MALEIC ANHYDRIDE DERIVATIVES

Reactions of the Double Bond

PREFACE

The chemistry of maleic acid and its *trans*-isomer, fumaric acid, has been the subject of studies made by many chemists for more than one hundred and thirty years.

For the last thirty years, during which time maleic anhydride has been freely available from the catalytic oxidation of benzene, industrial chemists have developed a surprisingly wide range of uses for it. Its importance in the production of different types of alkyd resins, of maleinized drying oils, and of various copolymers is well known. Less widely known are its valuable uses in the manufacture of organic pigments, rubber, deemulsifying agents, oil additives, pharmaceuticals, tanning agents, detergents, wetting agents, abrasives, adhesives, cellophane, and other important technical products.

Only small amounts of maleic acid, fumaric acid, or their salts have been employed as such. By far the greatest interest has been centered in the use of maleic anhydride as a building block in chemical synthesis. The many types of reactions which it undergoes are indeed intriguing to the organic chemist. Its structure is ideally suited for synthetic purposes because, if suitable conditions are chosen, any atom in the molecule can be induced to react. Furthermore, the activity of the unsaturated ethylene bond, enhanced by the two adjacent carbonyl groups, is such that it can be depended upon to undergo almost any reaction that is characteristic of unsaturated organic compounds.

We found these characteristic reactions of the carbon-carbon double bond as well as the other reactions of the maleyl group so fascinating that it seemed desirable to gather them together in their simplest book form so that they could be quickly reviewed, much as one might review a series of reference cards. Our discussions with many chemists indicated a very general interest in these reactions, most of which have to do with the double bond. The chemistry of the double bond is indeed basic to the synthesis of almost all industrial organic chemicals, such as dyes, detergents, perfumes, gasolines, and flavors. In this book, selected types of reactions are graphically portrayed on the right-hand pages. Only the reactants and the end products are shown; any attempt to portray the reaction mechanism has been avoided as being beyond this simple presentation.

It is our intention that the reader should be able to thumb through this book until a reaction that interests him is uncovered. Because the reader will wish to know how the products are made, we describe their preparation briefly. The reader will also wish to know what the products are like and what they are used for; that information is given on the facing page. Any more comprehensive information is beyond the scope of our book, but a series of references is given to assist in further study. No reference citations are included in the abbreviated text.

This book is intended for students and research workers interested in synthetic organic chemistry, and for industrial chemists confronted with the problem of finding suitable chemicals to solve specific problems. It is not designed as a textbook to be studied from cover to cover, nor is it in any sense an encyclopedia or a monograph. It is written particularly for the busy investigator who is already overburdened by the rapidly expanding chemical literature, but who likes to browse through chemical reactions looking for thoughts to stir his creative imagination.

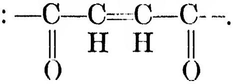
LAWRENCE H. FLETT
WILLIAM HOWLETT GARDNER

July, 1952

CONTENTS

Introduction

This book consists of a simplified presentation of 116 different types of chemical reactions involving maleic anhydride or one of its simple unsaturated derivatives. The reaction is given whether it takes place with maleic acid, fumaric acid, their esters, amides, or other unsaturated derivatives. In most cases the reactions can be carried out with any one of them; collectively, they are referred to as having the maleyl group:



$$-\underset{\underset{O}{\|}}{C}-\underset{H}{C}=\underset{H}{C}-\underset{\underset{O}{\|}}{C}-.$$

Each reaction selected has been treated as the representative of a particular type. The reactions are grouped into chapters according to the elements contained in the compound reacting with the maleyl group. Those containing only carbon and hydrogen are to be found in the first chapter. This chapter is followed by chapters on compounds containing other elements arranged in alphabetical order. Reactions with bromine, chlorine, or compounds containing these elements are covered in the chapter on halogen compounds. Those reactions involving metallic catalysts that take a prominent part in the reaction, such as Friedel-Craft catalysts, sodium alkoxides, and the like, appear in the chapter on metallic compounds. Many other valid classifications could have been chosen. A brief discussion of the various reactions within each group introduces each chapter.

Every effort has been made to keep the format as simple as possible. Each preparation is confined to a set of two open pages, with the net equation and a brief description of the method appearing on the right-hand page. Comments, a description of the reaction products, and possible uses are given on the left-hand page.

The class of compounds reacting with maleic anhydride or its derivatives is shown in the upper right-hand corner of the right-hand pages, as illustrated in the figure on page 3. In the left-hand corner of the page is a general formula for the group to which the reactant belongs. Only one reaction is given for the group, unless the reactants yield different products under varied experimental conditions, as, for example, is the case with the Grignard reagents. In such cases, separate preparations are included for each different type of reaction.

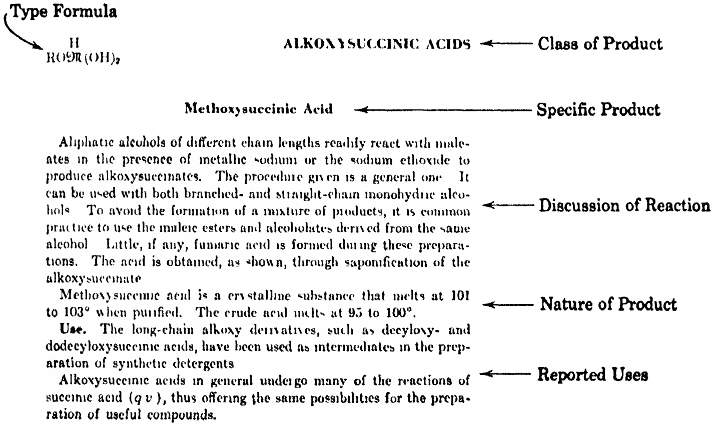
The specific reactant selected as being typical of the class is shown in the center of the page. In most cases this is the simplest member of the series. Because chemical reactions are most easily understood by studying the structural formulas of the reactants and the reaction product, the net equation is given directly below the name of the reactant.

Anyone interested in a particular reaction will then wish to know how it is carried out. Beneath the equation, there is a brief description of the preparation selected directly from the literature. This is not intended as a laboratory procedure. Those undertaking the preparation should first consult the original references.

After the description of the reaction, there are a few selected references to assist the reader who wishes to pursue the study of any reaction beyond the scope of this book. The first reference is the source of the method. To this has been added a list of selected references covering not only the method of preparation and the properties, but also the possible uses of the product. Most of the patent numbers cited pertain to uses.

The arrangement of the opposite or left-hand page is similar to that of the right-hand one. In the right-hand corner is given the class of product formed from the class of reactants shown in the same corner of the opposite page. In the illustration on this page, for example, alkoxysuccinic anhydrides are formed from aliphatic alcohols.

The left-hand corner of the left page in a similar manner shows a general formula for the products. This formula is designed to indicate at a glance what has been added, by the reaction, to the maleyl group. The following symbols have been employed in both sets of general



$RO\overset{H}{\mathfrak{M}}(OH)_2$

ALKOXYSUCCINIC ACIDS

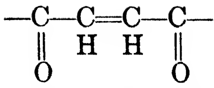
Methoxysuccinic Acid

Aliphatic alcohols of different chain lengths readily react with maleates in the presence of metallic sodium or the sodium ethoxide to produce alkoxysuccinates. The procedure given is a general one. It can be used with both branched- and straight-chain monohydric alcohols. To avoid the formation of a mixture of products, it is common practice to use the maleic esters and alcoholates derived from the same alcohol. Little, if any, fumaric acid is formed during these preparations. The acid is obtained, as shown, through saponification of the alkoxysuccinate.

Methoxysuccinic acid is a crystalline substance that melts at 101 to 103° when purified. The crude acid melts at 95 to 100°.

Use. The long-chain alkoxy derivatives, such as decyloxy- and dodecyloxysuccinic acids, have been used as intermediates in the preparation of synthetic detergents.

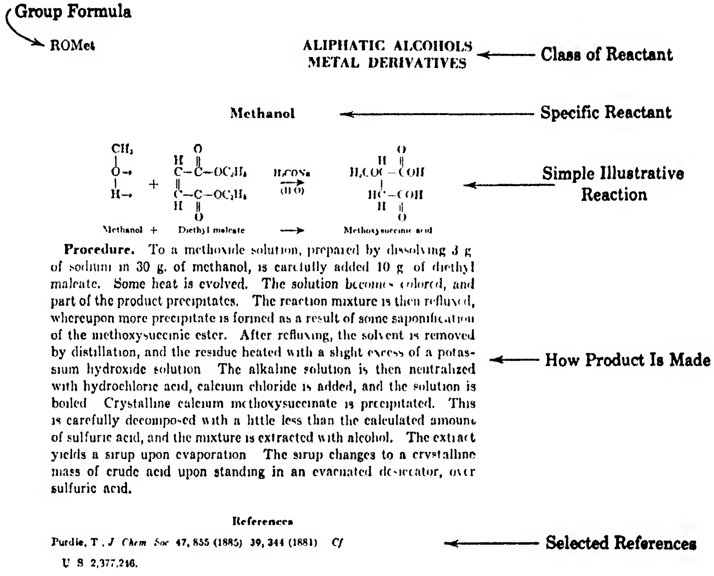
Alkoxysuccinic acids in general undergo many of the reactions of succinic acid (*q v*), thus offering the same possibilities for the preparation of useful compounds.



formulas: $\mathfrak{M}$ represents the maleyl grouping, $\underset{O}{\overset{\|}{—C}}—\underset{H}{C}=\underset{H}{C}—\underset{O}{\overset{\|}{C—}}$, which is present in maleic anhydride and each of the maleic derivatives used as reactants in these preparations. Maleic anhydride is thus represented by the combination $\mathfrak{M}>O$; maleic or fumaric acid by $\mathfrak{M}(OH)_2$; and their esters by $\mathfrak{M}<^{OR}_{OH}$ or $\mathfrak{M}(OR)_2$. Groups adding to the double bond to produce succinic acid derivatives are shown above or to the left of the symbol $\mathfrak{M}$, viz., $H_2=\mathfrak{M}>O$, $R\mathfrak{M}(OH)_2$, etc. Different alkyl groups are indicated by R, R′, R″, etc.; aryl substituents by Ar; halogens by X; and metals by Met. The chemical symbols have their usual significance when in combination with these symbols.

On the next line is the name of the specific product formed in the selected preparation. This is followed by general comments on the method of preparation, the reaction, and a brief description of the product itself. The page is concluded with a discussion of uses, not only of the product but of homologous compounds that may be prepared by this method.

Names of the chemicals are as far as possible those used in the latest edition of *Chemical Abstracts*. All temperatures refer to the Centigrade scale.



ROMet

**ALIPHATIC ALCOHOLS
METAL DERIVATIVES**

Methanol

$$\begin{array}{c}CH_3\\|\\O\rightarrow\\|\\H\rightarrow\end{array} + \begin{array}{l}\overset{H}{C}—\overset{O}{\overset{\|}{C}}—OC_2H_5\\ \|\\ \underset{H}{C}—\underset{O}{\underset{\|}{C}}—OC_2H_5\end{array} \xrightarrow[(H_2O)]{H_3CONa} \begin{array}{l}H_3CO\overset{H}{C}—\overset{O}{\overset{\|}{C}}OH\\ \quad\;\;|\\ \quad\underset{H}{HC}—\underset{O}{\underset{\|}{C}}OH\end{array}$$

Methanol + Diethyl maleate ⟶ Methoxysuccinic acid

Procedure. To a methoxide solution, prepared by dissolving 3 g of sodium in 30 g. of methanol, is carefully added 10 g of diethyl maleate. Some heat is evolved. The solution becomes colored, and part of the product precipitates. The reaction mixture is then refluxed, whereupon more precipitate is formed as a result of some saponification of the methoxysuccinic ester. After refluxing, the solvent is removed by distillation, and the residue heated with a slight excess of a potassium hydroxide solution The alkaline solution is then neutralized with hydrochloric acid, calcium chloride is added, and the solution is boiled Crystalline calcium methoxysuccinate is precipitated. This is carefully decomposed with a little less than the calculated amount of sulfuric acid, and the mixture is extracted with alcohol. The extract yields a sirup upon evaporation The sirup changes to a crystalline mass of crude acid upon standing in an evacuated desiccator, over sulfuric acid.

References

Purdie, T. *J Chem Soc* 47, 855 (1885) 39, 344 (1881) *Cf* U S 2,377,246.

CHAPTER
1

Hydrocarbons

This chapter describes the reactions of maleyl compounds with various types of hydrocarbons. The different hydrocarbons react in one manner or another to saturate the ethylene bond of the maleyl group.

With mono-olefins, such as propene and its higher homologs, a methylene carbon adjacent to the unsaturated ethylene group adds to one of the carbons of the double bond of the maleyl reactant. This is accompanied by transfer of a hydrogen from the reacting methylene group to the other carbon of the double bond. Alicylic mono-olefins, non-conjugated polyolefins, and non-conjugated olefins containing unreactive substituents, such as some of the fatty esters, behave similarly. Polyolefins containing unsaturated bonds separated by only a single methylene group generally undergo partial conversion to the conjugated isomers during this addition, giving rise to mixed types of products, as described under *Maleinized Oils* in Chapter 6, page 192. Such would be expected, since conjugated hydrocarbons react in a different manner as outlined below.

The resonating aromatic ring in alkylaromatic compounds, like toluene and its homologs, apparently serves to activate the adjacent methyl group in much the same manner as the double bond of the olefin activates the methylene group. If all the hydrogens of the methyl group are replaced by substituents, no reaction occurs, as in the case cited, with *tert*-butylbenzene.

Conjugated polyolefinic hydrocarbons add far more readily to maleyl compounds than do the non-conjugated types. In most instances, reaction easily takes place at temperatures below 100°, in contrast to most of the above reactions. In the case of conjugated dienes, for example, addition occurs between the terminal carbons of the diene grouping and those of the ethylene bond of the maleic reactant to yield tetrahydrophthalic acids or similar alicyclic adducts. These reactions are known as the Diels-Alder syntheses. The products contain a single unsaturated group in what was the 2-position of the original diene grouping. Various types of conjugated chain polyenes, cyclic conjugated dienes, certain arylvinyls, aromatics lacking a complete Kekulé structure such as anthracene, highly methylated naphthalenes, and dienynes react in this manner.

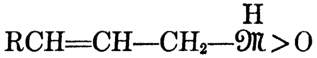
The reaction of arylvinyls, such as 1-vinylnaphthalene, is particularly interesting, since it is an example of how the conjugation may be furnished in these reactions by one of the unsaturated groups of an aromatic ring adjacent to an ethylene bond. Compounds containing the dienyne group, —CH═CH—C≡C—CH═CH—, react as if they were tetraenes in these reactions to give derivatives of 1,2,3,5,6,7-hexahydronaphthalene. Several other interesting modifications where the reactants contain other elements are described in the chapters which follow.

Hexaphenylethane, in contrast, appears to react by dissociating into its triphenylmethyl free radicals that add to both carbons of the ethylene bond of the maleyl compound. Similar α,β-bis-substituted succinic acid derivatives are produced by hexaphenyldilead, and by carbon tetrachloride in the presence of benzoyl peroxide.

Ethylene and compounds containing a vinyl group generally do not react with maleyl compounds except in the presence of polymerization catalysts. Under such conditions, the major products of the reactions are copolymers that are formed by the hydrocarbon uniting to produce bridges between the ethylene carbons of separate maleyl molecules. Such carbon-carbon linked bridges are formed at both carbons of the ethylene bond to give products of long chain structures. Resinous materials of a similar nature are also produced as by-products in other reactions described in this chapter.

Included also in this chapter is the polymerization of maleates because of the close similarity to the reaction with ethylene. This particular reaction might have been included in Chapter 6, since maleates are carboxy-substituted ethylenes. It seemed desirable, however, to make an exception in the arrangement in this case.

Products containing groups derived from both the catalyst and the solvents have been found among the products of these polymerization reactions, indicating that several different side reactions may also take place during these polymerizations. It has been shown that these reactions take place by a kinetic chain mechanism, apparently involving the formation of free radicals [Marvel, Prill, and De Tar, *J. Am. Chem. Soc.* **69,** 52 (1947)].



$RCH{=}CH{-}CH_2{-}\overset{H}{\mathfrak{M}}{>}O$

ALKENYLSUCCINIC ANHYDRIDES

Allylsuccinic Anhydride

The procedure given on the opposite page is a general one. It may be used also for preparing branched-chain alkenyl, cycloalkenyl, and non-conjugated polyenyl derivatives of succinic anhydride. Use of a solvent is convenient but not always essential, but high temperatures are required unless a small amount of a catalyst, such as a peroxide or a finely divided metal, is added. Small amounts of iodine produce saturated products, probably cycloalkylsuccinic anhydrides. Various amounts of resinous polymers are also formed. It is good practice to use freshly distilled olefins and to dissolve the anhydride completely before raising the temperature to 250°.

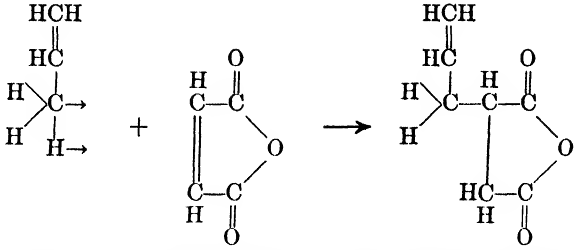
The addition of the olefin to the maleic compound usually occurs at one of its α-methylene carbons, as has been pointed out; but the ethylene bond may shift during this addition if other unsaturated groups are present in the olefin. This is the case with allylbenzene and biallyl. These compounds therefore yield 3-phenylallyl- and 2,5-hexadien-1-ylsuccinic anhydrides, respectively. These exceptions may readily be explained if a free radical mechanism is assumed for the reaction.

Allylsuccinic anhydride is a colorless oil that has not been solidified. It can be distilled under 16-mm. pressure at 135 to 142°. It is insoluble in water, but is slowly converted to the acid in contact with it. The acid melts at 99 to 100°. With hypobromous acid it yields a bromolactone.

Uses. Alkenylsuccinic anhydrides are valuable intermediates in the manufacture of certain synthetic detergents. The acids have been used as rust-inhibiting agents in lubricants. Ethylene esters have been employed in emulsions used for oiling textiles, in the treating of leather, and in the preparation of hard-water-soluble oils. Alkyl esters yield plasticizers for vinyl chloride copolymers.

When hydrogenated, alkenylsuccinic anhydrides produce the saturated alkyl derivatives, and when oxidized they yield carballylic or other tribasic acids. Most of them can be readily lactonized with sulfuric acid at normal temperatures.

Propene



Propene + Maleic anhydride ⟶ Allylsuccinic anhydride

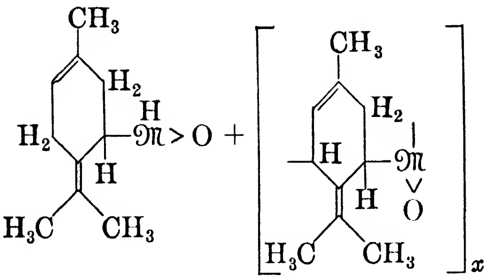
Preparation. A solution of 50 g. of maleic anhydride and 40 g. of propene in 50 ml. of benzene is allowed to react for 12 hours at 250° in an autoclave. This produces a maximum overpressure of 74 atmospheres. After the reacted mixture is cooled, the pressure is 13 atmospheres.

The product is a mixture containing a dark brittle resin, maleic anhydride and allylsuccinic anhydride. It is distilled under reduced pressure at 16 mm. The 44 g. of unreacted maleic anhydride distills below 132°, and the allylsuccinic anhydride is obtained at 135 to 142°. The yield of allylsuccinic anhydride is 26 g. or 35% of theory.

Homologs of propene react more easily, giving yields of 70 to 80% of theoretical amounts of substituted succinic anhydrides.

References

Alder, K., Pascher, F., and Schmitz, A., *Ber.* **76B**, 27 (1943). *Cf.*:
Arnold, R. T., and Dowdall, J. F., *J. Am. Chem. Soc.* **70**, 2590 (1948).
Farmer, E. H., *Trans. Faraday Soc.* **38**, 340 (1942).
Rodestvedt, C. S., Jr., *Org. Syn.* **31**, 85 (1951).
U.S. 2,055,456; 2,124,628; 2,133,734; 2,230,005; 2,294,259; 2,297,039; 2,380,699; 2,381,852; 2,402,825; 2,411,215; 2,440,985; 2,452,321; 2,454,862; 2,467,958; 2,527,081; 2,561,232; Fr. 801,919.



3-Terpinolenesuccinic Anhydride

The reaction of terpinolene with maleic anhydride is typical of non-conjugated monocyclic hydrocarbons. All the terpenes yield mixtures of monomers and resinous polymers. Rearrangement to a conjugated terpene takes place very readily if small amounts of maleic acid or other acids are present in the anhydride. When this occurs, the reaction product also contains relatively large proportions of the crystalline Diels-Alder addition product of α-terpinene (*q.v.*).

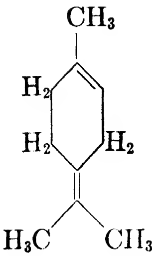
3-Terpinolenesuccinic anhydride is a pale yellow oil. When crystallized it melts at 182°. That it contains two ethylene bonds, in contrast to one of the Diels-Alder adduct, has been proved by ozonolysis and hydrogenation. Terpinolenesuccinic anhydride serves as a plasticizer for the resin formed during its preparation.

Uses. The reaction described here is utilized commercially in the production of products sold under the trade name Petrex Acid.* This acid is a uniform mixture of 50% monomer and 50% polymer. The acid is used in the manufacture of Petrex Resins, which have a number of unique properties. These resins are employed for various industrial purposes.

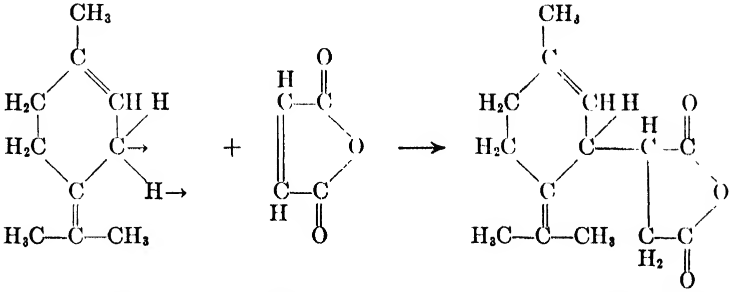
Terpenesuccinic anhydrides offer several possibilities for preparing many new and useful compounds as, for example, agents for controlling the vulcanization of rubber.

---

* Hercules Powder Company.



Terpinolene



Terpinolene + Maleic anhydride → 3-Terpinolenesuccinic anhydride

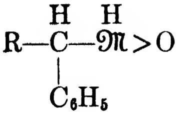
Procedure. A mixture of 68 g. of pure terpinolene and 49 g. of acid-free maleic anhydride is heated with good agitation to 185°. The reaction mixture is then allowed to reflux for 1 to 2 hours. The vigorous reaction is largely completed during the first half hour, as shown by the disappearance of the two layers and the rise in boiling temperature. The mixture is then distilled under reduced pressure. The portion b_{14} 180 to 200° is dissolved in a potassium hydroxide solution by heating the mixture of the two for a short period of time. The unsaponifiable material is removed by filtration, and the solution when cooled is acidified with acid. The oil that separates is dissolved in ether. The ether solution is washed with water, dried, and allowed to evaporate. The oily product so obtained is then allowed to crystallize from a mixture of ethyl acetate and petroleum ether, and recrystallized from ethyl acetate. The yield of pure crystalline adduct is 16%.

The non-volatile portion of the products consists of resinous copolymers ranging in molecular weight from 500 to 3000 and containing an excess of combined anhydride in a ratio of 5:4 to 4:3 moles of maleic anhydride to terpene.

References

Hultzsch, K., *Ber* 72B, 1173 (1939). *Cf.*:
Diels, O., Koch, W., and Frost, H., *Ber.* 71B, 1163 (1938).

