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MEDICINAL CHEMISTRY RESEARCH

A CONVENIENT ROUTE FOR THE SYNTHESIS OF *CIS* -1-SUBSTITUTED 1,2,3,4,4a,5,11,11a-OCTAHYDRO-6H-PYRIDO[3,2-*b*]CARBAZOLES AND 4-SUBSTITUTED 1,2,3,4,4a,5,6,11c-OCTAHYDRO-7H-PYRIDO[2,3-*c*] CARBAZOLES AS POTENT DOPAMINE AGONISTS.#

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Abstract. The *cis*-1/4 substituted octahydropyrido[(3,2-*b*)/(2,3-*c*)]carbazoles have shown potent dopamine agonistic activity *in vitro* and *in vivo*. The reported method[1] of their synthesis involves hydrogenation at high temperature and pressure. Some attempts have been made to develop new methods.[2] So in order to explore an alternative method, the key intermediate 4-benzoyloxy cyclohexanone obtained from 1,4-cyclohexanediol by its benzoylation followed by oxidation is used. The 4-benzoyloxycyclohexanone on condensation with acrylamide through enamine intermediate gave 6-benzoyloxy-1, 2,3,4,5,6,7,8-octahydroquinoline-2-one, which on hydrolysis followed by reduction afforded 6-hydroxy-1,2,3,4,4a,5,6,7,8,8a-decahydroquinoline-2-one which on oxidation, Fischer Indolisation and LAH reduction followed by alkylation yielded the desired octahydropyrido-[(3,2-*b*)/(2,3-*c*)] carbazoles.

Introduction

Apomorphine (1) is the prototype of dopamine agonist drugs. It is used against central dopamine deficiency diseases as Parkinson's disease. Recently it has found use against erectile dysfunction.[3] In spite of having strong dopaminergic activity Apomorphine has clinical limitation due to its high emetic activity. In view of it and the observed bioisosterism between indole and dopamine, the analogues

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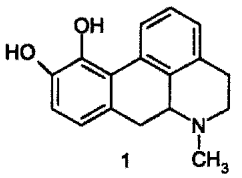
cis/trans-1-substituted-1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole and -4-substituted-1,2,3,4,4a,5,6,11c-octahydro-7H-pyrido[2,3-*c*]carbazoles have been reported.[1] Later similar carbazoles have also been synthesized as conformationally rigid seratonin analogues.[2] The reported synthetic routes for these carbazoles suffer with limitation of the use of high pressure and temperature hydrogenation process in the former and cumbersome work up in later.

Hence, an alternative approach to the synthesis of above carbazoles, which circumvents high pressure and temperature hydrogenation and complex and difficult work up, is reported here.



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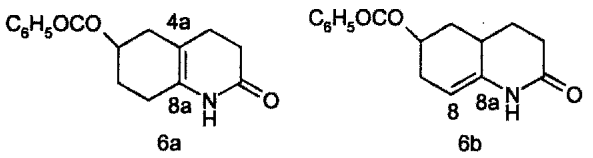
Chemistry

