THE CONDENSATION OF CITRACONIC AND MALEIC ANHYDRIDES WITH CHLOROPRENE AND ETHOXYPRENE

by

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I.

INTRODUCTION

This research was undertaken with a view toward developing new methods for the preparation of ring systems related to the steroids through use of the Diels-Alder reaction. It was also felt that a careful study of Diels-Alder reactions involving unsymmetrical components would prove of value both in determining some general characteristics of the reaction and in extending our ability to predict the structure of the product and rate of a particular reaction.

Of the possible diene components, 2-ethoxy butadiene (ethoxyprene) and 2-chloro butadiene (chloroprene) were chosen because of their availability and reactivity in the diene synthesis. Another diene which was not utilized but which shows considerable promise is 2-acetoxy butadiene.
The first of these dienes was prepared by H. Dykstra\(^{(1)}\) in 1935 by a method which involved hydration of mono-vinyl acetylene to methyl vinyl ketone which was converted by the following series of reactions to 2-ethoxy butadiene:

\[
\begin{align*}
\text{CH}_3\text{C} & \quad \text{CH} = \text{CH} \quad \text{EtOH} \quad \text{CH}_3 \quad \text{C} \quad \text{CH}_2\text{CH}_2\text{OEt} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 = \text{C} - \text{CH} = \text{CH}_2 \quad \Delta \quad \text{CH}_3 \quad \text{C} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OEt} \\
\text{(EtO)}_2 \text{CH} \quad \text{KHSO}_4 \quad \text{HCOEt} \\
\end{align*}
\]

The structure of the product was proven to be correct by its reaction with 1,4 napthoquinone, and subsequent oxidation of the resulting adduct to 2-ethoxy anthraquinone, a known compound. More recently A.A. Petrov\(^{(2)}\) has succeeded in synthesizing 2-ethoxy butadiene by a process which is far more feasible for laboratory preparation than that of Dykstra. It involves the following reactions:
Petrov has also investigated the role of 2-ethoxy butadiene as the diene component. He has allowed this diene to react with acrolein, (3)(5a) acrylonitrile (4) and methyl vinyl ketone (5) and has succeeded in proving the structures of the adducts obtained. In each case the 1-x-4 ethoxy-1,2,3,6-tetrahydrobenzene (X-CHO, CN, and COCH₃ respectively) isomer was formed exclusively.

H. L. Holmes and K. M. Mann (6) also made use of 2-ethoxy butadiene in a diene synthesis to obtain compound II from methyl 5-bromo-7,8 dimethoxy-3,4 dihydro napthoate (I).
The structure of II was proven and, indeed, seems reasonable in view of Petrov's work and later work done by B. M. Bloom.\(^7\)

All of the above adducts are vinyl (or enol) ethers and hence are readily hydrolyzed to the corresponding keto compounds by dilute acid. This ease of conversion strongly suggests the possibility of attaching the A ring of steroids to the rest of the molecule by means of a Diels-Alder reaction with ethoxyprene.

The second of the aforementioned dienes, chloroprene, has been known since 1931 - the date of its discovery by Carothers.\(^8\) It has in recent years been produced in large quantities by E. I. du Pont de Nemours and Co. by the addition of hydrochloric acid to mono vinyl-acetylene, and is available from that company. Chloroprene reacts with a number of dienophiles - most of the work having been done by Carothers\(^8\)(\(^9\)) himself. Among the dienophiles used by Carothers are maleic anhydride, maleic acid, 1,4-napthoquinone, methyl vinyl ketone, acrolein, ethyl fumarate, ethyl maleate and p-benzoquinone. It is significant that in no case in which the diene addition involved unsymmetric dieno-
philes was it possible to isolate more than one of the two possible position isomers. The structures of these compounds, however, were not proven. Recently A. A. Petrov(17) has(apparently unknowingly) repeated the work of Carothers on the chloroprene-acrolein reaction and shown the structure of the product to be 4-chloro-1,2,5,6-tetrahydro benzaldehyde.

The adducts formed with chloroprene contain a vinyl chloride unit, which is of course very resistant to hydrolysis. In order to make these adducts useful intermediates in steroid syntheses, and in order to compare the modes of addition of chloroprene and ethoxyprene, an investigation of possible methods of effecting the following conversion was undertaken:

\[
\begin{array}{c}
\text{Cl} \\
\text{C} \quad \rightarrow \\
\text{O}
\end{array}
\]

The use of 2-acetoxy butadiene was not considered principally because of the difficulties involved in its preparation. It has been made(21) by the action
of boron trifluoride, mercuric acetate and acetic acid on mono-vinylacetylene (which is not available commercially) and has been reacted with maleic anhydride and 1,4-napthoquinone. The principle advantage of 2-acetoxy butadiene over 2-ethoxy butadiene lies in its slightly greater stability toward acidic substances, (vide infra).

