THE SYNTHESIS AND REACTIONS OF
HINDERED ACRIDINES

DISSERTATION

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WARREN HOWARD POWELL, B. S.

The Ohio State University

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Approved by

Melvin S. Newman
Adviser
Department of Chemistry
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>General Methods of Acridine Syntheses</td>
<td>11</td>
</tr>
<tr>
<td>Discussion of Results</td>
<td></td>
</tr>
<tr>
<td>Syntheses of 4,5-dimethylacridine</td>
<td>19</td>
</tr>
<tr>
<td>Syntheses of 1,4,5,8-tetramethylacridine</td>
<td>33</td>
</tr>
<tr>
<td>Attempted synthesis of 2,4,5,7-tetramethylacridine</td>
<td>38</td>
</tr>
<tr>
<td>Reactions of Hindered acridines with boron</td>
<td></td>
</tr>
<tr>
<td>trifluoride and diborane</td>
<td>40</td>
</tr>
<tr>
<td>4,5-Dimethylacridine as a dehydrohalogenation agent</td>
<td>41</td>
</tr>
<tr>
<td>Experimental</td>
<td></td>
</tr>
<tr>
<td>Generalizations</td>
<td>47</td>
</tr>
<tr>
<td>1,2,3,6-Tetrahydro-3-methyl-3,6-endoxophthalic anhydride</td>
<td>48</td>
</tr>
<tr>
<td>3-Methylphthalic anhydride</td>
<td>48</td>
</tr>
<tr>
<td>3-Methylanthranilic acid</td>
<td>48</td>
</tr>
<tr>
<td>N-Acetyl-o-toluidine</td>
<td>49</td>
</tr>
<tr>
<td>N-Formyl-o-toluidine</td>
<td>49</td>
</tr>
<tr>
<td>Di-o-tolyacetamide</td>
<td>49</td>
</tr>
<tr>
<td>Di-o-tolyldiformamide</td>
<td>50</td>
</tr>
<tr>
<td>Di-o-tolylamine</td>
<td>51</td>
</tr>
<tr>
<td>N,N-Di-o-tolyloxamic acid</td>
<td>54</td>
</tr>
<tr>
<td>Methyl N,N-di-o-tolyloxamate</td>
<td>54</td>
</tr>
<tr>
<td>1-o-Tolyl-7-methylisatin</td>
<td>55</td>
</tr>
<tr>
<td>2',6-Dimethyl diphenylamine-2-carboxylic acid</td>
<td>56</td>
</tr>
<tr>
<td>9-Chloro-4,5-dimethylacridine</td>
<td>58</td>
</tr>
<tr>
<td>4,5-Dimethylacridone</td>
<td>59</td>
</tr>
<tr>
<td>4,5-Dimethylacridine-9-carboxylic acid</td>
<td>60</td>
</tr>
<tr>
<td>4,5-dimethylacridine</td>
<td>61</td>
</tr>
<tr>
<td>2-Nitro-1,4-xylene</td>
<td>64</td>
</tr>
<tr>
<td>2,5-Dimethylaniline</td>
<td>65</td>
</tr>
<tr>
<td>Di-2,5-xylamine</td>
<td>65</td>
</tr>
<tr>
<td>N,N-Di-2,5-xylyoxamic acid</td>
<td>66</td>
</tr>
<tr>
<td>Methyl N,N Di-2,5-xylyoxamate</td>
<td>66</td>
</tr>
<tr>
<td>1-(2,5)-Xylyl-4,7-dimethylisatin</td>
<td>68</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridine-9-carboxylic acid</td>
<td>69</td>
</tr>
<tr>
<td>2',3,5',6-Tetramethyl diphenylamine-2-carboxylic acid</td>
<td>70</td>
</tr>
<tr>
<td>9-Chloro-1,4,5,8-Tetramethylacridine</td>
<td>72</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridone</td>
<td>74</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridine</td>
<td>74</td>
</tr>
<tr>
<td>9-Chloroacridine</td>
<td>79</td>
</tr>
<tr>
<td>Name</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridone</td>
<td>74</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridine</td>
<td>74</td>
</tr>
<tr>
<td>9-Chloroacridine</td>
<td>79</td>
</tr>
<tr>
<td>Acridone</td>
<td>79</td>
</tr>
<tr>
<td>Acridine</td>
<td>79</td>
</tr>
<tr>
<td>Di-assym-m-xylidinomethane</td>
<td>79</td>
</tr>
<tr>
<td>Cholestanol</td>
<td>80</td>
</tr>
<tr>
<td>Cholestan-3-one</td>
<td>80</td>
</tr>
<tr>
<td>2-Bromocholestan-3-one</td>
<td>81</td>
</tr>
<tr>
<td>Reaction of Substituted Pyridines with Boron Trifluoride and Diborane</td>
<td>81</td>
</tr>
<tr>
<td>Dehydrohalogenation of 2-Bromocholestan-3-one with 4,5-dimethylacridine</td>
<td>81</td>
</tr>
</tbody>
</table>

Summary 85

Suggestions for Future Work 87

Autobiography 89
TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Association Constants for the Reaction of Substituted Pyridines with Phenol</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>Activation Energies of t-Aromatic Amines with Methyl Iodide</td>
<td>5</td>
</tr>
<tr>
<td>3.</td>
<td>Positions of the Maxima and Corresponding Intensities in the Ultraviolet Absorption Spectra of Acridine, 4,5-Dimethyl- and 1,4,5,8-Tetramethylacridine</td>
<td>43</td>
</tr>
<tr>
<td>4.</td>
<td>Positions of the Maxima and Corresponding Intensities in the Ultraviolet Absorption Spectra of Acridone, 4,5-Dimethyl- and 1,4,5,8-Tetramethylacridone</td>
<td>44</td>
</tr>
<tr>
<td>5.</td>
<td>Positions of the Maxima and Corresponding Intensities in the Ultraviolet Absorption Spectra of 9-Chloroacridine, 9-Chloro-4,5-dimethyl- and 9-Chloro-1,4,5,8-Tetramethylacridine</td>
<td>45</td>
</tr>
<tr>
<td>6.</td>
<td>$\Delta T$ Values for the Reactions of Boron Trifluoride and Diborane with t-Aromatic amines</td>
<td>83</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1.</td>
<td>Interconversions of Acridines, Acridones and Acridans</td>
<td>13</td>
</tr>
<tr>
<td>2.</td>
<td>Syntheses of the Acridine Ring System (Part I)</td>
<td>16</td>
</tr>
<tr>
<td>3.</td>
<td>Syntheses of the Acridine Ring System (Part II)</td>
<td>17</td>
</tr>
<tr>
<td>4.</td>
<td>Synthesis (A) of 4,5-Dimethylacridine</td>
<td>23</td>
</tr>
<tr>
<td>5.</td>
<td>Syntheses of Di-o-tolylamine</td>
<td>29</td>
</tr>
<tr>
<td>6.</td>
<td>Synthesis (B) of 4,5-Dimethylacridine</td>
<td>31</td>
</tr>
<tr>
<td>7.</td>
<td>Synthesis (A) of 1,4,5,8-Tetramethylacridine</td>
<td>35</td>
</tr>
<tr>
<td>8.</td>
<td>Synthesis (B) of 1,4,5,8-Tetramethylacridine</td>
<td>37</td>
</tr>
<tr>
<td>9.</td>
<td>Ultraviolet Absorption Spectra of Acridine, 4,5-Dimethyl- and 1,4,5,8-Tetramethylacridine</td>
<td>46</td>
</tr>
<tr>
<td>10.</td>
<td>Apparatus for Measuring Heats of Reaction</td>
<td>82</td>
</tr>
</tbody>
</table>
INTRODUCTION

The base strengths of pyridine, 2-picoline, and 2,6-lutidine, as measured by heat of reaction with methanesulfonic acid in nitrobenzene solution, were shown to be in the order 2,6-lutidine > 2-picoline, > pyridine.¹ These results agreed closely with the corresponding pKₐ values of these bases in aqueous solution² However, when measured against diborane, the order was reversed.³ The reason for this reversal was attributed to steric strains imposed on the transition state by the size of the substituent and the reference acid.

Another estimate of base strengths of substituted pyridines has been made by measuring the association constants with phenol⁴


(see Table 1). It was found that although a good correlation of the association constants with base strength could be obtained for pyridines unsubstituted in the 2 and 6 positions, no such correlation
TABLE 1

<table>
<thead>
<tr>
<th>Amine</th>
<th>$K \text{ (l.-mol.$^{-1}$)}$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>42</td>
<td>4.4</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>84</td>
<td>5.2</td>
</tr>
<tr>
<td>2-Methylpyridine</td>
<td>63</td>
<td>5.2</td>
</tr>
<tr>
<td>2,6-Dimethylpyridine</td>
<td>78</td>
<td>5.6</td>
</tr>
<tr>
<td>3,5-Dimethylpyridine</td>
<td>107</td>
<td>5.2</td>
</tr>
<tr>
<td>2-t-Butylpyridine</td>
<td>19</td>
<td>4.6</td>
</tr>
<tr>
<td>2,6-di-t-Butylpyridine</td>
<td>3</td>
<td>3.6</td>
</tr>
</tbody>
</table>
could be drawn with 2,6-lutidine, 2-t-butylpyridine, or 2,6-di-t-butylpyridine. The deviations were attributed to the steric effects of the ortho substituents.

The magnitude of steric strains in ortho substituted aromatic compounds, such as o-t-butyltoluene (I), 2,6-dimethyl-t-butylbenzene (II) and o-di-t-butylbenzene (III), has been estimated from the heats of formation of "homomorphic" molecular complexes of ortho substituted pyridines with trimethylboron, boron trifluoride, and diborane.

(5) This term has been proposed [H. C. Brown, G. K. Barbaras, H. L. Berneis, W. H. Bonner, R. B. Johannesen, M. Grayson, and K. L. Nelson, J. Am. Chem. Soc., 75, 1 (1953)] to designate molecules which have similar molecular dimensions. For example, IV and V would be homomorphs of o-t-butyltoluene.
Studies of the energies of activation for the reaction of methyl iodide with ortho substituted pyridines gave comparable results.\(^\text{10}\)

The results of this work have been excellently summarized.\(^\text{11}\) Recently

a study of the reaction of suitably substituted quinoline derivatives with methyl iodide has provided information on the steric strains of substituted naphthalenes.\(^\text{12}\) Table 2 lists the energies of activation for the reaction of some substituted pyridine and quinoline compounds with methyl iodide. The activation energies for the reaction of methyl iodide with pyridine and isoquinoline are in quite close agreement as would be expected because of the unhindered nitrogen in each case.

In assessing the steric effects of substituents ortho to a group G, we have assumed that a methyl group and a fused aromatic ring are roughly equivalent (compare VI and VII). The fact that the energy of activation for the reaction of quinoline with methyl iodide is of
<table>
<thead>
<tr>
<th>Compound</th>
<th>$E_a$ (kJ/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>13.9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>13.7</td>
<td>12</td>
</tr>
<tr>
<td>2-Methylpyridine</td>
<td>14.0</td>
<td>11</td>
</tr>
<tr>
<td>2,6-Dimethylpyridine</td>
<td>15.1</td>
<td>11</td>
</tr>
<tr>
<td>2-t-Butylpyridine</td>
<td>17.5</td>
<td>11</td>
</tr>
<tr>
<td>Isoquinoline</td>
<td>13.5</td>
<td>12</td>
</tr>
<tr>
<td>Quinoline</td>
<td>14.8</td>
<td>12</td>
</tr>
<tr>
<td>8-Methylquinoline</td>
<td>18.8</td>
<td>12</td>
</tr>
<tr>
<td>2-Methylquinoline</td>
<td>16.0</td>
<td>12</td>
</tr>
</tbody>
</table>
about the same magnitude as that for 2-picoline indicates that this approximation is correct (see Table 2).

In a similar way the steric effect of an ortho t-butyl group should be approximated by a methyl group on the adjacent peri position.\(^\text{(13)}\) (compare VIII and IX). The fact that the energy of

---

\(^\text{(13)}\) In this dissertation, the phrase "adjacent peri position" refers to the position on a fused ring that is adjacent to the group in question.
activation for the reaction of 8-methylquinoline with methyl iodide is about the same as that for 2-t-butylpyridine supports this approximation (see Table 2).

Since the energy of activation for the reaction of quinoline with methyl iodide is slightly greater than that for the corresponding reaction of 2-picoline, the steric effect of a fused ring is probably slightly greater than that of a methyl group. Furthermore, the energy of activation for the reaction of 8-methylquinoline with methyl iodide is slightly greater than that for the corresponding reaction of 2-t-butylpyridine. These facts have been explained by assuming that the rigidity of the fused ring does not permit as much relief of strain by rotation or bending.

It was stated above that the steric effect of an ortho t-butyl group should be approximated by a methyl group on the adjacent peri position. To extend the same reasoning, the steric effect of a methyl group on the adjacent peri position should be approximated by a benzene ring fused on the adjacent peri position. In other words, the group G in structures VIII, IX, and X should be subject to approximately the same steric effect.

\[ \text{VIII} \hspace{1cm} \text{IX} \hspace{1cm} \text{X} \]
The synthesis of 2,6-di-t-butylpyridine (XI) has been reported.\textsuperscript{14}


This unusual base reacted with hydrogen chloride but failed to react with boron trifluoride or methyl iodide.

Bearing in mind the above analogy, we decided to make 4,5-dimethylacridine (XII) and 1,4,5,8-tetramethylacridines (XIII) to see if these hindered bases approximated the behavior of 2,6-di-t-butylpyridine.

Specifically, these two hindered acridines (XII and XIII) were synthesized for three reasons. First, to study qualitatively their behavior with protonic and Lewis acids. Secondly, to supply these compounds to Dr. Szwarc of Syracuse University for his studies of methyl affinities of aromatic compounds.\textsuperscript{15} Thirdly, to study these

compounds as dehydrohalogenation reagents.

The elimination of hydrogen bromide from some bromo steroids with pyridine or collidine has been unsatisfactory because of undesirable side reactions such as quaternization. For example, treatment of 4-bromocoprostanone with pyridine gave only a low yield of \( \Delta^4 \)-cholesten-3-one along with a sparingly soluble, nitrogen-containing salt.\(^{16}\)

\[ \text{(16) A. Butenandt and A. Wolff, Ber. 68, 2091 (1935).} \]

Treatment of 2-bromocholestanone with pyridine gave no \( \Delta^1 \)-cholesten-3-one and a high yield of a similar salt.\(^{16}\) Originally assumed to be pyridine hydrobromide, these salts were later\(^{17,18}\) shown to have resulted from quaternization at the position occupied by the bromine.