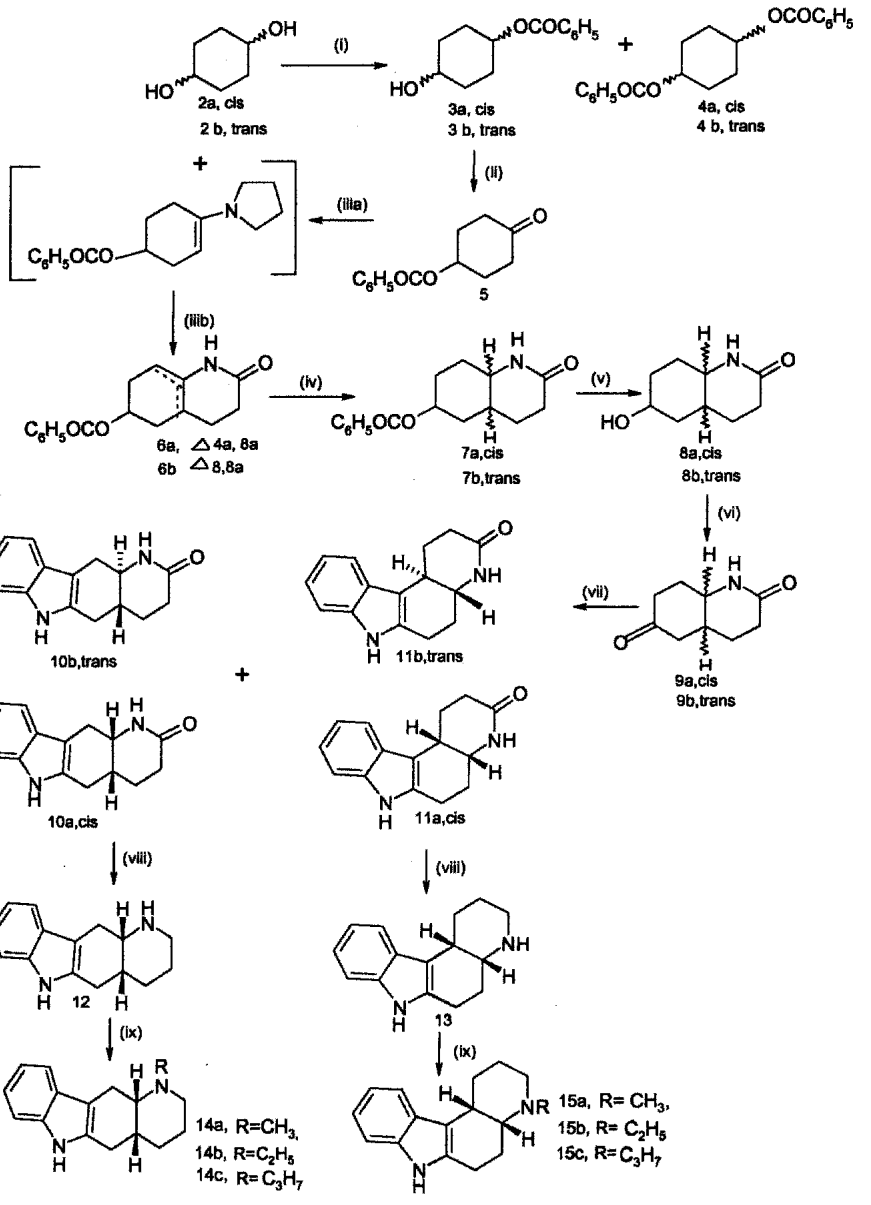
The title compounds (**14a-c** and **15a-c**) were synthesized (scheme 1), starting from the mixture of *cis*- and *trans*-1, 4-cyclohexanediol (**2**), which was benzoylated with benzoyl chloride to give a mixture of *cis*- and *trans*-4-benzoyloxycyclohexanol (**3a** and **3b**) and *cis*- and *trans*-1, 4-dibenzoyloxycyclohexane (**4a** and **4b**). This mixture was separated by vaccum distillation where mixture of **3a** and **3b** was distilled and **4a** and **4b** remained as residual. This mixture of **3a** and **3b** on oxidation with chromium trioxide gave 4-benzoyloxycyclohexanone (**5**). The compound **5** on treatment with pyrrolidine formed the enamine intermediate which was reacted with acrylamide to yield the mixture of key intermediates 6-benzoyloxy-3,4,5,6,7,8-hexahydro-2(1H)-quinolinone (**6a**) and 6-benzoyloxy-3,4,4a,5,6,7-hexahydro-2(1H)-quinolinone (**6b**).



Existence of these two isomers **6a** and **6b** is explainable according to Dyke[4], who concluded that depending on their structures enamines may participate in tautomeric equilibria involving two different C=C moieties and the relative amounts of each tautomer depends upon several steric and electronic factors. The ^{1}H and ^{13}C NMR spectra indicated that variable amount of **6a** and **6b** existed in the mixture ranging from 67% to almost >90% amount of 6a. The presence of a multiplet at δ 4.98 (0.33H) for H-8 of **6b**, a broad singlet at δ 5.47 (0.33H) for H-6 of **6b** and a quintet (J=5.8 Hz) at δ 5.31 (0.67 H) for H-6 of **6a** proved that **6a** and **6b** were present in the mixture in a ratio of 2:1.The existence of **6a** and **6b** was further supported by the presence of 9 peaks for methylene carbons, peaks at δ 28.56 and δ 106.41 for C-4a of **6b** and **6a** respectively, and at δ 100.07 for C-8 of **6b**.

