Chapter Three

Steroidal Lactam
Theoretical
The Beckmann rearrangement and Schmidt reaction are the two most frequently employed method for the insertion of nitrogen atom into the steroidal frame work. Other methods for preparation of such hetero steroids include imide synthesis, curtuis and Hofmann rearrangement, total synthesis etc. Photochemical reaction and microbiological amidition\textsuperscript{15-16} have also been used for the preparation of diffa- azasteroids analogues. The photochemical rearrangement which usually require strongly acidic condition cause serious problems such as low regioselectivity of the reaction or decomposition of products\textsuperscript{6-8}. Limitation of Schmidt reaction for the synthesis of number of substituted lactams led the scientists to replace hydrazoic acid with alkyl azide\textsuperscript{9-13}. In 1991 Aube \textit{et al.}\textsuperscript{14-15} accomplished intramolecular reaction of alkyl azides with ketone under remarkably mild and straightforward reaction condition.

Recent reports\textsuperscript{16} of obtaining various N-hydroxy lactam, and our continued interest in synthesis steroids prompted us to study the similar reaction with some steroidal substrates. This chapter deals with some of the more recent and pertinent examples regarding the preparation of lactams and the studies made for preparation of N-hydroxy lactams in the cholestane series.

The Schmidt reaction of 5\textalpha-cholestan-3-one (Ia) and its 5\textbeta-isomer (Ib) with sodium azide and polyphosphoric acid or the Beckmann rearrangement of their oximes (Ic) and (Id) afforded the 3-azasteroids (IIa) and (IIb)\textsuperscript{17} respectively.

\begin{align*}
\text{(I)} & \quad \text{(II)} \\
\text{(Ia)} & \quad \text{O; 5\textalpha-H} \\
\text{(Ib)} & \quad \text{O; 5\textbeta-H} \\
\text{(Ic)} & \quad \text{NOH; 5\textalpha-H} \\
\text{(Id)} & \quad \text{NOH; 5\textalpha-H} \\
\text{(IIa)} & \quad \text{5\textalpha-H} \\
\text{(IIb)} & \quad \text{5\textbeta-H}
\end{align*}
The photo-Beckmann rearrangement of the oxime (III) gave two isomeric lactams (IV) and 3-aza-A-homo-4a, 4a-dimethyl-5α-cholestan-4-one (V)\(^8\).

The Schmidt reaction of 3β-acetoxy-5α-bromocholan-6-one (VIa) afforded 3β-hydroxy-6-aza-B-homo-5α-bromocholan-7-one (VIIa) while 5α-bromo-cholan-6-one (VIa) gave the lactams (VIIb) and 7-aza-B-homocholestan-4-en-6-one (VIII)\(^9\).

Doorenbos and Singh carried out the schmidt reaction of 5α-cholestan-3,6-dione (IX) using excess of sodium azide and obtained 3,6-diaza-A,B-bishomo-5α-cholestan-4,7-dione (X)\(^20\).
Ahmad and Co-workers\textsuperscript{21} carried out the schmidt reaction of cholesta-4,6-di-en-3-one (XI) and 6\textbeta-bromocholesta-4-en-3-one (XII) and obtained the same product, 3-aza-A-homo-cholesta-4a, 6-dien-4-one (XIII).

Cholesta-3,5-dien-7-one (XIV\textsubscript{a}) gave a single oxime (XIV\textsubscript{b}) which on the Beckmann rearrangement gave 7a-aza-B-homo-cholesta-3,5-dien-7-one (XV)\textsuperscript{22}.

\[
\begin{align*}
(X) & \\
(IX) & \rightarrow
\end{align*}
\]
Beckmann rearrangement of 26-acetoxyfurost-3,5-20(22)-trien-7-one oxime (XVI) furnished the lactam 26-acetoxy-7a-aza-B-homofurost-3,5,20(22)-trien-7-one (XVII)²³.

\[ \text{(XVI)} \quad \text{OAc} \quad \text{OAc} \quad \text{NOH} \quad \text{(XVII)} \]

The Beckmann rearrangement of 7-oximinodiosgeninacetate (XVIII) afforded 3β-acetoxy-7a-aza-B-homo-22a-spirost-5-en-7-one (XIX)²⁴.

\[ \text{(XVIII)} \quad \text{AcO} \quad \text{AcO} \quad \text{(XIX)} \]

Black and Johnstone²⁵ reported the synthesis of medium sized oxo-lactams (XXII) by opening of fused tricyclic oxaziridines (XXI) and nitrones (XXIII).

\[ \text{(XX)} \quad \text{OH} \quad \text{(CH₂)ⁿ} \quad \text{Me} \quad \text{Me} \quad \text{N} \quad \text{O} \quad \text{Fe}^{2+} \]

\[ \text{(XXa)} \quad n = 2 \]
\[ \text{(XXb)} \quad n = 1 \]

\[ \text{(XXI)} \quad \text{OH} \quad \text{(CH₂)ⁿ} \quad \text{Me} \quad \text{Me} \quad \text{N} \quad \text{O} \quad \text{Fe}^{2+} \]

\[ \text{(XXIa)} \quad n = 2 \]
\[ \text{(XXIb)} \quad n = 1 \]
Photo rearrangement of hydroxy nitrones (XXIIIa-d) in ethanol by mean of light of wavelength 254nm afforded mixture of isomeric oxaziridines (XXIII) which on treatment with iron (II) sulphate afforded the keto lactams (XIVa-d).

