PART I

THE SYNTHESSES AND REACTIONS OF METHYL 2-METHYL-3-OXO-1-CYCLOPENTENE-1-CARBOXYLATE AND ETHYL 2-METHYL-3-OXOCYCLOPENTANECARBOXYLATE

PART II

A STUDY OF THE REACTIONS OF GRIGNARD REAGENTS WITH ESTERS OF LEVULINIC ACID

DISSERTATION

Presented in Partial Fulfillment of the Requirements
for the Degree Doctor of Philosophy in the
Graduate School of the Ohio State University

By

James L. McPherson, B.S., M.A.
The Ohio State University

1953

Approved by:

Melvin J. Abraham
Adviser
It is a pleasure to express my deep appreciation to Dr. Melvin S. Newman who suggested this problem, and whose advice and encouragement were an invaluable aid throughout this investigation, and to extend to the Upjohn Company, Kalamazoo, Michigan, my sincere appreciation for a fellowship in connection with this work.
# TABLE OF CONTENTS

Acknowledgement

Part I

The Syntheses and Reactions of Methyl 2-methyl-1-oxo-1-cyclopentene-1-carboxylate (IX) and ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
</tr>
<tr>
<td>II</td>
<td>Synthesis</td>
</tr>
<tr>
<td></td>
<td>1. Discussion of Results</td>
</tr>
<tr>
<td></td>
<td>2. Flow Sheet (Fig. 3)</td>
</tr>
<tr>
<td></td>
<td>3. Diethyl 2-cyano-3-methylbutanedicarboxylate (II)</td>
</tr>
<tr>
<td></td>
<td>4. Diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedicarboxylate (III)</td>
</tr>
<tr>
<td></td>
<td>5. Triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV)</td>
</tr>
<tr>
<td></td>
<td>6. Diethyl 2-methyl-3-oxo-1,4-cyclopentane dicarboxylate (V)</td>
</tr>
<tr>
<td></td>
<td>7. Ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI)</td>
</tr>
<tr>
<td></td>
<td>8. 2-Methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII)</td>
</tr>
<tr>
<td></td>
<td>9. 2-Methyl-3-oxocyclopentanecarboxylic acid</td>
</tr>
<tr>
<td></td>
<td>10. Methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX)</td>
</tr>
<tr>
<td></td>
<td>11. Ethyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (VII)</td>
</tr>
</tbody>
</table>

III Reactions

|        | 1. Acetal Formation | 34 |
|        | 2. Flow Sheet (Fig. 4) | 35 |
|        | 3. Ethynylation | 41 |
|        | 4. Diels-Alder Reaction | 48 |
5. Table
6. Reaction with Hydrazine

IV An Unsuccessful Route to the Synthesis of Methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate

1. Introduction
2. Flow Sheet (Fig. 5)
3. Diethyl 2-acetonylpentanedicarboxylate (I)
4. Diethyl 2-(1-cyano-1-hydroxyethyl)pentanedicarboxylate (II)
5. 4-Hydroxy-1,3,4-pentanetricarboxylic acid (III)
6. Triethyl 3-pentene-1,3,4-tricarboxylate (V)
7. Attempted cyclization of triethyl 3-pentene-1,3,4-tricarboxylate (V)

V Summary

Part II
A Study of the Reaction of Grignard Reagents with Esters of Levulinic Acid

I Introduction 68
II Discussion of Results 73
III Preparation of Levulinyl Chloride 76
IV Preparation of Esters
1. Methyl Levulinate 77
2. Ethyl Levulinate 77
3. Isopropyl Levulinate 78
4. Isobutyryl Levulinate 78
5. Diisopropylmethyl Levulinate 79
6. Tert-amyl Levulinate 80
V  Preparation of Grignard Reagents
  1. Methylmagnesium Bromide  83
  2. Ethylmagnesium Bromide    85
  3. Phenylmagnesium Bromide   86

VI  Reaction of Grignard Reagents with Esters
  1. Experimental Conditions   87
  2. Table                    89

VII Summary  90

Autobiography  91
Part I

The Syntheses and Reactions of Methyl 2-Methyl-3-Oxo-1-cyclopentene-1-Carboxylate and Ethyl 2-Methyl-3-Oxocyclopentane-carboxylate

Introduction

Since this work is concerned with the synthesis of Cortisone something should be mentioned of the importance of this compound and of the family of compounds of which it is a member.

The main use of Cortisone and the one for which it became famous is in the treatment of rheumatoid arthritis. When patients suffering from this disease are given Cortisone they show a dramatic recovery.

The discovery of this use for Cortisone dates back to the clinical researches of Hench\(^1\) at Mayo Clinic (1933-1938) where he noted that rheumatoid arthritic women usually experienced considerable relief during pregnancy, and arthritics of both sexes improved during attacks of jaundice. From these observations it was considered that the antirheumatic substance found in both cases might be a hormone, and the adrenal cortex was investigated as a possible source of this antirheumatic substance. Out of this hypothesis and the work of Hench, Kendall, Slocumb, Polley and Sarett, the clinical trials with Cortisone were made.

It should be noted here that Cortisone has also found success in the treatment of over forty-six different diseases or conditions.

Besides Cortisone five other active steroids have been isolated from adrenal extracts. They have a very similar structure to Cortisone and showed life prolonging activity for adrenolectonized animals. The

adrenal glands control many important functions and fundamental processes of the body such as carbohydrate metabolism and if these two glands are removed the animal dies in a few days.

In the future it may be found that some of the compounds related to Cortisone may have an even more dramatic effect on the body than Cortisone itself and the study of Cortisone and related compounds and their reactions may provide fundamental information concerning the mode of action and metabolism of the adrenocortical hormones in the body.

Something should be mentioned here about the structure of Cortisone. It belongs to the chemical family of steroids, which are widely spread through plant and animal life. Examples are cholesterol from wool fat, the unsaponifiable portion of animal and vegetable fats and oils, sex hormones, bile acids, and toad poisons. Because of the complexity of these molecules the structure has only recently been unraveled. The basic structure is a 4 ring compound called cyclopentanoperhydrophenanthrene. Each ring is designated by a letter, and the carbons are numbered as indicated for Cortisone. The

\[
\text{Structure A (Cortisone Acetate)}
\]

molecule is a 3 dimensional puckered structure. This puckering accounts for the steric hindrance encountered when attempts are made to attach groups to certain positions. This is important since groups that are introduced in improper spatial configuration are frequently medicinally inactive. An example is the methyl groups in positions C-10 and C-15 and the H at C-5 and C-8 and the side chain at C-17 which all project forward from the general plane of the ring system (assuming the so-called A configuration which is represented by a full line). Also the H atoms at C-9, C-14 and C-17 positions assume the B-configuration, i.e., they lie behind the general plane of the ring system which is represented by a dotted line.

The purpose of this research problem was to synthesize ring D or an analog of it and bring about a new ring C and D fusion.

Since we were interested in synthetic approaches to Cortisone, it is of interest to review the literature with regard to synthesis of Cortisone. At the time this work was begun no successful synthesis of Cortisone had been reported. However, during the course of this work three total\textsuperscript{1,2,3} syntheses of Cortisone and several syntheses involving natural steroids as starting material in


partial syntheses of Cortisone have been announced.

The synthetic approach has been along two lines. One involved the utilization of natural steroids (which already have the correct configurations) as starting material in a partial synthesis of Cortisone and the other involved the total synthesis of Cortisone.

The primary concern of the partial synthesis method is the introduction of functions which are necessary for the antirheumatoid arthritis activity. These functions are: a) double linkage between C-4 and C-5, b) oxygen at C-3, C-11 and C-17, and c) a \(-\text{CO-CH}_2\text{OH}\) side chain at C-17. The main difficulty was the introduction of oxygen at C-11. Lately this has been done rather spectacularly by a microbiological oxidation.¹

We, however, were more concerned with problems connected with the total synthesis of Cortisone. Here the problem was two fold,


the synthesis of the ring system with the correct stereochemical configurations at the ring junctions, and the suitable transformations after the ring structure had been elaborated.

Before going into our proposed method of synthesis of Cortisone it would be well to cover two of these total syntheses briefly and to see what methods the authors used, especially with regard to the junction of ring C and D in Cortisone since this is the problem with which we were concerned.

The first total synthesis of Cortisone to be announced was that of Woodward and co-workers (Fig. 1). In this synthesis the five membered ring D was classically formed by the treatment of the dl-3 keto-16, 17-dihydroxy-\(\Delta^4,9(11)\)-\(^1\)-\(^2\)-D-homoandrostadiene acetonide (VII) with periodic acid to form a di-aldehyde (VIII) which was cyclized to form the ring D in \(\Delta^1\)-\(^1\)-\(^2\)-norprogesterone. This was eventually converted to Cortisone by a more-or-less standard procedure.

Several months later "The stereospecific total synthesis of Cortisone" (Fig. 2) by L. H. Sarett and co-workers was published. One notable feature was the new method for the attachment of ring D. This involved the condensation of methyl iodide followed by the

WOODWARD SYNTHESIS OF CORTEISONE

1. H₂, Pd, SrCO₃
2. HCOOEt, NaOEt
3. Methyl aniline
4. Acrylonitrile
5. Triton
6. HOH, OH⁻
1. H₂, Pd, SrCO₃
2. HCOOEt, NaOEt
3. Methyl aniline
4. Acrylonitrile
5. Triton
6. HOH, OH⁻
condensation of methallyl iodide with dl-4b-methyl-7-ethylenedioxy-1,2-3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol-one (III), (Fig. 2) to give 2β, 4b-dimethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-one (IV). This was oxidized with chromium trioxide-pyridine complex and then condensed with ethoxyacetylenemagnesium bromide to yield 2β, 4b-dimethyl-2-methallyl-1-ethoxyethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (V). By a series of reactions this compound was transformed into 2β, 4b-dimethyl-1β-(β-p-toluenesulfonyloxyethyl)-2-acetonyl-7-ethylene-dioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (VII). Treatment with sodium methoxide converted this tricyclic compound into a sterol derivative, 3-ethylenedioxy derivative of dl-ketoprogesterone. This represents a new method for the attachment of ring D. The conversion of this to Cortisone acetate was done by a more-or-less conventional procedure.

To summarize we have discussed a few of the things which show the importance of Cortisone. We have discussed the stereo structure of Cortisone, and we have briefly gone through two of the total syntheses of Cortisone. We now come to our proposed work toward the synthesis of Cortisone.

It is obvious that any successful synthetic approach to Cortisone will require reactions which are stereospecific for the formation of linkages between rings.
FIGURE 2
SARETT SYNTHESIS OF CORTISONE
Corticosterone acetate

\[ \text{Preceded by standard methods} \]
A route of synthesis was proposed which involved the Diels-Alder condensation of 5-(1-ethoxyvinyl)-4a, 7, 8-tetrahydro-4a-methyl-2(3H)-naphthaleneone (I) with a substituted cyclopentene-carboxylate (II). It was proposed to use a masked ketone, i.e., an acetal or the Cortisone side chain (C-17) at F.

The Diels-Alder reaction would give a cis arrangement of the C-18 angular methyl and the C-14 carboxyl group. If the two cis groups were in the β position, i.e., above the plane of the ring, then the carboxyl group could probably be replaced by a bromo group which after dehydrohalogenation and hydrogenation should give the correct α-configuration at C-14. However, if the cis arrangement of the C-18 angular methyl group and the C-14 carboxyl group were in the α position, i.e., below the plane of the ring then this route of synthesis would have to be abandoned, since there is no method of converting α, β forms of angular methyl groups.

The purpose of having a masked ketonic group at F, i.e., a group which does not have an electron attracting effect and enters into resonance with the conjugated carbethoxy system was to insure that the carboxyl group predominate in determining the polarity of the dieneophile (II) and would direct the addition of the diene (I) as
to give the product III rather than a structure in which the carboxyl group would be at a position C-18 and the methyl group at C-14.

The failure of Dane\(^1\) to get the desired product from the reaction below was undoubtedly due to the wrong orientation of the Diels-Alder reaction.

\[
\begin{align*}
\text{HC} &= \text{CH}_2 \\
\text{H}_2\text{C} &= \text{O} \\
\text{HC} &= \text{O} \\
\text{H}_2\text{C} &= \text{O} \\
\end{align*}
\]

To test this proposed route of synthesis it was decided to make methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate and to mask the ketone by formation of an acetal or by introduction of the Cortisone side chain. A Diels-Alder reaction of this compound with various dienes as butadiene, 2,3-dimethylbutadiene, and 2-methoxybutadiene would then give the necessary information for the reaction of the dieneophile (II) with the diene (I).

The new compound, methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate was prepared and various attempts were made to mask the ketone group.

The Diels-Alder reaction of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate with various dienes was tried and no reaction occurred. Attempts were then made to prepare the hydrazide of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate for conversion to the 2-methyl, 1,3-cyclopentanediene which could have been used in an alternate Cortisone synthesis, but this also failed.

---

Discussion of Results

A survey of the literature for possible routes of synthesis for methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) showed that similar type compounds had been made by Haworth and Perkins,\(^1\) and Peak and Robinson\(^2\) by the Dieckman condensation reaction of substituted esters. Two routes of synthesis were proposed using this reaction. They both involved the building up of properly substituted adipic esters, which after cyclization by the Dieckman reaction, would yield the desired product. The first of these methods involved the formation of a double bond in the aliphatic ester before cyclization. This method was unsuccessful. (See flow sheet Fig. 5, Chapter IV).

The second method was successful. (See flow sheet, Fig. 3). It involved the preparation of a properly substituted ester which was cyclized to give a substituted cyclopentanone. This was in turn brominated and dehydrobrominated to give the desired cyclopentenone.

Methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) was prepared and an effort was made to determine the conditions for the best yield in each step of the synthesis.

Ethyl cyanoacetate was condensed with ethyl \(\alpha\)-bromopropionate to give diethyl 2-cyano-3-methylbutanedicarboxylate (II) in 73\% yield (average of 6 experiments of which the highest yield was 78\%). The order of addition of the reactants and the work up of the product was varied, and the effect on the yield was noted.

