Synthesis of biogenetically possible 2-phenyl-4-oxopyrano[2,3-a]carbazoles

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Synthesis of 2-cinnamoyl-1-hydroxycarbazoles 2 by the condensation of 1-hydroxycarbazoles with aluminium chloride and phosphorosy chloride in good yield followed by acid catalysed cyclisation and dehydrogenation with DDQ to obtain the biogenetically possible 2-phenyl-4-oxopyrano[2,3-a]carbazoles 4 is described.

The indole nucleus is associated with a wide spectrum of pharmacological properties such as antibacterial1,2, anticancer1,2, antibiotic3, in the functioning of central nervous system4, hallucinogenic5, antifungal6, antiviral7, etc. Currently, we are interested in the synthesis of indoloflavones, since flavones are compounds eliciting considerable interest because of inhibition of aflatoxin cytotoxicity8. In particular they too show anticancer activity and are being investigated as potential chemopreventive agents9. These compounds have numerous physiological functions, which are of interest from an ecological point of view and as regards their potential pharmacological applications10,11.

However, indole moiety fused with flavone nucleus (known as 2-phenyl-4-oxopyrano[2,3-a]carbazole) has not been reported so far. So we focussed our attention on this problem, since the combination of these two may play a vital role in medicinal chemistry. Apart from this, carbazoles having γ-pyrone as a part of their structures with [2,3-a] fusion, are biogenetically possible from the naturally available mupamine12.

In achieving our target, we opted 1-hydroxy-carbazoles I as precursors. 8-Methyl-1-hydroxy-carbazole 1a was reacted with cinnamic acid using anhydrous aluminium chloride and phosphorusy chloride. After work-up, it yielded a single product. Its IR spectrum showed >C=O, -NH and -OH stretching frequencies at 1630, 3380 and 3424 cm\(^{-1}\), respectively. In its \(^1\)H NMR spectrum, the methyl protons appeared as a singlet at δ 2.50. The aromatic cluster accountable for ten protons and two olefinic protons appeared as a multiplet at δ 7.25-7.86. The NH and OH signals appeared as two broad singlets at δ 8.52 and 13.73, respectively. The molecular ion peak at m/z 327 with 62% abundance was consistent with the molecular formula C\(_{22}\)H\(_{17}\)NO\(_2\). This was further supported by the elemental analysis (C, 80.64; H, 05.23; N, 04.28%). Based on the above facts, the structure to the product was assigned as 8-methyl-2-cinnamoyl-1-hydroxycarbazole 2a. A series of similar reaction was carried out with 1b-d and similar results, as discussed above, were obtained (Scheme I). The physical and spectral data of the compounds 2b-d are given in Table I.

The 2-H chromanone ring appears as a doublet of doublets centered at δ 5.92 due to free rotation between C-2-H and C-3-H (C-3-Hax and C-3-Heq). The protons at C-3 give rise to 4 signals each due to spin-spin interaction with each other and with C-2-H. The double doublets centered at δ 3.40 were assignable to C-3-Hax and a doublet of doublets centered at δ 2.95 was assigned to C-3-Heq forming an ABX system. The coupling constant of proton C-2-Hax with J\(_{ax}=12.36\) Hz (axial-axial) and J\(_{ax}=2.42\) Hz (axial-equitorial) indicated to be in axial-position in the quasi-chair conformation of the chromanone ring with phenyl equitorial.

The formation of the cyclised product, namely 2,3-dihydro-10-methyl-2-phenyl-4-oxopyrano[2,3-a]carbazole 3a (flavone derivative) was confirmed by the following tests: (±ve) Shinoda test (Mg-
HCl), a deep yellow colour with ammonia vapour and negative ferric chloride test\(^\text{13}\). The absorption at 1668 cm\(^{-1}\) in its IR spectrum was assignable to carbonyl group. The main features of its structure were confirmed by its \(^1\)H NMR spectrum in DMSO-\(d_6\). The mass spectrum showed the molecular ion peak at m/z 327, and the base peak at m/z 223 due to the loss of styrene moiety from the molecular ion. Elemental analysis (C, 80.69; H, 05.20; N, 04.39%) was in good agreement with the molecular formula C\(_{22}\)H\(_{17}\)NO\(_2\). Based on the above mentioned facts, the structure of the compound was attested to be 2,3-dihydro-10-methyl-2-phenyl-4-oxopyrano[2,3-\(\alpha\)]carbazole 3a \text{(Scheme I, Table I)}. A series of similar compounds 3b-d were realised from 2b-d.

