Preliminary Studies in the Synthesis of the Polynuclear Hydroaromatic Ring Systems

by

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Table of Contents

I. Introduction and Statement of Problem.............................. 1
II. Plan of Attack..................................................... 2
III. The Aims of the Investigation..................................... 8
IV. The Investigation................................................... 9
   1. p-methoxycinnamic acid........................................ 10
      a. The method of Knoevenagel................................ 10
      b. Oxidation of anisalacetone................................ 11
      c. By the Claisen Reaction.................................... 11
   2. p-methoxycinnamoyl chloride................................... 14
   3. diethyl isosuccinate............................................. 15
   4. diethyl acetyl isosuccinate.................................... 17
   5. diethyl p-methoxycinnamoyl isosuccinate...................... 18
      a. By the malonic ester synthesis............................. 18
      b. By the Claisen Condensation............................... 19
   6. The Grignard Reactions of diethyl p-methoxy
      cinnamoyl isosuccinate........................................ 20
   7. Laevulinic acid.................................................. 23
      a. $\delta$-anisallaevulinic acid............................... 24
      b. ethyl $\delta$-anisallaevulinate............................ 25
      c. ethyl $\delta$-anisallaevulinate............................ 25
   8. diethyl hydrochelidonate......................................... 25
      a. $\beta$-(\(\alpha\)-furyl) acrylic acid........................ 26
      b. ethyl $\beta$-(\(\alpha\)-furyl) acrylate..................... 27
      c. diethyl hydrochelidonate.................................. 28
9. Condensations of hydrochelidonic acid.................28
   a. hydrochelidonic anhydride..........................29
   b. potassium hydrochelidonate.........................29
10. Synthesis of ethyl \( \gamma \)-ethoxalyl-\( \alpha \)-methyl
crotonate..................................................30
    a. \( \alpha \)-hydroxy-\( \alpha \)-methyl-n-butyronitrile.....31
    b. ethyl \( \alpha \)-hydroxy-\( \alpha \)-methyl-n-butyrate.....32
    c. ethyl 4-dimethyl acrylate............................33
    d. ethyl \( \gamma \)-ethoxalyl-\( \alpha \)-methyl crotonate.....34
11. Condensations of ethyl \( \gamma \)-ethoxalyl-\( \alpha \)-methyl
crotonate..................................................35
12. \( \alpha \)-(\( \beta \)-phenylethyl) furane.........................37
    a. \( \alpha \)-phenyl-\( \beta \)-(\( \alpha \)-furyl) acrylic nitrile...37
    b. \( \alpha \)-(\( \beta \)-phenylethyl) furane................38
13. Another method for \( \alpha \)-(\( \beta \)-phenylethyl) furane...39
    a. \( \alpha \)-phenyl-\( \beta \)-(\( \alpha \)-furyl) ethylene........40
    b. \( \alpha \)-(\( \beta \)-phenylethyl) furane.................41
14. \( \alpha \)-(\( \beta \)(m-methoxyphenyl)ethyl) furane............41
    a. m-methoxybenzoic acid..............................43
    b. m-methoxybenzyl alcohol............................43
    c. m-methoxybenzyl chloride.........................44
    d. m-methoxyphenylacetonitrile.......................45
    e. \( \alpha \)-(\( \beta \)(m-methoxyphenyl)ethyl) furane........45
15. Addition of maleic anhydride to \( \alpha \)-(\( \beta \)-phenyl-
    ethyl) furane..........................................46
    a. 3-(\( \beta \)-phenylethyl)-3,6-endoxo-\( \alpha \)^{\#}-teta-
        hydrophthalic anhydride............................46
V. Conclusion..............................................48
VI. References............................................49
I. INTRODUCTION AND STATEMENT OF THE PROBLEM

Organic chemical research in the past decade has revealed a most suggestive coincidence. A considerable number of naturally occurring substances has been shown to possess a hitherto unsuspected fundamental structure, namely, the phenanthrene nucleus. This unit is common to the sex hormones, morphine and the related alk aloids, bile acids, sterols, and cardiac aglucones.

\[ \text{\includegraphics[width=0.8\textwidth]{compound structures}} \]

The structure of these compounds, but recently elucidated, remains to be proven by synthesis.

The total synthesis of any of the above substances is quite beyond the scope of this problem. On the other hand, the consistent application of one of the more general reactions of organic chemistry to the synthesis of substances containing the partially hydrogenated phenanthrene nucleus, or substances easily transformed by well known reactions into the latter, might well yield valuable information. Such an investigation would naturally be pursued with especial reference to the foundation of a substantial basis for future work on the more difficult problem of total synthesis.

Particularly favorable to a project of this sort, in
virtue of its wide applicability in the synthesis of cyclic systems, is the reaction of Diels and Alder (1). The choice of this vehicle entails the preparation of conjugated dienes suitable for condensation to substances of the type desired. The problem, then, assumes the character of an effort to obtain, by the usual methods of organic synthesis, certain compounds suitable for Diels-Alder condensation to adducts capable of ultimate transformation into one or more of the naturally occurring phenanthrene derivatives.

II. PLAN OF ATTACK

There are but three diene structures which afford the possibility of condensation to the oestrine ring system.

\[ \text{I.} \quad \text{II.} \quad \text{III.} \]

Of these, I. is fundamentally not dissimilar from the more readily accessible III. A desirable simplification of the problem, without loss of completeness, is consequently effected by the exclusion of the former. It remains to formulate suitable derivatives of II. and III., and to devise methods of synthesis for these substances.

A. Certain substances of type II. are known (24); none of these has been investigated in relation to its participation in the Diels-Alder reaction. Since its condensation pro-
3.

Products would be closely related to oestrone, the compound IV. is a suitable goal for synthetic work.

IV.

A number of methods of synthesis are available.

1. The reaction of the ketonic ester V, obtained by the malonic ester synthesis, with the Grignard reagent, MgI₂CH₂CH₂COOEt, should yield the hydroxy acid VI, which upon saponification, decarboxylation, and dehydration, gives IV.

V.

VI.

The method is subject to certain weaknesses. The Grignard reaction is not confined to the ketonic function. The ester groups of V. may well be sensitive to the action of organo-magnesium compounds. By careful adjustment of experimental conditions, however, previous investigators have been successful in isolating the ketonic reactions products from ketonic esters (2). Should this be impossible, the substitution of the magnesium compound by an organo-zinc derivative, as ZnBr₂CH(COOEt)CH₂COOEt, may overcome this difficulty, since the Reformatsky Reaction is specific for carbonyl
4.

groups (3). In any case, in the execution of the experimental work, it is advisable to study first the simpler reaction of V. with methyl magnesium iodide.

Again, V. is an \( \alpha \)-ethylenic ketone. This immediately calls to mind the possibility of 1,4-addition of the Grignard or Reformatsky reagents. This problem has occasioned a great deal of investigation (4), but no general rules may be formulated from which the reactions of V. may be inferred.

Finally, in order to allay all suspicion as to the structure of V., itself as yet unknown, an alternative method of synthesis is advisable. This is available in the condensation of diethyl acetylisosuccinate and anisic aldehyde in the presence of anhydrous hydrogen chloride.

\[ \text{R}_3\text{CH} - \text{CO} \rightarrow \text{R}_3\text{CH} - \text{CH} - \text{CO} \]

2. The reaction of ethyl \( \alpha \)-bromopropionate with ethyl \( \beta \)-anisallevulinate, VII., in the presence of zinc, should yield an hydroxy acid VIII., the transformation of which into IV. should not be difficult.

\[ \text{VII.} \quad \text{VIII.} \]

This method is similar in type to that mentioned above, and has certain of its drawbacks. In other respects it is advantageous; it involves only the selective Reformatsky
5.

Reaction, and employs readily accessible compounds (5).

3. Finally, it must be borne in mind that IV. exists in four geometrically isomeric configurations. Should any of the above methods of synthesis yield a mixture of two or more of these isomers, the situation would be complicated considerably. In such an event, the usual methods of separation by physical or chemical means must be relied upon.

