

THE REACTION BETWEEN UNSATURATED ANILS

AND MALEIC ANHYDRIDE

BY

THE UNIVERSITY OF MANITOBA
LIBRARY

IRVING LEVI B. Sc.

APRIL 1939

A THESIS PRESENTED TO
THE COMMITTEE ON POST-GRADUATE STUDIES
OF THE UNIVERSITY OF MANITOBA
IN CANDIDACY FOR THE DEGREE OF
MASTER OF SCIENCE

APRIL 1939

The writer wishes to acknowledge his indebtedness to Dr. H. P. Arnes for the suggestion of this problem and to express sincere gratitude for his helpful advice and generous interest with which he has directed the investigation.

Thanks are also gratefully offered to Dr. A. N. Campbell for the loan of apparatus and valuable advice.

CONTENTS

	Page.
Reaction Between Cinnamal-o-Toluidine and Maleic Anhydride - - - - -	89
Degradation of Product with KOH - - - - -	90
Nitrogen Analysis - - - - -	91
Preparation of Maleic Acid Mono-o-Toluidide - - - - -	92
Preparation of Benzal-p-Phenetidine - - - - -	93
Reaction Between Benzal-p-Phenetidine and Maleic Anhydride - - - - -	93
 SUMMARY - - - - -	 96
 BIBLIOGRAPHY - - - - -	 -97

INTRODUCTION

The work described in this thesis was undertaken with the object of ascertaining whether conjugated, unsaturated anils of the type $R-N=CH-CH=CH-R$ would enter into a Diene Synthesis with maleic anhydride.

Isolated examples of the Diene Synthesis have been known for forty years, but early workers had wrongly interpreted the reaction. The true course was first recognized by Euler and Josephson (1) and has been extensively developed by Diels and Alder (2).

In a series of investigations which extended over a number of years, Diels, Alder, and their co-workers, observed repeated instances where a combination between certain types of unsaturated compounds took place. These combinations consist of the direct addition of one unsaturated substance to another, and often take place simply on mixing the components at room temperature, and in the absence of any catalyst or condensing agent. This reaction has come to be known as the "Diene Synthesis" because many of the starting materials are dienes. It is characterized by its general applicability to unsaturated substances containing conjugated systems. In general, the Diene Synthesis consists of a philodiene component, that is, a suitable partner having a double or triple bond, adding to a diene with the formation of a hydroaromatic six atom ring. This reaction is in no way limited to open chain dienes. No principal difference seems to exist in its applicability

to acyclic and isocyclic dienes, as well as to heterocyclic systems such as furan. This has led to the production of complex, hitherto rare, or inaccessible organic compounds in excellent yield, with negligible formation of undesirable by-products. When the diene is cyclic, bridged ring products result which are closely related to, or identical with, natural substances such as the terpenes, sesquiterpenes, alkaloids, and camphors.

Because the Diene Synthesis offers the possibility for the synthetic production of complicated substances by a very easy method, it has become one of the newest methods of investigation in the field of organic chemistry. It can be used especially for solving complicated structures, or for bringing such problems nearer to a solution.

Apart from being interesting from a practical point of view, the Diene Synthesis is very significant from a theoretical point of view, such as for example, the discussion of the relationships of strain in polycyclic systems.

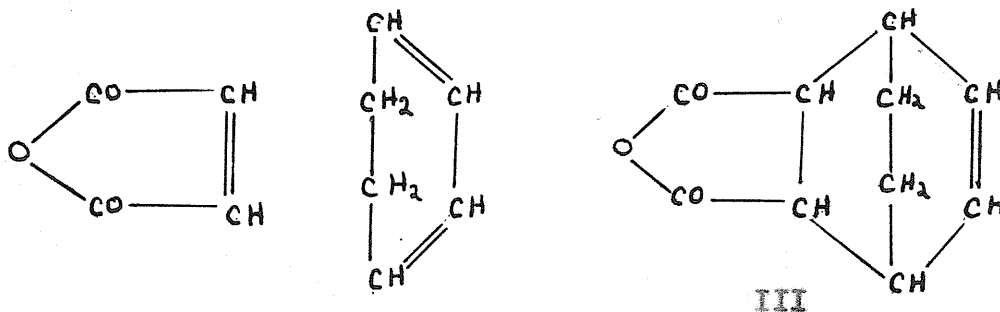
(3) Sachse's modification of Bayer's Strain Theory, (4) which was elaborated by Mohr (5) advances the theory that so called negative strain did not exist in large rings, but that they were strainless. In recent years this theory has been almost fully confirmed by experiment. Illustrating Sachse's idea by models of tetrahedral atoms, it is found that when such models are constructed for rings containing more than five members, the atoms forming the ring do not

lie in a plane as they do with smaller rings. For example, six tetrahedral atoms may be united as in diagrams I or II. These models can be constructed without distortion of the tetrahedral form of the atoms involved. Such strainless rings have been found to possess stabilities comparable with those of open chain compounds.



Until recently it has not been found possible to prepare synthetically bicyclic systems with a two membered bridge. This is rather noteworthy, since such compounds according to the views of Aschan (6) and Mohr(5) seem to be a basic system of rings free from strain, and therefore this factor would offer no opposition to their formation.

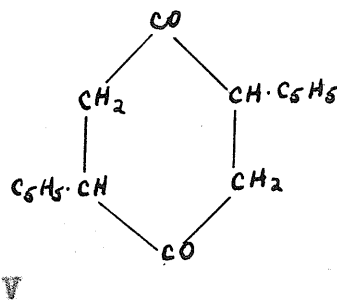
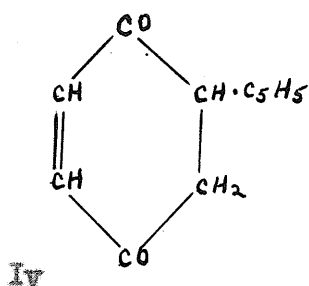
The principle of the Diene Synthesis has now placed at our disposal, for the first time, a method whereby syntheses of such systems can be carried out. It has been shown (2), for example, that dienes such as $\Delta^{1,3}$ -cyclohexadiene react smoothly with maleic anhydride, acrolein, crotonaldehyde, or quinone, with the formation of such types as III.



Much value can also be obtained in the field of physical chemistry by carrying out investigations with the compounds resulting from the Diene Synthesis or with the course of the Diene Synthesis itself. Thus, Kistiakowski and Lacher (7) in their study of the kinetics of gaseous reactions employed the Diene Synthesis. For four of these systems studied, acrolein-butadiene, acrolein-isoprene, acrolein-cyclopentadiene, and crotonaldehyde-butadiene, the reactions were found to be of the second order, homogeneous, and only slightly complicated by side processes.

HISTORICAL

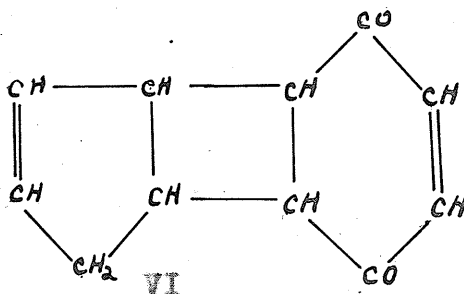
In 1906 Albrecht (8) first reported the addition of cyclopentadiene and p-quinone. He observed that when the two are brought together, a crystallized, stable compound is formed with extreme ease. This compound is the result of the addition of one molecule of the diene to one molecule of quinone, which Albrecht called cyclopentadiene-quinone and assigned to it formula IV. By the further action of cyclopentadiene on cyclopentadiene-quinone, the latter goes over very easily into a new product which consists of the addition of two molecules of diene to one of quinone. This second product Albrecht called dicyclopentadiene-quinone and assigned to it formula V.



Thus Albrecht indicates that the molecules of cyclopentadiene add to the quinone at the methylene groups and that both double bonds of the cyclopentadienes are still present in the reaction product. In both cases however, he admits that there are several strong objections to these formulae.

Staudinger (9), (10), on the basis of his observations of the addition of ketenes to cyclopentadiene, has come to the conclusion that Albrecht's conception is wrong, and he suggests that quinone and cyclopentadiene combine to

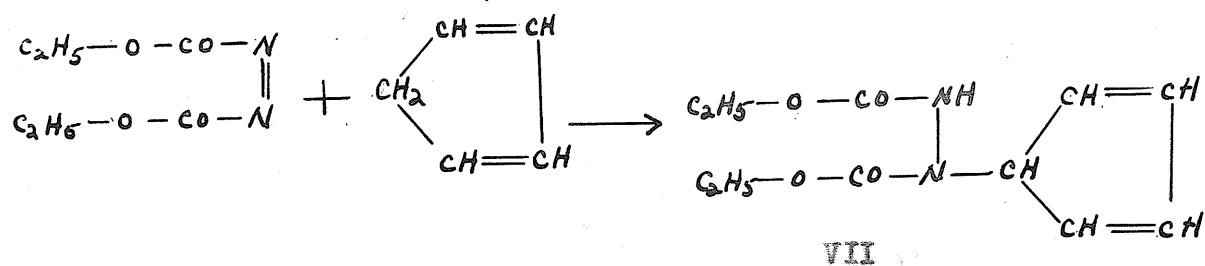
form a cyclobutane derivative for which he prefers expression VI. The cyclobutane ring in this formula would explain the easy reformation of quinone and cyclopentadiene, which has been observed to take place.



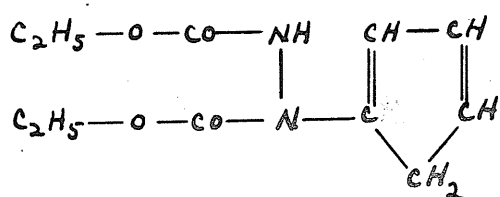
It has long been known that esters of azo-dicarboxylic acid $\text{ROOC}-\text{N}=\text{N}-\text{COOR}$ combine very easily with numerous classes of substances (11). This reaction also extends to the hydrocarbons. These react especially smoothly if they contain a system of conjugated double bonds, such as are found in methyl isoprene or cyclopentadiene.

Diels, Blom, and Koll, (12) studied the addition of methyl isoprene and azo-ester, and of cyclopentadiene and azo-ester. They have shown that both of these hydrocarbons add one molecule of azo-ester with great ease. The reaction does not stop there, but a second molecule of azo-ester can be taken up.

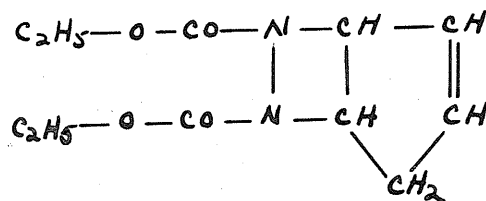
These observations can be compared with Albrecht's results of the study of the action between cyclopentadiene and p-quinone. If Albrecht's interpretation is applied to the azo-ester addition, then we will have to represent the addition of cyclopentadiene as follows;



But it was found that formula VII does not conform to the properties of the reaction product and therefore this assumption is excluded. Other possibilities such as VIII and IX suggested by the same line of reasoning are also strongly objected to for the same reasons.

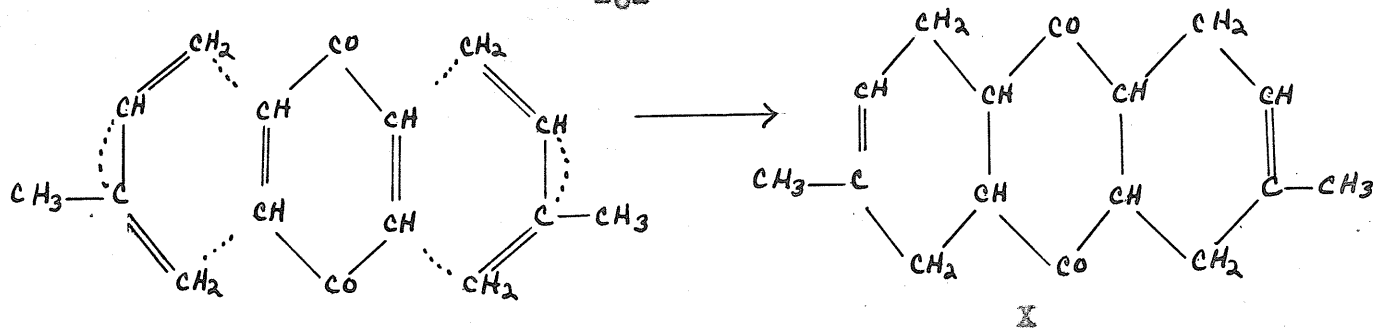


VIII

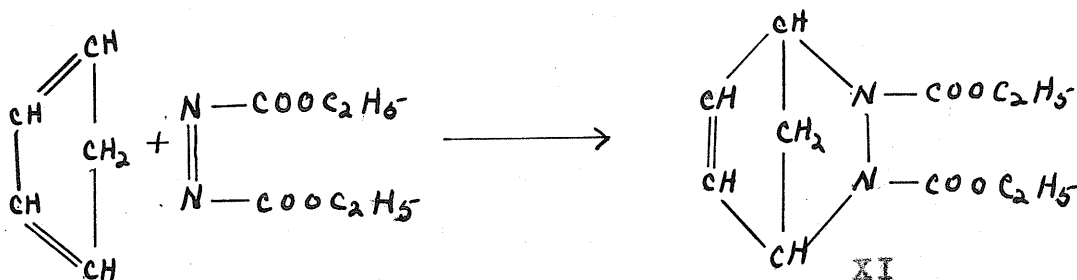


IX

Earlier, Euler and Josephson (1) had studied the action of isoprene on quinone and have shown that these two substances undergo a 1,4-addition, whereby two molecules of the hydrocarbon add to one molecule of quinone giving a product represented by X. They attribute this reaction to the systems of conjugated double bonds present in the isoprene molecules, and explain the mechanism of the reaction as follows. Each of the two isoprene molecules combine at the terminal carbon atoms by means of one partial valence, to the strong subsidiary valence of the quinone, whereby there takes place a redistribution of affinity, and the double bonds in the quinone are opened. Thus a partially hydrogenated dimethyl-anthraquinone is formed X.

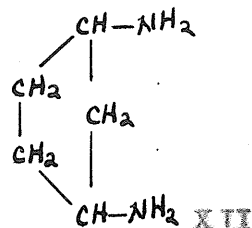


Diels, Blom, and Koll therefore explain the addition of cyclopentadiene to azo ester according to the above formulation discovered by Euler and Josephson, and consequently arrive at formula XI for the resulting product, which they call *N,N'*-dicarboxethyl-endomethylene-pyridazine.

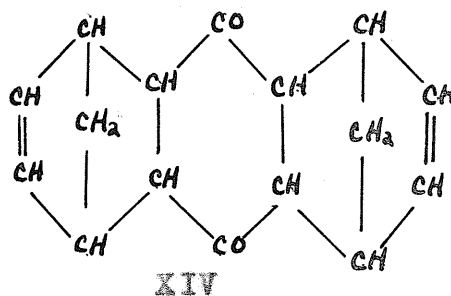
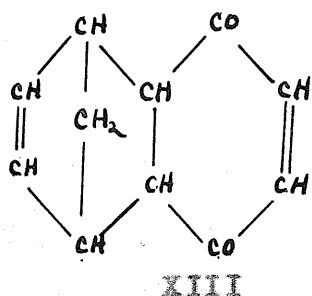


Further investigation by these workers eventually showed that this conception is the correct one for the cyclopentadiene-azo ester addition. The addition takes place in the 1,4-positions, at the ends of the conjugated system, and the two double bonds disappear with the formation of a new double bond. The presence of this double bond, and the fact that there is only one double bond present was established by bromination and hydrogenation. Not more than two atoms of bromine or two atoms of hydrogen were taken up in each case. The structure of the product was determined by catalytically reducing the C=C linkage, hydrolyzing,

and reducing the resulting product to the known 1,3-diamino-cyclopentane XII.



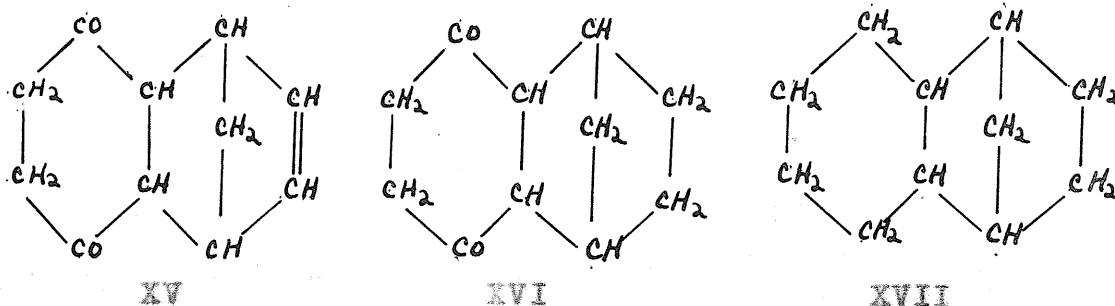
This result of Diels Blom and Koll threw strong doubt on the formulation suggested by Albrecht for the compounds obtained from quinone and cyclopentadiene. By analogy they suggested that the above expressions IV and V should be replaced by XIII and XIV respectively. These latter compounds represent the results of 1,4-addition. The first product contains one methylene bridge and the second two such bridges. Although Diels Blom and Koll suggested this formulation for the addition of cyclopentadiene and quinone, they did not prove it.