The mixture of **6a** and **6b** was catalytically hydrogenated over Pd-C in methanol to give the mixture of *cis*- and *trans*-6-benzoyloxy-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-quinolinone (**7a** and **7b**). The appearance of a singlet at δ 3.48 (0.33H) for H-8a of **7b** and a broad singlet at δ 3.62 (0.67H) for H-**8a** of **7a** in ^{1}H NMR of mixture of **7a** and **7b** suggested that the ratio of **7a** and **7b** in the mixture was 2:1.The formation of *cis*- and *trans*-isomers **7a** and **7b** may be explained on the basis of findings of Nelson group[5] which states that catalytic hydrogenation proceeds exclusively by *cis* addition across the C-C double bond. The formation of *cis* isomer **7a** is through both **6a** and **6b** but the formation of **7b** is decided by the approach of hydrogen during hydrogenation to **6b** at C-8a relative to C-4a proton.

Scheme 1



(i) C_6H_5COCl, dry pyridine, dry $CHCl_3$, 0-5°C ; (ii) CrO_3, CH_3COOH, H_2O, 0-10°C; (iii) Benzene, Pyrrolidine, PTSA, reflux; (b) Acrylamide, dry dioxane, reflux; (iv) 10% Pd-C, MeOH, 50 psi, r.t.; (v) NaOH, H_2O, MeOH, $CHCl_3$, r.t.; (vi) Jones reagent, dioxane, r.t.;(vii) $PhNHNH_2$, C_2H_5OH, conc. HCl, reflux; (viii) $LiAlH_4$,dry THF,reflux; (ix) RI, K_2CO_3, Acetone.

The mixture of **7a** and **7b** was hydrolysed using sodium hydroxide to yield a mixture of *cis*- and *trans*-6-hydroxy-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-quinolinone (**8a** and **8b**). Oxidation of above mixture using Jones reagent[6] in dioxane as solvent produced a mixture of *cis*- and *trans* –1,3,4,4a,5, 7,8,8a-octahydro-2,6-quinolinedione (**9a** and **9b**). The mixture of **9a** and **9b** was found to be in a ratio of 7.3:1 according to ^{1}H NMR of mixture of **9a** and **9b** [(δ 3.81;brs, 0.89 H, H-8a; 9a)] and [(δ 3.65;s, 0.12H,H-8a; 9b)], which showed a singlet at δ 3.65 for H- 8a of *trans* isomer **9b** and a broad singlet at δ 3.81 for H- 8a of *cis* isomer **9a**. The mixture of **9a** and **9b**, on Fischer Indolisation with phenylhydrazine yielded the required mixture of *cis*- and *trans* –1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*] carbazole-2-one (**10a** and **10b**) and *cis*- and *trans* –1,2,3,4,4a,5,6,11c- octahydro-7H- pyrido[2,3-*c*]carbazole-3-one (**11a** and **11b**). These *cis*- and *trans* –linear isomers (**10a** and **10b**), and *cis*- and *trans* – angular isomers (**11a** and **11b**) were separated by coloumn chromatography (the *trans* angular isomer could not be separated due to its poor concentration in the mixture) and their structures and stereochemistry were assigned by ^{1}H and ^{13}C NMR spectroscopic analyses. The differentiation between linear and angular isomers was made on the basis that H-11c of angular isomer (**11a**), which corresponded to H-4a of **10a** and **10b**,appeared downfield at δ 3.42 (as H-11c lied in the deshielding zone of aromatic indole) relative to H-4a linear isomers **10a** and **10b** (δ 2.50-2.57 for **10a** and δ 1.93-2.12 for **10b**). The H-4a of angular isomer **11a** (corresponding to H-11a of linear isomer **10a** and **10b**) appeared as multiplet at δ 3.90 and H-11a of **10a** and **10b** appeared as multiplets at δ 3.91 and δ 3.54 respectively. In ^{13}C NMR, C-6a (δ 133.76) and C-11b (δ 109.82) of angular isomer **11a** (corresponding to C-5a and C-10b of linear isomers **10a** and **10b** respectively) appeared downfield relative to C-5a (δ 131.95 for both **10a** and **10b**) and C-10b (δ 105.91 and δ 106.23 for **10a** and **10b** respectively) of linear isomers **10a** and **10b**.The chemical shifts of the methelyne carbons of linear and angular isomers were also characteristic.The C-5 and C-6 of angular isomer **11a** appeared at δ 28.48 and δ 20.66 respectively, whereas C-5 of linear isomers **10a** and **10b** (corresponding to C-6 of **11a**) appeared at δ 25.45 and δ 28.09 respectively.The *cis* isomers **10a** and **11a** were distinguished from *trans* isomers **10b** and **11b** on the basis of the chemical shifts and total signal widths (the coupling constants were not explicit in ^{1}H NMR of 200 MHz) of ring junction proton H-11a of **10a and 10b** and H-4a of **11a** .The H-11a of **10a** and H-4a of **11a** appeared downfield at δ 3.91 with total signal width ~ 22 Hz and at δ 3.90 with total signal width ~ 24 Hz respectively relative to H-11a (δ 3.54 with total signal width ~ 34Hz) of **10a**.

