

SYNTHESIS OF 3-(PYRIDYL)-3,3A,4,9-TETRAHYDRO-2H-PYRAZOLINO[3',4':5,4]CYCLOPENT[B]INDOLE

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ABSTRACTS

Mixed aldol condensation of 1-oxo-1,2,3,8-tetrahydrocyclopent[b]- indole (**1a-d**) with pyridine-2-aldehyde (**2**) under basic condition led to formation of 2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**3a-d**). To an ethanolic solution of 2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole(**3a-d**) is refluxed with hydrazine hydrate resulted 3-pyridyl-3,3a,4,9-tetrahydro-2H-pyrazolino[3',4':5,4]cyclopent[b]indole (**4a-d**).

Key words : 1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole, pyridine-2-aldehyde, 2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole, 3- pyridyl- 3,3a, 4,9- tetrahydro- 2H- pyrazolino [3',4':5,4] cyclopent [b]indole.

1. INTRODUCTION

There has been a great deal of interest in annelated heterocycles for designing novel structures capable of performing multiple functions. Among the numerous indole alkaloids those containing b-fused cycloalkanes (Benoit Joseph *et al.*, 2001), unit in general and b-fused cyclopentane (Elisabeth Conchon *et al.*, 2008), unit in particular are reported to possess potential pharmacological activities (Julien Debray *et al.*, 2010). Indole is main constituent unit in many of the alkaloids of the natural origin. Indole and its derivatives are shown to exhibit antitumour, antiinflammatory, antibacterial (Sangeetha Velusamy *et al.*, 2003), and antifungal (Sangeetha Velusamy *et al.*, 2003), activities. Pyrazolines have also been reported to possess excellent

antibacteria (Sangeetha Velusamy *et al.*, 2003), antifungal (Sangeetha Velusamy *et al.*, 2003), and antiviral activities (Thomas Lemster, *et al.*, 2009). These compounds owe their activities to the heterocyclic ring present in the structure. The structural and biosignificance of indoles as well as pyrazolines (Youssef Hajbi, *et al.*, 2010), has infused interest in us to synthesize some unknown pyrazolino[3',4':5,4]cyclopent[b]indole derivatives (**3a-d**) utilizing 2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**2a-d**) as synthons to construct pyrazolino annelated rings on the cyclopent[b]indole skeleton. The new products have been characterized by C,H,N analysis, IR, ¹H NMR and mass spectral studies.

2. RESULTS AND DISCUSSION

2.1. Synthesis of 2-Pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (3a).

1-Oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**1a-d**) obtained were considered to be an efficient

precursor for the synthesis of many novel heterocyclic fused cyclopent[b]indoles. Mixed-aldol condensation of 5-methyl-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**1a**) with pyridine-2-aldehyde (**2**) under basic condition led to the formation of 5-methyl-2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**3a**) in 90% yield (**Scheme - 1**).

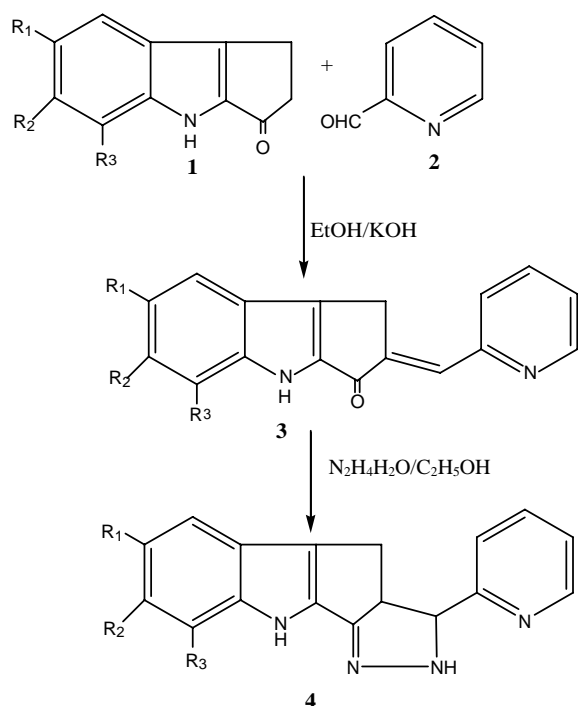
The IR spectrum of **3a** exhibited a strong absorption bands at 1675cm⁻¹ characteristic of α,β -unsaturated carbonyl group and at 3118 cm⁻¹ ascribable to -NH group. The ¹H-NMR spectrum showed the disappearance of C2 methylene proton signal and appearance of olefinic proton signal as a singlet at δ 7.21, which proved the mixed aldol condensation of 5-methyl-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**1a**) with pyridine-2-aldehyde (**2**) to give 5-methyl-2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**3a**). A singlet for three protons appeared at δ 2.38 was assigned to C5-CH₃ protons. The seven aromatic protons appeared as a multiplet at δ 7.34 to δ 8.74. The resonance owing to C3 methylene protons appeared as a singlet at δ 4.11, while that of -NH proton appeared as a broad singlet at δ 11.75. The molecular ion peak in its mass spectrum at m/z 275 and elemental analysis C 79.28% H 05.08% N 10.28% in accordance with the molecular formula C₁₆H₁₄N₂O. A series of compounds (**2b-d**) on reaction with pyridine-2-aldehyde. The characterization data of compounds (**2a-d**) are given in the Table 1.

