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Application of Pfitzinger Reaction in Synthesis of Hetero Ring Annelated Quinoline Carboxylic Acid Derivatives

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The diazotized 8-aminoquinoline (**4**) was reacted with 2-(hydroxymethylidine)cyclohexanone and N-benzyl 3-(hydroxymethylidine)-piperidine-4-one (**5, 6**) (generated from the reaction of cyclohexanone and N-benzyl-4-piperidone with ethyl formate in the presence of NaOEt) under the conditions of Japp-Klingemann reaction, followed by Fisher-indolization of the resulting hydrazones in acid, formed the quinolinooxocarbazole (**7**) and N-benzyl quinolinooxoazacarbazole (**8**), respectively. Pfitzinger reaction of compounds **7** and **8** with isatin in alkali afforded the corresponding quinoline carboxylic acid derivatives **10** and **11**, respectively. In accord to generally accepted mechanism of Pfitzinger reaction, we suggest that the reaction of compounds **7** and **8** with isatin in alkali proceeds with the formation of isatoic acid which undergoes instantaneous cyclocondensation with carbonyl species **7** and **8** to generate compounds **10** and **11**, respectively.

Keywords: Quinoline, Carbazole, Azacarbazole, Japp-Klingemann reaction, Pfitzinger reaction, Quinoline 4-carboxylic acid.

INTRODUCTION

Ubiquitous presence of carbazoles and azacarbazoles [1] in a vast array of bio-active molecules (such as ellipticine and olivacine) has stimulated intense research efforts to develop their structural analogues where different constitution and chemical reactivity could allow them to be used as novel chemotherapeutic agents. Heterocycles that incorporate the quinoline ring have been known in the literature to exhibit a wide array of biological activities including antimicrobial, antibacterial, antifungal [2-4], antiulcer [5], antitumor [6], antimalarial [7], anticancer [8], antihypertensive [9] and antiprotozoal activities [10]. Quinoline nucleus exhibits antitumor activity due to the formation of a stable complex with DNA.

Recent demonstrations [11] that quinoline carboxylic acid can be used as potential anti-HIV agents has stimulated further interest on these molecules with yet another perspective. Heterocyclic scaffolds bearing pyrazole nucleus in their molecular framework are endowed with a wide array of biological activities. It was therefore, considered of interest to prepare some examples of quinolino condensed carbazole and azacarbazole derivatives to which quinoline nucleus was appended into their molecular framework, to examine if such an association enhanced the DNA binding abilities of the system and produced a favourable impact on cytotoxicity in the new materials.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on CE (SHIMADZU) FTIR-8400S. ^{1}H NMR spectra were recorded on model AC-300F (Brucker) using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm. Mass spectra were taken on a Joel SX-102(EI/CI/FAB) mass spectrometer at 70 eV. 8-Amino-4-methyl quinolin-2-ol required in synthesis was prepared from the reduction of 4-methyl-8-nitro quinolin-2-ol.

Preparation of 2-hydroxymethylidine cyclohexanone and 1-benzyl-3-hydroxymethylidine-4-piperidone (5, 6): A mixture of NaOEt (0.06 g, 0.01 mol), dry ether (10 mL), redistilled cyclohexanone (0.9 g, 01 mol) or 1-benzylpiperidine-4-one (1.8 g, 01 mol), ethyl formate (10 mL) were placed in a two necked flask equipped with a stirrer and stopper. The reaction was initiated by the addition of 3 mL of ethanol to the stirred mixture, which was then placed in an ice cold water bath. Stirring was continued for 6 h. After standing overnight, 2.5 mL of ethanol was added. The mixture was stirred for additional 1 h. After the addition of 20 mL of water the mixture

was shaken in a separatory funnel. The combined aqueous extracts were washed with ether. The aqueous layer was acidified with 5 mL of 6 N HCl and the mixture was extracted twice with ether. The ether solution was washed with 5 mL saturated NaCl solution. The solid was dried by the addition of approximately 5 g of anhydrous $MgSO_4$ powder. The drying agent was removed by filteration and the ether was evaporated on the steam bath. The residue was distilled under reduced pressure to give **5**. Yield 0.5 g, 66 %, m.p. 295-96 °C.

