CHAPTER – III

DISCUSSION OF THE EXPERIMENT LEADING TO THE SYNTHESIS OF β-APOPICROPODOPHYLLIN ANALOGUES 43, 44 AND 45

Plan of synthesis:

Formylation of the tetralone esters 57a-c with ethyl formate using sodium hydride as the base yielded the hydroxy methylene tetralone esters 58a-c and hydroxymethylene tetralone acids 59a-c. Reduction of 58a-c and 59a-c with sodium borohydride in methanol gave the dihydroxy esters 60a-c and dihydroxy acids 61a-c respectively in excellent yields.

Saponification of the dihydroxy esters 60a-c with 5% aqueous sodium hydroxide and methanol gave the dihydroxy acids 61a-c. Treatment of the dihydroxy acids 61a-c with p-toulene sulfonyl chloride in pyridine gave the β-apopicropodophyllin analogues 43, 44 and 45 in good yields (Scheme-5).
1. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF THE HYDROXY METHYLENE TETRALONE ESTERS 58a-c AND HYDROXY METHYLENE TETRALONE ACIDS 59a-c

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\text{R} & \\ R^1=R^2=OCH_3 \\
a: R = p-NO_2-C_6H_4 \\
b: R = p-Cl-C_6H_4 \\
c: R = p-F-C_6H_4
\end{align*}
\]
Walker has synthesized 2-hydroxy methylene-3-ethyl carboxy-4-(3',4'-dimethy phenyl)-6,7-dimethy-1-tetralone 58d by formylation of the tetralone ester, 57d using ethyl formate in the presence of sodium methoxide\textsuperscript{112}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{57d_58d.png}
\caption{Conversion of 57d to 58d.}
\end{figure}

Gensler and co-workers\textsuperscript{113} prepared the hydroxy methylated tetralone ester 58e from 57e using ethyl formate and sodium hydride.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{57e_58e.png}
\caption{Conversion of 57e to 58e.}
\end{figure}
Formylation of the presently synthesized tetralone esters 57a-c with ethyl formate using sodium hydride as the base at room temperature gave two products\textsuperscript{114}. The hydroxy methylene tetralone esters 58a-c the major products were sodium hydroxide soluble and the other hydroxy methylene tetralone acids, 59 a-c of the minor product were sodium bicarbonate soluble. In view of the chemical properties, there was no question that the compounds 58a-c and 59a-c have keto-enol formula as shown below.

\[ R^1=R^2=OCH_3 \]
\[ a : R= p-\text{NO}_2-C_6H_4 \]
\[ b : R= p-\text{Cl-C}_6H_4 \]
\[ c : R= p-\text{F-C}_6H_4 \]

The IR spectra of 58a-c showed characteristic absorptions in the region of 3600-3200 cm\textsuperscript{-1} and 1620-1595 cm\textsuperscript{-1} assigned to vinylic hydroxyl and conjugated double bond groups respectively. The IR absorptions for the tetralone carbonyl group and ester carbonyl were not much displaced when compared to that of the
tetralone esters 57a-c. Compounds 59a-c showed broad peaks at 3600-3200 cm$^{-1}$ and a sharp peak in the range 1635-1615 cm$^{-1}$ due to the vinylic hydroxyl as well as carboxylic hydroxyl groups and conjugated double bonds respectively. The carbonyl group of the carboxylic acid absorbed in the range of 1715-1710 cm$^{-1}$ and the tetralone carbonyl at 1700-1685 cm$^{-1}$.

