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STEREOCHEMISTRY OF THE MICHAEL ADDITION
TO ANGELIC AND TIGLIC ACID
DERIVATIVES

by

Michael P. Hughes

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy

Thesis Director's Signature:

[Signature]

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The author is grateful for a National Science Foundation Cooperative Fellowship during 1962-1964 without which this work might never have been completed.
To my wife Eloise
and
my daughter Beth
TABLE OF CONTENTS

Introduction  . . . . . . . . . . . . . 1

Section I

The Michael Addition to Angelic and Tiglic Acid Derivatives  . . . . . 4

Experimental  . . . . . . . . . . . . . 27

Section II

Synthesis of Angelic and Tiglic Acid Derivatives  . . . . . 52

Experimental  . . . . . . . . . . . . . 58

Section III

Synthesis of the erythro and threo-2,3-Dimethylglutaric Acids  . . . . 66

Experimental  . . . . . . . . . . . . . 71

Bibliography  . . . . . . . . . . . . . . 79
INDEX OF TABLES

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>The Michael Adducts from Angelonitrile and Tigonitrile</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE II</td>
<td>The Addition of Diethyl malonate to Angelonitrile and Tigonitrile</td>
<td>34</td>
</tr>
<tr>
<td>TABLE III</td>
<td>The Addition of Ethyl cyanoacetate to Angelonitrile and Tigonitrile</td>
<td>38</td>
</tr>
<tr>
<td>TABLE IV</td>
<td>The Addition of Di-(t)-butyl malonate to Angelonitrile and Tigonitrile</td>
<td>40</td>
</tr>
<tr>
<td>TABLE V</td>
<td>The Michael Adducts from Ethyl angelate and Ethyl tiglate</td>
<td>41</td>
</tr>
<tr>
<td>TABLE VI</td>
<td>Addition of Diethyl malonate to Ethyl angelate and Ethyl tiglate</td>
<td>42</td>
</tr>
<tr>
<td>TABLE VII</td>
<td>Addition of Ethyl cyanoacetate to Ethyl angelate and Ethyl tiglate</td>
<td>44</td>
</tr>
<tr>
<td>TABLE VIII</td>
<td>Addition of Di-(t)-butyl malonate to Ethyl angelate and Ethyl tiglate</td>
<td>45</td>
</tr>
<tr>
<td>TABLE IX</td>
<td>The Michael Adducts from t-Butyl angelate and t-Butyl tiglate</td>
<td>46</td>
</tr>
<tr>
<td>TABLE X</td>
<td>The Additions to t-Butyl angelate and t-Butyl tiglate</td>
<td>47</td>
</tr>
<tr>
<td>TABLE XI</td>
<td>Dehydration of Methyl Ethyl Ketone Cyanohydrin</td>
<td>56</td>
</tr>
<tr>
<td>TABLE XII</td>
<td>The N.M.R. Spectra of Angelic and Tiglic Acid Derivatives</td>
<td>64</td>
</tr>
</tbody>
</table>
Introduction

The Michael reaction (1) is the addition of a nucleophile, $B^-$, to a carbon-carbon double bond activated by an electron withdrawing group, $X$ (e.g., $-\text{COOR}$, $-\text{CO}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}_2$). The nucleophile $B^-$ becomes attached to the carbon atom $\varnothing$ to the activating substituent. The resulting carbanion is stabilized by the electron withdrawing group.

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{B}^− + \text{C} = \text{C} \quad & \quad \left\{ \begin{array}{c} R_1 \quad R_2 \\
\text{R}_3 \\
\text{R}_2 \quad \text{R}_3 \\
\text{C} = \text{C} \quad \text{X} \\
\text{B} \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
\text{HA} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{H}
\end{array} \right. \\
\end{align*}
\]

In these reactions, diastereomeric products can arise involving asymmetry at atoms in the R groups or in the newly added base. These systems will not be considered in this work. Generally, in systems where $R_2$ is not $X$ or hydrogen and $R_1$, $R_3$, and $B$ are all different, the carbon atoms $\varnothing$ and $\varnothing$ to the activating group become asymmetric. If the anion II has a relatively long life, configurational equilibrium would be obtained before protonation. Reaction of cis and trans
isomers of I with the same nucleophile would lead to a common intermediate and thus the same product. If, however, the anion II is not a discrete intermediate or has a relatively short life, i.e., if configurational equilibrium is not reached before protonation, then the initial products from cis and trans isomers of I would be diastereomeric.

trans-Addition to an activated cyclohexene to give the cis-disubstituted cyclohexane has been observed in the reactions of diethyl malonate with 1-acetylcyclohexene (2), nitromethane with 1-acetylcyclohexene (3), and diethyl malonate with 1-cyanocyclohexene (4). The observed stereoselectivity can be explained on the basis of steric control of ketonization as discussed by Zimmerman (5). Stereoselective trans-addition has also been observed in the reaction of p-toluenethiol with 1-p-tosylcyclohexene in ethanol (6). The investigators proposed a concerted mechanism, where any intermediate anion would have only a fleeting existence. The nucleophilic additions of thiols to substituted acetylenes (7) have also been shown to be usually trans and again a concerted mechanism has been suggested. In the last two examples, the carbanions that might be formed could exist as geometric isomers. Since only one isomer is possible in a cyclohexene or an acetylene, any addition can only be stereoselective but never stereospecific and usually affords less direct evidence about the lifetime of any ionic intermediate.

The first stereospecific Michael reaction was proposed by Kennedy (8). He discovered that the products from reaction of diethyl sodiomalonate with ethyl α-bromocrotonate and ethyl
\(\alpha\)-bromoisocrotonate in ethanol were configurationally different cyclopropanes and showed that for stereospecificity the proton-donating solvent was important. A trans Michael addition was postulated for the first step. Kagan (9) and Stephenson (10) have extended the work to prove that the initial reaction was a stereospecific Michael addition and show that there was also solvent-dependent stereoselectivity in aprotic media.

This work was undertaken to establish the stereochemistry of the addition of malonic ester to derivatives of the isomeric 2-methyl-2-butenoic acids and to determine some of the factors which influence this stereochemistry. This system was chosen for study because it allows direct determination of the stereochemistry of the Michael reaction and does not have the problems of postulating the stereochemistry of the ring closure and proving that a Michael reaction was indeed the first step as was required in the system studied by Kennedy, Kagan and Stephenson.
Section I
The Michael Addition
to Angelic and Tiglic Acid Derivatives

The Michael addition of diethyl malonate to angelate derivatives (I) and tiglate derivatives (II) gives an ethyl 4-carboethoxy-2,3-dimethylglutarate derivative (III) [for a discussion of the structures and synthesis of I and II see Section II].

\[
\begin{align*}
\text{I} & : & \text{CH}_3 & \text{C} = \text{C} & \text{X} \\
& & \text{H} & \text{C} = \text{C} & \text{CH}_3 \\
& & & \text{CH}_3 & \text{CH}_3 \\
\text{II} & : & \text{CH}_3 & \text{C} = \text{C} & \text{X} \\
& & \text{H} & \text{C} = \text{C} & \text{CH}_3 \\
& & & \text{CH}_3 & \text{CH}_3 \\
\text{III} & : & (\text{C}_2\text{H}_5\text{OOC})_2\text{CH}-\text{CH}-\text{CH}-\text{X} \\
\left[\text{X} = \text{CN}, \text{COOC}_2\text{H}_5, \text{COOC(CH}_3)_3\right]
\end{align*}
\]

The adduct (III) possesses two asymmetric carbon atoms and can exist in two racemic forms: the *erythro* form (III A) and the *threo* form (III B).
The asymmetric carbon atoms in III are the atoms of the carbon-carbon double bond in (I) and (II). The asymmetry is formed by the Michael addition.

If one assumes the addition across the double bond to be in a trans manner, then the **threo** form (III A) would be obtained from the angulate derivative (I), and the **erythro** form (III B) would be obtained from the tiglate derivative (II).

\[
(C_2H_5OOC)_2CH_2 + I \rightarrow \begin{array}{c}
\text{(threo)} \\
\text{CH}_3 \\
\text{H} \\
\end{array}
\]

\[
(C_2H_5OOC)_2CH_2 + II \rightarrow \begin{array}{c}
\text{(erythro)} \\
\text{CH}_3 \\
\text{H} \\
\end{array}
\]

Another possible mechanistic path could be the addition of the di-ethyl malonate anion to I to form the anion (IV), which then by a fast 1,3-proton shift would give the anion (V). The proton shift would have to be on the same side as the addition of diethyl malonate anion and would give stereoisomers from cis addition to the carbon-carbon double bond.
In this case the angelate derivative (I) would give the erythro form (III A) and the tiglate derivative (II) would give the threo form (III B).

Another possible stereochemical course could be the addition of the diethyl malonate anion to (I) or (II) to give a common long-lived anion (VI). This anion could attain configurational equilibrium before protonation and lead to common products from (I) and (II). Resonance in (VI) with the group X forces the configuration about the \( \alpha \)-carbon to be planar (5,11). The anion could exist in several conformations but the most stable conformation would be difficult to predict (12).
Since the addition takes place under basic conditions, enolization at the carbon $\alpha$ to the group $X$ in III can also occur. This would equilibrate the erythro and threo forms. For this reason the reactions were not carried to completion but were run for shorter periods of time to determine the stereochemistry in the initial addition.

The additions of ethyl cyanoacetate and di-$t$-butyl malonate to (I) and (II) were also studied to determine what effect the steric requirement of the nucleophile had on the stereochemistry of addition. Addition of ethyl cyanoacetate to (I) and (II) would give derivatives of ethyl 4-cyano-2,3-dimethylglutarate (VII).
This adduct possesses three asymmetric carbon atoms and can exist in four racemic forms. However, under the basic conditions of the reaction, the configuration at the carbon atom \( \alpha \) to the nitrile and carboethoxy groups would be easily equilibrated. Acid hydrolysis of VII gives 2,3-dimethylglutaric acid, the same as from hydrolysis of III.

The stereochemical results of the Michael reactions were determined by acid hydrolysis of the adducts to 2,3-dimethylglutaric acid (VIII). If the stereochemistry of the two asymmetric carbon atoms was not changed during hydrolysis, the amounts of erythro and threo forms of the 2,3-dimethylglutaric acid would be the amounts of erythro and threo forms in III and would tell the stereochemistry of addition during formation of VII. The erythro and threo-2,3-dimethylglutaric acids were synthesized [see Section III]. Gas chromatographic analysis of the dimethyl esters was used to determine the erythro and threo composition of the 2,3-dimethylglutaric acids.

\[
\begin{align*}
\text{III or VII} & \xrightarrow{\text{H}_2\text{O}^+} \text{HOOC-C}_2\text{CH}_2-\text{CH-CO-H}^+ \\
& \text{CH}_3 \quad \text{CH}_3 \\
\text{VIII} & 
\end{align*}
\]

To show that the stereochemistry of the two asymmetric carbon atoms was not greatly changed, the following experiments were run. The pure dimethyl threo-2,3-dimethylglutarate was refluxed for twenty hours in 1:1 dioxane-6 N hydrochloric acid (the most vigorous conditions used in hydrolysis of VII). The isolated 2,3-dimethylglutaric acid was still the pure threo form. Dimethyl erythro-2,3-dimethylglutarate was also unchanged by the acid hydrolysis.
of III (X = -CN) or of VII could give first the 2,3-dimethylglutar-imide (IX). The erythro form (III A) would give the cis imide.

Enolization at the \( \alpha \)-carbon leading to the trans imide would relieve steric strain and further hydrolysis would give threo-2,3-dimethylglutaric acid. To check this possibility, the cis and trans-2,3-dimethylglutarimides were hydrolyzed for twenty hours in 1:1 dioxane-6 N hydrochloric acid. The cis-imide gave 2,3-dimethylglutaric acid containing 30% of the threo isomer (by v.p.c. of the dimethyl ester). The trans-imide gave 2,3-dimethylglutaric acid containing 18% of the erythro isomer. However, the enolization of any imide formed during the hydrolysis of the Michael adducts must not have occurred to a great extent because of the following observation. The adducts from diethyl sodiomalonate and the unsaturated nitriles could be resolved by gas chromatography into two peaks. If the peak which emerged first is assigned to the erythro isomer, then as determined by areas of the peaks, the amount of erythro isomer in the initial adduct was within 5% of the amount in the hydrolysate.
The only prior investigation of the stereospecificity of addition to angelic and tiglic acid derivatives was made by Blaise (13), who studied the addition of ethyl cyanoacetate to ethyl angelate and ethyl tiglate. The addition to ethyl angelate was run at room temperature to reduce the conversion of ethyl angelate to the more stable ethyl tiglate and the unreacted unsaturated ester was isolated and shown to be ethyl angelate. The addition to ethyl tiglate was run at steam bath temperature for thirty hours. The adduct from ethyl tiglate was saponified with aqueous potassium hydroxide and the triacid was decarboxylated at 150° to give "cis" 2,3-dimethylglutaric acid, m.p. 84-85° (shown in the present work to be the third isomer). The adduct from ethyl angelate also gave "cis" 2,3-dimethylglutaric acid and an impure liquid thought to be another 2,3-dimethylglutaric acid. Blaise concluded that, contrary to his expectation, the addition was non-stereospecific. No yields were given and no stereochemical assignment of the adduct was made. Since no adequate analytical methods were available to Blaise, it was impossible to determine whether equilibration took place during the Michael addition or during hydrolysis. The method of work-up used might equilibrate any stereoisomers.

