CHAPTER - II

Synthesis of Steroidal 1’, 3’-Dioxolan -2’-One and 1’, 3’-Oxathiolan -2’-Thione
THEORETICAL
Epoxide ring-opening reactions have been reported at large in the literature. The epoxide ring is very sensitive and opens, generally under mild condition when it comes in contact with acid or base. A number of papers dealing with the reaction of epoxides with a variety of reagents have appeared where anionic and cationic cleavages of epoxide ring followed by some novel rearrangements in certain cases have been reported.

Kihara et al. reported the reaction of 2,3-epoxypropyl phenyl ether (I) with carbon dioxide in the presence of N-methylpyrrolidinone (NMP) under atmospheric pressure at 100 °C in 5 mol % of various salts which gave selectively five membered cyclic carbonate (4-phenoxy methyl-1,3-dioxolan -2-one (II).

\[
\text{PhO} \quad \begin{array}{c}
\text{O} \\
\end{array} \quad \text{PhO}
\]

Josef et al. reported the reaction of ethylene oxide (III) with CO₂ [10 Molar] at 40-250 °C in the presence of various salts to form ethylene cyclic carbonate (IV) (yield 83.1%).

\[
\begin{array}{c}
\text{O} \\
\end{array} + \text{CO}_2 \quad \rightarrow \quad \begin{array}{c}
\text{O} \\
\end{array}
\]

Kihara et al. later reported the reaction of phenyl-ethylene oxide (V) with carbon disulfide in the presence of lithium bromide in THF which gave a mixture of regioisomeric cyclic dithiocarbonates (VI), (VII) and (VIII).
Kuper et al.\textsuperscript{13} reported the reaction of cyclohexane oxide (IX) with carbon dioxide in the presence of chromium metallo-prophyrinates at 75°C for 18 h to form \textit{cis} and \textit{trans}-cyclohexane 1,2-cyclic carbonates (Xa) and (Xb).

\[
\text{O} + \text{CO}_2 \rightarrow \text{CrTTPCI} \rightarrow \begin{cases} \text{(Xa)} \\ \text{(Xb)} \end{cases}
\]

Margherita et al.\textsuperscript{14} reported the reaction of 1,3-dithiolan-2-thione (XI) with epoxide (XII) in the presence of HBF$_4$ Et$_2$O in anhyd. CH$_2$Cl$_2$ or anhyd. C$_6$H$_5$Cl which gave 1,3-dithiolan-2-one (XIII) (yield 66-85%).

\[
\begin{array}{c}
R^1 = \text{H, Me} \\
R^2 = \text{H, Me, C}_{10}\text{H}_{21} \\
R^1R^2 = \text{(CH}_2\text{)}_4
\end{array}
\]

\[
\begin{array}{c}
R^3 = \text{H, Me} \\
R^4 = \text{H, Me, C}_{10}\text{H}_{21} \\
R^1R^2 = \text{(CH}_2\text{)}_4
\end{array}
\]
The reaction of 5,6α-oxido-5α-cholestan (XIV) and its 3β-substituted derivatives with 1-phenyl-1H-tetrazole-5-thiol in the presence of lithium bromide and dimethyl formamide provided respective products (XV).\(^{15}\)

![Chemical structure of XIV and XV](image)

Taguchi et al.\(^{16}\) reported that an equimolar reaction of 2-hexyl oxirane (XVI) with carbon disulphide in hexane and in the presence of triethylamine at 100 °C for 20 h provided 5-hexyl-1,3-oxathiolane-2-thione (XVII) (5%), 4-hexyl-1,3-dithiolane-2-thione (XVIII) (21%) and 4-hexyl-1,3-dithiolane-2-one (XIX) (63%).

![Chemical structures of XVI, XVII, XVIII, XIX](image)
Didier et al.\textsuperscript{17} reported that $\alpha$-acetylenic alcohols (XX) on reaction with carbon disulphide in the presence of KF on Al\textsubscript{2}O\textsubscript{3} (without solvent) gave selectively 4-alkylidene-1,3-oxathiolane-2-thione (XXI).

\[ R + \text{CS}_2 \rightarrow R^1 \text{C} \equiv R^2 \text{OH} \rightarrow \begin{array}{c} \text{O} \\ \text{S} \end{array} \text{S} \]

(XXI)

$R = \text{H, Me, 1-propynyl}; R^1 = \text{Me, H}$

$R^2 = \text{Et, Me}_2\text{CH}; R^1R^2 = (\text{CH}_2)_3$

Brasseur\textsuperscript{18} reported the reaction of alkylene oxides (XXII) with carbon disulphide in the presence of various catalysts to form cyclic dithiocarbonates (XXIII) which were decomposed in second stage to give thiiranes (XXIV).

\[ \begin{array}{c} \text{O} \\ \text{S} \end{array} \text{S} \rightarrow \begin{array}{c} \text{O} \\ \text{S} \end{array} \text{S} \]

(XXII)

(XXIII)

(XXIV)

$R = \text{H, Me, Et}; R^1 = \text{H}; RR^1 = (\text{CH}_2)_4$

Catalyst-LiCl, LiBr, MeI or I\textsubscript{2}

Taguchi et al.\textsuperscript{19} reported the reaction of episulphides (thiiranes) (XXV) and (XXVII) with malononitrile and diethyl malonate and obtained (XXVIa) $(\Rightarrow)$ (XXVIb) and (XXVIII) as the products, respectively.
Taguchi and coworkers\textsuperscript{20} also carried out the reaction of episulphide (XXIX) with carbon disulphide in the presence of triethylamine and obtained 4,4-dimethyl 1,3-dithiolane-2-thione (XXX) as the product.

\[
\text{Et}_3\text{N} + \text{CS}_2 \rightarrow \text{Et}_3\text{N} \quad \text{(XXX)}
\]

