CHAPTER – II

A. DISCUSSION OF THE EXPERIMENT LEADING TO THE SYNTHESIS OF TETRALONE ESTER INTERMEDIATES 57a-c BY GENSLER’S METHOD

Plan of Synthesis

The substituted benzophenones 51a-c were prepared by Friedel-Craft’s acylation of Veratrole 49 with acyl chlorides 50a-c using aluminium chloride as the catalyst in dichloromethane. Stobbe condensation of the benzophenones 51a-c with diethyl succinate gave itaconic acid half esters 52a-c as a mixture of cis and trans products which were hydrolyzed to give the itaconic acids 53a-c as a mixture of cis and trans isomers in good yields (Scheme-1).

Hydrogenation of the itaconic acids 53a-c as a mixture of cis and trans isomers using 5% sodium-amalgam to furnish the respective benzhydryl succinic acids 54a-c, which on dehydration with acetyl chloride gave the anhydrides 55a-c in 93% yields. Intramolecular Friedel-Crafts acylation of the anhydrides 55a-c using stannic chloride as the catalyst gave the tetralone acids 56a-c, which were esterified to give the respective tetralone esters 57a-c in high yields (Scheme-2).
1. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF THE BENZOPHENONES 51a-c...

Veratrole 49 was the starting material prepared by the reaction of catechol in dimethyl sulphate as the solvent and sodium hydroxide as the base to give compound by methylation, using Banthrone et al. procedure.\textsuperscript{95}

Friedel-Crafts acylation of veratrole 49 with acyl chlorides 50a-c using aluminium chloride as the Lewis acid in dry dichloromethane gave the benzophenones 51a-c in excellent yields (70%).

In all the cases acylation took place at position 1 as shown in the structure 51a-c, which was proven by PMR spectra of these compounds. As a specific
example, compound 51a showed PMR absorption at $\delta$ 7.2 as a doublet assigned to C$_5$ proton, which clearly indicated that C$_5$ proton had an ortho coupling with C$_6$ proton. The other benzophenones 51b-c showed similar PMR spectra. Compounds 51a-c showed IR stretching frequencies in the range 1674–1680 cm$^{-1}$ due to the carbonyl group.
2. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF THE ITACONIC ACIDS 53a-c

Stobbe condensation has been frequently used to construct the basic lignan skeleton. Batterbee et al have synthesized dihydrocubebin by Stobbe
condensation of the starting aldehyde to frame the lignan skeleton. In contrast, Japanese group Harri et al have used the Stobbe condensation of benzophenone derivative to prepare aryl naphthalene ketones, an approach pioneered by Gensler et al. A similar approach was adopted to construct the lignan skeleton required in the present analogues.

Stobbe condensation of the benzophenones with diethyl succinate in potassium t-butoxide as the base, furnished a mixture of cis and trans isomeric itaconic acid half esters in high yields. These itaconic acid half esters showed IR stretching absorptions in the range 1720-1733 cm$^{-1}$ assigned to the carboxyl carbonyl group. The absorption for the conjugated double bond appeared at 1610-1620 cm$^{-1}$ and for the aromatic double bonds in 1590-1600 cm$^{-1}$. The PMR spectra of compounds were consistent with the structure assigned. The ester functional group showed the PMR signals, a triplet at $\delta$ 0.95 - 1.35 assigned to the methyl protons and a quartet centered at the range $\delta$ 4.0-4.3 assigned to
methylene protons of ester group, a keto methylene protons showed a broad singlet centered at the range of $\delta$ 3.3-3.5.

Saponification of the itaconic acid half esters 52a-c with sodium hydroxide in methanol and water at reflux temperature afforded the itaconic acids 53a-c in good yield as a mixture of cis and trans isomers.

