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# SYNTHESIS OF ISOXAZOLO AND PYRAZOLINO ANNELATED CARBAZOLES FROM 2-(3'-(2'-CHLORO) QUINOLIDINE)-1-OXO-1, 2, 3, 4-TETRAHYDROCARBAZOLE AND 2-CHLORO-3-FORMYLQUINOLINE.

**Sangeetha, V.**
Department of Chemistry, Kongunadu Arts and Science College, Coimbatore 641 029, India.
*E.mail: vsangeetha@rediffmail.com

## ABSTRACT

1-Oxo-1,2,3,4-tetrahydrocarbazole (**1**) on mixed aldol condensation with 2-chloro-3-formylquinoline (**2**) yielded 2-(3'-(2'-chloro)quinolidine)-1-oxo-1,2,3,4-tetrahydrocarbazole (**3**), which was further treated with hydroxylamine hydrochloride and hydrazine hydrate in separate reactions to afford 4,5-dihydro-3-3'-(2'-chloro) quinoline -isoxazolo [3,4-*a*]carbazole (**4**) and 3'-(2'-chloro)- quinoline- 3,3a,4,5- tetrahydro- 2*H*-pyrazolino [3,4-*a*]carbazole (**5**). The prepared compounds were elaluated for their invitro antibacterial and antifungal activities against certain pathogenic fungal and bacterial strains.

**Key words:** 1-Oxo-1,2,3,4-tetrahydrocarbazole, 2-chloro-3-formylquinoline, 2-(3'-(2'-chloro)quinolidine)-1-oxo-1,2,3,4-tetrahydrocarbazole, 4,5-dihydro-3-3'-(2'-chloro)quinoline-isoxazolo[3,4-*a*]carbazole, 3'-(2'-chloro)-quinoline-3,3a,4,5-tetrahydro-2*H*-pyrazolino[3,4-*a*]carbazole.

## 1. INTRODUCTION

Among the nitrogenous plant constituent's carbazole derivatives, a special class of indole alkaloids has attracted considerable attention owing to their diverse physiological activities. There has been a great deal of intrest in annelated heterocycles for designing novel structures capable of performing multiple functions. Among the numerous indole alkaloids those containing *b*-fused cycloalkanes (Benoit *et al.,* 2001), unit in general and *b*-fused cyclopentane (Elisabeth *et al.,* 2008), unit in particular is reported to possess potential pharmacological activities (Julien *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 and Jayaram Pillai, 2003) and antifungal activities (Sangeetha and Jayaram Pillai, 2003). Pyrazolines have also been reported to possess excellent antibacterial (Sangeetha and Jayaram Pillai, 2003), antifungal (Sangeetha and Jayaram Pillai, 2003), and antiviral activities (Thomas *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 *et al.,* 2010), has infused interest in us to synthesize some unknown 3'-(2'-chloro)-quinoline-3,3a,4,5-tetrahydro-2*H*-pyrazolino [3,4-*a*] carbazole and 4,5-dihydro-3-3'-(2'-chloro) quinoline-isoxazolo [3,4-*a*] carbazole utilizing 2-(3'-(2'-chloro) quinolidine)-1-oxo-1,2,3,4-tetrahydro carbazole as synthons to construct pyrazolino- and oxazolo-annelated rings on the carbazole skeleton. The new products have been characterized by C, H, N analysis, IR, 1H NMR and mass spectral studies.

