CHAPTER 3
Section A
CHAPTER 3
SECTION A
Synthesis of Mukonine

Introduction

Carbazoles are a series of natural products which are widely distributed in higher plants. Although carbazole (1) (Fig. 1) itself is a natural product isolated from coal tar in 1872 by Graebe and Glaser, the first simple carbazole from plant sources was not discovered until the 1960s.\(^1\)

![Fig. 1](image)

A large number of biologically active carbazole alkaloids have been isolated from natural sources.\(^2\)-\(^10\) Many of these natural products display biological properties such as antitumor, psychotropic, anti-inflammatory, anti-histaminic, antibiotic and antioxidative activities.\(^11\)-\(^18\) As synthetic materials, many carbazole derivatives exhibit photoreactive, photo conductive and light emitting properties.\(^19\)-\(^20\) Carbazoles have also been recognized as useful scaffold in anion binding studies.\(^21\) Their useful bioactivities and their interesting structural features attracted the attention of synthetic chemists and led to the development of many different synthetic strategies. Since 1979, new highly substituted carbazole alkaloids have been found by several groups in different terrestrial plants.

The first carbazole alkaloid to be isolated from plant source was murrayanine (2) extracted from the stembark of the small tree Murraya Koenigii (Fam. Rutaceae)\(^22\) an Indian medicinal plant commonly known as “curry-leaf tree” and used externally to cure eruptions.\(^23\) Since then, the field has expanded enormously large due to the promising biological activities of many of the carbazole alkaloids.
The carbazole alkaloids have primarily been isolated from plants of the genus Murraya, Glycosmis and Clausena from the family Rutaceae, particularly 1-oxygenated carbazole alkaloids like murrayanine (2), mukoeic acid (3) and mukonine (6). Extracts of the leaves and bark of this tree have been used as a folk medicine for analgesia and local anesthesia, as well as for the treatment of eczema, rheumatism and dropsy. The shrub clausena excavata is traditionally used in China for the treatment of snakebites, abdominal pain and as a detoxification agent. Extensive studies of the clausena genus have resulted in several compounds with interesting biological activities.

The isolation of several 3-methyl carbazole derivatives from higher plants and of carbazole (1) from Glycosmis pentaphylla shows that the aromatic methyl group can be eliminated oxidatively from the key intermediate 3-methyl carbazole via -CH₂OH, -CHO and -COOH functionalities. The isolation of 3-methyl carbazole from the genus clausena, the co-occurrence of murrayanine (2), mukoeic acid (3), murrayafoline A (4), koenoline (5) in M.Koenigii, as well as the subsequent isolation of mukonine (6) (Fig. 2) support the hypothesis of biomimetic hydroxylation of 3-methyl carbazole. Congeners that differ in the oxidation state of the C-3 methyl group, i.e -CH₂OH, -CHO, -COOH and -COOMe, were found for various alkaloids, a fact which indicates an in vivo oxidation of carbazole alkaloids.

![Chemical structures](image)

2. Murrayanine  
   \( R = \text{CHO} \)

3. Mukoeic acid  
   \( R = \text{COOH} \)

4. Murrayafoline A  
   \( R = \text{Me} \)

5. Koenonline  
   \( R = \text{CH}_2\text{OH} \)

6. Mukonine  
   \( R = \text{COOMe} \)

Fig. 2
Thus a systematic classification of tricyclic carbazole alkaloids has been suggested based on their oxygenation pattern.²⁷

Bringmann et al.²⁸ have successfully transformed mukonine(6) to seven further 1-oxygenated carbazole alkaloids like murrayanine (2), mukoic acid (3), murrayafoline A (4), koenoline (5), clausine E (7), o-demethyl murrayanine (8) and 1-hydroxy-3-methyl carbazole (9) (Scheme I). Some of them show antibiotic,²⁹ antifungal³⁰ and cytotoxic³¹ properties and neoplasm inhibitory effects on mitosis³² as well as a good activity against the malaria parasite Plasmodium falciparum also exhibited by some dimeric carbazoles.³³

![Scheme I](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>LAH, Et₂O/CH₂Cl₂, r.t. 2 h</td>
</tr>
<tr>
<td>b</td>
<td>DIBAL, Et₂O, -78°C, 3.5 h</td>
</tr>
<tr>
<td>c</td>
<td>MnO₂, CCl₄, r.t. 6 h</td>
</tr>
<tr>
<td>d</td>
<td>BBr₃, CH₂Cl₂, 0°C, 3 h</td>
</tr>
<tr>
<td>e</td>
<td>KOH, EtOH/H₂O, 78°C, 4 h</td>
</tr>
</tbody>
</table>
A Literature Review

Given the biological importance of natural carbazole alkaloids, an intensive effort has been directed towards their total synthesis. Widely used methods for synthesis of 1-oxygenated carbazoles include the classical Fischer indolisation with appropriate phenylhydrazones,\textsuperscript{34} intramolecular cyclisation of indoles,\textsuperscript{35} and oxidative cyclisation of diarylamines.\textsuperscript{36} Increasingly important are transition metal-mediated and -catalyzed processes for preparation of carbazoles.\textsuperscript{8}

Literature methods for the synthesis of mukonine (6) are mentioned below-

Knolker et al.\textsuperscript{37} have prepared mukonine based on iron-mediated construction of the carbazole ring system. They carried out electrophilic substitution of the commercial arylamine using iron-complex cation in acetonitrile at room temperature to get the corresponding iron complex regio and stereoselectively in 36% yield. Oxidative cyclisation of this complex with very active manganese dioxide (v.a. MnO\textsubscript{2}) at room temperature in toluene afforded mukonine in 54% yield (Scheme II).

![Scheme II](image-url)
Brenna et al. reported the synthesis of mukonine starting from 3-formylindole via a base promoted cyclization. They carried out reaction of 3-formylindole with dimethyl succinate and sodium methylate in methanol to afford corresponding product through a Stobbe condensation. In a one-pot operation this product was then transformed to the aromatic derivative by reacting with ethyl chloroformate in the presence of triethylamine. After deacetylation of the aromatic derivative, the corresponding hydroxy derivative was methylated to give mukonine (Scheme III).