The first reactions studied in this work were the additions to angelonitrile (X) and tigonitrile (XI). It was hoped that by using the linear nitrile group instead of the carboethoxy group, conformational problems would be avoided and the steric requirement would be lessened so that a more stereospecific addition would be favored.
Diethyl sodiomalonate added to X in ethanol at 6° to give ethyl 2-carboethoxy-4-cyano-3-methylpentanoate (XII) containing 85% of the threo isomer. Under identical conditions, diethyl sodiomalonate and XI gave XII containing 75% of the erythro isomer. The reagents in the Michael additions were used in the ratio of two moles of diethyl malonate to one mole of unsaturated nitrile and one of base to give the stoichiometry:

\[
\text{CH}_2\text{(COOC}_2\text{H}_5\text{)}_2 + \text{CH}_3\text{CH=CH-CN} \rightarrow \text{C}_2\text{H}_5\text{OOC} \text{CH} - \text{CH} - \text{CH} - \text{CN} + \text{NACH(COOC}_2\text{H}_5\text{)}_2
\]

The use of a one mole excess of diethyl malonate was found to give better stereospecificity. When diethyl malonate was used in only 10% excess, the adduct XII from addition to X at 6° contained 77% of the threo isomer. The addition to XI under the same conditions gave XII containing 65% of the erythro isomer.
Prolonged reaction in refluxing ethanol gave XII containing about equal amounts of the erythro and threo isomers. Thus, there is no steric difference in the two isomers which would favor one form over the other.

The stereospecificity of the Michael addition was found to depend mainly upon the solvent and the temperature. Changing the concentrations did not greatly affect the stereospecificity. In general, lower temperature gave better stereospecificity but also less yield of XII. Long standing at room temperature decreased the stereospecificity, but at 6° the isomer composition remained the same even after 45 days.

Oxygen had to be excluded from the reactions. In the reactions at 6°, when oxygen was not completely removed, the yield of XII was much lower and a new product, pentaethyl 1,1,2,3,3-propanepentacarboxylate (XIII), was obtained. The pentaester was also obtained when an ethanol solution of diethyl sodiomalonate was saturated with oxygen and let stand at 6°.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{OOC} & \quad \text{COOC}_2\text{H}_5 \\
\text{CH} & \quad \text{CH} \\
\text{C}_2\text{H}_5\text{OOC} & \quad \text{COOC}_2\text{H}_5 \\
\end{align*}
\]

The structure of XIII was proved by synthesis and by hydrolysis to 1,2,3-propanetricarboxylic acid.
Diethyl potassiombomalonate and diethyl lithiomalonate were added to X and XI in ethanol to determine if the cation affected the stereochemistry. Diethyl ethoxymagnesiomalonate did not add to X or XI even after 55 days at room temperature. The results are shown in the following table. The use of sodium proved best. The cation was not a critical factor in stereospecificity, but the less ionic or dissociated salts reacted very slowly.

Effect of Cation on the Addition of Diethyl Malonate to Angelonitrile and Tiglonitrile in Ethanol at Room Temperature

<table>
<thead>
<tr>
<th>Cation</th>
<th>Time</th>
<th>( % ) yield of XII from X</th>
<th>( % ) erythro from XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>73 hr.</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Sodium</td>
<td>142 hr.</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Lithium</td>
<td>35 days</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Magnesium</td>
<td>55 days</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\( X = \text{Angelonitrile}; \ XI = \text{Tiglonitrile} \)

Stereospecificity was found even when \( \text{t-butyl alcohol} \) was used as the solvent. This was unexpected since the Michael addition of diethyl sodiomalonate to ethyl \( \text{\textalpha-} \)bromocrotonate and ethyl \( \text{\textalpha-} \)bromo-isocrotonate in \( \text{t-butyl alcohol} \) was not stereospecific (9). The proton transfer would be expected to be slower than in ethanol because the \( \text{t-butyl alcohol} \) is a weaker and more hindered acid than ethanol. Diethyl sodiomalonate added to angelonitrile to give XII
containing 65% of the threo isomer and diethyl sodiomalonate added to tiglonitrile to give XII containing 77% of the erythro isomer.

The Michael reaction in aprotic solvents was much slower and retained little stereospecificity. By using two equivalents of diethyl malonate to one equivalent of unsaturated nitrile and one of base, diethyl malonate could act as proton donor. The results are summarized below. Although the difference in composition was small, the trend was still towards a stereospecific addition.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time (days)</th>
<th>% yield of XII X</th>
<th>% yield of XII XI</th>
<th>% of erythro X</th>
<th>% of erythro XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>3</td>
<td>23(^a)</td>
<td>20</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>48</td>
<td>8</td>
<td>11</td>
<td>47</td>
<td>59</td>
</tr>
<tr>
<td>Dioxane</td>
<td>32</td>
<td>6</td>
<td>16</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>50</td>
<td>8</td>
<td>8</td>
<td>43</td>
<td>55</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>25</td>
<td>11</td>
<td>7</td>
<td>38</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^a\) Reaction run for 6 days.

The observed stereochemistry in ethanol required that the major reaction path of diethyl sodiomalonate with X and XI be a stereospecific trans addition. The reaction can be viewed as a concerted addition with the proton being donated by the solvent as the malonate anion adds to the double bond. The decreases in the rate and in
stereospecificity in aprotic solvents show that the proton addition is important in determining the energetics and stereochemistry.

Even at 6°, the stereospecificity in ethanol was about the same as in the room temperature runs for three days. Epimerization of the adduct at the carbon α to the nitrile group is possible but would not seem to explain a limit to the stereospecificity, since the isomer composition at 6° does not change after 45 days but the yield of XII does increase. Interconversion of unsaturated nitriles before addition also doesn't explain a limit of stereospecificity because the recovered nitriles from the reactions at 6° for 15 days were still more than 96% pure. The results would be observed if a minor amount of anion XIV was formed. Protonation could then occur from either side to give a mixture of isomers, or protonation might occur on nitrogen to give a ketenimine which would rearrange to the isomer mixture.
The decrease in stereospecificity in ethanol as the reaction proceeds at room temperature and at reflux can come from equilibration of the adduct at the asymmetric carbon atom \( \alpha \) to the nitrile group and by greater stereomutation of the double bond before addition. The unreacted unsaturated nitriles were recovered and analyzed. When the addition to X was run at reflux for 5 hours, the recovered nitrile contained 22% of XI. Under the same conditions, the recovered nitrile from the addition to XI contained 74% of X. Thus, the interconversion favored angelonitrile. At room temperature the interconversion was not as rapid but still favored angelonitrile.

The unreacted nitriles from the reactions in aprotic solvents were also recovered and checked for purity. Angelonitrile underwent little stereomutation. In tetrahydrofuran, dimethylformamide and
dimethyl sulfoxide, tiglonitrile slowly underwent conversion to anelonitrile. Dioxane was not a good aprotic solvent for the Michael reaction. Tiglonitrile was largely converted into anelonitrile after 30 days and the reaction was very slow, i.e., the yield of XII from anelonitrile had not greatly increased after 76 days.

No experiments were performed to determine the stability of the erythro and threo isomers in the presence of diethyl sodiomalonate in the aprotic solvents. There was some equilibration in dimethyl sulfoxide because the degree of stereospecificity decreased at longer reaction times.

When ethyl sodiocyanoacetate was added to X in ethanol at 6°, the Michael adduct, ethyl 2,4-dicyano-3-methylpentanoate (XV), contained 72% of the threo isomer. Under identical conditions, addition to XI gave XV containing 69% of the erythro isomer.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{OOC-CH-CH-CH-CN} \\
\text{CN} & \text{CH}_3 & \text{CH}_2
\end{align*}
\]

\[\text{XV}\]

The same trends were found using ethyl cyanoacetate in ethanol as using diethyl malonate in ethanol; however, the stereospecificity was less. The lower stereospecificity could possibly be due to the smaller steric requirement of the ethyl cyanoacetate anion, allowing more "cis" protonation of an intermediate anion, or could be due to more epimerization at the carbon α to the nitrile group during hydrolysis to the 2,3-dimethylglutaric acids. The adduct XV contained two nitrile groups, and stronger acid was required for
hydrolysis. Unfortunately, the adduct XV could not be analyzed by
gas chromatography so it is not known how much, if any, equilibration
occurred during hydrolysis.

Ethyl sodioacyanoacetate was insoluble in t-butyl alcohol and
tetrahydrofuran and the additions in these solvents were not completed.
The Michael reaction of di-t-butyl sodiomalonate with X and XI could
not be run in ethanol. Even at 6°, ester exchange to t-butyl alcohol
and diethyl sodiomalonate was complete. In t-butyl alcohol, di-t-
butyl sodiomalonate added to the unsaturated nitriles to give t-butyl
2-carbo-t-butoxy-4-cyano-3-methylpentanoate (XVI).

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

The results of using nucleophiles with different steric requirements
are shown in the table below.

The Michael Additions to Angelonitrile
and Tigonitrile at Room Temperature

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Solvent</th>
<th>% \text{erythro}</th>
<th>\text{% from}</th>
<th>X</th>
<th>XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl malonate</td>
<td>C_2H_5OH</td>
<td>20</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CH_3)_3COH</td>
<td>35</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CH_3)_2SO</td>
<td>38</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl cyanoacetate</td>
<td>C_2H_5OH</td>
<td>29</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CH_3)_2SO</td>
<td>31</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di-t-butyl malonate</td>
<td>(CH_3)_3COH</td>
<td>51</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CH_3)_2SO</td>
<td>35</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is evident that the increase in the steric requirement of the nucleophile did not increase the stereospecificity in the addition. However, the reactions with di-\(\tau\)-butyl malonate were faster than the reactions with diethyl malonate. The rate increase can be seen from the increase in the yield of the Michael adduct under about equal conditions. The results are shown in the table below.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Solvent</th>
<th>Time (days)</th>
<th>% yield of Michael Adduct X</th>
<th>% yield of Michael Adduct XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl malonate</td>
<td>(C_2H_5OH)</td>
<td>6</td>
<td>23(^a)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>42</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>((CH_3)_3COH)</td>
<td>16</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>((CH_3)_2SO)</td>
<td>45</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Di-(\tau)-butyl malonate</td>
<td>((CH_3)_3COH)</td>
<td>7</td>
<td>37</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>((CH_3)_2SO)</td>
<td>39</td>
<td>39</td>
<td>24</td>
</tr>
</tbody>
</table>

\(^a\)Reaction time was 8 days.

Di-\(\tau\)-butyl sodiomalonate must be less solvated and be a stronger base than diethyl sodiomalonate and thus have more free carbanion character.

Diethyl sodiomalonate added to ethyl angelate (XVII) and ethyl tiglate (XVIII) to give diethyl 4-carboxethoxy-2,3-dimethylglutarate (XIX).
The addition to XVII, but not to XVIII, gave also diethyl 4-carboethoxy-2-ethylglutarate (XX).

\[
\text{CH}_3\text{C}=\text{C}\text{CH}_3
\]

\[
\text{C}_2\text{H}_5\text{OOCC}_{\text{CH}-\text{CH}-\text{CH}-\text{COC}_{\text{H}_5}}\text{CH}_3\text{C}=\text{C}\text{CH}_3
\]

\[
\text{C}_2\text{H}_5\text{OOCC}_{\text{CH}_3}\text{C}=\text{C}\text{CH}_3
\]

\[
\text{XX}
\]

The amount of XX in the product increased as the reaction temperature was decreased. The results are given below.

The Product Composition from the Michael Addition of Diethyl Sodiomalonate to Ethyl Angelate and Ethyl Tiglate in Ethanol

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Composition(^a) of Michael Adducts from XVII</th>
<th></th>
<th>Composition(^a) of Michael Adducts from XVIII</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% XX</td>
<td>% erythro</td>
<td>% three</td>
<td>% erythro</td>
</tr>
<tr>
<td>Reflux</td>
<td>0</td>
<td>56</td>
<td>44</td>
<td>72</td>
</tr>
<tr>
<td>25(^\circ)</td>
<td>6</td>
<td>33</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>6(^\circ)</td>
<td>38</td>
<td>18</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>-20(^\circ)</td>
<td>85</td>
<td>3</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

\(^a\)Composition determined by v.p.c. of hydrolysis product.
The structure of XX was determined from analysis of the n.m.r. spectra of the adduct formed at -20° and of the ester of the hydrolysis product. Dimethyl 2-ethylglutarate was prepared from ethyl 2-carboxethoxy-4-cyano-2-ethylbutyrate, obtained by ethylation of the adduct of diethyl malonate and acrylonitrile.

\[
\begin{align*}
\text{CH}_2(\text{COOC}_2\text{H}_5)_2 + \text{CH}_2 = \text{CH} - \text{CN} & \rightarrow (\text{C}_2\text{H}_5\text{OOOC}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CN} \\
\text{CH}_2 = \text{CH} - \text{CN} & \rightarrow \text{CH}_2 = \text{CH}_2 \\
\text{CH}_3\text{COOC}-\text{CH}-\text{CH}_2\text{CH}_2 & \rightarrow (\text{C}_2\text{H}_5\text{OOOC}_2\text{CH}_2\text{CH}_2\text{CN} \\
\text{COOC}_2\text{CH}_3 & \rightarrow (\text{C}_2\text{H}_5\text{OOOC}_2\text{CH}_2\text{CH}_2\text{CN}
\end{align*}
\]

The authentic dimethyl 2-ethylglutarate and the ester from degradation of the Michael adduct formed at -20° were identical in n.m.r. spectra and gas chromatographic retention times.

The adduct XX would be obtained if ethylangelate in the presence of base would rearrange to ethyl 2-ethylacrylate (XXI) and XXI add diethyl sodiomalonate.

\[
\begin{align*}
\text{CH}_3 & \rightarrow \text{CH}_2 \\
\text{H'-C=CH}_{-\text{CH}_3} & \rightarrow \text{CH}_2\text{CH}_2\text{C}-\text{COOC}_2\text{H}_5 \\
\text{XXI} & \rightarrow \text{CH}_2\text{CH}_3 \\
(\text{C}_2\text{H}_5\text{OOOC}_2\text{CH}-\text{CH}_2-\text{CH}-\text{COOC}_2\text{H}_5 & \rightarrow XX
\end{align*}
\]
This is a novel process, since the hydrogen of the \( \alpha \)-methyl group would not be thought to be acidic. Removal of a proton by base would give the allylic carbanion (XXII).

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} \quad \text{C} \quad \text{COOC}_2\text{H}_5 \\
\text{H} & \quad \text{C} \quad \text{C} \quad \text{CH}_2 & \quad \xrightarrow{\text{XXII}} & \quad \text{CH}_3 & \quad \text{C} \quad \text{C} \quad \text{COOC}_2\text{H}_5 \\
\text{H} & \quad \text{C} \quad \text{C} \quad \text{CH}_2
\end{align*}
\]

Although the negative charge cannot be distributed by resonance to the carboethoxy group, it can still be stabilized by the close proximity to the electropositive carbon of the carbonyl (XXII C). Some driving force for a rearrangement in this manner would be the relief of steric strain of the cis methyl and carboethoxy groups.