In selecting the dienophiles for reaction with ethoxyprene and chloroprene several factors are considered to be important. It is desirable to use a simple, reactive dienophile which could serve both as a model for more complicated cases and which would yield an adduct of potential utility as a steroid intermediate. The introduction of an angular methyl group should also be accomplished.

The dienophile chosen was citraconic anhydride which, has the double advantage of being readily accessible and directly analogous to the somewhat simpler and more reactive maleic anhydride. It was also decided that certain quinones such as p-xyloquinone, in spite of their extreme unreactivity\(^{(10)(11)}\) in other cases, were deserving of investigation.
The methods used previously in proofs of structure of adducts obtained from the diene synthesis have involved either: (1) direct comparison with known compounds; (2) synthesis, or (3) conversion to known compounds by dehydrogenation or transformation of certain functional groups. In this research the last of these methods was utilized since it appeared to be the easiest and most direct under the circumstances. And, indeed, it should be noted that of the twenty or so cases\(^{(3)(3a)(6)(7)(5)(12-17)}\) in which the structures of adducts from unsymmetrical Diels-Alder reactions have been proven, almost all have taken advantage of this method.
II.

DISCUSSION

Preparation of Starting Materials.— The 2-ethoxy butadiene used was prepared by a method which is essentially that used by Petrov(2) — the only modifications being such as to make larger scale preparation more feasible and to obtain a purer product. The physical constants obtained for the purified product were in much better agreement with those reported by Holmes and Mann(6) than with those reported originally by Petrov.

The citraconic anhydride used was prepared according to the method described in "Organic Synthesis."(13) Special precautions were taken to assure a pure product which was absolutely acid free. Pure maleic anhydride was obtained by purification of the Eastman product.

The preparation of 4-chloro-1,2,3,6-tetrahydrophthalic acid, which was used as starting material in test reactions, was carried out according to the method of Carothers.(8)
Diazomethane was prepared from N-nitrosomethylurea which was made according to the method described in "Newer Methods of Preparative Organic Chemistry" (19) and purified by distillation in ether solution. This compound was used in subsequent esterifications of some acid adducts for purposes of structure proofs.

Palladium on charcoal catalyst for use in catalytic dehydrogenation was prepared in the fashion described by Newman (20). It was carefully dried and kept bone dry at all times.

All solvents used in the various operations described herein were purified by standard procedures, and, in the cases of solvents like benzene, toluene, xylene, ligroin, hexane, cymene and α-methyl naphthylene, were kept strictly anhydrous by storage over sodium wire.

Reaction of Maleic Anhydride with 2-Ethoxy Butadiene. - Initial attempts to prepare the adduct resulting from the reaction of 2-ethoxy butadiene and maleic anhydride resulted only in formation of a brown resinous polymer similar to that described by Fieselman (2a) who re-
ported the reaction as yielding nothing but indefinite polymeric materials. The reaction of the two components without a solvent was very vigorous, and the polymerization accompanied with the evolution of much heat - even at -20°C. In the presence of solvents the rate of polymerization at temperatures of from 0° to 90° was found to be a function of the concentration - being very great for high reactant concentrations and much slower for low reactant concentrations. Certain solvents, like ether, were found to be more effective in decreasing the rate of polymerization than others. It was also discovered that the smallest traces of acidic substances, like hydrochloric acid, accelerated the polymerization reaction greatly. Upon refluxing the reactants in high boiling solvents, like xylene, even at high dilution only polymer was produced. It was determined that the causes of the failures encountered might lie with a number of things: (a) The acidic nature of the anhydride itself; (b) Minute amounts of impurities in the anhydride (as free acid); (c) The conditions of the reaction (temperature, dilution, etc.). In the light of these possibilities certain experiments were designed to eliminate them.
A toluene solution of the reactants to which a little anhydrous sodium carbonate had been added was refluxed for a long period of time. A slow reaction took place with the formation of a brown, rubbery, insoluble polymer. Upon working up the reaction mixture essentially all the maleic anhydride was recovered. The polymer formed was clearly of a different nature than those formed in the previous runs. Whereas the first polymers encountered were soluble in organic solvents, dilute sodium hydroxide solution and concentrated sulfuric acid, the rubbery polymer obtained from this last reaction was insoluble in all these liquids and definitely not acidic. It indeed appeared as though a polymerization of the diene was taking place instead of a copolymerization of diene with anhydride, as was probably the case in the earlier runs. This, then, clearly showed that the presence of a basic substance could inhibit to a remarkable extent the formation of the copolymer. On a theoretical basis this is not too surprising since the ethoxy group, which is extremely labile, might be lost by ethoxyprene to form methyl vinyl
ketone, which would undoubtedly initiate some sort of polymerization reaction. That this effect can be induced by other basic substances was shown by the substitution of calcium oxide for sodium carbonate, in which case a similar reaction occurred.