In the ^{13}C NMR, ring junction carbons C-4a (δ 32.08) and C-11a(δ 51.11) of **10a** appeared upfield relative to C-4a (δ 36.77) and C-11a (δ 55.62) of **10b**. Reduction of linear *cis* - 1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*] carbazole-2-one and angular *cis*- 1,2,3,4,4a,5,6,11c- octahydro-7H- pyrido[2,3-*c*]carbazole-3-one with $LiAlH_4$ gave *cis* - 1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*] carbazole (**12**) and *cis*- 1,2,3,4,4a,5,6,11c-octahydro-7H- pyrido[2,3-*c*]carbazole (**13**) respectively. The compounds **12** and **13** on alkylation with alkyl iodides in presence of potassium carbonate yielded the corresponding *N*-alkyl compounds (**14a-c** and **15a-c**) as reported in literature[1].

Conclusion

The above method is relatively a convenient route for the synthesis of the title compounds as it avoids the use of high pressure and temperature hydrogenation and cumbersome work up. The method may be useful for the bulk synthesis of this important class of compounds of high medicinal value.

Experimental

General methods and materials:

Melting points were determined in open capillaries on an electrically heated melting point apparatus and are uncorrected. Progress of reactions and purity of compounds were monitored by thin layer chromatography, which was performed by self made plates of silica gel G or Aluminium oxide or 0.25 mm readymade plates of silica gel and compounds were detected with iodine vapours and Dragondrof solution. Separation or purification of the compounds was achieved by column chromatography, using silica gel (60-120 or higher, mesh size) or Aluminium oxide. The compounds were analyzed for C, H and N and the results obtained within ±0.4% of calculated values. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE DPX 200 MHz spectrometer. Chemical shifts have been described in ppm with reference to TMS. IR spectra were recorded on Perkin-Elmer infrared models 557,881 or Shimadzu FTIR model PC spectrophotometer. Electron Impact mass spectra (EIMS) and Fast Atomic Bombardment mass spectra (FABMS) were recorded on JEOL-JMSD-300 spectrometer and JEOL-JMS-SX102 spectrometer.

***cis*- and *trans*-4-*b*enzoyloxycyclohexanol (3a and 3b) -**

Benzoyl chloride (196 mL, 1.69 mol) in dry chloroform (496 mL) was added drop wise to a solution of a mixture of **2a** and **2b** (200g, 1.72 mol) in dry pyridine (468 mL, 5.80 mol) and dry chloroform (616 mL) with continuous stirring and cooling (0-5°C) during 5 h .The reaction mixture was washed with water (2 x 200 mL) followed by its washing with 5% H_2SO_4 solution (4 x 200 mL) and water (3 x 200 mL) to make it pyridine free. Drying over Na_2SO_4 and concentration followed by vaccum distillation of the mixture yielded cis-trans mixture of monobenzoate as viscous colorless oil and the residue contained dibenzoate. Yield: 60.6%; b.p.: 175-180/0.2 mm; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 1.42-2.15 (m,9H, CH_2, OH),3.81-3.86 (m, 1H, H-1),5.00-5.07,5.12-5.18 (both m. 1H (0.5 H, 0.5 H),H-4),7.40-7.59 (m,3H,ArH-3',4',5'), 8.01-8.15 (m, 2H, ArH-2',6');FTIR(neat): cm^{-1}759, 1064,1114,1217,1278, 1402, 1448,1614,1645,1706, 2868, 2947, 3022, 3411; MS (EI): m/z 220 (M^+); Anal. Calcd. for $C_{13}H_{16}O_3$: C.70.91; H, 7.27%. Found: C, 70.55; H, 7.10%.