In ethanol, the Michael reaction of diethyl sodiomalonate with XVII and XVIII was stereospecific. The \textit{erythro} isomer of XIX seemed to be more stable than the \textit{threo} form, for when the Michael reaction was run at reflux for 11 hours the composition was 56-72\% of the \textit{erythro} isomer. The equilibrium position must be between 56\% and 72\% and probably more towards the higher value.

Ethyl sodiocyanooacetate added to ethyl tiglate in ethanol at 6\(^\circ\) to give diethyl 4-cyano-2,3-dimethylglutarate (XXIII) containing 89\% of the \textit{erythro} isomer. Ethyl sodiocyanooacetate and ethyl angelate
under the same conditions gave XXIII and the adduct corresponding to XX. Hydrolysis of the mixture showed the XXIII to contain 55% of the erythro isomer.

\[
\text{CN CH}_3 \text{ CH}_3 \\
\text{C}_2\text{H}_5\text{OOC-CH-CH-CH-COOCC}_2\text{H}_5
\]

**XXIII**

Stereospecificity was also observed when diethyl sodiomalonate was added to \textit{t}-butyl angelate and \textit{t}-butyl tiglate in ethanol. Whereas di-\textit{t}-butyl malonate exchanged in ethanol to give diethyl malonate, the adducts from the \textit{t}-butyl angelate and \textit{t}-butyl tiglate showed little if any exchange (analysis by n.m.r.). Diethyl sodiomalonate added to \textit{t}-butyl angelate at room temperature to give the adduct XXIV containing 71% of the \textit{three} isomer. Under identical conditions, the adduct XXIV from \textit{t}-butyl tiglate contained 91% of the erythro isomer.

\[
(\text{C}_2\text{H}_5\text{OOC})_2 \text{CH-CH-CH-COOCC}_2\text{H}_5
\]

**XXIV**

The effect of the size of the activating group is shown on the following page.
Michael Addition of Diethyl Sodiomalonate to the Angelic and Tiglic Acid Derivatives in Ethanol at Room Temperature

<table>
<thead>
<tr>
<th></th>
<th>% erythro isomer from Angelic Configuration</th>
<th>Tiglic Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH=CH(CH₃)CN</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>CH₃CH=CH(CH₃)COOC₂H₅</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>CH₃CH=CH(CH₃)COOC(CH₃)₃</td>
<td>29</td>
<td>91</td>
</tr>
</tbody>
</table>

The Michael additions to the ethyl esters and t-butyl esters of angelic and tiglic acids in t-butyl alcohol or dimethyl sulfoxide were no longer stereospecific but were stereoselective. The results are shown in the table above.

The Michael Addition to Ethyl Angelate and Ethyl Tiglate at Room Temperature

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Solvent</th>
<th>% erythro isomer from XVII</th>
<th>XVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl malonate</td>
<td>(CH₃)₃COH</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Ethyl cyanoacetate</td>
<td>(CH₃)₂SO</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>Di-t-butyl malonate</td>
<td>(CH₃)₃COH</td>
<td>83</td>
<td>88</td>
</tr>
<tr>
<td>Di-t-butyl malonatea</td>
<td>(CH₃)₃COH</td>
<td>75</td>
<td>91</td>
</tr>
</tbody>
</table>

aAddition to t-butyl angelate and t-butyl tiglate.

Kennedy (8) and Kagan (9) reported that the reaction of diethyl sodiomalonate with ethyl α-bromocrotonate or ethyl α-bromoisocrotonate in aprotic solvents was stereoselective. Kagan (9) observed that the amount of cis isomer increased in the more polar solvents.
Because in aprotic solvents only stereoselectivity was found with ethyl angelate or ethyl tiglate but stereospecificity was observed with angelonitrile or tigonitrile, it must be assumed there is a difference in the steric requirement and the basicity of the intermediate anion (VI).

\[
(ROOC)_2CH + CH_3\cdot C=\overset{\text{H}}{\text{C}}\text{H}_3 \rightarrow (ROOC)_2CH\cdot CH\cdot C=\overset{\text{CH}_3\cdot CH_3}{\text{x}}
\]

Assuming an order of base strength (14) to be

\[
\overset{\text{x}}{\text{C}}\cdot \text{CN} > \overset{\text{c}}{\text{C}}\cdot \text{COOR} > \overset{\text{c}}{\text{C}}(\text{COOR})_2
\]

then it may be said that when \( X = \text{CN} \) the anion does not exist long enough to obtain configurational equilibrium before protonation but when \( X = \text{COOR} \) the anion does exist long enough to attain configurational equilibrium and proceeds mainly to the erythro isomer.

Zimmerman and Chang (12) have proposed a model to explain the stereoselectivity observed in the ketonization of acyclic enols of the type XXV.

\[
\text{Path 1}
\]

\[
\text{Path 2}
\]

(where \( L = \) large group, \( M = \) medium group, \( S = \) small group)
The authors proposed that, when \([ =C(OH)R_2]\) is only slightly larger than \(R_1\), the proton is added to the side marked path 1 to give the \textit{erythro} form, but when \([ =C(OH)R_2]\) is very much larger than \(R_1\), the proton is added to the side marked path 2 to give the \textit{threo} form.

By using this model to assign the stereochemistry of protonation of the anion \(XXVI\) and assuming that a methyl group is slightly larger than the carboethoxy group \((15)\), one would predict the \textit{erythro} isomer as the major product. This is observed.

The addition of di-\(t\)-butyl sodiomalonate to angelonitrile and tiglonitrile in dimethyl sulfoxide could be called a stereoselective reaction (angelonitrile gave adduct \(XVI\) containing 35\% \textit{erythro}, tiglonitrile gave adduct \(XVI\) containing 41\% \textit{erythro} form). In this case the model would require that \([ =C(OH)R_2]\) be very much larger than \(R_1\) or that the nitrile group be larger than a methyl group. Recent evidence by Ritchie and Pratt \((16)\) indicates that in dimethyl sulfoxide the nitrile group is so solvated that it might be larger than a methyl group.

This work is the second demonstrated stereospecific Michael reaction and is the first example of a general class of possible stereospecific Michael reactions. Some of the variables which affect the stereochemistry of the Michael adduct were determined.
Experimental

All melting points were corrected and boiling points were uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Carbon tetrachloride solutions or potassium bromide disks were used for solids and thin films on salt plates were used for liquids. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal reference (the chemical shifts are recorded as parts per million below tetramethylsilane). The spectra of liquids were obtained in the neat form or in carbon tetrachloride solutions and the spectra of solids in carbon tetrachloride solutions. Vapor phase chromatographic analyses were obtained on a Perkin-Elmer Model 154 chromatograph using a 2-meter column packed with 30% silicone oil on Chromosorb W or on a Wilkens Aerograph Hy-Fi equipped with a hydrogen flame ionization detector and using a 508-foot stainless steel capillary column (0.03 inch i.d.) coated with Ucon 50-HB-660 glycol (Union Carbide Corp.). Analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

The Michael reactions were run under the following conditions: The reagents were distilled before use. All solvents were carefully dried by standard procedures. The glassware was dried in an oven and care was taken to exclude moisture during the reaction. The reactions at room temperature or at 6° were run in tightly stoppered flasks that
had been purged well with dry nitrogen to exclude oxygen. The reagents were normally used in the proportion: two moles of malonic ester or cyanoacetic ester to one mole of unsaturated acid derivative to one mole of base. In ethanol or t-butyl alcohol, the alkoide was prepared from metallic sodium. In the aprotic solvents, sodium hydride was used to prepare the sodiomalonate or sodiocyaanoacetate. The procedure for work-up was the same for all runs. The following experiments typify the Michael additions.

Di-t-butyl malonate was prepared in 45% yield from 50 g. of malonic acid and isobutylene by the method of Fonken and Johnson (17) to give material with b.p. 96-98° at 14 mm.; 21°D 1.4184 .

Addition of Diethyl malonate to Angelonitrile:

In Ethanol: Metallic sodium (1.15 g. 0.048 mole) was dissolved in 50 ml. of absolute ethanol, 16.120 g. (0.1005 mole) of diethyl malonate added and the mixture heated to reflux and let cool to room temperature. Angelonitrile (4.086 g.. 0.0504 mole) was added and the flask was purged with dry nitrogen, stoppered tightly and let stand for 146 hours. Six milliliters of glacial acetic acid was added and the mixture was poured into 150 ml. of water and extracted with three 75-ml. portions of ether. The ethereal solution was washed with water, saturated sodium bicarbonate and brine and dried over anhydrous sodium sulfate. The ether was evaporated and the yellow residue distilled at 0.6 mm. to give a forerun, b.p. 25-55°, 12.95 g. of diethyl malonate, b.p. 55-70°, and 2.564 g. (21%) of ethyl 2-carboethoxy-4-cyano-3-methylpentanoate, b.p. 123-126°, 22°D 1.4388. Vapor phase chromatographic analysis of the low boiling fraction showed that the unreacted nitrile contained 10% of tiglonitrile.
In Dimethyl Sulfoxide: A mixture of 50 ml. of dimethyl sulfoxide and 16.024 g. (0.100 mole) of diethyl malonate was cooled in ice and 2.322 g. of a 51.2% dispersion of sodium hydride* in mineral oil added in one portion. The mixture was warmed until solution was complete, then cooled to room temperature. Angelonitrile (3.980 g., 0.0499 mole) was added and the flask was purged with dry nitrogen, stoppered tightly and let stand for 45 days. Six milliliters of glacial acetic acid was added and the mixture was poured into 100 ml. of water and extracted with three 75-ml. portions of ether. The ethereal solution was washed with water, saturated sodium bicarbonate and brine and dried over anhydrous sodium sulfate. Evaporation of the ether and distillation at 0.8 mm. gave a low boiling fraction, b.p. 25-60°, 11.80 g. of diethyl malonate, b.p. 60-75°, and 2.575 g. (21%) of ethyl 2-carboethoxy-4-cyano-3-methylpentanoate, b.p. 120-126°, n\textsuperscript{22}D 1.4386. Vapor phase chromatographic analysis of the low boiling fraction showed that the unreacted nitrile contained 13% of tiglonitrile.

Hydrolysis of the Michael Adducts: The Michael adducts which contained two nitrile functions were hydrolyzed in 1:1 dioxane-6 N hydrochloric acid for twenty hours. The Michael adducts which contained only one nitrile function were hydrolyzed in 1:1 dioxane-3 N hydrochloric acid for twenty hours and the Michael adducts which contained only ester functions were hydrolyzed in 1:1 dioxane-1.5 N hydrochloric acid for twenty hours. The following experiment typifies the hydrolysis procedure.

Hydrolysis of the Michael Adduct: Ethyl 2-carboethoxy-4-cyano-3-methylpentanoate (2.02 g.), 25 ml. of purified dioxane and 25 ml. of 3 N hydrochloric acid were refluxed for twenty hours. The solvent was evaporated and the salts extracted with four 25-ml. portions of ether. The combined ether fractions were treated with excess diazomethane (18) and the ether was evaporated and the remaining oil distilled under vacuum to give 0.849 g. (53%) of dimethyl 2,3-dimethylglutarate, b.p. 64-66° at 0.8 mm., n^22_D 1.4308.

Determination of the erythro and threo Isomer Composition in the Dimethyl 2,3-dimethylglutarates: The 508-foot stainless steel capillary column was coated with Ucon 50-HB-660 by forcing a 1% (by weight) solution of the glycol in chloroform slowly through the column. At 103° and a flow rate of 27 ml. per minute, a 0.3 μl. sample gave two partially resolved peaks after 40 minutes with the erythro diester emerging three minutes before the threo diester. Mixtures of known composition (prepared from the pure erythro and threo 2,3-dimethylglutaric acids) were chromatographed to establish a calibration curve.

\[
\begin{bmatrix}
\text{known % erythro vs.} & \text{peak height erythro} \\
\text{peak height erythro + peak height threo}
\end{bmatrix}
\]

The following experiments were run to test for equilibration between erythro and threo 2,3-dimethylglutaric acids.
Hydrolysis of Dimethyl erythro-2,3-dimethylglutarate: Twenty-five milliliters of 6 N hydrochloric acid, 25 ml. of purified dioxane and 0.817 g. of dimethyl erythro-2,3-dimethylglutarate were refluxed for 20 hours. The solvent was evaporated and the residue dried overnight at oil pump pressure. Excess ethereal diazomethane was added, the solvent evaporated and the residue distilled to give 0.623 g. of dimethyl 2,3-dimethylglutarate, b.p. 68-70° at 0.6 mm., n"D 1.4320. Gas chromatographic analysis on the capillary column at 103° and 18 psi carrier gas pressure gave one sharp peak after 35.5 minutes.

Hydrolysis of Dimethyl threo-2,3-dimethylglutarate: The above procedure was followed using 0.816 g. of dimethyl threo-2,3-dimethylglutarate. Distillation under vacuum gave 0.736 g. of dimethyl 2,3-dimethylglutarate, b.p. 70-72° at 0.8 mm., n"D 1.4324. Gas chromatographic analysis on the capillary column at 103° and 18 psi carrier gas pressure gave one sharp peak after 37.5 minutes.

Hydrolysis of threo-2,3-dimethylglutarimide: Ten milliliters of 6 N hydrochloric acid, 8 ml. of purified dioxane and 0.131 g. of threo-2,3-dimethylglutarimide were refluxed for 20 hours. The solvent was carefully evaporated and the salts extracted with three 20-ml. portions of ether. The ethereal solution was treated with excess diazomethane, the ether evaporated and the residue distilled to give 0.089 g. of dimethyl 2,3-dimethylglutarate, b.p. 70-72° at 0.8 mm., n"D 1.4320. Gas chromatographic analysis on the capillary column at 103° showed the diester to contain 17% of the erythro isomer.