The PMR spectra of 58a-c resembled each other except for the differences due to the substituents. A broad singlet centered in the range δ 6.2 due to the vinylic hydroxyl proton which was exchangeable with D$_2$O and a broad singlet in the range of δ 8.2-8.5 due to the vinylic proton. Compounds 59a-c showed a similar type of PMR spectra in which the signal due to ethyl group was absent, but a broad singlet in the range δ 9.9 and out of scale absorption for carboxylic OH proton. The PMR spectra of 59a-c showed broad peaks centered in the range of δ 5.9-6.2 and δ 9.9 and out of scale absorption assigned to the vinylic hydroxyl proton and the carboxylic proton respectively.
2. DISCUSSION OF THE EXPERIMENT LEADING TO PREPARATION OF THE 1-HYDROXY-2-HYDROXYMETHYL-3-ETHYL CARBOXY-4-SUBSTITUTED-1,2,3,4-TETRAHYDRO NAPHTHALENE ANALOGUES 60a-c.

Sodium borohydride has been extensively used to reduce ketones as well as \(\alpha,\beta\) unsaturated ketones to \(1,3\)-diols without affecting the ester functional group\(^{112, 115}\). The methylene hydroxy esters 58a-c were reduced to the corresponding dihydroxy esters 60a-c by sodium borohydride. Compounds 58a-c were dissolved in absolute methanol and then excess sodium borohydride in absolute methanol was added during 1h at room temperature. The reaction mixture was stirred for 5h at room temperature which on usual work up gave a brown
DISCUSSION

pasty mass in good yields. Based on Walker's work \(^{112}\) in a similar reduction, it was assumed that a mechanism involving 1, 4-attack on the keto enol system is involved in the sodium borohydride reduction of 58a-c to 60a-c. The substituent groups at positions 1 and 2 in 60a-c were assumed to be cis to each other similar to the views of Walker.

The IR spectrum of 1-hydroxy-2-hydroxy methyl-3-ethyl carboxy-4-(p-nitropheyl)-1, 2, 3, 4 tetrahydro naphthalene 60a showed a broad absorption in the region 3650-3200 cm\(^{-1}\) which is assigned to the OH groups and a sharp absorption at 1735 cm\(^{-1}\) assigned to the ester carbonyl group. Compounds 60b and 60c showed the IR spectra almost similar to that of 60a.
3. DISCUSSION OF THE EXPERIMENT LEADING TO PREPARATION OF THE 1-HYDROXY-2-HYDROXY METHYL-3-CARBOXY-4-SUBSTITUTED-1,2,3,4-TETRAHYDRON APHTHALENE ANALOGUES 61a-c

Hydrolysis of the esters 60a-c with 5% aqueous sodium hydroxide in methanol was affected smoothly at reflux temperature to give the dihydroxy carboxylic acids 61a-c in 70-78% yield. During alkaline hydrolysis of 60a-c, inversion of the carboxyl group did not occur under these conditions since the compounds 59a-c on reduction with sodium borohydride in absolute methanol
gave the identical products 61a-c. The hydroxy methylene tetralone acids 59a-c were dissolved in absolute methanol and then sodium borohydride in absolute methanol was added during 1h at room temperature. The excess of sodium borohydride was decomposed by dil. HCl and the separated solid on recrystallization from methanol gave white feathery crystals.

The IR spectra of 61a-c from both the routes were identical. An absorption in the region 3550-3200 cm\(^{-1}\) was assumed to the carboxylic hydroxyl groups and other primary and secondary hydroxyl groups.
4. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF \( \beta \)-APOPICROPODOPHYLLIN ANALOGUES 43, 44 AND 45.

\[
\text{R}^1 = \text{R}^2 = \text{OCH}_3 \\
a : \text{R} = \text{p-NO}_2\text{-C}_6\text{H}_4 \\
b : \text{R} = \text{p-Cl-C}_6\text{H}_4 \\
c : \text{R} = \text{p-F-C}_6\text{H}_4
\]

