CHAPTER V.

A GENERAL DISCUSSION OF THE REACTIONS USED IN THIS WORK FOR THE SYNTHESIS OF ACRIDINES.

Acridine derivatives can be prepared by a number of methods, the chief amongst them being:


\[
\text{aryl} - N^+ - \text{aryl} \xrightarrow{\text{ZnCl}_2} \text{acridine}
\]

2. o-Amino di-phenyl-methane is converted into acridine on oxidation (Fischer and Schute, Ber., 26, 3085, (1893)).

\[
\text{arylCH}_2\text{aryl} + \text{oxidation} \rightarrow \text{acridine}
\]

3. By the cyclisation of an N-phenyl-anthranilic acid.

\[
\text{aryl} - \text{COOH} \rightarrow \text{aryl} - \text{N}^+ \xrightarrow{\text{R}} \text{acridine}
\]
The phenylanthranilic acids can be obtained by:

(i) Ullmann's condensation, or

(ii) Jamison and Turner's synthesis - which is an extension of Chapmann's inversion of imino-ethers to a diphenyl amine derivative by heat.

The first two methods are only of academic interest and may lead to ambiguity.

We have therefore followed the third method for the synthesis of various 2-iodo-5 (6 or 7)-substituted-9-chloro acridines. Ullmann's reaction has been used in the present work for the synthesis of 12 out of the 14 nuclei. This route is simple, straightforward and unambiguous. The intermediates are easily available and yields excellent in most cases. Jamison and Turner's synthesis was resorted to in the case of 2-iodo-6-methoxy( or ethoxy)-9-chloro-acridines which would have been difficult to prepare by the Ullmann's condensation.

Ullmann (1907, AI, 648) found that o-halogen substituted benzoic acids reacted with primary amines in the presence of copper, to give N-phenylanthranilic acid.

\[
\text{\begin{align*}
\text{Cl} & \quad \text{N} \quad \text{R'} \\
\to & \\
\text{C} & \quad \text{H} \\
\text{N} & \quad \text{R'}
\end{align*}}
\]

This on cyclisation with zinc chloride, aluminium chloride, phosphorus pentoxide, or sulphuric acid gave acridine, which on reduction yielded the corresponding acridine. This method is
of general application and has been extensively employed by
various workers for the synthesis of substituted acridine
derivatives.

Albert and Ritchie, J.C.S., 459, (1943)
Bradbury and Linnel, J.C.S., 23, 47, (1942)
Dupre and Robinson, J.C.S. 549, (1945)
Garbakhsh Singh et al. J.I.C.S., 23, 224, 466, (1946)
24, 51, 79, (1947)
25, 227, (1948)
Magidson and Grigoveshki, Br. 62, 396, (1936)
Mauss and Mietzsch, D.R.P., 553, 072, (1932) etc.

For other methods of acridine synthesis, see
Becker and Danant, 1906, A1, 901.
For, B.C.A., 1904, T, 522, 1905, T, 1058, 1 06, T, 482, 1472;
1906, A1, 699, 901, 881.
Mayer, 1918, A1, 37.
Bamberger, Ber. 1909, 42, 170.
See also, The Acridines, by Albert;E.Arnold, (1951).
Goldberg and Ullmann (D.R.P. 173, 523; Ber. 33, 1691, (1906) obtained arylantranilic acid by condensing a substituted anthranilic acid with an aryl bromide in presence of cupric chloride.

Various modifications of Ullmann reaction have been described and it has been found that the reaction proceeds more smoothly at higher temperatures and also there is greater decomposition of the N-phenylanthranilic acid into diphenylamine and carbon dioxide if heating is prolonged. Potassium carbonate gives better results as potassium phenyl anthranilate is stable. (Ullmann Annalen, 1907, 325, 315, 358). Reaction occurs more readily with o-bromo- and o-iodo acids and better yields are obtained using amyl alcohol or nitro-benzene as diluents. (Ullmann, loc. cit). Iso-amyl alcohol gives even better results and cyclo-hexanol (Albert and Gladhill, J.Soc.Chem. 45, 149, (1945) has also been used when the reaction does not proceed smoothly at low temperatures.

