CHAPTER 2
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Synthesis of 2, 2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinolines

Introduction

Quinoline derivatives represent the major class of heterocycles and a number of preparations have been known since the late 1800s. These are important compounds for synthetic and biological chemists.\(^1\) The quinoline ring system occurs in various natural products especially in alkaloids, and its skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties, being used as anti-malarial, anti-inflammatory, antiasthamatic, antibacterial, antihypertensive and tyrosine kinase inhibiting agents.\(^2\) In addition, quinolines are valuable synthons used for the preparation of nano and mesostructures with enhanced electronic and photonic properties.\(^3\)

Alkaloids containing the pyranoquinoline and furoquinoline core constitute a significant group of the quinoline alkaloids. In the case of furo[2,3-b]quinoline alkaloids, the furan ring is fused to \(b\) bond of quinoline (I) and in case of pyrano[2,3-b]quinoline alkaloids, pyran ring is fused to the \(b\) bond of quinoline (II) (Fig.1).

![Fig. 1](image)

The plant family *rutaceae* especially *Balfourodendron riedelianum* a small Brazilian tree is known\(^4,5\) to be a prolific source of pyranoquinoline and furoquinoline alkaloids. These class of natural products have been reported\(^6,7\) to be associate with interesting pharmacological as well as biological activities such as antiallergic, anti-inflammatory, antipyretic, analgesic, antiplatelet, psychotropic and estrogenic activity.\(^8\)
Some examples of natural products containing the pyranoquinoline and furoquinoline core structures are shown in Fig. 2:

![Chemical structures of natural products](image)

**Geibalansine 1**

**Flindersin 2**

**Ribalinine 3**

**Helietidine 4**

**Dutadrupine 5**

**Simulenoline 6**

**Huajiosimuline 7**

**Zanthodioline 8**

**Teclealbine 9**

**Flindersiamine 10**

**Fig. 2**
The development of efficient synthesis of pyranoquinolines and furoquinolines has been the focus of much research for several decades and continues to be an active and rewarding research area.

In this section, we have directed our efforts towards developing a general synthesis of 2,2-dimethyl pyranoquinoline skeleton 11 (Fig. 3).
Literature Review

Owing to the potent biological activities of these pyranoquinoline and furoquinoline alkaloids, numerous methods have been developed for their synthesis. The synthetic method for the preparation of pyranoquinoline system is based on either oxidative cyclization of 4-hydroxy-3-(3'-methylbut-1'-enyl)-2-quinolinones 12 with DDQ\textsuperscript{10} or the Prevost reaction of 3-prenyl-2-quinolones 13\textsuperscript{11} (Fig. 4). Though these methods have proven to be fairly satisfactory, the overall yield of the alkaloids was only 15-35\% because the routes to obtain the precursor prenylquinolines gave low yields (21-35\%)\textsuperscript{12,13} and often were attended by undesired side reactions (such as the formation of unwanted 3-(3'-methylbut-1'-enyl)-2-quinolinones as the major product).\textsuperscript{14}

Corral \textit{et al.}\textsuperscript{15} have reacted \textit{N}-methyl aniline with diethyl-(3-methylbut-2-enyl)-malonate to obtain the prenylquinoline which they have further treated with peroxyauric acid to give furoquinolone. They have also prepared pyranoquinolone from furoquinolone using acetic anhydride and base (Scheme I).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig4.png}
\caption{Fig. 4}
\end{figure}
Grundon et al.\textsuperscript{16} have treated 2,4-dimethoxyaniline with diethyl (3-methylbut-2-enyl) malonate in boiling diphenyl ether to get 4-hydroxy-2-quinolone. Subsequently they treated this 4-hydroxy-2-quinolone with ethereal solution of diazomethane in methanol followed by oxidation with \textit{m}-chloroperoxybenzoic acid in chloroform at 0 °C to give a mixture of pyranoquinoline and furoquinoline products (\textbf{Scheme II}).
Rajendra Prasad et al.\textsuperscript{17} have synthesized pyranoquinolines by treating carboxy derivative of the 2-quinolinone with polyphosphoric acid at 140 °C (Scheme III).
Kametani et al.\textsuperscript{18} reported indium chloride catalysed cycloaddition of aldimines with various enol ethers to afford the corresponding pyranoquinoline derivatives (Scheme IV).

\begin{center}
\begin{align*}
\text{NH}_2 \quad \text{InCl}_3 \quad \text{NH}_2 \\
| \quad \quad \quad | \\
R \quad \quad \quad R \\
\text{ArCHO} + (\text{enol ether})_n \quad \rightarrow \quad \text{pyranoquinoline} \\
\text{Scheme IV}
\end{align*}
\end{center}

Yadav et al.\textsuperscript{19} have described that ionic liquids are found to catalyse efficiently the three component-coupling reactions of aldehydes, amines and cyclic enol ethers such as 3,4-dihydro-2\textit{H}-pyran and 2,3-dihydrofuran under mild and convenient conditions to afford corresponding pyranoquinolines (Scheme V).

\begin{center}
\begin{align*}
\text{NH}_2 \quad [\text{bmim}]\text{BF}_4 \\
| \quad \quad | \\
R \quad \quad R \\
\text{ArCHO} \quad \text{enol ether} \quad \rightarrow \quad \text{pyranoquinoline} \\
\text{Scheme V}
\end{align*}
\end{center}

Maiti & Kundu\textsuperscript{20} have reported the synthesis of substituted pyrano and furoquinolines via an imino Diels-Alder reaction using antimony trichloride (SbCl\textsubscript{3}) as a catalyst (Scheme VI).

\begin{center}
\begin{align*}
\text{NH}_2 \quad \text{SbCl}_3 (10 \text{~mol\%}) \\
| \quad \quad | \\
R \quad \quad R \\
\text{ArCHO} + \text{enol ether} \quad \rightarrow \quad \text{pyranoquinoline} \\
\text{Scheme VI}
\end{align*}
\end{center}
Kalita et al.\textsuperscript{21} have prepared tetrahydroisoxazolo-, dihydroisoxazolo-, and dihydropyrazolo-pyran[2-3-b]quinolines from acetanilides via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones, nitrile oxides and nitrile imines as 1,3-dipoles (Scheme VII).

Wei-Min and co-workers\textsuperscript{22} have reported the aza-Diels Alder reaction of 2-aminophenol in combination with substituted benzaldehyde and electron rich cyclic alkenes under controlled microwave heating in presence of catalytic amount of CF$_3$COOH to afford corresponding pyranoquinolines (Scheme VIII).

Akiyama et al.\textsuperscript{23} have reported enantioselective aza Diels-Alder reactions by using chiral phosphoric acid derived from chiral BINOL and demonstrated its catalytic activity as chiral bronsted acid catalyst (Scheme IX).
Lin et al.\textsuperscript{24} have developed highly efficient method for the synthesis of pyranoquinoline and furoquinoline derivatives via a molecular iodine catalyzed domino reactions of anilines with cyclic enol ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2H-pyran (Scheme X).