Ishibashi and Ikeda accomplished a novel synthesis of five, six and seven membered lactams (XXVI, XXVII, XXVIII, XXXI, XXXII and XXXIII) by alkene cyclization of N-alkenyl-α (methyl sulphinyl) acetamide (XXV, XXVa) and N-alkenyl-α-chloro-α- (methylthio)-5-acetamide (XXIX, XXX).
Hoffman and Salvador\cite{27} gave one flask conversion of cyclic ketones to N-methyl lactams (XXXVI). They reacted ketone with triethyl orthoformate to generate an acetal (XXXIV) which is reacted in situ with N(p-nitrobenzene- sulfonyl) oxy methyl amine (MeNH-OSO₂C₆H₄NsO₂). Dealkylation of the resulting O-ethylimidate (XXXV) with sodium iodide gave the lactam (XXXVI).
This method was considered as versatile and more efficient as compared to other methods effecting direct conversion of cyclic ketones with N-substituted lactams. (XXXVI). Conversion of cyclopropanes to N-substituted β-lactams by Wesserman's carbinol amine method is excellent but this procedure is not adaptable to large rings. This method is superior to photochemical rearrangement of oxaziridines and nitrones as the former requires preparation and isolation of oxaziridines by two step procedure followed by photolysis. The latter require isolation of N-methyl nitrone and gives much poorer yield.

Aube et al. have given the TiCl₄ mediated reaction of alkyl azides with cyclic ketones (XXXVII, XXXIX and XLII) resulting in formation of the product (XXXVIII, XL and XLI, XLIII and XLIV) respectively:

\[
\begin{align*}
\text{XXXVII} & \quad \rightarrow \quad \text{XXXVIII} \\
\text{R} &= \text{n-Hex}
\end{align*}
\]
Suda et al. reported manganese (III) tetraphenylporphyrin chloride \([\text{Mn(tpp)}] \) is a new and specific catalyst for stereo and regio-selective rearrangement of N-phenyl-spiro oxaziridine (XLV and XLVa) into lactams (XLVI, XLVIa and XLVIb).

Takacs and Weidener reported the synthesis of pentadienyl substituted lactams (L and LII) by the reaction of pentadienyl trimethylsilane, PDS with N-acyliminium ions (XLVII) intermediate and (XLVIIa) respectively.
Evan and Modi\textsuperscript{31} described a novel approach to Lactam (LV) via photo induced Schmidt rearrangement of the $\alpha$-azidotriisopropylsilyl ethers (LIV) which were obtained by direct azidonation of the triisopropylsilyl enol ethers (LIII).

\[ \text{LIII} \xrightarrow{\text{PPTS, TMSN}} \text{LIV} \xrightarrow{\text{hv}} \text{LV} \]

\[ \text{LVI} \xrightarrow{\text{PPTS, TMSN}} \text{LVII} \xrightarrow{\text{hv}} \text{LVIII} \]

\[ \text{LIX} \xrightarrow{\text{PPTS, TMSN}} \text{LX} \xrightarrow{\text{hv}} \text{LXI} + \text{LXII} \]

\[ \text{LXIII} \xrightarrow{\text{PPTS, TMSN}} \text{LXIV} \xrightarrow{\text{hv}} \text{LXV} \]

\[ X = \text{CH}_2 / \text{O} / \text{S} \]
Robert and Alper\textsuperscript{32} has developed the cobalt mediated carbonylation of 2-vinyl azetidines (LXVI) to afford ring expanded seven membered lactams (LXXII). The formation is explained as shown below.

\[
\begin{align*}
&\text{Co}_2(\text{CO})_8 \quad \text{Co}_4(\text{CO})_4 \quad \text{Co}_4(\text{CO})_4 \\
&(\text{LXVI}) \quad (\text{LXVII}) \quad (\text{LXVIII}) \\
&\text{Co}_4(\text{CO})_4 \quad \text{Co}_4(\text{CO})_4 \\
&(\text{LXX}) \quad (\text{LXXI}) \\
&\text{R'} = \text{H/CH}_2\text{CH}_2\text{COMe/CH}_2\text{CH}_2\text{COOMe/CH}_2\text{CH}_2\text{CN}
\end{align*}
\]

The Schmidt reactions on the chloro derivative of dimedone (LXXIII) give the lactams (LXXIV) and (LXXV) respectively. On the other hand, oxime of isophorone (LXXVIII) can be rearranged to the corresponding caprolactams (LXXIX) and (LXXX) respectively\textsuperscript{33}. These compounds shows central nervous system activity.\textsuperscript{33}
It is not clear whether the absence of the alternative rearrangement product (LXXXV) is due to the ready isomerizations of the (E)-oxime to the (Z)-oxime under the reaction condition or to the possibility that (LXXXV) does form but polymerizes under the reaction conditions.
Vedejs and Sano\textsuperscript{34} reported the preparation of N-methoxy lactams (XCII) and (XCIV), by use of ketones (XCI) and (XCIII) in the Beckmann type rearrangement.

Roberson and Noerpel\textsuperscript{35} have reported the synthesis of β-lactams (XCVII) by the use of [3+2] Annulation of Allylsilanes (XCVI) and chlorosulfonyl isocyanate. Chlorosulfonyl isocyanate reacted with the α-substituted allylsilane at room temperature in toluene to give pyrrolidinone (XCVI), the product on reduction provided the stable lactam (XCVII).
Averra et al.\textsuperscript{36} have reported the synthesis of enantiopure 4-[1-alkylsulfinyl vinyl]-1,2-dihydronaphthalenes (XCIX, C, CI and CII) and their Diels-Alder reaction are described. Cycloaddition with N-phenylmaleimide occur under thermal condition, very slowly but with notable stereoselection, giving in each just one of the two endo adducts in high yield. The 16-azasteroids skeleton (XCIX, C, CI and CII) derivative undergo chiral auxiliary removal in the presence of iodotrimethylsilane (TMSI).