---

FIGURE 3 - SYNTHESIS OF METHYL 2-METHYL-3-OXO-1-CYCLOPENTENE-1-CARBOXYLATE (IX) AND ETHYL 2-METHYL-3-OXOCYCLOPENTANE CARBOXYLATE (VII)
The addition of diethyl 2-cyano-3-methylbutanedicarboxylate (II) to acrylonitrile to give diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedicarboxylate (III) was done in 94% yield.

It was found more desirable to prepare triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV) by starting from diethyl 2-cyano-3-methyl butanedicarboxylate (II) and to go directly to (IV) without isolation of the diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedicarboxylate (III) or any of the other intermediates. The apparatus was so set up as to accommodate the addition of acrylonitrile to (II), the following hydrolysis, decarboxylation, and esterification, without the disassembly of the apparatus or transfer of the material. An over-all yield of 93% was obtained in going from diethyl 2-cyano-3-methylbutanedicarboxylate (II) to triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV).

The hydrolysis, decarboxylation and esterification of diethyl 2-methyl-3-oxo-2,4-cyclopentanedicarboxylate (V) to give ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) in 93% yield was done without isolation of the intermediate products. It was noted here that further study would probably make it possible to preferentially hydrolyze and decarboxylate the ester group in the 4 position of diethyl 2-methyl-3-oxo-2,4-cyclopentanedicarboxylate (V) without affecting the ester group in position 1.

The introduction of a double bond in the 1 position of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) was accomplished by halogenation followed by dehydrohalogenation. Various halogenating agents were used under varying conditions, and the dehydrohalogenation
was studied with different bases. The use of sulfuryl chloride as the halogenating agent and triethylamine as the dehydrohalo-
genation agent gave a mixture of the starting saturated ester (VI) and ethyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (VII). This mixture of product and starting material was always obtained regardless of the halogenation-dehydrohalogenation procedure used. Saponification of the mixture gave the unsaturated acid, 2-methyl-
3-oxo-1-cyclopentene-1-carboxylic acid (VIII), in a conversion of 59% (a net yield of 80% if based on recovered starting material) and the saturated acid, 2-methyl-3-oxocyclopentanecarboxylate in a yield of 28%.

The unsaturated methyl ester, methyl 2-methyl-3-oxo-1-cyclopen-
tene-1-carboxylate (IX) was obtained in 95% yield by the treatment of the unsaturated acid (VIII) with diazomethane.
Experimental

Diethyl 2-cyano-3-methylbutanedioate (II)

\[ \text{CH}_2(\text{CN})\text{-COOCH}_3 + \text{CH}_2\text{-CH(Br)}\text{-COOCH}_3 \xrightarrow{\text{NaOCH}} \text{CH}_3\text{-CH}\text{-CH-COOCH}_3 \]

The procedure which was found to be best suited for experiments involving three mole quantities is as follows: With caution, 69 g. (3 moles) of sodium cut into pieces of approximately .7 cm. on a side, was placed in a three-neck 3000 cc. round bottom flask which had been flushed with nitrogen and equipped with a Hershberg stirrer, a dropping funnel, and an efficient condenser. While stirring, 1000 cc. of absolute ethanol was added at such a rate as to maintain a rapid alcohol reflux. If the reaction is kept at reflux temperature at all times, the addition can be done in approximately 1.5 hours. A much longer time is required for solution of the sodium if the flask is allowed to cool below the reflux temperature. To the stirred solution was added 341.6 g. (3.02 moles) of ethyl cyanoacetate at a fast drop rate. It took approximately 1 hour for the addition. A thick creamy precipitate was formed and cooling was necessary at the end of the addition.

1. Several experiments were done in which 3 moles of sodium sand in toluene was used. The procedure has some advantages in that it gives a more rapid solution of the sodium.

2. In two experiments the order of addition was changed. The sodium ethylate solution was added to a mixture of the ethyl cyanoacetate and ethyl \( \alpha \)-bromopropionate. The yield in both experiments was 65\%—an 8\% drop in yield over the normal method of addition. Considerably less heat and precipitate was evolved.

3. Obtained from Kay Fries Chem. Inc., West Haverstraw, N. Y.
The ethyl α-bromopropionate, 54.3 g. (2.99 moles), b.p. 62-64° at 14 mm., was added at a fast drop rate with vigorous stirring. This took approximately 2 hours. Intermittent cooling was necessary to keep the temperature just below reflux. The material was refluxed for 1 hour,¹ allowed to stand for 1 hour, and then cooled in an ice bath.

A wide variation of procedure may be used here in isolation of the product with very little effect on yield. The simplest procedure was to filter the precipitated sodium bromide, wash the salt with ether, combine the ether with the filtrate, and remove the alcohol and ether by vacuum distillation. With the removal of the solvent the dissolved sodium bromide precipitated and was filtered. The filtrate was washed with 20 cc. of a saturated salt solution. A small quantity of benzene was added and the distillation was continued. There was obtained 466 g. (75%)² of diethyl 2-cyano-3-methylbutanedioate (II), b.p. 156° at 17 mm.³

---

1. In cases where the material was allowed to stand overnight without refluxing for 1 hour, the yield dropped to 46%, which is a 27% drop in yield compared with the average yield.

2. This is the average of six experiments for which the highest yield was 78%.

Diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedicarboxylate (III)

\[
\begin{align*}
&\text{COOC}_2\text{H}_5 \\
&\text{CH}_3-\text{CH}-\text{CH}-\text{COOC}_2\text{H}_5 \\
&\text{CN} \quad \text{II} \\
\end{align*}
\]

1. NaOCC₂H₅

\[
\begin{align*}
&\text{CH}_3-\text{CH}-\text{COOC}_2\text{H}_5 \\
&\text{CN} \quad \text{II} \\
\end{align*}
\]

2. CH₂=CH-CN at 34°C

\[
\begin{align*}
&\text{H}_5\text{C}_2\text{OOC}-\text{C}^{-} \\
&\text{CN} \quad \text{III} \\
\end{align*}
\]

A piece of sodium the size of a pea and 100 cc. of absolute ethanol were added to a 250 cc. flask equipped with a dropping funnel and a thermometer. To this solution was added 42.6 g. (0.2 mole) of the diethyl 2-cyano-3-methylbutanedicarboxylate (II). This was followed by the addition of (portion-wise) of 12.2 g. (0.2 mole plus 15% excess) of acrylonitrile. The temperature was maintained between 26°C and 34°C. Heat was evolved after each portion of acrylonitrile was added, up to the last addition when the temperature remained constant. After standing for 1.5 hours at room temperature, acetic acid was added to neutralize the sodium ethylate. Distillation gave 50 g. (94%) of diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedicarboxylate (III), b.p. 176-179°C at 2-3 mm.

---

1. Experimental done by Dr. M. S. Newman.
Triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV)

\[
\begin{align*}
\text{COOC}_2\text{H}_5 & \quad \text{1. NaOC}_2\text{H}_5 \\
\text{CH}_3-\text{CH}-\text{CH}=& \quad \text{2. CH}_2-\text{CH}-\text{CN} \\
\text{CN} & \quad \text{at 34°} \\
\end{align*}
\]

II

III 1. HCl, HHOH  
2. -CO₂  
3. C₂H₅OH + H⁺

\[
\begin{align*}
\text{CH}_3 & \quad \text{COOC}_2\text{H}_5 \\
\text{CH} & \quad \text{CH}_{2}-\text{COOC}_2\text{H}_5 \\
\text{CN} & \quad \text{CH}_{2}-\text{COOC}_2\text{H}_5 \\
\text{H}_5\text{C}_2\text{OOC}-\text{CH} & \quad \text{CH}_2
\end{align*}
\]

IV

In the preparation of triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV) it was found more convenient to go directly from the diethyl 2-cyano-3-methylbutanedioate (II) to (IV) without isolation of the intermediate nitrile or tricarboxylic acid. A solution of 853 g. (4 moles) of diethyl 2-cyano-3-methylbutanedioate (II) in 1000 cc. of absolute ethanol was placed in a three-neck 5000 cc. round bottom flask having ground glass joints. The flask (hood)¹ was equipped with a stirrer with a ground glass shaft and a glass blade, a three foot bead-packed column with a phase separating head, and a thermometer. Several pea-sized pieces of sodium were dissolved in 50 cc. of absolute ethanol and added to the flask. The color of the

1. Since the evolution of carbon dioxide from the reaction carries with it a considerable quantity of hydrogen chloride, it is necessary to either conduct the gas to a hood or to use some other means of removing the hydrogen chloride. This can be done very simply by taking the outer jacket of a two piece water condenser with the inner tube removed. This outer jacket is 2/3 filled with cut glass tubing of varying lengths. The gas enters through the top of the tube, and a stream of water enters through the top water connection for the condenser jacket.
reaction mixture went from colorless to slightly yellow. Keeping the temperature between 26° and 34°, 244 g. (4.6 moles - 15% excess) of acrylonitrile was added in four portions. With cooling this addition required 1 hour. Stirring at room temperature was continued for 2 hours, and enough acetic acid was added to neutralize the sodium ethylate. Here the solution became colorless. The reaction material was allowed to stand overnight. The alcohol, 1800 cc., was removed by distillation and saved for use later.

The flask was then cooled in an ice bath, and 2650 cc. of conc. hydrochloric acid was added in 500 cc. portions over a period of 1 hour. With the bottom of the flask immersed in an ice bath the temperature rose to 60°. The ice bath was withdrawn, and the mixture was allowed to stand for 2 hours and then heated to 70-80°. At this point the heating bath was withdrawn, and the reaction proceeded without further heating for two to three hours. A temperature just below the reflux temperature was maintained till the evolution of carbon dioxide ceased. This required 48-72 hours. The solid reaction product was distilled to dryness by the help of a water aspirator. Stirring was continued as long as the solid would permit. At this point an oil bath at 65-75° was used for heating in preference to an

1. In one case in which the temperature rose to 40° there was considerable darkening of the material, and after the addition of the nitrile this darkening continued until the addition of the acetic acid. The yield of the final product was 79% compared to an average yield of 92%.

2. A slight increase in yield was noted in the experiments in which the material was allowed to stand overnight.

3. Here a 2 hour period of standing or better an overnight period of standing helps dissipate some of the heat and the reaction is more easily controlled.
electric heating mantle, since in the latter case the slow heat transfer of the solid caused decomposition of the product around the walls of the flask. After the removal of apparently all of the water, 1000 cc. of benzene was added and the distillation was continued until the distillate came over at 80°.

The 1800 cc. of the previously recovered alcohol was added, and the solid was broken up, and all except approximately 200 g. 1 dissolved in the alcohol-benzene solution. The solution was then saturated with dry hydrogen chloride gas and the esterification begun. Periodically during the esterification more alcohol and benzene were added. The water azeotrope was removed by means of the phase separating head. Eight to ten days were required for completing the esterification.

At the completion of the esterification, the excess alcohol and benzene were removed by distillation, and the solid was filtered and washed with benzene. It is to be noted that this is the first time the apparatus has been moved or dismantled since it was originally set up. Distillation afforded 1072 g. (93% over-all yield) 2 of triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV), b.p. 150-155° 3 at 3 mm.

---

1. It is useless to filter this solid for more dissolved ammonium chloride always precipitates during the esterification.

2. This is an average of 4 experiments for which the best yield was 95%.

Diethyl 2-methyl-3-oxo-1,4-cyclopentanedicarboxylate (V)

With caution 97.2 g. (4 moles plus 1.2% excess) of sodium hydride (hood) was added to a 5000 cc. three-neck round bottom flask which had been flushed with nitrogen and equipped with a mechanical stirrer, a dropping funnel with a pressure equalizer tube, and an efficient condenser with a calcium chloride drying tube. After the addition of 2400 cc. of dry ether, a small quantity (5 cc.) of absolute ethanol was added. A gentle ether reflux occurred. The flask was cooled with an ice bath, and 1153.3 g. (4 moles) of triethyl 4-methyl-1,3,4-pentanetricarboxylate (IV) was added with stirring at a slow drop rate over a period of 20 hours. The solution became milky-white and later became clear greenish brown near the end of the addition. The product, while being cooled in an ice bath and stirred, was worked up by adding (dropwise at first) 1000 cc. of 6 N hydrochloric acid. The acidic mixture was allowed to stand 2-3 hours. The ether layer was decanted, and more water was added to the acidic aqueous layer to dissolve the remaining solid.

1. The large quantity of hydrogen evolved should be conducted to a hood.

2. In experiments in which the ester (IV) was added at such a rate as to maintain ether reflux (requires 6 hours to add) the yields were 20-30% lower than for the slow addition at ice bath temperature.
The aqueous layer was washed six times with 20 cc. portions of ether. The combined ether fractions was washed with one 30 cc. portion and six 10 cc. portions of a 10% sodium carbonate solution. The sodium carbonate wash removed most of the coloring matter. The wash was then extracted with three 20 cc. portions of ether and the ether added to the main ether fraction. Following the addition of 100 cc. of benzene the material was distilled. There was obtained 892 g. (92.1%) of diethyl 2-methyl-3-oxo-1,4-cyclopentanedicarboxylate (v), b.p. 153-156° at 6-7 mm.  

Ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI)

\[
\text{H}_3\text{C}_2\text{OOC} \quad \text{COOC}_2\text{H}_5 \\
\text{CH}_3
\]

1) 10% HCl
2) \text{CO}_2
3) \text{C}_2\text{H}_5\text{OH} + \text{H}^+

To 780 g. (3.2 moles) of diethyl 2-methyl-3-oxo-1,4-cyclopentanedicarboxylate (V) in a 3000 cc. three-neck round bottom flask equipped with a stirrer and reflux condenser was added 2000 cc. (approximately 4 times the volume of ester) of 10% hydrochloric acid. The mixture was stirred and heated on a steam bath overnight. The reflux condenser was replaced with a distillation column and distillate was collected till the temperature reached 95°. This required 8-9 hours. A total of 280 cc. of material was collected. After cooling, the content of the flask was saturated with ammonium sulfate and extracted with ether. The ether extract was dried over sodium sulfate (anhydrous). One hundred cc. of benzene was added and the ether and benzene removed by distillation. A solution of 1000 cc. of absolute ethanol and 500 cc. of benzene was added to the acid. This was saturated with hydrogen chloride gas and the esterification was begun. The water was removed by means of a phase separating head. The esterification required approximately 72 hours for completion.