4-*b*enzoyloxycyclohexanone (5) –

The mixture of **3a** and **3b** (140g, 0.64 mol) was dissolved in glacial acetic acid (238 mL). Chromium trioxide (61.6 g, 0.62 mol) in glacial acetic acid (143 mL) and distilled water (35 mL), was added dropwise to the above cooled (0-10°C) and stirred solution, so that temperature of the reaction mixture did not rise above 25°C during addition. Reaction mixture was stirred continuously for 4-5 h after completion of addition. Diethyl ether (2 x 200 mL) was used for extraction and the ether layer was washed with distilled water (2 x 50 mL),10% sodium hydroxide solution (3 x 50 mL) and again with distilled water (3 x 50 mL).Concentration of the solvent followed by crystallization of the crude in petroleum ether resulted in plate like crystals of **5**. Yield: 80.7%; mp.: 60°C; ^{1}H NMR ($CDCl_3$.200 MHz): δ 2.16-2.71(m,8H, CH_2),5.44 (distorted qn,1H, H-4),7.43-7.63 (m, 3H , ArH-3',4',5'),8.06 (d,J=8.6,2H,ArH-2',6'); FTIR (KBr): cm^{-1}714, 910,1024, 1116,1276,1442, 1496,1594, and 1714, 2960, 3070; MS (EI): m/z 218 (M^+); Anal. Calcd. For $C_{13}H_{14}O_3$: C.71.56; H, 6.42%. Found: C, 71.93; H, 6.65%.

6-*b*enzoyloxy-3, 4,5,6,7,8-hexahydro-2(1H)-quinolinone (6a) and 6-*b*enzoyloxy-3,4,4a,5,6,7- hexahydro-2(1H)-quinolinone (6b) –

A solution of **5** (100 g, 0.46 mol), pyrrolidine (60 mL, 0.72 mol) and few crystals of PTSA monohydrate in benzene (1000 mL) was refluxed for 1.5 h under dean-stark water separator. Benzene was distilled off avoiding moisture to enter in the system to get light yellow colored enamine as solid. Acrylamide (85.0 g, 1.2 mol) in dry dioxane (500 mL) was added to a solution of enamine in dry dioxane (1500 mL) and the resulting mixture was refluxed for 20-24 h. Dioxane was distilled off completely and methanol was added to the crude to have white crystals of compound. The solid was filtered and the filtrate was subjected to column chromatography to get compound (mixture of **6a** and **6b**). Yield: 80.7%; mp.:125-130°C; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 1.94-2.61,4.98(m,brs,10H (9.67H, 0.33 H), H-3,4,4a,5,7,8),5.31,5.47 (qn,br s ,J=5.8 Hz,1H (0.67 H ,0.33H), H-6),7.40-7.60 (m, 3H , ArH-3',4',5'),8.03(d,J=8.4Hz,2H,ArH-2',6'),8.43,9.14 (both brs,ex,1H,NH); FTIR(KBr):cm^{-1} 713, 806, 885, 947, 1018, 1060, 1110,1168,1213,1272, 1394,1450, 1487, 1608, 1668, 1718, 2860, 3072, 3400. MS(EI): m/z 271 (M^+); Anal. Calcd. for $C_{16}H_{17}NO_3$: C,70.85; H, 6. 27; N, 5.17%. Found: C, 70.84; H, 6.76; N, 4.99%. For 8a > 90% in concentration: - ^{1}H NMR ($CDCl_3$.200 MHz) : δ 2.02-2.56,4.88(both m,10H, H-3,4,4a,5,7,8),5.32,5.46 (qn,m ,J=5.6 Hz,1H , H-6),7.12 (brs, ex , 1H , NH),7.36-7.60 (m,3H,ArH-3',4',5'),8.02(d,J=8.4Hz,2H, ArH-2',6'); FTIR(KBr):cm^{-1} 714, 806, 972, 1108, 1194, 1272, 1388, 1450, 1668, 1716, 2942, 3092, 3182. MS(EI): m/z 271 (M^+).

