SYNTHESIS AND SELECTIVITY OF SCHMIDT REACTIONS OF DISUBSTITUTED TEREPTHALIC AND ISOPTHALIC ACIDS

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By
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*****
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This work is dedicated to the author's sons, David Ward and Paul
Jonathon, and to the future they deserve.
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I. INTRODUCTION

Reaction of hydrazoic acid with a carboxylic acid in the presence of concentrated sulfuric acid (the Schmidt reaction) yields the corresponding amine, carbon dioxide, and nitrogen (Equation 1). Sulfuric acid is usually used as the catalyst; it frequently serves also as the solvent.

\[
R\text{-CO}_2\text{H} + \text{HN}_3 \xrightarrow{\text{H}_2\text{SO}_4} R\text{-NH}_2 + \text{CO}_2 + \text{N}_2
\]  

(Mono-substituted benzenedicarboxylic acids in which the substituent is adjacent to one of the carboxyl groups undergo highly selective reactions with one equivalent of hydrazoic acid. In general the more sterically-hindered carboxyl group (the one adjacent to the substituent) is converted to an amine. Thus 3-substituted phthalic acids or their anhydrides in sulfuric acid react to give 3-substituted anthranilic acids (Equation 2). Reactions of 2- or 2,6-disubstituted terephthalic acids

\[
\begin{align*}
\text{OC-O} & \quad \xrightarrow{\text{HN}_3} \quad \text{CO}_2\text{H} \\
\text{CO} & \quad \text{NH}_2 \\
\text{G} & \quad + \text{N}_2 + \text{CO}_2
\end{align*}
\]

(Equation 3),

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \xrightarrow{\text{HN}_3} \quad \text{NH}_2 \\
\text{CO}_2\text{H} & \quad + \text{N}_2 + \text{CO}_2
\end{align*}
\]
and of 4-substituted isophthalic acids (Equation 4) also result in selective replacement of the hindered carboxyl groups.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{HN}_3 \\
\text{CO}_2\text{H} & \quad \text{H}_2\text{SO}_4 \\
\text{CO}_2\text{H} & \quad \text{N}_2 + \text{CO}_2
\end{align*}
\]

Reactions of hydrazoic acids with 2,5-disubstituted terephthalic acids and 4,6-disubstituted isophthalic acids, in which each carboxyl group is assisted by different substituents, might supply information about relative proximity and electrical effects of vicinal groups in the Schmidt reaction. To study these factors, syntheses and reactions of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids with hydrazoic acid were investigated. The course of the Schmidt reaction on each dicarboxylic acid was determined by isolation and identification of the products. An analysis has been made of possible factors which control the selectivity of reaction of the acids in the present study.
II. HISTORICAL

The Schmidt Reaction of Carboxylic Acids

The reaction between carbonyl compounds and hydrazoic acid in strong mineral acid is known as the Schmidt reaction (1,2).


The Schmidt reaction of carboxylic acids in strong mineral acid (Equations 5 and 6)

\[ R-CO_2H + HN_3 \rightarrow RNCO + N_2 \]  \hspace{1cm} (5)

\[ RNCO + H_2O \rightarrow RNH_2 + CO_2 \]  \hspace{1cm} (6)

yields amines having one less carbon atom, carbon dioxide and nitrogen; a presumed intermediate is the isocyanate which is subsequently hydrolyzed in the aqueous medium. Confirmation that isocyanates are probable intermediates was obtained when 4-phenanthryl isocyanate was isolated in 95 per cent yield from reaction of 4-phenanthrene-carboxylic acid with hydrazoic acid (50/50 trifluoroacetic acid-trifluoroacetic anhydride was used as solvent, no mineral acid or water being present) (3). Earlier,

Coronna had isolated isatoic anhydride as one of the products of reaction of phthalic anhydride with hydrazoic acid (4).

(4) G. Coronna, Gazz. chim. ital., 71, 189 (1941); C.A., 36, 3173 (1942).

A summary of the Schmidt reaction encompassing other carbonyl molecules which react with hydrazoic acid is given by Wolff (5).


Several investigators have proposed mechanisms for Schmidt reactions of aldehydes, ketones and carboxylic acids. Schmidt (6)

(6) K. F. Schmidt, Ber., 58, 2413 (1925).

suggested that imine, NH, and nitrogen are produced in cleavage of hydrazoic acid by a strong mineral acid; imine subsequently adds to the carbonyl group of aldehydes and ketones. Oliveri-Mandala criticized this proposal and postulated addition of hydrazoic acid to the carbonyl group of an aldehyde or ketone, followed by loss of nitrogen to give an unstable imino derivative, which undergoes a rearrangement of the Beckmann-type to yield amides (Equation 7), (7).

\[
\begin{align*}
R_2C = O + HN_3 & \rightarrow R-\overset{0^-}{N-H}^+ \rightarrow R-\overset{0^-}{N-N_2^+} \rightarrow R-\overset{0^-}{N-N_2} + N_2 \\
R-\overset{0^-}{C-N-N_2^+} & \rightarrow R-\overset{0^-}{C-N-R} + N_2 \\
\end{align*}
\]

Hurd extended this mechanism to carboxylic acids and proposed activation of hydrazoic acid by concentrated sulfuric acid (Equation 8):

\[
\text{H-} + \overset{\ddots}{\text{N}} = \overset{\ddots}{N} = \overset{\ddots}{N}_2 \overset{\ddots}{\text{H}} \overset{\ddots}{\text{N}} \rightarrow \text{H} + \overset{\ddots}{N} = \overset{\ddots}{N}_2
\]  

(8)

---


---

Reaction of "activated" hydrazoic acid with a carboxyl group and subsequent rearrangement with loss of nitrogen yields the carbamic acid (Equations 9, 10 and 11). Decomposition of the carbamic acid gives the amine and carbon dioxide.

\[
\begin{align*}
\text{R-C-OH} + \overset{\ddots}{\text{H}} \overset{\ddots}{\text{N}} = \overset{\ddots}{\text{N}}_2 & \rightarrow \left[ \begin{array}{c} \overset{\ddots}{\text{O}} \overset{\ddots}{\text{H}} + \\ \text{R-C-N-N=Ns} \end{array} \right] \\
\left[ \begin{array}{c} \overset{\ddots}{\text{O}} \overset{\ddots}{\text{H}} + \\ \text{R-C-N=N=Ns} \end{array} \right] & \rightarrow \left[ \begin{array}{c} \overset{\ddots}{\text{O}} \overset{\ddots}{\text{H}} + \\ \text{R-C-N+} \end{array} \right] + \overset{\ddots}{\text{N}}_2
\end{align*}
\]

(9)

(10)

(11)

Evidence for a linear structure for the azide ion was obtained by X-ray data (9) and confirmed by Raman spectra (10). The following resonance-hybrid was proposed for the azide ion (7):

\[
\overset{\ddots}{\text{N}} + \overset{\ddots}{\text{O}} \overset{\ddots}{\text{H}} \overset{\ddots}{\text{N}} \overset{\ddots}{\text{N}} \overset{\ddots}{\text{N}} \overset{\ddots}{\text{N}} = \overset{\ddots}{\text{N}} + \overset{\ddots}{\text{N}} \overset{\ddots}{\text{N}} \overset{\ddots}{\text{N}}
\]

(12)

---


The structure of methyl azide was subsequently determined (11) by


electron diffraction. The important contributing resonance structures that were suggested for hydrazoic acid are:

\[ \overset{+}{\text{N}} = \overset{-}{\text{N}} = \overset{+}{\text{N}} \quad \overset{-}{\text{N}} = \overset{+}{\text{N}} \equiv \overset{+}{\text{N}} \]

Bond parameters in methyl azide are (9):

\[ \text{H}_3\text{C} \quad 1.47\text{Å} \quad 1.26\text{Å} \quad 1.10\text{Å} \]

Hurd's proposal of "activated" hydrazoic acid is thus redundant, since the structures are identical with those suggested for the two most important resonance contributions.

Briggs and Lyttleton (12) conducted a qualitative rate study of


Schmidt reactions of benzoic acid and various substituted benzoic acids. The half-times of reaction indicate the rates are approximately in the reverse order of the ionization constants of the carboxylic acids in water. The order of decreasing rate of reaction of the meta-substituted acids was -CH₃ > -H > -OC₂H₅ > -OCH₃ > -OH > -Br > -Cl > -I > -CO₂H > -CN > -NO₂; the order of acid strengths is -NO₂ > -CO₂H > -CN > -Br > -Cl > -I > -OH > -OCH₃ > -OC₂H₅ > -H > -CH₃. The results of this
investigation were greatly subject to experimental errors however.

The mechanism proposed by Briggs and Lyttleton (12) is similar to that of Hurd (8). The rate determining step involves evolution of nitrogen and was pictured as follows (Equation 14):

\[
\begin{align*}
\text{R} + &\quad \begin{array}{c}
\text{H-O-C-} \text{N-N}^+\\
\text{O}^-
\end{array} \\
\rightarrow &\quad \begin{array}{c}
\text{H-O-C-} \text{N}^+\\
\text{O}^-
\end{array} + \text{N}_2
\end{align*}
\]

(14)

In this representation the positive charge on the central nitrogen atom is neutralized by transfer of an electron pair from the rest of the molecule. If R is nucleophilic, rearrangement should be facilitated and nitrogen evolution will be rapid; conversely, if R is electrophilic, the rate of evolution of nitrogen will be relatively slower.

The nitro group is strongly electrophilic; in the ortho position, however, it led to a relatively rapid reaction. Briggs and Lyttleton suggested that acceleration by the nitro group may occur as indicated (Equation 15):

\[
\begin{align*}
\text{HO-C-} \text{N-N}^+ \\
\rightarrow &\quad \begin{array}{c}
\text{HO-C-} \text{N}^+ \\
\text{N}^-
\end{array} + \text{N}_2
\end{align*}
\]

(15)

Newman and Gildenhorn found that reaction of 2,6-dimethylterephthalic acid with hydrazoic acid gave 4-amino-3,5-dimethylbenzoic acid exclusively (13). This observation led them to postulate a

\[
\begin{align*}
\text{HO-C-} \text{N-N}^+ \\
\rightarrow &\quad \begin{array}{c}
\text{HO-C-} \text{N}^+ \\
\text{N}^-
\end{array} + \text{N}_2
\end{align*}
\]

mechanism involving acid catalysis and formation of oxocarbonium ions. Initial protonation of the carboxyl group occurs to give the hydroxy-carbonium ion which is dehydrated by the sulfuric acid to the oxocarbonium ion. This view has strong support in the observation that similar hindered benzenecarboxylic acids have "$i$" values greater than 2 (14),

\[ \text{Equations 16 and 17} \]

\[ \text{Equations 18, 19, and 20} \]

In this mechanism, the migrating R-group carries its pair of bonding electrons to the electron deficient nitrogen atom resulting from loss of nitrogen; subsequent reaction with the hydroxylic solvent leads to
the amine. It was suggested that dihydroxycarhonium ions might also react with hydrazoic acid (Equations 21, 22 and 23).

\[
\begin{align*}
R-\overset{+}{C-CH} + \overset{+}{N-N_2} & \rightarrow R-\overset{+}{C-N-N_2} \quad (21) \\
&\quad \text{OH} \quad \text{OH} \\
\text{OH-}\overset{+}{C-N-N_2} & \rightarrow R-\overset{+}{N-C} + \overset{+}{OH} + N_2 \quad (22) \\
&\quad \text{OH} \quad \text{OH} \\
R-\overset{+}{N-C} + \overset{-}{\text{H}_2\text{O}} & \rightarrow R\text{NH}_3 + \text{CO}_2 \quad (23) \\
&\quad \text{OH} \\
\end{align*}
\]

Oxocarbonium ions were believed, however, to be more reactive than dihydroxycarhonium ions.

Selectivity of Schmidt Reactions of Substituted Aromatic Acids

Barkemeyer (15) repeated work by Caronna (16) on the Schmidt reaction of 3-nitrophthalic acid in sulfuric acid and confirmed that reaction occurred exclusively at the internal carboxyl group. Barkemeyer (15) and Moritsugu (17) determined the selectivity of


\(16\) G. Caronna, Gazz. chim. ital., 71, 475 (1941); C. A., 37, 118 (1943).

\(17\) T. Moritsugu, unpublished results.
Schmidt reactions of other phthalic acid derivatives with various electronegative and electropositive substituents in the 3-position. The only product isolated in each case was that derived by reaction of the relatively hindered (internal) carbonyl group (Equation 24).

\[
\begin{align*}
\text{G} = -\text{OH}, -\text{OCH}_3, -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{F}, -\text{Cl}, -\text{Br}, -\text{I}, -\text{CO}_2\text{H}, -\text{NO}_2
\end{align*}
\]

The product isolated from the reaction of 3-hydroxyphthalic anhydride was 2-oxo-4-benzoxazolinecarboxylic acid.

The study indicated that the electrical effects of the 3-substituent play a minor role in directing reaction at the hindered carboxyl group. Barkemeyer also showed that the presence of an amine group (presumably as the ammonium ion in sulfuric acid) prevented Schmidt reaction of 3-aminophthalic acid, anthranilic acid and m-aminobenzoic acid in 95.5% sulfuric acid at 45-50° (15). Therefore the electrical nature of a powerful electron-withdrawing group does become important in affecting Schmidt reactions in systems in which there is steric assistance.

Moritsugu subsequently found that 2,6-dibromoterephthalic and 2,6-dinitrotetraphthalic acids reacted selectively to give 4-amino-3,5-dibromobenzoic (90.7% yield) and 4-amino-3,5-dinitrobenzoic
(59.2% yield) acids, respectively (18). From the latter acid, 2,6-dinitro-

---


Moritsugu also studied the reactions of 2-substituted terephthalic acids and 4-substituted isophthalic acids with one equivalent of hydrazoic acid in concentrated sulfuric acid (18). In each case the carboxyl group in the hindered position reacted exclusively (Equations 25 and 26).

\[
\begin{align*}
\text{G} & = -\text{OCH}_3, -\text{CH}_3, -\text{C(CH}_3)_3, -\text{I}, -\text{Br}, -\text{F}, -\text{NO}_2 \\
\end{align*}
\]

The electrical effects of substituents on the Schmidt reaction in the absence of changing steric effects were determined from the product ratios in reactions of various 4-substituted phthalic acids (18) (Equation 27). The ortho-para-directing groups, -OCH$_3$, and -F, allowed reaction only at the carboxyl group (I) para to the substituent.
The meta-directing groups, -NO₂ and -CO₂H, gave replacement only of the meta-carboxyl group (II). Mixed isomers were obtained from compounds with -Br, -CH₃, and -C(CH₃)₃ substituents; preferential attack occurred at the para-carboxyl group however.

Tetrachlorophthalic anhydride, 1,2-naphthalic and 1,6-naphthalic acids were found to react with hydrazoic acid (17) (Equations 28, 29 and 30), contrary to an earlier report that the first two compounds were unreactive (19), presumably because of steric hindrance (20).

(19) G. Caronna, Gazz. chim. ital., 71, 475 (1941).

It was necessary to use fuming sulfuric acid to dissolve tetrachlorophthalic anhydride. Both 1,2- and 1,6-naphthalic acids gave reaction at the more sterically hindered -carboxyl group. These results thus
extended the concept of an activating proximity effect to substituted polynuclear aromatic acids.

The use of fuming sulfuric acid as a solvent permits the reaction of hydrazoic acid with otherwise resistant aromatic amino acids and most quinolinecarboxylic acids (Equation 31, Table 1). Reactions of
Table I
Schmidt Reactions of Quinolinecarboxylic Acids

<table>
<thead>
<tr>
<th>Position of Carboxyl Group</th>
<th>Yield %</th>
<th>Time of Reaction (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>trace</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>86.4</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>90.9</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>98.2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>90.4</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>91.2</td>
<td>4</td>
</tr>
</tbody>
</table>

4-aminoisophthalic (Equation 32) and 2-aminoterephthalic (Equation 33) acids gave 2,5-diamino- and 2,4-diaminobenzoic acids in 87.9 and 82.0 per cent yields, respectively.

\[
\text{Equation 32:} \quad \begin{array}{c}
\text{CO}_2\text{H} \\
\text{H} \\
\text{N}_3 \\
\text{H}_2\text{SO}_4(30\%\text{SO}_3) \\
\text{CO}_2\text{H}
\end{array} \quad \xrightarrow{\text{HN}_3} \quad \begin{array}{c}
\text{NH}_2 \\
\text{N}_3 \\
\text{H}_2\text{SO}_4(30\%\text{SO}_3) \\
\text{NH}_2 \\
\text{CO}_2\text{H}
\end{array}
\]

\[
\text{Equation 33:} \quad \begin{array}{c}
\text{CO}_2\text{H} \\
\text{NH}_2 \\
\text{H}_2\text{SO}_4(30\%\text{SO}_3) \\
\text{NH}_2 \\
\text{CO}_2\text{H}
\end{array} \quad \xrightarrow{\text{HN}_3} \quad \begin{array}{c}
\text{NH}_2 \\
\text{NH}_2 \\
\text{NH}_2 \\
\text{NH}_2
\end{array}
\]
These represent the first and only examples of selective competitive reaction at less hindered carboxyl groups.

The equilibria for reactions of amino acids with sulfuric acid are probably greatly in favor of the positively charged ammonium species; the presence of this group with a positive charge should decrease the ionization of a carboxyl group adjacent to the dihydroxy or oxocarbonium ions. In view of this, it is interesting to find that anthranilic and several substituted-anthranilic acids will react with hydrazoic acid in fuming sulfuric acid to give \( \alpha \)-phenylenediamines (Equations 34, 35, and 36) (16).

\[ \text{CO}_2\text{H} \quad \text{NH}_2 \quad \text{HN}_3 \quad \text{H}_2\text{SO}_4(30\% \text{ SO}_3) \quad \text{NH}_2\text{NH}_2 \]  

Equation 34

\[ \text{CO}_2\text{H} \quad \text{NH}_2 \quad \text{CH}_3 \quad \text{HN}_3 \quad \text{H}_2\text{SO}_4(30\% \text{ SO}_3) \quad \text{NH}_2\text{NH}_2 \quad \text{CH}_3 \]  

Equation 35

\[ \text{CO}_2\text{H} \quad \text{NH}_2 \quad \text{N(CH}_3)_3\text{C} \quad \text{HN}_3 \quad \text{H}_2\text{SO}_4(30\% \text{ SO}_3) \quad \text{NH}_2\text{NH}_2 \quad \text{N(CH}_3)_3\text{C} \]  

Equation 36
The reactivities of aromatic and aliphatic carboxylic acids appear to be of similar magnitude. Homoterephthalic acid reacts with hydrazoic acid to give a 91.7 per cent yield of two isomeric amino acids (17), the composition of which is approximately 25 per cent \( p \)-aminophenylacetic acid (I) and 61 per cent 4-(aminomethyl)-benzoic acid (II) (Equation 37).

![Chemical structure of I and II](attachment:image.png)

**Equation 37**

\[
\begin{align*}
\text{CO}_2\text{H} & \text{HN}_3 \\
\text{H}_2\text{SO}_4 & \rightarrow \\
\text{NH}_2 & \text{CO}_2\text{H} + \\
\text{CH}_2 & \text{CO}_2\text{H} \quad I \\
\text{CH}_2 & \text{NH}_2 \quad II
\end{align*}
\]

**Kinetics and Mechanism of Schmidt Reactions of Substituted Benzoic Acids**

The kinetics of reaction of benzoic and \( p \)-toluic acids with hydrazoic acid were first investigated by Bak (21); the second-order rate constants (95.4 per cent sulfuric acid, \( 25^\circ \), \( c = 0.05 \text{ M} \)) are \( 0.188 \times 10^{-3} \text{ l./mole-sec.} \) (0.0119 l./mole-min.) and \( 0.371 \times 10^{-3} \text{ l./mole-sec.} \) (0.0223 l./mole-min.) respectively. Bak concluded that the reaction must have a "comparatively great negative rho value" if the Hammett equation is followed. He did not determine the kinetics of Schmidt reactions of other acids.

\[\text{(21)} \quad \text{T. Bak, Acta. Chem. Scand., 8, 1733 (1954).}\]
Recently, a spectrophotometric study of the kinetics of reaction of benzoic and 26 substituted benzoic acids with hydrazoic acid in sulfuric acid was completed (22). Relative rates and activation parameters which were obtained are summarized in Table II. The reactions

\[ k_2 = \frac{k'_i}{K_T} \left( 1 + \frac{h_o}{K} + \frac{c_o}{K_T} \right) \left( 1 + \frac{h_o}{K_2} + \frac{h_o h_+}{K_2 K_3} \right) \]  

The correlation equation incorporates the high degree of protonation of hydrazoic acid (21) and the relatively low concentration of oxocarbonium ion; \( k'_i \) is the rate constant for reaction of unprotonated hydrazoic acid with oxocarbonium ion; \( K' \) is the hydrolysis constant for reaction of oxocarbonium ion with water to give unprotonated

\[ \text{(22) M. E. D. Hillman, Ph. D. dissertation, The Ohio State University, 1958.} \]

\[ \text{(23) N. C. Deno, J. Jaruzelski and A. Schriesheim, J. Am. Chem. Soc., 77, 3044 (1955).} \]
Table II
Relative Rates and Activation Parameters for Reaction of Hydrazoic Acid with Substituted Benzoic Acids in 96 per cent Sulfuric Acid (22).