4. The compound IX. differs but slightly from IV. Its two extra carbon atoms are advantageously situated for subsequent ring closure with the formation of the oestrone nucleus. IX. can conceivably be obtained by the second method for the preparation of IV. by the substitution of derivatives of hydrochelidonic acid for those of levulinic acid.

\[
\text{HOOC-CH}_2\text{CH}_2\text{CO-CH}_2\text{CH}_2\text{COOH} \quad \text{HOOC-CH}_2\text{CH}_2\text{COCH}_3 \\
\text{hydrochelidonic acid} \quad \text{laevulinic acid}
\]

5. Another representative of type II. is obtained by the condensation of ethyl \(\gamma\)-ethoxalyl-\(\alpha\)-methylcrotonate X. with anisic aldehyde to XI.
This reaction may follow one of two courses, judging from the analogous condensation of ethyl oxalacetate with aromatic aldehydes (6). In the latter case, either cyclic lactones (A) or unsaturated substances (B) are produced.

\[
\begin{align*}
\text{(A)} & \quad \text{(B)} \\
\end{align*}
\]

Compounds analogous to (B) would belong to type II. and would be suitable for the purposes of the problem. Should the reaction follow the alternative course, the products would be quite inapplicable to Diels-Alder condensation.

B. The addition of maleic anhydride to dienes of type III. has been shown recently to proceed with great difficulty, if at all. (7). This abnormality is attributed to a prototropic change with the formation of derivatives of vinyl tetralin; under the influence of maleic anhydride the latter substance would be expected to polymerise with great ease. Indeed, the p-methoxy derivatives, extremely sensitive to prototropic changes of this sort gave only polymeric products to the exclusion of any true diene adduct.

\[
\begin{align*}
\text{(A)} & \quad \text{(B)} \\
\end{align*}
\]

Now, the isomerisation, \((A) \rightarrow (B)\), requires, besides a labile hydrogen atom, an active double bond. Could we
reduce the activity of the $\Delta^{-3,4}$ bond without inhibiting the reactivity of the conjugated system in the Diels-Alder Reaction, we might well expect to avoid the unfavorable results of the previous investigations.

Substances which conform, at least in theory to this requirement are the substituted $\alpha-(\beta$-phenylethyl)-furanes. These compounds possess the basic structure of substances of class III. Their $\Delta^{-3,4}$ bond is relatively inactive as a consequence of the aromaticity of the furane ring, whereas the ability of the members of the furane series to undergo conjugate addition has been amply demonstrated (8).

1. Only the parent substances $\alpha-(\beta$-phenylethyl) furane is known. The reaction of this substance and its $m$-methoxy derivative with maleic and with citraconic anhydride, then, should yield derivatives of a type capable of transformation into hydrogenated phenanthrene derivatives by subsequent prototropic isomerisation under the influence of various inorganic reagents (9). With regard to the reactions with citraconic anhydride, we should expect from steric considerations that of the two possible products, XII. and XIII., the latter would be formed with greater ease.

\[ \text{XII.} \]

\[ \text{XIII.} \]
2. Finally, it has been shown that the reactions of substituted succinic anhydrides involve the carbonyl group attached to the least substituted carbon atom. (10). The reduction of XIII, or its cyclisation product, then, should give products capable of ultimate transformation into oestrone or its derivatives.

III. THE AIMS OF THE INVESTIGATION

It is hoped that the investigation will demonstrate the applicability of the Diels-Alder Reaction to the ultimate synthesis of oestrogenic substances. The work is preliminary in nature; it is hoped that a firm foundation may be constructed upon which future work may be based.

In virtue of this end, one salient fact must be kept in mind throughout the investigation. If any organic chemical is to be used as the starting point of a more or less lengthy synthesis, it is absolutely essential that its acquisition in quantity be a matter of relative ease. Reactions, then, which consistently yield the desired product in diminishing amounts are quite unsuitable for the purposes of this research.

No doubt in the course of this work, as in most organic research, compounds will be obtained which are quite irrelevant to the specific purpose of the investigation. Such substances are derivatives useful in the identification or chemical examination of unknown materials. The tabulation of the properties of such derivatives is of definite value.
9.

Again, it is not unreasonable to suppose that in some cases, known methods may be somewhat improved; certainly the best method for the preparation of certain compounds may be ascertained by comparison of the available procedures.

IV. THE INVESTIGATION

1. For the preparation of diethyl isosuccinate and p-methoxy cinnamoyl chloride must be obtained. P-methoxy cinnamic acid, p-cumaric acid methyl ether, has been prepared by a number of chemists (11). The more promising of these methods were investigated. The condensation of anisic aldehyde with malonic acid in the presence of alcoholic ammonia (Knoevenagel) proceeded very smoothly and gave excellent yields. The high cost of malonic acid, however, eliminated the use of the method on a preparative scale. The preparation of anisalacetone and its subsequent oxidation provided another convenient route to the acid, but its application on a large scale would be very troublesome, as a result of the excessively large volumes of reagent which would be necessary.

The best preparative method was found to be the condensation of anisic aldehyde with ethyl acetate in the presence of metallic sodium, followed by saponification of the resultant ester. The method has previously been employ-
ed by Vorländer, who gives no details. The yield was
fair (67 percent), the operations are not awkward even
on a very large run, and a pure product is easily obtained.

Experimental Part

p-methoxy cinnamic acid

CH₃O·C₆H₄·CH·CH·COOH  C₁₁H₁₁O₃  178.0

To a mixture of anisic aldehyde (2.0 gr.) and malonic
acid (1.9 gr.) eight percent alcoholic 1 ammonia
(8.0 c.c.) is added. The precipitate which forms dissolves
slowly, when heated on a vigourously boiling water bath, to
a clear yellow solution resembling nitrobenzene in appear-
ance. In one hour the mass becomes quite viscous, while
gas bubbles can be seen evolving. In eighty minutes fairly
rapid gas evolution begins, crystals can be seen on the
sides of the vessel, and an odor reminiscent of cinnamic
acid can be detected. In ninety-six minutes the reaction
mixture solidifies to a white crystallin mass. The solid
is dissolved in hot water (350-400 c.c.) and acidified
with dilute sulphuric acid (1:5). The p-methoxycinnamic
acid (1.7 gr.) separates in white flocks, which are
filtered off, washed well with water and dried. Crystall-
ized from dilute alcohol, it forms yellowish needles melt-
ing to a cloudy liquid at approximately 169°

1. Prepared by dissolving concentrated ammonia (20.0 c.c.)
in ethyl alcohol (250 c.c.).
anisal acetone

\[ \text{CH}_3\text{O.C}_6\text{H}_4\text{.CH:CH.CO.CH}_3 \quad \text{C}_{11}\text{H}_{12}\text{O}_2 \quad 176.0 \]

Anisic aldehyde (10.0 gr.) and acetone (12.0 gr.) are dissolved in a solution of sodium hydroxide (1.5 gr.) in water (500 c.c.). At the end of an hour yellow flocks begin to separate from the clear solution. In twelve hours, precipitation is complete. The ketone (9.5 gr.) is filtered off and recrystallised from petroleum ether. Splendid silver plates. (mp. 71-72\(^\circ\))

p-methoxycinnamic acid

\[ \text{CH}_3\text{O.C}_6\text{H}_4\text{.CH:CH.CO.OH} \quad \text{C}_{16}\text{H}_{10}\text{O}_3 \quad 179.0 \]

For conversion to the acid, p-methoxybenzalacetone (5.0 gr.) is heated on a vigourously boiling water bath with a large excess of freshly prepared sodium hypochlorite solution until evolution of chloroform ceases. The reaction mixture is filtered to remove unchanged ketone, and the p-methoxycinnamic acid (3.5 gr.) precipitated with dilute sulphuric acid (1:5), washed, dried and crystallised from dilute alcohol. Needles melting at 168\(^\circ\) to a cloudy liquid.

ethyl p-methoxy cinnamate

\[ \text{CH}_3\text{O.C}_6\text{H}_4\text{.CH:CH.CO.OH} \quad \text{C}_{12}\text{H}_{14}\text{O}_3 \quad 206. \]

Into a three-necked flask equipped with a thermometer
and an efficient motor stirrer, sodium \(_1\) (28.0 gr.) is introduced, followed by anhydrous ethyl acetate (500 c.c.) containing absolute alcohol (7.0 c.c.). Approximately one cubic centimeter of anisic aldehyde is immediately added, at room temperature \(_2\). Reaction begins at once as evidenced by the formation of a red deposit on the sodium particles. The contents of the flask are now cooled rapidly to 0\(^\circ\) at which temperature the remainder of the anisic aldehyde (136.0 gr.) is dropped in slowly, addition requiring about two hours in all. During this time the temperature is never allowed to exceed 10\(^\circ\). When the addition of the aldehyde has been completed, the reaction mixture, a somewhat viscous deep red liquid, is allowed to cool to room temperature, stirring being continued one to two hours to dissolve any unreacted sodium. At the end of this time, acetic acid (100 c.c.) is added cautiously, then water, and the mixture shaken thoroughly. The deep red ethyl acetate layer is separated, shaken once with six normal hydrochloric acid, twice with water, and is dried over anhydrous sodium sulphate. After

1. Finely divided sodium prepared in usual manner by stirring the molten metal under xylene.

2. If this is not done, the reaction is delayed so considerably that, once begun, it proceeds so violently as to occasion serious fires.
distillation of the solvent and excess acetic acid from a water bath under somewhat reduced pressure, the residue is fractionated in vacuo. The ester (130 gr.) is a slightly yellow highly refractive liquid (bp. 168°) which solidifies in the receiver to large colorless stout prisms, (mp. 42°) sufficiently pure for all practical purposes.