2.2. Synthesis of 3-(pyridyl)-3,3a,4,9-tetrahydro-2H-pyrazolino[3',4':5,4]cyclopent[b]indole (4a).

Reaction of 2-pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**3a**) with hydrazine hydrate in ethanol, gave 3-pyridyl-3,3a,4,9-tetrahydro-2H-pyrazolino [3',4':5,4] cyclopent [b] indole (**4a**) in 65% yield. The IR spectrum revealed

the presence of $>C=N$ (1537 cm^{-1}) and absence of carbonyl absorption. The $^1\text{H-NMR}$ spectrum of 6-methyl-3-(pyridyl)-3,3a,4,9-tetrahydro-2H-pyrazolino[3',4':5,4]cyclopent[b]indole in CDCl_3 showed a singlet three protons at 2.78 corresponding to C6-CH_3 protons. The multiplet observed in the region δ 2.47-2.88 was assigned to C3 and C3a protons. The signal due to C4 methylene protons appeared as a singlet at δ 3.70. The resonance due to pyrazolino $-\text{NH}$ appeared as a broad singlet at δ 4.51 and indole $-\text{NH}$ was found at δ 8.47 as a broad singlet. A multiplet appeared in the region at δ 6.92-7.58 have been assigned to aromatic protons based on their integrations corresponding seven protons respectively. The mass spectrum showed the molecular ion peak at m/z 289. The elemental analysis agreed well with the proposed molecular formula $\text{C}_{18}\text{H}_{16}\text{N}_4$. The compounds (**4b-d**) were synthesized similarly from 2-pyridylidene-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**2b-d**). The characterization data of compounds (**4a-d**) are given in the Table 2.

Scheme 1



1,3,4 a : $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{R}_3 = \text{H}$; **b** : $\text{R}_2 = \text{CH}_3$, $\text{R}_1 = \text{R}_3 = \text{H}$; **c** : $\text{R}_3 = \text{CH}_3$, $\text{R}_1 = \text{R}_2 = \text{H}$; **d** : $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$

3. EXPERIMENTAL SECTION

Melting points were determined on mettler FP-5 instrument and are uncorrected. IR spectra of the new compounds have been recorded as KBr pellets on a Perkin-Elmer model 1600 FT-IR instrument in the region $4000 - 400\text{ cm}^{-1}$ and ^1H NMR spectra were recorded on a varian AMX-400 instrument using TMS as an internal standard. C, H, N analyses were performed on carlo erba 1108 model elemental C H N analyser. Electron impact mass spectrum was recorded using Jeol(D)-300 EI mass spectrometer.

3.1. Preparation of 2-Pyridylidene-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (3)

A mixture of 1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**1**) (0.001 mol) and pyridine-2-aldehyde (0.001 mol) was treated with 4% alc. KOH stirred 12 hrs at room temperature. The product precipitated as crystalline solid that was filtered off and washed with 50% aq ethonal. Another quantum of the same crystalline condensation compounds was obtained from the filtrate on neutralization with acetic acid followed by dilution with water. Pure crystals are crystallized from methanol. The product was obtained were separated through colum packed with silica gel and eluting with peteroleum ether – ethyl acetate mixture [85 : 15]. The product obtained by the removal of solvent mixture offered 2-Pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole.