U.S. 1,992,249; 1,993,033; 2,047,004; 2,067,859; 2,070,553; 2,080,436; 2,118,925; 2,118,926; 2,268,501; 2,268,524; 2,294,651; 2,298,470; 2,321,750; 2,322,542; 2,354,993; 2,366,317; 2,371,235; 2,411,237. Fr. 842,991



$$R-\underset{C_6H_5}{\overset{H}{C}}-\overset{H}{\mathfrak{M}}>O$$

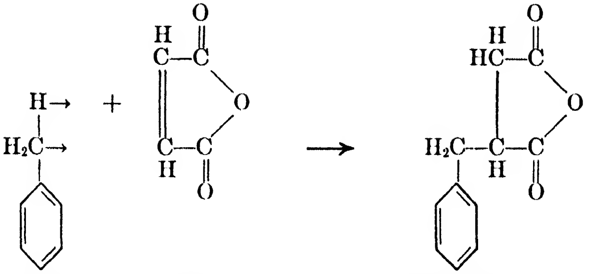
Benzylsuccinic Anhydride

Alkylaromatic hydrocarbons react with maleic anhydride at elevated temperatures under pressure, at the carbon atom adjacent to the aromatic nucleus. In this respect they resemble the mono-olefins in their manner of addition. Compounds that have been found to react in this manner, besides toluene, are ethylbenzene, isopropylbenzene, *p*-xylene, cumene, cymene, tetrahydronaphthalene, 2-methylnaphthalene, diphenylmethane, dibenzyl, fluorene, indan, and acenaphthalene. These reactions apparently involve the formation of free radicals as part of their mechanism. 9-Phenylmethylanthracene and 1,2,3,4-tetramethylnaphthalene react like aromatics (*q.v.*) to give diene-type adducts, whereas *tert*-butylbenzene, lacking an α-methylene group, fails to react.

Benzylsuccinic anhydride is a crystalline solid that melts at 100 to 101°. It dissolves gradually in hot water to produce on cooling a crystalline acid melting at 160 to 161°.

Use. Compounds of similar type of structure to the aralkylsuccinic acids are described as intermediates in the manufacture of dyes, resins, and synthetic detergents.

Toluene



Toluene + Maleic anhydride ⟶ Benzylsuccinic anhydride

Procedure. A solution of 1000 g. of toluene and 98 g. of maleic anhydride is placed in a pressure vessel and heated gradually over a period of a half hour to 305 to 315° and then held at this temperature for 20 minutes. An overpressure of 32 atmospheres is developed. Upon cooling, the mixture becomes lighter in color. The solution is then fractionally distilled to free it of the unreacted toluene and the small amount of maleic anhydride.

References

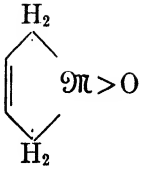
Binapfl, J., Ger. patent 607,380 and 623,338 (1935). Fr. patent 775,363 (1934). *Cf.*: Alder, K., Pascher, F., and Vagt, H., *Ber.* **75B**, 1501 (1942).

Barnett, E. de B., Goodway, N. F., Higgins, A. G., and Lawrence, C. A., *J. Chem. Soc.* **1934**, 1224.

Bickford, W. G., Fisher, G. S., Dollear, F. G., and Swift, C. E., *J. Am. Oil Chem. Soc.* **25**, 251 (1948).

Clar, E., *Chem. Ber. Proof* (*U.S. Dept. Commerce O.T.S., Rept.* PB 52017).

Kloetzel, M. C., Dayton, R. P., and Herzog, H. L., *J. Am. Chem. Soc.* **72**, 273 (1950).



DIELS-ALDER OLEFIN-ADDUCTS (TETRAHYDROPHTHALIC ANHYDRIDES)

cis-4-Cyclohexene-1,2-dicarboxylic Anhydride

(*cis*-4-Tetrahydrophthalic Anhydride)

This reaction is a very general one. It is used as a test for ascertaining the conjugation of unsaturated groups. Care should be taken, however, in what conclusions are drawn from this reaction alone, since certain conjugated compounds, such as the pyrroles, add maleic anhydride in an unusual manner (*q.v.*) and others, like the thiophenes, are usually completely non-reactive. Several non-conjugated olefins readily isomerize during reaction, to produce adducts of the conjugated isomers. Vinylcyclopropane, which shows many of the properties of conjugated diolefins, does not react with maleic anhydride at the usual temperatures. In the presence of nitrobenzene, dehydrogenation occurs so that substitute phthalic anhydrides are obtained in place of the partially hydrogenated derivatives.

cis-4-Cyclohexene-1,2-dicarboxylic anhydride, like most Diels-Alder adducts, is a crystalline solid. It melts at 103 to 104°. It is soluble in most organic liquids but only partially soluble in ligroin and petroleum ether. The acid may be obtained by heating the anhydride with water. When recrystallized from water, it melts at 166°.

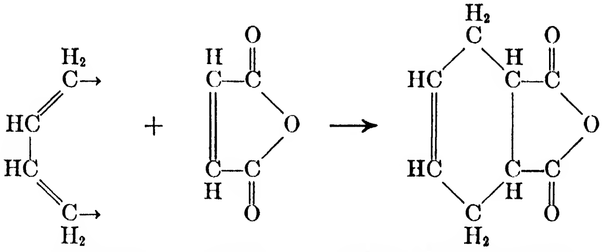
Uses. The adduct with cyclopentadiene, namely, bicyclo-[2.2.1]-5-heptene-2,3-dicarboxylic anhydride is known commercially by the trade name, Carbic Anhydride.* It is an important reactant in the preparation of oil-reactive resins, which are used in overprint varnishes, ink, waterproof coatings, and emulsion paints. Adducts with crotonaldehyde acetate have been suggested for use in the preparation of dyes, pharmaceuticals, and softening agents; and those from dimethyl muconate and from isoprene, as plasticizers for cellulose acetate. When sulfonated, these adducts have surface-active properties.

These adducts are also valuable in the synthesis of several pure chemicals. For example, *cis*-4-tetrahydrophthalic anhydride may be oxidized to butanetetracarboxylic acid with permanganate, and biphenyl compounds may be obtained by decarboxylation of the phenyl derivatives.

The reaction itself has been used as a means to remove conjugated compounds in separating fatty-acid mixtures and in separating neovitamin A from vitamin A, and to purify benzene of dienes.

* Bakelite Division, Carbide and Carbon Chemical Corporation.

1,3-Butadiene



1,3-Butadiene + Maleic anhydride ⟶ *cis*-4-Cyclopentene-1, 2-dicarboxylic anhydride

Procedure. A solution of 2.5 g. of 1,3-butadiene and 4 g. of maleic anhydride in 10 ml. of pure benzene is allowed to stand for 12 hours and is then heated on a water bath at 100° for 5 hours. The reaction mixture crystallizes completely upon cooling. The product is recrystallized from hot ligroin, giving practically a quantitative yield of *cis*-4-tetrahydrophthalic anhydride.

References

Diels, O., and Alder, K., *Ann.* **460**, 98 (1928); *Ber.* **62B**, 2087 (1929). *Cf.*:

Bergmann, E., Haskelberg, L., and Bergmann, F., *J. Org. Chem.* **7**, 303 (1942).

Buu-Hoï and Dat-Xuong, *Bull. soc. chim. France* **1948**, 751.

Craig, D., *J. Am. Chem. Soc.* **72**, 1678 (1950).

Cope, A. C., and Herrick, E. C., *J. Am. Chem. Soc.* **72**, 984 (1950).

Cosgrove, C., and Earhart, K. A., *Ind. Eng. Chem.* **41**, 1492 (1949).

Diels, O., *Z. angew. Chem.* **42**, 911 (1929).

Dufraisse, C., and Mathieu, J., *Bull. soc. chim. France* **1947**, 307.

Farmer, E. H., and Warren, F. L., *J. Chem. Soc.* **1929**, 903.

Frank, R. L., Emmick, R. D., and Johnson, R. S., *J. Am. Chem. Soc.* **69**, 2313 (1947).

Kloetzel, M. C., *Org. Reactions* **4**, 1 (1948). A Review.

Kohler, E. P., and Kable, J., *J. Am. Chem. Soc.* **56**, 2757 (1934).

Korolev, A., and Mur, V., *Doklady Akad. Nauk SSSR* **59**, 71 (1948); *Zhur. Obshcheĭ Khim.* (*J. Gen. Chem.*) **18**, 1977 (1948); C. A. **42**, 6776i (1942).

Kuhn, R., and Wagner-Jauregg, T. A., *Ber.* **63B**, 2662 (1930).

Norton, J. A., *Chem. Revs.*, **31**, 319 (1942). A Review.

Paul, R., and Tchelitcheff, S., *Bull. soc. chim. France* **1948**, 108.

Robeson, C. D., and Baxter, J. G., *J. Am. Chem. Soc.* **69**, 136 (1947).

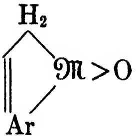
Robey, R. F., *Science* **96**, 470 (1942).

Snyder, H. R., Stewart, J. M., and Meyers, R. L., *J. Am. Chem. Soc.* **71**, 1055 (1949).

Tyutyunnikov, G. N., *Coke & Chem.* (*USSR*) **9**, (No. 1), 31 (1939); *C. A.* **34**, 2953^8 (1940).

Van Volkenburg, R., Greenlee, K. W., Derfer, J. M., and Boord, C. E., *J. Am. Chem. Soc.* **71**, 3596 (1949).

U.S. 2,314,846; 2,381,969; 2,384,855; 2,389,136; 2,397,240; 2,423,234; 2,432,586. Brit. 300,130; 552,644; 578,867.



POLYCYCLIC TETRAHYDROPHTHALIC ANHYDRIDES

1,2,3,10a-Tetrahydro-1,2-phenanthrenedicarboxylic Anhydride

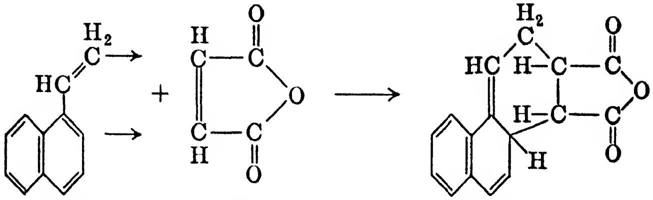
Certain arylvinyl compounds, such as 1-vinylnaphthalene, are capable of adding maleic anhydride, at least in part, in the manner of a chain-conjugated diene, as shown on the opposite page. Such compounds include, besides 1-vinylnaphthalene, certain 1-cyclopentenylnaphthalenes, several 9-vinylphenanthrenes, *p*-vinylveratroles, and *p*-vinylisosafroles (*q.v.*). Most arylvinyl compounds, such as styrene, however, can form only copolymers. Diarylethylenes add two moles of maleic anhydride to produce labile bis-adducts. See, for example, the reaction of 1-phenyl-1-(3,4-dimethoxyphenyl)ethylene. Indene also forms a similar cyclic adduct, but addition takes place in such a manner as to produce 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-dicarboxylic anhydride.

The reaction between 1-vinylnaphthalene and fumaric acid is slower than the one with maleic anhydride, but it gives a higher yield of monomeric adducts.

The *cis*-1,2,3,10a-tetrahydro-1,2-phenanthrenedicarboxylic anhydride formed in this reaction with maleic anhydride melts at 187.3 to 190°, after softening at 186°, according to Bachmann and Scott. When evaporatively distilled under reduced pressure, or refluxed with acetic or propionic acid, or treated with acetic anhydride and hydrogen chloride, it is isomerized to the naphthalenic anhydride, *cis*-1,2,3,4-tetrahydro-1,2-phenanthrenedicarboxylic anhydride. This compound melts at 170.3 to 170.8°.

Use. These anhydrides may be used to prepare the corresponding pure polycyclic hydrocarbons by dehydrogenation and decarboxylation. Aromatic dicarboxylic acids, such as 1,2-phenanthrenedicarboxylic acid, are obtained by dehydrogenation alone, and compounds such as 4*H*-cyclopenta[*a*]phenanthrene-15,17-dione by allowing these anhydrides to react with ethyl acetate. Adducts with 1-vinylnaphthalene have been employed in synthesizing sex hormones.

1-Vinylnaphthalene



1-Vinylnaphthalene + Maleic anhydride ⟶ 1,2,3,10a-Tetrahydrophenanthrene-1,2-dicarboxylic anhydride

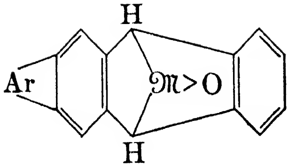
Procedure. A solution of 8.5 g. of 1-vinylnaphthalene and 5.7 g. of maleic anhydride in 17 ml. of xylene is heated on a steam bath for 3 hours. A deposit of the adduct begins to form in the yellow solution after 10 minutes' heating. Upon completion of the reaction, the mixture is allowed to stand for 12 hours at 0° and then is filtered. The yield of crude product is 13 g., or 91.5% of theory.

References

Bachmann, W. E., and Kloetzel, M. C., *J. Am. Chem. Soc.* **60**, 2204 (1938). *Cf.*:

Alder, K., Pascher, F., and Vagt, H., *Ber.* **75B**, 1501 (1942).
Arnold, R. T., and Coyner, E. C., *J. Am. Chem. Soc.* **66**, 1542 (1944).
Bachmann, W. E., and Deno, N. C., *J. Am. Chem. Soc.* **71**, 3062 (1949).
Bachmann, W. E., and Scott, L. B., *J. Am. Chem. Soc.* **70**, 1462 (1948).
Bergmann, E., and Bergmann, F. J., *J. Am. Chem. Soc.* **59**, 1443 (1937).
Bergmann, F., and Szmuszkovicz, J., *J. Am. Chem. Soc.* **70**, 2748 (1948).
Bergmann, F., and Weizmann, A., *J. Org. Chem.* **11**, 592 (1946).
Cohen, A., *Nature* **136**, 869 (1935).
Cohen, A., and Warren, F. L., *J. Chem. Soc.* **1937**, 1318.
Szmuszkovicz, J., and Bergmann, F., *J. Am. Chem. Soc.* **69**, 1779 (1947).
Szmuszkovicz, J., and Modest, E. J., *J. Am. Chem. Soc.* **70**, 2542 (1948).

U.S. 2,430,109.



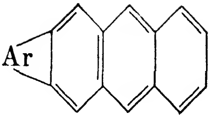
9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic Anhydride

(9,10-Dihydroanthracene-9,10-endo-α,β-succinic Anhydride)

Aromatic hydrocarbons, such as benzene, naphthalene, and phenanthrene, usually do not react with maleic anhydride. As a general rule, it is only the polynuclear aromatic compounds, for which a complete Kekulé structure cannot be drawn, that readily condense with this dienophile. Such compounds include anthracene, naphthacene, 1,2-benzanthracene, and the like. Chrysene and 1,2,3,4-tetramethylnaphthalene are the exceptions. The methyl groups in the latter compound probably so activate the aromatic rings that addition can take place under proper experimental conditions. This led Norton to predict that even benzene and naphthalene might add dienophiles if they could be made unusually reactive, provided of course that they formed sufficiently heat-stable adducts. (See reference to Kloetzel and Herzog.) Benzathrene adds maleic anhydride but rearranges in doing so. 9-Methyleneanthrone and its derivatives add the anhydride in a manner similar to that of vinylnaphthalenes.

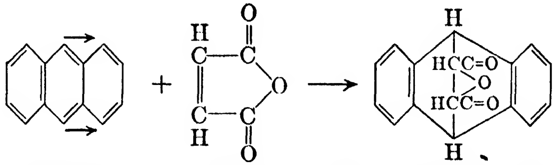
Anthracene forms a well-defined crystalline adduct that shows no fluorescence under an arc lamp, such as is observed with anthracene itself. This adduct melts at 223°.

Uses. Little study as yet has been given to possible uses for these compounds except for methods of separating polynuclear hydrocarbons. Treated with alcoholic potassium hydroxide, the anthracene adduct yields the corresponding anthrone derivative.



POLYNUCLEAR AROMATIC HYDROCARBONS

Anthracene



Anthracene + Maleic anhydride ⟶ 9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic anhydride

Procedure. Forty-two g. of anthracene and 25 g. of maleic anhydride are allowed to react in a boiling solution of 250 ml. of *o*-dichlorobenzene for one hour. Crystals of the adduct separate readily during the cooling of the reaction mixture. They are recrystallized, first from *o*-chlorobenzene and then from xylene.

References

Barnett, E. de B., Goodway, N. F., Figgins, A. G., and Lawrence, C. A., *J. Chem. Soc.* **1934,** 1224. *Cf.*:

Allen, C. F. H., and Bell, A., *J. Am. Chem. Soc.* **64,** 1253 (1942).

Bachmann, W. E., and Scott, L. B., *J. Am. Chem. Soc.* **70,** 1458 (1948).

Bickford, W. G., Fisher, G. S., Dollear, F. G., and Swift, C. E., *J. Am. Oil Chemists' Soc.* **25** (No. 7), 251 (1948).

Clar, E., *Ber.* **76B,** 609 (1943); **81,** 163 (1948).

Jones, R. N., Gogek, C. J., and Sharpe, R. W., *Can. J. Research* **26B,** 719 (1948).

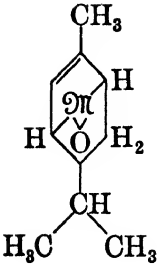
Kloetzel, M. C., Dayton, R. P., Herzog, H. L., *J. Am. Chem. Soc.* **72,** 273 (1950).

Kloetzel, M. C., and Herzog, H. L., *J. Am. Chem. Soc.* **72,** 1991 (1950).

Norton, J. A., *Chem. Revs.* **31,** 319 (1942).

Szmuszkovicz, J., and Modest, E. J., *J. Am. Chem. Soc.* **72,** 566 (1950).

U.S. 2,511,577. Ger. 623,338.



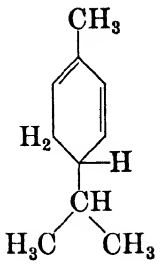
5-Isopropyl-7-methylbicyclo[2.2.2]-7-octene-2,3-dicarboxylic Anhydride

(7-Isopropyl-3,6-ethano-4-hexene-1,2-dicarboxylic Anhydride)

The formation of a Diels-Alder type of adduct with monocyclic terpenes containing conjugated double bonds is far from quantitative in most cases. Although the yield here is 90% with α-phellandrene, it is usually only 30 to 50% with other conjugated monocyclic terpenes, such as α-terpinene. The remainder of the products are chain copolymers that vary in their ratio of maleic anhydride to terpene. The copolymer of α-phellandrene, for instance, has a molecular weight of 1220 and a molar ratio of 6 parts of anhydride to 5 of terpene. Compounds of these types are also present in the reaction products of maleic anhydride with a non-conjugated monocyclic terpene (*q.v.*), if small amounts of acid are present to cause isomerization.

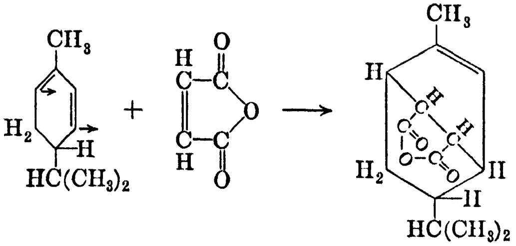
5-Isopropyl-7-methylbicyclo[2.2.2]-7-octene-2,3-dicarboxylic anhydride melts at 126 to 127°. It forms a crystalline acid and ammonium salt. It can be completely distilled under reduced pressure.

Use. These crystalline adducts, or the reaction mixtures of them with the copolymers formed simultaneously, may be combined with polyhydric alcohols to produce polyesters. These polyesters are used in coatings, inks, plasticizers, adhesives, linoleum, and food wrappers. The glycol ester has been employed as a rubber substitute. Deemulsifying agents for petroleum, sudsing and wetting agents, and synthetic tanning agents can be prepared from them.



CONJUGATED TERPENES

α-Phellandrene



α-Phellandrene + Maleic anhydride ⟶ 5-Isopropyl-7-methyl-bicyclo [2.2.2]-7-octene-2,3-dicarboxylic anhydride

Procedure. To a solution of 10 g. of α-phellandrene in 10 ml. of benzene 7 g. of maleic anhydride is added, and the mixture is thoroughly shaken. The shaking causes the liquid to turn yellow. The reaction mixture is then heated at 40 to 50° for one hour, during which time the maleic anhydride dissolves completely. The solution is filtered, evaporated, and the residue recrystallized from boiling methanol. The resulting crystals are dried at 100° under reduced pressure. The yield is approximately 90% of theory.

The reaction may also be carried out without solvent at 55°. The 10% polymeric by-product may be recovered also.

References

Diels, O., and Alder, K., *Ann.* **460**, 116 (1928). *Cf.*:

Diels, O., Koch, W., and Frost, H., *Ber.* **71B**, 1163 (1938).

Hopfield, J. J., Hall, S. A., and Goldblatt, L. A., *J. Am. Chem. Soc.* **66**, 115 (1944).

Hultzsch, K., *Ber.* **72B**, 1173 (1939).

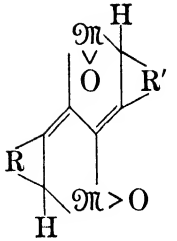
Ipatieff, V. N., and Pines, H., *J. Am. Chem. Soc.* **66**, 1120 (1944).

Kienle, R. H., *Ind. Eng. Chem.* **22**, 590 (1930).

Littmann, E. R., *J. Am. Chem. Soc.* **58**, 1316 (1936); *Ind. Eng. Chem.* **28**, 1150 (1936).

Norton, J. A., *Chem. Revs.* **31**, 417 (1942).

U.S. 1,993,025; 1,993,034; 1,993,035; 1,993,037; 2,081,753; 2,126,944; 2,347,923; 2,347,970; 2,348,575; 2,354,993; 2,373,413; 2,383,791; 2,403,098; 2,407,937; 2,436,048. Ger. 625,903; 627,783; 633,420. Brit. 563,238.



HEXAHYDRONAPHTHALENETETRACARBOXYLIC DIANHYDRIDES

1,2,3,4,5,6,7,11,12,13,16,17-Dodecahydro-15-cyclopenta [*a*]-phenanthrene-6,7,11,12-tetracarboxylic Dianhydride

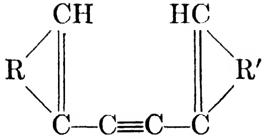
(Steradiene-6,7,11,12-tetracarboxylic Dianhydride)

This reaction illustrates how maleic anhydride may combine with certain dieneynes. Here the acetylene bond is the equivalent of two olefin groups, thus giving rise to a double Diels-Alder addition. In this respect, these dieneynes are similar to conjugated tetraenes, except that tetraenes do not produce conjugated bicyclic derivatives. 2,5-Dimethyl-1,5-hexadien-3-yne also reacts with two moles of maleic anhydride in a like manner, indicating that the reaction is a general one for both chain and cyclic dienynes of this type. That the products contain a conjugated group with the unsaturated bonds in different rings has been shown by comparing their absorption spectra with compounds known to contain such structures. The parent aromatic hydrocarbons have been prepared from these adducts by heating them with palladium and charcoal.

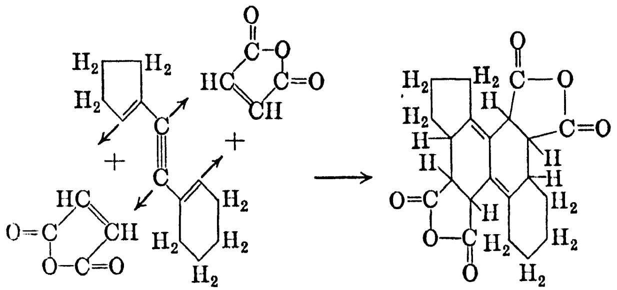
These dienynes do not react with maleic anhydride at temperatures much below 100°. Side reactions also occur that would account for the relatively low yields. It has been noted that small amounts of impurities in the reactants markedly affect the results.