<table>
<thead>
<tr>
<th>Acid</th>
<th>Relative Rates (0°)</th>
<th>$\Delta H^\ddagger$ kcal/mole</th>
<th>$\Delta S^\ddagger$ E.u.</th>
<th>$\Delta F^\ddagger$ kcal/mole (30°)</th>
<th>$\Delta E_a$ kcal/mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic</td>
<td>1</td>
<td>21.7</td>
<td>-2.37</td>
<td>22.5</td>
<td>22.3</td>
</tr>
<tr>
<td>o-Toluic</td>
<td>300</td>
<td>19.2</td>
<td>-0.25</td>
<td>19.3</td>
<td>19.6</td>
</tr>
<tr>
<td>o-Ethylbenzoic</td>
<td>753</td>
<td>17.7</td>
<td>-3.95</td>
<td>18.9</td>
<td>18.3</td>
</tr>
<tr>
<td>o-Isopropylbenzoic</td>
<td>2,260</td>
<td>17.0</td>
<td>-4.28</td>
<td>18.3</td>
<td>17.6</td>
</tr>
<tr>
<td>o-Tert-Butylbenzoic</td>
<td>15,900</td>
<td>16.9</td>
<td>0.72</td>
<td>17.2</td>
<td>17.5</td>
</tr>
<tr>
<td>2,5-Dimethylbenzoic</td>
<td>388</td>
<td>18.6</td>
<td>-2.03</td>
<td>19.2</td>
<td>19.2</td>
</tr>
<tr>
<td>2,4-Dimethylbenzoic</td>
<td>358</td>
<td>18.6</td>
<td>-2.07</td>
<td>19.3</td>
<td>19.2</td>
</tr>
<tr>
<td>2,3-Dimethylbenzoic</td>
<td>2,310</td>
<td>16.7</td>
<td>-5.41</td>
<td>18.3</td>
<td>17.3</td>
</tr>
<tr>
<td>2,6-Dimethylbenzoic</td>
<td>28,800</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>2,4,6-Trimethylbenzoic</td>
<td>117,000</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>o-Fluorobenzoic</td>
<td>0.659</td>
<td>22.8</td>
<td>+0.82</td>
<td>22.6</td>
<td>23.4</td>
</tr>
<tr>
<td>o-Chlorobenzoic</td>
<td>28.8</td>
<td>21.2</td>
<td>+2.63</td>
<td>20.5</td>
<td>21.9</td>
</tr>
<tr>
<td>o-Bromobenzoic</td>
<td>60.2</td>
<td>20.9</td>
<td>+2.76</td>
<td>20.1</td>
<td>21.5</td>
</tr>
<tr>
<td>o-Iodobenzoic</td>
<td>295</td>
<td>19.0</td>
<td>-0.95</td>
<td>19.3</td>
<td>19.6</td>
</tr>
<tr>
<td>o-Nitrobenzoic</td>
<td>5.94</td>
<td>19.8</td>
<td>-6.03</td>
<td>21.6</td>
<td>20.4</td>
</tr>
<tr>
<td>Phthalic Anhydride</td>
<td>0.222</td>
<td>23.1</td>
<td>-0.75</td>
<td>23.3</td>
<td>23.7</td>
</tr>
<tr>
<td>m-Toluic</td>
<td>1.73</td>
<td>21.3</td>
<td>-2.79</td>
<td>22.2</td>
<td>21.9</td>
</tr>
<tr>
<td>p-Toluic</td>
<td>1.55</td>
<td>21.5</td>
<td>-2.20</td>
<td>22.2</td>
<td>22.2</td>
</tr>
<tr>
<td>m-Tert-Butylbenzoic</td>
<td>2.17</td>
<td>20.9</td>
<td>-3.76</td>
<td>22.1</td>
<td>21.5</td>
</tr>
<tr>
<td>p-Tert-Butylbenzoic</td>
<td>1.60</td>
<td>21.7</td>
<td>-1.60</td>
<td>22.2</td>
<td>22.3</td>
</tr>
<tr>
<td>m-Fluorobenzoic</td>
<td>0.220</td>
<td>22.2</td>
<td>-3.87</td>
<td>23.3</td>
<td>22.7</td>
</tr>
<tr>
<td>p-Fluorobenzoic</td>
<td>0.399</td>
<td>22.8</td>
<td>-0.18</td>
<td>22.9</td>
<td>23.4</td>
</tr>
<tr>
<td>m-Chlorobenzoic</td>
<td>0.220</td>
<td>22.5</td>
<td>-2.70</td>
<td>23.3</td>
<td>23.1</td>
</tr>
<tr>
<td>p-Chlorobenzoic</td>
<td>0.407</td>
<td>22.7</td>
<td>-0.47</td>
<td>22.9</td>
<td>23.3</td>
</tr>
<tr>
<td>m-Bromobenzoic</td>
<td>0.197</td>
<td>23.3</td>
<td>-0.09</td>
<td>23.3</td>
<td>23.9</td>
</tr>
<tr>
<td>m-Methoxybenzoic</td>
<td>0.252</td>
<td>23.4</td>
<td>+0.92</td>
<td>23.1</td>
<td>24.0</td>
</tr>
</tbody>
</table>

carboxylic acid; $h/K$ is the ratio of dihydroxycarbonium ion to unprotonated carboxylic acid; $c/K$ is the ratio of oxocarbonium ion to unprotonated carboxylic acid ($c$ is related to $C_0$ by $C_0 = - \log c$); $h_h/K_2$ is the ratio of protonated to unprotonated hydrazoic acid; $h_hK_2K_3$ is
the ratio of diprotonated to unprotonated hydrazoic acid; $pK'$

$$\text{(RC(OH)}_2^+ \rightleftharpoons \text{RCO}_2\text{H} + \text{H}^+)$$

for \(\alpha\)-toluic acid is assumed to be -7.6.

The conclusions from the \(C_o\) correlation were that only unprotonated hydrazoic acid undergoes appreciable Schmidt reaction and reaction of \(\alpha\)-toluic acid proceeds by way of the oxocarbonium ion.

The kinetic results for \(\alpha\)-substituted benzoic acids show a striking proximity effect which must be due primarily to steric acceleration and enhancement by electron donation; only fluorine gave a minor deceleration (Table II) (22). The greater reactivity of 2,3-dimethylbenzoic acid than of 2,5-dimethylbenzoic acid appears to come from buttressing effects. Benzoic acids containing 2,6-dimethyl groups were even more reactive than \(\alpha\)-tert-butylbenzoic acid.

The kinetic results for \(m\)- and \(p\)-substituted benzoic acids show acceleration by electron-donating and deceleration by electron-withdrawing substituents. The results were correlated by the Hammett equation: $\rho = -1.773$ for \(m\)-substituents (expecting \(m\)-methoxy which is probably highly protonated), and $\rho = -1.538$ when both \(m\)- and \(p\)-substituents are included.

Three linear relationships between the enthalpies and entropies of activation were found (Equation 39) (24).

$$\Delta H^\ddagger = \Delta H_o^\ddagger + \beta \Delta S^\ddagger$$  \hspace{1cm} (39)


In the equation presented by Leffler, the constant $\beta$ (the slope of a linear plot of $\Delta H^\ddagger$ and $\Delta S^\ddagger$) is called the isokinetic temperature and represents the theoretical temperature at which all the substituted benzoic acids (falling on a line of slope $\beta$) would have the same rate constants for the Schmidt reaction.
Fairly parallel lines correlated (1) m-halobenzoic acids (larger enthalpies than benzoic acid), (2) other m- and all p-substituted benzoic acids (enthalpies similar to benzoic acid) and (3) o-substituted benzoic acids (enthalpies less than benzoic acid) with the exception of o-nitro, o-fluoro (fall on the m, p-line) and o-tert-butylbenzoic acids (falls below the ortho-line). The linear relationship of each isokinetic line implies a similar mechanism for all compounds in each correlation (24). The separation of the data into three linear correlations was interpreted on the basis of dihydroxycarbonium ions as ground states. Thus an ortho-substituent interferes with resonance in the ground state giving it an energy closer to that of the transition state than that of the meta and para-substituted aryldihydroxy carbonium ions. The meta-halo substituents are believed to have greater quantities of unprotonated carboxylic acid at equilibrium and this is reflected in a lower energy content of the ground state giving these compounds high enthalpies of activation.

Overall consideration of various aspects of the kinetic investigation lead to the belief that the rate-determining step in the Schmidt reaction of aromatic carboxylic acids is decomposition of protonated benzanide (22), perhaps with some participation of the aryl nucleus as modified by various substituent groups; electron-donating groups in general assist and electron-withdrawing groups (except as ortho-substituents) slow decomposition and migration.
III. THE PRESENT INVESTIGATION

The present investigation is a study of the syntheses and the selectivities of reaction of nine 2,5-disubstituted terephthalic acids and three 4,6-disubstituted isophthalic acids with hydrazoic acid in sulfuric acid (the Schmidt reaction). A discussion of specific syntheses for the acids that were prepared is first presented which includes new methods or modified and improved procedures followed by a summary and discussion of the data obtained from Schmidt reactions of these acids.

The Synthesis of 2,5-Disubstituted Terephthalic and 4,6-Disubstituted Isophthalic Acids

There are few existing published preparations of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids in which the substituents are not identical (25).

(25) Methods published for synthesis of disubstituted terephthalic and isophthalic acids or of intermediates of possible advantage to the present investigation are: (a) 2-amino-5-nitroterephthalic acid (6 steps) from dimethyl terephthalate, H. Kaufmann and L. Weissell, Ann., 393, 1 (1912); (b) 2-bromo-5-nitroterephthalic acid from p-toluidine (5 steps), A. Claus and J. Hubabny, Ann., 265, 367 (1891), and from 2-bromo-p-xylene (3 steps), H. Schindhelm, German Patent 512,228, C. A., 25, 970 (1931); also U.S. Patent 1,832,247, C. A., 26, 855 (1932); (c) 2-bromo-5-methoxy-terephthalic acid (4 steps from p-xylene, A. Marsin, J. prakt. Chem., 138, 103 (1933); (d) 2-bromo-5-chloroterephthalic acid (3 steps) from p-xylene, C. Willgerodt and R. Wolfien, J. prakt. Chem., II, 59, 410 (1889), and from p-cymene, G. Plancher, Gazz. chim. ital. 23II, 71 (1893); (e) 4-acetamido-6-nitroisophthalic acid (4 steps) from 2,4-dimethylaniline, R. Maltese and G. Errera, Gazz. Chim. Ital. 33II, 385 (1903); (f) 4-methoxy-6-nitroisophthalic acid (4 steps) from 2,4-dimethylaniline, R. Maltese, Gazz. Chim. Ital., 37III, 284 (1907); and (g) 4-chloro-6-nitroisophthalic acid (4 steps) from m-xylene, H. C. Beyerman and G. L. G. Wielart, Rec. trav. chim., 71, 1215 (1952).
At the beginning of this investigation it was believed that these desired dibasic acids would not be difficult to prepare and it was anticipated that the major portion of the research would be spent on studies of the Schmidt reaction. This objective was modified when it became apparent that the synthesis of pure disubstituted terephthalic and isophthalic acids in reasonable quantities was a difficult task. It should be explained that most of the procedures which follow are original syntheses or greatly improved modifications of those in the literature.

In this investigation 2-bromo-5-nitroterephthalic acid was first prepared by decomposition of the diazonium bromide of 2-amino-5-nitroterephthalic acid in the presence of copper. The method was unsatisfactory since the overall yield of dimethyl 2-amino-5-nitroterephthalate (Figure 1, Structure VI) was only 17.7 per cent and the diazotization of 2-amino-5-nitroterephthalic acid is difficult because of its insolubility in hydrobromic acid. 2-Amino-5-nitroterephthalic acid, a potential advantageous intermediate for synthesis of various disubstituted terephthalic acids, was also difficult to prepare in large quantities because nitration of dimethyl 2-acetamidoterephthalate (Figure 1, Structure IV) gives both the 3-nitro and 5-nitro derivatives.

A much more direct synthesis of 2-bromo-5-nitroterephthalic acid was accomplished by nitrating 2-bromoterephthalic acid (26). This

---

(26) This method was mentioned in a patent (footnote 25b); however, no experimental details were included. It was found upon experimentation that slow addition of an exactly equivalent amount of conc. nitric acid (dinitration resulted if an excess was used) to a hot sulfuric acid solution of 2-bromoterephthalic acid produced excellent results.
FIGURE 1. INITIAL ROUTE FOR SYNTHESIS OF 2-SUBSTITUTED 5-NITROTEREPHTHALIC ACIDS
Figure 2. Synthesis of 2-substituted-5-nitroterephthalic acids
method was found to be applicable to other terephthalic acids having an ortho-para-directing substituent in the 2-position. 2-Chloro-5-nitrotetraphthalic acid, 2-methyl-5-nitrotetraphthalic acid and 2-methoxy-5-nitrotetraphthalic acid were thus prepared by nitration of the appropriate substituted terephthalic acid (Figure 2).

A specific improvement in preparing 2-bromotetraphthalic and 2-chlorotetraphthalic acids, intermediates in the above synthesis, was realized by the use of aqueous sodium or potassium dichromate in 50 per cent excess at 250° for the oxidation of substituted p-xylanes. The yields and purity of product are greatly superior to that of any other published method (for details, see Experimental) (27).

(27) This procedure was brought to the attention of the author by Friedman, who successfully employed it to prepare polycyclic aromatic carboxylic acids from the corresponding hydrocarbons.

As part of a program to determine the general applicability of the oxidation method, several substituted benzoic acids (Table III) were prepared in excellent yields.

2-Bromo-5-chlorotetraphthalic acid was synthesized in 79 per cent yield (see Experimental) by oxidizing 2-bromo-5-chloro-p-xylene with hot aqueous potassium permanganate buffered with potassium bicarbonate (28); 2-bromo-5-chloro-p-xylene was prepared by chlorinating and then

(28) (a) The yields were greatly reduced when potassium bicarbonate was omitted. (b) Willgerodt and Wolfien (25d) had previously reported oxidation of 2-bromo-5-chloro-p-xylene to 2-bromo-5-chlorotetraphthalic acid with nitric acid in a sealed tube at 200°; the yield was not stated.
Table III
Preparation of Substituted Benzoic Acids by Aqueous Dichromate Oxidation

<table>
<thead>
<tr>
<th>Substituted Toluene</th>
<th>Product</th>
<th>Yield %</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-fluorotoluene</td>
<td>tars(^a)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>m-fluorotoluene</td>
<td>m-fluorobenzoic acid</td>
<td>36</td>
<td>120-122</td>
</tr>
<tr>
<td>p-fluorotoluene</td>
<td>p-fluorobenzoic acid</td>
<td>55</td>
<td>180-181</td>
</tr>
<tr>
<td>o-chlorotoluene</td>
<td>o-chlorobenzoic acid</td>
<td>98</td>
<td>139-140</td>
</tr>
<tr>
<td>m-chlorotoluene</td>
<td>m-chlorobenzoic acid</td>
<td>60</td>
<td>154-156</td>
</tr>
<tr>
<td>p-chlorotoluene</td>
<td>p-chlorobenzoic acid</td>
<td>88</td>
<td>235-237</td>
</tr>
<tr>
<td>m-methoxytoluene(^b)</td>
<td>m-methoxybenzoic acid</td>
<td>66</td>
<td>107-108</td>
</tr>
<tr>
<td>o-nitrotoluene</td>
<td>tars(^a)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>m-nitrotoluene(^b)</td>
<td>m-nitrobenzoic acid</td>
<td>82</td>
<td>140</td>
</tr>
<tr>
<td>p-nitrotoluene(^b)</td>
<td>p-nitrobenzoic acid</td>
<td>94</td>
<td>238</td>
</tr>
</tbody>
</table>

\(^a\) A phenolic odor was present in the tar; it is believed that nucleophilic replacement of fluorine by base occurred.
\(^b\) Sodium dihydrogen phosphate added in 10 per cent excess as a buffer (initial pH ~4.5).

brominating p-xylene. In an analogous manner, 4-bromo-6-chloroiso-phthalic acid was prepared (81.6%) by the buffered permanganate oxidation of 4-bromo-6-chloro-m-xylene.

2-Bromo-5-methoxysterephthalic acid (29) was synthesized from 2-methoxy-p-xylene by two routes which give products indistinguishable by their infrared spectra or X-ray powder diffraction diagrams but which have melting points differing by 15°.

\(^{(29)}\) An impractical synthesis of 2-bromo-5-methoxysterephthalic acid was reported by Marzin (25c); p-xylene was dibrominated and the 2,5-dibromo-p-xylene oxidized with refluxing nitric acid to 2,5-dibromo-4-methylbenzoic acid. By refluxing the monobasic acid in an anhydrous solution of sodium hydroxide in methanol with a copper catalyst for eight days, 5-bromo-5-methyl-2-methoxybenzoic acid was obtained; oxidation with permanganate gave 2-bromo-5-methoxysterephthalic acid. This route was followed in this laboratory; 50 grams of 2,5-dibromo-p-xylene gave only traces of the terephthalic acid.
In Method I, 2-methoxy-p-xylene was brominated to give 2-bromo-5-methoxy-p-xylene, identical with that obtained by methylating 2-bromo-5-hydroxy-p-xylene. Oxidation of 2-bromo-5-methoxy-p-xylene with refluxing aqueous permanganate gives 2-bromo-5-methoxyterephthalic acid, m.p. 265° in agreement with the literature (25c). In the second route the order of operations is reversed. 2-Methoxy-p-xylene is oxidized with aqueous permanganate to 2-methoxyterephthalic acid which is brominated "cationically" (30) to give 2-bromo-5-methoxyterephthalic acid.


This method appears to be of wide application for introducing halogens into strongly deactivated aromatic nuclei. In a discussion of the reactivity of this brominating agent it was postulated that Br⁺ is the attacking species. Evidence was presented for a much higher reactivity than that which is observed in brominating procedures in which ion pairs (Br⁺FeBr₃⁻) or complex ions (Br₂Fe) are involved.

m.p. 280°. The halogenation was effected by adding bromine to a stirred solution of 2-methoxyterephthalic acid and silver sulfate in sulfuric acid at room temperature (for details see Experimental) (Figure 3).

Bromination in the presence of silver sulfate and sulfuric acid was also used to prepare 2-bromo-5-methylterephthalic acid from 2-methylterephthalic acid; in this reaction a higher temperature (70-80°) was necessary to achieve sufficient conversion. The product was purified as the dimethyl ester by chromatography and recrystallization before saponification (Figure 3).

Synthesis of 4-chloro-6-nitroisophthalic acid was accomplished by oxidizing 4-chloro-6-nitro-m-xylene with hot aqueous potassium
2-BROMO-5-METHOXYTEREPHTHALIC ACID

4 steps, see FIGURE

2-BROMO-5-METHYLTEREPHTHALIC ACID

2-BROMO-5-CHLOROTEREPHTHALIC ACID

FIGURE 3. SYNTHESIS OF 2-BROMO-5-SUBSTITUTED-TEREPHTHALIC ACIDS
permanganate. The preparation was greatly complicated because a mixture of both toluic acid derivatives is formed by partial oxidation of the disubstituted m-xylene (31). A satisfactory quantity of 4-chloro-6-nitroisophthalic acid was obtained only by repeated recrystalli-

(31) Synthesis of 4-methoxy-5-nitroisophthalic acid by oxidation of 4-methoxy-5-nitro-m-xylene with permanganate also resulted in a mixture of the toluic acids as well as the dibasic acid. It was not possible to separate the isophthalic acid in a satisfactorily pure state. Use of excess permanganate for the oxidation resulted in complete degradation of the organic material.

tations of the crude material from two large oxidation reactions.

4-Chloro-6-nitro-m-xylene was prepared from 2,4-dimethylaniline by nitrating, then diazotizing in hydrochloric acid and adding copper to decompose the diazonium chloride.