1. Solution of the ester usually required 6-8 hours.

2. In one experiment in which the alcohol formed, one equivalent, from the hydrolysis was collected, as the diester (V) went into solution, there was obtained the ester (VI) in 92% yield directly, without esterification. In other words, with caro, the ester group in position 4 can be preferentially hydrolyzed and decarboxylated before the ester group in position I is hydrolyzed. This fact could be used to advantage since the esterification is rather slow and takes considerable time especially for large quantities.
There was obtained 500 g. (92.5%) of ethyl\textsuperscript{1} 2-methyl-3-oxocyclo-
pentane carboxylate (VI), b.p. 124-125° at 16 mm., \textsuperscript{2} \textit{N}^D_25 1.4489.

\textbf{Anal.} Calcd. for C\textsubscript{9}H\textsubscript{14}O\textsubscript{3}: C, 63.50; H, 8.23

\textit{Found}: C, 63.48; H, 7.95

1. The methyl ester, methyl 2-methyl-2-oxocyclopentanecarboxylate, b.p. 116-118° at 16 mm. was obtained in 83% yield by esterification using carbon tetrachloride and methyl alcohol.

2-Methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII)

\[ \text{CH}_3\ \overset{\text{VI}}{\longrightarrow} \overset{1. \text{Br}_2, 0^\circ}{\text{CH}_3} \overset{2. \text{Triethylamine}}{\longrightarrow} \overset{\text{VII}}{\text{CH}_3} \overset{1) 10\% \text{NaOH}}{\longrightarrow} \overset{2) \text{HCl}}{\text{VIII}} \text{COOH} \]

A solution of 524 g. (3.08 moles) of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) and 2300 cc. of dry redistilled carbon tetrachloride was placed in a 5000 cc. three-neck round bottom flask equipped with a mechanical stirrer, a dropping funnel with a pressure equalizer tube, and a reflux condenser. The contents of the flask was kept at 0°. With stirring, 491.2 g. (5.07 moles) of bromine in 767 cc. of carbon tetrachloride was added at a fast rate. The bromine color disappeared immediately. Five hours were required for the addition. There was very little hydrogen bromide evolution until approximately half of the bromine had been added. After the addition

1. In an experiment in which the bromine in carbon tetrachloride and the starting ester in carbon tetrachloride were simultaneously dropped down the condenser with resulting mixing into a flask containing an excess of triethylamine, the yield of the mixed esters was somewhat lower with the formation of some solid m.p. 128°. See p. 3 below.

2. In experiments in which the bromine was added to a mixture of the saturated ester (VI), acetic acid, and 2 moles of sodium acetate per mole of bromine the reaction mixture had to be heated to 50° before any reaction occurred. The sodium bromide was filtered, the acetic acid solvent removed, and the product distilled. Here again the product was a mixture of the saturated and unsaturated esters. Saponification gave the unsaturated acid in essentially the same yield as the bromine, carbon tetrachloride, triethylamine method.

3. If the rate of bromine addition greatly exceeds the rate of which the color is removed, there is obtained on distillation a small amount of unidentified yellow solid, m.p. 128° which comes over with a fraction boiling at 138° at 16 mm.
of bromine\(^1\) a water aspirator\(^2\) was connected and run for 5 hours to remove hydrogen bromide. At the end of this period 435 cc. of triethylamine\(^3\) was added to the ice cooled reaction flask. The resulting precipitate was stirred overnight, then heated to reflux for 2 hours and filtered. The triethylamine hydrobromide salt weighed 476 g. After removal of the excess triethylamine and carbon tetrachloride, the product was washed with 10% sodium carbonate, dried over Na\(_2\)SO\(_4\) (anhydrous), and distilled\(^4\) first from a Claisen flask at as low a pressure as possible and then through a packed column. The distillation gave the following fractions:

<table>
<thead>
<tr>
<th>Boiling Range</th>
<th>Pressure</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>126-128</td>
<td>16 mm.</td>
<td>9.2 g.</td>
</tr>
<tr>
<td>128-130</td>
<td>16 mm.</td>
<td>25.1 g.</td>
</tr>
<tr>
<td>130-133</td>
<td>16 mm.</td>
<td>24.7 g.</td>
</tr>
<tr>
<td>133</td>
<td>16 mm.</td>
<td>31.0 g.</td>
</tr>
<tr>
<td>134</td>
<td>16 mm.</td>
<td>50.9 g.</td>
</tr>
<tr>
<td>135</td>
<td>16 mm.</td>
<td>50.9 g.</td>
</tr>
<tr>
<td>Total weight</td>
<td></td>
<td>369.0 g.</td>
</tr>
<tr>
<td>Residue</td>
<td></td>
<td>50 g.</td>
</tr>
</tbody>
</table>

1. The intermediate bromo compound loses hydrogen bromide spontaneously and can be directly distilled to yield mostly the unsaturated ethyl ester, but it is contaminated with some bromo compound and must be treated with triethylamine to prevent polymerization.

2. Excess triethylamine may be used in lieu of the use of the water aspirator to remove the unattached hydrogen bromide. It should be noted here that the product (unsaturated ester) polymerizes on standing in the presence of hydrogen bromide.

3. Various reagents besides the triethylamine were tried for the removal of hydrogen bromide such as pyridine, diethylaniline, sodium ethylate, sodium carbonate and Amberlite IR + B acid absorbent anion exchange resin. In general the yields of mixed esters were about the same except for the sodium ethylate which gave considerably lower yields.

4. The use of a Todd mercury still in connection with a water aspirator gives the desired vacuum without the use of a vacuum pump which would soon be corroded by hydrogen bromide.
Each of these distillation fractions was found to be a mixture of the saturated ester (VI) (starting material) and the unsaturated ester (VII). These distillation fractions contained from 30 to 85% of the unsaturated ester (VII). Repeated redistillation through a packed column did not give a good separation.

The combined distillate was treated with 1240 cc. of 10% sodium hydroxide and stirred vigorously. The temperature rose to 65°, and after 1 hour of stirring only a very small amount of an insoluble top layer remained. After cooling, the material was extracted once with 50 cc. of ether. The ether extract was discarded. The main fraction was saturated with ammonium sulfate, and concentrated hydrochloric acid was added till a precipitate no longer came down. The light yellow colored acid was filtered and air-dried. This acid was dissolved in hot water and treated with Darco. After filtering the Darco, there was obtained 215 g. (50% yield from starting ester) of a white crystalline solid, 2-methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII), m.p. 175-175.5°, semicarbazone, m.p. 251-256°, 2,4-dinitrophenylhydrazone, m.p. 205°.

Anal. Calcd. for C₇H₈O₃: C, 59.99; H, 5.77

Found: C, 59.83; H, 5.70

1. A portion of each fraction was saponified and the amounts of the saturated acids quantitatively determined by fractional crystallization of the saturated and unsaturated acids.

2. When the starting ester was methyl, i.e., methyl-2-methyl cyclopentanone-3-carboxylate, the yield of unsaturated acid (VIII) was 62% and the recovered saturated acid (VIIIA) 22%.

The aqueous filtrate was concentrated, saturated with ammonium sulfate, and ether extracted. This white crystalline acid was recrystallized from petroleum ether (b.p. 65-110°C) and there was obtained 130 g. (30%) of the acid of the starting ester (VI), 2-methyl-3-oxocyclopentanecarboxylic acid, m.p. 94.1°C

Anal. Calcd. for C_7H_10O_3: C, 59.14; H, 7.08

Found: C, 59.60; H, 7.07

2-Methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII) (alternate procedure)

A solution of 170 g. (1 mole) of the ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI), b.p. 125° at 16 mm.\(^1\) and 400 cc. of freshly distilled carbon tetrachloride was added to a 1000 cc. three-neck, ground glass joint, round bottom flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel with a pressure equalizer tube. A thermometer dipping in the liquid was hung inside the condenser (hood). A solution of 135 g. (1 mole) of redistilled sulfuryl chloride,\(^2\) b.p. 69-70°, in 150 cc. of carbon tetrachloride was added at such a rate as to maintain a temperature of 55\(^0\) \(\pm\) 5°. The addition required 1.5 hours. The material was then refluxed for 1.5 hours, cooled in an ice bath, and 101 g. (1 mole) of triethylamine\(^3\) added in a small stream. After stirring in the cold for 1 hour, the

---

1. To explain the fact that in all cases some of the ester does not react, it was considered that there might be a difference in steric structure of the distillate fractions of the starting saturated ester. A large quantity of this ester was distilled and one of the first fractions boiling at 124\(^0\) was compared with one of the latter fractions boiling at 125\(^0\). An experiment was also run in addition to the above using a sample of the ester boiling at 124\(^0\) at 16 mm. and essentially the same yield of unsaturated acid was obtained as for the 125\(^0\) at 16 mm. above.

2. The use of Cl\(_2\) gas was unsatisfactory, since it gave mixtures of chlorinated products boiling over a wide range which on saponification gave a very low yield of the unsaturated acid (VIII).

3. Gas evolution started at approximately 40°, but, as in the use of bromine, there is a considerable induction period before the hydrogen chloride or hydrogen bromide was liberated in quantity.

4. The use of sodium carbonate in place of triethylamine did not offer any advantages and was slower and less efficient in the removal of the hydrogen chloride.
reaction material was heated to reflux for 1 hour. Most of the triethylamine hydrochloride precipitated during this latter period of heating. After cooling, some solid was filtered. The carbon tetrachloride was then removed by distillation and a total of 136 g. (theoretical 137.5 g.) of triethylamine hydrochloride was obtained. A rapid distillation\(^1\) from a Claisen flask gave 137 g. of boiling range 76-88° at 1 mm.

With vigorous shaking, 400 cc. of 10% sodium hydroxide was added. The temperature rose to 65°, and in 20 min. all but a very small amount of material had gone into solution. After cooling to 0° the mixture was extracted with 50 cc. of ether to remove the insoluble material. The aqueous portion was saturated with ammonium sulfate, and concentrated hydrochloric acid was added till a precipitate no longer came down. The straw colored crude acid was filtered, washed, and dissolved in a minimum of hot water and treated with Darco. After removal of the Darco there crystallized out upon cooling 62 g., and upon concentration of the mother liquor there was obtained an additional 20 g. This made a total of 82 g. (59%) of the 2-methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII) m.p. 174.5°.

Ether extraction of the filtrate followed by removal of the ether and recrystallization from petroleum ether (b.p. 65-100°) gave 40 g. (28%) of the 2-methyl-3-oxocyclopentanecarboxylic acid, m.p. 94°.

\(^1\) The material could be saponified without prior distillation, but involved much more work in purification, for two treatments with Darco were required to remove the dark color. The yield of the unsaturated acid (VIII) was about the same.
Methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX)

An ethereal solution of diazomethane (hood) was prepared by the portion-wise addition of 103 g. (1 mole) of nitrosomethylurea\(^1\) to 1000 cc. of ether over 300 cc. of 40% potassium hydroxide solution. The mixture was vigorously shaken during the addition, and the temperature was maintained at 0° to 5°. This light yellow colored ethereal solution of diazomethane was decanted onto dry potassium hydroxide pellets. After standing at 0° for 30 min. it was added portion-wise to an ether slurry of 91 g. (.65 mole) of 2-methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII) also cooled to 0°. The flask was vigorously shaken during the addition, and the temperature was maintained at 0°-5°. When the light yellow color of the diazomethane persisted, the addition was stopped. A small amount of acetic acid was added to remove the excess diazomethane. Distillation gave 94.6 g. (95%)\(^2\) of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX), b.p. 126.5°-127° at 16 mm., 84° at 2 mm., \(n_D^{26}\) 1.4954.

Anal. Calcd. for C\(_9\)H\(_{10}\)O\(_3\): C, 62.32; H, 6.40

Found: C, 62.49; H, 6.42

---

1. See Gilman, "Organic Syntheses", Coll. Vol. II, p. 462 (prep. No. 2), John Wiley and Sons, Inc., New York, N.Y., 1944. In this preparation if care is taken to keep the temperature at -5° to -10° instead of 0° to 5° in the diazotization step, the over-all yield of nitrosomethylurea can be raised to 61% compared to the 51% obtained in the reference.

2. The standard acid-esterification method using carbon tetrachloride methanol, and hydrogen chloride as the catalyst afforded a considerable quantity of a solid containing halogen and only a 50% yield of the methyl ester (IX).
Ethyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (VII)

A solution of 12 g. (0.086 mole) of 2-methyl-3-oxo-1-cyclopentane-1-carboxylic acid (VIII) and 150 cc. of absolute ethanol and 100 cc. of benzene were added to a 250 cc. flask, and the contents saturated with hydrogen chloride gas. The material was esterified for 17 hours without any water being collected. The solvent was removed by distillation, and a halogen containing solid m.p. 125-126° came out of solution. The filtrate was washed with 10% sodium carbonate and dried over sodium sulfate (anhydrous). Distillation gave 10 g. (69%) of ethyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (VII), b.p. 131-133° at 16 mm., n° 1.4875.

Anal. Calcd. for C₉H₁₂O₃: C, 64.26; H, 7.18

Found: C, 64.33; H, 7.19

1. A better acid catalyst for this reaction would be p-toluene-sulphonic acid, since the solid chloro compound that was isolated evidently resulted from the interaction of the hydrogen chloride with the unsaturated acid (VIII) or ester (VII).
Reactions of Methyl 2-methyl-1-oxo-1-cyclopentene-1-carboxylate (IX) and Ethyl 2-methyl-3-oxocyclopentanecarboxylate (V)

**Acetal Formation (Discussion of Results)**

Acetal formation was the first method used to try to block the ketone group and thus to neutralize its polar effect in directing the course of the proposed Diels-Alder reaction. The diethyl acetal of ethyl 2-methyl-3-oxocyclopentanecarboxylate (XVIII) see Figure 4, p. 35 was formed in 86% yield by the ethyl orthoformate procedure. The ethylene acetal of ethyl 2-methyl-3-oxocyclopentanecarboxylate (XIX) was formed in 81% yield by using an equivalent of ethylene glycol with ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI), an acid catalyst, and benzene. The water from the reaction was removed by distillation with benzene through a column equipped with a phase separating head.

