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A Facile Synthesis Of Rutaecarpine

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ABSTRACT

Total synthesis of rutaecarpine, a unique indoloquinazoline alkaloid from rutaceous plants, has been achieved from 2,3,4,9-tetrahydro-β-carbolin-1-one. The key step is the Japp-Klingmann condensation between aniline and ethyl 2-[2-(1,3-dioxo-2,3- dihydro-1H-2-isoindolyl ethyl]-3-oxobutanoate.Treatment of 2,3,4,9-tetrahydro-β-carbolin-1-one with methyl anthranilate gives the rutaecarpine.

KEYWORDS

Rutaecarpine;
β-Carboline;
Japp-Klingmann condensation;
Alkaloid;
Zolmitriptan.

INTRODUCTION

Rutaecarpine **(1)** is an indolopyridoquinazoline alkaloid that has been isolated from rutaceous plants[1], such as *Evodia ruraecarpa*, and has long been used to treat inflammation related disorders in traditional oriental medical practice. It is one of the constituents of the Chinese herbal drugs Wou-hou-Yu[2] and Shih-Hu[3], which have been used for gastrointestinal disorders, headache and dysentery. In addition to its anti-inflammatory activity, there are reports that rutaecarpine has cytotoxic, anti-platelet aggregation, vasorelaxation, and anti-anoxic activities. Owing to its pharmaceutical activities, attention still focused on development of new synthetic methods for rutaecarpine. 10-bromo rutaecarpine, 11-methoxy rutaecarpine and 10, 11-methylenedioxy rutaecarpine have been shown to possess cytotoxic activity[4]. The first total synthesis of rutaecarpine (1) was achieved by Tetsuji Kametan[5] et al in the year 1976.We now wish to report a more efficient synthesis of rutaecarpine **(1)**, which will be suitable for the large scale production of rutaecarpine, an important tool in the studies of plant physiology.

As a continuation of our interest in the synthesis of biologically active molecules utilizing different methodology, we envisioned a short synthesis of β-carbolines. β-Carboline moieties is the core

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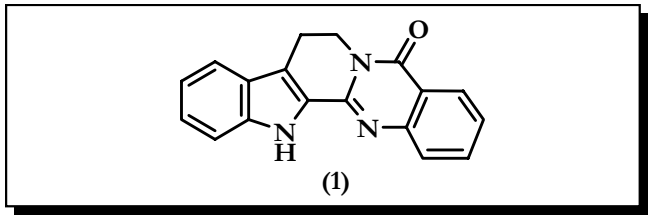


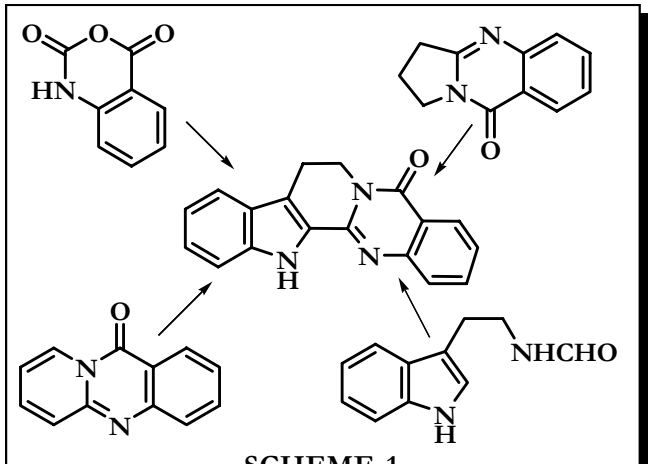
(1)

structure of various synthetic pharmaceuticals displaying a broad spectrum of biological activities, which is conformationally constrained tryptamine analogues, very fascinating and under-investigated class of compounds.

As a part of our process research on Zolmitriptan[6], we developed an in-house process for Zolmitriptan in which we encountered with an impurity that was identified as a derivative of 2,3,4,9-tetra hydro-β-carboline-1-one **(4)**. This observation encouraged us 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 such as Incasan[7], Canthin[8], Bauerine A-C[9], and rutaecarpine **(1)** derivatives possess this skeleton.