A selection of azapeptidomimetics containing constraining lactam ring (CIV) have been prepared by Mitsunobu cyclization\textsuperscript{37,38} of serine/homologated serivazaalanine derivatives. A novel azaaminoacid acylation method was developed to sterically
demanding α-benzyl-serine-azaalaming precursor. The Mitsunobu condition were highly efficient in forming the desired azapeptidomimetic lactams (CIV).

\[
\begin{align*}
\text{(CIII)} & \quad \text{(CIV)} \\
\end{align*}
\]

Cremonesi et al.\(^1\) have reported the synthesis of spiro-β-lactams (CVIII and CIX) which were prepared by means of a staudinger ketone-imine reaction starting from optically active N-Boc-1,3-thiazolidine-2-carboxylic acid derivatives (CV) and imines (CVI). The reaction was stereoselective and afforded spiro-β-lactams (CVIII and CIX) with a relative trans-configuration. The absolute configuration of the new stereocentres was assigned on the basis of the well-accepted mechanism and confirmed by means of X-ray crystals structure analysis.

\[
\begin{align*}
\text{(CV)} & \quad \text{(CVI)} \\
\text{(CVII)} & \quad \text{(CVIII)} \\
\text{(CIX)} & \quad R = \text{Me} / \text{Ph} / \text{OtBu} \\
R_1 = \text{CH}_2\text{Ph} / \text{Ph} / \text{MeOPh} / \text{SO}_2\text{Ph}
\end{align*}
\]
Banik et al.\(^4\) have reported the stereocontrolled synthesis of novel β-lactams (CXII). It is prepared by using polyaromatic imines (CXI) with acid chloride (CX) (equivalent) under the staudeger reaction\(^2\). The effect of the domestic microwave irradiation on this type of reaction has been investigated. The presence of an acetoxy group has proven obligatory for their anticancer activity\(^4\).

\[
\text{ZCH}_2\text{COCl} + \text{(CXI)} \xrightarrow{\text{TEA/CH}_2\text{Cl}_2} \text{CXII}
\]

\[Z = \text{OAc/OPh}\]

Rachid Touzani and Howard Alper\(^3\) have reported the synthesis of five, six or seven membered ring lactones and lactams by cyclocarboxylation methodology using PAMAM dendrimer-palladium complex catalyzed. Palladium complexes immobilized onto generation 0-3 PAMAM dendrimers supported on silica in the presence of 1,4-bis(diphenylphosphino) butane, were used as catalysts for the cyclocarboxylation of 2-allylphenols, (CXIII) affording lactons (CXV) and lactams (CXVI) respectively.

\[
\begin{align*}
\text{(CXIII)} & \rightarrow \text{(CXIV)} + \text{(CXV)} + \text{(CXVI)} \\
\end{align*}
\]

Carvalho de Souza and Kelly Chibale\(^\alpha\) have given a synthesis of a new series of 4-aminoquinoline γ- and δ-lactams (CXIX) synthesized via Ugi 3-component 4-centre multicomponent is described by the following reaction.
Troisi et al.\textsuperscript{45} have reported the synthesis of 4-heterosubstituted β-lactams (CXXIV). It is prepared by use a palladium-catalyzed \( [2+2] \) carbonylative cycloaddition of allylbromide (CXXI) with heteroaryliden-anilines (CXX) afforded 2-azetidinones N-phenyl substituted (CXXII), with a heteroaryl moiety linked at the C\(_4\) carbon, and an alkenyl group at C\(_3\) carbon. The C\(_3\) and the C\(_4\) positive could be further functionalized inserting alkyl and hydroxyl group in the azetidinone ring, through the generation of a stable azetidinyl anion then captured by various electrophiles.

Penhoat et al.\textsuperscript{46} have given a new Mayer's bicyclic lactam (CXXVI) which is structurally related to circumdatins, benzomalvins and asperlicins. An alternative procedure making use of the activating agent of carboxylic acid (CXXV) (Mukaiyama reagent and FEP) allowed the lactamization process to take place under milder condition (CH\(_2\)Cl\(_2\)/20°C) affording trans-(\(aS, R, S\)) (CXXVI) in a fair good yield (\(50-85\%\)).
Arumugam et al. have reported a highly regio- and stereoselective synthesis of novel spiro pyrrolidines/pyrrolizidines containing β-lactam and oxazolone moieties (CXXX) different conditions.

Liu et al. reported an efficient synthesis of functionalized α-amino caprolactams (CXXXIII) using ring-closing metathesis (RCM). The key intermediate is α-amino α,β-unsaturated caprolatam (CXXXII), and this was obtained from (CXXXI) by
RCM of α-amino acrylamide as a key step using Grubbs' second-generation-catalyst B.

Kayser et al.\textsuperscript{49} described the homochiral 3-hydroxy-4-substituted β-lactams (CXXXVII-CXL), which serve as precursors to corresponding α-hydroxy-β-amino acids—key components of many biological and therapeutically important compounds.

A bicyclic N-substituted β-lactams (CXLIV and CXLV) were prepared by the condensation of cyclic alkene (CXL) with chloro-sulfonyl isocyanates (CXLII) gave an intermediate N-chlorosulfonyl β-lactams (CXLIII) in 70% yield. Hydrolysis of (CXLIII) gave the resultant products (CXLIV and CXLV) respectively.\textsuperscript{50}
Koutsourea et al.\textsuperscript{51} have given a new synthetic procedure for the preparation of steroidal B-D bilactams (CLIV and CLV) respectively. 3β-Hydroxy-7α, 17α-diaza-B,D-dihomo-5-androsten-7,17-dione (CLV), prepared by using the 3β-acetoxy-5-androsten-17-one (CXLVI) as starting material and ketalization of the 17-ketone and allylic oxidation to the 7-ketone which followed by the Beckmann rearrangement at the B and D-steroid ring.
(CXLVIII) → iii. → (CXLIX) → iv. → (CL) ← v. → (CLI) → vi. → (CLII) → vii. → (CLIII) → viii. → (CLIV) → (CLV)
Reagent and conditions

i. P-TsOH / TEOF / ethylene glycol 90°C one hour.

ii. CrO₃ / 3,5-DMP / dry dichloromethane, -20°C five hours.

iii. H₂NOH. HCl / C₅H₅N, EtOH, R.T. ten hours.

iv. SOCl₂ / THF, 0°C eight hours.

v. aq HCl, RT, 1h 30 min.

vi. H₂NOH. HCl / C₅H₅N, EtOH reflux, two hours.

vii. SOCl₂ / dioxane R.T. five hours.