The saturated ester (VI) gave the expected acetals. However, the unsaturated ester, methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) gave the enol ethers instead.

The reaction of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) with trimethyl orthoformiate gave an 89% yield of the enol ether, methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate (X). Likewise, the reaction of ethylene glycol with methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) gave an 83% yield of the enol ether, methyl 3-(2-hydroxyethoxy)-2-methyl-1,3-cyclopentadiene-1-carboxylate (XII).
FIGURE 4
REACTIONS OF METHYL 2-METHYL-1-OXO-1-CYCLOPENTENE-1-CARBOXYLATE (IX) AND ETHYL 2-METHYL-3-OXOCYCLOPENTANECARBOXYLATE (XVII).
FIGURE 4 (CONT'D)
Diethyl Acetal of Ethyl 2-methyl-3-oxocyclopentanecarboxylate (XVII)

\[
\begin{align*}
\text{CH}_3 & \quad \overset{\text{O}}{\text{COOC}_2\text{H}_5} \\
\text{VI} & \quad + (\text{C}_2\text{H}_5\text{O})_3\text{CH} \quad \overset{\text{H}^+}{\longrightarrow} \\
\text{H}_5\text{C}_2\text{O} & \quad \overset{\text{OC}_2\text{H}_5}{\text{COOC}_2\text{H}_5} \\
\text{XVIII} & \quad \text{CH}_3
\end{align*}
\]

A solution of 8.5 g. (0.05 mole) of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) and 14.8 g. (0.10 mole) of freshly distilled triethyl orthoformate,\(^1\) b.p. 144°,\(^2\) was added to a small Erlenmeyer flask containing 11.5 g. (0.25 mole) of absolute ethanol and a trace\(^3\) of dry hydrogen chloride gas.\(^4\) It was noted that the temperature rose 5-6° upon mixing the reagents and remained there for 8-10 minutes. A slight tan coloration occurred. After standing overnight\(^5\) the mixture was poured over sodium carbonate (anhydrous), warmed a few minutes with shaking, and filtered after cooling.

Distillation gave 10.6 g. (86%) of the diethyl acetal of ethyl 2-methyl-3-oxocyclopentanecarboxylate (XVIII), b.p. 137-138.5° at 16 mm., \(n^\text{D}_{25} 1.4385\).

Anal. Calcd. for \(\text{C}_{13}\text{H}_{24}\text{O}_4\): C, 63.90; H, 9.90

Found: C, 64.00; H, 9.88

1. The use of trimethyl orthoformate to prepare the methyl ketal gave a methyl ketal with a mixture of methyl and ethyl esters.

2. Redistillation of triethyl orthoformate which had been distilled 12 hours previously gave a low boiling impurity of approximate 5\% by volume of the total. This may be due to decomposition during distillation. However, freshly distilled triethyl orthoformate did give a cleaner reaction with a slightly greater yield of product.

3. If much more than a trace of hydrogen chloride is used there is considerable darkening in color of the mixture, and a lower yield of ketal results. The use of hydrochloric acid has the same effect.

4. A small amount of dry hydrogen chloride gas was bubbled through 50 cc. of absolute ethanol and a stirring rod was dipped into this and transferred to the flask containing the alcohol to be used in the ketal formation.

5. Experiments which were worked up one hour after mixing gave only slightly lower yields than the ones worked up after standing overnight.
Ethylene acetal of ethyl 2-methyl-3-oxocyclopentanecarboxylate (XIIa)

\[
\begin{align*}
\text{CH}_3 - CH_2 \quad \text{COOC}_2H_5 \\
\text{VI} \\
\end{align*}
\]

\[
\begin{align*}
+ \text{HOCH}_2-\text{CH}_2\text{OH} \quad \text{H}^+ \\
\text{CH}_3 - CH_2 \quad \text{COOC}_2H_5 \\
\text{XIX} \\
\end{align*}
\]

A solution of 17 g. (0.1 mole) of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI)\(^1\) and 6.82 g. (0.11 mole)\(^2\) of freshly distilled ethylene glycol, b.p. 103-104° at 16 mm. was mixed with 200 cc.\(^3\) of dry thiophene free benzene containing 0.5 grams of p-toluenesulfonic acid. The apparatus used was similar to the standard set up for acid esterification using a column equipped with a phase separating head for the continuous removal of the benzene azeotrope. By the end of 12 hours the ethylene glycol layer had gone into solution and approximately the theoretical amount of water had been collected. After cooling, the product was poured over sodium carbonate (anhydrous), warmed, again cooled, and then filtered.

Distillation gave 17 g. (81%) of the ethylene acetal of ethyl 2-methyl-3-oxocyclopentanecarboxylate (XIX)\(^4\), b.p. 141-143° at 16 mm., \(n^D_25\) 1.4534.

**Anal.** Calcd. for C\(_{11}\)H\(_{18}\)O\(_4\): C, 61.66; H, 8.42
            Found: C, 61.66; H, 8.42

---

1. The procedure was first tested with cyclopentanone.
2. In one experiment in which a large excess of ethylene glycol was used there was so much ester interchange that the yield of desired product was practically zero.
3. This excess quantity of benzene served the purpose of cutting down any ketal formation involving two molecules of the starting ketone.
4. This compound showed no noticeable reaction with freshly cut sodium.
Methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate (X)

\[
\begin{align*}
\text{CH}_3 & \quad + \quad (\text{CH}_3\text{O})_3\text{CH} + \text{H}^+ \\
\text{IX} & \quad \Rightarrow \quad \text{CH}_3 \\
\text{COOCH}_3 & \quad \text{O-CH}_3 \\
\text{COOCH}_3 & \quad \text{COOCH}_3
\end{align*}
\]

To a solution of 7.7 g. (0.05 mole) of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and 10.6 g. (0.10 mole) of freshly distilled trimethyl orthoformate, b.p. 99-100°, was added 8 g. of absolute methanol containing a trace of hydrogen chloride gas. Mixing was accompanied by a rise in temperature with the formation of a light tan color. After standing overnight the mixture was poured over sodium carbonate (anhydrous), warmed, and after cooling, filtered.

Distillation gave 7.5 g. (89%) of methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate (X), b.p. 126° at 16 mm., m.p. 29°, \( n^25_D \) 1.5026.

**Anal.** Calcd. for C\(_9\)H\(_{12}\)O\(_3\): C, 64.26; H, 7.18

Found: C, 63.86; H, 7.29

1. On redistillation 10% by volume of the total came over as a low boiling impurity.

2. In this experiment considerable discoloring and polymerization with resulting low yield occurs if much more than a trace of acid is used.

3. See note 4, p.37

4. Contrary to the preparation of the diethyl acetal of ethyl 2-methyl-3-oxocyclopentane-carboxylate (XVIII) a much lower yield of the enol ether (X) occurred if the product was worked up in less than four hours after mixing.
Methyl 3-(2-hydroxyethoxy)-2-methyl-1,3-cyclopentadiene-1-carboxylate (XII)

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{COOCH}_3 & \quad \text{CH}_2 \\
\text{IX} & \quad \text{CH}_3 \\
\end{align*}
\]

A solution of 7.73 g, (0.05 mole) of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and 3.41 g, (0.055 mole) of freshly distilled ethylene glycol was added to a flask containing 100 cc. of dry thiophene free benzene and 1 g. of Dowex 50 (acid ion exchange resin). The apparatus used was similar to the standard set up for acid esterification using a column equipped with a phase separating head for the continuous removal of water. At the end of 15 hours 1 cc. of water had been collected, and the ethylene glycol layer had disappeared. There was very little coloration. The resin catalyst was recovered by filtering. Distillation gave 8.3 g. (83%) of the methyl 3-(2-hydroxyethoxy)-2-methyl-1,3-cyclopentadiene-1-carboxylate (XII), b.p. 133° at 16 mm., 93.5 at 2 mm., n\text{D}^25 1.4895.5

Anal. Calcd. for C\textsubscript{10}H\textsubscript{14}O\textsubscript{4}: C, 60.59; H, 7.11
Found: C, 60.64; H, 6.81

1. The acid ion exchange resin was used because decomposition occurred when other acid catalysts were used.
2. This is in contrast to the experiments using hydrogen chloride as a catalyst in which a dark brown color resulted and the yield was very low.
3. This enol ether showed a pronounced reaction with sodium with the liberation of H\textsubscript{2} gas, as contrasted to the unreactivity of the cyclic ketal of the saturated ester (XIX).
4. This b.p. is only 6° higher than the starting ester (IX) whereas the cyclic ketal of the saturated ester (XIX) has a b.p. 17° above its starting ester.
5. For some reason this particular compound, being perfectly clear, gave an index of refraction reading which was so dim as to be barely perceptible.
Ethynylation (Discussion of Results)

Since the unsaturated ester, methyl 2-methyl-3-oxo-1-cyclo-
pentene-1-carboxylate (IX) formed enol ethers instead of the expected
acetals, it was decided to try blocking the ketone by ethynylation.
This would serve an additional purpose, for the ethynyl group could
be modified to give the Cortisone side chain on carbon 17. (See
Structure A page 2). Two methods (with conditions varied) of
ethylation were tried: a) sodium, liquid ammonia, and acetylene,
b) acetylene-magnesium bromide and acetylene. These two methods were
used on the saturated ester, ethyl 2-methyl-3-oxocyclopentane-
carboxylate (VI) and on the unsaturated ester, methyl 2-methyl-3-
oxo-1-cyclopentene-1-carboxylate (IX). None of the expected ethynyl
products could be isolated. Varying amounts ranging from 59-82% of
the starting material were recovered. In one case, method (a) -
using sodium liquid ammonia and acetylene with the unsaturated
ester (IX) no starting material was recovered.
Attempted preparation of ethyl 3-ethynyl-3-hydroxy-2-methylcyclopentane carboxylate

(a) Sodium acetyllde method.

Approximately 50 cc. of liquid ammonia (hood) was added to a 250 cc. three-neck round bottom flask equipped with a Hershberg stirrer, a gas inlet tube extending to the bottom of the flask, and a wide bore copper tube condenser running through a dry ice acetone bath. The flask was covered with a thickness of several inches of packing material for insulation. A small piece of sodium was added, followed by the addition of a few crystals of hydrated ferric nitrate. After a few minutes the remainder of the sodium, totalling 2.33 g. (0.1 mole plus 1.3% excess) was added portion-wise. The acetylene was passed through a series of bubbler and drying towers to remove the acetone and water impurities. The purification train consisted of two sulphuric acid bubbler traps followed by a drying tower containing soda lime and a final drying tower containing phosphorus pentoxide. The material was stirred during the passage of acetylene gas. The disodium acetyllde was formed at first as noted by the increased stirring difficulty, followed by the formation of monosodium acetyllde. Here the stirring became easy. After 1.5 hours, acetylene was no longer absorbed. The acetylene bubbler was then withdrawn from the liquid and connected to the top of the dropping funnel with a pressure equalizer tube and the funnel connected to the reaction flask. A slow

1. As a preliminary to this experiment the same procedure above was first carried out with cyclopentanone.

2. Design taken from K. Greenlee, Ph.D. dissertation, Ohio State University, 1942.
flow of acetylene was maintained during the 1.5 hour addition of 17 g. (0.1 mole) of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI).

After the addition, the dropping funnel was removed, and the acetylene bubbled through the liquid for 2 hours. Ten g. (excess) of ammonium chloride was added, the condenser disconnected, and the unstoppered flask set up in the hood. After the evaporation of the ammonia, dilute acid was added to dissolve the solid, and this solution was then ether extracted. The ethereal extract was dried over sodium sulfate (anhydrous). After the removal of the ether, distillation gave 10 g. (59%) of recovered starting ester (VI), b.p. 124-126 at 16 mm., $^2_{25}$ 1.4485. A slight positive ethynyl test was obtained for practically all of the distillation fractions possibly only indicating the presence of small amounts of acetylene. Saponification of the recovered ester gave quantitatively the saturated acid, 2-methyl-3-oxocyclopentanecarboxylic acid, m.p. 95°.

---

1. This time was varied up to 8 hours to increase the reaction time, but the per cent of recovered starting ester remained essentially the same.

2. One experiment was run in which this distillation was carried out at as low a vacuum as possible in hopes of preventing the decomposition of any ethynyl compound, but the results were the same as above.

3. Several methods were used for testing for the ethynyl group, such as (a) the addition of a silver nitrate solution which gives a precipitate and liberates nitrous acid which turns universal litmus paper red. (b) The addition of ammoniacal silver nitrate solution which gives a precipitate in the presence of an ethynyl grouping.
Attempted preparation of ethyl 3-ethynyl-3-hydroxy-2-methylcyclo-
 pentane carboxylate

(b) Acetylenic Grignard method.

The general procedure was patterned after Grignard and co-workers.\(^1\) Approximately 25 cc. of dry ether and 3.4 g. (0.14 mole) of magnesium were placed in a 250 cc. three-neck flask with ground glass joints, which had been flushed with nitrogen, and equipped with a condenser, a dropping funnel with a pressure equalizer tube, and a Hershberg stirrer with a ground glass shaft. A slight pressure of nitrogen gas was maintained during the Grignard preparation. With stirring, 14.17 g. (0.13 mole)\(^2\) of freshly distilled ethyl bromide in 40 cc. of dry ether was added drop-wise at first till the reaction had started and then at such a rate as to maintain a rapid ether reflux. This required 30-40 minutes. The mixture was then refluxed for 1.5 hours and cooled with an ice bath (used throughout the remainder of the experiment). The solution was grey to black with the presence of colloidal magnesium. The dropping funnel was replaced with a bubbler tube extending below the surface of the Grignard reagent. The flask was immersed in an ice bath, and all of the joints and connections were wired to withstand pressure, acetylene was passed through the bubbler tube, and the pressure was maintained at 1.5 atm. In approximately 3 hours the dark Grignard solution became suddenly clear.


