A facile synthesis of novel 2-acetyl-1-hydroxycarbazoles– synthesis of biogenetically possible 2-phenyl-4-oxopyrano[2,3-*a*]carbazoles and annelated carbazoles

Vandana and Karnam Jayarampillai Rajendra Prasad*

Department of Chemistry, Bharathiar University, Coimbatore, Tamilnadu, India

Using trifluoroacetic acid as the condensing agent, the synthesis of novel 2-acetyl-1-hydroxycarbazoles has been achieved in moderate yield from 1-hydroxycarbazoles and acetyl chloride. Further, 2-acetyl-1-hydroxycarbazoles on base condensation with benzaldehyde followed by Prevost reaction with I_2 – AgOAc in glacial AcOH yielded 2,3-dihydro-3-iodo-2-phenyl-4-oxopyrano[2,3-*a*]carbazoles which upon dehydroiodination afforded the biogenetically possible 2-phenyl-4-oxopyrano[2,3-*a*]carbazoles. Also, 2-acetyl-1-hydroxycarbazoles have been employed as synthones for the synthesis of annelated carbazoles viz. 3-methyl-pyrazolino- and 3-methyl-isoxazolo- [2,3-*a*]carbazoles.

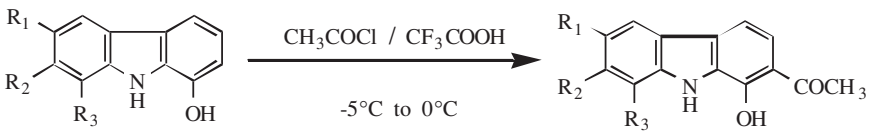
Keywords: 2-acetyl-1-hydroxycarbazoles, 2-phenyl-4-oxopyrano[2,3-*a*]carbazoles, 3-methyl-pyrazolino- and 3-methyl-isoxazolo-[2,3-*a*]carbazoles

Carbazole nucleus had received considerable interest owing to its significant and diverse biological activity.[1-4] Recently, the synthesis and structure–activity relationships of tricyclic α-ethoxy-phenylpropionic acid derivatives guided by *in vitro* PPARα and PPARγ transactivation data and computer modelling led to the identification of novel carbazole analogues with hypolipidemic and antidiabetic activity.[5] This interest was further heightened by the discovery of pyridocarbazoles and their anti-tumor activities.[6,7] Replacement of the pyridine ring in the pyridocarbazole by other heterocyclic rings may lead to interesting variations in the biological activities.[8-10] Among the 10 naturally occurring simple carbazoles, five have oxygen function on C_1 [or its equivalent C_8] and also so far 2-aryl-4-oxopyrano[2,3-*a*] or [3,2-*a*] carbazoles have not been isolated from plant body. But there exists naturally occurring carbazole substrates like murrayafoline A,[11] murrayainine,[12-13] koenoline,[14] mukoeic acid[15-16] and mukonine[17] on which 2-aryl-4-oxopyrano[2,3-*a*]carbazoles can be built up in the plant body and yet none of the 2-aryl-4-oxopyrano[2, 3-*a*] carbazoles are isolated so far. Keeping these facts in mind, we now report a concise route for synthesising novel 2-acetyl-1-hydroxycarbazoles which were then utilised to synthesise biogenetically possible 2-phenyl-4-oxopyrano[2, 3-*a*]carbazoles and annelated carbazoles viz. 3-methyl-pyrazolino- and 3-methyl-isoxazolo- [2,3-*a*]carbazoles.

Much interest centres around 2-acetyl-1-hydroxycarbazoles **2** because they are the suitable intermediates to derive various biogenetically possible naturally occurring heterocylco- fused carbazoles and annelated carbazoles. Therefore, we have undertaken much effort towards the establishment of efficient methodologies for the synthesis of the above mentioned synthons.

To achieve our target, 1-hydroxycarbazoles[18] was used as precursors. Thus, 8-methyl-1-hydroxycarbazole **1a** was dissolved in trifluoroacetic acid and acetyl chloride was added to at –5 to 0 °C. After 10 h, it gave a single product which was purified by column chromatography over silica gel by using petroleum ether: ethyl acetate (99:1) as eluant. Its ^{1}H NMR spectrum gave two '3H' singlets at δ 2.59 and δ 2.73 corresponding to C_8-CH_3 and C_2-$COCH_3$ respectively. It showed a five protons aromatic envelop at δ 7.10–8.08 and two broad singlets at δ 8.58 and δ 13.17 corresponding to carbazole NH and phenolic OH protons respectively. The compound gave positive ferric chloride test further confirming the presence of phenolic OH group. On the basis of physical and spectral data, the compound was attested to be 2-acetyl-8-methyl-1-hydroxycarbazole **2a**. The applicability of the reaction was successfully tested with **1b**, **1c** and **1d** (Scheme 1).