Potassium metal (G. Singh, J.I.C.S. 23, 224, (1946) in absolute alcohol instead of potassium carbonate, glycerol etc. has been claimed to give better results and purer products. Nitro substituted o-haloacids are condensed with amines only with difficulty. An intimate mixture of the amine and acid is usually heated with or without the addition of copper. (G. Singh et al. J.Ind. Chem. Soc. 25, 227, (1948).
Effect of substituents on the yield of aryl anthranilic acid (Goldberg & Kelly, J. Chem. Soc. 102, (1946) has been discussed but no general predictions can be made. However, from the general literature available on this subject (i.e. condensation of a negatively substituted arylamine and 2-halogen benzoic acid) [Ullmann, Ann. 350, 312, (1907); Tuttle, J.A.O.C., 45, 1905-1923; Magidson and Irawin, Ber. 69, 537, (1935); Albert and Linnell, J. Chem. Soc., 89, 1614, (1935); Lehmann and Schrader, Ber. 70, 836, (1937); etc.] it can be seen that the presence of negative substituent in either of the reactants exerts an inhibitive influence on the reaction, resulting in poor yields of the N-phenylanthranilic acid while substituents such as methoxy, or methyl, facilitate the reaction, the yields being excellent.

For ring closure of the N-phenylanthranilic acids, concentrated sulphuric acid and aluminium chloride have been used with success. (Ullmann, loc. cit.). Zinc chloride, phosphorus pentoxide and phosphorus oxy-chloride have also been used, the last named being the best agent for ring closure with simultaneous introduction of 9-chloro group.

\[ \text{[Diagram]} \]

\[ \text{[Chemical structure]} \]
Ring closure of N-phenyl anthranilic acid does not proceed in the normal way with phosphorus oxychloride when there are electro-negative substituents like chloro or nitro etc. in position 2 & 7. Normally 9-chloro derivative is the expected derivative, in such cases, but either the acridone only is formed, or poor yields of 9-chloro-acridine are obtained, large amount of acridone being formed as a by-product. The explanation forwarded for this is that the presence of two electro-negative substituents in the nucleus activates the chloro grouping at position 9. (Bradbury & Linnell, J. Chem. Soc. 777, (1942); and Singh & Singh, J. Ind. Chem. Soc. 25, 228, (1948).

A number of iodo-acridines of the following type have been synthesised:

A. 2-Iodo-5-(or 7)-substituted 9-chloro acridines.
B. 2-Iodo-6-methoxy (or ethoxy)-9-chloro acridines.
C. Condensation products of the above acridines with various aromatic, heterocyclic and dialkylamino alkyl amines.

A. 2-Iodo-5-(or 7)-substituted 9-chloro acridines.

Ullmann's reaction has been successfully used in the present work in condensing 2:5 di-iodo benzoic acid with aniline (a); p-toluidine (b); p-anisidine (c); p-phenetidine (d); o-anisidine (e); and o-phenetidine (f) using potassium metal in absolute alcohol, anhydrous potassium carbonate and the desired amine in presence of copper powder at a suitable temperature for 2-3 hours.
Ortho toluidine, however, did not condense in this way. Condensation was effected using potassium carbonate and A.R. glycerol at 160°C with copper powder as a catalyst (g). The haloanilines (p-chloro, bromo and iodo anilines, h,i,j) also condensed as in the case of o-toluidine, whereas o- and p-nitro-anilines (k, l) condensed only by fusing the two components near the melting point.
Alternative syntheses of products, a, c, d & 1, have also been carried out. Thus 3-methoxy-6-bromo-acid and the corresponding ethoxy compound condensed very readily with p-iodoaniline using isoamyl alcohol as the reaction medium along with potassium carbonate and copper powder to yield products identical with c, & d. On ring closure with phosphorus oxy-chloride, o-chloro benzoic acid under identical conditions gave a.

2-Nitro-1-iodo-9-chloro acridine was prepared by fusing 2-chloro-5-nitro-benzoic acid with p-iodoaniline and the intermediate cyclised with phosphorus oxy-chloride. This was found to be identical with product 1.

Cyclisation of the N-phenanthranilic acids presented no difficulties except in the case of 5-iodo-N-o- or p-nitro-phenyl and 5-iodo-N-p'-iodo( and bromo) phenanthranilic acids when large amount of acridones were formed as by-products using phosphorus oxy-chloride.
B. 2-Iodo-6-methoxy (or ethoxy)-9-chloro acridines.

Jamison & Turner synthesis of acridine.