2-Chloro-5-methylterephthalic acid, 2-isopropyl-5-methylterephthalic acid and 4-methoxy-6-methylisophthalic acid were synthesized by a novel route. As an example, p-chlorotoluene was dibrominated to 2,5-dibromo-p-chlorotoluene; the position of the bromine atoms was assumed by analogy with chlorination of 2,4-dichlorotoluene and 3,4-dichlorotoluene, both of which give as the predominant isomer, 2,4,5-trichlorotoluene (32). Confirmation of the 1,2,4,5 tetrasubstitution


of the benzene ring was later accomplished from the infrared spectrum
of the dibromide (50% solution in chloroform) in the 5,6-micron region (Plate I, Figure 6) (33).

(33) C. W. Young, R. B. DuVall and N. Wright, Anal. Chem., 23, 709 (1951), have found by empirical examination of a large number of spectra of variously substituted aromatic compounds that patterns characteristic of the number and position of groups on the benzene ring were consistent for a wide range of substituents. Both the number and intensity of peaks in this region show great regularity although fluorine and the nitro group will cause perturbations which are more noticeable in less substituted than in highly substituted benzene rings. Groups with a primary absorption in this region will mask the effect, e.g., the carbonyl frequency. Although no theoretical treatment is presented it is postulated that these patterns are made up of overtone and combination bands.

Conversion of 2,5-dibromo-p-chlorotoluene to 2-chloro-5-methyldibenzothiophenoneitrile was effected by reaction with cuprous cyanide in dimethyl formamide (34). It is believed that this is the first

(34) The preparation of nitriles from aromatic bromides and cuprous cyanide has been found to give uniformly good yields when dimethylformamide is used as the solvent (L. Friedman, unpublished results). Dimethyl formamide has also been used as solvent in the preparation of nitriles from aliphatic halides and sodium cyanide, H.B. Copelin, U.S. Patent 2,715,137, C.A., 50, 7126 (1956).

example of preparation of an aromatic dinitrile by direct replacement of two halogen atoms.

Hydrolysis of 2-chloro-5-methyldibenzothiophenonitrile was effected with refluxing acetic acid-sulfuric acid-water to give 2-chloro-5-methyldibenzothiophenal acid (Figure 10).

In syntheses analogous to that just described 2-isopropyl-5-methyldibenzothiophenal acid was prepared from p-cymene and 4-methoxy-6-methyldibenzothiophenal acid was prepared from m-methylanisole (Figure 10). It was found necessary to hydrolyse 4-methoxy-6-methyldibenzothiophenaltrile with base, however, to avoid acid degradation.
PLATE I. INFRA-RED SPECTRA IN THE 5 TO 6 MICRON REGION FOR 1, 2, 4, 5 TETRA-SUBSTITUTED BENZENE COMPOUNDS
FIGURE 10. SYNTHESIS OF ACIDS VIA THE NITRILES

\[
\begin{align*}
\text{CH}_3 \: & \xrightarrow{[\text{Br}_2]} \: \text{BrCH}_3 \: \xrightarrow{[\text{Cu}_2(\text{CN})_2]} \: \text{CNCH}_3 \: \xrightarrow{[\text{H}_2\text{SO}_4/\text{H}_2\text{O}]} \: \text{CO}_2\text{H} \\
\end{align*}
\]

\[G = -\text{Cl} \text{ and } -\text{CH(\text{CH}_3)_2}\]
The studies of Schmidt reactions of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids were made to determine the relative effects of substituents on the reactivities of the carboxyl groups. Since 2-substituted terephthalic and 4-substituted isophthalic acids gave specific amino acids in Schmidt reactions (18), it was expected that reactions of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids with hydrazoic acid would give information concerning the relative effects of substituents in directing Schmidt processes. In principle reactions of the disubstituted terephthalic and isophthalic acids may result in formation of single or both possible amino acids (Equations 40 and 41). Determinations of

\[ CO_2H \quad + \quad HN_3 \quad \rightarrow \quad G' H_2N \quad + \quad G' CO_2H \] (40)

\[ G' CO_2H \quad + \quad HN_3 \quad \rightarrow \quad G' H_2N \quad + \quad G' CO_2H \] (41)

which of the two possible amino acids is formed, or their relative proportions, should provide insight into substituent effects on the
Schmidt reactions of aromatic carboxylic acids and help establish a more detailed mechanism for the reactions.

Reactions of both carboxyl groups to give diamines are also possible but were not anticipated for reactions in concentrated sulfuric acid because it had previously been observed that only in fuming sulfuric acid were diamines formed (Equations 42 and 43).

\[
\begin{align*}
\text{CO}_2\text{H} + 2 \text{HN}_3 & \xrightarrow{\text{fuming}} \text{HN}_2\text{G} \\
\text{CO}_2\text{H} & \xrightarrow{\text{fuming}} \text{H}_2\text{SO}_4
\end{align*}
\]

In the present study, it was found that all but one of the nine 2,5-disubstituted terephthalic acids reacted with hydrazoic acid to give single amino acids resulting from replacement of one of the carboxyl groups. Diamines resulting from replacement of both carboxyl groups were also obtained but as minor products from seven of the 2,5-disubstituted terephthalic acids. Reaction of 2-chloro-5-methyl-terephthalic acid with hydrazoic acid gave the diamine, 2-chloro-5-methyl-p-phenylenediamine, as the major product (ca. 55%) along with 4-amino-2-chloro-5-methylbenzoic acid. 2-Isopropyl-5-methylterephthalic
acid could not be reacted selectively to give an amino acid; it gave only 2-isopropyl-5-methyl-\(p\)-phenylenediamine.

Of the three 4,6-disubstituted isophthalic acids investigated, single amino acids were obtained from 4-chloro-6-nitroisophthalic acid and 4-bromo-6-chloroisophthalic acid; diamines could not be isolated although several reaction variables were changed. The products of Schmidt reactions of 4-methoxy-6-methylisophthalic acid were not isolable.

The products and best yields in Schmidt reactions of the present study are summarized in Table IV. From these results, all the acids for which amino acids were obtained can be placed in one of three series. It was found that the carboxyl group proximal to a nitro group undergoes selective replacement to form the amino acid in reactions of 2-bromo-5-nitrotetraphthalic acid, 2-chloro-5-nitrotetraphthalic acid, 2-methyl-5-nitrotetraphthalic acid, 2-methoxy-5-nitrotetraphthalic acid (Equation 44), and 4-chloro-6-nitroisophthalic acid (Equation 45). The carboxyl groups proximal to the methyl group were

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{G} & \quad \text{G} \\
+ \text{HN}_3 & \quad \xrightarrow{\text{H}_2\text{SO}_4} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{G} & \quad \text{G}
\end{align*}
\]

(44)

\(G = \text{Br, Cl, CH}_3, \text{OCH}_3\)
Table IV

Products of Schmidt Reactions of 2,5-Disubstituted Terephthalic and 4,6-Disubstituted Isophthalic Acids

<table>
<thead>
<tr>
<th>Compound</th>
<th>Products</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-bromo-5-chloroterephthalic acid</td>
<td>2-bromo-5-chloro-p-phenylenediamine</td>
<td>61.0(^a)</td>
</tr>
<tr>
<td></td>
<td>4-amino-5-bromo-2-chlorobenzoic acid</td>
<td>87.9</td>
</tr>
<tr>
<td>2-bromo-5-nitroterephthalic acid</td>
<td>2-bromo-5-nitro-p-phenylenediamine</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-bromo-5-nitrobenzoic acid</td>
<td>86.0</td>
</tr>
<tr>
<td>2-chloro-5-nitroterephthalic acid</td>
<td>2-chloro-5-nitro-p-phenylenediamine</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-chloro-5-nitrobenzoic acid</td>
<td>57.5</td>
</tr>
<tr>
<td>2-methyl-5-nitroterephthalic acid</td>
<td>2-methyl-5-nitro-p-phenylenediamine</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-methyl-5-nitrobenzoic acid</td>
<td>74.3</td>
</tr>
<tr>
<td>2-methoxy-5-nitroterephthalic acid</td>
<td>2-methoxy-5-nitro-p-phenylenediamine</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-methoxy-5-nitrobenzoic acid</td>
<td>52.0</td>
</tr>
<tr>
<td>2-bromo-5-methoxyterephthalic acid</td>
<td>2-bromo-5-methoxy-p-phenylenediamine</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>4-amino-5-bromo-2-methoxybenzoic acid</td>
<td>85.6</td>
</tr>
<tr>
<td>2-bromo-5-methylterephthalic acid</td>
<td>2-bromo-5-methyl-p-phenylenediamine</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-bromo-5-methylbenzoic acid</td>
<td>64.2</td>
</tr>
<tr>
<td>2-chloro-5-methylterephthalic acid</td>
<td>2-chloro-5-methyl-p-phenylenediamine</td>
<td>54.2</td>
</tr>
<tr>
<td></td>
<td>4-amino-2-chloro-5-methylbenzoic acid</td>
<td>39.5</td>
</tr>
</tbody>
</table>

\(^a\) The diamine was prepared in a separate experiment using a large excess of hydrazoic acid.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Products</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-isopropyl-5-methylterephthalic acid</td>
<td>2-isopropyl-5-methyl-(p)-phenylenediamine no amino acid</td>
<td>81.2</td>
</tr>
<tr>
<td>4-chloro-6-nitroisophthalic acid</td>
<td>no diamine 5-amino-2-chloro-4-nitrobenzoic acid</td>
<td>65.0</td>
</tr>
<tr>
<td>4-bromo-6-chloroisophthalic acid</td>
<td>no diamine 5-amino-4-bromo-2-chlorobenzoic acid</td>
<td>96.0</td>
</tr>
<tr>
<td>4-methoxy-6-methylisophthalic acid</td>
<td>the products could not be isolated</td>
<td>----</td>
</tr>
</tbody>
</table>
selectively replaced in 2-bromo-5-methylterephthalic acid and 2-chloro-5-methylterephthalic acid (Equation 46); replacement of the carboxyl group proximal to bromine occurred in the Schmidt reactions of 2-bromo-

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{Cl} & \quad \text{Cl} \\
\text{O}_2\text{N} & \quad \text{O}_2\text{N} \\
+ \text{HN}_3 & \quad + \text{HN}_3 \\
\rightarrow & \quad \rightarrow \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

(Equation 46)

G = Br, Cl

5-chloroterephthalic acid, 2-bromo-5-methoxyterephthalic acid (Equation 47), and 4-bromo-6chloroisophthalic acid (Equation 48).

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{G} & \quad \text{G} \\
\text{Br} & \quad \text{Br} \\
+ \text{HN}_3 & \quad + \text{HN}_3 \\
\rightarrow & \quad \rightarrow \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

(Equation 47)

G = Cl, OCH₃

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{G} & \quad \text{G} \\
\text{Br} & \quad \text{Br} \\
+ \text{HN}_3 & \quad + \text{HN}_3 \\
\rightarrow & \quad \rightarrow \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{HO}_2\text{C} & \quad \text{HO}_2\text{C}
\end{align*}
\]

(Equation 48)
Isolation and Identification of Products;
Proof of Homogeneity

The experimental details for individual Schmidt reactions are described in Chapter IV (35). Reaction products were isolated in as quantitative a manner as possible (usually by continuous extraction). Melting points were compared with literature values after recrystallization; all new compounds were analyzed. The infrared spectra of all amino acids were always checked for \(-\text{CO}_2\text{H}\) and \(-\text{NH}\) group frequencies, Appendix, Figures 12 through 47.

For all 2-substituted-5-nitroterephthalic acids of this study it was shown that the isomeric amino acids which might be formed in the Schmidt reactions were not present in chromatographically detectable amounts. Only zones corresponding to the diamine and amino acid obtained by recrystallization of the crude product were formed. Proof of identity was made by comparison of the infrared spectra and melting points of the compounds eluted from the chromatographic column with those of the purified diamine and amino acid.

The structures of the amino acids were confirmed by deamination to the corresponding disubstituted benzoic acids, (Equations 49 and 50).
The disubstituted benzoic acids were identified by comparing their melting points with literature values and when possible by mixed melting points. The products obtained from the deamination reactions are listed in Table V. Four of the deamination products (denoted by asterisks in Table V) could not be identified unambiguously by comparison of melting point data alone.

The recorded melting point for 5-bromo-2-chlorobenzoic acid is 155-156°, whereas (isomeric) 2-bromo-5-chlorobenzoic acid is reported to melt at 153° (36); the deamination product of the aminobromo-chlorobenzoic acid derived from 2-bromo-5-chloroterephthalic acid melted at 152-153°. In order to identify the deamination product, authentic 5-bromo-2-chlorobenzoic acid was synthesized by brominating o-chlorobenzoic acid (36). Mixed melting point determination and

Table V
Deamination Products of Amino Acids Obtained from the Schmidt Reactions

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Deamination Product</th>
<th>Yield, %</th>
<th>m.p. °</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-amino-5-bromo-2-chlorobenzoic</td>
<td>5-bromo-2-chlorobenzoic acid</td>
<td>93.0</td>
<td>152-153</td>
</tr>
<tr>
<td>4-amino-2-bromo-5-nitrobenzoic</td>
<td>2-bromo-5-nitrobenzoic acid</td>
<td>81.5</td>
<td>180-182</td>
</tr>
<tr>
<td>4-amino-2-chloro-5-nitrobenzoic</td>
<td>2-chloro-5-nitrobenzoic acid</td>
<td>75.0</td>
<td>164-165</td>
</tr>
<tr>
<td>4-amino-2-methyl-5-nitrobenzoic</td>
<td>2-methyl-5-nitrobenzoic acid</td>
<td>71.0</td>
<td>174-177</td>
</tr>
<tr>
<td>4-amino-2-methoxy-5-nitrobenzoic</td>
<td>*2-methoxy-5-nitrobenzoic acid</td>
<td>75.5</td>
<td>148</td>
</tr>
<tr>
<td>4-amino-5-bromo-2-methoxybenzoic</td>
<td>5-bromo-2-methoxybenzoic acid</td>
<td>81.9</td>
<td>119.2-119.6</td>
</tr>
<tr>
<td>4-amino-2-bromo-5-methylbenzoic</td>
<td>2-bromo-5-methylbenzoic acid</td>
<td>80.0</td>
<td>153-154.5</td>
</tr>
<tr>
<td>4-amino-2-chloro-5-methylbenzoic</td>
<td>*2-chloro-5-methylbenzoic acid</td>
<td>75.5</td>
<td>145-148.5</td>
</tr>
<tr>
<td>5-amino-2-chloro-4-nitrobenzoic</td>
<td>*2-chloro-4-nitrobenzoic acid</td>
<td>72.0</td>
<td>139-140</td>
</tr>
<tr>
<td>5-amino-4-bromo-2-chlorobenzoic</td>
<td>4-bromo-2-chlorobenzoic acid</td>
<td>91.0</td>
<td>163.8-165.2</td>
</tr>
</tbody>
</table>

* See text
comparison of infrared spectra proved the identity of the deamination product as 5-bromo-2-chlorobenzoic acid.

The amino acid from Schmidt reaction of 2-methoxy-5-nitroterephthalic acid melted at 248-249.5° which agrees with that reported for 4-amino-2-methoxy-5-nitrobenzoic acid (37). Melting points of 168° (38) and 162° (37) have been reported for the expected deamination product, 2-methoxy-5-nitrobenzoic acid; (isomeric) 5-methoxy-2-nitrobenzoic acid melts at 132° (39). The deamination product melted at 148°. Further confirmation of the structure for the amino acid, 4-amino-2-methoxy-5-nitrobenzoic acid, was obtained by converting it to the known 4-ido-2-methoxy-5-nitrobenzoic acid, m.p. 227°(37).

The amino acids which might be obtained from reaction of 2-chloro-5-methylterephthalic acid with hydrazic acid are unknown. The possible isomeric deamination products, 2-chloro-5-methylbenzoic acid and 5-chloro-2-methylbenzoic acid, are variously reported to melt from 163-173° (40). An authentic sample of 5-chloro-2-methylbenzoic acid (41),

(41) Obtained from L. Wood, Chemistry Department, The Ohio State University, Columbus, Ohio.
synthesized by chlorinating 2-methylbenzoic acid, melted at 168-169°; the mixed melting point with the deamination product from the amino-chloromethylbenzoic acid was depressed. Since 4-chloroisophthalic acid is the only product isolable from permanganate oxidation of the deamination product, its structure is 2-chloro-5-methylbenzoic acid. The amino acid from Schmidt reaction of 2-chloro-5-methylterephthalic acid is therefore 4-amino-2-chloro-5-methylbenzoic acid.

The amino acid from Schmidt reaction of 2-chloro-4-nitroisophthalic acid and its acetyl derivative had melting points corresponding to those for 5-amino-2-chloro-4-nitrobenzoic acid and 5-acetamido-2-chloro-4-nitrobenzoic acid (42). The structure assignment was based on these data since identical melting points (139°) are reported for the possible isomeric deamination products, 2-chloro-4-nitrobenzoic (43) and 4-chloro-2-nitrobenzoic acids (44).

(43) F. Tiemann, Ber., 24, 707 (1891).

Effect of Solvent Acidity on the Ratio of Amino Acid
and Diamine Formed in Schmidt Reactions

Since Moritsugu observed that 2-aminoterephthalic and 4-aminoisophthalic acids react with hydrazoic acid in fuming sulfuric acid, it is to be expected that the proportions of diamine to amino acid
produced from a dibasic acid will increase with the sulfur trioxide content of the sulfuric acid used as solvent (17) if the intermediate amino acid undergoes reaction as it a ammonium derivative. This effect was observed for several 2,5-disubstituted terephthalic acids; 4,6-disubstituted isophthalic acids for which products were obtained, however, did not yield diamines under the experimental conditions investigated. Acids which gave an increase in ratio of diamine to amino acid when the concentrations of sulfuric acid or sulfur trioxide were increased were; 2-bromo-5-chloroterephthalic acid and 2-bromo-5-nitroterephthalic acid.

It was not possible to isolate any amino acid from reactions of 2-isopropyl-5-methylterephthalic acid with hydrazoic acid regardless of the concentration of sulfuric acid used; the use of a smaller relative quantity of hydrazoic acid only resulted in a lower conversion to 2-methyl-5-isopropyl-Å-phenylenediamine. The yield of diamine (45) was definitely dependent upon the concentration of sulfuric acid used.

---

(45) The yield is calculated on the basis of 2-isopropyl-5-methylterephthalic acid which underwent reaction; i.e., initial acid minus the acid recovered. This method of calculating yields is used for all products listed in Tables VI through IX.

however. Thus a 44 per cent yield of 2-isopropyl-5-methyl-Å-phenylene-diamine was obtained when 80 per cent sulfuric acid was used, whereas an 82 per cent yield was realized when the concentration of sulfuric acid was increased to 104 per cent (excess sulfur trioxide is calculated as "H₃SO₄"). When the reaction temperatures in this series of experiments were lowered from 45° to 0° the intermediate aminomethylisopropylbenzoic acids (Table VI, Equation 51) were still not obtained.
Table VI
Effect of Sulfuric Acid Concentration on the Yield of
2-Isopropyl-5-methyl-p-phenylenediamine From Schmidt
Reactions of 2-Isopropyl-5-methylerterephthalic Acid

\[
\text{Temp.} \quad \text{H}_2\text{SO}_4 \quad \text{Mole Ratio of} \quad \% \quad \% \quad (\text{Acid (a)})
\]

<table>
<thead>
<tr>
<th>Temp. °</th>
<th>H$_2$SO$_4$ Conc., %</th>
<th>Mole Ratio of HN$_2$/Dibasic Acid</th>
<th>Diamine</th>
<th>Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>80</td>
<td>1.8</td>
<td>44.0</td>
<td>92.5</td>
</tr>
<tr>
<td>45</td>
<td>96</td>
<td>1.8</td>
<td>60.0</td>
<td>17.0</td>
</tr>
<tr>
<td>0</td>
<td>99</td>
<td>1.02</td>
<td>76.5</td>
<td>34.0</td>
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<tr>
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<td>104</td>
<td>1.02</td>
<td>81.2</td>
<td>33.5</td>
</tr>
<tr>
<td>0</td>
<td>104</td>
<td>1.5</td>
<td>80.0</td>
<td>24.5</td>
</tr>
</tbody>
</table>

(a) 2-isopropyl-5-methylerterephthalic acid.