In 1928 Diels and Alder (2) published a paper, the first of a long series which was to follow, in which they definitely prove the correctness of this conception.

By reducing "cyclopentadiene-quinone" with zinc dust and glacial acetic acid two atoms of hydrogen are taken up giving XV. Further catalytic hydrogenation of XV opens

the second double bond and two more atoms of hydrogen enter the molecule yielding XVI. Reducing XVI by Clemmensen's method both oxygen atoms are replaced by hydrogen, and the final product obtained is 1,4-endomethylene-decahydro-naphthalene $C_{11}H_{18}$ XVII.

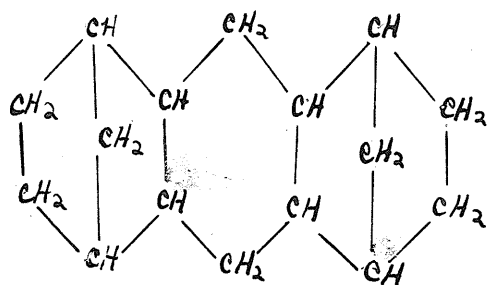


Albrecht's formula IV, however, by complete hydrogenation must lead to a hydrocarbon $C_{11}H_{20}$, which as we have just seen is not the case. Diels and Alder have observed that in such structures in which a bridge is formed, there is a very strong inclination for the reformation of the systems with conjugated double bonds, and that this often happens on heating. (15) (page 23).

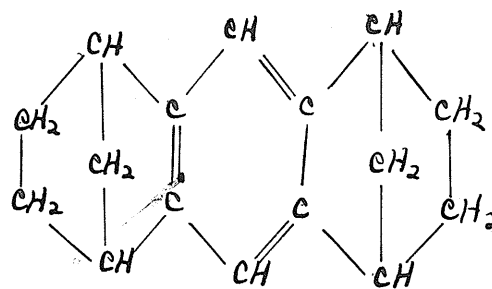
Staudinger's main objection to the Diels-Alder formulation was based on the very fact that the product decomposed into its components so readily. This last observation by Diels and Alder satisfies the last objection to the formulae they suggested.

When "dicyclopentadiene-quinone" is subjected to a similar series of reductions, 1,4-5,8-diendomethylene-tetradecahydroanthracene XVIII is obtained, which on dehydrogenation with selenium loses six atoms of hydrogen yielding an octahydroanthracene with two methylene bridges,

the probable structure of which is XIX.



XVIII



XIX

"Cyclopentadiene-quinone" is therefore, according to Diels and Alder, a derivative of a hydrogenated -naphtha-quinone containing a methylene bridge, and "dicyclopentadiene-quinone" a derivative of a hydrogenated anthraquinone containing two methylene bridges.

All of these observations could not be brought into agreement with any of the formulae suggested by the various workers described above, except with the last suggestion of Diels and Alder.

Cyclic dienes have been shown to react in a similar manner (14).

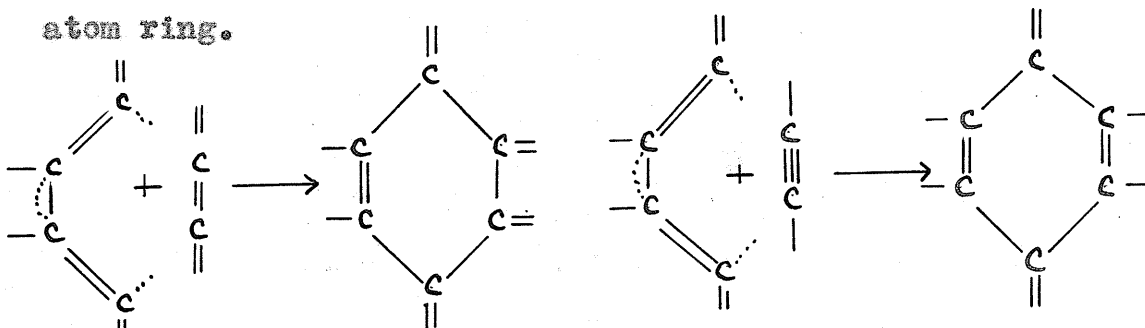
THEORETICAL

THIELE THEORY OF PARTIAL VALENCE.

Although Thiele's theory of partial valence (15), (16) is no longer held today as a general theory, it is still used as a valuable working rule to explain 1,4-addition to conjugated systems.

As has already been shown, the Diene Synthesis, in its typical course consists of the 1,4-addition of an α, β -unsaturated carbonyl compound - acid, ester, or anhydride - to a conjugated diene. In attempting to explain the mechanism of this reaction, Diels and Alder (17) make use of Thiele's theory of partial valence, and generalize the course of the reaction as follows.

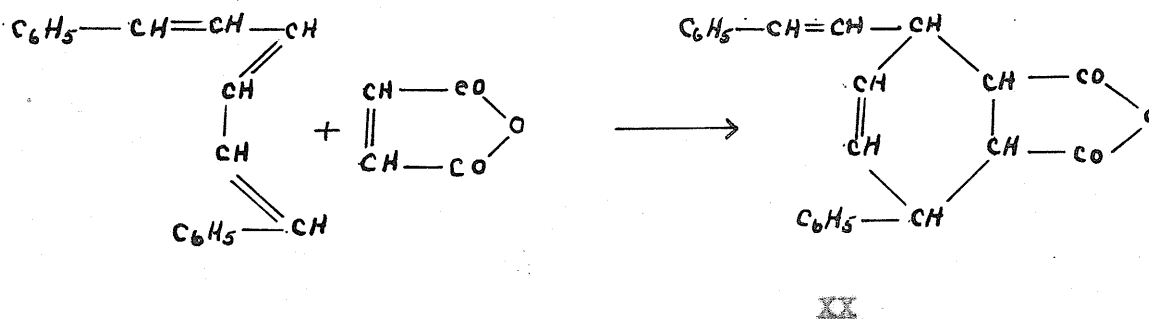
A suitable substance having a double or triple bond adds to a diene, with the formation of a hydroaromatic six atom ring.



The double or triple bonds, as the case may be, of the unsaturated anhydrides, acids, or esters, open up and there results in every case a joining up of the free valence in a 1,4-position with the hydrocarbon, because the effective unsaturation is localized at the ends of the conjugated system as shown. Since the substance being added requires more affinity than is available from the partial valences present at the ends of the diene system, the

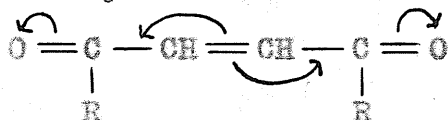
double bonds are broken, and a redistribution of affinity takes place in the molecule, with the formation of a new double bond between the carbon atoms 2 and 3 of the diene. In the cyclic compound that results, the diene has not broken.

It has been found however that polyenes always gave 1,4-addition products, regardless of the length of the conjugated system. For example, 1,6-diphenyl - hexatriene adds maleic anhydride in a 1,4-position (18) although according to Thiele's theory a 1,6-addition is available. The formulation advanced by Diels and Alder does not explain such cases very well.



ELECTRONIC THEORY

More recently an attempt has been made to explain the mechanism of the Diene Synthesis based on modern electronic concepts of valence. It will be noticed that the substances which add to the dienes in this synthesis usually contain two carbonyl groups or similar types, united by means of an intervening ethylenic system, giving rise to 1,4-quinonoid systems XXI.

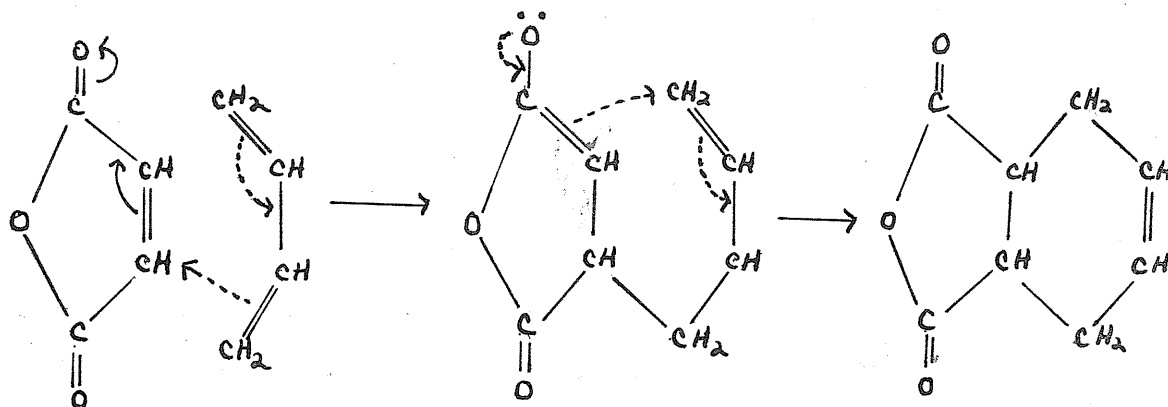


XXI

The two end groups tend to promote electromeric changes in opposite directions thus rendering such systems highly reactive (19). This group of 1,4-quinonoid systems includes p-benzoquinone, maleic acid, citraconic acid, and other similar compounds which have been found to be very valuable reactants for the Diene Synthesis. The reactivity of these substances may be regarded as manifestations of the tendency of a quinonoid system to revert to one in which the tension of the opposed electromeric effects has been relieved.

The enhanced reactivity of quinonoid systems is illustrated by the easy addition of 1,3-dienes to quinones and maleic anhydride. The Diels-Alder reaction may be regarded as a direct attack by an active donor centre of the reagent. Such active donor centres are found in the double bonds of reacting dienes. The Diene Synthesis may

therefore be formulated as shown.



The reaction is thus considered to consist of two stages, the second being a ring closure. In connection with the last statement it is interesting to note an observation made by Farmer and Warren (20) . They state that the addition of maleic anhydride to cyclohexadiene appears to be a two stage process in which the second stage , that of ring closure, is marked by the liberation of heat, and is capable of acceleration or retardation, within limits, at will.

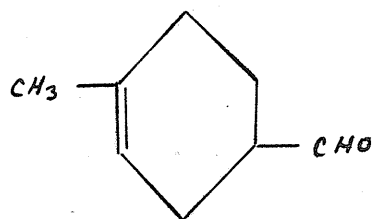
EXAMPLES OF THE DIENE SYNTHESIS -- 1,4-ADDITION

A number of examples will now be given to show the wide applicability of the Diene Synthesis. It will be seen that the complexity of the molecule in which the conjugated system is found does not interfere with the reaction. The various types of philodiene components which can be used in the Diels-Alder reaction will also be indicated. By using suitable components, the number of cyclic systems obtainable by this reaction is practically unlimited.

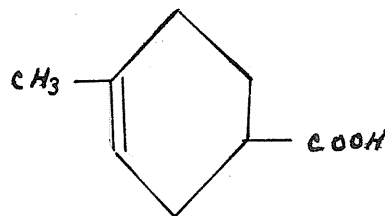
Maleic anhydride, acrolein, acrylic ester, p-benzoquinone, α -naphthaquinone, and other substances possessing the group $\text{CH}=\text{CH}-\text{C}=\text{O}$ unite almost quantitatively with open chain and cyclic dienes, frequently when the reactants are merely mixed at room temperature. The group $\text{C}=\text{O}$, however, does not appear to have any special significance.

FORMATION OF HYDROCARBON RINGS.

Isoprene condenses with acrolein (2), and Acrylic acid (21) yielding para derivatives of tetrahydrobenzene, XXII and XXIII respectively.

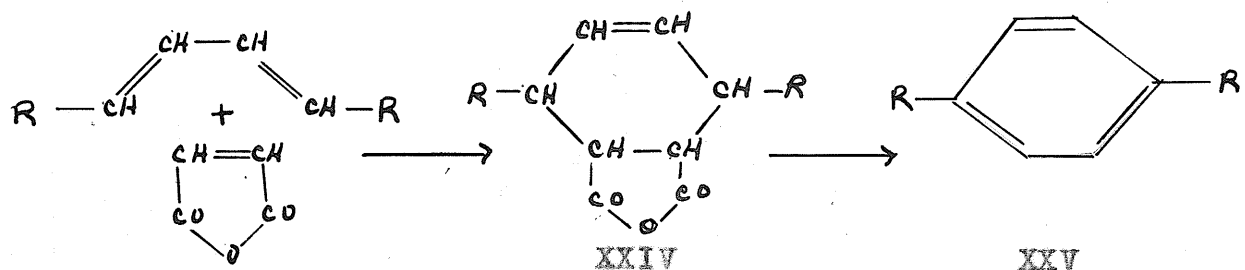


XXII



XXIII

Maleic anhydride adds smoothly to all arylated dienes, trienes, and fulvenes (18), (24). For example, 1,4-diphenyl butadiene adds to maleic anhydride to give XXIV which can be converted to XXV.

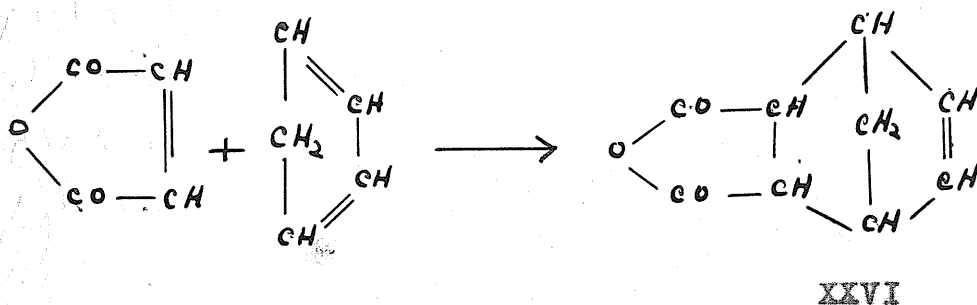


The butadiene acids such as sorbic and muconic acids and their derivatives such as sorbic acid chloride (23) yield tetrahydrophthalic anhydrides with maleic anhydride.

The hexatrienes and higher polyene hydrocarbons also yield cyclohexene derivatives. Polyenes add one molecule of maleic anhydride for each independent conjugated system. Thus, diphenyldodecahexaene adds three molecules of the anhydride (25). Each conjugate system unites with one molecule by a Diene Synthesis to form a separate six membered ring.

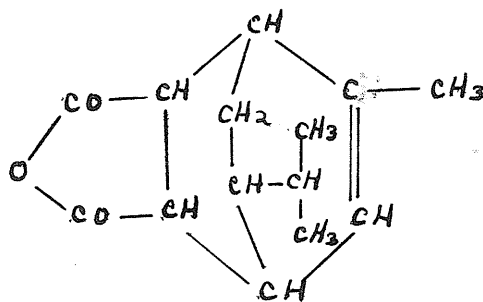
METHYLENE BRIDGE.

Maleic anhydride and cyclopentadiene (2) give a quantitative yield of 3,6-endomethylene- Δ^4 -o-phthalic-anhydride XXVI.



ETHYLENE BRIDGE.

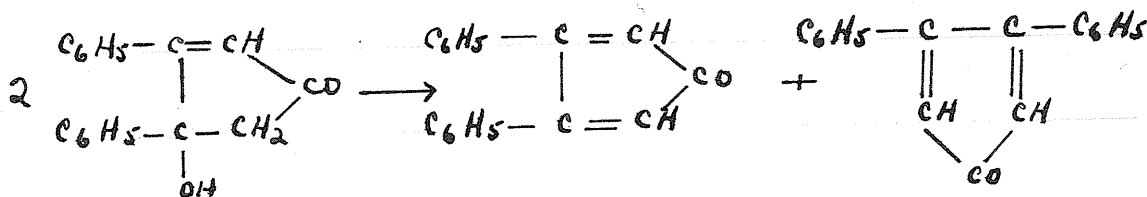
α -Phellandrene and maleic anhydride (2) react readily at elevated temperatures to form a product which contains a two membered bridge. XXVII.



XXVII

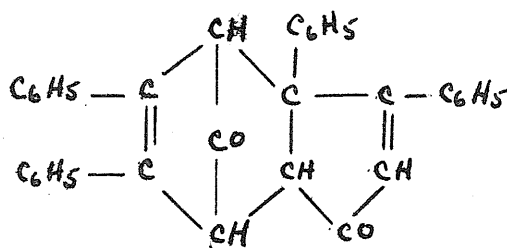
CARBONYL BRIDGE.