**p-methoxycinnamic acid**

\[ \text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4\text{CH:CH}_2\text{COOH} \quad \text{C}_{10}\text{H}_{10}\text{O}_3 \quad 178.0 \]

For conversion to the acid, ethyl p-methoxycinnamate (126.0 gr.) is allowed to stand overnight with potassium hydroxide (40 gr.) in alcohol (400-500 c.c.) The precipitated salt is filtered, dissolved in water, and acidified with six-normal sulphuric acid (170 c.c.). The p-methoxycinnamic acid is washed, dried overnight at 110°, and crystallised from methyl alcohol. Long needles melting at 169° to a cloudy liquid.

2. The conversion of p-methoxycinnamic acid into its chloride by the action of phosphorus pentachloride was accomplished by Perking in 1880 (12). Since that time, the less vigorous thionyl chloride has found great application in the preparation of acyl chlorides. All attempts to convert cumeric acid methyl ether by this method were unsuccesful, even when solvents were used. Only high
melting products and a substance melting at 136° (probably an allomeric modification of the acid) could be obtained.

The reaction with phosphorus pentachloride, on the other hand, ran very smoothly, giving excellent yields of the desired chloride. The separation of the latter from the admixed phosphorus compounds offered no difficulty. The material was identified by conversion the amide and the methyl ester.

**Experimental Part**

**p-methoxy cinnamoyl chloride**

\[
\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH} \cdot \text{COCl} \quad \text{C}_{10}\text{H}_{10}\text{O}_2\text{Cl} \quad 196.5.
\]

Pure p-methoxycinnamic acid (10.0 gr.) and phosphorus pentachloride (12.0 gr.) are shaken in an open vessel (hood) until a homogeneous emerald-green liquid is obtained. Phosphorus oxychloride and excess phosphorus pentachloride are removed by heating on a vigourously boiling water bath, for two hours at forty-five millimeters, then for an equal period at fifteen millimeters. The residue is now allowed to stand over-night, when it crystallises in dark striated masses. The chloride (10.0 gr.) is crystallised from petroleum ether. Beaut-

\[1.\text{ As an alternative procedure, the residue may be fractioned in vacuo at this point. p-methoxycinnamoyl chloride distils as a clear slightly yellow liquid, solidifying on cooling to a crystalline mass. (mp. 50°)}\]
iful white crystals, small nodular cluster, having much
the appearance of snow (mp. 50°).

Amide. A small sample of the chloride treated with alcohol-
ic ammonia gave the sparingly soluble amide, crystallising
from hot ethyl alcohol in long colorless needles. (mp. 136°).

Methyl ester. In similar manner the methyl ester, crystall-
isng from methyl alcohol in plates (mp. 89°) was prepared.

3. Diethyl ososuccinate was prepared in the usual manner
by the action of methyl iodide on diethyl sodiomalonate (13.).
The yield of ester is considerably increased by the use of
carefully prepared alcohol. Since diethyl malonate and
diethyl isosuccinate are indistinguishable by the ordinary
boiling point determinations, density measurements were
employed to establish the identity of the product.

Experimental Part
diethyl isosuccinate

\[ \text{CH}_3\text{CH(COOEt)}_2 \quad \text{C}_8\text{H}_{14}\text{O}_4 \quad 174.0 \]

Sodium (14.0 gr.) dissolved in absolute ethyl
alcohol (200.0 gr.) with diethyl malonate (100 gr.)
Methyl iodide (90.0 gr.) is added from time to time

1. Previously distilled from one tenth its weight of met-
   allic sodium.
in small portions, while the reaction mixture is refluxed vigourously. The original voluminous white precipitate dissolves completely, giving place toward the later stages of the reaction to a heavy crystalline precipitate of sodium iodide. In ninety minutes, the reaction mixture is neutral, and heating is discontinued. The alcohol is now distilled from the water bath in the vacuum of the water pump. The residue is fractionated at barometric pressure, a small portion distilling below 100° being discarded. The ester (33.0 gr.) is a colorless liquid of peculiar odor, distilling at 194-197°.

In order to distinguish from diethyl malonate, whose boiling point is practically identical with that of diethyl isosuccinate, density measurements were made.

\[
\begin{array}{ccc}
\text{Wt. tube and ester} & \text{4.796} & \text{Wt. tube and water} & \text{4.777} \\
\text{Wt. tube} & \frac{3.705}{1.091 \text{ gr.}} & \text{3.705} & \text{1.072} \\
T. = 22° & & & \\
\end{array}
\]

\[D_{22} = 1.017\]

Known densities.

\[
\begin{array}{ccc}
\text{CH}_2(\text{COOEt})_2 & \text{CH}_3\text{CH( COOEt)}_2 \\
D_{18} & 1.06104 & 1.02132 \\
D_{25} & 1.05248 & 1.01295 \\
\end{array}
\]

2. Small pieces of tile must be added to prevent very violent bumping.
4. Diethyl p-methoxycinnamoyl isosuccinate was prepared by two methods. One, the condensation in the presence of anhydrous hydrogen chloride of anisic aldehyde with diethyl acetylisosuccinate (Claisen Reaction) necessitated the preparation of the latter substance. This was obtained by the usual malonic ester synthesis (14).

**Experimental Part**

**diethyl acetyl isosuccinate**

\[
\begin{align*}
\text{CH}_3\text{CO} & \quad \times \quad \text{COOEt} \\
\text{CH}_3\text{CO} & \quad \text{COOEt}
\end{align*}
\]

C\(_{10}\)H\(_{16}\)O\(_5\) 196

Finely divided sodium (2.63 gr.) suspended in anhydrous ether (200 c.c.) is treated with diethyl isosuccinate (19.9 gr.). The precipitation of the flocculent white diethyl sodio-isosuccinate is allowed to proceed to completion in the refrigerator, about twenty-four hours being required. At the end of this time, acetyl chloride (9.0 gr.) in anhydrous ether (50 c.c.) is added with mechanical stirring during the course of two hours. When the reaction mixture has been allowed to stand over night, the ethereal solution is shaken with water, then with aqueous copper acetate, filtered, and dried over sodium sulfate. After evaporation of the ether, the residue is fractionated in vacuo. Diethyl acetylisosuccinate (10.0 gr.) is a colorless liquid with the pleasant odor peculiar to ketonic esters. (bp.\(_2\) 125-135\(^\circ\))

1. Diethyl acetylisosuccinate has been shown to possess no definite boiling point, as ordinarily obtained. This has been explained on the assumption of a keto-enol equilibrium constant hypersensitive to temperature changes.
5. A similar reaction that between diethyl isosuccinate and p-methoxy cinnamoly chloride, gave the new ester. The latter could also be obtained as mentioned above by the Claisen Reaction. This method is less involved than the malonic ester synthesis, but has the disadvantage that the reaction proceeds rather slowly.

The identity of the diethyl p-methoxycinnamoyl isosuccinate was established by quantitative saponification to sodium p-methoxycinnamate, and sodium isosuccinate.