Bringmann et al. started the synthesis from N-protected indole-3-carbaldehyde. The key steps in their synthesis are Horner-Emmons reaction, cyclization with sodium acetate in acetic anhydride followed by methanolysis and o-methylation with dimethyl sulphate in acetone to yield mukonine (Scheme IV).
Zempoalteca et al.\textsuperscript{38} have described synthesis of mukonine based on a regioselective Diels-Alder reaction of \(N\)-phenyl-4,5-dimethylidene-2-oxazolidinone with methyl propiolate. Successive transformation of the cycloadduct in one step to the corresponding phenyl aryl amine and palladium promoted cyclisation of the latter provided mukonine (Scheme V).
Knolker et al.\textsuperscript{39} started synthesis of mukonine from arylamine. Reaction of the iron complex cation with the arylamine by refluxing in acetonitrile gave the corresponding iron complex. The iron complex is subjected to smooth cyclodehydrogenation by reacting with air in trifluoroacetic acid to afford the 4a, 9a-dihydro-9\textsubscript{H}-carbazole complex. Aromatization of this complex with concomitant demetalation by using ferricenium hexafluorophosphate in the presence of sodium carbonate provided mukonine in 50\% yield (route A: three steps, 15\% overall yield). An alternative method was also attempted wherein they carried out demetalation and subsequent catalytic dehydrogenation to get mukonine (route B: three steps, 17\% overall yield) (Scheme VI).

Kuwahara et al.\textsuperscript{40} synthesized mukonine via the double \textit{N}-arylation starting from methyl vanillate and the pinacol ester of 2-hydroxyphenylboronic acid. Bromination of methyl vanillate followed by the Suzuki-Miyaura coupling with the pinacol ester of 2-hydroxyphenylboronic acid gave biphenyldiol. Biphenyldiol was converted to the corresponding ditriflate, which was subjected to the double \textit{N}-arylation with \textit{o}-tert-butyl carbamate. Using xantphos as the ligand, the desired product was obtained in 70\% yield, which was then deprotected using TFA to get mukonine quantitatively (Scheme VII).
Liu et al.\textsuperscript{41} prepared mukonine in three steps from commercially available 4-amino-3-methoxybenzoic acid. 3-Methoxy-4-amino benzoic acid was reacted with methanol to afford methyl 3-methoxy-4-aminobenzoate in 98% yield. Iodination using ICI in dichloromethane afforded methyl 4-amino-3-iodo-5-methoxybenzoate in 82% yield. Methyl 4-amino-3-iodo-5-methoxybenzoate was allowed to react with silylaryltriflate and CsF at room temperature in acetonitrile. Then Pd(OAc)\textsubscript{2} and PCy\textsubscript{3} were added and the reaction was heated to 100 °C for 12 hr under argon to get mukonine (Scheme VIII).
Scheme VIII
Present Work

Our continued interest in the application of Wittig reaction prompted us to investigate the usage of phosphorane chemistry towards the synthesis of carbazole alkaloid mukonine 6. The essential elements of our simple approach to the mukonine ring system is shown in Scheme IX.

As depicted in Scheme IX, first is preparation of homoskatolidene phosphorane 12. This preparation of homoskatolidene phosphorane 12 by alkylation of stable carboethoxymethylene triphenyl phosphorane 10 is reported in literature. In the next step, glyoxylic acid (13) on condensation with homoskatolidene phosphorane 12 could give the product 14 having both the acid and the ester group. Subsequent cyclisation of this product 14 with sodium acetate in acetic anhydride could give the
carbazole framework (15). Subsequent methanolysis and o-methylation with dimethyl sulphate in acetone could give the target molecule mukonine (6).

Accordingly, we started with the synthesis. The homoskatolidene phosphorane 12 was prepared in two steps. The first step was preparation of stable carboethoxymethylenetriphenyl phosphorane 10 which is already been discussed in chapter 1. In the second step, this stable phosphorane 10 was alkylated with gramine (11) in toluene under nitrogen atmosphere to get white solid of homoskatolidene phosphorane 12 in 93% yield (Scheme X).

![Scheme X](image)

The homoskatolidene phosphorane 12 was then refluxed with 50% aqueous solution of glyoxylic acid (13) in methanol for 10.0 hrs (Scheme XI).

![Scheme XI](image)

TLC of the reaction mixture showed appearance of new spot along with triphenylphosphine oxide spot. The solvent was evaporated followed by the corresponding workup for acid. The crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to obtain a white solid.
Its IR spectrum showed two strong bands one at $\delta$ 1681 cm$^{-1}$ and another at $\delta$ 1724 cm$^{-1}$ indicating the presence of two carbonyl groups. The broad band due to hydroxyl group of acid was observed at 3053 cm$^{-1}$. In addition to this, the absorption due to N-H bond of indole ring was observed at 3394 cm$^{-1}$.

The $^1$H-NMR spectrum (CDCl$_3$, 300 MHz, $\delta$ ppm) (Fig. I) showed signals at $\delta$ 1.24 (t, $J$ = 7.2 Hz, 3H) and $\delta$ 4.20 (q, $J$ = 7.2 Hz, 2H) which was attributed to -OCH$_2$CH$_3$ group of ester moiety. The peak observed at $\delta$ 4.38 (s, 2H) was due to -CH$_2$- attached to the third position of indole ring. The vinylic proton was observed at $\delta$ 7.05 (s, 1H). The downfield shift of this proton indicated it to be cis to the -COOCH$_2$CH$_3$ group ($E$ geometry). Peaks due to aromatic protons were observed at $\delta$ 6.82 (s, 1H), $\delta$ 7.12 (t, $J$ = 7.2 Hz, 1H), $\delta$ 7.19 (t, $J$ = 6.9 Hz, 1H), $\delta$ 7.33 (d, $J$ = 7.8 Hz, 1H), $\delta$ 7.72 (d, $J$ = 7.5 Hz, 1H) and proton attached to nitrogen was observed at $\delta$ 8.03 (br.s., 1H).