Taguchi and coworkers\textsuperscript{21} also reported the reaction of 2,2-dimethyloxirane (XXXI) with carbon disulphide in the presence of triethylamine under high pressure to give 5,5-dimethyl-1,3-oxathiolane-2-thione (XXXIII) in high yield and (XXXII) as a minor product, while 2-hexyl oxirane (XXXIV) under the same reaction conditions formed (XXXV), (XXXVII) and (XXXVIII) as minor product and 4-hexyl-1,3-dithiolane-2-thione (XXXVI) as the main product.

\[
\text{Et}_3\text{N} + \text{CS}_2 \xrightarrow{800\text{M Pa, } 100^\circ\text{C}} \text{Et}_3\text{N} \quad \text{(XXXII)}
\]

77
Fieser and Rajagopalan\textsuperscript{22} reported the reaction of cholesterol-epoxide (XXXIX) with N-bromosuccinimide which afforded 3\(\beta\), 5-dihydroxy-5\(\alpha\)-cholestan-6-one (XL) and 3\(\beta\)-hydroxy-7-bromocholest-4-en-6-one (XLI).

Fieser\textsuperscript{23} reported an exhaustive dichromate oxidation of cholesterol epoxide (XXXIX) in presence of acetic acid but only 16 \% yield of hydroxy diketone (XLII) was recovered but with cholesterol epoxide (XLIII) its yield was 90 \%.
James and Shoppee\textsuperscript{24} studied the bromination of 3\(\beta\)-acetoxy-5, 6\(\alpha\)-epoxy-5\(\alpha\)-cholestan (XLIV) by using 1\textsuperscript{st} mol bromine in acetic acid under varying conditions and obtained only one product 3\(\beta\)-acetoxy-5-bromo-6\(\beta\)-hydroxy-5\(\alpha\)-cholestan (XLV) which on chromic acid oxidation gave 3\(\beta\)-acetoxy-5-bromo-5\(\alpha\)-cholestan-6-one (XLVa).
Sondheimer et al.\textsuperscript{25} studied the reaction of 3-ethylene dioxy-5\(\alpha\), 6\(\alpha\)-oxidopregnan-20-one-17\(\alpha\), 21-diol-21-acetate (XLVI) with perchloric acid and allopregnan-3, 20-dione-5\(\alpha\), 6\(\beta\), 17\(\alpha\), 21-tetrol-21-monoacetate (XLVII) was obtained as a product.

Shaw and Stevenson\textsuperscript{26} discovered a simple method for the preparation of 4-bromocholest-4-en-3-one (IL) by the treatment of 4\(\beta\), 5-epoxy-5\(\beta\)-cholest-3-one (XLVIII) with hydrobromic acid.

Shoppee et al.\textsuperscript{27} reported the halogenation of 5, 6\(\beta\)-epoxy-5\(\beta\)-cholestane (L) in the presence of hydrogen chloride in chloroform at 15 °C to afford 5-chloro-5\(\alpha\)-cholestan-6\(\beta\)-ol (LI) which was oxidised by chromium trioxide-acetic acid at 15 °C to 5-chloro-5\(\alpha\)-cholestan-6-one (LII).
Collin²⁸ studied the rearrangement of 4α, 5α-epoxy-cholest-3-one (LIII) with BF₃-etherate and reported the formation of 5β-A-norcholestan-3-one (LIV).

Bowers et al.²⁹ reported the formation of cynosteroids (LVI) and (LVII) when 3β-acetoxy-5α, 6α-epoxy steroid (LV) was treated with potassium cyanide at 150 °C.
Kirk\textsuperscript{30} reported the BF\textsubscript{3}-etherate catalysed rearrangement of \(3\beta\)-acetoxy-5\(\alpha\), 6\(\alpha\)-epoxy-6\(\beta\)-methyl steroid (LVII) which gave \(3\beta\)-acetoxy-6\(\beta\)-methyl-A-homo-B-nor-5\(\alpha\) ketone (LIX). Transformation of 2\(\alpha\), 3\(\alpha\)-oxido-3\(\beta\)-acetoxy-5\(\alpha\)-cholestane (LX) into (LXI) was also reported\textsuperscript{31}.

Batres et al.\textsuperscript{32} reported the reaction of 5\(\alpha\), 6\(\alpha\)-oxido-3-cycloethylene dioxyandrostan-17\(\beta\)-ol (LXII) with ethylene glycol and piperidine and obtained (LXIII\(a\)) as a product which on further treatment with acetone-water in the presence of \(p\)-TsOH gave the ketone (LXIII\(b\)).
Ellis et al.\textsuperscript{33} reported the reaction of 3β-acetoxy-5, 6α-epoxy-6β-methyl-5α-androstan-17-one (LXIV) with hydriodic acid (under anhydrous condition) to obtain 3β-acetoxy-5, 6β-dihydroxy-6α-methyl-5α-androstan-17-one (LXV) as a product.

Djerassi et al.\textsuperscript{34} studied the reaction of 3-keto-1, 2-epoxy-5α-cholestane (LXVI) with hydrazine hydrate and sodium hydroxide and obtained Δ^2-cholesten-1α-ol (LXVII). Wharton and Bohlen\textsuperscript{35} also reported the hydrazine hydrate reduction of (XLVIII) into Δ^3-cholesten-5β-ol (LXVIII).
Hallsworth and Henbest\textsuperscript{36} reported the effect of a hydroxyl group on metal reduction of vicinal epoxides and obtained different products (LXIXa), (LXIXb), (LXXIa), (LXXIb), (LXXIII) with 5β, 6β-epoxycholestane (XLIII), 6β, 7β-epoxycholestane-3β-ol (LXX) and 3-methoxy-1β, 2β-epoxide (LXXII).
Kirk et al.\textsuperscript{37} reported the reaction of 6\(\beta\), 7\(\beta\)-epoxide (LXXIV) with lithium aluminium hydride in tetrahydrofuran which afforded triol (LXXV).