***cis*- and *trans*- 6-*b*enzoyloxy-3, 4,4a, 5,6,7,8,8a-octahydro-2(1H)-quinolinone (7a and 7b) –**

A mixture of **6a** and **6b** (2.0 g, 7.38 mmol) was dissolved in methanol (30 mL) and 10% Pd-C (0.5 g) was added to it .The solution was hydrogenated at 50 psi for 30 h. Filtration of catalyst and concentration of solvent followed by triturition with acetone gave white solid. Yield: 79.6%; m.p: 130-135°C;^{1}H NMR ($CDCl_3$.200MHz): δ 1.77-2.39(m, 11H, H-3, 4,4a, 5,7,8), 3.48, 3.62 (s,brs , (the two merging),1H (0.33H,0.67 H), H-8a),5.06,5.30-5.38 (m, 1H, (0.67 H ,0.33H),H-6), 6.26, 6.38(both brs (the two merging),1H.NH),7.41-7.57(m,3H, ArH-3',4',5') ,8.03(distorted d,J=7.0 Hz, 2H,ArH-2',6'); FTIR (KBr): cm^{-1} 713, 806, 927, 962, 989, 1024, 1070,1114, 1278,1315, 1407, 1450, 1629,1712, 2869, 2937, 3205; MS (EI): m/z 273 (M^+). Anal. Calcd. for $C_{16}H_{19}NO_3$: C.70.33; H, 6. 96; N, 5.13%. Found: C, 70.72; H, 6.59; N, 5.09%.

***cis*- and *trans* –6-hydroxy –3,4,4a, 5,6,7,8,8a-octahydro-2(1H)-quinolinone (8a and 8b)-**

Sodium hydroxide (4.43 g, 0.11 mol) in distilled water (20 mL) was added to solution of **7a** and **7b** (30 g, 0.11 mol) in methanol (150 mL) and dichloromethane (70 mL), and the reaction mixture was stirred for 8-10 h at r.t. Solution was concentrated to dryness and the product was extracted from the reaction mixture by repeated extraction with chloroform (20x50 mL) and ethyl acetate (10x50 mL). Combined organic layer washed with water and dried over sodium sulphate was subjected to concentration under vaccum to give white solid. Yield: 64.8%; mp.: 172-175°C; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 1.71-2.53(both m, 11H (10.84 H,0.16H), H-3,4,4a,5,7,8,OH),4.02 (m, 1H, H-6), 7.15 (brs,ex,1H,NH); FTIR (KBr): cm^{-1}752, 806, 1014, 1055, 1188, 1234, 1284, 1334, 1400, 1519, 1649, 2842, 2893, 3074, 3390; MS(EI): m/z 167 (M^+). Anal. Calcd. for $C_9H_{13}NO_2$; C.64.67; H, 7.78; N,8.38%.Found: C,65.11; H, 7.52 ; N ,8.85%.

***cis*- and *trans* –1,3,4,4a.5, 7,8,8a-octahydro-2, 6-quinolinedione (9a and 9b)-**

The mixture of **8a** and **8b** (8.0g, 0.047mol) was dissolved in dry dioxane. Jones reagent (35mL) was added dropwise to it with continuous stirring at r.t. during 15 min. Green sticky material was separated out which was isolated by decanting dioxane layer. Addition of water (20 mL) to green crude, and extraction with chloroform (10x30 mL) and ethyl acetate (10x30 mL) followed by crystallization in acetone yielded colorless crystals of **11a** and **11b**. Yield: 50.6%; mp.: 140°C; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 1.76-2.52 (m, 11H, H-3, 4, 4a, 5, 7, 8), 3.65, 3.81 (s, brs ,1H, (0.12 H,0.88H), H-8a), 7.79 (brs, ex, 1H, NH); FTIR (KBr): cm^{-1} 508, 772, 811, 1062, 1101, 1142, 1205, 1269, 1303, 1343, 1408, 1448, 1475, 1659, 1717, 2899, 2950, 3185; MS(FAB): m/z 168 ($M+H^+$), base), 190($M+Na^+$); Anal. Calcd. for $C_9H_{13}NO_2$: C,64.67; H, 7.78 ; N,8.38%. Found: C, 65.11; H, 7.52; N, 8.85%.