The IR spectra of the compounds 53a-c showed the carboxylic OH group absorption in the range 3200-3600 cm$^{-1}$ where as the conjugated carbonyl and the methylene carbonyl of carboxyl groups showed the absorptions in the range of 1680-1695 and 1700-1715 cm$^{-1}$ respectively. An absorption in the range 1600-1620 cm$^{-1}$ was assigned to the conjugated double bond. The presence of methylene protons to carbonyl group was evident with PMR signal in the range $\delta$ 3.6-3.7 and the presence of an absorption in the range $\delta$ 9.8 and above confirming the existence of carboxylic protons which were exchangeable with D$_2$O. The presence of carboxyl groups were also confirmed by usual chemical test.
3. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF THE BENZHYDRYL SUCCINIC ACIDS 54a-c

\[
\begin{align*}
\text{Cis / trans } 53a-c \\
R^1 &= R^2 = \text{OCH}_3 \\
a : R = \text{p-NO}_2 \text{-C}_6 \text{H}_4 \\
b : R = \text{p-Cl-} \text{C}_6 \text{H}_4 \\
c : R = \text{p-F-} \text{C}_6 \text{H}_4
\end{align*}
\]

Shirvaiker and Kulkarni \textsuperscript{101} reported the reduction of a mixture of substituted cis and trans itaconic acids into the diastereomeric benzhydryl succinic acid by 5% sodium-amalgam in alkali. Earlier Gensler and co workers \textsuperscript{100} have separated the cis and trans isomeric itaconic acids (with different substituents in the aromatic ring) by fractional crystallization and reduced separately by catalytic hydrogenation into two diastereomeric benzhydryl succinic acids in fairly good yields. Since in our synthesis, only one diastereomeric form of benzhydryl
succinic acid was obtained, the itaconic acids 53a-c were reduced as a mixture of cis and trans isomer to the respective benzhydryl succinic acids 54a-c following the procedure described by Shirvaiker and Kulkarni \(^{101}\).

The itaconic acids 53a-c were dissolved in 5% sodium hydroxide and cooled to around 5 °C and then powdered 5% sodium-amalgam was added in portions and stirred over night. On usual work up the products 54a-c were obtained as white solid which contain only one diastereomer.

The IR spectra of compounds 54a-c clearly showed the absence of a conjugated double bond in the region 1590-1600 cm\(^{-1}\). The spectra showed an absorption in the region 1700-1710 cm\(^{-1}\) assigned to the carboxyl carbonyl stretching frequencies. The carboxylic OH stretching absorption was found in the range of 3100-3600 cm\(^{-1}\). The PMR spectra of the compounds 54a-c showed a broad singlet centered in the range of δ 2.35-2.50, which is assigned to Cc-H (structures 54a-c), a quartet in the range of δ 3.5-3.8 due to Cb- H and a doublet centered at the range δ 3.7-3.8 with the coupling constant of around 7Hz due to the dibenzylic proton Ca-H. The large coupling constant value revealed that Ca-H and Cb-H should be trans to each other, a configuration being thermodynamically stable.
4. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF THE TETRALONE ACIDS $56a-c$

Dry acetyl chloride has been used as the dehydrating agent in a number of experiments and it has also been used to prepare the anhydrides from 1,2-dicarboxylic acids. Dehydration of the benzhydryl succinic acids $54a-c$ by dry acetyl chloride at reflux temperature afforded the anhydrides $55a-c$ in almost quantitative yields. The compounds $55a-c$ obtained as gummy solid could not be crystallized and were found to be neutral. The IR spectra of these compounds showed the presence of two carbonyl stretching frequencies, one in the range of
1780-1785 cm\(^{-1}\) and the other at 1874-1880 cm\(^{-1}\) which correspond to a five
membered cyclic anhydride.\(^{103}\)

Intramolecular Friedel-Crafts acylation reaction of the anhydrides 55a-c to
the corresponding tetralone acids 56a-c was achieved by aluminium chloride in
dry dichloromethane as described by Gensler and co workers\(^{100}\). Cyclisation took
place easily at the ring A (structures 56a-c) because the presence of electron
donating methoxy groups in ring A would activate the ring A towards
intramolecular Friedel-Crafts acylation to form corresponding tetralone acids
56a-c.

\[
\begin{align*}
\text{CH}_2\text{CO}_2\text{H} \\
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R} \\
\text{R} \\
\end{array}
\end{align*}
\]

56d

One more possible product that could be expected was the indanone acid
56d considering the stability of the product to parallel the stability of the transition
state, tetralone acid structures 56a-c with adjacent substituents trans and six
membered ring was the most favored. Since the two cis opposed groups in
indanone acid 56d are close to each other and are both rigidly axial, and hence this
form was ranked least likely.
The anhydrides 55a-c are cyclised to form the tetralone acids 56a-c in moderate yields. All the compounds 56a-c showed a broad absorption at IR region 3200-3600 cm\(^{-1}\) assigned to the carboxylic acid OH group and two sharp absorptions in the region 1710-1715 cm\(^{-1}\) and 1675-1688 cm\(^{-1}\) which were assigned to the carboxyl carbonyl group and the tetralone carbonyl group respectively. Since the indonone carbonyl group usually absorbs in the IR region 1730-1740 cm\(^{-1}\) because of decreased ring size\(^{104}\), it is clear that the ring carbonyl was in a six membered ring.