Anhydracetone-benzil XXVIII forms a bimolecular product $C_{34}H_{24}O_2$ in the following manner. (26). Dehydration of XXVIII first forms a cyclopentadiene XXIX, two molecules of which enter into a Diene Synthesis. One molecule adds to the end of the conjugated system in the second molecule in a 1,4-position. A tricyclic system containing a C=O bridge is thus formed, XXX.



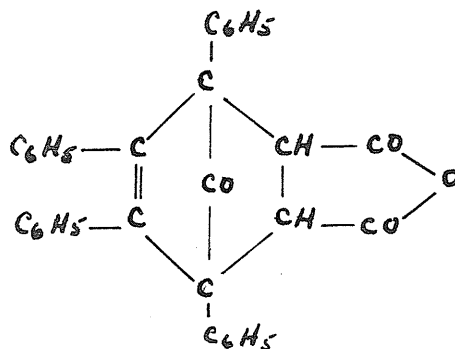
XXVIII

XXIX



XXX

When tetraphenylcyclopentadieneone and maleic anhydride are cautiously warmed together an addition product is formed which contains a carbonyl bridge, XXXI. When the temperature is raised the bridge is lost as carbon monoxide (27).



XXXI

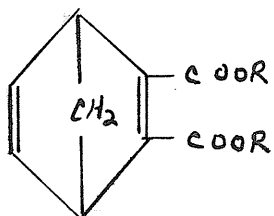
ACETYLENE DICARBOXYLIC ESTERS.

Other unsaturated substances which have been found to be very useful for the Diene Synthesis are carbonyl compounds with triple bonds.

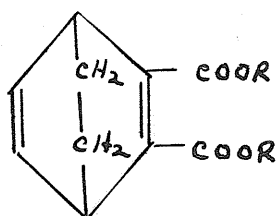
Acetylene dicarboxylic acid and its esters combine readily with diene hydrocarbons such as cyclopentadiene, cyclohexadiene and butadiene (28) producing substances whose structures are similar to those obtained through the use of maleic anhydride, except that the rings formed in these cases contain two double bonds instead of one.

Cyclopentadiene and $\Delta^{1,3}$ -cyclohexadiene react with acetylene dicarboxylic ester (28) forming products which contain a methylene bridge and two double linkages XXXII, and an ethylene bridge and two double bonds XXXIII respectively. Likewise the simplest diene, butadiene,

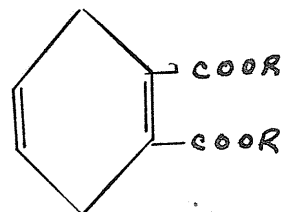
undergoes a normal diene synthesis (1,4-addition) with the ester producing XXXIV.



XXXII



XXXIII



XXXIV

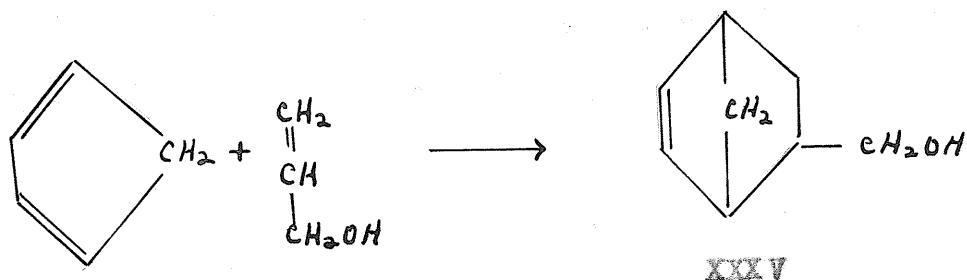
These unsaturated systems so easily obtained through the Diene Synthesis from unsaturated carbonyl compounds with triple bonds form valuable initial material for further study.

Other examples of the use of acetylene dicarboxylic esters in the Diels-Alder reaction will be brought forth in the course of this thesis.

SYNTHESIS WITH ALLYL COMPOUNDS.

Allyl compounds and their homologues can react extremely smoothly with dienes (29). This is basically, a new type of Diene Synthesis, since, here for the first time, a double bond $R-CH=CH_2$ which does not belong to the types $C=C-C=O$, $C=C-C=C$ or $C=C-C\equiv N$, and which is free from any special constitutional hypothesis possesses a tendency to participate in the Diene Synthesis.

Allyl alcohol, its esters and homologues such as crotyl alcohol combine with cyclopentadiene at $175-180^\circ$ leading to unsaturated products of the type XXXV.



Allyl chloride, bromide, amine, cyanide, as well as vinyl acetic acid and allyl mustard oil, react in the same way with cyclopentadiene. The steric arrangement of all these compounds is the same. The groups $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{COOH}$, and $-\text{CH}_2\text{CN}$, all take up the same spatial arrangement as the $-\text{CH}_2\text{OH}$ group of the alcohol does.

It thus becomes evident that the activity of allyl compounds in the Diene Synthesis is independent of the nature of the groups $-\text{OH}$, $-\text{Cl}$, $-\text{Br}$, $-\text{CN}$, $-\text{NH}_2$. The following conclusion can therefore be drawn. The activities of the double bond in an olefinic and of the triple bond in an acetylenic body, $\text{C}=\text{C}-\text{R}$ and $\text{C}\equiv\text{C}-\text{R}$ are independent of the nature of R and are able to undergo addition of dienes. The ease of the Diene Synthesis is a general function of the double and triple bonds respectively, and in no way connected with any special constitution of the molecule. Therefore, all that is necessary is the selection of proper experimental conditions and components.

The observed inactivity of many olefines to the Diene Synthesis is in general not dependent on the nature of R but rather on other factors such as the degree of

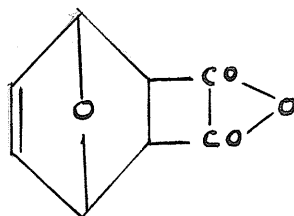
substitution, spatial arrangement of the substituents,
at the double bond, ring closure, and others.

DIENE SYNTHESIS WITH HETERO RINGS

CONTAINING OXYGEN

FURAN.

Furan which contains an oxygen atom in its ring behaves as a true diene. With maleic anhydride and acetylene dicarboxylic esters it forms compounds which are the result of 1,4-addition. Typical structures such as XXXVI result. Furfuralcohol in the form of its acetate and α,α' -dimethyl furan undergoe similar Diene Syntheses. (13), (30)



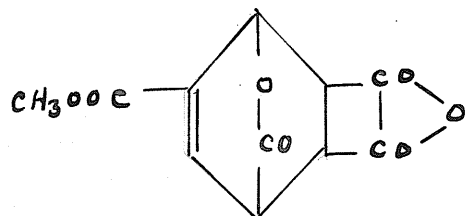
XXXVI

Such structures in which a bridge is formed, (the bridge need not be O, it can be $-\text{CH}_2-$, $-\text{CH}-\text{CH}-$, or something similar), have a strong tendency for the reformation of the original systems with the double bonds. (see page 10). This often happens on heating the addition compound. (31)

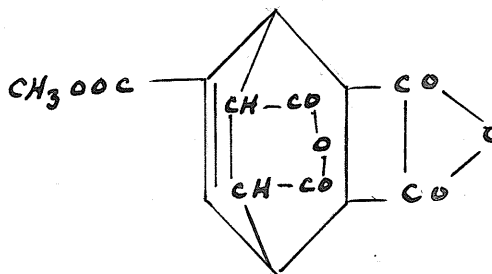
COUMALINS.

The coumalins can also be used as true dienes for the diene synthesis. Coumalic ester and maleic anhydride react with each other in boiling toluol (32) with the formation of a compound that contains an $-\text{O}-\text{CO}-$ bridge, XXXVII. In boiling xylene however, the reaction is more complex. The bridge is replaced by a second molecule of maleic anhydride and compound XXXVIII is the

chief product of the synthesis. This process is characteristic for coumalins in general.

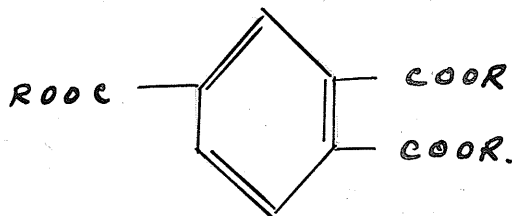


XXXVII



XXXVIII

When coumalins react with acetylene dicarboxylic ester, the -O-CO- bridge of the addition products splits off very easily as CO_2 , with the result that a benzene ring is formed (31). From coumalic ester we thus obtain trimellitic ester XXXIX.



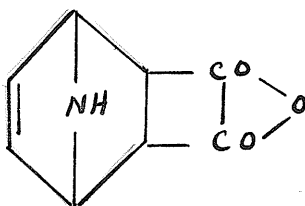
XXXIX.

DIENE SYNTHESIS WITH HETERO RINGS

CONTAINING NITROGEN

PYRROLE AND ITS HOMOLOGUES.

According to its structural formula, pyrrole appears to be a diene. It was therefore expected that it would be a suitable reagent for the Diene Synthesis just as other similar cyclic and non-cyclic types have been in numerous other cases. Moreover, since furan, which is analogous in structure to pyrrole, actually reacts as a true diene, it was believed that a similar reaction with pyrrole would lead to a compound of structure XL. (22).



XL.

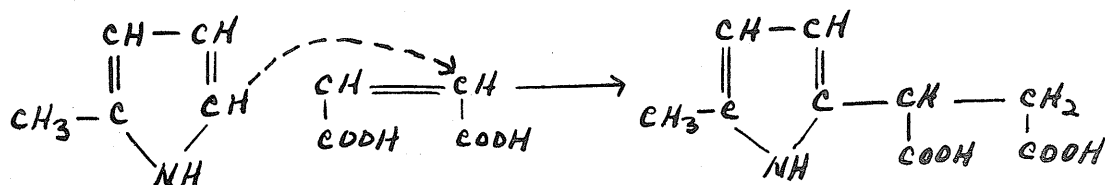
However, in the actual Diene Synthesis of pyrrole and pyrrole homologues, the products resulting are constituted differently from the corresponding products of cyclic hydrocarbons or of furans and their homologues. The addition processes are of an entirely different character and do not result in the formation of polycyclic derivatives.

MECHANISM OF THE REACTION---ADDITION BY DISPLACEMENT
OF HYDROGEN

The addition product of α -methyl-pyrrole and maleic acid, which can be isolated, contains both

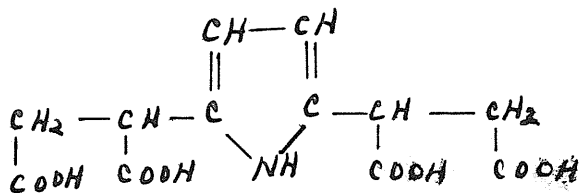
components in the ratio 1:1, and is a dicarboxylic acid. Pyrrole on the other hand enters into the reaction with two molecules of maleic acid with the formation of a tetra-carboxylic acid.

The maleic acid enters the α' -position in the α -methyl pyrrole and is accompanied by a wandering of the hydrogen from this position into the maleic acid molecule, and an opening of the double bond in the latter (33). This is represented schematically in diagram XLI.

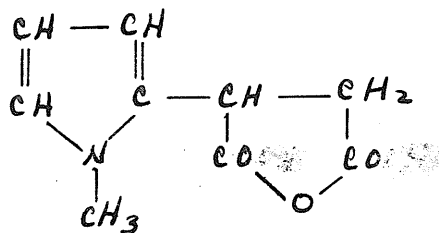


XLI.

In complete analogy with the above described process, pyrrole, and N-methyl pyrrole add two molecules of maleic acid and maleic anhydride by hydrogen displacement from the α and α' positions. Structures such as XLII and XLIII are formed ~~from~~ ^{WITH} the acid and anhydride respectively.



XLII



XLIII

PYRROLE AND ACETYLENE DICARBOXYLIC ESTERS.

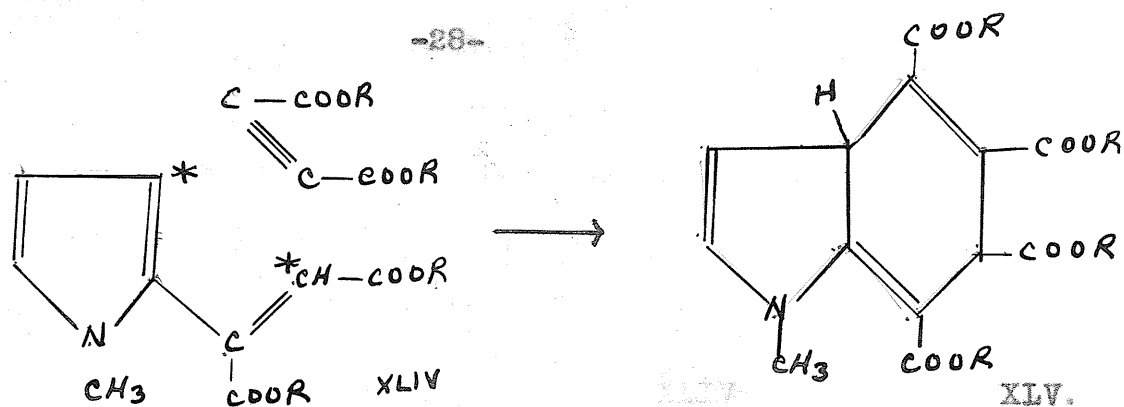
The Diene Synthesis with pyrrole and acetylene dicarboxylic acid and esters takes place principally in the same way. But in these cases small changes in the composition of one or other of the components will cause different types of products to be formed (22). Three reaction types have been established in which the ratios of pyrrole to ester are 1:1, 1:2, 2:1.

I. Addition of Components Takes Place in Molecular Proportion.

This type takes place in the same way as that described for the addition of maleic acid to pyrroles. One molecule of ester adds to one molecule of pyrrole with displacement of the α -hydrogen.

II. Addition in 1:2 Ratio With Formation of a Partially Hydrogenated Indole Derivative.

N-methyl-pyrrole and acetylene dicarboxylic dimethyl-ester yield a compound that contains two molecules of ester and one of pyrrole and possesses structure XLV. The first step of the reaction is the addition of one molecule of ester to the pyrrole in the α -position by hydrogen displacement similar to the above type. The resulting compound contains a new diene system indicated by asterisks in XLIV. To this diene a second molecule of ester adds in a true Diene Synthesis by 1,4-addition to yield XLV.



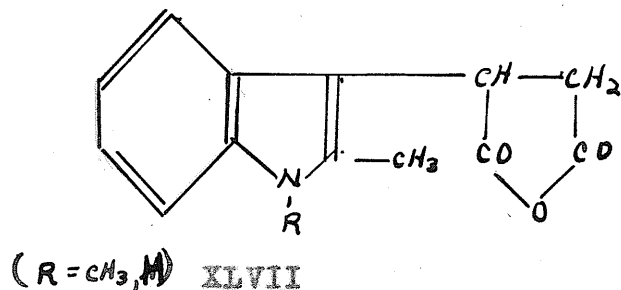
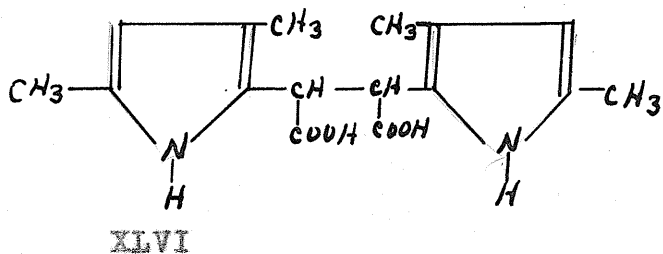
III. Two Molecules Pyrrole and One Molecule Ester.

This type is made possible by the triple bond in the ester molecule. Two molecules of 2,4,-dimethyl pyrrole add to one of ester by displacement of the α -hydrogen in each molecule of the pyrrole giving product XLVI. (34).

INDOLE.

The fusion of the pyrrole ring with the benzene ring as in indole does not change the process of the Diene Synthesis very much from that of pyrrole itself. Indole, α -methyl indole, and N, α -dimethyl indole behave in the same way (35).

The following observation is noteworthy. In all cases observed till now the maleic anhydride entered the pyrrole nucleus in the α position to the nitrogen. In indole derivatives with a substituted α position the β -carbon atom is attacked. Diagram XLVII



The increased mobility of the β -hydrogen atom in α -methyl indole has been reported by numerous investigators in connection with other lines of research. Fischer (36), Freund and Lebach (37), and Mohlau and Redlich (38), are among those who observed this fact.

Imidazoles and pyrazole react with acetylene dicarboxylic esters in the same way as do the pyrroles (34).