It became clear at this point that the activation energy of the Diels-Alder reaction in this case was fairly great - sufficiently large at any rate to warrant a much higher reaction temperature. The activation energy of the copolymerization was apparently fairly small on the other hand, since the reaction took place readily even at low temperatures. This implied that at a sufficiently high temperature some adduct would be formed, or, in other words, higher temperatures would favor the Diels-Alder reaction. On the basis of the dilution-polymer formation rate relationship it also appeared that high dilution would favor the Diels-Alder reaction over polymerization, since the polymerization was probably a polymolecular reaction whereas the Diels-Alder was bimolecular.

To verify the implications resulting from these hypotheses three experiments were carried out - all
at the same temperature. The temperature chosen was 200° since it was felt that higher temperatures might favor the reverse Diels-Alder reaction and cause considerable decomposition.

Run one was made at moderate concentration in benzene solution and resulted in a small yield of a colorless crystalline substance which proved to be the adduct.

Run two was made at high dilution in benzene, and resulted in a somewhat higher yield of the same substance.

Run three was made at high dilution in benzene in the presence of pure calcium oxide. The yield of adduct in this case was much higher. Further experimenting with these conditions enabled the yield to be increased to over 50%.

The compound isolated gave no test for ethyl alcohol, upon treatment with sodium hypoidite after digestion with strong acid. The compound was also recovered unchanged after treatment with hydrochloric acid and removal of the acid under vacuum. This indicated that the compound actually isolated was cyclohexanone-3,4-dicarboxylic acid (III).
These indications were fully corroborated by virtue of a neutralization equivalent and comparison of physical constants with those reported by Klebanski, who prepared it by reacting 2-formoxy butadiene with maleic anhydride.

Reaction of Citraconic Anhydride with 2-Ethoxy Butadiene.- Here again it was found that the only conditions under which the reaction would proceed were those employed successfully in the reaction of 2-ethoxy butadiene with maleic anhydride. In the case of this reaction, however, two reaction products were possible. The structures of these products (after hydrolysis of the ethoxy group) are shown below.
In spite of the fact that two isomers are possible, and in spite of the fact that the reaction product here, as in the case of the ethoxyprene-maleic anhydride adduct (III) was isolated and purified only with difficulty, it was determined that only one of the two possible products was formed. As was the case with adduct III, the product actually isolated in this reaction had lost its ethoxy group during purification and indeed was the keto compound given either by structure IV or V. The melting point of the purified compound was somewhat below that of III, but this is not too unreasonable in view of the fact that maleic anhydride (or acid) melts considerably above the melting point of citraconic anhydride (or acid).

Reaction of Citraconic Anhydride with Chloroprene.—This reaction turned out to be much more straightforward than those of ethoxyprene with anhydrides, and the product was much more easily isolated and purified. A considerable difference was discovered
in the reactivities of citraconic and maleic anhydrides. Whereas maleic anhydride reacts very vigorously when heated to only 50°C, citraconic anhydride did not react even at 100°C. The yields obtained in this reaction under optimum conditions were also much lower than those obtained with maleic anhydride. The following table reports the yields obtained under different conditions. These runs were all made in sealed tubes under an atmosphere of nitrogen using phenothiazine as stabilizer and xylene as solvent.

<table>
<thead>
<tr>
<th>Temp. (°C.)</th>
<th>Time (hrs)</th>
<th>Parts Solvent</th>
<th>Parts Dieno</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>110</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>118</td>
<td>21</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>125</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>125</td>
<td>18</td>
<td>4</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>135</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>140</td>
<td>4.5</td>
<td>1</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>140</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>200</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>200</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
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Here again two possible reaction products were possible, VI or VII. Only one

![Chemical Structure](image)

of these was isolated. This case, along with that encountered in the ethoxyprene-citraconic anhydride reaction, serves to confirm the theory of high stereo-selectivity in the Diels-Alder reaction.

