CHAPTER - 3

Vilsmeier reagent as an effective geminal dichlorinating agent.
Introduction

Geminal dihalides are chemically important organic synthons and are ideal templates for synthesis of various carbocycles as well as heterocycles. Oxidation of an aldehyde or a ketone with a chlorinating agent in presence of a suitable catalyst, is the usual way for preparation of geminal dichlorides.

One of the earliest report of geminal dichloride preparation was forwarded by B.B.Carroll's group. They made 1,1-dichlorides by the action of phosphorous pentachloride on cyclohexanone without a solvent.\(^1\)

\[
\text{PCI}_5 \rightarrow \text{ClCl}
\]

2-Chloropropene on treatment with dry HCl in presence of catalytic amount of FeCl\(_3\) affords geminal dichlorides in good yields.\(^2\)

\[
\begin{align*}
\text{Cl} & \quad \text{HCl} \quad \text{FeCl}_3 \\
\text{Cl} & \quad \text{77\% - 94\%}
\end{align*}
\]

The addition of HCl to terminal alkynes generally produces 2-chloro-1-alkenes together with 2,2-dichloro alkanes.\(^3\)

\[
\begin{align*}
R & \quad \text{HCl} \\
\text{Cl} & \quad \text{RCl} \\
\text{Cl} & \quad \text{RCl}
\end{align*}
\]

Treatment of squaric acid with excess amount of thionyl chloride and catalytic amount of dimethyl formamide in benzene under reflux for 2 h gave perchloro cyclobutanone in 76 % yield.\(^4\)

\[
\begin{align*}
\text{HO} & \quad \text{Cl} \\
\text{Cl} & \quad \text{HO} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

Aromatic and \(\alpha,\beta\)-unsaturated aldehydes are converted to geminal dichlorides in good yields by treating with a mixture of thionyl chloride and dimethyl formamide in dichloromethane.\(^5\)

\[
\text{C}_6\text{H}_5\text{CHO} + (\text{CH}_3)_2\text{NCHO} + \text{SOCl}_2 \rightarrow \text{C}_6\text{H}_5\text{CHCl}_2
\]
Imines have been conveniently halogenated in the α-position of the carbon-nitrogen double bond by using N-chlorosuccinimide in carbon tetrachloride. A typical example is the reaction of N-1-(1-arylalkylidene)anilines with two molar equivalents of N-chlorosuccinimide in carbon tetrachloride to afford N-1-(2,2-dichloro-1-arylalkylidene)anilines.⁶

The (2+2) cycloaddition of dichloroketene to a series of 1-substituted cyclohexenes is shown to proceed in a highly regio and stereospecific manner to afford the geminal dichloride.⁷

Synthesis of 2,2-dichloro indane-1,3-dione has been accomplished from naphthaquinone by treatment of FeCl₃/HClO₄ in refluxing acetic acid.⁸

Hydrazones of ketones or aldehydes react with copper(ii) chloride / triethyl amine in methanol to afford conveniently the corresponding geminal dichlorides.⁹

Few important reactions of geminal dichlorides
Beckmann ring expansion reaction of cyclobutanone with Tamuras reagent [o-
(mesitylenesulfonyl)hydroxylamine] gives regioselectively α,α-dichloro-γ-lactone which on treatment with trifluoro acetic acid yields a statine derivative.\(^{10}\)

A general procedure for cyclopentenone synthesis is achieved by the acid treatment of dichlorohomoallyl alcohol.\(^{11}\)

In a closely related reaction, a divinyl chloride is generated by chelatropic extrusion of sulfur dioxide from the dichlorocarbene 3-sulfolene adduct. Under the reaction conditions the divinyl dichloride solvolyzes to the cyclopentenone.\(^{12}\)

Heating of 1-(Benzyliminomethyl)-2,2-dichloro-1-phenyl cyclopropane at 220°C (in biphenyl ether or in benzene) in an autoclave for 40 h affords a mixture of 2,5-disubstituted pyridine and 4-chloro-2,5-disubstituted pyridine.\(^{13}\)

Oxidation of 2,2-dichlorocyclobut-3-enone with VO(OEt)Cl\(_2\) in refluxing ethanol leads to regioselective ring fission giving a non conjugated ester(ethyl 2,4,4-trichlorobut-3-enoates) with regioselective introduction of a chloro group at 2-position.\(^{14}\)
Thermolysis of N-t-butyl- and N-cumyl-2,2-dichlorocyclopropyl imines gives selectively 3-chloropyrroles in polar solvents while 2-chloro derivatives are obtained with added base.\textsuperscript{15}

A convenient synthesis of 3,3-dichloro azetidines, a new class of azetidine was achieved by a three step reaction sequence starting from a geminal dichlorinated aryl ketimines.\textsuperscript{16}

Reactivity of enamino ketones and aldehydes.