Fig. I: $^1$H-NMR spectrum of Compound 14
The $^{13}C$-NMR spectrum (CDCl$_3$, 75 MHz, δ ppm) (Fig. II) spectrum showed peaks at δ 13.96 (CH$_3$), δ 29.66 (CH$_2$), δ 61.74 (OCH$_2$), δ 109.96 (C), δ 113.57 (CH), δ 119.68 (CH), δ 120.47 (CH), δ 122.63 (CH), δ 124.76 (2 X CH), δ 128.70 (C), δ 136.03 (C), δ 148.62 (C), δ 166.60 (C=O), δ 166.98 (C=O).

![Fig. II: $^{13}C$-NMR spectrum of Compound 14](image)

The high resolution mass spectrum of the compound displayed strong peak at $m/z$ 296.0887 presumably due to [M+Na]$^+$ pseudo ions. The elemental composition of which was determined to be C$_{15}$H$_{15}$NO$_4$. HRMS $m/z$ calculated for C$_{15}$H$_{15}$NO$_4$ Na [(M+Na)$^+$] was 296.0899, found : 296.0887. The melting point of this compound was found to be 108-111 °C.
Hence, based on the mode of formation and spectral data, compound 14 was confirmed to be the predicted one. The yield of the product was found to be 80%.

Our next aim was to carry out the cyclisation to get the carbazole framework Scheme XII.

\[
\begin{align*}
\text{Scheme XII} \\
\text{To achieve this we refluxed compound 14 with sodium acetate in acetic anhydride for 24 hrs, after which there was seen disappearance of the starting materials on TLC. Evaporation of the solvent followed by column chromatographic purification over silica gel using hexanes:ethyl acetate(7:3) as an eluent furnished a white solid.}
\end{align*}
\]

The IR spectrum of this compound showed absence of band due to N-H stretching and presence of three bands at 1712 cm\(^{-1}\), 1718 cm\(^{-1}\) and 1774 cm\(^{-1}\) indicating the presence of three carbonyl groups.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. III) showed signals at \(\delta\) 1.38 (t, \(J = 7.2\) Hz, 3H) and \(\delta\) 4.40 (q, \(J = 7.2\) Hz, 2H) which was due to -OCH\(_2\)CH\(_3\) group of ester moiety. The peak observed at \(\delta\) 2.38 (s, 3H) was attributed to -CH\(_3\) group of -OAc moiety, and another peak at \(\delta\) 2.80 (s, 3H) was attributed to -CH\(_3\) group of -NAc moiety. The signals due to remaining aromatic protons were observed at \(\delta\) 7.46 (t, \(J = 7.2\) Hz, 1H, H-6), \(\delta\) 7.60 (t, \(J = 7.2\) Hz, 1H, H-7), \(\delta\) 7.85 (s, 1H, H-2), \(\delta\) 8.00 (d, \(J = 8.4\) Hz, 1H, H-8), \(\delta\) 8.38 (d, \(J = 7.8\) Hz, 1H, H-5), \(\delta\) 8.70 (s, 1H, H-4).
Fig. III: $^1$H-NMR spectrum of Compound 15

The $^{13}$C-NMR spectrum (DMSO-d6, 75 MHz, δ ppm) spectrum (Fig. IV) showed peaks at δ 14.67, δ 21.16, δ 27.15, δ 61.51, δ 114.84, δ 119.38, δ 121.55, δ 122.99, δ 124.16, δ 124.74, δ 126.32, δ 128.92, δ 129.07, δ 133.20, δ 137.87, δ 139.27, δ 165.46, δ 168.67, δ 170.91.
The high resolution mass spectrum of this compound displayed strong peak at $m/z$ 362.1003 presumably due to [M+Na]$^+$ pseudo ions. The elemental composition of which was determined to be C$_{19}$H$_{17}$NO$_5$. HRMS $m/z$ calculated for C$_{19}$H$_{17}$NO$_5$Na[( M + Na)$^+$] was 362.1004, found : 362.1003.

The melting point of the compound was found to be 118-121 °C.

Hence, based on the mode of formation and spectral data structure (15) was assigned to the compound. The yield of the product was found to be 65%.
Now, as we obtained the required moeity in hand, there was a need to knock off both the acetyl groups followed by hydrolysis of ester to get the acid which is our next target compound. Hence, the compound 15 was refluxed with NaOH in methanol for 2 hrs (Scheme XIII).

Scheme XIII

TLC indicated disappearance of starting material and appearance of a new spot. The reaction was neutralized with 1:1 HCl solution. It was then extracted in diethyl ether. The solvent was evaporated followed by column chromatographic purification over silica gel using hexanes:ethyl acetate (8:2) as an eluent to obtain a white solid.

This solid in its IR spectrum showed strong peaks at 3350 cm\(^{-1}\) and 3300 cm\(^{-1}\) due to N-H stretching and O-H stretching, and peak at 1653 cm\(^{-1}\) indicating the presence of carbonyl group.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, δ ppm) (Fig. V) showed signals at δ 1.48 (t, \(J = 7.2\) Hz, 3H) and δ 4.47 (q, \(J = 7.2\) Hz, 2H) which was due to presence of -CH\(_2\)CH\(_3\) group of ester moiety, which indicated that the ester group did not hydrolyse to acid. Another broad signal was observed at δ 6.17 (br.s., 1H) indicating the presence of -OH group. The aromatic protons were observed at δ 7.30 (t, \(J = 7.8\) Hz, 1H, H-6), δ 7.46-δ 7.50 (m, 2H, H-7 & H-8), δ 7.72 (s, 1H, H-2), δ 8.13 (d, \(J = 7.8\) Hz, 1H, H-3).
Hz, 1H, H-5), δ 8.47 (s, 1H, H-4) and signal due to proton on nitrogen was observed at δ 8.54 (br.s., 1H, NH).

