SYNTHESIS OF 2-HYDROXYPYRIDO[2,3-*a*]CARBAZOLES AND 2-HYDROXYPYRIMIDO[4,5-*a*]CARBAZOLES FROM 1-HYDROXYCARBAZOLES

Kandasamy Shanmugasundaram and Karnam J. Rajendra Prasad*

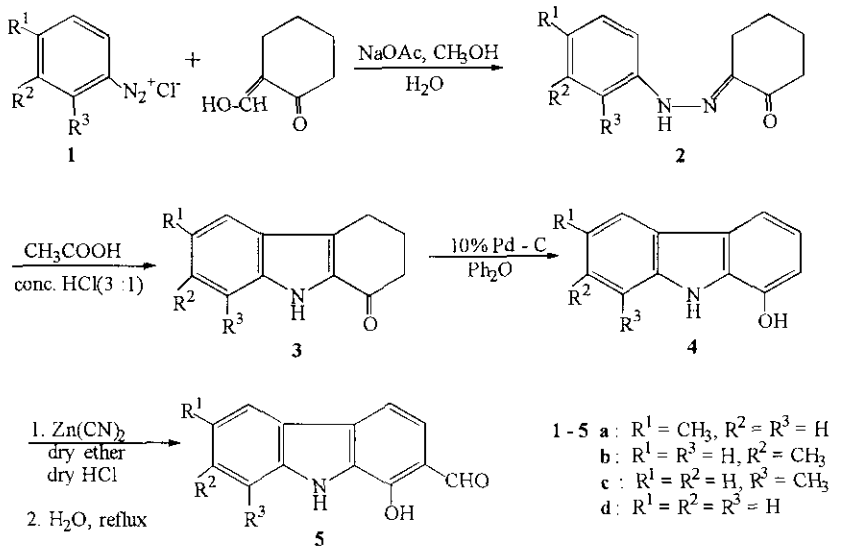
Department of Chemistry, Bharathiar University, Coimbatore - 641 046, India

Abstract - Gattermann reaction on substituted 1-hydroxycarbazoles (**4a-d**) afforded substituted 1-hydroxycarbazole-2-carbaldehydes (**5a-d**) from which synthesis of either 2-hydroxypyrido[2,3-*a*]carbazoles (**7a-d**) *via* Perkin reaction or 2-hydroxypyrimido[4,5-*a*]-carbazoles (**8a-d**) *via* condensation with urea could be achieved.

It is well established that the pyridocarbazole ring is an appropriate skeleton to design DNA intercaling drugs.[1] Some compounds such as ellipticine, olivacine and pyridazino[4,5-*b*]carbazoles, representing 3-aza analogs of pyrido[4,3-*b*]-carbazoles elicit high antitumour properties.[1-4] Since the discovery of the potent activity of 11*H*-pyrido[2,3-*a*]carbazoles[1] and 6*H*-pyrido[3,2-*b*]carbazoles,[3] numerous syntheses have been reported.[1,5] Indoles,[5a-e] but also 3-amino carbazoles,[5h] stilbenes,[5e] substituted benzenes[5g] or quinolines[1,5f] were often used as starting materials. These methods, however, often have low yields due either to the large number of steps[5g] or to the presence of several isomers.[5c-d,5i] This fact and the promising antitumour properties of these tetracyclic compounds have induced us to develop a synthetic strategy directed towards the synthesis of the titled system.

The precursors opted for this study were 1-hydroxycarbazole-2-carbaldehydes (**5a-d**), prepared as shown in Scheme 1.[6-8] Substituted 1-hydroxycarbazoles (**4a-d**) have been prepared by the dehydrogenation of 2,3,4,9-tetrahydrocarbazol-1-ones (**3a-d**) with palladium-charcoal.[6] 2,3,4,9-Tetrahydrocarbazol-1-ones (**3a-d**) have been prepared by Fischer indole synthesis of the monophenylhydrazones of cyclohexane-1,2-dione (**2a-d**) using CH_3COOH - HCl (3 : 1, v/v).[7] Phenylhydrazones have been made by Japp-Klingemann condensation of corresponding diazonium chlorides (**1a-d**) with 2-hydroxymethylidenecyclohexanone.[8] Though hydroxyformylcarbazoles (**5**) have already been reported in the literature, the synthetic methods directed towards them suffers from either multitudiness of the steps involved[9] or low yields due to undesired side reactions and recovery of starting material.[10] In order to overcome the aforesaid difficulties, the Gattermann reaction on 1-hydroxycarbazoles (**4a-d**) was achieved and it led to the formation of 1-hydroxycarbazole-2-carbaldehydes (**5a-d**) in good yields and these were used to build pyridine and pyrimidine blocks.