4,5-Diarylisoaxazoles are efficiently prepared by submitting enamiones to oximation condition.\textsuperscript{17}
Enaminones has been prepared and submitted to conjugate reduction with LAH to give β-amino ketones.\(^{18}\)

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{Ar}_2 \quad \text{Ar}_1 \\
\text{Me}_2\text{N} & \quad \text{Ar}_2 \quad \text{Ar}_1 \\
\text{Me}_2\text{N} & \quad \text{Ar}_2 \quad \text{Ar}_1 \\
\end{align*}
\]

One example of pyridopyrimidine synthesis utilising enamo ketone was cited in the introduction of the thesis as below.\(^{19}\)

\[
\begin{align*}
\text{R}_2 \quad \text{R}_1 \\
\text{DMF} & \quad \text{DMA} \\
\end{align*}
\]

Reaction of enamo aldehyde with urea afforded pyrimidine.\(^{20}\)

\[
\begin{align*}
\text{Cl} & \quad \text{NMe}_2 \\
\text{H}_2\text{N} & \quad \text{CO} \\
\text{H}_2\text{N} & \quad \text{OH} \\
\end{align*}
\]

Benzyltrimethyl ammonium dichloro iodate (BTMA.ICl\(_2\)) has been reported to be an efficient α-iodinating agent for secondary enaminones.\(^{21}\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{NMe}_2 & \quad \text{H}_2\text{N} \\
\text{H}_2\text{N} & \quad \text{Cl} \\
\end{align*}
\]

Reaction of BTMA.ICl\(_2\) with tertiary enaminones exclusively affords α-chlorination product.\(^{22}\)
Incorporation of a geminal dichloride moiety into a lead molecule is a topic of recent interest. Since steroidal skeleton itself is well known to exhibit tremendous biological activities, therefore it is planned to functionalize the steroidal D-ring with a geminal dichloride moiety utilising the chemistry of steroidal azadienes.

**Steroidal oxime (1)**

Various derivatives of steroidal oximes were prepared by reacting commercially available 16-DPA with hydroxylamine following the procedure discussed in the chapter (1a).

**Steroidal 16-formyl-17-enamide (2a)**

Reaction of conjugated oxime (1a) with Vilsmeier reagent prepared from a mixture of POCl₃ and DMF(1:10:10 eq.) at 15-20°C for 3 h afforded 3β-acetoxy-17-acetamido-16-formylandrost-5,16-diene (2a) in 75% yield. The same product was also obtained from the reaction of 17-acetamido-androst-5,16-diene-3β-acetate with Vilsmeier reagent. The product was characterised and discussed in details in chapter-2.
Similarly other derivatives of 16-DPA oxime viz. 3β-formyloxy-16-dehydro-pregnenolone oxime (1b) and 3β-benzoyloxy 16-dehydropregnenolone oxime (1c) also gave the corresponding 16-formyl-17-acetamido derivative (2b and 2c) in good yields.

The products gave satisfactory IR, 1H NMR, Mass spectra and elemental analysis.

Steroidal enamine

Alkaline hydrolysis of (2a) under the influence of ethanolic KOH resulted 17-amino-16-formyl-3β-hydroxyandrost-5,16-diene 3a in 60% yield.
The IR(KBr) spectrum of the compound showed an absorption band at 3250 cm\(^{-1}\) assigned to the NH-stretching. The absence of a strong absorption band at 1725 cm\(^{-1}\) indicated hydrolysis of acetyl groups. Also, the strong band at \(\nu_{\text{max}}\) 1625 cm\(^{-1}\) indicated the presence of C-16-formyl group. The \(^1\)HNMR (\(\text{d}_6\)-DMSO) of the product showed a sharp singlet at \(\delta\) 9.45 integrated for one proton due to C-16 formyl group. Finally in the mass spectrum (EI) the fragmentation ion peak at m/z 297 and 282 were assigned to the loss of H\(_2\)O and CH\(_3\) group from the molecular ion.

The identity of the product 3a was also ascertained by acetylation of the steroidal enamine 3a to 2a using acetic anhydride in pyridine.

\[\text{3a} \xrightarrow{\text{Ac}_2\text{O} / \text{Py}} \text{2a}\]

The product was characterised by comparison of spectral data, mixture TLC and mixture melting point with a standard sample of 2a.

**Steroidal-16-formyl-17-N-alkyl enamide**

Another C-17 nitrogen derivative, 3\(\beta\)-acetoxy-17-(ethylacetamido)-16-formyl androst-5,16-diene 3b was prepared by alkylation of \(\beta\)-formyl enamide (2a) with ethyl bromide under phase transfer catalytic condition.

\[\text{2a} \xrightarrow{\text{C}_2\text{H}_5\text{Br} / \text{PTC}} \text{3b}\]

Dichloromethane solution of 2a was stirred at room temperature with two molar equivalent of ethyl bromide, tetrabutyl ammonium bromide and KOH(40% aqueous), for 24 h. The organic layer was separated by using a separatory funnel and the aqueous layer was extracted again with dichloromethane. The combined extract was
washed with water, dried over sodium sulphate and removal of solvent afforded the product 3b in 46% yield. The product 3b melted at 168-70°C and gave Rf value 0.3 in TLC (ethyl acetate:hexane=20:80). The IR (KBr) spectrum of the compound did not show the characteristic strong band at 3250 cm⁻¹ for NH stretching of 2a. The peak at ν max 1730 and 1650 cm⁻¹ were assigned to the C=O stretching of the acetyl groups. The ¹H NMR spectrum of the compound showed absence of broad singlet at δ 10.75 for amide proton of 2a indicating that the alkylation took place at C-17 nitrogen, which was further supported by the appearance of a quartet signal at δ 3.80 integrated for two protons due to the CH₂ of ethyl group. The mass spectrum (EI) of the compound showed fragmentation peaks at m/z 367 and 352 which were assigned to the loss of CH₃COOH and CH₃ group from the molecular ion. The compound gave satisfactory elemental analysis for molecular formula C₂₆H₃₇NO₄ of 3b.

Similarly 3β-acetoxy-17-(allylacetamido)-16-formyl-androst,5-16-diene(3c) and 17- (propargyl acetamido)-16-formyl-androst,5-16-diene (3d) were prepared from 2a in good yields under phase transfer catalytic condition and were characterised satisfactorily as discussed in the chapter 2.