Various other reagents are also reported for this sequence. Yadav et al.\textsuperscript{25} have reported montmorillonite-clay as a catalyst. Lakshmikantham et al.\textsuperscript{26} reported polyaniline supported indium trichloride as a reusable catalyst, Zang et al.,\textsuperscript{27a} Chen et al.,\textsuperscript{27b} extensively studied cycloaddition reaction of anilines with various enol ethers to afford corresponding pyranoquinolines.

Yadav et al.\textsuperscript{28} have described a synthesis of pyrano and furoquinoline derivatives via aza-Diels Alder reaction using 1 mol % of phosphomolybdic acid (PMA, F.W.: \( H_3PMO_{12}O_{40} \)) as a catalyst (Scheme XI).
Marco-Contelles et al.\textsuperscript{29}, have described synthesis of pyranoquinolines from 3-pyridine carboxaldehydes. They treated 3-pyridine carboxaldehydes with malononitrile and ethyl acetoacetate in presence of piperidine to get 4H-pyran units, which were further reacted with cyclohexanone in presence of aluminium trichloride to afford the corresponding pyranoquinolines (Scheme XII).

Zhang et al.\textsuperscript{30} have prepared pyranoquinolines from 1-acetyl-N-aryl cyclopentanecarboxamides via tandem cyclization/ring-opening/recyclization reaction using sulphuric acid at 50 °C (Scheme XIII).
Majumdar et al.\textsuperscript{31} have carried out alkylation of hydroxylquinolines with substituted benzyl bromide followed by palladium-catalyzed cyclization to give benzannulated pyranoquinolines (\textbf{Scheme XIV}).
Present Work

Retrosynthesis

In view of the importance of pyranoquinoline ring system for various biological activities and very few synthetic methods being available we found it interesting to use our experience in phosphorane chemistry to develop a convenient method for the synthesis of pyranoquinolines. Our simple four step disconnection approach towards pyranoquinoline is shown in Scheme XV.

The pyranoquinoline (A) could be obtained from the corresponding amino lactone (B). The amino lactone (B) has a Z geometry which is difficult to obtain but if the corresponding E compound (C) is obtained during cyclization, it can be converted to (B). The compound (C) can be obtained from corresponding nitro compound (D) which in turn can be obtained from uncyclised (E). Compound (E) could easily be prepared from \(\alpha\)-nitrobenzaldehyde (F) by condensing it with Wittig reagent (G).

![Scheme XV](image-url)
Synthetic plan

The synthetic plan envisaged by us is depicted in Scheme XVI. We envisaged that o-nitrobenzaldehyde (14) on condensation with Wittig reagent 15 will give the key intermediate ester 16. It was thought that the o-nitrocinnamate ester 16 on lactonisation followed by reduction could form 19 via intermediate 17 which on acid cyclisation should provide 20. The other slightly shorter route was ester 16 to be reduced first to give 18 which then on acid cyclisation would provide directly 20.

Scheme XVI

The first step in our projected synthesis was Wittig reaction for which we required the corresponding prenyl phosphorane 15. The preparation of this is already described in the first chapter.

To start with we took o-nitrobenzaldehyde (14a) and it was refluxed with prenyl phosphorane 15 in chloroform for 3.0 hrs (Scheme XVII).
TLC of the reaction mixture showed the disappearance of the starting aldehyde and appearance of a new spot along with triphenylphosphine oxide. The crude product was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a pleasant smelling viscous liquid.

As expected the IR spectrum of the compound exhibited strong band at 1713 cm\(^{-1}\) due to the carbonyl bond of \(\alpha,\beta\)-unsaturated ester group.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) showed peaks at \(\delta\) 1.35 (t, 3H, \(J = 7.2\) Hz) \(\delta\) 4.30 (q, 2H, \(J = 7.2\) Hz) which were attributed to the ester group (-OCH\(_2\)CH\(_3\)) while the signal at \(\delta\) 1.42 (s, 3H) and \(\delta\) 1.64 (s, 3H) were assigned to the two methyl groups of the prenyl moiety. The peaks observed at \(\delta\) 2.98 (d, 2H, \(J = 6.3\) Hz) and at \(\delta\) 5.03 (m, 1H) were assigned to the prenyl moiety (-CH\(_2\)CH=C\(<\)). The peaks observed at \(\delta\) 7.37 (d, \(J = 7.5\) Hz, 1H), \(\delta\) 7.51 (t, \(J = 7.5\) Hz, 1H), \(\delta\) 7.65 (t, \(J = 7.8\) Hz, 1H) and at \(\delta\) 8.13 (d, \(J = 8.1\) Hz, 1H) were attributed to aromatic protons, while the signal at \(\delta\) 7.9 (s, 1H) was assigned to the benzylic proton.

The \(^{13}\)C-NMR spectrum (CDCl\(_3\), 75 MHz, \(\delta\) ppm) showed peaks at \(\delta\) 14.23 (CH\(_3\)), \(\delta\) 17.64 (CH\(_3\)), \(\delta\) 25.66 (CH\(_3\)), \(\delta\) 27.06 (CH\(_2\)), \(\delta\) 61.04 (OCH\(_2\)), \(\delta\) 120.97 (CH), \(\delta\) 124.72 (CH), \(\delta\) 128.90 (CH), \(\delta\) 131.18 (CH), \(\delta\) 132.07 (C), \(\delta\) 132.81 (C), \(\delta\) 133.28 (CH), \(\delta\) 133.91 (C), \(\delta\) 135.59 (CH), \(\delta\) 147.71 (C), \(\delta\) 167.28 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

In GC/MS molecular ion peak was shown at \(m/z\) 289.
Thus on the basis of mode of formation and above spectral analysis, structure 16a (E-isomer) was assigned to the product formed. The yield of the product was found to be 90%.

![16a](image)

We thought to exploit first route A from our projected synthesis. Accordingly, the pleasant smelling α,β-unsaturated ester 16a was subjected to the PPA cyclization for 5 minutes to furnish δ lactone (Scheme XVIII).

![Scheme XVIII](image)

The progress of the reaction was monitored by TLC. The crude product obtained after workup was then purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a white solid.

The IR spectrum of this compound showed strong band at 1774 cm\(^{-1}\) which was attributed to the carbonyl group of α,β-unsaturated six membered lactone.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, δ ppm) showed peaks at δ 1.46 (s, 6H), δ 1.85 (t, \(J = 6.9\) Hz, 2H) and δ 2.56 (dt, \(J = 6.9\) Hz & 2.4 Hz, 2H) were attributed to the two methyl groups (2 X CH\(_3\)) and two methylene groups (-CH\(_2\)-CH\(_2\)-) of the six membered lactone respectively. The peaks observed at δ 7.39 (d, \(J = 7.5\) Hz, 1H), δ 7.55 (t, \(J = 7.5\) Hz, 1H), δ 7.69 (t, \(J = 7.5\) Hz, 1H) and at δ 8.17 (d, \(J = 8.1\) Hz, 1H)
were assigned to aromatic ring protons. While the signal at $\delta$ 8.11 (br.s, 1H) was attributed to the benzylic proton.

