SYNTHESIS OF 16-aza and 15,16-diaza-steroids
As mentioned in the introductory chapter, numerous modifications of steroidal functional groups and the steroidal nucleus itself have been carried out in search of compounds with improved biological activities. However, with a few notable exceptions, presence of nitrogen has often led to a decrease in the original physiological activity. To explain this, it has been proposed that at the physiological pH the basic aza-steroids are present as salts and their cell wall permeability, which is dependent on lyophilic character, decreases. Thus lack of activity could be due to the fact that these compounds do not reach the reaction sites. The presence of a non-basic nitrogen, as an amidic group, in the hormonal analogues seemed more likely to lead to useful compounds as they may not be capable of forming salts under physiological conditions. With this end in view synthesis of some amidic azasteroids was undertaken in the present work. In this chapter approaches for obtaining the \( \text{16-aza-steroidal systems CLVII and CLVIII} \) are discussed. Syntheses of some \( \text{16-aza-steroids} \) and connected pharmacological activity have been referred to

\[
\begin{align*}
\text{CLVII} & \quad R = H \\
\text{CLVIII} & \quad R = \text{OH}
\end{align*}
\]
in the introductory chapter\textsuperscript{189}. It may be pointed out that the amidic compound CLVII is not expected to be non-basic due to the presence of the second nitrogen atom.

Synthesis of 3-deoxy-15,16-diaza-18-norequilenin (CLVII) was first examined along the following lines.

The acid CLX was prepared by the known procedure\textsuperscript{190} involving acylation and reduction steps. Its ester was formylated by treating with sodium ethoxide and ethylformate, and then cyclised
to the phenanthrene derivative CLXIII using a mixture of sulphuric acid and phosphoric acid. The identity of the compound CLXIII was confirmed by converting it to the known dihydrophenanthrene carboxylic acid CLXV.

The ester CLXIII was refluxed, for 40 hrs., with hydrazine hydrate in ethanol. It was hoped that this procedure will directly lead to the tetracyclic compound CLVII. Work up of the reaction mixture afforded a solid, m.p. 162-64°, mass spectrum of which exhibited the molecular ion peak at m/e 238 and other prominent peaks at m/e 207 (M - 31) and m/e 179 (M - 59). On this basis, it was assigned the structure CLXIV. The elemental analysis and the IR spectrum were also in accord with this structure.
The failure of the ester CLXIII to directly afford CLVII was surprising in view of the fact that Carpino had earlier reported\(^{192}\) the cyclisation of ethylcinnamate (CLXVI) to 5-phenyl-3-pyrazolidine (CLXVIII) in 80-90 % yield under similar conditions.

The postulated\(^{192}\) intermediate (CLXVII) in the transformation CLXVI $\rightarrow$ CLXVIII arises from attack of a hydrazine molecule on the $\beta$-carbon atom of the $\alpha$, $\beta$-unsaturated carbonyl system whereas in the present case, the attack occurs on the carbonyl carbon itself. The resulting product CLXIV resists cyclisation under the reaction conditions. A possible explanation for the different behaviour of CLXIII and CLXVI can be an increased mesomeric interaction, of the type shown, in the naphthalene compound resulting in lower positive charge on the carbon atom. Greater ability of naphthalene, as compared to benzene, to disperse an...
Alternatively, the incorporation of the double bond in the ring system or steric factors associated with the naphthalene ring could be responsible for this behaviour. A similar observation was made in another reaction also which is mentioned at a later stage.

Nevertheless, more vigorous conditions were tried to cyclise the hydrazide CLXIV. Stirring the hydrazide with sodium hydride in tetrahydrofuran gave a complex mixture from which no pure component could be isolated even after column chromatography over alumina. Attempts to cyclise the compound under acidic conditions, refluxing a benzene solution of CLXIV in the presence of p-toluenesulphonic acid, were also unrewarding. Photolysis in benzene : methanol (20:1) solution under a nitrogen atmosphere, for 18 hrs., left the hydrazide CLXIV unaltered.

