CHAPTER – II

A. DISCUSSION OF THE SYNTHESIS OF TETRALONE ESTER INTERMEDIATES 49a-c BY GENSLER’S METHOD

The Plan of Synthesis

The substituted benzophenones 43a-c were prepared by Friedel-Crafts acylation of 41 with acyl chlorides 42a-c using anhydrous aluminium chlorides as catalyst in dry dichloromethane. Stobbe condensation of the benzophenones 43a-c with diethyl succinate gave the itaconic acid half esters 44a-c as a mixture of cis and trans products which were hydrolyzed to give the itaconic acids 45a-c as a mixture of cis-trans isomers in good yields. (Scheme - 1).

The cis and trans itaconic acids 45a-c were reduced by using 5% sodium amalgam to furnish the respective benzhydryl succinic acids 46a-c which were dehydrated with acetyl chloride gave the anhydrides 47a-c in about 88% yields.

The intramolecular Friedel-Crafts acylation reaction of the anhydrides 47a-c with anhydrous aluminium chloride as catalyst gave tetralone acids 48a-c which were esterified to give the respective tetralone esters 49a-c in high yields.
1. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF BENZOPHENONES 43a-c

a) 1,3- Benzodioxole 41 is a starting material which was prepared by the reaction of catechol with dry dichloromethane in presence of sodium hydroxide in dimethyl sulfoxide using Bonthrone et al. procedure.

b) p-Chlorobenzoic acid, p-flurobenzoic acid and p-nitrobenzoic acid were refluxed separately with thionyl chloride in dry benzene to give the respective acyl chlorides 42a-c which are also the starting materials for the preparation of benzophenones 43a-c.

c) Friedel-Crafts acylation reaction of 41 with acyl chlorides 42a-c seperately using anhydrous aluminium chloride as the Lewis acid in dry dichloromethane gave the benzophenones 43a-c in excellent yields (about 80-90%).

In all the cases acylation took place at the position 1 as shown in structures 43a-c, which was proven by PMR spectra. As a specific example, compound 43a showed PMR spectra at 7.3 as a doublet assigned to the C5

\[ \text{Anhyd. AICI}_3 \text{ Dry CH}_2\text{Cl}_2 \rightarrow \]

41 \[ \text{RCOCI} \]

42a-c

43a-c

\[ a : \text{R= p-Cl-C}_6\text{H}_4 \]

\[ b : \text{R= p-F-C}_6\text{H}_4 \]

\[ c : \text{R= p-NO}_2\text{-C}_6\text{H}_4 \]
proton that clearly indicated that C₆ proton had an ortho coupling with the C₆ proton. All the other benzophenones 43 b&c showed similar PMR spectra. Compounds 43a-c showed IR stretching frequencies in the range 1685 – 1695 cm⁻¹ due to carbonyl group.

2. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF ITACONIC ACIDS 45a-c

Stobbe condensation⁸³ has been frequently used to construct the basic lignan skeleton (A.S.R. Anjaneyalu et al and Batterbee et al.)⁸⁴⁻⁸⁸.
Dihydrocubebin is prepared by the Stobbe condensation of the starting aldehyde to frame the lignan skeleton\(^8\). In contrast, the Japanese group Harii et al.\(^9\) have used the stobbe condensation of a benzophenone derivative to prepare the aryl naphthalene ketones, an approach pioneered by Gensler et al.\(^4\). A similar approach was adopted to construct the required lignan skeleton in the present analogues.

Stobbe condensation of the benzophenones 42a-c with diethyl succinate using potassium t-butoxide as a base furnished a mixture of cis and trans isomeric itaconic acid half esters 43a-c in high yields. Itaconic acid half esters 43a-c showed IR stretching absorption in the range of 1735-1725 cm\(^{-1}\) assigned to the ester carbonyl and at 1715-1700 cm\(^{-1}\) assigned to the carboxy-carbonyl group. The absorption for the conjugated double bond appeared at the range of 1645-1630 cm\(^{-1}\) and for the aromatic double bond in the range of 1600-1590 cm\(^{-1}\). The PMR spectra of compounds 43a-c were consistent with the structure assigned. The PMR spectra for the ester functional group showed a triplet at 0.80-1.1 assigned to the methyl protons and a quartet at the range of 3.7-3.9 assigned to the methylene protons. The keto methylene protons showed a broad singlet at the range of 3.5 – 3.6.
Saponification of the itaconic acid half esters **43a-c** with sodium hydroxide in methanol and water mixture at reflux temperature afforded the itaconic acids **45a-c** in good yields as a mixture of cis and trans isomers.