Blunt et al.\textsuperscript{5} reported the reaction of BF\(_3\)-etherate with 5, 6\(\alpha\)-epoxy-5\(\alpha\)-cholestane (LXXVI) and obtained rearranged product (LXXVII).
Blacket et al. studied the reaction of 4α, 5α-(LXXVIII) and 5β, 6β-(L) epoxycholestanes with BF₃-etherate in benzene and obtained rearranged products, cholestan-4α-ol (LXXIX) and 6α-ol (LXXX) respectively.

Iwasaki et al. treated various oxiranes (LXXXI) with carbon dioxide at 100 °C using sodium bromide as catalyst under atmospheric pressure to obtain the corresponding five-membered cyclic carbonates (LXXXII) quantitatively.
The reaction of 5, 6α-epoxy-5α-cholestan (LXXXIII-a) its 3β-chloro- (LXXXIII-b) and acetoxy (LXXXIII-c) analogues with carbon disulphide in triethylamine furnished 5α-cholestan-6α, 5α-1', 3'-oxathiolane-2'-thione (LXXXIV-a), its chloro (LXXXIV-b) and acetoxy analogues (LXXXIV-c).
Baba et al.\textsuperscript{39} reported the reaction of oxiranes (LXXXIV) with carbon dioxide using 1: 1 complex Bu$_3$SnI and Bu$_4$PI as a catalyst to produce five membered cyclic carbonates (LXXXV).

\[
\text{R}^1 \quad \begin{array}{c}
\text{R}^2 \\
\text{O} \\
\text{O} \\
\end{array}
\begin{array}{c}
+\text{CO}_2 \\
\rightarrow \\
\text{R}^1 \\
\text{R}^2 \\
\text{O} \\
\text{O} \\
\end{array}
\]

(LXXXV) \quad (LXXXVI)

Takeda et al.\textsuperscript{40} reported the reaction of propylene oxide (LXXXVII) with carbon dioxide in the presence of $\alpha,\beta,\gamma,\delta$-tetraphenylprophynato-aluminium methoxide to produce propylene carbonate (LXXXVIII).

\[
\begin{array}{c}
\text{TPPA} \text{OMe} \\
+\text{CO}_2 \\
\rightarrow \\
\text{O} \\
\end{array}
\]

(LXXXVII) \quad (LXXXVIII)

5,6$\alpha$-Epoxy-5$\alpha$-cholestane (LXXXIX-a) its 3$\beta$-chloro (LXXXIX-b) and 3$\beta$-acetoxy (LXXXIX-c) analogues when treated with allyl isothio cyanate (using AlCl$_3$ as catalyst) provided 5-hydroxy-5$\alpha$-cholestane-6$\beta$-isothiocyanates (XC a-c) and oxazolidin-2-thiones (XCI a-c).\textsuperscript{41}
Ritter reaction of \(3\beta\)-chlooro-5, 6\(\alpha\)-epoxy-5\(\alpha\)-cholestan (XCII) in acetonitrile-BF\(_3\) etherate provided 3\(\beta\)-chlooro, 5,6;5-dihydroxy-5\(\alpha\)-cholestan (XCIII-a) and 3\(\beta\)-chlooro-5-hydroxy-6\(\beta\)-acetylamino-5\(\alpha\)-cholestan\(^{42}\) (XCIII - b).

Hewett and coworkers\(^{43}\) reported the preparation of aminosteroids (XCV a-c) from 3\(\beta\)-acetoxy-5, 6\(\alpha\)-epoxy-5\(\alpha\)-androstan-17-one (XCIV). Condensation
of $2\alpha, 3\alpha$-epoxy-5$\alpha$-cholestan-17$\beta$-ol (XCVI) with secondary amine in water gave the corresponding 2$\beta$-amino-5$\alpha$-androstane-3$\alpha$, 17$\beta$-deiol (XCVII).

2$\alpha, 3\alpha$-Epoxy-5$\alpha$-cholestan (XCVIII) when treated with dimethylamine afforded 2$\beta$-dimethylamino-5$\alpha$-cholestan-3$\alpha$-ol (XCIX). A similar synthesis of 2$\beta$-dimethyamino-3$\alpha$-hydroxy-5$\alpha$-androstan-17-one (CI) from $2\alpha, 3\alpha$-epoxy-5$\alpha$-androstan-17-on (C) has been reported.$^{44}$
Shafiuullah and Hussain\textsuperscript{45} reported the synthesis of N-(2'-hydroxy-2-methyl) acetyl-3\(\beta\)-substituted-5\(\beta\)-cholestanooaziridines (CIV a-c) from corresponding epoxides (CII a-c) through the following sequence of reaction.
The reaction of steroidal epoxides (CV a-c) with thioglycolic acid provided steroidal hydroxyformates (CVI a-c) and diols (CVII a-c). 

Reaction of 3β-chloro 5,6α-epoxy-5α-cholestanе (CVII-a) and its 3β-acetoxy analogue (CVII a-b) with nitrosylchloride gas provided the respective isomeric chlorohydrins (CIX a-b), (CX a-b) and diols (CXI a-b).
The reaction of 5,6α-epoxy-5α-cholestan-3-ol (CXII-a), its 3β-chloro (CXII-b) and 3β-acetoxy analogues (CXII-c) with acrylonitrile (BF₃-etherate as catalyst) provided 5,6β-dihydroxy-5α-cholestane (CXIII-a), its 3β-chloro (CXIII-b) and 3β-acetoxy analogue (CXIII-c) and 5-hydroxy-6β-acrylamido-5α-cholestan-3-ol (CXIV-a), its 3β-chloro (CXIV-b) and 3β-acetoxy analogues (CXIV-c).