Recently, Baldwin has presented some empirical rules to predict the relative facility of ring forming reactions. According to these rules, the process CLXIV $\rightarrow$ CLVII would be...
classified as a 5-Endo-Trigonal ring closure. The prefix Endo means that the breaking bond is endocyclic to the smallest so formed ring and trigonal indicates the geometry of the carbon atom undergoing ring closure reaction (marked by asterick).

\[
\begin{align*}
\text{5-Endo-Trigonal} \\
\text{Such processes are kinetically disfavoured}, \text{ which may explain the failure of the present cyclisation.}
\end{align*}
\]

Further, according to the Baldwin rules 5-Exo-Trigonal ring closures are favoured processes.

\[
\begin{align*}
\text{5-Exo-Trigonal} \\
\text{Thus the intermediate CLXVII should undergo ready}
\end{align*}
\]
cyclisation to CLXVIII.

\[
\begin{align*}
\text{CLXVII} & \quad \text{CLXVIII}
\end{align*}
\]

It was, therefore, decided to modify the route and attempt the cyclisation with CLXX which would involve a 5-Exo-Trigonal ring closure. In fact, similar reactions of β-ketoesters with hydrazine are known.\(^{146}\)

\[
\begin{align*}
\text{CLXX} & \quad \text{CLXXIII}
\end{align*}
\]

The substrate CLXX was prepared according to the
following scheme.

The acid chloride of 1-naphthylbutyric acid (CLX) was cyclised to 1-keto-1,2,3,4-tetrahydrophenanthrene (CLXXI) using stannic chloride. The cyclised ketone was reacted under basic conditions (sodium methoxide) with dimethyloxalate to get the glyoxalate CLXXII which was decarbonylated, by heating at 170°, to give the ketoester CLXX.

Reaction of the ketoester CLXX with hydrazine hydrate in ethanol readily led to 3-deoxy-14,15,-16-diaza-18-norequilenin (CLXXIII).
The NMR spectrum of CLXXIII could not be recorded as it was insoluble in the common organic solvents. Its mass spectrum showed the molecular ion peak at m/e 236 and fragment ion peaks at m/e 207 and m/e 179. This fragmentation pattern may be rationalised as follows.

Attempts to reduce or hydrogenate CLXXIII to CLVII were unsuccessful.

Attention was then diverted to the synthesis of the 11-keto-16-azasteroid CLVIII. Azasteroids functionalised at C-11 are of special interest because of the biological activity associated with this position.

For the synthesis of CLVIII the route investigated
The naphthaldehyde CLXXIV was synthesised essentially according to the literature procedures as shown below.
The identity of this aldehyde (CLXXIV) was established on the basis of spectroscopic evidence and correct elemental analysis. The NMR spectrum showed a singlet at $\delta$ 4.06 (3H, OCH$_3$), a multiplet at $\delta$ 7.25-8.5 (6H, aromatic) and a very low field singlet, at $\delta$ 11.75 (H, -CHO), characteristic of aldehydic protons. In the mass spectrum the molecular ion peak was present at m/e 186 (base peak) and other prominent peaks appeared at m/e 185, 157 and 142.

The reaction of the aldehyde CLXXIV with ethyl acetate in absolute ethanol in the presence of sodium ethoxide afforded the $\alpha,\beta$-unsaturated ester (CLXXV). The geometry across the double bond was inferred to be trans on the basis of the large coupling constant ($J = -16$ Hz) observed for the olefinic proton appearing as a doublet at $\delta$ 6.55 in the NMR spectrum. A triplet and a quartet corresponding to -COOCH$_2$CH$_3$ and -COOCH$_2$CH$_3$ appeared at $\delta$ 1.35 and $\delta$ 4.35 respectively while a singlet at $\delta$ 4.0 was assigned to the methoxy protons. One olefinic proton was merged with the aromatic protons$^{203}$ in the $\delta$ 7.2-8.0 region.