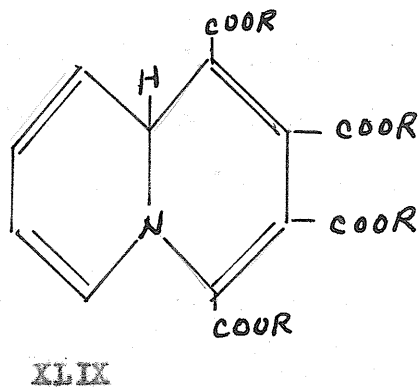
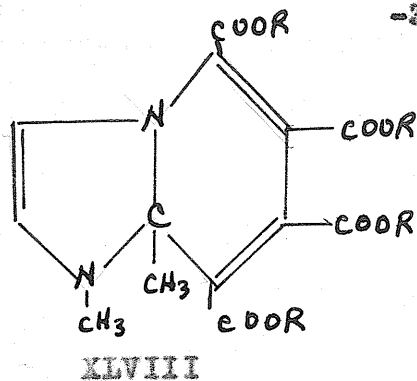
HETEROCYCLIC TERTIARY BASES.

The products obtained in the Diene Synthesis from six membered heterocyclic substances of the pyridine type and acetylene dicarboxylic ester are formed in a manner different from that observed in the pyrrole series. In this reaction type the double bond between nitrogen and carbon in the group $-N=C-$ is opened and the ester adds at these positions.

Although the reaction is characteristic for all nitrogenous heterocyclic rings of the pyridine type, it was first observed in the case of 1,2-dimethyl imidazole (34), which behaves differently than other imidazoles.

In the reaction between 1,2-dimethyl imidazole methylated at the nitrogen atom, and the ester, product XLVIII is produced.

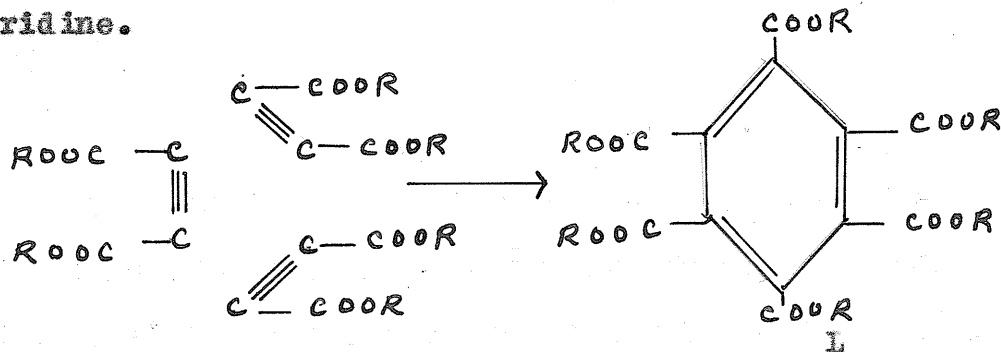
Pyridine unites with two molecules of acetylene dicarboxylic ester in the same way (39) forming XLIX.



This type of Diene Synthesis is typical for quinoline, quinaldine, isoquinoline, and pyridine bases in general. In these substances there has never been observed the formation of products combined in any other way. They always combine exclusively with two molecules of acetylene dicarboxylic ester to give intensely colored and very characteristic compounds.

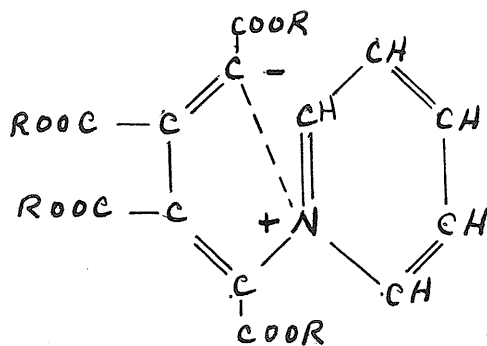
MECHANISM OF THE REACTION.

The above reactions are usually carried out in ethereal solution. If in place of ether, acetic acid is used as the solvent, mellitic ester is formed. Three molecules of ester polymerize under the influence of the pyridine.

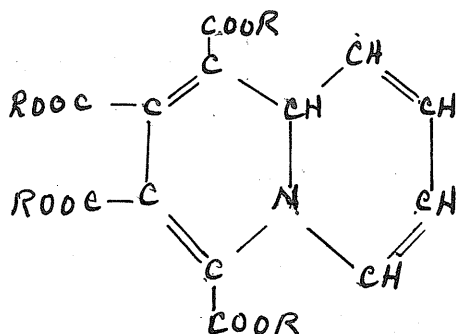


In ethereal solution it is assumed by analogy,

which is represented by structure LII for pyridine and acetylene dicarboxylic ester. This is followed by isomerization. The double bond is opened up and the other end of the chain is attached to the carbon atom resulting in the stable yellow product which has structure LIII.



LII



LIII.

Quinoline, α -picoline, (43), isoquinoline (44), and stilbazol (45) also yield two isomers with acetylene dicarboxylic ester which are represented by similar structures.

In the quinaldine series however, the stable and labile products which formed were different from those of pyridine and the others in that both isomers formed in approximately equal amounts, and once they were formed could not be converted into each other under any circumstances. Comparison of the absorption curve of the stable quinaldine product with those of the corresponding pyridine and quinoline compounds indicated that the former had a different structure.

Further work proved that this was so. (42).

APPLICATIONS OF THE DIENE SYNTHESIS

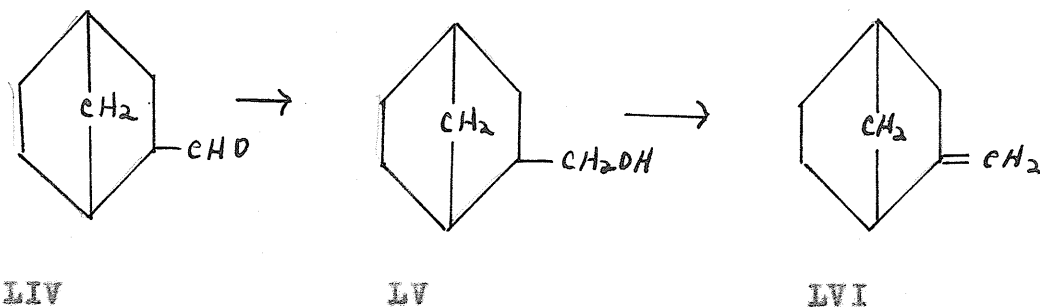
SYNTHESIS

The Diene Synthesis allows the synthesis of complex substances previously unknown, or obtainable only with extreme difficulty. It leads to new types of compounds which may ultimately be of great commercial value. The superiority of this new principle is shown in the fact that rings with internal bridges which are present in a large group of important natural products such as the terpenes, camphors, and others, are synthesized without difficulty. A few examples will be given here to show the large variety of products obtainable by this reaction.

CAMPHORS AND CAMPHENES.

2,5-Endomethylene-hexahydrobenzaldehyde LIV which is easily prepared by the Diene Synthesis is the starting material used by Diels and Alder for the synthesis of norcamphore, camphore, norcamphene, camphene, and camphenilon (46) (47).

The camphene type of structure according to speculation and investigation appears to play a very important role in the terpene series. Since norcamphene is a forerunner of this series it is interesting and important to note that Diels and Alder have succeeded in synthesizing it in a most simple manner by this new method. The aldehyde LIV is converted to the alcohol LV, the sodium compound of which, acted on by CH_3I and followed by dry distillation yields norcamphene LVI.



IRONE SERIES.

Diels and Alder made an investigation into the series of the β -irones by means of the Diene Synthesis. Although they were not able to obtain β -irone itself, they succeeded in producing substances which were similar to β -irone. The reason for their failure was that the starting diene which they thought possessed the structure of 1,1-dimethyl butadiene, actually possessed the structure of 1,3-dimethyl butadiene.(46)

Derivatives of Benzaldehyde.

Many examples have already been given to show that dienes such as acrolein and crotonaldehyde which contain conjugated double bonds react with unsaturated aldehydes yielding derivatives of tetrahydrobenzaldehyde. These by hydrogenation can be converted to the corresponding derivatives of hexahydrobenzaldehyde.

Diels and Alder have applied the Diene Synthesis to the formation of conine, norlupinane, and cantharidins, (13), (42), (43), (48).

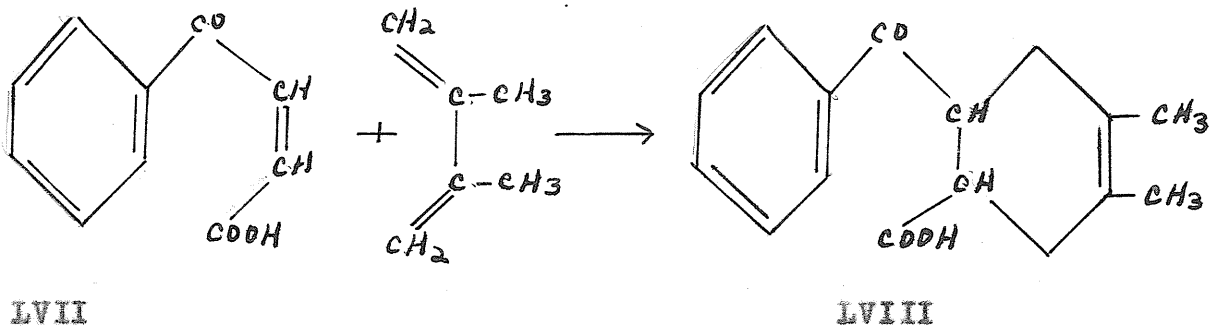
ANTHRACENES AND PHENANTHRENES.

The Diene Synthesis has made possible the easy conversion of the naphthalene ring system into the anthracene or phenanthrene ring systems. One of the many applications of the Diels-Alder reaction has become the basis of an established method for the synthesis of anthraquinones, hydrophenanthrenes, and related compounds. The main application of the Diene Synthesis to these substances is due to L. F. Fieser and his co-workers.

For the synthesis of anthraquinones, the general method consists of adding a diene to α -naphthaquinone, or of adding two molecules of a diene to p-benzoquinone, and converting the resulting product to an anthraquinone by isomerisation and oxidation (2).

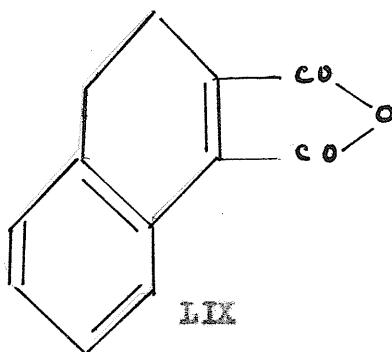
Fieser and his co-workers have developed another route to the members of the anthraquinone series by a somewhat different application of the Diene Synthesis.

Acrylacrylic acids such as benzoylacrylic acid LVII are readily prepared by the Friedel and Crafts' condensation of suitable aromatic substances with maleic anhydride, and by other syntheses. These unsaturated keto acids combine smoothly and almost quantitatively with butadiene or 2,3-dimethyl butadiene (49) in alcoholic solution at 100° yielding addition products of type LVIII. These products can be converted to anthraquinone derivatives by dehydration and ring closure.



The generality of this synthesis was demonstrated by using the acrylaic acids resulting from benzene, toluene, m-xylene, p-xylene, and anisole.

It has been found that the derivatives of maleic anhydride in which the active ethylenic linkage is incorporated in an alicyclic ring such as in structure LIX are capable of entering into the Diels-Alder reaction with dienes(50), (51). The products resulting can be converted to pure phenanthrene derivatives



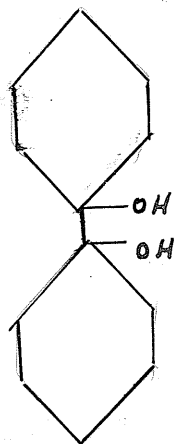
Similar condensations have been effected with cyclic dienes leading to 3,4-benzphenanthrene derivatives(51). These are of interest because of the discovery that the parent hydrocarbon (52) has cancer-producing properties (53).

The scope of this process has been extended to substances of oestrogenic activity by the development of

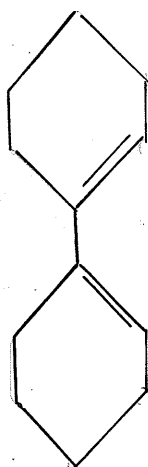
a method for the introduction of hydroxyl or methoxyl groups into the phenanthrene dicarboxylic anhydrides (54), (55).

The reverse of this method employed by Fieser, namely the addition of maleic anhydride or a similar compound to a dicyclic or potentially dicyclic hydrocarbon containing a diene unit was used by Barnett and Lawrence (56), and by Gruber and Adams (57).

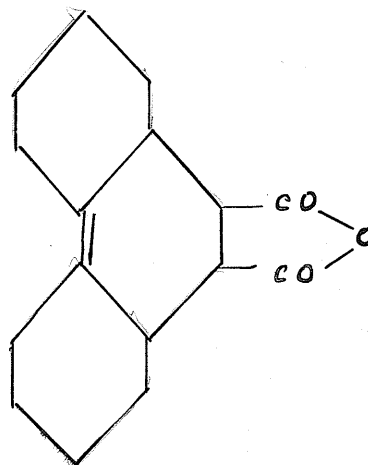
Barnett and Lawrence dehydrated the pinacol LX derived from cyclohexanone to a diene LXI, which yielded addition products of the usual type with maleic anhydride, benzoquinone, and naphthaquinone. Thus with maleic anhydride LXII was obtained.



LX



LXI



LXII

Gruber and Adams independently studied the addition of maleic anhydride and acrolein to the same diene and obtained similar results.

By extending the method of Barnett and Lawrence, Cohen (58) (59) made use of the Diene Synthesis in his attempts to synthesize aetrogenic compounds.

The sterols, bile acids, sex hormones, and other natural substances contain an angular methyl group, i.e. a methyl group attached to a carbon atom which is a common member of two rings. Chuang and Han (60) attempted to prepare such a system by the addition of dienes to alkylated quinones but were unsuccessful. They ascribe their failure to the steric hindrance of the methyl groups. Fieser and Seligman (61) found however, that the dimethyl derivatives of ortho quinone react with 2,3-dimethyl butadiene by heating an alcoholic solution of the two in a sealed tube at 100-105°. The Diene Synthesis follows the normal course in spite of the presence of the blocking methyl group attached to the quinone nucleus. Experiments with other substituted quinones indicate that the reaction is quite general.

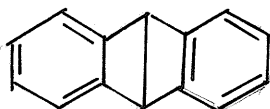
From the above examples we see that the present extension of the Diene Synthesis offers a promising method of approach to substances bearing some relationship to certain of the important sterols and sex hormones.

DETERMINATION OF STRUCTURE

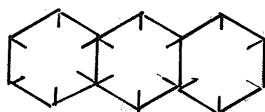
The Diene Synthesis gives us a valuable method for determining the structure of complicated substances. It enables us to detect, and in some cases, to locate the exact position of conjugated double bonds in a molecule. Several examples will be given to show the applicability of the Diels-Alder reaction in this direction.

ANTHRACENE.

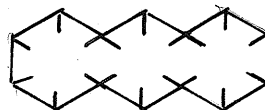
The following formulae have been suggested for anthracene.



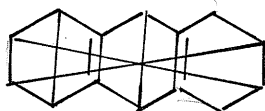
A (62)



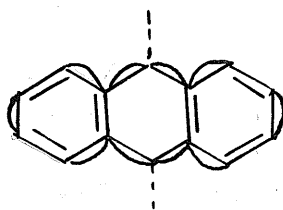
B (63)



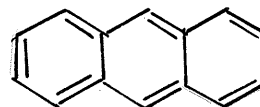
C (64)



D (65)



E (66)

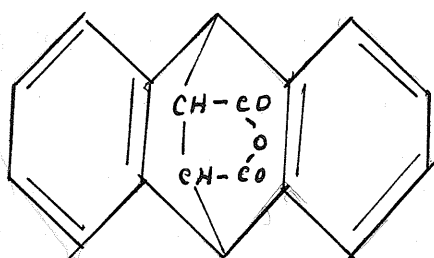


F (67)

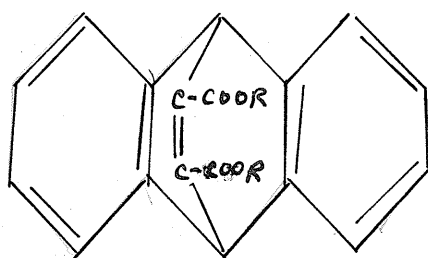
Anthracene contains a peculiar reactivity of the meso 9,10-carbon atoms. The explanation of this fact would be the best argument by which we may arrive at the solution of the structure. A, B, C, and D, do not satisfactorily indicate this reactivity, while E may give a possible explanation. The best evidence points to the Armstrong-

Hinsberg anthracene formula F. Meyer (68) , Scholl (69), and Schlenk (70), all made use of the structure F in their investigations, with great success. Exhaustive spectrochemical investigations by Auwers (71), (72), also point to this formula.