Preparation of 2-hydroxy-4-methyl-7,8,9,11-tetrahydro-4aH-pyrido[2,3a]carbazol-10(5*H*)-one (7, 8)

(A) Preparation of hydrazone: A solution of **3** (1.6 g, 005 mol) in aqueous hydrochloric acid (0.5 mL conc. HCl in 1 mL water) was treated with a cold saturated solution of sodium nitrite (0.1 g in 2 mL water) while the temperature was kept at 0-5 °C. It was then added portion wise to an ice cooled mixture containing **5** (0.05 mL), sodium acetate trihydrate (0.3 g), methanol (1.5 mL) and water (1 mL) over a period of 5 h with stirring. The contents were allowed to stand for further 5 h and the resulting solid mass was filtered, washed with water, dried and recrystallized from ethanol to give the hydrazone. Hydrazone was used as such in the second step without further purification.

(B) Cyclization of hydrazone: A solution of hydrazone (1.7 g, 005 mol) in a mixture of acetic acid (0.5 mL) and hydrochloric acid (0.2 mL) was refluxed on an oil bath preheated to 125-130 °C for 0.5 h. The content were then cooled and poured in ice cooled water with continous stirring. The separated brown solid **7** was purified by passing through a column of silica gel using 50 % benzene in petroleum ether as eluant to give 1.23 g. Yield-67 %, 297-99 °C.

Similarly compound **8** was prepared. Yield: 0.92 g, 58 %, m.p. 318-320 °C.

Spectral data of compound 7: IR (KBr, ν_{max}, cm^{-1}): 3555 (OH str.), 3110 (NH str.), 2920, 2850 (CH str.), 1720 (C=O str.), 1660 (C=N str.),1570-1475 (C=C str.), 1332 (NH def.), 1080 (C-N), 946 (CH def.). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.07 (1H, s, OH), 11.63 (1H, s, NH), 8.12 (1H, d, CH), 7.69 (1H, d, CH), 6.31 (H, s, CH), 3.01 (2H, t, CH_2), 2.61 (3H, s, CH_3), 2.58 (2H, t, CH_2), 2.11 (2H, m, CH_2). MS (*m/z*): 266.29 [M^+].

Spectral data of compound 8: IR (KBr, ν_{max}, cm^{-1}): 3540 (OH str.), 3110 (NH str.), 2940, 2845 (CH str.), 1705 (C=O str.), 1640 (C=N str.), 1578-1480 (C=C str.), 1331 (NH def.), 1076 (C-N), 949 (CH def.). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.07 (1H, s, OH), 11.63 (1H, s, NH), 8.12 (1H, d, CH), 7.69 (1H, d, CH), 7.33-7.23 (5H, m, ArH), 6.31 (H, s, CH), 4.51 (2H, s, CH_2), 3.39 (2H, t, CH_2), 2.63 (2H, s, CH_2), 2.61 (3H, s, CH_3). MS: *m/z* 357.40 [M^+].

Preparation of 11-hydroxy-9-methyl-6,13-dihydro-5*H*-diquinolino[2,3-a:3',2'-i]carbazole-4-carboxylic acid (10, 11): A solution of compound **7** (1 g, 0.004 mol), isatin (0.9 g, 0.005 mol) and 1.2 g of KOH in 5 mL of ethanol was refluxed for 24 h. After distillation of most of the solvent, water was added, the netural impurities were removed by ether extraction and the aqueous layer was acidified with acetic acid and solid **10** was isolated by repeated crystallization from ethanol. 0.74 g, Yield 74 %, m.p. 231-233 °C.

Similarly compound **11** was prepared. 0.76 g. Yield 76 %, m.p. 204-206 °C.