The ester CLXXV was added to the anion of nitromethane generated by potassium metal in t-butanol. Work up of the reaction mixture, after 72 hrs., gave back the starting ester CLXXV.
(TLC, IR, NMR). The failure of the Michael addition is in contrast to the known facile addition of nitromethane to ethyl cinnamate and, as mentioned earlier, could be a result of decreased reactivity at the $\beta$-carbon atom in CLXXV.

In view of this failure the original scheme was slightly modified.

The presence of an additional electron withdrawing $R=CH$. 

The presence of an additional electron withdrawing
carbethoxy group in CLXXVII could make the $\beta$-position more reactive towards attack by the nitromethane anion. The adduct CLXXVIII could then be elaborated to CLVIII.

Reaction of the aldehyde CLXXIV with ethyl malonate afforded the diester CLXXVII almost quantitatively. Its reaction with sodium salt of nitromethane in methanol furnished, on acidification, a reddish oil which was found to be a mixture of two major components (TLC). It defied all attempts at purification by crystallisation. Kohler and Engelbrecht had earlier reported similar problems in the reaction involving the simple benzene analog. They considered the red oil to be a secondary product arising from subsequent reaction of the type shown.

To overcome the difficulty these workers had suggested acidification of the reaction mixture with hydrogen chloride.
gas immediately after the addition of nitromethane solution. Following this procedure, consistently good yields of the adduct CLXXVIII were obtained. Its NMR spectrum exhibited two triplets at $\delta$ 1.0 and 1.25 (3H each, 2 x $-\text{COOC}_2\text{CH}_3$, $J = 6$ Hz), two quartets at $\delta$ 4.15 and 4.3 (2H each, 2 x $-\text{COOC}_2\text{CH}_3$, $J = 6$ Hz) and a singlet at $\delta$ 4.0 (3H, $-\text{OCH}_3$). A doublet for $-\text{CH}_2$-$\text{NO}_2$ protons was observed at $\delta$ 5.10 ($J = 7$ cps) and the six aromatic protons showed up as a multiplet extending from $\delta$ 7.1-7.9. The remaining two protons appeared as a multiplet centred around $\delta$ 4.05. The mass spectrum and elemental analysis were also in accord with the structure CLXXVIII. This product was also obtained by first condensing nitromethane with the aldehyde CLXXIV to give 2-(6-methoxy-2-naphthyl)-1-nitroethylene (CLXXXIII) followed by reaction with ethyl malonate, although the overall yield of CLXXVIII by this procedure was lower.

The nitro group in CLXXVIII was reduced with zinc dust in refluxing acetic acid. The product spontaneously cyclised to give 4-(6-methoxy-2-naphthyl)-3-carbethoxy-2-pyrrolidone (CLXXIX). Its NMR spectrum showed a triplet at $\delta$ 1.35 (3H, $-\text{COOC}_2\text{CH}_3$, $J = 6$ Hz), a singlet at $\delta$ 3.95 (3H, $-\text{OCH}_3$), a quartet at $\delta$ 4.25 (2H, $-\text{COOC}_2\text{CH}_3$)
and a broad signal at $\delta$ 6.85 (1H, $-\text{NH}$). The aromatic protons showed up as a multiplet at $\delta$ 7.7 (6H) and the $-\text{CH}_2\text{NH}$ and two remaining protons of pyrrolidone ring appeared as a multiplet around $\delta$ 3.6. In the IR spectrum a broad band at $\nu_{\text{max}}^{\text{nujol}}$ 3300 cm$^{-1}$ for the $-\text{NH}$ group, and sharp signals at 1750 cm$^{-1}$ and 1685 cm$^{-1}$, due to ester and amidic functions respectively, were observed. The mass spectrum showed the molecular ion peak at m/e 313 (M$^+$, 45%) and other peaks at m/e 268 (16%), 240 (base peak) and 189 (23%) which may be rationalised as shown below.