**Reaction of Diethyl Citraconate with 2-Ethoxy-Butadiene.**--This reaction was attempted in order to determine whether the absence of any acidic nature in the dienophile would have a direct effect upon the reaction or stability of the product. The one trial made was run at 165° with no solvent present for a period of ten hours. Only a small amount of polymerization was evident upon completion of the reaction. When the reaction mixture was subjected to vacuum distillation, though, most of the diethyl citraconate used was recovered unchanged and a good deal of polymer remained in the distilling
flask. No product was isolated. It is probable, even in view of the fact that the temperature did not rise over 120° at any point in the distillation, that the product was actually formed but decomposed into the reaction components - one of which (the diene) polymerized. The other possibility, of course, is that the reaction did not go and that the amount of polymerization appeared to be smaller than it actually was. The reaction was not investigated beyond this point, but further research would be of interest.

Reaction of p-xyloquinone with 2-Ethoxy Butadiene.- In the light of previous reactions run with 2-Ethoxy Butadiene, it appeared that it was a much less active diene than butadiene (which is reasonable when resonance effects are considered) and that the chances of it reacting with p-xylo quinone were slight (in view of attempted reactions of p-xylo quinone with butadiene(10)(11)). The reaction was carried out under varied conditions in cyclohexane, which appeared to be an elegant solvent for recovering unreacted p-xylo quinone. In every case no product could be isolated.
Reaction of 1-Methyl-4 or 5-Chloro-1,2,3,6-Tetrahydrophthalic Acid (VI or VII) and 4-Chloro-1,2,3,6-Tetrahydrophthalic Acid (VIII) with Boron Trifluoride and Acetic Acid.— This reaction was undertaken with a view toward adding acetic acid across the double bond according to the following scheme:

\[ \text{CH}_3\text{COOH} + \text{BF}_3 \xrightarrow{} \text{CH}_3\text{C} = \text{O} \text{S} \]

This reaction has been found to work in the above case under fairly mild conditions (100°) to give a good yield of the acetate (60%). (22) It was hoped that a similar reaction could be effected with the chloroprene adducts to give a chloroacetate which would in all probability hydrolyze easily to give the corresponding keto compounds. This would, if successful, show unequivocally the relationship between the chloroprene and the ethoxyprene series. The reaction was tried with no success. At temperatures below 110° no reaction occurred, at temperatures much above 110° a great deal of poly-
merization took place in spite of the fact that a large excess of acetic acid was used.

**Attempted Dehydrogenations.**—The first attempt to prove the structures of the adducts obtained from the reactions of ethoxyprene and chloroprene with citraconic anhydride were via dehydrogenation with sulfur. Because of the highly substituted nature of these adducts, it was recognized that dehydrogenation would go in low yields if at all. In view of its accessibility and because it represented the simplest case, 4-chloro-1,2,3,6-tetrahydrophthalic acid was also used in dehydrogenation experiments. Three attempts - all under different conditions - were made to dehydrogenate the chloroprene-maleic anhydride adduct and all were unsuccessful. In each case only a small fraction of the theoretical amount of hydrogen sulfide was given off and much decomposition took place. On one run though a few milligrams (corresponding to 0.1% yield) of a white crystalline substance was isolated by sublimation. Although the substance melted at approximately the same place as 4-chlorophthalic anhydride, it was only slightly
acidic and could not be converted to the acid which melts much higher. The chloroprene-citraconic anhydride product under the same conditions yielded nothing identifyable.

Attempts were then made to dehydrogenate these compounds catalytically with palladium on charcoal. Runs were tried with the two adducts mentioned above and with the ethoxyprene citraconic anhydride adduct and its dimethyl ester. These runs were made in cymene as solvent, in methyl napthalene as solvent and without a solvent. In none of these cases was any reaction other than decomposition observed. In the runs in which solvent was used a good portion of the starting material was recovered. The activity of the catalyst used was checked by using it to dehydrogenate tetralin.

Attempted Decarboxylations.— In view of the fact that the chloroprene and ethoxyprene-citraconic anhydride adducts contained tertiary carboxyl groups it was hoped that they could be decarboxylated and thence converted into known compounds. Attempts
were, therefore, made to decarboxylate these compounds by heating with fine copper powder, both without a solvent and in diethyl aniline. In each case some decomposition took place, and only a part of the starting material was isolated. The failure of these decarboxylations probably was due to the ease with which the compounds formed anhydrides. It is thought that conversion to the transform would greatly facilitate decarboxylation.