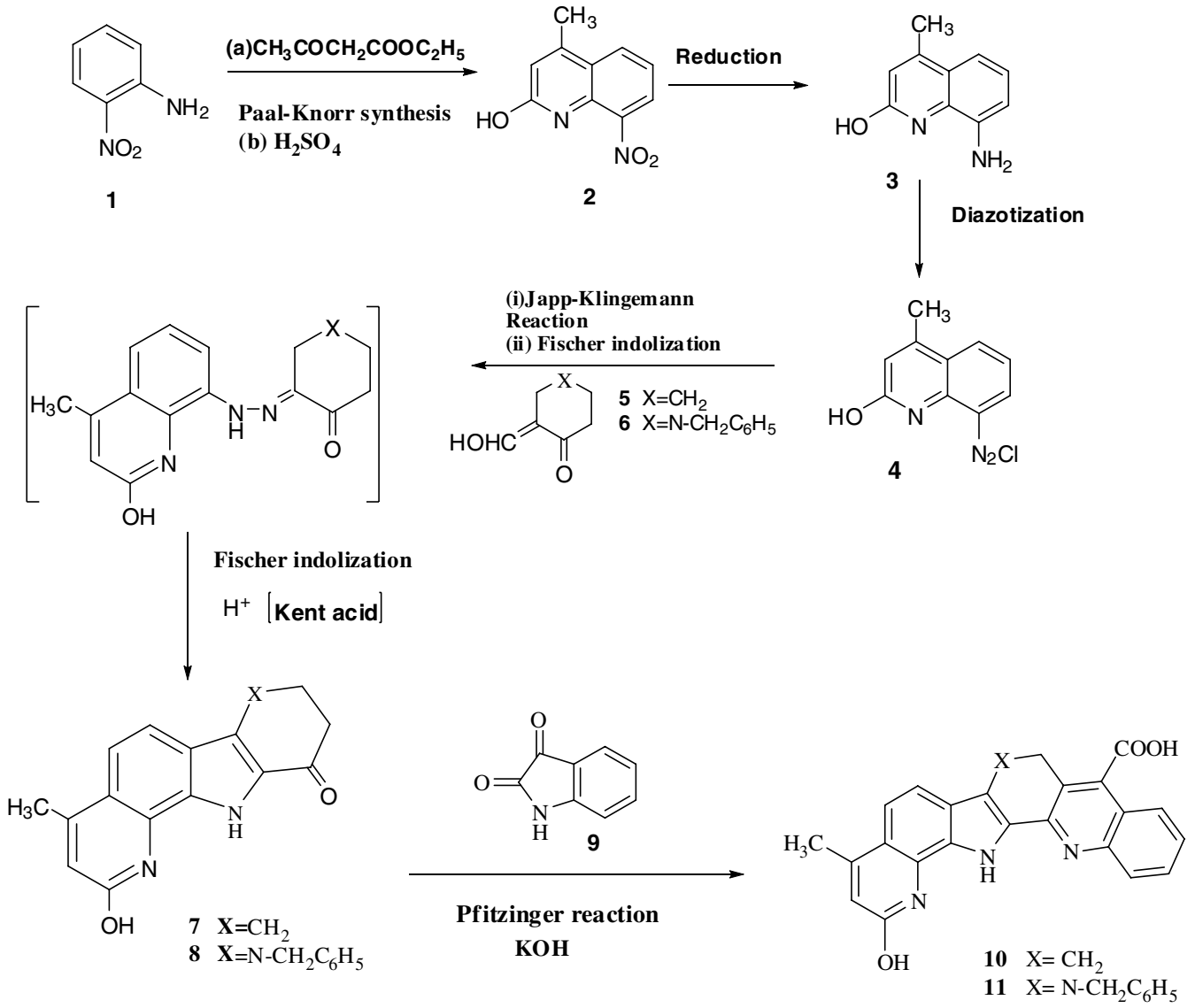
Spectral data ofcompound 10: IR (KBr, ν_{max}, cm^{-1}): 3450 (OH str.), 3010-2505 (CO and OH overtones), 2920, 2850 (CH str.), 1640 (C=N str.), 1570 (NH str.), 1455 (C-H bend.), 755 (C-H str.). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.74 (1H, s, OH), 12.06 (1H, s, OH), 11.33 (1H, s, NH), 8.23-7.93 (4H, m, ArH), 8.12 (1H, d, CH), 7.67 (1H, d, CH), 6.32 (1H, s, CH), 2.93 (2H, t, CH_2), 2.88 (2H, t, CH_2), 2.63 (3H, s, CH_3). MS: *m/z* 395.41 [M^+].