viii. LiOH / MeOH IN RT one hour.
Discussion
After the discovery of the penicillins and the cephalosporin, the past few decades have witnessed a remarkable growth in the field of β-lactams chemistry, as this heterocycle is a strategic component of various antibacterial agents. The need for potent and effective β-lactam antibiotic, as well as more effective enzyme inhibitors, has motivated synthetic organic chemists to design new functionalized 2-azetidinones. Application of β-lactams in medicinal chemistry include their use as therapeutic agent for lowering the cholesterol level in plasma, as antitumor agent and as enzyme inhibitors (for example inhibitors of cysteine proteases), the substituted hydroxy β-lactams have been the starting materials in the semisynthesis of paclitaxel (taxol) and docetaxel (taxotere). Our continuing studies, more specifically, spiro-β-lactams are interesting because they can act as antiviral, antibacterial agent and also inhibit cholesterol absorption. They are also β-lurn mimetics, the 4-spiro-β-lactams in particular being synthetic precursor of cyclic α,α-disubstituted β-amino acids and peptide derivatives. Recently, J.D. Hansen et al. have described the synthesis of spirolactams (CLVI) that display high binding affinity towards CCR4, which is a G-protein coupled receptor that binds, two chemokines, macrophage derived chemokine (MDC) and thymus and activation regulated chemokins (TARC). CCR4 antagonists as novel agent for treatment of asthma and atopic dermatitis. To extend our study, in the last years several papers have been published on the synthesis of caprolactams which shown to exhibit biological as well as physiological activities. In this regards, recently L.A. Thompson et al. reported a variety of substituted amino caprolactams (CLVII) inhibitors of the Alzheimer's disease-γ-secretase. Genetic evidence obtained from familial form of AD suggest that increased production of 42 amino acid form of Aβ has a primary role in the disease. The Aβ peptides are generated by successive cleavages of amyloid precursor protein (APP), by β and γ-secretase which have emerged as strong therapeutic targets for AD intervention. The most potent hit identified was SR 973 (CLVII) and amino caprolactam succinate derivative which block Aβ formation with IC₅₀ = 0.2μm.
J.C. Pelletier et al.\textsuperscript{71} have given the preparation of highly substituted \(\gamma\)-lactams (CXLVI) follicle stimulating hormone receptor agonists. Follicle stimulating hormones (FSH) is a 38KDA protein that triggers maturation of ovarian follicles in women and spermatogenesis in men.

Recently M. Nivasarkar et al.\textsuperscript{72} have reported a series of bicyclic N-substituted and unsubstituted \(\beta\)-lactams which were synthesized and evaluated as targeted potential antimalerials. The compounds MNR4 (CLIX) and MNRS (CLX) were found to have highest potency against Plasmodium falciparum in vitro. Hetero-steroids are regarded by synthetic chemists as attractive target molecules because of their important bioactivities and the effect that even minor structural modifications of their skeleton can play on their biological role. For instance, the incorporation of a nitrogen atom in the steroidal system helps the formation of stable substrate-enzyme complexes which are the foundations of antibacterial, antifungal, and many other kind of activities shown by azasteroids\textsuperscript{73-77}. These compounds were found to display a broad spectrum of biological activities\textsuperscript{78-85}. The survey of literature reveals that the several papers dealing with the preparation of steroidal lactams have appeared from our laboratories\textsuperscript{86-91} following different procedures.

\[
X_1 \quad \text{CCR4 receptor antagonists (CLVI)}
\]
Follicle stimulating hormone; FSH (CLVII)

Alzheimer's disease \( \gamma \)-secretase (CLVIII)

MNR4 (CLIX)

MNR5 (CLX)
Despite the development of a variety of new methods the Schmidt and Beckmann reaction remain the most convenient and general methods for steroidal lactams synthesis. In this chapter we reported the use of slightly modified version of Schmidt reaction as described by Aube et al.\textsuperscript{92,93} where hydrazoic acid has been replaced by hydroxy alkyl azide \textsuperscript{16, 28,92,93}. The purpose of this investigation is to extend the scope of these reactions in the preparation of hetero N-hydroxy alkyl lactams from easily accessible steroidal \(\alpha,\beta\)-unsaturated ketones such as 3\(\beta\)-acetoxycholest-5-en-7-one (CLXI) 3\(\beta\)-chlorocholest-5-en-7-one (CLXII) 3\(\beta\)-hydroxycholest-5-en-7-one (CLXIII) and cholest-4-en-3-one (CLXIV). The ketones (CLXI-CLXIV) were 2-hydroxy-2-phenylethylazide and the products obtained were characterized on the basis of their spectral and chemical methods.

\[
\begin{align*}
\text{(CLXI)} & \quad X = \text{AcO} \\
\text{(CLXII)} & \quad X = \text{Cl} \\
\text{(CLXII)} & \quad X = \text{OH}
\end{align*}
\]
Reaction of 3β-acetoxycholest-5-en-7-one (CLXI) with 2-hydroxy-2-phenylethylazide in presence of BF₃-etherate: N-2-phenylethenyl-7a-aza-B-homo-3β-acetoxycholest-5-en-7-one (CLXV)

3β-Acetoxycholest-5-en-7-one (CLXI: 200mg: 0.45mmol) was allowed to react with 2-hydroxy-2-phenylethylazide (250mg: 1.54mmol) in dichloromethane (15ml) the reaction mixture was cooled to 0°C. BF₃-etherate (0.5ml) was added dropwise over 5 minutes immediate gas evaluation was noticed upon addition. The reaction mixture was stirred. The progress of the reaction was determined by the TLC. After the completion of the workup, evaporation of solvent obtained residual oil which crystallized with methanol afforded a solid (CLXV) m.p. 110°.
Characterization of the compound m.p. 110\(^\circ\) as N-2-phenylethenyl-7a-aza B-homo-3\(\beta\)-acetoxycholest-5-en-7-one (CLXV)

The compound m.p. 110\(^\circ\) was analysed for C\(_{37}\)H\(_{53}\)NO\(_3\) indicating that the reagent 2-hydroxy-2-phenylethylazide is incorporated. The I.R. spectrum of the compound showed a weak absorption band at 3033, 1626 cm\(^{-1}\) could be assigned for the aromatic ring. Bands at 1715 and 1248 cm\(^{-1}\), were assigned for (OAc,\(\beta\)-oriented) and at cm\(^{-1}\) 1660 for \(\alpha,\beta\)-unsaturated lactam. Other bands were exhibited at 1605 for (C=C) and 1350 cm\(^{-1}\) for (C-N). These values supported the presence of lactam moiety\(^94\).