Normal dehydrohalogenation was effected in better yield with collidine.\(^{19}\) In general, collidine has proved to be a better reagent than pyridine for dehydrohalogenation reactions, but it is still very poor in many cases, as some yields of unsaturated ketone are less than ten percent.\(^{20}\) A reason for improved yields with collidine seems to be the steric effect of the methyl groups which decreases quaterni-
zation.

Since the steric effects in the acridines (XII and XIII) proposed for synthesis should be greater than in collidine, greater yields of unsaturated ketones might be expected from \(\alpha\)-haloketones.
Acridine (I) was first found in the anthracene fraction of coal tar. It got its name from its acrid smell and its irritating action on the skin and mucous membranes. Many systems of numbering the simple acridine ring system have been used, especially in the older literature. At the present time only two systems are commonly used, I and II. Chemical Abstracts has used I since 1937. This system is the preferred one in most of the current literature and will be used in this dissertation.

Most acridines have been synthesized from one of three types of compounds, diphenylamines, diphenylamine-2-carboxylic acids or their derivatives, and aromatic amines. Since each general method can give
rise to the acridine system at various levels of oxidation, interconversions of acridones (III), acridans (V) and acridines (VI) will first be discussed. These reactions are summarized in Figure 1.

Acridones (III) may be converted directly to acridines (VI) by distillation with zinc dust\(^3\) (path 5, Fig. 1), but the reaction gives variable results, tends to become uncontrollable on large scale runs, and is limited to distillable acridines.

Acridones (III) may be reduced to acridans (V) by reagents such as sodium and alcohol, sodium amalgam, and aluminum amalgam\(^4\) (path 3, Fig. 1). However, this method is not very satisfactory when reducible groups are present on the acridine ring system.

A much more satisfactory method is to convert the acridone (III) to the 9-chloroacridine (IV) by means of phosphorous oxychloride (path 1, Fig. 1).\(^5\) The 9-chloroacridines (IV) are easily reduced to acridans (V) by hydrogenation over Raney Nickel in the presence of an equivalent amount of a suitable base such as potassium hydroxide or pyridine\(^5\) (path 4, Fig. 1). The reduction does not occur in the absence of base.\(^6\)

\(^{(3)}\) Ref. 1, p. 9-12; Ref. 2, p. 11, 17-18.


\(^{(5)}\) Ref. 1, p. 10-12; Ref. 2, p. 9-10, 13, 17-18.

FIG. I INTERCONVERSIONS OF ACRIDINES, ACRIDANS, AND ACRIDONES
The only known direct method of converting a 9-chloroacridine (IV) to acridine (VI) is by alkaline decomposition of the N-(9-acridyl)-N'-p-toluenesulfonhydrazide\(^7\) (path 6, Fig. 1). Nitrogen and sodium p-toluenesulfinate are eliminated to produce the acridine (VI). The yields by this method do not appear to be superior to the catalytic hydrogenation of 9-chloroacridines (IV) to acridans (V) followed by oxidation to the acridine (VI). The usefulness of the p-tosylhydrazide method is in the preparation of acridines having reducible substituents, such as nitro or cyano.

Since the reduction of acridines (VI) to acridans (V) (path 8, Fig. 1) proceeds more easily than the reduction of acridones (III) or 9-chloroacridines (IV) to acridines, no reducing agent has yet been found that will give acridines directly. Hence, an oxidation step from acridans (V) to acridines (VI) is necessary (path 7, Fig. 1). This is easily accomplished by a variety of methods.\(^8\) The more easily oxidized acridans are air-oxidized during the workup of the reduction product. For other acridans the best procedure seems to be oxidation with potassium dichromate (one oxygen equivalent) and dilute sulfuric acid. Addition of excess dichromate allows the product to be isolated as the dichromate salt.

Two other methods of oxidation have been successfully used especially when sensitive groups are present on the molecule. The
first is aeration of a hot suspension of the acridan in aqueous alkali and the second is boiling an acid suspension of the acridan with excess ferric chloride.

The general methods usually used for the synthesis of the acridine ring system are summarized in Figures 2 and 3.

Aromatic amines with the p-position blocked, such as in p-toluidine, react with formaldehyde to give various products depending on the reaction conditions.\(^9\) In acid solution, a diaminodiphenylmethane (VIII) is produced while in basic solution a methylenediamine (VII) is formed. Both products are reported to cyclize to acridans (IX) on heating with mineral acid.

Methylene halides also react with amines to form methylene diamines (VII).

Only a small number of acridines have been synthesized from diphenylamine-2-aldehydes or ketones (X)\(^10\) even though the acridine system (XI) is formed directly. Since the starting materials are difficult to prepare, and since a more convenient method is available through the diphenylamine-2-carboxylic acids (see below), this method has not been used very much.

The Bernthsen reaction, one of the earliest methods of acridine synthesis, consists of heating a diphenylamine (XII) and an organic acid with zinc chloride at 200-270°.\(^11\) The fact that poor yields are
A. From Aromatic Amines and Formaldehyde

\[
\begin{align*}
R \text{NH}_2 \xrightarrow{(1) \text{KOH, CH}_2\text{O}} & \rightarrow [ \text{R} \text{NHCH}_2\text{NH}] & \text{VII} \\
\text{CH}_2\text{O} \quad \text{or} \quad \text{HCl} & \rightarrow [ \text{R} \text{NHCH}_2\text{NH}] & \text{VII} \\
\text{NH}_2\text{H}_2\text{N} \xrightarrow{\Delta} & \rightarrow \text{R} \text{N} & \text{IX} \\
\end{align*}
\]

B. From Diphenylamine-2-aldehydes or ketones

\[
\begin{align*}
\text{COR} & \xrightarrow{\text{H}^+} \rightarrow \text{R} \\
\text{NH} & \rightarrow \text{R} \\
\end{align*}
\]

\[R = \text{H or alkyl}\]

FIG. 2. SYNTHESSES OF THE ACRIDINE RING SYSTEM (PART I)
C. From Diphenylamines and Organic Acids or their derivatives.

\[ \text{C}_{16} \text{H}_{14} \text{N} \quad \xrightarrow{\text{RCOOH, ZnCl}_2, \Delta} \quad \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \]

\[ \text{C}_{16} \text{H}_{14} \text{N} \quad \xrightarrow{(1) (\text{COCl})_2, (2) \text{AlCl}_3} \quad \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \]

\[ \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \quad \xrightarrow{\text{OH}^-} \quad \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \]

D. From Diphenylamine-2-carboxylic acids.

\[ \text{C}_{16} \text{H}_{14} \text{N} \text{COOH} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \]

\[ \text{C}_{16} \text{H}_{14} \text{N} \text{COOH} \quad \xrightarrow{\text{POCl}_3} \quad \text{C}_{16} \text{H}_{12} \text{N}_2 \text{O}_2 \text{Cl} \]

FIG. 3 SYNTHESSES OF THE ACRIDINE RING SYSTEM (PART II)
obtained with formic acid, and the rather drastic conditions limit the usefulness of the reaction to the preparation of 9-substituted acridines (XIII) without sensitive groups.

Diphenylamines (XII) can be converted to the corresponding isatin (XIV) by reaction with excess oxalyl chloride followed by cyclization with aluminum chloride.\(^1\) Rearrangement of the isatin to the acridine-9-carboxylic acid (XV) occurs readily in a refluxing basic solution.\(^2\) Although this reaction has been very little used, it could be of considerable importance because acridine-9-carboxylic acids are easily decarboxylated.

By far the most general method of the synthesis of the acridine ring system is the cyclization of diphenylamine-2-carboxylic acids (XVI) either with sulfuric acid to the acridone (XVII) or with phosphorous oxychloride to the 9-chloroacridine\(^3\) (XVIII). Since

the preparation of diphenylamine-2-carboxylic acids is relatively easy by means of the Jordan-Ullman reaction\(^4\) it is not surprising that this method is widely used.
DISCUSSION OF RESULTS

Syntheses of 4,5-Dimethylacridine

The synthesis of 4,5-dimethylacridine has been reported\(^1\) by the route outlined below. Our first synthesis of 4,5-dimethylacridine (I) followed this method very closely.

\[\text{3-Methylanthranilic acid (II) has been prepared by nitration of } m\text{-toluic acid from which 2-nitro-} m\text{-toluic acid was isolated in 50\%.}\]
yield\textsuperscript{2} followed by quantitative hydrogenation over Raney Nickel.\textsuperscript{3}

\begin{equation}
\text{yield} \rightarrow \text{hydrogenation over Raney Nickel}.
\end{equation}


\begin{equation}
\begin{array}{c}
\text{COOH} \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{COOH} \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{COOH} \\
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{COOH} \\
\text{CH}_3
\end{array}
\end{equation}

A second method which has been used in this laboratory\textsuperscript{4} is that

(4) Dr. F. Zeelan of this laboratory has prepared a quantity of 3-methyl anthranilic acid by this method. At this time his results are not available.

\begin{equation}
\begin{array}{c}
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{CH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{NH}_2
\end{array}
\end{equation}

of Sandmeyer.\textsuperscript{5,6} 7-Methylikisatin, prepared in 93\% yield from o-toluidine,\textsuperscript{7}


was oxidized in 90\% yield to 3-methylanthranilic acid (II) by aqueous hydrogen peroxide.\textsuperscript{8}

Reactions previously studied in these laboratories\textsuperscript{9,10} were

\textsuperscript{9} E. P. Moore, Ph. D. dissertation, The Ohio State University, 1957.

\textsuperscript{10} H. R. Barkemeyer, M. S. thesis, The Ohio State University, 1952.

used to obtain 3-methylantranilic (II) acid by a third method.
Commercial 2-methylfuran and maleic anhydride in ether solution gave the Diels-Alder adduct, 1,2,3,6-tetrahydro-3-methylphthalic anhydride (III) in 90% yield.\(^9\) Aromatization of III to 3-methylphthalic anhydride (IV) in concentrated sulfuric acid was achieved in 51% yield. A large number of reagents have been tried for this aromatization,\(^9\) but concentrated sulfuric acid seems to be the best.

A Schmidt reaction on 3-methylphthalic anhydride (IV) gave in 76% yield\(^{10}\) 3-methylantranilic acid (II) which was taken to 4,5-dimethylacridine (I) in 52-56% overall yield as shown in Fig. 4.

The condensation between 3-methylantranilic acid (II) and o-bromotoluene was reported\(^1\) to give a 70% yield of V after three hours of heating at 185°. In our hands, under these conditions, only very low yields of 2',6-dimethyldiphenylamine-2-carboxylic acid (V) were obtained. However, on heating with stirring at 185° ± 5° for twenty-four hours, a 76% yield of the desired acid was produced along with tarry by-products. Possibly the activity of our copper catalyst was at fault.

Cyclization of 2',6-dimethyldiphenylamine-2-carboxylic (V) acid with phosphorous oxychloride afforded a quantitative yield of crude 9-chloro-4,5-dimethylacridine (VI). Purification by chromatography on alumina gave an 89% yield of pure 9-chloro-4,5-dimethylacridine (VI) and a small amount (6%) of its hydrolysis product, 4,5-dimethylacridone (VII).

Acid hydrolysis of pure 9-chloro-4,5-dimethylacridine (VI) gave 4,5-dimethylacridone (VII) in 83% yield, which could be readily
FIG. 4. SYNTHESIS (A) OF 4,5-DIMETHYLACRIDINE
converted back to the chloroacridine (VI) in 89% yield by refluxing with phosphorous oxychloride.

The hydrogenation of 9-chloro-4,5-dimethylacridine (VI) over Raney Nickel catalyst occurred readily at room temperature under about three atmospheres of hydrogen pressure, as well as at 35-45° and one atmosphere hydrogen pressure over Raney Nickel as reported.\(^1\) Oxidation of the crude reduction product with potassium dichromate (one oxygen equivalent) and dilute sulfuric acid gave an 83% yield of 4,5-dimethylacridine (I) accompanied by a small amount of the corresponding 9,9'-biacridine.\(^1\)

The reduction does not proceed without the presence of an equivalent amount of base, such as pyridine or potassium hydroxide, to neutralize the hydrogen chloride produced.\(^11\) Ethanoic potassium hydroxide solutions either alone or mixed with benzene have usually been used as solvents. However, 9-chloro-4,5-dimethylacridine (VI) is not very soluble in the mixed (1:1) solvent, ethanol and benzene (2.4 g. requires 80 ml. of mixed solvent). Since a large volume of solvent is required unless special equipment is used, a limitation is placed on the size of the run. Thus, a number of experiments were attempted in order to find a more suitable method for larger scale runs.

Lithium aluminum hydride has been used to reduce phenanthridine or 9-chlorophenanthridine to 9,10-dihydrop phenanthridine.\(^12,13\)

A chlorine in the 9 position of acridine should be similar to a chlorine in the 9 position of phenanthridine in reactivity. As expected, reduction of 9-chloro-4,5-dimethylacridine (VI) with lithium aluminum hydride in refluxing tetrahydrofuran, followed by oxidation of the crude acridan with potassium dichromate (one oxygen equivalent) and dilute sulfuric acid gave a 77% yield of 4,5-dimethylacridine (I). This method is much more convenient for large scale runs.

Treatment of 4,5-dimethyl-9-chloroacridine (VI) with sodium borohydride in refluxing methanol gave back somewhat impure starting material.

Two other methods of dehalogenation of 9-chloro-4,5-dimethylacridine (VI) were attempted without success. An attempt to prepare the organolithium derivative which could be hydrolysed to 4,5-dimethylacridine (I), gave a very low yield of (I) along with very high melting organic material. Treatment of 4,5-dimethyl-9-chloroacridine
(VI) with palladium on charcoal in boiling tetralin gave similar results.

These results were not too surprising since 9,9'-biacridines (very high melting substances) are prepared from 9-chloroacridines by a number of methods. The addition of an ethereal solution of 9-chloroacridine to phenylmagnesium bromide gave an almost theoretical yield of 9,9'-biacridine. It was also obtained by refluxing 9-

chloroacridine and Raney Nickel in an inert solvent, by heating 9-chloroacridine and catalytic copper at 140°C, and by heating 9-chloroacridine with palladium on barium sulfate in xylene at 130°C.\(^{14}\)

Although the synthesis outlined above was entirely adequate, a shorter route for preparation of hindered acridines in the best possible yields was sought.