***cis*- and *trans* –1,2,3,4,4a, 5,11,11a-octahydro-6H-pyrido[3,2-*b*] carbazole-2-one (10a and 10b) and *cis*- and *trans*–1,2,3,4,4a, 5,6,11c-octahydro-7H-pyrido[2,3-*c*]carbazole-3-one (11a and 11b)-**

Phenylhydrazine (1.5g, 0.014mol) and conc. HCl (0.6 mL) were added to a solution of a mixture **9a** and **9b** (2.0g, 0.012 mol) in ethanol (100 mL) and the resulting solution was refluxed for 4-5 hours. Solvent was concentrated and then poured over ice to get yellow

colored solid .The crude was subjected to column chromatography to get *cis* and *trans* linear isomers **10a and 10b** and *cis* and *trans* angular isomers **11a** and **11b**.

***cis*- 1,2,3,4,4a, 5,11,11a-octahydro-6H-pyrido[3,2-*b*] carbazole -2-one (10a)**- Yield: 8.0%; mp.: 170-172°C; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 1.89-2.03(m,2H,H-4),2.50-2.57 (t,3H ,H-3,4a),2.69-2.79 ,2.94-3.20(both m, 4H ,H-5,11),3.91(m,1H,H-11a),5.85(brs, ex,1H,lactam NH),7.09-7.18 (m,2H,H-8,9),7.26-7.36(m,1H,H-7), 7.44(d,J=7.3Hz, 1H,H-10), 7.78 (br s, ex, 1H, indole NH); FTIR (KBr): cm^{-1} 748, 1014, 1222,1328, 1404, 1467, 1645, 2858, 2918, 3068, 3280, 3404; MS (FAB): m/z 240 (M^+), 241 $(M+H)^+$, 279 $(M+K)^+$. Anal. Calcd. for $C_{15}H_{16}N_2O$: C,75.00; H, 6.67; N, 11.67%. Found: C, 74.71; H, 6.81; N, 12.03%.

***trans*–1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole-2-one(10b)**-
Yield: 7.3%; mp.: 305°C; ^{1}H NMR ($CDCl_3$.200MHz) :δ1.68-1.81,1.93-2.12(both m, 3H,H-4,4a), 2.48-2.69,2.92-3.12 (both m ,4H,2H,H-3,5,11),3.54(m, 1H ,H-11a),5.94(brs, ex.1H.lactam NH), 7.07-7.19 (m,2H,H-8,9),7.26-7.36(m,1H,H-7),7.45(d, J=7.4Hz,1H,H-10), 7.85(brs, ex, 1H, indole NH); FTIR(KBr): cm^{-1} 665,742,1014, 1326,1371,1409,1460, 1533,1656,2731,2844, 2916, 3010,3301,3369;MS(EI): m/z 240 (M^+);Anal. Calcd. for $C_{15}H_{16}N_2O$: C,75.00; H, 6.67; N, 11.67%. Found: C, 75.12; H, 6.44; N, 11.87%.

***cis*- 1,2,3,4,4a,5,6,11c- octahydro-7H- pyrido[2,3-*c*]carbazole-3-one (11a)**-
Yield : 48.8%; mp.: 237°C; ^{1}H NMR ($CDCl_3$.200 MHz) : δ 2.02-2.42(m,6H,H-1,2,5),2.75-2.81 (m ,2H,H-6),3.42 (m, 1H ,H-11c),3.90 (m,1H,H-4a), 6.00(brs,ex.1H.lactam NH),7.06-7.19(m,2H,H-9,10), 7.26-7.33 (m, 1H, H8), 7.53 (d,J=6.9Hz,1H,H-11), 7.85(brs,ex,1H, indole NH); FTIR(KBr): cm^{-1} 618, 663, 736, 811, 1021, 1136, 1183, 1222, 1288, 1328, 1404, 1426, 1468, 1601, 2883, 2927, 2980, 3053, 3199, 3270;MS(EI):m/z 240 (M^+, base);Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.00; H, 6.67; N,11.67%. Found: C, 74.80; H, 6.33; N, 11.46%.

