CHAPTER - 4
THEORETICAL

Preparation of $\gamma$-Butyrolactones and Thiolactones

$\gamma$-Butyrolactones are known for the antifungal\textsuperscript{44}, anthelmintic\textsuperscript{45}, anticonvulsant\textsuperscript{46} sedative, hypnotic\textsuperscript{47} agent for stimulating microorganism in producing known antibiotic- staphylomycin\textsuperscript{48}, anticancer, antibacterial and antihypertensive\textsuperscript{49} properties. Naturally occurring antifungal compounds\textsuperscript{50} like anenaciolide, isoanenaciolide and canadensolide have butyrolactone ring in their framework\textsuperscript{51}. Various types of lower fatty $\gamma$-lactones are also reported as perfumes and flavouring materials\textsuperscript{52,53}.

Syntheses of lactones are well known\textsuperscript{54-61}. Preparative methods of $\gamma$-lactones from lower fatty acids and epoxides were reported\textsuperscript{52}.

Recently a variety of new $\gamma$-butyrolactones were obtained by hydrogenation and cyclization of unsaturated acid in vapour phase with metal catalyst\textsuperscript{62}. An oxidative cyclization method for the preparation of $\gamma$-lactone from saturated and/or unsaturated carboxylic acids in the presence of alkali metal ions\textsuperscript{64,65} or ammonium peroxysulphate in CuCl\textsubscript{2} was also reported\textsuperscript{51,63}.
By condensing diacetone alcohol with alkyl substituted cyano acetic esters gave $\delta$-lactone$^{66}$. Dihydroxy compound on oxidation with KMnO$_4$ yielded $\gamma$-lactone$^{67}$. The substituted lactones$^{68}$ were obtained from the reaction of halogen substituted compounds with $\gamma$-keto acids. Lactones were also synthesized acetylenic acid$^{69}$. From N-iodoamide/N-chloroamide, $\gamma$-lactones were synthesized by thermolysis or photochemical transformation$^{70,71}$. Trans - (2-decenyl) succinic anhydride were reduced with sodium borohydride in dimethyl methanol at room temperature to afford $\gamma$-butyrolactones$^{72}$. $\gamma$-Butyrolactones was prepared from maleic anhydride or succinic anhydride in presence of metal catalyst$^{73}$. Simple keto acid on cyclization with HCHO and MeCHO gave $\gamma$-lactone$^{74}$. On heating acylate ester with alcohol and t-butylperoxide$^{75}$ and allylic 4-pentynoates cyclization$^{76}$, alkynoic acids with PhSCI/PhSeCl in presence of HCl and Et$_3$N$^{77}$ afforded lactones. The cis and trans lactones were prepared by sodium borohydride reduction of olefinic acid with aldehyde$^{78}$. In our laboratory $\gamma$-butyro-
lactones were prepared by the reaction of undecenoic acid and magnese triacetate or lead tetracetate\textsuperscript{82,83}.

Cyclopentadione:

Five member cyclic saturated compound having two carboxyl groups attached to it is called cyclopentadione. Cyclopentadione and cyclopentanone were successfully prepared by reacting aldehyde and shortchain alpha,beta unsaturated esters\textsuperscript{84}. Prostaglandis synthon, 2-(w-carboxyhexyl) cyclopentenone, has been conveniently converted from undecylenic acid in several steps\textsuperscript{55,88}. Treatment of dioic acid with acid chloride in presence of AlCl\textsubscript{3}\textsuperscript{85}, pentenolides and Me\textsubscript{3}COOK with triethylamine\textsuperscript{86} and hydroxy cyclopentene carboxylate in acidic medium\textsuperscript{87} gave acyclopentanedione derivatives. Quantitative yield of cyclopentadione was reported by refluxing\textsuperscript{89} EtCOCH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}Et with NaOMe -MeOH in xylene Me\textsubscript{2}SO.