One possibility involved the easy, but little used, rearrangement of N-phenylisatins.\(^ {15,16,17}\)

Diphenylamine condenses with oxalyl chloride to produce the half acid chloride and the tetrasubstituted oxamide.\(^{15}\) The half acid chloride

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\(^{15}\) R. Stolle, J. prakt. chem. N.F. 105, 137 (1922).

\(^{16}\) P. Friedlander and K. Kunz, Ber. 55, 1597 (1922).

cyclizes easily with aluminum chloride to N-phenylisatin. Refluxing the isatin with aqueous alkali produces acridine-9-carboxylic acid,\textsuperscript{15,16}

which is easily decarboxylated to the parent hydrocarbon.

The mechanism of the rearrangement has not been studied but is presumed to proceed as outlined below.
An analogous mechanism has been proposed\textsuperscript{18} for the reaction

\begin{equation}
(18) \text{C. K. Bradsher and S. T. Webster, J. Am. Chem. Soc., 72, 393 (1957).}
\end{equation}

of phenyllithium with o-benzylbenzoic acid to yield 9-phenylanthracene.

![Chemical structure](image)

Di-o-tolylamine (X) required for the synthesis of 4,5-dimethylacridine (I) by this method, has been reported to be formed in low yield (6-10\%) from o-toluidine and o-toluidine hydrochloride\textsuperscript{19} and in good yield from N-acetyl-o-toluidine and o-bromotoluene.\textsuperscript{20}

\begin{equation}
(19) \text{M. Battegay, H. Silbuman, and J. Fischer, Chimie and Industrie Spec. No. B 27, 525 (1932).}
\end{equation}

"good" yield from N-acetyl-o-toluidine and o-bromotoluene.\textsuperscript{20} Fig. 5 summarizes our work on the synthesis of di-o-tolylamine (X). The condensation of N-acetyl-o-toluidine and o-bromotoluene in the presence of potassium carbonate and a precipitated copper catalyst\textsuperscript{21}

\begin{equation}
(20) \text{H. Wieland and A. Susser, Ann. 392, 176 (1912).}
\end{equation}

\begin{equation}
(21) \text{R. Brewster and T. Groenig, Org. Syn. 14, 67 (1934); Coll. Vol. 2, 446 (1943).}
\end{equation}

in refluxing nitrobenzene for fifty hours gave only a 24\% yield of
FIG. 5. SYNTHESSES OF DI-o-TOLYLAMINE
di-o-tolylacetamide (VIII), along with considerable amounts of recovered starting material and tars. Catalytic amounts of iodine did not affect the yield nor did the absence of solvent as in cases reported.\textsuperscript{20,22} The use of N-formyl-o-toluidine in the condensation gave a yield of $\frac{42}{\text{vol}}\%$ of di-o-tolylformamide (IX).

Hydrolysis of di-o-tolylacetamide (VIII) in alcoholic potassium hydroxide as reported\textsuperscript{20} failed to go to completion even on long periods of refluxing. Refluxing for several hours with $\frac{40}{\text{vol}}\%$ sulfuric acid produced di-o-tolylamine (X) in 76\% yield (overall yield from N-acetyl-o-toluidine, 18\%).

Di-o-tolylformamide (IX) was easily hydrolyzed in 91\% yield in a refluxing mixture of hydrochloric acid-glacial acetic acid to di-o-tolylamine (X) (overall yield from N-formyl-o-toluidine, 38\%).

Approximately the same yields of di-o-tolylamine (X) (22\% and 37\% respectively) were obtained in one step by hydrolysis of the crude, distilled reaction product of the condensation.

The conversion of di-o-tolylamine (X) to 4,5-dimethylacridine (I) in an overall yield of 78\% is summarized in Fig. 6. Addition of di-o-tolylamine (X) to excess oxalyl chloride gave excellent yields of the corresponding acid chloride (not isolated pure) as shown by conversion to the corresponding acid (XI) and its methyl ester (XII) in 87\% and 94\% yields respectively when treated with water or methyl alcohol, respectively. No tetrasubstituted oxámidas were found as
FIG. 6 SYNTHESIS (B) OF 4,5-DIMETHYLACRIDINE
previously reported.\textsuperscript{15} 1-o-Tolyl-7-methylisatin (XIII) was also obtained in excellent yield, 93%, on treatment of the crude acid chloride with aluminum chloride.

1-o-Tolyl-7-methylisatin (XIII) was oxidized to 2',6-dimethyl-diphenylamine-2-carboxylic acid (V) in 88% yield by alkaline hydrogen peroxide. This reaction provides a link between syntheses A and B of 4,5-dimethylacridine (I).

The rearrangement of the isatin (XIII) in aqueous potassium hydroxide went quantitatively to 4,5-dimethylacridine-9-carboxylic acid (XIV), which was decarboxylated at its melting point in 87% yield to 4,5-dimethylacridine (I). A small amount of high melting solid (300\textdegree) was also obtained.

Summarizing briefly, we have synthesized 4,5-dimethylacridine (I) by two routes, A (Fig. 4) and B (Fig. 6). Synthesis A resulted in an overall yield of 52-56% from 3-methylanthranilic acid (II).\textsuperscript{23}

\textsuperscript{23} A. Albert and J. B. Willis, ref. 1 obtained I in 56% overall yield by the same method.

Synthesis B resulted in an overall yield of 78% from di-o-tolylamine (X), but only 34% from o-toluidine. Synthesis B is much more convenient in the laboratory and would be ideal if a good synthesis for di-o-tolylamine could be found.

Lithium aluminum hydride has been used for the first time to reduce a 9-chloroacridine. This method gave approximately the same yield as catalytic hydrogenation over Raney Nickel and is more convenient for larger scale runs.
3-Methylantranalnic acid (II) was prepared in 35% overall yield from 2-methylfuran and maleic anhydride. It can also be obtained in 50% and 80% yields by the methods outlined earlier.

The ultraviolet absorption spectra of 4,5-dimethylacridine, 4,5-dimethylacridone and 4,5-dimethyl-9-chloroacridine are summarized in Tables 3, 4, and 5 and Fig. 9.

Syntheses of 1,4,5,8-Tetramethylacridine

The rearrangement of isatins to acridine-9-carboxylic acids has been little used for the syntheses of acridine derivatives. Encouraged by the success of this method in the synthesis of 4,5-dimethylacridine and in order to gain additional information about the generality of this method, the synthesis of 1,4,5,8-tetramethylacridine (XV) was undertaken.

\[
\text{CH}_3 \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{CH}_3
\]

XV

A survey of the literature revealed that this tetramethylacridine has been synthesized, although in unstated yield and of questionable purity, from p-xylidine, p-xylenol, and methylene chloride.\(^{(24)}\)

The starting material for the synthesis of this compound by the isatin route was di-2,5-xylylamine (XVI) prepared in 74% yield by the condensation of 2-amino-p-xylene and 2-bromo-p-xylene in the presence of metallic potassium.

The conversion of di-2,5-xylylamine (XVI) to 1,4,5,8-tetramethylacridine (XV) is summarized in Fig. 7. An excellent yield of the half acid chloride (not isolated pure) was obtained as shown by excellent yields (94% and 96% respectively) of the corresponding acid (XVII) and ester (XVIII) when treated with water, or methyl alcohol, respectively. 1-(2,5)-Xylyl-4,7-dimethylisatin (XIX) was prepared in 96% yield by treatment of the crude half acid chloride with anhydrous aluminum chloride.

The rearrangement of the isatin (XIX) to 1,4,5,8-tetramethylacridine-9-carboxylic acid (XX) in boiling aqueous potassium hydroxide
FIG. 7 SYNTHESIS (A) OF 1,4,5,8-TETRAMETHYLACRIDINE
was effected in 79% yield only after 300 hours.

Decarboxylation of 1,4,5,8-tetramethyl-9-carboxylic acid (XX) at its melting point afforded 1,4,5,8-tetramethylacridine (XV) in 94% yield. This material readily sublimes and the evolution of carbon dioxide had to be carefully controlled by the rate of heating to prevent the product from being carried away by the gas.

An alternate synthesis used to synthesize 1,4,5,8-tetramethylacridine (XV), is summarized in Fig. 8.

Alkaline hydrogen peroxide oxidation of 1-(2,5)-xylyl-4,7-dimethylisatin (XIX) gave 2',3,5,6-tetramethyldiphenylamine-2-carboxylic acid (XXI) in 92% yield.

Cyclization of 2',3,5',6-tetramethyldiphenylamine-2-carboxylic acid (XXI) with phosphorous oxychloride gave 9-chloro-1,4,5,8-tetramethylacridine (XXII) in only 56% yield along with 1,4,5,8-tetramethylacridone (XXIII) in 26% yield. Cyclization with phosphorous oxychloride followed by acid hydrolysis of the crude 9-chloroacridine (XXII) gave 1,4,5,8-tetramethylacridone (XXII) in 72% yield whereas acid hydrolysis of the pure 9-chloroacridine (XXII) gave the corresponding acridone (XXIII) in 88% yield. 1,4,5,8-Tetramethylacridone (XXIII) could be converted to the 9-chloroacridine (XXII) in 85% yield with phosphorous oxychloride.

The conversion of 9-chloro-1,4,5,8-tetramethylacridine (XXII) to 1,4,5,8-tetramethylacridine (XV) was effected in the same manner as for 4,5-dimethylacridine (I). Reduction with hydrogen and Raney Nickel catalyst in the presence of potassium hydroxide followed by oxidation with potassium dichromate and dilute sulfuric acid gave a 76% yield of
FIG. 8. SYNTHESIS (B) OF 1,4,5,8-TETRAMETHYLACRIDINE
the desired acridine (XV). Reduction with lithium aluminum hydride in tetrahydrofuran followed by oxidation with potassium dichromate and dilute sulfuric acid gave a 74% yield of 1,4,5,8-tetramethylacridine (XV).

Synthesis A is a much more convenient method even though there is the long period of time necessary for the basic rearrangement of the isatin, since in synthesis B considerable time is necessary in working up reaction products.

The ultraviolet absorption spectra of 1,4,5,8-tetramethylacridine (XV) 1,4,5,8-tetramethylacridone (XXIII) and 1,4,5,8-tetramethyl-9-chloroacridine (XXII) are summarized in Tables 3, 4, and 5 and in Fig. 9.

**Attempted Syntheses of 2,4,5,7-Tetramethylacridine**

An attempt was made to synthesize 2,4,5,7-tetramethylacridine (XXIV) by the reaction of 2,4-dimethylaniline with formaldehyde.²⁷,²⁸

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Under acid conditions,\textsuperscript{27} the reaction gave 55\% of the starting material, 2,4-dimethylaniline along with high boiling tarry products. Under basic conditions,\textsuperscript{28} about 65\% of starting material was recovered, the remainder being high-boiling tarry products. Furthermore, the preparation of di-p-toluidinomethane (XXV) as reported\textsuperscript{28} could not be repeated, although starting material was not recovered.

![Structure of di-p-toluidinomethane (XXV)](image)

Reaction of 2,4-dimethylaniline with methylene diiodide\textsuperscript{29} at 150° gave a 40\% yield of yellow crystals, presumably di-2-4-ocylidino-methane (XXVI). Rearrangement of this material in acid solution followed by the usual dichromate-sulfuric acid oxidation gave only a very small amount of (\(<1\%\)) product presumably 2,4,5,7-tetramethyl-
Reactions of Hindered Acridines with Boron Trifluoride and Diborane

Both 4,5-dimethylacridine and 1,4,5,8-tetramethylacridine formed trinitrobenzene complexes in high yield. They also formed hydrochlorides and hydrobromides in high yield. Since a satisfactory method of purification for these salts was not found, they were not obtained analytically pure.

Acridine, 2,4,6-collidine, and pyridine showed substantial heats of reaction with boron trifluoride (8-10°) and diborane (4-5°). However, under the same conditions, neither 4,5-dimethylacridine nor 1,4,5,8-tetramethylacridine showed any heat of reaction with either Lewis acid.

In charge transfer complexes of the type formed between aromatic compounds and such compounds as trinitrobenzene or picric acid, the aromatic compound can be considered to be a very weak Lewis base. Interestingly, both hindered acridines form complexes with trinitrobenzene but do not react with boron trifluoride or diborane, much stronger Lewis acids in the normal sense. Thus, we cannot generalize about "acid strength," but must specify the basic component.

The geometry of these hindered acridines is such that the nitrogen atom can be attacked in the plane of the rings only by a very small species such as a proton. Thus, since the trinitrobenzene moiety cannot be attached directly to the acridine nitrogen atom in these cases, we have additional evidence for the view that these types of complexes are of the layer type.
It was stated earlier (see introduction) that 2,6-di-t-butylpyridine failed to react with either boron trifluoride or methyl iodide. It has also been shown that diborane is a homomorph of methyl iodide.\(^{30}\) Since 4,5-dimethylacridine failed to react with boron trifluoride or diborane, it has been demonstrated that the steric hindrance afforded by a methyl group on the adjacent peri position to a group is equivalent to that of a t-butyl group ortho to the group.

4,5-Dimethylacridine as a Dehydrohalogenation Agent

It was brought out earlier (see introduction) that the reason for low yields in dehydrobrominations of keto-steroids with pyridine or 2,4,6-collidine might be due to quaternization of the base with the steroid molecule. If this is true, a highly hindered base such as 2,6-di-t-butylpyridine or 4,5-dimethylacridine should give rise to improved yields of the desired unsaturated ketone.

Treatment of 2-bromocholestan-3-one with 4,5-dimethylacridine either in dimethylacetamide at reflux temperature (164\(^{\circ}\)) for 30 minutes or in N-methylpyrrolidone at 170-175\(^{\circ}\) (bath temperature) for 15 minutes afforded 65\% and 94\% yields, respectively, of 4,5-dimethylacridine hydrobromide. The crude (once recrystallized) \(\Delta^1\)-cholesten-3-one, m.p. 88-93\(^{\circ}\), isolated from these reaction mixtures in 68\% and 72\% yields respectively, showed two carbonyl bands in the infrared and
a maximum at 236-237 m\(\mu\) in the ultraviolet spectra. Chromatography on alumina or recrystallization of this material failed to improve the purity as measured by these methods.

Collidine effected an almost quantitative removal of hydrogen bromide from 2-bromocholestan-3-one\(^{31}\) but only 37-44\% of crude

\(\Delta^1\)-cholesten-3-one, m.p. 89-92\(^\circ\), \(\lambda_{\text{max.}}\) 231-234 m\(\mu\), was isolated.