Fig. V: $^1$H-NMR spectrum of Compound 17

The high resolution mass spectrum of this compound displayed a strong peak at m/z 278.0792 presumably due to [M+Na]$^+$ pseudo ions. The elemental composition of which was determined to be C$_{15}$H$_{13}$NO$_3$. HRMS m/z calculated for C$_{15}$H$_{13}$NO$_3$Na[(M+Na)$^+$] was 278.0793, found:278.0792.

The melting point of the compound was found to be 165-167 °C.

Hence, based on the mode of formation and spectral data, the compound should have structure 17. The yield of the product was found to be 98%.
Hence, we succeeded to knock off both the acetyl groups but failed to hydrolyse the ester. In order to achieve both our aims, i.e. to knock off the acetyl groups as well as to hydrolyse the ester we thought to reflux the reaction mixture for longer duration (Scheme XIV).

The compound 15 was refluxed with NaOH in methanol for 4 hrs. TLC of the reaction mixture showed disappearance of both, the starting compound 15 as well as the compound 17, and there was seen one new spot on TLC. The reaction was neutralized with 1:1 HCl solution. It was then extracted in diethyl ether. The solvent was evaporated and the residue obtained was analyzed by IR spectroscopic technique, as it was difficult to purify this residue.

The IR spectrum of this residue showed strong band at 1703 cm\(^{-1}\) due to carbonyl group of acid moiety. The broad band was observed at 3250 cm\(^{-1}\) due to hydroxyl group.

The high resolution mass spectrum of this residue displayed strong peak at \(m/z\) 250.0454 presumably due to \([M+Na]^+\) pseudo ions. The elemental composition of which was determined to be \(C_{13}H_{19}NO_3\). HRMS \(m/z\) calculated for \(C_{13}H_{19}NO_3Na[(M+Na)^+]\) was 250.0480, found:250.0454.
Hence, based on the mode of formation and above spectral data formation of compound 16 was confirmed.

\[
\begin{align*}
&\text{COOH} \\
&\text{H} \\
&\text{OH} \\
&\text{16}
\end{align*}
\]

To get our target molecule mukonine, the crude compound 16 without further purification (as it was difficult to purify) was treated with \( \text{K}_2\text{CO}_3 \) and dimethyl sulphate in dry acetone (Scheme XV).

\[
\begin{align*}
\text{N} & \text{H} \\
\text{COOH} \\
\text{OH} \\
\text{16}
\end{align*}
\]

\[
\begin{align*}
\text{COOCH}_3 \\
\text{OCH}_3 \\
\text{DMS} \\
\text{Acetone} \\
\text{K}_2\text{CO}_3 \\
\text{Acetone}
\end{align*}
\]

\[
\begin{align*}
&\text{COOCH}_3 \\
&\text{OCH}_3 \\
&\text{DMS} \\
&\text{K}_2\text{CO}_3 \\
&\text{Acetone}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{H} \\
\text{COOCH}_3 \\
\text{OCH}_3 \\
\text{DMS} \\
\text{K}_2\text{CO}_3 \\
\text{Acetone}
\end{align*}
\]

\[
\begin{align*}
&\text{COOCH}_3 \\
&\text{OCH}_3 \\
\text{DMS} \\
\text{K}_2\text{CO}_3 \\
\text{Acetone}
\end{align*}
\]

**Scheme XV**

The reaction mixture was refluxed for 8 hrs, after which there was seen appearance of a new spot on TLC. The solvent was evaporated and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to obtain a white solid.
The IR spectrum of this compound showed presence of a band at 1697 cm\(^{-1}\), which was attributed to the presence of the carbonyl group of ester. There was seen disappearance of N-H and O-H peaks.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. VI) showed signals at \(\delta\) 3.99 (s, 3H), \(\delta\) 4.07 (s, 3H) and \(\delta\) 4.22 (s, 3H) which were attributed to -NCH\(_3\), -OCH\(_3\) and -COOCH\(_3\) group. Aromatic protons were observed at \(\delta\) 7.30-\(\delta\) 7.57 (m, 3H, H-6, H-7, H-8), \(\delta\) 7.61 (s, 1H, H-2), \(\delta\) 8.12 (d, \(J\) = 8.1 Hz, 1H, H-5), \(\delta\) 8.49 (s, 1H, H-4).

![Fig. VI: \(^1\)H-NMR spectrum of Compound 18](image)

The high resolution mass spectrum of this compound displayed strong peak at \(m/z\) 292.0947, presumably due to [M+Na]\(^+\) pseudo ions. The elemental composition of which was determined to be C\(_{16}\)H\(_{15}\)NO\(_3\), HRMS \(m/z\) calculated for C\(_{16}\)H\(_{15}\)NO\(_3\)Na[(M+Na)]\(^+\): 292.0950, found: 292.0947.

The melting point of the compound was found to be 122-125 °C.
Hence, based on the mode of formation and above spectral data the formation of N-methylated compound 18 was confirmed. The yield of the product was found to be 58%.

Since, we did not succeed to get the mukonine molecule in hand, we thought of an alternate approach for it. The crude compound 16 was refluxed with a few drops of sulphuric acid in methanol for 10.0 hrs (Scheme XVI).

The solvent was evaporated and the residue obtained was dissolved in ether. The ether layer was dried over sodium sulphate, ether was evaporated and the residue was purified by column chromatography over silica gel using hexanes:ethyl acetate (9:1) as an eluent to get a white solid. In IR spectrum of this compound there was seen a strong band at 1703 cm\(^{-1}\) indicating the presence of carbonyl group of ester. There was also seen a strong band at 3392 cm\(^{-1}\) due to N-H stretching.
The $^1$H-NMR spectrum (CDCl$_3$, 300 MHz, δ ppm) (Fig. VII) showed signals at δ 3.51 (s, 3H) and δ 3.98 (s, 3H) which was attributed to -OCH$_3$ and -COOCH$_3$ group. Aromatic protons were observed at δ 7.28-7.50 (m, 3H, H-6, H-7 & H-8), δ 7.62 (s, 1H, H-2), δ 8.11 (d, $J = 7.5$ Hz, 1H, H-5), δ 8.45 (s, 1H, H-4) and signal due to proton on nitrogen was observed at δ 8.68 (br.s., 1H, NH).