Spectral data of compound 11: IR (KBr, ν_{max}, cm^{-1}): 3420 (OH str.), 3020-2550 (CO and OH over tones), 2955, 2870 (CH str.), 1655 (C=N str.), 1580 (N-H bend), 1470 (C-H bend.), 720 (CH out of plane-1, 2-disub. ring). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm: 12.74 (1H, s, OH), 12.07 (1H, s, OH), 11.34 (1H, s, NH), 8.23-7.93 (4H, m, ArH), 8.12 (1H, d, CH), 7.69 (1H, d, CH), 7.33-7.23 (4H, m, ArH), 6.31 (1H, s, CH), 4.71 (2H, s, CH_2), 4.32 (2H, s, CH_2), 2.61 (3H, s, CH_3). MS: *m/z* 486.52 [M^+].

RESULTS AND DISCUSSION

The synthetic plan adopted for the preparation of the compounds **10** and **11** (**Scheme-I**) required it to be accomplished in two stages. The first stage of this strategy involved the conversion of quinolinyldiazonium chloride (**4**) to the quinolino fused oxocarbazole and oxoazacarbazole derivatives **7** and **8**, respectively. These were realized by the interaction of **1** with (a) 2-hydroxymethylidene cyclohexanone (**5**) and (b) N-benzyl-3-hydroxymethylidene-4-piperidone (**6**), respectively, under the conditions of Japp-Klingemann reaction, followed by Fischer indolization of the resulting crude hydrazones with Kent's acid (HCl:AcOH; 1:4 v/v). The compounds **5** and **6** required in the synthesis were in turn obtained, following the reported procedure [12] which consisted of treating cyclohexanone and N-benzyl-4-piperidone, respectively with ethyl formate in presence of sodium ethoxide. The second stage of the strategy required the conversion of **7** and **8** to the corresponding quinoline carboxylic acid derivatives **10** and **11**, respectively. The Pfitzinger reaction of isatin on compounds containing the $COCH_2$ group is known to provide a very convenient one pot synthetic entry to quinoline-4-carboxylic acid [13] derivatives. It is reported [14] that enolizable ketones show great facility to condense with isatin in strongly alkaline medium to subsequently cyclize to give quinoline products. Application of this strategy on **7** and **8** allowed **10** and **11** to be formed in moderate to good yield.

The structure of compounds **7**, **8**, **10** and **11** were established on the basis of their microanalysis (for N), IR, ^{1}H NMR and MS spectral data. The data shown in experimental section were found in good agreement to the assigned structures. The IR spectrum of all the compounds showed the presence of a strong absorption band near 1710 cm^{-1} for CO group. The presence of carboxylic acid group in **10** and **11** was ascertained by the appearance of a broad band of OH group in the region of 3510-3420 cm^{-1}. The ^{1}H NMR spectrum displayed the corresponding peak for OH proton of carboxylic acid in the region of δ 12.71-1274 ppm. The most diagnostic evidence which established the formation of the compounds **7**, **8**, **10**



Scheme-I

and **11** was the appearance of the proton of indole NH in the regionof 11.33 in all the compounds. The appearance of the M^+ peaks corresponding to their molecular formula in MS spectrum sustained further the formation of the compounds and unequivocally established their structures.

The mechanistic pathway that can rationalize the formation of **10** and **11** from **7** and **8** has been shown in **Scheme-II**. It is assumed that the reaction proceeds through the formation of a non-isolable isatoic acid from isatin which undergoes instantaneous cyclocondensation with **7** and **8** to generate **10** and **11**, respectively.