At this time, it can only be said that 4,5-dimethylacridine does not seem to be any better than 2,4,6-collidine for the dehydrohalogenation of 2-bromocholestan-3-one to \(\Delta^1\)-cholesten-3-one. More work on dehydrobromination of \(\alpha\)-bromoketones is needed before the effectiveness of 4,5-dimethylacridine can be evaluated.

**TABLE 3**

Positions of the Maxima ($\lambda_{max}$) and Corresponding Intensities ($\log \epsilon$) in the Ultraviolet Absorption Spectra of Acridine, 4,5-Dimethyl- and 1,4,5,8-Tetramethylacridine in 95% Ethanol.\(^a\)

<table>
<thead>
<tr>
<th>Maximum</th>
<th>Acridine(^b)</th>
<th>4,5-Dimethyl</th>
<th>1,4,5,8-Tetramethyl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\lambda_{max}$</td>
<td>$\log \epsilon$</td>
<td>$\lambda_{max}$</td>
</tr>
<tr>
<td>1</td>
<td>(243)</td>
<td>4.90</td>
<td>(247)</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>5.25</td>
<td>255</td>
</tr>
<tr>
<td>3</td>
<td>323</td>
<td>3.53</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>330</td>
<td>3.62</td>
<td>(333)</td>
</tr>
<tr>
<td>5</td>
<td>338</td>
<td>3.78</td>
<td>(341)</td>
</tr>
<tr>
<td>6</td>
<td>346</td>
<td>3.80</td>
<td>349</td>
</tr>
<tr>
<td>7</td>
<td>354</td>
<td>3.93</td>
<td>356</td>
</tr>
<tr>
<td>8</td>
<td>(365)</td>
<td>3.66</td>
<td>(367)</td>
</tr>
<tr>
<td>9</td>
<td>(380)</td>
<td>3.39</td>
<td>390</td>
</tr>
</tbody>
</table>

\(^a\) Numbers in parentheses are points of inflection.

TABLE 5

Positions of the Maxima (λ max) and Corresponding Intensities (log ε) in the Ultraviolet Absorption Spectra of 9-Chloroacridine, 4,5-Dimethyl-9-chloro- and 1,4,5,8-Tetramethyl-9-chloroacridines in 95% Ethanol. a

<table>
<thead>
<tr>
<th>Maximum</th>
<th>9-Chloroacridine</th>
<th>4,5-Dimethyl-9-chloro</th>
<th>1,4,5,8-Tetramethyl-9-chloro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>λ max</td>
<td>log ε</td>
<td>λ max</td>
</tr>
<tr>
<td>1</td>
<td>(246)</td>
<td>4.90</td>
<td>(250)</td>
</tr>
<tr>
<td>2</td>
<td>253</td>
<td>5.32</td>
<td>257</td>
</tr>
<tr>
<td>3</td>
<td>(328)</td>
<td>3.54</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>343</td>
<td>3.80</td>
<td>(345)</td>
</tr>
<tr>
<td>5</td>
<td>(350)</td>
<td>3.84</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>358</td>
<td>4.02</td>
<td>360</td>
</tr>
<tr>
<td>7</td>
<td>(370)</td>
<td>3.80</td>
<td>375</td>
</tr>
<tr>
<td>8</td>
<td>388</td>
<td>3.62</td>
<td>397</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a. Numbers in parentheses are points of inflection.
FIG. 9. ULTRAVIOLET ABSORPTION SPECTRA OF ACRIDINE, 4,5-DIMETHYLACRIDINE AND 1,4,5,8-TETRAMETHYLACRIDINE
EXPERIMENTAL

Generalizations

1. All melting points are uncorrected unless otherwise stated.

2. Microanalyses were by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

3. The phrase "worked up in the usual manner" used throughout this section means that the organic solvent layer was washed successively with water, acid or base as indicated, saturated sodium chloride solution, and the solvent removed by distillation.

4. The term "ether-benzene" refers to a 3:2 mixture (by volume) of ethyl ether and benzene.

5. The Skellysolves (petroleum ether fractions) used for recrystallizations and chromatographic elution were redistilled and had the following boiling ranges: Skellysolve F, b.p. 35-55°; Skellysolve B, b.p. 65-69°; Skellysolve C, b.p. 90-97°.

6. Infrared spectra were recorded on a Baird double-beam spectrophotometer. The significant bands for each new compound prepared in this section are given at the end of each experiment in microns and the μ is omitted. A letter w, m, or s in parentheses following the wavelength indicates the intensity of the band as weak, medium, or strong, respectively.
7. Ultraviolet spectra were measured on a Carey recording spectrophotometer.

1,2,3,6-Tetrahydro-3-methyl-1,6-endoxophthalic anhydride (III)

Compound III was prepared essentially as described by Moore,\textsuperscript{1}

\textsuperscript{(1)} E. P. Moore, Ph. D. dissertation, The Ohio State University, 1957.

who obtained a quantitative yield from pure 2-methylfuran. Using technical 2-methylfuran (Dupont) we were able to prepare III in 88\% yield as a white powder, m.p. 79.5-81.0\degree, lit.\textsuperscript{1} m.p. 82-83\degree.

3-Methylphthalic anhydride (IV)

Aromatization of III with concentrated sulfuric acid according to the procedure of Moore\textsuperscript{1} gave a 51\% yield of IV as white needles, m.p. 116-118\degree, lit.\textsuperscript{1} m.p. 117-118\degree.

3-Methylanthranilic acid (II)\textsuperscript{2}

\textsuperscript{(2)} The method used was essentially that of H. R. Barkenmeyer, M. S. thesis, The Ohio State University, 1952, except on a much larger scale.

To a solution of 100 g. (0.62 mol.) 3-methylphthalic anhydride (IV) in 500 ml. concentrated sulfuric acid contained in a 2-liter, 3-necked flask equipped with a mechanical stirrer and maintained at 40\degree by means of a water bath, was added portionwise over a one-hour period, 44.2 g. (0.68 mol.) of powdered sodium azide. Stirring was continued at 40\degree for two hours and the dark solution poured onto four liters of crushed ice with rapid stirring. The mixture was neutralized
with 25% potassium hydroxide solution and made barely acid with 5% hydrochloric acid. The whole mixture was diluted to 12 liters and stirred for 2 hours. The tan solid was filtered, washed thoroughly with ice-cold water, and dried under vacuum to yield 63.0 g. (68%) of crude amino acid, m.p. 171-174°. Ether extraction of the aqueous filtrates produced an additional 15.0 g. (16%) tan solid, m.p. 170-174°. Recrystallization from about 30% aqueous ethanol gave three crops of II as light tan needles as follows: 55.6 g. (60%), m.p. 175-176°; 6.8 g. (7%) m.p. 174-176°, and 6.3 g. (7%) m.p. 173-175°, lit.2 m.p. 173-174°.

N-Acetyl-o-toluidine

The method of Feiser3 was used to obtain N-acetyl-o-toluidine


in 80% yield as white needles, m.p. 109-110°, lit.4 m.p. 110°.

N-Formyl-o-toluidine

The method of Tyson5 gave N-formyl-o-toluidine in 89% yield as


white needles, m.p. 57-58°, lit.5 m.p. 55-58°.

Di-o-tolylacetamide (VIII)

A mixture of 37.3 g. (0.25 mol.) N-acetyl-2-toluidine, 20.7 g. (0.15 mol., 0.30 eq.) anhydrous potassium carbonate, 43.0 g. (0.25 mol.)
o-bromotoluene, 200 ml. redistilled nitrobenzene and approximately 1 g. of precipitated copper\(^6\) was refluxed with stirring at 185-200\(^\circ\)


for fifty hours. The black mixture was cooled and steam distilled. The cooled residue was treated with 500 ml. ether-benzene and the mixture filtered. After separation of the layers, the aqueous phase was extracted with two 200 ml. portions of ether-benzene. The combined organic layers were washed with one 300 ml. portion of water and worked up in the usual manner. The resulting black oil was fractionated through a short column (12\(\text{"} \times \text{"} 1\)) as follows:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>wt. (g.)</th>
<th>b.p.(^\circ)/l mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.2</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>12.6</td>
<td>120-150</td>
</tr>
<tr>
<td>3</td>
<td>19.0</td>
<td>150-160</td>
</tr>
<tr>
<td>4</td>
<td>4.8</td>
<td>160-170</td>
</tr>
<tr>
<td>5 (residue)</td>
<td>10.0</td>
<td>&gt; 170</td>
</tr>
</tbody>
</table>

Fractions 3 and 4 solidified on standing, were combined and recrystallized from Skellysolve B to yield 14.3 g. (24\%) of VIII as white crystals, m.p. 86-88\(^\circ\). The infrared spectrum showed a carbonyl band at 5.99 (s) and no NH band in the 2.5-3.0 region. Recrystallization from Skellysolve B gave the analytical sample, m.p. 87.1-88.2\(^\circ\) (corr.).

**Anal. Calc'd. for C\(_{16}\)H\(_{17}\)NO: C, 80.3; H, 7.2; N, 5.9**

**Found: C, 80.0; H, 7.3; N, 5.9**

**Di-o-tolylformamide (IX)**

A mixture of 25.0 g. (0.18 mol.) N-formyl-2-toluidine, 34.0 g.
(0.20 mol.) o-bromotoluene, 13.8 g. (0.10 mol. 0.20 eq.) anhydrous potassium carbonate, 100 ml. redistilled nitrobenzene, and about 1 g. precipitated copper was refluxed with stirring for fifty hours. The black mixture was cooled, steam distilled, the residue treated with 400 ml. ether-benzene, and filtered. The layers were separated and the aqueous phase extracted with two 200 ml. portions of ether-benzene. The combined organic layers were washed with a 300 ml. portion of water and worked up in the usual manner. The black oil was fractionated through a short column (12″ x 2″) column as follows:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>wt. (g.)</th>
<th>b.p.°/2 mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>154</td>
</tr>
<tr>
<td>2</td>
<td>11.1</td>
<td>154-164</td>
</tr>
<tr>
<td>3</td>
<td>13.7</td>
<td>164-174</td>
</tr>
<tr>
<td>4 (residue)</td>
<td>4.0</td>
<td>&gt; 174</td>
</tr>
</tbody>
</table>

Fractions 2 and 3 solidified on cooling, were combined and recrystallized from Skellysolve B to give, in two crops, 16.4 g. (40%) white solid, m.p. 87-88.5°, and 1.8 g. (4%) slightly off-white solid, m.p. 86-88°. Recrystallization of the combined crude product from Skellysolve B gave 17.4 g. (42%) of IX as white crystals, m.p. 87.5-88.5°. The infrared spectrum showed a carbonyl band at 6.01 (s) and no NH band in the 2.5-3.0 region. An analytical sample, m.p. 88.0-89.0 (corr.), was obtained by recrystallization from Skellysolve B.

**Anal. Calc'd. for Cl5H15NO:** C, 80.0; H, 6.7; N, 6.2

**Found:** C, 79.9; H, 6.9; N, 6.2

**Di-o-tolylamine (X)**

1. **From Di-o-tolylacetamide VIII:** A solution of 14.3 g. (0.060
mol.,) di-o-tolylacetamide (VIII) and 200 ml. of 40% sulfuric acid was refluxed for 24 hours and poured onto 1 kg. crushed ice and neutralized with 40% potassium hydroxide solution. The lightly colored mixture was extracted with two 200 ml. portions of ether-benzene. The combined organic extracts were worked up in the usual manner. Distillation of the residue gave 9.2 g. (76%) of X as a colorless oil that solidified on standing, b.p. 134-138°/2 mm., m.p. 49-50°; lit.7 b.p. 192°/23 mm., m.p. 48-49° (crude); m.p., 52-53° (pure); lit.8 b.p. 185°/13 mm.


2. From Di-o-tolylformamide (IX): A solution of 33.3 g. (0.161 mol.,) di-o-tolylformamide (IX) in 150 ml. concentrated hydrochloric acid and 150 ml. glacial acetic acid was refluxed for 12 hours. The cooled solution was poured into crushed ice and filtered. The resulting bluish-white solid was triturated with a mixture of dilute ammonium hydroxide solution and ether-benzene. After separation of the layers, the aqueous phase was extracted with two 100 ml. portions of ether-benzene. The combined organic layers were worked up in the usual manner. Distillation afforded 29.6 g. (94%) of X as an almost colorless oil, b.p. 145-160°/3 mm. Recrystallization from Skellysolve F (80 ml.) gave 28.7 g. (91%) of X as very slightly off-white crystals, m.p. 48-50°.

3. From N-acetyl-o-toluidine: A mixture of 25.0 g. (0.167 mol.) N-acetyl-o-toluidine, 29.0 g. (0.170 mol.) o-bromotoluene, 12.0 g. (0.087 mol., 0.174 eq.) potassium carbonate, 100 ml. redistilled
nitrobenzene, and one gram of catalytic copper\textsuperscript{6} was refluxed for fifty hours, cooled, and steam distilled. The residue was triturated with ether-benzene, filtered, and worked up as in (1) above. The black oil was distilled from a Claisen flask, to give 18.5 g., (56\%) of yellow oil, b.p. 140-165\(^\circ\)/2 mm, which only partially solidified on standing. This material was refluxed with 200-ml. of 40\% sulfuric acid overnight, poured on 1 kg. ice, neutralized with 20\% KOH solution, and extracted with two 200 ml. portions of ether-benzene. The combined organic layers were worked up in the usual manner. The dark oil was distilled to yield 7.1 g. (22\%) of crude X as a light yellow oil, that solidified on standing, b.p. 131-136\(^\circ\)/2 mm., m.p. 40-45\(^\circ\). Recrystallization from Skellysolve F produced 5.9 g. (18\%) of X as white crystals, m.p. 47-48.5\(^\circ\).

4. From N-formyl-o-toluidine: A mixture of 25.0 g. (0.182 mol.) N-formyl-o-toluidine, 34.0 g. (0.199 mol.) o-bromotoluene, 13.8 g. (0.10 mol., 0.20 eqs.) potassium carbonate, 100 ml. nitrobenzene, and one gram catalytic copper\textsuperscript{6} was refluxed for fifty hours and worked up as in (2) above. Distillation from a Claisen flask gave 25.7 g. (61\%) of yellow oil, b.p. 130-170\(^\circ\)/2 mm. This material was refluxed with a mixture of 250 ml. glacialacetic acid and 250 ml. concentrated hydrochloric acid for ten hours and cooled. It was poured into 200 ml. ice-water and extracted three times with 100 ml. portions of ether-benzene. The combined organic extracts were worked up in the usual manner and distilled to obtain 14.2 g. (43\%) of crude X as a colorless oil, b.p. 145-170\(^\circ\)/4 mm. Recrystallized from Skellysolve F to give
13.5 g. (37%) of X as white crystals, m.p. 46-48°.