**Attempted Reaction of the Ethoxyprene Citraconic Anhydride Adduct with Phosphorus Pentachloride.**

This reaction was undertaken again in the hope that the relationship between the chloroprene and ethoxyprene series could be established. The reaction was tried under varied conditions but no pure reaction product could be isolated. The acid chloride was formed readily but evidence for a reaction of the keto group was negative. After hydrolysis of the acid chloride in ice water very little halogen (if any) remained since the oil resulting from the hydrolysis gave very little potassium chloride upon treatment with hot alcoholic potassium hydroxide.
Attempted Reaction of the Chloroprene Citraconic Anhydride Adduct with Hydrogen Chloride.— Hydrogen bromide reacts with 1-chloro cyclohexene to give 1-chloro, 2-bromo cyclohexane.\(^{23}\) It was thought that by analogy HBr should behave in a similar manner. Hydrochloric acid, however, if it could be added successfully, would most certainly give the gem-dichloride. This reaction was tried but no conclusion could be reached because of the complex nature of the resulting substance. It is thought that under the circumstances of the reaction (12-N hydrochloric acid, 100\(^\circ\)) there would be some conversion to trans acids along with decomposition and polymerization.
III.

EXPERIMENTAL

Preparation of Benzenesulfonamide. - Two hundred forty grams of benzenesulfonyl chloride was added dropwise with stirring to 400 ml. of concentrated ammonium hydroxide solution. After the addition was completed the mixture was heated to boiling, cooled, and the colorless crystals separated by filtration. The benzenesulfonamide was purified by crystallization from hot water. The yield of a product melting at 155-156° was 205 g. (97%).

Benzenesulfondibromamide. - The preparation was done in several batches, each of which was carried out as follows: Two hundred forty g. (75.3 ml.) of bromine was added dropwise to a 0° suspension of 160 g. of orange mercuric oxide in 3 l. of water. The resulting mercuric bromide was collected on a mat which was prepared by putting a layer of filtering asbestos upon glass wool which was supported by glass cloth
on a Buchner funnel. The cold filtrate was used directly in bromination of the sulfonamide.

To a cold, well stirred solution of hypobromous acid was added a solution of 60 g. of benzene-
sulfonamide dissolved in 600 ml. of hot water. The reaction mixture was stirred for one hour, the solid
dibromide collected on a funnel and washed with cold water. The yellow product, while still wet, was
dissolved in 300 ml. of chloroform and the resulting water layer was separated. The chloroform solution
was then dried over sodium sulfate and worked up to give yellow-orange crystals of the dibromide melting
at 110-111°. The yield was 92 g. (73%).

4 Bromo-3-ethoxy-butene-1.- One hundred and five grams of the dibromamide was added in small portions
to a stirred and cooled (-20°) solution of 51.0 g. (75 ml.) of butadiene in 300 ml. of freshly prepared
absolute ethanol. The reaction mixture was stirred for one hour after the last addition. The product
was removed by steam distillation. The heavy oil was extracted with ether, washed with water and
dried over calcium chloride. The compound was distilled at 27 m.m. pressure and the fraction boiling in the range 65-66° was collected. The yield of this product was 80 g. (66%), and its index of refraction was 1.4565 at 20°.

2-Ethoxy Butadiene. - Forty grams of 4-bromo-3-ethoxy butene were added to a stirred solution of 38 g. of potassium hydroxide in 75 ml. of ethanol. A little water was added and the mixture steam distilled. The resulting oil was separated, washed with saturated sodium carbonate solution and dried over anhydrous sodium carbonate. The yield of a product boiling at 55° under 160 m.m. pressure was 20.1 g. (75%); \( \frac{N}{D}^2 = 1.4397 \). Holmes and Mann: b.p. 95°, 760 m.m.; \( \frac{N}{D}^2 \) 1.4372.

Citraconic Anhydride. - One kilogram of citric acid was pyrolized in five 200 g. portions, and the resulting mixture of itaconic and citraconic anhydrides converted to citraconic anhydride by distillation at
atmospheric pressure. The product was purified by distillation at 23 m.m. pressure; b.p. 108-111°. The yield was 187 g. (28.8% based on citric acid). The anhydride was further purified by drying over sodium, and distillation at 2 m.m. and 70°C.

4-Chloro-1,2,3,6-Tetrahydrophthalic Acid.—A mixture of 43.2 g. chloroprene* and 39.2 g. of maleic anhydride in 50 c.c. of xylene was heated to 50°, at which point the reaction proceeded vigorously without further heating. After two hours the reaction mixture was poured into 500 ml. of hot water and boiled until all the xylene was removed. The remaining insoluble material was removed by filtration and the solution allowed to stand. The resulting colorless crystalline compound was collected by filtration and dried in a vacuum desiccator. The yield of a product melting at 170.8 to 171.3° was 62 g. (76%).