**Experimental Part**

**Diethyl p-methoxycinnamoyl isosuccinate**

\[
\text{CH}_3\text{CH} = \text{CH-CO-C(CH}_3\text{)(COOH)}_2 \quad \text{C}_{18}\text{H}_{22}\text{O}_6 \quad 334.0
\]

Finely divided sodium (2.63 gr.) suspended in anhydrous ether (200. c.c.) is treated with diethyl isosuccinate (19.9 gr.). The precipitation of the flocculent white diethyl sodyl isosuccinate is allowed to proceed to completion in the refrigerator, about twenty-four hours being required. At the end of this time, p-methoxycinnamoyl chloride (22.3 gr.) in anhydrous ether (50 c.c.) is added slowly, with mechanical stirring, during the course of three hours. The reaction is strongly exothermic, and will occasion excessively vigorous boiling of the ether if the addition is too rapid. The reaction mixture assumes a bright orange-yellow colour, and the light flocculent precipitate of the sodium derivative
19.
gives place to a heavy granular deposit of sodium chloride. After standing over night, the reaction mixture is shaken with water, the ethereal solution is shaken with aqueous copper acetate, filtered and dried over anhydrous sodium sulphate. After evaporation of the ether, the residue is fractionated in vacuo. The new ester (9.5 gr.) is a thick viscous yellow oil, of peculiar and lasting odor. (bp2 200-205°). Although on standing several months, a very small quantity of crystals appears, the ester cannot be induced to solidify completely. The crystals may well be p-methoxy-cinnamic acid, present as an impurity in the ester, or from hydrolysis on standing.

Saponification Equivalents

<table>
<thead>
<tr>
<th>Millequivalents ester used</th>
<th>0.1032 gr.</th>
<th>0.0920 gr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.c. 0.1037 n NaOH</td>
<td>20.00</td>
<td>20.00</td>
</tr>
<tr>
<td>C.c. 0.0929 n HCl</td>
<td>11.96</td>
<td>13.09</td>
</tr>
<tr>
<td>Millequivalents NaOH used</td>
<td>0.964</td>
<td>0.859</td>
</tr>
</tbody>
</table>

**diethyl p-methoxycinnamoyl isosuccinate**

\[ \text{CH}_3\text{O.C}_6\text{H}_4\text{CH:CH.CO.C(COOEt)}_2\text{CH}_3 \quad \text{C}_{18}\text{H}_{22}\text{O}_6 \quad 334.0 \]

Anisic aldehyde (13.6 gr.) and diethyl acetylisosuccinate (19.6 gr.) were saturated at 5° with anhydrous hydrogen

Although 0° is a more favorable temperature, the mixture is prone to solidification if it is allowed to become so cold.
chloride. The brilliant scarlet reaction mixture is allowed to stand at this temperature for one week. At the end of this time, the reaction product is shaken with water, the separated oil is taken up in ether, and the ethereal solution is dried over anhydrous sodium sulphate. After removal of the ether, the residual oil is fractionated in vacuo. ( bp\textsubscript{2} 199-205° ) ( cf. above. )

6. The discussion in the preliminary section indicated that the reaction between diethyl \( p \)-methoxycinnamoyl isosuccinate and Grignard reagents might well be complex. Preparatory to the use of the relatively complicated MgI\( _2 \).CH\(_2\)CH\(_2\).COOEt, the simpler methyl magnesium iodide was employed. The above conclusion was indeed justified. In no case could homogeneous reaction products be isolated in appreciable yield. The reaction-mixture contained unsaturated substances, but the method of Kohler (4), was ineffectual in the separation of the latter from any saturated substances which may have been present. Attempts at hydrolysis in the hope of obtained saturated acids were likewise unsuccessful.

**Experimental Part**

In a typical experiment the Grignard solution from magnesium ( 0.5 gr.\textsuperscript{2} ), methyl iodide ( 3.0 gr.\textsuperscript{2} ) and anhydrous

1. The low temperature is maintained in order to minimise the formation of trimolecular reaction products.

2. Freshly turned bar magnesium was used.
ether (15 c.c.) was added slowly, with mechanical stirring, to a solution of diethyl p-methoxycinnamoyl isosuccinate (7.0 gr.) in anhydrous ether (30 c.c.). Reaction took place with the evolution of heat. No gas evolution was observed. When the addition had been completed, the reaction mixture was heated on the steam bath for one hour. Decomposition with water, followed by ether extraction, drying, and evaporation of the solvent in the usual manner gave a pleasant-smelling very viscous yellow oil, from which no desired homogeneous produce could be isolated. Upon vacuum distillation, to be sure, a small amount of diethyl isosuccinate, probably formed by the following reaction

\[
\text{Cu}_2(\text{CO}_3)_2 + \text{Cu}_2\text{O} \rightarrow \text{Cu}_3(\text{CO}_3)_2 + \text{Cu}_2\text{O}(\text{CO})
\]

(cf. Kohler, Herriage, Am. 46 222)
could be identified. This indicated that some of the desired hydroxyacid had been formed, but a long series of experiments was unsuccessful in isolating it.

Variation of all the above factors did not yield more favorable results.

7. The first method for the preparation of substances of type II. having proven futile, efforts were now directed towards the second process, viz. the Reformatsky reactions of ethyl -anisal-levulinate. It was, of course, necessary to prepare the latter substance. This had been prepared by Borsche (5) and it was supposed that its preparation on a
scale suitable for synthetic work would be a simple matter. This did not prove to be the case. The preparation of levulinic acid, though laborious and time-consuming, offered no particular difficulties (5). Condensation of the acid with anisic aldehyde (or benzaldehyde) gave sticky, tarry, yellow masses which could under no circumstances be induced to crystallise, except in small amounts and very slowly. This difficulty has also been encountered by Erlenmeyer and Borsche. Variation of experimental conditions was likewise unsuccessful. An attempt to convert the crude acid into the ester and purify the latter was futile. The use of condensing agents other than sodium hydroxide was precluded by the versatility of laevulinic acid in such condensations.

As a last resort the tars were thrown under vacuum distillation. Indeed, by this process pure δ-anisallaevulinic acid was obtained. The coincident formation of a beautiful red-orange resin, however, tended to make the amounts of the desired ketonic acid vanishingly small.

1. In the presence of anhydrous hydrogen chloride, β-condensation products are obtained, whereas acetic anhydride sodium acetate, and similar more vigourous reagents gives α-condensation products.

2. The resinification of such arylicene ketones has been shown to be quite common.
From the pure ketonic acid prepared by vacuum distillation, ethyl δ-anisellaevulinate was prepared, and found to agree completely in properties with the compound obtained by Borsche.

Since, however, the method had shown itself entirely unsuited to further synthetic work, it was abandoned at this point.

**Experimental Part**

**laevulinic acid**

\[ \text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH} \quad \text{C}_5\text{H}_8\text{O}_3 \quad 116.0 \]

To a solution of cane sugar (500 gr.) in water (1000 c.c.) in a two liter flask is added concentrated hydrochloric acid spec. grav. 1.16 (250 c.c.). The flask is heated on a steam bath for twenty-four hours, during which time considerable carbonization takes place. The black solid is filtered off with suction and washed with water (300 c.c.). The filtrate is placed in a large evaporating dish on a steam bath and allowed to evaporate over night. The black solid residue obtained on the following morning is ground to a powder and placed in a folded filter paper of 34 cm. diameter. This is placed in a 25 cm. funnel fitted with a water-cooled twelve liter flask. The solid is extracted with ether (500 c.c.) for six to eight hours. The ether is distilled and the residue fractionated under reduced pressure. The fraction distilling at 150-160° 15 mm. forms a rather dark liquid which does not completely solidify.
on cooling

On redistillation under reduced pressure fraction boiling over a range of not more than 2° ( e.g., 137-139° (10 mm.) ) is obtained with very little loss; this fraction solidifies almost completely at 30°. The yield is 72 - 76 gr. ( 22-23 per cent of the theoretical amount ).

δ-anisal laevulinic acid

\[ \text{CH}_3\text{O} \overset{\text{C}}{\text{CH}}\text{:CH.CO.CH}_2\text{CH}_2\text{COOH} \]

\[ \text{C}_{13}\text{H}_{14}\text{O}_4 \quad 234.0 \]

Laevulinic acid ( 130 gr. ) are dissolved in water ( 300 c.c. ), a solution of sodium hydroxide ( 12.4 gr. ) in water ( 200 c.c. ) is added, and the whole mixed in a flask with anisic aldehyde ( 21.1 gr. ) in ethyl alcohol ( 150 c.c. ). This mixture is heated, with vigorous stirring, on the steam bath; a clear solution is formed in a short time. The heating is discontinued in one half hour, the reaction mixture is rapidly cooled, and neutralised with hydrochloric acid. The bright yellow, sticky, tarry precipitate is taken up in ether and the ethereal solution is dried over night over sodium sulphate, the ether is distilled, and the residue distilled in the best obtainable vacuum. -anisallaevulinic acid ( 4.8 gr. ) distills as yellow oil which solidifies in the receiver to thick yellow prism. Crystallised from dilute alcohol, it forms beautiful fine yellow needles melting at 131-132°.
25.

ethyl δ-anisallaevulinate
m-CH₃O.C₆H₄.CH₂CH₃CO₂H₂CH₂CO₂Et C₁₅H₁₅O₄ 262.0

Pure δ-anisallaevulinic acid (5.0 gr.) is heated on the steam bath for two hours with five percent alcoholic sulphuric acid (15.0 gr.). Upon cooling ethyl anisallaevulinate (3.9 gr.) crystallises in long shining white needles. Washed with a small amount of cold alcohol and recrystallised from this solvent, they melt at 64.5-65.0°.