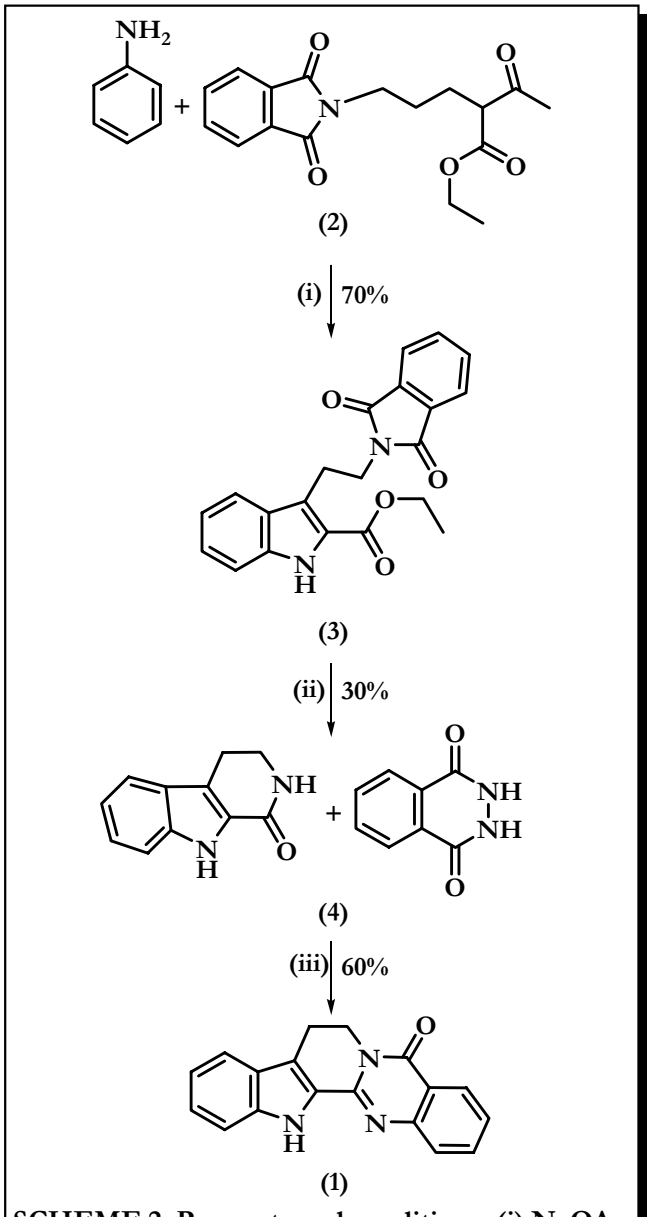
RESULTS AND DISCUSSION

The various approaches for the total synthesis of rutaecarpine have been reported in the literature; Subhash et. al[10] approach involves the isatoic anhydride as starting material and comprises a sequence of seven synthetic steps. An alternative total synthesis of rutaecarpine was reported by Josef Kokosi et al.[11], which involves pyridoquinazoline and deoxyvasicinone alkaloid as starting material. Tetsuji et al, which involves N-formyltryptamine as a starting material. Most of these synthetic process for rutaecarpine involves the more synthetic steps, used costly raw materials and not feasible for large-scale preparation. The starting materials for this synthesis by various approaches is outlined in SCHEME 1



SCHEME 1

Our synthetic method is able to over comes these limitations, and provides an easy access to rutaecarpine and its derivatives. In addition, this process will be



SCHEME 2: Reagents and conditions: (i) NaOAc, EtOH, Conc. HCl, $NaNO_2$; (ii) NH_2NH_2 and HCl; (iii) Methyl anthranilate, $POCl_3$

Note

easy to operate in large-scale preparation. The synthesis is outlined in SCHEME 2.