Then, 2-acetyl-8-methyl-1-hydroxycarbazole **2a** was subjected to mixed aldol reaction with benzaldehyde under basic condition to give 2-cinnamoyl-8-methyl-1-hydroxycarbazole **3a**. Earlier method[19] to derive 3 adopted by us directly from 1-hydroxycarbazole by cinnamoylation afforded only around 50%. But in the present method, the yield of **3** has been realised around 92% from the easily accessible 1-hydroxy-2-acetylcarbazoles and benzaldehyde. In the ^{1}H NMR spectrum, the methyl protons appeared as a singlet at δ 2.50. The aromatic cluster accountable for 10 protons and olefinic protons accountable for 2 protons appeared at δ 7.25–7.86. The NH and OH signals appeared as a broad singlet at δ 8.52 and δ 13.73 respectively. Mass spectrum showed molecular ion peak at *m*/*z* 327 with 62 % abundance, base peak at *m*/*z* 223 was obtained by loss of styrene molecule. Based on the above facts, the structure was assigned to be

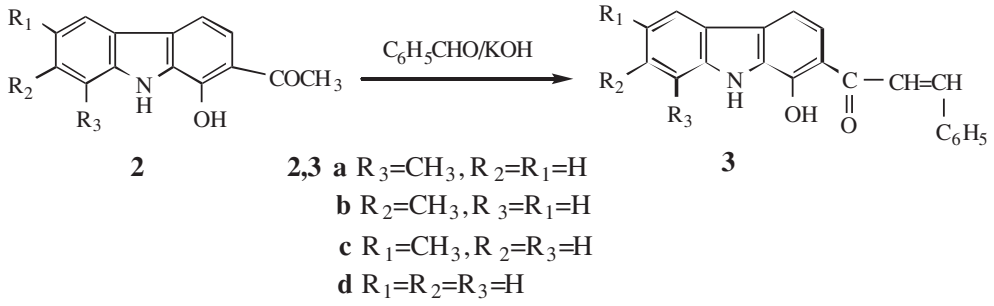


1 **2**

1,2 a :R_3= CH_3,R_1=R_2=H
b:R_2= CH_3,R_1=R_3=H
c:R_1= CH_3,R_2=R_3=H
d:R_1=R_2=R_3=H

Scheme 1

* Correspondence. E-mail: prasad_125@yahoo.com



2 **2,3** **a** R_3=CH_3, R_2=R_1=H **3**

b R_2=CH_3, R_3=R_1=H

c R_1=CH_3, R_2=R_3=H

d R_1=R_2=R_3=H

Scheme 2

8-methyl-2-cinnamoyl-1-hydroxycarbazole **3a**. A series of similar reaction was carried out with **2b–2d** to realise **3b**–**3d**, respectively (Scheme 2).

Further, 2-cinnamoyl-8-methyl-1-hydroxycarbazole **3a** was treated with iodine and silver acetate in presence of acetic acid at room temperature. The reaction mixture was maintained under stirring for 24 h and a crude product obtained was purified using column chromatography. The ^{1}H NMR spectrum registered the following significant resonance signals

(a) a '3H' singlet at δ 2.45 corresponding to C_{10}–CH_3.
(b) a '1H' doublet with J=15.96 Hz at δ 6.46 corresponding to C_2–$H^{21, 22}$.
(c) a '1H' doublet with J=15.96 Hz at δ 7.80 corresponding to C_3–$H^{21,22}$.
(d) an aromatic envelop between δ 7.16–7.73 for nine protons.
(e) a '1H' broad singlet at δ 8.17 (NH).

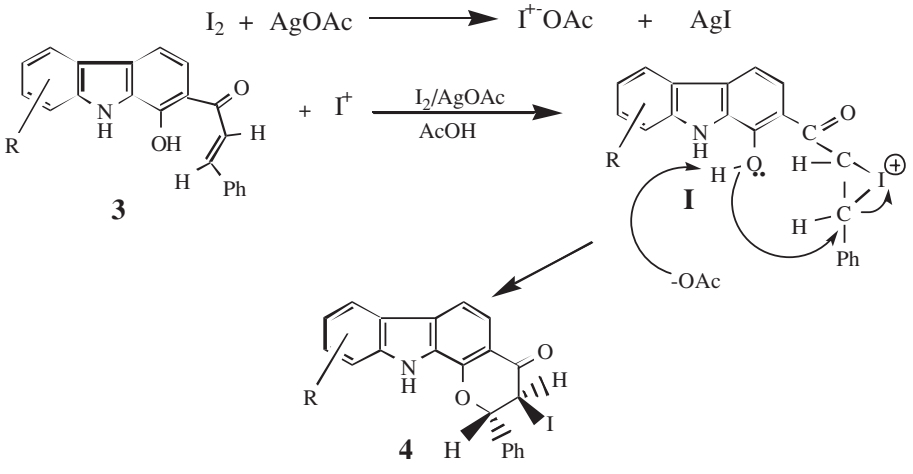
On the basis of molecular ion peak at m/z 453, in its mass spectrum, the molecular formula has been found to be $C_{22}H_{16}NO_2I$.

The elimination of neutral species like $C_{20}H_{15}NO$ gives a fragment ion radical at m/z 168, which clearly suggests the presence of iodine. A conclusive proof for the presence of iodo group is derived from the elemental analysis C, 58.29 H, 03.55 N, 03.08% which is compatible with the molecular formula $C_{22}H_{16}NO_2I$.