3. Concurrent with experiments on the preparation of laevulinic acid, diethyl hydrochelidonate was being prepared. This was obtained in excellent yield by the reaction of Merckwald (15) ¹.

\[
\text{CH₂CH₂COOH} + 2\text{H₂O} \rightarrow \text{EtOOC.CH₂CH₂COEt}
\]

Although the first experiments involved the use of \(\beta-(\alpha\text{-furyl})\) acrylic acid, which was prepared from furfuraldehyde and acetic anhydride by the Perkin reaction (16), it was later found that ethyl \(\beta-(\alpha\text{-furyl})\) acrylate could be used with equally good results. Since the latter, through the medium of the Claisen Reaction is more easily obtained than the free acid, this modification offers slight advantages.

¹ This reaction has been extended recently as a general method of synthesis of \(\gamma\)-ketonic acids by Tchitchibabine (17).
\[ \beta-(\alpha\text{-furyl})\text{acrylic acid} \]

\[ C_4H_3O.CH:CH.COCH \quad C_7H_6O_3 \quad 138.0 \]

Acetic anhydride (109.0 gr.), pure furfuraldehyde (47.0 gr.) and fused anhydrous sodium acetate (109.0 gr.) are placed in a flask equipped with a reflux condenser containing a drying tube at the upper end. The flask is immersed in an oil bath at 180-190°. In six hours, most of the solid mass has dissolved to give a vigorously refluxing deep brown liquid. When the reaction has run for ten hours, heating is discontinued, and the reaction-mixture is poured into cold water. The dark granular mass obtained in this way is repeatedly extracted with saturated sodium carbonate solution. After decolourisation with charcoal, this solution is acidified with hydrochloric acid, the precipitated white acid is filtered, dried, and recrystallised from boiling water. \( \beta-(\alpha\text{-furyl})\text{-acrylic acid} \) (33.0 gr.) crystallises from water in beautiful long yellowish needles (mp. 140-141°).

1. The solution must not be kept at the boiling point longer than is necessary to dissolve the acid. Should this precaution be disregarded, the tendency for decomposition into \( \alpha\)-vinylfuran and its polymers can give an impure product.

2. The acid polymerises on exposure to light for long periods. This results in a disintegration of the crystal form, and a darkening of colour.
ethyl \( \beta-(\alpha\text{-furyl})\)acrylate

\[
\text{CH:CH.COOC}\text{Et} \quad \text{C}_9\text{H}_8\text{O}_3 \quad 156.0
\]

Same as ethyl \( p \)-methoxycinnamate (vide Section 1) with the exception of the substitution of furfur aldehyde (96.0 gr.) for the anisic aldehyde. Ethyl furylecrylate (100 gr.) is a yellow liquid of very pleasant odor reminiscent of oranges. (bp. 223-230°).

diethyl hydrochilidonate

\[
\text{EtOOC}CH_2CH_2COCH_2CH_2COOC}\text{Et} \quad \text{C}_{11}\text{H}_{18}\text{O}_5 \quad 219.0
\]

A mixture of furfur acrylic acid (50.0 gr.), or ethyl furylecrylate (62.0 gr.) and absolute alcohol (100 gr.) is heated to boiling and then allowed to cool. As soon as crystals of the acid appear, a vigorous stream of anhydrous hydrogen chloride is passed into the solution. The momentary delicate pink colour rapidly gives way to a beautiful emerald green hue. The reaction mixture is refluxed for two hours, hydrogen chloride being passed in all the time. When the reaction is complete, most of the alcohol is driven off by heating on the steam bath. The residual dark liquid is poured into concentrated sodium carbonate solution, the oil which separates is taken up in ether, and the ethereal solution dried over sodium sulphate over night. After the removal of the ether the diethyl hydrochilidonate (90.0 gr.) is distilled in vacuo. (bp. 14 174-175°) The ester is a
colorless highly refractive liquid of very faint, but pleasant fruity odor.

9. A preliminary attempt to condense ethyl hydrochelidonate with anisic aldehyde in the presence of anhydrous hydrogen chloride gave a heavy deep yellow oil distilling undecomposed in the molecular still. Because of other considerations this compound was not more thoroughly investigated.

A few experiments on the condensation of free hydrochelidonic acid were made. One point of interest was uncovered. Since the alkaline condensation of lαevulinic acid yields δ-products, the α-methylene groups of the acid might be supposed to be inactive in alkaline solution. Should this be the case, we should expect hydrochelidonic acid to be quite incapable of condensation under these conditions. This proved to be quite true.

The condensation by anhydrous hydrogen chloride could not be accomplished because of mechanical difficulties resulting from the fact that hydrochelidonic acid is a solid of rather high molecular weight. An attempt to overcome this difficulty by the use of solvents led only to the formation of the dilactonic hydrochelidonic anhydride.

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{O} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{O}
\]

Although other condensing agents remained to be tried, the failure of the concurrent attempt to prepare ethyl δ-anisallaevulinate on a synthetic scale made the continuation of these correlative experiments unprofit-
nable. They were therefore abandoned.

Experimental Part

\[
\text{hydrochelidonie anhydride}
\]

\[
\text{CH}_2\text{CH}_2\text{OC(CH}_2\text{CH}_2\text{OOC} \rightleftharpoons \text{CH}_2\text{CH}_2\text{O} \rightleftharpoons \text{OCO} \rightleftharpoons \text{C} \rightleftharpoons \text{O}
\]

\[
\text{C}_7\text{H}_8\text{O}_4
\]

156.0.

Anisic aldehyde (6.3 gr.) and hydrochelidonie acid (8.0 gr.) are dissolved in glacial acetic acid (50. c.c.). The solution is now saturated with anhydrous hydrogen chloride at 10°, and allowed to stand for several days in the cold. The crystalline precipitate which has separated at the end of this time is filtered, washed with a small quantity of cold glacial acetic acid, and recrystallised from the hot boiling acid. (mp. 64-66°).

\[
\text{potassium hydrochelidonate}
\]

\[
\text{KOOC.CH}_2\text{CH}_2\text{OC.CH}_2\text{CH}_2\text{COOK}
\]

\[
\text{C}_7\text{H}_8\text{O}_3\text{K}_2
\]

230.0

Diethyl hydrochelidonate (57.5 gr.) is added gradually to a solution of potassium hydroxide (37.0 gr.) in ethyl alcohol (500 c.c.). The solution assumes a reddish-orange hue; in a short time a mass of white crystals is deposited, the color of the solution lightening considerably at this time. The reaction mixture refluxed for 0.75 hr. cooled, the crystalline precipitate was filtered, washed, with alcohol, then with anhydrous ether, and finally
dried at 110° for 2-3 hours. An almost colorless microcrystalline powder (50.0 gr.) which was obtained, was dissolved immediately in water (250 c.c.) to give a clear orange solution. The aqueous solution obtained in this way is boiled for a few minutes with decolorising carbon and filtered. The clear colorless solution thus prepared was used for all attempted alkaline conclusions with aromatic aldehydes. Whenever it was necessary to obtain free hydrochelidonic acid (as in condensations by acid agents) one of two methods was used. The silver salt, easily precipitated, after neutralisation with HCl gave an aqueous solution from which upon evaporation crystals of hydrochelidonic acid (mp. 141-142°) separated. Again, direct neutralisation of the potassium salt solution slow evaporation to dryness, followed by Soxhlet extraction with ether of the solid mixture, gave this free acid (mp. 142°).

10. The work was now continued with a view to obtaining the remaining member of group II. Methyl ethyl ketone was converted into the cyanohydrine, α-hydroxy-α-methyl-n-butyronitrile. The technique of this reaction was improved

1. This salt must not for any reason be allowed to stand in air, since it is extremely hygroscopic and in less than an hour will liquify completely under ordinary atmospheric conditions.
over that of previous investigators by certain experimental modifications. The hydrolysis of the nitrile to
\( \alpha \)-hydroxy-\( \alpha \)-methyl-n-butyric acid, the conversion of the latter to its ethyl ester, and the transformation of this ester to ethyl \( \alpha,\beta \)-dimethyl acrylate followed the excellent directions in the literature very accurately (13). The reaction of the unsaturated ester with ethyl oxalate in the presence of potassium ethylate gave the expected ethyl \( r \)-ethoxalyl-\( \alpha \)-methyl crotonate.