Amino acids and diamines were obtained from Schmidt reactions of 2-bromo-5-chloroterephthalic and 2-bromo-5-nitroterephthalic acids. The increases in the ratios of diamine to amino acid (Equation 52) with an increase in sulfuric acid acidity as obtained from 2-bromo-5-chloroterephthalic acid are summarized in Table VII. The ratio of hydrazoic acid to 2-bromo-5-chloroterephthalic acid was increased in this series of experiments from 1.4 to 3.2 to allow a larger proportion
Table VII

Effect of Sulfuric Acid Concentration on the Amino Acid-Diamine Ratios for Schmidt Reactions of 2-Bromo-5-Chloroterephthalic Acid

<table>
<thead>
<tr>
<th>Temp., °C</th>
<th>H₂SO₄ Conc. %</th>
<th>Mole Ratio of HN₃/Dibasic Acid</th>
<th>Amino Acid % (a)</th>
<th>Diamine % (b)</th>
<th>Recovered Acid % (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>96</td>
<td>1.4</td>
<td>87.9</td>
<td>---</td>
<td>35.0</td>
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<tr>
<td>45</td>
<td>98</td>
<td>1.8</td>
<td>71.3</td>
<td>4.5</td>
<td>8.0</td>
</tr>
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<td>45</td>
<td>100</td>
<td>3.2</td>
<td>26.8</td>
<td>61.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

(a) 4-amino-5-bromo-2-chlorobenzoic acid
(b) 2-bromo-5-chloro-p-phenylenediamine
(c) 2-bromo-5-chloroterephthalic acid

of the starting material to react. That this does not appear to be the controlling factor in the change of the ratio of diamine to amino acid is assumed by analogy with the results of reactions of 2-bromo-5-nitroterephthalic acid, Table VIII (Equation 53). When the ratio of hydrazoic acid to 2-bromo-5-nitroterephthalic acid was changed from 1.20 to 4.11, there was little change in the ratio of 2-bromo-5-
\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{Br} & \quad + \text{HN}_3 & \quad \xrightarrow{96 - 102\%} \quad \text{CO}_2\text{H} & \quad \text{Br} \\
\text{O}_2\text{N} & \quad \text{CO}_2\text{H} & \quad \xrightarrow{\text{H}_2\text{SO}_4} & \quad \text{O}_2\text{N} & \quad \text{NH}_2 \\
\end{align*}
\]

Table VIII

**Effect of Sulfuric Acid Concentration on Amino Acid-Diamine Ratio for Schmidt Reactions of 2-Bromo-5-nitroterephthalic Acid**

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>H(_2)SO(_4) Conc. %</th>
<th>Mole Ratio of HN(_3)/Dibasic Acid</th>
<th>Amino Acid % (a)</th>
<th>Diamine % (b)</th>
<th>Recovered Acid % (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>96</td>
<td>1.20</td>
<td>81.0</td>
<td>6.0</td>
<td>20.0</td>
</tr>
<tr>
<td>45</td>
<td>98</td>
<td>4.11</td>
<td>85.0</td>
<td>10.0</td>
<td>-----</td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>1.60</td>
<td>86.0</td>
<td>11.2</td>
<td>-----</td>
</tr>
<tr>
<td>45</td>
<td>102</td>
<td>5.45</td>
<td>-----</td>
<td>91.0</td>
<td>-----</td>
</tr>
</tbody>
</table>

(a) 4-amino-2-bromo-5-nitrobenzoic acid  
(b) 2-bromo-5-nitro-p-phenylenediamine  
(c) 2-bromo-5-nitroterephthalic acid

Nitro-p-phenylenediamine to 4-amino-2-bromo-5-nitrobenzoic acid formed (the sulfuric acid concentration was constant at 96%). Similarly a change in the ratio of hydrazoic acid to aromatic acid affects only the total conversion and not the yield of diamine formed from 2-methyl-5-isopropylterephthalic acid (Table VI, the sulfuric acid concentration was constant at 104%).
An exception to the generalization that an increase in solvent acidity leads to an increase in the ratio of diamine to amino acid, was found for reaction of 2-bromo-5-methoxyterephthalic acid. The diamine, 2-bromo-5-methoxy-p-phenylenediamine, was the only product for reactions in 96 per cent sulfuric acid; an increase in concentration of sulfuric acid led to a decrease in the yield of diamine. The amino acid, 4-amino-5-bromo-2-methoxybenzoic acid, could be isolated only when 30 per cent fuming sulfuric acid (107% "H₂SO₄") was used, Table IX, Equation 54.

\[
\begin{align*}
\text{H}_2\text{CO}_2\text{H} & \quad \text{Br} \quad \text{H}_2\text{SO}_4(30\% \text{SO}_3) \quad \text{HN}_3 \quad \text{H}_2\text{CO}_2\text{H} \\
\text{H}_3\text{CO} & \quad \text{CO}_2\text{H} \quad \text{Br} \quad \text{NH}_2 \quad \text{Br} \quad \text{H}_3\text{CO} \quad \text{NH}_2 \quad \text{Br} \quad \text{H}_3\text{CO} \quad \text{CO}_2\text{H}
\end{align*}
\]

(96-100% H₂SO₄) (107% H₂SO₄)

Table IX

Effect of Sulfuric Acid Concentration on Schmidt Reactions of 2-Bromo-5-methoxyterephthalic Acid

<table>
<thead>
<tr>
<th>Temp., o</th>
<th>H₂SO₄</th>
<th>Mole Ratio of HN₃/Dibasic Acid</th>
<th>Amino Acid % (a)</th>
<th>Diamine % (b)</th>
<th>Recovered Acid % (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>96</td>
<td>1.10</td>
<td>----</td>
<td>93.0</td>
<td>54.4</td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>1.64</td>
<td>----</td>
<td>61.0</td>
<td>----</td>
</tr>
<tr>
<td>0</td>
<td>107</td>
<td>1.01</td>
<td>85.6</td>
<td>6.6</td>
<td>7.1</td>
</tr>
</tbody>
</table>

(a) 4-amino-5-bromo-2-methoxybenzoic acid
(b) 2-bromo-5-methoxy-p-phenylenediamine
(c) 2-bromo-5-methoxyterephthalic acid
Failure to obtain any amino acid from reactions of 2-bromo-5-
methoxyterephthalic acid in sulfuric acid of concentrations lower than
107 per cent is probably due to the greater reactivity imparted by
electron donation from the methoxyl group. The methoxyl group may
also be protonated and is probably the predominant form in fuming
sulfuric acid (Equation 55). Protonation of the more basic methoxyl

group can probably be realized over a certain range of solvent acidity
(here demonstrated to be at least 107% H₂SO₄) to the exclusion of pro-
tonation (or formation of the oxocarbonium ion) of the adjacent carboxyl
group. Although the amino-group in the **para**-position is probably also
highly protonated even at much lower range of acidity, the fact that
it is removed from the vicinity of the reaction gives it much less
influence in preventing protonation of the carboxyl group. If a small
amount of the oxocarbonium ion could form adjacent to the protonated
methoxyl group, subsequent reaction with hydrazoic acid would give an
intermediate with even more unfavorable distribution of charge
(Equation 56).

In Structure II, Equation 56, the positive charge on the oxocarbazide
group is largely located on nitrogen and is quite proximal (45) to the
protonated methoxyl group (e.g. the Newman "Rule of Six"). It is improbable, therefore, that this reaction would occur.

These experiments indicate that two separate reactions are favored by increasing sulfuric acid concentration. Formation of the reactive precursor in Schmidt reactions of carboxylic acids, the oxocarbonium ion, is enhanced as is protonation of other basic groups on the molecule. When a substituent which may be protonated, such as the methoxyl group, is proximal to a carboxyl group, protonation of the carbonyl group or reaction with hydrazoic acid may be prevented by using conditions of high acidity. Removal of the basic group from the vicinity of the carboxyl group lowers the inhibiting effect of positive charge sufficiently to allow the Schmidt reaction to proceed; this apparently occurs when diamines are formed from amino acids.
Possible Routes for Formation of Diamines

For all 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids studied, only one of the two possible isomeric amino acids could be isolated from the reaction mixtures. The most obvious conclusion is that the Schmidt reactions of these acids is highly specific.

The isolation of diamines for all the 2,5-disubstituted terephthalic acids, however, allows the argument that the isomeric amino acids are formed concurrently. The amino acid which does not appear among the products could be assumed to react rapidly to give the diamine, whereas the amino acid which is isolated reacts only slowly to give the diamine, thus accounting for the absence of one amino acid in the products (Equation 57).

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{G} \quad \text{CO}_2\text{H} \\
\text{G'} & \quad \text{NH}_2 \quad \text{G'} \\
\text{CO}_2\text{H} & \quad \text{G} \quad \text{CO}_2\text{H} \\
\text{G'} & \quad \text{NH}_2 \quad \text{G'} \\
\text{CO}_2\text{H} & \quad \text{G} \\
\text{G'} & \quad \text{NH}_2 \\
\end{align*}
\]

(Equation 57)
This concept must assume a fundamental difference in the effects of an amine group in reactions of isomeric amino acids with hydrazoic acid. The substituent groups \( G \) and \( G' \) can not be directly responsible; they would not be expected to have markedly different relative effects on the rates of reaction of a given carboxyl group in the amino acid as compared to the same carboxyl group in the parent terephthalic acid (substituent constants do not vary). In the strongly acidic media for the Schmidt reaction it is expected that an amine group is highly protonated (Equation 58). The strongly electron-attracting ammonium group should decelerate the Schmidt reaction at a carboxyl group in the ortho- or para-position. If protonation is inhibited in some way concentration of the free base could be appreciable and reaction of the para-carboxyl group would be accelerated by electron donation from the amine group.

The degree of protonation of the amine group could be reduced by steric factors (solvation, size) or strong electron withdrawal by the ortho-group, as for example with a nitro group (Equation 59). If the
group ortho to the amine group were small or possessed electron-donating tendencies, the ability of the amine group to protonate would be increased.

From these arguments crude predictions of the reactivities of isomeric amino acids can be made and compared with the experimental results. For 2-nitroterephthalic acids substituted in the 5-position with bromine, chlorine, methyl or methoxyl groups, it is predicted that the amino acid with the nitro group adjacent to the amine group would be less able to protonate than would its isomer. It should give the diamine more rapidly than the isomeric amino acid in which the nitro group is meta and the other substituent ortho to the amine group (Equation 60). If both isomeric amino acids were formed, the one which

should be isolated is the 4-amino-5-substituted-2-nitrobenzoic acid if the arguments are valid. The isomer that is actually found is the 4-amino-2-substituted-5-nitrobenzoic acid.
These considerations coupled with the inability to obtain isomeric amino acids by chromatographic analysis make it highly unlikely that the diamine is derived from the isomeric amino acids which are not isolated. The correlation of the ratio of amino acid to diamine with the acidity of the reaction medium (in which the amount of diamine formed increases with increasing acidity) is further evidence that the diamine is formed by reaction of the amino acid which is isolated and that it is the only amino acid formed.

The Mechanics of Schmidt Reactions of 2,5-Disubstituted Terephthalic and 4,6-Disubstituted Isophthalic Acids

The mechanism of reaction of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids with hydrazoic acid to give amino acids is probably similar to that of substituted benzoic acids. The kinetic results (22) for Schmidt reactions of mono-substituted benzoic acids provided strong evidence for a mechanism involving formation of a protonated benzazide as an intermediate, followed by rate-determining loss of nitrogen with rearrangement. As applied to 2,5-disubstituted terephthalic acids this mechanism is illustrated by Equations 61 to 64.

The presence of two carboxyl groups in disubstituted terephthalic acids thus allows possible reaction sequences involving each of the carboxyl groups or both to give isomeric amino acids or the diamine corresponding to the replacement of both carboxyl groups (Equation 65).
\[
\begin{align*}
\text{CO}_2\text{H} + 2\text{H}_2\text{SO}_4 & \rightleftharpoons \text{CO}_2\text{H}^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^- \quad (61) \\
\text{CO}_2\text{H} + 2\text{H}_2\text{SO}_4 & \rightleftharpoons \text{CO}_2\text{H}^+ + \text{H}_3\text{O}^+ + 2\text{HSO}_4^- \\
\text{CO}_2\text{H}^+ + \text{N}_2 & \rightarrow \text{CO}_2\text{H} + \text{N}_2 \quad (62) \\
\text{CO}_2\text{H}^+ + \text{N}_2 & \rightarrow \text{CO}_2\text{H} + \text{N}_2 \quad (63) \\
\text{CO}_2\text{H}^+ + \text{H}_2\text{O} & \rightarrow \text{CO}_2\text{H} + \text{H}_3\text{O}^+ \quad (64)
\end{align*}
\]
Substituent effects of $G$ and $G'$ on the ground state of the dicarboxylic acid and on the rearrangement step of its protonated carboxylic azide intermediates determine the amino acid formed in the reaction. Although all species leading to and including the protonated benzazides are affected by the substituents, their concentrations depend upon equilibrium reactions and thus do not simply determine the products formed. Reaction sequences involving 4,6-disubstituted isophthalic acids are similar to the above.

If only proximity effects of $G$ and $G'$ are important, it should be possible to correlate the amino acids obtained from selective Schmidt reactions of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids with the relative rates of reaction of hydrazoic and ortho-substituted benzoic acids. On the basis that proximity effects are completely controlling in the acids of the present research, the order of decreasing effects of substituents on a proximal carboxyl group is:

$$-\text{NO}_2 > -\text{CH(CH}_3)_2 > -\text{CH}_3 > -\text{Br} > -\text{Cl} > -\text{OCH}_3$$

Thus for 2-nitro-5-substituted-terephthalic acids, the carboxyl group proximal to the nitro group is replaced preferentially. Since only 2-methyl-5-isopropyl-2-phenylenediamine was obtained from 2-methyl-5-isopropylterephthalic acid, it is impossible to rank methyl and
isopropyl groups in this system; it is known (22) however in ortho-
alkylbenzoic acids that an isopropyl group has a much greater activating proximal effect than does a methyl group. In the present systems
the carboxyl group adjacent to a methyl group is replaced preferentially
to that proximal to bromine or chlorine. Similarly, the carboxyl group
proximal to bromine in 2-bromo-5-chloroterephthalic and 2-bromo-5-methoxy-
therphthalic acids is that which reacts in formation of the amino acids.

When the above series is compared with the relative rates of
reaction (22) of ortho-substituted benzoic acids with hydrazoic acid
(Table X, see also Table III0, the orders are similar with the exception
of the nitro group. From the great disparity in the positions of the
nitro group, and because of the inability to isolate an amino acid from

<table>
<thead>
<tr>
<th>Benzoic acid,</th>
<th>Relative Rate of reaction, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ortho substituent</td>
<td></td>
</tr>
<tr>
<td>-H</td>
<td>1</td>
</tr>
<tr>
<td>-NO₂</td>
<td>5.94</td>
</tr>
<tr>
<td>-CH(CH₃)₂</td>
<td>2,260.0</td>
</tr>
<tr>
<td>-CH₃</td>
<td>300.0</td>
</tr>
<tr>
<td>-Br</td>
<td>60.2</td>
</tr>
<tr>
<td>-Cl</td>
<td>28.8</td>
</tr>
<tr>
<td>-OCH₃</td>
<td>1.5</td>
</tr>
</tbody>
</table>

reaction of 2-methyl-5-isopropylterephthalic acid and hydrazoic acid
(o-isopropylbenzoic acid is more than seven times as reactive as
o-methylbenzoic acid), it appears that the selectivity of reactions of
the isophthalic and terephthalic acids involves much more than just an analysis of proximity effects.

The fact that the accelerating kinetic effect of a nitro group is the smallest for the above ortho-substituted benzoic acids is perhaps to be anticipated since a negative rho was obtained (22) in the Hammett correlation (Equation 66) of the rates of Schmidt reactions of meta- and para-substituted benzoic acids. The negative sign of rho indicates that the reaction is accelerated by electron-donating and decelerated by electron-attracting groups (46).

\[
\log \frac{k_2}{k_2^0} = \sigma \rho
\]  

(66)

(a) In Equation 66, \(k_2\) is the second order rate constant for the meta or para-substituted benzoic acid; \(k_2^0\) is the rate constant for benzoic acid. Sigma, \(\sigma\), the substituent constant, depends on the nature of the substituting group and its position on the benzene ring with respect to the reacting center. Rho, \(\rho\), the reaction constant, is a measure of the susceptibility of the reaction to substituent effects (mainly electrical). (b) H. H. Jaffe, Chem. Rev., 53, 217 (1953).

Although the Hammett equation cannot usually be used to correlate effects of ortho-substituents, the qualitative direction of electrical effects of an ortho group will be the same as when in the meta or para positions. Since the nitro group is a very strong electron attracting substituent (large positive meta and para substituent constants) and thus functions electrically in opposition to steric assistance, the low relative rate for ortho-nitrobenzoic acid may be rationalized.
It then becomes apparent that a satisfactory explanation of the specific replacement of carboxyl groups in Schmidt reactions of 2,5-disubstituted terephthalic and 4,5-disubstituted isophthalic acids must include the relative total effects of substituents upon each carboxyl group in a given acid. The selectivity of reaction of 2-methyl-5-nitrotetraphthalic acid to yield 4-amino-2-methyl-5-nitrobenzoic acid can be explained qualitatively on the basis that a meta-nitro group (electron-withdrawing) will slow Schmidt reaction of an ortho-toluic acid (fast) to such an extent that reaction of an ortho-nitrobenzoic acid (slow) accelerated minorly by a meta-methyl group (electron-donating) will occur relatively more rapidly. Similarly, in reaction of 2-bromo-5-nitrotetraphthalic acid to give 4-amino-2-bromo-5-nitrobenzoic acid, the decelerative effect of a meta-nitro group on reaction of an ortho-bromobenzoic acid (fast), is much greater than that for a meta-bromo group on an ortho-nitrobenzoic acid (slow) and thus the carboxyl group ortho to nitro is selectively replaced. In reaction of 2-bromo-5-methylterephthalic acid to yield 4-amino-2-bromo-5-methylbenzoic acid, it may be rationalized that the deactivation of meta-bromine on an ortho-toluic acid (fast) is insufficient to allow competitive reaction of an ortho-bromobenzoic acid (slow) as activated by a meta-methyl group. Similar arguments may be used to explain the selectivities of reaction of 2-bromo-5-chlorotetraphthalic and other related acids.

A quantitative analysis of the total effects of all substituents upon each carboxyl group of a given acid is very difficult with the acids of the present research because the necessary direct kinetic
information is not yet available; however, certain attempts have been made on the basis of simplifying and highly idealized assumptions.