3.2. Preparation 3-(pyridyl)-3,3a,4,9-tetrahydro-2H-pyrazolino[3',4':5,4]cyclopent[b]indole (4).

To an ethanolic solution of 2-Pyridelydine-1-oxo-1,2,3,8-tetrahydrocyclopent[b]indole (**3**) (0.001 mol) (20 ml), hydrazine hydrate (0.5 ml) was added and mixture was refluxed. After a period of 2hrs the solvent was removed under reduced pressure and the residue was washed with water and extracted with chloroform (3 x 15 ml), and the combined organic layer was dried over anhydrous sodium sulphate. Evaporation of the solvent followed by crystallization yielded the desired 3-(pyridyl)-3,3a,4,9-tetrahydro-2H-pyrazolino[3',4':5,4]cyclopent[b]indole as yellow powder.

Table 1. Characterization of compounds 3a-d

Compd.	mp°C	Yield(%)	Mol.Formula (Mol. Wt)	Calcd % (Found)		
				C	H	N
3a	257	70	C ₁₈ H ₁₄ N ₂ O	79.39	05.14	10.21
3b	244	68	C ₁₈ H ₁₄ N ₂ O	79.28	05.08	10.28
3c	222	57	C ₁₈ H ₁₄ N ₂ O	79.18	05.02	10.26
3d	234	54	C ₁₇ H ₁₂ N ₂ O	78.30	04.58	10.67

¹H NMR (CDCl₃) (δ ppm) of compounds 3a-d

2.38 (s, 3H, C ₅ -CH ₃), 4.11 (s, 2H, C ₃ -H), 7.34-8.54(m, 7H, C ₄ -H, C ₆ -H, C ₇ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 7.67 (s, 1H, olefinic - H), 11.75 (bs, 1H, carbazole H)
2.40 (s, 3H, C ₆ -CH ₃), 4.15 (s, 2H, C ₃ -H), 7.34-8.54(m, 7H, C ₄ -H, C ₅ -H, C ₇ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 7.73 (s, 1H, olefinic - H), 11.69 (bs, 1H, carbazole H)
2.32 (s, 3H, C ₇ -CH ₃), 4.25 (s, 2H, C ₃ -H), 7.46-8.55(m, 7H, C ₄ -H, C ₅ -H, C ₆ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 7.80 (s, 1H, olefinic - H), 11.75 (bs, 1H, carbazole H)
4.33 (s, 2H, C ₃ -H), 7.42-8.55(m, 7H, C ₄ -H, C ₅ -H, C ₆ -H, C ₇ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 7.98 (s, 1H, olefinic - H), 11.77 (bs, 1H, carbazole H)

Table 2. Characterization of compounds 4a-d

Compd	mp°C	Yield(%)	Mol.Formula (Mol. Wt)	Calcd% (Found)		
				C	H	N
4a	185	74	C ₁₈ H ₁₆ N ₄ (288)	74.97	05.59	19.43
4b	140	68	C ₁₈ H ₁₆ N ₄ (288)	74.88	05.57	19.36
4c	204	77	C ₁₈ H ₁₆ N ₄ (288)	74.87	05.56	19.44
4d	198	64	C ₁₈ H ₁₆ N ₄ (274)	74.46	05.25	20.48

¹H NMR (CDCl₃) (δ ppm) of compounds 4a-d

2.47-2.88 (s, C ₃ -H, C _{3a} -H), 2.78 (s, 3H, C ₆ -CH ₃), 3.70(m, 2H, C ₄ -H ₂), 4.51 (s, 1H, pyrazolino-NH), 6.92-7.58(m, 7H, C ₅ -H, C ₇ -H, C ₈ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 8.47(bs, 1H, Indole -NH)
2.37-2.80 (s, C ₃ -H, C _{3a} -H), 2.79 (s, 3H, C ₇ -CH ₃), 3.70(m, 2H, C ₄ -H ₂), 4.51 (s, 1H, pyrazolino-NH), 6.92-7.58(m, 7H, C ₅ -H, C ₆ -H, C ₈ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 8.47(bs, 1H, Indole -NH)
2.47-2.88 (s, C ₃ -H, C _{3a} -H), 2.78 (s, 3H, C ₈ -CH ₃), 3.70(m, 2H, C ₄ -H ₂), 4.51 (s, 1H, pyrazolino-NH), 6.92-7.58(m, 7H, C ₅ -H, C ₆ -H, C ₇ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 8.47(bs, 1H, Indole -NH)
2.47-2.88 (s, C ₃ -H, C _{3a} -H), 3.70(m, 2H, C ₄ -H ₂), 4.51 (s, 1H, pyrazolino-NH), 6.92-7.58(m, 8H, C ₅ -H, C ₆ -H, C ₇ -H, C ₈ -H, C _{3'} -H, C _{4'} -H, C _{5'} -H, C _{6'} -H), 8.47(bs, 1H, Indole -NH)

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