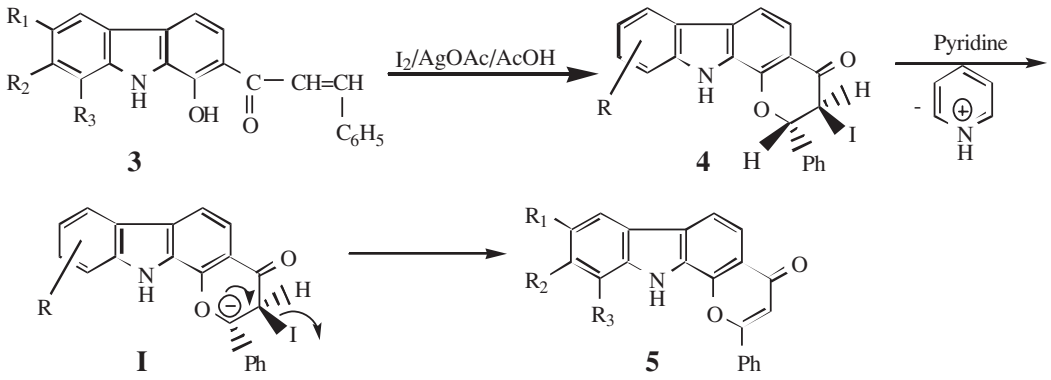
The unique action of iodine with silver acetate in the conversion of 2-cinnamoyl-1-hydroxycarbazole **3** to 2, 3-dihydro-3-iodo-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **4** is of considerable mechanistic interest. The formation of 2, 3-dihydro-3-iodo-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **4** from 2-cinnamoyl-1-hydroxycarbazole **3** can be assumed to proceed via the cyclic iodonium ion **I** formed by electrophilic attack of +ve iodine species on the double bond. The iodonium ion intermediate **I** is then regiospecifically cleaved, by intramolecular nucleophilic attack by the phenoxide ion which in turn was formed the abstraction of OH proton by the base to give the final iodo derivative 2,3-dihydro-3-iodo-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **4** (Scheme 3).

Based on the above mentioned physical and spectral data, the compound was attested to be 2,3-dihydro-3-iodo-10-methyl-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **4a**. A series of similar compounds **4b–4d** were realised from **3b–3d** (Scheme 4).

Further, the treatment of 2,3-dihydro-3-iodo-10-methyl-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **4a** with dry pyridine at refluxing temperature for 8 h under nitrogen atmosphere, after work up, gave a single product as indicated by tlc which was then purified using column chromatography**.** A sharp singlet at δ 2.22 in its ^{1}H NMR spectrum was due to the methyl group at C_{10} and a singlet in the downfield region at δ 7.00 corresponding to C_3-H olefinic proton. The downfield shift was due to deshielding effect of the phenyl ring at C_2 position. An aromatic envelope at δ 7.20–8.52 was consistent with ten aromatic protons and a broad singlet at δ 10.11 for the NH proton. Elemental analysis, C, 81.22 H, 04.54 N, 04.21% was in good agreement with the molecular formula $C_{22}H_{15}NO_2$. On this basis, the structure of the product was assigned to be 10-methyl-2-phenyl-4-oxopyrano[2,3-*a*]carbazole **5a**. A series of similar compounds **5b–d** were realised from **4b–d.** In a mechanistic view the formation of **5** might be due to the cis-elimination[20] initiated by the abstraction of proton at C-2 by pyridine at refluxing temperature followed by the elimination (so a low yield of ≈ 45%), of the iodide ion. It is pertinent to mention here that the resulting carbanion (**I**) is stabilised by the delocalisation of the negative charge over the C-2 phenyl ring which, looses I^- to yield the final product **5** (Scheme 4)**.**



Scheme 3



3-5 **a** R_3=CH_3, R_2=R_1=H
b R_2=CH_3, R_3=R_1=H
c R_1=CH_3, R_2=R_3=H
d R_1=R_2=R_3=H

Scheme 4

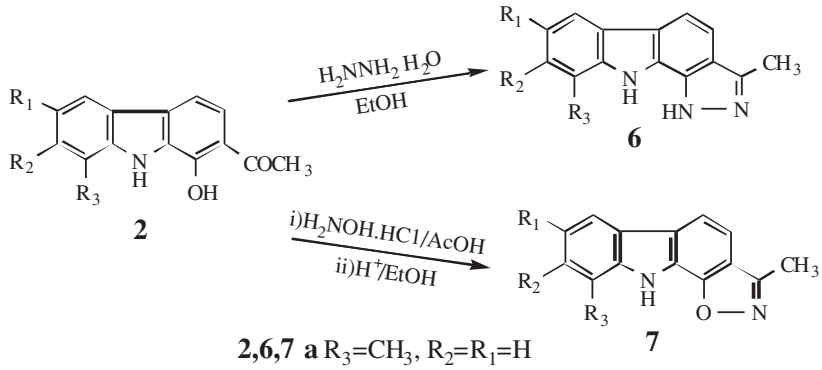
After achieving the synthesis of 2-acetyl-1-hydroxycarbazoles, an efficient precursor for the synthesis of many novel heterocyclo- fused carbazoles and and to prove its synthetic utility, 2-acetyl-8-methyl-1-hydroxycarbazole **2a** was reacted with hydrazine hydrate in ethanol, to afford a brown solid, m.p. 191°C. Its ^{1}H NMR spectrum showed two '3H' singlets at δ 2.33 and δ 2.52 corresponding to C_9-CH_3 and C_3-CH_3. The aromatic cluster accounting for 5 protons appeared as a multiplet at δ 6.99–8.03. The proton of carbazole NH was found to resonate as a broad singlet at δ 8.23 and that of pyrazolino NH at δ 5.23. The mass spectrum showed the molecular ion peak at *m/z* 235. The elemental analysis, C, 76.53 H, 05.62 N, 17.83% agreed well with the proposed molecular formula $C_{15}H_{13}N_3$ augmenting the structure of the compound to be 3,9-dimethyl-pyrazolino[2,3-*a*]carbazole **6a**. The generality of the above reaction was tested with **2b**, **2c** and **2d** (Scheme 5).