2. An approximately 20% excess of Grignard reagent was prepared to take care of the expected yield of 80%.
The acetylene pressure was maintained overnight. The bubbler was replaced by a dropping funnel, and 50 cc. of dry thiophene free benzene was added followed by the fast drop-wise addition with stirring of 17 g. (0.1 mole) of ethyl 2-methyl-3-oxocyclopentane-carboxylate (VI) in 30 cc. of benzene. A mud-colored precipitate formed immediately. After stirring for 1.5 hours a Michler's ketone test was negative for unreacted Grignard reagent. The mixture was allowed to set over the weekend under several pounds of acetylene pressure. The material was worked up by adding dilute hydrochloric acid and ice and ether extracting the mixture. The extract was washed with 10% sodium carbonate solution and dried over sodium sulfate (anhydrous). Distillation gave 14 g. (82% recovery) of starting ester (VI).
Attempted preparation of methyl 3-ethynyl-3-hydroxy-2-methyl-1-cyclopentene-1-carboxylate.

(a) Sodium acetylide method.

The procedure was the same as for the attempted preparation of ethyl 3-ethynyl-3-hydroxy-2-methylcyclopentanecarboxylate by method (a) page 42. Here, however, upon the addition of 15.4 g. (0.1 mole) of the methyl 2-methyl-3-oxo-1-cyclopentane-1-carboxylate (IX) to the sodium acetylide a great deal of brown coloration\(^1\) occurred. The product\(^2\) was worked up as for the saturated ester (VI), page 42. Distillation gave only black polymeric residue.

Attempted preparation of methyl 3-ethynyl-3-hydroxy-2-methyl-1-cyclopentene-1-carboxylate.

(b) Acetylenic Grignard method.

The general procedure and apparatus were the same as for the attempted preparation of ethyl 3-ethynyl-3-hydroxy-2-methylcyclopentanecarboxylate by method (b), page 44. The Grignard reagent was prepared by adding 13.1 g. (0.12 mole) of freshly distilled ethyl bromide and 100 cc. of ether to 3.16 g. (0.13 mole) of magnesium covered with 25 cc. of dry ether at a fast drop rate. This required 30 minutes. After refluxing for 1.5 hours, an ice bath was added (used throughout the remainder of the experiment) and acetylene added under a 1.5 atm. pressure for 1.5 hours. The acetylene pressure was

---

1. It was expected that the strong alkali would decompose this starting ester (IX), but since the method (b) had given negative results, the above method was tried anyway.

2. The product isolated for distillation gave a negative test for nitrogen and a weak test for the ethynyl group.
removed and 15.4 g. (0.1 mole) of methyl 2-methyl-2-oxo-1-cyclopentene-1-carboxylate (IX) was added drop-wise with stirring. A heavy yellow precipitate formed and 60 cc. of benzene had to be added to facilitate stirring. Stirring was continued for 1 hour \(^1\) after the addition, and 7 g. of ammonium chloride in 25 cc. of water was added with stirring with the temperature still at \(0^\circ\). The work up of product was continued by adding 100 cc. of water and filtering off the excess magnesium. There was recovered 0.45 g. (15%) of unreacted magnesium. The benzene-ether layer was decanted and the aqueous portion ether extracted. This extract was washed with 10% sodium carbonate solution, and after the removal of the solvent there remained 17 g. of a light tan-colored liquid (gave a weak test for ethynyl group) which on distillation gave 9.7 g. (63% recovery) of the starting ester (XI) with no ethynyl compound isolated.

\(^1\) One experiment was run in which the reaction product was refluxed for 4.5 hours after the ester (IX) had been added. The resulting final product was essentially the same as for the experiment above.
Diels-Alder Reaction (Discussion of Results)

Since all attempts to satisfactorily block the ketone group of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) by acetal formation or ethynylation had failed, it was decided to proceed with the Diels-Alder reaction without further attempts to block the ketone group. A study of the reaction was made using three dienes, butadiene, 2-methoxybutadiene, and 2,3-dimethylbutadiene. Butadiene is the least reactive diene of the three and 2,3-dimethylbutadiene the most active. The use of 2-methoxybutadiene as a diene would give two possible products depending on whether the ketone or the carboxyl group had the stronger polar affect. Under the wide range of conditions that were used no Diels-Alder adduct between the methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and the dienes resulted. The results showing the diene and the experimental conditions used are summarized in Table I, page 50.
Attempted Diels-Alder reaction of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) with various dienes.¹

The equation for the expected Diels-Alder reaction is as follows:

\[ \text{CH}_3 + \text{CH}_2=\text{CH}_2 \xrightarrow{\text{COOCH}_3} \text{CH}_3\text{COOCH}_3 \]

IX

The general procedure for the reactions summarized in Table I was as follows:

A weighed quantity (0.05 mole) of the methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and varying amounts (0.025 to 0.125 mole) of the diene were added to a nitrogen or carbon dioxide flushed pyrex bomb tube (1.5 cm. x 30 cm.). Five cc. of benzene were added in those cases where a solvent was used. The tube was sealed and placed in a 2" x 14" iron pipe with a screw cap at the top and bottom. A 0.5 cm. hole was drilled in the top cap. The iron tube was lined inside with several layers of asbestos paper-between which the thermocouple lay protected after extending through the hole in the cap. The pipe containing the bomb tube and thermocouple was

1. (a) Butadiene was obtained from Dr. K. Greenlee, A.P.I. at Ohio State University.
   (b) 2-Methoxybutadiene was prepared according to Helen Lloyd, Ph.D. dissertation, Ohio State University, 1951.
   (c) 2,3-Dimethylbutadiene was prepared from acetone through the intermediate of pinacol according to Gilman "Organic Syntheses" Coll. Vol. I page 459, John Wiley and Sons, New York, N.Y. 1938. The O.S. preparation of pinacol hydrate was modified so as to give the pinacol instead of pinacol hydrate. This was done by directly distilling the pinacol from the reaction mixture at the point where O.S. says to add water to form the pinacol hydrate. The yields were essentially the same for the pinacol as was recorded by O.S. for the pinacol hydrate.
<table>
<thead>
<tr>
<th>Addend</th>
<th>Ratio of Diene to Dienophile</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time Hrs.</th>
<th>Yield of Adduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butadiene</td>
<td>2.0</td>
<td>Benzene</td>
<td>80°</td>
<td>10.5</td>
<td>0</td>
</tr>
<tr>
<td>Butadiene</td>
<td>1.0</td>
<td>Benzene</td>
<td>100</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>Benzene</td>
<td>200</td>
<td>10.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>Benzene</td>
<td>200</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>Benzene</td>
<td>220</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>Benzene</td>
<td>200</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>2-Methoxybutadiene</td>
<td>.5</td>
<td>&quot;</td>
<td>200</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>&quot;</td>
<td>200</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>None</td>
<td>200</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>2,3-Dimethylbutadiene</td>
<td>1.0</td>
<td>Benzene</td>
<td>200</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>200</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>200</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>200</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>None</td>
<td>200</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>Room temp.</td>
<td>2 months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>.1</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
</tr>
</tbody>
</table>

*Dienophile was 2-Methyl-3-oxo-1-cyclopentene-1-carboxylic acid*
placed in an electrically heated shaker. The temperature was accurately controlled by a Brown thermoregulator. The time of heating was recorded as beginning when the temperature inside the iron tube reached the desired temperature and ending when the heating unit was cut off. It took approximately 1 hour for the heater to reach 200° and 2 hours for the heater to cool to 60°.

The glass bomb was opened and the contents (usually a dark brown color with an odor ranging from a fish odor for butadiene to a pine oil odor for the 2,3-dimethylbutadiene) washed with benzene into a small distillation flask. The various distillation fractions obtained were found to be made up of a main fraction of recovered ester (IX) ranging from 75% recovered ester for cases where the time of heating did not exceed 12 hours to 10-20% where the time of heating exceeded 40 hours. Saponification of each fraction collected over the range from 70 to 140° at 2 mm. gave the 2-methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII) and polymeric material. The preparation of the 2,4-dinitrophenylhydrazone derivative of each fraction indicated the presence of only one ketone compound, the starting ester (IX). The remaining fractions boiling 140 - 220° at 2 mm. were all polymeric and would not give a ketone derivative and did not show the presence of an acid group. The results showing the diene and the experimental conditions used are summarized in Table I, page 50. Under the conditions that were used, no Diels-Alder adduct between the methyl-2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and any of the three dienes was indicated.
Reaction with hydrazine (Discussion of results)

Since methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) did not undergo a Diels-Alder reaction with various dienes under the conditions used, it was decided to investigate the reaction of this compound with hydrazine. The extreme ease with which the ester (IX) is saponified suggested the idea that perhaps the hydrazide might be preferentially formed in preference to the hydrazone as:

\[
\text{CH}_3\text{C} = \text{O} + \text{H}_2\text{NN}_2 \rightarrow \text{CH}_3\text{C} = \text{O} + \text{HOCH}_3
\]

If it were possible to form this hydrazide it possibly could be converted to the azide which could then be used in a Curtius reaction to give 2-methyl 1,3-cyclopentanedione.

\[
\text{CH}_3\text{C} = \text{O} \xrightarrow{\text{Curtius Reaction}} \text{CH}_3\text{C} = \text{O}
\]

This would offer a new route to the synthesis of this potentially very valuable compound which could possibly be used in an alternate synthesis of Cortisone.

The only products that could be isolated from the reaction of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) with hydrazine were: the hydrazone (XV), see Fig. 4, p. 35, the hydrazide-

---

hydrazone (XVI), and the azine (XIV) of the ester (IX). The reaction of methyl 3-methoxy-2-methyl-1, 3-cyclopentadiene-1-carboxylate (X) with hydrazine gave the hydrazide-hydrazone of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XVI).

All attempts to prepare the acid chloride of 2-methyl-3-oxo-1-cyclopentene-1-carboxylic acid (VIII) gave only a polymer. If the acid chloride could have been prepared it would probably have reacted with sodium azide to form the azide which would then undergo the Curtius reaction to give the 2-methyl-1,3-cyclopentanedione.
Hydrazide-hydrazone of methyl-2-methyl-3-oxo-cyclopentene-1-carboxylate (XVI)

With stirring, 7.7 g. (0.05 mole) of the methyl-2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) was mixed with 5.28 g. (0.15 mole plus 10% excess) of hydrazine (anhydrous). A straw color developed on first mixing, heat was evolved, and a white solid precipitated. This was filtered and after washing with methanol and drying weighed 3.0 g. The original filtrate was mixed with 10 cc. of cellosolve, and 10 drops of hydrazine were added. The mixture was warmed, and upon cooling a white precipitate was collected which after washing and drying weighed 2.9 g. This was repeated four more times. A total of 8.4 g. (theoretical 100% yield of a mixture of crude hydrazide-hydrazone (XVI) and hydrazone (XV) was collected. This material was mixed with a large excess of benzene, and the solid remaining was filtered and recrystallized from pyridine. There was obtained 4 g. (47.6%) of the white hydrazide-hydrazone of methyl-2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XVI), m.p. 217-218°.

Anal. Calcd. for C_{7}H_{12}ON_{4}; C, 49.98; H, 7.19; N, 33.31
Found: C, 50.17; H, 7.24; N, 33.07

1. Supplied by Mathieson, Coleman and Bell, Inc., Norwood, Ohio.
2. After removal of the benzene there was obtained 4.2 g. (crude) (50%) yield of the hydrazone of methyl-2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XV) (identified later after the crude material was chromatographed).
Hydrazone of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XV)

\[
\begin{align*}
\text{N-NH}_2 \\
\text{CH}_3 \\
\text{COOCH}_3
\end{align*}
\]

XV

With stirring, 3.85 g. (0.025 mole) of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) was mixed with 0.88 g. (0.025 mole) plus 10\% excess of hydrazine (anhydrous) at 0\°.\textsuperscript{1} The mixture was kept in a refrigerator overnight, and the solid that was formed was filtered and washed with methanol. There was obtained 1 g. of material. This was shaken with 3000 cc. of benzene (cold). There remained .4 g. of white insoluble material of m.p. 217-218\° dec. which by mixed melting points proved to be the hydrazide-hydrazone (XVI). The benzene solution was chromatographed\textsuperscript{2} using a column 4cm. x 30 cm. filled with a mixture of pre-dried\textsuperscript{3} silicic acid celite 1.55:1.

The column which required 400 cc. of solvent to fill it, was pre-washed first with 250 cc. of petroleum ether (b.p. 65-110\°) then with 250 cc. of benzene. The benzene solution containing the material

\textsuperscript{1} The primary purpose of this experiment was to obtain the pure hydrazone of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XV) without particular regard to the yield.

\textsuperscript{2} The best procedure was first worked out using 1 cm. x 10 cm. chromatographic tubes. The location of the compound in the extruded column was clearly indicated by streaking with .025\% KMnO\textsubscript{4} solution.

\textsuperscript{3} Or the mixture may be pre-washed according to E. W. Malmberg, K. N. Trueblood, Anal. Chem., 21, 1055-8 (1949).
to be chromatographed was passed through the column, and the column was developed with 1000 cc. of a solution containing 500 cc. of ether, 250 cc. of benzene, and 250 cc. of petroleum ether (b.p. 65-110°). The developer was collected in six portions; evaporation to dryness showed no appreciable residue. The chromatographic column was extruded and streaked with 0.025% KMnO₄. Two bands were evident, a narrow 5 mm. band at the top of the column and the main 25 mm. band in the middle of the column. The two bands were eluted separately with ether. Upon evaporation of the ether the extract of the top 5 mm. band gave a very small amount of material which after crystallization from methanol had a m.p. of 153°. The residue from the ether solution of the main band gave a very light yellow solid which after recrystallization from methanol gave 0.4 g. of an ivory colored material of sharp m.p. 155-156° which gave the correct analysis for the hydrazone of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XV).