## 2. RESULTS AND DISCUSSION

Mixed aldol reaction of 1-oxo-1,2,3,4-tetra hydrocarbazole (1a) with 2- chloro- 3-formyl quinoline (2) under basic condition gave the expected 2- (3'- (2'-chloro) -quinolidine) -1- oxo-1,2,3,4- tetrahydrocarbazole (3a) in a good yield. The IR spectrum of 3a exhibited two sharp and strong absorption bands at 3253 and 1643 $cm^{-1}$ characteristic of –NH group and α,β-unsaturated carbonyl group respectively. Its $^1H$ NMR spectrum showed the disappearance of $C_2$ proton signal and appearance of quinolinic proton signal as a singlet at δ 7.71 proved the validity of mixed aldol reaction of 1a with 2-chloro-3-formyl quinoline to give 3a. The $C_3$ and $C_4$ protons resonated as two multiplets centered at δ 3.09 and δ 3.16 respectively and a broad singlet at δ 11.87 for carbazole-NH. Further it exhibited a multiplet at δ 7.07 - 8.12 due to eight aromatic protons. A sharp singlet appeared at δ 8.60 shows presence of $C_4$' proton. The mass spectrum (m/z = 358) and the elemental analysis was compatible with the molecular formula $C_{22}H_{15}N_2OCl$. A series of similar compounds 3b-3d were realized with 1b-1d. (Scheme 1)

### *2.1. Synthesis of 4,5-dihydro-3-(3'-(2'-chloro)quinolin)isoxazolo[3,4-a]carbazole (4a-4d)*

In an another experiment, 2-(3'-(2'-chloro)quinolidine)-1-oxo-1,2,3,4-trahydrocarbazole

3a was condensed with hydroxylamine hydrochloride in dry pyridine. The reaction mixture, after work up, afforded the compound 4a, as a solid mass which was purified by column chromatography. The IR spectrum of 4a of this compound exhibited two absorptions at 3222 $cm^{-1}$ and 1604 $cm^{-1}$ which were ascribable to –NH and >C=N stretching vibrations respectively. Its $^1H$ NMR spectrum registered a multiplet at δ 3.30 – 3.32 corresponding to $C_4$ and $C_5$ protons in addition, a multiplet appeared at δ 7.15 – 8.96 for nine aromatic protons and a broad singlet at δ 12.01 corresponding for carbazole – NH proton. Its mass spectrum and the elemental analysis agreed well with the molecular formula $C_{22}H_{14}N_3OCl$. Based on the above mentioned spectral data the structure of the compounds was proposed as 4,5-dihydro-3-(3′-(2′-chloro) quinoline) isoxazolo[3,4-*a*]carbazole 4a. Similarly following the above condition, the compounds 8b-8d afforded the corresponding isoxazalo[3,4-*a*]carbazoles (4b-4d).

*2.2. Synthesis of 3'-(2'-chloro)-quinoline-3,3a,4,5-tetrahydro-2H-pyrazolino-[3,4-a]carbazole (5b-5d)*

Reaction of 2-(3'-(2'-chloro)quinolidine)-1-oxo-1,2,3,4-tetrahydrocarbazole (8a) with hydrazine hydrate in ethanol afforded the expected 3-(3'-(2'-chloro)quinolin)-3,3a,4,5-tetrahydro-2*H*-pyazolino [3,4-*a*]carbazole 9a in a moderate yield. Its IR spectrum (Fig. 4) revealed the formation of >C=N (1637$cm^{-1}$), thereby indicating the absence of carbonyl absorption. The $^1H$ NMR spectrum (Fig. 5) of 9a in DMSO showed as a multiplet resonated at δ 2.48 and δ 2.49 for $C_4$ and $C_5$ protons. $C_3$ and $C_{3a}$ protons appeared as a multiplet at δ 2.50. A broad singlet at δ 3.50 accounts for pyrazolino-NH proton and the nine aromatic protons resonated at δ 7.05-8.60 as a multiplet. Carbazole-NH appeared as a broad singlet at δ 8.65. Further the mass spectrum m/z =372 (fig.6) and elemental analysis agreed well with the molecular formula $C_{22}H_{17}N_4Cl$. On the basis of the aforesaid data, the product was attested to 3-(3'-(2'-chloro)quinolin)-3,3a,4,5-tetrahydro-2*H*-pyrazolino[3,4-*a*]carbazole 9a. Similarly following the above conditions the compounds 8b-8d afforded the corresponding pyrazolino[3,4-*a*]carbazoles, 9b-9d (Scheme 5).

