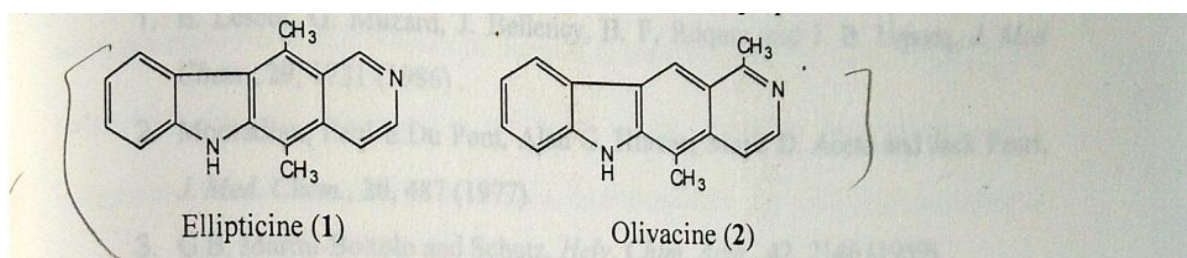


Synthetic Studies on 6-Phenyl-Quino Carbazole

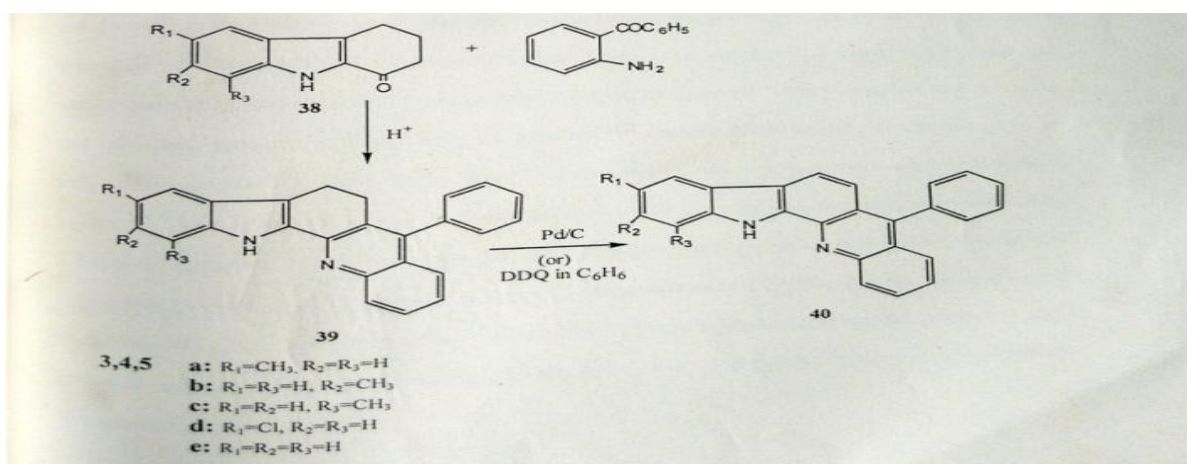
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ABSTRACT: Much interest centres around carbazoles because of the aim high level of pharmacological properties. Carbazoles derivatives in general, pyridocarbazoles in particular, (Ellipticine(1) and Olivacine(2) exhibit anti – cancer properties.



In the present case, the reaction of 1-oxo -1,2,3,4 – tetrahydro carbazoles with o-amino benzophenone in the presence of acids as catalyst is taken as objective. Then the resulting 7,8 – dihydro derivative of carbazoles can be used as synthons to derive quino(2,3- b) carbazoles using either Pd/C in diphenyl ether or DDQ in benzene. The is outline below



All the compounds have been characterized by IR ,NMR and elemental analysis.

Keywords: Carbazoles derivatives, 1-oxo -1,2,3,4 tetrahydrocarbazoles, 7,8-dihydro- 6-phenyl – quino (2,3-a)carbazole using Pd/C.

I. INTRODUCTION

Nitrogen hetero cyclic compounds play vital role in the metabolism of all living cells, which are widely distributed in nature and are essential to life.