* The chloroprene used came as a 50% solution in xylene.
Palladium on Charcoal Catalyst.— Darco G-60 charcoal was warmed with dilute nitric acid (7.5 c.c. 16 N acid in 100 c.c. water) until fumes of nitrogen dioxide were evolved. After standing one hour the charcoal was collected, washed thoroughly with hot and cold distilled water and dried at 100° for two days and at 200° for two hours. Three grams of this charcoal was then stirred into a cold solution of 1 g. of palladium chloride in 6 c.c. of water and .6 cc of 12 N hydrochloric acid. A small mechanical stirrer was then introduced and 6 cc. of 40% formalin followed by a cold solution of 6 g. of potassium hydroxide in 6 cc. of water, the temperature being held below 5°. After all the alkali was added, the temperature was raised to 60° for one-half an hour. The catalyst was collected on a filter, washed thoroughly with dilute acetic acid and hot water and finally dried in a vacuum at 100°.

Reaction of Maleic Anhydride with 2-Ethoxy Butadiene.—Five grams of maleic anhydride and 5 g. of 2-ethoxy butadiene in 100 ml. of anhydrous, thiophene free
benzene along with 5 g. of finely powdered, freshly prepared calcium oxide was heated in a sealed pyrex tube at 200°C. for ten hours. The sealed tube was then opened (after cooling) and the calcium oxide removed by filtration. The benzene was removed under vacuum and the resulting syrup poured into 50 ml. of hot water. The mixture was boiled for ten minutes, cooled to 10° and the insoluble polymer removed by filtration. The resulting solution was extracted with five 5 ml. portions of chloroform and the chloroform extracts discarded. After boiling the water solution for a few minutes with decolorizing charcoal and filtering off the carbon, the water was removed under reduced pressure (20 m.m.) and the resulting oil set in a desiccator over phosphorus pentoxide to crystallize. After crystallization (which usually takes a few days), the tan solid was boiled with 20 c.c. of chloroform containing 2 c.c. of amyl alcohol. The white insoluble solid was filtered, washed with chloroform and dried. The yield of a product melting at 159-160° was 5.3 g. (55%). The compound was further purified by sublimation at
150° under 0.03 m.m. After hydrolysis of the resulting anhydride (M.P. 104-104.5°) the acid was obtained in about 95% recovery. Upon drying over phosphorus pentoxide a colorless crystalline product was obtained which melted at 160.8-161.5° (m.p. reported by Klebanski for III 161-162°).

Six tenths of a gram of this compound was added to 3 ml. of 6-N hydrochloric acid and the solution allowed to stand at room temperature for one hour. One half of this solution was made basic by the addition of 6-N sodium hydroxide solution. A few drops of freshly prepared sodium hypodite was added and the mixture allowed to stand. No precipitate was observed - indicating the absence of an ethoxy group.

The remaining portion of this solution was evaporated at 1 m.m. pressure and the resulting white solid washed a few times with 1 ml. portions of diethyl ether. The product after drying melted at 161-161.8°, and was shown by mixed melting point to be identical with the starting compound (m.p. of the mixture: 161-161.5°). The neutralization equivalent was found to be 183. (The calculated value is 186.16).
Reaction of Citraconic Anhydride with 2-Ethoxy Butadiene. - This reaction was carried out in the manner described in the previous section. Five and six-tenths grams of citraconic anhydride and 5 g. of 2-ethoxy budadiene furnished 6.7 g. of crude product (after solidification from oil). In this case the crude acid was boiled with pure chloroform and the yield of white crystals after filtration, washing and drying was 5.9 g. (56%) of a product melting at 139.5-140°. The chloroform solution contained only polymer and was discarded.

The product was further purified by the following procedure: One part of adduct was heated with two parts of chloroform to 120° in a sealed tube. The tube was removed from the furnace after all the solid had dissolved, and opened (after cooling). To the clear solution after filtration was added a quantity of ligroin just sufficient to cloud the solution. Upon scratching and alternate cooling and heating, colorless crystals were formed which, after drying, melted at 140.8-140.9°.

This acid was shown to be the keto acid by the procedure described in the previous section.
The neutralization equivalent was found to be 200.5 (Calculated 199.2).

Anal. Calcd. for C₉H₁₁O₅: C, 54.28; H, 54.28, O, 40.16

Found: C, 53.48; H, 6.03; O, 40.48.