Anal. Calcd. for C₈H₁₂O₂N₂: C, 57.12; H, 7.19; N, 16.65

Found: C, 57.22; H, 7.19; N, 16.71
Azine of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XIV)

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

XIV

A solution of 7.7 g. (0.05 mole) of methyl-2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and 1.76 g. (0.051 mole plus 10% excess) of hydrazine (anhydrous) was added to a 100 cc. flask equipped with a reflux condenser. After the addition of 50 cc. of absolute methanol the mixture was refluxed 12 hours. A bright yellow material precipitated. This crude material weighed 6.6 g. Repeated recrystallizations from methanol and cellosolve gave a yellow crystalline material which behaved in many respects like a mixture of compounds. A benzene solution of 0.5 g. of this recrystallized yellow compound was chromatographed using the same procedure and quantities of wash and developer as were used in the chromatography of the hydrazone of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XV)

In the development of the column the yellow colored band containing the main fraction of the material was moved through the column and collected in 6 fractions. These upon removal of the solvent gave 0.4 g. of a yellow crystalline material of m.p. 193-193.5°.

1. At the time this experiment was run the product of the reaction was not known. It would have been better to have used 0.025 mole of hydrazine.

2. After developing the column itself had only one small band at the top. This upon working up gave a very small amount of a yellow solid of m.p. 190°.
This material gave the correct analysis for the azine of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (XIV).

**Anal.** Calcd. for C_{10}H_{20}O_{4}N_{2}: C, 63.14; H, 6.80; N, 9.20

Found: C, 63.21; H, 6.80; N, 9.24

**Attempted preparation of the hydrazide of methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate**

A solution of 3 g. (0.018 mole) of the methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate (X), 2.3 g. (0.072 mole) of hydrazine (anhydrous), and 5\(^{1}\) cc. of absolute methanol was refluxed for 2 hours. After standing overnight 1.2 g. of an ivory colored solid precipitated. This compound after recrystallization from pyridine gave a m.p. of 217\(^{0}\) dec. and on mixing with a known sample of the hydrazide-hydrazone (XV) gave no depression in m.p.

---

1. Some of this same product was isolated when no alcohol was used as a solvent. Evidently the alcohol formed from the reaction of the hydrazine with the ester is sufficient to convert the enol ether to the ketone.
An unsuccessful route to the synthesis of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate

Introduction

In the course of deciding the best route of synthesis for this compound the literature was searched for similar compounds. It was found that saturated cyclopentanone compounds had been made by Haworth and Perkin in 1908 by a Dieckman condensation reaction of saturated tricarboxylic esters. Therefore, if the properly substituted unsaturated tricarboxylic compound were cyclized it should give a cyclopentanone type compound.

The synthesis outlined on the flow sheet (Fig. 5, p. 60) was studied.

The first step in this sequence, the preparation of diethyl-2-acetylpentanediode (I) went in 59% yield using ethyl β-chloropropionate and 77% yield using the ethyl β-bromopropionate. The next step involving the addition of hydrogen cyanide to give the diethyl 2-(1-cyano-1-hydroxyethyl) pentanediode (II) went with a yield of 84%. Various attempts to convert the cyano group to an ester always resulted in mixtures of the dehydrated cyano compound, the starting cyano compound (II), and a very small amount of the tri-ester (V). Consequently, the diethyl 2-(1-cyano-1-hydroxyethyl) pentanediode (II) was hydrolyzed to 4-hydroxy-1,3,4-pentanetricarboxylic acid (III) in 59% yield (no effort was made to improve this yield).

ATTEMPTED SYNTHESIS OF ETHYL 2-METHYL-1-3-OXO-1-CYCLOPENTENE-1-CARBOXYLATE
Esterification of the tricarboxylic acid (III) using sulphuric acid as a catalyst gave two products, the triethyl 4-hydroxy-1,3,4-pentanetricarboxylate (IV) and triethyl 3-pentene-1,3,4-tricarboxylate (V) in 22% and 32% yields respectively.

The triethyl 3-pentene-1,3,4-tricarboxylate (V) was used in a Dieckman condensation reaction. Repeated experiments using both the methyl and ethyl esters of the 3-pentene-1,3,4-tricarboxylic acid gave oils which proved to be so difficult to separate that this scheme of preparing the compound was abandoned.
Diethyl 2-acetylpentanedicote (I)

The procedure followed for the preparation of diethyl 2-acetylpentanedicote (I) was patterned after the method of Kuster.\(^1\)

To 368 g. (8 moles) of absolute ethanol in a three-neck 1000 cc. round bottom flask equipped with a Hershberg mechanical stirrer, a reflux condenser with a calcium chloride drying tube, and a separatory funnel was added 23 g. (1 mole) of sodium portion-wise maintaining a rapid alcohol reflux. Periodic cooling with an ice bath was necessary. It took approximately 2-3 hours for all of the sodium to go into solution.

With vigorous stirring, 126 g. (1 mole) of redistilled acetoacetic ester was added at a fast drop rate. Some heat was evolved and an ice bath was used. Immediately after this addition, 136 g. of redistilled ethyl \(\beta\)-chloropropionate was added at a fast drop rate. The product took on a copper-like color and was heated on a steam bath for 2.5 hours with stirring. After this digestion period the reaction product was filtered to remove the salts, and the filtrate (wine colored) was transferred to a 1000 cc. Claisen flask for distillation. Distillation gave 133 g. (59\%),\(^2\) of diethyl 2-acetylpentanedicote (I), b.p. 165-170\(^\circ\) at 22 mm.\(^3\)

---

2. This yield was increased to 77\% by the use of 1.2 moles methyl \(\beta\)-bromopropionate and 1.5 moles of acetoacetic ester.
3. W. Kuster and J. Weller, Ber., 47, 534 (1914), records b.p. 169-170\(^\circ\) at 22-25 mm.
Diethyl 2-(1-cyano-1-hydroxyethyl)pentanedioate (II)

The general procedure was patterned after Kuster.\(^1\) A mixture of 152 g. (0.66 mole) of diethyl 2-acetylpentanedioate (I), 608 cc. of dry ether, and 120 g. (1.34 moles) of mortared potassium cyanide was added to a three-neck 2000 cc. round bottom flask equipped with a dropping funnel and a gas delivery tube connected to a bubbler trap containing sodium hydroxide solution (hood). The flask was cooled with an ice bath, and 140 cc. (1.5 moles) of concentrated hydrochloric acid was slowly added over a period of 4 hours with the flask being occasionally shaken. At the end of this period the escape tube was pinched off and the material let stand for 48 hours. The flask was then placed on a water bath, and a stream of air passed through the flask to remove excess hydrogen cyanide. The mixture remained essentially clear.\(^2\) The ether layer was decanted, and the solid mixture extracted 3 times with 25 cc. portions of ether and the ether extract combined with the decanted ether and dried over sodium sulfate (anhydrous). Distillation gave 144, (84%)\(^3\) of diethyl 2-(1-cyano-1-hydroxyethyl)pentanedioate (II), b.p. 143° at 15 mm.

---

2. The use of wet commercial ether resulted in a brown colored mixture.
3. The yield was essentially the same when the methyl ester was used.
Hydroxy-1,3,5-pentanetricarboxylic acid (III)

The general procedure was patterned after Kuster. A mixture of 33.4 g. (1.3 moles) of diethyl 2-(1-cyano-1-hydroxyethyl) pentanedicarboxylate (II) and 1000 cc. of 25% hydrochloric acid was added to a 2000 cc. round bottom flask equipped with a reflux condenser and heated at reflux for 16 hours. The material was then hand extracted twenty times with 25 cc. portions of ether. This extraction gave 107 g. of material after removal of the ether. A continuous ether extraction for 50 hours gave an additional 128 g. of material.

A portion of this crude material was purified by recrystallization of the barium salt and then dehydrated by heating to 100\(^\circ\) under vacuum to give the unsaturated acid 3-pentene-1,3,4-tricarboxylic acid, m.p. 96\(^\circ\). This showed the crude material above, total 235 g. (59\%)\(^3\) to be essentially pure.

2. H. Fischer and Costin Nenitzeeca, Z. Physical Chem., 145, 306 (1925) reported m.p. 96-97\(^\circ\).
3. The procedure was repeated for the methyl ester with a corresponding yield of 63\%.
Triethyl 3-pentene-1,3,4-tricarboxylate (V) (Ethyl Hematinate)

A mixture of 220 g. (1 mole) of 4-hydroxy-1,3,4-pentane-tricarboxylic acid (III), 1000 cc. of absolute ethanol, 500 cc. of benzene and 3 cc. of concentrated sulphuric acid was esterified. After 9 hours approximately 75 cc. of azeotrope was collected. The mixture was poured over solid sodium carbonate, filtered, and distilled. There were obtained two main fractions, 67 g. (22%) of triethyl 4-hydroxy-1,3,4-pentanetricarboxylate (IV), b.p. 104-112° at 20 mm., which gave a negative bromine test for unsaturation and 92 g. (32%) of triethyl 3-pentene-1,3,4-tricarboxylate (V), b.p. 112-115° at 20 mm. which gave a positive bromine test for unsaturation. Saponification of a portion of the unsaturated ester (V) gave 3-pentene-1,3,4-tricarboxylic acid (Hematinic acid) m.p. 96°. Preliminary attempts to dehydrate the hydroxy ester (IV) by means of distillation over potassium acid sulfate or iodine gave back unchanged saturated hydroxy ester (IV).
**Attempted cyclization of triethyl 3-pentene-1,3,4-tricarboxylate (V)**

With vigorous stirring, 31.1 g. (0.108 mole) of the triethyl 3-pentene-1,3,4-tricarboxylate (V) was added to 2.84 g. (0.108 mole) of sodium sand in 200 cc. of toluene in a three-neck 500 cc. round bottom flask equipped with an efficient condenser, a Hershberg stirrer, and a dropping funnel. The exothermic reaction was maintained at reflux by the rate of addition of the ester (V). After the addition the mixture was refluxed for 3 hours. The excess toluene was removed by distillation, and ice and 10% hydrochloric acid were added to the yellowish white solid. The solution was ether extracted. After removing the ether by distillation there remained 13.4 g. of a light yellow oil. Various attempts to purify this oil and to obtain any sizable quantity of the cyclized product, diethyl 2-methyl-3-oxo-1-cyclopentene-4-dicarboxylate (VI) were unsuccessful. It was therefore decided to abandon this route of synthesis.
Summary

The syntheses of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) and ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) has been made.

Ethyl 2-methyl-3-oxocyclopentanecarboxylate (VI) reacted with ortho formates and ethylene glycol to form acetals, whereas methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) reacted to give only the enol ethers.

Ethynylation did not give any reaction product.

Methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) failed to undergo a Diels-Alder reaction with butadiene, 2-methoxybutadiene, or 2,3-dimethylbutadiene under a wide range of conditions.

The reaction of methyl 2-methyl-3-oxo-1-cyclopentene-1-carboxylate (IX) with hydrazine gave three products, the hydrazone, the hydrazide-hydrazone, and the azine.
A Study of the Reaction of Grignard Reagents with Esters of Levulinic Acid

Introduction

Frequently in the synthesis of organic compounds, the worker is faced with the problem of using a reagent with a compound having two functional groups either of which will react with the reagent. Sometimes it is possible to protect one functional group, as is frequently done with an hydroxy group by acetylation. Aldehydes and ketones are frequently protected by the formation of acetals. The methods of blocking a group are usually limited to those methods which enable the functional group to be regenerated after the reagent has reacted with the other functional group.

Another means of reducing the activity of one functional group in the presence of another is to render one functional group less reactive by attaching a group which by its steric hindrance prevents the reaction of the function group with the reagent. Usually this method is limited to the protection of the alcohol function by a sterically hindering acid group or the protection of an acid group by a sterically hindering alcohol group.

One of the most complete works showing the steric effect of the acid portion of the molecule on the rate of esterification is the work of Loening, Garrett and Newman\(^1\) in which the acid catalyzed esterification of 26 branched chain aliphatic acids was discussed. This work

showed that there is over a 7000 fold decrease in the rate of esterification of \((\text{CH}_3)_3\text{C-C(\text{CH}_3)_2-COOH}\) as compared to acetic acid due to the steric hindrance of the carboxyl group to the addition of alcohol across the carbonyl oxygen.

The alcohol portion of an ester can likewise show a steric effect and prevent or decrease the addition of a reagent across the carbonyl oxygen bond. This is illustrated by the difference in magnitude of the base hydrolysis constant \(K\) for primary, secondary, and tertiary aliphatic esters.\(^1\)

<table>
<thead>
<tr>
<th>Ester</th>
<th>(K) (base hydrolysis constant, moles/min.) aqueous 20°</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{-COOCH}_2-(\text{CH}_2)_2\text{-CH}_3)</td>
<td>3.93</td>
</tr>
<tr>
<td>(\text{CH}_3\text{-COOCH(\text{CH}_3)CH}_2\text{CH}_3)</td>
<td>0.816</td>
</tr>
<tr>
<td>(\text{CH}_3\text{COOC(\text{CH}_3)}_3)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

Another example\(^2\) of the hindrance of the ester group to hydrolysis is:

<table>
<thead>
<tr>
<th>Ester</th>
<th>(K) (base hydrolysis constant moles/hr.) 75% alc. 69°</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH(\text{CH}_3)}_2)</td>
<td></td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{-COOCH(\text{CH(\text{CH}_3)}_2)})</td>
<td>0.16</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{-COO-CH-CH}_2\text{CH}_2\text{CH}_3)</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Since the reaction of a Grignard reagent with an ester group involves this same type of addition across a carbonyl group, one

---

1. L. Smith, K. S. Olsson, Z. Physik. Chem., 118, 99 (1925); ibid, 102, 26 (1922); ibid, 125, 243 (1927).
would expect the same steric factors to hold true. An example of
the steric hindrance of the acid portion of the ester molecule to
Grignard addition is illustrated by Whitmore and Lewis.¹

\[
\begin{array}{ll}
\text{Ester} & \% \text{Grignard addition} \\
(C_2H_5)\text{C}-\text{COOC}_2H_5 & 0 \\
(C_2H_5)_2\text{CCOOCH}_3 & 0 \\
(C_2H_5)_2\text{CHCOOCH}_2H_5 & 45 \\
(C_2H_5)(CH_3)_2\text{CCOOCH}_2H_5 & 100
\end{array}
\]

It is of interest to note here that the ethyl group is more effective
as a sterically hindering group than is a methyl group.