Hortshorn et al. carried out the reaction of 4β,5-epoxy-4α-methyl-5β-cholestan-3-ol (CXV) with BF₃-etherate in benzene and obtained 5β-methyl-5α-cholestan-4-one (CXVI) and 5β-acetyl-A-nor-cholestan (CXVII) as the product.
Blunt et al.\textsuperscript{50} have studied the reaction of 3\textalpha-acetoxy-4\alpha,5-epoxy-5\alpha-cholestane (CXVIII) with BF\textsubscript{3}-etherate in benzene and obtained 3\alpha-acetoxy-5\alpha-cholestan-4-one (CXIX) along with rearranged product 3\alpha-acetoxy-4\alpha-hydroxy compound (CXX).

The reaction of 3\beta-chloro-5, 6\alpha-epoxy-5\alpha-cholestane (CXXI) with BF\textsubscript{3}-etherate in benzene furnished ketones (CXXII) and rearranged product (CXXIII), westphalen rearranged products (CXXIV) and fluorohydrins (CXXV).\textsuperscript{51}
Ponsold and Preibsch\textsuperscript{52} synthesized 2$\beta$, 3$\beta$-imino-5$\alpha$-androstan-17$\beta$-ol (CXXVIII) from 2$\alpha$, 3$\alpha$-epoxy-5$\alpha$-cholesatn-17-one (CXXVI) via the corresponding azidoalcohol tosylate (CXXVII) and converted into 2$\beta$-amino-3$\beta$-chloro-5$\alpha$-androstan-17$\beta$-ol (CXXIX).
Wicha\textsuperscript{53} studied the reaction of epoxide (CXXX) with BF\textsubscript{3}-etherate in benzene for 10 minute at ambient temperature and obtained (CXXXI).

\[
\begin{align*}
\text{(CXXX)} & \quad \text{BF}_3 - \text{etherate} \\
& \quad \text{Benzene, 10 min} \\
\end{align*}
\]

Shafiullah \textit{et al.}\textsuperscript{54} studied the reaction of 5\textalpha{}, 6\textalpha{}-epoxycholestane (CXXXII-a), its 3\textbeta{}-acetoxy (CXXXII-b) and 3\textbeta{}-chboro (CXXXII-c) analogues with glycine in dimethylformamide using AlCl\textsubscript{3} as catalyst which gave 5\textalpha{}-cholestano [6\textalpha{}, 5\textalpha{}-d] oxazolidine-2-one (CXXXIII-a), its 3\textbeta{}-acetoxy (CXXXIII-b) and 3\textbeta{}-chboro (CXXXIII-c) analogues respectively.

\[
\begin{align*}
\text{(CXXXII-a)} & \quad \text{H} \\
\text{(CXXXII-b)} & \quad \text{OAc} \\
\text{(CXXXII-c)} & \quad \text{Cl} \\
\end{align*}
\]

Ahmad \textit{et al.}\textsuperscript{55} studied the reaction of 4\textbeta{}, 5-epoxy-5\textbeta{}-cholestan-3-one (CXXXIV) with thiourea to afford 5\textbeta{}-hydroxycholest-3-eno [3,4-\textalpha{}]-2'-aminothiazole (CXXXV) while with thiacetamide it furnished 3,5-cholestadieno [3,4-\textalpha{}] 2'-methylthiazole (CXXXVI) and 5\textbeta{}-hydroxycholest-3-eno [3,4-\textalpha{}]-2'-methylthiazole (CXXXVII).
Ahmad et al.\textsuperscript{35} studied the reaction of 6\(\beta\)-chloro-5-hydroxy-5\(\alpha\)-cholestane (CXXXVIII) on treatment with KSCN in dimethylformamide which gave cholesta-4, 6-diene (CXXXIX), 5\(\alpha\)-cholestan-6-one (CXL), 5-hydroxy-5\(\alpha\)-cholestan-6\(\alpha\)-yl isothiocynate (CXLI), 5-hydroxy-5\(\alpha\)-cholestan -6-one (CXLII) and 5\(\alpha\)-cholestano [6\(\alpha\), 5-\(\delta\)] 1,3-oxazolidine-2-thione (CXLIII).
Saleem et al. studied the reaction of 5, 6α-epoxy-5α-cholestane (CXLIV-a), its 3β-acetoxy (CXLIV-b) and 3β-chloro (CXLIV-c) analogues with thioacetamide in THF at room temperature in the presence of LiBr as a catalyst which afforded selectively the corresponding substituted steroidal 1,3-oxathiolanes (CXLV a - c) in high yield.
6-Nitrocholest-5-ene-\((4\alpha,3\alpha\text{-d})-2'-\text{vinyl}-2\text{-oxazoline}\) (CXLVII) and 3\(\alpha\)-hydroxy-4\(\beta\)-acrylamido-6-nitrocholest-5-ene (CXLVIII) were obtained when 3\(\alpha\), 4\(\alpha\)-epoxy-6-nitrocholest-5-ene (CXLVI) was treated with acrylonitrile in the presence of BF\(_3\)-etherate.\(^{57}\)

Ducker and Lazer reported the formation of aziridine (CL) from the \(\beta\)-epoxide (CXLIX) via Ritter reaction.\(^{58}\)
Oxazolidinone (CLII-a) and trans-dihydroxy compound (CLII-b) were obtained when 3α, 4α-epoxy-6-nitrocholest-5-ene (CLI) was treated with phenylisocyanate (AlCl₃ as catalyst)⁵⁹, when same epoxide (CLI) was treated with urea in DMF, oxazolidinone (CLII-a) and its isomer (CLII-c) were obtained.⁶⁰

