PART VII
SYNTHESIS OF SOME AMIDES AND
ESTERS OF 1-STACHYDRINE
SYNTHESIS OF SOME ESTERS AND AMIDES OF 1-STACHYDRINE

Hunt and Taveau (1911) investigated the derivatives and homologs of choline and showed that muscarinic effect (stimulation of the inhibitory nerves to the heart and the organs with the result of lowering of blood pressure) is most marked in compounds that depart least from the choline type of structure i.e. having the group \( (\text{CH}_3)_2^+ \text{CH}_2\text{CH}_2-0^+ \). Betaine salts \( (\text{CH}_3)_2^+ \text{CH}_2\text{COOH} \) have the structural similarity to choline and are still inert. The inert property of these compounds has been attributed due to the presence of carboxylic group. Number of cases are known in literature where introduction of carboxylic group has altered the physiological properties of the substance and some examples of such inactivations are the reported non-toxic characters of benzobetaine \( \text{CH}_3\text{NO}_2\text{H}_4\text{COO}^- \), taurobetaine \( \text{CH}_3\text{NCH}_2\text{SO}_2^- \), and stachydrine \( \text{CH}_3\text{NCH}_2\text{SO}_2^- \). All these compounds are quaternary ammonium compounds with basic similarity to choline but are not physiologically active like choline.

Renshaw and Hotchkiss described the physiological inactivity of betaine in the blood stream due to its existence as electrically neutral and hence physiologically inert bipolar ion \( (\text{CH}_3)_2^+ \text{NCH}_2\text{COO}^- \). They prepared number of esters and amides of betaine to see if these compounds, devoid of free carboxylic group would show any muscarinic effect. These esters and amides were examined for their physiological activity by Hunt and Renshaw, and they reported the esters and amides to be physiologically active. Ethyl ester of betaine was found to have more muscarinic effect.
than choline. Renshaw and Hotchkiss\(^7\) prepared series of alkyl and aryl \(N\)-substituted betaine amides. It was found that in the alkyl series, the maximum muscarinic action was observed, but the phenyl derivatives gave a remarkable strong stimulating nicotinic action.

Taking into consideration the structural similarity of stachydrine and betaine, both are quaternary ammonium compounds and have carboxylic group and both as such are physiologically inactive. The inactivity of stachydrine in the blood stream may also be due to its electrically neutral bipolar ion (1)

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Some esters and amides of stachydrine were prepared with a view to get compounds devoid of free carboxylic group, and were tested for some physiological activity.

**PREPARATION OF AMIDES**

For the preparation of amides, 1-stachydrine was converted to 1-stachydrine acyl chloride and then condensed with different amines or amine hydrochloride.

**Preparation of 1-stachydrine acyl chloride**

Thionyl chloride is considered to be the most convenient reagent for the preparation of acyl chlorides\(^9\). The acyl halides are formed in excellent yield at room temperature or upon refluxing gently for a short time. The other products of the reaction are gases as hydrogen chloride and sulphurdioxide. Benzene is used as the solvent\(^{10}\), and
sometimes a few drops of pyridine are added. Trial was thus made to prepare acyl chloride derivative of 1-stachydrine using thionyl chloride. But the residue after the completion of the reaction was found to be black resinous mass. To avoid this the reaction was tried at different temperatures using different time period. In all the cases the results were the same.

But the stachydrine acyl chloride could be prepared successfully using oxalyl chloride. The oxalyl chloride used was prepared as below:

(Preparation of oxalyl chloride)

90 gm. of finally powdered anhydrous oxalic acid was mixed thoroughly with 400 gm. of powdered phosphorous pentachloride. The mixing was done at low temperature by keeping the mortar immersed in an ice bath. The mixture was then kept at room temperature for two to three days or till sufficient liquification of the mass had taken place. The reaction product was then distilled fractionally. The fraction which distilled over between 60-100°C. was collected. This fraction when redistilled and collected at 60-70°C. gave approximately 45-50% yield of oxalyl chloride.

Preparation of 1-stachydrine acyl chloride (using oxalyl chloride)

20 gm. of anhydrous stachydrine was refluxed with 20 gm. of oxalyl chloride for three hours. The excess of oxalyl chloride and other volatile matter was removed from the reaction mixture by distilling it under slightly reduced pressure. Stachydrine acyl chloride was obtained as brown oily compound which was used further as such.
Preparation of 1-stachydrine methylamide

2 gm. of stachydrine acyl chloride and 1 gm. of methylamine hydrochloride were refluxed on a water bath for 4 hours. Mixture of chloroform (25 ml. and pyridine 4 ml.) was used as a solvent for the reaction. After reaction was over, distillation was carried out under reduced pressure to remove volatile matter. The residue was viscous oily mass. It was taken in a small volume of absolute ethyl alcohol 20 ml. and was passed through column of alumina (containing 100 gm. alumina E.M. for chromatography). The elution was done with ether, chloroform, acetone and absolute ethyl alcohol respectively. Fractions of 10 ml. each were collected till the last few drops of the eluate left no residue on evaporation. It was found that the test with the alkaloidal reagent was positive only in alcoholic fractions. All the alcoholic fractions were combined and concentrated to a small volume. The concentrated solution was kept in a refrigerator, when needle shaped crystals of stachydrine methylamide chloride were obtained. Filtered and dried under vacuum over calcium chloride, m.p. 166°C.
The product was found to be highly hygroscopic.

