

Note

A facile synthesis 2,3,4,9-tetrahydro- β -carbolin-1-ones

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A short and efficient synthesis and characterization of various tetrahydro- β -carboline derivatives have been synthesized using Japp-Klingmann condensation followed by cyclization. A new two-pot reaction sequence is used to furnish these compounds in good overall yield. Some of the compounds are screened for their antibacterial activity.

Keywords: β -carbolines, Japp-Klingmann condensation, anti-microbial activity, 2,3,4,9-tetrahydro- β -carbolin-1-ones, and cyclization

A number of 2,3,4,9-tetrahydro- β -carbolin-1-ones have been known as potential biologically active compounds such as bauerine A-C **2-4** which possess central nervous depressant activity¹. These β -carboline moieties is the core structure of various synthetic pharmaceuticals displaying a broad spectrum of biological activities such as hortiamine² (hypotensive), canthins³ (cytotoxic and antileukemic activity), rutaecarpine⁴ **1** (anti-inflammatory and cytotoxic) and several other β -carboline derivatives⁵ show the anti HIV and antitumor activity.

β -Carbolines are conformationally constrained tryptamine analogues, very fascinating and under-investigated compounds. As a continuation of interest in the synthesis of biologically active molecules utilizing different methodology, a short synthesis of β -carbolines was carried out.

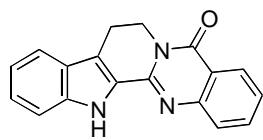
Results and Discussion

As a part of research on zolmitriptan⁶, a process for synthesizing zolmitriptan was developed which encountered with an impurity that was identified as a derivative of 2,3,4,9-tetra hydro- β -carboline-1-one. This observation led encouraged to investigate this methodology thoroughly and apply in the synthesis of various biologically active compounds. It is worth mentioning that the basic skeleton (β -carboline) present in the impurity isolated in the process of zolmitriptan is very interesting, as many biologically active compounds possess this skeleton.

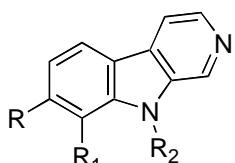
A number of approaches for the preparation of β -carboline derivatives have been reported in the literature. The 2,3,4,9-tetrahydro- β -carbolin-1-one can be prepared by using various different types of starting materials like ethyl 2-carbeethoxy-4-cyanopentanoate⁷, harmaline⁸, glycine⁹, 5-methoxytryptamine-2-carboxylic acid¹⁰, phenylhydrozone¹¹ and *N*-substituted indole carboxylic acid¹².

The earlier reported synthetic methods involve lengthy procedure, costly raw materials and not suitable for commercialization. The present methodology can overcome these limitations and can be extended to the synthesis of the various biologically active molecules like hortiamine, 6-methoxyrhetsinine, canthins, bauerine C, and several other β -carboline derivatives.

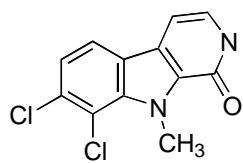
A more efficient approach for the synthesis of 2,3,4,9-tetrahydro- β -carbolin-1-ones from easily available starting materials amines **1** (**Scheme I**) were subjected to Japp-Klingmann condensation with readily available intermediate ethyl-2-acetyl-5-phthalimido pentanoate **2** (ref. 13) give the corresponding intermediate **3** in 80-92% yield. The indole derivatives **3** on treatment with hydrazine hydrate and hydrochloric acid furnished the crude 2,3,4,9-tetrahydro- β -carbolin-1-ones **4**. The crude compounds were purified by column chromatography



Rutaecarpine I



Bauerine-A ($R = Cl$, $R_1 = H$, $R_2 = CH_3$) **II**
 Bauerine-B ($R = Cl$, $R_1 = Cl$, $R_2 = CH_3$) **III**



Bauerine-C IV

using ethyl acetate and petether mixture as an eluent to give pure 2,3,4,9-tetrahydro- β -carbolin-1ones in 50-70% yield. 1,2,3,4-tetrahydro 1,4-phthalazine dione is isolated as a minor product in every cyclization. During the preparation of 1-oxo-2,3,4,9-tetrahydro-1H- β -carboline-5-carboxylic acid **4c**, formation of substantial amount of ethyl 1-oxo-2,3,4,9-tetrahydro-1H- β -carboline-5-carboxylate **4d** has been observed. The longer reaction time has been recorded for the Japp-klingman condensation with halogen substituted starting materials (amines).