3β-Acetoxy-5α-fluoro-4α-methylcholestan-4β-ol (CLIV-a) 3-acetoxy-4-methylcholesta-3, 5-diene (CLIV-b) and 3β-acetoxy-5α-methylcholestan-4-one (CLIV-c) and compound (CLIV-d) were obtained when 3β-acetoxy-4β, 5-
epoxy-4α-methyl-5β-cholestane (CLIII) was treated with BF₃-etherate in benzene.⁶¹

Chandrasekaran and coworkers⁶² reported the reaction of 2, 3-dihydroxy-2, 3-dimethylbutane (CLV-a) with 4-(dimethylamino) pyridine (DMAP) (1 equiv) and acetic anhydride (2.2 equiv) at ca. 85 °C for 3 h which gave 2-oxo-4, 4, 5, 5-tetramethyl-1, 3-dioxolane (CLV-b)

Trost and coworkers⁶³ reported the synthesis of 4-methylene-1, 3-dioxolan-2-one (CLVIII) by the following sequence of reaction.
Shamsuzzaman and Salim\textsuperscript{64} reported the reaction of 5, 6\(\alpha\)-epoxy-5\(\alpha\)-cholestane (CLIX-a), its 3\(\beta\)-acetoxy (CLIX-b) and 3\(\beta\)-chloro (CLIX-c) analogues with carbon disulphide in THF at room temperature in the presence of LiBr as catalyst which afforded selectively the corresponding 1, 3-oxathiolane-2-thiones (steroidal cyclic cis-dithiocarbonates) (CLX a-c) in high yields.

Bettadaiah \textit{et al.}\textsuperscript{65} reported the synthesis of \(\alpha\)-bromoketone (CLXII) by the reaction of terpene epoxide (CLXI) with bromine and dimethyl sulfide.
Similarly benzylic epoxide (CLXIII) on reaction with bromine and dimethyl sulphide gave $\alpha$-bromoaldehyde (CLXIV) in good yield.\textsuperscript{65}

\[ \text{Br}_2 / \text{DMS} \rightarrow \]

(CLXIII) \hspace{1cm} (CLXIV)

Madhusudhan \textit{et al.}\textsuperscript{66} treated epoxide (CLXV) with sodium azide to give azide alcohol (CLXVI) followed by its hydrogenation with 5\% Pd/C in ethyl acetate to afford amino alcohol (CLXVII) which was further treated with carbonyldiimidazole to give phenyl-2-oxo-1, 3-oxazolidine-5-carboxylates (CLXVIII).

\[ \text{NaN}_3 / \text{NH}_3\text{Cl} \rightarrow \text{H}_2\text{O} - \text{EtOH} \]

(CLXV) \hspace{1cm} (CLXVI)

\[ \text{Pd - C} / \text{H}_2 \text{Ethylacetate} \]

(CLXVII) \hspace{1cm} (CLXVIII)
DISCUSSION
Five membered cyclic carbonates have many synthetic uses and have generally been synthesized from corresponding diols and phosgene or related compounds. The reaction of oxirane with carbon dioxide has received much attention because of its simple operation, high yield and harmless nature of the reagents. Further, the reaction is one of the most effective methods to incorporate carbon dioxide into organic molecules. Although the reaction of oxirane with carbon dioxide so far had been carried out at high pressure > 50 atm. Recently lithium bromide or sodium bromide can be the effective catalyst for the reaction of oxiranes and carbon dioxide under atmospheric pressure.

Here, we have applied a convenient stereoselective method for the preparation of steroidal 1,3-dioxolan-2-ones and steroidal 1,3-oxothiolane-2-thiones at 100 °C in high yields by the reaction of 3β-acetoxy-5, 6α-epoxy-5α-cholestane (CLXIX), 3β-chloro-5, 6α-epoxy-5α-cholestane (CLXX), 3β-acetoxy-5α-bromo-6α-hydroxycholestan (CLXXI) and 3β-chloro-5α-bromo-6α-hydroxycholestan (CLXXII) with carbon dioxide and carbon disulphide in DMF and THF using sodium bromide as a catalyst. Here, the cis-isomers were selectively obtained as single product.
Reaction of $3\beta$-acetoxy-5, 6$\alpha$-epoxy-5$\alpha$-cholestone (CLXIX) with carbon dioxide:

$3\beta$-Acet oxy-5, 6$\alpha$-epoxy-5$\alpha$-cholestone (CLXIX) was taken in dimethyl formamide and treated with carbon dioxide gas in the presence of NaBr as catalyst at 100 °C with continuous stirring for 30 min. After completion of reaction, solvents were removed under reduced pressure and the residue was taken in diethyl ether. After usual work-up and chromatography over silica gel column a semi-solid compound (CLXXIII) was obtained in 70% yield.

Characterization of semi-solid compound as $3\beta$-acetoxy-5$\alpha$-cholestan $[S, 6\alpha$-$d][1', 3'-dioxolan-2'-one (CLXXIII):

The elemental analysis of the compound corresponded to the molecular formula C$_{30}$H$_{48}$O$_{5}$. Its IR spectrum showed characteristic absorption bands at 1735 (OCOCH$_{3}$)$_{2}$, 1710 (C=O) and 1030 cm$^{-1}$ (C–O). The $^1$HNMR spectrum of the compound (CLXXIII) showed a one-proton broad multiplet at $\delta$ 4.8 (w$\alpha$ = 16 Hz, axial) for C$_3\alpha$-proton, a double doublet for one proton at 3.9 (J = 8.4, 3.6 Hz) for C$_6\beta$-proton and a sharp singlet for three (acetoxy) protons at 2.02. Angular and side-chain methyl protons appeared at $\delta$ 1.15 (C$_{10}$–CH$_{3}$), 0.71 (C$_{13}$–CH$_{3}$), 0.89 and 0.81 (other methyl protons). Thus, on the basis of these
data the structure of the compound (LXV) was established as 3β-acetoxy-5α-cholestan [5,6α-d] 1',3'-dioxolan-2'-one.