On the basis of elemental analysis and I.R. two isomeric structure are possible for compound m.p. 110\(^\circ\). The distinction between the two structures (CLXV) and (CLXVI) could be made on the basis of its \(^1\)HNMR spectral study which showed a multiplet at \(\delta 7.46\) integrating for the five protons which can be assigned to the protons of aromatic ring. Another multiplet ranging \(\delta 6.30-6.39\) integrating for two protons could be assigned to the protons of N-CH\(_2\) and \(=\mathrm{CH}-\mathrm{Ar}\). A singlet at \(\delta 5.8\) integrating for one proton indicated the presence of a vinylic hydrogen at \(\mathrm{C}_6-\mathrm{H}\) as in structure (CLXV). A multiplet centered at \(\delta 2.6\) integrating for one proton is assigned to \(\mathrm{C}_8-\beta\mathrm{H}\) although one expected it to be at \(\sim \delta 3.3\) but in the alternate structure the same proton would not be shifted down beyond \(\delta 2.3\) therefore this is taken as \(\mathrm{C}_8-\beta\mathrm{H}\) structure (CLXV) and the slight upfield shift may be due to the field generated by the aromatic ring. A multiplet was observed, integrating for one proton at \(\delta 3.9\) (\(J_\alpha/\beta=16\)Hz) which could be attributed to \(\mathrm{C}_3-\alpha\mathrm{H}\), axial proton (A/B ring junction trans)\(^95\). The acetate methyl protons were seen at \(\delta 2.1\) as sharp singlet. The angular and side chain methyls were observed at \(\delta 1.16, 1.14, 1.10\) and 0.94.

In the light of foregoing discussion the compound, m.p. 110\(^\circ\), is tentatively characterized as N-2-phenylethenyl-7a-aza-B-homo-3\(\beta\)-acetoxycholest-5-en-7-one (CLXV).
Reaction of 3β-chlorocholest-5-en-7-one (CLXII) with 2-hydroxy-2-phenylethylazide in presence of BF₃-etherate: N-2-phenylethenyl-7α-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII)

The ketone (CLXII) was allowed to react with 2-hydroxy-2-phenylethylazide in dichloromethane as described earlier. After the completion of the workup, evaporation of solvents, residual oil obtained was crystallized from methanol which afforded a solid m.p. 103°.

\[ \text{CLXII} \]

\[ \text{CLXVII} \]

\[ \text{CLXVIII} \]
Characterization of the compound solid m.p. 103° as N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII)

The compound m.p. 103° was analysed for C_{35}H_{50}NOCl indicating that the reagent 2-hydroxy-2-phenylethylazide is incorporated. The I.R. spectrum of the compound showed bands 3024, 1623 could be assigned for aromatic ring, 1665 for α,β-unsaturated lactams, 1597 (C=C), 1360 (C-N) and 708 cm\(^{-1}\) (C-Cl). These values supported the presence of lactam moiety.

On the basis of the elemental analysis and I.R. two possible isomeric structures (CLXVII) and (CLXVIII) can be written the m.p. 103°. The distinction is based on its \(^1\)HNMR spectral study. \(^1\)HNMR spectrum showed a multiplet at δ 7.40 integrating for five protons can be assigned to the protons of aromatic ring. Another multiplet in the range δ6.07-6.16 integrating for two protons could be assigned to the proton of N-CH\(_2\) and =CH-Ar. A singlet at δ 5.6 integrating for one protons indicated the presence of a vinylic protons at C\(_6\)-H. A multiplet was observed integrating for one proton at δ3.4 (\(^1\)J\(_{\text{HH}}\)=16Hz) which could be attributed to C\(_3\)-α-H, axial proton (A/B ring junction trans). The angular and side chain methyl protons were observed at δ1.11, 1.02, 0.93, 0.91, 0.87 and 0.71. These values discarded the structure (CLXVIII) in favour of (CLXVII).

In the light of foregoing discussion and in analogy with the previous compound (CLXV) the compound m.p. 103° is tentatively characterized as N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII).

Reaction of 3β-hydroxycholest-5-en-7-one (CLXIII) with 2-hydroxy-2-phenylethylazide in the presence of BF\(_3\)-etherate: N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX)

The ketone (CLXIII) was allowed to react with 2-hydroxy-2-phenylethylazide in dichloromethane as described earlier. After the completion of the workup, evaporation of solvents, residual oil obtained failed to crystallize. The oil was subjected to column chromatography and elution with petroleum ether gave N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX) as a pure entity.
Characterization of the compound oil as N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX)

The oil (CLXV) was analysed for C_{35}H_{51}NO_{2} indicating that the reagent 2-hydroxy-2-phenylethylazide is incorporated. The I.R. spectrum of the compound showed band at 3185-3366 cm\(^{-1}\) which can be assigned to (-OH), the bands at 3070, 1631 cm\(^{-1}\) could be assigned for aromatic ring, 1662 cm\(^{-1}\) for α,β-unsaturated lactam. Other bands were exhibited at 1615 (C=C) and 1348 (C-N) cm\(^{-1}\). These values supported the presence of lactam moiety.

On the basis of the elemental analysis and I.R. two possible isomeric structures (CLXIX) and (CLXX) can be written the oil. The distinction is based on its \(^1\)HNMR spectral study. \(^1\)HNMR spectrum showed a multiplet at δ 7.18 integrating for five protons can be assigned to the protons of aromatic ring. Another multiplet at δ 6.23-6.31 integrating for two protons could be assigned to the proton of N-CH and =CH-Ar. A singlet at δ 5.29 integrating for one proton indicated the presence of a vinlylic
protons at C₆-H. A multiplet was observed integrating for one proton at δ 4.7 (W/2=17Hz) which could be attributed to C₃-αH, axial proton (A/B ring junction trans). The hydroxy proton was seen at δ 4.1 as singlet. The angular and side chain methyl protons were observed at δ 1.0, 0.96, 0.90, 0.84 and 0.72. These values discarded the structure (CLXX) in favour of (CLXIX).