The $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz, $\delta$ ppm) showed peaks at $\delta$ 21.66 (CH$_2$), $\delta$ 27.96 (2 X CH$_3$), $\delta$ 33.13 (CH$_2$), $\delta$ 80.94 (C), $\delta$ 125 (CH), $\delta$ 127.04 (C), $\delta$ 129.41 (CH), $\delta$ 130.66 (CH), $\delta$ 131.21 (C), $\delta$ 133.43 (CH), $\delta$ 138.15 (CH), $\delta$ 147.72 (C), $\delta$ 165.79 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

The high resolution mass spectrum of the compound displayed strong peak at $m/z$ 284.0893 presumably due to [M+Na]$^+$ pseudo ions. The elemental composition of which was determined to be C$_{14}$H$_{15}$NO$_4$. HRMS $m/z$ calculated for C$_{14}$H$_{15}$NO$_4$Na[(M+Na)$^+$] was 284.0899, found : 284.0893.

The melting point of the compound was found to be 96-98 °C.

Based on the above spectral data and mode of formation structure 17a was assigned to the expected lactone having $E$ geometry. The yield of the product was found to be 85%.

Since reduction and cyclisation are the next two consecutive steps leading to pyranoquinoline core structure, we thought to exploit domino approach wherein both reduction and cyclisation can take place in one pot.

In this regard we planned to use a method$^{32}$ which was published by our group wherein Fe and conc. HCl were used for reductive cyclisation. The nitrolactone 17a
was treated with Fe and conc. HCl and was refluxed on water bath, till the starting material disappeared as indicated by TLC (Scheme XIX).

![Scheme XIX](image)

The usual basic workup followed by column chromatographic purification over silica gel using hexanes-EtOAc (8:2) as an eluent afforded a white solid.

The IR spectrum of this compound showed bands at 1622, 1562, 1492 and 1415 cm$^{-1}$.

The $^1$H-NMR spectrum (CDCl$_3$, 300 MHz, δ ppm) (Fig. I) showed peaks at δ 1.50 (s, 6H), δ 1.96 (t, $J = 6.6$ Hz, 2H) and δ 3.04 (t, $J = 6.3$ Hz, 2H) which were attributed to the two methyl groups (2 X CH$_3$) and two methylene groups (-CH$_2$-CH$_2$-) of the pyran ring respectively. The peaks at δ 7.36 (t, $J = 7.8$ & 7.2 Hz, 1H), δ 7.58 (t, $J = 8.1$ & 7.2 Hz, 1H), δ 7.68 (d, $J = 7.5$ Hz, 1H), δ 7.85 (d, $J = 8.7$ Hz, 1H) and δ 7.88 (s, 1H) were assigned to the five aromatic protons of quinoline ring.
Fig. I: $^1$H-NMR spectrum of Compound 20a

The $^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz, δ ppm) (Fig. II) showed peaks at δ 22.62 (CH$_2$), δ 27.36 (2 X CH$_3$), δ 32.41 (CH$_2$), δ 77.08 (C), δ 117.66 (C), δ 123.88 (CH), δ 125.19 (C), δ 126.56 (CH), δ 127.22 (CH), δ 129.02 (CH), δ 137.51 (CH), δ 146.42 (C), δ 159.72 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.
The high resolution mass spectrum (HRMS) of the compound showed strong peak at $m/z$ 236.1049 presumably due to [M+Na]$^+$ pseudo ions. The elemental composition of which was determined to be C$_{14}$H$_{15}$NO. HRMS, $m/z$ calculated for C$_{14}$H$_{15}$NONa [(M+Na)$^+$] was 236.1051, found : 236.1049.

Melting point of the compound was found to be 103-105 °C.

Based on the spectral data and mode of formation structure 20a was assigned to the pyranoquinoline core structure. The yield of the product was found to be 54%.

Here, the reduction of nitro to amino, isomerisation of $E$ to $Z$ lactone and cyclisation took place in one pot in a domino fashion. Thus, we succeeded in getting the 3,4-dihydro-pyranoquinoline compound in good yield.
Furthermore, in order to make our synthesis more concise an alternate method i.e. route B was attempted, wherein Wittig product (16a) was directly subjected to reductive cyclisation employing Fe and conc. HCl to get the corresponding dihydropyranooquinoline (20a) without isolating the lactone intermediate.

Thus, the α,β-unsaturated ester 16a was subjected to Fe and conc. HCl and was heated on boiling water bath till the starting material disappeared as indicated by TLC. The usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent afforded a white solid.

The appearance of this compound on TLC and its spectral analysis such as IR, $^1$H-NMR, $^{13}$C-NMR and HRMS were matching with that of the 3,4-dihydropyranooquinoline (20a) prepared by the previous route A. Hence formation of it was confirmed.

However, the yield of isolated product during this one-pot concurrent reduction/isomerisation/cyclisation was found to be only 19%.

Once establishing a protocol for the synthesis of pyranooquinoline 20a, we decided to generalize the method to make more such analogues of pyranooquinolines. For this purpose, we selected three nitrobenzaldehydes namely 5-substituted-2-nitrobenzaldehyde (14b), 3,4-dimethoxy-6-nitrobenzaldehyde (14c) and 3,4-methylenedioxy-6-nitrobenzaldehyde (14d) as depicted in Scheme XX.
We thought to start with 5-substituted-2-nitrobenzaldehyde (14b). It was prepared by referring literature method from 3-hydroxy benzaldehyde (21).

Thus, hydroxyl group protection of 3-hydroxybenzaldehyde (21) was carried out with ethylchloroformate in presence of pyridine as per reported procedure (Scheme XXI). The spectral data of the product was found to be identical with that of the reported in literature.\(^{33}\)
The nitration on $O$-protected benzaldehyde (22) was carried out by subjecting it to sulphuric acid/ nitric acid mixture. After usual workup the crude product was recrystallized from hexanes to get pale yellow needles of ethyl-3-formyl-4-nitrophénylcarbonate (14b). The crystallized product was melted at 61 °C (Lit. 34 m.p.- 60-61 °C) (Scheme XXII)

\[
\begin{align*}
\text{EtOOCO} & \quad \text{CHO} & \quad \text{HNO}_2/H_2\text{SO}_4 & \quad \text{EtOOCO} & \quad \text{CHO} \\
\text{22} & & & & 14b
\end{align*}
\]

Scheme XXII

The Wittig olefination reaction of this 5-substituted-2-nitrobenzaldehyde (14b) with prenyl phosphorane (15) was done in refluxing chloroform for 3.0 hrs. The product was obtained as a pleasant smelling viscous liquid after column chromatographic purification.