Hydrolysis of erythro-2,3-dimethylglutarimide: The above procedure was followed using 0.060 g. of erythro-2,3-dimethylglutarimide.
After treatment with diazomethane and careful drying, the ether was evaporated to leave 0.025 g. of light yellow oil. Gas chromatographic analysis on the capillary column showed the dimethyl 2,3-dimethylglutarate to be 70% of the erythro isomer and 30% of the threo isomer.

Gas Chromatographic Analysis of Ethyl 2-carboethoxy-4-cyano-3-methylpentanoate: The Michael adduct from diethyl malonate and angelonitrile or tiglonitrile was separated on the 508-foot capillary column maintained at 150° and a flow rate of 27 ml. per minute into two peaks emerging after 45 minutes and 52 minutes. The major peak from the angelonitrile adduct emerged after 52 minutes. The major peak from the tiglonitrile adduct emerged after 45 minutes. The results are summarized below.

<table>
<thead>
<tr>
<th>Reaction Vol.</th>
<th>Results from VPC</th>
<th>Results from Hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (ml.)</td>
<td>% of area of peak</td>
<td>% erythro</td>
</tr>
<tr>
<td></td>
<td>after 45 min</td>
<td>A</td>
</tr>
</tbody>
</table>

I. Reactions at Room Temperature:

18 140 hr. 26 75 23 63
18 280 hr. 26 74 26 70
50 73 hr. -- 77 -- 74
50 142 hr. 19 72 18 70
50 26 day 27 66 26 63
100 26 days 35 62 32 57
200 172 hr. 29 72 31 67

II. Reactions at 6°:

18 15 day -- 76 17 74
18 44 day 18 80 18 76
50 15 day 17 78 15 73
50 45 day 16 78 16 75
100 15 day 19 76 19 76
100 45 day -- 75 19 75

A = Angelonitrile; T = Tiglonitrile
<table>
<thead>
<tr>
<th>Compound</th>
<th>b.p.(mm.)</th>
<th>$n^2 \Delta$</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calculated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>%C</td>
</tr>
<tr>
<td>$\text{CH}_3 \text{CH}_3^3$</td>
<td>$\text{NO-CH-CH-CH(COOC}_2\text{H}_5\text{)}_2$</td>
<td>123-126°(0.6)</td>
<td>1.4388</td>
</tr>
<tr>
<td>From: Angelonitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiglonitrile</td>
<td>120-124°(0.6)</td>
<td>1.4386</td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_3 \text{CH}_3^3$</td>
<td>$\text{CN}$</td>
<td>122-124°(0.4)</td>
<td>1.4480</td>
</tr>
<tr>
<td>From: Angelonitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiglonitrile</td>
<td>120-123°(0.5)</td>
<td>1.4478</td>
<td></td>
</tr>
<tr>
<td>$\text{CH}_3 \text{CH}_3^3$</td>
<td>$\text{NC-CH-CH(CH(COOC}_3\text{CH}_3\text{)}_2}$</td>
<td>128-132°(0.4)</td>
<td>1.4360</td>
</tr>
<tr>
<td>From: Angelonitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiglonitrile</td>
<td>125-130°(0.5)</td>
<td>1.4358</td>
<td></td>
</tr>
</tbody>
</table>
TABLE II

The Addition of Diethyl malonate to Angelonitrile and Tiglonitrile

(All reactions were run using 0.10 mole of diethyl malonate, 0.05 mole of nitrile, and 0.05 mole of base.)

A = Angelonitrile; T = Tiglonitrile

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Nitrile</th>
<th>Composition of recovered nitrile</th>
<th>Yield</th>
<th>Adduct Composition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>% Tig.</td>
<td></td>
<td>% erythro</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1.25 hr.</td>
<td>A</td>
<td>19</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>2.5 hr.</td>
<td>A</td>
<td>29</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5 hr.</td>
<td>A</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>12 hr.</td>
<td>A</td>
<td>60</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>48 hr.</td>
<td>A</td>
<td>61</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>5 hr.</td>
<td>A</td>
<td>22</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>18</td>
<td>1.25 hr.</td>
<td>T</td>
<td>25</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>2.5 hr.</td>
<td>T</td>
<td>32</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5 hr.</td>
<td>T</td>
<td>47</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>12 hr.</td>
<td>T</td>
<td>61</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>48 hr.</td>
<td>T</td>
<td>70</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>5 hr.</td>
<td>T</td>
<td>26</td>
<td>41</td>
<td>58</td>
</tr>
</tbody>
</table>

A. In ethanol at reflux:

B. In ethanol at room temperature:
<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>26 d.</td>
<td>A</td>
<td>12</td>
<td>51</td>
<td>26</td>
</tr>
<tr>
<td>100</td>
<td>190 hr.</td>
<td>A</td>
<td>16</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>26 d.</td>
<td>A</td>
<td>16</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>200</td>
<td>172 hr.</td>
<td>A</td>
<td>14</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>18</td>
<td>70 hr.</td>
<td>T</td>
<td>91</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>18</td>
<td>140 hr.</td>
<td>T</td>
<td>77</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>18</td>
<td>280 hr.</td>
<td>T</td>
<td>69</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>50</td>
<td>73 hr.</td>
<td>T</td>
<td>85</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>50</td>
<td>146 hr.</td>
<td>T</td>
<td>80</td>
<td>32</td>
<td>70</td>
</tr>
<tr>
<td>50</td>
<td>26 d.</td>
<td>T</td>
<td>44</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>100</td>
<td>73 hr.</td>
<td>T</td>
<td>69</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>100</td>
<td>146 hr.</td>
<td>T</td>
<td>65</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>100</td>
<td>26 d.</td>
<td>T</td>
<td>35</td>
<td>53</td>
<td>57</td>
</tr>
<tr>
<td>200</td>
<td>172 hr.</td>
<td>T</td>
<td>69</td>
<td>14</td>
<td>67</td>
</tr>
</tbody>
</table>

C. In ethanol at 5-8°:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>15 d.</td>
<td>A</td>
<td>1</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>18</td>
<td>44 d.</td>
<td>A</td>
<td>6</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>15 d.</td>
<td>A</td>
<td>3</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>50</td>
<td>45 d.</td>
<td>A</td>
<td>12</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>100</td>
<td>15 d.</td>
<td>A</td>
<td>6</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>100</td>
<td>44 d.</td>
<td>A</td>
<td>12</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>200</td>
<td>43 d.</td>
<td>A</td>
<td>10</td>
<td>12.5</td>
<td>16</td>
</tr>
<tr>
<td>18</td>
<td>16 d.</td>
<td>T</td>
<td>96</td>
<td>8</td>
<td>74</td>
</tr>
<tr>
<td>18</td>
<td>46 d.</td>
<td>T</td>
<td>94</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>Nitrile</td>
<td>% Tig.</td>
<td>Yield %</td>
<td>% erythro</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>---------</td>
<td>--------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>50</td>
<td>15 d.</td>
<td>T</td>
<td>96</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>50</td>
<td>45 d.</td>
<td>T</td>
<td>87</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td>100</td>
<td>15 d.</td>
<td>T</td>
<td>94</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>100</td>
<td>45 d.</td>
<td>T</td>
<td>84</td>
<td>14</td>
<td>75</td>
</tr>
<tr>
<td>200</td>
<td>44 d.</td>
<td>T</td>
<td>87</td>
<td>11.5</td>
<td>74</td>
</tr>
</tbody>
</table>

D. In ethanol at 5-8° using 1:1 diethyl malonate : nitrile:

<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>46 d.</td>
<td>A</td>
<td>19</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>50</td>
<td>58 d.</td>
<td>T</td>
<td>85</td>
<td>31</td>
<td>65</td>
</tr>
</tbody>
</table>

E. In ethanol at -20°:

<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>71 d.</td>
<td>A</td>
<td>1</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>100</td>
<td>71 d.</td>
<td>T</td>
<td>99</td>
<td>2</td>
<td>--</td>
</tr>
</tbody>
</table>

F. In ethanol at room temperature using K:

<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>73 hr.</td>
<td>A</td>
<td>16</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>75</td>
<td>73 hr.</td>
<td>T</td>
<td>52</td>
<td>25</td>
<td>64</td>
</tr>
</tbody>
</table>

G. In ethanol at room temperature using Li:

<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>35 d.</td>
<td>A</td>
<td>7</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>35 d.</td>
<td>T</td>
<td>90</td>
<td>7</td>
<td>61</td>
</tr>
</tbody>
</table>

H. In t-butyl alcohol at room temperature:

<table>
<thead>
<tr>
<th>Vol. (ml.)</th>
<th>Time</th>
<th>Nitrile</th>
<th>% Tig.</th>
<th>Yield %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>144 hr.</td>
<td>A</td>
<td>5</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>50</td>
<td>16 d.</td>
<td>A</td>
<td>4</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>50</td>
<td>30 d.</td>
<td>A</td>
<td>4</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>100</td>
<td>144 hr.</td>
<td>T</td>
<td>94</td>
<td>6</td>
<td>--</td>
</tr>
<tr>
<td>50</td>
<td>16 d.</td>
<td>T</td>
<td>92</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>50</td>
<td>30 d.</td>
<td>T</td>
<td>93</td>
<td>53</td>
<td>70</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>Nitrile</td>
<td>% Tig.</td>
<td>Yield %</td>
<td>% erythro</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
<td>---------</td>
<td>--------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>I. In tetrahydrofuran at reflux:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>36 hr.</td>
<td>A</td>
<td>6</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>80</td>
<td>36 hr.</td>
<td>T</td>
<td>85</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>J. In tetrahydrofuran at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>48 d.</td>
<td>A</td>
<td>2</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td>50</td>
<td>48 d.</td>
<td>T</td>
<td>90</td>
<td>11</td>
<td>59</td>
</tr>
<tr>
<td>K. In dioxane at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>15 d.</td>
<td>A</td>
<td>4</td>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>50</td>
<td>76 d.</td>
<td>A</td>
<td>2</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>50</td>
<td>15 d.</td>
<td>T</td>
<td>56</td>
<td>12</td>
<td>59</td>
</tr>
<tr>
<td>L. In dimethylformamide at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>50 d.</td>
<td>A</td>
<td>2</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>50</td>
<td>50 d.</td>
<td>T</td>
<td>90</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>M. In dimethyl sulfoxide at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>25 d.</td>
<td>A</td>
<td>3</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>50</td>
<td>45 d.</td>
<td>A</td>
<td>13</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>50</td>
<td>60 d.</td>
<td>A</td>
<td>8</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>25 d.</td>
<td>T</td>
<td>94</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>50</td>
<td>45 d.</td>
<td>T</td>
<td>72</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>50</td>
<td>60 d.</td>
<td>T</td>
<td>84</td>
<td>18</td>
<td>51</td>
</tr>
</tbody>
</table>
TABLE III
The Addition of Ethyl cyanoacetate to Angelonitrile and Tiglonitrile

(All reactions were run using 0.10 mole of ethyl cyanoacetate, 0.05 mole of nitrile, and 0.05 mole of base.)

A = Angelonitrile; T = Tiglonitrile

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Nitrile</th>
<th>Composition of recovered nitrile</th>
<th>Adduct Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>% Tig.</td>
<td>% erythro</td>
</tr>
<tr>
<td>A. In ethanol at reflux:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>5 hr.</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td>75</td>
<td>4.3 hr.</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td>40</td>
<td>5 hr.</td>
<td>T</td>
<td>--</td>
</tr>
<tr>
<td>75</td>
<td>4.3 hr.</td>
<td>T</td>
<td>--</td>
</tr>
<tr>
<td>B. In ethanol at room temperature:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>70 hr.</td>
<td>A</td>
<td>7</td>
</tr>
<tr>
<td>20</td>
<td>186 hr.</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td>20</td>
<td>360 hr.</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td>75</td>
<td>70 hr.</td>
<td>T</td>
<td>92</td>
</tr>
<tr>
<td>20</td>
<td>186 hr.</td>
<td>T</td>
<td>--</td>
</tr>
<tr>
<td>20</td>
<td>360 hr.</td>
<td>T</td>
<td>--</td>
</tr>
<tr>
<td>C. In ethanol at 6°:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>20 d.</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>49 d.</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>75</td>
<td>20 d.</td>
<td>T</td>
<td>95</td>
</tr>
<tr>
<td>100</td>
<td>49 d.</td>
<td>T</td>
<td>92</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>Nitrile</td>
<td>% Tig.</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>50</td>
<td>10 d.</td>
<td>A</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>34 d.</td>
<td>A</td>
<td>29</td>
</tr>
<tr>
<td>50</td>
<td>10 d.</td>
<td>T</td>
<td>79</td>
</tr>
<tr>
<td>50</td>
<td>34 d.</td>
<td>T</td>
<td>78</td>
</tr>
</tbody>
</table>

D. In dimethyl sulfoxide at room temperature:
TABLE IV

The Addition of Di-t-butyl malonate to Angelonitrile and Tiglonitrile

(All reactions were run using 0.08 mole of di-t-butyl malonate, 0.04 mole of nitrile, and 0.04 mole of base.)

\[ A = \text{Angelonitrile}; \ T = \text{Tiglonitrile} \]

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Nitrile</th>
<th>Composition of recovered nitrile</th>
<th>Adduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>% Tig. % erythro</td>
<td>Yield %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. In t-butyl alcohol at room temperature:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>7 d.</td>
<td>A</td>
<td>37</td>
</tr>
<tr>
<td>100</td>
<td>20.5 d.</td>
<td>A</td>
<td>56</td>
</tr>
<tr>
<td>100</td>
<td>7 d.</td>
<td>T</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>20.5 d.</td>
<td>T</td>
<td>62</td>
</tr>
<tr>
<td>B. In dimethyl sulfoxide at room temperature:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>39 d.</td>
<td>A</td>
<td>39</td>
</tr>
<tr>
<td>50</td>
<td>39 d.</td>
<td>T</td>
<td>24</td>
</tr>
</tbody>
</table>
### TABLE V

The Michael Adducts from Ethyl angelate and Ethyl tiglate

<table>
<thead>
<tr>
<th>Compound</th>
<th>b.p.(mm.)</th>
<th>( n^\circ \text{D} )</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calculated</td>
</tr>
<tr>
<td></td>
<td>%C</td>
<td>%H</td>
<td>%C</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{CH}_3 & \text{CH}_3 \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH}-\text{CH}-\text{CH}(&\text{COOC}_2\text{H}_5)_2 \\
\text{From:} & \text{ Ethyl angelate} & 124-126^\circ(0.4) & 1.4362 & [\text{lit. (46,57) b.p. 150}^\circ (3 \text{ mm.})] \\
& \text{Ethyl tiglate} & 128-132^\circ(0.6) & 1.4366 \\
\text{CH}_3 \text{ CH}_3 \text{ CN} \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH}-\text{CH}-\text{CH}-\text{COOC}_2\text{H}_5 \\
\text{From:} & \text{ Ethyl angelate} & 120-124^\circ(0.4) & 1.4440 & [\text{lit. (47) b.p. 148}^\circ (3 \text{ mm.})] \\
& \text{Ethyl tiglate} & 120-125^\circ(0.5) & 1.4410 & [\text{lit. (13) b.p. 172}^\circ(17 \text{ mm.})] \\
\text{CH}_3 \text{ CH}_3 \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH}-\text{CH}-(&\text{COOC(CH}_3)_2)_2 \\
\text{From:} & \text{ Ethyl angelate} & 125-130^\circ(0.4) & 1.4340 \\
& \text{Ethyl tiglate} & 128-132^\circ(0.4) & 1.4338 & 62.76 & 9.36 & 62.67 & 9.27
\end{align*}
\]
TABLE VI

Addition of Diethyl malonate to Ethyl angelate and Ethyl tiglate

(The reactions with ethyl angelate were run using 0.06 mole of diethyl malonate, 0.03 mole of ester and base. The reactions with ethyl tiglate were run using 0.10 mole of diethyl malonate, 0.05 mole of ester and base.)

