A NEW ROUTE TO 4-OXYGENATED β-CARBOLINES: THE TOTAL SYNTHESIS OF CRENATINE[1]

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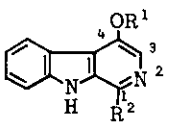
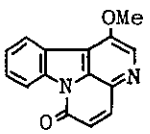
Abstract—— Crenatine, a new type of β-carboline alkaloid having an oxygen function at its C_4-position, was synthesized using ethyl 1-benzylindole-2-carboxylate as a starting material via cyclization of C_2-substituent to C_3-position of indole nucleus and $AlCl_3$-catalyzed debenzylation for N-protected indoles.

Recently, a number of new type of β-carboline alkaloids having an oxygen function at their C_4-position as illustrated in Figure 1 were isolated from Simaroubaceae by Ohmoto[2] and others.[3] These are expected to have interesting biological activities, because 4-hydroxy-β-carboline-1-carboxaldehyde (1b) has been reported[4] 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 Cook[5], 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

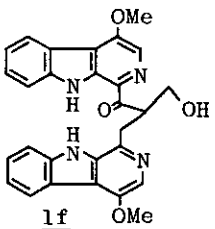


1a: R^1=Me, R^2=Et (Crenatine)
b: R^1=H, R^2=CHO
c: R^1=Me, R^2=CO_2Me
d: R^1=Me, R^2=CH(OH)CH_2OH

Figure 1

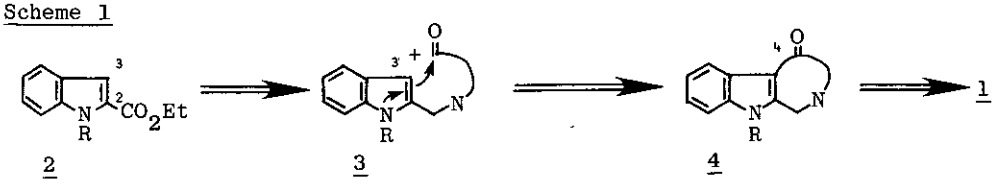


1e

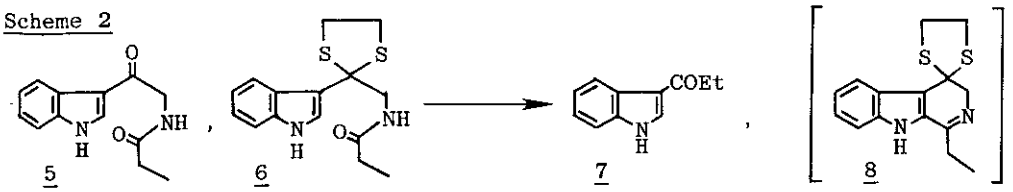


1f

Scheme 1



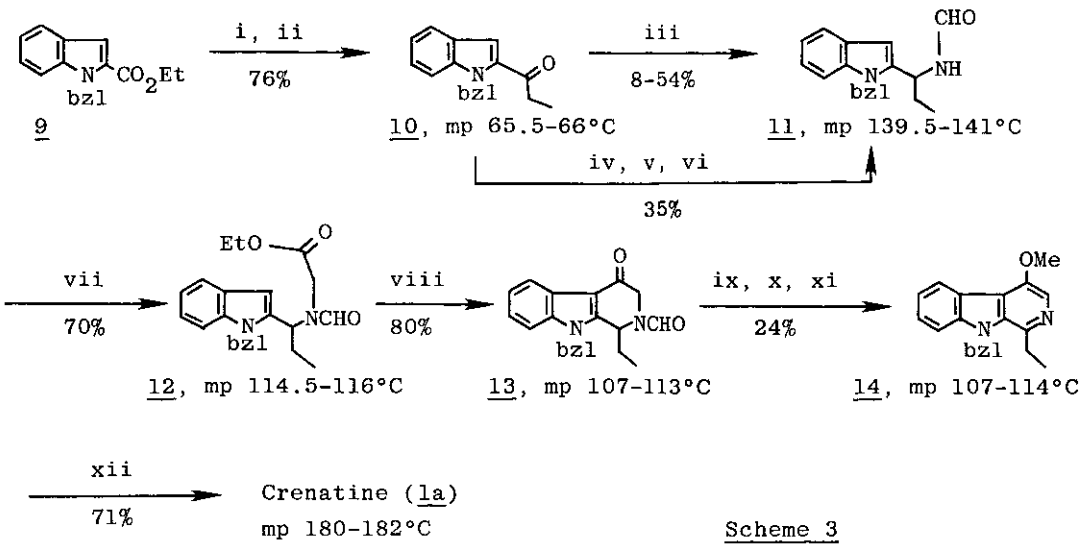
Scheme 2



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 us[6], 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-propionylindole[8] (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



9
10, mp 65.5-66°C
11, mp 139.5-141°C
12, mp 114.5-116°C
13, mp 107-113°C
14, mp 107-114°C

Scheme 3

Reagents: i) LDA/$CH_3CH_2CO_2Et$, ii) 30% H_2SO_4 in AcOH, iii) $HCO_2H/HCONH_2/(NH_4)_2SO_4$, 190°C, 42-90 atm, iv) $NH_2OH \cdot HCl$/AcONa, v) $NaBH_4/TiCl_4$, vi) HCO_2Et, vii) NaH/$ClCH_2CO_2Et$, viii) PPA, ix) conc.HCl, x) Pd-C/decalin, xi) Me_2SO_4/Na_2CO_3, xii) $AlCl_3$/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] $AlCl_3$-catalyzed debenzylation 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 debenzylation step for the synthesis of crenatine[11] (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.

REFERENCES AND NOTES

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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.

10) S. Kano, Y. Tanaka, E. Sugino, and S. Hibino, Synthesis, 695 (1980).

11) This debenzylation 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 debenzylation of various indoles stable to $AlCl_3$.

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