The product obtained in this preparation occurs as colorless crystals that melt in an evacuated tube at 252 to 253° without decomposition. Heated with ethyl alcohol, it yields the monoethyl ester. This melts at 223 to 230°, with discoloration and evolution of gas. The acid can be obtained in 94% yield from the anhydride. It melts at 231 to 232° with decomposition. The tetraethyl ester melts at 117.5 to 120.5°. Hydrogenation with an Adams catalyst gives 89% of sterene-6,7,11,12-tetracarboxylic acid, which melts at 164.5 to 170.5°.

Use. Some of these compounds were prepared for studying the metabolism of steroids in animals.



(1-Cyclohexen-1-yl)(1-cyclopenten-1-yl)acetylene



(1-Cyclohexen-1-yl) (1-cyclopenten-1-yl)acetylene + Maleic anhydride ⟶ 1,2,3,4,5,6,7,11,12,13,16,-17-Dodecahydro-15-cyclopenta [*a*] phenanthrene-6,7,11,12-tetracarboxylic dianhydride

Preparation. Three moles of freshly distilled maleic anhydride and one of (1-cyclohexen-1-yl) (1-cyclopenten-1-yl) acetylene are heated at 150° for 3 hours in a sealed tube, in an atmosphere of nitrogen. The reaction mixture, after cooling, is extracted with ether, and the residue from the ether extract is then recrystallized from ethyl acetate or dioxane. This yields 15 to 17% of the above dianhydride.

References

Butz, L. W., and Joshel, L. M., *J. Am. Chem. Soc.* **63**, 3344 (1941); **64**, 1311 (1942). *Cf.*:
Butz, L. W., Gaddis, A. M., Butz, E. W. J., and Davis, R. E., *J. Am. Chem. Soc.* **62**, 995 (1940); *J. Org. Chem.* **5**, 379 (1940).
Joshel, L. M., Butz, L. W., and Feldman, J., *J. Am. Chem. Soc.* **63**, 3348 (1941).
Klebanskii, A. L., Popov, L. D., and Tsukerman, N. Ya., *J. Gen. Chem.* (*USSR*) **16**, 2083 (1946); C. A. **42**, 858g (1948).

U.S. 2,031,481.

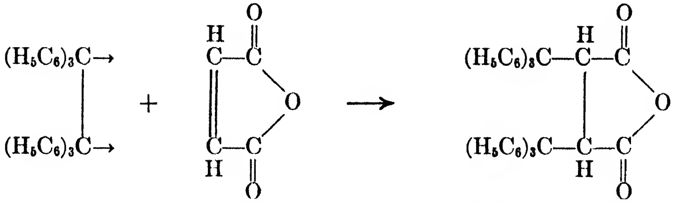
α,β-Bis(triphenylmethyl)succinic Anhydride

Compounds capable of splitting into free radicals will react with derivatives of ethylene such as maleic anhydride, either in an inert solvent or in the molten condition to produce the disubstituted products. Two reactions of this type have been carried out with maleic anhydride, namely, the above reaction with hexaphenylethane and the reaction with hexaphenyldilead (*q.v.*). A similar addition takes place with trichloromethyl radicals when produced by the reaction of carbon tetrachloride with benzoyl peroxide. (See Reaction of Carbon Tetrachloride.) In contrast, chlorotriphenylmethane reacts with silver fumarate to yield only the triphenylmethyl ester, without affecting the unsaturation of the fumarate.

α,β-Bis(triphenylmethyl)succinic anhydride is a crystalline solid that melts at 232° when crystallized from acetone. The acid is readily soluble in ether and can be separated from the anhydride by this solvent. Crystallized from acetic acid, it decomposes at 148°. The dimethylester melts at 212 to 213°.

Use. No commercial use has yet been made of these reactions.

Hexaphenylethane



Hexaphenylethane + Maleic anhydride ⟶ α,β-Bis(triphenylmethyl)succinic anhydride

Procedure. To 200 ml. of a benzene solution of hexaphenylethane, which has been prepared by allowing finely divided silver to react with 120 g. of chlorotriphenylmethane, 40 g. of maleic anhydride is added. The reaction mixture is refluxed in an atmosphere of nitrogen for several hours. The reacted mixture is then extracted with a 3% sodium hydroxide solution. An insoluble salt forms at the interface of the two solutions. This salt and the aqueous solution are then separated, acidified, and extracted with ether. Whereupon, 60 g. of acid and 12 g. of the anhydride are obtained from the extract.

References

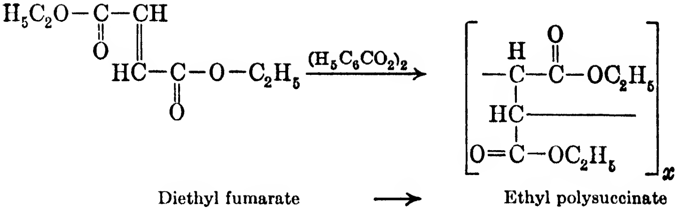
Conant, J. B., and Chow, B. F., *J. Am. Chem. Soc.* 55, 3475 (1933). *Cf.*: Leeper, R. W., *Iowa State Coll. J. Sci.* 18, 57 (1943).

Ethyl Polysuccinates

Polymerization of this type occurs to varying degrees in the preparation of several compounds of maleic and fumaric acids, especially if catalysts, such as benzoyl peroxide (*q.v.*), are present that can induce self-addition of the maleic compound. Such addition polymerization takes place very readily in the preparation of esters with polyhydric alcohols; it occurs after two or more moles of maleic acid have reacted to form a polymaleate. Air may accelerate such a reaction under certain conditions by producing peroxides.

Ethyl polysuccinate is a soft, colorless resin that is soluble in ethyl alcohol, acetone, ethyl acetate, butyl acetate, benzene, toluene, xylene, and aromatic naphthas. It is insoluble in aliphatic hydrocarbons.

Uses. Coating compositions of good color stability and excellent characteristics are obtained from ethyl polysuccinate. Use is also made of this type of reaction by admixing maleic anhydride in small amounts with other anhydrides in manufacturing several important types of mixed alkyd resins. Glycol polysuccinates give coatings that dry in air when siccatives are added. Esters from dienols have been suggested as drying-oil substitutes. Nitroalkyl esters produce combustible plastics and binders for explosives. Unsaturated esters from allyl alcohol and its homolog yield an important group of cast plastics, rubbers, and fibers. Emulsion polymers of this type have been recommended as plasticizers for synthetic rubber, and the diethylene glycol polyesters as binders for low-pressure molding compounds.



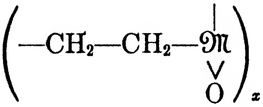
Diethyl Fumarate

Procedure. A solution of 4 g. of benzoyl peroxide in 200 g. of diethyl fumarate is heated on a water bath for 7 hours. The unpolymerized ethyl fumarate is then removed by distillation, leaving 179 g. (89% of theory) of ethyl polysuccinate.

References

Dykstra, H. B., U.S. 1945307 (1934). *Cf.*:
Doscher, C. K., *Colloid Chem.* **6**, 1068 (1946); J. Alexander, Editor.
Gabriel, A. E., *Modern Plastics* **25** (No. 8), 145 (1948).
Marvel, C. S., Prill, E. J., and De Tar, D. F., *J. Am. Chem. Soc.* **69**, 52 (1947).

U.S. 2,254,382; 2,319,575; 2,319,576; 2,370,565; 2,379,247; 2,392,621; 2,404,688; 2,410,074; 2,410,425; 2,411,136; 2,415,366; 2,425,144; 2,442,330. Brit. 552,228; 572,777; 589,861. Dutch 59,166. Ger. 699,445.



$$\left(-CH_2-CH_2-\overset{|}{\underset{\underset{O}{V}}{\mathfrak{M}}}\right)_x$$

Polyethylenesuccinic Anhydride

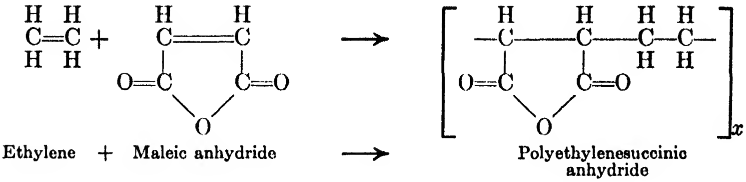
This copolymerization is typical of many of the catalyzed reactions of maleyl compounds with those containing vinyl or substituted ethylene groups. Several arylvinyl compounds, like α-vinylnaphthalene, indene, and propenylphenyl ethers such as isosafrole, however, undergo the typical Diels-Alder condensation in the absence of peroxides (*q.v.*); but stilbene, 9-benzylidenefluorene, 9-anisylidenefluorene, 1,4-diphenyl-1-butene, and 1,10-diphenyl-1,3,5,7,9-decapentaene form chain compounds similar to those of ethylene even when no peroxide is added to the reactants.

Many of these reactions yield products that are of constant composition and molecular weight irrespective of initial concentrations of reactants. Some reactions require a solvent, whereas other reactants will unite only in the presence of themselves. The molecular proportion of succinyl groups in the product varies with the particular ethylene derivative. Some can be made to react in molecular proportions, such as propylene, isobutylene and diisobutylene. Others contain only an excess of one or the other of the reactants. In general, maleyl compounds show a reaction selectivity that favors the alternating 1:1-type of copolymer.

Polyethylenesuccinic anhydride is a solid that dissolves readily in warm water and hydrolyzes slowly to give the polyacid. A 10% solution at 25° has a *p*H of 5.2 and a viscosity of 11.6 centipoises. The copolymer is also soluble in alkalies.

Use. Polyalkylenesuccinic anhydrides have been used as tanning agents, photographic chemicals, gelatin substitutes, textile agents, petroleum chemicals, protein hardeners, alkyd resin ingredients, and as an intermediate in producing naphthol dyes for color photography. Polyphenylethylenesuccinates may be used for coatings, resins, lacquer, base-exchange resins, and plastics; mixed vinyl copolymers when sulfonated, as detergents; and methyl methacrylate copolymers, as solvents and plasticizers. Copolymers with vinyl compounds have adhesive and other properties that are not readily obtained in other ways, whereas maleinized rubbers not only adhere better to metals but are partially vulcanized during the copolymerization.

Ethylene



Procedure. A solution containing 30 g. of maleic anhydride and 1.5 g. of benzoyl peroxide in 200 ml. of toluene is placed in an autoclave, and ethylene is added until the weight increases 40 g. Heat is then applied, initiating an exothermic reaction at about 100°, at which point the temperature rises rapidly to 150°. The mixture is carefully held at the higher temperature for one hour before being cooled. The product formed is insoluble in toluene and is thus recovered by filtration. The yield is 35 g., or 88% of theory.

References

Hanford, W. E., U.S. 2,378,629 (1945). *Cf.*:
Alder, K., Pascher, F., and Vagt, H., *Ber.* **75B**, 1051 (1942).
Alfrey, T., and Lavin, E., *J. Am. Chem. Soc.* **67**, 2044 (1945).
Bartlett, P. D., and Nozaki, K., *J. Am. Chem. Soc.* **68**, 1495 (1946).
Bachmann, W. E., and Scott, L. B., *J. Am. Chem. Soc.* **70**, 1462 (1948).
Ebers, E. S., et al., *Ind. Eng. Chem.* **42**, 114 (1950).
Lewis, F. M., Walling, C., Mayo, F. R., et al., *J. Am. Chem. Soc.* **70**, 1519, 1529, 1533, 1543, 1544 (1948); **71**, 1930 (1949); **73**, 2819 (1951).
Marvel, C. S., et al., *J. Am. Chem. Soc.* **64**, 1675 (1942); **69**, 52 (1947).
Rust, J. B., *Ind. Eng. Chem.* **32**, 64 (1940).
Starkweather, H. W., et al., *Ind. Eng. Chem.* **39**, 210 (1947).
Tong, L. K. J., and Kenyon, W. O., *J. Am. Chem. Soc.* **71**, 1925 (1949).
Wagner-Jauregg, T., *Ber.* **63B**, 3213 (1930).

U.S. 2,365,717; 2,373,067; 2,375,960; 2,384,085; 2,384,595; 2,384,855; 2,391,621; 2,392,139; 2,394,527; 2,396,785; 2,403,213; 2,436,256; 2,438,102; 2,439,227; 2,439,953. Brit. 561,800; 562,092; 563,288; 583,474; 584,622; 585,969. Can. 437,996.

CHAPTER
2

Halogens and Their Compounds

The hydrocarbon reactions described in the first chapter were limited to the saturation of the carbon-carbon double bond of maleic compounds. Halogens and their compounds offer a wider variety of reactions. Included in this chapter are reactions involving not only the ethylene bond, but also those embracing the hydroxyl and carbonyl groups. In fact, a halogen reaction can be carried out with every atom of the maleyl group.

The addition of halogens, themselves, is an interesting study of the effect of reaction conditions upon the yield of different optical isomers. Whereas α,β-dichlorosuccinic acid may be obtained as either the racemic acid or the *meso*-acid, α,β-dibromosuccinic acid is produced only as a mixture of isomers under all conditions. Dichlorosuccinic acids, like tartaric acids, are often cited as a classical example of optical activity.

Addition of a dehydrohalogenating agent in the reaction with chlorine produces chloromaleic acid, which acts in many syntheses as if it were acetylenedicarboxylic acid as a result of the ease with which it splits off hydrogen chloride during many of its reactions.

Considerable difficulty is encountered in effecting the addition of halo acids. Hydrogen chloride, for example, can be caused to react only in excess in an anhydrous solution, whereas very poor yields are reported for the reaction of hydrogen bromide by various methods. Hypochlorous acid, in marked contrast, readily adds to the ethylene bond of maleates even in an aqueous solution to give β-chloromalic acid. This product readily splits off hydrogen chloride, especially in alkaline solution, to give the interesting dicarboxyethylene oxide, epoxysuccinic acid.

The reaction with mixed alkyl chlorides through a splitting off of hydrogen chloride gives the alkenylsuccinic acids. This affords a convenient means of adding olefinic groups to the ethylene bond of maleic anhydride by starting with saturated hydrocarbons.

Compounds such as 2-bromo-1,1-diphenylethylene probably first undergo a multiple Diels-Alder reaction, but the product not only loses hydrogen bromide and some maleic anhydride but also undergoes autodehydrogenation upon sublimation during the purification.

No evidence has as yet been obtained that acid chlorides are capable of adding to the ethylene bond of maleyl compounds. With maleic and fumaric acids, fumaryl chloride is the product formed. With maleamic acid, imides and amides are produced. When maleic acid is treated with phosphorus pentachloride and the reaction mixture is immediately distilled under reduced pressure, a product isomeric with the unknown maleyl chloride has been reported. This compound is a lactone having the ring structure of maleic anhydride where two chloro groups replace an oxygen of one of the carbonyls.

Carbon tetrachloride in the presence of benzoyl peroxide treated with maleates gives α,β-bis(trichloromethyl)succinates as one of the products of the reaction. The catalyst apparently reacts with the carbon tetrachloride to produce trichloromethyl free radicals, which, like triphenylmethyl, add to both carbons of the ethylene bond of the maleate. As is pointed out in the discussion of that reaction, dioxane forms, in contrast, the dioxanylsuccinate.

meso-α,β-Dichlorosuccinic Acid

α,β-Dichlorosuccinic acids may be obtained either as the racemic acid mixture or the inseparable *meso*-acid. The product formed in this preparation is reported to be exclusively the *meso*-acid produced by what is known as a trans-addition. The racemic α,β-dichlorosuccinic acid has been made in a similar manner from maleic acid. A cis-addition occurs when chlorine is added to aqueous solutions of the soluble neutral salts in the presence of an excess of chloride ions. Commercially, molten maleic anhydride is treated with chlorine under pressure to produce the α,β-dichlorosuccinic anhydride.

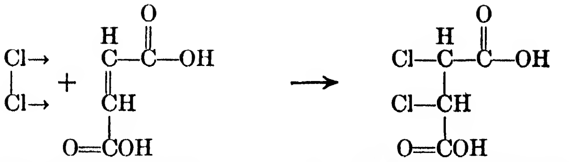
Bromine, in contradistinction, yields mixtures of the isomers under all conditions. The *meso*-acid is the predominant product when this halogen is added to aqueous solutions of the neutral salts of either maleic or fumaric acid. The racemic acid is usually prepared by carrying out the reaction in anhydrous ether.

meso-α,β-Dichlorosuccinic acid occurs as bright hexagonal, bilateral pointed prisms, which sinter at 190° and melt at 215°. The acid is soluble in water, alcohol, ether, acetone, and chloroform, but only slightly soluble in benzene and ligroin. The racemic acid melts at 166 to 167°, as does both the *d*- and the *l*-acids.

Use. α,β-Dihalosuccinic acids have been extensively used in the synthesis of a large number of chemical compounds. Propargylic acid; acetylenedicarboxylic acid; α,β-dihalosuccinamic acids; α,β-dichloro-N-phenylsuccinimides; α-bromo-N-(*p*-tolyl)maleimide; halomaleic and halofumaric acids; α-chloro-β-iodoacrylic acid; α,α,β,β-tetrachloro-N-phenylsuccinimide; α,β-diarsonosuccinic acid; α,β-diphenoxysuccinic acid; 2,3,4,5-thiophenetetracarboxylic acid; hydrazinomalehydroxamic acid; 4-oxo-1,4-benzopyrancarboxylic acid; 4-pyrone; 2,3-dihydro-5-phenyl-2,3,4-furantricarboxylic acid; *meso*-α,β-diaminosuccinic acid; and 1,2,3-cyclopropanetricarboxylic acid are some of the types of substances that have been prepared from these acids.

The alkyl esters of dichlorosuccinic acids are valuable fungicides.

Chlorine

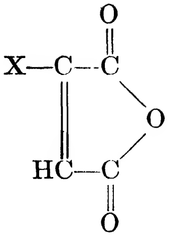


Chlorine + Fumaric acid ⟶ *meso*-α,β-Dichlorosuccinic acid

Procedure. A mixture of 10 g. of fumaric acid and 5 g. of ice is placed in a heavy-walled, heat-resistant flask. The flask is then placed in a cooling bath of solid carbon dioxide and ether, and an excess of chlorine is passed through the reaction mixture, being fed in a strong stream into the flask at or below the level of the cooling fluid. Practically all the chlorine condenses to a liquid within the flask. The reaction mixture is then exposed to bright sunlight for 4 days, while being agitated vigorously. The excess of chlorine is blown out of the flask after the contents have been cooled in an ice-salt mixture, and the mushy product is transferred to a filter and sucked free of liquid. What remains in the filtrate is then extracted with ether, and the combined recovery of dichlorosuccinic acid is recrystallized from water. The total yield in this way is practically quantitative.

References

Kirchhoff, H., *Ann.* 280, 210 (1894). *Cf.*:
Frankland, E. P., *Proc. Chem. Soc.* 27, 206 (1911); *J. Chem. Soc.* 99, 1775 (1911).
I. G. Farbenindustrie, A–G., *U.S. Dept. Commerce OTS Report PB* 84252.
Robinson, H. V. W., and Lewis, D. T., *J. Chem. Soc.* 1933, 1260.
Ruhemann, S., and Stapleton, H. E., *J. Chem. Soc.* 77, 1179 (1900).
Terry, E. M., and Eichelberger, L., *J. Am. Chem. Soc.*, 47, 1067 (1925).
Wenner, W., *J. Org. Chem.* 13, 26 (1948).



HALOMALEIC ANHYDRIDES

Chloromaleic Anhydride

The barium chloride in this preparation serves as a dehydrochlorinating agent. It has no effect on the rate of chlorination. Benzoic anhydride, phthalic anhydride, or benzoyl peroxide may be used also for the same purpose.

Pure chloromaleic anhydride is a solid at ordinary temperatures, melting at 33° to a liquid that boils at 196.3°.

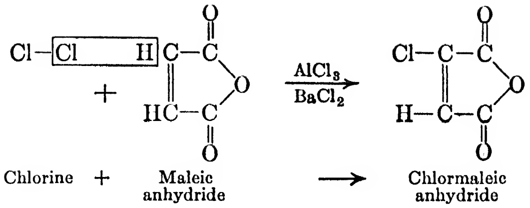
Use. The dialkyl esters of this anhydride copolymerize with 1,3-butadiene to give valuable synthetic rubbers.

Chloromaleic anhydride is itself also a valuable reagent in many organic syntheses. With conjugated drying oils, it gives infusible soluble resins. With substituted propenylbenzenes, this anhydride yields a substituted dihydronaphthalenedicarboxylic anhydride. With conjugated dienes, and cyclic hydrocarbons such as anthracene, it gives chlorinated Diels-Alder type of adducts. In the presence of sodium alkoxides, however, chloromaleic esters condense with keto esters, malonates, and substituted phenols to yield derivatives of maleic acid by splitting off sodium chloride without affecting the unsaturation. Thus diethyl chlorofumarate and ethyl acetoacetate form triethyl acetoaconitate. This product reacts with concentrated ammonia to give 1,2,3,4-tetrahydro-3-hydroxy-6-methyl-2-oxocinchomeric acid.

Halomaleic esters react with ammonia to form aminomaleimides, halomaleamic acids, and aminomaleamides. Aniline yields halomaleanilic acids, α-anilino-N-phenylmaleimide, and α-anilinofumaramides. Phenylhydrazine gives phenylhydrazonosuccinamide.

Chloromaleic acid reacts with chlorine in the presence of a small amount of water to produce α,α,β-trichlorosuccinic acid. Cements and adhesives may be had from condensation of the acid with glycerol or polyamines.

Chlorine



Procedure. A mixture of 306 g. of maleic anhydride, 6 g. of barium chloride, and 6 g. of anhydrous aluminum chloride is heated to 140 to 150° and then treated with chlorine at this temperature, with vigorous agitation, for 8 hours. The reaction mixture is then distilled under partial vacuum, and the portion is collected that boils at 97 to 103° under 35 mm. of pressure. An excellent yield of chloromaleic anhydride is obtained in this manner.

The anhydride may also be prepared under similar conditions without the use of barium chloride. In this case, nearly 24 hours is required instead of 8 for the gain in weight to equal that calculated for the necessary conversion to the monochloromaleic anhydride. The technical product obtained in this preparation has a slightly narrower boiling range of b_{50} 111–114°.

References

Wise, P., and Milone, C., U.S. 2,342,174 (1944). *Cf.*:

Alfrey, T., Muiz, E., and Mark, H., *J. Polymer Research* **1,** 37 (1946).

Claus, A., and Voeller, F., *Ber.* **14,** 150 (1881).

Mast, W. C., and Fisher, C. H., *Ind. Eng. Chem.* **40,** 107 (1948).

Putnam, S. T., Moss, M. L., and Hall, R. T., *Ind. Eng. Chem.*, Anal. Ed., **18,** 628 (1946).

Ruhemann, S., et al., *J. Chem. Soc.* **69,** 530,532,1386 (1896); **71,** 323 (1897); **79,** 1186 (1901); **81,** 1212 (1902).

Synerholm, M. E., *J. Am. Chem. Soc.* **67,** 345, 1229 (1945).

Thomas-Mamert, R., *Compt. rend.* **117,** 167 (1893).

van der Riet, S. J., *Ann.* **280,** 216 (1894).

Am. Chem. J. **9,** 180 (1888); *Ber.* **21,** 2718 (1887); *J. prakt. Chem.* (2), **52,** 289 (1896).

U.S. 2,370,055; 2,391,226; 2,391,261; 2,404,411; 2,422,470; 2,436,902. Brit. 570,216; 570,263; 570,867; 572,137.

Chlorosuccinic Acid

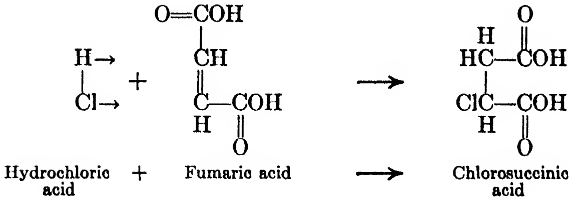
Other halosuccinic acids may be prepared in similar manner to that given on the opposite page for chlorosuccinic acid. Bromosuccinic acid, for example, has been prepared by using fuming hydrobromic acid at 100°. Fittig claimed to have obtained complete conversion under these conditions, but Dunn and Fox report poor yields, not only for this but also for other methods.