PMR spectral data further confirmed the tetralone acid structure of the cyclised products. As a specific example tetralone acid 56a exhibited a distinct singlets at \(\delta\) 6.8 and 7.4 assigned to the aromatic C\(_5\) proton and C\(_8\) proton respectively. The C\(_5\) proton was relatively shielded because of the free rotation of the benzyl group and the C\(_8\) proton is relatively deshielded because of the electronegative effect of the neighboring tetralone carbonyl group. A doublet at \(\delta\) 4.1 with a coupling constant \(J\) of 7 Hz was assigned to the dibenzylic C\(_4\) proton. The large coupling constant indicated that the C\(_3\) proton and C\(_4\) proton in 56a were diaxial.

Hence the C\(_3\) carboxyl and C\(_4\) benzyl groups should be trans to each other, a configuration being thermodynamically stable.
5. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF TETRALONE ESTERS 57a-c

The tetralone acids 56a-c were esterified to the corresponding tetralone esters 57a-c using a catalytic amount of conc. sulphuric acid in dry ethanol and reflux for 5h. The stereochemical disposition of the functional groups were unaltered during the esterification process.

The IR spectra of 57a-c did not show any absorption in the region 3200-3600 cm\(^{-1}\) confirming the absence of the acid functional group, where as two sharp distinct absorptions in the region 1730-1738 cm\(^{-1}\) and 1670-1685 cm\(^{-1}\) due to the ester carbonyl and tetralone carbonyl group respectively were present. The PMR spectra of the compounds 57a-c further proved the presence of ethyl ester group
DISCUSSION

by showing a triplet at δ 1.0-1.3 with coupling constant J of 5 Hz and a quartet at δ 4.0-4.2 with almost same coupling constant. The mass spectra of the tetralone esters, 57a-c showed the molecular ion peaks at their respective mass numbers m/z 399, 388 and 372 respectively.
B. DISCUSSION OF THE SYNTHESIS OF THE TETRALONE ESTERS 57a-c BY SHORTER ROUTE

Plan of synthesis

Acetophenone 63 was prepared in good yields by the acylation of veratrole with acetic anhydride 62 using zinc chloride as the catalyst. Acetophenone further reacts with 64a-c in presence of a strong base in ethanol and water mixture to give the substituted chalcones (Benzal acetophenone) 65a-c (Scheme-3).

The substituted chalcones 65a-c on treatment with ethyl chloroacetate 66 in presence of powdered sodium in dry benzene give the cyclopropyl keto esters 67a-c in high yields. Intra molecular alkylation of the cyclo propyl ketoesters 67a-c using stannic chloride as the catalyst in dry dichloromethane give good yields of the tetralone esters 57a-c (Scheme-4).
1. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF ACETOPHENONE 63

Veratrole 49 was the starting material used for the preparation of acetophenone 63. Veratrole 49 was prepared in good yield by the reaction of catechol with dimethyl sulphate in presence of sodium hydroxide gave a liquid compound veratrole.

Acylation of veratrole 49 with acetic anhydride 62 using zinc chloride as the catalyst in dichloromethane give the acetophenone 63 in excellent yields as brown solid product. The compound 63 showed IR stretching absorption at 1683 cm\(^{-1}\) this clearly indicated that the product contain a carbonyl group.
2. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF CHALCONES 65a-c

The substituted chalcones 65a-c were prepared in high yields by Claisen reaction of 63 with substituted aldehydes 64a-c separately in the presence of dilute alkali at room temperature. The products 65a-c were recrystallised from rectified spirits. The IR spectra of these compounds were observed around 1665 and 1600 cm⁻¹ which is assigned to the stretching vibration frequencies of the carbonyl group and the carbon-carbon double bond respectively.
3. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF CYCLOPROPYL KETO ESTERS 67a-c

Cyclopropyl ketoesters are important intermediates for the synthesis of analogues of β-apopiropodophyllin 9. K.M. Lokanatha Rai and co workers developed a new method in which cyclopropyl keto esters are formed in excellent yield.
yields. The above method was used for cyclopropanation of chalcones 65a-c. Reaction of chalcones 65a-c with ethyl chloroacetate 66 using powdered sodium as catalyst in dry benzene furnished cyclopropyl keto esters 67a-c in about 70% yields.