**Steroidal-16-formyl-17-N-pyrrolidineline**

Another strategy towards synthesis of C-17 nitrogen containing heterosteroid was by chloroformylation of 3β-acetoxy-androst-5-ene-17-one(A) to chloroformyl
derivative (B) followed by nucleophilic substitution with pyrrolidine base.

3β-Acetoxy-androst-5-ene-17-one (A) was prepared by Beckmann rearrangement of 16-DPA oxime under the influence of POCl₃/pyidine, and acid hydrolysis following a reported procedure.

Androstenone A was found to give satisfactory spectral and elemental analyses. The product melted at 160°C and showed Rf value 0.26 in TLC (CHCl₃).

Chloroform solution of androstenone (A) was then treated with 3 molar equivalents of chloromethyleneiminium salt under reflux for 2 h to obtain 17-chloro-16-formyl-androst-5-ene-3β-acetate (B). The product B was refluxed with equimolar amount of pyrrolidine in ethanol for 3 h, during which colourless reaction mixture changed into yellowish colour. The work up of the reaction was made by reducing ethanol to half of its volume in a rotavapour, pouring it into ice cold water. Extraction with chloroform, drying over sodium sulphate and removal of solvent gave a red semi solid mass which on column chromatographic separation (eluting solvent chloroform:methanol=99:1) rendered a white solid of 4 in 69% yield. The product 4 melted at 227-28°C and showed an Rf value of 0.3 in TLC (chloroform:methanol=99:1).

The IR(KBr) spectrum of the product showed a medium absorption band at \( \nu_{\text{max}} \) 2940 cm\(^{-1}\), assigned to the alkane CH-stretching of the steroidal skeleton. The strong absorption band at \( \nu_{\text{max}} \) 1725 cm\(^{-1}\) was assigned to the C=O stretching vibration of the 3-acetyl group. The \(^1\)HNMR (CDCl₃) spectrum of the compound showed a sharp singlet at \( \delta \) 9.34 integrated for one proton which was assigned to the C-16 formyl proton. An additional multiplet signal at \( \delta \) 3.48 integrated for four protons was a clear indication of pyrrolidine substitution on the molecule. Finally the mass spectrum (El) showed molecular ion peak at m/z 411 and the peak at m/z 383 was assigned to the loss of CO group from the molecular ion. The compound gave satisfactory elemental analysis for...
Few other C-17 nitrogen containing derivatives were prepared from 3β-acetoxy 17-acetamido-16-formyl androst-5,16-diene(2a) by derivatisation of aldehyde at C-16 position.

3β-Acetoxy-17-acetamido-androst-5,16-diene-16-formylidinemalononitrile(5a)

Ethanol solution of (2a) was stirred with equimolar amount of malononitrile in presence of KOH(ethanolic) at 10-15°C for 0.75 hr. The product 5a was obtained in 75 % yield after usual work, it had a mp 201°C and Rf value 0.98 in TLC (toluene:acetone=95:5).

The IR (KBr) spectrum of the compound 5a showed characteristic absorption band at $\nu_{\text{max}}$ 2230 cm$^{-1}$ for CN stretching. The $^1$HNMR spectrum of the compound showed a sharp singlet at $\delta$ 7.75 for C-16 olefinic proton. The upfield shift of the proton from $\delta$ 9.5 was an indication of blocking of formyl group. The broad singlet at $\delta$ 9.35 integrated for one proton was assigned to the amide proton at C-17 position as it was exchangeable with D$_2$O. Finally the mass spectrum (EI) of the compound showed fragment ion peak at m/z 387 accountable for the loss of CH$_3$COOH from the molecular ion. The fragment ion peaks at m/z 372, 345 were assigned to the successive loss of a CH$_3$ and a CH$_2$=C=O fragments.

3β-Acetoxy-17-acetamido-androst-5,16-diene-16-formylidine-ethylcyanomalonate (5b)

The preparation product 5b by procedure followed for 5a led to low yields and side reaction products. It was prepared by treating a dioxane solution of 2a with equimolar amount of ethyl cyanoacetate under the influence of piperidine base for 1 h at room temperature. The yellowish white solid product of 5b was obtained after usual work up. The product melted sharply at 180°C and had an Rf value of 0.18 in
CHCl₃/MeOH(98:2). It gave satisfactory spectral and elemental analysis.

Analogous reaction with diethyl malonate and chloroacetonitrile with 2a failed to give the desired condensation product.

All these prepared C-17 nitrogen substituted steroids from 2a to 5b consisted of a conjugated exocyclic diene moiety at D-ring bearing an amine derivative at 4-position of the diene. It was planned to study their behaviour towards Vilsmeier reagent. Few unexpected and interesting results were obtained as recorded below.

A mixture of 2a and chloromethyleneimium salt (3 molar equivalent) was refluxed at 65°C in chloroform solution for 2 h under nitrogen atmosphere. Colourless reaction mixture changed to deep red during 2 h reflux. The reaction was worked up by pouring the content into ice cold water. Extraction with CHCl₃, washing with water, drying over Na₂SO₄, removal of solvent and chromatographic purification (eluant toluene) rendered two product 6a and 6b in 60% and 10% yield.