When recrystallized from water or acetic acid, chlorosuccinic acid melts at 151.5 to 152°. It is very soluble in water and hot acetic acid. It is only slightly soluble in cold acetic acid, however, and very slightly soluble in chloroform.

Use. Halosuccinic acids are convenient starting substances for synthesizing a number of compounds. They are used, for instance, in the preparation of mercaptosuccinic acid, which is employed for making the medicinal, aurothiomalic acid. Ethylmercaptosuccinic acid can be prepared in a similar manner. It can be oxidized to ethylsulfonylsuccinic acid, which in turn can be converted to β-bromo-β-ethylsulfonylpropionic acid. The halogen group of the halosuccinic acid can also be readily replaced by an xantho group or by an iodo group. Ethyl iodosuccinate reacts with benzophene and zinc to give ethyl γ,γ-diphenylparaconate. With aqueous ammonia, bromosuccinic acid forms β-malamic acid.

Halosuccinic acids also readily undergo condensation in the presence of sodium ethoxide. Ethyl 2-oxocyclopentanecarboxylate reacts with diethyl bromosuccinate, for example, to produce 1-carboxy-2-oxo-1-cyclopentylsuccinic acid.

Hydrochloric Acid



Procedure. A convenient quantity of fumaric acid is placed in a flask and cooled to 0°. An excess of a saturated solution of hydrogen chloride in acetic acid is added and the mixture is heated on a water bath for 12 to 14 hours, with constant agitation. Part of the chlorosuccinic acid that is formed separates when the solution is cooled. This is removed, and the mother liquor is then evaporated under reduced pressure to incipient crystallization in order to recover the remainder of the product.

The acid may also be prepared from malic acid.

References

Anschütz, R., and Bennert, C., *Ber.* **15,** 640 (1882). *Cf.*:

- Baker, J. W., *J. Chem. Soc.* **1931,** 1546.
- Dunn, M. S., and Fox, S. W., *J. Biol. Chem.* **101,** 493 (1933).
- Fitger, P., *Ber.* **54B,** 2943 (1921).
- Fittig, R., *Ber.* **10,** 513 (1877); **9,** 1192 (1876).
- Freudenberg, K., Piazolo, G., and Knoevenagel, C., *Ann.* **537,** 197 (1939).
- Grove, J. F., and Bovington, H. H. S., *Ann. Applied Biol.* **34,** 113 (1947).
- Holmberg, B., *J. prakt. Chem.* **88,** (2) 553 (1913).
- Levene, P. A., and Mikeska, L. A., *J. Biol. Chem.* **60,** 685 (1924).
- Lutz, O., *Chem. Zentr.* **1900,** (II), 1009.
- Moffatt, J. S., Newberry, G., and Webster, W., *J. Chem. Soc.* **1946,** 451.
- Walden, P., *Ber.* **26,** 210 (1893).

U.S. 2,358,130; 2,380,061; 2,385,018.

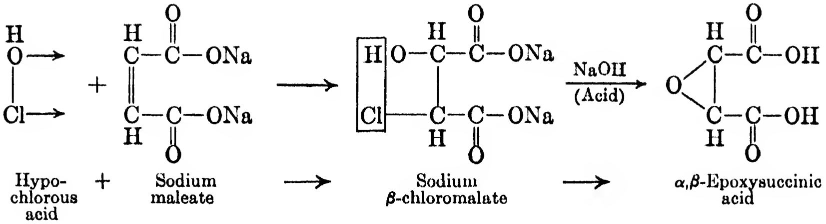
dl-trans-α,β-Epoxysuccinic Acid

The preparation as described here yields *dl-trans-α,β*-epoxysuccinic acid. This acid can be readily resolved into its optical isomers. Fumaric acid when substituted for maleic acid in the reaction gives a 72% yield of a mixture of the *dl-trans*-acid and the *cis*-acid. The latter acid comprises only 27% of the mixture. Upon hydrolysis, the *dl-trans*-acid yields a mixture of 37% *dl*-tartaric acid and 63% of *meso*-tartaric acid.

The *dl-trans-α,β*-epoxysuccinic acid melts at 209°; the *d*- and the *l*-acids melt at 180°. A mixture of equal quantities of the optically active acids has the same melting point as the racemic acid. The *cis*-acid melts at 149°. No success has been had in resolving it into its active isomers.

Use. Little study has been given to the reactions of this acid. It should be an interesting reagent, since it contains the ethylene oxide grouping.

Hypochlorous Acid



Procedure. A solution containing 80 g. of maleic acid in 1 liter of water is neutralized with 55.2 g. of sodium hydroxide in a 20-liter flask. To this is added a solution of 63 g. of chlorine in 11 liters of water. The flask then is sealed with a rubber stopper and permitted to stand for 22 hours. A glass stopper should be avoided. The reaction mixture is then treated with 60 g. of sodium hydroxide, and, upon further standing for 2 days, 170 g. of barium chloride hydrate is added. This causes 105 g. of the barium salt of *dl-trans-α,β*-expoxysuccinic acid to precipitate. Twenty grams of sodium hydroxide is then added to the mother liquor, and an additional 45 g. of the barium salt is obtained upon standing several days. The combined product is then decomposed with sulfuric acid in the usual manner. The yield is 75% of theory. An ether extraction of the mother liquor yields only small amounts of impure *cis-α,β*-epoxysuccinic acid.

Reference

Kuhn, R., and Ebel, F., *Ber.* **58B**, 919 (1925).

trans-β-Chloromalic Acid

(α-Chloro-β-hydroxysuccinic Acid)

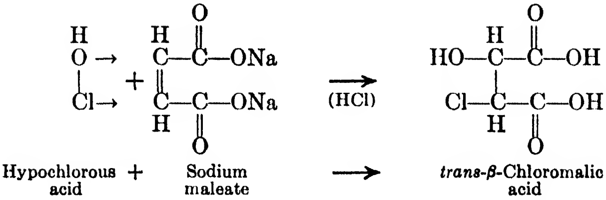
Maleic acid when treated with hypochlorous acid in absence of excess caustic yields exclusively the *trans*-chloromalic acid, whereas fumaric acid gives a mixture of 80% of the *trans*-acid and 20% of the *cis*-acid. It should be possible to resolve both of these acids into optical isomers, yielding a total of four optically active acids.

These acids can also be prepared in very high yields by treating the respective epoxysuccinic acids with concentrated hydrochloric acid at 0°. The yield of *cis*-acid, for example, is 95% by this method. Other halomalic acids can be prepared in a similar manner.

trans-Chloromalic acid occurs as a crystalline solid that melts at 146°. The *cis*-acid melts at 153.5°.

Use. These acids are valuable starting materials for the synthesis of several compounds. When treated with concentrated ammonium hydroxide, for example, they yield the various isomers of β-hydroxyaspartic acid.

Hypochlorous Acid



Procedure. A suspension of 110 g. of maleic acid in water is neutralized with sodium hydroxide. This is then diluted to a 1% solution with ice water, and a few milliliters of it are poured rapidly into a 20-liter bottle filled with chlorine. The chlorine bottle is closed quickly with a stopper carrying a rubber tube, which is dipped into the remainder of the maleate solution. Chlorine is rapidly absorbed when the bottle is shaken, causing the rest of the maleate solution to be drawn into the bottle. The reaction mixture is allowed to stand overnight, when it is neutralized by adding one-half the amount of sodium hydroxide originally required for neutralization of the acid. Two and one-half equivalents of barium chloride are added next, and the whole is shaken for half an hour. After standing, the easily filtered precipitate is removed. It is washed with water, air-dried, and crushed. This material is then placed in a thick-walled bottle, covered with ether, and shaken with small additions of concentrated hydrochloric acid until there is a 10% excess, care being taken to cool the solution between additions. After separating the ether layer, the aqueous one is extracted five times with fresh portions of ether. The combined extracts are allowed to evaporate after washing with a few drops of water. Chloromalic acid is thus obtained as an oil, but it quickly solidifies to a solid crystalline mass. The yield is 40 to 50%. The filtrates contain 20 to 25% of epoxysuccinic acid (*q.v.*)

References

Dakin, H. D., *J. Biol. Chem.* **48**, 279 (1921). *Cf.*:
Kuhn, R., and Ebel, F., *Ber.* **58B**, 919 (1925).
Lossen, W., Schörk, W., and Niehrenheim, M., *Ann.* **348**, 273 (1906).
Timmermans, J., and Jaffe, J., *Bull. soc. chim. Belg.* **46**, 471 (1937).
Timmermans, J., van Lancker, T., and Jaffe, J., *Bull. soc. chim. Belg.* **48**, 33 (1939).

Decenylsuccinic Acid

This is an industrial type of preparation employing practical grades of reagents such as are used in the manufacture of certain types of chemical products. The decyl chloride employed here is a mixture of similar chlorides, since it is prepared from a petroleum distillate. Even very narrow fractions of petroleum products consist of a mixture of isomeric hydrocarbons. The use of such chlorides causes no difficulty when the product is to be used for purposes such as those suggested below. For most industrial uses, the extra cost of starting with a pure chloride would not be warranted. For the same reason, no attempt is made to isolate and characterize the individual isomeric decenylsuccinic acids of which the product is undoubtedly composed. Often such mixtures of similar compounds have characteristics superior to those of their individual constituents for many practical uses.

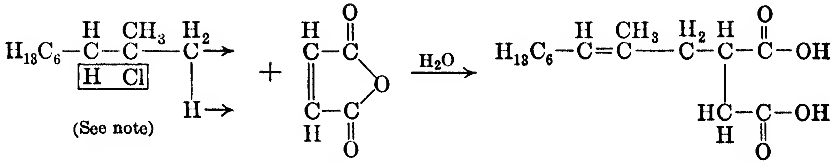
There is no reason to believe, however, that this method could not be employed to produce a pure decenylsuccinic acid, if the starting chloride were an individual compound. It shows that alkyl chlorides do not have to be converted to olefins (*q.v.*) to obtain alkenylsuccinic acids from maleic anhydride.

Almost any alkyl chloride or mixture of them may be used in this preparation. When the chloride has a low boiling point, it is best to add a higher-boiling inert solvent, or 1 to 5% of a catalyst such as aluminum chloride, zinc chloride, or the like. It is also well to use underchlorinated hydrocarbons, even if it requires steam distillation to remove the unchlorinated material.

The product obtained in this preparation is a dark gummy mass. Neutral salt solutions of any desired concentration can be obtained by titrating a suspension of it with a solution of alkali.

Use. These salt solutions have wetting, emulsifying, and washing properties if the alkenyl groups contain five to twelve carbons.

Decyl Chloride Mixture



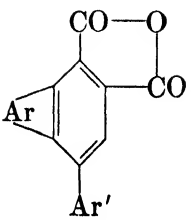
Decyl chloride + Maleic anhydride ⟶ Decenylsuccinic acid

Procedure. Thirty-five and three-tenths grams of decyl chloride prepared by chlorinating a suitable petroleum fraction is refluxed with 20 g. of maleic anhydride for 50 hours at 178°. Hydrogen chloride begins to be evolved when the temperature reaches 170°, and has practically ceased by the end of the heating period. A 5% solution of sodium hydroxide is added to render the reaction mixture alkaline. A light oily layer separates and is removed. The remaining aqueous solution is made acid to Congo red with 10% hydrochloric acid, which causes the decenylsuccinic acids to precipitate. These acids are removed by filtration, and both the product and the aqueous layer are then extracted with chloroform. Whereupon, evaporation of the chloroform solution gives a yield equivalent to 85% of the theoretical amount of decenylsuccinic acids.

Reference

Kyrides, L. P., U.S. 2,360,426 (Oct. 17, 1945).
The above formula is representative of the mixture.

Note. This single isomer is used purely to illustrate the general type of reaction. Similar reactions occur with each of the other isomers.



1-PHENYLNAPHTHALENEDICARBOXYLIC ANHYDRIDES

1-Phenyl-3,4-naphthalenedicarboxylic Anhydride

Only in a comparatively limited number of cases have compounds containing halogens been successfully employed in Diels-Alder syntheses. In many of the reactions studied, the hydrogen halide is split off during the preparation, giving adducts that are more unsaturated than those obtained with the corresponding hydrocarbons, as is the case in this instance.

The particular reaction shown on the opposite page, however, undoubtedly may take place in two stages, with the hydrogen bromide being evolved and autooxidation occurring during the sublimation of the reaction product. The initial amorphous material contains bromine and probably two moles of maleic anhydride, as there is no reason to believe that diarylvinyl halides would react differently from diarylvinyl compounds in general. See, for example, the reaction of 1-phenyl-1-(3,4-dimethoxyphenyl)ethylene with maleic anhydride. 1,1-Diaryl-2,2-dihalogenoethylenes and ω-bromostyrene, in contrast, do not react with maleic anhydride.

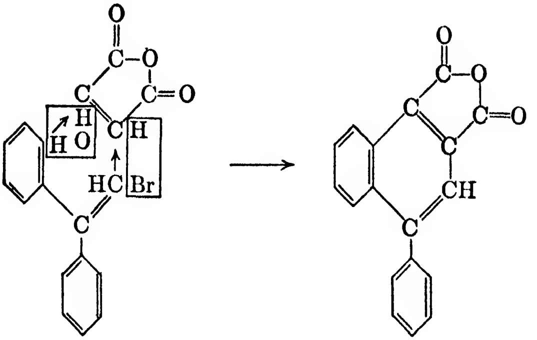
1-Chloro-3-methyl-1,3-butadiene and 1-chloro-3-methyl-1,3-pentadiene add maleic anhydride, with a loss of hydrogen chloride, to give products that yield upon hydrolysis a mixture of acids. The former adds both one and two moles of maleic anhydride. In general, only acyclic dienes containing a single halogen in the 3-position $(>C{=}CCl{-}\underset{|}{C}{=}C<)$ add dienophiles as readily as do the parent hydrocarbons. The highly reactive hexachloropentadiene adds maleic anhydride without loss of halogen. Derivatives of hexachlorocyclopentadiene, in which the allylic chlorine atoms are replaced by alkoxy groups, react similarly. This reactivity is attributed to their *cis*-butenoid configuration. Octachloro-5-ethylidenecyclopentadiene and its isomers do not react with maleic anhydride under ordinary conditions.

Chloromaleic anhydride when used as a dienophile yields derivatives of maleic anhydride through the loss of hydrogen chloride.

1-Phenyl-3,4-naphthalenedicarboxylic anhydride occurs as clusters of needles when crystallized from ligroin (b.p. 130°). These needles melt at 172°.

Use. These reactions are a convenient means for producing certain substituted cyclic carboxylic acids and their decarboxylated products.

2-Bromo-1,1-diphenylethylene
(Diphenylvinyl Bromide)



2-Bromo-1,1-diphenylethylene + Maleic anhydride + Oxygen ⟶ 1-Phenyl-3,4-naphthalenedicarboxylic anhydride

Procedure. A dark brown reaction mass is obtained when a mixture of 1 g. of 2-bromo-1,1-diphenylethylene and ten equivalents or 4 g. of maleic anhydride is allowed to react, upon heating for 4 hours at 160 to 180°. This dark brown product is broken up by dissolving it in alcohol and precipitating with water. The precipitate is separated, thoroughly dried, and then sublimed at 270 to 340°, under 2 mm. of pressure. The sublimate is finally purified by triturating it with ethanol, followed by crystallization from ligroin. The yield is 400 mg. or 38% of theory.

References

Bergmann, F., and Szmuszkovicz, J., *J. Am. Chem. Soc.* **69**, 1777 (1947). *Cf.*:
Bergmann, F., and Szmuszkovicz, J., *J. Am. Chem. Soc.* **72**, 1035 (1950).
Bergmann, F., *J. Am. Chem. Soc.* **64**, 176 (1942).
Favorskaya, T. A., et al., *J. Gen. Chem.* (*USSR*) **9**, 386 (1939); **10**, 446, 451, 461 (1940); *Chem. Abst.* **33**, 9281 (1939); **34**, 7844–7845 (1940).
Favorskiĭ, A., and Favorskaya, T., *Compt. rend.* **200**, 839 (1935).
Fieser, L. F., and Dunn, J. T., *J. Am. Chem. Soc.* **59**, 1016, 1024 (1937).
I. G. Farbenindustrie, *Monthly Repts.; U.S. Dept. Commerce O.T.C. Rept.* PB73894, frame 5174–5194.
Klebanshiĭ, A. L., Sorokina, R. M., and Khavin, Z. Y., *J. Gen. Chem.* (*USSR*) **17**, 235 (1947); *Chem. Abst.* **42**, 515g (1948).
Koebner, A., Robinson, R., and Cardwell, H. M. E., *J. Chem. Soc.* **1941**, 566.
Newcomer, J. S., and McBee, E. T., *J. Am. Chem. Soc.* **71**, 946, 952 (1949).
Norton, J. A., *Chem. Revs.* **31**, 379 (1942).
Prill, E. A., *J. Am. Chem. Soc.* **69**, 62 (1947).
Synerholm, M. E., *J. Am. Chem. Soc.* **67**, 345, 1229 (1945).

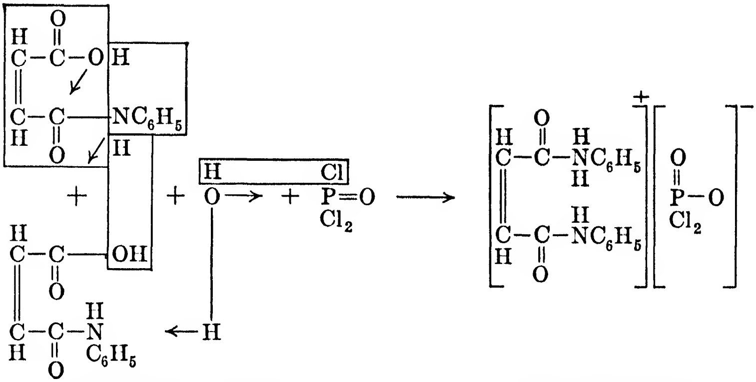
Brit. 320,375 (1929). I. G. Farbenindustrie, *Monthly Repts.*; *U.S. Dept. Commerce O.T.C. Rept.* PB73894, frame 5174–5194.

Maleanilide Dichlorophosphate

This preparation is interesting in that it would indicate that even at 100° dichlorophosphoric acid or phosphoryl chloride shows no evidence of adding to the unsaturated bond of maleyl compounds. The maleanilidium dichlorophosphate when treated with cold water is almost quantitatively hydrolyzed to maleanilide, phosphoric acid, and hydrochloric acid. If addition had occurred at the unsaturated bond, hydrolysis should have produced the anilide of malic acid. Instead the only other compound found to be formed by reaction with phosphoryl chloride is a small amount of α-chloro-N-phenylsuccimide (m.p. 118 to 90°), which can be isolated from the original mother liquor. This is undoubtedly produced by the hydrogen chloride splitting off during the reaction.

Maleanilidium dichlorophosphate is very unstable. Upon being heated rapidly, it decomposes at 142°, at which temperature it turns brown. The maleanilide formed upon hydrolysis varies in melting point, depending upon the conditions under which the melting point is determined, since at the fusion temperature it is converted in part to the isomeric fumaranilide. Heated rapidly, it melts at 175°. In the third edition of Bielstein's *Organischen Chemie* this compound is listed both as maleanilide and as phenylaspartanil. When heated with hydrochloric acid it produces N-phenylmaleimide (m.p. 90 to 91°) and anilinium chloride.

Phosphoryl Chloride



Maleanilic acid + Phosphoryl chloride + Water ⟶ Maleanilide dichlorophosphate

Procedure. A mixture of 19 g. of maleanilic acid and 115 g. of phosphoryl chloride is carefully heated at 100° in a hood, and held at this temperature for several minutes, until all the maleanilic acid is dissolved in the oxychloride. The reaction mixture is then cooled and is diluted with carbon disulfide, whereupon yellow needles of the product are deposited. These are separated, washed with ether, and then dried over concentrated sulfuric acid.

References

van Dorp, W. A., and van Haarst, P. M., *Rec. trav. chim.* **19**, 311 (1900). *Cf.*: Anschütz, R., and Wirtz, Q., *Ann.* **239**, 137 (1887).

α-Chloro-N-phenylsuccinimide

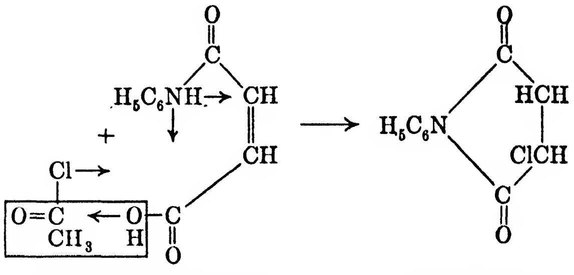
(α-Chlorosuccinanil)

This preparation is another example of the failure of acid chlorides to add to the C:C unsaturated bond of maleyl compounds. (*Cf.* Reaction of Phosphoryl Chloride.) Here α-chloro-N-phenylsuccinimide is the usual product of the reaction. At elevated temperatures even the hydrogen chloride that is evolved during the reaction fails to add to the ethylene group. (See N-Phenylmaleimide Preparation.) Under such conditions, the acetyl chloride acts only as a dehydrating agent leading to ring closure.

α-Chloro-N-phenylsuccinimide is a colorless crystalline compound melting at 117 to 118° or 118 to 119°.

Use. Its structure suggests that it should be an interesting reactant for chemical synthesis.

Acetyl Chloride



Acetyl chloride + Maleanilic acid ⟶ α-Chloro-N-phenyl-succinimide

Procedure. A mixture of 19 g. of maleanilic acid and an excess of acetyl chloride are digested for 45 minutes. The reaction mixture is then cooled and diluted with benzene or ligroin, which causes the α-chloro-N-phenyl-succinimide to precipitate as fine needles. These are recovered and dried in the usual manner.

References

von Auwers, K., *Ann.* **309**, 347 (1899). *Cf.*:
Giustiniani, E., *Gazz. chim. ital.* **28** (II), 191 (1898).

Fumaryl Chloride

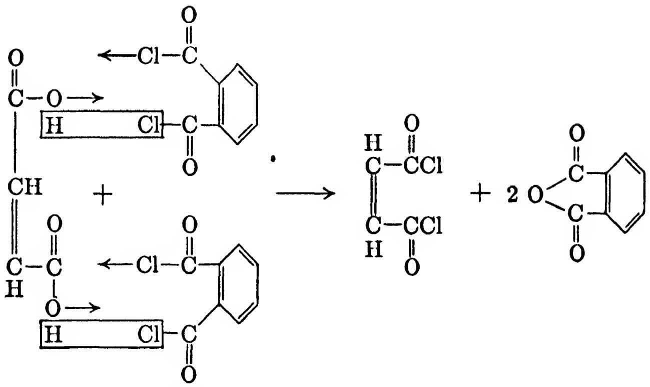
Fumaryl chloride has been prepared by a number of other different methods, for example, by the reaction of thionyl chloride with fumaric acid and of phosphorus pentachloride with maleic acid or anhydride. However, none of these methods has given as good yields as either the one described here or the reaction of phthalyl chloride with maleic anhydride in the presence of zinc chloride. When maleic acid is allowed to react with phthalyl chloride, large amounts of maleic anhydride are formed that do not react with the acid chloride except in the presence of a catalyst. In consequence, only very poor yields of fumaryl chloride are obtained.

Maleyl chloride, the optical isomer, is unknown, but under proper conditions maleic acid may be caused to react with phosphorus pentachloride to give the isomeric dichloride, γ,γ-dichloro-γ-hydroxyisocrotonic lactone (*q.v.*). This compound isomerizes slowly to fumaryl chloride.

Fumaryl chloride is a liquid that boils at 161 to 164° (60° at 16 mm.). It has the following densities at different temperatures: d_{15}^{15} 1.4202, d_{20}^{20} 1.4149 and d_{25}^{25} 1.4095.