Fig. VII : $^1$H-NMR spectrum of Compound 6

The melting point of the compound was found to be 198-200°C.

Hence, based on the above spectral data, structure 6 was assigned to the product. The yield of the product was found to be 41%.
This completed the synthesis of carbazole alkaloid mukonine (6), which also constitute the formal synthesis of alkaloids murrayanine (2), mukoeic acid (3), murrayafoline A (4) and koenoline (5).
Conclusion

We have developed a convenient synthesis of carbazole alkaloid mukonine using Wittig reaction and cyclisation with sodium acetate in acetic anhydride as key steps.
Experimental

3.1 Preparation of Triphenyl-α-ethoxycarbonylhomoskatolidene phosphorane (12)

A solution of gramine (11) (2.5 g, 0.014 moles) in toluene (20 mL) was added to a solution of carboethoxymethylenetriphenyl phosphorane (10) (5.0 g, 0.014 moles) in toluene (50 mL). The reaction mixture was refluxed for 12 hrs under nitrogen atmosphere. The mixture was chilled, the precipitate was filtered off and consecutively washed with cold toluene and petroleum ether. It was recrystallized from ethyl acetate to get the white solid of triphenyl-α-ethoxycarbonylhomoskatolidene phosphorane 12 (6.37 g, 93%); m.p. 189-190 °C.

3.2 Preparation of (2E)-4-Ethoxy-3-(1H-indol-3-ylmethyl)-4-oxobut-2-enoic acid (14)

A mixture of glyoxylic acid (50% solution in water) (3.19 g, 0.022 moles), homoskatolidene phosphorane (6.85 g, 0.014 moles) was refluxed in methanol (25 mL) for 10.0 hrs. Methanol was evaporated, and the residue was dissolved in ethyl acetate (30 mL). The ethyl acetate layer was extracted with sat. sodium carbonate (3 X 30 mL). The sodium carbonate extract was then cooled, acidified using 1:1 HCl solution to pH- 2-3 and extracted with diethyl ether (3 X 30 mL). The diethyl ether
layer was dried over anhydrous sodium sulphate, the solvent was evaporated and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to furnish a white solid (14) (3.13 g, 80%); m.p. 108-111 °C.

3.3 Preparation of 1-Acetoxy-9-acetyl-3-ethoxycarbonylcarbazole (15)

\[
\begin{align*}
\text{14} & \xrightarrow{\text{NaOAc, Ac}_2\text{O}} \text{15} \\
\end{align*}
\]

The compound 14 (2.5 g, 9.15 mmol) was refluxed with sodium acetate (1.62 g, 20 mmol) in acetic anhydride (33 mL) for 24.0 hrs. The acetic anhydride was removed under vacuum pump and purification of the remaining residue by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent gave a white solid (15) (2.0 g, 65%); m.p. 118-121 °C.

3.4 Preparation of Ethyl 1-hydroxy-9H-carbazole-3-carboxylate (16)

\[
\begin{align*}
\text{15} & \xrightarrow{\text{NaOH, MeOH, Reflux, 2 hrs}} \text{17} \\
\end{align*}
\]

A mixture of compound 15 (0.64 g, 1.89 mmol) in methanol (8 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 2 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained was purified by column chromatography over silica gel using
hexanes:EtOAc (8:2) as an eluent to get a white solid (17) (0.47 g, 98%); m.p. 165-167 °C.

3.5 Preparation of Methyl 1-methoxy-9-methyl-9H-carbazole-3-carboxylate (18)

\[
\begin{align*}
\text{15} & \quad \text{COOEt} \\
\text{COCH}_3 \\
\text{NaOH} & \quad \text{MeOH} \\
\text{Reflux, 4 hr} \\
\text{16} & \quad \text{COOH} \\
\text{OH} \\
\text{17} & \quad \text{K}_2\text{CO}_3 \\
\text{DMS} & \quad \text{acetone} \\
\text{18} & \quad \text{COOCH}_3 \\
\text{OCH}_3 \\
\end{align*}
\]

A mixture of compound 15 (0.5 g, 1.47 mmol) in methanol (6 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 4 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained without further purification was dissolved in dry acetone (6 mL) and to it K\textsubscript{2}CO\textsubscript{3} (0.2 g, 1.47 mmol) and dimethylsulphate (0.19 g, 1.47 mmol) were added. The reaction mixture was refluxed for 8.0 h and solvent was evaporated to dryness. The residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to afford a white solid (18) (0.22 g, 58%); m.p. 122-125 °C.
3.6 Preparation of Methyl 1-methoxy-9\textit{H}-carbazole-3-carboxylate (6)

A mixture of compound 15 (0.5 g, 1.47 mmol) in methanol (6 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 4 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained without further purification was refluxed with conc. H\textsubscript{2}SO\textsubscript{4} (1 mL) in methanol (10 mL) for 10.0 hrs. The solvent was evaporated under vacuum, and the residue obtained was dissolved in ether (10 mL). The ether layer was dried over sodium sulphate, ether was evaporated and the residue obtained was purified by column chromatography over silica gel using hexanes: EtOAc (9:1) as an eluent to get a white solid (6) (0.23 g, 41%); m.p. 198-200 °C.
References

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CHAPTER 3
Section B
**CHAPTER 3**

**SECTION B**

An unusual synthesis of indole 2-carboxylates

**Introduction**

Indoles are known to possess various biological properties including antibacterial, cytotoxic, antioxidative and insecticidal activities.\(^1\) Some indole derivatives are used as antibiotics in pharmaceuticals.\(^1b\) The preparation of different indole compounds and evaluation of their bioactivity is of great interest. We have attempted the synthesis of 2-prenyl indole and 2,3’-bis(indolyl)methane derivative in this section which eventually lead to the synthesis of ethyl indole 2-carboxylates. These ethyl indole-2-carboxylates are valuable starting materials for the synthesis of various alkaloids,\(^2\) heterocyclic compounds\(^3\) and biologically active compounds.\(^4\)

The chemistry of indole is dominated by electrophilic substitution reaction. The heterocyclic ring of indole is very electron rich in comparison with its benzene counterpart, hence, there is a strong preference for electrophilic substitution in the 5-membered ring. Attack on the nitrogen would destroy the aromaticity of pyrrole ring, hence the two other positions C-2 and C-3 are only the alternatives. When considering the stability of the two generalised cations, A and B, it is realised that the intermediate B cannot derive further resonance stabilisation without disrupting the aromatic ring, whereas A can derive contribution from the lone pair of nitrogen (Fig. 1). Due to the higher resonance stabilization of Wheland intermediate A the preference for electrophilic position is at 3-position rather than at 2-position.