Cyanocyclopentenone derivative was obtained from trione in three steps. In this route hydrocyanation of 2-alkyl-3-methoxy 4-hydroxy-2-cyclopentenone with diethylaluminum cyanide was a key step\textsuperscript{90}. Attempts were made to utilize the cyanocyclopentenone as a starting material for the total synthenia of prostaglandin - F\textsubscript{1} (PGF\textsubscript{1}) or prostaglandin - E\textsubscript{1} (PGE\textsubscript{1}) which are now known to be physiologically important lipids, widely distributed in nature and to show diverse
pharmacological properties. Several other methods for the synthesis of cyclopentenedione and cyclopentadione starting from easily accessible triones (3-alkyl-1,2,4-cyclopentanetrione, occurring in enol form) were also described. Base catalysed aldol condensation of aldehyde, ketones and the alkylation of cyclopentadione with butyliodide in presence of K$_2$CO$_3$ in dimethylformamide (DMF) gave methoxycyclopentanone. Substituted 1,3-cyclopentenedione may be easily obtained by base induced cyclization of -ketoester. 2-Hydroxy cyclobutanone undergoes ring expansion to substitute cyclopentane 1,3-diones in presence of silver ion.

The long-chain fatty compounds were cyclized and gave quantitative yields and showed various activities. Keeping in view these points, the reaction of alpha,beta unsaturated fatty acid with various reagents were carried out in the present study and the results of these reactions are discussed.

Thiolactones:

Thiolactones are useful intermediate for bactericides, antiinflammatory agents, anticonvulsant and antibiotic (+)-thiolactomyclin. Their pharmaceutical acceptable salts were prepared as blood platelet aggregation inhibitor useful as antithromboitics.
Synthesis of thiolactone was done by heating tetrahydro-thienopyridinone and alcohol\textsuperscript{104} and chloro derivative in presence of Amberlyst-15 ion exchange resin\textsuperscript{105} and with triethylamine and \( \text{H}_2\text{S}\)\textsuperscript{102,103,106}. Diethyl malonate is converted to thiolactone in presence of sodium ethoxide in ethanol\textsuperscript{100}. \( \gamma \)-butyrolactone reacted with MeCoNMe\textsubscript{2} gave thiolactone\textsuperscript{101} and again treatment \( \gamma \)-butyrolactone with PhCH\textsubscript{2}SNa and (CF\textsubscript{3}CO)\textsubscript{2}O gave thiolactone\textsuperscript{107}. Acid containing sulphur was also converted into thiolactones\textsuperscript{108}. 
DISCUSSION

Preparation of methyl 4-oxohexadecanoate (19):

Methyl 4-oxohexadec-2(\(E\))-enoate(18) when hydrogenated in presence of 10% palladium charcoal at 25 psi for 4 hr. gave a white solid product. After final filtration and fractionation over silica gel column, the product (19) was obtained in 70% yield.

\[
\text{CH}_3 - (\text{CH}_2)_{11} - \text{CH} - \text{CH} = \text{CH} - \text{COOCH}_3 \\
\text{CrO}_3/\text{AcOH} \\
\text{CH}_3 - (\text{CH}_2)_{11} - \text{C} = \text{CH} - \text{COOCH}_3 \\
Pd/C/H_2 \\
\text{CH}_3 - (\text{CH}_2)_{11} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{COOCH}_3
\]

Characterization of Product (19)

The compound (19) responded DNP test positive for chemical evidence of oxo function. Microanalysis of compound (19) corresponded to the formula C_{17}H_{32}O_3. The IR spectrum gave characteristic bands at 1735 and 1700 cm\(^{-1}\) for ester carbonyl and isolated carbonyl group respectively. Its NMR spectrum showed a triplet at \(\delta 2.64 (J=4 \text{ Hz})\) integrating for 51
four protons of C-2 and C-3 methylene and another triplet at 2.45 (J=7Hz) for C-5 methylene protons besides the usual fatty ester signals. On the basis of above data structure (19) was assigned as methyl 4-oxohexadecanoate.

Reaction of methyl 4-oxohexadecanoate (19) with sodium borohydride:

When methyl 4-oxohexadecanoate (19) was stirred with sodium borohydride in ethanolic sodium hydroxide afforded a solid product (20).