In the Armstrong-Hinsberg formula the centre ring contains a conjugated system of double bonds and therefore anthracene should react in the Diene Synthesis. Diels, Alder, and Beckmann (73), found that under the usual conditions of the Diene Synthesis anthracene combines smoothly with one molecule of crotonic acid, maleic, dibromomaleic, and citraconic anhydrides, as well as with esters of acetylene dicarboxylic acid, p-benzoquinone (74), and azo dicarboxylic esters (75), to form perfectly stable products. These are firmly joined compounds which consist of a saturated central ring with a bridge and a true benzene nucleus on each side of the central ring. Two such examples from maleic anhydride and acetylene dicarboxylic ester are indicated in LXV and LXVI respectively.

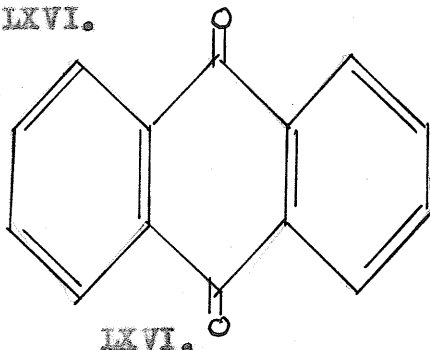


LXV



LXVI

Support for LXV and therefore for structure F, is obtained by oxidative decomposition carried out stepwise under the mildest possible conditions. This finally leads to anthraquinone. LXVI.



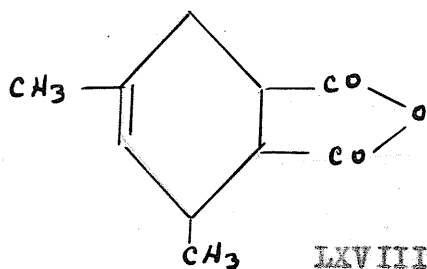
These observations lead to the following conclusions. Anthracene is a typical diene and as such adds the typical philodienes of the Diene Synthesis. The latter become attached at the 9,10-positions in the hydrocarbon with the formation of corresponding bridge compounds. A pair of conjugate bonds are present in anthracene which show the characteristic reactions of such bonds found in aliphatic and alicyclic systems. The ends of these pairs lie in the 9,10-positions and the formula suggested by Armstrong and Hinsberg show these as such.

MYRCENE.

Myrcene adds maleic anhydride (46) to give the anhydride of iso-hexenyl-4-cis-4⁴-tetrahydro-phthalic-acid LXVII. From our knowledge of the course of the Diene Synthesis we have here evidence for the presence of conjugate double bonds in myrcene. The structure of LXVII

DETECTION OF CONJUGATE SYSTEMS.

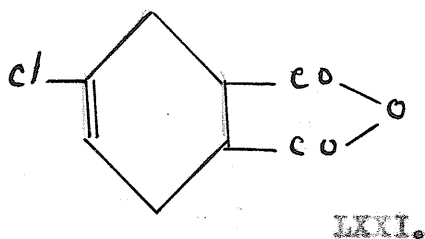
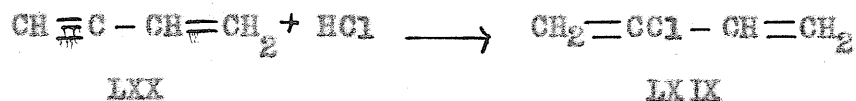
An interesting example of the applicability of the Diene Synthesis to the proving of structure was shown by Diels and Alder in their observations of the irone series (46) (page 35). Since they obtained a pseudo-irone instead of the desired β - irone it was concluded that the starting diene was 1,3-dimethyl butadiene instead of 1,1-dimethyl butadiene. Oxidation and hydrogenation reactions suggested that this assumption was right but the final proof was obtained by an application of the Diene Synthesis. It was observed that a substance which was known to be 1,3-dimethyl butadiene reacted with maleic anhydride to form crystals of 3,5-dimethyl- Δ^4 -tetrahydro-phthalic-anhydride LXVIII. Carrying out the same reaction with their starting diene they got the identical compound.



Other dienes such as isoprene, piperylene, 1,4-^{DIMETHYL} and 2,3-[^] as well as 1,1,3-trimethyl butadiene can be identified in the same way by this reaction.

Carothers and his co-workers (77) made use of this reaction in proving the structure of 2-chloro-1,3-butadiene LXIX, which was produced from vinyl acetylene LXX

by the action of HCl. LXX reacts with maleic anhydride to form LXXI whose structure can be determined.



It has been found however that not all conjugated systems will enter into the Diene Synthesis (77). Coffman and Carothers have observed that a number of open chain chloro compounds which contain at least one pair of conjugated double bonds fail to react either with naphthoquinone or with maleic anhydride at 100⁰. Therefore the Diene Synthesis can be regarded as diagnostic only if it leads to positive results.

DIENE SYNTHESIS IN NATURE

Diels is very much impressed with the ease with which the Diene Synthesis takes place and offers the suggestion that the process is going on in nature. We have seen the ease with which compounds similar to or identical with natural substances such as terpenes, camphors, and alkaloids could be synthesized by this new method. The Diene Synthesis with pyrrole leads to compounds in the region of the blood and plant coloring matter, and is therefore worthy of note in biological investigations. These compounds are synthesized in the laboratory under the mildest conditions possible. The complex products found in the living cell are likewise produced without the use of high temperatures or pressures and in the absence of vigorous chemical reagents such as bromine.

The polymerization of certain butadienes is a Diene Synthesis. Thus, isoprene dimerizes to dipentene and diprene (78), while cyclopentadiene polymerizes in two steps (79), (80), yielding dicyclopentadiene first and finally tricyclopentadiene. Isoprene polymerizes spontaneously and therefore the energy required for this process must be very small. Since the hydrocarbons comprising the terpenes, sesquiterpenes, their homologues and derivatives, found in natural products are considered to be made up of isoprene units, it might easily be considered that the spontaneous polymerization of these units is taking place in the living cell, leading to these compounds. Considering

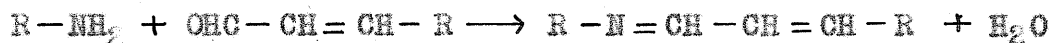
the conditions under which the Diene Synthesis takes place to produce so many complex substances, makes such an assumption very plausible.

DISCUSSION OF THE PROBLEM

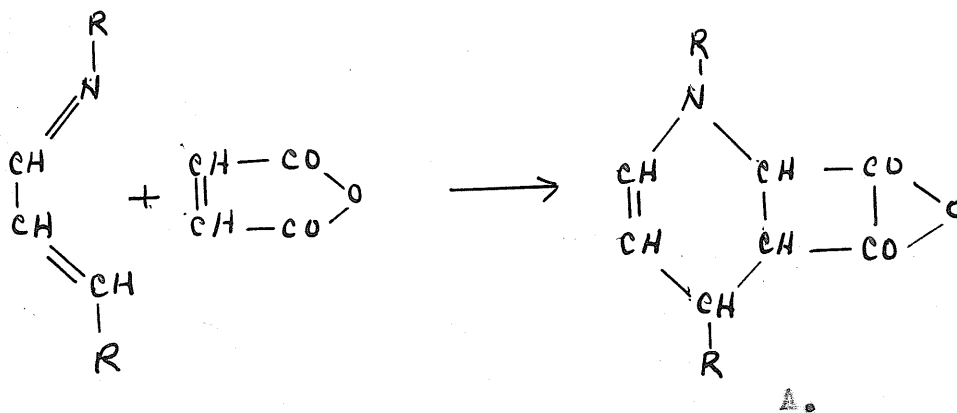
On searching through the literature with reference to the Diene Synthesis, it was noticed that no cases have been reported in which the reaction has been attempted with unsaturated conjugated anils.

It was therefore decided to make a study of the reaction between compounds that contain the system $-N=CH-CH=CH-$ and maleic anhydride in order to determine whether such compounds would enter into a Diene Synthesis. The results of this investigation are reported in this thesis.

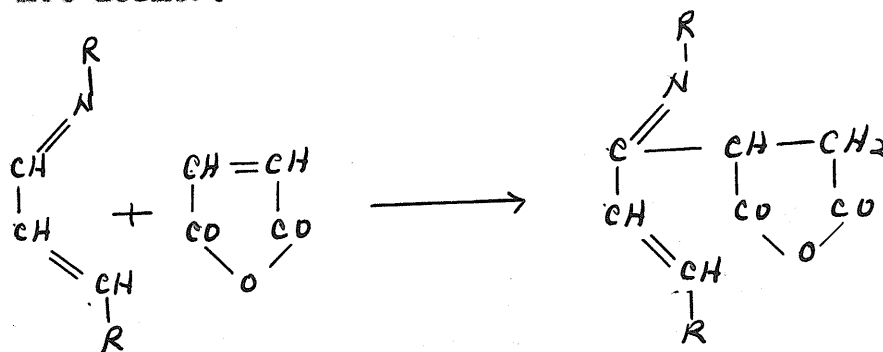
Several compounds containing the desired grouping were prepared by condensing a primary base with an unsaturated aldehyde.



From our knowledge of the Diene Synthesis two possible reactions can be formulated. The first would be the result of a 1,4-addition of the maleic anhydride to the conjugated system, with the formation of a heteroring containing nitrogen. This is formulated as shown.



The second type of reaction may be formulated according to the reaction which takes place between pyrrole and maleic anhydride. In this case the hydrogen atom which is attached to the carbon next to the nitrogen, wanders into the anhydride molecule, opening the double bond in the latter, which then joins to the carbon atom from which the hydrogen has wandered. In this case a ring structure is not formed.



In both formulations the resulting product consists of the addition of one molecule of anhydride to one molecule of anil.

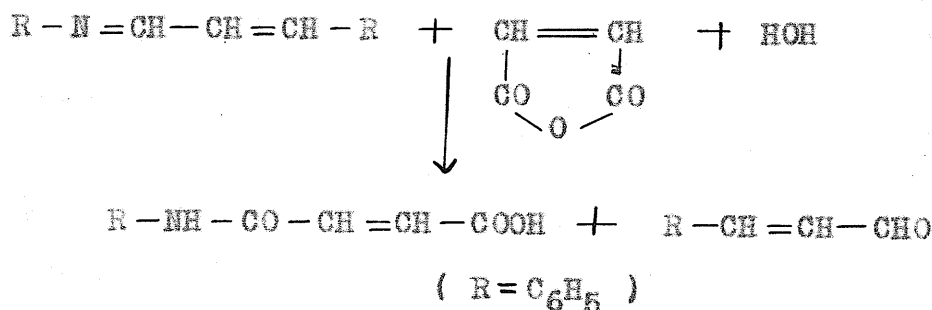
REACTIONS BETWEEN ANILS AND MALEIC ANHYDRIDE IN SOLVENTS.

In the first attempt, a reaction was carried out between cinnamal-aniline $C_6H_5 - N = CH - CH = CH - C_6H_5$ and maleic anhydride in solution at room temperature. In one case ether was used as solvent and a yellow solid compound was produced immediately. By repeating the reaction in acetone a red compound was obtained which appears to be an isomer of the yellow compound. The two substances are

exactly alike in all respects, except that the red changes into the yellow on warming. This change takes place in the solid phase, i.e. below the melting point of either substance and it is not reversible.

It was found that neither of the above reactions took place. In addition to the solid which was formed, cinnamic aldehyde was produced and this was isolated from the ethereal solution. The yellow solid was shown to be maleic acid mono-anilide. By boiling with a 20% KOH solution it yielded aniline and fumaric acid.

This type of reaction between cinnamyl-aniline and maleic anhydride was shown to be due to the presence of water in the solvents employed. Apparently the maleic anhydride acts as a catalyst for the hydrolysis of the anil, since it was found that water itself without the presence of the anhydride did not cause the reformation of the base and aldehyde from the anil. The aniline thus formed reacts with the maleic anhydride producing the solid anilide and the cinnamic aldehyde is left in solution.



The above procedure was repeated using cinnamal-
o-toluidine and maleic anhydride in place of ^{THE} aniline product.

A similar reaction took place producing in this case in addition to cinnamic aldehyde, maleic acid mono-o-toluidide. By boiling with 20% KOH solution the maleic acid mono-o-toluidide yielded fumaric acid and o-toluidine. Here again, the water which was present in the ether, which was used as the solvent, was responsible for the reaction and the maleic anhydride acted as a catalyst for the hydrolysis of the anil.

Since it became evident that the conjugated system in the the group $-N=CH-CH=CH-$ did not function as a unit in these reactions, but that only the double bond attached to the nitrogen atom in the group $-N=CH-$ was concerned, similar reactions with anils that contained only this double bond were carried out to verify this observation and thus establish the course of the reaction. For this purpose benzal-aniline $C_6H_5-CH=N-C_6H_5$, and benzal-p-phenetidine $C_2H_5-O-C_6H_4-N=CH-C_6H_5$, were prepared. From benzal-aniline and maleic anhydride it was expected that according to the reaction indicated above that maleic acid mono anilide would also be formed in this case and that the aldehyde would be benzaldehyde. This was actually found to be the case. In a similar manner benzaldehyde and maleic acid mono-p-phenetidide were obtained from benzal-p-phenetidine and maleic anhydride.

It has already been stated that for the reaction to take place as indicated, i.e. the opening of the anhydride ring and the splitting off of aldehyde requires the presence

of water and since no water was added during the reaction, it must have been present in sufficient quantity in the organic solvents employed.

The reaction between cinnamal-aniline, and maleic anhydride, benzal-aniline and maleic anhydride, cinnamal-o-toluidine and maleic anhydride, and benzal-p-phenetidine and maleic anhydride were repeated using absolutely dry materials and apparatus in order to determine what effect the absence of water had on the course of the reaction, and to attempt thereby to alter it to a Diene Synthesis. No reaction took place after allowing a mixture of each set of components stand at room temperature for several days. A few drops of water were then added to each flask and shaken and a solid compound was formed immediately. The compound in the case of cinnamal-aniline and maleic anhydride for example, was as in the first case, maleic acid mono-anilide and again cinnamic aldehyde was isolated from the solvent. Similar reactions took place in the other cases.

It is thus established that when an unsaturated anil of the type used above and maleic anhydride are brought together in solution in the presence of water, an anilide and aldehyde are formed in the following manner, The anil is hydrolyzed by the water to a base and aldehyde. For this hydrolysis the maleic anhydride acts as a catalyst. The free base then reacts with the anhydride to form the anilide, while the aldehyde remains in solution.

A reaction was carried out between cinnamal-aniline and maleic anhydride in dry ether in the presence of anhydrous $AlCl_3$, at room temperature. A compound formed which was different from that obtained in the first case. This compound is still under investigation and nothing can be stated about its structure at the present time.

REACTION IN THE ABSENCE OF SOLVENTS.

Cinnamal-aniline and maleic anhydride were next heated together in the absence of solvent, at temperatures varying between $120 - 200^{\circ}$ and for periods of time varying from a few minutes to an hour. In all cases the same compound was obtained which was different from any obtained previously.

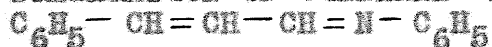
An analysis of this compound indicates that it is composed of one molecule of maleic anhydride and one molecule of cinnamal-aniline. These analyses are in agreement with either formula A or B, both of which necessarily have the same percentage composition. This compound is still under investigation at the present time, but from the information already obtained formula A, i.e. a 1,4-addition is favored. For example, the action of KOH does not decompose it to yield aniline as would be expected from the open chain compound B, thus indicating a stable ring as is present in A. The compound is also acidic in character showing that the anhydride grouping is still present.

We thus have in this last reaction product an

indication that a Diene Synthesis has taken place between cinnamal-aniline which contains a conjugated system and maleic anhydride. This compound is still being investigated at the present time and it is believed that definite proof will shortly be obtained to show that this is actually a Diene Synthesis.

EXPERIMENTAL

PREPARATION OF CINNAMAL-ANILINE (81)



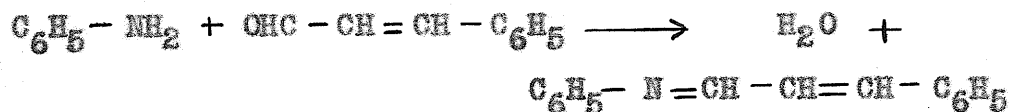
52 grams cinnamic aldehyde.

36 grams aniline.

The cinnamic aldehyde and aniline were purified by distillation and allowed to cool. The aniline was slowly added to the aldehyde with constant stirring. A reaction set in at once with evolution of much heat. The vessel was cooled and everything solidified completely yielding an orange yellow solid. The product was recrystallized from alcohol in the form of fine yellow flakes.

Melting point 108°

Yield 49 grams.



REACTION BETWEEN CINNAMAL-ANILINE AND MALEIC ANHYDRIDE.