In the light of forgoing discussion the compound as oil is tentatively characterized as N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX).

**Reaction of cholest-4-en-3-one (CLXIV) with 2-hydroxy-2-phenylethylazide in the presence of BF₃-etherate: N-2-phenylethenyl-4-aza-A-homocholest-4a-en-3-one (CLXXI)**

The ketone (CXLIV) was allowed to react with 2-hydroxy-2-phenylethylazide in dichloromethane as described earlier. After the completion of the workup, evaporation of the solvents, residual oil obtained failed to crystallize. The oil was subjected to column chromatography and elution with petroleum ether gave N-2-phenylethenyl-4-aza-A-homocholest-4a-en-3-one (CLXXI) as a pure entity.
Characterization of the compound oil as N-2-phenylethenyl-4-aza-A-homocholest-4a-en-3-one (CLXXI)

The compound (CLXXI) was analysed for C_{35}H_{49}NO indicating that the reagent 2-hydroxy-2-phenylethylazide is incorporated. The I.R. spectrum of the compound showed bands at 3050, 1630 cm^{-1} which could be assigned for aromatic ring. Bands at 1658 cm^{-1} is ascribed to \( \alpha,\beta \)-unsaturated lactam. Other bands were exhibited at the 1600 (C=C) and 1352 cm^{-1} (C-N). These values supported the presence of lactam moiety.

On the basis of the elemental analysis and I.R. two possible isomeric structures (CLXXI) and (CLXXII) can be written the oil. The distinction is based on its \(^1\)HNMR spectral study. \(^1\)HNMR spectrum showed a multiplet at \( \delta \) 6.92-7.35 integrating for five protons which can be assigned to the protons of aromatic moiety. Another multiplet ranging \( \delta \) 6.07-6.15 integrating for two protons could be assigned to the proton of N-CH and =CH-Ar. A singlet at \( \delta \) 5.5 integrating for one proton indicated the presence of a vinylic proton at C_{4a}-H. The angular and side chain methyl protons were observed at \( \delta \) 1.18, 1.11, 1.06, 0.91, 0.87, 0.85, 0.8 and 0.71. These values discarded the structure (CLXXII) in favour of (CLXXI).

In the light of forgoing discussion the oil is tentatively characterized as N-2-phenylethenyl-4-aza-A-homocholest-4a-en-3-one (CLXXI).
Experimental
All the melting point are uncorrected. Infrared spectra (I.R) were measured in KBr with perkin-Elmer 237 and unichem SP 300 spectrophotometers. The I.R. values are given in cm\(^{-1}\) (s-strong, m-medium w-weak, br-broad). The \(^1\)HNMR spectra were run in CDCl\(_3\) on various 300Hz instrument with TMS as internal standard. The \(^1\)HNMR value were given in ppm (s-singlet, d-doublet, t-triplet br-broad mc-multiplet centred at). Thin layer chromatography plates were coated with silica gel G and developed in an iodine chamber. Light petroleum ethers to fraction bp 60-80°.

3β-Acetoxycholest-5-ene (CLXXIII)
A mixture of cholesterol (100g) pyridine (150ml) and freshly distilled acetic-anhydride (100ml) was heated on a water bath for two hours. A light brown solution was obtained which after allowing to cool at room temp was poured on to crushed ice with stirring. 3β-acetoxycholest-5-ene (CLIII) was obtained as a white precipitate which was filtered under suction and washed with water and air dried. The crude product was recrystallized from acetone as needles, m.p. 114-115° (reported\(^6\) m.p. 116°).

3β-Chlorocholest-5-ene (CLXXIV)
Freshly purified thionylchloride (37ml) was added gradually to cholesterol (50g) at room temperature. A vigorous reaction ensued with the evolution of gaseous product. When the reaction slackened the mixture was gently heated at a temperature 50-60° on a water bath for one hour and then poured on to crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cold water and air-dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (47 g), m.p. 98-96° (reported\(^7\) m.p. 96-97°).

Cholest-5-ene (CLXXV)
3β-Chlorocholest-5-ene (10.0g) was dissolved in warm amylalcohol to the solution with the stirring over a period of eight hours. During this period of addition of sodium. The reaction mixture was warmed occasionally so as to facilitate the
dissolving of sodium metal. When all the sodium metal was dissolved the reaction mixture was poured into water. Acidified with hydrochloric acid and allowed to stand over night. A white crystalline solid was obtained which was filtered under suction and washed thoroughly with water and air dried. The crude product was recrystallized from acetone to provide the desired compounds as cubes (7.5g), m.p. 94° (reported m.p. 95°).

3β-Hydroxy 5α, 6β-dibromocholestan (CLXXVI):

3β-Hydroxycholest-5-ene (14g) was added in (100ml) of ether to this solution add (50ml) of bromine solution with continue stirring. The solution turn yellow and promptly set to stiff paste of dibromide. The mixture was cooled to 20°C by stirring with a glass rod for 5 minutes to ensure complete crystallization. The product was then collected by filtration under suction and washed with cold ether acetic acid mixture (3:7) until the filtrate completely colourless, m.p. 112° (reported m.p. 112°).

5α, 6β-Dibromocholestan-3-one (CLXXVII)

3β-Hydroxy 5α, 6β-dibromocholestan (10g) was suspended in acetone (300 ml-distilled over KMnO₄) in a three necked round bottom flask fitted with a stirrer and dropping funnel. Jone’s reagent (15ml) was then added in small portion from dropping funnel in the course of 30 minutes. The temperature of the reaction mixture during the oxidation was maintained between 0-5° by external cooling. After the addition was completed stirring was continued for 15 minutes and cold water (200 ml) was added. The product was filtered under suction and washed thoroughly with water, methanol and air dried, m.p. 73° (reported m.p. 73-75°).