Reaction of Citraconic Anhydride with Chloroprene.-

Twelve grams of 50% chloroprene solution, 5 g. citraconic anhydride, 0.25 g. of phenothiazine (stabilizer) and 15 ml. of benzene was heated in a sealed tube, which had been flushed thoroughly with nitrogen, for five and one-half hours. At the end of this time the tube was opened (after cooling) and the solution placed in a concentrater. The solvent was then removed under vacuum (2 m.m.) and the resulting syrup poured into 60 ml. of hot water. The solution was boiled for five minutes, cooled, and the brown polymer removed by filtration. Decolorizing carbon was added to the filtrate and the mixture boiled until the volume of solution was reduced to 25 cc. The carbon was removed by filtration and the clear solution set aside over-night to crystallize. The white, powdery, substance
was collected, washed and recrystallized from hot water. The yield of a product melting at 169.5-170° was 4.5 g. (46%). The neutralization equivalent was found to be 221 (calculated 218.5).

Anal. Calcd for C₉H₁₁O₄Cl: C, 49.48; H, 5.08; Cl, 16.23

Found : C, 49.30; H, 5.08; Cl, 16.19.

Reaction of Diethyl Citraconate with 2-Ethoxy Butadiene. - Twelve grams of diethyl citraconate and 5 g. of 2-ethoxy butadiene was heated in a sealed tube at 165° for ten hours. The resulting light brown solution was subjected to a vacuum distillation at 1.5 m.m. pressure. The only substance which could be isolated was diethyl citraconate - 9.5 g. of which was collected. Remaining in the distilling flask was a dark brown polymer which was insoluble in benzene, ether or water and slightly soluble in acetone.

Reaction of 4-Chloro-1,2,3,6-Tetrahydrophthalic Acid with Boron Trifluoride and Acetic Acid. - Five grams of 4-Chloro-1,2,3,6-tetrahydrophthalic acid, 20 g. of glacial acetic acid and 2 g. of a 45% solution of
boron trifluoride in diethyl ether were heated in a sealed tube at 90° for one hundred twenty hours. The acetic acid was removed under reduced pressure and the white product left behind was identified as starting material by mixed melting point.

The same procedure was used in other runs. However, when the reaction temperature was above 110° some polymer was also formed.

**Attempted Dehydrogenations with Sulfur.**—Four grams of 4-chloro-1,2,3,6-tetrahydrophthalic acid and 1.4 g. sulfur was heated at 240° for one-half hour and then at 270° for ten minutes. Only about one-fourth of the theoretical amount of hydrogen sulfide was given off. The brown residue was heated to 110° at 0.05 mm. pressure and 4 mgm. of a white crystalline substance was obtained which melted in the range 95-100° (m.p. 4-chloro phthalic acid 99°). However, this compound was recovered unchanged upon heating with water, and appeared to be only slightly acidic.

The other dehydrogenations attempted with sulfur were carried out in much the same manner. All were unsuccessful.
Attempted Catalytic Dehydrogenations.— Five grams of compound to be dehydrogenated and 0.1 g. Pd. on Carbon catalyst with 5 g. solvent or without solvent was heated to the reflux temperature of the mixture in an atmosphere of nitrogen. The compounds used include the chloroprene adducts, the citraconic anhydride-2-ethoxy butadiene adduct and its dimethyl ester and the solvents used were p-cymene and α methyl naphthalene. In no case was hydrogen evolved. Starting materials were recovered by removing solvent under reduced pressure and subjecting the residue to sublimation at 105 m.m. and 150°C.

Attempted Reaction of the Ethoxyprene Citraconic Anhydride Adduct with Phosphorus Pentachloride.— One gram of the adduct was heated on a steam bath with 1.5 g. of phosphorus pentachloride. A vigorous reaction began and considerable hydrogen chloride was evolved. The clear solution was heated on an oil bath at 110° for two hours, cooled and poured on to ice. The resulting oil was treated with 10 c.c. of 20% potassium hydroxide solution in methanol.
Very little potassium chloride was formed however. The solution was acidified with hydrochloric acid and evaporated to dryness under a vacuum. The resulting solid was extracted with acetone and the acetone removed from the extract on a steam bath. A few drops of a yellow oil remained which could not be identified. No product could be isolated from the reaction.

Attempted Reaction of the Chloroprene Citraconic Anhydride Adduct with Hydrogen Chloride.— Two grams of the adduct was heated with 10 c.c. of concentrated hydrochloric acid at 100° in a sealed tube for twenty-four hours. The solution resulting was evaporated under vacuum (20 m.m.) and the resulting light tan colored product was dried in a desiccator over concentrated sulfuric acid. The solid was quite impure (m.p. 120-140°) and could not be purified since it decomposed on sublimation (190° at .03 m.m.) and had very unfavorable solubility characteristics.
IV.

SUMMARY

Adducts resulting from the condensation of maleic and citraconic anhydrides with ethoxyprene, and citraconic anhydride with chloroprene have been prepared.