Use. It is a valuable intermediate in the preparation of a number of derivatives of fumaric acid, as, for example, fumaryl peroxide, fumaryl bisaspartic acid, bis(4-phenoxybenzoyl)ethylene, and other substituted dibenzoylethylenes (*q.v.*).

Phthalyl Chloride



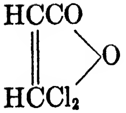
Fumaric acid + Phthalyl chloride ⟶ Fumaryl chloride + Phthalic anhydride

Procedure. A mixture of 48 g. of fumaric acid and 184 g. of phthalyl chloride is heated cautiously in a hood to about 120°. At this point the fumaric acid begins to dissolve slowly in the acid chloride with a copious evolution of fumes of hydrogen chloride. The temperature is then gradually raised to 160° and held at this temperature until the amount of gas emitted is greatly diminished. The reaction mixture is then fractionally distilled at ordinary pressures. The amount of fumaryl chloride formed is practically equivalent to the amount of fumaric acid in the original mixture. Only a very small amount of maleic anhydride is formed as the other product of fumaric acid.

References

van Dorp, W. A., and van Dorp, G. C. A., *Rec. trav. chim.* **25,** (2), 96 (1906). *Cf.*:
Anschütz, R., and Wirtz, Q., *Ann.* **239,** 137 (1887).
Kyrides, L. P., *J. Am. Chem. Soc.* **59,** 207 (1937); *Org. Syn.* **20,** 51 (1940).
Lutz, R. E., *J. Am. Chem. Soc.* **52,** 3423 (1930).
Meyer, H., *Monatsh.* **22,** 421 (1901).
Michael, A., *J. prakt. Chem.* **46,** (2), 392 (1892); **52,** (2), 292 (1896).
Mousseron, M., Granger, R., and Claret, J., *Bull. soc. chim. France* **1947,** 868.
Perkin, W. H., *Ber.* **14,** 2540 (1881).
Piutti, A., *Gazz. chim. ital.* **17,** 126, 185 (1887); **16,** 278 (1886); *Ber.* **19,** 1693 (1886).
Vanino, L., and Thiele, E., *Ber.* **29,** 1724 (1896).

U.S. 2,437,867.



γ,γ-Dichloro-γ-hydroxyisocrotonic Lactone

(5,5-Dichloro-2,5-dihydro-2-oxofuran or Maleïn Chloride)

This unsymmetrical maleyl chloride is relatively unstable. It readily rearranges to fumaryl chloride, even upon standing for several days at room temperature. When the product is distilled at 24 mm. instead of 11 mm. pressure, it partially decomposes into maleic anhydride and fumaryl chloride. This mixture is very difficult to separate. The lactone has not been prepared from maleic anhydride nor from maleic acid with other acid chlorides.

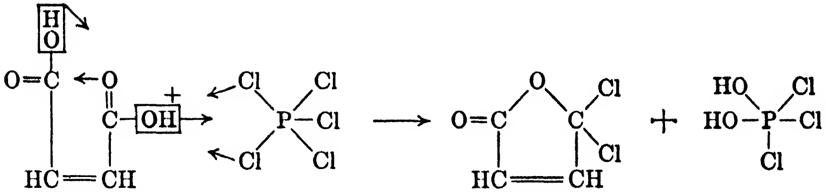
The usual method for preparing chlorides of a similar structure is to heat the symmetrical acid chlorides with aluminum chloride. This is the method that has been used in the preparation of *asym-o*-phthalyl chloride, α-bromomaleyl chloride and α,β-dibromomaleyl chloride. When fumaryl chloride, however, is treated with aluminum chloride, only very small amounts of the asymmetric chloride are obtained. The major products of the reaction are carbon monoxide and hydrogen chloride.

These asymmetric chlorides markedly differ from the symmetrical acid chlorides in their slower rate of reaction, the type of products formed, their effect upon hydrogen catalysts, the color of metal complexes with aluminum chloride, and their dimorphism. The last property is characteristic of lactones in general.

γ,γ-Dichloro-γ-hydroxyisocrotonic lactone boils at 70 to 71° under 11 mm. pressure, according to Anschütz and Wirtz. Lutz obtained a redistilled product boiling at 65° under 2 mm. by the same method.

Use. It may be used for preparing γ-hydroxy-γ,γ-diphenylcrotonic acid by allowing it to react with benzene in the presence of aluminum chloride. *asym*-α,β-Dibromomaleyl chloride under similar conditions produces 2-bromo-1,1-diphenyl-3-indenecarboxylic acid, through loss of hydrogen bromide, which results in the cyclization.

Phosphorus Pentachloride



Maleic acid + Phosphorus chloride ⟶ γ,γ-Dichloro-γ-hydroxyisocrotonic lactone + Trichlorophosphoric acid

Procedure. A mixture of 38.6 g. of maleic acid and 69 g. of phosphorus pentachloride is placed in a 250-ml. Claisen distilling flask in a hood and the flask is connected to a highly efficient pump. The products are then distilled from the reaction mixture, not allowing the pressure to exceed 11 mm. The product is redistilled at a pressure of approximately 2 mm.

References

Anschütz, R., and Wirtz, Q., *Ber.* **18**, 1947 (1885). *Cf.*:
Lutz, R. E., *J. Am. Chem. Soc.* **52**, 3405, 3436 (1930).
Ott, E., *Ber.* **46**, 2172 (1913); *Ann.* **392**, 267 (1912).
Vandevelde, J., *Bull. Classe Sci., Acad. Belg.* **37**, (3), 680 (1900).
van Dorp, W. A., and van Dorp, G. C. A., *Rec. trav. chim.* **25**, (2), 98 (1906).

Diethyl α,β-Bis(trichloromethyl)succinate

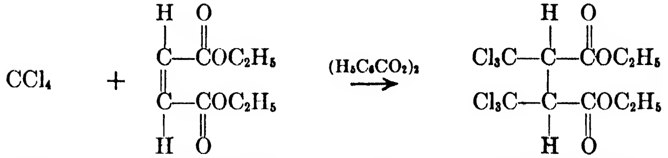
Diethyl α,β-bis(trichloromethyl)succinate is one of the products formed when diethyl maleate is allowed to react in the presence of large amounts of benzoyl peroxide in carbon tetrachloride. Chlorobenzene and hexachloroethane are also found in the volatile portion of the products. This reaction is similar in several respects to that of hexaphenylethane (page 23) and to that of maleates with benzoyl peroxides in the absence of a solvent (page 209).

An excess of carbon tetrachloride such as used here apparently is needed in order to obtain any appreciable yield of α,β-bis(trichloromethyl)succinate; but it is questionable whether so large an excess of peroxide is required for the formation of such polychloro compounds, judging from analogous reactions of ethylene compounds in carbon tetrachloride where benzoyl peroxide is used as the catalyst.

Should conditions be found for increasing the yields, this method would offer a most convenient procedure for adding various groups derived from solvents to the ethylene bond of maleic compounds. Dimethyl dioxanylsuccinate, for example, has been identified as one of the products of the reaction of dimethyl maleate with benzoyl peroxide in dioxane.

Diethyl α,β-bis(trichloromethyl)succinate is obtained as colorless needles that melt at 93.5 to 94.5°. The acid melts at 183 to 184.5°, and the anhydride at 117 to 118.5°. The diethyl ester, when refluxed 12 hours with a 20% potassium hydroxide solution, presumably loses two moles of hydrogen chloride to produce what is apparently α,β-bis(dichloromethylene)succinic acid. This product occurs as colorless cubes that melt at 219°.

Carbon Tetrachloride



Carbon tetrachloride + Diethyl maleate ⟶ Diethyl α,β-bis(trichloromethyl)succinate

Procedure. A solution of 109 g. of benzoyl peroxide and 172 g. of diethyl maleate in 1200 ml. of carbon tetrachloride is refluxed for 36 hours. The residue obtained upon removal of the solvent is extracted with ether. The extract is washed with a sodium bicarbonate solution, dried, and then fractionally distilled with the aid of reduced pressure. This yields a total of 87 g. of liquid products boiling up to 200° under 1 mm. pressure and 131 g. of dark non-volatile resin. Crystals separate from fraction boiling at b_1 130 to 150°. These are separated, sublimed under reduced pressure, and recrystallized from 50% ethanol to give pure diethyl α,β-bis(trichloromethyl)succinate.

References

Marvel, C. S., Prill, E. J., and De Tar, D. F., *J. Am. Chem. Soc.* **69**, 52 (1947). *Cf.*: Kharasch, M. S., Jensen, E. V., and Urry, W. H., *J. Am. Chem.* **69**, 1102 (1947).

CHAPTER
3

Hydrogen

The size of this chapter should in no manner detract from its importance, since the single example given is a typical one for a large number of compounds containing the unsaturated maleyl group. This reaction with hydrogen is another example of the ease with which many different reagents add to the carbon-carbon double bond of maleyl compounds. In this instance, the reaction may be carried out under a variety of different conditions with excellent yields. Even a mild reducing agent, such as zinc and sulfuric acid, may be employed as the source for the hydrogen.

In most cases, these reductions apparently involve only the simple addition of hydrogen atoms to the carbons of the ethylenic double bond of the maleyl compound. However, this cannot be true for all such reactions, as indicated by the studies of Ott, and of Lutz and co-workers. It is possible, as postulated by Conant and Lutz, that during the reduction of maleates to succinates under certain conditions, hydrogen first adds to the carbonyls of the conjugated maleyl grouping to give a dienol that isomerizes irreversibly by a shift of hydrogens to the stable keto form of succinic acid, viz.,

$$\underset{1}{\mathrm{O}}{=}\underset{2}{\mathrm{C}}\mathrm{(OH)}{-}\underset{3}{\mathrm{CH}}{=}\underset{4}{\mathrm{CH}}{-}\underset{5}{\mathrm{C}}\mathrm{(OH)}{=}\underset{6}{\mathrm{O}} + 2\mathrm{H} \rightleftharpoons$$

$$\mathrm{HO{-}C(OH){=}CH{-}CH{=}C(OH)OH} \longrightarrow$$

$$\mathrm{O{=}C(OH){-}CH_2{-}CH_2{-}C(OH){=}O}$$

The initial addition of hydrogen to the carbonyl groups is assumed to occur as a reversible reaction. It can take place as a 1,2-, as a 1,4- or, as shown, as a 1,6-addition similar to that of Grignard reagents described in Chapter 4. For example, such type of addition would readily account for the apparent oxidation-reduction potential observed in the hydrogenation of fumaric acid, for the varying proportions of isomers obtained in hydrogenating sodium dimethylmaleate under different conditions, and for the dimeric and cyclic compounds obtained from diaroylethylenes under certain conditions.

Both succinic acid and its anhydride are produced commercially in this country by the hydrogenation of maleic anhydride. Many important chemicals can be prepared from them, as can be seen on the following page.

Probably the most interesting reactions of succinic acid are those involving its methylene groups. The ease with which the hydrogens may be replaced from these two groups may be due to their juxtaposition to its carbonyl groups. Esters of succinic acid, for example, are unusual in their strong tendency to undergo aldol condensation with ketones to produce itaconic acids, *methylenesuccinic acids.* This reaction is known as the Stobbe condensation. The failure of diethyl malonate to condense in a similar manner, even though it contains a more reactive methylene group, would indicate that this type of reaction involves more than the reactivity of the methylene groups alone. Paraconic acids are possibly first formed as intermediates in the production of itaconic acids. They are the usual products of reaction with aldehydes.

The recent preparation of several methylbenz[*a*]anthracenes for physiological studies is a typical example of how reactions of succinic acid can be employed in a series of syntheses leading to products of a particular interest.

Succinic Acid

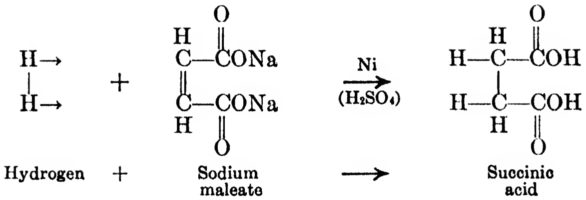
Pure succinic acid consists of colorless monoclinic crystals with a d_4^{15} of 1.564. When pure, it melts at 189 to 190°. The commercial practical grade consists of crystals that melt at 186 to 188°. The anhydride melts at 119.6° to give a liquid that boils at 261°. The acid is soluble in water and alcohol, only slightly soluble in ether, and practically insoluble in benzene and chloroform.

Uses. Succinic acid is the starting material for the synthesis of a large number of very useful substances. Its esters have been employed as plasticizers for adhesives, vinyl plastics, rubber, and lacquers; as ingredients in bitumen products; as additives in lubricating and cutting oils; as perfumes; as water-repellent agents; and as aids in the dyeing of vinyl yarns. The succinyl peroxide and N-chlorosuccinimide derivatives are powerful germicides. The succinyl peroxide has been suggested for the bleaching of food products; and the N-chlorosuccinimide is used in the purification of drinking water. N-Bromosuccinimide is employed as a brominating agent, particularly where it is desired to introduce bromine into unsaturated compounds without affecting the double bond. (See Djerassi.) Several oil-soluble dyes, alkyd resins, ester-type elastomers, sulfa-drugs, arsenicals, other pharmaceuticals, synthetic musks, detergents, and wetting agents also depend upon succinic acid for their manufacture.

Succinic acid may be used as a reagent in photographic processes and in chemical analysis.

A wide variety of other chemicals can also be prepared starting with this acid. They include, for example, succinosuccinic esters; acetonediacetic anhydride; aroylpropionic acids; substituted itaconic acids; paraconic acids; fulgides; 4-(*p*-methoxyphenyl)-3-butenoic acids; 1,8-diphenyl-1,3,5,7-octatetraene; 3,3′-dicoumarin; pyrocinchonic anhydride; ethyl formylsuccinate; levulinic acid; 3-acetyl-2,5-dimethylfuran; 2-(alkylmercapto)thiophenes; α,β-dichloromaleimide; 5-hydroxy-6-methylcinchomeronic acid; N-*p*-phenetylsuccinimide; 2-alkylbutadienes; 8,9,11-trimethylbenz[*a*]anthracene; methyl 2,5-dioxo-1-pyrrolidene acetate; and equilein.

Hydrogen



Procedure. A solution containing 25 g. of sodium hydroxide in 100 ml. of water is placed in a 325-ml. autoclave. To this is added 58 g. of maleic acid and, when dissolved, 5 to 8 g. of Raney nickel catalyst. Hydrogenation is then carried out with proper precautions at 2500 lb. per sq. in. and at 100°. Upon completion, the catalyst is removed by filtration, the filtrate acidified and evaporated to dryness under reduced pressure. The product is purified by extraction with absolute alcohol and recrystallization from water. The yield is 98% of theory.

The above reaction may be carried out at ordinary temperatures, if a palladium catalyst is used. Reduction with zinc and sulfuric acid is also practical.

References

Allen, B. B., Wyatt, B. W., and Henze, H. R., *J. Am. Chem. Soc.* **61**, 843 (1939). *Cf.*:
Backer, H. J., and van der Zanden, J. M., *Rec. trav. chim.* **50**, 645 (1931).
Carrière, E., *Ann. chim.* **17**, 38 (1921).
Ciamician, G. L., and Silber, P., *Gazz. chim. ital.* **13**, 403 (1883).
Cook, J. W., and Robinson, A. M., *J. Chem. Soc.* **1938**, 505.
Curtius, T., and Raschig, K., *J. prakt. Chem.* **125**, 466 (1930).
Djerassi, C., *Chem. Revs.* **43**, 271 (1948) (Rev. of bromosuccinimide, 125 ref.).
Fittig, R., et al., *Ber.* **30**, 2148 (1897); *Ann.* **250**, 166 (1888); **255**, 1, 18, 257, 275 (1898); **267**, 204 (1892); **331**, 160, 191 (1904)
Hughes, E. D., and Watson, H. B., *J. Chem. Soc.* **1930**, 1733.
Johnson, W. S., et al., *J. Am. Chem. Soc.* **67**, 430, 1360, 1366 (1945); **69**, 74, 2942 (1947); **70**, 418 (1948); **71**, 1384 (1949); **72**, 501, 505, 511, 514, 2398 (1950).
Kharasch, M.S., and Fuchs, C. F., *J. Org. Chem.* **9**, 359 (1944).
Kuhn, R., and Winterstein, A., *Helv. Chim. Acta* **11**, 109 (1928).
Linstead, R. P., and Mann, J. T. W., *J. Chem. Soc.* **1930**, 2064.
Lutz, R. E., et al., *J. Am. Chem. Soc.* **57**, 1947, 1953, 1957 (1935).
Magnanini, G., and Bentivoglio, T., *Gazz. chim. ital.* **24** (I), 435 (1894).
Marvel, C. S., Meyers, R. L., and Saunders, J. H., *J. Am. Chem. Soc.* **70**, 1694 (1948).
McQuillin, F. J., and Robinson, R., *J. Chem. Soc.* **1941**, 586.
Morgan, G. T., and Walton, E., *J. Chem. Soc.* **1931**, 615.
Neuberg, C., *Z. physiol. Chem.* **31**, 574 (1901).
Piutti, A., *Gazz. chim. ital.* **20**, 167 (1890).
Reddish, G. F., and Pauley, A. W., *Bull. Natl. Formulary Comm.* **13**, 11 (1945).
Robinson, R., and Seijo, E., *J. Chem. Soc.* **1941**, 582.
Shaefer, W. E., *Ind. Eng. Chem.*, Anal. Ed., **2**, 115 (1930).
Steinkopf, W., and Leonhardt, P., *Ann.* **495**, 166 (1932).
Stobbe H., et al., *Ann.* **315**, 219 (1901); **314**, 111 (1901); **380**, 1 (1911).
Werbin, H., and Spoerri, P. E., *J. Am. Chem. Soc.* **69**, 1681 (1947).
Wojcik, B., and Adkins, H., *J. Am. Chem. Soc.* **56**, 2424 (1934).

U.S. 1,621,757; 1,939,217; 2,368,765; 2,371,102; 2,384,068; 2,407,726; 2,445,006; 2,447,325. Brit 274,095. Indian 31,437.

CHAPTER
4

Metallic Compounds

The reactions between organometal compounds and maleic derivatives, as described in this chapter, comprise three general classes of preparations, namely:

(1) Reactions that give final products that contain the metal bound to one or both of the carbons of the maleyl group.

(2) Reactions involving the use of a metal compound or salt that for practical purposes serves as a catalyst, although it may form an essential complex or metal derivative with the substance reacting with the maleic derivative.

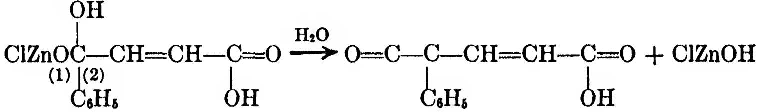
(3) Grignard reactions where the metal is removed from the product by hydrolysis during the preparation.

The first group of reactions includes those of maleic anhydride with mercuric acetate and with hexaphenyldilead. Both these reactants yield α,β-disubstituted succinic acids. Mercuric acetate in aqueous solution, for example, yields the mercuric salt of β-acetoxymercurimalic acid, whereas hexaphenyldilead produces the bis(triphenyllead)succinic anhydride. The latter reactant, like hexaphenylethane, apparently dissociates into free radicals during the reaction.

The second, by far the most important of the three groups of reactions, involves the use of such auxiliary substances as sodium alkoxides and anhydrous aluminum chloride, which are known in some cases to form definite metallo complexes with one of the reactants. Hence they have been included in this chapter rather than treated separately elsewhere. The reactions with sodium alkoxides are a very convenient means of causing a variety of substances to add to the ethylene bond of maleic derivatives. Examples given include the addition of alcohols, β-keto esters, malonates, and nitriles. Such reactions with keto esters are known as Claisen syntheses, while those with malonates and nitriles are known as Michael syntheses. Some of these reactions can also be carried out in the presence of strongly alkaline catalysts other than sodium alkoxides, but the usual procedure is to add either metallic sodium to the reactant in the presence of an alcohol or a sodium alkoxide, before incorporating the maleyl compound in the reaction mixture as shown in the preparations selected. Reactions with nitroparaffins and with potassium cyanide are included under nitrogen compounds, since they may be carried out under somewhat different conditions from those generally employed here.

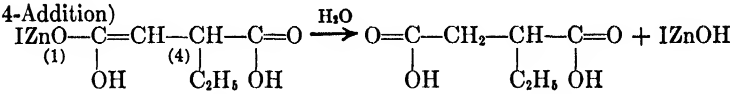
The third group is limited to the Grignard reactions. Seven examples illustrating the different end products that may be obtained from the Grignard synthesis are given. A variety of products may be formed by these reagents, depending upon the conditions, upon the proportions used, and upon whether the reagent adds to the maleyl group at the 1,2-(*5,6-*) or 1,4-(*3,6-*) positions, namely:

(1,2-Addition)



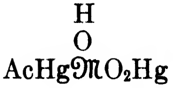
$$ClZnO\underset{\substack{(1)\,|\,(2)\\ C_6H_5}}{\overset{OH}{C}}-CH=CH-\underset{OH}{C}=O \xrightarrow{H_2O} O=C-\underset{C_6H_5}{C}-CH=CH-\underset{OH}{C}=O + ClZnOH$$

(1,4-Addition)



$$IZnO-\underset{\substack{(1)\\ OH}}{C}=CH-\underset{\substack{(4)\\ C_2H_5}}{CH}-\underset{OH}{C}=O \xrightarrow{H_2O} O=\underset{OH}{C}-CH_2-\underset{C_2H_5}{CH}-\underset{OH}{C}=O + IZnOH$$

For example, phenylzinc chloride undergoes a 1,2-addition with maleic anhydride to produce β-benzoylacrylic acid, but isopropylcadmium bromide adds to the 1,4-positions of maleates to yield the isopropylsuccinates. In a like manner, two moles of a Grignard reagent may produce either γ-hydroxycrotonic acid as a result of a 1,2-1,2-addition, a γ-ketopropionic acid from a 1,2-1,4-addition, or a diketoalkene from a 1,2-5,6-addition. An even greater number of compounds are theoretically possible when larger amounts of Grignard reactant are employed, as illustrated in some of the other examples given. There is also some evidence that a 1,6-addition may occur to a limited extent under certain conditions.



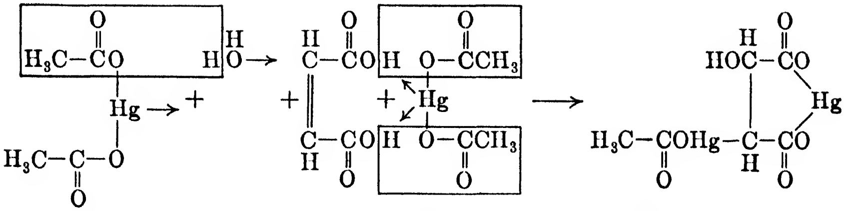
$AcHg\overset{\overset{H}{O}}{\mathfrak{M}}O_2Hg$

Mercuric β-Acetoxymercurimalate

Maleic acid is the only maleyl compound that has been reported to react with mercuric acetate to form this type of product. Fumaric acid under identical conditions reacts by metathesis to yield only mercuric fumarate. Apparently, the carboxyl group of the *trans*-configuration leads to a steric hindrance that prevents the large mercuric ion from reacting with the olefin bond of this acid.

Mercuric β-acetoxymercurimalate is a colorless solid that is insoluble in both water and alcohol. It dissolves in most of the acids but not in dilute acetic acid. It also dissolves in alkaline solutions but with the complete destruction of the addition compound, whereas a sodium chloride solution yields a mixture of disodium β-chloromercurimalate, sodium acetate, and mercuric chloride. The latter solution is strongly acidic. Potassium iodide solutions, like those of alkalies, destroy the complex malate.