Scheme 1



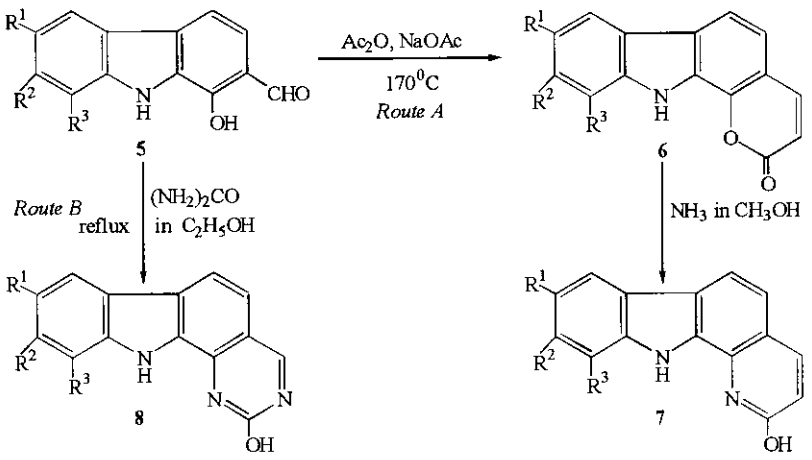
Perkin reaction of **5a-d** with acetic anhydride and anhydrous sodium acetate afforded the corresponding pyrano[2,3-*a*]carbazol-2-ones (**6a-d**). The formation of α-pyrone ring in **6a-d** has been evidenced from the appearance of absorption peak at ~1760 cm^{-1} corresponding to carbonyl group. In the NMR spectra of **6a-d**, the disappearance of resonances owing to formyl proton as well as hydroxyl proton and the appearance of unresolved aromatic multiplet owing to seven protons in **6a-c** and eight protons in **6d** further strengthen our belief that α-pyrone ring is formed in **6a-d**. The analytical data obtained for **6a-d** were also in good agreement with the proposed structures. The treatment of **6a-d** with ammonia in methanol gave 2-hydroxypyrido[2,3-*a*]carbazoles (**7a-d**) (Scheme 2, *Route A*).The disappearance of the carbonyl absorption in the IR spectra of the compounds (**7a-d**) revealed the formation of the pyridine ring with hydroxyl group in the second position. The presence of hydroxyl group in **7a-d** is further substantiated by the appearance of resonance signals in their ^{1}H-NMR spectra. The analytical values were also corroborated with the structures assigned to them. Furthermore, the condensation of 1-hydroxycarbazole-2-carbaldehydes (**5a-d**) with urea in boiling ethanol yielded 2-hydroxypyrimido[4,5-*a*]carbazole derivatives (**8a-d**) (Scheme 2, *Route B*). The IR and ^{1}H- NMR spectra of the products suggested the formation of pyrimidine ring in **8a-d**. The elemental analysis obtained also attested the structures (**8a-d**).

From 1-hydroxycarbazoles, pyridocarbazoles (**7a-d**) and pyrimidocarbazoles (**8a-d**) could be prepared with good yields.

EXPERIMENTAL

General Information. Melting points were determined with a Boetius microheating table and are uncorrected. The

Scheme 2



5 - 8 **a** : $R^1 = CH_3$, $R^2 = R^3 = H$
b : $R^1 = R^3 = H$, $R^2 = CH_3$
c : $R^1 = R^2 = H$, $R^3 = CH_3$
d : $R^1 = R^2 = R^3 = H$

IR spectra were recorded in KBr pellets with a Shimadzu FTIR 8002 spectrophotometer and only noteworthy absorption levels (cm^{-1}) are listed. The ^1H NMR spectra were obtained on a Varian AMX 400 FT spectrometer and were recorded in ppm downfield from an internal standard tetramethyl silane in $CDCl_3$. J values are reported in Hertz (Hz). MS were obtained on a Jeol D 300 instrument and elemental analyses were performed on a Heraeus Carlo Erba 1108 apparatus. Column chromatography was performed on silica gel (60 - 120 mesh). TLC was performed on silica gel. Petroleum ether used was generally the fraction bp 60 - 80°C.