E.A. = Ethyl angelate; E.T. = Ethyl tiglate

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ester</th>
<th>Composition of recovered ester</th>
<th>Adduct</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% E.T.</td>
<td>Yield</td>
<td>% erythro</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. In ethanol at reflux:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>11 hr.</td>
<td>E.A.</td>
<td>65</td>
<td>56</td>
</tr>
<tr>
<td>50</td>
<td>11 hr.</td>
<td>E.T.</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>B. In ethanol at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>90 hr.</td>
<td>E.A.</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>24 hr.</td>
<td>E.T.</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>72 hr.</td>
<td>E.T.</td>
<td>96</td>
<td>42</td>
</tr>
<tr>
<td>C. In ethanol at 6°:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>38 d.</td>
<td>E.A.</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>50</td>
<td>50 d.</td>
<td>E.T.</td>
<td>96</td>
<td>66</td>
</tr>
<tr>
<td>75</td>
<td>82 d.</td>
<td>E.T.</td>
<td>97</td>
<td>72</td>
</tr>
<tr>
<td>75</td>
<td>136 d.</td>
<td>E.T.</td>
<td>97</td>
<td>83</td>
</tr>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td>Ester</td>
<td>% E.T.</td>
<td>Yield %</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>D. In ethanol at -20°:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>41 d.</td>
<td>E.A.</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>50</td>
<td>39 d.</td>
<td>E.T.</td>
<td>97</td>
<td>7</td>
</tr>
<tr>
<td>E. In t-butyl alcohol at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>24 d.</td>
<td>E.A.</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>75</td>
<td>15 d.</td>
<td>E.T.</td>
<td>90</td>
<td>70</td>
</tr>
</tbody>
</table>
Addition of Ethyl cyanacetate to Ethyl angelate and Ethyl tiglate
(The reactions with ethyl angelate were run using 0.06 mole of ethyl cyanacetate,
0.03 mole of ester and base. The reactions with ethyl tiglate were run using 0.10
mole of ethyl cyanacetate, 0.05 mole of ester and base.)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ester</th>
<th>Composition of recovered ester</th>
<th>Adduct Yield</th>
<th>Composition % erythro % xx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. In ethanol at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>E.A.</td>
<td>1</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td>75</td>
<td>E.T.</td>
<td>98</td>
<td>29</td>
<td>90</td>
</tr>
<tr>
<td>B. In ethanol at 6°:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>E.A.</td>
<td>1</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>100</td>
<td>E.T.</td>
<td>99</td>
<td>37</td>
<td>89</td>
</tr>
<tr>
<td>C. In dimethyl sulfoxide at room temperature:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>E.A.</td>
<td>41</td>
<td>53</td>
<td>91</td>
</tr>
<tr>
<td>50</td>
<td>E.T.</td>
<td>99</td>
<td>82</td>
<td>97</td>
</tr>
</tbody>
</table>
TABLE VIII

Addition of Di-t-butyl malonate to Ethyl angelate and Ethyl tiglate

(The additions were run using 0.06 mole of di-t-butyl malonate, 0.03 mole of ester and 0.03 mole of base.)

E.A. = Ethyl angelate; E.T. = Ethyl tiglate

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ester</th>
<th>Composition of recovered ester</th>
<th>Adduct</th>
<th>Composition erythro %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.)</td>
<td>Time</td>
<td></td>
<td>Yield</td>
<td>% E.T.</td>
</tr>
<tr>
<td>50</td>
<td>13 d.</td>
<td>E.A.</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>70</td>
<td>100 hr.</td>
<td>E.T.</td>
<td>--</td>
<td>71</td>
</tr>
<tr>
<td>50</td>
<td>11 d.</td>
<td>E.T.</td>
<td>--</td>
<td>76</td>
</tr>
</tbody>
</table>

In t-butyl alcohol at room temperature:
<table>
<thead>
<tr>
<th>Compound</th>
<th>b.p. (mm.)</th>
<th>n°D</th>
<th>Analysis</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%C</td>
<td>%H</td>
</tr>
<tr>
<td>(CH₃)₃COOC-CH-CH-CH(COOC₂H₅)₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From: t-Butyl angelate</td>
<td>115-120°(0.4)</td>
<td>1.4338</td>
<td></td>
<td>60.73</td>
<td>8.92</td>
</tr>
<tr>
<td>t-Butyl tiglate</td>
<td>120-122°(0.5)</td>
<td>1.4342</td>
<td></td>
<td>60.31</td>
<td>8.73</td>
</tr>
<tr>
<td>(CH₃)₃COOC-CH-CH-CH(COOC(CH₃)₃)₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From: t-Butyl angelate</td>
<td>135-140°(0.7)</td>
<td>1.4330</td>
<td></td>
<td>64.48</td>
<td>9.74</td>
</tr>
<tr>
<td>t-Butyl tiglate</td>
<td>128-132°(0.4)</td>
<td>1.4328</td>
<td></td>
<td>64.46</td>
<td>9.64</td>
</tr>
</tbody>
</table>
TABLE X

The Additions to t-Butyl angelate and t-Butyl tiglate

(The reactions with t-butyl angelate were run using 0.04 mole of malonic ester, 0.02 mole of t-butyl angelate and 0.02 mole of base. The reactions with t-butyl tiglate were run using 0.08 mole of malonic ester, 0.04 mole of t-butyl tiglate and 0.04 mole of base.)

t-B.A. = t-Butyl angelate; t-B.T. = t-Butyl tiglate

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ester</th>
<th>Adduct</th>
<th>Yield</th>
<th>Composition %</th>
<th>% erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. (ml.) Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. In ethanol at room temperature using diethyl malonate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 15 d.</td>
<td>t-B.A.</td>
<td>7</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 18 d.</td>
<td>t-B.T.</td>
<td>16</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. In t-butyl alcohol at room temperature using di-t-butyl malonate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 26 d.</td>
<td>t-B.A.</td>
<td>20</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 25 d.</td>
<td>t-B.T.</td>
<td>72</td>
<td>91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following experiments were run to isolate the erythro and threo 2,3-dimethylglutaric acids from the Michael adducts.

Hydrolysis of the Dimethyl 2,3-dimethylglutarate from the Addition of Diethyl malonate to Angelonitrile at 8°: Dimethyl 2,3-dimethylglutarate (1.351 g.), 15 ml. of purified dioxane and 20 ml. of 3 N hydrochloric acid were refluxed for twelve hours. The solvent was carefully evaporated and the thick oil seeded with threo-2,3-dimethylglutaric acid and dried at oil pump pressure overnight. The semi-solid residue, 1.207 g., was recrystallized three times from carbon tetrachloride to give 0.623 g. (55%) of threo-2,3-dimethylglutaric acid, m.p. 87-87.5°. A mixture with authentic threo-diacid melted at 86-87°.

Hydrolysis of the Dimethyl 2,3-dimethylglutarate from the Addition of Diethyl malonate to Tiglonitrile at 8°: Dimethyl 2,3-dimethylglutarate (0.926 g.), 15 ml. of purified dioxane and 20 ml. of 3 N hydrochloric acid were refluxed for twelve hours. The solvent was carefully evaporated and the thick oil was seeded with erythro-2,3-dimethylglutaric acid and dried overnight at oil pump pressure. The semi-solid residue, 0.779 g., was recrystallized from 1 ml. of water and 1 ml. of concentrated hydrochloric acid to give material of m.p. 58-60°. Two recrystallizations from benzene--carbon disulfide gave 0.295 g. (37%) of erythro-2,3-dimethylglutaric acid, m.p. 68-69°. A mixture with authentic erythro diacid melted at 69-70°.

Hydrolysis of the Dimethyl 2,3-dimethylglutarate from the Addition of Diethyl malonate to Ethyl tiglate: Dimethyl 2,3-dimethylglutarate (2.203 g.), 25 ml. of dioxane and 25 ml. of 1 N hydrochloric acid were
refluxed for twenty hours. The solvent was evaporated and the residue
dried in a vacuum desiccator. The semi-solid residue was recrystal-
lized twice from benzene--carbon disulfide to give 0.876 g. (49\%) of
erthro-2,3-dimethylglutaric acid, m.p. 68-69\°.

**Preparation of 2-Ethylglutaric acid:**

**Ethyl 2-carboethoxy-4-cyanobutyrate:** Metallic sodium (0.15 g.)
was dissolved in 5 ml. of anhydrous ethanol, 16.0 g. of diethyl malon-
ate added, the flask cooled in an ice bath, 5.30 g. of acrylonitrile
added and the mixture let stand for one and one-half hours. Twenty
milliliters of ether and 3 ml. of glacial acetic acid were added and
the ethereal solution was washed with 20 ml. of water, 10 ml. of
saturated sodium bicarbonate and 20 ml. of brine and filtered through
anhydrous magnesium sulfate. Evaporation of the ether and distil-
lation gave 8.45 g. (40\%) of ethyl 2-carboethoxy-4-cyanobutyrate,
b.p. 138-142\° at 0.5 mm., n$_25$$^0$ 1.4353 (lit. (19) b.p. 104-110\° at
0.6 mm.).

The n.m.r. spectrum in carbon tetrachloride solution showed
bands at 4.21 $\delta$ (quartet) for four protons, 3.43 $\delta$ (triplet) for
one proton, 2.30 $\delta$ (multiplet) for four protons and 1.27 $\delta$ (triplet)
for six protons.

**Ethyl 2-carboethoxy-2-ethyl-4-cyanobutyrate:** Metallic sodium
(0.768 g.) was dissolved in 10 ml. of anhydrous ethanol, 7.00 g. of
ethyl 2-carboethoxy-4-cyanobutyrate added and the mixture let stand
for thirty minutes. Ten milliliters of ethyl iodide was added, the
solution warmed until it tested neutral to litmus, then poured into
20 ml. of ether. The ethereal solution was washed with
20 ml. of water, 20 ml. of brine and filtered through anhydrous
magnesium sulfate. Evaporation of the ether and distillation gave
5.90 g. (75%) of ethyl 2-carboethoxy-2-ethyl-4-cyanobutyrate, b.p.
127-129° at 0.7 mm., m.p. 44-45° (lit. (20) m.p. 47°).

The n.m.r. spectrum in carbon tetrachloride solution showed
bands at 4.21 δ (quartet) for four protons, 2.28 δ (multiplet) for
four protons, 1.95 δ (quartet) for two protons, 1.27 δ (triplet)
for six protons and 0.86 δ (triplet) for three protons.

2-Ethylglutaric acid: Ethyl 2-carboethoxy-2-ethyl-4-cyano-
butyrate (4.50 g.) was refluxed in 30 ml. of concentrated hydro-
bromic acid for thirty hours. The solvent was evaporated and the
residue dried overnight at oil pump pressure. The semi-solid mass
was recrystallized from benzene--petroleum ether to give 1.92 g.
(65%) of 2-ethylglutaric acid, m.p. 54-57°. A second recrystal-
lization from benzene-petroleum ether gave material of m.p. 60-61°
(lit. (21) m.p. 60.5°).

A sample was esterified with diazomethane to give dimethyl
2-ethylglutarate, b.p. 70-72° at 0.6 mm., n_24^D 1.4274. The n.m.r.
spectrum of the neat liquid showed bands at 3.68 δ (singlet) for
three protons, 3.66 δ (singlet) for three protons, 2.3 δ (multi-
plet) for three protons, bands from 1.0-2.0 δ (multiplet) for four
protons, and 1.88 δ (triplet) for three protons.

Reaction of Diethyl sodiomalonate with Oxygen: Sodium metal
(1.15 g.) was dissolved in 100 ml. of absolute ethanol, 16.56 g. of
diethyl malonate added, and the mixture chilled in an ice bath and
saturated with oxygen. The flask was stoppered and let stand at
5-8° for 47 days. Six milliliters of glacial acetic acid was added,
the mixture poured into 700 ml. of water, extracted with three 100-ml. portions of ether and the ethereal solution washed with saturated sodium bicarbonate, water and brine and dried with anhydrous sodium sulfate. Evaporation of the ether and distillation gave 9.70 g. of diethyl malonate, b.p. 65-75° at 0.3 mm., and 1.53 g. (11.5%) of pentaethyl propane-1,1,2,3,3-pentacarboxylate, b.p. 183-186° at 0.8 mm., n\textsuperscript{22}D 1.4440 (lit. (22) b.p. 223° at 10 mm.).