A modified form of the Hammett equation (Equation 67) has been used to correlate reaction series involving constant ortho-substituents and varied meta- and para-substituents (46)

\[
\log \frac{k_2}{k_2^0} = \rho \sigma + X
\]  

(67)

The last term, \(X\), represents the contribution to the overall rate by the ortho-substituent and is equivalent to the logarithm of the ratio of the rate constants for the ortho-substituted and the unsubstituted species (Equation 68).

\[
X = \log \frac{k_2^{ortho}}{k_2^0}
\]  

(68)

In theory, the use of Equation 67 assumes that the ortho-substituent will not affect the mechanism or the reaction constant, \(\rho\), for the analogous reaction series without an ortho-substituent (47). In fact, \(\rho\) does vary to an extent which is a measure of the interference or assistance by the ortho-substituent with transmission of electrical effects from the rest of the molecule. Variation in \(\rho\), however, for ortho-substituted compounds from that for the corresponding unsubstituted compounds has not been large for reactions that have been correlated by Equation 67.
Equation 67 may be rewritten as Equation 69 in which the reference structure is the ortho-substituted compound without meta or para-substituents.

\[ \log \frac{k_2}{k_2} \text{ortho} = -\sigma^o \]  

(69)

Upon assuming that rho for the Schmidt reactions of benzoic acid is not changed appreciably by an ortho-substituent (therefore assuming the rho values obtained for meta- and para-substituted benzoic acids) and using the rate constants for ortho-substituted benzoic acids (22) as \( k_2 \text{ortho} \), reaction rate constants, \( k_2 \), can be calculated for each carboxyl group of a specific 2,5-disubstituted terephthalic or 4,6-disubstituted isophthalic acid. The larger value from each pair of reaction rate constants should indicate the carboxyl group which actually reacts to give the observed amino acid from a given dibasic acid, if the reaction mechanism is similar to that for the corresponding meta- and para-substituted benzoic acids. A summary of calculated rate constants for Schmidt reactions of pairs of 2,5- and 2,4-disubstituted benzoic acids is included in Table XI. The kinetic predictions in principle should be applicable to 2,5-disubstituted terephthalic and 2,4-isophthalic acids; the relative effects of the additional carboxyl group in the latter acids will be constant with constant values of rho. Available accurate data were insufficient for calculation of "theoretical" rate constants for 5-methyl-2-isopropylbenzoic, 2-methoxy-5-nitrobenzoic, 2-bromo-5-methoxybenzoic acids and their isomers. Details of the calculations are given in the Appendix II.
Table XI

Calculated Rate-constants for Schmidt Reactions of 2,5- and 2,4-
Disubstituted Benzoic Acids Using Equation 69\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substituted Benzoic Acid</th>
<th>$k_2$</th>
<th>Experimental Results;\textsuperscript{c} Carboxyl Replaced, ortho to</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-bromo-5-nitro</td>
<td>0.0718</td>
<td>NO$_2$</td>
</tr>
<tr>
<td>5-bromo-2-nitro</td>
<td>0.0205</td>
<td></td>
</tr>
<tr>
<td>2-chloro-5-nitro</td>
<td>0.0357</td>
<td>NO$_2$</td>
</tr>
<tr>
<td>5-chloro-2-nitro</td>
<td>0.0223</td>
<td></td>
</tr>
<tr>
<td>2-methyl-5-nitro</td>
<td>0.275</td>
<td>NO$_2$</td>
</tr>
<tr>
<td>5-methyl-2-nitro</td>
<td>0.134</td>
<td></td>
</tr>
<tr>
<td>5-bromo-2-methyl</td>
<td>1.01</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>2-bromo-5-methyl</td>
<td>1.72</td>
<td></td>
</tr>
<tr>
<td>5-chloro-2-methyl</td>
<td>1.09</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>2-chloro-5-methyl</td>
<td>0.856</td>
<td></td>
</tr>
<tr>
<td>2-bromo-5-chloro</td>
<td>0.284</td>
<td>Br</td>
</tr>
<tr>
<td>5-bromo-2-chloro</td>
<td>0.155</td>
<td>Br</td>
</tr>
<tr>
<td>2-bromo-4-chloro</td>
<td>0.581</td>
<td>Br</td>
</tr>
<tr>
<td>4-bromo-2-chloro</td>
<td>0.284</td>
<td>Br</td>
</tr>
<tr>
<td>2-chloro-4-nitro</td>
<td>0.041</td>
<td>NO$_2$</td>
</tr>
<tr>
<td>4-chloro-2-nitro</td>
<td>0.045</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} $k_2$ ortho$^*$ rate constant at 30° for the corresponding ortho-
substituted benzoic acid; rho = -1.77 for 2,5-disubstituted benzoic acids, -1.54 for 2,4-disubstituted benzoic acids. \textsuperscript{b} Calculated rate constants for 2,5- and 2,4-disubstituted benzoic acids. \textsuperscript{c} Carboxyl group which is actually replaced experimentally in Schmidt reactions of the corresponding 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids.
In Schmidt reactions of 2-chloro-5-methylterephthalic, 2-bromo-5-chloroterephthalic, 4-bromo-6-chloroisophthalic, and 4-chloro-6-nitroisophthalic acids, the carboxyl group which is replaced is in agreement with that for which the calculated rate constants for the corresponding disubstituted benzoic acids are larger. There is, however, lack of correlation between possible isomer distribution in the Schmidt reactions of the present study and that predicted on the basis of the kinetic calculations. Much worse, however, for each 2,5-disubstituted terephthalic acid containing a nitro group and for 2-bromo-5-methylterephthalic acid, the Schmidt product is the reverse of that predicted from the simplified kinetic analysis. The lack of correlation of isomer distribution and the reversal of the predicted reactivity for 2,5-disubstituted terephthalic and 2,4-disubstituted isophthalic acids thus implies that the rho values for reaction of certain of these compounds are significantly different from that of meta- and para-substituted benzoic acids.

A similar analysis of the selectivity of reactions of 2,5-disubstituted terephthalic and 4,6-disubstituted isophthalic acids has been made in terms of isomeric pairs of 2,4- and 2,5-disubstituted benzoic acids using the relative rate constants of ortho-substituted benzoic acids as reference values and computing meta- and para-effects of substituents on relative rates using $\sigma^+$ values (Table XII). Previous correlation of Schmidt reactions of meta- and para-substituted benzoic acids has been made using $\sigma$ values (22); however, it might be expected that the ground states of the isophthalic and terephthalic
Table XII

<table>
<thead>
<tr>
<th>Benzoic acid, ortho-substituent</th>
<th>Relative rate of reaction, $0^\circ$</th>
<th>$\sigma_m$</th>
<th>$\sigma_m^+$</th>
<th>$\sigma_p$</th>
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<td>$-\text{H}$</td>
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<tr>
<td>$-\text{NO}_2$</td>
<td>5.94</td>
<td>0.710</td>
<td>0.662</td>
<td>0.778</td>
<td>0.777</td>
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<tr>
<td>$-\text{CH(CH}_3\text{)}_2$</td>
<td>2,260.0</td>
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</tr>
<tr>
<td>$-\text{CH}_3$</td>
<td>300.0</td>
<td>-0.069</td>
<td>-0.0652</td>
<td>-0.170</td>
<td>-0.306</td>
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<tr>
<td>$-\text{Br}$</td>
<td>60.2</td>
<td>0.391</td>
<td>0.399</td>
<td>0.232</td>
<td>0.148</td>
</tr>
<tr>
<td>$-\text{Cl}$</td>
<td>25.8</td>
<td>0.373</td>
<td>0.391</td>
<td>0.227</td>
<td>0.112</td>
</tr>
<tr>
<td>$\text{OCH}_3$</td>
<td>1.5</td>
<td>0.115</td>
<td>0.0465</td>
<td>-0.268</td>
<td>-0.764</td>
</tr>
</tbody>
</table>

Acids are considerably less protonated than are benzoic acids and therefore bring out much greater resonance substituent effects in the rearrangement step. The results of the attempted correlations were similar however to those obtained with $\sigma$ values in that they do not predict that carboxyl groups ortho to the nitro group react selectively in these Schmidt systems. More complicated correlations were attempted in which various different rho values were assumed for each of the ortho-substituted series of benzoic acids. Partial correlation could be made between the kinetic results of Hillman (22) and the selectivities of reaction of the present acids; depending on the assumed rho values, the correlations were unsatisfactory in general however for many of the systems studied.
The results of the present investigation imply that there are appreciable differences in the reaction constant for ortho-nitrobenzoic acids to that for other ortho-substituted acids. The differences in the rho values are presumably reflected in the absolute changes in reaction mechanism. Kinetic studies of Schmidt reactions of systems such as 4- and 5-substituted-2-nitrobenzoic acids, etc., designed to determine their reaction constants will possibly provide important information concerning the differences in reaction mechanics. In lieu of such information, possible ideas which may account for the apparent greatly different reaction constant for substituted ortho-nitrobenzoic acids (and other ortho-substituted benzoic acids) will be considered.

The proposed rate-determining step of decomposition of a protonated benzazide in a Schmidt reaction involves: (1) loss of nitrogen with a bonding pair of electrons and (2) transfer of a migrating aryl group with its electrons to the remaining electron-deficient nitrogen atom (Equation 70). It is not known whether this sequence occurs concertedly or stepwise; however, it may be used to speculate how an ortho-nitro group could modify the reaction mechanism sufficiently to determine
exclusive replacement of the adjacent carboxyl group in the acids of the present study. In the usual sense the nitro group is electron-withdrawing and will be expected to inhibit the transfer of electrons in step 2 of Equation 70. However, the oxygen atoms of the nitro group are in an excellent position to supply electrons to the protonated nitrogen atom to facilitate loss of nitrogen as in step 1, Equation 71.

\[
\begin{align*}
\text{O}_2H & \quad \text{H}^+ \quad \text{N}^+ \quad \text{N}_2 \quad \text{O}^- \quad \text{G} \quad \text{CO}_2\text{H} \\
\text{O} & \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{H}^+ \quad \text{N}^+ \quad \text{N}_2 \quad \text{O}^- \quad \text{G} \quad \text{CO}_2\text{H} \quad + \quad \text{N}_2 \quad (71)
\end{align*}
\]

The spatial arrangement for such electron transfer is ideal if the nitro and the protonated carbo-azinium groups were both in the plane of the ring. This contribution to the rearrangement step will be further aided if an electron-donating group, G, were in the 3- or the 5-position on the ring. In this event participation by the electron-donating group in terms of contributions as in Equations 72 and 73 will accelerate electron release by the nitro group.

\[
\begin{align*}
\text{O} & \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{H} \quad \text{G} \quad \text{CO}_2\text{H} \\
\text{O} & \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{H} \quad \text{G} \quad \text{CO}_2\text{H} \quad (72)
\end{align*}
\]
In the present study, all the substituents in the 5-position of 5-substituted-2-nitroterephthalic acids can supply electrons by either resonance (−Br, −Cl, −OCH₃) or inductive (−CH₃) effects. The above argument does not imply the separate existence of intermediates as in Equations 72 and 73 but does attach importance to the facility of loss of nitrogen in determining the course of reaction. Such an effect is not unexpected since loss of nitrogen could occur without appreciable change in the spatial configuration of the remaining atoms, whereas the subsequent step involves molecular rearrangement. It is assumed then that the rearrangement step follows immediately or is almost simultaneous with the loss of nitrogen or that bond-breaking involving loss of nitrogen plays the major role in the activation step.

This picture of how the nitro group might control the course of the Schmidt reactions of 5-substituted-2-nitroterephthalic acids suggests certain experiments which will test the hypothesis. The accelerative effect of introducing a strongly electron donating group into the 5-position on the rates of reaction of 2-nitrobenzoic acids with hydrazoic acid should be markedly greater than the effects on the rates of reaction of other 2-substituted benzoic acids upon introducing the same electron donating substituent into the 5-position. Conversely,
introducing an electron attracting group into the 5-position should have a greater decelerative effect on the rate of reaction of 2-nitrobenzoic acid than for other ortho-substituted benzoic acids.

The difference in mechanism of Schmidt reactions of 2-nitrobenzoic acids should also be apparent when the reaction constant, rho, is determined for reactions of 4- and 5-substituted 2-nitrobenzoic acids. Rho for the reactions of 5-substituted-2-nitrobenzoic acids should have a more negative value (acceleration by electron donating groups) than for 4-substituted-2-nitrobenzoic acids if the effect postulated in Equations 72 and 73 is important. Furthermore, rho for the series of 2-nitrobenzoic acids should be markedly different for that of other 2-substituted acids which cannot contribute electrically in the manner postulated.

It may be similarly argued for Schmidt reactions of substituted ortho-toluic acids that the reaction constant is relatively large (large negative rho). Such a circumstance will thus allow simple explanation of the fact that 2-methyl-5-nitroterephthalic acid is converted to 4-amino-2-methyl-5-nitroterephthalic acid by hydrazoic acid. The relatively high rho for ortho-toluic acids is perhaps to be expected since the methyl group cannot donate electrons through space as possibly can nitro halogen and methoxyl groups. (It is also to be considered that the internal inconsistencies in the present results or the differences in results of the present study from that of Hillman (22) are due to great relative differences in ground states with respect
to protonation of carboxyl groups to dihydroxycarbonium ions; such differences are expected to be expressed significantly in the rho values for reaction).

The reaction of 2-methyl-5-isopropylterephthalic acid to give 2-methyl-5-isopropyl-£-phenylenediamine is of interest; all efforts to control the Schmidt reaction to yield intermediate amino acids were unsuccessful (48). It is thus to be concluded that the rate of

\[ \text{(48) The relative rates of reaction of benzoic, o-toluic, and o-isopropylbenzoic acids at } 0^\circ \text{ are: } 1; 300; 2,260; \text{ see Table II, p. 18.} \]

Schmidt reaction of 4-amino-2-methyl-5-isopropylbenzoic acid, the expected intermediate, is greater than that of the parent dibasic acid. The apparent reasons for this result, in contrast to that of the other acids of the present study, lie in the facts that in the amino acid intermediate there is present a strong ortho accelerating substituent, a minor meta accelerating group, and a very bulky alkyl group which tends to minimize conversion of the activating amine group to the deactivating ammonium ion.
IV. EXPERIMENTAL

Preparation and Purification of Dibasic Acids

1. Synthesis of 2-bromo-5-nitroterephthalic acid, Method I.

(a) Synthesis of dimethyl 2-nitroterephthalate. Powdered dimethyl terephthalate (97.2 g., 0.5 moles) was added to stirred fuming sulfuric acid (230 g., 30% $\text{H}_2\text{SO}_4$) at $0^\circ$. When solution was complete, "mixed acid" (fuming nitric acid, 100 g., mixed with fuming sulfuric acid, 100 g.) was added in 4 hours at such a rate that the temperature remained below $10^\circ$. The mixture was poured on ice and let stand 20 hours, then filtered, washed and dried. Recrystallization from acetone/water gave pure dimethyl 2-nitroterephthalate (114 g., 0.47 moles, 94%), m.p. 74-76°, lit. (49) m.p. 76°.

(49) H. Kauffmann and L. Weissel, Ann., 393, 1 (1912).

(b) Synthesis of dimethyl 2-acetamidoterephthalate. A mixture of dimethyl 2-nitroterephthalate (24 g., 0.1 moles), anhydrous stannous chloride (57 g., 0.3 moles) and acetic anhydride (29 g.) in a Claisen flask was heated cautiously until reaction began. Boiling was maintained for 20 minutes by the heat of reaction. Acetic acid and excess acetic anhydride were removed by distillation at reduced pressure; water (200 ml.) was added and the solid collected on a filter, washed and dried. Recrystallization from methanol gave pure dimethyl 2-acetamidoterephthalate (16 g., 0.063 moles, 63%), m.p. 161-163°, lit. (49) m.p. 166°. Further purification was unnecessary.
(c) **Synthesis of dimethyl 2-acetamido-5-nitroterephthalate.**

A mixture of sulfuric and nitric acids (50/50; 100 ml.) was added in 8 hours to a stirred solution (made up at 5°) of dimethyl 2-acetamidoterephthalate (32.7 g., 0.13 moles) in sulfuric acid (100 ml.) at 0°. The mixture was poured on ice (500 g.), let stand one hour and filtered, washed and dried. Recrystallization from methanol gave pure dimethyl 2-acetamido-5-nitroterephthalate (22.2 g., 0.075 moles, 57.5%), m.p. 142°, lit. (50) m.p. 142°.

---

(50) A. Claus and J. Herbabny, Ann., 265, 367 (1891).

(d) **Synthesis of dimethyl 2-amino-5-nitroterephthalate.** A mixture of dimethyl 2-acetamido-5-nitroterephthalate (22.5 g., 0.075 moles), sulfuric acid (70 g.) and methanol (100 ml.) was refluxed 3 hours. The solution was allowed to cool slowly and gave pure dimethyl 2-amino-5-nitroterephthalate (10 g., 0.039 moles, 52%), m.p. 187°, lit. (50), m.p. 187°.

(e) **Synthesis of dimethyl 2-bromo-5-nitroterephthalate.** Sodium nitrite (2.5 g., 0.036 moles) was added in one hour to a stirred suspension of finely powdered dimethyl 2-amino-5-nitroterephthalate (9 g., 0.035 moles) in hydrobromic acid (60 ml., 48%) at 0-5°. After the mixture had been stirred for 2 hours, copper bronze powder (1 g.) was added and the mixture was warmed to 50° in one hour. The mixture was poured into ice and filtered, washed and dried. Recrystallization from ethanol/water gave pure dimethyl 2-bromo-5-nitroterephthalate (5.0 g., 0.016 moles, 45%), m.p. 110-111°.)
A nal. Calcd. for C$_{10}$H$_8$BrNO$_6$ Found:

<p>| | | |</p>
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<tr>
<td>N</td>
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</table>

(f) Synthesis of 2-bromo-5-nitroterephthalic acid. A mixture of dimethyl 2-bromo-5-nitroterephthalate (3.0 g., 0.009 moles), methanol (100 ml.) and aqueous potassium hydroxide (100 ml., 10%) was refluxed 10 hours. The mixture was acidified and methanol was stripped. After cooling overnight, crystals of pure 2-bromo-5-nitroterephthalic acid were obtained (1.0 g., 0.003 moles, 33%), m.p. 261-262°, lit. (50) m.p. 260-261°.

1. Synthesis of 2-bromo-5-nitroterephthalic acid, Method II.

(a) Synthesis of 2,5-dimethylbromobenzene. Bromine (1.5 kg., 9.4 moles) in carbon tetrachloride (1.5 kg.) was added in 8 hours to a stirred mixture of p-xylene (1 kg., 96% pure, 9.12 moles), powdered iron (5 g.) and carbon tetrachloride (1 kg.) at 0-5° with exclusion of light. The reaction mixture was then stirred for 10 hours while being slowly heated to room temperature. The stirred organic solution was washed successively by decantation 3 times with sodium hydroxide solution (1 l. portions, 5%) and twice with water. After the carbon tetrachloride had been distilled, potassium hydroxide (150 g.) in methanol (1.2 l.) was added, and the mixture was heated to boiling and let stand for 24 hours. The organic product was dissolved in ether, washed several times with water and dried (sodium sulfate). The ether was distilled and the product fractionated at reduced
pressure to give 2-bromo-1,4-dimethylbenzene (1560 g., 8.42 moles, 92.5%), b.p. 78°/8 mm., lit. (51) b.p. 205-210°/770 mm., nD25 1.551, lit. (52) nD18.5 1.5514.

(52) K. V. Auwers and J. Jacobsen, Ann., 422, 164 (1921).

(b) Synthesis of 2-bromoterephthalic acid (new method of preparation). A mixture of 2,5-dimethylbromobenzene (37 g., 0.2 moles), potassium dichromate (136 g., 0.45 moles), potassium aluminum sulfate (30 g.) and water (200 ml.) was heated in a rocking steel bomb (450 ml. volume) at 250° for 31 hours. The bomb was opened at room temperature (no excess pressure), and the chromium oxide (Cr₂O₃) was filtered and washed with water. The basic (pH ~10.0) aqueous filtrate was extracted with methylene chloride to remove unreacted material (2.1 g. recovered), boiled to remove traces of solvent and then acidified (sulfuric acid, 40%). The crude product was filtered, washed with water and air-dried. Reprecipitation from ammonium hydroxide after decolorization gave pure white 2-bromoterephthalic acid (32.0 g., 0.13 moles, 68.5%), m.p. 301° (sealed tube), lit. (53) m.p. 302-303°; neut. equiv. (calc'd), 122.52, (found) 122.5.

(53) R. Wegscheider and K. Bittner, Monatsh., 21, 640 (1900).

(e) Synthesis of 2-bromo-5-nitroteterephthalic acid (improved preparation). Nitric acid (2.5 g., 0.0278 moles, sp.gr. 1.42) was added in 30 minutes to 2-bromoterephthalic acid (4 g., 0.0163 moles)
in sulfuric acid (50 ml., 96.5%) at 90-95°. After 10 minutes the
reaction mixture was poured into ice, refrigerated several hours and
filtered. The product was washed with ice water, then dissolved in
boiling water (ca. 10 ml.), decolorized (Darco) and allowed to
crystallize as colorless needles of 2-bromo-5-nitroterephthalic acid
(3.31 g., 0.0144 moles, 70.0%), m.p. 263-264° (uncorr.) lit. (54)
m.p. 260-262°, m.p. (50) 260-261° (uncorr.), neut. equiv. (calc'd.),
14.02, (found) 144.5.

(54) H. Schindhelm, U.S. Patent 1,832,247; C.A. 855° (1932).

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<tr>
<th>Anal.</th>
<th>Calc'd. for C₈H₄BrNO₆</th>
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<tr>
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</tbody>
</table>


(a) Synthesis of 2-chloroterephthalic acid (new method of
preparation). A mixture of 2,5-dimethylchlorobenzene (28 g., 0.2 moles),
sodium dichromate (180 g., 0.6 moles, 50% excess) and water (180 ml.)
was rocked in a steel bomb (capacity 450 ml.) at 250° for 10-1/2 hours,
The bomb was opened at room temperature and the chromium oxide (Cr₂O₃)
was filtered and washed with water. The basic filtrate (pH≈9.0) was
extracted with ether to remove unreacted material (2.0 g., recovered),
boiled to remove traces of ether and acidified with hydrochloric acid.
The product was filtered, washed with cold water to remove dichromate,
and air-dried (33 g., 0.1645 moles, 88.5%), m.p. 304-310°, lit. (55) m.p. 300°; neut. equiv. (calc'd.), 100.25, (found) 100.3. This new method of preparing 2-chloroterephthalic acid gives higher yields than any in the literature.

(55) F. Ahrens, Ber., 19, 1637 (1886).

(b) Synthesis of 2-chloro-5-nitroterephthalic acid (improved preparation). Nitric acid (11 ml., sp. gr. 1.42) was added in 5 minutes to 2-chloroterephthalic acid (20 g., 0.1 moles) in fuming sulfuric acid (80 ml., 5% SO₃) at 90-95°. After one-half hour the mixture was poured into ice (350 g.), cooled and filtered. The crude solid was washed with cold water (80 ml.) and dried. The combined filtrates were extracted continuously with chloroform; the material obtained after distilling the chloroform was combined with that on the filter and recrystallized from 40% ethanol to give 2-chloro-5-nitroterephthalic acid (22 g., 0.0896 moles, 89.6%), m.p. 263-265°, lit. (54) m.p. 265°; neut. equiv. (calc'd.), 122.79, (found) 123.0.