Mercuric Acetate



Mercuric acetate + Water + Maleic acid ⟶ Mercuric β-acetoxymercurimalate

Procedure. A solution containing 5 g. of maleic acid in 40 ml. of water is added to one containing 20 g. of mercuric acetate in 60 ml. of water. A small amount of a yellow precipitate is formed, which is removed after adding acetic acid. The filtrate is diluted with water and heated upon a water bath. To this is added 4 g. of maleic acid in 40 ml. of water. Further heating produces a white, microcrystalline precipitate that increases in amount when the reaction mixture is allowed to cool. This precipitate is collected and thoroughly washed with very dilute acetic acid, then with pure water, followed by alcohol, and then ether. It is then air-dried. The initial washing must be carried out with acidulated water, since pure water causes a material to precipitate from the mother liquor that contaminates the product. The yield is 7.5 g.

Reference

Biilmann, E., *Ber.* **35,** 2576 (1902).

$(Ar_3Pb)_2\mathcal{M}(OH)_2$ α,β-BIS(TRIARYLLEAD)SUCCINIC ACIDS

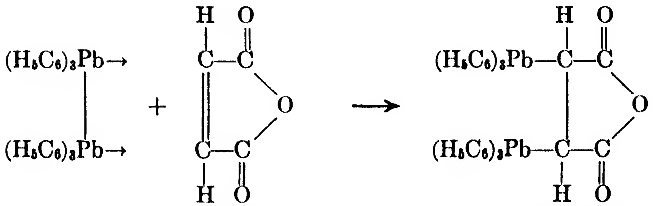
α,β-Bis(triphenyllead)succinic Anhydride

This reaction apparently is very similar to that of hexaphenylethane (*q.v.*). Leeper reports that it also occurs when a chloroform solution of the two reactants is allowed to stand for 5 months.

The product does not melt below 330° but only darkens at 265 to 270°. It is insoluble in acetone, dioxane, benzene, chloroform, carbon tetrachloride, and petroleum ether. It is only slightly soluble in boiling water but dissolves in glacial acetic acid. When refluxed with a 10% solution of sodium hydroxide, it slowly forms a sodium salt that is also insoluble in water.

In contrast, the salt, triphenyllead acid maleate, melts at 207°. This salt can be obtained from triphenyllead hydroxide and maleic anhydride. The neutral salt sinters at 189 to 199°.

Hexaphenyldilead

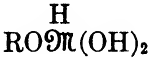


Hexaphenyldilead + Maleic anhydride → α,β-Bis(triphenyllead)-succinic anhydride

Procedure. An equivalent amount of hexaphenyldilead is slowly added to molten maleic anhydride, and the product obtained is progressively extracted with benzene, alcohol, water, and an aqueous solution of ammonium acetate to effect purification.

Reference

Leeper, R. W., *Iowa State Coll. J. Sci.* **18**, 57 (1943).



$RO\overset{H}{\mathfrak{M}}(OH)_2$

ALKOXYSUCCINIC ACIDS

Methoxysuccinic Acid

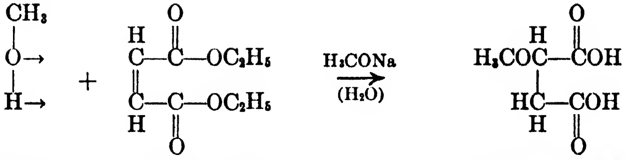
Aliphatic alcohols of different chain lengths readily react with maleates in the presence of metallic sodium or the sodium ethoxide to produce alkoxysuccinates. The procedure given is a general one. It can be used with both branched- and straight-chain monohydric alcohols. To avoid the formation of a mixture of products, it is common practice to use the maleic esters and alcoholates derived from the same alcohol. Little, if any, fumaric acid is formed during these preparations. The acid is obtained, as shown, through saponification of the alkoxysuccinate.

Methoxysuccinic acid is a crystalline substance that melts at 101 to 103° when purified. The crude acid melts at 95 to 100°.

Use. The long-chain alkoxy derivatives, such as decyloxy- and dodecyloxysuccinic acids, have been used as intermediates in the preparation of synthetic detergents.

Alkoxysuccinic acids in general undergo many of the reactions of succinic acid (*q.v.*), thus offering the same possibilities for the preparation of useful compounds.

Methanol



Methanol + Diethyl maleate ⟶ Methoxysuccinic acid

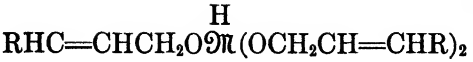
Procedure. To a methoxide solution, prepared by dissolving 3 g. of sodium in 30 g. of methanol, is carefully added 10 g. of diethyl maleate. Some heat is evolved. The solution becomes colored, and part of the product precipitates. The reaction mixture is then refluxed, whereupon more precipitate is formed as a result of some saponification of the methoxysuccinic ester. After refluxing, the solvent is removed by distillation, and the residue heated with a slight excess of a potassium hydroxide solution. The alkaline solution is then neutralized with hydrochloric acid, calcium chloride is added, and the solution is boiled. Crystalline calcium methoxysuccinate is precipitated. This is carefully decomposed with a little less than the calculated amount of sulfuric acid, and the mixture is extracted with alcohol. The extract yields a sirup upon evaporation. The sirup changes to a crystalline mass of crude acid upon standing in an evacuated desiccator, over sulfuric acid.

References

Purdie, T., *J. Chem. Soc.* **47**, 855 (1885); **39**, 344 (1881). *Cf.*:

U. S. 2,377,246.

ALKENYLOXYSUCCINATES



$$RHC{=}CHCH_2O\overset{H}{\mathfrak{M}}(OCH_2CH{=}CHR)_2$$

Diallyl Allyloxysuccinate

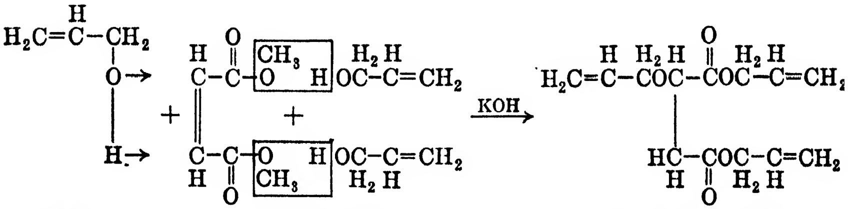
Maleic esters undergo both addition and ester exchange with unsaturated alcohols in the presence of alkaline catalysts to yield the dialkenyl alkenyloxysuccinic esters. Containing three olefin groups, these products readily polymerize in the presence of siccatives, such as cobalt and manganese linoleates. In this respect, they resemble the vegetable drying oils.

The procedure appears to be a general one. Dimethallyl methallyloxysuccinates have also been prepared by it. If desired, the time of reaction can be shortened by using a high-boiling inert solvent to increase the reaction temperature. Continuous removal of the lower boiling alcohol that is formed assures complete conversion to the dialkenyl ester.

Both diallyl allyloxysuccinate and dimethallyl methallyloxysuccinate are high-boiling liquids that cannot be distilled without change at ordinary pressures. The former boils under 4 mm. pressure at 124 to 136°. The latter has a boiling point of b_3 150–155°.

Use. These unsaturated esters have been used as synthetic vehicles for paint and varnish and as plasticizers for lacquer. Products of similar structure have been valuable in the preparation of resins and of copolymers of various types.

Allyl Alcohol

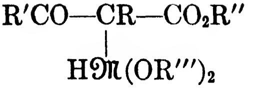


Allyl alcohol + Dimethyl maleate ⟶ Diallyl allyloxysuccinate

Procedure. A toluene solution of 144 g. of dimethyl maleate and 58 g. of allyl alcohol is placed in a flask carrying a fractionating column and refluxed for 6 to 10 hours in the presence of a strongly alkaline catalyst, such as potash. The methanol that is formed is removed by distillation during the refluxing. Upon completion of the reaction, the solvent is distilled off and the product purified by fractionation under reduced pressure.

Reference

Rothrock, H. S., U.S. 2,346,612 (1944).



$$\begin{array}{l}R'CO\text{—}CR\text{—}CO_2R''\\ \qquad\;\; | \\ \qquad H\mathfrak{M}(OR''')_2\end{array}$$

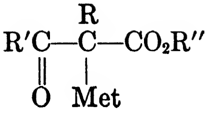
KETOTRICARBOXYLIC ESTERS

Triethyl α-Acetotricarballylate

Keto esters, such as acetoacetic ester and benzoylacetic ester and their homologs, readily combine with maleic esters in the presence of sodium alkoxides as shown by this preparation. Reaction takes place by the carbon adjacent to the carbonyl groups adding to the double bond of the maleate. The free acids can readily be obtained through saponification of the resulting esters. When maleic acid is employed in place of the maleates, a very poor yield is obtained. Chlorosuccinic esters, however, can be readily substituted for the maleic esters.

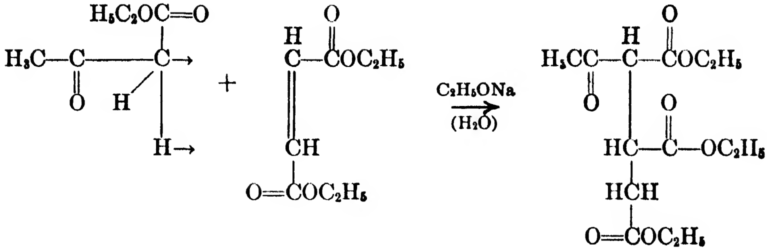
Triethyl α-acetotricarballylate is a liquid that boils without decomposition at 187 to 189°, under 11 mm. pressure.

Use. These products should form some interesting resins with polyhydric alcohols and other resinifying substances, since they contain a keto and three carboxyl groups, which should impart a high degree of functionality to the reactants.



$$R'\underset{\underset{O}{\|}}{C}-\overset{R}{\underset{\underset{Met}{|}}{C}}-CO_2R''$$

Ethyl Acetoacetate



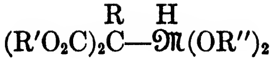
Ethyl acetoacetate + Diethyl fumarate ⟶ Triethyl α-acetotricarballylate

Procedure. Sixty-eight grams of dry sodium ethoxide is suspended in ether that has been freed of all traces of water and alcohol. To this solution is first added 118 g. of ethyl acetoacetate and then 172 g. diethyl fumarate. Considerable heat is evolved during the addition. The reaction mixture is allowed to stand for 12 to 14 hours and is then acidified with dilute sulfuric acid. This produces two layers. The ether layer is separated and shaken with a sodium carbonate solution, again separated, dried, and allowed to evaporate. The oily residue obtained is then fractionated under reduced pressure to obtain a relatively pure product. The yield of triethyl acetotricarballylate obtained in this manner is 75% of theory.

References

Ruhemann, S., and Browning, K. C., *J. Chem. Soc.* **73**, 727 (1898). *Cf.*:
Emery, W. O., *Ber.* **23**, 3757 (1890).
Trephiliev, H., *J. Russ. Phys. Chem. Soc.* **39**, 1618 (1908), *Ber.*, **39**, 1859, 2129 [1906].

Brit. 594,182.



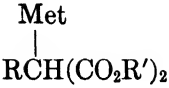
$(R'O_2C)_2\overset{R}{C}—\overset{H}{\mathfrak{M}}(OR'')_2$

Tetraethyl 1,2,3,3-Pentanetetracarboxylate

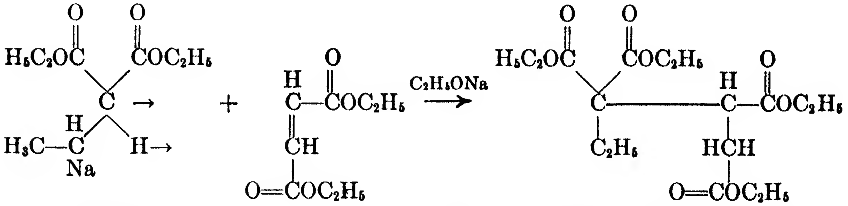
Malonic esters and their homologs readily condense with maleic esters in the presence of sodium ethoxide to yield the $\alpha,\beta,\gamma,\gamma$-tetracarboxylic acids. The procedure is a general one for preparing both the aliphatic and the aromatic homologs. Dialkyl dibromosuccinates may be substituted for the maleic ester in these preparations. In like manner, the molecular compound obtained by treating dipropyl acetal with potassium hydroxide (Brit. 594,182) may be substituted for sodium ethoxide.

Tetraethyl 1,2,3,3-pentanetetracarboxylate is a liquid that boils at 197° under 13.5 mm. pressure. The 1,2,3-pentanetricarboxylic acid obtained upon saponifying it melts at 153° when pure.

Use. Compounds of this general type have produced some interesting resins and plasticizers.



Diethyl Ethylmalonate



Diethyl ethylmalonate + Diethyl fumarate ⟶ Tetraethyl 1,2,3,3-pentanetetracarboxylate

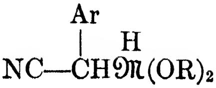
Procedure. A sodium ethoxide solution is prepared by dissolving 2.1 g. of sodium in 25 g. of absolute alcohol. To this solution is carefully added, at 20 to 50°, 17.5 g. of diethyl ethylmalonate and then 16 g. of diethyl fumarate. The reaction mixture is allowed to stand for 12 hours. After this, most of the solvent is distilled off under reduced pressure, and the residue is treated with water in the usual manner. The aqueous mixture is shaken three times with fresh ether, and the combined extracts are washed first with dilute alkali and then with water. They are then dried and allowed to evaporate. The residue obtained is separated by distilling under reduced pressure. The major portion, boiling at 196 to 198° under 14 mm., is collected. It is redistilled at the same pressure to yield 20.6 g. or 62% of the tetraethyl ester of 1,2,3,3-pentanetetracarboxylic acid.

The 1,2,3-pentanetricarboxylic acid is obtained when this ester is hydrolyzed with twice the theoretical amount of concentrated hydrochloric acid. It can be obtained pure by crystallizing thrice from hot acetic acid.

References

Michael, A., *Ber.* 33, 3769 (1900). *Cf.*:
Duff, D. A., and Ingold, C. K., *J. Chem. Soc.* 1934, 87.
Gardner, J. A., and Rydon, H. N., *J. Chem. Soc.* 1938, 42.
Ingold, C. K., *J. Chem. Soc.* 119, 329 (1921).
Koelsch, C. F., *J. Am. Chem. Soc.* 65, 437 (1943).
Malachowski, R., Bilbel, E., and Biliński-Tarasowicz, M., *Ber.*, 69B, 1295 (1936)
Michael, A., and Ross, J., *J. Am. Chem. Soc.* 52, 4598 (1930).
Ruhemann, S., and Cunnington, A. V., *J. Chem. Soc.* 73, 1010 (1898).
Rydon, H. N., *J. Chem. Soc.* 1935, 420.

Brit. 594,182.



$$\mathrm{NC{-}\overset{Ar}{\overset{|}{C}}H\overset{H}{\mathfrak{M}}(OR)_2}$$

CYANOMETHYLSUCCINATE

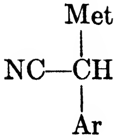
Methyl (α-Cyanobenzyl)succinate

Phenylacetonitriles, like the malonates, contain an active α-methylene group. Hence they also undergo the Michael reaction in the presence of alkoxides. In this particular preparation a solvent is not needed. Superior yields are generally obtained by omitting it, as is done in the procedure selected. With diethyl maleate, for example, only a 46% yield was obtained in ethanol, compared to 52 to 58% yields without the use of solvent. By omitting the solvent, the formation of complex compounds such as that obtained by Henze may be largely avoided, as well as the excessive formation of alkoxysuccinates (*q.v.*), which are readily produced in the presence of larger amounts of alcohol containing a basic catalyst.

Compounds with a carboxyl group in place of the phenyl substituent, such as the alkyl cyanoacetates, are much less reactive than α-tolunitrile. In this case it is necessary to add a suspension of the sodium derivative of the cyano compound to an alcoholic solution of the maleate, heating the whole on a water bath for 36 hours. Yields equivalent to that obtained with α-tolunitrile can be had in this way. The products in this case are esters of the tricarboxylic acid, α-cyanotricarballylic acid.

Dimethyl (α-cyanobenzyl)succinate boils at 198 to 203° under 10 mm. pressure. The diethyl ester has a boiling point of 187° at 1 mm. pressure.

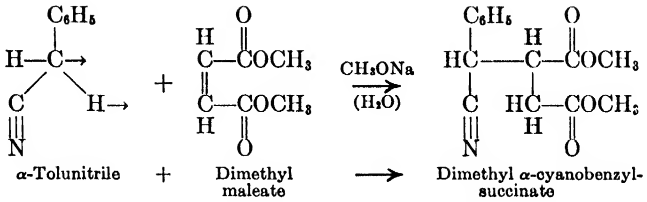
Use. Compounds of similar structures generally have valuable insecticidal and fungicidal properties. When reduced, such compounds give amino acids, which can be used in the preparation of polymers and synthetic detergents.



$NC—CH(Met)(Ar)$

α-Tolunitrile

(Benzyl Cyanide)



Procedure. A mixture of 58 g. of α-tolunitrile and 72 g. of dimethyl maleate is kept agitated while a solution of 1 g. of sodium in 20 ml. of methanol is added, two to three drops at a time. The temperature is carefully kept below 50° by external cooling during this operation. When all the sodium methoxide solution has been added and the temperature continues to drop even upon further addition of catalyst, it is a sign that the reaction is complete. The reaction mixture is then acidified with acetic acid and worked up in the usual manner. This yields 50% of the cyanobenzylsuccinic ester.

References

Koelsch, C. F., *J. Am. Chem. Soc.* **65,** 437 (1943). *Cf.*:
Henze, M., *Ber.* **33,** 966 (1900).
Ingold, C. K., *J. Chem. Soc.* **119,** 329 (1921).

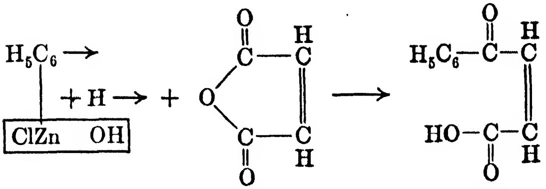
β-Benzoylacrylic Acid

The Grignard synthesis is generally considered to be superior to the Friedel-Craft method for preparing certain aroylacrylic acids. This is not true, however, for reactions involving maleic anhydride or its derivatives. Except for the less reactive reagents, like phenylzinc chloride, no aroylacrylic acids have been isolated from the mixture of products resulting from the reactions with such maleyl compounds. Even under the most favorable conditions as outlined in this preparation only 26% of benzoylacrylic acid is obtained. More reactive reagents, such as phenylmagnesium bromide, when allowed to react in equal molecular proportions, yield only saturated compounds such as β-benzoyl-α-phenylpropionic acid and 1,2,4-triphenyl-1,4-butanedione.

Ethylzinc iodide, when allowed to react with diethyl fumarate, has been reported to add only in the 1,4-positions to the $\underset{1}{O}{=}\underset{2}{C}{-}\underset{3}{C}{=}\underset{4}{C}{-}\underset{5}{C}{=}\underset{6}{O}$ grouping, to give upon hydrolysis the ester of ethylsuccinic acid. Diethylzinc is described as behaving similarly but full experimental details are lacking. The same is true with ethylzinc iodide. Further study should be given, therefore, to reactions employing equal molecular proportions of these reactants.

The properties of β-benzoylacrylic acid are described under the Friedel-Craft reaction (*q.v.*).

Phenylzinc Chloride



Phenylzinc chloride + Maleic anhydride ⟶ β-Benzoyl-acrylic acid

Preparation. Phenylzinc chloride is prepared by adding 16.4 g. of freshly fused zinc chloride in 40 ml. of dry ether to phenylmagnesium bromide from 15.7 g. of bromobenzene and 2.4 g. of magnesium. A solution of 8.8 g. of maleic anhydride in 90 ml. of dry ether is then carefully added dropwise to the gray solid mass, while the reaction mixture is allowed to reflux and is kept thoroughly agitated. The reaction is usually complete within an hour, half of which time is required for the addition of the anhydride. During the last half hour, the mixture turns yellow and becomes slightly sticky. The products are then treated in the usual manner by separating them into two fractions with a sodium carbonate solution. This yields 0.9 g. of diphenyl and 10.2 g. of a red oil. The red oil is then purified by dissolving it in benzene, precipitating with ligroin, and crystallizing the oily yellow solid so obtained, first from ligroin, and then from a benzene-petroleum ether solution, yielding 1.9 g. of β-benzoylacrylic acid. An additional 2.3 g. of impure product can be obtained from the mother liquor of the original benzene solution, giving a maximum yield of crude acid of 26% of theory.

References

Tarbell, D. S., *J. Am. Chem. Soc.* **60,** 215 (1938). *Cf.*:
Michael, A., *Ber.* **29,** 1791 (1896).
Pétrieff, B., *Bull. soc. chim. France* **41,** (2), 309 (1884).
Tarbell, D. S., and Weaver, C., *J. Am. Chem. Soc.* **62,** 2747 (1940).

Diethyl Isopropylsuccinate

This product results from a 1,4-addition of an alkylating reagent to the maleyl group, $\underset{1}{O}{=}\underset{2}{C}{-}\underset{3}{C}{=}\underset{4}{C}{-}\underset{5}{C}{=}\underset{6}{O}$, in contrast to the 1,2-addition described for phenylzinc chloride (*q.v.*) in the preparation of β-benzoylacrylic acid, where equal molecular amounts are also employed. The reaction is similar in this respect to the one with ethylzinc iodide.

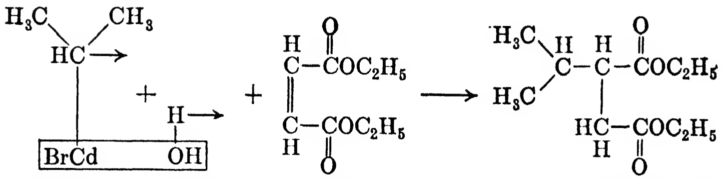
Practically the same yield is obtained when isopropylmagnesium bromide is substituted for the cadmium reagent in this preparation, or diethyl fumarate for the maleate. Use of a 50% mole excess of the diethyl fumarate with isopropylmagnesium bromide does not increase the yield. A longer time for reaction between the isopropyl bromide and magnesium, or the isopropylmagnesium bromide and cadmium chloride also has no effect in this preparation.

Diethyl isopropylsuccinate may be prepared also, by reducing diethyl isopropylidenesuccinate with hydrogen in the presence of Raney nickel. Although it is a two-step procedure, starting with succinic acid, it has several advantages over this Grignard method for preparational use.

Diethyl isopropylsuccinate obtained here boils at 118 to 126° under 20 mm. pressure. Redistilled, it gives a pure product boiling at 123 to 125° (20 mm.) with n_D^{20} 1.4284 and d_4^{20} 0.9925. Adkins and Wojcik prepared the product from diethyl isopropylidenesuccinate and report b_8 110–112°; and Neklutin obtained it in a similar manner, $b_{0.8}$ 71–78° n_D^{29} 1.4288. The acid when recrystallized from acetone and water melts at 115.5 to 116.5°. Roser reports 114°, and Henry and Paget 117°, as the melting point for the same acid.

Use. Alkylsuccinic acids have been studied for their effect on the growth of dibenzanthracene-induced tumors in mice. Although they do not cause complete repression of any of the tumors, definite inhibitory effects were observed in the case of methylsuccinic acid and cyclohexylsuccinic acid.

Isopropylcadmium Bromide



Isopropylcadmium bromide + Water + Diethyl maleate ⟶ Diethyl isopropylsuccinate

Procedure. Isopropylmagnesium bromide is first prepared by adding 143 g. of isopropyl bromide to 28.6 g. of magnesium and 1 liter of dry ether. This is converted to the cadmium reagent by adding 212 g. of anhydrous cadmium chloride in the customary manner. A solution of 200 g. of diethyl maleate in 500 ml. of ether is then added dropwise to the reagent. This addition requires approximately 3½ hours. The agitation is then continued for 5 hours to complete the reaction.

The products are treated in the usual manner, and the resulting oil is separated by distillation. The yield of diethyl isopropylsuccinate is 48 g., or 29.3% of theory.