Carbazole derivatives represent a new interesting variant in the large number of indole alkaloids, which have yielded several important drugs. Several reports have appeared on the synthesis of carbazoles derivatives, in the

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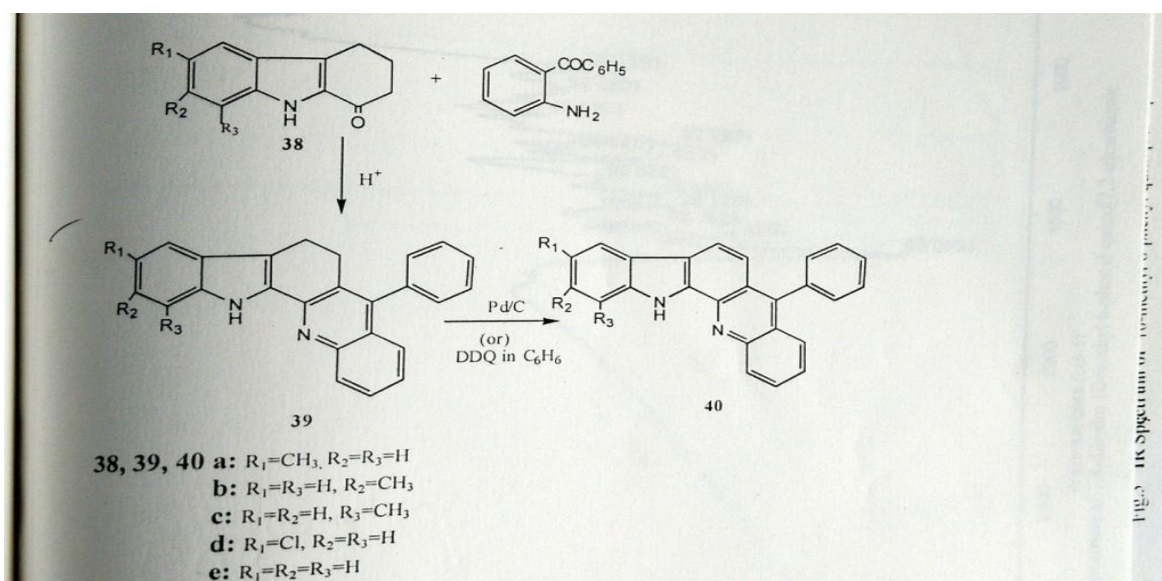
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connection with the search for newer physiologically active compounds. Chowdhury, et al¹, have studied the toxicity and structure activity relationships of fourteen carbazoles derivatives. Carbazomycin A and Carbazomycin B have been found to be useful as antibacterial and anti – fungal agents.²⁻⁴ The ochrosia and Aspidosperma 6H- pyrido(4,3-b) carbazole alkaloids, namely, ellipticine is used clinically as a drug to treat advanced breast cancer, myeloblastic leukemia and some solid tumors.⁵⁻⁸ Recently 7H –pyrido(4,3-c)ncarbazoles were reported to elicit anti HIV activity, Antidepressant, Anticonvulsant and diuretic, Trypanocidal, Anticancer, etc.,

II. RESULT AND DISCUSSION

The potential precursors, 1-oxo-1,2,3,4 – tetrahydrocarbazoles (2) prepared in our laboratory have opened new avenues for the synthesis of highly functionalized carbazoles derivatives viz., mukonine isomers⁴², oxazolocarbazoles⁵⁷, girinimbine isomers⁵⁸, 2,2-dimethyl – 2H – Pyrocarbazoles⁵⁹, indolocoumarins⁶⁰, carbazolyloxypropanolamines^{55,3-acetyl – 2-hydroxy – 1-N,N-diacetylaminocarbazoles⁶¹, benzocarbazoles⁴³, and pyrazinocarbazoles⁴⁹, in excellent yields.}

The 1-oxo-1,2,3,4 – tetrahydrocarbazoles (38) thus obtained were utilized as synthons to derive 6-Phenyl – quino(2,3 – a) carbazoles (40).



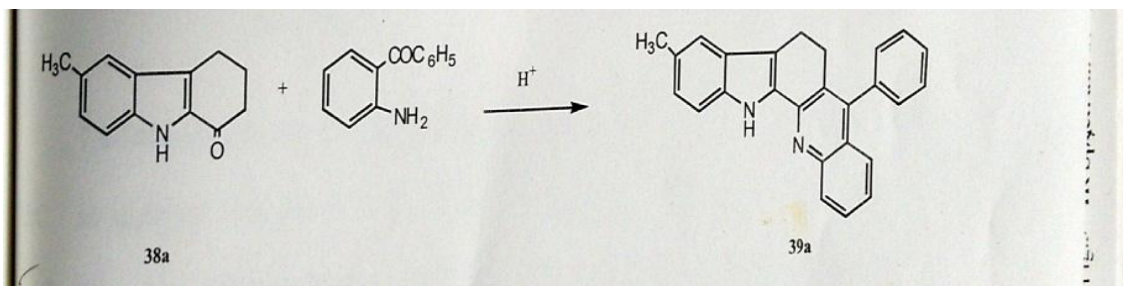
6- Methyl -1-oxo-1,2,3,4 – tetrahydrocarbazole (38a) on treatment with o-aminobenzophenone in glacial acetic acid yielded an orange coloured solid. This on purification using column chromatography over silica gel yielded yellow colour solid melted at 156⁰C. Its IR spectrum showed strong stretching at 3275cm⁻¹ due to the presence of N-H group. A band between 2980 and 2895cm⁻¹ was due to C –H stretching's. A group C=N stretching's appeared at 1640 cm⁻¹ Its ¹H- NMR spectrum in CDCl₃ exhibited in various singlet and multiplet band.