In another typical experiment, the reaction of 2-acetyl-8-methyl-1-hydroxycarbazole **2a** with hydroxylamine hydrochloride in acetic acid followed by acid catalysed cyclisation using H^+ / ethanol gave brown crystals which melted at 201°C. Its ^{1}H NMR spectrum exhibited two-three proton singlets at δ 2.49 and δ 2.87 corresponding to C_9-CH_3 and C_3-CH_3. Five aromatic proton envelop appeared as a multiplet at δ 7.25–7.71 and –NH proton resonates as a broad singlet at δ 7.99. The molecular ion peak in its mass spectrum appeared at *m/z* 236. The elemental analysis, C, 76.31 H, 05.18 N, 11.81% was compatible with the molecular formula $C_{15}H_{12}N_2O$. A conclusive proof was derived from negative ferric chloride test. On the basis of the above mentioned facts, the compound was attested to be 3,9-dimethyl-isoxazolo[2,3-*a*]carbazole **7a.** A series of similar compounds were obtained from **2b–d** (Scheme 5).

Experimental

Acetylation of 1-hydroxycarbazoles **1**: To a solution of the respective 1-hydroxycarbazole (**1**, 0.01 mol) in trifluoroacetic acid, acetyl chloride (0.01 mol) was added. Stirred well and maintained at –5 to 0°C for 10 h. Excess acid of was removed using rotary evaporator and the residue was poured into ice water, extracted with ethyl acetate and washed with water. The combined organic layers were dried over anhydrous sodium sulfate. Removed of the solvent and purification by passing through a column of silica gel afforded yellow crystals of the corresponding 2-acetyl-1-hydroxycarbazole

2-Acetyl-8-methyl-1-hydroxycarbazole **(2a)**: M.p.: 173–175°C, Yield: 0.979g (41%), IR (KBr) [ν_{max} cm^{-1}] 3270, 3025, 1635, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.59 (s, 3H, C_8–CH_3), 2.73 (s, 3H, C_2–$COCH_3$), 7.10–8.08 (m, 5H, aromatic H), 8.58 (b s, 1H, carbazole NH), 13.17 (b s, 1H, phenolic-OH, D_2O exchangeable) Analysis ($C_{15}H_{13}NO_2$) Calcd : C, 75.30%; H, 05.47%; N, 05.85% Found : C, 74.88%; H, 06.74%; N, 05.81%



2,6,7 **a** R_3=CH_3, R_2=R_1=H
b R_2=CH_3, R_3=R_1=H
c R_1=CH_3, R_2=R_3=H
d R_1=R_2=R_3=H

Scheme 5

2-Acetyl-7-methyl-1-hydroxycarbazole (**2b**): M.p.: 150–152°C, Yield: 0.860g (36%), IR (KBr) [ν_{max} cm^{-1}] 3406, 2923, 1665,, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.63 (s, 3H, C_7 -CH_3), 2.91 (s, 3H, C_2 -$COCH_3$), 7.01–8.01 (m, 5H, aromatic H), 8.54 (b s, 1H, carbazole NH), 13.10 (b s, 1H, phenolic-OH, D_2O exchangeable), Analysis ($C_{15}H_{13}NO_2$) Calcd : C, 75.30%; H, 05.47%; N, 05.85% Found : C, 74.91%; H, 06.71%; N, 05.81%

2-Acetyl-6-methyl-1-hydroxycarbazole (**2c**): M.p.: 169–173°C, Yield: 0.955g (40%), IR (KBr) [ν_{max} cm^{-1}] 3400, 2999, 1640, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.52 (s, 3H, C_6–CH_3), 2.57 (s, 3H, C_2–$COCH_3$), 7.21–8.04 (m, 5H, aromatic H), 8.59 (b s, 1H, carbazole NH), 13.11 (b s, 1H, phenolic-OH, D_2O exchangeable) Analysis ($C_{15}H_{13}NO_2$) Calcd : C, 75.30%; H, 05.47%; N, 05.85% Found : C, 74.99%; H, 06.65%; N, 05.88%

2-Acetyl-1-hydroxycarbazole (**2d**): Mp: 174–176°C, Yield: 0.949g (38%), IR (KBr) [ν_{max} cm^{-1}] 3375, 3000, 1655, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.73 (s, 3H, C_2–$COCH_3$), 7.20–8.08 (m, 6H, aromatic H), 8.58 (b s, 1H, carbazole NH), 13.10 (b s, 1H, phenolic-OH, D_2O exchangeable)Analysis ($C_{14}H_{11}NO_2$) Calcd : C, 74.65%; H, 04.92%; N, 06.22% Found : C, 74.59%; H, 04.87%; N, 06.15%

Synthesis of 2-cinnamoyl-1-hydroxycarbazoles **3**: An equimolar solution of the respective 2-acetyl-1-hydroxycarbazole (**2**, 0.001 mol) and benzaldehyde (0.0005 mol) was treated with 4% alc KOH solution (10 ml) and was refluxed for 1 h. Then the reaction mixture was cooled and poured into crushed ice. The precipitate obtained was filtered, recrystallised from methanol and identified as of 2-cinnamoyl-1-hydroxycarbazoles **3** based on physical and spectral data.