N,N Di-o-tolyloxamic acid (XI) and Methyl N,N Di-o-tolyloxamate (XII).

A solution of 7.5 g. (0.038 mol.) di-o-tolyamine (X) in 40 ml. purified carbon disulfide was added dropwise over a 15 minute period to a stirred, gently refluxing, solution of 5.5 g. (0.043 mol.) oxalylchloride (Matheson, Coleman and Bell) in 25 ml. purified carbon disulfide. The evolution of hydrogen chloride was rapid. After one hour refluxing with stirring, the solvent and excess oxalyl chloride were removed under reduced pressure. The resulting yellow oil was taken up in 30 ml. Skellysolve F, filtered and refrigerated. In two crops, 10.0 g. (91%) of pale yellow solid, m.p. 68-70° was isolated.

1. N,N Di-o-tolyloxamic acid (XI): A mixture of 5.00 g. (0.017 mol.) of the above crude acid chloride and 25 ml. water was heated to boiling and immediately cooled in ice. The brittle, pale yellow solid was removed by filtration, powdered in a mortar, and dried under vacuum over P₂O₅ to give 4.45 g. (95%) of pale yellow powder, m.p. 145-150° w. dec. This crude product was taken up in 10% potassium hydroxide solution, brought to almost neutral with dilute hydrochloric acid, treated with charcoal, filtered and acidified. Filtration produced 4.05 g. (87%), of XI as a white powder, m.p. 154-155° w. dec. The infrared showed carbonyl at 5.85 (s) and no NH band in the 2.5-3.0 region. Two recrystallizations from chloroform-
Skellysolve B afforded the analytical sample, m.p. 154-155° w. dec.

**Anal. Calc'd. for C_{16}H_{15}NO_{3}:**
- C, 71.4; H, 5.6; N, 5.2
  - Neut. Eq. 269
  - Found: C, 71.0; H, 5.7; N, 5.3
  - Neut. Eq. 267, 268, 269

2. **Methyl N,N Di-o-tolyl oxamate (XII):** A solution of 5.00 g. (0.017 mol.) of the above crude acid chloride and 25 ml. absolute methanol was allowed to stand for 30 minutes. Evaporation of the solvent left 4.90 (100%) of white solid, m.p. 94-96°. Recrystallization from Skellysolve B (100 ml.) gave 4.60 g. (94%) of XII as white crystals, m.p. 97-98°. The infrared spectrum showed two carbonyl bands, 5.85 (s); 6.05 (s) and no NH absorption in the 2.5-3.0 region. Another recrystallization from Skellysolve B gave the analytical sample, m.p. 96.8-98.2° (corr.).

**Anal. Calc'd. for C_{17}H_{17}NO_{3}:**
- C, 72.1; H, 6.1; N, 4.9
  - Found: C, 71.9; H, 5.8; N, 5.2

1-o-Tolyl-7-methyliasin (XIII)

A solution of 12.3 g. (0.063 mol.) of di-o-tolylamine (X) in 60 ml. purified carbon disulfide was added dropwise over a 40 minute period to a stirred, gently refluxing solution of 9.0 g. (0.071 mol.) oxalyl chloride in 45 ml. purified carbon disulfide. The evolution of hydrogen chloride was rapid. The yellow solution was gently refluxed with stirring for one hour and the solvent and excess oxalyl chloride stripped off under reduced pressure.

Pumping was continued for one hour after the solvent was gone. Then, 100 ml. purified carbon disulfide was added followed by 26.6 g.
(0.20 mol.) anhydrous aluminum chloride portionwise over a 15 min. period. As the black complex separated, stirring became impossible but refluxing was continued for one hour. After stripping off the solvent, the black complex was decomposed by cautious addition of ice followed by dilute hydrochloric acid. The red mixture was extracted with three 100 ml. portions of ether-benzene and the combined organic extracts worked up in the usual manner. The resulting red solid was recrystallized from benzene-cyclohexane (3:5) to give 14.6 g. (93%) of XIII as red crystals, m.p. 172-174°. The infrared spectrum showed a wide carbonyl band at 5.82 (s) and a band at 2.9 (v.w.). The analytical sample, m.p. 172.6-173.9° (corr.) was prepared by recrystallization from benzene-cyclohexane.

Anal. Calc'd. for C_{16}H_{15}NO_{2}: C, 76.5; H, 5.2; N, 5.6
Found: C, 76.4; H, 5.3; N, 5.8

2',6-Dimethyldiphenylamine-2-carboxylic acid (V)

1. From 3-Methylantranilic acid (II): A mixture of 65.8 g. (0.435 mol.) 3-methylantranilic acid (II), 114.5 g. (0.666 mol.) o-bromotoluene, 94 g. (0.68 mol., 1.36 eq.) anhydrous potassium carbonate, 375 ml. redistilled nitrobenzene and 2 g. precipitated copper was heated at 185°± 5° for 26 hours, cooled, and the nitrobenzene removed by steam distillation. The dark-brown residue was filtered hot, the filtrate made almost neutral with concentrated hydrochloric acid (charcoal) filtered, and acidified by dropwise addition with stirring to a mixture of ice and hydrochloric acid. Filtration and air drying produced 105 g. (quant.) of dirty brown-green solid,
Recrystallization from benzene (charcoal) gave 74.5 g. (72%) of V as yellow crystals, m.p. 187-188°. From the mother liquors there was obtained, in two crops, 3.4 g. (3%) of V as light brown crystals, m.p. 186-187°, lit.10 m.p. 185°.


The methyl ester was prepared by treatment of a solution of 4.84 g. (0.020 mol.) of 2',6-dimethyldiphenylamine-2-carboxylic acid (V) with an ethereal solution of diazomethane (about 0.04 mol.).11 The solution was allowed to stand for three hours and then the excess diazomethane decomposed with a few drops of acetic acid. The ethereal solution was washed with water, twice with 5% potassium bicarbonate solution, water and worked up in the usual manner. On distillation 4.5 g. (90%) of the ester as a light yellow oil, b.p. 210-235°/5 mm., that solidified on cooling to a yellow solid, m.p. 60-62°, was obtained. Two recrystallizations from methanol produced the ester as a pale yellow solid, 3.1 g. m.p. 61-62° (if cooled and retaken, 67.5-68.5). The low melting point appears to be that of a polymorphic form. The infrared spectrum showed a carbonyl band, 5.90 (m) and NH, 2.97 (m). The analytical sample was recrystallized from methanol and melted 68.2-68.9° (corr.).

Anal. Calc'd. for C_{16}H_{17}NO_{2}: C, 75.3; H, 6.7; N, 5.5

Found: C, 75.5; H, 6.5; N, 5.6
2. From 1-o-tolyl-7-methylisatin (XIII): Twenty-five ml. of a 3% hydrogen peroxide solution was added with stirring to a solution of 1.0 g. (0.004 mol.) N-o-tolyl-7-methylisatin (XIII) in 170 cc. of 3% potassium hydroxide solution at room temperature. The yellow mixture was allowed to stand for 3 hours, acidified with concentrated hydrochloric acid, and filtered to obtain 0.93 g. (96%) of V as a white solid, m.p. 185-187°. Recrystallization from benzene-Skellysolve B gave 0.85 g. (88%) of V as a white solid, m.p. 186-187°.

9-Chloro-4,5-dimethylacridine (VI)

1. From 2',6-Dimethyldiphenylamine-2-carboxylic acid (V): A mixture of 43.6 g. (0.181 mol.) 2',6-dimethyldiphenylamine-2-carboxylic acid (V) and 350 g. phosphorous oxychloride was heated slowly to 70°. After the vigorous reaction subsided, the black mixture was refluxed (bath temperature 120°), for one hour and the excess removed under reduced pressure at 100°. The complex was decomposed with ice and 5% ammonium hydroxide. After allowing the yellow mixture to stand overnight, filtration and drying under vacuum gave 43.6 g. (100%) of yellow-green solid, m.p. 144-149°. This crude product was dissolved in chloroform, adsorbed on a large column of alumina (2" x 24"), and eluted with Skellysolve B. Recrystallization of the yellow solid, obtained on evaporation of the solvent, from 1200 ml. Skellysolve F gave 38.9 g. (89%) of VI as yellow, fluffy, silky needles, m.p. 149-151°, lit. 12 m.p. 149-150°. Further elution of the column with chloroform and

acetone gave 3.5 g. of dirty brown solid, m.p. 200-214°. Two recrystallizations from chloroform-Skellysolve B gave 2.5 g. (6%) of yellow crystals, m.p. 232-233°. The infrared spectrum showed a carbonyl band, 6.15 (vs) NH band, 2.90 (m), and vicinal trisubstituted benzene, 13.55 (vs). Analysis of a sample, m.p. 233.6-234.9° (corr.), obtained by recrystallization from chloroform-Skellysolve B, was correct for the hydrolysis product of 9-chloro-4,5-dimethylacridine (VI), 4,5-dimethylacridone (VII).

Anal. Calc'd. for C_{15}H_{13}NO:  C, 80.7; H, 5.9; N, 6.2

Found: C, 80.7; H, 5.7; N, 6.3

2. From 4,5-Dimethylacridone (VII): A mixture of 5.8 g. (0.026 mol.) 4,5-dimethylacridone (VII) and 50 g. phosphorous oxychloride was refluxed for one hour and the excess phosphorous oxychloride removed under reduced pressure at 100°. The black complex was cooled and decomposed with ice and dilute ammonium hydroxide. After standing for several hours, the yellow solid was filtered and dried under vacuum over phosphorous pentoxide to give 6.2 g. (98%) yellow-brown solid, m.p. 146-149°. This crude material was dissolved in chloroform, adsorbed on a short column of alumina (1" x 12") and eluted with Skellysolve B. Evaporation of the eluates gave 5.7 g. (89%) of VI as yellow, fluffy needles, m.p. 150-151°.

Elution of the column with chloroform and acetone gave 0.3 g. (5%) of recovered (VII), m.p. 227-230°.

4,5-Dimethylacridone (VII)

A mixture of 5.0 g. (0.025 mol.) 9-chloro-4,5-dimethylacridine (VI)
and 100 ml. of 10% hydrochloric acid was heated on the steam bath for two hours, cooled, and filtered. Recrystallization of the resulting brown-yellow solid twice from chloroform-Skellysolve B gave, in two crops, 3.8 g. (83%) of VII as light yellow needles, m.p. 230-231°.

4,5-Dimethylacridine-9-carboxylic acid (XIV)

A solution of 47.0 g. (0.187 mol.) 1-o-tolyl-7-methylisatin (XIII) in 500 ml. of 10% potassium hydroxide solution was refluxed for 12 hours, cooled, and poured onto a mixture of crushed ice and concentrated hydrochloric acid. The orange mixture was extracted with three 1-liter portions of ether-benzene. The combined organic extracts were worked up in the usual manner. On removal of the solvent, solid separated out at a volume of about one liter. Filtration gave 37.5 g. (78%) of XIV as a yellow solid, m.p. 230-236°, w. dec. Concentration of the filtrate produced 9.0 g. (19%), of XIV as yellow solid, m.p. 229-234° w. dec. Total yield of XIV, 46.5 g. (99%) m.p. 229-236° w. dec. Total yield of XIV, 46.5 g. (99%) m.p. 229-236° w. dec. The infrared spectrum showed a carbonyl band, 5.87 (s). Two recrystallizations from aqueous alcohol (about 1:1) gave the analytical sample, m.p. 230-235° w. dec.

**Anal. Calc'd. for C_{16}H_{13}NO_{2}:**

<table>
<thead>
<tr>
<th>C</th>
<th>76.5</th>
<th>H</th>
<th>5.2</th>
<th>N</th>
<th>5.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neut. Eq.</td>
<td>251</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Found:</th>
<th>C</th>
<th>76.5</th>
<th>H</th>
<th>5.3</th>
<th>N</th>
<th>6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neut. Eq.</td>
<td>246, 249, 246</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The methyl ester was prepared by treating a solution of 3.6 g. (0.014 mol.) 4,5-dimethylacridine-9-carboxylic acid in 500 ml. anhydrous with an ethereal solution of diazomethane\(^{11}\) (about 0.04 mol.). After standing for four hours the excess diazomethane was decomposed with acetic acid and the organic solution worked up in the usual manner.
Recrystallization of the resulting yellow solid from chloroform-Skellysolve B gave 3.3 g. (87%) of the ester as yellow needles, m.p. 123-124°. The infrared spectrum showed a carbonyl band at 5.81 (s). Two recrystallizations from Skellysolve B gave the analytical sample, m.p. 123.6-124.4° (corr.).

Anal. Calc'd. for C₁₇H₁₅NO₂:  \( \text{C}, \, 77.0\);  \( \text{H}, \, 5.7\);  \( \text{N}, \, 5.3 \)

Found:  \( \text{C}, \, 76.7\);  \( \text{H}, \, 5.9\);  \( \text{N}, \, 5.2 \)

4,5-Dimethylacridine (I)

1. From 4,5-Dimethylacridine-9-carboxylic acid (XIV): 4,5-Dimethylacridine-9-carboxylic acid (XIV) (20.8 g., 0.083 mol.) was heated at 240-250° for 15 minutes. Carbon dioxide was rapidly evolved. The cooled residue was dissolved in 40 ml. chloroform, adsorbed on a short column of alumina (1" x 12") and eluted with Skellysolve F. Evaporation of the solvents gave 16.5 g. (96%) of yellow powder, m.p. 60-75°. This crude I was treated with 150 ml. absolute methanol and filtered from 0.8 g. yellow powder, m.p. > 300°. The filtrate was concentrated to 100 ml. and refrigerated. In two crops, 14.9 g. (87%) of I as yellow needles, m.p. 77.5-79.5° (corr.) was obtained, lit.¹² m.p. 78-80°.

The trinitrobenzene complex of I was prepared by mixing a hot solution of 1.00 g. (0.0048 mol.) 4,5-dimethylacridine (I) in 10 ml. absolute ethanol with a hot solution of 1.05 g. (0.0049 mol.) trinitrobenzene in 20 ml. absolute ethanol and cooling to yield 1.88 g. (93%) yellow needles, m.p. 136-138°. Recrystallization from absolute ethanol gave 1.74 g. (86%) yellow needles, m.p. 137.5-139.5°. The
analytical sample, m.p. 138.8-140.4° (corr.), was prepared by recrystallization from absolute alcohol.

