Reactions of heterocyclic quinone methides: A facile entry to synthesize the alkaloid, flindersine and its analogues

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A concise synthesis of pyranoquinoline based alkaloids, flindersine, 8-methoxy flindersine and N-methyl flindersine, from the respective 4-hydroxy-3-methyl-2(1H)-quinolines, using 2,3-dichloro-5,6-dicyano-p-benzoquinone and dimethyl acrylic acid generated through quinone methide intermediates is reported.

In the present age of nutraceuticals too, the pyranoquinoline alkaloids have been given more importance because of their interesting and varying pharmacological properties that belong to the plant family Rutaceae. Flindersine la, a member of a family of pyrano quinoline alkaloids, was first isolated from the wood of Flindersia australis in 1914. Several reports have appeared in the literature for their synthesis.

Herein we report a convenient one-pot synthesis of flindersine la, 8-methoxyflindersine lb and N-methylflindersine lc. The synthesis of la was realized through a two-step procedure based on the methylene-substituted quinones. The designed synthetic route is outlined in Scheme I.

As a first step, 4-hydroxy-3-methyl-2(1H) quinoline 2a was prepared from aniline and diethyl(methyl) malonate under the nitrogen atmosphere for 3 hr. Generation of the required 3-methylene-2,4(1H, 3H)-quinoline dione 3 was made out by refluxing a solution of quinoline 2a in benzene in the presence of DDQ. To the refluxing solution, dimethyl acrylic acid was added and the mixture refluxed for 45 hr, cooled, filtered, dried and extracted with ethyl acetate. The residue was then triturated with petroleum ether-ethyl acetate and the solid thus obtained was recrystallized from ethanol. Here the methylene quinone can be regarded as an electron deficient enone and in the presence of electron rich DMAA, it preferentially underwent an inverse electron demand cycloaddition reaction.

\[
\begin{align*}
\text{a: } R &= R = H \\
\text{b: } R_i &= \text{OCH}_3, R = H \\
\text{c: } R_i &= H, R = \text{CH}_3
\end{align*}
\]

(a) DDQ, Benzene; (b) DMAA, reflux, 45 hr

Scheme I

leading to the formation of la. Similarly starting from 2b and 2c, lb and lc were synthesized.

In accordance with our expectation, this approach proved to be successful and resulted in the desired flindersine and its analogues in good yield. In its IR spectral data, angular annulation has been indicated by the presence of a 2-quinolinone-carbonyl signal at 1655 cm\(^{-1}\). It also indicated a peak at 3390 cm\(^{-1}\) for –OH group. The physical and spectral data of la-c are presented in Table I which supports the structural assignment.

Experimental Section

General information. TLC was used to assess the reactions and purity of products. Melting points were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu-8201 FT instrument in KBr disc and only noteworthy absorption levels (reciprocal centimeter) are listed. \(^1\)H NMR spectra were recorded in AMX-400 MHz spectrometer in CDCl\(_3\) solution (chemical shifts are expressed in ppm (\(\delta\)) relative TMS). Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin-Elmer models 240 CHN analyzer. Mass spectra were recorded on a Jeol–300 mass spectrometer.
Table I—Physical and spectral data of flindersine and its analogues (la-c)

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
<th>IR (Kar) (μm)</th>
<th>MS (70 eV)</th>
<th>δH NMR (CDCl₃) ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flindersine</td>
<td>195</td>
<td>68</td>
<td>C₁₄H₁₄NO₂</td>
<td>3390, -OH</td>
<td>1655</td>
<td>1.45(s, 6H, 2 × CH₃)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1620, C=N</td>
<td>257</td>
<td>6.7-7.5 (m, 6H, Ar-H)</td>
</tr>
<tr>
<td>8-Methoxy flindersine</td>
<td>178</td>
<td>70</td>
<td>C₁₂H₁₂NO₃</td>
<td>2995, -OH</td>
<td>1660</td>
<td>1.40(s, 6H, 2 × CH₃)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1600, C=N</td>
<td>241</td>
<td>3.9(s, 3H, OCH₃)</td>
</tr>
<tr>
<td>N-Methyl flindersine</td>
<td>85</td>
<td>80</td>
<td>C₁₂H₁₄NO₂</td>
<td>1670, C=O</td>
<td></td>
<td>6.8-7.7 (m, 6H, Ar-H)</td>
</tr>
</tbody>
</table>

Synthesis of flindersine la. Equal moles of 4-hydroxy-3-methyl-2(1H)-quinoline 1a (0.001 mole), 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.001 mole) and dimethyl acrylic acid (0.001 mole) in 50 mL of benzene were refluxed for 45 hr. After cooling, the reaction mixture was filtered, the solvent evaporated and the residual mass extracted with ethyl acetate. The combined organic extracts were then subjected to silica gel column chromatography using pet. ethyl ether-ethyl acetate (85:15) when the desired product, flindersine 1a was obtained in 68% yield. The similar procedure was adopted for the synthesis of 8-methoxyflindersine 1b (70%) and of N-methylflindersine 1c (80%).

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References
4 Mathes H & Schreiber E, Ber dext pharm ges, 24, 1914, 385.
7 Huffman J W & Hsu T M, Tetrahedron, 1972, 141.