SYNOPSIS

PART I

SYNTHESIS OF 4-THIAZOLIDONES

Several thiasolidone derivatives have been found to exhibit a wide variety of physiological activities. 2-Imino-4-thiazolidone has been found to possess antithyroid action similar to that of thiouracil. Han-Hoi et al. synthesized several 4-oxo-\( \Delta^2 \)-thiazolin-2-yl-hydrazones possessing tuberculostatic activity.

In light of the observations that 2-aryl-3-alkyl-4-thiazolidones show anticonvulsant properties and hydrazones of 2,4-thiazolin-diones have been found to be tuberculostatic, the synthesis of various 4-oxo-3-aryl/benzyl-5-alkyl/aryl-thiazolin-2-yl-hydrazones was undertaken with a view to investigate their tuberculostatic and anti-convulsant effects.

To synthesise 4-oxo-3-aryl/benzyl-5-alkyl/aryl-thiazolin-2-yl-hydrazones, first various thiosemicarbazides were prepared, and condensed with different aldehydes to get thiosemicarbazones. These thiosemicarbazones were then condensed with chloro-acetic, \( \alpha \)-bromo-propionic and \( \alpha \)-bromo-phenylacetic acid, the 4-oxo-3-aryl/benzyl-5-alkyl/aryl-thiazolin-2-yl-hydrazones being obtained directly.

The synthesis of thiosemicarbazones is described in Section I and Section II describes the condensation of these thiosemicarbazones with chloro-acetic, \( \alpha \)-bromo-propionic and \( \alpha \)-bromophenylacetic acid.
SECTION I: SYNTHESIS OF 4-ARYL/BENZYL-THIOSEMICARBAZIDES AND THIOSEMICARBAZONES

The 4-aryl/benzyl thiosemicarbazides required for the purpose of this work were prepared from the corresponding aryl/benzyl isothiocyanates by the action of hydrazine hydrate in ethanol.

\[ R - N = C = S + H_2N.NH_2.H_2O \rightarrow R - NH - CSNHNH_2 \]

where \( R \) is \( C_6H_5^- \), o-, m- and p-\( CH_3 \cdot C_6H_4^- \), p-\( CH_2O \cdot C_6H_4^- \), or p-\( CH_2CH \cdot C_6H_4^- \).

These 4-substituted thiosemicarbazides, when condensed with different aldehydes in ethanol and a few drops of glacial acetic acid, afforded the corresponding 4-aryl/benzyl-thiosemicarbazones.

\[ R - NHCSNHNH_2 + OHCR' \rightarrow R - NHCSNNR = CH.R' + H_2O \]

where \( R \) is the same as above.

while \( R' \) is \( C_6H_5^- \), o- and p-\( CH_3 \cdot C_6H_4^- \), o- and p-\( HO \cdot C_6H_4^- \), p-\( CH_2O \cdot C_6H_4^- \), o-\( CH_2CH \cdot C_6H_4^- \), m-\( O_2N \cdot C_6H_4^- \), \( 2,4\)-\( Cl_2 \cdot C_6H_5^- \), 3,4-(\( CH_3 \cdot OH \cdot C_6H_5^- \), 3,4-(\( CH_2O \cdot C_6H_5^- \) and \( \sim -C_10H_7^- \).

SECTION II: SYNTHESIS OF 4-OXO-3-ARYL/BENZYL-5-ALKYL/ARYL-THIAZOLIN-2-YL-HYDRAZONES

Several 4-oxo-3-aryl/benzyl-5-alkyl/aryl-thiazolin-2-yl-hydrazone have been prepared and described in this section.

The 4-aryl/benzyl thiosemicarbazones were condensed with chloroacetic, \( \sim \)-bromo-propionic and \( \sim \)-bromo-phenylacetic acid in
presence of fused sodium acetate and absolute ethanol, when 4-oxo-3-aryl/benzyl-5-alkyl/aryl-thiazolin-2-yl-hydrazones of the general formula given below were obtained, cyclisation taking place simultaneously with the condensation.

\[
\begin{align*}
R - \text{NH} - C - \text{NHN} = \text{CHR}^1 & \quad \xrightarrow{\text{condensation}} \quad R - N \left[ \text{H} - \right] C = N . N = \text{CHR}^1 \\
\text{S} & \\
\text{H}_2\text{O} & \quad \text{C}=\text{O} \\
R - \text{N} - C = N . N = \text{CHR}^1 & \\
O=C & \quad \text{CH} \quad \text{S} \\
R^1 & \\
\end{align*}
\]

where \( R \) and \( R^1 \) are the same as before and \( R'' = \text{H}, \text{CH}_3^- \) and \( \text{C}_6\text{H}_5^- \).