Product 6a had melting point 155°C and Rf value 0.9 in TLC (CHCl₃). The IR(KBr) spectrum of the compound showed a strong absorption band at $\nu_{\text{max}}$ 1735 cm⁻¹ which was assigned to the C=O stretching frequency of 3-acetyl group. Absence of the strong absorption band at $\nu_{\text{max}}$ 1635 cm⁻¹ for the formyl group of 2a was an indication of the participation of formyl group in the rearrangement. In the ¹H NMR spectrum of the product the signals for formyl and the amide protons of (2a) were absent, however a sharp singlet had appeared at $\delta$ 6.40 integrated for one proton which was assigned to the (E)-chloromethylene group.²³ The absence of the sharp singlet at $\delta$ 2.12 for N-acetyl proton further supported the proposed rearrangement. Finally the mass spectrum (EI) of the product showed characteristic trichloro compound pattern (27:27:9:1). Fragmentation peak at m/z 370 (98%) was assigned to the loss of
CH$_3$COOH fragment from the molecular ion. The ion peaks at m/z 372 (100%) and 374 (33%) were assigned to [(M$^+$-CH$_3$COOH)+2] and [(M$^+$-CH$_3$COOH)+4] fragment respectively. Based on all these spectral data and satisfactory elemental analysis the product was assigned to be 3β-acetoxy-17,17-dichloro-16(E)-chloromethyleneandrost-5-ene(6a).

The product 6b had melting point 170°C and Rf value 0.78 in TLC (CHCl$_3$). The IR (KBr) spectrum of the compound showed characteristic band at $\nu_{\text{max}}$ 1720 and 1623 cm$^{-1}$ assigned to the C=O stretching of the 3-acetyl and 17-keto groups. The $^1$HNMR spectrum of the compound showed characteristic triplet signal at $\delta$ 6.86 for 16(E)-vinyllic proton of the conjugated enone.$^{23}$ It showed absence of the signals at $\delta$ 10.5, 9.1 and 2.2 for amide, formyl and acetyl proton at D-ring of (2a). Finally the mass spectrum (El) of the product showed characteristic one chlorine bearing fragmentation pattern. The peaks at 316(100%) and 318(33%) were assigned to the (M$^+$-CH$_3$COOH) and [(M$^+$+2)-CH$_3$COOH] fragments respectively. Based on all the spectral data and satisfactory elemental analysis the structure of the compound was assigned as 3β-acetoxy-16(E)chloromethylene-androst-5-ene-17-one.(6b)

Similarly compound 2b and 2c when treated with the Vilsmeier reagent at an elevated temperature afforded corresponding trichloro derivative 7 and 8 as sole products. Products were characterised satisfactorily with the help of spectral and elemental analysis.

![Reaction of steroidal enamine with Vilsmeier reagent](image)

**Reaction of steroidal enamine with Vilsmeier reagent**

A chloroform solution of 3a was treated with Vilsmeier reagent (10 molar equivalent) at 65°C for two hours. After completion of reaction it was worked up by usual procedure of water treatment and solvent extraction. Solvent removal and
column chromatographic separation of the product rendered 3β-formyloxy-16-(E)-chloromethylene-5-androstene-17-one (9a) and 3-chloro-16-(E)-chloromethylene-17-ketoandrost-5,16diene(9b) in 40% and 35% yield respectively. However it was of interest to note that corresponding trichloro derivatives did not form in this cases.

Product 9a had a melting point of 165-66°C and TLC in toluene showed Rf = 0.4; The IR(KBr) spectrum of the compound showed strong absorption bands at v max 1730 and 1623 cm⁻¹ which was assigned to the C=O stretching of 3-formyloxy and 17-keto group. The ¹HNMR spectrum of the product showed a sharp singlet at δ 7.78 integrated for one proton which was assigned to the 3-formyloxy proton and the characteristic triplet having J=2.45 Hz at δ 6.92 was due to the 16(E)-chloromethylene proton. Finally the mass spectrum (El) of the product showed peak at 316(42%) and 318(18%) which were assigned to the characteristic fragmentation pattern(3:1) of the compound 9a due to loss of HCOOH from the molecular ion.

Product 9b melted at 198-99°C and had an Rf value of 0.8 in TLC CHCl₃. The IR(KBr) spectrum of the compound showed strong absorption bands at v max 1623 cm⁻¹ which was assigned to the C=O stretching of 17-keto group. The ¹HNMR spectrum of the product showed a triplet having J=2.50 Hz at δ 6.90 due to the 16(E)-chloromethylene proton. Finally the mass spectrum (El) of the product showed molecular ion peaks at m/z 252, (M⁺,70%), 254(M⁺+2,42%) and 256(M⁺+4,9%) were characteristic of compounds bearing two chlorine atoms (9:6:1).

Vilsmeier reaction with the substrate 3b, 3c, 3d and 4 in a similar reaction condition afforded both the trichloro and keto product 6a and 6b.
In order to investigate the role of electron withdrawing formyl group in the above reaction, the steroidal formylidine malononitrile 5a was treated with Vilsmeier reagent (10 molar equivalent) at 110°C for 2 h. The reaction afforded a white solid product 10 after usual work up and purification.

The product did not melt up to 240°C but decomposed above this temperature. It gave an Rf value of 0.3 in Toluene:acetone(95:5). The IR(KBr) spectrum of the product showed characteristic sharp absorption band at ν max. 2240 cm⁻¹ assigned to the CN group in the molecule. The strong bands at ν max. 1735 and 1650 cm⁻¹ were assigned to the C=O stretching of 3-acetyl and the enamino formyl group. The bands at 1590 and 1540 cm⁻¹ were assigned to the characteristic absorption bands of a pyridine nucleus and also an out of plane -CH deformation band was observed at 780 cm⁻¹ for the pyridine ring. The ¹HNMR (Acetone- d₆) spectrum of the product showed sharp singlet at δ 8.70, 8.01 and 7.68 integrated for one proton each, these three signals were accounted for the pyridine ring proton, formyl proton and enamino proton respectively. The mass spectrum(EI) of the product showed a peak m/z 487 assigned to the molecular ion peak. The elemental analysis of the product gave satisfactory
result for the assigned structure 10.