One gram of pentaester was refluxed for 24 hours in 25 ml. of 3 N hydrochloric acid. Removal of the solvent left 0.43 g. of solid, m.p. 120-140°. Two recrystallizations from acetone-chloroform gave propane-1,2,3-tricarboxylic acid, m.p. 155.5-156.5°, neutral equivalent 57.4 (lit. (23) m.p. 162°, neutral equivalent required 58.6).

A mixture with an authentic sample melted at 155-156°.

**Pentaethyl propane-1,1,2,3,3-pentacarboxylate**: Diethyl sodiomalonate was prepared from 2.30 g. of sodium metal and 16.10 g. of diethyl malonate in 100 ml. of absolute ethanol and refluxed with 8.0 g. of ethyl dichloroacetate for eight hours. Then 10 g. of sodium metal in 20 ml. of absolute ethanol was added and refluxing continued another two hours. Glacial acetic acid (15 ml.) and 250 ml. of water were added and the mixture extracted with three 100-ml. portions of ether. The ethereal solution was washed with water and saturated sodium bicarbonate and dried with anhydrous sodium sulfate. The ether was evaporated and the residue distilled to give 9.83 g. (48%) of pentaethyl propane-1,1,2,3,3-pentacarboxylate, b.p. 179-183° at 0.8 mm., n\textsuperscript{23}D 1.4445, d\textsuperscript{30} 1.0606. The n.m.r. spectrum in carbon tetrachloride showed bands at 1.3 \delta (multiplet) for fifteen protons, 3.7 \delta (multiplet) for three protons and 4.2 \delta (multiplet) for ten protons.
Section II
Synthesis of Angelic and Tiglic Acid Derivatives

2-Methyl-2-butenoic acid exists as two geometric isomers: angelic acid (I) and tiglic acid (II).

The structure assignments were proposed on the basis of their chemical and physical properties (24,25) and have been confirmed by X-ray crystallographic analysis (26).

Since tiglic acid is the more stable isomer (24), a stereo-specific synthesis for tiglic acid is not necessary so long as the isolation method is conducive to isomerization. However, any preparation of angelic acid must involve a stereospecific synthesis and employ mild isolation conditions (27).

Tiglic acid has been prepared from methyl ethyl ketone cyano-hydrin by dehydration followed by hydrolysis (28), by hydrolysis to the \( \alpha \)-hydroxy acid and dehydration (29), and by combined dehydration-hydrolysis in concentrated sulfuric acid (30,31), the latter being the preferred synthetic method. Tiglic acid, as methyl tiglate,
has also been obtained in 90% yield from reaction of acetaldehyde and the ylide (III) (32). Other methods of synthesis (24) of tiglic

\[
\left(\text{C}_6\text{H}_5\right)_3\text{P} = \text{C} - \text{C} = \text{OOCCH}_3
\]

\[
\text{CH}_3
\]

acid are more involved or give lower yields.

Angelic acid has been prepared by two methods which use the criteria of stereospecific reactions and mild isolation conditions. Bromination of tiglic acid, dehydrobromination and sodium amalgam reduction of the bromo acid gave angelic acid in 33% overall yield (30, 33).
Carboxylation of $\text{trans}$-2-butenyl-2-lithium (27,32) or $\text{trans}$-2-butenyl-2-magnesium bromide (34) gave angelic acid in 65% and 47% yield, respectively.

In this work angelic acid was prepared by the method of Dreiding and Pratt (27). 2,3-Dibromobutane was dehydrobrominated with potassium hydroxide and the cis and $\text{trans}$-2-bromo-2-butenes separated. 2-Bromo-$\text{trans}$-2-butene, treated with two equivalents of lithium metal, gave $\text{trans}$-2-butenyl-2-lithium which was carboxylated to give angelic acid. The angelic acid was esterified with ethyl iodide and anhydrous potassium carbonate using conditions which do not isomerize the acid or ester (35). Some ethyl angelate was obtained after esterification from the liquid acidic by-product from synthesis of tiglic acid according to Buckles and Mock (30). The amount of angelic acid in the acidic by-product varied (as measured by gas chromatographic analysis of the esterified material) but could be as much as 40% if, during the addition of methyl ethyl ketone cyanohydrin to concentrated sulfuric acid, the temperature was raised to 100°. However, the fact that the total yield of isolated material (tiglic acid and by-product) was much less and the difficulty in purifying the ethyl angelate (after esterification of the by-product) made this an unacceptable method for preparation of ethyl angelate. Ethyl angelate could not be prepared directly from angelonitrile by ethanolation with dry hydrogen chloride and ethyl alcohol because hydrogen chloride added to the double bond (35). Angelic acid has been reported, but in low yield, from ultraviolet induced isomerization of tiglic acid (36), but irradiation of ethyl tiglate for
fifty-three hours with ultraviolet light gave only 4% ethyl angelate in the ethyl tiglate. t-Butyl angelate was prepared from angelic acid and isobutylene.

Angelonitrile and tiglonitrile have been prepared by dehydration of methyl ethyl ketone cyanohydrin with phosphorus pentoxide (37), thionyl chloride (37), or phosphorus oxychloride in pyridine (38). Phosphorus pentoxide was reported to give low yields of angelonitrile and tiglonitrile. This was found to be true (see Table XI). Heilman and Bonnier (38) reported using phosphorus oxychloride in pyridine but gave no experimental details and did not mention any chlorine-containing impurity. Bruylants, Ernould and Dekoker (37) reported that thionyl chloride gave a mixture of products which could not be separated but was treated with hydrogen chloride to give a mixture of three isomeric chloro-2-methylbutanonitriles. These isomers were separated by distillation and angelonitrile and tiglonitrile prepared by dehydrochlorination of 3-chloro-2-methylbutanonitrile with quinoline.

In this work angelonitrile could be prepared by dehydration of methyl ethyl ketone cyanohydrin with thionyl chloride or phosphorus oxychloride in pyridine but the tiglonitrile could not be separated from 2-chloro-2-methylbutanonitrile. A number of different dehydrating agents were tried (see Table XI) and the best conditions gave angelonitrile in fair yield.

The actual isolated yield of angelonitrile was lower than that given in the Table since to obtain material of at least 99% purity required repeated fractional distillations. Because separation was
<table>
<thead>
<tr>
<th>Dehydrating Agent</th>
<th>% Yield of Reaction Products&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methyl α-Ethyl-ethyl ketone acrylonitrile</td>
</tr>
<tr>
<td>Phosphorus Pentoxide:</td>
<td>24</td>
</tr>
<tr>
<td>Phosphorus Oxychloride in Pyridine:</td>
<td>10</td>
</tr>
<tr>
<td>Thionyl Chloride in Benzene:</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>B. Thionyl Chloride in Pyridine:</td>
</tr>
<tr>
<td></td>
<td>A. SOCl&lt;sub&gt;2&lt;/sub&gt; added to cyanohydrin in pyridine</td>
</tr>
<tr>
<td></td>
<td>B. Cyanohydrin added to SOCl&lt;sub&gt;2&lt;/sub&gt; in pyridine</td>
</tr>
</tbody>
</table>

<sup>a</sup>The % yields are calculated from v.p.c. analysis of the crude material.
never complete between the lower boiling 2-ethylacrylonitrile and angelonitrile, some angelonitrile was lost with the lower boiling fractions.

Since tiglonitrile could not be isolated pure from dehydration of methyl ethyl ketone cyanohydrin, the unsaturated nitrile was prepared from tiglic acid. The acid chloride, prepared from tiglic acid and phosphorus trichloride, was added to concentrated ammonium hydroxide to give tiglamide in 75% yield. Dehydration of tiglamide with phosphorus pentoxide gave pure tiglonitrile in 75% yield.

A second synthesis of angelonitrile and tiglonitrile was attempted. The plan was to dehydrate the cyanohydrin from sodium cyanide and 3-chloro-2-butanol. 3-Chloro-2-butanol was prepared from 2-butene and t-butyl hypochlorite (39), but conditions were not found for preparation of the cyanohydrin.
Experimental
Experimental

Methyl ethyl ketone cyanohydrin was prepared in 87% yield on a six mole scale by the method of Baily, Naylor and Hewitt (40) to give material with b.p. 98-100° at 37 mm., n\textsuperscript{21}D 1.4140 (lit. (40) b.p. 108.4° at 40 mm., n\textsuperscript{25}D 1.4127).

Angelonitrile: Two hundred and fifty milliliters of anhydrous ether, 360 g. of pyridine and 250 g. of practical grade thionyl chloride were mixed in a 3-l. flask fitted with a mechanical stirrer, condenser and dropping funnel. The flask was immersed in an ice bath and 200 g. of methyl ethyl ketone cyanohydrin added dropwise. Then 250 ml. of ether was added and the mixture stirred overnight. Water was added (carefully at first) and the organic layer was separated and extracted with 200 ml. of 6 N hydrochloric acid, then with 30% sodium hydroxide until the wash remained basic, and brine and dried with anhydrous potassium carbonate. The mixture was distilled through a 2 x 30 cm. column packed with glass helices, collecting the fraction, b.p. 110-135°. Repeated fractionation through a 31-cm. center rod column gave 63 g. (39%) of angelonitrile, b.p. 119-120°, n\textsuperscript{22}D 1.4214 (lit. (38) b.p. 121-122°, n\textsuperscript{20}D 1.4224) and an after-run, b.p. 135-137°, containing 10% of angelonitrile, 49% of tiglonitrile and 41% of 2-chloro-2-methylbutanonitrile (by v.p.c.). The n.m.r. spectrum in carbon tetrachloride solution of a sample of 2-chloro-2-methylbutanonitrile, n\textsuperscript{23}D 1.4131 (lit. (41) b.p. 135-136°, n\textsuperscript{25}D 1.4158), separated on a Wilkens Model A-700 Auto-prep using a 6 foot silicone
oil column at 137°, gave bands at 1.25 δ (triplet) for three protons, and 1.90 δ (singlet) and 2.1 δ (unresolved quartet) for five protons.

**Tiglic acid** was prepared by the method of Buckles and Mock (30) using 660 g. of methyl ethyl ketone cyanohydrin. The yield of tiglic acid, m.p. 64-65°, varied between 25 and 45%. The oily yellow by-product was distilled, collecting the fraction of b.p. 180-195°, to give in 10-25% yield a colorless partially crystalline acidic material. This fraction was esterified with absolute ethanol and a trace of sulfuric acid. Slow distillation through a 31-cm. center rod column gave some ethyl angelate, b.p. 141-144°, n°D 1.4290 (lit. (59) b.p. 140-141°, n°D 1.4304), and ethyl tiglate, b.p. 153-155°, n°D 1.4324 (lit. (30) b.p. 154°, n°D 1.4324).

**Tiglamide:** Eighty grams of tiglic acid was placed in a 500-ml. flask, the flask heated on a steam bath and 30 ml. of phosphorus trichloride slowly added. The mixture was heated gently for fifteen minutes, then stirred for one hour at room temperature. The top layer was decanted into a well dried 500-ml. separatory funnel and added dropwise to 250 ml. of cold concentrated ammonium hydroxide. After evaporating off the water, the salts were extracted with three 100-ml. portions of ether and 100 ml. of boiling benzene. The combined ether and benzene extract was concentrated to about 75 ml., chilled and vigorously scratched to give 60 g. (75%) of product, m.p. 67-70°. Recrystallization from benzene gave tiglamide, m.p. 70-71.5° (lit. (17) m.p. 75°).

**Tiglonitrile:** Fifty grams of powdered tiglamide was mixed with 60 g. of phosphorus pentoxide in a 500-ml. flask. The flask was heated to 150° under water pump pressure and the distillate
collected in a receiver cooled in a Dry Ice-acetone bath. Distillation of the colorless liquid gave 30.4 g. (75%) of tiglonitrile, b.p. 137-137.5°, n\(^{22}\)D 1.4304 (lit. (37) b.p. 138-138.4°, n\(^{20}\)D 1.4319).

2,3-Dibromobutane was prepared from 1 lb. of bromine and 2-butene (Matheson, mixture of cis and trans) in 99% yield to give material with b.p. 154-156° (lit. (23) b.p. 155°).

2-Bromo-2-butene was prepared from 2,3-dibromobutane (430 g.) and potassium hydroxide (140 g.) in ethylene glycol by the method of Dreiding and Pratt (27). The crude yield (84%) was kept in the sunlight before final distillation through a micro spinning band column. Slow distillation gave 180 g. of 2-bromo-trans-2-butene, b.p. 85.5-86°, n\(^{22}\)D 1.4570 (lit. (27) b.p. 83° at 740 mm., n\(^{25}\)D 1.4561; (42) b.p. 85.5°, n\(^{20}\)D 1.4579). A sample of 2-bromo-cis-2-butene, b.p. 94-95°, n\(^{22}\)D 1.4610 (lit. (27) b.p. 90.2-91.2° at 740 mm., n\(^{25}\)D 1.4606; (42) b.p. 94°, n\(^{20}\)D 1.4620) for n.m.r. analysis was obtained by careful distillation of another crude product from 40 g. of 2,3-dibromobutane.

Angelic acid: The procedure is a modification of the method of Dreiding and Pratt (27). Lithium wire (3.83 g., 0.55 mole) cut in very small pieces was suspended in 500 ml. of anhydrous ether under oxygen-free nitrogen. The flask was chilled in an ice-salt bath and 2-bromo-trans-2-butene (34.63 g., 0.26 mole) was added in small portions. The solution was stirred for two hours and poured onto an excess of powdered Dry Ice. Any particles of lithium were removed and 50 ml. of 6 N hydrochloric acid was added. The organic layer was separated and dried with anhydrous sodium sulfate. Evaporation of the ether gave a thick yellow oil, which solidified when chilled.
in ice. Recrystallization from petroleum ether gave 15.3 g. (59%) of angelic acid, m.p. 42-44° (lit. (27) m.p. 44.5-46°).