**Anal. Calc'd. for C_{21}H_{16}N_{4}O_{6}:** C, 69.0; H, 3.8; N, 13.3  
**Found:** C, 59.7; H, 3.8; N, 13.8  
12.8

The hydrochloride was prepared by saturating a solution of 1.00 g. (0.0048 mol.) 4,5--dimethylacridine in 100 ml. anhydrous ether with dry hydrogen chloride. Recrystallization from 1 N hydrochloric acid gave 1.06 g. (91%) of yellow orange needles, m.p. 195-205° w. dec. The analytical sample was prepared by recrystallization from 1 N hydrochloric acid and dried to constant weight under vacuum over phosphorous pentoxide.

**Anal. Calc'd. for C_{15}H_{13}NCl:** C, 73.9; H, 5.8; N, 5.8; Cl, 14.6  
**Found:** C, 72.4; H, 6.4; N, 5.4; Cl, 15.6

The hydrobromide was obtained in the same manner as the hydrochloride salt; Yield, 1.30 g. (94%), m.p. 290-300° w. dec. The analytical sample was prepared by recrystallization from 1 N hydrobromic acid.

**Anal. Calc'd. for C_{15}H_{13}NBr:** C, 62.5; H, 4.9; N, 4.9; Br, 27.7  
**Found:** C, 61.8; H, 5.4; N, 5.2; Br, 27.3

These analytical results are not good, although the nitrogen to halogen ratio calculated out to be 1:1. A more satisfactory method of purification is needed.

2. **From 9-Chloro-4,5-dimethylacridine (VI):**  
   a. **Reduction with Raney Nickel and hydrogen:** A solution of 4.84 g. (0.020 mol.) 9-chloro-4,5-dimethylacridine VI in 80 ml. dry, thiophene-free benzene was mixed with a solution of 1.12 g. (0.020 mol.)
mol.) potassium hydroxide in 80 ml. absolute ethanol and shaken at room temperature with about 2 g. Raney Nickel catalyst\textsuperscript{13} at an initial hydrogen pressure of 3 atmospheres (45 lbs.). After three hours 3.5 lbs. hydrogen had been absorbed (theory, 3.3 lbs.). The reaction mixture was heated to boiling, filtered hot and the catalyst washed thoroughly with hot benzene and absolute ethanol. Evaporation of the solvent left a yellow residue which was taken up in ether-benzene and worked up in the usual manner to obtain 4.10 g. (98%) crude 4,5-dimethylacridan, m.p. 85-92; lit.\textsuperscript{12} m.p. 92-93°. This material was suspended in 40 ml. of a gently boiling, stirred, 20% sulfuric acid solution and treated in two portions 5 minutes apart with a hot solution of 2.12 g. (0.0067 mol., 0.020 eq.) potassium dichromate in 25 ml. water. After gentle boiling for 10 minutes, a hot solution of 5.4 g. (0.18 mol.) potassium dichromate in 60 ml. water was added. After 10 minutes additional gentle boiling, with stirring, the orange mixture was refrigerated overnight. The orange dichromate salt was filtered and triturated with 50 ml. 10% ammonium hydroxide solution. The crude product was extracted with ether-benzene and worked up in the usual manner to give 3.80 g. (92%) crude I as a yellow solid, m.p. 74-77°. Recrystallization from methanol (charcoal) gave, in two crops, 3.45 g. (83%) of I as yellow needles, m.p. 78-79°.

b. Reduction with lithium aluminum hydride: A solution of 24.2 g. (0.10 mol.) 9-chloro-4,5-dimethylacridine (VI) in 400 ml. purified tetrahydrofuran was added dropwise over a 90 minute period to a stirred

slurry of 19.0 g. (0.50 mol.) lithium aluminum hydride in 100 ml. purified tetrahydrofuran. The resulting mixture was refluxed for 45 hours, cooled, and the excess hydride decomposed by adding drop-wise 100 ml. of a 1:1 mixture of tetrahydrofuran and water, followed by 200 ml. water and 200 ml. concentrated hydrochloric acid. The layers were separated and the aqueous layer extracted with two 100 ml. portions of ether-benzene. The combined organic layers were washed with three 300 ml. portions of water and worked up in the usual manner to give 20.5 g. (98%) of the crude acridan as brown-yellow solid, m.p. 84-95°. This material was suspended with stirring in 200 ml. of hot 20% sulfuric acid and treated in two portions 5 minutes apart with a solution of 10.0 g. (0.034 mol., 0.102 eq.) potassium dichromate in 120 ml. hot water. After boiling for 10 minutes, a solution of 27 g. (0.092 mol.) potassium dichromate in 300 ml. hot water was added, the mixture boiled for 10 minutes and refrigerated overnight. The dichromate salt was filtered, triturated with 500 ml. of 10% ammonium hydroxide, refrigerated, and filtered to obtain 18.8 g. (91%) crude I as a yellow-brown solid, m.p. 72-77°. Recrystallization from 150 ml. absolute methanol (charcoal) gave, in two crops, 16.0 g. (77%) of I as yellow needles, m.p. 78-79°.

2-Nitro-1,4-xylene

The method of Snyder and Pilgrim\(^\text{14}\) gave an 86% yield of 2-nitro-

1,4-xylene as a light yellow liquid, b.p. 117-118°/13 mm. lit.\textsuperscript{14} b.p. 64-65°/0.35 mm.

2,5-Dimethylaniline

In two batches, 124 g. (0.82 mol.) 2-nitro-1,4-xylene in 120 ml. absolute ethanol was shaken with 600 mg. platinum oxide catalyst at an initial hydrogen pressure of 3 atm. About 3 hours per batch was required to absorb the theoretical amount of hydrogen. The catalyst was filtered and washed thoroughly with absolute ethanol. Distillation through a short column (12" x 1") gave 92.0 g. (93\%) of 2,5-dimethylaniline as a colorless liquid, b.p. 61-63°/1 mm.; \( N_D^{23} \), 1.5579, lit.\textsuperscript{15} b.p. 213.5; \( N_D^{20} \), 1.5591.


Di-2,5-xylylamine XVI

A solution of potassium p-xylidide in 2-amino-p-xylene was prepared by adding 12.5 g. (0.32 mol.) metallic potassium to 440 ml. refluxing 2-amino-p-xylene under nitrogen. After two hours of refluxing a clear red solution was obtained. To this solution was added dropwise over a 1 hour period 55.5 g. (0.30 mol.) of 2-bromo-p-xylene. The mixture was refluxed with gentle stirring for four hours and cooled. Fifty milliliters of water was added cautiously, then 300 ml. water added and the layers separated. The aqueous layer was extracted with three 100 ml. portions of ether-benzene. The combined organic layers were washed with four 250 ml. portions of water and
worked up in the usual manner. The residue was distilled through
a short column (12" x 1") as follows:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Quantity</th>
<th>b. range</th>
<th>N&lt;sub&gt;p&lt;/sub&gt; 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165 ml.</td>
<td>61-70°/2 mm.</td>
<td>1.5560</td>
</tr>
<tr>
<td>2</td>
<td>220 ml.</td>
<td>70-72°/2 mm.</td>
<td>1.5572</td>
</tr>
<tr>
<td>3</td>
<td>6 g.</td>
<td>72-148°/2 mm.</td>
<td>1.5618</td>
</tr>
<tr>
<td>4</td>
<td>58.1 g.</td>
<td>148-152°/2 mm.</td>
<td>solidified</td>
</tr>
<tr>
<td>5</td>
<td>3.2 g.</td>
<td>152-180°/2 mm.</td>
<td>oil</td>
</tr>
<tr>
<td>Residue</td>
<td>5.9 g.</td>
<td>&gt; 180°/2 mm.</td>
<td>-</td>
</tr>
</tbody>
</table>

Fraction 4 (58.1 g., 96%) was recrystallized from Skellysolve F
to give 43.6 g. (65%) of XVI as white crystals, m.p. 51-53°.

From the mother liquors, by evaporation to dryness, precipitation of
the hydrochloride from dry ether with dry hydrogen chloride, decomposi­
tion of the salt with water and work up in the usual manner, followed
by distillation gave 8.0 g. additional crude XVI as a colorless oil,
b.p. 155-159°/3 mm. Recrystallization of the solidified oil from
Skellysolve F gave 6.2 g. (9%) of additional XVI, as white crystals, m.p.
50-53°. The total yield of XVI was 49.8 g. (74%), m.p. 50-53°. The
infrared spectrum showed a NH band at 2.94 (m) and 1,2,4 substitution,
12.65 (vs). Two recrystallizations from Skellysolve F followed by a
micro distillation gave the analytical sample, m.p. 53.4-54.8° (corr.)

**Anal. Calc'd. for C<sub>16</sub>H<sub>19</sub>N:**

C, 85.3; H, 8.5; N, 6.2

**Found:** C, 85.0; H, 8.6; N, 6.2

* N,N Di-2,5-xylyloxamic acid (XVII) and Methyl N,N Di-2,5-xylyloxamate
  *(VIII)*

A solution of 2.6 g. (0.012 mol.) di-2,5-xylylamine (XVI) in 15 ml.
purified carbon disulfide was added dropwise, with stirring, over a 10
minute period to a gently refluxing, solution of 2.0 g. (0.016 mol.)
oxalyl chloride in 10 ml. purified carbon disulfide. The evolution of hydrogen chloride was rapid. Gentle refluxing with stirring was continued for 30 minutes and the solvent and excess oxalyl chloride removed at reduced pressure. The resulting oil was taken up in 50 ml. Skellysolve F, filtered and concentrated to 30 ml. Refrigeration produced 3.5 g. (95%) light yellow crystals, m.p. 113.0-113.5°.

1. N,N Di-2,5-xylyloxamic acid (XVII): A mixture of 1.48 g. (0.0049 mol.) of the above crude acid chloride and 10 ml. of 20% potassium hydroxide solution was shaken for four hours. The resulting suspension was diluted to 50 ml. with water, heated briefly to dissolve the salt, and acidified with 10% hydrochloric acid. The mixture was extracted with two 50 ml. portions of ether—benzene and the combined organic extracts worked up in the usual manner. The resulting solid was triturated with Skellysolve B to give 1.30 g. (94%) of XVII as white powder, m.p. 132-134° w. dec. Recrystallization from chloroform—Skellysolve B (charcoal) gave, in two crops, 1.16 g. (84%) of XVII as white powder, m.p. 133-134° w. dec. The infrared spectrum showed carbonyl bands at 5.75 (s) and 5.95 (s). The analytical sample was prepared by recrystallization from chloroform—Skellysolve B and melted 133-134° w. dec.

Anal. Calc'd. for C_{18}H_{19}NO_{3}:  C, 72.7;  H, 6.4;  N, 4.7
Neut. eq. 297

Found:  C, 72.3;  H, 6.6;  N, 4.3
Neut. Eq. 314, 320

The neutral equivalent was not run on the analytical sample and gave a fairly good value for a monohydrate. It is possible, therefore, that the low carbon and nitrogen values are due to incomplete removal
of water of hydration even after long periods of drying.

2. Methyl N,N di-2,5-xylyloxyxamate (XVIII): A mixture of 2.00 g. (0.00635 mol.) of the above crude acid chloride and 2 ml. absolute methanol was warmed briefly to effect solution and refrigerated. Filtration gave 1.90 g. (96%) of XVIII as white powder, m.p. 96-97°. Two recrystallizations from Skellysolve B gave 1.50 g. (76%) of XVIII as white needles, m.p. 97-98°. The infrared spectrum showed carbonyl bands at 5.75 (s) and 5.95 (s). Recrystallization from Skellysolve B afforded the analytical sample, m.p. 97.2-97.8° (corr.).

Anal. Calc'd. for \( \text{C}_{19}\text{H}_{21}\text{NO}_3 \): C, 73.3; H, 6.8; N, 4.5

Found: C, 73.2; H, 6.8; N, 4.5

1-(2,5)-Xylyl-4,7-dimethylisatin (XIV)

A solution of 45.0 g. (0.20 mol.) di-2,5-xylylamine (XVI) in 300 ml. purified carbon disulfide was added dropwise with stirring over a 120 min. period to a gently refluxing solution of 33.1 g. (0.26 mol.) oxalyl chloride in 180 ml. purified carbon disulfide. Gentle refluxing with stirring was continued for one hour and the solvent and excess oxalyl chloride removed under reduced pressure. The resulting oil solidified and 200 ml. purified carbon disulfide was added followed by 94.0 g. (0.71 mol.) anhydrous aluminum chloride portionwise over a 30 minute period. The separation of a black complex made stirring impossible but the mixture was gently refluxed for one hour and the solvent stripped off at reduced pressure. Decomposition of the complex with ice and dilute hydrochloric acid gave a red solid which was extracted from the aqueous mixture with three 200 ml. portions of ether-benzene.
The combined organic extracts were worked up in the usual manner and the resulting red solid recrystallized from 200 ml. cyclohexane to give, in two crops, 53.4 g. (96%) of XIX as red needles, m.p. 140-142°. The infrared spectrum showed carbonyl bands at 5.75 (s) and 5.80 (s). Two recrystallizations from cyclohexane gave the analytical sample, m.p. 141.5-142.0° (corr.).

Anal. Calc'd. for C_{15}H_{17}NO_2: C, 77.4; H, 6.1; N, 5.0

Found: C, 77.7; H, 6.3; N, 5.2

1,4,5,8-Tetramethylacridine-9-carboxylic acid (XX)

A solution of 10.0 g. (0.0358 mol.) 1-(2,5)-xylyl-4,7-dimethyl-isatin (XIX) in 150 ml. water containing 20.0 g. (0.358 mol.) potassium hydroxide was refluxed for a total of 305 hours, cooled, and a small amount of insoluble material removed by filtrations. Acidification and filtration gave an orange powder which was triturated with hot benzene and filtered. Evaporation of the filtrate gave 0.6 g. (6%) of an almost white powder, m.p. 190-200°, presumably 2',3,5',6-tetramethyldiphenylamine-2-carboxylic acid (XXI).

The benzene insoluble portion

(16) Treatment of the isatin (XIX.) with potassium hydroxide in xylene led to predominantly 2',3,5',6-tetramethyldiphenylamine-2-carboxylic acid (XXI.) m.p. 193-199° w. dec.

was treated with hot 10% potassium carbonate solution and filtered from some insoluble material, 0.9 g., m.p. >300°. Acidification of the filtrate with concentrated hydrochloric acid, filtration, and drying under vacuum gave 7.9 g. (79%) m.p. 229-233° w. dec. of XX as an orange powder. This material was sufficiently pure for further
work. The infrared spectrum showed carbonyl at 5.80 (m). Two recrystallizations from 95% ethanol gave the analytical sample in poor recovery, m.p. 229-233° w. dec.