Similar reaction of substrate 5b with Vilsmeier reagent did not afford the corresponding pyridine product.

**Mechanism**

The plausible mechanism of the reaction may proposed as below.

Formation of the product 6a and 6b can be attributed to the facile tautomerism of the lone pair of nitrogen in C-17 with enolisable C-16 formyl group. Attack of the tautomerised intermediate on chloromethyleneiminium salt possibly gives intermediate A followed by attack of a chloride ion resulting B. Further nucleophilic attack of two chloride ion on tautomerised imine bond at C-17 position leads to 6a whereas concomitant hydrolysis at C-17 position leads to 6b.

The 16-formyl-16-DPA oxime also afforded the corresponding trichloro and keto product in a similar reaction condition confirming participation of enamide via Beckmann rearrangement.
The formation of the pyridosteroid 10 may be proposed by the nucleophilic attack of the chloride ion on tautomeric form C of the amide to intermediate D followed by the cyclization through elimination of cyanogen chloride and biformylation of activated methyl group of pyridine nucleus in presence of Vilsmeier reagent at elevated temperature.

Conclusion

A large number of highly stable C-17 nitrogen containing steroid molecules were synthesised and employed for the first time to study their behaviour towards Vilsmeier reagent. Vilsmeier regent acted as geminal dichlorinating agent for β-formyl primary, secondary and tertiary amine however when the tautomerisation of C-17 amide group with C-16 formyl group was blocked by derivatisation of formyl group with malononitrile, the reaction leads to a completely unexpected D-ring fused pyridine derivative.
Experimental section

The preparation of the compounds is outlined below in the order they have been discussed in the text.

Compound 16-Dehydropregnenoloneformate, 16-Dehydropregnenolone benzoate, 16-dehydro pregnenolone acetate-20-oxime(1a), 16-Dehydro pregnenolone formate-20-oxime(1b), 16-Dehydro pregnenolone benzoate-20-oxime(1c) were prepared as described in chapter 1.

Synthesis of 3β-acetoxy-17-acetamido-16-formyl-androst-5,16-diene(2a):

To an oven dried 250 mL round bottomed flask was added a solution of POCl₃(11.2 mL, 0.012 mol) and DMF(10 mL, 0.013 mol) at 0°C and flushed with nitrogen. The reaction mixture was stirred vigorously until a white chloromethylene-iminium salt separated out. A cold solution of 1a(1.16g, 0.003 mol) in chloroform(100 mL) was prepared and added to this salt at -5°C under nitrogen atmosphere. Stirring was continued for 3 h when the temperature gradually raised to 15°C. The reaction mixture was immediately poured into ice cold water and stirred vigorously. Removal of the solvent under reduced pressure at 20°C gave an aqueous mixture which was basified with powered KOH to pH 10 and then warmed on a water bath at 60°C for 2 h. Extraction with dichloromethane (3 x 20 mL) and washing with water (2 x 50 mL) gave a light yellow solution which was dried over Na₂SO₄. Removal of the solvent gave 2b as white solid, Yield 760 mg (61%); mp 236-37°C(ethyl acetate); TLC in chloroform(Rf = 0.3); IR(KBr): v max 3250, 2940, 1725, 1625, 1500, 1240 cm⁻¹; ¹H NMR(CDCl₃): δ 10.75(s,1H), 9.08(s,1H), 5.10(m,1H), 4.33(m,1H), 2.05(s,3H), 1.80(m,3H), 0.98(s,3H), 0.85(s,3H), 2.55-1.15(m,17H); mass spectrum(EI) m/z 339, 311, 297, 282, 269; Anal. Calcd for C₂₄H₃₃NO₄: C, 72.18; H, 8.27; N, 3.51. Found: C, 72.25; H, 8.30; N, 3.40.

3β-Formyloxy-17-acetamido-16-formyl-androst-5,16-diene(2b):

Yield 911mg(76%); mp 190°C; TLC in chloroform(Rf=0.5); IR(KBr)v max 3350, 2950, 1725, 1630, 1260 cm⁻¹; ¹H NMR(CDCl₃) δ 11.03(s,1H), 9.23(s,1H), 7.72(s,1H), 5.28(bs,1H), 4.55(s,1H), 2.09(s,3H), 1.10(s,3H), 1.00(s,3H), 2.45-1.25(m,17H); mass spectrum(EI) m/z 385, 357, 339, 311, 297, 282; Anal. Calcd. for C₂₃H₃₁NO₄:...
3\(\beta\)-Benzoyloxy-17-acetamido-16-formyl-androst-5,16-diene (2c):

Yield 1.01 g (70%); mp. 245°C (decomp); TLC in chloroform (Rf = 0.2); IR (KBr) \(\nu_{\text{max}}\) 3345, 2945, 1730, 1625, 1255 cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)) \(\delta\) 10.08 (bs, 1H), 9.25 (s, 1H), 7.60–7.10 (m, 5H), 5.20 (bs, 1H), 4.30 (m, 1H), 2.15 (s, 3H), 1.85 (s, 3H), 0.92 (s, 3H), 0.78 (s, 3H), 2.20–1.10 (m, 17H); mass spectrum (El) m/z 339, 311, 297, 282; Anal. Calcd. for C\(_{29}\)H\(_{35}\)NO\(_4\): C, 75.46; H, 7.64; N, 3.04. Found: C, 75.38; H, 7.58; N, 2.99.