A novel synthesis of acridine has been described by Jamison and Turner (J.C.S. 1954, 1937) which in reality is an extension of Chapmann's (J.C.S. 569, 1929) inversion of benzimidichloride diphenyl ether into a diphenyl amine derivative.

Ulmann's synthesis required the difficultly accessible 4-methoxy-3-chloro-benzoic acid for the preparation of 3-methoxy-7-iodo-9-chloro-acridine or its substituted products. It can be readily obtained by the following series of reactions.

4-Methoxy methyl salicylate was condensed with imidochlorid of benzoyl p-iodo aniline to obtain N-p-iodo-phenyl benzimid-5'-methoxy-2'-carbo-methoxy phenyl ether (I). This on heating at 270°C underwent Chapmann's re-arrangement with the formation of methyl-N-benzoyl-4-iodo-5'-methoxy-diphenyl amine-2'-carboxylic acid (II). (II) on hydrolysis with alkali gave 4-methoxy N-p'-iodo-phenyl anthrolic acid (III) which on subsequent ring closure gave the required 3-methoxy-7-iodo-9-chloro-acridine (IV) in good yields. 3-Methoxy-7-iodo-acridone (V) can be directly prepared by heating (I) at 320°C for ten minutes, when through an intre-molecular change a molecule of methyl benzoate is eliminated. 3-Ethoxy-7-iodo-9-chloro acridine was prepared in exactly the same way using 4-ethoxy-ethyl salicylate as the starting substance.
1. o-ethyltoluidines.
2. o-phenylanisidines.
3. o-phenetidines.
4. p-chloro, bromo, iodo-anilines.

In addition, the following aliphatic amines have been condensed with 2-iodo-6 (or 7)-methoxy-9-chloro-acridine to yield acridines of possible antimalarial activity.

1. $\text{H}_2\text{N} - (\text{CH}_2)_3 \text{N} / \text{CH}_3 \cdot \text{CH}_3$

2. $\text{H}_2\text{N} - (\text{CH}_2)_3 \text{N} / \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$

3. $\text{H}_2\text{N} - (\text{CH}_2)_3 \text{N} / \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$

4. $\text{H}_2\text{N} - (\text{CH}_2)_3 \text{N} / \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$

5. $\text{H}_2\text{N} - (\text{CH}_2)_3 \text{N} / \text{iso amyl}$

6. $\text{H}_2\text{N} - (\text{CH}_3)_3 \text{N} / \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2$

7. $\text{H}_2\text{N} - \text{CH} - (\text{CH}_2)_3 \text{N} \text{Et}_2$. 
The selection of $\text{H}_{2}\text{N-}(\text{CH}_{2})_{3}-\text{NR}_{2}$ is based on the extensive work carried out by Magidson and Grigrovski, (Ber. 62, 401, 1936) Meitzch and Meuss, (Klin, Wochenschr. 12, 1375, 1933), Adams and co-workers etc, (A recent survey of antimalarials (1940-45) by Wissloge, Edward Bros. Mich. U.S.A.), who have found that maximum antimalarial activity is associated with the amines of above type.

Interesting compounds of the **bisacridyl** type have been obtained by the interaction of 2-iodo-7-methyl-9-amino acridine with 2-ido-7-chloro (or ethoxy) 9-chloro acridines respectively.

Most of the compounds synthesised have been screened for their antiseptic action against several pathogens including *Staph. aureus*, *Bact. Coli*, *siga*, *flexner*, *Bact. typhosum*, para-typhoid A & B, *Vibrio cholerae*, *Fs. pyocyanea*, *Proteus vulgaris* etc. Many of these compounds have been found to exhibit powerful antibacterial action against several organisms and in some cases anticipated results could be obtained. These screening tests are described more fully in part II of this thesis. Toxicities of the more active derivative have also been determined. Basicity of some of these compounds have also been found out and recorded in the experimental part.
It has not been possible to get these compounds assayed for their antimalarial action. Arrangements have been made with the Malaria Institute of India to carry out the antimalarial tests of a few selected dialkyl-amino alkyl derivatives in Monkey Malaria.

In the end we may conclude that iodo acridines have shown good deal of activity and some of the compounds have shown powerful antiseptic action and sometimes marked specificity against one or another pathogen. Toxicities are also much less than that of acriflavine and 9-amino-acridine and some of these derivatives may possibly be used clinically with success.