**Anal. Calc'd for C_{18}H_{17}NO_2:** C, 77.4; H, 6.1; N, 5.0

**Found:** N, 5.2

The methyl ester was prepared by treatment of a solution of 2.0 g. (0.0072 mol.) 1,4,5,8-tetramethylacridine—9-carboxylic acid (XX) in 500 ml. anhydrous ether with an ethereal solution of diazomethane (about 0.020 mol.). As the yellow suspension stood it gradually cleared to a yellow solution. After standing overnight, the excess diazomethane was decomposed with acetic acid and the solution concentrated to 100 ml. The solution was washed with water and 5% potassium bicarbonate solution, and worked up in the usual manner. Recrystallization of the resulting yellow solid from 95% ethanol gave 1.9 g. (91%) of the ester as yellow solid, m.p. 126.0-127.5°.

The infrared spectrum showed a carbonyl band at 5.77 (s). Two recrystallizations from 95% ethanol gave the analytical sample, m.p. 127.2-128.3° (corr.).

**Anal. Calc'd for C_{19}H_{19}NO_2:** C, 77.8; H, 6.5; N, 4.8

**Found:** C, 77.6; H, 6.7; N, 5.0

**2',3',5',6-Tetramethyldiphenylamine-2—carboxylic acid (XXI)**

A mixture of 8.0 g. (0.0286 mol.) 4,7-dimethyl-N-p-xylylisatin (XIX), 16.0 g. (0.286 mol.) potassium hydroxide and 145 ml. water was heated at 60° until the red solid turned to a yellow solid. Then
10 ml. (about 0.1 mol.) of 30% hydrogen peroxide was added in two portions 2 hours apart. Stirring was continued at 60° for 3 more hours and the clear yellow solution cooled and acidified with concentrated hydrochloric acid and ice. A light brown solid, 7.5 g. (97%), m.p. 194-197° was obtained by filtration and drying under vacuum. This crude product was dissolved in hot 10% potassium carbonate, cooled, and the aqueous solution extracted twice with ether-benzene. The basic solution was brought to almost neutral with concentrated hydrochloric acid, treated with charcoal and acidified with hydrochloric acid. Filtration and air drying gave 7.1 g. (92%), of XXI as a white powder, m.p. 197-199°. The infrared spectrum showed a carbonyl band at 5.95 (s) and NH absorption at 2.90 (m). Two recrystallizations from benzene-Skellysolve B gave the analytical sample, m.p. 197.5-199.0°.

**Anal. Calc'd. for C_{17}H_{19}NO_{2} :**
C, 75.8; H, 7.1; N, 5.2
Neut. Eq. 269

**Found: C, 75.8; H, 7.1; N, 5.3**
Neut. Eq. 265, 268, 271

The methyl ester was prepared by treatment of a solution of 1.0 g. (0.0035 mol.) 2',3,5',6-tetramethyldiphenylamine-2-carboxylic acid (XXI) in 50 ml. anhydrous ether with an ethereal solution of diazomethane (about 0.02 mol.). After standing for four hours the excess diazomethane was decomposed with acetic acid and the solution worked up in the usual manner to yield 0.93 g. (89%) of the methyl ester as a white powder, m.p. 124-128°. Two recrystallizations from aqueous methanol gave 0.75 g. (72%) of the ester as white, fluffy needles, m.p. 127.0-128.5°. The infrared spectrum showed a carbonyl band at
5.30 (s) and NH absorption at 2.97 (s). Another crystallization from aqueous methanol gave the analytical sample, m.p. 128.0-128.5° (corr.).

**Anal. Calc'd. for C_{18}H_{21}NO_{2}: C, 76.3; H, 7.5; N, 4.9**

**Found: C, 75.9; H, 7.4; N, 5.2**

9-Chloro-1,4,5,8-tetramethylacridine (XXII)

1. From 2',3,5',6-Tetramethylidiphenylamine-2-carboxylic acid (XXI):

A mixture of 7.0 g. (0.026 mol.) 2',3,5',6-tetramethylidiphenyl-amine-2-carboxylic acid (XXI) and 70 ml. phosphorous oxychloride was refluxed for 90 minutes at 120° (bath temperature) and the excess solvent pumped off at 100°. The resulting slurry was decomposed with ice and concentrated ammonia hydroxide. After standing for two hours the mixture was extracted with three 300 ml. portions of ether-benzene. The combined organic layers were worked up in the usual manner to yield 6.0 g. yellow-green solid, m.p. 150-180°. This material was dissolved in 40 ml. benzene and adsorbed on a large column of alumina. Development with 2 liters of Skellysolve B gave 4.2 g. (60%) of crude XXII as yellow solid, m.p. 168-171° on evaporation of the solvent from the eluates. Recrystallization from Skellysolve B gave, in two crops 3.9 g. (58%) of XXII as yellow needles, m.p. 170.0-171.5°. The infrared spectrum showed no NH absorption in the 2.5-3.0 region, no carbonyl in the 5.3-6.0 region, ¹ 1,2,3,4 substitution at 12.4 (s), and presumably C-Cl absorption at 12.1 (s). An analytical sample was obtained by rechromatography in Skellysolve B on alumina followed by recrystallization from Skellysolve B, m.p. 171.5-172.0° (corr.).
Anal. Calc'd. for C_{17}H_{16}NCl:  C, 75.7; H, 6.0; N, 5.2; Cl, 13.1

Found:  C, 75.7; H, 5.9; N, 5.2; Cl, 13.0

Washing the column down with one liter chloroform gave 1.9 g. (29%) light brown solid, m.p. 214-220°. Recrystallization from benzene gave, in two crops, 1.7 g. (26%) of yellow needles, m.p. 220-221°. The infrared spectrum showed NH absorption at 2.85 (m), carbonyl absorption at 6.1 (vs) and 1,2,3,4 absorption at 12.5 (s). The analytical sample, prepared by recrystallization from benzene, m.p. 220.0-221.4° (corr.) analyzed correctly for the hydrolysis product of 9-chloro-1,4,5,8-tetramethylacridine (XXII), 1,4,5,8-tetramethylacridone (XXIII).

Anal. Calc'd. for C_{17}H_{17}NO:  C, 81.2; H, 6.8; N, 5.6

Found:  C, 81.1; H, 6.8; N, 5.7

2. From 1,4,5,8-tetramethylacridone (XXIII): A mixture of 2.00 g (0.00798 mol.) 1,4,5,8-tetramethylacridone (XXIII) and 20 ml. of phosphorous oxychloride was refluxed for 90 minutes at 120° (bath temperature) and the excess phosphorous oxychloride removed under reduced pressure at 100°. The resulting complex was decomposed with ice and concentrated ammonium hydroxide with stirring. After allowing to stand for two hours, the yellow mixture was extracted with three 100 ml. portions of ether-benzene. The combined organic layers were worked up in the usual manner, concentrated to about 25 ml., and adsorbed on a short column (1" x 12") of alumina. Elution with Skellysolve B gave 1.9 g. (89%) of XXII as a yellow solid, m.p. 164-168° on evaporation of the solvent. Recrystallization from Skellysolve B gave, in two crops, 1.31 g. (85%) of XXII as yellow needles, m.p. 171-172°.
Development of the column with benzene gave 0.15 g. (8%) of recovered XXIII as light tan solid, m.p. 210-217°. Recrystallization from benzene gave 0.10 g. (5%) m.p. 219-221°, recovered 1,4,5,8-tetramethylacridone (XXIII).

1,4,5,8-Tetramethylacridone (XXIII)

1. From 9-chloro-1,4,5,8-tetramethylacridine (XXII): A mixture of 5.4 g. (0.02 mol.) 9-chloro-1,4,5,8-tetramethylacridine (XXII) and 100 ml. of dilute hydrochloric acid (1:1) was heated at 100° for 2 hours and cooled. Filtered to obtain 4.8 g. (96%) yellow-green solid, m.p. 215-218°. Recrystallized from benzene (charcoal) to obtain, in two crops, 4.4 g. (88%) of XXIII as light yellow needles, m.p. 219-220°.

2. From 2',3',5',6-Tetramethyldiphenylamine-2-carboxylic acid (XXI): A mixture of 5.0 g. (0.0186 mol.) 2',3',5',6-tetramethyldiphenylamine-2-carboxylic acid (XXI) and 50 ml. phosphorous oxychloride was refluxed for 90 minutes at 120° (bath temperature) and the excess solvent removed under reduced pressure at 100°. The resulting complex was refluxed with 1:4 hydrochloric acid for two hours, cooled overnight, and filtered to obtain 3.7 g. (79%) of dirty green solid, m.p. 205-218°. Recrystallization from benzene (charcoal) gave, in three crops, a total of 3.4 g. (72%) of XXIII as pale yellow needles, m.p. 219-221°.

1,4,5,8-Tetramethylacridine (XV)

1. From 1,4,5,8-Tetramethylacridine-2-carboxylic acid (XX): 1,4,5,8-Tetramethyl-9-carboxylic acid (XX) (7.8 g., 0.025 mol.) was slowly heated to 200° where carbon dioxide evolution was first noticed.
In order to minimize sublimation of the product the heating was regulated so as to keep the gas coming off slowly. After about 20 minutes the temperature was 240° and no more gas was being evolved. The cooled residue was taken up in chloroform, concentrated to about 50 ml, adsorbed on a short column (1" x 12") of alumina and eluted with Skellysolve B. Evaporation of the solvent from the eluates gave 6.3 g. (95%) of yellow solid, m.p. 186-189°. Recrystallization from Skellysolve B (400 ml.) gave, in two crops, 6.2 g. (94%) of XV as yellow needles, m.p. 187-189°. The infrared spectrum showed 1,2,3,4 substitution absorption at 12.35 (s). The analytical sample, m.p. 188.7-189.2° (corr.), was prepared by recrystallization from Skellysolve B followed by sublimation.

**Anal. Calc'd. for C_{17}H_{17}N:** C, 86.8; H, 7.3; N, 6.0

**Found:** C, 86.7; H, 7.3; N, 6.2

The trinitrobenzene complex of XV was prepared by mixing a hot solution of 1.20 g. (0.0051 mol.) 1,4,5,8-tetramethylacridine in 20 ml. benzene and a hot solution of 1.10 g. (0.0052 mol.) trinitrobenzene in 10 ml. benzene, boiling for five minutes, and cooling. Filtration produced 2.10 g. (92%) of orange needles, m.p. 179-181°. Two recrystallizations from benzene gave the analytical sample, m.p. 180.6-182.0° (corr.)

**Anal. Calc'd. for C_{23}H_{20}N_{4}O_{6}:** C, 61.6; H, 4.5; N, 12.6

**Found:** H, 4.6; N, 12.5

The hydrochloride was prepared by saturating a solution of 0.50 g. (0.0021 mol.) 1,4,5,8-tetramethylacridine (XV) in 100 ml. anhydrous ether with dry hydrogen chloride. Recrystallization from 1 N hydrochloric
acid gave 0.54 g. (93%) of yellow-orange needles, m.p. 290—300°. The analytical sample was prepared by recrystallization from 1 N hydrochloric acid and dried to constant weight under vacuum and over phosphorous pentoxide.

**Anal. Calc'd. for C_{17}H_{18}NCl:**  C, 75.1; H, 6.7; N, 5.2; Cl, 13.1

**Found:**  C, 65.3; H, 6.3; N, 4.6; Cl, 19.7

The hydrobromide was obtained in the same manner as the hydrochloride. Yield, 0.64 g. (96%) of orange needles, m.p. 310-315°. The analytical sample was prepared by recrystallization from 1 N hydrobromic acid.

**Anal. Calc'd. for C_{17}H_{18}NBr:**  C, 64.6; H, 5.7; N, 4.4; Br, 25.3

**Found:**  C, 63.2; H, 5.7; N, 4.8; Br, 26.0

The analyses for these salts were not satisfactory. It is apparent that a satisfactory method of purification is needed.

2. **From 9-chloro-1,4,5,8-tetramethylacridine (XXII):**

   a. **By reduction with Raney Nickel and hydrogen:** A mixture of 3.0 g. (0.011 mol.) 9-chloro-1,4,5,8-tetramethylacridine (XXII) in 50 ml. dry, thiophene-free benzene and 0.62 g. (0.011 mol.) potassium hydroxide in 30 ml. absolute alcohol was shaken with about 2 g. Raney Nickel catalyst under an initial hydrogen pressure of 45 lbs. The theoretical amount of hydrogen was absorbed in one hour. The resulting almost colorless suspension was heated to boiling, filtered, and the catalyst thoroughly washed with hot benzene and hot ethanol. The yellow solid obtained on removal of the solvent was taken up in ether-benzene and worked up in the usual manner to yield 2.5 g. (96%) of yellow solid, m.p. 182—205°. This crude reduction product was suspended
In another run this material was shown to be a mixture of 1,4,5,8-tetramethyl-9,10-dihydroacridine and 1,4,5,8-tetramethylacridan in about a 2:1 ratio as follows: The solid was triturated with hot dilute (1:4) hydrochloric acid and filtered. The filtrate was made alkaline with concentrated ammonium hydroxide and filtered to obtain 1.10 g. (42.4%) of light tan solid, m.p. 180-189°C. This material was triturated with Skellysolve B (100 ml.) and filtered from 0.20 g. (8.4%) of brown solid, m.p. > 300°C. Concentration of the filtrate to about 30 ml. and cooling produced, in two crops, 0.81 g. (31%) of XV as yellow needles, m.p. 187-188°C. The acid insoluble fraction from above 1.45 g. (55%) was a yellow solid, m.p. 221.5-222.0°C (mixed melting point with authentic 1,4,5,8-tetramethylacridone, 190-205°C), that showed no carbonyl band in the infrared at 5.8-6.1 and had a maxima in the ultraviolet at 289 μ, log ε 3.10. This material was 1,4,5,8-tetramethyl-9,10-dihydroacridine.