The elemental analysis was also in good agreement with the proposed molecular formula C₂₆H₂₀N₂. All these spectral and analytical details attest the compound as 7,8 – dihydro -10-methyl -6-phenyl-quino(2,3-a) carbazole (39a).

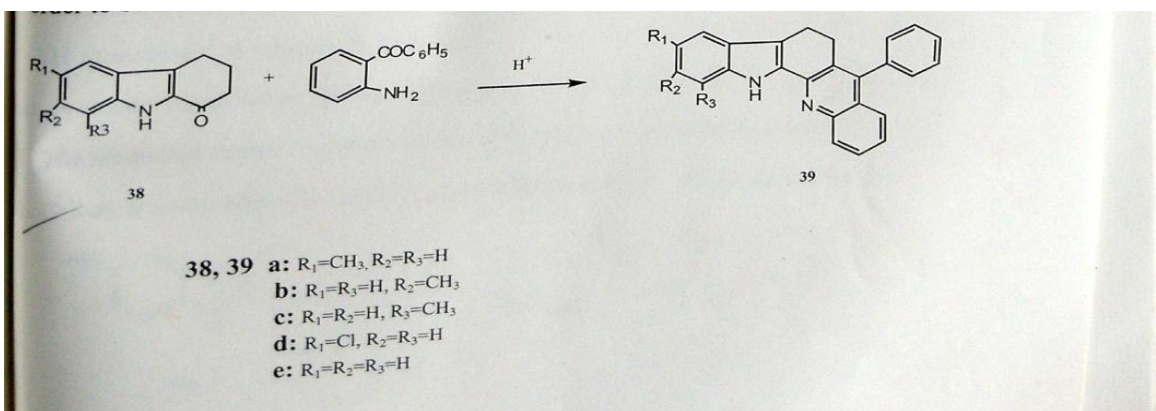
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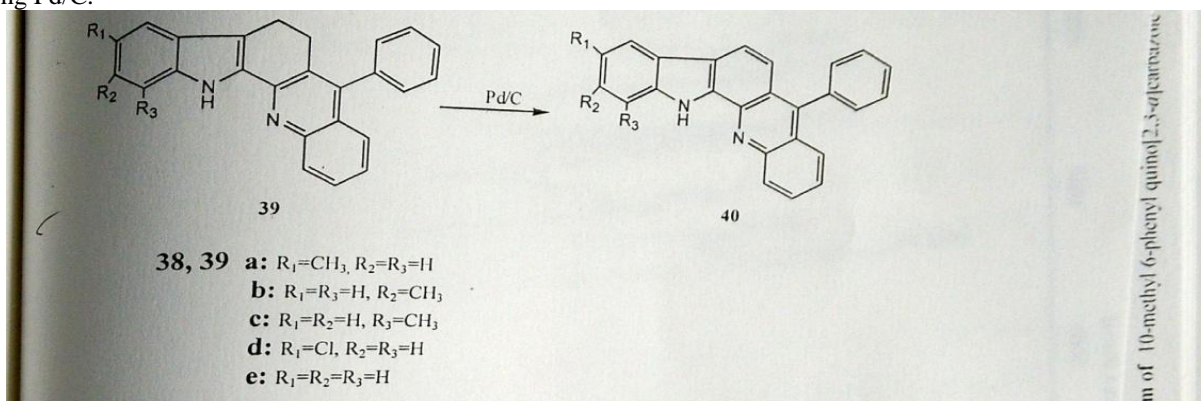
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The above reaction was generalized for other carbazole derivatives 38 (b-e) in order to obtain the respective products 39 (b-e)



The spectral and analytical data infer the obtained product as 7,8-dihydro-6-phenyl-quinolizino[2,3-a]carbazole(39). Therefore We planned to get 6-phenyl quinolizino[2,3-a]carbazole(40) from 7,8-dihydro-6-phenyl-quinolizino[2,3-a]carbazole using Pd/C.