Further, 3a was dehydrogenated using DDQ in benzene to yield a single product. Its IR spectrum showed strong absorptions at 3379, 1605 (shouldering starts at 1690) and 1254 cm\(^{-1}\) corresponding to -NH, C=O and C-O-C stretching vibrations respectively. A sharp singlet at \(\delta 2.22\) in its \(^1\)H NMR spectrum was due to the methyl group at C10 and a singlet in the downfield region at \(\delta 7.00\) corresponding to C3-H olefinic proton. The downfield shift was due to deshielding effect of the phenyl ring at C2 position. An aromatic envelope at \(\delta 7.20-8.52\) was consistent
with ten aromatic protons and a broad singlet at δ 10.11 for the NH proton. Elemental analysis (C, 81.22; H, 0.454; N, 0.21%) 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-oxopyranophenolic acid 4a. A series of similar compounds 4b-d were realised from 3b-d. The physical and spectral data of compounds 4a-d are given in Scheme I and Table I.

### Experimental Section

Melting points were determined using Mettler FP 5 apparatus and are uncorrected. $^1$H NMR spectra in CDCl$_3$ were recorded on a Varian AMX 400 FT-

### Table I — Physical and spectral data of compounds 2, 3, and 4.

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Caled % (Found)</th>
<th>MS (70 eV)</th>
<th>$^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>226</td>
<td>50</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.64)</td>
<td>327</td>
<td>2.50 (s, 3H, C$_9$-CH$_3$), 7.25-7.86(m, 12H, 10 Ar-H and 2×CH), 8.52(b s, 1H, NH), 13.73(s, 1H, OH).</td>
</tr>
<tr>
<td>2b</td>
<td>215</td>
<td>51</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.62)</td>
<td>327</td>
<td>2.54(s, 3H, C$_9$-CH$_3$), 7.03-7.99(m, 12H, 10 Ar-H and 2×CH), 8.67(b s, 1H, NH), 13.79(s, 1H, OH).</td>
</tr>
<tr>
<td>2c</td>
<td>220</td>
<td>50</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.50)</td>
<td>327</td>
<td>2.53(s, 3H, C$_9$-CH$_3$), 7.31-7.98(m, 12H, 10 Ar-H and 2×CH), 8.50(b s, 1H, NH), 13.79(s, 1H, OH).</td>
</tr>
<tr>
<td>2d</td>
<td>232</td>
<td>55</td>
<td>$C_{21}H_{15}NO_2$</td>
<td>80.49 (80.52)</td>
<td>313</td>
<td>7.27-8.10(m, 13H, 11 Ar-H and 2×CH), 8.60(b s, 1H, NH), 13.79(s, 1H, OH).</td>
</tr>
<tr>
<td>3a</td>
<td>191</td>
<td>92</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.69)</td>
<td>327</td>
<td>2.60 (s, 3H, C$_9$-CH$_3$), 2.95 (d d, 1H, C$<em>9$-H$</em>{eq}$, $J$=2.84 and 16.70 Hz), 3.40 (d d, 1H, C$<em>7$-H$</em>{eq}$, $J$=12.64 and 16.70 Hz), 5.92 (d d, 1H, C$_5$-H, $J$=2.42 and 12.36 Hz), 7.11-7.15 (m, 1H, C$_7$-H), 7.26(d, 1H, C$_6$-H, $J$=6.98 Hz) 7.41-7.74 (m, 5H, C$_2$-H, C$_3$-H, C$_4$-H, C$_6$-H, C$_8$-H), 7.59 (d, 1H, C$_7$-H, $J$=8.26 Hz), 7.80 (d, 1H, C$_3$-H, $J$=8.26 Hz), 7.99 (d, 1H, C$_9$-H, $J$=7.78 Hz), 11.53 (bs, 1H, carbazolo NH)</td>
</tr>
<tr>
<td>3b</td>
<td>182</td>
<td>90</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.73)</td>
<td>327</td>
<td>2.52 (s, 3H, C$_9$-CH$_3$), 2.94 (d d, 1H, C$<em>9$-H$</em>{eq}$, $J$=2.80 and 16.80 Hz), 3.22 (d d, 1H, C$<em>7$-H$</em>{eq}$, $J$=13.08 and 16.70 Hz), 5.65 (d d, 1H, C$_5$-H, $J$=2.56 and 13.36 Hz), 7.09 (d, 1H, C$_5$-H, $J$=8.04 Hz), 7.23 (s, 1H, C$<em>7$-H$</em>{eq}$), 7.41-7.56 (m, 5H, phenyl protons), 7.67 (d d, 1H, C$_6$-H, $J$=8.32 Hz), 7.77 (d, 1H, C$_3$-H, $J$=8.28 Hz), 7.94 (d, 1H, C$_9$-H, $J$=8.04 Hz), 8.37 (b s, 1H, carbazolo NH)</td>
</tr>
<tr>
<td>3c</td>
<td>189</td>
<td>91</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.72 (80.66)</td>
<td>327</td>
<td>2.47 (s, 3H, C$_9$-CH$_3$), 2.93 (d d, 1H, C$<em>9$-H$</em>{eq}$, $J$=2.86 and 16.70 Hz), 3.40 (d d, 1H, C$<em>7$-H$</em>{eq}$, $J$=13.08 and 16.72 Hz), 5.90 (d d, 1H, C$_5$-H, $J$=2.52 and 12.84 Hz), 7.29 (d, 1H, C$_5$-H, $J$=8.24 Hz), 7.42-7.50 (m, 5H, phenyl protons), 7.56 (d d, 1H, C$_6$-H, $J$=8.32 Hz), 7.72 (d, 1H, C$_3$-H, $J$=7.16 Hz), 7.77 (d d, 1H, C$_9$-H, $J$=8.28 Hz), 7.94 (d, 1H, C$<em>7$-H$</em>{eq}$), 11.64 (b s, 1H, carbazolo NH)</td>
</tr>
<tr>
<td>3d</td>
<td>178</td>
<td>91</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>80.49 (80.52)</td>
<td>313</td>
<td>2.96 (d d, 1H, C$<em>9$-H$</em>{eq}$, $J$=2.84 and 16.80 Hz), 3.25 (d d, 1H, C$<em>7$-H$</em>{eq}$, $J$=13.48 and 16.80 Hz), 5.68 (d d, 1H, C$_5$-H, $J$=2.64 and 13.40 Hz), 7.25-7.29 (m, 2H, C$_2$-H and C$_4$-H), 7.41-7.50 (m, 5H, phenyl protons), 7.57 (d d, 1H, C$<em>9$-H$</em>{eq}$, $J$=7.57 Hz), 7.73 (d, 1H, C$_3$-H, $J$=8.32 Hz), 7.80 (d, 1H, C$_9$-H, $J$=8.32 Hz), 8.08 (d, 1H, C$_9$-H, $J$=7.88 Hz), 8.47 (b s, 1H, carbazolo NH)</td>
</tr>
<tr>
<td>4a</td>
<td>&gt;300</td>
<td>82</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>81.21 (81.22)</td>
<td>325</td>
<td>2.22 (s, 3H, C$_9$-CH$_3$), 7.00(s, 1H, C$_7$-H), 7.20-8.52(m, 10H, Ar-H), 10.11(b s, 1H, NH).</td>
</tr>
<tr>
<td>4b</td>
<td>298</td>
<td>81</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>81.21 (81.72)</td>
<td>325</td>
<td>2.17(s, 3H, C$_9$-CH$_3$), 7.13(s, 1H, C$_7$-H), 7.17-8.51(m, 10H, Ar-H), 10.10(b s, 1H, NH).</td>
</tr>
<tr>
<td>4c</td>
<td>&gt;300</td>
<td>83</td>
<td>$C_{22}H_{17}NO_2$</td>
<td>81.21 (81.11)</td>
<td>325</td>
<td>2.49(s, 3H, C$_9$-CH$_3$), 7.11(s, 1H, C$_7$-H), 7.25-8.36(m, 10H, Ar-H), 10.05(b s, 1H, NH).</td>
</tr>
<tr>
<td>4d</td>
<td>282</td>
<td>81</td>
<td>$C_{21}H_{15}NO_2$</td>
<td>80.01 (80.28)</td>
<td>311</td>
<td>7.16(s, 1H, C$_7$-H), 7.21-8.70(m, 11H, Ar-H), 10.21(b s, 1H, NH).</td>
</tr>
</tbody>
</table>
NMR spectrometer using TMS as an internal reference (chemical shift in δ, ppm); and mass spectra on Jeol-JMS-D 300 Mass spectrometer. Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin-Elmer Model 240 CHN analyzers.