In 50 ml. of gently refluxing 20% sulfuric acid. While stirring, a hot solution of 1.09 g. (0.0037 mol., 0.011 eq.) potassium dichromate in 13 ml. water was added in two portions 10 minutes apart. After boiling for 30 minutes, a hot solution of 3.0 g. (0.010 mol.) potassium dichromate in 35 ml. water was added. The orange suspension of the dichromate was boiled 15 more minutes, refrigerated overnight and filtered. The orange solid was suspended in 50 ml. hot water, made basic with concentrated ammonium hydroxide, and refrigerated. The tan solid, obtained on filtration, was triturated with 100 ml. of hot dilute hydrochloric acid (1:5), filtered hot, cooled, and made basic with concentrated ammonium hydroxide. The cooled suspension was filtered to yield 2.3 g. (89%) light tan solid, m.p. 175-185°C. This crude product was dissolved in Skellysolve B containing a little chloroform, adsorbed on a short column (1" x 12") of alumina, and eluted with Skellysolve B. The yellow solid obtained on removal of solvent from the eluates, 2.1 g. (81%), m.p. 183-188°C, was recrystallized from Skellysolve B (100 ml.) to yield in two crops, 2.0 g. (76%) of XV as yellow needles, m.p. 188-189°C.
b. Reduction with lithium aluminum hydride: A solution of 2.00 g. (0.0074 mol.) 9-chloro-1,4,5,8-tetramethylacridine XXII in 100 ml. purified tetrahydrofuran was added dropwise over a 30-minute period to a stirred slurry of 2.85 g. (0.075 mol.) lithium aluminum hydride in 50 ml. purified tetrahydrofuran and the mixture refluxed for 20 hours. Fifty ml. of water followed by 200 ml. dilute hydrochloric acid (1:1) was added dropwise to the cooled mixture. The yellow mixture was extracted with three 200 ml. portions of ether-benzene. The combined organic extracts were washed with three 200 ml. portions of water and worked up in the usual manner. Removal of the solvent gave 1.65 g. (94%) tan solid, m.p. 192-217°. This crude acridan was suspended in 25 ml. of hot 20% sulfuric acid with stirring and treated in two portions 15 minutes apart with a hot solution of 2.20 g. (0.075 mol.) potassium dichromate in 15 ml. water was added, the orange mixture boiled for 15 more minutes and refrigerated overnight. The orange dichromate salt, obtained by filtration, was suspended in hot water, treated with concentrated ammonium hydroxide, and refrigerated. The light tan solid was triturated with about 200 ml. hot dilute hydrochloric acid (1:4) and filtered hot. The filtrate was made basic with concentrated ammonium hydroxide and refrigerated. Filtration gave 1.50 g. (86%) light tan solid, m.p. 175-187°. This material was taken up in about 400 ml. hot Skellysolve B containing a little chloroform, adsorbed on a short (1" x 12") column of alumina, and eluted with Skellysolve B. Recrystallization of the yellow solid, obtained by evaporation of the elutes, from Skellysolve B (50 ml.) gave, in two crops, 1.29 g. (74%) of (XV) as yellow needles, m.p.
9-Chloroacridine

The method of Albert and Ritchie\(^\text{18}\) gave an 83\% yield of 9-chloroacridine as pale yellow solid, m.p. 120.5-121.5\(^\circ\), lit.\(^\text{18}\) m.p. 119-120\(^\circ\).

Acridone

A mixture of 12.0 g. (0.056 mol.) 9-chloroacridine and 200 ml. dilute hydrochloric acid (1:1) was refluxed for 3 hours, cooled, and filtered to yield 10.6 g. (97\%) brown solid, m.p. 348-351\(^\circ\). Recrystallization from about 500 ml. glacial acetic acid (charcoal) gave, in two crops 10.0 g. (92\%) of acridone as yellow needles, m.p. 358-362\(^\circ\), lit.\(^\text{19}\) m.p. 348-352\(^\circ\).

Acridine

The method of Albert and Willis\(^\text{20}\) was used to convert 9-chloroacridine to acridine. A yield of 72\% was obtained of acridine as pale yellow needles, m.p. 110-111\(^\circ\), lit.\(^\text{20}\) m.p. 110\(^\circ\).

Di-assym-m-xylidinomethane (XXVI)

A mixture of 24.2 g. (0.20 mol.) 2,4-dimethylaniline, 26.8 g. (0.10 mol.) methylene diiodide, and 29 g. (0.21 mol., 0.42 eq.)
potassium carbonate was heated at 150° (bath temperature) for four hours. The cooled reaction mixture was dissolved in a mixture of ether-benzene and water. After separation of the layers, the aqueous phase was extracted with two 100 ml portions of ether-benzene, and the combined organic layers worked up in the usual manner. Two recrystallizations of the gum from ethanol gave 8.3 g (33%) of (XXVI) as yellow needles, m.p. 125.5-126.5°. The analytical sample was prepared by recrystallization from ethanol, m.p. 126.8-128.2° (corr.), lit. 21 m.p. 127-128°.


Anal. Calc'd. for C_{17}H_{22}N_{2}: C, 80.3; H, 9.0
Found: C, 80.0; H, 9.0

Cholestanol

Commercial cholesterol was reduced by the method of Hershberg 22


to yield 87% of cholestanol as white needles, m.p. 140.0-140.5 (corr.), lit. 22 m.p. 139-142°, lit. 23 m.p. 138-141°.

(23) L. F. Feiser and X. A. Dominguez, ibid., 75, 1704 (1953).

Cholestan-3-one

Cholestanol was oxidized by the method of Feiser and Dominguez 23

to give a 64% yield of cholestan-3-one as white needles, m.p. 128.0-
128.5° (corr.), lit.23 m.p. 127-128°.

2-Bromocholestan-3-one

Cholestan-3-one was brominated according to the method of Feiser and Dominguez23 to give a 51% yield of 2-bromocholestanone as white needles, m.p. 169.0-169.5°, lit.23 m.p. 168-169°.

Reaction of Substituted Pyridines with Boron Trifluoride and Diborane

Heats of reaction of boron trifluoride and diborane with substituted pyridines were crudely measured in the apparatus shown in Fig. 9. Boron trifluoride was obtained from a cylinder, and diborane was generated by the dropwise addition of a solution of sodium borohydride in redistilled diglyme to a solution of boron trifluoride etherate in redistilled diglyme.

The general procedure used was as follows. A solution of 0.002 mol. of the base in 10.0 ml. of sodium-dried, thiophene-free benzene was charged into the reaction tube and a stream of dry nitrogen passed through for exactly five minutes. Boron trifluoride or diborane was then bubbled through the solution for five minutes at a rapid rate. The temperature rise was noted and timed by means of a stopwatch. Finally the system was thoroughly flushed with nitrogen. Two runs were made for each base with each Lewis acid and the results agreed within 0.5° C. The average temperature rise is shown in Table 6. Correction has been made for the temperature effect of the solvent.

Dehydrobromination of 2-Bromocholestan-3-one with 4,5-Dimethylacridine

1. In Dimethylacetamide: A solution of 2.00 g. (0.0044 mol.)
FIG. 10. APPARATUS FOR MEASURING HEATS OF REACTION

To Hg pressure release

To BF₃ or B₂H₆ source

To N₂ source

Mineral Oil

Pyridine

Thermometer

Reaction tube

Safety trap
### TABLE 6

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta T_{\text{HF}_3}, ^\circ C$</th>
<th>$\Delta T_{\text{BH}_3}, ^\circ C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>-0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Pyridine</td>
<td>9.7</td>
<td>5.2</td>
</tr>
<tr>
<td>2,4,6-Collidine</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Acridine</td>
<td>8.3</td>
<td>4.3</td>
</tr>
<tr>
<td>4,5-Dimethylacridine</td>
<td>0.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>1,4,5,8-Tetramethylacridine*</td>
<td>-0.3</td>
<td>-</td>
</tr>
</tbody>
</table>

*Concentration was only 0.001 mol./10 ml. benzene because of solubility problems in benzene.
2-bromocholestan-3-one, 1.00 g. (0.0048 mol.) 4,5-dimethylacridine (I) and 20 ml. redistilled dimethylacetamide (b.p. 163—164°) was refluxed for 30 minutes and solvent removed under reduced pressure at 120° (bath temperature). Ether was added and the orange salt, 0.80 g. (65%), m.p. > 250°, removed by filtration. The filtrate was diluted to about 100 ml. with ether, saturated with dry hydrogen chloride, and the salt removed by filtration. The filtrate was washed with two 25 ml. portions of dilute hydrochloric acid and worked up in the usual manner to yield 1.55 g. (95%) of an orange-yellow oil that solidified on standing. Recrystallization from aqueous ethanol gave 1.19 g. (73%) of a light yellow solid, m.p. 88—93°, $\lambda_{\text{max}}$ (95% EtOH), 237 m$\mu$, log $\epsilon$ 3.91, lit. m.p. 89—93° (crude), m.p. 98-100° (pure), $\lambda_{\text{max}}$ 231, log $\epsilon$ 3.99.


2. In N-Methylpyrrolidone: A solution of 1.98 g. (0.00435 mol.) 2-bromocholestan-3-one, 1.00 g. (0.0048 mol.) 4,5-dimethylacridine (I), and 20 ml. redistilled N-methylpyrrolidone (b.p. 96°/22 mm.) was heated at 170—175° (bath temperature) for 15 minutes and the solvent removed under reduced pressure at 140° (bath temperature). Ether was added and the orange salt, 1.14 g. (94%) removed by filtration. The filtrate was worked up as in (1) above to yield, after recrystallization from aqueous ethanol, 1.11 g. (68%), of tan solid, m.p. 91-94°, $\lambda_{\text{max}}$ (95% EtOH) 236 m$\mu$, log $\epsilon$ 3.82.
SUMMARY

The hindered acridines, 4,5-dimethylacridine (I) and 1,4,5,8-tetramethylacridine (II) were found to form hydrochlorides and hydrobromides as well as trinitrobenzene complexes, but showed no reaction with either boron trifluoride or diborane. Solutions of pyridine, 2,4,6-collidine and acridine in benzene showed significant temperature rises, 8-10° and 4-5° respectively when treated with boron trifluoride or diborane. Solutions of I and II in benzene showed no temperature rise under the same conditions.

3-Methylanthranilic acid was obtained in 34% overall yield in three steps from commercial 2-methylfuran and maleic anhydride.

4,5-Dimethylacridine (I) was synthesized by two routes. 3-Methylanthranilic acid was condensed with o-bromotoluene to give 2',6-dimethyl-diphenylamine-2-carboxylic acid (III) in 76% yield. Cyclization of III with phosphorous oxychloride gave 9-chloro-4,5-dimethylacridine (IV) in 89% yield. Reduction of IV with either Raney Nickel and hydrogen or lithium aluminum hydride followed by oxidation with potassium dichromate and dilute sulfuric acid gave I in 83% and 77% yields respectively. The overall yield of I was 52-56%.

Condensation of N-formyl-o-toluidine with o-bromotoluene followed by hydrolysis with a hydrochloric-acetic acid mixture gave di-o-tolylamine (V) in 38% yield. Condensation of V with oxalyl-chloride gave di-o-tolylxamid acid chloride which was cyclized to 1-o-toly-7-methyl-
isatin (VI) in 92% yield by aluminum chloride. Rearrangement of VI in dilute base gave 4,5-dimethylacridine-9-carboxylic acid (VII) in 99% yield, which was decarboxylated in 87% yield to give I. The overall yield of I was 30%.

2,5-Dimethylaniline was condensed with 1-bromo-2,5-xylene in the presence of metallic potassium to give di-2,5-xylylamine (VIII) in 74% yield. Condensation of VIII with oxalyl chloride gave di-(2,5)-xylyloxamide acid chloride which was cyclized to 1-(2,5)-xylyl-4,7-dimethylisatin (IX) in 96% yield by aluminum chloride. 1,4,5,8-Tetramethylacridine (II) was synthesized from this isatin by two routes.

Rearrangement of IX in dilute base gave 1,4,5,8-tetramethylacridine-9-carboxylic acid (X) in 79% yield which was decarboxylated in 94% yield to give II. The overall yield from 2,5-dimethylaniline was 53%.

Oxidation of IX with alkaline hydrogen peroxide gave 2',3,5',6-tetramethylene-1,4-diphenylamine-2-carboxylic acid (XI) in 92% yield. Cyclization of XI with phosphorus oxychloride afforded 9-chloro-1,4,5,8-tetramethylacridine (XII) in 58% yield along with 1,4,5,8-tetramethylacridone (XIII) in 26% yield. Reduction of XII either with Raney Nickel and hydrogen or lithium aluminum hydride followed by oxidation with potassium dichromate and dilute sulfuric acid gave II in 76% and 74% yields respectively. The overall yield from 2,5-dimethylaniline was 28%.

Treatment of 2-bromocholestan-3-one with 4,5-dimethylacridine in refluxing dimethylacetamide or in N-methylpyrrolidone at 170-175° gave 65% and 94% yields of 4,5-dimethylacridine hydrobromide. In each case, about 70% crude △-cholesten-3-one was isolated.
SUGGESTIONS FOR FUTURE WORK

During the course of this investigation several points of interest for future work arose.

1. Development of methods for measuring the small differences in steric effect between a t-butyl group and a methyl group on a benzene ring. Small differences in basicity cannot be easily measured by reaction with protonic acids. Further, since no reaction occurs between 2,6-di-t-butylpyridine or 4,5-dimethylacridine and Lewis acids such as boron trifluoride, no comparative measurements can be made. The measurement of equilibrium constants for the interaction of suitably substituted pyridine bases with phenol may be one method.\(^1\) The value for 2,6-di-t— butylpyridine has already been determined.

Another method might be kinetic studies of rates of esterification or rates of hydrolysis of the esters of the following acids:

\(\text{CH}_3\)
\(\text{CH}_3\)
\(\text{COO}^-\)
\(\text{COO}^-\)

\(\text{COOH}\)
\(\text{COOH}\)

---

2. Syntheses of the dibenzacridines shown below to extend the hypothesis developed in the present work.

![Dibenzoacridine structures]

3. Development of a suitable synthesis for substituted diphenylamines in high yields.

4. Additional studies on reducing acridones or 9-chloroacridines directly to the acridine ring system without over reduction. Theoretical quantities of lithium aluminum hydride might work well.
I, Warren Howard Powell, was born in North Collins, New York, on January 1, 1934. I received my secondary school education at Bemus Point Central School, Bemus Point, New York, and Johnson City High School, Johnson City, New York. My undergraduate training was obtained at Antioch College, Yellow Springs, Ohio, which granted me a Bachelor of Science in Chemistry degree in June, 1955. In September, 1955, I entered the graduate school of The Ohio State University and while completing the requirements for the degree Doctor of Philosophy, I held the following positions: Assistant (1955-57); Assistant Instructor (1957-58); Instructor (Fall Quarter, 1958); Research Fellow (Summer Quarters 1957 and 1958) in the Department of Chemistry; and Research Fellow supported by a grant from the Office of Ordnance Research, U. S. Army (1959).