3\(\beta\)-Hydroxy-17-amino-16-formyl-androst-5,16-diene (3a):

A 30% KOH (1 mL) solution was added slowly to 1a (399 mg, 0.001 mol) in ethanol (25 mL) at room temperature and stirred for 3.5 h. On completion of reaction the solvent was removed in a rotavapor at 40°C. It was treated with water (50 mL) and extracted with chloroform (2 X 40 mL). The organic solution was washed with water, dried over Na\(_2\)SO\(_4\) and solvent removed to afford 3a as white solid. Yield, 205 mg (65%); mp 185–90°C; TLC in MeOH/CHCl\(_3\): 99/1 (Rf = 0.3); IR (KBr) \(\nu_{\text{max}}\) 3350, 1625, 1590 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 9.45 (s, 1H), 5.30 (bs, 1H), 3.52 (m, 1H), 1.12 (s, 3H), 0.93 (s, 3H), 2.25–1.30 (m, 17H); mass spectrum (El) m/z 297, 282; Anal. Calcd. for C\(_{20}\)H\(_{29}\)NO\(_2\): C, 76.19; H, 9.21; N, 4.44. Found: C, 76.02; H, 9.10; N, 4.25.

Acetylation was carried by adding a solution of 3a (357 mg, 0.001 mol) to a mixture of dry pyridine (5 mL) and acetic anhydride (0.37 mL, 0.004 mol) under nitrogen atmosphere. After stirring for 12 h at room temperature the reaction was poured into cold water (50 mL), acidified with dil HCl, extracted with CHCl\(_3\) (3 x 30 mL), washed with water and dried over Na\(_2\)SO\(_4\). Removal of the solvent yielded 2a as white solid, 298 mg (75%). TLC in CHCl\(_3\) (Rf = 0.3); mp 236–37°C. The product was characterised by comparison of spectroscopic data and mixture melting point with a standard sample.

3\(\beta\)-Acetoxy-17-(ethylacetamido)-16-formyl-androst-5,16-diene (3b):

To a stirred solution of 1a (300 mg, 0.0008 mol) and ethyl bromide (112 mL, 0.0015 mol) in dichloromethane (100 mL) was added a solution of aqueous KOH (30%, 20 mL) and tetrabutylammonium bromide (241 mg, 0.0008 mol) at room temperature. The reaction was monitored by TLC using ethyl acetate/hexane (20:80) as eluant.
completion of 12h stirring, the organic layer was separated and the alkaline aqueous layer was extracted with dichloromethane(2 x 20 mL). The combined organic extract was washed with water(3 x 30 mL), dried over Na$_2$SO$_4$ and the solvent removed to afford 3b as white solid. Yield, 150 mg (46%); mp 168-70°C; TLC in ethyl acetate/hexane(20:80)(Rf=0.3); IR(KBr) v$_{\text{max}}$ 2900, 1730, 1650, 1600, 1250 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 9.35(s,1H), 5.20(bs,1H), 4.35(m,1H), 3.80(q,2H), 2.00(bs,6H), 1.08(bs,6H), 2.30-1.25(m,20H); mass spectrum (EI) m/z 367, 352; Anal Calcd for C$_{26}$H$_{37}$NO$_4$: C, 73.03; H, 8.72; N, 3.27. Found: C, 73.29; H, 8.55; N, 3.11.

3β-Acetoxv-17-(allylacetamido)-16-formyl-androst-5,16-diene(3c) and 3β-acetoxv-17-(propargylacetamido)-16-formyl-androst-5,16-diene(3d) were prepared as described in chapter 2.

3β-Acetoxv-16-formyl-17-pyrrolidino-androst-5,16-diene(4):

3β-Acetoxv-17-chloro-16-formyl-androst-5,16-diene(B) was prepared according to the literature method.$^{24}$

To a solution of 3β-Acetoxv-17-chloro-16-formyl-androst-5,16-diene(1g, 0.0026 mol) in ethanol(100 mL) was added pyrrolidine(0.5 mL, 0.003 mol) under stirring and then refluxed for 2h. On completion of reaction it was concentrated in a rotavapor and poured into cold water. It was extracted with chloroform(3 x 30 mL), washed with dilute hydrochloric acid and then with water. Drying over Na$_2$SO$_4$ and removal of the solvent gave a red semi solid mass which was purified by passing through a silica gel column with chloroform/MeOH(99:1) as eluant to yield 4 as white solid. Yield 751mg(69%); mp 227-28°C(ethyl acetate); TLC in chloroform/methanol(99:1)(Rf= 0.3); IR(KBr) v$_{\text{max}}$ 2940, 1725, 1630 cm$^{-1}$; $^1$H NMR(CDCl$_3$) δ 9.34(s,1H), 5.25(bs,1H), 4.30 (m,1H), 3.48 (m,4H), 1.92(s, 6H), 1.0(s,6H), 2.55-1.10(m, 21H); mass spectrum (EI) m/z 351, 336; Anal. Calcd. for C$_{26}$H$_{37}$NO$_3$: C, 75.87; H, 9.05; N, 3.40. Found: C, 75.99; H, 9.25; N, 3.57.