**Reaction of 3β-chloro-5, 6α-epoxy-5α-cholestan (CLXX) with carbon dioxide:**

3β-Chloro-5, 6α-epoxy-5α-cholestan (CLXX) was similarly treated with carbon dioxide gas. After usual work-up and chromatography over silica gel column an oily compound (CLXXIV) was obtained in 68% yield.

![Chemical structures](CLXX to CLXXIV)

**Characterization of oily compound as 3β-chloro-5α-cholestan [5, 6α-d] 1', 3'-dioxolan-2'-one (CLXXIV):**

The elemental analysis of the compound corresponded to the molecular formula C_{28}H_{45}O_{3}Cl. It gave positive Beilstein test for chlorine. The IR spectrum showed absorption bands at 1715 (C = O), 1040 (C–O) and 710 cm\(^{-1}\) (C–Cl). The \(^1\)HNMR spectrum of the compound (CLXXIV) showed a broad multiplet for one proton at δ 4.11 (w \(\nu/2 = 15\) Hz, axial) for C₃α - H, a double doublet for one proton at 3.87 (\(J = 7.2, 2.8\) Hz) for C₅β-proton. Angular and side-chain methyl protons were observed at δ 1.10 (C₁₀–CH₃), 0.70 (C₁₃–CH₃), 0.95 and 0.81 (other methyl protons). Thus, these data suggested the structure
of oily product (CLXXIV) as 3\(\beta\)-chloro-5\(\alpha\)-cholestan [5, 6\(\alpha\)-d] 1', 3'-dioxolan-2'-one.

**Mechanism of the reaction:**

The following mechanism (Scheme-1) has been proposed for the stereoselective conversion of steroidal epoxides into the corresponding cyclic cis-carbonates.

![Scheme-1](image)
Stereochemistry of steroidal-1',3'-dioxolan-2'-one (steroidal cis-carbonates) (CLXXIII) and (CLXXIV):

It is proposed that this reaction proceeds via nucleophilic attack of bromide ion at the less substituted (C-6) position of the steroidal epoxides (CLXIX) and (CLXX) and cyclization of the resulting carbonate anion by the nucleophilic attack of oxygen at C-6 (Scheme-1). The reaction of epoxide with sodium bromide is the rate determining step for the reaction of epoxide with carbon dioxide. These cis carbonates (CLXXIII) and (CLXXIV) were obtained selectively from the reaction of epoxide (CLXIX) and (CLXX) with carbon dioxide by double SN2 inversion on the epoxide ring at C-6.

Reaction of 3β-acetoxy-5α-bromo-6α-hydroxycholestan (CLXXI) with carbon disulphide:

3β-Acetoxy-5α-bromo-6α-hydroxycholestan (CLXXI) in THF was treated with carbon disulphide at room temperature, and the reaction was stirred for 5-6 h. After completion of reaction, the reaction mixture was concentrated, cooled and taken in diethyl ether. It was usually worked up and chromatographed over silica gel column to give a semi-solid compound (CLXXV) in 73.65 % yield.
Characterization of semi-solid compound (CLXXV) as 3β-acetoxy-5α-cholestan [5, 6α-d] 1',3'-oxathiolan-2'-thione:

The elemental analysis of the compound corresponded to the molecular formula C_{30}H_{48}O_{3}S_{2}. The IR spectrum showed characteristic absorption bands at 1730 (OCOCH₃), 1190 (C=S), 1035 (C−O) and 610 cm⁻¹ (C−S). The ¹HNMR spectrum of the product (CLXXV) showed a broad multiplet at δ 4.9 (w ½ = 17 Hz, axial) for C₃α - proton, a double doublet for one proton at 3.98 for (J = 7.4, 3.2 Hz) C₆β - proton and a sharp singlet for three protons (acetoxy group) at 2.01. Angular and side – chain methyl protons appeared at δ 1.12 (C₁₀–CH₃), 0.68 (C₁₃–CH₃), 0.98 and 0.88 (other methyl protons). Thus, the above data suggested the structure for compound (LXVII) as 3β-acetoxy-5α-cholestan [5, 6α-d] 1',3'-oxathiolane-2'-thione.

Reaction of 3β-chloro-5α-bromo-6α-hydroxycholestan (CLXXII) with carbon disulphide:

3β-Chloro-5α-bromo-6α-hydroxycholestan (CLXXII) in THF on similar treatment with carbon disulphide at room temperature and after usual workup and chromatography over silica gel column provided an oily compound (CLXXVI) in 71 % yield.

![Chemical Structures](image)
Characterization of oily compound (CLXXVI) as 3\(\beta\)-chloro-5\(\alpha\)-cholestan [5, 6\(\alpha\)-d] 1',3'-oxathiolan-2'-thione:

The elemental analysis of the compound corresponded to the molecular formula \(\text{C}_{28}\text{H}_{45}\text{OS}_{2}\text{Cl}\). It gave positive Beilstein test for chlorine. The IR spectrum showed characteristic absorption bands at 1180 (C=S), 1030 (C-O), 710 (C-Cl) and 600 cm\(^{-1}\) (C-S). The \(^1\text{HNMR}\) spectrum of compound (CLXXVI) exhibited a broad multiplet for one proton at \(\delta 4.12\) (\(\gamma/2 = 15\) Hz, axial) for C\(_3\alpha\) - H, a double doublet for one proton at 3.9 (J = 8.1, 3.4 Hz) for C\(_6\beta\)-proton. Angular and side-chain methyl protons were observed at \(\delta 1.16\) (C\(_{10}\)-CH\(_3\)), 0.68 (C\(_{13}\)-CH\(_3\)), 0.94 and 0.84 (other methyl protons). Thus, on the basis of the above data the oily product (CLXXVI) has been characterized as 3\(\beta\)-chloro-5\(\alpha\)-cholestan [5, 6\(\alpha\)-d] 1',3'-oxathiolan-2'-thione.