\( p \)-Toluene sulfonyl chloride in pyridine has been used as a dehydrating agent in many organic synthesis. The same reagent was used to convert podophyllotoxin 1 to \( \beta \)-apopropicropodophyllin 9 in a single step by Murthy et al.\textsuperscript{116} Following the same procedure, the dihydroxy acids 61a-c were successfully dehydrated with concomittant isomerization to the corresponding \( \beta \)-apopoporopodophyllin analogues 43, 44 and 45 respectively.
Compounds 61a-c in dry benzene were mixed with p-toluene sulfonyl chloride in pyridine and refluxed for 3h. After the usual work up, the crude products were column chromatographed over silica gel using chloroform as the eluent. The products 43 and 44 were isolated as pale yellow solids and 45 as the pale brown solid. They showed the absence of OH groups in their respective IR spectra but a strong absorption in the region of 1775–1770 cm\(^{-1}\) due to the presence of an \(\alpha, \beta\) unsaturated \(-\gamma\)-lactone carbonyl group and a shoulder in the range 1647-1640 cm\(^{-1}\) due to the tetra substituted C=C bond stretching. These observations corresponded very well to those of \(\beta\)-apoporopodophyllin 9 as observed by Gensler\(^{110}\) and Murthy\(^{112}\). The PMR spectra of 43 showed singlets at \(\delta\) 4.2 for C\(_3\)-H, 2.8 for C\(_9\)-H, 3.1 for C\(_8\)-H, 7.3 for C\(_4\)-H and 6.8 for C\(_7\)-H. The other two analogues 44 and 45 showed a similar type of PMR spectra. The mass spectra of 43, 44 and 45 and showed molecular ion peaks (M\(^+\)) 367, 356 and 340 respectively.
5. DISCUSSION OF THE EXPERIMENT LEADING TO THE PREPARATION OF \(6,6a\)-DIHYDRO-2,3,Dimethoxy-9-
SUBSTITUTED-11b\(H\)-BENZO [C] FLUOREN-5,7-DIONE \(46, 47\) AND \(48\).

\[\begin{align*}
R^1 &= R^2 = OCH_3 \\
a \ &\& 46 : R = NO_2 \\
b \ &\& 47 : R = Cl \\
c \ &\& 48 : R = F
\end{align*}\]
DISCUSSION

The diones 46, 47 and 48 were synthesized by Friedel-Crafts intramolecular acylation reaction of 68a-c. This method has two steps. First the benzhydryl succinic acids 54a-c were converted separately into benzhydryl succinyl chlorides 68a-c, which were cyclised by using anhyd. aluminium chloride as catalyst in dry dichloromethane.

The compounds 46, 47 and 48 were formed in 59-73% yields, which were characterized by IR, PMR, Mass spectra and elemental analysis data (Scheme-6). The IR absorption in the region 1715-1697 cm\(^{-1}\) assigned to the six membered carbonyl group and 1742-1730 cm\(^{-1}\) assigned to the five membered carbonyl groups.

PMR of 46, 47 and 48 showed a doublet of a doublet in the region \(\delta\) 2.5 assigned to C\(_6\)-H, a quartet at \(\delta\) 3.3-3.4 assigned to 6aH and a doublet at \(\delta\) 4.0-4.2 assigned to 11b-H. Mass spectra of the products showed molecular ion peaks (M\(^{+}\)) at their respective mass number m/z, 353, 342 and 326.
EXPERIMENTAL RESULTS

INTRODUCTION

All the starting materials and reagents were purchased from Sigma-Aldrich and Merck Company. Melting points were determined on a SONAR melting point apparatus and are uncorrected. Reactions were monitored by TLC on 0.2mm precoated silica gel 60 F_{254} plates (E. Merck). Infrared spectra were recorded on Perkins Elmer spectrum-1000 (450-4000cm^{-1}) spectrometer on KBr disc or Nujol mull. The $^1$H NMR spectra were recorded with a Varian T-60 and Brucker DRX-300 (300MHz FT NMR) spectrometer using tetra methyl silane (Me$_4$Si, $\delta$=0) as an internal standard in CDCl$_3$, $J$ values are given in Hz. The mass spectra have recorded on a JEOL SX102A spectrometer. Elemental analysis data were recorded in on Elemental Analyzer Vario EL III.

All the products were purified either by repeated recrystallization or by column chromatography using silica gel (60-120/70-230 mesh, Merck) as an adsorbent.