Preparation of 2-cinnamoyl-1-hydroxycarbazoles 2. A mixture of the respective 1-hydroxycarbazole (1, 0.001 mol), cinnamic acid (0.001 mole), anhydrous aluminum chloride (3 g) and phosphorous-oxy chloride (4 mL) was kept at room temperature for 24 hr, with occasional shaking. The reaction mixture was then poured into crushed ice and the precipitate obtained was filtered, washed with water, dried over anhydrous sodium sulphate and concentrated. The resulting residue was purified by passing through a silica gel column and eluting with petroleum ether-ethyl acetate (98:2) to afford dark brown crystals of the respective 2-cinnamoyl-1-hydroxycarbazole 2.

Preparation of 2,3-dihydro-2-phenyl-4-oxopyrano[2,3-a]carbazoles 3. To an ethanolic solution of the respective 2-cinnamoyl-1-hydroxycarbazole (2, 0.001 mole), added a few drops of conc. sulphuric acid and refluxed for 5 hr. Evaporated off excess ethanol, poured into crushed ice and extracted with ethyl acetate. The combined organic layers were then dried over anhydrous sodium sulphate and purified by passing through a column of silica gel and eluting with petroleum ether-ethyl acetate (99:1).

Preparation of 2-phenyl-4-oxopyrano[2,3-a]carbazoles 4. A mixture of the respective 2,3-dihydro-4-oxo-pyrano[2,3-a]carbazole (3, 0.001 mole) and DDQ (0.001 mole) in benzene (5 mL) was refluxed for 1 hr, cooled and filtered, and washed with excess benzene. On removal of the solvent, it gave a residue, which was purified by passing through silica gel column and eluting with petroleum ether-ethyl acetate, to afford the corresponding product (99:1).

References