2-Cinnamoyl-8-methyl-1-hydroxycarbazole (**3a**): M.p.**:** 224–226°C, Yield: 0.297g (91%), IR (KBr) [ν_{max} cm^{-1}] 3424, 3380, 1630, 1597, 1496, 757, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.50 (s, 3H, C_8–CH_3), 7.32(d, 1H, H, J=16.8 Hz, H merged along with aromatic region) 7.25–7.86 (m, 12H, 10 aromatic-H and 1 olefinic-H), 8.52 (b s, 1H, carbazole NH), 13.73 (s, 1H, OH) Analysis ($C_{22}H_{17}NO_2$) Calcd : C, 80.72%; H, 05.23%; N, 04.28% Found: C, 80.64%; H, 05.23%; N, 04.48%

2-Cinnamoyl-7-methyl-1-hydroxycarbazole (**3b**): M.p.: 213–216°C, Yield: 0.294g (90%), IR (KBr) [ν_{max} cm^{-1}] 3422, 3381, 1629, 1595, 1492, 1352, 759, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.54 (s, 3H, C_7–CH_3), 7.29(d, 1H, H, J=16.9 Hz, H merged along with aromatic region), 7.51(s, 1H, C_8–H) 7.03–7.99 (m, 10H, 9 aromatic-H and 1 olefinic-H), 8.67 (b s, 1H, carbazole NH), 13.79 (s, 1H, OH) Analysis ($C_{22}H_{17}NO_2$) Calcd: C, 80.72%; H, 05.23%; N, 04.28% Found: C, 80.62%; H, 05.77%; N, 04.12%

2-Cinnamoyl-6-methyl-1-hydroxycarbazole (**3c**): M.p.: 219–221°C, Yield: 0.300g (92%), IR (KBr) [ν_{max} cm^{-1}] 3420, 3381, 1630, 1595, 1495, 1353, 1073, 758, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.53 (s, 3H, C_6–CH_3), 7.61(d, 1H, H, J=16.8 Hz, H merged along with aromatic region) 7.31(s, 1H, C_5–H), 7.39–7.98 (m, 10H, 9 aromatic-H and 1olefinic-H), 8.50 (b s, 1H, carbazole NH), 13.79 (s, 1H, OH) Analysis ($C_{22}H_{17}NO_2$) Calcd: C, 80.72%; H, 05.23%; N, 04.28% Found: C, 80.50%; H, 05.12%; N, 04.51%

2-Cinnamoyl-1-hydroxycarbazole (**3d**): M.p.: 230–233 °C, Yield: 0.287g (92%), IR (KBr) [ν_{max} cm^{-1}] 3412, 3384, 1626, 1592, 1493, 1356, 1072, 759, ^{1}H NMR ($CDCl_3$) [δ ppm]: 7.27(d, 1H, H , J=16.8 Hz, H merged along with aromatic region) 7.43–8.10 (m, 13H, 11 aromatic-H and 2 olefinic-H), 8.60 (b s, 1H, carbazole NH), 13.79 (s, 1H, OH) Analysis ($C_{21}H_{15}NO_2$) Calcd: C, 80.49%; H, 04.82%; N, 04.47% Found: C, 80.52%; H, 04.73%; N, 04.50%

Prevost reaction of 2-cinnamoyl-1-hydroxycarbazoles **3**: A mixture of the appropriate 2-cinnamoyl-1-hydroxycarbazole (**3**, 0.001 mol), silver acetate (0.002 mol) and iodine (0.25g, 0.001 mol) in acetic acid (25 ml), was stirred well at room temperature. The reaction was monitored by tlc. It showed a single spot. The precipitated silver iodide was filtered, washed with chloroform, washings were combined and extracted with chloroform. The extract was successively washed with dilute solutions of sodium thiosulphate followed by sodium bicarbonate and finally with water and dried over anhydrous sodium sulfate. The residue thus obtained was chromatographed over silica gel and eluted with petroleum ether – ethyl acetate mixture (90:10).

2,3-Dihydro-3-iodo-10-methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole (**4a**): M.p.: 131–133°C, Yield: 0.308g (68%), IR (KBr) [ν_{max} cm^{-1}] 3305, 2924, 1751, ^{1}H NMR ($CDCl_3$) [δ ppm] 2.45 (s, 3H, C_{10}–CH_3), 6.46 (d, 1H, C_2-H, J=15.96 Hz), 7.16–7.73 (m, 10H, aromatic H), 7.80 (d, 1H, C_3–H, J=15.96 Hz), 8.17 (b s, 1H, carbazole NH) Analysis ($C_{22}H_{16}NO_2I$) Calcd : C, 58.30%; H, 03.56%; N, 03.09%Found : C, 58.22%; H, 03.49%; N, 03.03%