The IR spectra of these compounds **45a-c** showed the carboxylic OH absorption in the range of 3600 – 3100 cm\(^{-1}\), whereas the conjugated carbonyl and the methylene carbonyl of carboxyl groups showed the absorption in the range of 1685 – 1670 and 1700 – 1690 cm\(^{-1}\) respectively. An absorption in the range 1630 – 1615 cm\(^{-1}\) was assigned to the conjugated double bond. The presence of methylene protons to the carboxyl group was evident with a PMR signal in the range of 3.7 – 3.8 and the carboxylic protons are absorbed in the out of scale (δ10.5-12). But they are characterized by usual chemical tests.

3. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF BENZHYDRYL SUCCINIC ACIDS **46a-c**

![Diagram](image)

\[ \text{Reaction Scheme: } \text{45a-c} \rightarrow \text{46a-c} \]

- **a**: \( R = \text{p-Cl-C}_6\text{H}_4 \)
- **b**: \( R = \text{p-F-C}_6\text{H}_4 \)
- **c**: \( R = \text{p-NO}_2\text{-C}_6\text{H}_4 \)

Shirvaiker and Kulkarni\(^{90}\) reported the reduction of a mixture of substituted cis and trans itaconic acids into one diastereomeric benzhydryl succinic acid by 5% sodium amalgam in alkali. Earlier Gensler and co-
workers had 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 required the itaconic acids 45a-c were reduced as a mixture of cis and trans isomer to the respective benzhydryl succinic acids 46a-c following the procedure described by Shirvaiker and Kulkarni. The itaconic acids 45a-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 overnight. On usual work up, the products 46a-c were separated as white crystalline solid consisting of only one diastereomer. The IR spectra of compounds 46a-c clearly showed the absence of a conjugated double bond (there is no absorption band in the region 1630-1615 cm⁻¹). The spectra showed an absorption in the region of 1725–1700 cm⁻¹ assigned to the carboxyl carbonyl stretching frequencies. The carboxylic OH stretching absorption was found in the range of 3600 – 3100 cm⁻¹. The PMR spectra of the compounds 46a-c showed a broad doublet centred in the range of δ 2.9 which is assigned to Cc-H (structure 45a-c), a quartet in the range of δ 3.4 due to the Cb-H and a doublet centred at the range of 4.0 with the coupling constant of around 9 Hz due to the dibenzylic proton Ca-H. The large coupling constant of 9 Hz revealed that Ca-H & 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 48a-c

Acetyl chloride was used as the dehydrating agent in a number of experiments and it was also used to prepare the anhydrides from 1, 2-dicarboxylic acids\(^9^1\). Dehydration of the benzhydryl succinic acids 45a-c by acetyl chloride at reflux temperature afforded the anhydrides 47a-c in almost quantitative yields. The compounds 47a-c obtained as gummy solid 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 1780-1747 cm\(^{-1}\) and the other at 1860-1815 cm\(^{-1}\) that corresponded to a cyclic anhydride \(^9^2,9^3\).

Intramolecular Friedel-Crafts acylation reaction of the anhydrides 47a-c to the corresponding tetralone acids 48a-c was achieved by anhydrous aluminium chloride in dry dichloromethane as described by Gensler et al.\(^4^6\).
Cyclisation had taken place easily on the ring A (structure 47 a-c) because the presence of electron donating substituents such as methoxy and chloro groups in the ring A would activate the ring A for the intramolecular Friedel–Crafts acylation to the corresponding tetralone acids 48a-c.