IR (KBr): 1770 cm\(^{-1}\) (C=O of carbonate group), 1712 cm\(^{-1}\) (C=O of ester group)

\(^1\)H-NMR (CDCl\(_3\), 300 MHz, \(\delta\) ppm):

<table>
<thead>
<tr>
<th>(\delta)</th>
<th>Multiplicity</th>
<th>Assignments</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.26-1.43</td>
<td>m</td>
<td>6 H</td>
<td>2 X - OCH(_2)CH(_3)</td>
</tr>
<tr>
<td>1.64</td>
<td>s</td>
<td>6 H</td>
<td>2 X - CH(_3)</td>
</tr>
<tr>
<td>2.93</td>
<td>d</td>
<td>2 H ((J = 6.6) Hz)</td>
<td>- CH(_2)-CH =</td>
</tr>
<tr>
<td>4.19-4.33</td>
<td>m</td>
<td>4 H</td>
<td>2 X - OCH(_2)CH(_3)</td>
</tr>
<tr>
<td>4.95</td>
<td>br. s.</td>
<td>1 H</td>
<td>- CH(_2)-CH =</td>
</tr>
<tr>
<td>7.15</td>
<td>d</td>
<td>1 H ((J = 2.4) Hz)</td>
<td>ArH</td>
</tr>
<tr>
<td>8.14</td>
<td>d</td>
<td>1 H ((J = 9.0) Hz)</td>
<td>ArH</td>
</tr>
<tr>
<td>7.29</td>
<td>dd</td>
<td>1 H ((J = 9.0) &amp; 2.4 Hz)</td>
<td>ArH</td>
</tr>
<tr>
<td>7.79</td>
<td>s</td>
<td>1 H</td>
<td>Ar-CH(_\text{= C})</td>
</tr>
</tbody>
</table>
$^{13}$C-NMR (CDCl$_3$, 75 MHz, $\delta$ ppm) :

$\delta$ 14.11 (CH$_3$), $\delta$ 14.20 (CH$_3$), $\delta$ 17.54 (CH$_3$), $\delta$ 25.61 (CH$_3$), $\delta$ 26.99 (CH$_2$), $\delta$ 61.11 (OCH$_2$), $\delta$ 65.56 (OCH$_2$), $\delta$ 120.65 (CH), $\delta$ 121.23 (CH), $\delta$ 123.52 (CH), $\delta$ 126.56 (CH), $\delta$ 133 (C), $\delta$ 134.11 (C), $\delta$ 134.40 (C), $\delta$ 134.72 (CH), $\delta$ 144.71 (C), $\delta$ 152.32 (C), $\delta$ 154.06 (C), $\delta$ 167.03 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

In GC/MS molecular ion peak was shown at $m/z$ 377.

Thus, on the basis of mode of formation and spectral data structure 16b was assigned to the product formed. The yield of the product was found to be 82%.

![Image of 16b]

This $\alpha,\beta$-unsaturated ester 16b was then subjected to PPA cyclisation followed by usual workup. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent, a white solid was obtained.

IR (KBr): 1774 cm$^{-1}$ (C=O of carbonate group), 1717 cm$^{-1}$ (C=O of lactone group)
**$^{1}$H-NMR (CDCl$_3$, 300 MHz, $\delta$ ppm):**

<table>
<thead>
<tr>
<th>$\delta$</th>
<th>Multiplicity</th>
<th>Number of Protons</th>
<th>Chemical Shift</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.34</td>
<td>$t$</td>
<td>3</td>
<td>$J = 7.2$ Hz</td>
<td>$-\text{OCH}_2\text{CH}_3$</td>
</tr>
<tr>
<td>1.40</td>
<td>$s$</td>
<td>6</td>
<td></td>
<td>$2\times\text{-CH}_3$</td>
</tr>
<tr>
<td>1.78</td>
<td>$t$</td>
<td>2</td>
<td>$J = 6.9$ Hz</td>
<td>$-\text{CH}_2\text{-CH}_2\text{-}$</td>
</tr>
<tr>
<td>2.53</td>
<td>$t$</td>
<td>2</td>
<td>$J = 6.9$ Hz</td>
<td>$-\text{CH}_2\text{C(\text{CH}_3)_2}$</td>
</tr>
<tr>
<td>4.30</td>
<td>$q$</td>
<td>2</td>
<td>$J = 7.2$ Hz</td>
<td>$-\text{OCH}_2\text{CH}_3$</td>
</tr>
<tr>
<td>7.18</td>
<td>$d$</td>
<td>1</td>
<td>$J = 2.4$ Hz</td>
<td>$\text{ArH}$</td>
</tr>
<tr>
<td>8.17</td>
<td>$d$</td>
<td>1</td>
<td>$J = 9.0$ Hz</td>
<td>$\text{ArH}$</td>
</tr>
<tr>
<td>7.32</td>
<td>$dd$</td>
<td>1</td>
<td>$J = 9.0 &amp; 2.4$ Hz</td>
<td>$\text{ArH}$</td>
</tr>
<tr>
<td>8.03</td>
<td>$s$</td>
<td>1</td>
<td></td>
<td>$\text{Ar-CH= C}$</td>
</tr>
</tbody>
</table>

**$^{13}$C-NMR (CDCl$_3$, 75 MHz, $\delta$ ppm):**

$\delta$ 14.11 (CH$_3$), $\delta$ 21.60 (CH$_2$), $\delta$ 27.95 (2 $\times$ CH$_3$), $\delta$ 33.08 (CH$_2$), $\delta$ 65.68 (CH$_2$), $\delta$ 81.00 (C), $\delta$ 121.56 (CH), $\delta$ 123.08 (CH), $\delta$ 126.89 (CH), $\delta$ 127.63 (C), $\delta$ 133.22 (C), $\delta$ 137.22 (CH), $\delta$ 144.66 (C), $\delta$ 152.31 (C), $\delta$ 154.10 (C), $\delta$ 165.48 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: $m/z$ [M + Na]$^+$ Calcd for C$_{17}$H$_{19}$NO$_7$Na: 372.1059; found: 372.1059.

The melting point of the compound was found to be 104-106 °C.

Based on the mode of formation and spectral data, structure 17b was assigned to the product formed. The yield of the product was found to be 95%.
Final step was reductive cyclisation. Here, both the routes of reductive cyclisation i.e. from δ-lactones as well as from α,β-unsaturated ester were attempted to get 3,4-dihydropyranooquinoline.

**Route A**
In this method δ lactone (17b) was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid product in 85 % yield.

**Route B**
In this method the corresponding α,β-unsaturated ester 16b was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid product in 36 % yield.

The two compounds obtained by these two methods were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 3300 (OH), 1612, 1517, 1434, 1367 cm⁻¹.

¹H-NMR (CDCl₃, 300 MHz, δ ppm) (Fig. III):

<table>
<thead>
<tr>
<th>δ</th>
<th>1.46</th>
<th>s</th>
<th>6 H</th>
<th>2 X- CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>1.93</td>
<td>t</td>
<td>2 H (J = 6.9 Hz)</td>
<td>-CH₂-CH₂-</td>
</tr>
<tr>
<td>δ</td>
<td>2.99</td>
<td>t</td>
<td>2 H (J = 6.9 Hz)</td>
<td>-CH₂-C(CH₃)₂</td>
</tr>
<tr>
<td>δ</td>
<td>5.58</td>
<td>br.s.</td>
<td>1 H</td>
<td>Ar-OH</td>
</tr>
<tr>
<td>δ</td>
<td>7.03</td>
<td>d</td>
<td>1 H (J = 2.7 Hz)</td>
<td>ArH</td>
</tr>
<tr>
<td>δ</td>
<td>7.21</td>
<td>dd</td>
<td>1 H (J = 9.0 &amp; 2.7 Hz)</td>
<td>ArH</td>
</tr>
<tr>
<td>δ</td>
<td>7.73</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>δ</td>
<td>7.76</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
</tbody>
</table>
$^{13}$C-NMR (CDCl$_3$, 75 MHz, $\delta$ ppm):
$\delta$ 22.59 (CH$_2$), $\delta$ 27.28 (2 X CH$_3$), $\delta$ 32.39 (CH$_2$), $\delta$ 70.19 (C), $\delta$ 108.46 (CH), $\delta$ 118.06 (CH), $\delta$ 120.69 (CH), $\delta$ 125.83 (CH), $\delta$ 128.52 (C), $\delta$ 136.16 (C), $\delta$ 141.62 (C), $\delta$ 152.02 (C), $\delta$ 158.20 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: $m/z$ [M + Na]$^+$ Calcd for C$_{14}$H$_{15}$NO$_2$Na: 252.1; found: 252.0999.