After a preliminary test on a small scale indicated that a reaction took place between maleic anhydride and cinnamal-aniline, the following was carried out on a larger scale.

40 grams cinnamal-aniline.

19 grams maleic anhydride.

Molecular proportions of the two components were dissolved separately in ether. Maleic anhydride yielded a colorless solution and the cinnamal-aniline

a light yellow solution. One solution was added to the other and immediately the mixture started to turn a reddish-brown color. The flask was tightly stoppered to prevent evaporation of ether. A yellow solid started to separate out from solution in about one minute after mixing and the color of the mother liquor started to change back to yellow. After thirty minutes the separation of more solid could no longer be detected and the solution had assumed a dull yellow color. The flask was allowed to stand for twenty four hours in order to make certain that the reaction had gone to completion.

The reaction product was removed by filtration. Evaporation of the ether from the mother liquor caused more of the same yellow product to separate. This substance will be referred to as the yellow product.

Yield 38 grams.

Melting point $195 - 196^{\circ}$.

After all the ether was removed by distillation on the steam bath a very dark colored liquid was left in the distilling flask. An attempt was made to isolate a pure sample of this liquid by distillation but it decomposed to a very great extent when the temperature reached about 150° . It was therefore distilled under reduced pressure. A pale yellow liquid came over between $138-140^{\circ}$ and at 20 mm. pressure. It had a faint cinnamon smell but after standing several days it turned dark red

and had a pronounced cinnamon smell. Yield 15 grams.

A fusion with sodium indicated that nitrogen was not present. It was shown that this substance was cinnamic aldehyde by preparing the semicarbazone, oxime, and phenylhydrazone, which melted at 214° , 138° , and 168° respectively. On standing the pale yellow cinnamic aldehyde is oxidized by the air, hence the change to the red color.

In the distilling flask there remained a dark tarry residue which was insoluble in the common solvents such as alcohol, acetone, ether, chloroform, benzene, carbon disulphide, petroleum ether, toluene, and xylene. This substance was not investigated further.

EXAMINATION OF THE YELLOW PRODUCT.

On close examination of the yellow product, which was in the form of a powder, it was observed that there was present also a very small amount of slightly darker crystals. Attempts to separate these by means of extracting with different solvents were unsuccessful since both substances were either soluble or insoluble, to the same extent, in the same solvents. The crystals were therefore separated by hand picking with the aid of a lens.

Melting point of the crystals 195° .

Melting point of yellow powder 195°.

Mixed melting point 195°.

When the crystals were crushed with a glass rod they also formed a yellow powder. Therefore the two substances are the same product in different forms - powder and well defined crystals.

An attempt was made to prepare the yellow substance in a state of purity suitable for analysis. For this purpose a search was made for a solvent which would be suitable for recrystallization. In the following solvents the product was either insoluble or so slightly soluble as to make them useless for the desired purpose; ether, chloroform, carbon disulphide, carbon tetrachloride, benzene, xylol, toluol, ethyl acetate, water, ligroin, and petroleum ether. Pyridine on the other hand could not be used for recrystallizing because the product was so extremely soluble in the cold.

The compound was refluxed with acetone for half an hour and went into solution. The solution was colored yellow. On cooling, a white crystalline compound settled out. The acetone remained yellow. A similar white compound was obtained when the yellow compound was refluxed with alcohol and nitrobenzene, the only other solvents found in which it dissolved in appreciable quantity. The compound dissolved more readily in nitro-

benzene than either in alcohol or acetone.

After separating the white recrystallized solid by filtration, the acetone was removed by distillation leaving an insignificant amount of dark red film on the inside wall of the flask. This was apparently impurity left in solution which colored it yellow. It was not considered necessary to investigate this further. The same results were obtained from the alcohol and nitrobenzene. The following results were therefore obtained on recrystallization:

Yellow product A M. P. 195°	acetone	→	White product B M.P. 194-5°
	alcohol	→	White product C M.P. 195°
	nitrobenzene	→	White product D M.P. 195-6°

Mixed melting points.

A - B	195°
A - C	195-6°
A - D	196°
B - C	195-6°
B - D	195°
C - D	195°

Thus the melting points indicate that we are still dealing with the same compound. The only explanation advanced so far for the change of color on recrystallizing is attributed to the removal of colored impurities, which apparently did not effect the melting point of the yellow substance.

ACETONE AS SOLVENT.

Since a white compound results when the yellow substance is recrystallized from acetone, the reaction between cinnamal-aniline and maleic anhydride was carried out in acetone solution to determine whether the white compound would be formed directly instead of the yellow compound.

20 grams cinnamal-aniline

9.5 grams maleic anhydride.

Molecular proportions of the two components were dissolved separately in acetone. The cinnamal-aniline dissolved in the acetone with the production of a yellow solution. On mixing the two solutions a dark red color was produced. After standing a few minutes a red precipitate started to separate out instead of the expected white solid, and continued to do so for several hours. The acetone was removed by filtration and the solid dried in a dessicator over sodium hydroxide. This substance will be referred to as the red compound.

Yield 21 grams.

Melting point $194-5^{\circ}$.

The acetone which was still colored red was removed by distillation leaving a dark reddish-brown mixture of solid substance and tarry dark red matter. Benzene which was added, dissolved everything except seven grams of red solid material. The benzene was filtered off and the solid dried in a dessicator and the melting point taken. It melted at $194-5^{\circ}$ and was evidently more of the red substance

obtained by concentrating the solution. These seven grams are included in the yield mentioned above.

The red benzene solution was distilled under reduced pressure. After the benzene was removed, a pale yellow liquid distilled over at 139-142° under 20 mm. pressure. This was identified as cinnamic aldehyde by the same methods as in the previous case.

yield 2.5 grams.

COMPARISON OF RED AND YELLOW PRODUCTS.

When the melting point of the red substance was determined it was noticed that at 145-150° the color changed from red to yellow without any melting taking place. On further raising the temperature the yellow product formed melted at 194-5°.

A little of the red substance was next placed on a watch glass and carefully warmed. The change from red to yellow started to take place at the outer edges of the substance first and rapidly spread throughout the mass. No melting occurred. The glass was allowed to cool to room temperature. The yellow color persisted, the reverse change from yellow to red not having taken place. Scratching the solid with a glass rod did not cause the change to take place.

A little of the red substance was then heated on a watch glass until it melted and then allowed to cool. Again it solidified to the yellow compound. Mixed melting

point of this compound and the original yellow compound was also $194-5^{\circ}$.

A relationship exists therefore between the red compound obtained when acetone is used as the solvent and the yellow compound obtained when ether is used as the solvent. The behavior of both substances to various reagents was compared with the hope of establishing this relationship.

The red and yellow solids are both soluble in the same solvents and insoluble in the same solvents. The organic solvents used were the same as those listed on page 58. No liquid was found in which ~~in which~~ only one of the substances was soluble and the other not. Except for pyridine, all solvents in which the substances were soluble had to be refluxed with the solid for solution to take place. It was also noticed that in each case the red substance went into solution with more difficulty than did the yellow product, requiring a larger volume of solvent and a longer period of boiling. In all cases the product that came out of solution on cooling was a white crystalline solid that melted at $194-5^{\circ}$, and was identical to the white solid described above. Mixed melting points of the recrystallized and original red and yellow substances showed no depression.

It was also observed that nitric and hydrochloric acids and KOH had no effect on both substances. They both decolorized bromine water, and acid KMnO_4 , and liberated CO_2 from NaHCO_3 . Bromine derivatives of the red and yellow

substances were prepared (method of preparation on page 72). Both derivatives were pale green in color.

Melting point of red bromine derivative 194° .

Melting point of yellow bromine derivative $194-5^{\circ}$.

Mixed melting point $194-5^{\circ}$.

Both the red and yellow substances yield therefore the same bromine derivatives.

Mixed melting point of bromine derivative and original yellow product $175-177^{\circ}$.

This indicates that the bromine derivative is a different compound than the original yellow one.

Except for the original colors of the two products they appear identical in all respects. The only explanation advanced so far for the conversion of the red product to the yellow on heating, is that an isomerisation takes place.

Since the red changes into the yellow substance and the reverse change does not take place, it was decided to continue with the further examination of the yellow product.

ANALYSIS.

A sodium fusion of the yellow compound indicated that nitrogen was present. The substance was analyzed for carbon, hydrogen, and nitrogen by the combustion method.

First determination;

Weight of CaCl_2 tube after combustion	40.2523 gms.
Weight of CaCl_2 tube before combustion	<u>40.2016</u> "
Increase due to H_2O	0.0509 "
Weight of KOH bulb after combustion	70.8027 gms.
Weight of KOH bulb before combustion	<u>70.5190</u> "
Increase due to CO_2	0.2837 "
Weight of combustion boat plus sample	5.0166 gms.
Weight of combustion boat	<u>4.8920</u> gms.
Weight of sample	0.1246 "

$$\text{Percentage of carbon} = \frac{12 \times .2837 \times 100}{44 \times .1246} = 62.10\%$$

$$\text{Percentage of hydrogen} = \frac{2 \times .0509 \times 100}{18 \times .1246} = 4.54\%$$

Second determination;

Weight of CaCl_2 tube after combustion	40.2429 gms.
Weight of CaCl_2 tube before combustion	<u>40.2034</u> "
Increase due to H_2O	0.0395 "

Weight of KOH bulb after combustion	70.7426 gms.
Weight of KOH bulb before combustion	<u>70.5134</u> "
Increase due to CO ₂	0.2292 "

Weight of combustion boat plus sample	3.5450 gms.
Weight of combustion boat	<u>3.4456</u> "
Weight of sample	0.0994 "

$$\text{Percentage of carbon} = \frac{12 \times .2292 \times 100}{44 \times .0994} = 62.87\%$$

$$\text{Percentage of hydrogen} = \frac{2 \times .0395 \times 100}{18 \times .0994} = 4.47\%$$

Mean percent carbon 62.49%

Mean percent hydrogen 4.51%.

First determination for nitrogen:

Weight of watch glass plus sample	7.0314 gms.
Weight of watch glass	<u>6.8024</u> "
Weight of sample	0.2290 "

Volume of nitrogen collected 15.6 c. c.

Barometer reading 732 mm.

Temperature 22° C.

$$\text{Percentage of nitrogen} = \frac{15.6 \times 273 \times 732 \times .126}{295 \times 760 \times .2290} = 7.65\%$$

Second determination for nitrogen:

Weight of watch glass plus sample	6.9963 gms.
Weight of watch glass	<u>6.8012</u> "
Weight of sample	0.1951 "

Volume of nitrogen collected 15.8 c.c.

Barometer reading 737 mm.

Temperature 23° C.

$$\text{Percentage of nitrogen} = \frac{15.8 \times 273 \times 737 \times .126}{296 \times 760 \times .1951} = 9.13\%$$

Third determination for nitrogen:

Weight of watch glass plus sample	7.0316 gms.
Weight of watch glass	<u>6.8012</u> "
Weight of sample	0.2304 "

Volume of nitrogen collected 19.0 c.c.

Barometer reading 743 mm.

Temperature 25° C.

$$\text{Percentage of nitrogen} = \frac{19 \times 273 \times 743 \times .126}{298 \times 760 \times .2304} = 9.29\%$$

The source of CO₂ for the nitrogen combustions was NaHCO₃. The NaHCO₃ used in the first determination was used up testing the combustion apparatus. The new

supply obtained for the second and third determinations gave the higher percentage results as shown. A nitrogen determination was therefore run with phenacetin as a check of the apparatus and materials used.

Determination of nitrogen in phenacetin $C_2H_5 \cdot O \cdot C_6H_4 - NH - CO - CH_3$.

Weight of watch glass plus sample	7.0220 gms.
Weight of watch glass	<u>6.8012</u> "
Weight of sample	0.2208 "

Volume of nitrogen collected 16.8 c.c.

Barometer reading 737 mm.

Temperature 22° C.

Percentage of nitrogen = $\frac{16.8 \times 273 \times 737 \times .126}{295 \times 760 \times .2208} = 9.63\%$

Theoretical value for nitrogen 7.62%

It is therefore apparent that the high values obtained in the second and third determinations are due to impurities in the $NaHCO_3$. The percentage of nitrogen was therefore redetermined by the Kjeldahl method and the following results were obtained.

First determination 7.20%

Second determination 7.57%

Mean 7.39%

The results obtained by the kjeldahl method agree with the first combustion determination and they are the ones accepted for the calculation below.

The following empirical formula was calculated for the yellow compound from the analytical data obtained.

$$N = 7.39\%$$

$$C = 62.49\%$$

$$H = 4.51\%$$

$$O = 26.61\% \text{ (by subtraction)}$$

$$N = \frac{7.39}{14} = .5278$$

$$C = \frac{62.49}{12} = 5.207$$

$$H = \frac{4.51}{1} = 4.51$$

$$O = \frac{26.61}{16} = 1.600$$

$$\frac{.5278}{.5278} = 1.00 = 1$$

$$\frac{5.2070}{.5278} = 9.86 = 10$$

$$\frac{4.5100}{.5278} = 8.63 = 9$$

$$\frac{1.6000}{.5278} = 3.15 \approx 3$$

Empirical formula $C_{10}H_9NO_3$

Analysis of the white product obtained on recrystallizing the yellow compound from acetone.

Carbon and Hydrogen.

First determination:

Weight of KOH bulb after combustion	74.2160	gms.
Weight of KOH bulb before combustion	<u>74.0494</u>	"
Increase due to CO ₂	0.1666	"
Weight of CaCl ₂ tube after combustion	42.9390	gms.
Weight of CaCl ₂ tube before combustion	<u>42.9120</u>	"
Increase due to H ₂ O	0.0270	"
Weight of combustion boat plus sample	3.5172	gms.
Weight of combustion boat	<u>3.4450</u>	"
Weight of sample	0.0722	"

$$\text{Percentage of carbon} = \frac{12 \times .1666 \times 100}{44 \frac{16}{18} \times .0722} = 62.93\%$$

$$\text{Percentage of hydrogen} = \frac{2 \times .0270 \times 100}{18 \times .0722} = 4.15\%$$

Second determination;

Weight of KOH bulb after combustion	74.4528 gms.
Weight of KOH bulb before combustion	<u>74.2160</u> "
Increase due to CO ₂	0.2368 "

Weight of CaCl ₂ tube after combustion	42.9764 gms.
Weight of CaCl ₂ tube before combustion	<u>42.9390</u> "
Increase due to H ₂ O	0.0374 "

Weight of combustion boat plus sample	3.5480 gms.
Weight of combustion boat	<u>3.4446</u> "
Weight of sample	0.1034 "

$$\text{Percentage of carbon} = \frac{12 \times .2368 \times 100}{44 \times .1034} = 62.24\%$$

$$\text{Percentage of hydrogen} = \frac{2 \times .0374 \times 100}{18 \times .1034} = 4.02\%$$

Mean percent carbon 62.59%

Mean percent hydrogen 4.08%

Nitrogen was determined by the Kjeldahl method.

First determination 7.58% nitrogen

Second determination 7.78% nitrogen

Mean 7.68% nitrogen

The following empirical formula was calculated for the white compound from the analytical data.

$$N = 7.68\%$$

$$C = 62.59\%$$

$$H = 4.08\%$$

$$O = 25.65\% \text{ (by subtraction).}$$

$$N = \frac{7.68}{14} = .5486 \qquad \frac{.5486}{.5486} = 1 = 1$$

$$C = \frac{62.59}{12} = 5.2160 \qquad \frac{5.2160}{.5486} = 9.6 = 10$$

$$H = \frac{4.08}{1} = 4.08 \qquad \frac{4.080}{.5486} = 7.6 = 8$$

$$O = \frac{25.65}{16} = 1.587 \qquad \frac{1.5870}{.5486} = 2.88 = 3$$

Empirical formula $C_{10}H_8NO_3$

Due to experimental errors it is quite possible that the formula of the white compound obtained from the yellow one on recrystallization ~~has the~~ is also $C_{10}H_8NO_3$. The two compounds therefore represent the same substance in different degrees of purity.

Preparation of the Bromine Derivative of the Yellow Compound.

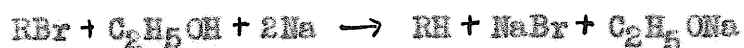
Two grams of the yellow product were dissolved in alcohol by heating under a reflux condenser. When the solid had all gone into solution sufficient alcohol was added to prevent precipitation on cooling. When the solution had cooled to room temperature a very small amount of the substance had recrystallized out. This was removed by filtration. Bromine water was slowly added to the solution and was decolorized instantly, raising the temperature of the solution. Addition was continued until no more decolorization took place. At this point a precipitate started to form. The solution was stirred vigorously and allowed to stand for some time until it had cooled to room temperature. The liquid was removed and the solid formed was recrystallized from alcohol.

The presence of bromine was confirmed by heating a little of the solid on a clean copper wire; a bluish-green coloration was produced due to the formation of volatile copper halides.

