mol(0.9 eq.)] / AcOEt, reflux, 1 h **c:** hexamethylenetetramine / CHCl₃, room temperature, 1 h **d:** c.HCl / EtOH, 55°, 1 h **e:** Et₃N / EtOH, room temperature, 10 h

Scheme V

The C₃-selective Friedel-Crafts acylation⁷ of **5** gave the 3-acetyl product (**11**), and selective bromination of the α -carbon of the carbonyl group with CuBr₂ 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 Et₃N 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 (IC₅₀ = 13.6 \pm 0.5 μ g / ml), HOC-21 human ovarian cancer cell (IC₅₀ = 25.2 \pm 1.3 μ g / ml) and MKN-28 human cancer cell (from human stomach) (IC₅₀ = 16.1 \pm 1.3 μ g / 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

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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.