![Fig. 1](image-url)
I) An attempt towards the synthesis of 2,3’-bis(indolyl)methane (BIM):

Introduction

The indole unit forms the basis for general BIM structures. BIMs are molecules containing two indolyl moieties connected to the same carbon atom (Fig. 2).

Bis(indolyl)methanes and their derivatives are known to be important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties. Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism, and induce apoptosis in human cancer cells. Therefore, there is great interest in the synthesis of these compounds. The indole ring is more reactive at 3-position, and therefore the majority of BIMs found in literature are 3,3’-BIMs.
A Literature Review

Usually the synthesis of 2,3’-BIMs is quite difficult due to the higher reactivity of the indole ring at position 3 as discussed before, and controlling this is not possible. To overcome the lack of nucleophilic reactivity at position 2 of the indole ring a completely different mechanism is required.

Some of the recent methods for the synthesis of 2,3’-BIMs are mentioned below –

Jackson et al.\textsuperscript{8} prepared 2,3’-bisindolyl methane derivative from indoline-2,3-dione. The ring-opening of isatin undergoing alkaline hydrolysis in DMSO produced the amine. Reaction of the amine with 2-chloro-1-(1\textit{H}-indol-3-yl)-ethanone followed by ring closure and ring opening yielded the corresponding methanone. Reduction of this methanone with LAH produced the 2,3’-bisindolyl methane derivative (Scheme I).

\begin{center}
\textbf{Scheme I}
\end{center}
Murakami et al.\textsuperscript{9} treated indole with PTSA in benzene to afford 2,3’-bisindolyl methane derivative (Scheme II).

\textbf{Scheme II}

Rossi et al.\textsuperscript{10} have reacted lithium derivative of 3-iodo-1-(phenylsulphonyl)-1\textit{H}-indole with 1-methoxymethyl-1\textit{H}-indole-3-carbaldehyde to get the corresponding alcohol which was then oxidised with active manganese dioxide to (1-benzenesulfonyl-3-iodo-1\textit{H}-indol-2-yl)(1-methoxymethyl-1\textit{H}-indol-3-yl)methanone (Scheme III).

\textbf{Scheme III}
Harigaya et al.\textsuperscript{11} reacted 3-methylindole with \textit{ortho}- or \textit{meta}-nitrobenzaldehyde in presence of Montmorillonite K-10 clay to yield 2,3’- and also 2,2’-bisindolyl methane derivatives (\textbf{Scheme IV}).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_IV.png}
\end{center}

\textbf{Scheme IV}

Bergman et al.\textsuperscript{12} have provided three different routes for the synthesis of 2,3’-BIMs as depicted in \textbf{Scheme V}. In the first route, Lewis acid-assisted acylation of the substituted indoles is used to produce the corresponding ketones, followed by reduction with LAH to yield corresponding 2,3’-BIM.

In the second approach, position 2 of \textit{N}-protected indole is lithiated, followed by reaction with 1-benzenesulfonylindole-3-carboxaldehydes to give the alcohol; the latter in turn was reduced to 2,3’- bisindolyl methane derivative.

In the third route, the indole derivative was treated with LDA in THF followed by addition of 1-benzenesulfonylindole-3-carboxaldehydes the alcohol, obtained was then reduced with LAH yielding corresponding 2,3’- bisindolyl methane derivative.\textsuperscript{13}
Giannini et al.\textsuperscript{14} have reported the synthesis of 2,3'-bisindolyl methane derivative by treating indole and 5-hydroxy-pentanal in methanolic hydrochloric acid (Scheme VI).

Gu et al.\textsuperscript{15} condensed indole and aldehyde in presence of iodine in acetonitrile at room temperature to afford 3,3'-bisindolyl methane derivative which after isomerisation gave 2,3'-bisindolyl methane derivative (Scheme VII).
Scheme VII
**Present Work**

Our aim was to synthesize 2,3’-bisindolyl methane derivative having structure 1 which could be tested for its biological activity. Again we were interested to use phosphorane chemistry for this purpose.

![Chemical structure of 1](image)

The methodology envisaged by us (Scheme VIII) is based on the literature method reported to synthesize 2-vinyl indoles. The steps involved are Wittig reaction followed by reductive cyclisation.

![Scheme VIII](image)

**Scheme VIII**

The first step in our projected synthesis was Wittig reaction of o-nitrobenzaldehyde (2) with homoskatolidene phosphorane (3) (Scheme IX).
Scheme IX

The preparation of homoskatolidene phosphorane (3) is discussed in section 1 of this chapter. This homoskatolidene phosphorane (3) was refluxed with o-nitrobenzaldehyde (2) in chloroform for 2.5 hrs. TLC of the reaction mixture showed the dissappearance of the aldehyde and apperance of new spot along with triphenyl phosphine oxide. The crude product was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a yellow viscous liquid.