2,3-Dihydro-3-iodo-9-methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole (**4b**): M.p : 129–132°C, Yield: 0.249g (55%), IR (KBr) [ν_{max} cm^{-1}] 3150, 2950, 1686,, ^{1}H NMR ($CDCl_3$) [δ ppm2.17 (s, 3H, C_9–CH_3), 6.46 (d, 1H, C_2–H, J=16 Hz), 7.25–7.56 (m, 10H, aromatic H), 7.79 (d, 1H, C–H, J=16 Hz) Analysis ($C_{22}H_{16}NO_2I$) Calcd: C, 58.30%; H, 03.56%; N, 03.09% Found : C, 58.25%; H, 03.51%; N, 03.05%

2,3-Dihydro-3-iodo-8-methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole (**4c**): M.p.: 130–134°C, Yield: 0.280g (62%), IR (KBr) [ν_{max} cm^{-1}] 3100, 1685, ^{1}H NMR ($CDCl_3$) [δ ppm 2.41 (s, 3H, C_8–CH_3), 6.46 (d, 1H, C_2–H, J=15.99 Hz), 7.25–7.57 (m,10H, aromatic H), 7.80 (d, 1H, C_3–H, J=15.99 Hz), 8.01 (b s, 1H, carbazole NH)) Analysis ($C_{22}H_{16}NO_2I$) Calcd : C, 58.30%; H, 03.56%; N, 03.09%Found : C, 58.09%; H, 03.35%; N, 03.08%

2,3-Dihydro-3-iodo-2-phenyl-4-oxopyrano[2,3-a]carbazole (**4d**): M.p.: 131–134°C, Yield: 0.268g (61%), IR (KBr) [ν_{max} cm^{-1}] 3150, 2920, 1683^{1}H NMR ($CDCl_3$) [δ ppm 6.46 (d, 1H, C–H, J=16 Hz), 7.21–7.57 (m, 11H, aromatic H), 7.80 (d, 1H, C_3–H J=16 Hz) Analysis ($C_{22}H_{16}NO_2I$) Calcd : C, 57.42%; H, 03.21%; N, 03.19%Found : C, 57.39%; H, 03.17%; N, 03.18%

Dehydroiodination of 2,3-dihydro-3-Iodo-2-phenyl-4-oxopyrano[2,3-a]carbazoles **4**: A solution of the iodo derivative (**4**, 226 mg, 0.001mol) in dry pyridine (10 ml) was refluxed under nitrogen atmosphere for 8 h. The excess of pyridine was removed under reduced pressure and then poured into water (50 ml) and extracted with chloroform (40 ml). The choroform extract was washed with dil.HCl, water and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by crystallisation of the residue obtained with petroleum ether: ethyl acetate mixture (99:1) furnished the respective 2-phenyl-4-oxopyrano[2,3-a]carbazole (**5**).

10-Methyl- 2-phenyl-4-oxopyrano[2,3-a]carbazole (**5a**): M.p.: >300 °C, Yield: 0.149g (46%), IR (KBr) [(max cm-1]: 3379, 1605, 1580, 1450, 777, 1H - NMR (DMSO) [δ ppm]: 2.22 (s, 3H, C_{10}–CH_3), 7.00 (s, 1H, C_3–H), 7.20–8.52 (m, 10H, aromatic –H), 10.11 (b s, 1H, carbazole NH) UV {ethanol} λ_{max}(log ε): 226(4.49), 248(4.89), 282(3.85), 294(4.05), 310(3.97), 326(3.94), 339(3.92), Analysis ($C_{22}H_{15}NO_2$) Calcd: C, 81.21%; H, 04.65%; N, 04.31% Found: C, 81.22%; H, 04.54%; N, 04.21%

9-Methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole (**5b**)**:** M.p.: 294–298 °C, Yield: 0.139g (43%), IR (KBr) [λ_{max} cm^{-1}]: 3380, 1601, 1450, 776, ^{1}H NMR (DMSO) [δ ppm]: 2.17 (s, 3H, C_9–CH_3), 7.13 (s, 1H, C_3–H), 7.17–8.51 (m, 10H, aromatic –H), 10.10 (b s, 1H, carbazole NH), UV {ethanol} λ_{max}(log ε): 238(4.64), 250(4.85), 282(3.87), 296(4.05), 307(3.98), 328(3.59), 339(3.54), Analysis ($C_{22}H_{15}NO_2$) Calcd: C, 81.21%; H, 04.65%; N, 04.31% Found: C, 81.72%; H, 04.52%; N, 04.23%

8-Methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole (**5c**): M.p.: >300°C, Yield: 0.156g (48%), IR (KBr) [λ_{max} cm^{-1}]: 3454, 1620 (shouldering starts at 1690), 1596, 1449, 772, ^{1}H NMR (DMSO) [δ ppm] : 2.49 (s, 3H, C_8-CH_3), 7.11 (s, 1H, C_3-H), 7.25–8.36 (m, 10H, aromatic –H), 10.05 (b s, 1H, carbazole NH), UV {ethanol} λ_{max}(log ε): 226(4.61), 248(4.68), 285(3.93), 295(4.16), 310(3.97), 333(3.71), 346(3.67), Analysis ($C_{22}H_{15}NO_2$) Calcd: C, 81.21%; H, 04.65%; N, 04.31% Found: C, 81.11%; H, 04.79%; N, 04.16%