Contrary to the observations of previous experimenters (19) the product did not appear to be completely homogeneous. Along with the desired crystalline form of the ester, a small quantity of an oily non-volatile substance was obtained. Again, attempts to dry the crystalline material over phosphorus pentoxide in vacuo at elevated temperatures converted the latter partially into the oily substance.

These two substances are undoubtedly the two stereoisomers possible in this series, since they are identical in their chemical reactions.

**Experimental Part**

ethyl \( \alpha \)-hydroxy-\( \alpha \)-methyl-n-butyronitrile

\[
\begin{align*}
\text{CH}_3 \quad & \quad \text{ON} \\
\text{CH}_2\text{CH}_2 \quad & \quad \text{CN}
\end{align*}
\]

\( \text{C}_5\text{H}_9\text{ON} \quad 99.0 \)
Methyl ethyl ketone (72.0 gr.) and water (200 c.c.) and pure sodium cyanide (93.0 gr.) were placed in an autoclave chamber. Sodium bicarbonate (116.0 gr.) was now added in one lot; the autoclave cover was quickly secured, and the mixture was allowed to shake without external heat for two hours. At the end of this time, the reaction mixture is made acid to methyl orange with dilute HCl. The cyanhydrin was extracted several times with ether (1 1/2 liters) and the ethereal solution dried over sodium sulphate. From pale yellow ethereal solution α-hydroxy-isovaleronitrile (86.0 gr.) was obtained as a light yellow oil of pleasant odor, by evaporation of the more volatile constituent through heating on the steam bath for some time (0.75 - 1.00 hr.)

ethyl α-hydroxy-α-methyl-n-butyrate

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 \text{CH}_2 \quad \text{C}_7\text{H}_{14}\text{O}_3 \\
\text{CH}_3 & \quad \alpha \quad \text{OH} \quad 146.0 \\
\text{H} & \quad \alpha \quad \text{C} \quad \text{C}O\text{Et}
\end{align*}
\]

A vigorous current of anhydrous hydrogen chloride was passed into a solution of crude oxyisovaleronitrile

1. Purified by fractionation thru a 15 ft Davis Column of Eastman Kodak Co's practical "methyl ethyl ketone" bp. ats. 79.2-80.0°.
( 86.0 gr. ) in absolute alcohol ( 100-110 c.c. ) and water ( 16.0 c.c. ). The reaction mixture became warm enough to reflux. In no less than 0.33-0.50 hr. the solution was appeared to be saturated, and it was necessary to filter the very copious precipitate of ammonium chloride. After remaining over night anhydrous hydrogen chloride was again passed into the vigourously boiling liquid, this time for a period of fifteen hours. After pouring the yellow alcoholic solution into water, the resulting aqueous solution is subjected to continuous extraction for a period of four days. The ether extract is shaken with the necessary quantity of sodium carbonate, and dried over anhydrous sodium sulphate. After removal of the ether the pure ethyl \( \alpha \)-hydroxy-\( \alpha \)-methyl-n-butyrate (40.0 gr. ) is obtained, by distillation in vacuo. ( bp. 7 49-51° )

**ethyl \( \alpha \beta \)-dimethyl acrylate**

\[
\text{CH}_3 - \text{CH:C(CH}_3\text{)}\text{COOEt} \quad \text{C}_7\text{H}_{12}\text{O}_2 \quad 130.0
\]

Phosphorus trichloride (27.0 gr. ) was added gradually to cold ethyl \( \alpha \)-oxyisovalerate (45.0 gr. ). In a short time (5 minutes) there was a sharp rise in temperature and hydrogen chloride was evolved. The whole, having subsequently been heated for some time (1.5 hrs. )
on the water bath, was distilled at atmospheric pressure. The portion distilling below 154° was washed with water to free from mineral acid, dissolved in ether and fractionated in vacuo. A mixture of unsaturated esters, ethyl tiglate and ethyl angelate (27.0 gr.) is obtained. (bp. 20° 54-61°).

\[ \text{ethyl- } \gamma\text{-ethoxalyl-} \alpha\text{-methyl-crotonate} \]
\[ \text{EtOOC.CO.CH}_2\text{CH:C(CH}_3\text{)COCEt} \]

Powdered metallic potassium (9.4 gr.) was suspended in cold anhydrous ether (150-200 c.c.) in a flask immersed in a freezing mixture. Anhydrous alcohol (11.0 gr.) was added with mechanical stirring over a considerable period (2 2/3 hr.). The whole was allowed to stand over night, when, the conversion of the metal into the finely divided ethoxide was complete. After the contents of the flask had been cooled below 0°, a mixture of ethyl oxalate (17.6 gr.) and pure ethyl 3,4 dimethyl-acrylate (15.5 gr.) was added very slowly, with mechanical stirring. As the reaction proceeded, the copious colorless ethoxide gave place to a crystalline orange-yellow precipitate. After four hours, the latter was fil-

1. The residue in the flask was spontaneously inflammable. During the distillation a distinct odor of phosphorus was noticeable.
tered at the pump and washed with anhydrous ether. After drying for two hours at 40°, the solid was dissolved in cold water and the solution extracted several times with ether to remove neutral impurities. On addition of acetic acid, nearly pure ethyl \( \gamma \)-ethoxalyl-1-\( \alpha \)-methyl crotonate (15.0 gr.) is precipitated. It is filtered at the pump and recrystallised in colorless prisms from aqueous alcohol (mp. 90-92°). Extraction of the filtrate with ether, drying of the ether solution, and fractionation of the solvents gives a small quantity of an oil, (mp. 0-5°) undoubtedly the isomeric ethyl \( \gamma \)-oxalyl-\( \alpha \)-methyl isocrotonate. This material is more easily obtained and in greater quantity by subjection of the solid ester to elevated temperatures (70-30°) over phosphorus pentoxide in vacuo \(^1\).

II. Finally, condensation of the ester (the solid material was used in all of the experiments) with anisic aldehyde in the presence of anhydrous hydrogen chloride gave a crystalline product. This is an interesting example of the much discussed ability of the ethylenic bond

\(^1\) In the abderholden apparatus. \( H \) eat transfer liquid, carbon tetrachloride.
to transmit the inductive effect of the carbonyl group. Since, however, the product could not be induced to react with maleic anhydride, it was assumed to be lactonic (type (A), preliminary section).

Experimental Part

\[\text{1-}(\text{p-methoxyphenyl})-1',2',3'\text{diketo-1,2,1',2'tetrahydrofurane}\]
\[\text{2-}(\alpha\text{-methyl)acrylic ester}\]

\[\text{C}_{17}\text{H}_{16}\text{O}_{6}\quad 313.0\]

A mixture of ethyl - \(\alpha\)-methyl\(\beta\)-ethoxalyl-crotonate (1.00 gr.) and anisic aldehyde (0.63 gr.) is saturated with anhydrous hydrogen chloride. In a week the deep scarlet reaction mixture crystallises. After washing with a small quantity of cold alcohol, the pro-

1. The so-called principle of vinylology.

2. This assumption is not necessarily correct. Since the conclusion of this work, it has been found that all four isomers of a conjugated diene must not necessarily react with maleic anhydride. The above substance may be such an unreactive diene. This angle of the investigation may, then, still offer fruitful possibilities for future work, especially since two isomers of the starting material have already been obtained.
duct is dissolved in ether. The ethereal solution is shaken with potassium carbonate until no chloride can be detected in the wash liquid. Evaporation of the ether gives crystalline product (0.40 gr.) melting at 127-129°.

12. The objective of the investigation now becomes the preparation of dienes of type III. Phenylacetonitrile condensed readily with furfuraldehyde to α-phenyl-β-(α-furyl) acrylic nitrile (20), although purification of this material was somewhat difficult. The reduction of the nitrile with molten sodium and absolute alcohol proceeded smoothly (21).

Since the isolation of the amine compound formed at the same time was unnecessary, the previous method was modified somewhat.