Characterization of Product (20):

Compound (20) was analysed for C₁₆H₃₀O₂. Its IR spectrum displayed band at 1765 cm⁻¹ for -lactone carbonyl function. The NMR displayed two characteristic multiplets at 4.49 for ring methine proton and 2.74 - 2.1 for ring methylene protons. On the basis of above evidence compound (20) was formulated as γ-dodecyl-γ-butyrolactone.
Mass spectrum of product (20) has further strengthened the formulated structure by showing molecular ion peak at m/z 254 (25) along with an ion at 255 (M + 1,2). The characteristic mass fragments are shown in the scheme (IX). The structure revealing fragments were observed at m/z 113 (M-141,40), 99 (M-155,10) and 85 (M-165,100). Other usual fragments were observed at m/z 236 (M - H²O, 60), 225 (M - C₂H₅, 10), 211 (M- C₃ H₇, 10), 195 (M- CH₃-CH₂ -C≡CH₂, 10), 168(M-86,10), 154(M-100,20) and 140(M-114,34).

Reaction of methyl 4-oxohexadecanoate (19) with sodium ethoxide:

Methyl 4-oxohexadecanoate (19) reacted promptly with sodium ethoxide in presence of boiling toluene.

\[
\text{CH}_3 - (\text{CH}_2)_{10} - \text{CH}_2 - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{COOCH}_3
\]

(19) \[ \xrightarrow{\text{NaOEt, Toulene}} \]

\[
\text{O} \quad \text{CH}_3 - (\text{CH}_2)_{10} - \text{CH}_3
\]

(21)

Characterization of Product (21):

The elemental analysis of product (21) corresponded to formula C₁₆ H₂₈ O₂. The diagnostic IR band at 1725 and
SCHEME - IX

\[ R = -(CH_2)_9-CH_3 \]
another at 1695 cm⁻¹ for ring carboxyl groups. The appearance of two bands in carbonyl region is due to keto-enol tautomeric forms of beta-diketones. The broad band was observed at 3000 due to bonded hydroxy group. The NMR spectrum exhibited sharp singlet peak at δ 2.6 for four methylene protons of the ring and 2.2 - 2.45 as a multiplet for methylene protons alpha to the ring. The methine proton was not free due to tautomerization and hence not observed in NMR spectrum. On the basis of above spectral characteristics the compound (21) was characterized as 2-undecyl-1,3-cyclopentandione.

The confirmatory evidence for product (21) was furnished by its mass spectrum. Molecular ion peak observed at m/z 252 (30) along with ions at 253 (M + 1, 20) and 251 (M-1, 5). The structure revealing fragments were observed at m/z 197 (96) and 97 (100). The other fragment ions were shown in the scheme (X) at m/z 179 (M-C₄H₇, 10), 155 (10), 141 (12), 126 (M-C₉H₁₈, 98) and 111 (17).

Reaction of compound (21) with borontrichloride in methanol

2-undecyl-1,3-cyclopentandione (21) reacted quickly with 10% borontrichloride in methanol to give enol ether (22).

\[ R = (\text{CH₂})_{10} - \text{CH₃} \]
\[ \text{R} \longrightarrow \text{CH}_2 \longrightarrow \text{CH} = \text{C} = \text{C} = \text{OH} \]

\[ \text{m/z 197} \]

\[ \text{R} = -(\text{CH}_2)_9 \longrightarrow \text{CH}_3 \]

\[ \text{m/z 111} \]

\[ \text{m/z 97} \]

\[ \text{m/z 252} (M^+) \]

\[ \text{m/z 155} \]

\[ \text{m/z 141} \]

\[ \text{SCHEME - X} \]
Characterization of Product (22):

This compound was analysed for \( \text{C}_{17} \text{H}_{30} \text{O}_2 \). The IR spectrum of compound (22) gave a weak band at 1660 cm\(^{-1}\) for vinyl group and 1200 cm\(^{-1}\) for ether linkage along with usual carbonyl signal at 1700 cm\(^{-1}\). The NMR exhibited a sharp singlet at \( \delta 3.62 \) for methoxy protons, a triplet at 2.53 for ring methylene protons alpha to carbonyl group and triplet at 2.38 \( (J = 6.5 \text{ Hz}) \) for ring methylene protons alpha to olefinic group. On the basis of above spectral data the structure (22) was assigned as 2-undecyl-3-methoxycyclopent-2-en-1-one.