The bromine derivative was a pale green crystalline compound. The crystals were very tiny and when examined with a hand lens appeared transparent. Melting point 194° . Mixed melting point of yellow product and bromine derivative $175 - 177^{\circ}$. It is thus established that we are dealing with a different compound here, and not with the original product thrown out of solution. The identical bromine derivative was obtained from the red product by the same method (see page 63).

BROMINE ANALYSIS.

The method of Stepanow was used to determine the amount of bromine in the bromine derivative of the yellow compound. A weighed sample of the substance (about 0.5 gms.) was dissolved in 50c.c. of absolute alcohol in a flask fitted with a reflux condenser. To the boiling solution was gradually added about 3 grams of metallic sodium (cut into clean strips). When all was added the mixture was heated with a free flame until all the sodium had reacted according to the equation;



The mixture was then cooled, diluted with water, acidified with dilute nitric acid, and titrated by the Volhard method.

In general the Volhard method is as follows. The bromide solution was treated with an excess of 0.1N $AgNO_3$ solution and titrated with ammonium thiocyanate using ferric alum as indicator. From the required volume of $AgNO_3$ the quantity of bromine was computed.

The following solutions were therefore prepared;

0.1N $AgNO_3$ solution.

0.1N ammonium thiocyanate solution.

First determination;

Weight of watch glass plus sample	9.3448 gms.
Weight of watch glass	<u>8.8841</u> "
Weight of sample	0.4607 "

100 c.c. of 0.1N AgNO_3 added.

Required 77.6 c.c. of 0.1N NH_4CNS

Therefore 22.4 c.c. of AgNO_3 were required to precipitate the bromine present in the sample.

1000 c.c. of 0.1N AgNO_3 solution = $\frac{\text{Br}}{10} = 7.992$ gms Br.

22.4 c.c. " " " " = $\frac{22.4 \times 7.992}{1000} = .1789$ gms Br.

Percentage of bromine = $\frac{.1789 \times 100}{.4607} = 38.86\%$

Second determination;

Weight of watch glass plus sample 9.4328 gms.

Weight of watch glass 8.8839 "

Weight of sample 0.5489 "

100 c.c. of 0.1N AgNO_3 added.

Required 75.3 c.c. of 0.1N NH_4CNS

Therefore 24.7 c.c. of AgNO_3 were required to precipitate the bromine present in the sample.

24.7 c.c. of 0.1N AgNO_3 = $\frac{24.7 \times 7.992}{1000} = .1974$ gms Br.

Percentage of bromine = $\frac{.1974 \times 100}{.5489} = 36.00\%$

Mean percent bromine 37.43%

Examining this result with the calculated empirical formula in mind $\text{C}_{10}\text{H}_9\text{NO}_3$, it becomes evident that two atoms of bromine were taken up by the yellow compound and therefore one double bond is present in this compound. The calculated value for two atoms of bromine is 45.5%, but the values obtained above are sufficiently accurate to indicate one double bond.

An attempt was made to determine the molecular weight of the yellow compound. The freezing point depression method was found to be of no value in this case since the substance was so slightly soluble in the ordinary solvents at room temperature.

The method of the elevation of the boiling point was therefore employed. An electrically heated apparatus was set up similar to that suggested by S. L. Bigelow (82). The heating coil consisted of a piece of resistance wire passing through the solvent. The solvent employed was acetone.

Pellets of the sample were used but it was found that the tightly packed pellets fell to the bottom of the vessel below the coil and did not dissolve at the boiling point of acetone.

The yellow product was next added as a powder but again it did not dissolve to any appreciable extent. Even after boiling for half an hour the small amount of substance that went into solution produced no appreciable elevation of boiling point.

Attempts to use benzene as the solvent were also unsuccessful due to the same difficulty.

It was therefore decided to prepare derivatives of the yellow compound which might be easily soluble in some solvent and thus determine the molecular weight.

The bromine derivative described above was also not sufficiently soluble in the volume of liquid employed to produce a satisfactory elevation of boiling point.

PREPARATION OF ETHYL ESTER OF YELLOW COMPOUND.

Ten grams of the yellow product were boiled with 150 c.c. of absolute ethyl alcohol and 5 c.c. of concentrated H_2SO_4 under a reflux condenser for four hours. The excess alcohol was distilled off and the remaining solution diluted with water. It was neutralized with solid Na_2CO_3 and shaken in a separating funnel with ether. The ethereal solution was withdrawn, washed with water, and dried over $CaCl_2$. The ether was removed by distillation leaving a red liquid behind, which yielded a pale yellow liquid on further distillation. This liquid boiled at $106-109^{\circ}$ and is presumably the ethyl ester of the yellow product. It had a strong characteristic smell. Yield 4.5 gms. Since the ester turned out to be a liquid, it could not be employed for a molecular weight determination by the freezing point depression or boiling point elevation methods.

PREPARATION OF THE BROMINE DERIVATIVE OF THE ETHYL ESTER.

The ester was dissolved in alcohol and bromine was added to the solution. The bromine dissolved with the disappearance of the red color and evolution of much heat. The flask was cooled and more bromine was added till it was no longer decolorized. A white solid formed. The flask was allowed to stand until it cooled to room temperature, when the liquid was filtered off and the solid was recrystallized from alcohol. Pure snow white needle-like crystals were obtained which melted sharply at 120° . Yield 2 grams.

The presence of halogen was confirmed by heating

a little of the solid on a clean copper wire. A blue coloration was produced.

Molecular weight determinations with this product were unsuccessful because of temperature fluctuations. The mercury thread of the Beckman thermometer fluctuated continuously over a range of 0.5° making it impossible to take an accurate reading. Apparently the heating apparatus required adjusting. By this time all of the material had been used up and it was decided to save the original yellow product for further investigations along different lines.

DEGRADATION OF THE YELLOW COMPOUND WITH KOH.

Three grams of the yellow compound were dissolved in alcohol producing a yellow solution. 80 c.c. of a 20% KOH solution were added causing the solution to turn pink. The mixture was refluxed over a free flame. As the boiling was continued the color gradually became dark red. After four hours it was noticed that the color did not change any more, and the heating was stopped. Most of the alcohol was removed by distillation and after cooling, the remaining liquid was shaken with ether and the ethereal solution separated. The ethereal solution was red and the aqueous solution remained yellow. The ether was distilled off leaving a red liquid, which upon further distillation yielded a colorless liquid which boiled at 183° and had the odour of aniline.

It was shown that this oil was aniline by its boiling point, bleaching powder test, and the azo- β -naphthol derivative which melted at 130° .

Therefore one degradation product is aniline.

The aqueous mother liquor from which the aniline was removed was acidified with dilute HCl and again shaken with ether. All the yellow color entered the ether leaving a colorless aqueous solution which was drawn off. The water was removed by distillation leaving a white solid in the flask. This was identified as inorganic KCl.

The ether was removed from the ethereal solution, leaving a white solid upon which the following tests were made:

Melting point; did not melt., sublimed at 200° .

Na fusion indicated that nitrogen was not present.

Insoluble in cold water, sparingly soluble in hot water, solution acidic to litmus.

Liberates CO_2 readily from NaHCO_3 .

Decolorizes acid KMnO_4 .

This substance is therefore an unsaturated acid, presumably a derivative of, or related to maleic acid. The sublimation of the compound suggested fumaric acid and it was actually shown to be this by preparing the p-nitro-benzyl-ester which melted at 150° . The same derivative of known fumaric acid was prepared which also melted at 150° and a mixture of the two melted at the same temperature.

Therefore the second degradation product is fumaric acid.

Searching through Beilstein it was found that maleic acid mono-anilide $C_6H_5-NH-CO-CH=CH-COOH$, resembled the yellow substance resulting from the reaction between cinnamal-aniline and maleic anhydride. A comparison between the two compounds is given below.

Maleic acid mono-anilide.

Melting point, 187, 198.

Breakdown products with KOH are aniline and fumaric acid.

Color- yellow



C = 62.82%

H = 4.71%

N = 7.33%

Yellow compound.

Melting point 195°.

Breakdown products with KOH are aniline and fumaric acid.

Color - yellow



C = 62.49%

H = 4.51%

N = 7.39%

PREPARATION OF MALEIC ACID MONO-ANILIDE.(83).

Aniline and maleic anhydride were dissolved in ether in molecular proportions and the solutions were mixed. The two reacted in the cold yielding the yellow compound. Recrystallized from alcohol. Melting point 196-7°. Mixed melting point of this compound and the original yellow compound 195-6°.

It is thus established that the reaction between cinnamal-aniline and maleic anhydride which has been

described above leads to the formation of cinnamic aldehyde and maleic acid mono-anilide. It is now possible to assign formulae to the various derivatives which have been prepared.

Bromine derivative: $C_6H_5-NH-CO-CHBr-CHBr-COOH$.

Ethyl ester: $C_6H_5-NH-CO-CH=CH-COOC_2H_5$

Bromine derivative of ester: $C_6H_5-NH-CO-CHBr-CHBr-COOC_2H_5$

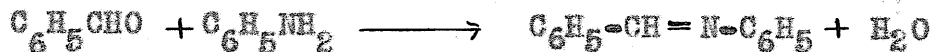
Since both double bonds in the anil did not take part in the reaction, but only the double bond to which the nitrogen was attached, a similar reaction was carried out between benzal-aniline and maleic anhydride. Benzal-aniline contains only the one double bond next to the nitrogen atom which is concerned in the reaction.

PREPARATION OF BENZAL-ANILINE.

20 c.c. Benzaldehyde.

20 c.c. Aniline.

The two substances were mixed and heated on the water bath for one hour. On cooling, crystals of benzal-aniline formed. Recrystallized from alcohol. Melting point 54° .



REACTION BETWEEN BENZAL-ANILIN AND MALEIC ANHYDRIDE.

10 grams benzal-aniline .

6 grams maleic anhydride.

Molecular proportions of both substances were

dissolved separately in ether and the two solutions were mixed. The mixture became cloudy at once and deposited a pale yellow solid. Yield 8 grams. Melting point 196° . Mixed melting point of this product and maleic acid mono-anilide $195-6^{\circ}$.

After the solid was removed by filtration, the ether was distilled off and 2.5 grams of benzaldehyde were isolated in the same way as the cinnamic aldehyde was isolated in the previous case. The benzaldehyde was identified by its characteristic smell, boiling point 179° , and its semicarbazone M. P. 214° .

DEGRADATION OF THE YELLOW SOLID OBTAINED FROM BENZAL-ANILINE AND MALEIC ANHYDRIDE.

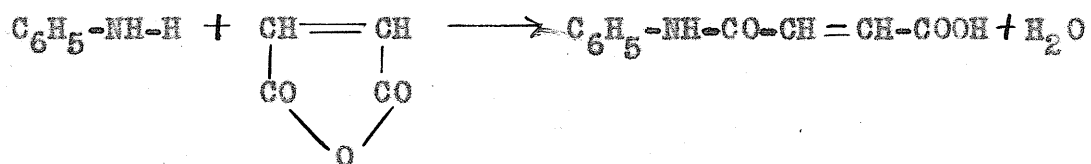
Three grams of the solid were dissolved in alcohol producing a pale yellow solution. 80 c.c. of 20% KOH solution were added and the mixture was refluxed for six hours. The solution gradually turned dark brown. The excess alcohol was distilled off, the remaining solution shaken with ether, and the ethereal solution separated. By fractionally distilling the ethereal solution a small amount of aniline was isolated. The aniline was identified by its boiling point, 185° , bleaching powder test, and the acetyl derivative M. P. 113° .

The aqueous solution from which the aniline was removed was acidified with dilute HCl, shaken with ether, and the ethereal layer removed. From this fumaric acid was isolated and identified as indicated in the previous case.

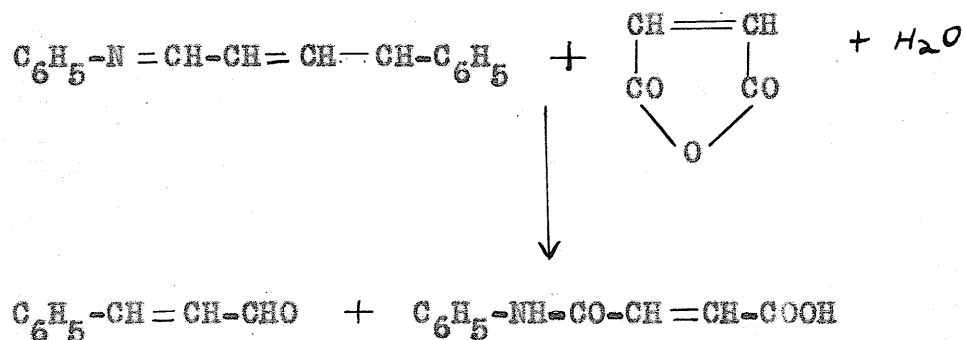
It did not melt but sublimed at about 200°, and the p-nitro-benzyl-derivative melted at 150°.

Thus the same product maleic acid mono-anilide, is obtained from benzal-aniline and maleic anhydride as well as from cinnamal-aniline and maleic anhydride.

The reaction between aniline and maleic anhydride is understandable from the following equation;



But for the reaction between cinnamal-aniline and maleic anhydride, or benzal-aniline and the anhydride, with the production of the same compound and the splitting off of the corresponding aldehydes, it will be seen that one molecule of water is required.



Since no water was added during the reaction, it must have been present in sufficient quantity in the ether for the reaction to take place. The reaction was therefore repeated using dry ether.

REACTION BETWEEN CINNAMAL-ANILINE AND MALEIC ANHYDRIDE
USING DRY SOLVENT.

The procedure was the same as that in the case previously described.

The ether was dried over sodium for 30 hours. The cinnamal-aniline was recrystallized from alcohol and thoroughly dried in a vacuum dessicator for three days. On mixing ethereal solutions of the two, a slow reaction took place compared to the fast reaction observed in the previous case. After 20 minutes a small amount of the yellow product was formed and the smell of cinnamic aldehyde could be detected. Evidently this represents imperfect drying and the faintest trace of water will cause the reaction to take place as indicated in the equation above. To show that water was the influencing factor, one drop of water was added to the flask and shaken. A large amount of the yellow product formed immediately.

An attempt was therefore made to obtain a perfectly dry solvent. Ether was dried over sodium for seven days, during which time the sodium was replaced several times by fresh sodium. The ether was finally distilled over CaCl_2 . Etheral solutions of the dry components were now mixed and allowed to stand. No immediate reaction took place. The flask was tightly stoppered and allowed to stand for three days. An insignificant amount of solid was formed. Sufficient product was obtained to give a melting point of 196° . The ether was evaporated in a vacuum dessicator and the original anil and aldehyde were recovered unchanged.

Similar results were obtained with dry benzal-aniline and maleic anhydride.

Similar results were obtained using dry benzene as the solvent.

Aniline and maleic anhydride on the other hand, reacted immediately even in dry ether to produce maleic acid mono-anilide.

REACTION BETWEEN CINNAMAL-ANILINE AND MALEIC ANHYDRIDE
IN THE PRESENCE OF ANHYDROUS $AlCl_3$

Molecular proportions of cinnamal-aniline and maleic anhydride were dissolved separately in dry benzene. $AlCl_3$ was added to the anhydride solution and then the anil. On mixing, the solution turned red and after standing 30 minutes a solid started to separate out. After standing three days the benzene was filtered off from the solid and evaporated in a vacuum dessicator. A solid mixture was left which consisted of transparent flakes and yellow - brown powder. Separation by fractional crystallization from various solvents was unsuccessful. A little of each product was separated by hand with the aid of a lens and ~~was~~ identified as original maleic anhydride and cinnamal-aniline by their respective melting points. This portion, therefore, did not react.

The first solid which formed was colored red. It

was successively treated with water, dilute HCl, and finally with water to remove $AlCl_3$.

In a search for a suitable recrystallizing solvent it was found that acetone dissolved out the red material leaving a white solid behind, which did not dissolve even on boiling. This white compound was found to be an inorganic residue containing aluminum and was not investigated further.

The red acetone solution was removed and the acetone evaporated in a vacuum desiccator. A yellow solid in small yield was obtained which melted at $146-148^\circ$. It is soluble in alcohol, acetone, and chloroform giving a yellow solution in each case, and is decomposed by boiling HCl. More work will have to be done on this compound before a statement can be made with regard to its structure.

REACTION BETWEEN CINNAMAL-ANILINE AND MALEIC ANHYDRIDE
IN THE ABSENCE OF SOLVENT.

10 grams cinnamal-aniline.

4.5 grams maleic anhydride.

The cinnamal-aniline and maleic anhydride were mixed as solids in a dry flask fitted with an air condenser and warmed in an oil bath at temperatures ranging from 120° to 200° , and for periods of time ranging from a few minutes to one hour. In each case the same product was obtained but it was finally found that heating the components for 15 minutes at 190° was the most satisfactory procedure.