<table>
<thead>
<tr>
<th>Anal. Calc'd. for C₈H₄ClNO₆</th>
<th>Founds</th>
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<td>H, 1.76</td>
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<tr>
<td>N, 5.71</td>
<td>N, 5.56</td>
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</table>


(a) Synthesis of 2,4-dimethylbromobenzene. Bromine (1.59 kg., 9.9 moles) in carbon tetrachloride (1.5 kg.) was added in 7 hours to a stirred mixture of m-xylene (1 kg., 95%, 9.12 moles), powdered iron
(5 g.) and carbon tetrachloride (1 kg.) at 0-5°C in the absence of light. The reaction mixture was then stirred 11 hours while warming to room temperature. The organic solution was washed successively by stirring and decantation, 3 times with sodium hydroxide (5%, 1 l. portions) and twice with water. The carbon tetrachloride was distilled and potassium hydroxide (150 g.) in methanol (1.2 l.) was added. The mixture was heated to boiling and let stand for 24 hours to hydrolyze side-chain bromination products. Water (3 l.) was added to the cold solution to extract the alkaline methanol; the organic layer was separated, dissolved in ether, washed with water several times and dried (sodium sulfate). The ether was distilled and the 2,4-dimethylbromobenzene fractionated at reduced pressure (1450 g., 7.85 moles, 86%) through a Vigreaux column (20 cm.), b.p. 72.5-73.5°C/7 mm., lit. (56) b.p. 84°C/13 mm.


(b) Synthesis of 2,4-dimethylbenzonitrile (new method of preparation). A stirred mixture of 2,4-dimethylbromobenzene (370 g., 2 moles), cuprous cyanide (206 g., 2.3 equiv.) and dimethyl formamide (300 ml.) was refluxed for 6 hours. The cooled mixture was slowly poured into a stirred solution of ferric chloride (200 g.) and hydrochloric acid (100 ml.) in water (500 ml.) at 0-10°C. The oil which separated was dissolved in ether and washed with sodium bicarbonate (100 ml., 5%) and water (two 300 ml. portions) and then dried over sodium sulfate. The ether was distilled and the crude 2,4-dimethyl-
benzonitrile (210 g., 1.6 moles, 80%) was distilled at reduced pressure through a Vigreaux column (20 cm.); b.p. 100-102°/9 mm., lit. (57) b.p. 222°/760 mm., (58) b.p. 223-224°/760 mm.; (59) b.p. 110-112°/16 mm.

(57) K. Gasiorowski and V. Merz, Ber., 18, 1012 (1885).
(58) W. Hinrichsen, Ber., 21, 3083 (1888).

The yield of 2,4-dimethylbenzonitrile by this method exceeds any other in the literature.

(a) Synthesis of 2,4-dimethylbenzoic acid. A stirred mixture of 2,4-dimethylbenzonitrile (60 g., 0.457 moles), potassium hydroxide (82 g., 1.46 moles), diethylene glycol (300 ml.) and water (20 ml.) was refluxed for 10 hours. The cooled mixture was poured into dilute sulfuric acid (300 ml., 40%) and filtered; the solid filter cake was washed with water and pressed. The damp solid was stirred with hot water (200 ml.), filtered and washed with cold water. Reprecipitation from ammonium hydroxide after decolorization gave pure 2,4-dimethylbenzoic acid (66.0 g., 0.44 moles, 96.0%), m.p. 124-126°, lit. (60, 61) m.p. 126°. This product was used in the next step without further purification.

(61) L. Gatterman and G. Schmidt, Ann., 244, 52 (1888).

(d) Synthesis of 2-methylterephthalic acid. A hot mixture of potassium permanganate (45 g., 0.293 moles) and water (300 ml.) was added in 10 minutes to a stirred solution of 2,4-dimethylbenzoic acid
(20.5 g., 0.135 moles) in sodium carbonate (400 ml., 10%) at 90-95°.
When the supernatant liquid became colorless (ca. 45 min.), the manganese
dioxide was filtered and washed with hot sodium carbonate (10%). The
filtrate was acidified with dilute sulfuric acid and the cooled slurry
of 2-methylterephthalic acid was filtered, washed and dried (13.7 g.,
0.076 moles, 56.0%), m.p. 320-325°, lit. (62) 320-324°, (63) 325-330°,
neut. equiv. (calc'd.) 90.1, (found) 90.1.

62, 2332 (1940).
(63) W. H. Beatley and W. H. Perkins, J. Chem. Soc., 177 (1897);

(e) Synthesis of 2-methyl-5-nitroterephthalic acid (new compound).
Nitric acid (2.4 g., sp. gr. 1.42) was added in one-half hour to a
solution of 2-methylterephthalic acid (3.0 g., 0.0166 mole) in sulfuric
acid (40 ml., 96.5%) at 90-95°. The clear solution was poured into
vigorously stirred crushed ice and allowed to stand for several hours.
The crude solid product was filtered, washed with cold water and dried
(3.2 g.). Recrystallization from water gave 2-methyl-5-nitroterephthalic
acid as colorless plates (2.9 g., 81.0%), m.p. 294-295.5° (uncorr.),
neut. equiv. (calc'd) 112.5, (found) 113.1.

<table>
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<tr>
<th>Anal.</th>
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<th>Found:</th>
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<td>N</td>
<td>6.22</td>
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</table>

The position of the nitro group was proven from the structure of known
products obtained in the Schmidt reaction, p. 98.

Bromine (15 g., 0.094 moles) was added in 90 minutes to a stirred solution of 2-methylterephthalic acid (16 g., 0.09 moles) and silver sulfate (15 g., 0.05 moles) in fuming sulfuric acid (110 ml., 10% SO₃) at 0-10°C. After standing 24 hours at room temperature the slurry was poured into ice, filtered and washed with cold water. The wet solid was triturated with sodium bicarbonate (20%) and filtered free of silver bromide. The alkaline filtrate was carefully acidified; the precipitate was filtered, washed and dried. Recrystallization from glacial acetic acid (500 ml.) gave crude 2-bromo-5-methylterephthalic acid (8.2 g., 0.032 moles, 35%), neut. equiv. (calc'd.) 129.5, (found) 126.0, m.p. 275° subl., 334-335° melts.

Crude 2-bromo-5-methylterephthalic acid (5.0 g.) was refluxed for 2 days with methanol (50 ml.) and 1,2-dichloroethane (100 ml.) to give the crude dimethyl ester (5.13 g.). The ester was chromatographed by elution through Woelm alumina ("activity 1", 2.5 cm. X 20 cm.) with benzene (100 ml.) and recrystallized from ethanol/water to give pure dimethyl 2-bromo-5-methylterephthalate (4.8 g.), m.p. 113-114°; saponification number (calc'd.) 143.0, (found) 141.5.

**Anal. Calc'd. for C₁₁H₁₁Br₄O₂**  
- C, 46.02  
- H, 3.86  
- Br, 27.82  

**Found**  
- C, 45.80  
- H, 3.99  
- Br, 27.99

Basic hydrolysis (potassium hydroxide, 15% in 50/50 methanol/water) gave pure 2-bromo-5-methylterephthalic acid, m.p. 335-336°, neut. equiv. (calc'd.) 129.5, (found) 128.
5. **Synthesis of 2-methoxy-5-nitroterephthalic acid.**

(a) **Synthesis of 2,5-dimethylanisole.** Dimethyl sulfate (126 g., 1.0 mole) was added in 1-1/2 hours to a stirred solution of 2,5-dimethylphenol (122 g., 1.0 mole) and sodium hydroxide (41 g., 1.02 moles) in water (600 ml.) at 45°. After addition of the dimethyl sulfate, aqueous sodium hydroxide (200 ml., 10%) was added in one portion and additional dimethyl sulfate (60 g.) was added over one-half hour. After the mixture had been stirred for 10 minutes, the oil which had separated was dissolved in ether. The aqueous layer was extracted twice with ether; the ether solution was washed 3 times with water. After drying and distilling the ether, benzene (5 ml.) was added and distilled to remove traces of water as an azeotrope. The oil was distilled through an open, vacuum-jacketed column (one decimeter) and gave colorless 2,5-dimethylanisole (112.5 g., 0.82 moles, 82.5% yield), b.p. 51-54°/772 mm.; lit. (64), b.p. 194°/772 mm.

(b) **Synthesis of 2-methoxyterephthalic acid (improved synthesis).** Potassium permanganate (94 g., 0.6 moles, 50% excess) was added in 4 equal portions in 2 hours to a stirred mixture of 2,5-dimethylanisole (13.2 g., 0.097 moles) and pyridine (80 ml.) in water (600 ml.) at 90°. After the permanganate had been used (disappearance of purple color), the manganese dioxide was filtered and washed with sodium bicarbonate (10%). The filtrate was made strongly acid with hydrochloric acid, cooled for several hours in a refrigerator and filtered. The 2-methoxyterephthalic acid was washed and air-dried (13 g., 0.0645 moles,
66.4%), m.p. 272-278°, lit. (65) m.p. 277-279°, neut. equiv. (calc'd.) 98.1, (found) 100.0. This acid was used in the next step without further purification.

(c) Synthesis of 2-methoxy-5-nitroterephthalic acid (new compound).
Nitric acid (5 ml., 0.078 moles, d. 1.42) was added in 5 minutes to a stirred solution of 2-methoxyterephthalic acid (12.0 g., 0.061 moles) in sulfuric acid (100 ml., 96.5%) at room temperature. The mixture was stirred until the temperature had dropped 30° from the maximum that was reached during reaction (about 20 minutes). The mixture was poured into stirred crushed ice and cooled in a refrigerator for 12 hours. The solid was filtered, washed with ice water and air-dried. Recrystallization from water gave pure 2-methoxy-5-nitroterephthalic acid as colorless needles (10.5 g., 0.0436 moles, 71.5%), m.p. 243-245°, neut. equiv. (calc'd.) 120.5, (found) 121.5.

<table>
<thead>
<tr>
<th>Anal.</th>
<th>Calc'd. for CgH7NO7</th>
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</tr>
</thead>
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<td>C, 44.66</td>
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<tr>
<td>H,</td>
<td>2.93</td>
<td>H, 2.72</td>
</tr>
<tr>
<td>N,</td>
<td>5.81</td>
<td>N, 5.98</td>
</tr>
</tbody>
</table>

The position of the nitro group was proven from the structure of known products obtained from the Schmidt reaction, p. 100.
6. **Synthesis of 2-bromo-5-methoxyterephthalic acid (new method of preparation).**

Bromine (11.0 g., 3.5 ml., 0.068 moles) was added in 2 hours to a stirred solution of 2-methoxyterephthalic acid (9.8 g., 0.05 moles) and silver sulfate (8.6 g., 0.027 moles) in sulfuric acid (110 ml., 96.5%) at 10°. The slurry which formed was stirred 3 hours, warmed to room temperature, and then poured into ice containing sodium bisulfite. The precipitate was filtered, washed with cold water, and then trituated with aqueous potassium hydroxide (5%) at 80-90°. The silver residue was filtered and washed with dilute base.

The combined filtrate was acidified with dilute sulfuric acid, cooled, filtered, washed with cold water and air-dried (10.18 g., 0.037 moles, 74%). Pure 2-bromo-5-methoxyterephthalic acid was obtained by recrystallization from acetic acid, m.p. 272-274°, lit. (66) 265-268°,
neut. equiv. (calc'd.) 137.5, (found) 137.5.


A sample of 2-bromo-5-methoxyterephthalic acid prepared by permanganate oxidation of 2-bromo-5-methoxy-p-xylene (Method II) gave an infrared spectrum and an X-ray diffraction pattern which were identical with those of the material synthesized above.

7. **Synthesis of 2-bromo-5-methoxyterephthalic acid, Method II.**

(a) **Synthesis of 2-bromo-5-methoxy-1,4-dimethylbenehhe.**

Bromine (80 g., 0.5 moles) in carbon tetrachloride (100 ml.) was added in 2 hours to a stirred mixture of 2,5-dimethylanisole (67.5 g., 0.5 moles),
iron powder (5 g.), iodine (0.5 g.) and carbon tetrachloride (400 ml.) at 0-5°. The mixture was stirred an additional 6 hours; the liquid layer was washed successively with water, potassium carbonate and saturated sodium chloride. After drying and stripping the solvent, the oil was fractionally distilled and gave starting material (10 g., 0.074 moles) and 2-bromo-5-methoxy-1,4-dimethylbenzene (83.8 g., 0.39 moles, 91.5% of unrecovered material), b.p. 100-102°/4 mm. This material was identical (infrared spectrum) with that obtained from methylation of authentic 2-bromo-5-hydroxy-1,4-dimethylbenzene.

(b) Synthesis of 2-bromo-5-methoxyterephthalic acid.

Potassium permanganate (127 g., 0.8 moles) was added in 2 hours to a stirred mixture of 2-bromo-5-methoxy-1,4-dimethylbenzene (28.8 g., 0.134 moles), pyridine (110 ml.), and water (1 l.) at 90°. Heating and stirring were continued until the supernatant liquid was colorless (4 hours). The manganese dioxide was filtered and washed. The filtrate was extracted with ether to remove unreacted starting material (3.0 g., 0.014 moles) and then acidified (hydrochloric acid), cooled, filtered, washed and dried. Recrystallization from glacial acetic acid gave pure 2-bromo-5-methoxyterephthalic acid (10.2 g., 0.037 moles, 30.8%), m.p. 263-266°, lit. (66) m.p. 265-268°, neut. equiv. (calc'd.) 137.5, (found) 137.5.

<table>
<thead>
<tr>
<th>Anal.</th>
<th>Calc'd. for C14H7BrO7</th>
<th>Found</th>
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<td>C</td>
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<tr>
<td>H</td>
<td>2.56</td>
<td>H</td>
</tr>
<tr>
<td>Br</td>
<td>29.05</td>
<td>Br</td>
</tr>
</tbody>
</table>

(a) Synthesis of 2-bromo-5-chloro-1,4-dimethylbenzene.
Bromine (41 g., 14 ml., 0.26 moles) in carbon tetrachloride (60 ml.) was added in one hour to a stirred mixture of 2-chloro-1,4-dimethylbenzene (35.3 g., 0.254 moles), ferric chloride (1 g.) and carbon tetrachloride (100 ml.) at 0-10°. After the mixture had been stirred for 12 hours at room temperature, the organic layer was washed with conc. potassium hydroxide and water. The solution was dried over sodium sulfate and the carbon tetrachloride was distilled to give crude product (56 g.). Recrystallization from methanol gave pure 2-bromo-5-chloro-1,4-dimethylbenzene (50 g., 0.228 moles, 90%), m.p. 66°, lit. (67) m.p. 66°.

(b) Synthesis of 2-bromo-5-chloroterephthalic acid (improved synthesis). Potassium permanganate (400 g., 2.53 moles) was added in portions (50 g.) in 3 hours to a stirred emulsion of 2-bromo-5-chloro-1,4-dimethylbenzene (49 g., 0.224 moles), pyridine (200 ml.) and saturated aqueous potassium bicarbonate (1 liter) at an initial temperature of 90-100°. The heat of reaction caused vigorous boiling for several minutes after each addition of permanganate but external heating was continued throughout the oxidation. The stirred reaction mixture was heated until all permanganate was used (disappearance of color) and then the manganese dioxide was filtered and washed with potassium bicarbonate. The clear filtrate was acidified with dilute hydrochloric
acid to pH ~ 3.0 and the thick slurry which resulted was cooled. The crude product was filtered, washed with cold water and air-dried (49.4 g., 0.177 moles, 79%). Recrystallization from acetic acid gave pure 2-bromo-5-chloroterephthalic acid, m.p. 306-308° corr., lit. (68) m.p. 308-310° corr., neut. equiv. (calc'd.) 139.7, (found) 139.7.


(a) Synthesis of 2,5-dibromo-4-chlorotoluene. Bromine (155 g., 0.97 moles) was added in 2 hours to a mixture of p-chlorotoluene (57.5 g., 0.456 moles), carbon tetrachloride (200 ml.) and aluminum amalgam (0.5 g.) at 5° (reaction was quite vigorous, bromine disappeared immediately and hydrogen bromide was liberated profusely). The solution was washed with sodium bisulfite, dilute sulfuric acid and water, then dried and stripped to the solid. Fractional distillation at reduced pressure gave a fore-run (13 g.), b.p. 60-93°/1.5 mm., a middle cut (60 g.), b.p. 113-120°/3.5 mm., and an after-run (18.2 g.) b.p. 120-127°/3.5 mm. Recrystallization of the middle portion gave pure 2,5-dibromo-4-chlorotoluene as colorless needles (55 g., 0.194 moles, 42.5%), m.p. 96.3-97.6°, lit. m.p. (69) 94°. An infrared


spectrum of a chloroform solution (40%, 0.2 mm cell) in the 5-6μ region indicated 1,2,4,5-tetrasubstitution, Plate I, Figure 6, p. 31(33).
(b) Synthesis of 2-chloro-5-methylterephthalonitrile (new compound). A mixture of 2,5-dibromo-4-chlorotoluene (30 g., 0.105 moles), cuprous cyanide (19 g., 0.212 equiv.), dimethyl formamide (57.6 g.) and pyridine (1 ml.) was refluxed for 12 hours. The hot solution was poured into a mixture of ammonium hydroxide (200 ml.) and ice (200 g.) and filtered. The solid was dried, extracted with boiling toluene, decolorized and cooled to give crystalline 2-chloro-5-methylterephthalonitrile (16 g., 0.09 moles, 86%), m.p. 202-204°. The crude nitrile was used without further purification.

(c) Synthesis of 2-chloro-5-methylterephthalic acid (new compound). A mixture of 2-chloro-5-methylterephthalonitrile (15 g., 0.085 moles), acetic acid (40 ml.), water (15 ml.) and sulfuric acid (50 ml., 96.5%) was refluxed for 18 hours, poured into ice-water, filtered, washed and dried. Reprecipitation from ammonium hydroxide after decolorization gave crude 2-chloro-5-methylterephthalic acid (12.5 g., 0.068 moles, 68.2%), neut. equiv. (calc'd.) 107.3, (found) 115.0. By boiling with concentrated potassium hydroxide, acidification and recrystallization from glacial acetic acid, pure 2-chloro-5-methylterephthalic acid was obtained, m.p. 160°, neut. equiv. (calc'd.) 107.3, (found) 109.0.

**Anal. Calcd. for C_{9}H_{7}ClO_{4}:**

- C, 50.35 \( \text{Found: C, 50.29} \)
- H, 3.28 \( \text{Found: H, 3.32} \)
- Cl, 16.52 \( \text{Found: Cl, 16.77} \)

Infrared spectrum, Figure 16, p. 117.

(a) Synthesis of 2,5-dibromo-£-cymene. Bromine (420 g., 2.62 moles) was vaporized in a stream of dry air and bubbled through a solution of iodine (0.5 g.) in p-cymene (160 g., 1.2 moles) at 5° in 60 hours. The oil was washed with sodium bisulfite, dilute sulfuric acid and water, dried and fractionally distilled at reduced pressure. Pure 2,5-dibromo-£-cymene (249.5 g., 0.85 moles, 71%) was obtained, b.p. 88-90°/0.5 mm., lit. (75) b.p. 135-140°/7 mm., d^24 1.58, lit. (70),

(b) Synthesis of 2-isopropyl-5-methylerephthalonitrile (new compound). A stirred mixture of 2,5-dibromo-£-cymene (61.0 g., 0.218 moles), cuprous cyanide (38.0 g., 0.425 equiv.), dimethyl formamide (68 g.) and pyridine (1 ml.) was refluxed for 14 hours. The hot mixture was poured into ammonium hydroxide (200 ml.) and ice (300 g.), filtered and pressed. The solid was extracted with boiling chloroform-acetic acid; the hot solution was decolorized and evaporated to the solid. Recrystallization from dilute acetic acid gave pure 2-isopropyl-5-methylerephthalonitrile (31.2 g., 0.17 moles, 77.5%), m.p. 119.2-119.8°.

Anal. Calc'd. for C_{12}H_{12}N_{2}: Found:

<p>| | | |</p>
<table>
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<tr>
<th></th>
<th></th>
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<td>H,</td>
<td>6.56</td>
<td>H,</td>
</tr>
<tr>
<td>N,</td>
<td>15.22</td>
<td>N,</td>
</tr>
</tbody>
</table>
(c) **Synthesis of 2-isopropyl-5-methylterephthalic acid**

(new compound). A stirred mixture of 2-isopropyl-5-methylterephthalonitrile (7.0 g., 0.038 moles), acetic acid (20 ml.), water (10 ml.) and sulfuric acid (40 ml.) was refluxed for 7 hours. The hot slurry was poured into ice-water (400 g.), filtered, washed and dried. Recrystallization from dilute acetic acid after decolorization gave crude 2-isopropyl-5-methylterephthalic acid (7.5 g., 0.034 moles, 89%), m.p. 288-294°, neut. equiv. (calc'd.) 111.1, (found) 113.5. Reprecipitation from ammonium hydroxide after additional decolorization and recrystallization from glacial acetic acid gave pure 2-isopropyl-5-methylterephthalic acid, m.p. 293-294°, neut. equiv. (calc'd.) 111.1, (found) 111.1.