Aniline was subjected to Japp-Klingmann condensation with readily available intermediate ethyl 2- [2-(1,3-dioxo-2, 3-dihydro-1H-2-isoindolyl ethyl]-3-oxo butanoate[12] 2 to give 2-{2-[2-(1-ethoxy vinyl) 1H-3-indolyl] ethyl}-1,3-isoindolinedione 3 in 70% yield. The intermediate ethyl 2-[2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl ethyl]-3-oxo butanoate **(2)** can be prepared according to the literature[12] in four simple steps. The cyclization of compound **(3)** using hydrazine hydrate and hydrochloric acid furnished the crude 2,3,4,9-tetrahydro-β-carbolin-1-one **(4)** in 30% yield, which was purified by column chromatography. Phthalyl hydrazide was the major byproduct in this reaction which on further treatment with methyl anthranilate in presence of $POCl_3$ gave the rutaecarpine **(1)** in 60% yield.

EXPERIMENTAL

General methods

^{1}HNMR spectra were determined in $CDCl_3$, DMSO-d_6 solution on Varian Gemini 200 MHz spectrometers. 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.

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

Part A: 3.5g (0.0107mmol) of ethyl 2- acetyl-5-phthalimidopentanoate and ethanol (36 ml) were taken into four-neck round-bottom flask. Next 7.2g (0.088mmol) of Sodium acetate was added to the reaction flask under stirring for 5min, and the solution were stirred at room temperature for 1 h.

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

The part-A mixture was cooled to 0°C and part-B mixture was added and maintained at room temperature for 3 h. reaction mixture was extracted to dichloromethane, evaporated the organic solvent. 10% of ethanolic hydrochloric acid was added to the solution under reflex condition. Reaction was maintained for 2h at reflex condition. Solid was filtered and washed with chilled ethanol to 3 in 70% yield. . ^{1}HNMR (200 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.04 (m, 1H), 7.87 (m, 1H), 7.27 (m, ΦH), 6.93 (s, 1H), 4.07 (t, 2H), 3.31 (t, 2H) Anal. Calcd. For $C_{21}H_{18}N_2O_4$ (362.38); C, 69.60; H, 5.01; N, 7.73. Found: C, 69.78; H, 5.12; N, 7.82. MS (CI method) 363 (M+1).

2,3,4,9-tetrahydro-1H-β-carbolin-1-one (4)

0.890g of ethyl 3-[2-(1,3-dioxo-2, 3 dihydro-1H-2-isoindolyl) ethyl]-1H-2indole carboxyl ate and (50ml) of ethanol were taken in four-necked round bottom flask. (3 ml) of hydrazine hydrate was added slowly at 40-45°C and maintained for two-hours.10% of hydrochloric acid was added 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) with 30% of yield. ^{1}HNMR (200 MHz, DMSO-d_6) δ 11.99(s, 1H), 11.77(s, 1H), 7.73(d, 1H), 7.26(m, ΦH), 3.25(t, 2H), 2.94(t, 2H), Anal. Calcd. For $C_{11}H_{10}N_2O$ (186.21); C, 70.95; H, 5.41; N, 15.04. Found: C, 70.97; H, 5.62; N, 15.13. MS (CI method) 187 (M+1).

Preparation of rutaecarpine (1)

2,3,4,9-tetrahydro-1H-β-carbolin-1-one (0.020g 0.0001mmol) was dissolved in toluene150 ml and heated the solution. Slowly $POCl_3$ (0.020g 0.0001 mmol) added. Methylanthranilate (0.030g 0.0002 mmol) was added under refluxed for two hours, cooled and filtered to yield the required compound:

^{1}HNMR (200 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.40 (d, 1H), 8.06 (s, 2H), 7.80-7.10 (m, ΦH), 4.26 (t, 2H), 3.23 (t, 2H), Anal. Calcd. For $C_{18}H_{13}N_3O$ (287); C, 75.25; H, 4.56; N, 14.63. Found: C, 75.40; H, 4.72; N, 14.87. MS (CI method) 288 (M+1).

Thus, we have achieved an efficient synthesis of rutaecarpine **(1)** in a seven steps with good yield. The overall procedure will be suitable for the large-scale production of this unique indoloquinazoline alkaloid derivative. The methodology involving the use of Japp-Klingman reaction will be useful for the synthesis of various rutaecarpine analogues. Utilizing this methodology prepared the β-Carboline derivatives, which are precursors for the total synthesis of Bauerine A-C, will be communicated shortly.

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