General procedure for the Gattermann reaction of substituted 1-hydroxycarbazoles (4a-d). The respective 1-hydroxycarbazole (**4**) (5.0 mmol) was dissolved in dry ether (75 mL) and freshly prepared zinc cyanide (0.59 g, 5.0 mmol) was added to the reaction mixture. This heterogeneous mixture was maintained at 0 to -5°C for 3 - 4 h with constant stirring to pass dry HCl. After saturating the ether with HCl, the HCl gas was passed more slowly and stirring was continued for another 0.5 h to ensure the completion of the reaction. The reaction mixture was then placed in a refrigerator for 48 h and the resulting precipitated imine hydrochloride was filtered, dissolved in water and heated under reflux for 1 h. Cooling, filtration, extraction with ethyl acetate, drying over anhydrous sodium sulfate followed by solvent removal afforded a crude product which was purified by column chromatography (petroleum ether / ethyl acetate, 96 : 4). The product thus obtained was recrystallised from the petroleum ether - ethyl acetate (96 :4) mixture.

6-Methyl-1-hydroxycarbazole-2-carbaldehyde (**5a**): Yield 85%; mp 129°C; ^1H NMR ($CDCl_3$) δ : 2.54(s, 3H, CH_3), 7.05 - 7.87(m, 5H, $H_{3\text{-}4\text{-}5\text{-}7\text{-}8}$), 8.47(br s, 1H, NH), 9.99(s, 1H, CHO), 11.75(s, 1H, OH); IR (KBr) : 1662, 1610, 1593, 1461, 1415, 1388, 1334, 1307, 1276, 1251, 1211, 1195, 1147. *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found : C, 74.38; H, 4.79; N, 6.15.

7-Methyl-1-hydroxycarbazole-2-carbaldehyde (**5b**): Yield 90%; mp 135°C; ^{1}H NMR ($CDCl_3$) δ : 2.57(s, 3H, CH_3), 6.99 - 7.82(m, 5H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}8}$), 9.37(s, 1H, CHO), 10.78(s, 1H, OH); IR (KBr) : 1666, 1610, 1595, 1485, 1461, 1456, 1398, 1350, 1288, 1253, 1226, 1166, 1112, 1093. *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found : C, 74.79; H, 4.82; N, 6.11.

8-Methyl-1-hydroxycarbazole-2-carbaldehyde (**5c**): Yield 85%; mp 140°C; ^{1}H NMR ($CDCl_3$) δ : 2.61(s, 3H, CH_3), 7.17 - 7.96(m, 5H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7}$), 8.48(br s, 1H, NH), 10.01(s, 1H, CHO), 11.82(s, 1H, OH); IR (KBr) : 1662, 1610, 1593, 1541, 1508, 1460, 1417, 1386, 1334, 1313, 1251, 1211, 1147, 1082. *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found : C, 74.47; H, 4.78; N, 6.10.

1-Hydroxycarbazole-2-carbaldehyde (**5d**): Yield 82%; mp 138°C; ^{1}H NMR ($CDCl_3$) δ : 7.08 - 8.11(m, 6H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{-}8}$), 8.57(br s, 1H, NH), 10.01(s, 1H, CHO), 11.75(s, 1H, OH); IR (KBr) : 1662, 1610, 1591, 1483, 1450, 1392, 1340, 1253, 1209. *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63. Found : C, 73.75; H, 4.16; N, 6.55.

General procedure for the synthesis of pyrano[2,3-*a*]carbazol-2-ones (6a-d). The appropriate 1-hydroxycarbazole-2-carbaldehyde (**5**) (2.0 mmol) was treated with 5 mL of acetic anhydride and 1 g of anhydrous sodium acetate at 170°C for 10 h under nitrogen atmosphere. The reaction mixture was then poured into crushed ice, the resulting semi solid separated was extracted with chloroform and the combined organic layers were subsequently dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product which was purified by column chromatography (petroleum ether / ethyl acetate, 90:10). The product thus obtained was recrystallised from petroleum ether - ethyl acetate mixture (96 :10).