As the temperature was raised the maleic anhydride

melted first at 53° and then the cinnamal-aniline melted at 108° (Approximately). All was liquid now and remained so until the temperature reached 120° when everything suddenly solidified. On raising the temperature to 190° the solid did not melt again but frothed in the flask.

The solid obtained was dark red in color. On re-crystallizing from alcohol a brown powder was obtained which melted at $222-224^{\circ}$ to a dark red liquid. Yield quantitative.

This compound decolorized acid $KMnO_4$, bromine water, liberated CO_2 from $NaHCO_3$, was insoluble in dilute HCl and soluble in dilute KOH. In dilute KOH it was soluble with difficulty, but when the solid was dissolved in alcohol and then KOH added it remained in solution. When this solution was then acidified with dilute HCl the original product was thrown out of solution. In addition to indicating thus that the substance is acidic in nature this was found to be good method of obtaining the product in a pure state.

ANALYSIS OF THE FUSION PRODUCT.

The percentage of nitrogen was estimated by the Kjeldahl method and the following results were obtained.

First determination 4.33% nitrogen

Second determination 4.14% nitrogen

Mean 4.24% nitrogen

Carbon and Hydrogen determinations.

First determination.

Weight of KOH bulb after combustion	69.0830	gms.
Weight of KOH bulb before combustion	<u>68.5920</u>	"
Increase due to CO ₂	0.4910	"

Weight of CaCl ₂ tube after combustion	43.0878	gms.
Weight of CaCl ₂ tube before combustion	<u>43.0070</u>	"
Increase due to H ₂ O	0.0808	"

Weight of combustion boat plus sample	5.1446	gms.
Weight of combustion boat	<u>4.9672</u>	"
Weight of sample	0.1774	"

$$\text{Percentage of hydrogen} = \frac{2 \times .0808 \times 100}{18 \times .1774} = 5.06\%$$

$$\text{Percentage of carbon} = \frac{12 \times .4910 \times 100}{44 \times .1774} = 75.34\%$$

Second determination.

Weight of CaCl ₂ after combustion	43.2020	gms.
Weight of CaCl ₂ tube before combustion	<u>43.0918</u>	"
Increase due to H ₂ O	0.1102	"

Weight of KOH bulb after combustion	69.7516 gms.
Weight of KOH bulb before combustion	<u>69.0920</u> "
Increase due to CO ₂	0.6596 "
Weight of combustion boat plus sample	5.2030 gms.
Weight of combustion boat	<u>4.9680</u> "
Weight of sample	0.2350 "

$$\text{Percentage of hydrogen} = \frac{2 \times .1102 \times 100}{18 \times .2350} = 5.21\%$$

$$\text{Percentage of carbon} = \frac{12 \times .6596 \times 100}{44 \times .2350} = 76.54\%$$

These analyses are in good agreement with the calculated values of the product which would be obtained if a diene synthesis took place between cinnamal-aniline and maleic anhydride. The calculated values given below are based on formula A_c given on page 48.

	<u>Found</u>	<u>Calculated</u>
Nitrogen	4.24%	4.59%
Hydrogen	5.06%	4.92%
Carbon	75.34%	74.75%

This compound is still under investigation at the present time and more information about it will have to be obtained in order to ascertain whether this compound is the result of a Diene Synthesis.

PREPARATION OF CINNAMAL-O-TOLUIDINE.

56 grams cinnamic-aldehyde.

42 grams o-toluidine.

Both substances were purified by distillation, cooled, and mixed in molecular proportions. A yellow compound formed immediately with the evolution of much heat. Recrystallization from alcohol yielded yellow flakes. Yield 57 grams. Melting point 74° .

REACTION BETWEEN CINNAMAL-O-TOLUIDINE AND MALEIC ANHYDRIDE.

33 grams cinnamal-o-toluidine.

26 grams maleic anhydride.

Molecular proportions of the two substances were dissolved separately in ether producing a yellow and colorless solution respectively. On mixing the two solutions the color slowly turned red. Thirty minutes after mixing a light yellow solid started to separate from solution and continued to do so for two hours. The reaction can be hastened by refluxing the components in ethereal solution for twenty minutes, cooling, and scratching the inside of the flask with a glass rod to start crystallization of the product. This product is soluble in ether to a certain extent and the yield can therefore be increased by concentrating the solution. The red ethereal solution was filtered off, and the solid recrystallized from alcohol.

Yield 15 grams.

Melting point 118° .

This will be referred to as the light yellow solid.

The red ethereal solution was distilled under reduced pressure. After the ether was removed a pale yellow liquid came over at 132° under 23 mm. pressure. This was identified as cinnamic aldehyde by its characteristic smell, boiling point, and semicarbazone which melted at 214° .

DEGRADATION OF THE LIGHT YELLOW PRODUCT WITH KOH.

Three grams of the light yellow solid were dissolved in alcohol producing a colorless solution. 80 c.c. of a 20% KOH solution were added and the mixture refluxed for six hours. During the boiling the solution assumed a dark red color. The excess alcohol was removed by distillation, the remaining solution shaken with ether, and the ethereal layer separated. From the ethereal solution o-toluidine was separated by fractional distillation. The toluidine was identified by its boiling point 196° , and the benzoyl derivative which melted at 143° .

The aqueous solution from which the o-toluidine was removed was acidified with dilute HCl, and extracted with ether. From the ethereal solution a white solid was obtained which was identified as fumaric acid just as in the previous cases mentioned. It did not melt but sublimed at 200° , and the p-nitro-benzyl-ester melted at 150° .

The reaction between cinnamal-o-toluidine and maleic anhydride is analogous therefore, to the former reactions described between unsaturated anils and maleic anhydride when carried out in wet solvents. In this case maleic acid mono-o-toluidide $\text{CH}_3\text{-C}_6\text{H}_5\text{-NH-CO-CH=CH-COOH}$ FORMED. This is a homologue of the compound obtained from cinnamal-aniline and maleic anhydride and is described in the literature (84).

ANALYSIS FOR NITROGEN BY COMBUSTION METHOD.

First determination:

Weight of watch glass plus sample	6.9820 gms.
Weight of watch glass	<u>6.8013</u> "
Weight of sample	0.1807 "

Volume of nitrogen collected 11.6 c.c.

Barometer reading 744 mm.

Temperature 20° C.

Percentage of nitrogen $= \frac{11.6 \times 273 \times 744 \times .126}{293 \times 760 \times .1807} = 7.38\%$

Second determination;

Weight of watch glass plus sample	6.9944 gms.
Weight of watch glass	<u>6.8014</u> "
Weight of sample	0.1930 "

Volume of nitrogen collected 12.1 c.c.

Barometer reading 740 mm.

Temperature 21°.

Percentage of nitrogen $-\frac{12.1 \times 273 \times 740 \times .126}{294 \times 760 \times .1930} = 7.14\%$

Mean percent nitrogen 7.26%

Percent nitrogen calculated from formula 6.83%

NOTE: Absolutely complete absorption of the CO₂ by the KOH is never reached in a combustion. This unabsorbed gas is actually a fine froth of CO formed by the action of the heat hot copper spiral upon the carbon dioxide. This volume of gas is usually equivalent to about 0.3% of nitrogen on a 0.2 gram of sample, leading to a correspondingly high analytical result.

PREPARATION OF MALEIC ACID MONO-O-TOLUIDIDE (84).

Maleic anhydride and aniline were mixed in molecular proportions and the pale yellow compound formed immediately. Recrystallized from alcohol. Melting point 118°.

Mixed melting point of this product and that obtained from cinnamal-o-toluidine and maleic anhydride 118° .

The procedure as outlined above was repeated using perfectly dry ether as solvent. The components were mixed and allowed to stand for five days. No reaction took place. The ether was removed in a vacuum dessicator and the unchanged original substances, maleic anhydride and cinnamal-o-toluidine were recovered. Therefore the reaction does not take place in the absence of water.

Maleic anhydride and o-toluidine however, react even in dry ether. The explanation for this case is the same as that given for the cinnamal-aniline reaction.

PREPARATION OF BENZAL-P-PHENETIDINE.

26 grams p-phenetidine.

20 grams benzaldehyde.

The two substances were mixed in a beaker, stirred, and allowed to stand for a few minutes. White needles of the anil were produced. Recrystallized from alcohol.

Melting point 75° .

Yield 33 grams.

REACTION BETWEEN BENZAL-P-PHENETIDINE AND MALEIC ANHYDRIDE.

10 grams benzal-p-phenetidine.

4.5 grams maleic anhydride.

The reaction was carried out just as in the former cases described. A yellow solid formed and was recrystallized from alcohol.

Yield 7 grams.

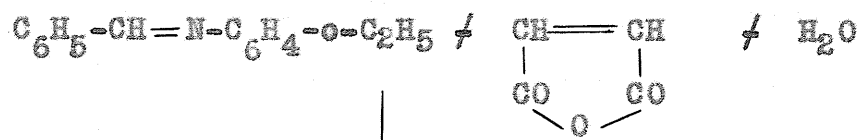
Melting point $181-2^{\circ}$.

From the ethereal solution, from which the above product was removed, benzaldehyde was isolated by fractional crystallization. The aldehyde was identified by its distinct smell, its boiling point 179° , and the semicarbazone melting point 215° .

This reaction ~~too~~ was repeated using dry ether as solvent. After standing three days only a very small amount of the solid had formed. This probably represents imperfect drying of the solvent. From the ethereal solution unchanged benzal-p-phenetidine and maleic anhydride were recovered.

The yellow solid obtained in the first reaction proved to be maleic acid mono-p-phenetidide. The latter compound was also prepared from p-phenetidine and maleic anhydride by simply mixing ethereal solutions of the two at room temperature. They reacted at once to give the same compound which melted at 182° . A mixed melting point of this compound and the one obtained above was also 182° .

The reaction between benzal-p-phenetidine and maleic anhydride can therefor be represented as shown below. This formulation requires water and is in complete analogy with the other reactions described.



SUMMARY

SUMMARY.

The historical development of the Diene Synthesis has been given and its wide application to synthesis and determination of structure indicated.

The type of reaction that takes place between unsaturated anils and maleic anhydride in the presence of water has been studied and the course of the reaction has been determined. It has also been shown that in the absence of water no reaction takes place.

A compound different than that obtained in the above reaction was obtained from cinnamal-aniline and maleic anhydride in dry solvent and in the presence of $AlCl_3$. Lack of time prevented a full investigation of this compound.

Still another compound was obtained from cinnamal-aniline and maleic anhydride when the two substances were fused above their melting points. This compound indicates that a Diene Synthesis may have taken place between the components and that it is the result of a 1,4-addition. This compound is going to be investigated further.

BIBLIOGRAPHY

1. Euler and Josephson; Ber. 52 822 (1920).
2. Diels and Alder; Annalen 460 98 (1928).
3. Sachse; Ber. 23 1563 (1890).
4. Bayer; Ber. 18 2277 (1885).
5. Mohr; J. Prakt. Chem. 103 316 (1922).
6. Aschan; Acta. Soc. Scient. Fennica.
21 No. 5 123 Helsingfors (1895).
7. Kistiakowski and
Lecher; J. Am. Chem. Soc. 58 123 (1936).
8. Albrecht; Annalen 348 31 (1906).
9. Staudinger; Die Ketene page 59 Stuttgart (1912).
10. Staudinger; Annalen 467 73 (1928).
11. Diels; Z. Angew. Chem. 42 480 913 (1929).
12. Diels Blom and Koll; Annalen 443 242 (1925).
13. Diels and Alder; Ber. 62B 554 (1929).
14. Diels Alder Peterson
and Querberitz; Annalen 478 137 (1930).
15. Thiele; Annalen 306 87 (1899).
16. Thiele; Annalen 308 333 (1899).
17. Diels; Ber. 69A 194 (1936).
18. Diels Alder and Pries; Ber. 62B 2081 (1929).
19. Gilman; Organic Chemistry vol. II page 1692.
John Wiley and Sons (1938).
20. Farmer and Warren; J. Chem. Soc. 897 (1929).
21. Lehmann and Paasche; Ber. 68 1068 (1935).
22. Diels Alder and
Winckler; Annalen 490 267 (1932).
23. Wagner-Jauregg and
Helmert; Ber. 71 2525 (1938).

24. Kohler and Kable; J. Am. Chem. Soc. 57 917 (1935).
25. Kuhn and Wagner-
Jauregg; Ber. 63 2662 (1930).
26. Allen and Spanagel; Can. J. Res. 8 414 (1933).
27. Allen and Sheps; Can. J. Res. 11 171 (1934).
28. Diels Alder and
Nienberg; Annalen 486 91 (1931).
29. Alder and Windemouth; Ber. 71 1939 (1928).
30. Diels, Alder, Nienberg,
and Schmalbeck; Annalen 490 243 (1932).
31. Alder and Rickert; Ber. 70B 1354 (1937).
32. Diels, Alder, and
Muller; Annalen 490 257 (1932).
33. Diels, Alder, and
Winter; Annalen 486 211 (1931).
34. Diels Alder Winckler
and Peterson; Annalen 498 1 (1932).
35. Diels, Alder, and
Lubbert; Annalen 490 277 (1932).
36. Fischer; Ber. 19 2988 (1886).
37. Freund and Lebach; Ber. 38 2640 (1905).
38. Mohlau and Redlich; Ber. 44 3605 (1911).
39. Diels Alder Kashimoto
Eckardt and Klare; Annalen 498 16 (1932).
40. Diels, Alder,
Friedrichsen, Klare,
Winkler and Schrum; Annalen 505 103 (1933).
41. Diels, Alder,
Friedrichsen, Peterson,
Brodersen, and Kech; Annalen 510 89 (1934).
42. Diels and Kech; Annalen 519 140 (1935).

43. Diels and Pistor; Annalen 530 87 (1937).
44. Diels and Harms; Annalen 525 73 (1936).
45. Diels and Moller; Annalen 516 45 (1935).
46. Diels and Alder; Annalen 470 62 (1929).
47. Diels, Alder, and Peterson; Annalen 486 202 (1931).
48. Diels and Schrum; Annalen 530 68 (1937).
49. Fieser and Fieser; J. Am. Chem. Soc. 57 1679 (1935).
50. Fieser and Hershberg; J. Am. Chem. Soc. 57 2192 (1935).
51. Fieser, Fieser, and Hershberg; J. Am. Chem. Soc. 58 1463 (1936).
52. Cook; J. Chem. Soc. 2524 (1931).
53. Barry, Cook, Hazelwood, Proc. Roy. Soc. (London)
Hewett, Rieger, and 117 B 318 (1935).
Kennaway;
54. Fieser and Hershberg; J. Am. Chem. Soc. 58 2314 (1936).
55. Fieser and Holmes; J. Am. Chem. Soc. 58 2319 (1936).
56. Barnett and Lawrence; J. Chem. Soc. 1104 (1935).
57. Gruber and Adams; J. Am. Chem. Soc. 57 2555 (1935).
58. Cohen; Nature 136 869 (1935).
59. Cohen; J. Chem. Soc. 429 (1935).
60. Chuang and Han; Ber. 68B 876 (1935).
61. Fieser and Seligman; J. Am. Chem. Soc. 56 2690 (1934).
62. Graebe and Liebermann; Ber. 1 50 (1868).
Ber. 6 63 (1873).
63. Obermuller; J. Pr. (2) 75 1 1907.
64. Bamberger; Annalen 257 52 (1890).
65. Lagerlof; J. Pr. (2) 96 35 (1917).

66. Thiele; Annalen 306 141 (1899).
67. Armstrong; P. Ch. S. 101 (1890).
Hinsberg; Annalen 319 284 (1902).
68. Meyer; Annalen 339 37 (1911).
Annalen 396 133 (1913).
69. Scholl; Ber. 41 2311 (1908).
70. Schlenk; Ber. 47 479 (1914).
71. Auwers; Ber. 53 941 (1920).
72. Auwers and Krollpfeffer; Annalen 430 254 (1923).
73. Diels Alder and Beckmann; Annalen 486 191 (1931).
74. Clar; Ber. 64B 2194 (1931).
75. Diels, Schmidt, and Witte; Ber. 71B 1186 (1938).
76. Lauer and Miller; J. Am. Chem. Soc. 57 520 (1935).
77. Coffman and Carothers; J. Am. Chem. Soc. 55 2040 (1935).
78. Tilden; J. Chem. Soc. 45 410 (1884).
79. Alder and Stein; Annalen 485 223 (1931).
80. Alder and Stein; Annalen 496 204 (1932).
81. Doebner and Miller; Ber. 16 1665.
Peine; Ber. 17B 2117.
82. Bigelow; Amer. Chem. J. 22 (1899) page 280.
83. Anschutz; Ber. 20 3215.
84. Dunlap and Phelps; Amer. Chem. J. 19 page 495.