Cholest-5-en-3-one (CLXXVIII)

To a solution of 5α, 6β-dibromocholestan-3-one (5gm) in ether (100ml) and acetic acid (2.5 ml) was added zinc dust (7.5gm) in small portion during 30 minutes with continuous shaking. After the complete addition, the ethereal solution containing suspended zinc dust was filtered in separating funnel. The ethereal phase was then washed with water dried over anhydrous sodium sulphate (Na₂SO₄). The oily
residue obtained, evaporation of the solvent was crystallized from methanol to give the desired product (3.5g), m.p. 127-120° (reported 129°).

**Cholest-4-en-3-one (CLVI)**

A solution of cholest-5-en-3-one (5.0gm) in ethanol (50 ml) and oxalic acid (0.6gm) heated under reflux for 15 minutes. The reaction mixture was poured into water and extracted with ether. Ether extract was washed with water and NaHCO₃ (5%) and again with water. Then dried over anhydrous sodium sulphate (Na₂SO₄). Evaporation of the solvent kept only residue which is crystallized from methanol in the cold to give ketone (3.2g), m.p. 80° (reported m.p. 81-82°).

**3β-Acetoxycholest-5-en-7-one (CLXI)**

A solution of t-butyl chromate [from t-butyl alcohol (60 ml), CrO₃ (20 g), acetic acid (84 ml) and acetic anhydride (10 ml)] was added at 0°C to a solution of 3β-acetoxycholest-5-ene (8 g) in carbontetrachloride (150 ml), acetic acid (30ml) and acetic anhydride (10 ml). The mixture was heated under reflux for three hour and diluted with water. The organic layer washed successively with water and sodium bicarbonate (NaHCO₃) solution (5%) and dried over anhydrous sodium sulphate (Na₂SO₄). Evaporation of the solvent under reduced pressure furnished an oil which was crystallized from methanol to give the desired ketone (4.0 g), m.p. 162° (reported m.p. 162°).

**Reaction of 3β-acetoxycholest-5-en-7-one (CLXI) with 2-hydroxy-2-phenylethylazide:**

3β-Acetoxycholest-5-en-7-one (CLXI:200mg:0.45mmol) was allowed to react with 2-hydroxy-2-phenylethylazide (250mg:1.54mmol) in dichloromethane (15ml) and reaction mixture and was cooled to 0°C. BF₃-etherate (0.5 ml) was added dropwise over five minutes, immediate gas evaluation was noticed upon addition. The reaction mixture stirred for four hours. The progress of the reaction was determined by TLC. After the completion of the reaction, oily residue obtained which were extracted with ether. The etheral layer washed with water and sodium bicarbonate (NaHCO₃) solution (5%). Further the organic layer was washed with water and
dried over anhydrous sodium sulphate (Na$_2$SO$_4$). Evaporation of the solvents, residual oil obtained was crystallized from methanol which afforded a solid as N-2-phenylethenyl-7a-aza-B-homo-3β-acetoxycholest-5-en-7-one (CLXV) m.p. 110°.

**N-2-phenylethenyl-7a-aza-B-homo-3β-acetoxycholest-5-en-7-one (CLXV)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>m.p.</td>
<td>110°</td>
</tr>
<tr>
<td>Yield</td>
<td>(182 mg:0.35mmol)</td>
</tr>
<tr>
<td>I.R.</td>
<td>3033, 1626 (aromatic), 1715 and 1248 (OAcβ-oriented) 1660 (α,β-unsaturated lactam), 1605 (C=C) and 1350 cm$^{-1}$ for (C-N).</td>
</tr>
<tr>
<td>HNMR spectrum</td>
<td>δ 7.46 mc(5H aromatic protons), δ 6.30-6.39 mc(2H, N-CH and =CH-Ar), δ 5.8 s(H, C$_6$-H vinylic proton), δ 2.6 mc(C$_3$-βH), δ 3.9 mc(H C$_3$-αH) and acetate methyl protons at 2.1 as sharp singlet. The angular and the side chain methyl protons were observed at δ 1.16, 1.14, 1.10 and 0.94.</td>
</tr>
<tr>
<td>Analysis found</td>
<td>C 80.39 H, 10.98 N, 6.05</td>
</tr>
<tr>
<td>C$<em>{37}$H$</em>{53}$NO$_3$ requires</td>
<td>C 80.41 H, 11.12% N, 6.06%</td>
</tr>
</tbody>
</table>

On the basis of the above evidence the compound can best be formulated as N-2-phenylethenyl-7a-aza-B-homo-3β-acetoxycholest-5-en-7-one (CLXV).

**3β-Chlorocholest-5-en-7-one (CLXII)**

A solution of t-butylchromate [from t-butyl alcohol (60 ml), CrO$_3$ (20 g), acetic acid (84 ml) and acetic anhydride (10 ml)] was added at 0°C to a solution (150ml), acetic acid (30 ml) and acetic anhydride (10 ml). The mixture was heated under reflux for three hour and diluted with water. The organic layer washed successively with water and sodium bicarbonate (NaHCO$_3$) solution (5%). Further the organic layer was washed with water and dried over anhydrous sodium sulphate (Na$_2$SO$_4$). Evaporation of the solvent under reduced pressure furnished an oil which was crystallized from methanol to give the desired ketone (4.0 g), m.p. 144° (reported$^{97}$ m.p. 142°).
Reaction of 3β-chlorocholest-5-en-7-one (CLXII) with 2-hydroxy-2-phenylethylazide in the presence of BF₃-etherate: N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII)

3β-Chlorocholest-5-en-7-one (CLXII:200mg:0.46mmol) was allowed to react with 2-hydroxy-2-phenylethylazide (300mg:1.85mmol) in dichloromethane (20ml) and reaction mixture was cooled to 0°C. BF₃-etherate (0.5 ml) was added dropwise over 5 minutes, immediate gas evaluation was noticed upon addition. The reaction mixture stirred for four hours. After the completion of the usually workup, evaporation of the solvents obtained residual oil which crystallized with methanol afforded a solid as N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one, m.p. 103°.