**Ethyl angelate:** Crude angelic acid prepared from 33.3 g. of 2-bromo-trans-2-butene was dissolved in 500 ml. of reagent grade acetone. Seventy-five grams of ethyl iodide and 100 g. of anhydrous potassium carbonate were added and the mixture was shaken for eight hours, an additional 75 g. of ethyl iodide was added and the shaking continued another twenty-four hours. The solid was filtered off, the solvent evaporated and the yellow oil distilled under vacuum on a micro spinning band column to give 13.1 g. (41%) of ethyl angelate, b.p. 88-92° at 140-145 mm., n\textsuperscript{25}D 1.4286 (lit. (58) b.p. 48.5-49.5° at 11 mm., n\textsuperscript{20}D 1.4304). Gas chromatographic analysis on the 30% silicone oil column at 145° and 25 psi carrier gas pressure gave one sharp peak after seven minutes.

**Ethyl tiglate:** Fifty grams of tiglic acid, 250 ml. of absolute ethanol and 5 ml. of concentrated sulfuric acid were refluxed for twenty-four hours. The solution was concentrated to one-half the original volume, poured into water and extracted with ether. The ethereal solution was washed with water, saturated sodium bicarbonate and brine and dried with anhydrous sodium sulfate. Removal of the ether and distillation gave 51 g. (89%) of ethyl tiglate, b.p. 154-156°, n\textsuperscript{25}D 1.4322 (lit. (30) b.p. 154°, n\textsuperscript{25}D 1.4324). Gas chromatographic analysis on the 30% silicone oil column at 145° and 25 psi carrier gas pressure gave one sharp peak after eight and one-half minutes.

**t-Butyl angelate:** Seven grams of angelic acid dissolved in 15 ml. of anhydrous ether, 1 ml. of concentrated sulfuric acid and
12 ml. of isobutylene were mixed in a 100-ml. pressure flask and let stand at 5-8° for twenty-five days. The mixture was poured into a separatory funnel containing 25 ml. of 3 N sodium hydroxide and 25 ml. of ether, the water layer was extracted with 25 ml. of ether and the combined ethereal solution washed with brine and filtered through anhydrous magnesium sulfate. After removing the ether, the clear liquid was distilled under vacuum to give 6.26 g. (57%) of \( t \)-butyl angelate, b.p. 43-44° at 8 mm., \( n^\text{D}^{21.5} \) 1.4275.

**Anal.** Calcd. for \( C_9H_{16}O_2 \): C, 69.19; H, 10.33. Found: C, 69.41; H, 10.36.

**t-Butyl tiglate:** Twenty-seven grams of tiglic acid dissolved in 50 ml. of anhydrous ether, 5 ml. of concentrated sulfuric acid and 35 ml. of isobutylene were mixed in a 100-ml. pressure bottle and let stand at room temperature for eighteen days. The mixture was poured into a separatory funnel containing 50 ml. of 3 N sodium hydroxide and 50 ml. of ether, the water layer extracted with 50 ml. of ether and the combined ethereal solution dried with anhydrous potassium carbonate. After evaporating the ether, the clear liquid was distilled under vacuum to give 14.6 g. (47%) of \( t \)-butyl tiglate, b.p. 58-60° at 9 mm., \( n^\text{D}^{22} \) 1.4330.

**Anal.** Calcd. for \( C_9H_{16}O_2 \): C, 69.19; H, 10.33. Found: C, 68.95; H, 10.36.

**Attempt to isomerize ethyl tiglate:** Twenty-three milliliters of ethyl tiglate, b.p. 154-155°, was irradiated for 53 hours with a water-cooled 250-watt Hanovia mercury lamp. Gas chromatographic analysis (30% silicone oil column at 145° and 25 psi) of the pale yellow liquid showed 4% of ethyl angelate and 96% of ethyl tiglate. Distillation gave 20 ml. of material, b.p. 154-156°.
Attempt to isomerize angelonitrile: Fifteen milliliters of angelonitrile, b.p. 119-121°, was irradiated in a quartz flask for 50 hours. Gas chromatographic analysis (30% silicone oil column at 110° and 25 psi) of the black liquid showed 65% angelonitrile and 35% tiglonitrile. However, when the reaction was scaled up to 170 ml. and irradiated for 50 hours the gas chromatographic analysis showed only 1% of tiglonitrile.

Vapor Phase Chromatographic Analysis of Isomers: Analyses were obtained on a Perkin-Elmer Model 154 chromatograph using a 2-meter x 1/4" column packed with 30% silicone oil on Chromosorb W. Helium was used as the carrier gas. The nitriles were analyzed at 110° and 25 psi carrier gas pressure. Angelonitrile emerged after five minutes and tiglonitrile emerged after seven minutes. The ethyl esters were analyzed at 145° and 25 psi carrier gas pressure with ethyl angelate emerging after seven minutes and ethyl tiglate emerging after eight and one-half minutes. The amount of each isomer was assumed to be proportional to the area under the peak due to that isomer. The peak area was determined by multiplying the peak height times the width at one-half the peak height. The percent of tiglic isomer was then calculated as

\[
\frac{\text{Area of tiglic isomer}}{\text{Area of angelic isomer + Area of tiglic isomer}} \times 100.
\]
TABLE XII

The N.M.R. Spectra of Angelic and Tiglic Acid Derivatives

(Chemical shifts are given in p.p.m. below tetramethylsilane and coupling constants are in cycles per second.)

\[
\text{CH}_3-\text{CH}=\text{C}-\text{COOR}
\]

<table>
<thead>
<tr>
<th>Compound (^a)</th>
<th>vinyl hydrogen (^A)</th>
<th>Chemical shifts</th>
<th>Coupling constants (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{C}^=\text{C}^\bigcirc \text{COOH}^b,c)</td>
<td>6.23</td>
<td>2.03</td>
<td>1.92</td>
</tr>
<tr>
<td>(\text{CH}_3\text{C}^=\text{C}^\bigcirc \text{COOH})</td>
<td>7.00</td>
<td>1.80</td>
<td>1.87</td>
</tr>
<tr>
<td>(\text{CH}_3\text{C}^=\text{C}^\bigcirc \text{COOC}_2\text{H}_5)</td>
<td>6.04</td>
<td>1.97</td>
<td>1.88</td>
</tr>
<tr>
<td>(\text{CH}_3\text{C}^=\text{C}^\bigcirc \text{COOC}_2\text{H}_5)</td>
<td>6.81</td>
<td>1.77</td>
<td>1.82</td>
</tr>
</tbody>
</table>

\(^a\) For compounds labeled with \(b,c\), the vinyl hydrogen is shifted to the left of the carbonyl group.
<table>
<thead>
<tr>
<th>Compound</th>
<th>J_{AB}</th>
<th>J_{AC}</th>
<th>J_{BC}</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$C≡C(COOCH$_3$)$_3$</td>
<td>5.93</td>
<td>1.93</td>
<td>1.85</td>
<td>1.50$^s$</td>
</tr>
<tr>
<td>CH$_3$C≡C$^\text{CN}$</td>
<td>6.27</td>
<td>1.88</td>
<td>1.86</td>
<td>--</td>
</tr>
<tr>
<td>CH$_3$C≡C$^\text{CN}$</td>
<td>6.39</td>
<td>1.77</td>
<td>1.84</td>
<td>--</td>
</tr>
<tr>
<td>CH$_3$C≡C$^\text{Br}$</td>
<td>5.64</td>
<td>1.65</td>
<td>2.20</td>
<td>--</td>
</tr>
<tr>
<td>CH$_3$C≡C$^\text{Br}$</td>
<td>5.85</td>
<td>1.58</td>
<td>2.17</td>
<td>--</td>
</tr>
</tbody>
</table>

$a$ spectra of neat liquids; $b$ saturated CCl$_4$ solution; $s$ singlet; $q$ quartet; $t$ triplet.


Section III
Synthesis of the
erythro and threo 2,3-Dimethylglutaric Acids

2,3-Dimethylglutaric acid can exist as two racemic diastereoisomers, erythro-2,3-dimethylglutaric acid (I) and threo-2,3-dimethylglutaric acid (II).

Blaise (43) has reported a 2,3-dimethylglutaric acid, m.p. 83°, from hydrolysis of the product of addition of hydrocyanic acid to 2,3-dimethylbutyrolactone. His material gave an anhydride, b.p. 275-283°, and an anilic acid, m.p. 147°. Blaise (13) also obtained the 2,3-dimethylglutaric acid, m.p. 84-85°, from hydrolysis of the condensation product of ethyl sodiocyanacetate and ethyl tiglate or ethyl angelate. His material gave an imide, m.p. 108°, and an anilic acid, m.p. 147°. Montemartini (44) has reported a liquid 2,3-dimethylglutaric acid as one product of the reaction of diethyl sodiomethylmalonate and ethyl y-chlorobutyrate. As proof for his structure assignment, the same liquid diacid was obtained after hydrolysis and reduction with
hydriodic acid of the cyanoxydrin of ethyl L-methyllevulinate. Thorpe and Young (45) have reported two 2,3-dimethylglutaric acids from hydrolysis of ethyl 2-cyano-2,3-dimethylglutarate. Methylation with methyl iodide of the reaction mixture of ethyl sodiocyanoacetate and ethyl crotonate, then acid hydrolysis gave a dimethylglutarimide, m.p. 113°, and a gummy diacid. Acid hydrolysis of the imide gave "cis"-2,3-dimethylglutaric acid, m.p. 87°. This diacid readily formed an anhydride, b.p. 255°, and an anilic acid, m.p. 149°. The gummy "trans"-2,3-dimethylglutaric acid slowly gave an anhydride with acetic anhydride but on hydrolysis the anhydride gave the "cis"-2,3-dimethylglutaric acid. Michael and Ross have reported isolation of the "cis" and "trans" 2,3-dimethylglutaric acids after hydrolysis of the adducts of diethyl malonate or ethyl cyanoacetate to ethyl tiglate (46) and after hydrolysis of the adduct of ethyl 2-cyano-propionate and ethyl crotonate (47). The "cis"-2,3-dimethylglutaric acid melted at 87° and gave an imide, m.p. 112-113°. The "trans"-2,3-dimethylglutaric acid was a liquid but gave a dianilide, m.p. 216°. Finally Ruhl (48) has reported a 2,3-dimethylglutaric acid, m.p. 64-66°, isolated in 19% yield from hydrolysis of the material from methylation of the reaction mixture of diethyl malonate and ethyl crotonate.

Since the configurations of the two diastereoisomers were not known, their stereospecific synthesis was undertaken. The approach was to begin with the known meso and dl-2,3-dimethylsuccinic acids (49) and, after preparation of the monoesters (59), to run the Arndt-Eistert reaction (50) and extend the carbon chain by a methylene group to a 2,3-dimethylglutaric acid with known configuration (51). The reaction scheme can be formulated as shown on the following page.
The meso and dl-2,3-dimethylsuccinic acids were prepared by acid hydrolysis of ethyl 2,3-dicyano-2-methylbutyrate (52). The higher melting meso diacid was purified by recrystallization from water. The diacid was readily converted to cis-2,3-dimethylsuccinic anhydride with acetyl chloride; however, prolonged refluxing slowly converted some material to the more stable trans anhydride. The lower melting dl-2,3-dimethylsuccinic acid was difficult to purify by crystallization. However, the dl diacid gave the more stable trans anhydride which could be isolated pure by distillation of the crude anhydride at atmospheric pressure. The cis and trans anhydrides were refluxed in anhydrous methanol to give the monomethyl meso and dl-2,3-dimethylsuccinates. Reaction with diazomethane and vapor chromatographic analysis showed the monoesters to be the pure diastereoisomers.

Reaction of the monoesters with thionyl chloride in benzene gave the crude monoester acid chlorides which were not isolated but were added to ethereal diazomethane to form the monoester diazo ketones. The crude monoester diazo ketones were decomposed in anhydrous methanol using silver benzoate in triethylamine (55) to give the dimethyl 2,3-dimethylglutarates.

Monomethyl meso-2,3-dimethylsuccinate gave dimethyl erythro-2,3-dimethylglutarate, b.p. 62-63° at 0.2 mm., n$^\text{25}_D$ 1.4294, in 77% yield. Monomethyl dl-2,3-dimethylsuccinate gave dimethyl threo-2,3-dimethylglutarate, b.p. 63-64° at 0.2 mm., n$^\text{25}_D$ 1.4300, in 75% yield. The infrared spectra, even in the fingerprint region, of the two dimethyl esters were identical. The only difference in the n.m.r.
spectra of the two diesters was seen in the C-methyl region. The erythro-diester showed two doublets having chemical shifts of 1.10 δ (J = 7 cps) and 0.90 δ (J = 7 cps). The three-diester showed two doublets with chemical shifts of 1.08 δ (J = 7 cps) and 0.90 δ (J = 7 cps). In a mixture of the erythro and three diesters, each band of the doublet centered at about 1.1δ was always split about 1 cps. Vapor phase chromatographic analysis on the capillary column gave single peaks for the pure diesters. A mixture gave two partially resolved peaks with the erythro diester emerging three minutes before the three diester.

Acid hydrolysis of the diesters gave the pure diacids. three-2,3-Dimethylglutaric acid melted at 87-87.5°, and its imide melted at 113°. The three diacid is therefore the known solid "cis" 2,3-di-ethylglutaric acid reported by Blaise, Thorpe and Young, and Michael and Ross. erythro-2,3-Dimethylglutaric acid melted at 69.5-70° and gave an imide, m.p. 59.5-60°. The erythro diacid could be the known liquid "trans" 2,3-dimethylglutaric acid but no satisfactory derivative of the "trans" diacid is reported in the literature. A number of derivatives of the two diacids were prepared and characterized.
Experimental
Experimental

Ethyl 2,3-dicyano-2-methylbutyrate was prepared by the method of Higson and Thorpe (52) using 17.7 g. of lactonitrile and 28.0 g. of ethyl cyanoacetate to give in 59% yield material with b.p. 153-155° at 20 mm., n\(^{22}\)D 1.4362, d\(^{32}\)4 1.025 (lit. (52) b.p. 152° at 23 mm.).

d1 and meso-2,3-Dimethylsuccinic acids: A mixture of ethyl 2,3-dicyano-2-methylbutyrate (58.8 g.) and 200 ml. of concentrated hydrochloric acid was refluxed for 24 hours. After cooling, the white solid was filtered off and recrystallized from water to give meso-2,3-dimethylsuccinic acid (17.77 g., 37%), m.p. 209-210° (lit. (49) m.p. 209°). The original filtrate was evaporated to dryness and the white solid was extracted with two 50-ml. portions of ether. The ethereal solution was treated with Norite, filtered and dried with anhydrous sodium sulfate. After removal of the ether and vigorous scratching of the thick oil, crystals, m.p. 123-125°, were obtained. Recrystallization from 6 N hydrochloric acid gave 16.5 g. (35%) of dl-2,3-dimethylsuccinic acid, m.p. 126.5-127° (lit. (49) m.p. 127°).

cis-2,3-Dimethylsuccinic anhydride: Twenty milliliters of acetyl chloride and 10.09 g. of meso-2,3-dimethylsuccinic acid were refluxed for one hour. After initial vigorous reaction, an additional 10 ml. of acetyl chloride was added. The excess acetyl chloride was distilled and the residue was dried in a vacuum desiccator over flake sodium hydroxide. Final drying at oil pump pressure...
gave solid \textit{cis}-2,3-dimethylsuccinic anhydride (8.8 g., 99%), m.p. 36-38° (lit. (49) m.p. 39-40°, (60) m.p. 36-37.2°).