References

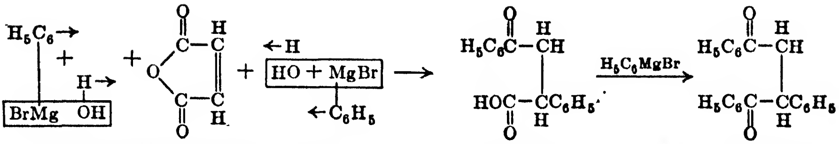
Marvel, C. S., Meyers, R. L., and Saunders, J. H., *J. Am. Chem. Soc.* **70**, 1695 (1948). *Cf.*:
Henry, T. A., and Pagent, H., *J. Chem. Soc.* **1928**, 70.
Neklutin (see Marvel, Meyers, and Saunders, above).
Roser, W., *Ann.* **220**, 271 (1883).
Wojcik, B., and Adkins, H., *J. Am. Chem. Soc.* **55**, 4939 (1933); **56**, 2424 (1934).
Woodhouse, D. L., *Cancer Research* **7**, 398 (1947).

β-Benzoyl-α-phenylpropionic Acid

The fact that only saturated products are obtained when equal molecular quantities of maleic anhydride are allowed to react with phenylmagnesium bromide is of interest in view of the results that are obtained when the Grignard reagents are present in large amounts (*q.v.*). Apparently, equal molecular quantities of this reagent favor a 1,4-addition of the second molecule of Grignard reagent, whereas the second molecule of an alkyl reagent tends to add in the 1,2-position to the keto group of the ketoacrylic acid. See γ,γ-diethyl-γ-hydroxycrotonic acid. Here at best the yields are poor for both the β-benzoyl-α-phenylpropionic acid and the by-product, 1,2,4-triphenyl-1,4-butanedione. Various side reactions also take place, as is evident from the large proportion of biphenyl in the neutral fraction.

β-Benzoyl-α-phenylpropionic acid, when prepared by this method and purified, melts at 145 to 148°. 1,2,4-Triphenyl-1,4-butanedione, *desylacetophenone,* melts at 125 to 127°. Compare these results with those given for β-benzoyl-α-phenylpropionic acid prepared by the Friedel-Craft reaction, as described on page 91. Mixtures of the propionic acids prepared by the two methods melt at 148 to 150°.

Phenylmagnesium Bromide

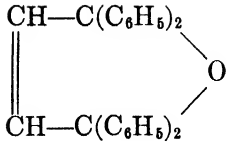


Phenylmagnesium bromide + Water + Maleic anhydride ⟶ β-Benzoyl-α-phenylpropionic acid 1,2,4- ⟶ Triphenyl-1,4-butanedione

Procedure. The Grignard reagent in this preparation is prepared in the customary manner from 2.4 g. of magnesium and 15.7 g. of bromobenzene. It is then added dropwise, with constant stirring, to an ether solution of 8.8 g. of maleic anhydride, which is constantly maintained at 0° by means of an ice-salt bath. Increasing amounts of a white solid separate instantaneously with each addition of the Grignard reagent. When the reaction is complete, the products are separated with sodium carbonate into a neutral fraction consisting largely of 1.2 g. of diphenyl, with small amounts of 1,2,4-triphenyl-1,4-butanedione and an acid fraction of 5.9 g. of a red oil. The red oil is dissolved in benzene and then fractionally precipitated with ligroin. This gives three batches of uncrystallized oil and then 1.7 g., or 26% of the theoretical amount, of crude β-benzoyl-α-phenylpropionic acid. The pure acid is obtained by recrystallization from an acetone-petroleum ether solution. The yield of 1,2,4-triphenyl-1,4-butanedione from the neutral fraction is 5.4%.

Reference

Tarbel, D. S., *J. Am. Chem. Soc.* **60**, 215 (1938).



ALKENEDIOL ANHYDRIDES

2,5-Dihydro-2,2,5,5-tetraphenylfuran

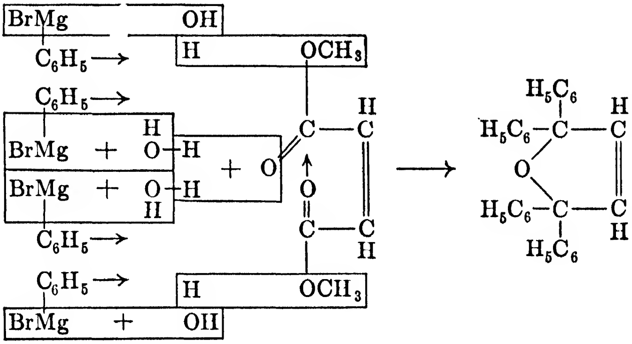
It would appear from this and the following preparations that the use of an excess of Grignard reagent distinctly favors the 1,2-type of additions to maleyl compounds. The fact that saturated by-products are obtained in the next preparation with phenyllithium, however, would indicate that a 1,4-addition of the second or third mole of Grignard reagent can still occur under certain experimental conditions. Compare this with the preceding preparation, where phenylmagnesium bromide is used in an equivalent amount.

Unfortunately, in the preparation given here only one substance so far has been obtained from the reaction mixture, and this is a dehydration product of the tetraarylalkenediol. This diol is undoubtedly formed during the reaction by the addition of four moles of reagent to the carbonyls of the maleate. To this extent, the reaction is similar to the one where eight moles of benzylmagnesium chloride is added to maleic anhydride (*q.v.*), except in that case the intermediate tetraaralkylalkenediol is a by-product of the reaction, and that dehydration gives rise to a highly unsaturated triene.

In view of the relatively low yields obtained in all cases, one cannot be certain, however, that the products isolated are the principal products of the reaction. All these preparations can be profitably restudied from the standpoint of what might be done to effect better methods of separation of the complex mixtures of products.

2,5-Dihydro-2,2,5,5-tetraphenylfuran when precipitated from ether melts at 190°.

Phenylmagnesium Bromide

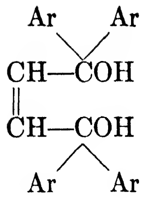


Phenylmagnesium bromide + Water + Dimethyl maleate ⟶ 2,5-Dihydro-2,2,5,5-tetraphenylfuran

Procedure. The reagent is prepared from 6.7 g. of magnesium and 44 g. of bromobenzene. This is added cautiously and dropwise to an ether solution of 10 g. of dimethyl maleate in the usual manner. A spontaneous vigorous reaction ensues. When the reaction has quieted down, the mixture is heated for one hour on a water bath. The product is then treated in the customary way, yielding a sirup upon evaporation of the ether layer. This sirup partially crystallizes upon standing. The crystals are freed of the adhering sirup by treating them with 2 g. of ether. They are purified by dissolving in benzene and precipitating with ether.

Reference

Purdie, T., and Arup, P. S., *J. Chem. Soc.* 97, 1537 (1910).



ALKENEDIOL AND BY-PRODUCTS

trans-1,1,4,4-Tetraphenyl-2-butene-1,4-diol

This preparation is interesting as giving fairly reasonable yields of the butenediol. That there is some competition with a 1,4-addition to the maleyl group is illustrated by the two by-products obtained, since β,γ,γ-triphenylbutyric lactone undoubtedly results from loss of water from a γ-hydroxy-β,γ,γ-triphenylbutyric acid intermediate, and tetrahydro-5-hydroxy-2,2,3,5-tetraphenylfuran could readily result from 3-hydroxy-2,3,3-triphenylpropyl phenyl ketone through a cyclization involving a transfer of hydrogen of the hydroxyl group. The *cis*-isomer of 1,1,4,4-tetraphenyl-2-butene-1,4-diol may be prepared in similar manner from diethyl maleate.

Small amounts of phenol and phenyl benzoate are also obtained from the aqueous solution left after the original extraction with ether. This would indicate that some addition to the 1,6-positions of the maleyl group may have occurred also during the reaction.

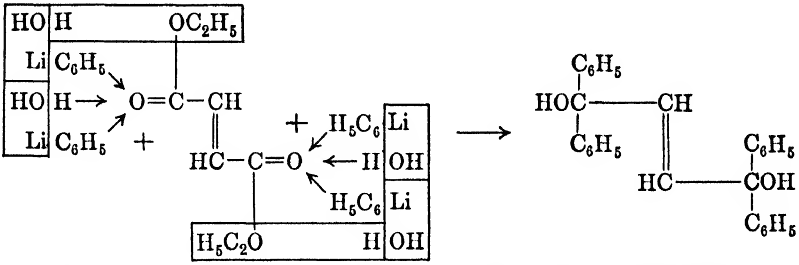
trans-1,1,4,4-Tetraphenyl-2-butenediol is obtained as colorless prisms that melt at 195 to 201°. When dissolved in concentrated sulfuric acid, it changes from red through violet, to blue and then green. The *cis*-isomer cannot be crystallized, but when boiled with acetic anhydride for 4 hours it yields 2,5-dihydro-2,2,5,5-tetraphenylfuran, m.p. 182 to 184° (*q.v.*).

β,γ,γ-Triphenylbutyric lactone occurs as needles that melt at 162.5 to 163.5° when recrystallized from methyl alcohol. They show no depression in melting point with the product isolated from the reaction with phenylmagnesium bromide. Dissolved in concentrated sulfuric acid, it imparts an intense yellow color to the solution.

Tetrahydro-5-hydroxy-2,2,3,5-tetraphenylfuran melts at 216 to 217° and gives no color in concentrated sulfuric acid. Treated with acetic acid and concentrated hydrochloric acid, it gives the 2,3-dihydro-2,2,3,5-tetraphenylfuran, and with hydriodic acid and red phosphorus, 1,2,4-triphenylnaphthalene.

GRIGNARD REAGENTS V
1,2-1,2-1,2-1,2-ADDITION (TO FUMARATES)

Phenyllithium



Phenyllithium + Water + Diethyl fumarate ⟶ *trans*-1,1,4,4-Tetraphenyl-2-butene-1,4-diol

Procedure. A solution of 1.9 g. of diethyl fumarate in 40 ml. of dry ether is cooled to —60 to —70°. This is added over a 5-minute period to 50 ml. of a 1 *N* ether solution of phenyllithium that has been cooled to the same temperature. After 30 minutes the reaction mixture is allowed to increase slowly to room temperature. After 25 minutes at the new temperature, it is decomposed with acidulated water, neutralized, and then extracted with ether. Upon standing, 0.3 g. of colorless needles of tetrahydro-5-hydroxy-2,2,3,5-tetraphenylfuran separate from the extract. These are recrystallized from an ethyl acetate–alcohol mixture.

The extract is then allowed to evaporate, and the residue is taken up in methyl alcohol. From the alcohol solution is obtained 1.55 g. of 1,1,4,4-tetraphenyl-2-butene-1,4-diol, which is recrystallized from a mixture of benzene and alcohol.

The mother liquor yields 0.4 g. of β,γ,γ-triphenylbutyric lactone.

References

Scholtis, K., *Ann.* **557**, 82 (1945). *Cf.*:
Purdie, T., and Arup, P. S., *J. Chem. Soc.* **97**, 1537 (1910).

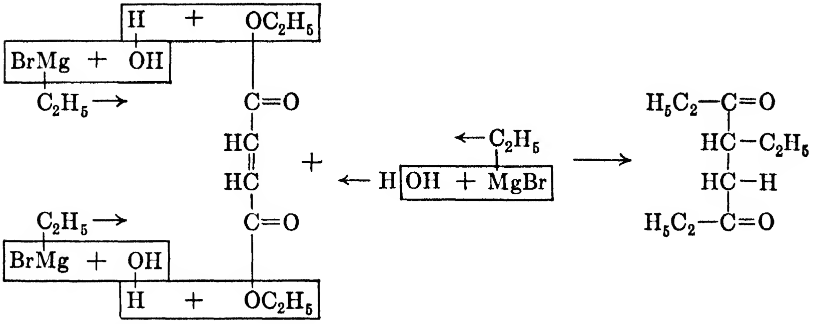
5-Ethyl-3,6-octanedione

Substituted aliphatic diketones are the major products when maleic esters are allowed to react with an eight-mole equivalent of alkylmagnesium bromides. These ketones result from the reaction of three moles of the Grignard reagent with one of the maleate, two moles adding to the carbonyl groups in the 1,2-positions and the third in the 1,4-position. It is also possible for all three moles to add in the 1,2-positions. For example, in the reaction with butylmagnesium chloride, small amounts of $Bu_2C(OH)CH{=}CHCOBu$ are formed as by-products in the reaction with maleic anhydride with butylmagnesium chloride.

5-Ethyl-3,6-octanedione is a colorless liquid with the following properties: b_{25} 143° (b_1 110°), n_D^{21} 1.438, and d_{21} 0.9661. The compound undergoes the pyrrole reaction characteristic of 1,4-diketones. It does not react with semicarbazide in aqueous alcoholic solutions, but can unite further with two moles of the Grignard reagent to yield a crystalline diol. The benzyl analog is sterically hindered in this respect from adding more than one molecule of reagent.

Use. This procedure is a convenient one for synthesizing certain substituted diketones and diols.

Ethylmagnesium Bromide



Ethylmagnesium bromide + Dimethyl maleate ⟶ 5-Ethyl-3,6-octanedione

Procedure. The Grignard reagent is prepared from 87 g. of pure ethyl bromide and 19 g. of magnesium. This is added dropwise, with constant stirring to a solution of 14.4 g. of dimethyl maleate in ether, which is maintained at 0°. The product is worked up in the usual manner for this type of reaction. Acidic constituents are removed with sodium carbonate solution, and the neutral fraction purified by distillation under reduced pressure.

Reference

Weizmann, C., and Bergmann, F., *J. Am. Chem. Soc.* **60**, 2647 (1938).

γ,γ-Diethyl-γ-hydroxycrotonic Acid

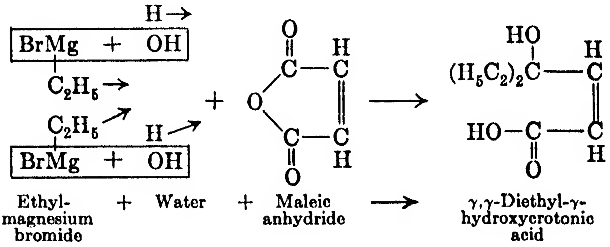
The use of maleic anhydride in place of maleic esters in reactions with large amounts of alkylmagnesium bromides leads to an asymmetric addition of the first two moles of the Grignard reagent to a single carbonyl group. Thus γ,γ-dialkylhydroxycrotonic acids are obtained as the major product of these reactions instead of the saturated 1,4-diketones formed in the previous preparation. Further addition of the Grignard reagent may also occur during these reactions. With ethylmagnesium bromide, this results in addition to the other carbonyl group as well as a 1,4-addition to saturate the C:C bond, giving 5,6-diethyl-6-hydroxy-3-octanone as the by-product. The less reactive butylmagnesium chloride, however, forms only the unsaturated 8-butyl-8-hydroxy-6-dodecen-5-one; whereas benzylmagnesium chloride gives, 2,5-dibenzyl-1,6-diphenyl-1,3,5-hexatriene. The last compound is undoubtedly produced by a dehydration of the unsaturated diol, 2,5-dibenzyl-1,6-diphenyl-3-hexene-2,6-diol. Thus complete alkylation of both carbonyl groups can occur only if the conjugated system is preserved throughout the series of four Grignard additions.

γ,γ-dialkyl-γ-hydroxycrotonic acids readily undergo dehydration. With the diethyl derivative, this takes place almost spontaneously so that these compounds can be isolated only as crystalline esters, such as the *p*-phenylphenacyl ester described in this preparation.

p-Phenylphenacyl γ,γ-diethyl-γ-hydroxycrotonate melts at 77 to 78°. The *p*-phenylphenacyl ester of γ-ethylsorbic acid, the dehydration product, occurs as quadratic plates melting at 138°. Purified 5,6-diethyl-6-hydroxy-3-octanone has the following properties: $b_{1.5}$ 75° (b_{37} 112°), n_D^{21} 1.457, and d_{21} 0.9269.

Use. This method offers several possibilities for preparing branched-chain fatty acids and other compounds from maleic anhydride.

Ethylmagnesium Bromide



Procedure. The Grignard reagent is prepared from 87 g. of pure ethyl bromide and 19 g. of magnesium, as in the previous preparations. This is added dropwise, with constant stirring, to a solution of 9.8 g. of maleic anhydride in ether at 0°. The reaction mixture is treated in the usual manner by separating it into neutral and acid fractions by extraction with a sodium carbonate solution. Since the major product γ,γ-diethyl-γ-hydroxycrotonic acid undergoes spontaneous dehydration, it is isolated as the well-defined *p*-phenylphenacyl ester by the addition of *p*-phenylphenacyl bromide. Small amounts of the phenylphenacyl ester of γ-ethylsorbic acid may be obtained from the filtrate after removing the above ester. 5,6-Diethyl-6-hydroxy-3-octanone is recovered from the neutral fraction that is left upon extraction with the carbonate solution.

Reference

Weizmann, C., and Bergmann, F., *J. Am. Chem. Soc.* **60**, 2647 (1938).

β-Benzoylacrylic Acid

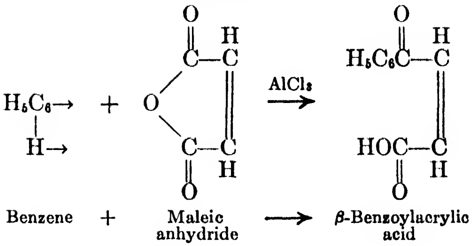
This is one of the general methods used for preparing arylketones. A considerable number of β-aryloylacrylic acids have been made by this or very similar procedures. The first step in the reaction is considered to be the formation of the complex compound of aluminum chloride and maleic anhydride, which reacts with the benzene to yield the keto acid. When allowed to react with two moles of benzene, the maleic anhydride complex yields β-benzoyl-α-phenylpropionic acid (*q.v.*).

β-Benzoylacrylic acid may also be prepared from maleic anhydride by the Grignard reaction (*q.v.*), but the yield is very poor. Esters have been prepared by removing hydrobromic acid from benzoylbromopropionates. The pure acid melts at 97°.

Use. The use of β-benzoylacrylic acid has been limited in the past because of its tendency to form Pechmann's dye. This dye may be prepared by refluxing β-benzoylacrylic acid with acetic anhydride. A copious precipitate of reddish needles or plates with a bronze luster is obtained. The exact structure of this dye eluded chemists for a period of 42 years. It is the diphenylacylfumaric lactone, a dimeric condensate of β-benzoylacrylic acid.

Studies of methods for processing β-benzoylacrylic acid have continued to be attractive because β-benzoylacrylic acid, like maleic anhydride, contains a series of highly reactive groups, which should undergo many of the reactions of the anhydride itself. (See discussions of Dibenzoylethylene and Reaction of Nitroparaffins.)

Benzene



Procedure. A mixture of 10 g. of maleic anhydride and 100 ml. of benzene is heated on a water bath, with constant agitation, to 55 to 60°. Fifteen grams of pulverized anhydrous aluminum chloride is then added in small portions, and the heating is continued for 6 hours. Hydrogen chloride is slowly evolved during the reaction, and the mixture forms two layers. Upon completion, 40 ml. of water containing a few milliliters of hydrochloric acid is cautiously added. This causes the lower viscous layer to disappear when the three-layer heterogeneous mixture is heated further. The mixture is then placed in a separatory funnel, and the acidic aqueous layer is drawn off. The remaining clear benzene layer is washed with water while still warm and extracted with a dilute alkali solution. A yield of 12 g., or 74% of the theoretical amount, of crude β-benzoylacrylic acid is obtained when hydrochloric acid is added to the extract. This crude acid is then recrystallized from the 480 ml. of hot water, yielding 9 g. of pure acid.

This method was first employed by von Pechmann.

References

Gabriel, S., and Colman, J., *Ber.* **32**, 395 (1899). *Cf.*:
Berliner, E., *Org. Reactions* **5**, 229 (1949).
Bogert, M. T., and Ritter, J. J., *J. Am. Chem. Soc.* **46**, 2871 (1924).
Bougault, J., *Compt. rend.* **146**, 140 (1908).
Cattelain, E., *Bull. soc. chim. France* **41**, (IV), 352 (1927).
Dave, K. P., et al., *J. Univ. Bombay* **7**, (III), 191 (1938); **10**, (III), 122 (1941).
Fieser, L. F., and Fieser, M., *J. Am. Chem. Soc.* **57**, 1679 (1935).
Groggins, P. H., *Unit Process in Organic Synthesis*, McGraw-Hill Book Co., New York (1947), pp. 729, 761.
Haller, A., and Guyot, A., *Compt. rend.* **119**, 139 (1894).
Koenigs, W., et al., *Ber.* **26**, 558 (1893); **28**, 1048 (1895).
Kohler, E. P., and Engelbrecht, H., *J. Am. Chem. Soc.* **41**, 768 (1919).
Kohler, E. P., and Woodward, D. W., *J. Am. Chem. Soc.*, **58**, 1933 (1936).
Kózniewski, T., and Marchlewski, L., *Bull. intern. acad. sci. Cracovie*, **1906**, 81; *J. Chem. Soc.* **90**, (I), 759 (1906).
Kugel, M., *Ann.* **299**, 50 (1897).
Lutz, R. E., *J. Am. Chem. Soc.* **52**, 3405 (1930).
Lutz, R. E., and Couper, M., *J. Org. Chem.* **6**, 77, 91 (1941).
McMullen, T. C., *J. Am. Chem. Soc.* **44**, 2055 (1922).
Oddy, H. G., *J. Am. Chem. Soc.* **45**, 2156 (1923).
Rice, G. P., *J. Am. Chem. Soc.* **45**, 222, 232 (1923); **48**, 269 (1926); **50**, 1481 (1928); **52**, 2094 (1930).
Ruhemann, S., and Stapleton, H. E., *J. Chem. Soc.* **77**, 1179 (1900).
von Pechmann, H., *Ber.* **15**, 881 (1882).

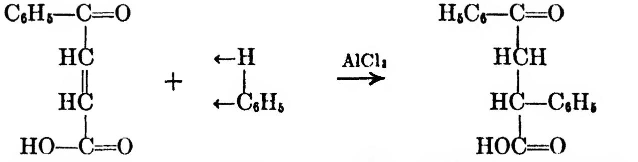
β-Benzoyl-α-phenylpropionic Acid

Aluminum chloride might also be expected to form a complex with benzoylacrylic acid, as well as with maleic anhydride.

The preparation of benzoylphenylpropionic acid from benzene and maleic anhydride under controlled conditions has also been reported. It would appear that the initial phase in any reaction between maleic anhydride and benzene in the presence of aluminum chloride is the formation of benzoylacrylic acid, and that addition to the C:C bond of maleic anhydride occurs only after the formation of the unsaturated keto acid. The yield, however, is very poor in this one-step procedure. That obtained by the method given on the opposite page, where benzoylacrylic acid is used as the starting material, in contrast, is practically quantitative.

β-Benzoyl-α-phenylpropionic acid, when recrystallized several times from acetic acid, melts at 148°. Prepared by either procedure, the keto acids obtained are identical.

Benzene



Benzoylacrylic acid + Benzene ⟶ β-Benzoyl-α-phenylpropionic acid

Procedure. A mixture of 2 g. of β-benzoylacrylic acid and 75 ml. of benzene is heated upon a water bath until the β-benzoylacrylic acid has dissolved. Then 20 g. of anhydrous aluminum chloride is added to it in small amounts over a period of half an hour. The mixture is kept thoroughly agitated during this period and for the following 12 hours. The solution changes from yellow to brown in forming a complex with the aluminum chloride, such as occurs in the preparation of β-benzoylacrylic acid. When the reaction is complete, the mixture is cooled and thoroughly extracted with dilute alkali. The product is recovered from the extract by precipitation with hydrochloric acid, and is then purified by three recrystallizations from 30% acetic acid. The yield is 4 g.

References

Pummerer, R., and Buchta, E., *Ber.* **69B**, 1005 (1936). *cf.*:
Bickel, C. L., *J. Am. Chem. Soc.* **60**, 927 (1938); **68**, 941 (1946).