**Experimental Part**

α-phenyl-β-(α-furyl) acrylic nitrile

\[ \text{C}_6\text{H}_5\text{C(CN)}:\text{CH}_2\text{C}_4\text{H}_3\text{O} \quad \text{C}_{15}\text{H}_{9}\text{ON} \quad 195.0 \]

To a mixture of phenylacetonitrile (50.0 gr.) and furfuraldehyde (42.0 gr.) twenty percent alcoholic sodium ethylate solution (20 c.c.) is added, in small por-
tions, with shaking. A great deal of heat is liberated, while the brown liquid which results solidifies on cooling to a hard crystalline mass. The latter is transferred to the pump, where it is washed several times with alcohol. In this way a product of tolerable purity is obtained, though with much loss by dissolution of the substance in the wash alcohol. This material is transferred to a vacuum disiccator where it is allowed to dry over night, while the filtrate is poured into water, and allowed to stand for about one hour and one half. The crystalline mass is then filtered at the pump, and the material so obtained is centrifuged to separate as much as possible from the large quantity of oil with which it is mixed. The centrifuged material is crystallised from aqueous alcohol, and the resulting product dried over night in the vacuum disiccator.

Pure $\alpha$-phenyl-$\beta$-($\alpha$-furyl)-acrylic nitrile (70.0 gr.) is a colorless, or slightly yellow crystalline substance. (mp. 42-43°).

$$\alpha$-($\beta$-phenylethyl)-fu rane$$

$C_4H_9O\cdot CH_2CH_2\cdot C_6H_5$ $C_{12}H_{12}O$ 172.0

$\alpha$-phenyl-$\beta$-($\alpha$-furyl)-acrylic nitrile (63.0 gr.) is dissolved in absolute alcohol (650 gr.), and the re
sulting solution is poured onto sodium (110 gr.) 2. When the reduction is complete, the greenish reaction-mixture is carefully made acid with hydrochloric acid, and subjected to a vigorous steam distillation. The distillate, which consists of alcohol, water, and the desired substance, is extracted with ether, the ethereal solution is dried over calcium chloride, the ether is carefully evaporated, and the residual oil purified by distillation. \( \alpha-(\beta\text{-phenylethyl})\text{-}fu\text{rane} \ (27.0 \text{ gr.}) \) is a colorless liquid (bp \(78^\circ \) 241-243\(^\circ\)) of pleasant aromatic odor, reminiscent of stilbene. The material turns yellow on standing for a few days. 3

13. Again, the desired \( \alpha-(\beta\text{-phenylethyl})\text{ furane} \) was obtained by a new method. With a view to obtaining compounds suitable for use in the reaction of Tchitchinabine (17), the reaction of furfuraldehyde with benzyl magnesium

1. A three-necked flask, equipped with two reflux condensers and one stopper is used for the reduction. If the reaction becomes too violent, the clogging of the condensers is easily remedied by removing the stopper for a moment.

2. This is an excess of two and one half times the theoretical amount for complete reduction to \( \beta\text{-phenyl-}\beta--(\alpha\text{-furfuryl})\text{-ethylamine.} \)

3. The same phenomenon has been noticed in the case of \( \alpha-(\gamma\text{-phenyl-n-propyl})\text{-fu rane.} \)
chloride had been investigated. From the reaction-mixture no homogeneous substance could be directly obtained. The oily products distilled uniformly over a long range. Distillation in vacuo over potassium hydrogen sulphate, however, gave an oil solidifying at room temperature. This material was suspected to be the hitherto unknown \( \alpha \)-phenyl-\( \beta \)-(\( \alpha \)-furyl) ethylene. The catalytic reduction of the new compound to \( \alpha \)-(\( \beta \)-phenylethyl)-furane not only confirmed this view, but offered a new route to the latter compound.

**Experimental Part**

\[
\alpha \text{-phenyl-}\beta \text{-}(\alpha \text{-furyl}) \text{ethylene}
\]

\[
\bigcirc \text{CH:CH} \quad C_4H_9O \quad C_{12}H_{16}O \quad 170.0
\]

To the Grignard solution from magnesium (122 gr.) benzyl chloride (63.0 gr.) and anhydrous ether (300 c.c.), furfuraldehyde (43.0 gr.) is added slowly, with mechanical stirring. When the addition has been completed the reaction-mixture is heated on the water bath for a short time. There is now suspended in the ether a yellow crystalline precipitate. The whole is poured into ice and stirred well to effect decomposition. The ethereal solution is separated, the residual sludge of magnesium oxychloride is dissolved in dilute acetic acid and the resulting solution is extracted with ether. The combined ethereal extracts are dried over sodium sulphate,
the ether is carefully removed. The deep yellow residual oil (35 gr.) is distilled in vacuo over pure potassium hydrogen sulphate (20.0 gr.) or anhydrous aluminium sulphate (7.0 gr.). The fraction (bp. 150-155°) solidifies on cooling and may be purified further by crystallisation from alcohol. (mp. 49-50°). α-phenyl-β-(α-furyl)-ethyline (10.0 gr.) forms long slightly yellowish needles, of pleasant aromatic odor reminiscent of stilbene.

\[ \alpha-(\beta\text{-phenylethyl})\text{furane} \]

\[ \text{CH}_2\text{CH}_2\text{CH}=\text{CHCHCH}=\text{CH}_{12} \]

\[ \text{C}_{12}\text{H}_{12} \]

\[ 172.0 \]

α-phenyl-β-(α-furyl) ethylene (5.0 gr.) dissolved in alcohol (100 c.c.) was reduced catalytically with hydrogen in the presence of platinum oxide in the usual manner. The reduction was complete in about two hours. The reaction mixture was subjected to distillation without further treatment. The lower fraction (bp. 50-80°) was discarded; the higher fraction (4.3 gr.) was a colorless oil of aromatic odor. (bp. 241-242°).

14. α-(β-phenylethyl) furane having been shown to undergo the Diels-Alder Reaction with great ease (vide

1. Much resinification was noticed during this distillation.

2. The Adams hydrogenation apparatus was used.
section 15). Experiments were now started on the preparation of \( \alpha-(\beta-(m\text{-methoxyphenylethyl}) \text{ furane. H-}
\text{tolyl methyl ether was oxidised to } m\text{-methoxybenzoic acid by alkaline permanganate (22). Although the acid was}
\text{ easily isolated in a state of great purity, the yield}
\text{ was rather unsatisfactory. Electrolytic reduction of}
\text{ the acid to the corresponding } m\text{-methoxybenzyl alcohol was}
\text{ easily accomplished (23). The conversion of the alcohol}
\text{ to the chloride by the action of thionyl chloride in}
\text{ pyridine proceeded smoothly. Reaction of the chloride}
\text{ with aqueous-alcoholic potassium cyanide gave the new}
\text{ } m\text{-methoxyphenylacetonitrile:}

\[
\begin{align*}
\text{Condensation of } m\text{-methoxybenzyl cyanide with furfur-
\text{aldehyde in the presence of sodium ethylate was not as}
\text{ rapid as in the similar reaction involving benzyl cyanide.}
\text{ Again, the product was an oil. Since experience in the}
\text{ simpler case has shown the difficulty of purification of}
\text{ these compounds, the crude material was submitted directly}
\text{ to reduction by sodium and absolute alcohol. Examination}
\text{ of the reaction mixture gave a high boiling oil with an}
\text{ aromatic odor reminiscent of cresyl ether, undoubtedly}
\text{ the desired } \alpha-(\beta-(m\text{-methoxyphenyl})\text{ethyl}) \text{ furane. Time,}
\text{ however, did not allow the further investigation of this}
\end{align*}
\]
Experimental Part

**m-methoxybenzoic acid**

\[ \text{CH}_3, \text{C}_6\text{H}_4, \text{CH}_2\text{O} \]

\[ \text{C}_8\text{H}_8\text{O}_3 \]

152.0

m-tolyl methyl ether (40 gr.) was heated for three hours on a steam bath with potassium permanganate (50 gr.) and sodium carbonate (50 gr.) in water (2500 c.c.). At the end of this time, potassium permanganate (100 gr.) dissolved in water (2500 c.c.) is added from time to time in the course of five hours. The reaction-mixture is then evaporated until crystals of sodium m-methoxybenzoate begin to separate, manganese dioxide being filtered from time to time as it separates. The hot solution is stirred for a few minutes with Norite, filtered, and carefully acidified with concentrated hydrochloric acid (125 c.c.). The precipitated m-methoxybenzoic acid (21.6 gr.) crystallises in shining plates melting at 106-109°.