The melting point of the compound was found to be 223-225 $^\circ$C.

Based on the mode of formation and spectral data, structure 20b was assigned to the product formed.
Interestingly during the reductive cyclisation the carbonate group was also cleaved.

Third aromatic nitroaldehyde which was used was 3,4-dimethoxy-6-nitrobenzaldehyde (14c). 3,4-dimethoxy-6-nitrobenzaldehyde (14c) was prepared from 3,4-dimethoxybenzaldehyde (23) by treating it with nitric acid. After usual workup, the crude product was recrystallized from ethanol to afford pale yellow needles of 3,4-dimethoxy-6-nitrobenzaldehyde (14c). The crystallized product was melted at 132 °C (Lit.34 m.p. 133°C) (Scheme XXIII).

Condensation of this 3,4-dimethoxy-6-nitrobenzaldehyde (14c) with phosphorane 15 was carried out in refluxing chloroform for 3.0 hrs. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent, the product was obtained as a thick viscous yellow liquid.

IR (KBr): 1709 cm\(^{-1}\) (C=O).
$^1$H-NMR (CDCl$_3$, 300 MHz, δ ppm) (Fig. IV):

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Chemical Shift</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.37</td>
<td>t</td>
<td></td>
<td>3H</td>
<td>OCH$_2$CH$_3$</td>
</tr>
<tr>
<td>1.49</td>
<td>s</td>
<td></td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>1.67</td>
<td>s</td>
<td></td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>3.00</td>
<td>d</td>
<td>6.0</td>
<td>2H</td>
<td>CH$_2$-CH =</td>
</tr>
<tr>
<td>3.92</td>
<td>s</td>
<td></td>
<td>3H</td>
<td>OCH$_3$</td>
</tr>
<tr>
<td>4.00</td>
<td>s</td>
<td></td>
<td>3H</td>
<td>OCH$_3$</td>
</tr>
<tr>
<td>4.31</td>
<td>q</td>
<td>7.2</td>
<td>2H</td>
<td>OCH$_3$CH$_3$</td>
</tr>
<tr>
<td>5.1</td>
<td>m</td>
<td></td>
<td>1H</td>
<td>CH$_2$-CH =</td>
</tr>
<tr>
<td>6.77</td>
<td>s</td>
<td></td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.75</td>
<td>s</td>
<td></td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.94</td>
<td>s</td>
<td></td>
<td>1H</td>
<td>Ar-CH = C</td>
</tr>
</tbody>
</table>

Fig. IV: $^1$H-NMR spectrum of Compound 16c
$^{13}$C-NMR (CDCl$_3$, 75 MHz, δ ppm) (**Fig. V**):

δ 14.24 (CH$_3$), δ 17.85 (CH$_3$), δ 25.62 (CH$_3$), δ 27.28 (CH$_2$), δ 56.33 (OCH$_3$), δ 56.40 (OCH$_3$), δ 60.99 (OCH$_2$), δ 107.70 (CH), δ 112.42 (CH), δ 121.77 (CH), δ 126.66 (C), δ 132.75 (C), δ 132.83 (C), δ 136.82 (CH), δ 140.15 (C), δ 148.55 (C), δ 152.97 (C), δ 167.41 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

![Fig. V: $^{13}$C-NMR spectrum of Compound 16c](image)

In GC/MS, molecular ion peak was shown at $m/z$ 349.

On the basis of mode of formation and spectral data, structure **16c** was assigned to the product formed. The yield of the product was found to be 66%.
The α,β-unsaturated ester 16c was further subjected to PPA cyclisation. The usual work up followed by column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent gave a yellow solid.

IR (KBr): 1692 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. VI):

<table>
<thead>
<tr>
<th>(\delta)</th>
<th>Multiplicity</th>
<th>Number of H</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.46</td>
<td>s</td>
<td>6 H</td>
<td>2 X-CH(_3)</td>
</tr>
<tr>
<td>1.85</td>
<td>t</td>
<td>2 H ((J = 6.9 \text{ Hz}))</td>
<td>-CH(_2)-CH(_2)-</td>
</tr>
<tr>
<td>2.55</td>
<td>dt</td>
<td>2 H ((J = 6.6 &amp; 2.1 \text{ Hz}))</td>
<td>-CH(_2)-C(CH(_3))(_2)</td>
</tr>
<tr>
<td>3.98</td>
<td>s</td>
<td>3 H</td>
<td>-OCH(_3)</td>
</tr>
<tr>
<td>4.00</td>
<td>s</td>
<td>3 H</td>
<td>-OCH(_3)</td>
</tr>
<tr>
<td>6.73</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.76</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>8.11</td>
<td>br.s.</td>
<td>1 H</td>
<td>Ar-CH = C</td>
</tr>
</tbody>
</table>
Fig. VI: $^1$H-NMR spectrum of Compound 17c

$^{13}$C-NMR (CDCl$_3$, 75 MHz, δ ppm) (Fig. VII):

δ 21.75 (CH$_2$), δ 27.98 (2 X CH$_3$), δ 33.20 (CH$_2$), δ 56.47 (OCH$_3$), δ 56.62 (OCH$_3$), δ 80.83 (C), δ 107.97 (CH), δ 111.63 (CH), δ 125.75 (C), δ 126.16 (C), δ 139.17 (CH), δ 140.33 (C), δ 148.88 (C), δ 153.14 (C), δ 166.02 (C=O).
HRMS: $m/z$ [M + Na]$^+$ Calcd for $C_{16}H_{19}NO_6Na$: 344.1110; found: 344.1113.

The melting point of the compound was found to be 181-182 °C.

Based on the spectral data and mode of formation structure $17c$ was assigned to the product. The yield of the product was found to be 80%.

For further reductive cyclisation both routes were attempted.
**Route A**
Corresponding δ lactone 17c was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent gave a white solid in 76 % yield.