2-Phenyl-4-oxopyrano[2,3-a]carbazole (**5d**): M.p.: 282–294°C, Yield: 0.143g (46%), IR (KBr) [ν_{max} cm^{-1}] : 3379, 1600, 1532, 1450, 779, ^{1}H NMR (DMSO) [δ ppm] : 7.16 (s, 1H, C_3-H), 7.21–8.70 (m, 11H, aromatic –H), 10.21 (b s, 1H, carbazole NH), UV {ethanol} λ_{max}(log ε): 225(4.44), 240(4.62), 251(4.46), 260(4.34), 295(4.21), 309(3.96), 326(3.94), 339(3.92), Analysis ($C_{21}H_{13}NO_2$) Calcd: C, 80.01%; H, 04.21%; N, 04.50% Found: C, 80.98%; H, 04.34%; N, 04.42%

Preparation of 3-methyl-pyrazolino[2,3-a]carbazoles (**6**): A mixture of the respective 2-acetyl-1-hydroxycarbazole (**2**, 0.001 mol) was dissolved in absolute ethanol (10 ml), 0.5 ml of hydrazine hydrate was added and refluxed for 2h. The excess solvent was distilled off, and 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 recrystallisation yielded the corresponding 3-methyl-pyrazolino[2,3-*a*]carbazole (**6**).

3,9-Dimethyl-pyrazolino[2,3-a]carbazole (**6a**) M.p.: 191–193°C, c IR (KBr) [ν_{max} cm^{-1}]: 3363, 1600, 1545, 1034, ^{1}H NMR ($CDCl_3$) [δ ppm] : 2.33 (s, 3H,C_3–CH_3), 2.52 (s, 3H, C_9–CH_3), 5.23 (s, 1H, pyrazolino NH), 6.99–8.03 (m, 5H, aromatic H), 8.23 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{13}N_3$) Calcd: C, 76.58%; H, 05.57%; N, 17.86% Found: C, 76.53%; H, 05.62%; N, 17.83%

3,8-Dimethyl-pyrazolino[2,3-a]carbazole (**6b**): M.p.: 189–193°C, Yield: 0.190g (81%), IR (KBr) [ν_{max} cm^{-1}]: 3383, 1605, 1500, 1388, 1326, 1242, 775, 740, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.32 (s, 3H,C_3–CH_3), 2.56 (s, 3H, C_8–CH_3), 5.23 (s, 1H, pyrazolino NH), 6.85–8.04 (m, 5H, aromatic H), 8.35 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{13}N_3$) Calcd: C, 76.58%; H, 05.57%; N, 17.86% Found: C, 76.32%; H, 05.53%; N, 17.91%

3,7-Dimethyl-pyrazolino[2,3-a]carbazole (**6c**): M.p.: 199–201°C, Yield: 0.193g (82%), IR (KBr) [ν_{max} cm^{-1}]: 3364, 1600, 1406, 827, 804, 600, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.32 (s, 3H,C_3–CH_3), 2.52 (s, 3H, C_7–CH_3), 5.23 (s, 1H, pyrazolino NH), 7.12–7.82 (m, 5H, aromatic H), 8.26 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{13}N_3$) Calcd: C, 76.58%; H, 05.57%; N, 17.86% Found: C, 76.44%; H, 05.35%; N, 17.83%

3-Methyl-pyrazolino[2,3-a]carbazole (**6d**): M.p.: 196–199°C, Yield: 0.195g (88%), IR (KBr) [ν_{max} cm^{-1}]: 3371,1610, 1508, 739, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.32 (s, 3H,C_3–CH_3), 5.23 (s, 1H, pyrazolino NH), 6.73–8.11 (m, 6H, aromatic H), 8.41 (b s, 1H, carbazole NH), Analysis ($C_{14}H_{11}N_3$) Calcd: C, 76.00%; H, 05.01%; N, 18.99% Found: C, 75.97%; H, 05.09%; N, 18.91%

Preparation of 3-methyl-isoxazolo[2,3-a]carbazoles **7**: The appropriate 2-acetyl-1-hydroxycarbazole (**2**, 0.001mol) was treated with hydroxylamine hydrochloride (1.5 g) in gla. acetic acid (5 ml) at 120°C for 10 h. The reaction mixture was then poured into crushed ice, the resulting semi solid was separated, and dissolved in ethanol (10 ml). A few drops of conc sulfuric acid was added to this mixture and refluxed for 24 h. The reaction was monitored by TLC. The excess of ethanol was removed and poured into crushed ice, extracted with ethyl acetate and washed with water, dried over anhydrous sodium sulfate. The residue thus obtained was purified by column chromatography over silica gel, petroleum ether-ethyl acetate as eluant (97:3).

3,9-Dimethyl-isoxazolo[2,3-a]carbazole (**7a**): M.p.: 200–203°C, Yield: 0.120g (51%), IR (KBr) [ν_{max} cm^{-1}]: 3290, 1640, 1608, 1369, 1319, 1246, 766, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.49 (s, 3H, C_9–CH_3), 2.87 (s, 3H, C_3–CH_3), 7.25–7.71 (m, 5H, aromatic H), 7.99 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{12}N_2O$) Calcd: C, 76.25%; H, 05.12%; N, 11.86% Found: C, 76.31%; H, 05.18%; N, 11.81%

3,8-Dimethyl-isoxazolo[2,3-a]carbazole (**7b**): M.p.: 201–205°C, Yield: 0.113g (48%), IR (KBr) [ν_{max} cm^{-1}]: 3165, 1642, 1605, 1401, 1327, 773, 669, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.51 (s, 3H, C_8–CH_3), 2.75 (s, 3H, C_3–CH_3), 6.95–7.74 (m, 5H, aromatic H), 8.05 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{12}N_2O$) Calcd: C, 76.25%; H, 05.12%; N, 11.86% Found: C, 76.11%; H, 05.01%; N, 11.83%