Reaction of methyl 10,11-epoxy undecanoate (23) with 2-mercaptoacetic acid:

Methyl 10,11-epoxy undecanoate (23) was allowed to react with 2-mercaptoacetic acid in chloroform. The reaction mixture was worked up. Column chromatographic purification of crude mixture yielded two products (24, 25).

\[
\text{CH}_2 - \text{CH} - (\text{CH}_2)_8 - \text{COOCH}_3 \\
(23)
\]

\[
\text{HSCH}_2\text{COOH, CHCl}_3 \\
\text{OH/COCH}_2\text{SH}
\]

\[
\text{(CH}_2)_8 - \text{COOCH}_3
\]

\[
\text{CH}_2 - \text{CH} - (\text{CH}_2)_8 - \text{COOCH}_3 \\
\text{OCOCH}_2\text{SH/OH}
\]

and

\[
\text{(CH}_2)_8 - \text{COOCH}_3 \\
(24)
\]

\[
\text{CH}_2 - \text{CH} - (\text{CH}_2)_8 - \text{COOCH}_3 \\
(25)
\]

55
Characterisation of Product (24)

Elemental analysis of (24) corresponded to formula C_{14}H_{24}O_{4}S. IR spectrum exhibited a strong band at 1745 and 1735 cm^{-1} for lactone carbonyl and ester carbonyl respectively. The NMR showed a characteristic multiplet signal at 4.04 integrated for methine proton of ring. In addition to usual ester and chain, the NMR also exhibited a sharp singlet at 3.1 for methylene protons present in between ring carbonyl and sulphur and a doublet at 2.6 (J = 4 Hz) for C-11 methylene protons. These data established the structure (24) as methyl 10,11-thiolactone undecanoate.

Mass spectrum of (24) further strengthened the formulated structure. It showed molecular ion peak at m/z 288 (10) along with ions at 289 (M+1, 10) and 286 (M-2H, 10). Characteristic mass fragment ions were observed at 229 (M-CH_{3}COO, 30), 214 (M-74 McLafferty cleavage, 25), 200 (214-CH_{2}, 40) and 182 (214-S, 10). Alpha cleavage of thiolactone ring moiety was also observed at 170 (20) which shows the position of ring at C_{10}-C_{11}. Other prominent peaks were present at m/z 215 (10), 214 (215-H, 20), 201 (10), 200 (201-H, 40), 169 (100) and 117 (10) (Scheme - XI).
Scheme XI
Characterization of Product (25):

The elemental analysis of the compound (25) corresponded to formula C_{14}H_{26}O_{5}S. IR spectrum of the compound has illustrated a couple of important bands at 3500 and 1745 cm^{-1} for hydroxy and carbonyl groups. The NMR spectrum showed a peak at 4.9 as a multiplet for methine proton (CH - O), and a doublet at 4.6 (J = 3 Hz) for methylene protons attached to oxygen (CH$_2$ - O). A broad singlet at 4.0 for methylene protons attached to sulphur (CH$_2$-SH). The sulphur proton and hydroxy proton appeared at 3.9 and at 3.7 respectively. Both are D$_2$O exchangeable. On the basis of these data compound (25) was characterised as methyl 11 (10) - acetomethyl mercaptan - 10 (11) - hydroxy undecanoate.

Mass spectrum of (25) was deprived of molecular ion peak at m/z 306. The ion peak at m/z 200 due to loss of methyl mercaptoacetate (M-C$_3$H$_6$O$_2$S, 20) in scheme - (XII). However the diagnostic mass ions were observed at m/z 201 (M - 105, 10) and McLafferty cleavage at 191 (M - 115, 20). In addition to these diagnostic ion peaks were observed at m/z 275 (10) prove the isomeric nature besides the other significant mass ions were present at m/z 243 (275 - 32, 10), 115 (20), 171 (10), 169 (201 - 32,96),135 (10), 114 (10), 110 (109 + H, 15), 109 (10) and 105 (12).
m/z 306 (M^+, absent)

R = (\text{CH}_2)_4\text{COOCH}_3

Scheme-XII
Reaction of methyl 9, 10-epoxy-octadecanoate (26) with 2-mercaptoacetic acid.