**Route B**
The α,β-unsaturated ester 16c was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid in 25 % yield.

The two compounds obtained by both these routes were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 1612, 1496, 1458, 1381 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz, δ ppm) (Fig. VIII):

<table>
<thead>
<tr>
<th>δ</th>
<th>Multiplet</th>
<th>Number of H</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.47</td>
<td>s</td>
<td>6 H</td>
<td>2 X- CH(_3)</td>
</tr>
<tr>
<td>1.93</td>
<td>t</td>
<td>2 H ((J = 6.6) Hz)</td>
<td>-CH(_2)-CH(_2)-</td>
</tr>
<tr>
<td>2.97</td>
<td>t</td>
<td>2 H ((J = 6.6) Hz)</td>
<td>-CH(_2)-C(CH(_3))(_2)</td>
</tr>
<tr>
<td>3.98</td>
<td>s</td>
<td>3 H</td>
<td>- OCH(_3)</td>
</tr>
<tr>
<td>3.99</td>
<td>s</td>
<td>3 H</td>
<td>- OCH(_3)</td>
</tr>
<tr>
<td>6.95</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.2</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.7</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
</tbody>
</table>
Fig. VIII: $^1$H-NMR spectrum of Compound 20c

$^{13}$C-NMR (CDCl$_3$, 75 MHz, $\delta$ ppm) (Fig. IX):

$\delta$ 22.43 (CH$_2$), $\delta$ 27.28 (2 X CH$_3$), $\delta$ 32.51 (CH$_2$), $\delta$ 55.87 (2 X CH$_3$), $\delta$ 76.53 (C), $\delta$ 104.69 (CH), $\delta$ 106.62 (CH), $\delta$ 114.85 (C), $\delta$ 119.92 (C), $\delta$ 136 (CH), $\delta$ 143.05 (C), $\delta$ 147.81 (C), $\delta$ 152.07 (C), $\delta$ 158.66 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.
The melting point of the compound was found to be 156-158°C.

Based on the mode of formation and spectral data structure 20c was assigned to the product formed.

Another nitrobenzaldehyde chosen for this purpose was 3,4-methylenedioxy-6-nitrobenzaldehyde (14d). 3,4-methylenedioxy-6-nitrobenzaldehyde (14d) was obtained from 3,4-methylenedioxybenzaldehyde (24) by treating it with nitric acid. After usual workup the crude product was recrystallized from ethanol to furnish pale
yellow needles of 3,4-methylenedioxy-6-nitrobenzaldehyde (14d). The crystallised product was melted at 87°C (lit. 34 m.p. 88°C) (Scheme XXIV).

The Wittig olefination reaction of 3,4-methylenedioxy-6-nitrobenzaldehyde (14d) with phosphorane 15 was performed in refluxing chloroform for 3.0 hrs. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent the product was obtained as a yellow viscous liquid.

IR (KBr): 1713 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz, \(\delta\) ppm):

<table>
<thead>
<tr>
<th>(\delta)</th>
<th>Multiplicity</th>
<th>Assignments</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.35</td>
<td>t</td>
<td>3H ((J=7.2) Hz)</td>
<td>- OCH(_2)CH(_3)</td>
</tr>
<tr>
<td>1.51</td>
<td>s</td>
<td>3 H</td>
<td>- CH(_3)</td>
</tr>
<tr>
<td>1.67</td>
<td>s</td>
<td>3 H</td>
<td>- CH(_3)</td>
</tr>
<tr>
<td>3.00</td>
<td>d</td>
<td>2 H ((J=6.6) Hz)</td>
<td>- CH(_2)-CH =</td>
</tr>
<tr>
<td>4.29</td>
<td>q</td>
<td>2 H ((J=7.2) Hz)</td>
<td>- OCH(_2)CH(_3)</td>
</tr>
<tr>
<td>5.06</td>
<td>m</td>
<td>1 H</td>
<td>- CH(_2)-CH =</td>
</tr>
<tr>
<td>6.17</td>
<td>s</td>
<td>2 H</td>
<td>- OCH(_2)O-</td>
</tr>
<tr>
<td>6.74</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.65</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.83</td>
<td>s</td>
<td>1 H</td>
<td>Ar-CH = C</td>
</tr>
</tbody>
</table>
\(^{13}\)C-NMR (CDCl\(_3\), 75 MHz, δ ppm):
δ 14.21 (CH\(_3\)), δ 17.68 (CH\(_3\)), δ 25.66 (CH\(_3\)), δ 27.15 (CH\(_2\)), δ 60.99 (OCH\(_2\)), δ 103.20 (CH\(_2\)), δ 105.50 (CH), δ 109.74 (CH), δ 121.02 (CH), δ 128.74 (C), δ 132.74 (C), δ 133.05 (C), δ 136.22 (CH), δ 141.87 (C), δ 147.78 (C), δ 151.77 (C), δ 167.30 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

GC/MS: \(m/z\) 333 [M\(^+\)].

On the basis of mode of formation and spectral data, structure 16d was assigned to the product formed. The yield of the product was found to be 68%.

The resulting α,β-unsaturated ester 16d was then subjected to PPA cyclisation. The usual workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent gave a yellow solid.

IR (KBr): 1697 cm\(^{-1}\) (C=O).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz, δ ppm):

<table>
<thead>
<tr>
<th>δ ppm</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
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<td>6 H</td>
</tr>
<tr>
<td>1.85</td>
<td>t</td>
<td>2 H ((J = 6.9) Hz)</td>
</tr>
<tr>
<td>2.56</td>
<td>dt</td>
<td>2 H ((J = 6.9) &amp; 2.4 Hz)</td>
</tr>
<tr>
<td>6.18</td>
<td>s</td>
<td>2 H</td>
</tr>
<tr>
<td>6.73</td>
<td>s</td>
<td>1 H</td>
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<tr>
<td>7.67</td>
<td>s</td>
<td>1 H</td>
</tr>
<tr>
<td>8.04</td>
<td>br.s.</td>
<td>1 H</td>
</tr>
</tbody>
</table>

2 X- CH\(_3\)
- CH\(_2\)-CH\(_2\)-
- CH\(_2\)-C(CH\(_3\))\(_2\)
- OCH\(_3\)-
ArH
ArH
Ar-CH = C
\(^{13}\)C-NMR (CDCl\(_3\), 75 MHz, \(\delta\) ppm):
\(\delta\) 21.65 (CH\(_2\)), \(\delta\) 27.94 (2 X CH\(_3\)), \(\delta\) 33.11 (CH\(_2\)), \(\delta\) 80.83 (C), \(\delta\) 103.38 (OCH\(_2\)O), \(\delta\) 105.79 (CH), \(\delta\) 109.00 (CH), \(\delta\) 126.14 (C), \(\delta\) 127.84 (C), \(\delta\) 138.91 (CH), \(\delta\) 142 (C), \(\delta\) 148.13 (C), \(\delta\) 151.94 (C), \(\delta\) 165.9 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: \(m/\text{z} \ [\text{M + Na}^+]\) Calcd for C\(_{15}\)H\(_{15}\)N\(_2\)O\(_6\)Na: 328.0797; found 328.0800.

The melting point of the compound was found to be 176-177 °C.

Based on the mode of formation and spectral data structure 17d was assigned to the product. The yield of the product was found to be 82%.

![Structure 17d](image)

Further reductive cyclisation was done using both the routes.

**Route A**
In this method the \(\delta\) lactone 17d was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent gave a white solid in 83% yield.