The reaction of maleic anhydride with ethoxyprene, which was ineffectually attempted by Fiesselmann, was allowed to take place under novel conditions and yielded cyclohexanone-2,4-dicarboxylic acid, a known compound. The condensation of ethoxyprene with citraconic anhydride was accomplished under the same conditions to give a single compound which is either 3-methyl-cyclohexanone-3, 4-dicarboxylic acid or 4-methyl-cyclohexanone-3, 4-dicarboxylic acid. The structure of this adduct was not proven, but upon the basis of theoretical considerations, (see appendix) the compound probably
is 3-methyl-cyclohexanone-3, 4-dicarboxylic acid. The reaction of citraconic anhydride with chloroprene furnished an adduct which probably is 1-methyl-5-chloro-1,2,3,6-tetrahydrophthalic acid. Attempts were made to prove the structures of the adducts obtained, and to show the relation between the ethoxyprene and chloroprene series.
V.

APPENDIX

The reaction of an unsymmetrical diene with an unsymmetrical dienophile has, in all cases studied, given either exclusively or predominantly one compound. If I reacts with II to give all possible isomers it can be seen that four compounds would result.

These four compounds would have the following structures (III, IV, V, VI):

III TRANS

IV TRANS
It has been demonstrated that the Diels-Alder reaction produces exclusively cis isomers. This is the first aspect of the high "stereo selectivity" shown by this reaction, and, in view of this fact, compounds III and IV can be discounted as possibilities.

The second aspect of this "stereo selectivity" involves structures V and VI, only one of which is usually formed. It is on this point that the literature is somewhat vague. Hudson and Robinson\(^{(24)}\) introduced the concept of polarized molecules and postulated an addition of the negative end of the diene to the positive end of the dienophile by an unpaired electron process. In addition, they postulated that the reaction of butadiene with maleic anhydride went through a single electron process of the following type:
It can be seen, however, that the postulation of a process involving unpaired electrons is completely unnecessary when unsymmetrical components are involved. The only assumption which must be made is that the diene, at the point of greatest electron "excess", attacks the dienophile at the point of greatest electron"deficiency." Upon this basis a consideration of electrical and steric effects will explain the results of Diels-Alder additions without the postulation of unpaired electrons.

Petrov(3) has shown that 2-ethoxy butadiene reacts with acrolein to give 4-ethoxy-1,2,3,6-tetrahydrobenzaldehyde. This reaction product can be explained by first considering the possible
resonance forms of the components involved and then the direction in which they are polarized.

From these resonance forms and from the inductive effects indicated, the molecules can be seen to be polarized and to react in the following manner.

The reaction product therefore is in full accord with this theory.
Only one case (25) among the twenty or so adducts of this type whose structures have been proven is not explained by consideration of simple electrical effects. This is the reaction of 1-phenyl butadiene with acrylic acid where the product is 3-phenyl-1,2,3,6-tetrahydrobenzoic acid (VII). Acrolein, however, gives the expected adduct (2-phenyl-1,2,5,6-tetrahydrobenzaldehyde (VIII). In this anomalous case, it is quite probable that a steric effect is in operation and normal addition does not occur because of the hindrance involved in the transition state.

\[
\begin{align*}
\text{VII} & : \text{\begin{align*}
& \text{C} \text{O} \text{H} \\
& \text{VII}
\end{align*}} \\
\text{VIII} & : \text{\begin{align*}
& \text{C} \text{H} \text{O} \\
& \text{VIII}
\end{align*}}
\end{align*}
\]

In the case of the reactions described in this paper, those of chloroprene and ethoxyprene with citraconic anhydride, no such steric effect is involved - i.e., one form of addition is not favored over another on steric grounds. It is virtually
certain, therefore, that the products actually isolated in these two cases are given by structures IX and X.

\[ \text{IX} \quad \text{X} \]

This is based on the polarization of citraconic anhydride indicated by the following important resonance forms:

\[ \text{Resonance Forms} \]

It is interesting to note that this argument furnishes an explanation for the greater reactivity of unsubstituted components in the Diels–Alder reaction other than that based on steric effects.
Citraconic anhydride, for example, would not be as reactive as maleic anhydride because resonance forms corresponding to (c) and (d) do not contribute as much to the polarizability of citraconic anhydride on account of its dissymmetry.
VI.

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The author was born in Methuen, Massachusetts, on July 12, 1928. He received his elementary school training at St. Laurence O'Toole Parochial School and his secondary schooling at the Lawrence Public High School whence he graduated in 1945. He entered Massachusetts Institute of Technology in July 1945 where he majored in Chemistry.