\[
\begin{align*}
&\text{[\includegraphics{m/e_313}} \text{]} \\
&\text{m/e 313 (M$^+$)}
\end{align*}
\]

\[
\begin{align*}
&\text{\textbf{-OC}_2\text{H}_5} \\
&\longrightarrow \\
&\text{[\includegraphics{m/e_268}} \text{]} \\
&\text{m/e 268 } \text{M-45}
\end{align*}
\]

\[
\begin{align*}
&\text{[\includegraphics{m/e_240}} \text{]} \\
&\text{m/e 240 } \text{M-73}
\end{align*}
\]

\[
\begin{align*}
&\longrightarrow \\
&\text{[\includegraphics{m/e_183}} \text{]} \\
&\text{m/e 183 } \text{M-130}
\end{align*}
\]
Treatment of CLXXIX with 0.2 N sodium hydroxide solution in acetone resulted in 30-35% conversion to the acid CLXXX. About 30% of the ester CLXXIX was recovered unchanged. Use of longer reaction periods or stronger hydrolysis conditions did not lead to any improvement of the yield. Because of low solubility in common solvents the NMR spectrum of the acid CLXXX could not be recorded. Its IR spectrum showed broad bands at $\nu_{\text{nujol}}$ 3200 cm$^{-1}$ and 1685-1715 cm$^{-1}$. The mass spectrum showed the molecular ion peak at m/e 285 (40%) and other peaks at m/e 270 (65%), 240 (base) and 183 (30%).

Attempted homologation of the acid CLXXX to CLXXXI, by first treating it with thionyl chloride and then reaction with diazomethane, resulted in a very complex mixture. The difficulty was traced to the acid chloride formation step, as the TLC of
the product at this stage showed a number of spots and the IR spectrum did not indicate the presence of $-\text{C} - \text{Cl}$ group. Several transformations are recorded in literature where thionyl-chloride can act as an oxidant. Use of oxalyl chloride, instead of thionyl chloride, did lead to the acid chloride formation (which was confirmed by its conversion to the ester CLXXIX on treatment with ethanol) but its subsequent reaction with diazo-methane again afforded a complex mixture from which no pure product could be isolated.

As far as the synthesis of CLVIII was concerned, this route seemed impracticable. It was, therefore, decided to synthesise the C-nor analogue CLXXXIV. Besides its inherent interest it could lead to CLVIII and/or CLXXXV through ring expansion.
A number of common cyclisation conditions (polyphosphoric acid\textsuperscript{209,210} at 150°, methane sulphonic acid\textsuperscript{209} at 50° and polyphosphate ester\textsuperscript{211} at room temperature) proved unrewarding. Finally, reaction of the acid CLXXX with P\textsubscript{2}O\textsubscript{5} in refluxing chloroform\textsuperscript{208} afforded CLXXXIV in a low yield (10 %). The identity of CLXXXIV was made on the basis of elemental and IR analysis and was confirmed from its mass spectrum which exhibited the molecular ion peak at m/e 267 and other peaks at m/e 210 and m/e 167. The genesis of these peaks may be attributed to the following fragmentation.

\[ \text{It may be mentioned that earlier Birch and SubbaRao}\textsuperscript{212} had worked on cyclodehydration of CLXXXVI to CLXXXVII. For unknown reasons, it was found to be a difficult process and only low yields of CLXXXVII could be obtained.} \]
Recently, Gary H. Posner and coworkers\textsuperscript{195} have reported HF promoted cyclisation of the keto acid CLXXXVIII to the tetracyclic steroid CLXXXIX in 10\% yield. However, HF promoted cyclisation of the ketal acid XCC produced the same steroid (CLXXXIX) in 65\% yield.

The low yield at the cyclisation stage in the present case precluded attempts at ring expansion of CLXXXIV. The prior ketal formation procedure suggested by Posner et al.\textsuperscript{195} was obviously not applicable to the amidic compound CLXXX.