*2.3. Preparation of 2-(3'-(2'-chloro)quinolidene)-1-oxo-1,2,3,4-tetrahydrocarbazoles (8a-8d)*

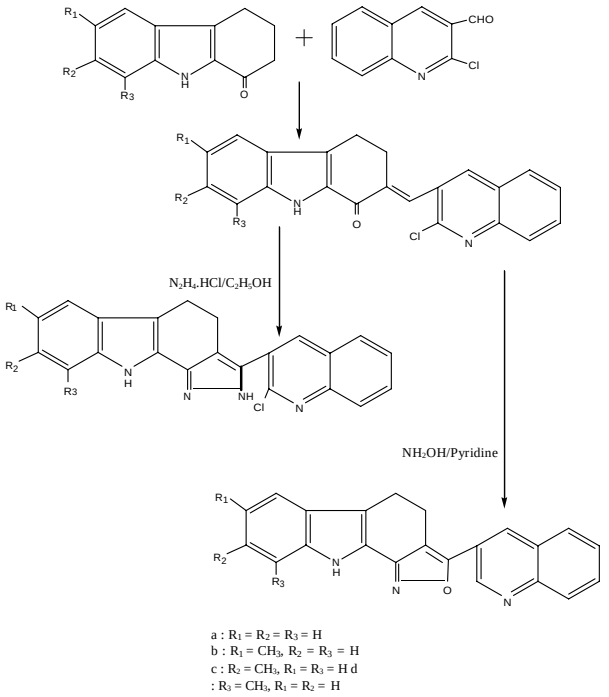
*2.3.1. General Procedure*

A mixture of the respective 1-oxo-1,2,3,4-tetrahydrocarbazole (6a-6d) 0.002 mol and 2-chloro-3-formyl quinoline 0.002 mol was treated with 4% alcoholic KOH (20 mL) and stirred for 12 hours at room temperature. The product precipitated as crystalline mass was filtered off and washed with 50% aqueous ethanol. Another quantum of the same crystalline compound was obtained from the filtrate on neutralization with acetic acid followed by dilution with water. Pure crystals of the respective products (8a-8d) were obtained by recrystallization with methanol.

*2.4. Preparation of 4,5-Dihydro-3-(3'-(2'-chloro)quinolin)isoxazolo[3,4-a]carbazole (9a-9d)*

*2.4.1. General Procedure*

A mixture of the respective 2-(3'-(2'-chloro) quinolidene) -1 -oxo- 1,2,3,4- tetrahydro carbazole (8, 0.001 mol) with hydroxylamine hydrochloride (0.139g, 0.002 mol) in pyridine (5 mL) was refluxed at 130ºC for 10 hours. The resulting reaction mixture was poured into crushed ice and stirred. The product separated as semisolid was extracted twice with chloroform (2×15mL), combined organic layers were washed with dilute hydrochloric acid and water successively and dried over anhydrous sodium sulphate. Evaporation of the excess solvent yielded a crude product and chromatographed over silica gel and eluted with petroleum ether-ethyl acetate mixture (80:20) to obtain the compound 4,5-dihydro-3-(3'-(2'-chloro)quinolin)isoxazolo[3,4-*a*]carbazole (9).




*2.5. Preparation of 3-(3'-(2'-chloro)quinolin)-3,3a,4,5-tetrahydro-2H-pyrazolino [3,4-a] carbazoles (9a-9d)*

*2.5.1. General procedure*

To an ethanolic solution of 2-(3-'(2-'chloro) quinolidene) -1 -oxo- 1,2,3,4- tetrahydrocarbazole (0.001mol) (20mL), hydrazine hydrate (1.5mL) was added and mixture was refluxed. After a period of 3h the solvent was removed under reduced pressure and the residue was washed with water and extracted with chloroform (3x15ml), and the combined organic layers were dried over anhydrous sodium sulphate. Evaporation of the solvent followed by crystallization yielded the desired product and chromatographed over silica gel and eluted with petroleum ether – ethylacetate mixture (80:20) to obtain the compound 3-(3'-(2'-chloro)quinolin)-3,3a,4,5-tetrahydro-*2H*-pyazolino[3,4-*a*] carbazole.

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