**Mechanism of the reaction:**

The following mechanism (Scheme-2) has been proposed for stereoselective conversion of 3\(\beta\)-acetoxy-5\(\alpha\)-bromo-6\(\alpha\)-hydroxycholestane (CLXXI) and its S/S'-chloro analogue (CLXXII) into corresponding cyclic cis dithiocarbonates (CLXXV and CLXXVI).

![Scheme 2](image-url)
EXPERIMENTAL
All melting points were recorded on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr / Nujol / Neat with Perkin Elmer 1600 FTIR spectrophotometer. The $^1$HNMR spectra were run in CDCl$_3$ on Varian VXR-300s machine with Me$_4$Si as the internal standard and its values are given in ppm ($\delta$). The abbreviations s, singlet; br, broad; m, multiplet centered at; d, doublet; dd, double doublet; t, triplet. Thin layer chromatographic (TLC) plates were coated with silica gel G and 20% aqueous solution of perchloric acid was used as spraying agent. Light petroleum ether refers to a fraction of b.p. 60-80°C and ether refers to diethyl ether. Sodium sulphate anhydrous was used as the drying agent.

**3β-Acetoxycholest-5-ene:**

A mixture of cholesterol (50 g), pyridine (75 ml) and freshly distilled acetic anhydride (50 ml) was heated on a water bath for 2 h. A brown solution was obtained which after being allowed to cool at room temperature was poured into crushed ice-water with stirring. A white solid thus obtained was filtered under suction, washed with water and air dried. The crude acetate was recrystallized from acetone which gave 3β-acetoxycholest-5-ene (45 g), m.p. 113-114°C (reported$^7$ m.p. 115-116°C).

**3β-Acetoxy-5, 6α-epoxy-5α-cholestan-16-ene (CLXIX):**

3β-Acetoxycholest-5-ene (11 g) in chloroform (100 ml) was treated with a solution of m- chloroperbenzoic acid (1.1 mol equivalent) in chloroform and left at – 8°C for 20 h. The reaction mixture was then washed successively with ice cooled water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent provided (CLXIX) as semi-solid which was crystallized from acetone as needles to afford epoxide (CLXIX) (8.4 g), m.p. 97°C (reported$^8$ m.p. 97°C).
Reaction of 3β-acetoxy-5, 6α-epoxy-5α-cholestan (CLXIX) with carbon dioxide: 3β-Acetoxy-5α-cholestan [5, 6α-d] 1',3'-dioxolan-2'-one (CLXXIII):

3β-Acetoxy-5, 6α-epoxy-5α-cholestan (CLXIX) (1.0 g, 2.252 mmol) in DMF (Dimethyl Formamide) (30 ml) was taken in two necked round bottom flask and added few crystals of sodium bromide as a catalyst. The solution was stirred for 10 min. at room temperature and then carbon dioxide gas was passed into the solution (carbon dioxide gas is prepared from CaCO₃ and dilute H₂SO₄) with continuous stirring and heating at 100 °C for 30 min. Progress of the reaction was monitored by the TLC. After completion of reaction, the solvent was removed under reduced pressure and the residue thus obtained was dissolved in ether, washed with water (4-5 times each with 30 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel column. Elution with light petroleum ether-diethyl ether (17:1) provided 3β-acetoxy-5α-cholestan [5, 6α-d] 1',3'-dioxolan-2'-one (CLXXIII) as a semi-solid (0.769 g).

Analysis found  :  C, 73.67; H, 9.93

C₃₀H₄₈O₅ requires  :  C, 73.72; H, 9.90%

IR  :  ν_{max} 1735 (OCOCH₃), 1710 (C = O) and 1030 cm⁻¹ (C – O).

¹H NMR (CDCl₃)  :  δ 4.8 (br, m, 1H, w ½ = 16Hz, axial, C₃α – H), 3.9 (dd, 1H, J = 8.4, 3.6 Hz, C₆β – H), 2.02 (s, 3H, OCOCH₃), 1.15 (C₁₀ – CH₃), 0.71 (C₁₃ – CH₃), 0.89 and 0.81 (other methyl protons).
3\textbeta-Chlorocholest-5-ene:

Freshly purified thionyl chloride (37 ml) was added gradually to cholesterol (50 g) at room temperature. A vigorous reaction ensured with evolution of gaseous products. When the reaction slackened, the reaction mixture was gently heated at a temperature of 50-60 °C on a water bath for one h and then poured into cold water with constant stirring. The yellow solid thus obtained was filtered under suction, washed several times with ice cold water and air dried. Recrystallization from acetone gave 3\textbeta-chlorocholest-5-ene (46 g), m.p. 95 °C (reported\textsuperscript{85} m.p. 96-97 °C).

3\beta-Chloro-5, 6\alpha-epoxy-5\alpha-cholestan (CLXX):

3\beta-Chlorocholest-5-ene (11 g) in chloroform (100 ml) was treated with a solution of m-chloroperbenzoic acid (1.1 mol equivalent) in chloroform and left at -8°C for 20 h. The mixture was then washed successively with ice cooled water, sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil, which was crystallized from acetone to give (CLXX) as needles (8.1 g), m.p. 89 °C (reported\textsuperscript{86} m.p. 89-90 °C).