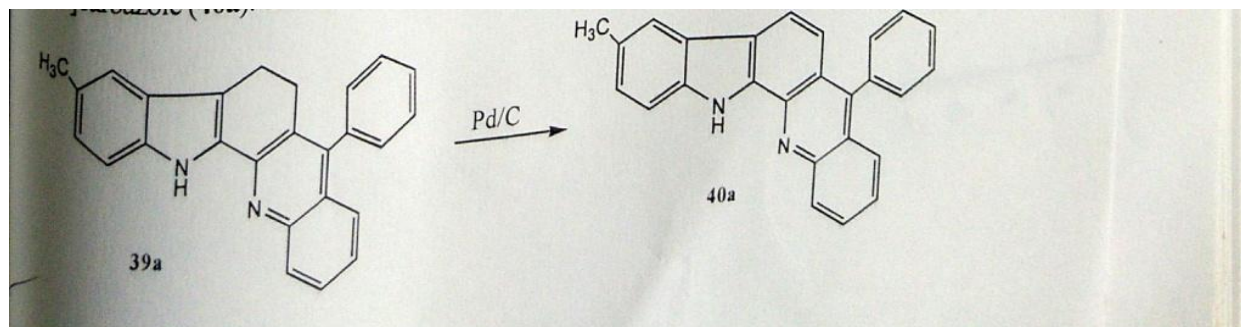
7,8-dihydro-10-methyl-6-phenyl-quinolizino[2,3-a]carbazole(39a) refluxed with Pd/C

In diphenyl ether for 5 h to yield a dark brown coloured product. This on purification using column chromatography over silica gel yielded a yellow coloured solid melted at 162^oC. Its IR spectrum showed a strong stretching at 3422cm⁻¹ showed the presence of C-H stretching. A stretching appeared at 1667cm⁻¹ was due to C=N group. The product is well supported by its mass spectrum. The molecular ion peak appeared at m/e 358. The elemental analysis agreed well with the assigned structure 10-methyl-6-phenyl-quinolizino[2,3-a]carbazole(40a). The sample has been submitted for its ¹H-NMR spectral data.

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III. EXPERIMENTAL

General:

The solvent and reagents used for the preparations were grade and were purified by standard methods, petroleum ether used was of boiling point range 60-80°C. Anhydrous sodium sulphate was used to dry the solution of organic extracts.

Thin layer chromatography was performed using glass plates coated with silica gel -G containing 13% calcium sulphate as binder. Ethyl acetate and petroleum ether were used as developing solvents. A chamber containing iodine vapour was used to locate the spots.

Preparation of 2-hydroxymethylcyclohexanone:

Cyclohexanone (51.7 mL, 0.50 mol) was added in portion over a period of 5 min. to a well cooled vigorously stirred mixture of sodium methoxide (12.25 g of sodium in 125 mL of methanol), dry ether (100 mL) and ethyl formate (45 mL, 0.50 mol). The mixture was stirred in the ice bath for another 1 h and then allowed to stand at room temperature for 24 h. At the end of the period, ice and water were added to the yellow solid mass and acidified with cold concentrated hydrochloric acid. The oil thus separated was extracted with ether, washed with cold water and brine solution and dried over anhydrous sodium sulphate. The residual oil after the removal of solvent was distilled under reduced pressure to give 2-hydroxymethylcyclohexanone.

b.p: 83-85°C/ 8 mm

Yield: 35 g (60%)

Preparation of cyclohexanone-1,2-dione-1-arylhydrazones (37):

General procedure:

A solution of appropriate aniline derivative (0.1 mol) in aqueous hydrochloric acid (27 mL of HCl in 53 mL solution) was diazotized with cold saturated aqueous solution of sodium nitrite (8.7 g in 20 mL water) while the temperature was kept at 0°C to 5°C. The solution was kept aside for 10 minutes. It was then added portion wise to an ice cold mixture containing 2-hydroxymethylcyclohexanone (38), 12.6 g, 0.1 mol, sodium acetate trihydrate (25 g), methanol (150 mL) and water (75 mL) over a period of 0.5 h with stirring. The contents were allowed to stand for further 0.5 h, and the resulting solid mass was filtered, washed with water, dried and crystallized from methanol. Finally we got 37a, 37b, 37c, 37d & 37e.

CYCLISATION OF THE HYDRAZONE (37):

General procedure:

A solution of the appropriate hydrazone (37, 0.001 mol) in a mixture of acetic acid (20 mL) and hydrochloric acid (5 mL) was refluxed on oil bath preheated to 125-130°C for 0.5 h. The contents were then cooled and poured into cold water with stirring. The separated brown solid was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (95:5).