3β-Acetoxv-17-acetamido-androst-5,16-diene-16-formylidiene malononitrile (5a):

To a solution of 1a(400mg, 0.001 mol) in ethanol(40 mL) was added malononitrile(264mg, 0.004 mol) and cooled to 5°C. Powdered KOH(500 mg) was
added slowly to it and the reaction mixture was stirred at 10°C for 1h. It was treated with ice cold water, neutralised with dilute hydrochloric acid (pH 7.6) and stirred for 15 minutes when a solid yellowish product separated out. The product was filtered, washed with water and dried. Recrystallisation from hexane-diethyl ether(8:2) afforded, 365 mg (78% yield) of the product 5a as yellowish white flakes. Yield 365 mg(78 %); mp 201°C (sharp); TLC in toluene:acetone=95:5 (Rf=0.1); IR (KBr) v max 3280, 2910, 2230, 1710, 1650, 1585, 1270. cm⁻¹; ¹H NMR(DMSO-d₆) δ 9.31(bs, 1H), 7.79(s, 1H), 5.23(bs, 1H), 4.45(m,1H), 4.15(q,2H), 2.10(s, 3H), 1.89(s,3H), 1.00(s,6H), 2.3-1.5(m,17 H); Mass spectrum (EI) m/z 387(M⁺-CH₃COOH), 372[(M⁺-CH₃COOH)-15], 345[(M⁺-CH₃COOH)-42], 330[(M⁺-CH₃COOH)-42]-15), 237, 121; Anal. calcd. for C₂₇H₃₃O₃N₃: C, 72.45; H, 7.43; N, 9.39. Found: C, 71.98; H, 7.60; N, 8.79.

3β-Acetoxv-17-acetamido-androst-5,16-diene-16-formyldinecyanoethvlmalonate (5b):

To a dioxane solution(10 mL) of 3β-acetoxy-16-fomyI-17-acetamido-androst-5,16-diene(399 mg, 0.001 mol) in a 150 mL round bottomed flask, ethyl cyanoacetate(0.15 mL, 0.0012 mol) and piperidine(1.5 mL) were added and stirred at room temperature for 0.5 h. After completion of the reaction the colourless reaction mixture turned to yellowish in colour. The reaction was worked up by pouring into ice cold water, 1mL concentrated HCl was added and stirred for 15 minutes when the product was precipitated out. It was filtered, washed with water, dried in air and recrystallised from methanol/water(9:1) to afford the product (5b) as yellow thin flakes. Yield, 375 mg(76%); mp 180°C (sharp); TLC in CHCl₃: MeOH=98:2 (Rf=0.21); IR(KBr) v max 3250, 2910, 2240, 1700, 1525-1575, 1230, 1035 cm⁻¹; ¹H NMR(CDC₁₃) δ 8.18(bs,1H), 7.8(s,1H), 5.2(bs, 1H), 4.4(m,1H), 4.15(q,2H), 2.2(s,3H), 1.95(s,3H), 1.25(t, 3H), 1.00(s,6H), 2.2-1.01(m,17H); mass spectrum(EI) m/z 494,434; Anal. calcd. for C₂₈H₃₆N₅O₅ : C, 70.45; H, 7.69, N, 5.66. Found: C,69.83; H, 7.63; N, 5.35.

**General procedure for synthesis of 3β-acetoxv-17,17-dichloro-16(E)-chloro methyleneandrost-5-ene(6a):**

To a chloromethyleneiminium salt prepared freshly from distilled phosphorous oxychloride(8.37mL, 0.009 mol) and dimethylformamide(7 mL, 0.009 mol) was added a solution of 2a(1.2g, 0.003 mol) in chloroform(100 mL) under nitrogen atmosphere.
The reaction was stirred first at room temperature for 0.25h and then at 65°C for 3h followed by pouring it into ice cold water. The organic solvent was removed in a rotavapor at 25°C and neutralised with powdered sodium bicarbonate to pH 6.5 at 15°C. Extraction with ethyl acetate(3 x 30 mL), washing with water, drying and removal of the solvent gave a white solid product. Column chromatography of the product using toluene as eluant afforded two distinct products.

a) 3β-acetoxv-17,17-dichloro-16(E)-chloromethylenandro-5-ene (6a):

Yield 774 mg (60%); mp. 155-56°C(methanol); TLC. in toluene(Rf= 0.6); IR(KBr) $\nu_{max}$ 2950,1735 cm$^{-1}$; $^1$H NMR(CDC$_3$) $\delta$ 6.40(s,1H), 5.20(bs,1H), 4.35(m,1H), 1.85(s,3H), 0.95(s,3H), 0.90(s,3H), 2.30-1.10(m,17H); mass spectrum (EI) m/z 370(98%), 372(100%), 374(33%); Anal. Calcd for C$_{22}$H$_{29}$O$_2$Cl$_3$: C, 61.40; H, 6.77. Found: C, 61.35; H, 6.82; and

b) 3β-acetoxv-17-keto-16(E)-chloromethylene androst-5-ene (6b):

Yield 112 mg(10%), mp 170-71°C(ethanol); TLC. in CHCl$_3$ (Rf= 0.65); IR(KBr): $\nu_{max}$ 2945, 1740, 1700 cm$^{-1}$; $^1$H NMR(CDC$_3$) $\delta$ 6.86(t,J=2Hz, 1H), 5.15(bs,1H), 4.30(m,1H), 1.90(s,3H), 0.85(s,3H), 2.30-1.10(m,17H); mass spectrum(EI) m/z 316(100%), 318(33%). Anal.Calcd. for C$_{22}$H$_{29}$ClO$_3$: C, 70.10; H, 7.76. Found: C, 70.22; H, 7.82.

Product 6a and 6b were also obtained from 3b,3c, 3d and 4 by employing same reaction condition.

17,17-Dichloro-16(E)-chloromethylene-3β-formyloxy-androst-5-ene (7):

Yield 831 mg (66%); mp 176-77°C; TLC in toluene(Rf = 0.7); IR(KBr) $\nu_{max}$ 2950, 1730 cm$^{-1}$; $^1$H NMR(CCl$_4$) $\delta$ 7.82(s,1H), 6.48(s,1H), 5.30(m,1H), 4.62(m,1H), 1.12(s,3H), 0.98(s,3H), 2.48-1.20(m,17H); mass spectrum El) m/z 370(99%), 372(100%), 374(33%); Anal.Calcd for C$_{21}$H$_{27}$Cl$_3$O$_2$: C, 60.58; H, 6.50. Found, C, 60.47; H, 6.61.