Conclusion

In conclusion, an efficient methodology for the synthesis of quinolino fused carbazolesazacarbazolo fused quinoline carboxylic acids was developed. Heterocyclic scaffolds bearing these structures are widely studied because of their impressive pharmacological activities. It was therefore reasoned, that the fusion of quinoline, azacrabazole and quinoline carboxylic acid may lead to novel heterocyclic scaffolds with interesting biological activities. Two noteworthy features of the strategy employed in synthesis of the reported compounds are apparent from our study. Firstly it has established that the Fisher indolization of the 5-quinolylhydrazones of cyclohexanone and N-substituted piperidin-4-ones provides a very convenient synthetic entry to the difficultly accessible fused azacarbazole derivatives. Secondly, it has established further, the versatility of the Japp-Klingemann reaction to provide a one pot synthetic approach to the preparation of heteroarylhydrazones (from an adjacent methylene carbon of a cyclic nitrogen containing carbonyl species) which are not normally accessible by the conventional procedures.

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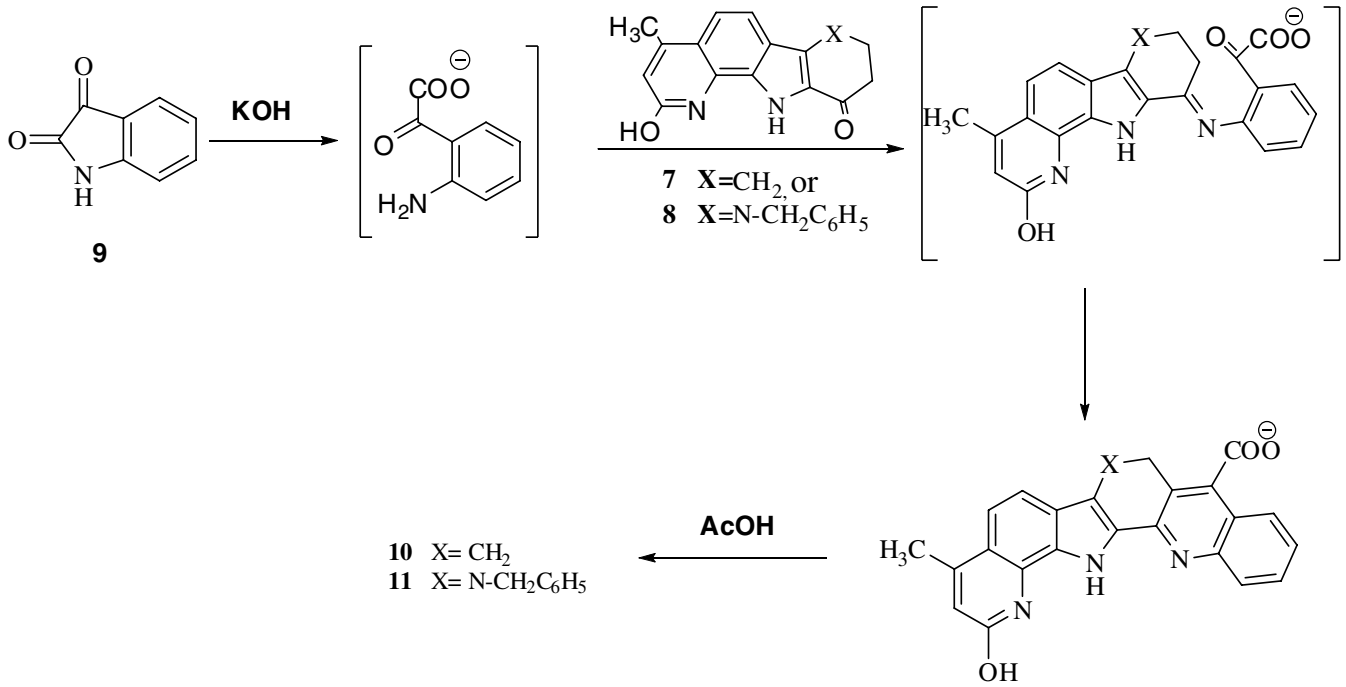

Scheme-II: Mechanism of formation of compounds **10** and **11** from compounds **7** and **8**

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