Methyl 9, 10-epoxy-octadecanoate (26) was treated with 2-mercaptoacetic acid in chloroform as described earlier. The products (27, 28) were isolated by silicagel column chromatography.

\[
\text{CH}_3-(\text{CH}_2)_7-\text{CH}-\text{CH}-(\text{CH}_2)_7-\text{COOCH}_3
\]

(26)

\hspace{1cm}

\[
\text{HS}-\text{CH}_2\text{COOH}, \text{CHCl}_3
\]

\[
\text{CH}_3-(\text{CH}_2)_7-\text{CH}-\text{CH}-(\text{CH}_2)_7-\text{COOCH}_3
\]

(27)

\[
\text{HSCH}_2\text{CO/HO}
\]

\[
\text{CH}_3-(\text{CH}_2)_7-\text{CH}-\text{CH}-(\text{CH}_2)_7-\text{COOCH}_3
\]

(28)

Characterization of Product (27):

The compound (27) was analysed for C\text{21} H\text{38} O\text{4} S. Its IR spectrum exhibited two characteristic bands in the region of 1725 and 1745 cm\textsuperscript{-1} for ester as well as thiolactone ring carbonyl groups. The NMR absorption at \textdegree 4.0 multiplet
integrating methine protons (CH-S, CH-O) and a singlet at 3.4 for methylene protons present in the ring. On the basis of these data compound (27) was formulated as methyl 9, 10-thiolactone-octadecanoate.

Mass spectrum of the compound (27) did not show the molecular ion peak at m/z 386. It has ion peak at m/z 352 due to loss of hydrogen sulphide (M - H₂S, 10) shown in scheme (XIII). The fragment ions at m/z 273 (10), 229 (10), 157 (10) and 113 (10) established the position of ring at C-9 and C-10. The peaks at m/z 216 (10) and 172 (15) were observed to show the isomeric nature. Thiolactone ring cleavage showed ion peaks at m/z 260 (10), 216 (40), 170 (10) and 126 (40) besides other peaks at m/z 261 (30), 244 (40), 214 (273 + COOCH₃, 35), 187 (248 - 61, 100), 155 (157 - 2H, 80) and 129 (10).

Characterization of Product (28):

The combustion data of compound (28) was equivalent to formula C₂₁H₄₀O₃S. Its IR spectrum exhibited characteristic bands of hydroxy group as well as ring carbonyl group at 3350 and 1720 cm⁻¹ respectively. The NMR showed a broad unresolved signal from 4.1 - 3.3, which was partly merged with a strong singlet ester protons at 3.6, is assigned for six protons. These data were consistent with (the structure of (28) formulated as methyl 9 (10) - hydroxy -10(9) - acetomethyl mercaptan octadecanoate. Further structure
$R = \text{CH}_3(-\text{CH}_2)_7$

$R' = (\text{CH}_2)_7\text{COOCH}_3$

Scheme-XIII
(28) was strengthened by mass spectrum which did not show molecular ion peak at m/z 404 (M⁺), but the ion peak observed at m/z 356 (10) due to the loss of methyl mercaptan (M – CH₃SH). The mass ion peaks at m/z 261 (10), 217 (10) 187 (10) and 143 (10) established the isomeric structure of (39).