The IR spectrum of the compound exhibited strong band at 3412 cm\(^{-1}\) which was due to N-H stretching of indole ring structure. Strong band at 1714 cm\(^{-1}\) was due to carbonyl bond of \(\alpha,\beta\)-unsaturated ester moiety.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. I) showed peaks at \(\delta\) 1.28 (t, \(J = 6.9\) Hz, 3H) and \(\delta\) 4.27 (q, \(J = 6.9\) Hz, 2H) were attributed to the ester group (\(-\text{OCH}_2\text{CH}_3\)). The peaks observed at \(\delta\) 3.83 (s, 2H) was attributed to methylene group attached to third position of indole ring. Signal at \(\delta\) 6.91 (s, 1H) was assigned to proton on 2-position of indole ring. The remaining aromatic protons were observed at \(\delta\) 7.08 (t, \(J = 6.9\) Hz, 1H), \(\delta\) 7.19 (t, \(J = 7.2\) Hz, 1H), \(\delta\) 7.34 (d, \(J = 8.1\) Hz, 1H), \(\delta\) 7.42 (t, \(J = 7.5\) Hz, 1H), \(\delta\) 7.44- \(\delta\) 7.56 (m, 3H) and \(\delta\) 8.13 (d, \(J = 7.8\) Hz, 1H). The broad signal at \(\delta\) 7.97 (br.s., 1H) was attributed to the proton on nitrogen of indole ring. While the signal exhibited at \(\delta\) 8.07 (s, 1H) was assigned to the benzylic proton. The downfield shift of this proton indicated it to be \textit{cis} to the \(-\text{COOEt}\) group (\(E\) geometry).
Fig. I: $^1$H-NMR spectrum of Compound 4

$^{13}$C-NMR spectrum (CDCl$_3$, 75 MHz, δ ppm) (Fig. II) showed peaks at δ 14.18 (CH$_3$), 23.52 (CH$_2$), 61.19 (OCH$_2$), 111.11 (CH), 113.76 (C), 118.62 (CH), 119.23 (CH), 121.76 (CH), 122.07 (CH), 124.82 (CH), 126.95 (C), 129.09 (CH), 130.95 (CH), 131.67 (C), 133.34 (C), 133.47 (CH), 136.08 (CH), 136.27 (C), 147.68 (C), 167.71 (C=O).
Based on the mode of formation and above spectral data structure 4 was assigned to the product formed. The yield of the product was found to be 93%.

In the next step compound 4 was refluxed with triphenyl phosphine in diphenyl ether for 5.0 hrs (Scheme X), after which there was seen dissappearance of compound 4 on TLC and appearence of a new spot.
The crude product was then purified by column chromatography over silica gel using hexanes-EtOAc (8:2) as an eluent to get a white solid.

The IR spectrum of the compound exhibited strong band at 3311 cm\(^{-1}\) which was due to N-H stretching of indole ring moiety. Strong band at 1693 cm\(^{-1}\) was due to carbonyl group of ethyl ester.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. III) showed peaks at \(\delta\) 1.44 (t, \(J = 7.2\) Hz, 3H) and \(\delta\) 4.44 (q, \(J = 7.2\) Hz, 2H) which was attributed to the ester group -OCH\(_2\)CH\(_3\). The aromatic protons were observed at \(\delta\) 7.18 (t, \(J = 7.2\) Hz, 1H), \(\delta\) 7.26 (s, 1H), \(\delta\) 7.35 (t, \(J = 7.5\) Hz, 1H), \(\delta\) 7.45 (d, \(J = 8.4\) Hz, 1H) and 7.72 (d, \(J = 7.8\) Hz, 1H). The peak observed at \(\delta\) 8.92 (br.s., 1H) was attributed to the proton on nitrogen of indole structure.
Looking at the above spectral data, it is confirmed that we could not synthesize the expected 3,3’-BIM molecule, but the product which actually we got in our hand was ethyl indole-2-carboxylate (5). It was further confirmed by its similarity with lit.\textsuperscript{16} m.p. 110-112 °C, found 109-111 °C. The yield of the product was found to be 35%.

A probable mechanism is postulated for this unusual formation of ethyl indole-2-carboxylate is depicted in Scheme XI. However, we did not isolated 3-methyl indole probably due to its oligomerisation under the reaction conditions.
Scheme XI
Conclusion

An unsuccessful attempt has been made to synthesize 2,3’-BIM molecule, actually leading to the synthesis of ethyl indole-3-carboxylates. A probable mechanism for its formation is also postulated.
Experimental

3.7 Preparation of Compound 4

A solution of o-nitrobenzaldehyde (2) (0.302 g, 2 mmol) and homoskatolidene phosphorane (3) (0.954 g, 2 mmol) in chloroform (15 mL) was refluxed for 2.5 hrs. The TLC of reaction mixture showed appearance of a new spot. 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 yellow viscous liquid (4) (0.651 g, 93%).

3.8 Preparation of Ethyl indole-3-carboxylate (5)

A mixture of compound 4 (0.350 g, 1 mmol) and triphenyl phosphine (0.524 g, 2.0 mmol) in diphenyl ether (10 mL) was heated under reflux for 5.0 hrs. The progress of the reaction was monitored by TLC. Diphenyl ether was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give solid ethyl indole-2-carboxylate (5) (0.066 g, 35%), m.p. 109-111 °C.
References


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II) An attempt towards the synthesis of 2-prenyl indole:

Introduction

Prenylated indole alkaloids are hybrid natural products containing indole/indoline and isoprenoid moieties or structures derived thereof. They are widely distributed in terrestrial and marine organisms, especially in the genera *Penicillium* and *Aspergillus* of ascomycota, and display broad structure diversity. These compounds often carry biological and pharmacological activities distinct from their non-prenylated aromatic precursors.1–3

In the structures of prenylated indole alkaloids, the prenyl moieties can be connected via its C-1 or C-3 to an aromatic nucleus which are referred to as regular or reverse prenyl moieties respectively (Fig. 1).

![Fig. 1](image)

These are some of the prenylated indole alkaloids having $\gamma,\gamma$-dimethyl allyl and $\alpha,\alpha$-dimethyl allyl system attached to C-2 of indole ring (Fig. 2).
In order to lay groundwork for the synthesis of these complex prenylated indole alkaloids, an attempt was made to synthesise the α-prenyl indole nucleus.
A Literature Review

Usually the regiospecific metallation of \( N \)-protected indoles is exploited for the synthesis of 2-substituted indoles. Nitrogen-protected 2-lithioindoles have been widely used in synthesis since the pioneering work of Sundberg and Russel,\(^5\) with phenylsulfonfyl protecting group.\(^6\) From \( N \)-protected indoles, deprotonation (lithiation) can be effected at C-2, which can result in various C-2 substituted indoles that subsequently act as precursors in the synthesis of biological active compounds.