8-Methylpyrano[2,3-*a*]carbazol-2-one (**6a**): Yield 70%; mp 205°C; ^{1}H NMR ($CDCl_3$) δ : 2.17(s, 3H, CH_3), 7.03 - 8.05(m, 7H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{-}9\text{-}10}$), 8.12(br s, 1H, NH); IR (KBr) : 3421, 1760, 1589, 1456, 1355, 1330, 1319, 1201, 1153, 1120; MS (m/z) : M^+ 249 (55). *Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found : C, 77.22; H, 4.32; N, 5.54.

9-Methylpyrano[2,3-*a*]carbazol-2-one (**6b**): Yield 64%; mp 162°C; ^{1}H NMR ($CDCl_3$) δ : 2.50(s, 3H, CH_3), 6.93 - 8.05(m, 7H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}10}$), 8.10(br s, 1H, NH); IR (KBr) : 3404, 1764, 1610, 1577, 1492, 1443, 1365, 1319, 1280, 1195, 1078. *Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found : C, 76.85; H, 4.38; N, 5.52.

10-Methylpyrano[2,3-*a*]carbazol-2-one (**6c**): Yield 65%; mp 197°C; ^{1}H NMR ($CDCl_3$) δ : 2.52(s, 3H, CH_3), 6.92 - 8.02(m, 7H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}9}$), 8.15(br s, 1H, NH); IR (KBr) : 3373, 1747, 1577, 1558, 1541, 1508, 1456, 1425, 1367, 1355, 1319, 1292, 1215, 1153, 1120, 1072. *Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found : C, 77.22; H, 4.33; N, 5.66.

Pyrano[2,3-*a*]carbazol-2-one (**6d**): Yield 70%; mp 169°C; ^{1}H NMR ($CDCl_3$) δ : 7.19 - 8.04(m, 8H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}9\text{-}10}$), 8.08(br s, 1H, NH); IR (KBr) : 3415, 1759, 1612, 1583, 1504, 1487, 1456, 1434, 1392, 1371, 1340, 1325, 1278, 1211, 1153, 1120, 1078. *Anal.* Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found : C, 76.35; H, 3.74; N, 5.89.

General procedure for the synthesis of 2-hydroxypyrido[2,3-*a*]carbazoles (7a-d). The respective pyrano[2,3-*a*]carbazol-2-one (**6**) (1.0 mmol) was dissolved in absolute methanol (50 mL). The solution was saturated with ammonia gas and kept at rt for about 5 h. The solvent was removed under reduced pressure. The residue was dissolved in chloroform and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by crystallisation from petroleum ether yielded 2-hydroxypyrido[2,3-*a*]carbazole (**7**).

2-Hydroxy-8-methylpyrido[2,3-*a*]carbazole (**7a**): Yield 90%; mp 182°C; ^{1}H NMR ($CDCl_3$) δ : 2.53(s, 3H, CH_3), 5.35(s, 1H, OH), 6.82(d, 1H, H_4, J = 7.8 Hz), 7.04, 7.06(d, 2H, H_5, H_6, J = 7.8 Hz), 7.25(d, 1H, H_9, J = 9.8 Hz), 7.35(d, 1H, H_{10}, J = 9.8 Hz), 7.64(d, 1H, H_3, J = 7.8 Hz), 7.85(s, 1H, H_7), 8.19(br s, 1H, NH); IR (KBr) : 3460, 3390, 1616, 1577, 1506, 1477, 1461, 1427, 1394, 1363, 1344, 1313, 1272, 1224, 1199, 1072,1051; MS (m/z) : M^+ 248 (33). *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found : C, 77.68; H, 4.78; N, 11.20.

2-Hydroxy-9-methylpyrido[2,3-*a*]carbazole (**7b**): Yield 92%; mp 157°C; ^{1}H NMR ($CDCl_3$) δ : 2.52(s, 3H, CH_3), 5.55(s, 1H, OH), 6.79 - 7.93(m, 7H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{—}8\text{-}10}$), 8.37(br s, 1H, NH); IR (KBr) : 3433, 3271, 1618, 1583, 1498, 1438, 1303, 1240, 1217, 1078, 1043. *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found : C, 77.15; H, 4.73; N, 11.14.