One more possible product that could be expected was the indanone acid 48d. Considering the stability of the product parallel to the stability of the transition state, the tetralone acid structures 48a-c with adjacent substituents trans on a six membered ring was the most favored. Since the two cis opposed groups in indanone acid 48d are close to each other and are both rigidly axial, and hence this form was ranked least likely.

\[
\text{48d}
\]

The anhydrides 47a-c were cyclised to form the tetralone acids 48a-c in good yields. All the compounds 48a-c showed a broad absorption in the IR region 3600-3200 cm\(^{-1}\) assigned to the carboxylic OH group and two sharp absorptions in the region 1700 – 1710 cm\(^{-1}\) and 1670-1695 cm\(^{-1}\) which were assigned to the carboxyl carbonyl group and the tetralone carbonyl group respectively. Since the indanone carbonyl group usually absorbs in the IR
region 1740-1730 cm\(^{-1}\) because of the decreased ring size\(^{94}\). It is clear that the ring carbonyl group is in a six membered ring.

PMR spectral data further confirmed the tetralone acid structures of the cyclised products. As a specific example tetralone acid 48a-c exhibited a distinct singlet at \(\delta\) 6.7 and 7.3 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 neighbouring tetralone carbonyl group. A doublet at \(\delta\) 4.1 with a coupling constant J 6 Hz was assigned to the dibenzyllic proton.

Hence the C\(_3\) carboxyl and C\(_4\) benzyl groups should be trans to each other, a configuration being thermodynamically stable. Mass spectra of the tetralone acids 48a-c showed the molecular ion peaks at their respective mass numbers.
5. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF TETRALONE ESTERS 49a-c

The tetralone acids 48a-c esterified to the corresponding tetralone ester 49a-c using a catalytic amount of concentrated sulphuric acid in dry ethanol and refluxing the mixture for 5 hr. The stereochemical disposition of the functional groups were unaltered during the esterification process.

The IR spectra of 49a-c did not show any absorption in the region 3600-3200 cm\(^{-1}\) confirming the absence of the acid functional group whereas two sharp distinct absorptions in the region 1740-1730 cm\(^{-1}\) and 1695-1690 cm\(^{-1}\) due to the ester carbonyl and tetralone carbonyl groups, respectively.

The PMR spectra of the compounds 49a-c further proved the presence of the ethyl ester group by showing a triplet at \(\delta 0.8 - 1.0\) with a coupling constant \(J\) of 6 Hz and a quartet at \(\delta 3.6\) with almost the same coupling constant.
B. DISCUSSION OF THE SYNTHESIS OF TETRALONE ESTERS 49a-c
BY SHORTER ROUTE

Plan of synthesis

Substituted acetophenone 55 is prepared by the acylation reaction of 41
(i.e. 1,3-benzodioxole) with acetic anhydride 54 using fused zinc chloride as
the catalyst, the substituted acetophenones further react with 56a-c (p-chloro,
p-fluoro, and p-nitro benzaldehyde) separately in the presence of a strong base
in ethanol and water mixture to give the substituted chalcones
(benzalacetophenones) 57a-c (Scheme 3). The substituted chalcones 57a-c
gave cyclopropyl ketoesters 59a-c on treatment with ethyl cyanoacetate 58 in
the presence of powdered sodium in dry benzene. The intramolecular
alkylation of the cyclopropyl ketoster by 59a-c using anhydrous stannic chloride
as the catalyst and acetic anhydride in dry dichloromethane gave good yields of
the tetralone esters 49a-c (Scheme 4).
1. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF ACETOPHENONE 55

1,3- Benzodioxole 41 is the starting material for the preparation of the substituted acetophenone 55, which is prepared in high yield by the reaction of catechol with dichloromethane in the presence of sodium hydroxide in dimethyl sulfoxide\textsuperscript{95}.