3,7-Dimethyl-isoxazolo[2,3-a]carbazole (**7c**): M.p.: 189–192°C, Yield: 0.111g (47%), IR (KBr) [ν_{max} cm^{-1}]: 3218, 1625, 1599, 1350, 1240, 745, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.49 (s, 3H, C_7–CH_3), 2.72 (s, 3H, C_3–CH_3), 7.29–8.02 (m, 5H, aromatic H), 8.10 (b s, 1H, carbazole NH), Analysis ($C_{15}H_{12}N_2O$) Calcd: C, 76.25%; H, 05.12%; N, 11.86% Found: C, 76.05%; H, 04.99%; N, 11.81%

3-Methyl-isoxazolo[2,3-a]carbazole (**7d**): M.p.: 189–193°C, Yield: 0.109g (49%), IR (KBr) [ν_{max} cm^{-1}]: 3185, 1635, 1590, 1325, 770, ^{1}H NMR ($CDCl_3$) [δ ppm]: 2.75 (s, 3H, C_3-CH_3), 7.21–7.79 (m, 6H, aromatic H), 8.22 (b s, 1H, carbazole NH), Analysis ($C_{14}H_{10}N_2O$) Calcd: C, 75.66%; H, 04.54%; N, 12.60% Found: C, 75.59%; H, 04.58%; N, 12.51%

Received 20 April 2004; accepted 3 September 2004
Paper 04/2478

References

1 D.P. Chakraborty *Prog. Chem. Org. Nat. Prod*., Eds. W. Herz, H. Grisebach and G.W. Kirby, Springer Verlag, Wien, 1977, Vol. 34, p. 299.
2 H.P. Husson, *The Alkaloids*, Ed. A. Brossi, Academic press, New York, 1985, Vol. 26, p.1.
3 P. Bhattacharya and D.P. Chakraborty, *Prog. Chem. Org. Nat. Prod*., Eds. W. Herz, H. Grisebach, G.W. Kirby and C. Tamm, Springer Verlag, Wien, 1987, Vol. 52, p. 159.
4 D.P. Chakraborty and S. Roy, *Prog. Chem. Org. Nat. Prod*, Eds, W. Herz, H. Grisebach, G.W. Kirby and C. Tamm, Springer Verlag, Wien, 1991, Vol. 57, p. 71.
5 P. Sauerberg, I. Pettersson, L. Jeppesen, P.S. Bury, J.P. Mogensen Wassermann, C.L. Brand, J. Sturis, H.F. Woldike, J. Fleckner, Anne-Sofie, T. Andersen, S.B. Mortensen, L. Anders Svensson, H.B. Rasmussen, S.V. Lehmann, Z. Polivka, K. Sindelar, V. Panajotova, L. Ynddal and E.M. Wulff, *J. Med. Chem*., 2002, **45**, 789.
6 D.N. Chowdhury, S.K. Basak and B.P. Das, *Curr. Sci.,* 1978, **47**,490
7 G.W. Gribble, *The Alkaloids*, Ed. A. Brossi, Academic Press, New York, 1990, Vol 39, p.239.
8 M. Suffness and G.A. Cordell, *The Alkaloids*, Ed. A. Brossi, Academic Press, New York, 1985, Vol. 25, p.1.
9 D. Joseph, L. Martarello, G. Kirsch, *J. Chem. Res*., (S) 1995, 350; *J. Chem. Res*., (M) 1995 2001.
10 F.M.C. Peixoto, M.J.R.P. Queiroz and G. Kirsch, *J. Chem. Res*. (M), 1998, 801.
11 T. Martin and C.J. Moody, *Tetrahedron Lett*., 1985, **26**, 5841.
12 D.P. Chakraborty, B.K. Barman and P.K. Bose, *Tetrahedron*, 1965, **21**, 681.
13 A.V. Rama Rao, K.S. Bhide and R.B. Mujumdar, *Chem. Ind*., (Lond.), 1980, 697.
14 D.P. Chakraborty and B.K. Chowdhury, *J. Org. Chem*., 1968, **33**, 1265.
15 B.K. Chowdhury and D.P. Chakraborty, *Chem. Ind*., (Lond.), 1969, 549.
16 B.K. Chowdhury and D.P. Chakraborty, *Phytochemistry*, 1971, **10**, 1967.
17 D.P. Chakraborty, P. Bhattacharyya, S. Roy, S.P. Bhattacharyya and A.K. Biswas, *Phytochemistry*, 1978, **17**, 834.
18 D. Sowmitran and K.J. Rajendra Prasad, *Hetrocycles*, 1986, **24**, 2195.
19 C. Kavitha and K.J. Rajendra Prasad, *J. Chem. Res* (*S*), 2003, 600; *J. Chem. Res*. (*M*), 2003, 1025.
20 Baciocchi, in Patai; Rappoport, *The Chemistry of Functional Groups*, *Supplement D*, pt.2; Wiley: New York, 1173, 1983.
21 K.J. Rajendra Prasad and M. Subramanian, *Ind. J. Chem*., **33B**, 696 (1994).