***cis* -1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole (12)**-
A solution of *cis* -1,2,3,4,4a, 5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole –2-one (0.20g,.8 mmol) in dry THF was added to a suspension of $LiAlH_4$ (0.120 g ,3.2 mmol) in dry THF and the mixture was refluxed for 24 h. Few drops of water were added to decompose $LiAlH_4$ and solution was filtered and concentrated. Purification of crude product by column

chromatography using Al_2O_3 as adsorbent in MeOH and $CHCl_3$ as eluent gave 12. Yield: 65%; mp.:189-190°C, lit. mp.:190°C; ^1H NMR ($CDCl_3$.200 MHz) : δ1.25-1.75(m,5 H, H-3.4.4a),2.2(m ,1H,NH exchangeable),2.63-3.48(m, 7H ,H-2,5,11,11a),7.02-7.44(m,4H,ArH),7.72(br s,1H, indole NH);IR(KBr):cm^{-1} 737, 807, 919, 1440, 1586, 1624, 2365, 2768, 2852, 2923, 3051, 3142, 3278, 3436; MS(EI): m/z 226 (M^+,);Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4%. Found: C, 79.7; H, 8.1; N, 12.1%.

***cis* -1,2,3,4,4a, 5,6,11c-octahydro-7H-pyrido[2,3-*c*] carbazole (13)-**

A solution of *cis* -1,2,3,4,4a,5,6,11a-octahydro-7H-pyrido[2,3-*c*]carbazole –3-one (0.20g,0.8mmol) in dry THF(50 mL) was added to a suspension of $LiAlH_4$ (0.12gm,3.2mmol) in dry THF(20 mL) and the mixture was refluxed for 24 h.Few drops of water were added to decompose $LiAlH_4$ and solution was filtered and concentrated .purification of crude by column chromatography using Al_2O_3 as adsorbent in MeOH and $CHCl_3$ as eluent gave 13.Yield: 69.1%; mp.:166°C;lit. mp.:167°C; ^1H NMR ($CDCl_3$+DMSO-D_6.200MHz):δ1.76-2.04(m,4H,H-1,5),2.21-2.59 (m,4H,H-2,6), 3.00-3.07(m,2H,H-3),3.21(distorted brs,ex,1H,NH),3.47(m,1H,H-11c),7.44(d,J,=9.4Hz,1H,H-11), 9.64 (brs,ex,1H, indoleNH); FTIR(KBr): cm^{-1}622,666, 734,926, 1052,1219, 1265,1329, 1405, 1457, 1582, 2852, 2940,3077,3258; MS(EI): m/z 226 (M^+); Anal. Calcd. for $C_{15}H_{18}N_2$: C.79.65; H, 7.96; N, 12.39 %. Found: C, 79.42; H, 7.60; N, 12.42%.

***cis*-1- methyl-1, 2,3,4,4a, 5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole (14a)-**

A mixture of **12** (0.90 g, 0.0035 mol) with K_2CO_3 (1.68 g, 0.012 mol) and methyl iodide (1.14 g, 0.008 mol) in acetone (40 mL) was refluxed for 72 h and concentrated. Water (20 mL) was added slowly and extracted with ether (3 x 20 mL). The organic extract was dried and concentrated to give **14a**, which was crystallized from ether. Yield: 60 %; mp.: 70-72°C; lit. mp: 72°C.

***cis*-1- ethyl-1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole (14b)-**

Alkylation of **12** by ethyl iodide as the method described for **14a** afforded **14b**.Yield: 65%; mp: 255-259 °C ; lit. mp: 258°C.

***cis*-1- propyl-1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[3,2-*b*]carbazole (14c)-**

Alkylation of **12** by propyl iodide as the method described for **14a** afforded **14c**.Yield: 75%; mp: 200 °C ; lit. mp: 200°C.

***cis*-4- methyl-1,2,3,4,4a,5,6,11c-octahydro-7H-pyrido[2,3-*c*]carbazole (15a)-**

Alkylation of **13** by methyl iodide as the method described for **14a** afforded **15a**.It was crystallized from ether. Yield: 80%; mp: 132-135 °C; lit. mp: 133°C.

***cis*-4- ethyl-1, 2,3,4,4a, 5,6,11c-octahydro-7H-pyrido[2,3-*c*]carbazole (15b)-**

Alkylation of **13** by ethyl iodide as the method described for **14a** afforded **15b**. It was crystallized from ether. Yield: 70%; mp: 287-290°C; lit. mp; 288°C.

***cis*-4- propyl-1, 2,3,4,4a, 5,6,11c-octahydro-7H-pyrido[2,3-*c*]carbazole (15c)-**

Alkylation of **13** by propyl iodide as the method described for **14a** afforded **15c**. It was crystallized from ether. Yield: 70% ;mp: 252-254 °C ; lit. mp; 252-254°C.

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