Acylation of 1,3-benzodioxole 41 with acetic anhydride 54 using fused zinc chloride as a catalyst gave the acetophenone 55 in excellent yield\textsuperscript{96} as pale yellow crystalline solid. The compound 55 showed IR stretching absorption in the region 1670 – 1674 cm\textsuperscript{-1} clearly indicating that the product contain a carbonyl group.
2. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF CHALCONES 57a-c

The substituted chalcones 57a-c were prepared as a pale yellow crystalline solids in high yields by the Claisen reaction of acetophenone 55 with 56a-c separately in dilute alkali at room temperature. The products 57a-c were recrystallized from rectified spirit. The IR spectra of these compounds were observed around 1665 cm$^{-1}$ and 1610 cm$^{-1}$, which were assigned to the stretching vibration frequencies of the carbonyl group & the carbon-carbon double bond respectively.

\[ \text{55} \quad \text{56a-c} \quad \text{NaOH} \quad \text{C$_2$H$_5$OH-H$_2$O} \quad \text{57a-c} \]

a : R= p-Cl-C$_6$H$_4$

b : R= p-F-C$_6$H$_4$

c : R= p-NO$_2$-C$_6$H$_4$
3. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF CYCLOPROPYL KETOESTERS 59a-c

Cyclopropyl ketoesters are important intermediates for the synthesis of analogues of β-apopicropodophyllin (11). K. M. Lokanatha Rai et al., developed a new method in which cyclopropyl ketoesters are formed in good yields. The above method was used for cyclopropanation of chalcones 57a-c. The reaction of chalcones 57a-c with ethyl cyanoacetate 58 using powdered sodium as catalyst in dry benzene furnished 59a-c in about 78% yield.

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

IR and PMR spectra were in accordance with the structures 59a-c. IR absorption occurs at 1673-1660 cm$^{-1}$ and 1739 cm$^{-1}$ and were assigned to the carbonyl and ester carbonyl groups stretching vibration frequencies respectively. The PMR signals observed as a triplet at $\delta$ 1.1 were assigned to the ester methyl protons and multiplet $\delta$ at 2.6 to C$_1$-H, C$_2$-H and C$_3$-H and quartet at $\delta$ 4.0 is assigned to the ester methylene protons.

![Scheme-7 Diagram](image-url)
4. DISCUSSION OF THE EXPERIMENTS LEADING TO THE PREPARATION OF TETRALONE ESTERS 49a-c

The aryl aroyl cyclopropanes are conveniently converted into 4-aryl-tetralones using anhydrous stannic chloride as a catalyst in dry dichloromethane at room temperature. However the cyclopropyl keto ester 61 on cyclization with anhydrous stannic chloride under a variety of reaction conditions, followed by work up gave 62 & 63 as the only products, but not the required tetralone esters 64. In this cyclization reaction the benzyl carbocation 65 was found to be the intermediate. W.S. Murphy and S. Wattanasin advanced two reasons for the reluctance of the cyclopropyl ketoester 61 to cyclize into tetralone ester 64. The reason being the three vicinal methoxy groups are sterically prohibited from stabilizing the benzyl carbocation and thus having a net deactivating effect, the cyclopropyl ketoster
61, as discussed by Gensler\textsuperscript{46} and ring A in 65 was deactivated by the neighbouring carbonyl group. In this context, attack of the carbonyl group on the initially formed carbocation intermediate 65 would stabilize it and lead to the formation of 62 & 63. 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 oxonium ion 66.

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 64 as the major product and hydroxyl ketoester 62 as the minor side product\textsuperscript{100}. The shift in equilibrium from 66 to 65 is most likely due to the solvent induced effect in which nitromethane is known to exhibit in Lewis acid catalyzed reactions\textsuperscript{101} (Scheme 8).
Scheme-8
Recently Vyas et. al.\textsuperscript{103}, have reported 95% yield of \textit{64} from \textit{61} by using two equivalents of acetic anhydride along with boron trifluoride etherate and nitromethane. The rearrangement occurred within an hour at room temperature. The acetic anhydride has been presumed to form the transient enol acetate \textit{67} and prevent the formation of oxocarbonium ion intermediate leaving the carbonium ion intermediate for the aryl ring attack which led to the formation of the tetralone ester \textit{64} (Scheme 8). Using the above method\textsuperscript{103}, a very high yield of the tetralone esters \textit{49a-c} were obtained.

IR absorption for the tetralone esters \textit{49a-c} occurs at 1734 cm\textsuperscript{-1} and 1703 cm\textsuperscript{-1} for the ester carbonyl and tetralone carbonyl stretching respectively. In PMR, a broad multiplet occurs in the region $\delta$ 2.5-4.2 for $C_2$-H, $C_3$-H and $C_4$-H.