**m-methoxy benzyl alcohol**

\[ \text{m-CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2\text{O} \]

\[ \text{C}_6\text{H}_10\text{O}_2 \]

133.0

m-methoxybenzoic acid (20.0 gr.) was dissolved in small portions from time to time in thirty percent alcohol.

It is advantageous to stir the evaporating solution rapidly with a motor stirrer. If this is not done, the heavy precipitate of manganese dioxide occasions troublesome bumping.
section 15). Experiments were now started on the preparation of \( \alpha\left(\beta-(\text{m-methoxyphenylethyl})\right) \) furane. Methyl methyl ether was oxidised to m-methoxybenzoic acid by alkaline permanganate (22). Although the acid was easily isolated in a state of great purity, the yield was rather unsatisfactory. Electrolytic reduction of the acid to the corresponding m-methoxybenzyl alcohol was easily accomplished (23). The conversion of the alcohol to the chloride by the action of thionyl chloride in pyridine proceeded smoothly. Reaction of the chloride with aqueous-alcoholic potassium cyanide gave the new m-methoxyphenylacetonitrile:

\[
\begin{array}{c}
\text{CN} \quad \text{H}_2 \quad \text{O} \\
\text{CN} \quad \text{H}_2 \quad \text{O} \\
\text{CN} \quad \text{H}_2 \quad \text{O} \\
\text{CN} \quad \text{H}_2 \quad \text{O} \\
\end{array}
\]

Condensation of m-methoxybenzyl cyanide with furfuraldehyde in the presence of sodium ethylate was not as rapid as in the similar reaction involving benzyl cyanide. Again, the product was an oil. Since experience in the simpler case has shown the difficulty of purification of these compounds, the crude material was submitted directly to reduction by sodium and absolute alcohol. Examination of the reaction mixture gave a high boiling oil with an aromatic odor reminiscent of cresyl ether, undoubtedly the desired \( \alpha\left(\beta-(\text{m-methoxyphenyl})\right. \) ethyl) furane. Time, however, did not allow the further investigation of this
material.

**Experimental Part**

*m*-methoxybenzoic acid

\[
\text{C}_8\text{H}_8\text{O}_3 \quad 152.0
\]

*m*-tolyl methyl ether (40 gr.) was heated for three hours on a steam bath with potassium permanganate (50 gr.) and sodium carbonate (50 gr.) in water (2500 c.c.). At the end of this time, potassium permanganate (100 gr.) dissolved in water (2500 c.c.) is added from time to time in the course of five hours. The reaction-mixture is then evaporated until crystals of sodium *m*-methoxybenzoate begin to separate, manganese dioxide being filtered from time to time as it separates. The hot solution is stirred for a few minutes with Norite, filtered, and carefully acidified with concentrated hydrochloric acid (125 c.c.). The precipitated *m*-methoxybenzoic acid (21.6 gr.) crystallises in shining plates melting at 106-108°.

**m-methoxy benzyl alcohol**

\[
\text{C}_8\text{H}_14\text{O}_2 \quad 133.0
\]

*m*-methoxybenzoic acid (20.0 gr.) was dissolved in small portions from time to time in thirty percent alcohol-1. It is advantageous to stir the evaporating solution rapidly with a motor stirrer. If this is not done, the heavy precipitate of manganese dioxide occasions troublesome bumping.
ic sulphuric acid (120 c.c.) contained in the lead cathode compartment of an electrolytic cell. The reduction was complete with the passage of sixty to seventy amperes hours at a current density of 0.12 amperes per square centimeter. The cathode portion was then poured into cold water, and the pleasant smelling oil which separated taken up in ether. After drying the ethereal solution over anhydrous sodium sulphate, the ether is fractionated, and the residual oil distilled in vacuo. m-methoxybenzyl alcohol (13.0 gr.) is a colorless liquid of pleasant aromatic odor (bp \_10130^\circ ).

\[ m\text{-methoxy benzyl chloride} \]

\[ m\text{-CH}_3\text{O.C}_6\text{H}_4\text{CH}_2\text{Cl} \quad C_6\text{H}_9\text{OCl} \quad 156.5。\]

To m-methoxybenzyl alcohol (11.5 gr.) dissolved in pure pyridine (10 c.c.), thionyl chloride (10.0 gr.) is added gradually 0\(^\circ\). After standing for one half hour at this temperature, the reaction mixture is refluxed for one half hour on the steam bath. The deep yellow product

The cell consisted of a lead cathode of one hundred square centimeters area, and a lead anode in a small porous cup containing thirty percent aqueous sulphuric acid. When used in the above reduction, it was placed in series with two resistances, themselves in parallel, and an ammeter; the current was maintained at twelve amperes throughout the reduction.
is poured into water, the oil is extracted with ether, and the ether solution dried over anhydrous sodium sulphate. After removal of the ether the m-methoxybenzyl chloride (8.0 gr.) is distilled in vacuo. It is a highly refractive liquid of characteristic pungent odor (bp. 10. 120°).

\[
m-\text{methoxyphenylacetonitrile}
\]

\[
m-\text{CH}_3\text{O}.\text{C}_6\text{H}_4.\text{CH}_2\text{CN} \quad \text{C}_9\text{H}_9\text{ON} \quad 163.0
\]

To a boiling solution of sodium cyanide (3.0 gr.) in water (3.5 c.c.) and alcohol (5.0 c.c.), m-methoxybenzyl chloride (7.0 gr.) is added gradually during the course of one half hour. The mixture is then refluxed vigorously for three hours. Alcohol is removed from the dark brown reaction-mixture by distillation from the water bath at somewhat reduced pressure. (Water pump.) After the addition of common salt to break up easily formed emulsions, the dark colored oil is separated and distilled directly in vacuo. The fraction (bp. 8 137-138°) is a yellowish highly refractive oil of characteristic odor, not unlike that of phenylacetonitrile.

\[
\alpha-(\beta-(\text{m-methoxyphenyl ethyl})furane
\]

\[
\text{C}_{13} \text{H}_{14} \text{O}_2 \quad 202.0
\]

To a mixture of m-methoxyphenyl acetonitrile (2.70 gr.)
and freshly distilled furfuraldehyde (1.77 gr.), twenty percent alcoholic sodium ethylate (1.0 c.c.) is added with shaking in 0.1 c.c. portions at intervals of five minutes. The reaction-mixture darkens somewhat; it is now heated on the steam bath for half an hour.

The dark viscous liquid was dissolved in absolute alcohol (30 c.c.). The alcoholic solution was poured quickly into pure finely sliced sodium (6.4 gr.). When the reduction is complete, the greenish reaction-mixture is carefully diluted with water, and made acid with dilute hydrochloric acid. Steam distillation gives an oil which taken up in ether and isolated in the usual manner gives a colorless oil (bp.8 146-148°), smelling much like the cresyl methyl ethers.

15. The reaction of benzylfurfuryl with maleic anhydride although slow, proceeds very satisfactorily, and gives an almost quantitative yield of a crystalline addition product.

Experimental Part

3-(p-phenylethyl)-3,6-endoxo-A-tetrahydrophthalic anhydride

\[
\text{C}_{16}\text{H}_{14}\text{O}_{4} \quad 270.0
\]

\[\alpha-(\beta-\text{phenylethyl})-\text{furene} \quad (5.4 \text{ gr.})\] and carefully
purified maleic anhydride (3.0 gr.) are dissolved in anhydrous ether (30-35 c.c.) in a flask equipped with a drying tube. After the reaction mixture has been allowed to stand for a week and a half, the ether is evaporated to one half its volume in vacuo at room temperature, when beautiful needles of the addition product separate. With little effort, a nearly theoretical yield of 3-(β-phenyl-ethyl-)-3,6-endoxo- A⁴-tetra-hydrodropthalic anhydride (7.7 gr.) is obtained. The anhydride forms small shining needles melting at 71-73°.

1. By crystallisation from chloroform which has been shaken with concentrated sulphuric acid and distilled. A preliminary run with ordinary EKC maleic anhydride gave no product other than maleic acid upon following the above procedure.

2. If some of the material obtained in this way is washed several times with anhydrous ether, a purer product (mp. 73-74°) is obtained. The substance cannot well be purified by recrystallisation, since the tendency towards dissociation into its components is very great in solution. Moreover, the material once melted does not solidify, again the result of dissociation. Upon standing for some weeks in air the material exhibited signs of extensive decomposition per se.
Conclusion

The extension of the Diels-Alder Reaction to a class of substances whose adducts bear close relationship to the naturally occurring phenanthrene derivatives establishes a firm basis for future work on the total synthesis of one or more of the latter.
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