The alcohol portion of an ester has likewise been shown to
exert a steric effect and prevent or decrease the addition of the
Grignard reagent across the carbonyl oxygen of the ester as illustrated
by the failure of CH₃COOC(C₂H₅)₃ to react with methylnitrogen
bromide.²

There are few examples in the literature where this method of
protecting one of two functional groups from the reaction of a
reagent capable of reacting with either function group has been
used. No systematic study had been made, so it was proposed to study
the reaction of various Grignard reagents with primary, secondary, and
tertiary alkyl esters of a β-keto acid such as levulinic acid. The
amount of product resulting from the reaction of the Grignard reagent

1. F. C. Whitmore and C. F. Lewis, J. Am. Chem. Soc., 64, 1681,
   2984, 1239, 1242, 1247, 1321 (1942).

with the \( \gamma \)-keto group would be a measure of the effectiveness of the primary, secondary, or tertiary alcohol group of the ester in preventing a side reaction of the Grignard reagent with the ester group.

The particular \( \gamma \)-keto ester type compound was chosen for this study because of its frequent use in the build-up of organic compounds.

The equation for the general reaction of the various esters of levulinic acid with Grignard reagents is given on the flow sheet, page 72.
Main Reaction

\[
\begin{align*}
\text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} + R'MgX &\rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \\
\text{OMgX} &\rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \\
\end{align*}
\]

Where \( R \) is methyl, ethyl, isopropyl, isobutyl, or \( t \)-amyl, or diisopropylmethyl.

\( R' \) is methyl, ethyl, or phenyl

\[ \gamma \text{-methyl, } \beta \text{-alkyl butyrolactone} \]

Side reaction

\[
\begin{align*}
\text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} + R'MgX &\rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \\
\text{OMgX} &\rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \\
\end{align*}
\]

The greater the yield of the product (the substituted butyrolactone) resulting from the reaction with the ketone group the more effective is the alkyl group of the ester in preventing a reaction of the Grignard reagent with the ester group.

In the preparation of the various esters of levulinic acid it is of interest to note here a problem that arose. Esters of levulinic acid may exist in two forms, the normal-ester, and the pseudo-ester, and often a preparation of the ester will yield a mixture of the two forms.

\[
\begin{align*}
\text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \quad \text{Normal-ester} &\quad \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} \quad \text{Pseudo-ester} \\
\end{align*}
\]

\[ \text{OR} \]
This according to Langlois and Wolf\textsuperscript{1} and is the first example of the occurrence of a pseudo-ester in the aliphatic series. Several examples of pseudo-esters occur in the aromatic series.\textsuperscript{2} The pseudo-ester is very sensitive to base and can be removed by titrating a mixture of the two esters with 0.1 N sodium hydroxide using phenolphthalein as an indicator.

**Discussion of results**

After a series of pure normal esters, methyl, ethyl, isopropyl, isobutyl, diisopropylmethyl, and t-amyl, of levulinic acid had been prepared, a procedure had to be worked out which was satisfactory for the reaction of one particular Grignard reagent with all of the esters in the series. It was found, for example, that the solubility of the Grignard addition complex for each ester greatly affected the yield of lactone. To avoid the precipitation of the Grignard complex, 1000 cc. of benzene per mole of ester was added to each ester before the addition of the Grignard reagent. Except for the ethyl ester essentially homogeneous reaction systems were obtained by this device. In nearly all cases in which benzene was added the yields of lactone were considerably higher than for the cases in which ether alone was used. However, this increase in yield varied with each individual ester. A similar improvement in yield by the


use of benzene was noted by Cason.\textsuperscript{1} The effect of solvent on the yield of product can be seen in Table II, page 89, for the reaction of ethylmagnesium bromide and phenylmagnesium bromide with various esters. The solvent may exert a gross effect through the solubility of the complex. Observations of differences in the behavior of the esters in the present investigation intimate that this solubility effect may be an important factor in determining the yield.

In the course of studying the reaction the effect on the yield of the rate of addition\textsuperscript{2} of the Grignard reagent was noted. See 6a, Table II, page 89. It was found that the method of isolation of the Grignard addition product affected the yield considerably and in many instances varied with the different esters. See conditions 1-5 on Table II, page 89.

The results of this study of the best conditions for reacting different Grignard reagents with various esters of levulinic acid showed that it was very difficult to find one set of experimental conditions which would apply equally well for the reactions of all of the esters of levulinic acid with a particular Grignard reagent.

The effect of solvent, rate of addition of the Grignard reagent, and the effect of time and temperature on the work-up of the Grignard addition product resulted in the selection of condition 5 at the bottom

\begin{enumerate}
\end{enumerate}
of Table II, page 89 as the best condition for comparing the reactivity of the Grignard reagents with esters of levulinic acid. The substituted lactone resulting from the reaction of the Grignard reagent with the keto group of each ester was determined and the yields showed that there was an advantage in using the ethyl ester over the methyl ester - an increase in yield of 15% of the substituted lactone. However, contrary to what might be expected the use of a secondary alkyl ester did not appreciable increase the yield of the substituted lactone. As expected the tertiary ester generally gave the best yield, but because of the difficulty associated with the preparation of the tertiary ester, the use of that compound to increase the yield would not be practical.
Levulinyl chloride (γ-chloro, γ-methylbutyrolactone)

\[
\begin{align*}
0 & \quad 0 \\
\text{CH}_3-\text{C}-\text{CH}_2-\text{CH}_2-\text{C}-\text{OH} & + \text{SOCl}_2 \rightarrow \text{CH}_3-\text{C}-\text{CH}_2-\text{CH}_2-\text{C}
\end{align*}
\]

To 600 g. (5.12 moles) of redistilled levulinic acid in a 200 cc. three-neck round bottom flask (hood) equipped with a reflux condenser containing a calcium chloride drying tube, a glass stirrer, and a dropping funnel was added 500 cc. (815 g. - 6.85 moles) of thionyl chloride (Eastman Kodak white label) at a fast drop rate with stirring. An ice bath was necessary at the very beginning of the reaction. However, the reaction soon became so endothermic that a layer of ice formed on the outer walls of the flask. This addition required 2-5 hours. After the addition the reaction product was refluxed for 45 minutes, and the excess thionyl chloride was removed by vacuum distillation with a water aspirator. Distillation afforded two fractions, 238 g., b.p. 85-90° at 30 mm. and 238 g., b.p. 90-95° at 30 mm. The combined fractions represented a yield of 69%.

1. A Hershberg stirrer may be used even though some corrosive action takes place.

2. A longer period of reflux lowered the yield.

3. Different distillation fractions of this 10° boiling range did not show any difference in yield of normal- or pseudo-ester.
Methyl levulinate

To 20 g. (0.15 mole) of the levulinyl chloride, b.p. 85-90° at 29-30 mm., was added, with stirring 20 cc. of a 1% methanolic potassium hydroxide solution. Heat was evolved and it was necessary to cool the flask. The material was refluxed for 30 minutes. After filtering off a small amount of white solid, the mixture was distilled. There was obtained 19 g. (98.4%) of the methyl levulinate, b.p. 90° at 15 mm., 82° at 10 mm., nD^26 1.4202. Titration with 0.1 N sodium hydroxide showed the ester to be .2% pseudo-ester.

Ethyl levulinate

To 348 g. (3 moles) of levulinic acid in a 2000 cc. flask equipped with a 3' packed column with a phase separating head was added a mixture of 500 cc. of absolute ethanol and 500 cc. of benzene. Three cc. of phosphoric acid was added as a catalyst. It took 6 hours of esterification to collect the theoretical amount of water. The mixture was poured over solid sodium carbonate and then filtered. After removal of the alcohol and benzene there was obtained by distillation 344 g. (80% of ethyl levulinate, b.p. 67° at 3 mm., 89° at 10 mm., nD^26 1.4189.

1. (a) The use of pyridine as a base gave a yield of only 25% -considerable complexing with the levulinyl chloride occurred. (b) The use of triethylamine as a base gave a yield of 73% - provided the amine was added after the alcohol had reacted with the ester.

2. The acid esterification method using levulinic acid, carbon tetrachloride and methanol gave a yield of 80%.


4. The methyl levulinate is very soluble in aqueous sodium carbonate solution.
Isopropyl levulinate

To 348 g. (3 moles) of levulinic acid in a 2000 cc. flask equipped with a 3' packed column with a phase separating head was added a mixture of 500 cc. of absolute isopropanol and 500 cc. of benzene. Three cc. of phosphoric acid was added as a catalyst. Seven hours of esterification were required to remove the theoretical amount of benzene water azeotrope. After neutralization of the acid catalyst with sodium carbonate followed by filtration there was obtained by distillation 420 g. (88%) of isopropyl levulinate, b.p. 89° at 10 mm., n_D^26 1.4175.²

Isobutyl levulinate

A mixture of 348 g. (3 moles) of levulinic acid, 600 cc. of isobutyl alcohol, 600 cc. of benzene, and 3 cc. of phosphoric acid was added to a 2000 cc. flask equipped with a column with a phase separating head for removal of the benzene-water azeotrope. Eight hours of esterification were required for the removal of the theoretical amount of water. The mixture was poured over sodium carbonate and then filtered. Distillation gave 500 g. (97%) of isobutyl levulinate, b.p. 108° in 10 mm., n_D^26 1.4230. This ester contained < 1% of pseudo-ester.

Anal. Calcd. for C_{9}H_{18}O_{3}: C, 62.76; H, 9.36

Found: C, 62.98; H, 9.11

1. The acid chloride of levulinic acid, triethylamine, and isopropyl also gave a yield of 81%.


3. The use of the acid chloride of levulinic acid, triethylamine, and isobutyl alcohol gave a 54% yield of the isobutyl ester boiling over a 5° range. It was a mixture of the pseudo- and normal-esters.
Diisopropylmethyl levulinate

To 500 g. (4.5 moles) of levulinic acid in a 2000 cc. three-neck round bottom flask equipped with a mechanical stirrer, a reflux condenser with a calcium chloride drying tube, and a dropping funnel of the pressure equalizer type, was added 500 cc. of thionyl chloride at a fast drop rate. The material was then heated on a steam bath till gas evolution had almost ceased (45 min.). The excess thionyl chloride was removed by distillation using a water aspirator. To the mixture was added 500 cc. of diisopropyl carbinal at a fast drop rate. The material was heated on a steam bath for 45 minutes and allowed to stand overnight. Distillation gave 500 g. (35%) yield\(^1\) of the diisopropylmethyl levulinate, b.p. 121-130\(^\circ\) at 10 mm. The various fractionation cuts from 121-130\(^\circ\) at 10 mm. were tested and their pseudo-ester content ranged from 7% for 121\(^\circ\) at 10 mm. to 15% for the 130\(^\circ\) at 10 mm. fraction. The normal ester after removal of the pseudo-ester had a b.p. of 126\(^\circ\) at 10 mm., \(n^D_26\) 1.4309.

1. If the acid chloride of levulinic acid is isolated a yield 30-40% of the ester is obtained, but the overall yield from levulinic acid is not as good as for the above. However, it should be noted here that if the acid chloride and triethylamine are used, the acid chloride and alcohol must first react before the addition of triethylamine. If the acid chloride is added to a mixture of the alcohol and triethylamine, the yield drops considerably (5-10% in some cases). In fact, for the preparation of this ester there appears to be no advantage in using triethylamine or any other base.

2. The pure normal ester b.p. 126\(^\circ\) at 10 mm. was prepared in 19% yield by the standard acid esterification method.
Tert-amyl levulinate

(a) successful synthesis

\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{CH}_2\text{-COOH} + \text{CH}_3\text{-CH}_2\text{C(CH}_3\text{)_2} & \quad \text{(amylene)} \\
\uparrow & \\
\text{CH}_3\text{C-CH}_2\text{CH}_2\text{-COO-C(CH}_3\text{)_2-CH}_2\text{-CH}_3 + \text{H}_2\text{O}
\end{align*}
\]

The procedure\(^1\) which was found to be best was as follows. Four cc. of 100% sulphuric acid was added to 114 g. (0.98 mole) of redistilled levulinic acid, b.p. 126\(^0\) at 4 mm. and the mixture added to 161.8 g. (1.8 mole) of amylene,\(^2\) b.p. 38-39\(^0\). The mixture was made homogeneous by the addition of approximately 85 cc. of tert-amyl alcohol. After setting for 48 hours in a stoppered flask, 100 cc. of amylene was added and the levulinic acid layer (70 cc.) then separated. The top layer containing the desired ester, tert-amyl alcohol, and amylene was decanted onto sodium carbonate. After filtering, there was obtained by distillation 26.5 g. of tert-amyl levulinate, b.p. 105-107\(^0\) at 10 mm. This was redistilled\(^3\) and there was obtained 22 g. of tert-amyl levulinate, b.p. 106\(^0\) at 10 mm., \(n^\text{D}_{26} 1.4256\). The yield was 12%.


3. Before redistillation the ester was extracted with 0.1 N sodium hydroxide solution to remove any pseudo-ester. The ester was essentially the pure normal form.
However, based on the recovered levulinic acid the yield was 70%.

Anal. Calcd. for C₁₀H₁₈₀₃: C, 64.68; H, 9.74

Found: C, 64.40; H, 9.75

In the olefin method of ester synthesis an ether such as dioxane or diethylether is usually used as a solvent with the additional purpose of preventing polymerization. Also, in working up the product water is introduced, and the acid of course, must be redistilled before any further use. For the particular case above it was found that the yield remained the same whether or not ether was used. Very little polymerization occurred if the sulphuric acid was first mixed with the levulinic acid before the olefin and alcohol were added. After the reaction equilibrium had been reached - < 24 hours - the homogeneous mixture of the alcohol, olefin, levulinic acid and H₂SO₄ separated into two layers upon the addition of an excess of the olefin. This made it possible to re-use the acid after separation of the top layer containing the ester, by simply adding more olefin, sulphuric acid and alcohol. The process was repeated several times with the result that the yield of the ester from the olefin was as high as 70%.