In order to prove the constitution, 4-oxo-3,5-diphenyl-thiazolin-2-yl-hydrazone of benzaldehyde was subjected to acid hydrolysis, when the following known diketone was obtained.

\[
\begin{align*}
\text{C}_6\text{H}_5^- & \quad \text{N} \quad C = N . N = \text{CH} . \text{C}_6\text{H}_5 \\
O=C & \quad \text{CH} \quad \text{S} \\
\text{C}_6\text{H}_5 & \\
\to \\
\text{C}_6\text{H}_5^- & \quad \text{N} \quad C = \text{O} \\
O=C & \quad \text{CH} \quad \text{S} \\
\text{C}_6\text{H}_5 & \\
\text{C}_6\text{H}_5 & \\
\end{align*}
\]

Further, I.R. Spectra of these compounds have been studied for assignment of the group frequencies.

Some of these compounds have been tested for their physiological activity.
PART II

SYNTHESIS OF BASIC LOCAL ANAESTHETICS:

The use of acetanilide and methyl-acetanilide (Exalgin) as antipyretic and analgesic drugs is based on observations which go back to the beginning of the history of synthetic drugs. There is some local anaesthetic activity in some of these simple aryl substituted amides, when \(-\text{COCH}_2\) group is substituted by \(-\text{COCH}_2\text{NR}_1\text{R}_2\), the group commonly present in the procaine series. Rohmann and Friedrich found this activity in simple compounds such as I and II.

\[
\begin{align*}
I & \quad \text{\(\alpha\)-dimethylamino-acetanilide} \\
II & \quad \text{\(\alpha\)-diethylamino-acetanilide}
\end{align*}
\]

The most active and satisfactory member of this simple series is Xylocaine (Lidocaine) \(\alpha\)-diethylamine-2,6-dimethyl acetanilide, which is extensively used as local anaesthetic. As it has very few side reactions, Xylocaine has become one of the most satisfactory local anaesthetics.

\[
\begin{align*}
\text{III} & \quad \text{\(\alpha\)-diethylamine-2,6-dimethyl acetanilide}
\end{align*}
\]

Borovansky, Sekera and Cenek Vrba prepared several chloracetanilides of aryloxy, benzylloxy and phenoxyacetanilides and
the corresponding diethylamino acetanilides and tested these compounds for their local anaesthetic activity. The pharmacological tests showed that:

i) Compared to Xylocaine, the lipophilization of the molecule caused by aryloxy groups increased surface anaesthetic activity.

ii) Ortho substitution was least advantageous; m-phenoxy, p-benzyloxy and p-phenylethoxy derivatives were the most active.

iii) These compounds were less toxic than lidocaine.

As is well known, the introduction of benzyloxy group in a molecule brings about the analgesic properties. With a view to study the effect of benzyloxy group in derivatives of benzyloxyaniline, the present work was undertaken. Several compounds containing the anaesthetic group (-NHCOCHNR_1R_2) have been synthesised from m- and p-benzyloxyanilines and are described in this part.

The sequence of the reactions is given below:
HO-NHCOCH$_3$ where OH is in meta and para position

alkali solution

ClH$_2$C-X where X = H, Cl and CH$_3$

alkaline hydrolysis

X-CH$_2$O-NHCOCH$_3$

ClC$_6$H$_4$Cl and CH$_3$CNBrCOCl

X-CH$_2$O-NHCOCH$_3$Cl

RR'NH

X-CH$_2$ONHCOCH$_2$N$_2$R R'HCl

X-CH$_2$ONHCOCH$_2$N$_2$R R'HCl
where $R$ and $R'$ for both series are:

\[ R \text{ and } R' = \text{dimethylamino}, \]
\[ = \text{diethylamino}, \]
\[ = \text{morpholino}, \]
\[ = \text{piperidino}, \]
\[ = \text{piperazino} \]

The physiological activity of these compounds is under investigation.