6-methyl-1-oxo-1,2,3,4-tetrahydrocarbazoles (38a): Cyclohexane-1,2-dione-1-p-tolylhydrazone (37a): 2.16 g, Glacial acetic acid and hydrochloric acid: 20 mL: 5 mL, M.p: 193°C, Yield: 1.25 g (63%), IR (KBr) cm⁻¹: 3380, 1635, 1530, 1475, 1460, 1375, 1250, 1195, 1180, 1130, 1035, 890.

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7-methyl – 1-Oxo-1,2,3,4-tetrahydrocarbazoles(38a):Cyclohexane-1,2-dione-1-p-tolylhydrazone(37b) :2.16 g, Glacial acetic acid and hydrochloric acid:20 mL:5mLM.p. :159 - 160°C, Yield:1.25g,(63%), IR(KBR)cm⁻¹:3250,1620,1550,1520,1460,1325,1350,1240,1120,1060,880.

8-methyl – 1-Oxo-1,2,3,4-tetrahydrocarbazoles(38c):Cyclohexane-1,2-dione-1-p-tolylhydrazone(37c) :2.16 g, Glacial acetic acid and hydrochloric acid:20 mL:5m,M.p.:163 - 163°C, Yield:1.85g,(57%), IR(KBR)cm⁻¹:3200,1630,1600,1530,1460,1370,1320,1240,1220,1180,1160,1120,1020,840.

1-oxo-1,2,3,4-tetrahydrocarbazole(38c)Cyclohexane-1,2-dione-1-phenylhydrazone(37c):2 gGlacial acetic acid and hydrochloric acid:20 mL:5mL,M.p:166 - 168°C, Yield:1.2 g(65%), IR(KBR)cm⁻¹ :3250,1620,1550,1520,1450,1320,1240,1220,1170,1150,1120,880.

Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles(38) with o-aminobenzophenone:

General procedure:

A solution of an 1-oxo-1,2,3,4-tetrahydrocarbazoles(38,0.005 mL) was refluxed for 8 hrs in the presence of a drop of sulphuric acid, The reaction was monitored by TLC. After the completion of the reaction, it was poured into crushed ice and extracted with chloroform and dried over anhydrous sodium sulphate. The crude product thus obtained on removal of the solvent, was purified by column chromatography over silica gel using per. ether: ethyl acetate(98:5) to yield the corresponding product.

7,8- Dihydro – 6-phenyl – quino(2,3-a) carbazole(39e):1-oxo 1,2,3,4

tetrahydrocarbazole(38e):0.925g(0.005mol),oaminobenzophenone:0.985g(0.005mL)M.p:>300°C, Yield:0.573g(62%) ,IR(KBR)V_{max}Cm⁻¹:3413,2922,2360,1639,1548,¹HNMR(CDCl₃,^δ12.30(b s, 1H, N₁₃-H),8.57- 6.96(m,13H,C₂⁻, C₃⁻, C₄⁻, C₅⁻, C₉⁻, C₁₀⁻, C₁₁⁻, C₁₂⁻, C₂⁻, C₃⁻, C₄⁻, C₅⁻,C₆⁻-H),3.08-2.93(m,4H,C₇-2H, C₈-2H),

Reaction of 7,8-dihydro –6-phenyl –quino (2,3-b) carbazole(39,0.001mol) Pd/C(0.050)in 6 ml of diphenyl ether was refluxed for about 5 h. The reaction was monitored by TLC. It was then filtered by Whatmann-41 filter paper to remove Pd/c. After the removal of solvent, the mixture was poured into crushed ice, extracted using ethyl acetate dried over anhydrous sodium sulphate. The crude product, Thus obtained was purified by column chromatography over silica gel per. ether: ethyl acetate(98:2) to yield the corresponding 6 – phenyl – quino(2,3-a) carbazole(40).

10- Methyl -6-phenyl-quino(2,3-a)carbazoles(40a):7,8-dihydro 10-methyl-6-phenyl quino(2,3-a)carbazole(39a):0.360 g(0.001 mol),Pd/C:0.050g,M.P:162-164°C, Yield :0.166g (46%) IR(KBR) V_{max} cm⁻¹ :3422,2965,2783,1667,1589,743,MS(m/e):358.

Analysis:	C ₂₆ H ₁₈ N ₂	C	H	N
Calculated		87.12	5.06	7.82
Found		87.23	5.01	7.76

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