1. Many unsuccessful attempts were made to shift this equilibrium by the removal of the ester formed in the reaction. A method of using a continuous extraction of the levulinic acid + H₂SO₄ mixture with amylene was not satisfactory since the catalyst (H₂SO₄) combined with the olefin and was extracted even though the levulinic acid was not appreciably extracted. It might be that ZnCl₂ which is also a catalyst for this type of reaction might not be removed by the olefin and a method of continuous extraction using amylene could be used. An ion exchange acid resin would probably work also, but because of the lack of time this problem was not pursued further.
(b) other synthesis

The usual method employed for the preparation of tertiary esters is to react the acid chloride of the acid with the tertiary alcohol in the presence of a hydrogen chloride acceptor, such as triethylamine or pyridine. This method was tried using levulinyl chloride and tert-amyl alcohol with various bases. The yield of t-amyl ester was as high as 30% with the use of triethylamine. However, this 30% yield of material had an 8° boiling range and over 50% of it was the pseudo ester. This might be expected since the acid chloride exists mainly as the γ-chloro, γ-methyl, β-butyrolactone. All efforts to shift the equilibrium to give more of the desired normal ester were unsatisfactory.

The reaction of the (α) Angelica lactone with tert-amyl alcohol gave a yield of 31% of a mixture of normal- and pseudo-tert-amyl levulinate. However, after removal of the pseudo-ester, this was reduced to a yield of < 12% for the normal ester.

\[
\text{CH}_3\text{C}==\text{CHCH}_2\text{CH}_3 + \text{tert-amyl alc.} \xrightarrow{\text{H}^+} \text{CH}_3\text{C}==\text{CHCH}_2\text{CH}_2\text{CH}_3\text{O}
\]

(α) Angelica lactone

1. The bases used were as follows: potassium hydroxide (solid), potassium hydroxide (alcoholic), sodium carbonate (solid), pyridine, N₂-O-t-amylate, diethylaniline, and triethylamine. In these cases the acid chloride was added to the mixture of the alcohol and base, since the presence of an acid causes some of the t-amyl ester to revert to amylene and levulinic acid.

4. Prepared in 75% yield according to A. Thiele, Ann., 319, 184 (1901) using levulinic acid, acetic anhydride and acetyl chloride.
The method of ester interchange was investigated. Isopropyl levulinate, an equivalent of sodium (also potassium was tried), and an excess of t-amyl alcohol were used. No t-amyl ester of levulinic acid was obtained on distillation nor was there any recovered isopropyl levulinate. The main product was sodium levulinate. The use of phosphoric acid as a catalyst did not give any t-amyl levulinate by ester interchange.

**Methyhemagnesium bromide (standard solution)**

To 146 g. (6 moles) of magnesium in a 5000 cc. three-neck, ground glass joint, round bottom flask which had been flushed with nitrogen and equipped with a Friedrich condenser, a mechanical stirrer with a blade made of a piece of glass tubing, and a bubbler tube extending just below the surface of the ether was added 2000 cc. of dry ether.

The ether was warmed (maintaining a slight nitrogen pressure) and 569.7 g. (6 moles) of methyl bromide was poured into a 1000 cc. stoppered Erlenmeyer flask with an outlet tube for conducting the gas through a sulphuric acid bubbler and then through a potassium hydroxide

1. And methyl levulinate.
2. This blade was made of a piece of glass tubing 3 cm. x 1 cm. with a hole 0.6 cm. in the center and bottom of the tubing. The shaft was fused to the center of the tubing opposite the hole in the bottom.

![](Shciff)

This type of stirrer efficiently circulated the liquid without moving the solid. In a reaction of the Grignard type this type of stirrer worked as well as a Hershberg stirrer and did not require as powerful a motor and did not splash the magnesium on the walls of the flask as did the Hershberg stirrer.

3. Better contact was obtained with the sulphuric acid when the bubbler was filled with glass beads.
(pellet) tower and finally the gas was bubbled below the surface of the ether in the reaction flask. In approximately 10 minutes the ether took on a cloudy appearance and the reaction began. The rate of evaporation of the methyl bromide was sufficient to maintain a rapid ether reflux. It required 9-10 hours for the addition of the methyl bromide. The mixture was then refluxed for 1 hour, cooled, and transferred by nitrogen pressure to a brown bottle which had been flushed with nitrogen.

The Grignard reagent was standardized as follows:

Five cc. of the Grignard reagent was added to 40 cc. of distilled water and allowed to stand for 1 hour. Twenty-five cc. of 1 N standard acid solution was added and back titrated with 1 N standard sodium hydroxide solution using methyl orange as an indicator. The molarity of the methyl magnesium bromide solution prepared above was 2.706.

Ethylmagnesium bromide (standard solution)

To 146 g. (6 moles) of magnesium in a 5000 cc. three neck, ground glass joint round bottom flask which had been flushed with nitrogen and equipped with a Friedrich condenser, a mechanical stirrer with a blade made of a piece of glass tubing,\(^1\) and a dropping funnel with a pressure equalizer tube was added 800 cc. of dry ether.

The material was heated to ether reflux maintaining a slight nitrogen pressure, and a small quantity of ethyl bromide was added. In a few minutes the mixture took on a milky appearance. A total of 942.1 g. of ethyl bromide of b.p. 57° mixed with 2400 cc. of dry ether was added at such a rate as to maintain a rapid reflux. A total of six hours was required for the addition. The mixture was then refluxed for one hour and transferred by nitrogen pressure to a nitrogen flushed brown bottle for storage.

The molarity of the standard Grignard solution was found by titration\(^2\) to be 2.720.

---

1. See note 2, page 83.
2. See page 84.
Phenylmagnesium bromide (standard solution)

A total of 146 g. (3 moles) of magnesium and 800 cc. of dry ether were added to a 500 cc. three-neck, ground glass joint, round bottom flask which had been flushed with nitrogen and equipped with a mechanical stirrer with a glass tube as a blade,\(^1\) a dropping funnel with a pressure equalizer tube, and a Friedrich condenser.

The ether was heated to reflux and a small quantity of bromobenzene was added. When the reaction had started as noted by the milky appearance, the remainder of the bromobenzene totalling 842.1 g. (3 moles) was added at such a rate as to maintain a rapid ether reflux. Six hours was required for the addition. The mixture was then refluxed for 1 hour and transferred by nitrogen pressure to a brown bottle which had been flushed with nitrogen. Titration\(^2\) of the Grignard reagent showed it to be 2.734 molar.

---

1. See note 2, page 83.
2. See page 84
The reaction of Grignard reagents with esters of levulinic acid

\[
\text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-OR} + R'\text{-MgX} \rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-C-O-OR} + HX
\]

Where \( R' \) is methyl, ethyl, or phenyl
\( R \) is methyl, ethyl, isobutyl, diisopropylmethyl, or tert-amyl
\( \gamma \)-methyl, \( \beta \)-alkyl-butyrolactone

The general procedure was as follows: A 250 cc. three-neck, ground glass joint round bottom flask, equipped with a Hershberg stirrer, a 250 cc. dropping funnel with a pressure equalizer tube, and a Friedrich condenser, was flushed with nitrogen gas and placed in an ice bath. A total of 0.14 mole of the ester and 140 cc. of solvent (ether or benzene) equivalent to 1000 cc. per mole of ester were added. The mixture was stirred for 1 hour. With care, 0.13 mole of the Grignard reagent was transferred to the dropping funnel, and the reagent added over a period of 1 hour to the stirred solution of the ester.
ester and solvent. A temperature of 0° was maintained and a slight nitrogen pressure was maintained during the addition. The mixture was then stirred at 0° for 2.5 hours, followed by a 30 minute period of reflux. After cooling to 0°, 100 cc. of a 20% sulphuric acid solution was added at a fast drop rate maintaining a temperature of 0°-5°. The two layer mixture was then transferred to a separatory funnel. The aqueous portion was withdrawn and extracted with 10-20 cc. portions of ether. These extracts were added to the main ether-benzene layer, and the combined extracts washed consecutively with 10 cc. of water, 10 cc. of 10% sodium bicarbonate solution, 10 cc. of water, and finally with 10 cc. of saturated sodium chloride solution. After drying over sodium sulfate (anhydrous) the material was distilled first from a Claisen flask at very low pressure and then through a column at 2 mm. pressure. The products of the reaction of the Grignard reagents with the esters of levulinic acid were as follows: The γ,γ-dimethylbutyrolactone was isolated as the product of the reaction of methyl Grignard reagent with the esters of levulinic acid, b.p. 57° at 2 mm., 95° at 17 mm., n_D²⁵ 1.4259.¹

The γ-methyl, β-ethylbutyrolactone was isolated as the product of the reaction of ethyl Grignard reagent with the esters of levulinic acid, b.p. 70° at 2 mm., 105° at 15 mm., n_D²⁵ 1.4395.²

The γ-methyl, γ-phenylbutyrolactone was isolated as the product of the reaction of phenyl Grignard reagent with the esters of levulinic acid, b.p. 129-130° at 2 mm., 148° at 5 mm., n_D²⁵ 1.5285.³

Table II

Reaction of Grignard Reagents with Various Esters of Levulinic Acid

<table>
<thead>
<tr>
<th>Grignard Reagent</th>
<th>Solvent</th>
<th>Methyl</th>
<th>Ethyl</th>
<th>Isopropyl</th>
<th>Isobutyl</th>
<th>Diisopropylmethyl</th>
<th>t-ethyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMgBr</td>
<td>Benzene</td>
<td>*</td>
<td>*</td>
<td>37.5 (1)</td>
<td>40.9 (1)</td>
<td>39.9 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.7 (2a)</td>
<td>50.4 (6)</td>
<td>53.2 (6a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ether</td>
<td>34.8 (2)</td>
<td></td>
<td>37.5 (1)</td>
<td>55.5 (1)</td>
<td>40.9 (1)</td>
<td>42.7 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.4 (2)</td>
<td></td>
<td>39.9 (3)</td>
<td></td>
</tr>
<tr>
<td>EtMgBr</td>
<td>Ether</td>
<td>26.1 (2)</td>
<td></td>
<td>13.3 (4)</td>
<td>21.7 (4)</td>
<td>52.6 (3)</td>
<td>53.9 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.4 (5)</td>
<td>61.9 (4)</td>
<td>46.9 (5)</td>
<td>61.9 (5)</td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
<td>34.5 (5)</td>
<td>49.5 (5)</td>
<td>43.2 (5)</td>
<td>35.8 (5)</td>
<td>37.1 (5)</td>
<td>49.8 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.8 (5)</td>
<td>28.8 (5)</td>
<td>36.7 (5)</td>
<td></td>
</tr>
<tr>
<td>C_{6}H_{5}MgBr</td>
<td>Ether</td>
<td>34.5 (5)</td>
<td></td>
<td>49.5 (5)</td>
<td>43.2 (5)</td>
<td>35.8 (5)</td>
<td>37.1 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49.1 (5)</td>
<td>39.8 (5)</td>
<td>28.8 (5)</td>
<td>36.7 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.93 (3)</td>
<td></td>
<td>49.1 (5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34.5 (5)</td>
<td></td>
<td>49.1 (5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
<td></td>
<td></td>
<td>49.1 (5)</td>
<td></td>
<td>49.8 (5)</td>
<td></td>
</tr>
</tbody>
</table>

*Difficulty of separating lactone made results here inaccurate.

Conditions

(1) Work up product 15 min. after addition of Grignard reagent (no heat used).
(2) Work up product 60 min. after addition of Grignard reagent (no heat used).
(2a) Work up product 2 hr. after addition of Grignard reagent (no heat used).
(3) reflux 30 min. before decomp. Grignard complex and reflux 45 min. after decomp.
(4) Work up product 2.5 hr. after addition of Grignard reagent and after decomp. of Grignard complex heat 15 min.
(5) Work up product 2.5 hr. after addition of Grignard reagent and reflux 30 min. before work up. (These conditions were believed to be the best).
(6) Work up product after setting overnight in refrigerator (no heat used).
(6a) Here the Grignard reagent was added in 1 min. instead of the customary 60 min., and the material was worked up in 1 hour (no heat used).
Summary

A series of primary, secondary, and tertiary alkyl esters of levulinic acid were prepared.

A study of the reaction of these esters with Grignard reagents was made.

The effectiveness of the alkyl group of the ester to block the side reaction of the Grignard reagent with the ester group was measured by the yield of the substituted lactone resulting from the reaction of the Grignard reagent with the γ-keto group. The more product resulting from the reaction with the γ-keto group, the more effective was the alkyl group in blocking the ester.

It was found with one set of experimental conditions that the tertiary alkyl ester was the most effective in sterically hindering the side reaction of the Grignard reagent with the ester group; the difference is small and is obscured by the varying effect of experimental conditions.

There was found to be very little difference in the effect of a primary or a secondary alkyl-ester. However, within the primary alkyl esters, the ethyl ester gave a better than 15% increase in yield of lactone over that obtained with the methyl ester, consequently there is an advantage in using the ethyl ester over the methyl ester to sterically hinder the reaction of the ester group with the Grignard reagent.
I, James L. McPherson, was born in Chattanooga, Tennessee, June 25, 1922. I received my secondary education in the schools of that city, and the degree of Bachelor of Science from The Georgia Institute of Technology of Atlanta, Georgia in June 1944. For the next two years I served as rifleman in the infantry in the South Pacific. In October 1947, I enrolled in the Graduate School of the University of Texas and was granted the degree of Master of Arts in June 1949. I entered the Graduate School of The Ohio State University in September 1949. While completing the requirements for the degree of Doctor of Philosophy I held the position of Research Fellow of the National Institute of Health from 1950 to 1951 and a Fellowship from Upjohn Company from 1951-1953.