

A NEW ROUTE TO 4-OXYGENATED β -CARBOLINES: THE TOTAL SYNTHESIS OF CRENATINE¹

Yasuoki Murakami*, Yuusaku Yokoyama, Chiyoko Aoki (nee Ishiyama),
Chiemi Miyagi, Toshiko Watanabe, and Taichi Ohmoto
School of Pharmaceutical Science, Toho University,
2-2-1, Miyama, Funabashi, Chiba 274, Japan

Abstract— Crenatine, a new type of β -carboline alkaloid having an oxygen function at its C₄-position, was synthesized using ethyl 1-benzylindole-2-carboxylate as a starting material via cyclization of C₂-substituent to C₃-position of indole nucleus and AlCl₃-catalyzed debenzylation for N-protected indoles.

Recently, a number of new type of β -carboline alkaloids having an oxygen function at their C₄-position as illustrated in Figure 1 were isolated from Simaroubaceae by Ohmoto² and others.³ These are expected to have interesting biological activities, because 4-hydroxy- β -carboline-1-carboxaldehyde (**1b**) has been reported⁴ to have anti-tumour and xanthin oxidase inhibitory activities. However, the biological activity of the other compounds has not been examined, because of the limited amount of isolation from natural sources. This situation prompted us to synthesize these alkaloids (**1**). There is no report for the synthetic approach of **1** except for the total synthesis of crenatine (**1a**) reported by Cook⁵, which involved DDQ oxidation of the tetrahydro- β -carboline derivative. We wish to report here a total synthesis of crenatine (**1a**) based on a new strategy leading

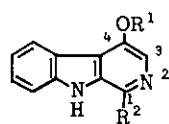
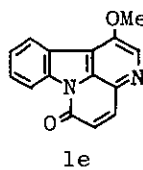
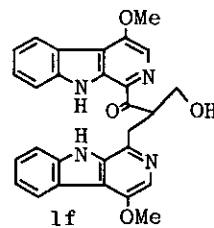


Figure 1

- 1a**: R¹=Me, R²=Et
(Crenatine)
b: R¹=H, R²=CHO
c: R¹=Me, R²=CO₂Me
d: R¹=Me, R²=CH(OH)CH₂OH