17,17-Dichloro-16(E)-chloromethylene-3β-benzoyloxy-androst-5-ene (8):

Yield 998 mg(67%); mp169-71°C; TLC in toluene(Rf = 0.7); IR(KBr) $\nu_{max}$ 2950, 1740cm$^{-1}$; $^1$H NMR(CDC$_3$) $\delta$ 7.82-7.35(m,5H, aromatic), 6.38(s,1H), 5.25(bs,1H),
4.65(m,1H), 1.02(s,3H), 0.85(s,3H,Me), 2.45-1.10(m,17H); mass spectrum (El) m/z 370(100%), 372(100%), 374(33%); Anal. Calcd for C_{27}H_{31}Cl_{30} : C, 65.85; H, 6.32. Found: C, 65.80; H, 6.42.

3β-Formyloxy-16(E)-chloromethylene-5-androsten-17-one(9a):-
Yield 634mg(54%); mp 165-66°C; TLC in toluene (Rf = 0.4); IR(KBr) \( \nu_{\text{max}} \) 2950, 1730, 1623 cm\(^{-1}\); \(^1\)H NMR(CDCl\(_3\)) \( \delta \) 7.78(s,1H), 6.92(t, 1H, J=2.45Hz), 5.32(bs,1H), 4.55(m,1H), 1.02(s,3H), 0.90(s,3H), 2.40-1.15(m,17H); mass spectrum (El) m/z 316(100%), 318(33%); Anal. Calcd for C_{21}H_{27}ClO_{3} : C, 69.61; H, 7.49. Found: C, 69.70; H, 7.23.

3-Chloro-16(E)-chloromethylene-17-ketoandrost-5-ene(9b):-
Yield 123 mg (35%) mp 198°C; TLC in CHCl\(_3\) (Rf=0.8); IR(KBr) \( \nu_{\text{max}} \) 2950, 1620, 1425 cm\(^{-1}\); \(^1\)HNMR(CDCl\(_3\)) \( \delta \) 6.90(t,1H, J=2.50Hz), 5.17(bs,1H), 3.51-3.45(m,1H), 0.86(s,3H), 0.71(s,3H), 2.7-1.1(m,17H); Mass spectrum(El) m/z 352(M\(^+\), 56%), 354(M\(^+\)+2, 36%), 356(M\(^+\)+4, 7%); Anal. calcd. for C_{19}H_{26}OCl_{2} : C, 68.18; H, 7.38. Found: C, 68.30; H, 7.41.

Preparation of steroidal(17,16-b)pyridine(10):-
A solution of 5a (447mg, 0.001 mol) in DMF(25 mL) was poured into 0.01 mol of Vilsmeier reagent(prepared from 0.93 mL of POCl\(_3\) and 0.78 mL of DMF) at 0°C under nitrogen atmosphere in a 150 mL round bottomed flask. The reaction mixture was stirred at room temperature for 30 minutes and then at 110°C for 1.5h. It was worked up by pouring the reaction mixture into ice cold water, basified with a mixture of powdered NaHCO\(_3\) and KOH to pH =9 and stirred at 45°C for 0.5 h when a solid separated out which was filtered through whatmann 40 filter paper under suction and was purified by silica gel column chromatography using Toluene:acetone=90:10 as eluting solvent. Yield, 350 mg (71.8%); mp 240°C(decomp); TLC in toluene:acetone=95:5 (Rf=0.3); IR(NaCl) \( \lambda_{\text{max}} \) 2960, 2240, 1735, 1650, 1590, 1540, 1385, 1260, 1125, 1050,780 cm\(^{-1}\); \(^1\)HNMR(acetone-d\(_6\)) \( \delta \) 8.70(s,1H), 8.01(s,1H), 7.68(s,1H), 5.43(bs,1H), 4.51(m,1H), 3.19(s,3H), 3.11(s,3H), 1.97(s,3H), 1.14(s,3H), 0.97(s,3H), 2.52-1.29(m,17 H); Mass spectrum(El) m/z 487(M\(^+\)), 461(M\(^+\)-26), 425, 380, 300, 288, 260; Anal. calcd. for C_{30}H_{37}N_{3}O_{3} : C, 73.92; H, 7.59; N, 8.62. Found: C, 73.60; H, 7.62; N, 8.51.
Vilsmeier reaction of 16-formyl-16-DPA oxime:

To a chloromethyleneiminium salt prepared freshly from distilled phosphorous oxychloride $8.37\text{mL, 0.009 mol}$ and dimethylformamide $7\text{mL, 0.009 mol}$ was added a solution of 16-formyl-16-DPA oxime $1.2\text{g, 0.003 mol}$ in chloroform $100\text{mL}$ under nitrogen atmosphere. The reaction was stirred first at room temperature for 0.25h and then at 65°C for 3h followed by pouring it into ice cold water. The organic solvent was removed in a rotavapor at 25°C and neutralised with powdered sodium bicarbonate to pH 6.5 at 15°C. Extraction with ethyl acetate $3 \times 30\text{mL}$, washing with water, drying and removal of the solvent gave a white solid product. Column chromatography of the product using toluene as eluant afforded two distinct products. The two products were confirmed as 6a and 6b by its spectral data and mixture melting point with standard samples.

References