In-vitro antibacterial screening

The reported compounds were tested for the *in-vitro* antimicrobial assay and tested against a panel of organisms consisting of reference Gram-positive bacteria and Gram-negative bacteria. These compounds were found inactive. linezolid and moxifloxacin were used as control antibiotics in the assay.

Experimental Section

General methods ^1H NMR spectra were determined in CDCl_3 , $\text{DMSO}-d_6$ solution on a Varian Gemini 200 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (J) are given in hertz.

Melting points were determined using scientific capillary melting point apparatus and are uncorrected. Mass spectra were obtained on a HP-5989A mass spectrometer. Thin layer chromatography was performed on silica gel plates (SRL 230-400 mesh). All the solvents used were commercially available and was distilled before use.

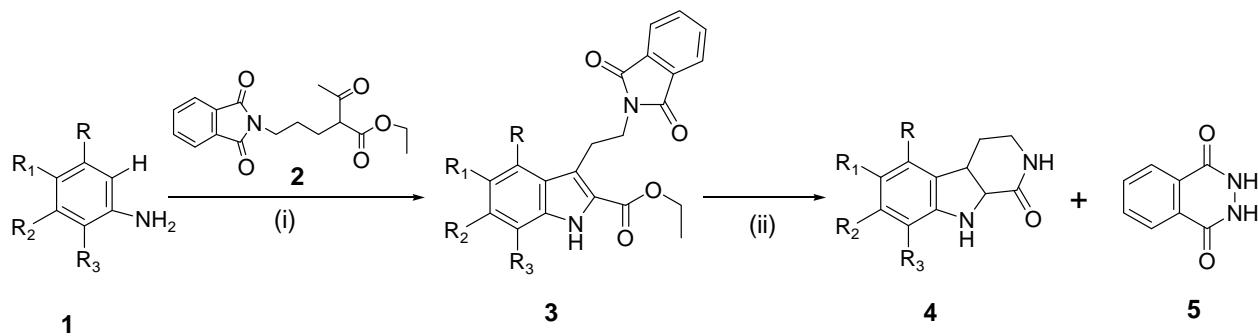
Representative procedure for the intermediate

Preparation of Ethyl 3-[2-(1,3-dioxo-2,3 dihydro-1H-2-isoindolyl)ethyl]-1H-2indole carboxylate

Part A. 3.5 g (0.0107 mole) of ethyl 2- acetyl-5-phthalimidopentanoate and ethanol (36 mL) were taken into four-necked round-bottom flask, 7.2 g (0.088 mole) of sodium acetate was added to the reaction-mixture while stirring the mixture for 5 min and the solution was stirred at room temperature for 1 hr.

Part B. 1g of aniline (0.0107 mole), 3 mL of ethanol, and 4.7 mL of water were taken in a four neck round bottom flask, stirred and cooled to 0°C . 3 mL of concentrated hydrochloric acid was added to the reaction mixture over 30 min while stirring. The reaction- mixture was stirred at 0°C for 10-15 min. Freshly prepared sodium nitrite 0.812 g (0.117 mole) solution was slowly added to the reaction-mixture at -5 to 10°C and stirred at this temperature for 30 min.

The Part A mixture was cooled to 0°C and Part B mixture was added to it and maintained at room



Reagents and conditions: (i) NaOAc , EtOH , Conc. HCl , NaNO_2 ; (ii) NH_2NH_2 and HCl

R	R ₁	R ₂	R ₃
4a	H	OCH_3	H H
4b	H	OH	H H
4c	COOH	H	H H
4d	COOC_2H_5	H	H H
4e	H	H	H H
4f	Br	H	H H
4g	H	H	Cl Cl
4h	H	Cl	Cl H
4i	H	H	Cl H

Scheme I

temperature for 3 hr. The reaction-mixture was extracted with dichloromethane. The organic solvent was evaporated; the residue was taken in ethanol and 10% of ethanolic HCl was added to the solution under reflux condition. Reaction-mixture was stirred for 2 hr at reflux condition. The separated solid was filtered and washed with chilled ethanol to give yellow powder. m.p : 233-38°C. ^1H NMR (200 MHz, DMSO- d_6): δ 8.20 (s, 1H), 8.04 (m, 1H), 7.87 (m, 1H), 7.27 (m, Ar-H), 6.93 (s, 1H), 4.07 (t, 2H), 3.31 (t, 2H). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4$: C, 69.60; H, 5.01; N, 7.73; O. Found: C, 69.78; H, 5.12; N, 7.82%; mass (CI): 363 (M+1).