**Route B**
In this method the corresponding \(\alpha,\beta\)-unsaturated ester 16d was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid in 33% yield.
The two compounds obtained by both these routes were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 1620, 1480, 1465, 1388 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$, 300 MHz, $\delta$ ppm) (Fig. X):

<table>
<thead>
<tr>
<th>$\delta$</th>
<th>$\delta$ ppm</th>
<th>$\delta$ ppm</th>
<th>$\delta$ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.44</td>
<td>s</td>
<td>6 H</td>
<td>2 X- CH$_3$</td>
</tr>
<tr>
<td>1.89</td>
<td>t</td>
<td>2 H ($J = 6.6$ Hz)</td>
<td>-CH$_2$-CH$_2$-</td>
</tr>
<tr>
<td>2.92</td>
<td>t</td>
<td>2 H ($J = 6.6$ Hz)</td>
<td>-CH$_2$-C(CH$_3$)$_2$</td>
</tr>
<tr>
<td>6.02</td>
<td>s</td>
<td>2 H</td>
<td>- OCH$_2$O-</td>
</tr>
<tr>
<td>6.91</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
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<td>7.15</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.65</td>
<td>s</td>
<td>1 H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

Fig. X: $^1$H-NMR spectrum of Compound 20d
$^{13}$C-NMR (CDCl$_3$, 75 MHz, $\delta$ ppm) (**Fig. XI**):
$\delta$ 22.32 (CH$_2$), $\delta$ 27.26 (2 X CH$_3$), $\delta$ 32.44 (CH$_2$), $\delta$ 76.65 (C), $\delta$ 101.26 (CH$_2$), $\delta$ 102.08 (CH), $\delta$ 104.40 (CH), $\delta$ 114.78 (C), $\delta$ 121.10 (C), $\delta$ 136.57 (CH), $\delta$ 144.24 (C), $\delta$ 145.83 (C), $\delta$ 150.21 (C), $\delta$ 158.60 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

**Fig. XI**: $^{13}$C-NMR spectrum of Compound 20d

HRMS: $m/z$ [M + Na]$^+$ Calcd for C$_{15}$H$_{15}$N O$_3$Na: 280.0950; found: 280.0958.
The melting point of the compound was found to be 177-179 °C.

Based on the mode of formation and spectral data structure 20d was assigned to the product formed.

![20d](image)
Thus, we have successfully completed the synthesis of four 3,4-dihydropyranoquinoline molecules (20a-d).

Some of the chlorinated compounds containing quinoline ring structure, such as chloroquine and quinine exhibit good antimalarial activity. Owing to the importance of these compounds, we thought to chlorinate our 3,4-dihydropyranoquinoline compounds in order to study the biological activity (if any) associated with it.

At this point the literature search on the chlorinating agents was performed and we found out that the acetyl chloride in presence of CAN in acetonitrile acts as an efficient chlorinating agent for activated aromatic system.\(^{35}\)

The 3,4-dihydropyranoquinoline compound selected for this purpose was 7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2\(H\)-pyrano[2,3-b]quinoline (20c). The substrate 20c was treated with acetyl chloride in acetonitrile in presence of CAN for 8.0 hrs, till the disappearance of the starting material (monitored by TLC) (Scheme XXV).

![Scheme XXV](image)

After workup the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) to furnish a pale yellow solid.

IR spectrum of this compound showed absorptions at 1593.20 cm\(^{-1}\), 1556.55 cm\(^{-1}\), 1485.19 cm\(^{-1}\), 1454.33 cm\(^{-1}\) and 1263.37 cm\(^{-1}\).

The \(^1\)H-NMR (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. XII) showed strong peak at \(\delta\) 1.48 (s, 6H) which was assigned to the two methyl groups 2 \(-\text{CH}_3\) on the pyran ring. The signal at \(\delta\) 1.94 (t, \(J\) = 6.6 Hz, 2H) and at \(\delta\) 3.04 (t, \(J\) = 6.6 Hz, 2H) was attributed to -\text{CH}_2-\text{CH}_2- group of pyran ring moiety. Whereas the signal at \(\delta\) 3.97 (s, 3H) and \(\delta\) 4.00
(s, 3H) was assigned to the two methyl groups 2 X (-CH₃) of two methoxy moieties on the benzene ring. The signal due to one aromatic proton was observed at δ 8.20 (s, 1H).

![Fig. XII: ¹H-NMR spectrum of Compound 25](image)

The ¹³C-NMR spectrum (CDCl₃, 75 MHz, δ ppm) (Fig. XIII) showed peaks at δ 22.64 (CH₂), δ 27.28 (2 X CH₃), δ 32.32 (CH₂), δ 61.27 (CH₃), δ 61.38 (CH₃), δ 77.96 (C), δ 118.58 (C), δ 120.58 (C), δ 121.32 (C), δ 122.79 (C), δ 134.76 (CH), δ 140.82 (C), δ 147.50 (C), δ 152.02 (C), δ 160.46 (C).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.
The high resolution mass spectrum (Fig. XIV) of the compound displayed strong peak at \( m/z \) 342.0662 presumably due to \([M+H]^+\) pseudo ions. The elemental composition of which was determined to be C\(_{14}\)H\(_{17}\)NO\(_3\)Cl\(_2\). HRMS \( m/z \) calculated for C\(_{14}\)H\(_{17}\)NO\(_3\)Cl\(_2\)H\([M+H]^+\] was 342.0663, found: 342.0662.
The melting point of the compound was found to be 98-100 °C.

Thus on the basis of mode of formation and spectral data the formation of dichlorinated compound 25 was confirmed. The yield of the product was found to be 73%.

Thus, we have prepared chlorinated 3,4-dihydropyranquinoline molecule (25) which could be tested for its biological activity.
Conclusion

We have developed a convenient synthesis of 2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinolines from o-nitrobenzaldehydes using Wittig reaction as a key reaction. The Wittig condensation product was converted to 2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinolines by two routes. The first route involves lactonisation using PPA followed by reductive cyclisation of the lactone. The overall yield of this two step approach was found to be good. While the direct reductive cyclisation to target compounds gave low overall yield. We also demonstrated the chlorination of pyranoquinoline (20c) takes place in the benzene nucleus of the quinoline ring which could be useful to make biologically active molecules.
2.1 Preparation of Ethyl (2E)-5-Methyl-2[(2-nitrophenyl)methylidene]hex-4-enoate (16a)

A solution of o-nitrobenzaldehyde (14a) (0.151 g, 1 mmol), phosphorane 15 (0.417 g, 1.0 mmol) in chloroform (10 mL) was refluxed for 3 hrs. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous yellow liquid (16a) (0.260 g, 90%).