Reaction of 3\beta-chloro-5, 6\alpha-epoxy-5\alpha-cholestan (CLXX) with carbon dioxide : 3\beta-Chloro-5\alpha-cholestan [5, 6\alpha-d] 1', 3'-dioxolan-2'-one (CLXXIV):

In a 100 ml two necked round bottom flask, 3\beta-chloro-5, 6\alpha-epoxy-5\alpha-cholestan (1.0 g, 2.375 mmol) in DMF (30 ml) was treated with catalytic amount of sodium bromide. The solution was stirred for 10 min. and then carbon dioxide gas was passed into the solution (carbon dioxide gas is prepared in another flask from CaCO\textsubscript{3} and dilute H\textsubscript{2}SO\textsubscript{4}) with continuous stirring and heating at 100 °C for 30 min. Progress of the reaction was monitored by the TLC. After completion of reaction, the solvent was removed under reduced
pressure and the residue thus obtained was dissolved in ether, washed with water (4 – 5 times each with 30 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel column. Elution with light petroleum ether-diethyl ether (16: 1) provided 3β-chloro-5α-cholestan [5, 6α-d] 1',3'-dioxolan-2'-one (CLXXIV) as an oily compound (0.748 g) (Beilstein positive).

Analysis found: C, 72.34; H, 9.79

C28H45O3Cl requires: C, 72.30; H, 9.75%

IR: νmax 1715 (C = O), 1040 (C – O) and 710 cm⁻¹ (C – Cl).

¹HNMR (CDCl₃): δ 4.11 (br, m, 1H, w ½ = 15Hz, axial, C₃α - H), 3.87 (dd, 1H, J = 7.2, 2.8 Hz, C₆β - H), 1.10 (C₁₀ - CH₃), 0.70 (C₁₃ - CH₃), 0.95 and 0.81 (remaining methyl protons).

3β-Acetoxy-5α-bromo-6α-hydroxycholestan (CLXXI):

3β-Acetoxycholestan-5-ene (12 g) was dissolved in ether (200 ml) and cooled to 0 °C. To this was added perchloric acid (1.6 ml) and N-bromosuccimide (9.6 g). The mixture was then stirred at room temperature for two h. The reaction mixture was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a solid which was recrystallized from petroleum-ether to give 3β-acetoxy-5α-bromo-6α-hydroxycholestan (CLXXI), (6 g), m.p. 161 °C (reported⁸⁷ m.p. 162 °C).
Reaction of 3β-acetoxy-5α-bromo-6α-hydroxycholestane (CLXXI) with carbon disulphide: 3β-Acetoxy-5α-cholestan [5, 6α-d] 1', 3'-oxathiolan-2'-thione (CLXXV):

3β-acetoxy-5α-bromo-6α-hydroxycholestane (CLXXI) (1.0 g, 1.904 mmol) in THF (30 ml) was treated with carbon disulphide (0.13 ml, 2.152 mmol) and the mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure and the residue thus obtained was dissolved in ether, washed with water (4-5 times each with 30 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel column. Elution with light petroleum ether - diethyl ether (15:1) provided 3β-acetoxy-5α-cholestan [5, 6α-d] 1', 3'-oxathiolan-2'-thione (CLXXV) as a semi-solid (0.729 g).

Analysis found : C, 69.15; H, 9.31

C_{30}H_{48}O_{3}S_{2} requires : C, 69.18; H, 9.28%

IR : \nu_{\text{max}} 1730 (OCOCH_{3}), 1190 (C = S), 1035 (C – O) and 610 cm^{-1} (C – S).

^1{H}NMR (CDCl_{3}) : \delta 4.9 (br, m, 1H, w \gamma/2 = 17Hz, axial, C_{3}\alpha - H), 3.98 (dd, 1H, J = 7.4, 3.2 Hz, C_{6}\beta - H), 2.01 (s, 3H, OCOCH_{3}), 1.12 (C_{10} - CH_{3}), 0.68 (C_{13} – CH_{3}), 0.98 and 0.88 (other methyl protons).

3β-Chloro-5α-bromo-6α-hydroxycholestane (CLXXII):

3β-Chlorocholest-5-ene (12 g) was dissolved in ether (200 ml) and cooled to 0 °C. To this was added perchloric acid (1.6 ml) and N-bromocessimide (9.6 g). The mixture was then stirred at room temperature for 2 h. The reaction mixture was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a solid,
which was recrystallized from petroleum-ether to give 3\(\beta\)-chloro-5\(\alpha\)-bromo-6\(\alpha\)-hydroxycholestane (CLXXII), (6 g), m.p. 161 °C (reported m.p. 162 °C).

**Reaction of 3\(\beta\)-chloro-5\(\alpha\)-bromo-6\(\alpha\)-hydroxycholestane (CLXXII) with carbon disulphide:**

3\(\beta\)-Chloro-5\(\alpha\)-bromo-6\(\alpha\)-hydroxycholestane (CLXXII) (1.0 g, 1.992 mmol) in THF (30 ml) was treated with carbon disulphide (0.13 ml, 2.152 mmol) and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure and the residue thus obtained was dissolved in ether, washed with water (4-5 times each with 30 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel column. Elution with light petroleum ether-diethyl ether (14:1) provided 3\(\beta\)-chloro-5\(\alpha\)-cholestan [5, 6\(\alpha\)-\(d\)] 1',3'-oxathiolan-2'-thione (CLXXVI) as a semi-solid (0.703 g) (Beilstein positive).

Analysis found : C, 67.66; H, 9.08

C\(_{28}\)H\(_{45}\)OS\(_2\)Cl requires : C, 67.63; H, 9.12%

IR : \(\nu_{\text{max}}\) 1180 (C = S), 1030 (C - O), 710 (C - Cl) and 600 cm\(^{-1}\) (C - S).

\(^1\)HNMR (CDCl\(_3\)) : \(\delta\) 4.12 (br, m, 1H, w \(\nu = 15\)Hz, axial, C\(_{3}\)\(\alpha\) - H), 3.9 (dd, 1H, J = 8.1, 3.4 Hz, C\(_{6}\)\(\beta\) - H), 1.16 (C\(_{10}\) - CH\(_3\)), 0.68 (C\(_{13}\) - CH\(_3\)), 0.94 and 0.84 (other methyl protons).
REFERENCES