N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellestain Test</td>
<td>positive</td>
</tr>
<tr>
<td>m.p.</td>
<td>103°</td>
</tr>
<tr>
<td>Yield</td>
<td>(142mg:0.37mmol)</td>
</tr>
<tr>
<td>I.R.</td>
<td>3024, 1623 (aromatic), 1665 (α,β-unsaturated lactam), 1597 (C=C), 1360 (C-N) and 708 cm⁻¹ (C-Cl)</td>
</tr>
<tr>
<td>¹HNMR CDCl₃</td>
<td>δ 7.40 mc(5H, aromatic protons), δ 6.07-6.16 mc(2H, N-CH and =CH-Ar), δ 5.6 s(H, C₆-H vinylic proton), δ 2.3 mc(H, C₅-βH) and δ 3.4 mc(H, C₅-αH). The angular and the side chain methyl protons were observed at δ1.11, 1.02, 0.93, 0.91, 0.87 and 0.71.</td>
</tr>
</tbody>
</table>

Analysis found: C 80:94  H, 10.79  N, 6.09
C₃₅H₅₀NOCl requires: C 80:99  H, 10.81%  N, 6.11%

On the basis of the above evidence the compound can best be formulitated as N-2-phenylethenyl-7a-aza-B-homo-3β-chlorocholest-5-en-7-one (CLXVII).
3β-Hydroxycholest-5-en-7-one (CLXIII)

3β-Hydroxycholest-5-en-7-one (500mg) was taken in ethanol (10 ml) and conc. hydrochloric acid (1.5ml) was added mixed together. The reaction mixture was refluxed for two hours. After the completion of the reaction crystals separated by filtration, washed thoroughly with water. Recrystallized with methanol gave 3β-hydroxycholest-5-en-7-one as solid (400 mg) as a solid m.p. 106-108°.

Reaction of 3β-hydroxycholest-5-en-7-one (CXLIX) with 2-hydroxy-2-phenylethylazide in presence of BF₃-etherate; N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX)

3β-Hydroxycholest-5-en-7-one (CLXVIII:250mg:0.62mmol) was allowed to react with 2-hydroxy-2-phenylethylazide (325mg:2.0mmol) in dichloromethane (20 ml) and reaction mixture and was cooled to 0°C. BF₃-etherate (0.5 ml) was added dropwise over 5 minutes, immediate gas evaluation was noticed upon addition. The reaction mixture stirred for four hours. The progress of the reaction was determined by the TLC. After the completion of the reaction, the reaction mixtures was extracted with ether. The ether layer washed with water and sodium bicarbonate (NaHCO₃) solution (5%). Further the organic layer was washed with water and dried over anhydrous sodium sulphate (Na₂SO₄). Evaporation of the solvents afforded as an oil which failed to crystallize. The oil was subjected to column chromatography and elution with petroleum ether gave N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX) as a pure entity.

N-2phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX):

<table>
<thead>
<tr>
<th>Elution</th>
<th>Yield</th>
<th>I.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petroleum ether</td>
<td>(200mg : 0.38 mmol)</td>
<td>3185-3366 (-OH), 3070, 1631 (aromatic), 1662</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(α,β-unsaturated lactam), 1615 (C=C) and 1348 cm⁻¹ (C-N).</td>
</tr>
</tbody>
</table>

¹HNMR (CDCl₃) : δ 7.18 mc(5H, aromatic protons), δ 6.23-6.31 mc(2H, N-CH and =CH-Ar), δ 5.29 (H, C₆-H vinylic protons), δ3.7 mc(H, C₃-αH) and δ 4.2 broad band (OH). The angular and
side chain methyl protons were observed at 1.0, 0.96, 0.90, 0.84 and 0.72.

Analysis found : C, 81:12  H, 11.01  N, 6.17

C_{35}H_{51}NO_{2} requires : C, 81:19  H, 11.13  N, 6.18%

On the basis of the above evidence the compound can best be formulated as N-2-phenylethenyl-7a-aza-B-homo-3β-hydroxycholest-5-en-7-one (CLXIX).

**Reaction of cholest-4-en-3-one (CL) with 2-hydroxy-2-phenylethylazide in presence of BF₃-etherate: N-2-phenylethenyl-4-aza-A-homo-cholest-4a-en-3-one (CLXXI)**

Cholest-4-en-3-one (CLXIV:200mg:0.52mmol) was allowed to react with 2-hydroxy-2-phenylethylazide (285mg;1.75mmol) in dichloromethane (20ml) and reaction mixture and was cooled to 0°C. BF₃-etherate (0.5 ml) was added dropwise over 5 minutes, immediate gas evaluation was noticed upon addition. The reaction mixture stirred for five hours. After the completion of the reaction, oily residue obtained which were extracted with ether. The etheral layer washed with water and sodium bicarbonate (NaHCO₃) solution (5%). Further the organic layer was washed with water and dried over anhydrous sodium sulphate (Na₂SO₄). Evaporation of the solvents residual oil obtained failed to crystallize. The oil was subjected to column chromatography and elution with petroleum ether gave N-2-phenylethenyl-4-aza-A-homo-cholest-4a-en-3-one (CLXXI) as a pure entity.

**N-2-phenylethenyl-4-aza-A-homo-cholest-4a-en-3-one (CLXXI)**

Elution : Petroleum ether
Yield : (78mg :0.34 mmol)

I.R. : 3050, 1630 (aromatic), 1658 (α,β-unsaturated lactam), 1600 (C=C) and 1352 cm⁻¹ (C–N)

¹HNMR (CDCl₃) : 86.92-7.35 mc(5H, aromatic protons), δ 6.07-6.15 (2H, N-CH and =CH-Ar), δ 5.5 (H, C₄-H vinylic protons). The angular and side chain methyl protons were observed at 1.18, 1.11, 1.06, 0.91, 0.87, 0.85, 0.8 and 0.71.
Analysis found : C, 81:12  H, 11.01  N, 6.21

C_{35}H_{49}NO requires : C, 81:19  H, 11.13  N, 6.23%

On the basis of the above evidence the compound can best be formulated as N-2-phenylethenyl-4-aza-A-homo-cholest-4a-en-3-one (CLXXI).
References


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