**Anal.**

<table>
<thead>
<tr>
<th></th>
<th>Calc'd. for C₁₂H₁₄O₄</th>
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<tr>
<td>C,</td>
<td>64.80</td>
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<tr>
<td>H,</td>
<td>6.35</td>
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</table>

11. **Synthesis of 4-chloro-6-nitrosophthalic acid.**

(a) **Synthesis of 2,4-dimethyl-5-nitroaniline.** Nitric acid (165 g., sp. gr. 1.42) was added in 2-1/2 hours to a stirred solution of 2,4-dimethylaniline (200 g., 1.65 moles) in sulfuric acid (2 kg., 96.0%) at 5°. After having been stirred for an additional 15 minutes, the mixture was poured into ice-water (3 kg.) and cooled to 5° for 2 hours. The solid was filtered, pressed, and triturated with potassium carbonate until the supernatant liquid was basic. The cold slurry was filtered, washed and dried to give crude 2,4-dimethyl-5-nitroaniline (190 g., 1.14 moles, 69%), m.p. 118-120°, lit. (71) m.p. 123-124°.

(b) Synthesis of 2,4-dimethyl-5-nitrochlorobenzene. Sodium nitrite (20 g., 0.29 moles) in water (50 ml.) was added in 90 minutes to a stirred slurry of finely-divided 2,4-dimethyl-5-nitroaniline (35 g., 0.21 moles) in hydrochloric acid (400 ml., 37%) at 9-5°. When reaction was complete (2 hours), the diazonium solution was poured in 15 minutes with vigorous shaking into a solution of cuprous chloride (100 g.) in hydrochloric acid (200 ml.) at 40°. When gas evolution had ceased (one hour), the mixture was cooled and extracted with methylene chloride. The organic solution was washed with dilute hydrochloric acid, sodium bisulfite (5%), sodium hydroxide (5%) and water, then dried and stripped. The crude oil was distilled at reduced pressure to give 2,4-dimethyl-5-nitrochlorobenzene (35 g., 0.19 moles, 90%), m.p. 40-41° (from ethanol), lit. (72) m.p. 40-41°.


(c) Synthesis of 4-chloro-6-nitroisophthalic acid. A solution of 2,4-dimethyl-5-nitrochlorobenzene (33 g., 0.179 moles) in pyridine (40 ml.) was added in 3 hours to a refluxing solution of potassium permanganate (140 g., 0.885 moles) in water (2 l.). After refluxing for 5-1/2 hours the supernatant liquid was colorless; the manganese dioxide was filtered and washed. Unreacted starting material (10 g., 0.054 moles) was extracted with methylene chloride, and the aqueous layer was concentrated (to 50 ml.) and acidified (hydrochloric acid). After standing 5 days at 0-5° crystals formed which were filtered and recrystallized from acetic acid (40%) to give pure
12. Synthesis of 4-bromo-6-chloroisophthalic acid.

(a) Synthesis of 4-chloro-1,3-dimethylbenzene. Chlorine (720 g., 10.1 moles) was bubbled through a solution of m-xylene (1 kg., 95%, 9.0 moles) in carbon tetrachloride (1 kg.) containing iron powder (10 g.) at 0-5°. After having been stirred for another 10 hours at room temperature the mixture was washed with water (2-1 l. portions) by stirring and decantation. Sodium hydroxide solution (1 l., 10%) was added, and the mixture was refluxed for 3 hours. The mixture was separated; the organic portion was washed with water (2, 1 l. portions), dried and stripped. The oil upon fractional distillation gave m-xylene (160 g., 1.5 moles) and 4-chloro-1,3-dimethylbenzene (860 g., 6.1 moles, 81% of unrecov. xylene), b.p. 94-98°/45 mm., lit. (59) b.p. 73-75°/16 mm. The infrared spectrum in the 5-6 μ region indicated that the initial distillate (300 g.) was contaminated with small amounts of 2-chloro-1,3-dimethylbenzene; this fraction was not used in subsequent work.

(b) Synthesis of 4-bromo-6-chloro-1,3-dimethylbenzene.
Bromine (80 g., 0.5 moles) in carbon tetrachloride (200 ml.) was added in 4 hours to a stirred mixture of 4-chloro-1,3-dimethylbenzene (70 g., 0.5 moles), carbon tetrachloride (500 ml.) and iron powder (5.0 g.) at 0-5°. The mixture was stirred 2 additional hours and poured into sodium bisulfite (500 ml., 5%). The organic portion was washed
successively with potassium carbonate (5%), ammonium chloride (5%) and water, dried and stripped of carbon tetrachloride. The oil, upon distillation at reduced pressure, gave a crude solid product (82.5 g.). Recrystallization from methanol yielded pure 4-bromo-6-chloro-1,3-dimethylbenzene (50.0 g., 0.228 moles, 45.5%), m.p. 67-68°, lit. (73) m.p. 68°.


(c) Synthesis of 4-bromo-6-chloroisophthalic acid (new compound). Potassium permanganate (200 g., 1.25 moles) was added in 3 hours to a stirred mixture of 4-bromo-6-chloro-1,3-dimethylbenzene (25 g., 0.114 moles), pyridine (150 ml.), and saturated potassium bicarbonate (800 ml.) at 90-100°. After stirring for 2 additional hours the supernatant liquid was colorless; the manganese dioxide was then filtered and washed. The filtrate was carefully acidified by pouring it into hydrochloric acid with vigorous stirring. The product was filtered, washed and dried. Reprecipitation from ammonia and drying at 110° for 30 hours gave crude 4-bromo-6-chloroisophthalic acid (26 g., 0.093 moles, 81.6%), m.p. 260-268°, neut. equiv. (calc'd.) 139.5, (found) 143.5.

Purification was effected by dissolving the product in boiling aqueous sodium dihydrogen phosphate (10%, pH ~ 3.5) and cooling the mixture rapidly. The first crop of solid was filtered and discarded; the filtrate was acidified (phosphoric acid) and heated to boiling to effect complete solution. The fine needle-like crystals obtained by slow cooling were filtered, washed with cold water and dried at 110°
for 20 hours to give pure 4-bromo-6-chloroisophthalic acid, m.p. 266-268°, neut. equiv. (calc'd.) 139.5, (found) 139.5.

**Anal. Calc'd. for C₈H₄BrC₆O₄:**

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<th>Calc'd.</th>
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<tr>
<td>total halogen as Br,</td>
<td>50.34</td>
<td>Br, 50.36</td>
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</table>

13. **Synthesis of 4-methoxy-6-methylisophthalic acid.**

(a) **Synthesis of 4,6-dibromo-3-methylanisole.** Bromine (300 g., 1.87 moles) in acetic acid (135 ml.) was added in 2 hours to a stirred mixture of m-methylanisole (100 g., 0.82 moles), acetic acid (100 ml.) and iron powder (3 g.) at 4-10° in the absence of light. After having been stirred an additional one-half hour, the mixture was poured into ice-water, filtered and dried. Recrystallization from ethanol/water gave large prisms of pure 4,6-dibromo-3-methylanisole (122 g., 0.435 moles, 53%), m.p. 75-76°, lit. (74) m.p. 75-76°.


(b) **Synthesis of 4-methoxy-6-methylisophthalonitrile.** A stirred mixture of 4,6-dibromo-3-methylanisole (40 g., 0.143 moles), cuprous cyanide (28 g., 0.31 equivalents), dimethyl formamide (60 g.) and pyridine (1 ml.) was refluxed for 12 hours. The hot solution was poured into ammonium hydroxide (200 ml.) and ice (200 g.) with vigorous stirring. The solid was filtered, washed and dried, then extracted several times with boiling toluene. Decolorization of the toluene solution and cooling gave fine white needles of pure 4-methoxy-6-methylisophthalonitrile (20 g., 0.116 moles, 81%), m.p. 182.5-183°.
(c) Synthesis of 4-methoxy-6-methylisophthalic acid. A stirred mixture of 4-methoxy-6-methylisophthalonitrile (24 g., 0.14 moles), potassium hydroxide (106 g., 1.9 moles), water (30 ml.) and diethylene glycol (200 ml.) was refluxed for 30 hours. The hot solution was poured into ice (500 g.) and hydrochloric acid (200 ml.), let stand for several hours, filtered and pressed. The moist solid was triturated with ammonium hydroxide; the silica from the flask was filtered. After decolorizing the filtrate, the 4-methoxy-6-methylisophthalic acid was reprecipitated with hydrochloric acid, filtered, washed and dried (6.5 g., 0.031 moles, 22%); neut. equiv. (calc'd.) 104, (found) 106.3, m.p. 254-255° (from methanol/water), lit. (75) m.p. 250-252°.

Reactions of 2,5-Disubstituted Terephthalic and 4,6-Disubstituted Isophthalic Acids with Hydrazoic Acid

Apparatus

Schmidt reactions were run in a modified Erlenmeyer flask (Figure 11, p. 95) similar to that used for catalytic hydrogenation at atmospheric pressure. The reaction vessel was heated by a regulated glycerine bath. Sodium azide was placed in the scoop and added as desired by partially rotating the side-arm joint. The gas outlet tube was attached to a bubbler trap leading to an inverted cylinder filled with water and clamped over a water reservoir.

1. Reaction of 2-bromo-5-nitrotetraphthalic acid with hydrazoic acid. Sodium azide (1.80 g., 0.0277 moles, 60% excess) was added in 30 minutes to a stirred solution of 2-bromo-5-nitrotetraphthalic acid (5.04 g., 0.0173 moles) in sulfuric acid (40 ml., 100%, f.p. 10.4°) at 45°. After gas evolution (1000 ml., 10 hours) was complete, the mixture was poured into ice (300 g.) and then made basic (sodium hydroxide, 75%). The diamine formed was separated by extracting with chloroform, drying the extract and stripping to the solid. Recrystallization from benzene/ligroin gave deep red crystals of pure 2-bromo-5-nitro-2-phenylenediamine (0.46 g., 0.00019 moles, 11.2%), m.p. 180-183°, lit. (76) m.p. 156°, infrared spectrum, Figure 37, p.128.

(76) W. Korner, Gazz. Chem. ital., 4, 414 (1874).

<table>
<thead>
<tr>
<th>Anal.</th>
<th>Calc'd. for C₈H₅BrN₃O₂</th>
<th>Found:</th>
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<tbody>
<tr>
<td>N,</td>
<td>18.10</td>
<td>N,</td>
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</table>
Fig. 11. APPARATUS FOR SCHMIDT REACTIONS
The aqueous solution was acidified (hydrochloric acid, pH≈3.0), filtered and extracted continuously. Concentration of the extract and recrystallization of the residue from ethanol/water gave yellow crystals of pure 4-amino-2-bromo-5-nitroterephthalic acid (3.90 g., 0.0149 moles, 86.0%), m.p. 263-265° C., lit. (77) m.p. 264°; infrared spectrum, Figure 27, p.123.


<table>
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<td>N,</td>
<td>10.75</td>
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Proof of structure of 4-amino-2-bromo-5-nitrobenzoic acid. Sodium nitrite (0.5 g., 0.0072 moles) was added to a suspension of 4-amino-2-bromo-5-nitrobenzoic acid (0.57 g., 0.00218 moles) in hydrochloric acid (30 ml.) at 5°. After 30 minutes the diazotized solution was poured into ice-cold hypophosphorus acid (50 ml.) and refrigerated for 20 hours. The product was obtained by filtering and extracting the filtrate with chloroform. After concentrating the extract all of the solid product was recrystallized from ethanol to give pure 2-bromo-5-nitrobenzoic acid (0.44 g., 0.00178 moles, 81.5%), m.p. 180-182°, lit. (78) m.p. 180°, (79) 180-181°.

(79) E. Bamberger, Ber., 57, 2090 (1924).
2. Reaction of 2-chloro-5-nitrotetraphalic acid with hydrazoic acid. Sodium azide (0.63 g., 0.0097 moles) was added in 15 minutes to a stirred solution of 2-chloro-5-nitrotetraphalic acid (2.00 g., 0.0082 moles) in fuming sulfuric acid (40 ml., 5% SO₃) at 45°. Gas evolution (400 ml.) was complete in 30 minutes. The mixture was poured on ice, made basic, and extracted with chloroform. Evaporation of the chloroform and recrystallization from ethanol/water gave red needles of 2-chloro-5-nitro-£-phenylenediamine (0.38 g., 0.00203 moles, 24.7%), m.p. 155-156°, lit. (80) m.p. 156-157°, infrared spectrum, Figure 38, p.128.


The aqueous solution was acidified (hydrochloric acid, pH<3.0) and extracted continuously with chloroform for 3 days. Recrystallization of the product from dilute acetic acid gave yellow prisms of 4-amino-2-chloro-5-nitrobenzoic acid (1.02 g., 0.00472 moles, 57.5%), m.p. 267°, lit. (81) m.p. 267°; infrared spectrum, Figure 28, p.123.


<table>
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<td>N</td>
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Proof of structure of 4-amino-2-chloro-5-nitrobenzoic acid.

A mixture of 4-amino-2-chloro-5-nitrobenzoic acid (0.50 g., 0.0023 moles) and hydrochloric acid (30 ml.) was treated with sodium nitrite (0.5 g.) at 0-5°. In 30 minutes the reaction mixture was poured into cold hypophosphorus acid (50 ml.) and refrigerated for 20 hours. The product was isolated by extracting the deamination mixture repeatedly with chloroform; the chloroform was evaporated and the solid recrystallized from ethanol/water to give pure 2-chloro-5-nitrobenzoic acid (0.35 g., 00174 moles, 75%), m.p. 164-165°, lit. (82) m.p. 164-165°.


3. Reaction of 2-methyl-5-nitrotetraphthalic acid with hydrazoic acid. Sodium azide (1.73 g., 0.0266 moles, 100% excess) was added in 6 minutes to a stirred solution of 2-methyl-5-nitrotetraphthalic acid (3.0 g., 0.0133 moles) in sulfuric acid (40 ml., 96.5%) at 45°. Gas evolution ceased after 10 hours (640 ml.); the reaction mixture was poured into ice and made basic (sodium hydroxide, 20%). The diamine fraction was isolated by filtration and extraction of the filtrate with chloroform. The crude product was recrystallized from water/ethanol to give dark red crystals of pure 2-methyl-5-nitro-p-phenylenediamine (0.40 g., 0.0024 moles, 18.0%), m.p. 171.5-173°, lit. (83) m.p. 173°; infrared spectrum, Figure 39, p.129.

The aqueous solution was acidified (hydrochloric acid, pH 3.0) after removal of the diamine, and the yellow crystalline solid which formed was filtered. The filtrate was extracted continuously with chloroform and gave additional yellow product. Recrystallization from ethanol gave pure 4-amino-2-methyl-5-nitrobenzoic acid (1.94 g., 0.0099 moles, 74.3%), m.p. 282-283.5°d., lit. (84) m.p. 280°d.; infrared spectrum, Figure 29, p.124.


<table>
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Proof of structure of 4-amino-2-methyl-5-nitrobenzoic acid. A mixture of crude 4-amino-2-methyl-5-nitrobenzoic acid (0.29 g., 0.0016 moles) and hydrochloric acid (40 ml.) was diazotized by addition of sodium nitrite (0.5 g.) in 30 minutes at 0-5°. The solution was added to ice-cold hypophosphorus acid (50 ml.) and refrigerated for 20 hours. The crystalline solid which formed was filtered; the filtrate was extracted with chloroform. After recrystallization from dilute ethanol, pure 2-methyl-5-nitrobenzoic acid (0.19 g., 0.00103 moles, 71%) was obtained, m.p. 174-177°, lit. (85) m.p. 176-178.6°, (86) 179°.

(85) M. L. van Scherpenzeel, Rec. trav. chim. (France), 20, 173 (1901).
(86) O. Jacobsen and F. Wierss, Ber., 16, 1958 (1883).
4. Reaction of 2-methoxy-5-nitrotetraphthalic acid with hydrazoic acid. Sodium azide (1.60 g., 0.0246 moles, 46% excess) was added in 5 minutes to a stirred solution of 2-methoxy-5-nitrotetraphthalic acid (4.055 g., 0.0168 moles) in sulfuric acid (20 ml., 96.5%) at 50°. The reaction was stopped after 12 hours (750 ml. gas evolved) by pouring the solution on cracked ice (300 g.). The cold solution was made basic (sodium hydroxide, 20%) and extracted with chloroform to remove the diamine fraction. The chloroform solution was washed with water, dried over sodium sulfate, and concentrated. The solid residue was recrystallized from ethanol/water as orange needles of 2-methoxy-5-nitro-1,2-phenylenediamine (0.32 g., 0.00175 moles, 9.6%), m.p. 200-201°, lit. (80) m.p. 190-191°; infrared spectrum, Figure 40, p. 129.

The aqueous solution from the chloroform extraction was acidified (hydrochloric acid) and extracted continuously (2 days) with chloroform. The chloroform solution was stripped to a solid which upon recrystallization from ethanol/water gave 4-amino-2-methoxy-5-nitrobenzoic acid (1.86 g., 0.00877 moles, 52%), m.p. 247-248°, lit. (87) m.p. 248°.


Proof of structure of 4-amino-2-methoxy-5-nitrobenzoic acid. A solution of 4-amino-2-methoxy-5-nitrobenzoic acid (0.50 g., 2.36x10^-4 moles) in hydrochloric acid (50 ml.) was diazotized at 5°. The diazonium solution was poured into ice-cold hypophosphorus acid (50 ml.) and refrigerated for 24 hours. The solid was filtered and
recrystallized from ethanol/water to give 2-methoxy-5-nitrobenzoic acid (0.35 g., \(1.78 \times 10^{-4}\) moles, 75.5%), m.p. 148°, lit. (88) m.p. 148°, (89) m.p. 148-150°.


5. Reaction of 2-bromo-5-chloroterephthalic acid with hydrazoic acid.

(a) Reaction with 40% excess hydrazoic acid. Sodium azide (1.30 g., 0.02 moles, 40% excess) was added in 30 minutes to a solution of 2-bromo-5-chloroterephthalic acid (4.00 g., 0.0143 moles) in sulfuric acid (70 ml., 96% at 48°. The mixture was poured over ice (400 g.) when gas evolution was complete (680 ml., 20 hours), neutralized (sodium hydroxide, 20%) and then adjusted to pH = 3.0 (sulfuric acid). The crude product (3.50 g.) was filtered, dried and titrated (neut. equiv. 191.2). Assuming that the crude product contained only starting acid (neut. equiv. 139.7) and amino acid (neut. equiv. 250.5), calculation indicates that 40% of the crude product was starting material; this was confirmed by diazotization, (see Proof of structure). Recrystallization of the ethanol-soluble portion gave pure 4-amino-5-bromo-2-chlorobenzoic acid (2.05 g., 0.00817 moles, 57.1%; yield based on material which reacted, 87.9%), m.p. 249-251°, infrared spectrum, Figure 33, p.126; 4-amino-5-bromo-2-chlorobenzoic acid is a new compound.
Proof of structure of 4-amino-5-bromo-2-chlorobenzoic acid.

A suspension of crude 4-amino-5-bromo-2-chlorobenzoic acid (0.540 g.) in hydrochloric acid (30 ml.) was diazotized with sodium nitrite (0.5 g.) at 5-10°. After unreacted material (0.22 g., 40.7%, m.p. 306°) had been filtered, the diazonium solution was poured into cold hypophosphorus acid (50 ml.) and refrigerated 20 hours. The solid obtained after filtering and extraction with chloroform was recrystallized from ethanol/water to give pure 2-chloro-5-bromo benzoic acid (0.281 g., \(1.19 \times 10^{-4}\) moles, 93% of diazotizable material), m.p. 152-153°, lit. (90) m.p. 155-156°, mixed m.p. 154-155°. Its infrared spectrum was identical


with that of authentic 2-chloro-5-bromobenzoic acid obtained by cationic bromination of o-chlorobenzoic acid (directions follow immediately).

Synthesis of 2-chloro-5-bromobenzoic acid (new preparation).

Bromine (5 ml., 15.5 g., 0.097 moles) was added in 2 hours to a stirred solution of o-chlorobenzoic acid (10 g., 0.064 moles) and silver sulfate (10 g., 0.032 moles) in sulfuric acid (80 ml., 96.5%) at room temperature. After stirring an additional 2 hours, the mixture
was poured on ice, filtered, washed and pressed. The moist solid was triturated with sodium bicarbonate and silver residues were removed by filtering. The filtrate was acidified; the product was filtered and dried. Recrystallization from acetic acid (70%) gave colorless needles of pure 2-chloro-5-bromobenzoic acid (11.0 g., 0.047 moles, 73.5%) m.p. 156°, lit. (90) m.p. 155-156°.