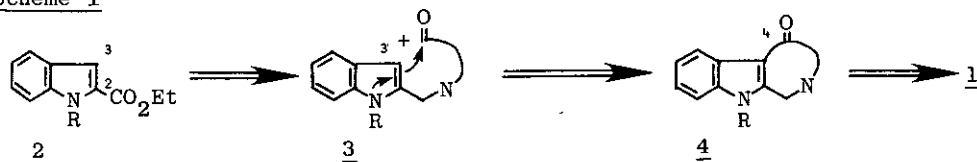


1e

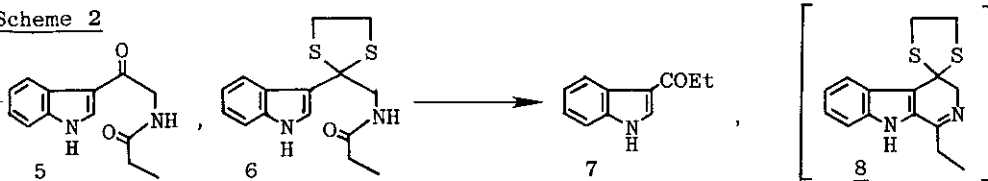


1f

Scheme 1



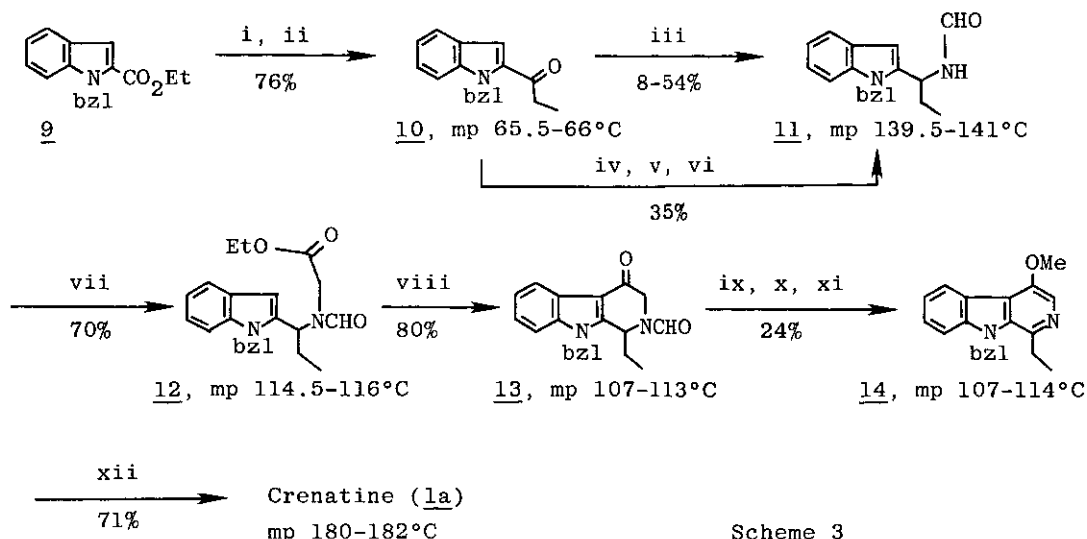
Scheme 2



to a general synthetic route of this type of alkaloids (**1**), using ethyl 1-benzylindole-2-carboxylate (**9**) as a starting material. Synthetic utility of **9** or corresponding NH compound has been extensively studied by us⁶, since it can be considered to be a stable synthetic equivalent or substitute of indole itself. The present strategy involves the use of a carboethoxy group of **9** as one-carbon unit and the cyclization of elongated C_2 -substituent to nucleophilic C_3 -position (Scheme 1). One of the advantage of our strategy is that the cyclization step from C_2 - to C_3 -position results in the simultaneous introduction of oxygen function at the C_4 -position of β -carboline skeleton.

Before starting with this route, we planned a route via Bischler-Napieralski reaction, which has been a representative β -carboline synthesis. We actually carried out the reaction on the 3-acylindole protected by thioketal (**6**), as the reaction on unprotected 3-acylindole such as **5** has been known to give an oxazole derivative.⁷ However, the reaction gave only 3-propionylindole⁸ (**7**) without a corresponding β -carboline (**8**).

The synthetic route of **1a** is shown in Scheme 3.⁹ The ester (**9**) was reacted with lithium salt of ethyl propionate, followed by hydrolysis and decarboxylation to give ethyl ketone (**10**). After all attempts for direct introduction of the glycine residue to the ethyl ketone (**10**) were failed, stepwise sequence was adopted. The amination to **11** was accomplished by two methods, that is, the Leuckart reaction and the NaBH_4 - TiCl_4 reduction of the oxime.¹⁰ The latter method was more advantageous than the former, because the operation is troublesome and yield was not reproducible in the former. Alkylation with ethyl chloroacetate and the subsequent cyclization of the amide ester (**12**) with PPA smoothly proceeded to give 4-oxo-tetrahydro- β -carboline (**13**) in good yield. Hydrolysis of **13**, followed by



Scheme 3

Reagents: i) LDA/CH₃CH₂CO₂Et, ii) 30% H₂SO₄ in AcOH, iii) HCO₂H/HCONH₂/(NH₄)₂SO₄, 190°C, 42-90 atm, iv) NH₂OH·HCl/AcONa, v) NaBH₄/TiCl₄, vi) HCO₂Et, vii) NaH/ClCH₂CO₂Et, viii) PPA, ix) conc. HCl, x) Pd-C/decalin, xi) Me₂SO₄/Na₂CO₃, xii) AlCl₃/anisole

aromatization and methylation gave N-benzylcrenatine (14). The methylation was successful by a combination of dimethyl sulfate and sodium carbonate, whereas diazomethane gave a poor result.

It has been known that benzyl group attached to indole nitrogen could be removed only by reduction with sodium in liquid ammonia (Birch reduction). However, the pyridine nucleus with methoxy group was considered to be sensitive under Birch condition. Recently we developed^{6e} AlCl₃-catalyzed debenylation of 2-acylindoles which are stable to Lewis acid, using benzene or anisole as solvent and trapping agent for benzyl cation generated. This method was applied to the last debenylation step for the synthesis of crenatine¹¹ (1a). The desired product (1a) was obtained in a good yield when anisole was used as a solvent. Synthetic crenatine (1a) was identical in all respects with the natural one,^{2b} mp 177-178°C.

We believe that our strategy provides a new route leading to general synthesis of 4-oxygenated-β-carboline alkaloids, and so syntheses of the other alkaloids (1) are now in progress.

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- 8) The mechanism of formation of the product will be discussed in a future paper.
- 9) All compounds with melting point in this paper showed satisfactory elemental analysis and spectral data.
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- 11) This debenzylolation method for 2-acylindoles was also found to be effective for other fully aromatized indoles, N-benzylcarbazole and N-benzyl- β -carboline, in 85 and 61% yields, respectively. This fact suggests that this method can be applied to debenzylolation of various indoles stable to $AlCl_3$.

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