Preparation of 2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4e. 0.890 g of ethyl 3-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl]-1*H*-2indole carboxylate and (50 mL) of ethanol was taken in four-necked round bottom flask. Hydrazine hydrate (3 mL) was added slowly to the mixture at temperature 40-45°C and maintained for 2 hr. Hydrochloric acid (10%) was added to the mixture and filtered. The filtrate was neutralized and extracted with ethyl acetate; the organic layer was evaporated and purified by column chromatography using ethyl acetate: pet ether (50:50 v/v) as eluent to give of fine yellow powder in 52% yield. ^1H NMR (200 MHz, DMSO- d_6): δ 11.99 (s, 1H), 11.77 (s, 1H), 7.73 (d, 1H), 7.26 (m, Ar-H), 3.25 (t, 2H), 2.94 (t, 2H). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.97; H, 5.62; N, 15.13%; mass: (CI): 187 (M+1).

Spectral data for the prepared compounds are given below:

6-Methoxy-2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4a: ^1H NMR (200 MHz, CDCl_3): δ 11.20 (s, 1H), 7.43 (d, 2H), 6.98 (s, 1H), 6.80 (d, 1H), 3.98 (s, 3H), 3.68 (t, 2H), 2.92 (t, 3H); mass (CI): 217 (M+1).

6-Hydroxy-2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4b: ^1H NMR (200 MHz, CDCl_3) δ 11.20 (1H, s), 7.43 (2H, d), 6.98 (1H, s), 6.80 (1H, d), 3.98 (3H, s), 3.68 (2H, t), 2.92 (3H, t); mass: (CI): 203 (M+1).

1-Oxo-2,3,4,9-tetrahydro-1*H*- β -carbolin-5-carboxylic acid 4c: ^1H NMR (200 MHz, CDCl_3): δ 10.21 (s, 1H), 7.89 (d, 2H), 8.06 (s, 1H), 7.64 (m, H), 5.69 (d, 1H), 3.67 (t, 2H), 2.57 (t, 2H); mass: (CI): 231(M+1).

Ethyl 1-oxo-2,3,4,9-tetrahydro-1*H*- β -carbolin-5-carboxylate 4d: ^1H NMR (200 MHz, CDCl_3): δ 12.03 (s, 1H), 11.54 (s, 2H), 8.06 (s, 2H), 7.91(m, 2H), 7.89 (d, 2H), 7.76 (d, 1H), 4.38 (q, 2H), 3.53 (t, 2H), 2.99 (t, 2H); 1.38 (t, 3H); mass (CI): 259 (M+1).

7-Bromo 2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4f: ^1H NMR (200 MHz, DMSO- d_6): δ 11.99 (s, 1H), 11.77 (s, 1H), 7.73 (d, 1H), 7.26 (m, Ar-H), 3.25 (t, 2H), 2.94 (t, 2H); mass (CI): 266 (M+1).

7,8-Dichloro 2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4g: ^1H NMR (200 MHz, CDCl_3): δ 12.04 (s, 1H), 7.68 (s, 1H), 7.54 (d, 1H), 7.19 (d, 1H), 3.56 (t, 2H), 2.97 (t, 2H); mass (CI): 256 (M+1).

6,7-Dichloro, 2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4h: ^1H NMR (200 MHz, CDCl_3): δ 12.20 (s, 1H), 11.90 (s, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.60 (s, 1H), 7.40 (s, 1H), 3.20 (t, 2H), 2.97 (t, 2H); mass (CI): 256 (M+1).

7-Chloro, 2,3,4,9-tetrahydro-1*H*- β -carbolin-1-one 4i: ^1H NMR (200 MHz, CDCl_3): δ 11.98 (s, 1H), 11.77 (s, 1H), 7.64 (s, 1H), 7.54 (d, 1H), 7.19 (d, 1H), 3.56 (t, 2H), 2.97 (t, 2H); mass (CI): 221(M+1).

Ethyl-2-acetyl-5-phthalimido pentanoate 2: ^1H NMR (CDCl_3): δ 7.79 (s, 1H), 7.36 (s, 1H), 6.55 (d, 1H), 5.41(d, 1H), 3.26 (t, 2H), 3.01 (t, 2H); mass (CI): 203 (M+1).

1,2,3,4-Tetrahydro 1,4-phthalazine dione 5: ^1H NMR (200 MHz, CDCl_3): δ 8.10 (m, Ar-H), 7.90 (m, Ar-H); mass (CI): 163 (M+1).

In summary, biologically important, tetrahydro- β -carboline derivatives were synthesized in good overall yield.

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