Quantitative analysis for nitrogen:

\[
\text{Found} = 14.20\% \\
\text{Calculated for } C_9H_{17}N_2OCl = 14.54\%
\]

Preparation of 1-stachydrine ethylamide

\[
\text{Cl} \quad \text{COCl} + \text{C}_2\text{H}_5\text{NH}_2\cdot\text{HCl} \rightarrow \text{Cl} \quad \text{CONH}_2\text{H}_5 \\
\text{stachydrine ethylamide chloride}
\]

The reaction was carried out in the same way as for methylamide but using ethylamine in place of methylamine. The needle shaped crystals obtained in this case had m.p. 163°C., and was highly hygroscopic.

Quantitative analysis for nitrogen:

\[
\text{Found} = 13.48\% \\
\text{Calculated for } C_9H_{19}N_2OCl = 13.55\%
\]

Preparation of 1,2-bis(hydrinamido)ethane methochloride

\[
\text{Cl} \quad \text{COCl} + \text{H}_2\text{N} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2 \rightarrow \text{Cl} \quad \text{CONH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH} \cdot \text{OC} \\
\text{l-stachydrine acyl chloride 2 gm. and ethylene diamine 0.25 gm. were refluxed in a mixture of chloroform 25 ml. and pyridine 4 ml. for 4 hours. After the completion of the reaction, distillation was carried out under reduced pressure to remove volatile matter and the residue obtained was dissolved in}
\]


small amount of absolute ethyl alcohol and purified as in
the case of methyleamide with the help of chromatographic
technique. Acetone fractions gave positive tests with alkaloidal-
al reagents. The combined acetone fractions were concentrated
and kept in a vacuum desiccator. The product crystallised
after few days, m.p. 205-206°C.
Quantitative analysis for nitrogen.

Found = 14.25 %

Calculated for

\[ \text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{Cl}_2 \]

14.6 %

"Preparation of esters of l-stachydrine"

Preparation of methyl ester

![Chemical Structure](image)

2 mg. of anhydrous stachydrine was dissolved
in 10 ml. of absolute methyl alcohol, and saturated with dry
hydrochloric acid gas and refluxed on a water bath for 6
hours. Removed the volatile matter under vacuum. The residue
obtained, was oily in nature and did not crystallise even
after keeping it in refrigerator for many days. Small amount
of the ester obtained above was treated with sodium bicarbonate
solution (1 % w/v) and then extracted with various solvents.
It was found that the esters could not be extracted by
petroleum ether, ether, benzene and chloroform. The chloroaurate
derivative of the small amount of ester was prepared by adding
auric chloride solution to aqueous solution of little of the
ester obtained above, when a crystalline mass immediately
separated out. Filtered and recrystallised from water. m.p. 85°C.

The reported melting point of chloroaurate derivative of methyl ester of 1-stachydrine is 85°C.

**Preparation of ethyl ester**

C\(_2\)H\(_5\)OH saturated with dry HCl gas

![Chemical structure of ethyl ester]

Ethyl ester was prepared in an analogous way as methyl ester, using absolute ethyl alcohol instead of methyl alcohol. Chloroaurate was prepared as above m.p. 59-60°C. The reported melting point of chloroaurate of 1-stachydrine ethyl ester is 59-60°C.

**Preparation of propyl ester**

C\(_3\)H\(_7\)OH saturated with dry HCl gas

![Chemical structure of propyl ester]

Propyl ester was also prepared in a similar way as methyl ester using propyl alcohol in place of methyl alcohol. Chloroaurate derivative was prepared as above m.p. 45°C.

**Analysis for Au.**

<table>
<thead>
<tr>
<th>Found</th>
<th>38.51 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated for</td>
<td></td>
</tr>
<tr>
<td>C(_6)H(_12)NCOO C(_2)H(_7).HAuCl(_4)</td>
<td>38.55 %</td>
</tr>
</tbody>
</table>

**Preparation of Butyl ester**

C\(_4\)H\(_9\)OH saturated with dry HCl gas

![Chemical structure of butyl ester]
It was also prepared by the same method as methyl ester using dry butyl alcohol in place of methyl alcohol. Chloroaurate derivative was prepared as above. Chloroaurate derivative in this case separated as an oily mass, which crystallised on keeping in refrigerator, m.p. 14-15 °C.

Analysis for Au.

\[
\text{Pound} = 37.48 \%
\]

Calculated for

\[
\text{C}_6\text{H}_{12}\text{NCOOC}_4\text{H}_4\cdot\text{HAuC}_4
\]

\[
= 37.52 \%
\]
REFERENCES


4. Ackerman, Z. Biol. 1914, 64, 44.


11. Staudinger, Ber., 1908, 41, 3363.