(b) Reaction of 2-bromo-5-chloroterephthalic acid with a large excess of hydrazoic acid. Sodium azide (1.50 g., 0.023 moles, 220% excess) was added in 30 minutes to a solution of 2-bromo-5-chloroterephthalic acid (2.00 g., 0.00716 moles) in sulfuric acid (35 ml., 100%, f.p. 10°) at 45°. When evolution of gases had ceased (740 ml., 48 hours), the mixture was poured over ice (400 g.) and made basic (sodium hydroxide, 20%). The solid was filtered, dried and recrystallized from ethanol/water to give pure colorless needles of 2-bromo-5-chloro-p-phenylenediamine (0.97 g., 0.00437 moles, 61.0%), m.p. 166-170.5°; infrared spectrum, Figure 44, p. 131; 2-bromo-5-chloro-p-phenylene diamine is a new compound.

Anal. Calc'd. for C16H16BrClN2: Found:

<table>
<thead>
<tr>
<th></th>
<th>Calc'd.</th>
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<tr>
<td>H</td>
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<td>2.50</td>
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<td>N</td>
<td>12.62</td>
<td>12.79</td>
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</table>

The diamine was converted to its bis-acetyl derivative by reaction with acetic anhydride and pyridine in chloroform. Recrystallization gave pure 2-bromo-5-chloro-bis(acetyl)-p-phenylenediamine, m.p. 306-306.5°, infrared spectrum, Figure 45, p. 132.
After removal of the diamine, the aqueous solution was acidified (hydrochloric acid) and filtered. Recrystallization of the crude material from ethanol/water gave pure 4-amino-5-bromo-2-chlorobenzoic acid (0.48 g., 0.00192 moles, 26.8%), m.p. 248-250°, mixed m.p. with previous sample, 248-250°.

6. Reaction of 2-bromo-5-methoxyterephthalic acid with hydrazoic acid.

(a) Using fuming sulfuric acid as solvent and catalyst.
Sodium azide (0.50 g., 0.0077 moles) was added in 45 minutes to a stirred solution of 2-bromo-5-methoxyterephthalic acid (2.00 g., 0.0076 moles) in fuming sulfuric acid (30 ml., 30% SO₃) at 0°. Gas evolution (330 ml.) was complete in 2 hours; the solution was poured into ice (400 g.) and made basic (sodium hydroxide, 15%). The diamine was removed by extraction with chloroform; since it oxidizes readily on contact with air, it was converted to the bis(acetyl) derivative which is stable. Acetic anhydride (5 ml.) and pyridine (2 drops) were added to the anhydrous chloroform solution. The chloroform was distilled after several hours; the solid obtained was recrystallized from ethanol/water to give pink crystals of pure 2-bromo-5-methoxy-bis(acetyl)-p-phenylenediamine (0.14 g., 4.65x10⁻⁴ moles, 6.1%), m.p. (218° soft) 241.5°d; infrared spectrum, Figure 46, p.132; 2-bromo-5-methoxy-bis(acetyl)-p-phenylenediamine is a new compound.
The aqueous solution was acidified, filtered and extracted continuously with chloroform to obtain the amino acid fraction. Material insoluble in cold ethanol/water was filtered; it was reprecipitated from ammonium hydroxide and dried to give starting material (0.15 g., 0.00054 moles, 7.1%); neut. equiv. (calc'd.) 137.5, (found) 143.0; m.p. 280°d; m.p. initial material 280°d. The infrared spectrum was identical with authentic material.

The ethanol-soluble portion was crystallized after decolorization (Norite) and concentration to give pure 4-amino-5-bromo-2-methoxybenzoic acid (1.49 g., 0.00605 moles, 79.5% conversion, the yield is 85.6% based on reacted starting material), m.p. 196°d., neut. equiv. (calc'd.) 246.0, (found) 245.0; infrared spectrum, Figure 34, p. 126; 4-amino-5-bromo-2-methoxybenzoic acid is a new compound.

Proof of structure of 4-amino-5-bromo-2-methoxybenzoic acid.
A mixture of crude 4-amino-5-bromo-2-methoxybenzoic acid (0.39 g.) in hydrochloric acid (30 ml.) was diazotized in 30 minutes with sodium
nitrite (0.5 g.) at 5-10°. Insoluble material was filtered (0.036 g.), and the filtrate mixed with cold hypophosphorus acid (50 ml.), then refrigerated for 20 hours. The product collected upon filtration and extraction with chloroform was recrystallized from ethanol/water to give pure 5-bromo-2-methoxybenzoic acid (0.272 g., 0.00018 moles, 81.9%), m.p. 119.2-119.6°, lit. (91) m.p. 120-120.5°


7. Reaction of 2-bromo-5-methylterephthalic acid with hydrazoic acid. Sodium azide (0.55 g., 0.0086 moles, 10% excess) was added in 15 minutes to a solution of 2-bromo-5-methylterephthalic acid (2.00 g., 0.0077 moles) in sulfuric acid (30 ml., 96.5%) at 45°. Evolution of gases (380 ml. total) ceased after 3 hours. The reaction mixture was then poured into ice, made basic (sodium hydroxide, 20%) and extracted with chloroform 4 times; this diamine also proved unstable in air. After drying the chloroform extract (sodium sulfate, then calcium hydride), the bis-acetyl derivative was prepared by treatment of the solution with acetic anhydride (5 ml.) and pyridine (2 drops). After 20 hours the white crystalline derivative was filtered, washed with chloroform and dried to yield pure 2-bromo-5-methyl-bis(acetyl)-p-phenylenediamine (0.375 g., 0.0013 moles, 16.9%), m.p. 306-306.5°, infrared spectrum, Figure 42, p. 130; 2-bromo-5-methyl-bis(acetyl)-p-phenylenediamine is a new compound.
The aqueous solution was acidified (hydrochloric acid, pH~3.0) after removal of the diamine and filtered. The filtrate was extracted continuously with chloroform in 20 hours. The ethanol-soluble portion upon recrystallization gave pure 4-amino-2-bromo-5-methylbenzoic acid (1.04 g., 0.0046 moles, 59.5% conversion; yield based on reacted starting material, see next paragraph, 64.2%), m.p. 225-225.5°, infrared spectrum, Figure , p. ; 4-amino-2-bromo-5-methylbenzoic acid is a new compound.

When the crude product was diazotized (see proof of structure) crude starting material was isolated. Assuming a representative sample was used for the diazotization, 8-1/2% of the crude weight (1.65 g.) is starting material (0.14 g., 0.00054 moles, 7%), m.p. 330-335°, m.p. (initial material) 334-335°.

Proof of structure of 4-amino-2-bromo-5-methylbenzoic acid. Crude 4-amino-2-bromo-5-methylbenzoic acid (0.47 g.) was diazotized in hydrochloric acid with sodium nitrite in 30 minutes at 0-5°.
Unreacted dibasic acid was filtered and identified (40 mg., see above). The solution was poured into ice-cold hypophosphorus acid (40 ml., 30%) and let stand over 20 hours. The product was isolated by filtration and extraction of the reaction mixture and then recrystallized from ethanol/water to give pure 2-bromo-5-methylbenzoic acid (0.32 g., 0.00015 moles, 80%), m.p. 153-154.5°, lit. (92) m.p. 152-153°, (93) m.p. 154-155°.

(93) A. Claus, J. prakt. Chem., 2, 46, 22 (1892).

8. Reaction of 2-chloro-5-methylterephthalic acid with hydrazoic acid. Sodium azide (1.10 g., 0.0169 moles, 80% excess) was added in 15 minutes to a stirred solution of 2-chloro-5-methylterephthalic acid (2.00 g., 0.0093 moles) in sulfuric acid (40 ml., 99%) at 45°. The mixture was poured on ice after 90 minutes (750 ml. of gas evolved) and made basic (sodium hydroxide, 20%). The diamine was extracted with methylene chloride, dried and converted to the stable bis-acetyl derivative with acetic anhydride and pyridine. Recrystallization from ethanol/water gave pure white 2-chloro-5-methyl-bis(acetyl)-p-phenylenediamine (1.12 g., 0.00505 moles, 54.2%), m.p. 302-303°; infrared spectrum, Figure 41, p.130; 2-chloro-5-methyl-bis(acetyl)-p-phenylenediamine is a new compound.

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<td>N</td>
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The aqueous solution was acidified (hydrochloric acid) and extracted continuously with chloroform for 24 hours. The solid was recrystallized from ethanol/water to give pure 4-amino-2-chloro-5-methylbenzoic acid (0.68 g., 0.00367 moles, 39.5%), m.p. 215-215.8°, infrared spectrum, Figure 32, p.125; 4-amino-2-chloro-5-methylbenzoic acid is a new compound.

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Proof of structure of 4-amino-2-chloro-5-methylbenzoic acid.
A mixture of 4-amino-2-chloro-5-methylbenzoic acid (0.28 g., 0.000151 moles) and hydrochloric acid (30 ml.) was diazotized in 30 minutes with sodium nitrite (0.5 g.) at 0-5°. The clear solution was poured into cold hypophosphorus acid (50 ml.) and refrigerated 20 hours. The product was isolated by extracting the acid solution with chloroform. Recrystallization once from ethanol/water gave 2-chloro-5-methylbenzoic acid (0.19 g., 1.12x10⁻⁴ moles, 73.5%), m.p. 145-148.5°, lit. (94) m.p. 163-166°, (95) 167°. The infrared spectrum was not the same as that of authentic 5-chloro-2-methylbenzoic acid.

(95) A. Claus, J. prakt. Chem. 2, 46, 27 (1892).
To prove further the structure of the deaminated product, a sample (0.10 g., 0.00059 moles) was oxidized with dilute potassium permanganate (1.0 g., 40 ml. of water) at 90-95°. Crude 4-chloroisophthalic acid (0.06 g., 0.0003 moles, 51%) was obtained, m.p. 290-293°, lit. (96) m.p. 294.5°; mixed melting point with authentic 4-chloroisophthalic acid, no depression. Its infrared spectrum was identical with that of authentic material.

(96) F. Ullmann and J. B. Uzbachian, Ber., 36, 1799 (1903).

9. Reaction of 2-isopropyl-5-methylterephthalic acid with hydrazoic acid. Sodium azide (0.6 g., 0.0092 moles) was added in 2 hours to a stirred solution of 2-isopropyl-5-methylterephthalic acid (2.00 g., 0.009 moles) in sulfuric acid (40 ml. 99%) at 0°. Gas evolution (420 ml.) ceased in 3 hours. The mixture was poured on ice, made basic and extracted with chloroform. Acetic anhydride (5 ml.) and pyridine (0.5 ml.) were added to the dried solution to prepare a stable derivative. After standing 20 hours the mixture was stripped of solvent. Recrystallization from ethanol/water gave pure 2-isopropyl-5-methyl-bis(acetyl)-p-phenylenediamine (1.26 g., 0.00506 moles, 56.3%, yield based on recovery was 81.2%), m.p. 260-261°, lit. (97) m.p. 260°, (98) 260°, infrared spectrum Figure 47, p. 133.

(97) F. Kehrmann and J. Messinger, Ber., 23, 3563 (1890).
The aqueous solution was acidified (hydrochloric acid), cooled and filtered to give starting acid (0.67 g., 0.000304 moles, 33.8%) m.p. 290-294°. Continuous extraction of the filtrate with chloroform failed to give any other organic product.

10. Reaction of 4-chloro-5-nitroisophthalic acid with hydrazoic acid. Sodium azide (0.45 g., 0.0069 moles) was added in 15 minutes to a stirred solution of 4-chloro-5-nitroisophthalic acid (1.5 g., 0.00613 moles) in sulfuric acid (30 ml., 100%) at 45°. The mixture was poured on ice after 4 hours (280 ml. gas evolved) and made basic (sodium hydroxide, 15%), then acidified (hydrochloric acid, adjusted to pH <3.0), and filtered. The filtrate was extracted with chloroform and the residue after evaporation of chloroform added to that on the filter. Recrystallization from dilute acetic acid gave orange needles of pure 5-amino-2-chloro-4-nitrobenzoic acid (0.97 g., 0.0045 moles, 66% yield), m.p. 236-238.5°d., sublimes, lit. (99) m.p. 239-240°d., sublimes; infrared spectrum, Figure 36, p.127.


Proof of structure of 5-amino-2-chloro-4-nitrobenzoic acid.
A solution of 5-amino-2-chloro-4-nitrobenzoic acid (0.30 g., 0.000139 moles) in hydrochloric acid (30 ml.) was diazotized with sodium nitrite (0.5 g.) at 0-5°. The clear solution which resulted was poured into
cold hypophosphorus acid (50 ml.) and refrigerated overnight. The product was extracted with chloroform (five 30 ml. portions) and the chloroform solution dried (sodium sulfate) and evaporated. The residue was recrystallized from benzene/ligroin to give light yellow needles of 2-chloro-4-nitrobenzoic acid (0.20 g., 0.0001 moles, 72% yield), m.p. 139-140°, lit. (100) m.p. 140-142°.


11. Reaction of 4-bromo-6-chloroisophthalic acid. Sodium azide (2.33 g., 0.0358 moles) was added in 15 minutes to a stirred mixture of 4-bromo-6-chloroisophthalic acid (4.00 g., 0.0143 moles) in sulfuric acid (40 ml., 96.5%) at 45°. The mixture was poured on ice when gas evolution was complete (760 ml., 6 hrs.) and made basic (sodium hydroxide, 20%); no diamine was obtained. The solution was acidified (hydrochloric acid, pH~3.0), cooled and filtered. The dry product was dissolved in ethanol/water; unreacted starting material was insoluble (0.52 g., 0.00185 moles), m.p. 266°, initial material, m.p. 266-268°. The ethanol/water solution upon decolorization and evaporation gave crystals of 5-amino-4-bromo-2-chlorobenzoic acid (3.00 g., 0.012 moles, 96.0% of reacted starting material), m.p. 189-190°; infrared spectrum, Figure 35, p.127; 5-amino-4-bromo-2-chlorobenzoic acid is a new compound.
Proof of structure of 5-amino-4-bromo-2-chlorobenzoic acid.

A mixture of 5-amino-4-bromo-2-chlorobenzoic acid (0.70 g., 0.0028 moles) and hydrochloric acid (30 ml.) was diazotized with sodium nitrite (1.0 g.) at 0-5° and added to ice-cold hypophosphorus acid (50 ml.). After standing 20 hours at 5° the product was separated by filtration and chloroform extraction. Recrystallization from ethanol/water gave 4-bromo-2-chlorobenzoic acid (0.60 g., 0.00255 moles, 91%), m.p. 163.8-165.2°, lit. (90) m.p. 167°.

12. Reaction of 4-methoxy-6-methylisophthalic acid with hydrazoic acid. Sodium azide (0.35 g., 0.0054 moles) was added in 10 minutes to a stirred solution of 4-methoxy-6-methylisophthalic acid (1.00 g., 0.0047 moles) in sulfuric acid (30 ml., 100%) at 0°. The mixture was poured on ice after gas evolution was complete (250 ml., 3 hours) and neutralized (sodium hydroxide, 20%) but not allowed to become basic. The aqueous solution rapidly became dark upon standing. A brown oil (0.29 g.) which could not be identified was obtained after continuous extraction with chloroform.

Several experiments were tried in which higher temperatures were used and in which variations in the work up were attempted. Nothing could be isolated from any of the reaction mixtures.
APPENDIX I

Infrared Spectrograms

The infrared spectrograms were obtained on a Perkin Elmer Double-Beam Recording Spectrophotometer equipped with sodium chloride optics.
2-METHYL-5-NITRO-TEREPHTHALIC ACID

2-METHOXY-5-NITRO-TEREPHTHALIC ACID

Fig. 15.
Fig. 18

Fig. 19
2-M ETHYL-5 -ISOPROPYL-TEREPHTHALIC ACID

4-B R O M O-6 -C H L O R O-ISOPHTHALIC ACID

Fig. 20.

Fig. 21.
Fig. 24.

Fig. 25.
Fig. 26.
Fig. 29.

Fig. 30.
Fig. 38.

Fig. 40.
2-Bromo-5-Methoxy-p-Phenylenediamine

Fig. 44.
Fig. 46.

2-BROMO-5-DIBROMO-5-HYDROXY-
[ACETYL]-2-PHENYLENE-
DIAMINE

NHCOCH₃

2-BROMO-5-METHOXY-
[ACETYL]-2-PHENYLENE-
DIAMINE

NHCOCH₃

H₂CO

NHCOCH₃

Fig. 45.
APPENDIX II

Calculations of Rate Constants for Schmidt Reactions of 2,5- and 2,4-Disubstituted Benzoic Acids.

Rate constants, "$k_2$", presented in Table XI, p. 62 for 2,5- and 2,4-disubstituted benzoic acids were calculated with the modified Hammett equation (Equation 69):

$$\log \frac{k_2}{k_2^{ortho}} = \sigma \rho$$

in which $k_2^{ortho}$ is the second order rate constant for the Schmidt reaction at $30^\circ$ (101) of the corresponding ortho-substituted benzoic acid in 96.5% sulfuric acid (22); $\rho$ is the reaction rate constant determined from kinetic studies.

(101) Rate data for ortho-substituted benzoic acids are available at temperatures of $0^\circ$, $10^\circ$, $20^\circ$ and $30^\circ$; to approximate more nearly the conditions of the present study, values at $30^\circ$ were used.

Calculations of "$k_2$" are illustrated for 2-bromo-5-nitrobenzoic and 5-bromo-2-nitrobenzoic acids.

"$k_2$" for 5-Bromo-2-nitrobenzoic Acid at $30^\circ$; $k_2^{ortho}$ (rate constant for ortho-nitrobenzoic acid) = 0.1009 l/mole min., $\sigma$ (m-bromo) = 0.391, $\rho = -1.77$

$$\log \frac{k_2}{k_2^{ortho}} = \sigma \rho$$

$$\log k_2 = \sigma \rho + \log k_2^{ortho}$$

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$k_2 = \text{anlog} (\sigma \rho + \log k_{2 \text{ortho}})$

$k_2 = \text{anlog} (-1.77 \times 0.391 + \log 0.1009)$

$k_2 = 0.0205 \text{ l/mole min.}$

"$k_2$" for 2-bromo-5-nitrobenzoic acid at 30°;

$k_{2 \text{ortho}}$ (rate constant for ortho-bromobenzoic acid) = 1.30 l/mole min., $\sigma_{(\text{m-nitro})} = 0.710$, $\rho = -1.77$.

$k_2 = \text{anlog} (\rho \sigma + \log k_{2 \text{ortho}})$

$k_2 = \text{anlog} (-1.77 \times 0.710 + \log 1.30)$

$k_2 = 0.0718 \text{ l/mole min.}$

Similar calculations were made for all compounds listed in Table XI. The values used for $k_{2 \text{ortho}}$ and $\sigma$ are listed in Table XIII.
Table XIII
Compilation of Rate\textsuperscript{a} and Substituent Constants

<table>
<thead>
<tr>
<th>Substituent</th>
<th>( \sigma )</th>
<th>( k_2^\text{ortho} )</th>
<th>( \log k_2^\text{ortho} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-bromo</td>
<td>-</td>
<td>1.30</td>
<td>0.114</td>
</tr>
<tr>
<td>o-chloro</td>
<td>-</td>
<td>0.647</td>
<td>-0.189</td>
</tr>
<tr>
<td>o-methyl</td>
<td>-</td>
<td>4.91</td>
<td>0.691</td>
</tr>
<tr>
<td>o-nitro</td>
<td>-</td>
<td>0.1009</td>
<td>-0.996</td>
</tr>
<tr>
<td>m-bromo</td>
<td>0.391</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>m-chloro</td>
<td>0.373</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>m-nitro</td>
<td>0.710</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>m-methyl</td>
<td>-0.069</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p-bromo</td>
<td>0.232</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p-chloro</td>
<td>0.227</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p-nitro</td>
<td>0.778</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Rate constants, \( k_2^\text{ortho} \), are experimental values determined at 30\textdegree for the indicated acids undergoing the Schmidt reaction in 96.5\% sulfuric acid.
I, Derry Lee Fishel, was born in Findlay, Ohio, July 15, 1929. My secondary school education was received in the public schools of Findlay, Ohio, and my undergraduate training at Bowling Green State University, which conferred the degree Bachelor of Arts in 1952. I began graduate study in chemistry at Ohio State University in October, 1952. While completing requirements for the degree Doctor of Philosophy I served as graduate teaching assistant in general and physical chemistry during the academic years from 1952 to 1958. I received three DuPont fellowships during the Summers of 1955, 1957 and 1958 while continuing my graduate study.