(scheme – XIV)

Reaction of methyl 12, 13-epoxy-9-octadecenoate (29) with 2-mercapto acetic acid :

Methyl 12, 13-epoxy-9-octadecenoate (29) was allowed to react with 2-mercapto acetic acid under similar conditions stated earlier. The two products (30, 31) were isolated and purified by column chromatography.

\[
\begin{align*}
R - CH - CH - R' &
\quad
\text{(29)}
\quad
\text{HSCH₂COOH, CHCl₃}

\quad
\text{OH/OOCOCH₂SH}

+ R - CH - CH - R' &
\quad
\text{(31)}

\quad
\text{OOCOCH₂SH/OH}
\end{align*}
\]

\[
\begin{align*}
R &= \text{CH₃} - (\text{CH₂})₄ \\
R' &= \text{CH₂} - \text{CH} = \text{CH} - (\text{CH₂})₇ - \text{COOCH₃}
\end{align*}
\]
Scheme XIV

$R' - CH = O - COCH_2SH$

$m/z 187$

$m/z 261$

$m/z 404$ (M$^+$, absent)

$R - CH = O - COCH_2SH$

$m/z 217$

$m/z 143$

$R = CH_3-(CH_2)_7$

$R' = (CH_2)_7-COOCH_3$
Characterization of Product (30):

Elemental analysis of (30) corresponded to formula \( C_{21}H_{36}O_{4}S \). Its IR spectrum showed two characteristic bands at 1740 and 1610 cm\(^{-1}\) for ring carbonyl and carbon-carbon double bond function respectively. NMR displayed three distinct multiplets centred at 5.5, 4.0 and 3.5 which were assigned to olefinic protons and two methine protons, one attached to oxygen and other to sulphur respectively. A singlet is also observed at 3.6 for methylene protons of ring moiety. These data characterised the product (30) as methyl 12, 13-thiolactone - 9- octadecenoate.

Mass spectrum of (30) gave more information to confirm the product. It did not show the molecular ion peak at \( m/z \) 384. The ion peak was at \( m/z \) 353 (10) due to loss of methoxy group (\( M^- - CH_3 O, 10 \)) and 354 (\( M-OCH_2 , 20 \)). The mass ion peaks at \( m/z \) 187 (10) and 313 (30) confirmed ring at C-12 and C-13. The characteristic peaks at \( m/z \) 255 (80) and 130 (10) were observed to show isomeric nature, besides other peaks at 201 (10), 197 (20) and 129(30) were present (scheme-XV).

Characterization of Product (31):

The compound (31) was analysed for \( C_{21}H_{38}O_{5}S \). The IR spectrum of (31) showed the presence of hydroxy band at 3400 cm\(^{-1}\), besides two important bands 1740 for ring carbonyl and
\[
CH - CH - CH_2 - CH = CH - R' \\
\downarrow \\
m/z 255
\]

\[
\begin{align*}
313 & \quad 187 & \quad 197 & \quad 201 & \quad 221 \\
R & \quad CH - CH & \quad CH_2 & \quad CH = CH & \quad R' \quad \text{+} \\
\downarrow & & \downarrow & \quad \downarrow &
\end{align*}
\]

\[
\begin{align*}
R - CH - CH - CH_2 - CH = CH - R' \quad \text{+} \\
\downarrow & & \downarrow & \quad \downarrow &
\end{align*}
\]

\[
m/z 384 (m^+, \text{absent})
\]

\[
R = CH_3 - (CH_2)_4 \\
R' = (CH_2)_7 - COOCH_3
\]

Scheme-XV
1620 for olefinic bond. The NMR spectrum showed at \( \delta 5.4 \) a multiplet for olefinic protons, 4.7 a multiplet for methine protons and 4.2 a singlet for methylene protons. Two D\(_2\)O exchangeable singlets were detected at 3.3 for one sulphur proton and other for hydroxy proton at 3.1. The structure (31) assigned from these spectral data was methyl 12(13)-hydroxy 13(12)-acetomethylmercaptan -9- ocatadecenoate.

Mass spectrum of (31) was more informative to confirm the isomeric nature of the product(scheme - XVI). Molecular ion peak at m/z 402 was non existent. The ion peak was at m/z 354 (20) due to loss of methyl mercaptan (M - CH\(_3\)SH). The mass ion peaks at m/z 301 (10), 227 (80), 175 (30) and 100 (35) confirm the isomeric nature of product (31). The other mass ion peaks were at m/z 241 (20), 209(15), 207(10), and 142 (30).
\[
\text{Scheme-XVI}
\]