2-Hydroxy-10-methylpyrido[2,3-*a*]carbazole (**7c**): Yield 84%; mp 178°C; ^{1}H NMR ($CDCl_3$) δ : 2.53(s, 3H, CH_3), 5.38(s, 1H, OH), 6.81 - 7.85(m, 7H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{—}8\text{-}9}$), 8.19(br s, 1H, NH); IR (KBr) : 3455, 3390, 1618, 1577, 1508, 1477, 1460, 1425, 1394, 1313, 1294, 1224, 1201, 1174, 1134, 1072, 1051. *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found : C, 77.17; H, 4.81; N, 11.16.

2-Hydroxypyrido[2,3-*a*]carbazole (**7d**): Yield 85%; mp 197°C; ^{1}H NMR ($CDCl_3$) δ : 5.76(s, 1H, OH), 6.86 - 8.07(m, 8H, $H_{3\text{-}4\text{-}5\text{-}6\text{-}7\text{—}8\text{-}9\text{-}10}$), 8.48(br s, 1H, NH); IR (KBr) : 3433, 3255, 1616, 1581, 1502, 1488, 1452, 1309, 1253, 1236, 1215, 1080. *Anal.* Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found : C, 76.69; H, 4.25; N, 11.87.

General procedure for the synthesis of 2-hydroxypyrimido[4,5-*a*]carbazoles (8a-d). To the solution of appropriate 1-hydroxycarbazole-2-carbaldehyde (**5**) (1.0 mmol) in absolute ethanol (20 mL), urea (0.5 g, 8.3 mmol) was added and this mixture was heated at reflux for 4 h . The solvent was removed under reduced pressure, then the crude reaction mixture was washed with water, extracted with chloroform and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent followed by crystallisation from petroleum ether gave 2-hydroxypyrimido[4,5-*a*]carbazole (**8**).

2-Hydroxy-8-methylpyrimido[4,5-*a*]carbazole (**8a**): Yield 88%; mp 207°C; ^{1}H NMR ($CDCl_3$) δ : 2.86(s, 3H, CH_3), 5.51(s, 1H, OH), 7.14 - 8.18(m, 6H, $H_{4\text{-}5\text{-}6\text{-}7\text{-}9\text{-}10}$), 8.50(br s, 1H, NH); IR (KBr) : 3450, 3390, 1616, 1577, 1558, 1541, 1508, 1488, 1419, 1363, 1313, 1224, 1201; MS (m/z) : M^+ 249 (43). *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found : C, 72.02; H, 4.38; N, 16.73.

2-Hydroxy-9-methylpyrimido[4,5-*a*]carbazole (**8b**): Yield 85%; mp 172°C; ^{1}H NMR ($CDCl_3$) δ : 2.52(s, 3H, CH_3), 5.28(s, 1H, OH), 6.79 - 7.93(m, 6H, $H_{4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}10}$), 8.16(br s, 1H, NH); IR (KBr) : 3440, 3388, 1618, 1577, 1560, 1541, 1508, 1488, 1458, 1303, 1078. *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found : C, 72.53; H, 4.49; N, 16.78.

2-Hydroxy-10-methylpyrimido[4,5-*a*]carbazole (**8c**): Yield 80%; mp 193°C; ^{1}H NMR ($CDCl_3$) δ : 2.52(s, 3H, CH_3), 5.16(s, 1H, OH), 6.80 - 7.84(m, 6H, $H_{4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}9}$), 8.16(br s, 1H, NH). IR (KBr) : 3483, 3390, 1616, 1577, 1508, 1477, 1460, 1425, 1394, 1344, 1294, 1224, 1201, 1174, 1072. *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found : C, 72.44; H, 4.35; N, 16.80.

2-Hydroxypyrimido[4,5-*a*]carbazole (**8d**): Yield 82%; mp 212°C; ^{1}H NMR ($CDCl_3$) δ : 5.16(s, 1H, OH), 6.83 - 7.69(m, 7H, $H_{4\text{-}5\text{-}6\text{-}7\text{-}8\text{-}9\text{-}10}$), 8.26(br s, 1H, NH); IR (KBr) : 3433, 3300, 1616, 1581, 1502, 1487, 1452, 1396, 1338, 1309, 1253, 1236, 1215, 1161, 1080. *Anal.* Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found : C, 71.21; H, 3.73; N, 17.72.

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