2.2 Preparation of (3E)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2H-pyran-2-one (17a)

To a flask containing compound 16a (0.289 g, 1 mmol) was added polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 min. Chilled water (15 mL) was added to the reaction mixture and it was subsequently extracted with diethyl ether (3 X 10 mL). The diethyl ether layer was washed twice with sat. NaHCO₃ solution and then dried over anhyd. sodium sulphate. The solvent was removed under vacuum pump and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a white solid (17a) (0.222 g, 85%), m.p. 96-98 °C.
2.3 Preparation of 2,2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (20a)

\[\text{Fe} / \text{conc. HCl} \quad \text{Reflex}\]

Concentrated HCl (8 mL) was added to a magnetically stirred mixture of esters 16a (0.289 g, 1 mmol) or 17a (0.261 g, 1 mmol) and Fe powder (0.838 g, 15 mmol). The reaction mixture was allowed to stir for 15 mins. and was subsequently refluxed on a water bath. After completion of the reaction (the progress of the reaction was monitored by thin TLC), the reaction mixture was filtered and the residue was washed with water (3 X 5 mL). This combined filtrate was washed with diethyl ether (2 X 10 mL) and filtered on celite. The filtrate was basified with solid NaOH pellets and the compound was subsequently extracted in diethyl ether (3 X 15 mL). The combined organic extracts were dried over anhyd. Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (20a) [0.040 g, (19 % from 16a), 0.115 g, (54 % from 17a)] m.p. 103-105 °C.

2.4 Preparation of Ethyl-3-Formylphenyl carbonate (22)
3-Hydroxybenzaldehyde (21) (15.0 g, 0.123 mol) was dissolved in dry pyridine (100 mL). The solution was cooled in an ice bath and ethyl chloroformate (20 mL) was added dropwise over a period of 30 mins. The resulting solution was stirred for 2 hrs at room temperature. The product was extracted into diethyl ether (3 X 25 mL), and the ether extract was washed consecutively with water, 5% HCl, 5% cold NaOH and again with water. The dried organic extract was evaporated to give the product (22) as yellow syrup (23 g, 97%) which was directly nitrated.

2.5 Preparation of Ethyl 3-Formyl 4-nitrophenyl carbonate (14b)

![Diagram](image)

Ethyl 3-formyl phenyl carbonate (22) (14.0 g, 0.0072 mol) was dissolved in conc. H₂SO₄ (135 mL). The solution was cooled to -5 °C and a solution 67.5 mL of fuming nitric acid (3.44 ml, sp.g. 1.49, 0.0814 mol) in 25 mL of conc. H₂SO₄ was added dropwise over 15 mins. at -5 to 0 °C. Stirring was continued at -5 to 0 °C for 1 hr. Water (500 mL) was added dropwise at -10 °C and the product was extracted into chloroform (3 X 50 mL). Evaporation of the dried solvent gave a gum which was crystallized from hexanes to give product (14b) as pale yellow needles (13 g, 76%, m.p. 60-61 °C).

2.6 Preparation of Ethyl (2E)-2-({5-[(ethoxycarbonyl)oxy]-2-nitrophenyl} methylidene)-5-methylhex-4-enoate (16b)

![Diagram](image)
Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous yellow liquid (16b) (82%).

2.7 Preparation of 3-[(E)-(6,6-Dimethyl-2-oxodihydro-2H-pyran-3(4H)-ylidene) methyl]-4-nitrophenyl ethyl carbonate (17b)

Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a white solid (17b) (95%) m.p. 104-106 °C.

2.8 Preparation of 2,2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-ol (20b)

Followed the same procedure as in Expt. 2.3, except the basification was carried out using liquid ammonia instead of solid NaOH pellets. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (20b) (36% from 16b, 85% from 17b) m.p. 223-225 °C.
2.9 Preparation of 3,4-Dimethoxy-6-nitrobenzaldehyde (14c)

Nitric acid (35 mL, 1.4 d) was cooled to 0 °C and 3,4-dimethoxybenzaldehyde (23) (5 g) was added to it in lots with constant stirring. The addition was complete in about 10 mins. During the addition the temperature of the reaction mixture was kept below 0 °C. The ice bath was removed and the reaction mixture was stirred for 5 mins. It was then warmed on water bath to get a clear reddish brown solution. This solution was kept in ice bath and stirred vigorously till the solid product separated out. The reaction mixture was then poured into ice cold water. The pale yellow solid thus obtained was filtered, washed with water and dried. It was recrystallized from ethanol to furnish 3,4-dimethoxy-6-nitrobenzaldehyde (14c) (5.2 g, 82%) m.p. 133 °C.

2.10 Preparation of Ethyl (2E)-2-[(4,5-dimethoxy-2-nitrophenoxy)methylidene]-5-methylhex-4-enoate (16c)

Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous yellow liquid (16c) (66%).
2.11 Preparation of \( (3E)-3-[(4,5\text{-Dimethoxy-2-nitrophenyl})\text{methylidene}]-6,6\text{-dimethyltetrahydro-2H-pyran-2-one} \) (17c)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{Et} & \quad \text{Et} \\
\end{align*}
\]

Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a yellow solid (17c) (80%) m.p. 181-182 °C.

2.12 Preparation of 7,8-Dimethoxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (20c)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{Et} & \quad \text{Et} \\
\end{align*}
\]

Followed the same procedure as in Expt. 2.3. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (20c) (25% from 16c, 76% from 17c), m.p. 156-158 °C.

2.13 Preparation of 3,4-Methylenedioxy-6-nitrobenzaldehyde (14d)

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\end{align*}
\]

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Nitric acid (35 mL, 1.4 d) was cooled to 0 °C and 3,4-methylenedioxybenzaldehyde (24) (5 g) was added to it in lots with constant stirring. The addition was complete in about 10 mins. During the addition the temperature of the reaction mixture was kept below 0 °C. The ice bath was removed and the reaction mixture was stirred for 5 mins. It was then warmed on water bath to get a clear reddish brown solution. This solution was kept in ice bath and stirred vigorously till the solid product separated out. The reaction mixture was then poured into ice cold water. The pale yellow solid thus obtained was filtered, washed with water and dried. It was recrystallized from ethanol to furnish 3,4-methylenedioxy-6-nitrobenzaldehyde (14d) (5.5 g, 97%) m.p. 87 °C.

2.14 Preparation of Ethyl (2E)-5-methyl-2-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]hex-4-en-1-yl) ethyl (16d)

Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous yellow liquid (16d) (68%).

2.15 Preparation of (3E)-6,6-Dimethyl-3-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]tetrahydro-2H-pyran-2-one (17d)

Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a yellow solid (17d) (82%) m.p. 176-177 °C.
2.16 Preparation of 7,8-Methylenedioxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (20d)

Followed the same procedure as in Expt. 2.3. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (20d) (33% from 16d, 83% from 17d) m.p. 177-179 °C.

2.17 Preparation of 6,9-Dichloro-7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b] quinoline (25)

To a stirred mixture of the 7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (20c) (0.200 g, 0.73 mmol) and freshly distilled acetylchloride (0.056 g, 0.73 mmol) in acetonitrile (5 mL) was added ceric ammonium nitrate (0.040 g, 0.073 mmol) in one portion under N₂ at room temperature. The reaction mixture was allowed to stir for 8 hrs. After completion of the reaction (the progress of the reaction was monitored by TLC), the reaction mixture was diluted with diethyl ether (15 mL) and washed thoroughly with sat. aqueous NaHCO₃ solution (3 X 5 mL), brine (3 X 5 mL) and dried over anhyd. Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to give a pale yellow solid (25) (0.180 g, 73%), m.p. 98-100 °C.
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