Chalcones are α, β unsaturated ketones, which act as Michael receptors. The resultant anion undergoes intramolecular nucleophilic attack (Scheme-7) on the carbon atom bearing chloro group to form the desired cyclopropyl keto esters (Scheme-4).

IR and PMR spectra were in accordance with the structures 67a-c. IR absorption occurs at 1674-1667 cm⁻¹ and 1735-1725 cm⁻¹ were assigned to the carbonyl and ester carbonyl groups stretching vibration frequencies respectively. The PMR signals observed as a triplet at δ 1.0-1.4 assigned to the ester methyl broad multiplet at δ 2.4-3.6 assigned to C₁-H, C₂-H and C₃-H and a quartet at δ 4.0-4.3 is assigned to the ester methylene protons.
Scheme - 7
4. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF TETRALONE ESTERS 57a-c

Aryl aroylcyclopropanes have been conveniently converted into 4-aryl-1-tetralones using anhydrous stannic chloride as a catalyst in dry dichloromethane at room temperature. However, the cyclopropyl ketoester 69 on cyclisation with anhydrous stannic chloride under a variety of reaction conditions, followed by basic work up, gave 70 and 71 as the only products, but not the tetralone ester 72.
For this cyclisation reaction, the benzyl carbocation 73 was found to be the intermediate. W. S. Murphy and S. Wattanasin\(^\text{108}\) have advanced two reasons for the reluctance of the cyclopropyl keto ester 69 to cyclise into tetralone ester 72. The reason to the three vicinal methoxy groups being sterically prohibited from stabilizing the benzyl carbocation and thus having a net deactivating effect. The cyclopropyl ketoester 69, as discussed by Gensler\(^\text{100}\), and ring A in 73 are deactivated by the neighboring carbonyl group. In this context, attack of the carbonyl group on the initially formed carbocation intermediate 73 would stabilize it and lead to the formation of 70 and 71. This route (route-b) will be much faster than the aryl ring attack (route-a). Due to the instability of the 3,4,5-trimethoxy benzyl carbocation system, the reaction will necessarily shift towards the oxonium ion 74. The use of nitro methane as solvent with either stannic chloride or boron trifluoride etherate as catalyst, the reaction being carried out at room temperature for 4-6 days, gave tetralone ester 72 as the major product and hydroxy keto ester 70 as the main side product\(^\text{109}\). The shift in equilibrium from 74 to 73 is most likely due to the solvent induced effect, in which nitro methane is known to exhibit in Lewis acid catalysed reactions\(^\text{110}\) (Scheme-8).
Scheme 8
DISCUSSION

Recently Vyas and co-workers\textsuperscript{111} reported a 95\% yield of 72 from 69 by using two equivalents of acetic anhydride along with boron trifluoride etherate and nitro methane. The rearrangement occurred within an hour at room temperature. The acetic anhydride is presumed to form the transient enol acetate 75 and prevent the formation of an oxocarbonium ion intermediate 74 for the aryl ring attack which led to the formation of the tetralone ester 72 (Scheme-8). Using the above method\textsuperscript{111} very high yields of the tetralone esters 57a-c were formed.

IR absorption for the tetralone esters 57a-c occurs at 1730-1739 cm\textsuperscript{-1} and 1680-1670 cm\textsuperscript{-1} for the ester-carbonyl and tetralone carbonyl stretching frequencies respectively. In PMR, a broad multiplet occurs in the region $\delta$ 2.3-4.4 for C\textsubscript{2}-H, C\textsubscript{3}-H and C\textsubscript{4}-H.

The mass spectra of the tetralone esters 57a-c showed the molecular ion peaks at their respective mass number m/z 399, 388 and 372.