Thus, 1-(phenylsulfonyl)indole is prepared from indole with \( n \)-butyllithium and benzenesulfonyl chloride. This is then lithiated at C-2 with lithium diisopropylamide (LDA), and the resulting 2-lithiospecies treated with various electrophiles to afford C-2 substituted indoles\(^7\) (Scheme I).

![Scheme I](image)

Swindell et al.\(^8\) metalated \( N \)-(benzene-sulfonyl) indole with lithium diisopropylamide. The resultant \( \alpha \)-lithio compound was treated with prenyl bromide to get the \( \alpha \)-prenylated derivative which was then reduced with sodium amalgam to liberate \( \alpha \)-prenyl indole (Scheme II).
Stanovnik et al.\textsuperscript{9} modified the procedure of Swindell et al.\textsuperscript{8}, wherein instead of benzene sulfonyl protecting group, they used tosyl protecting group. The protecting group was knocked off by magnesium powder in methanol under ultrasonic condition (Scheme III).

Danishefsky et al.\textsuperscript{10} treated the solution of 3-chloroindolenine in dichloromethane with stannane in presence of 2 equiv. of BCl\textsubscript{3} at -78\degree\textsuperscript{C} to get the $\alpha$-prenylated indole derivative (Scheme IV).
Stanovnik et al.\textsuperscript{11} prepared $\alpha$-isoprenylindole using 9-BBN. They converted 9-BBN first to 9-(3-methylbut-2-enyl)-9-borabicyclo[3.3.1]nonane using 3-methylbuta-1,2-diene in THF at room temperature. This was then reacted with 3-chloroindole in THF in presence of triethyl amine at room temperature (Scheme V).
Prabakar et al.\textsuperscript{12} started their synthesis from $N^a$-acetyltryptamine. They converted first it to a $N^a$-prenyl-$N^b$-acetyl tryptamine derivative with prenyl bromide in presence of NaH in DMF. Further, the $N^a$-prenylated derivative was treated with BF$_3$.Et$_2$O at $-4\,^\circ\text{C}$ for 18 hrs. to yield 2-prenylated tryptamine nucleus (Scheme VI).

Scheme VI
Present Work

Most of the reported methods for the synthesis of α-prenyl indole make use of preformed indoles, however we have attempted the synthesis which need not require preformed indoles. Our intention was to prepare α-prenyl indole derivative having structure 1 which could be further converted to bioactive prenylated indole alkaloids having complex structural framework.

The methodology envisaged by us (Scheme VII) is based on the literature method reported to synthesise 2-vinyl indoles\(^{13}\) wherein the steps involved are Wittig reaction and reductive cyclisation.

Scheme VII

The Wittig reaction of 3,4-methylenedioxy benzaldehyde (2) with prenyl phosphorane (3) was performed in refluxing chloroform for 3.0 hrs to get the α,β-unsaturated ester 4 (Scheme VIII). This α,β-unsaturated ester 4 is synthesised and characterised in Chapter 2.
As per planned methodology compound 4 was then refluxed with triphenyl phosphine in diphenyl ether for 4.0 hrs, after which there was seen dissappearance of compound 4 on TLC and appearence of new spot (Scheme IX).

The crude product was then purified by column chromatography over silica gel using hexanes-EtOAc (8:2) as an eluent to get the white solid.

The IR spectrum of the compound exhibited strong band at 3307 cm\(^{-1}\) which was due to N-H stretching of indole ring moiety. Strong band at 1687 cm\(^{-1}\) was due to carbonyl group of ethyl ester.

The \(^1\)H-NMR spectrum (CDCl\(_3\), 300 MHz, \(\delta\) ppm) (Fig. I) showed peaks at \(\delta\) 1.41 (t, \(J = 7.2\) Hz, 3H) and \(\delta\) 4.39 (q, \(J = 7.2\) Hz, 2H) which was attributed to the ester group -OCH\(_2\)CH\(_3\). The signal due to methylene proton was observed at \(\delta\) 5.99 (s, 2H). The aromatic protons were observed at \(\delta\) 6.84 (s, 1H), \(\delta\) 7.01 (s, 1H) and \(\delta\) 7.12 (s, 1H). The peak observed at \(\delta\) 8.79 (br.s., 1H) was attributed to the proton on nitrogen of indole ring structure.
Looking at the above spectral data, we can say that we failed to synthesize the expected α-prenyl indole nucleus, but the product formed was ethyl-5,6-methylenedioxyindole-2-carboxylate (5). It was further confirmed by its similarity with lit.\textsuperscript{14} m.p. 175-178 °C, found 174-176 °C. The yield of the product was found to be 32%.

A probable mechanism is postulated for this unusual formation of ethyl-5,6-methylenedioxyindole-2-carboxylate (5) is depicted in Scheme X.
Scheme X
Experimental

3.9 Preparation of Compound 4

\[ \text{NO}_2 \text{CHO} + \text{EtOOCC} + \text{PPh}_3 \xrightarrow{\text{Reflux}} \text{COOEt} \]

Please refer Chapter 2, Expt. No. 2.3.

3.10 Preparation of Ethyl-5,6-methylenedioxyindole-2-carboxylate (5)

\[ \text{COOEt} + \text{Ph}_2 \text{O, Reflux} \]

A mixture of compound 4 (0.333 g, 1 mmol) and triphenyl phosphine (0.524 g, 2.0 mmol) in diphenyl ether (10 mL) was heated under reflux for 4.0 hrs. The progress of the reaction was monitored by TLC. Diphenyl ether was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give ethyl-5,6-methylenedioxyindole-2-carboxylate (5) (0.075 g, 32%), m.p. 174-176 °C.
Conclusion

An attempt has been made to synthesise α-prenyl indole nucleus, which actually lead to the synthesis of ethyl-5,6-methylenedioxyindole-2-carboxylate.
References