\textit{Monomethyl meso-2,3-dimethylsuccinate:} \textit{cis}-Dimethylsuccinic anhydride (8.8 g.) was refluxed in 30 ml. of anhydrous methanol for five hours. The excess methanol was boiled off and the light yellow residue was distilled in vacuum, collecting the fraction boiling at 112-116° at 0.20 mm. The monomethyl \textit{meso}-2,3-dimethylsuccinate (10.83 g., 98%) solidified in the flask; m.p. 42-46°. Recrystallization from petroleum ether gave 8.50 g. of material, m.p. 47-48° (lit. (53) m.p. 49°, (60) m.p. 46-47.5°).

\textit{trans-2,3-Dimethylsuccinic anhydride:} Twenty milliliters of acetyl chloride and 14.06 g. of \textit{dl}-2,3-dimethylsuccinic acid were refluxed for four hours. The excess acetyl chloride was distilled and the residue was dried in a vacuum desiccator over sodium hydroxide. Final drying at oil pump pressure gave solid \textit{trans}-2,3-dimethylsuccinic anhydride, m.p. 74-80°. The material could be recrystallized from benzene--petroleum ether to give a 60% yield, m.p. 85.5-86.5°, or distilled in 80-95% yield; b.p. 235-236°, m.p. 88° (lit. (54) m.p. 88°, (52) m.p. 87°).

\textit{Monomethyl \textit{dl}-2,3-dimethylsuccinate:} \textit{trans}-2,3-Dimethylsuccinic anhydride (11.7 g., m.p. 74-80°) was refluxed in 30 ml. of anhydrous methanol for four hours. The excess methanol was boiled off and the colorless thick residue dried at oil pump pressure for twenty-four hours. Recrystallization from acetone--petroleum ether gave 13.4 g. (93%) of monomethyl \textit{dl}-2,3-dimethylsuccinate, m.p. 36-38° (lit. (53) m.p. 38°, (60) m.p. 33-36.5°).
Dimethyl erythro-2,3-dimethylglutarate: The acid chloride of monomethyl meso-2,3-dimethylsuccinate was prepared by the reaction of 5.007 g. of the monoester, 7.0 ml. of purified thionyl chloride and one drop of triethylamine in 10 ml. of anhydrous benzene for one hour at room temperature. The excess thionyl chloride and benzene were removed under vacuum, 10 ml. of anhydrous benzene was added and the solution evaporated under vacuum. The crude acid chloride was dissolved in 10 ml. of anhydrous benzene and added dropwise with rapid mixing to an ethereal solution of diazomethane, prepared from 35.0 g. of N-methyl-N-nitroso-p-toluenesulfonamide (18). After standing for three hours, the yellow solution was concentrated under vacuum and the residue dissolved in 100 ml. of absolute methanol. A solution of 1.0 g. of silver benzoate in 9.0 g. of triethylamine was added dropwise to the cooled, stirred methanolic solution (55). After nitrogen evolution had ceased, the black solution was kept overnight in the freezer. Silver particles were removed by filtering through a Celite pad, most of the methanol was removed under vacuum at room temperature and the remaining black liquid was dissolved in ether. The ethereal solution was washed with saturated sodium bicarbonate, 1 N hydrochloric acid, again with saturated sodium bicarbonate and finally brine, and dried with anhydrous sodium sulfate. Evaporation of the ether and distillation under vacuum of the yellow oil gave 4.506 g. (77%) of dimethyl erythro-2,3-dimethylglutarate, b.p. 62-63° at 0.2 mm., n D 1.4294. Gas chromatographic analysis on the capillary column at 103° and 27 ml. per minute flow rate gave one sharp peak.
Anal. Calcd. for C₉H₁₆O₄: C, 57.43; H, 8.58. Found: C, 56.96; H, 8.50.

A liquid film had infrared bands at 3.40(m), 5.75(s), 6.85-6.95(s) doublet, 7.25(m), 7.8-9.3(s), 9.50(m), 9.90(m) and 11.65(m) μ. The n.m.r. spectrum of the neat liquid showed bands (chemical shifts in ppm below tetramethylsilane) at 3.66 δ (singlet) for six protons, 2.30 δ (multiplet) for four protons, 1.10 δ (doublet) for three protons and 0.90 δ (doublet) for three protons.

Dimethyl threo-2,3-dimethylglutarate: The above procedure for dimethyl erythro-2,3-dimethylglutarate was followed using 6.016 g. of monomethyl dl-2,3-dimethylsuccinate and 44.0 g. of N-methyl-N-nitroso-p-toluenesulfonamide (18). Vacuum distillation gave 5.305 g. (75%) of colorless dimethyl threo-2,3-dimethylglutarate, b.p. 63-64° at 0.2 mm., n₂⁵ 1.4300. Gas chromatographic analysis on the capillary column at 103° and a flow rate of 27 ml. per minute gave one sharp peak.

Anal. Calcd. for C₉H₁₆O₄: C, 57.43; H, 8.58. Found: C, 56.98; H, 8.49.

A liquid film had infrared bands at 3.40(s), 5.75(s), 6.85-6.95(s-doublet), 7.30(m), 7.8-9.3(s), 9.55(νw), 9.90(m) and 11.65(νw) μ. The n.m.r. spectrum of the neat liquid showed bands at 3.66 δ (singlet) for six protons, 2.26 δ (multiplet) for four protons, 1.08 δ (doublet) for three protons and 0.90 δ (multiplet) for three protons.

Erythro-2,3-Dimethylglutaric acid: Dimethyl erythro-2,3-dimethylglutarate (2.403 g.) was refluxed in 3 ml. of purified dioxane and 15 ml. of 1 N hydrochloric acid for four hours. Most of the solvent was distilled off and the last traces of water removed by
azeotropic distillation with benzene. The remaining acid was re-
crystallized twice from benzene--carbon disulfide to give 1.213 g.
(60%) of **erythro**-2,3-dimethylglutaric acid, m.p. 68-69.5°. A final
recrystallization from benzene--carbon disulfide gave material of
m.p. 69.5-70.0°. A mixed melting point with **threo**-2,3-dimethyl-
glutaric acid melted at 55-65°.

Anal. Calcd. for C\textsubscript{7}H\textsubscript{12}O\textsubscript{4}: C, 52.49; H, 7.55. Found: C, 52.48;
H, 7.56.

Infrared bands (potassium bromide disk) were observed at 3.45
(broad), 5.85(s), 6.8(m), 7.0-7.05(s) doublet, 7.25(m), 7.7(s),
7.85(ms), 8.10(ms), 8.40(ms), 8.60(w), 9.05(w), 9.25-9.35(w-doublet),
9.25(m) and 10.55(m) μ. The n.m.r. spectrum in carbon tetrachloride
solution showed bands at 12.90 $\delta$ (singlet) for two protons,
2.37 $\delta$ (multiplet) for four protons and 1.18 $\delta$ (doublet) for six
protons.

**threo**-2,3-Dimethylglutaric acid: Dimethyl **threo**-2,3-dimethyl-
glutarate (2.972 g.) was refluxed in 20 ml. of 3 N hydrochloric acid
for eight hours. The solvent was boiled off and the last traces of
water removed by azeotropic distillation with benzene. Removal of
the benzene gave a solid, m.p. 84-86°. Recrystallization from carbon
tetrachloride gave 1.931 g. (76%) of **threo**-2,3-dimethylglutaric acid,
m.p. 87-87.5° (lit. (45) m.p. 87°). Infrared bands (potassium bro-
mide disk) were observed at 3.40(broad), 5.85(s), 6.80(w), 7.0-
7.10(m) doublet, 7.20(m), 7.5(w), 7.70(s), 7.90(m), 8.05-8.10(ms)
doublet, 8.25(w), 8.80(vw), 8.95(m), 9.30(m), 9.90(vw) and 10.85(m) μ.
The n.m.r. spectrum in carbon tetrachloride solution showed bands at
12.90 $\delta$ (singlet) for two protons, 2.37 $\delta$ (multiplet) for four pro-
tons and 1.17 $\delta$ (doublet) for six protons.
**erythro-2,3-Dimethylglutarimide:** Five milliliters of acetyl chloride and 0.509 g. of erythro-2,3-dimethylglutaric acid were refluxed for forty-five minutes. The excess acetyl chloride was boiled off and the yellow oily anhydride kept overnight in a vacuum desiccator over sodium hydroxide. The thick oil was dissolved by warming in 3 ml. of concentrated ammonia and let stand. After two hours, the solution was acidified with concentrated hydrochloric acid and evaporated to dryness. The solid was extracted with three 10-ml. portions of ether and the ethereal solution was dried with anhydrous sodium sulfate. After removing the ether, the light yellow oil was refluxed in 4 ml. of acetyl chloride for forty-five minutes. The excess acetyl chloride was distilled, the residue was dissolved in 30 ml. of ether, and the solution washed with aqueous sodium bicarbonate and brine and dried with anhydrous sodium sulfate. The ether was evaporated and the remaining solid recrystallized twice from ether--petroleum ether to give erythro-2,3-dimethylglutarimide; 0.158 g. (35%), m.p. 59.5-60°.

*Anal.* Calcd. for C_7_H_11NO_2: C, 59.55; H, 7.86; N, 9.92. Found: C, 59.38; H, 7.87; N, 10.27.

**threo-2,3-Dimethylglutarimide** was prepared from threo-2,3-dimethylglutaric acid by the method described above. Recrystallization from ether--petroleum ether gave threo-2,3-dimethylglutarimide, m.p. 113-114° (lit. (45) m.p. 113°).

**erythro-N-Phenyl-2,3-dimethylglutarimide:** Five milliliters of acetyl chloride and 0.303 g. of erythro-2,3-dimethylglutaric acid were used to prepare the anhydride. The oily anhydride was dissolved in 5 ml. of anhydrous ether and 2 ml. of freshly distilled aniline was added. After an hour at room temperature, the mixture was
acidified with 3 N hydrochloric acid, separated and the water phase extracted with two 20-ml. portions of ether. The combined ethereal solution was dried with anhydrous sodium sulfate. Five milliliters of acetyl chloride was added to the ether and the resulting solution was allowed to stand for two days. Water was added, slowly at first, and the layers were separated. The ethereal layer was extracted with saturated sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. The ether was evaporated and the oil that remained crystallized by vigorous scratching. Recrystallization from ethanol—petroleum ether gave 0.305 g. (75%) of erythro-N-phenyl-2,3-dimethylglutarimide, m.p. 69-70.5°. After a second recrystallization, the product melted at 70-70.5°.

Anal. Calcd. for C_{13}H_{15}NO_{2}: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.13; N, 6.38.

threo-N-Phenyl-2,3-dimethylglutarimide was prepared from threo-2,3-dimethylglutaric acid by the above procedure. Recrystallization from ethanol—petroleum ether gave threo-N-phenyl-2,3-dimethylglutarimide in 43% yield: m.p. 107.5-108°.

Anal. Calcd. for C_{13}H_{15}NO_{2}: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.85; H, 7.07; N, 6.70.

Di-p-phenylphenacyl erythro-2,3-dimethylglutarate was prepared from erythro-2,3-dimethylglutaric acid and p-phenylphenacyl bromide by the method of Shrinier, Fuson and Curtin (56). Recrystallization from benzene—ethanol gave pale yellow crystals, m.p. 139-140°.

Anal. Calcd. for C_{35}H_{32}O_{6}: C, 76.62; H, 5.88. Found: C, 76.65; H, 5.86.
**Di-p-phenylphenacyl threo-2,3-dimethylglutarate** was recrystallized from benzene-ethanol to give pale yellow crystals, m.p. 126.5-127.5°. A mixture with the **erythro-diester** melted at 105-110°.

**Anal.** Calcd. for C$_{35}$H$_{32}$O$_6$: C, 76.62; H, 5.88. Found: C, 76.51; H, 5.91.

**Di-p-nitrobenzyl erythro-2,3-dimethylglutarate** was prepared from **erythro**-2,3-dimethylglutaric acid and **p**-nitrobenzyl chloride (56). Sodium iodide was added to the mixture during the reaction. Recrystallization from benzene-ethanol gave crystals, m.p. 62-63°.

**Anal.** Calcd. for C$_{21}$H$_{22}$N$_2$O$_8$: C, 58.59; H, 5.15; N, 6.52. Found: C, 58.41; H, 5.17; N, 6.51.

**Di-p-nitrobenzyl threo-2,3-dimethylglutarate** was isolated as an oil which slowly solidified; m.p. 42.5-44°. An analytical sample also gave an oil from ethanol which solidified; m.p. 44-44.5°.

**Anal.** Calcd. for C$_{21}$H$_{22}$N$_2$O$_8$: C, 58.59; H, 5.15; N, 6.52. Found: C, 58.61; H, 5.24; N, 6.54.

The di-p-bromophenacyl esters were prepared (56) and after recrystallization from ethanol gave material with m.p. 88.5-89° from **erythro**-2,3-dimethylglutaric acid and material with m.p. 92.5-93° from **threo**-2,3-dimethylglutaric acid. A mixture melted at 80-83°.
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Bibliography


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