2,4-Dimethoxyphenylsuccinic Anhydride

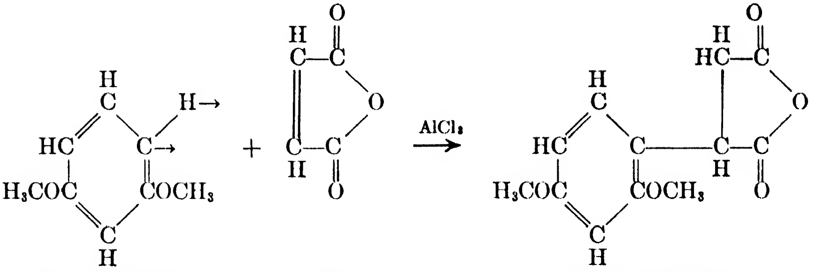
Unlike other aromatic compounds, *m*-dimethoxybenzene reacts with maleic anhydride in the presence of aluminum chloride to form largely the saturated substituted succinic anhydride instead of the benzoylacrylic acid derivative. Veratrole, *p*-dimethoxybenzene and methylanisoles, in contrast, react in the normal manner. Small amounts of β-(2,4-dimethoxybenzoyl)acrylic acid and β-(2,4-dimethoxybenzoyl)-α-(2,4-dimethoxyphenyl)propionic acid are also formed during the reaction with *m*-dimethoxybenzene, but it is clear from the yields that the addition reaction is the one that predominates in this preparation. When *m*-dimethoxybenzene is added to β-(2,4-dimethoxybenzoyl)acrylic acid, the isomeric, β-(2,4-dimethoxybenzoyl)-β-(2,4-dimethoxyphenyl)propionic acid is formed in addition to the β,α-compound. The β,β-compound, however, has not been reported as one of the products of the maleic anhydride reaction.

(2,4-Dimethoxyphenyl)succinic anhydride occurs as fine colorless needles that melt at 147°. It is soluble in acetone, benzene, toluene, and chloroform. The acid melts at 160°.

β-(2,4-Dimethoxyphenyl)acrylic acid is yellow, losing its color at 180° and decomposing at 189°. The β,α- and β-(2,4-dimethoxybenzoyl)-β-(2,4-dimethoxyphenyl)propionic acids melt at 160 and 157°, respectively.

m-Dimethoxybenzene

(Resorcinol Dimethyl Ether)



m-Dimethoxybenzene + Maleic anhydride ⟶ (2,4-Dimethoxyphenyl) succinic anhydride

Procedure. A dark yellowish-green solution of 53.6 g. of purified maleic anhydride in 71.5 g. of *m*-dimethoxybenzene is stirred rapidly while 150 g. of carbon disulfide is added. The reaction mixture is then cooled in an ice bath, and anhydrous aluminum chloride is added in small portions. The mixture is kept thoroughly agitated with the mechanical stirrer until the dark red product begins to set to a complete solid mass. It is then decomposed in the usual manner with ice and concentrated hydrochloric acid. The product is removed by filtration, air-dried, pulverized, and then extracted with several small portions of ether. The yellowish residue is dissolved in acetone, from which crystallizes 37.4 g. of the colorless anhydride. Additional (2,4-dimethoxyphenyl)succinic anhydride can be obtained by treating the residue from this solvent with toluene, giving a total yield of 49.2 g. or 40% of theory, based upon the weight of dimethoxybenzene originally taken.

Small amounts of (2,4-dimethoxyphenyl)succinic acid, β-(2,4-dimethoxybenzoyl)acrylic acid, and β-(2,4-dimethoxybenzoyl)-α-(2,4-dimethoxyphenyl)propionic acid may also be obtained from the acetone filtrate.

Reference

Rice, G. P., *J. Am. Chem. Soc.* **53**, 3153 (1931).

trans-Dibenzoylethylene

(1,4-Diphenyl-2-butene-1,4-dione)

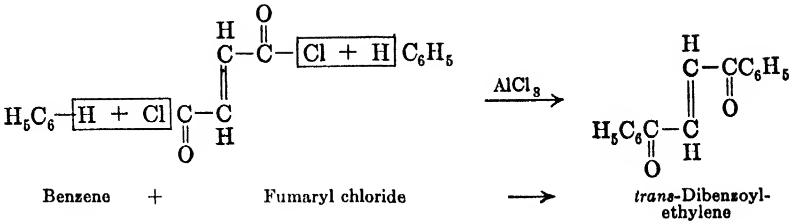
This preparation is by far the most convenient and economical one for the synthesis of *s*-diaryloylethylenes. An excess of aluminum chloride is required to obtain products of good color. The rate of addition of the fumaryl chloride is also important. If the benzene suspension is not warmed before the chloride is added, the reaction starts slowly, and frothing with boiling over may result when the temperature begins to rise suddenly. Should the stirrer stop for any reason, it must be started again very cautiously.

tran-*s*-Dibenzoylethylene crystallizes from alcohol as yellow needles that melt at 109 to 110°. It is insoluble in ligroin, only partially soluble in alcohol, but readily dissolves in acetic acid, benzene, and chloroform. This is the only *trans*-*s*-diaryloylethylene that has been reported to melt below its *cis*-isomer (m.p. 134°).

It undergoes many reactions that are similar to maleic anhydride, including the addition of dienes, malonates, halogens, Grignard reagents, sodium bisulfite, amines, hydroxylamine, oxygen from hydrogen peroxide, and the like. In the presence of acetic anhydride and a little sulfuric acid it produces 1,4-diphenyl-3-furanol acetate, and with sodium ethoxide in benzene, 1,4-dibenzoyl-2,6-diphenyl-6-fulvenol. It is extremely easily reduced, being capable of forming upon reduction either the saturated monomer or a saturated dimer.

Use. *s*-Diaryloylethylenes have been employed as the starting materials in the synthesis of various substituted furanes; fulvenes; dihydrobenzofurans; cyclohexenes; bicyclo [2·2·1]-2,5-heptadienes; cyclopropanes; furanones; pyrazoles and pyrazolines; 4,4-dibenzoyl-1-phenyl-2,2-butanedicarboxylic acid; *o*-dibenzoylbenzene; 3,6-diphenylpyridazine; 1,4-diphenyl-2-piperidino-1,4-butanediol; dibenzoylacetylene; dibenzoylethanol; dibenzoylethylene oxide and 1,2-dibenzoyl-2-chloroethanol.

Benzene



Procedure. A mixture of 350 g. of finely powdered anhydrous aluminum chloride and 1800 ml. of thiophene-free benzene is heated on a water bath while vigorously agitated. To this is slowly added 153 g. of fumaryl chloride until the mixture reaches 50 to 60°. The chloride is run into it at a fairly rapid rate over a period of 15 to 25 minutes. During this time the reaction mixture becomes dark red and begins to boil rapidly. The refluxing is continued for 10 minutes after the evolution of gas has practically ceased. It is then decomposed in the usual manner and brought to room temperature by adding hot water. The benzene layer is separated and washed. The solvent is then removed on a water bath under reduced pressure until crystallization ensues. A yield of 78% of the theoretical amount of dibenzoylethylene is obtained.

References

Lutz, R. E., *Org. Syn.* 20, 29 (1940). *Cf.*:
Bailey, P. S., and Lutz, R. E., *J. Am. Chem. Soc.* 69, 498 (1947).
Blatt, A. H., *J. Am. Chem. Soc.* 56, 2774 (1934).
Campbell, N., and Khanna, N., *Nature* 161, 54 (1948).
Dupont, G., *Bull. soc. chim. France* 41 (IV), 1167, (1927).
Fuson, R. C., et al., *J. Am. Chem. Soc.* 67, 2054 (1945); *J. Org. Chem.* 10, 121 (1945).
Geiger, W. B., *Arch. Biochem.* 16, 423 (1948).
Jolles, E., *Gazz. chim. ital.* 68, 488 (1938).
Kharasch, M. S., Nudenberg, W., and Fields, E. K., *J. Am. Chem. Soc.* 66, 1276 (1944).
Kohler, E. P., and Woodward, D. W., *J. Am. Chem. Soc.* 58, 1933 (1936).
Lutz, R. E., *J. Am. Chem. Soc.* 48, 2905, 2916 (1926); 49, 1106 (1927); 51, 3008, (1929); 52, 3405, 3410, 3421, 3423, 3432 (1930).
Lutz, R. E., et al., *J. Am. Chem. Soc.* 55, 1168, 1599 (1933); 56, 1341, 1980, 1987, 2065, 2145, 2679, 2698 (1934); 57, 1947, 1953, 1957 (1935); 58, 1885 (1936); 59, 2316 (1937); 60, 716 (1938); 61, 3007, 3010 (1939); 62, 1520 (1940); 63, 1148, 3171, 3175, 3189 (1941); 64, 2585 (1942); 67, 2229 (1945); 68, 2224 (1946); 72, 2002 (1950).
Oddy, H. G., *J. Am. Chem. Soc.* 45, 2156 (1923).
Smith, L. I., and Howard, K. L., *J. Am. Chem. Soc.* 65, 159 (1943).

CHAPTER

5

Compounds Containing Nitrogen

This chapter covers possibly one of the most interesting groups of substances reacting with maleyl compounds from the standpoint of synthesis of products with different types of structures. In general, compounds containing nitrogen react quite readily with either the ethylene bond or the carboxyl groups of the maleyl compound or combinations of these three groups.

The reactions of ammonia and hydrazine are unique to the extent that numerous individual compounds can be readily obtained by varying the experimental conditions as shown in the several preparations given. Generally, when reactive groups are capable of forming such numerous combinations, the products are difficultly separable resinous mixtures. Although the reactions of ammonia and hydrazine are quite similar, both have been included to show the different reaction conditions and some deficiencies in the end products.

The reaction of benzalazine with two molecules of maleic anhydride is one of the few examples of a 1,3-addition of a conjugated unsaturated grouping to maleic anhydride, leading to what has been termed a criss-cross addition to the two moles of anhydride. In the presence of water, this compound behaves like a Schiff's base, splitting off benzaldehyde to yield only the substituted maleyl hydrazide.

Another unusual reaction is that of benzaldehyde oxime with maleic anhydride to form N-benzoylaspartic anhydride, where a rearrangement has the net effect of the oxime isomerizing to the amide during the reaction. Schiff's bases from aniline and 2-alkenals apparently are tautomeric mixtures of the base and conjugated N-alkadienylanilines, since they undergo what amounts to a Diels-Alder addition with the nitrogen forming an amide group in producing bicyclopyrrolidonecarboxylic acids.

Pyrroles also react in an unexpected manner to produce substituted succinic acids instead of undergoing the usual Diels-Alder type of addition of cyclic dienes such as takes place with the oxygen analogs, the furans. When both the methylene carbons adjacent to the imide group are substituted, addition takes place at the 3-pyrrole carbon, which is one carbon removed from the nitrogen atom.

The nitrogen ring of benzyl azide is opened in its addition to ethylene bond of fumarates to yield the 1-benzyl-Δ^2-1,2,3-triazoline-4,5-dicarboxylates, but carbamyl azide loses a mole of nitrogen in the same type of addition to form the 1-carbamyl-2,3-aziridinedicarboxylate. Diazomethane, like azides, also forms a heterocyclic ring upon addition. In this case, it is the 1-pyrrolidine ring that is formed. Diazonium chloride, like carbamyl azide, loses a molecule of nitrogen during reaction in producing the α-aryl-β-chlorosuccinates.

Two molecules of fumaric ester are involved when hydrogen cyanide adds to the ester in potassium cyanide solutions. This addition is accompanied by either decarboxylation or cyclization, depending upon experimental conditions. Since no direct method is known for producing the simple nitrile, this should be a fruitful field for further study.

Additional study might also be given to the reactions of both primary and secondary nitroparaffins, since these reaction products have interesting possibilities for further synthesis.

Aspartic Acid

Most of the methods given in the literature for preparing aspartic acid directly from maleyl compounds and ammonia give very poor yields owing to the formation of other products and to losses during separation. Manufacturing methods have been developed, however, that do not have these defects so that aspartic acid is now a commercial product. Temperature, pressure, and the use of catalysts are apparently the most effective means for increasing the yield as shown in the procedure given. The highest yield reported, however, is obtained by the hydrolysis of 2,5-dioxopiperazinediacetamide, which can be prepared in almost quantitative yields from diethyl fumarate and ammonia (*q.v.*).

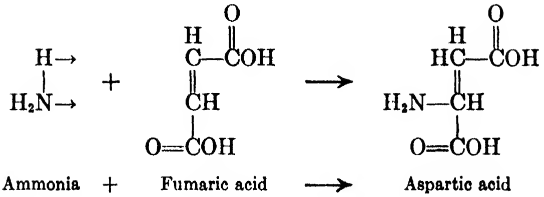
Ammonia appears to react more readily with the carboxyl groups of maleyl compounds than to add to the unsaturated bond. There is some evidence that the addition of an amino group to the carbonyl activates the ethylene bonds in the maleyl radical. This may account for the greater readiness with which aspartamides and imides are frequently formed.

dl-Aspartic acid is a monoclinic crystalline solid melting at 270°. It is very soluble in water, alcohol, and ether. It may be separated into the two optical forms. The *d*-acid melts at 251°, and the *l*-acid at 269 to 271°. The latter acid occurs as columnar rhombic leafs.

Uses. Aspartic acid is a valuable intermediate for organic syntheses. 5-Hydantoinacetic acid, carbamylaspartic acid, 2-amino-1,1,4,4-tetraphenyl-1,4-butanediol, diazosuccinic acid, and fumaryldiaspartic acid are a few of the products that have been made from it.

Aspartic acid is also used therapeutically as an amino acid, as a growth substance for yeast, in the production of penicillin, and to stabilize vitamin C and soap.

Ammonia

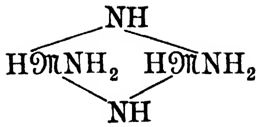


Procedure. One hundred and sixteen grams of fumaric acid and 214 g. of ammonium chloride are placed in an autoclave, and 34 g. of ammonia is run in. The contents are carefully heated to 180°, which gives a pressure of 10 atmospheres. The temperature is then held at this point for one hour, giving a yield of aspartic acid of 60 to 65% of the theoretical amount, when the product is recovered in the usual manner.

Other methods of preparing aspartic acid by treating maleic, fumaric, or bromosuccinic acids with alcoholic or aqueous ammonia yield only 15 to 30% of the acid.

References

Tutiya, Y., *J. Agr. Chem. Soc. Japan* **17,** 706–710 (1941); *Bull. Agr. Chem. Soc. Japan* **17,** 87 (1941) (in English). *Cf.*:
Dunn, M. S., and Smart, B. W., *J. Biol. Chem.* **89,** 41 (1930).
Engel, R., *Bull. soc. chim. France* **48,** (2), 97 (1887).
Enkvist, T., *Finska Kemistsamfundets Medd.* **46,** 165 (1937); *C. A.* **32,** 2816^7 (1938).
Enkvist, T., and Laasonen, L., *Ber.* **72B,** 1927 (1939).
Fischer, E., and Koenigs, E., *Ber.* **37,** 4585 (1905).
Fischer, E., and Raske, K., *Ber.* **40,** 1051 (1907).
Körner, G., and Menozzi, A., *Gazz. chim. ital.* **17,** 226 (1887).
Stadnikoff, G., *Ber.* **44,** 44 (1911).



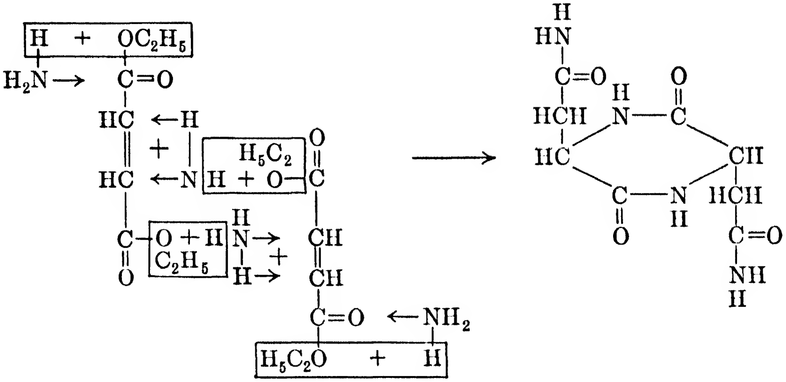
2,5-Dioxo-3,6-piperazinediacetamide

This lactam is very readily formed whenever there is a large excess of ammonia. It crystallizes as needles from water. These do not melt but decompose above 250°. The compound is insoluble in alcohol and ether. It is easily saponified to give crude sodium aspartate when refluxed with 6 *N* sodium hydroxide solution. An overall yield of 96% of crude aspartate is obtained in this manner.

Use. To prepare pure aspartic acid, the saponified mixture is treated with copper acetate, and the crystalline copper salt formed is removed by filtration. This salt is then converted to the acid by dissolving it in a normal solution of acetic acid and treating with hydrogen sulfide. C.P. *dl*-acid (57% theory) may be prepared by repeating this purification procedure.

2,5-Dioxo-3,6-piperazinediacetamide has an interesting structure from the standpoint of chemical synthesis. The compound contains a large number of hydrophilic groups that might be used to advantage in surface active compounds.

Ammonia



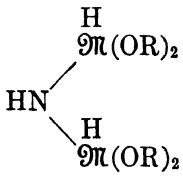
Diethyl fumarate + Ammonia ⟶ 2,5-Dioxo-3,6-piperazinediacetamide

Procedure. A solution of 172 g. of diethyl fumarate and 82 g. of dry ammonia gas in 1100 ml. of 99.85% ethanol is heated for 24 hours at 100° in a suitable pressure vessel. Proper precautions should be taken in handling such a mixture.

The reaction mixture is then transferred to another vessel, and the solvent removed under reduced pressure. Any solids left in the pressure vessel are added to the residue, and the combined solids are crystallized from water. The yield of crude 2,5-dioxo-3,6-piperazinediacetamide is practically quantitative by this method.

References

Dunn, M. S., and Fox, S. W., *J. Biol. Chem.* **101**, 493 (1933). *Cf.*: Fischer, E., and Koenigs, E., *Ber.* **37**, 4585 (1905).



IMINOTETRACARBOXYLIC ESTER

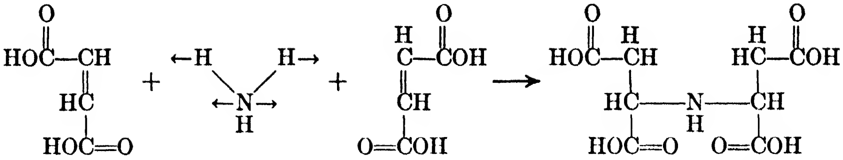
Tetraethyl Iminobissuccinate

This reaction illustrates another manner in which ammonia can combine with maleyl compounds to give different products. The procedure obviously needs further study in view of the low yields, but clearly shown is the effect of high temperature and excess ammonia in favoring the addition of ammonia to two moles of the maleyl compound. The formation of amides is evidently partially prevented by the large amount of water present.

The tetraethyl ester of iminobissuccinic acid is a viscous liquid, b_5 215–217°. It is soluble in alcohol and ether but insoluble in water. The acid has not yet been isolated.

This compound would offer interesting possibilities as a polybasic ester for commercial organic synthesis if it could be obtained in favorable yields.

Ammonia

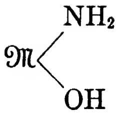


Fumaric acid + Ammonia ⟶ Iminobissuccinic acid

Procedure. Twenty grams of fumaric acid is dissolved in 38 ml. of aqueous ammonia of sp. gr. 0.908, to which 50 ml. of water has been added. This is placed in a pressure flask and heated with necessary precautions at 120 to 130° for 20 hours. Then the reacted mixture is heated in an open vessel on a water bath to free it of ammonia. It is then made acid to tropaeolin with hydrochloric acid and evaporated to a paste. The paste is extracted with cold water, the unreacted fumaric acid filtered off, and the extract allowed to evaporate upon a water bath. The residue is dried over concentrated sulfuric acid in a vacuum desiccator, extracted with absolute alcohol, filtered, and converted to esters in the customary manner. The mixture of esters is separated by distillation in vacuo after removal of the solvent. Three fractions are obtained in this way, namely, 3 g. of crude diethyl aspartate, b_7 130–170°; a small amount of liquid of b_7 170–215°; and 2 g. b_7 215–220°. The last fraction when redistilled yields pure tetraethyl iminobissuccinate.

Reference

Stadnikoff, G., *Ber.* 44, 52 (1911); *J. Rus. Chem. Phys. Soc.* 41, 900 (1911).



$\mathfrak{M}\langle^{NH_2}_{OH}$

Maleamic Acid

The monoamides, maleamic and maleanilic acids, are formed when maleyl compounds react with ammonia, or primary or secondary amines under anhydrous conditions.

N-Alkylmaleamic acids when heated at elevated temperatures are converted to the imides, whereas the *trans*-isomers, the fumaramic acids, produce largely N-alkylaspartic acids. N-Methylmaleimide volatilizes readily, yielding lachrymose vapors that are readily recognized as characteristics of this compound.

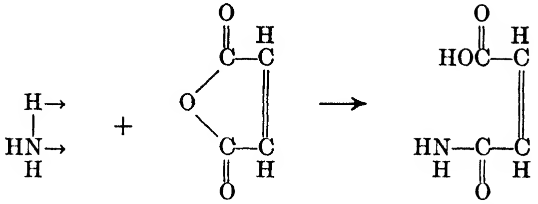
Maleamic acid crystallizes as plates from water. These decompose at 152 to 153°, but melt at 172 to 173° if heated rapidly. Maleamic acid is soluble in water and hot alcohol. It is insoluble in ether, benzene, and chloroform.

Use. This reaction of maleyl compounds in forming maleamic acids is important in the syntheses of certain sulfa-drugs, such as 4,4′-bis(β-carboxyacrylylamino)diphenylsulfone, *p*-(2-thiazolyl)sulfamylmaleanilic acid, and the like.

N-Alkylmaleamic acids, as N-dodecylmaleamic acid, can be sulfonated to give valuable lathering aids when added to detergents. Resins are readily produced from alkylmaleamic acid by polymerization.

N-Ethylmaleanilic acid is used in the separation of mixtures containing methyl, ethyl, and methyl ethyl alkylated toluidines. Maleanilic acid reacts with phosphorus oxychloride to give maleanilide dichlorophosphate. This anilinium salt is easily hydrolyzed to the maleanilide.

Ammonia



Ammonia + Maleic anhydride ⟶ Maleamic acid

Procedure. A solution of 10 g. of maleic anhydride in 350 g. of dry benzene is saturated in a hood with anhydrous ammonia gas until the precipitation of the gummy ammonium salt is complete. The salt is removed and dissolved in water. This solution is heated until no further odor of ammonia is detected. It is then acidified with hydrochloric acid, which causes the maleamic acid to precipitate as fine crystals. The yield is 70% of the theoretical amount.

N-Substituted maleamic acids may be prepared by similar procedures. They may also be synthesized by heating the reactants without a solvent at elevated temperatures under pressure; by treating maleimide with alcohols; and by allowing N-alkylfurfurylideneamines to react with maleic acid.

References

Anschütz, R., *Ann.* **259**, 137 (1891). *Cf.*:
Herz, W., *J. Am. Chem. Soc.* **67**, 1854 (1945).
Hoogwverff, S., and van Dorp, W. A., *Rec. trav. chim.* **18**, 358 (1899).
Kappelmeier, C. P. A., and van Goor, W. R., *Verfkroniek* **21**, 136 (1948).
Michael, A., and Palmer, G. M., *Ber.* **19**, 1375 (1886).
Moore, M. L., and Miller, C. S., *J. Am. Chem. Soc.* **64**, 1572 (1942).
Pressman, D., Bryden, J. H., and Pauling, L., *J. Am. Chem. Soc.* **70**, 1352 (1948).
Piutti, A., and Giustiniani, E., *Gazz. chim. ital.* **26** (I), 431 (1896).
Snyder, H. R., and Robinson, J. C., *J. Am. Chem. Soc.* **63**, 3279 (1941).

U.S. 2,268,754; 2,459,964. Brit. 542,874; 617,810.

N-Phenylmaleimide

(Maleanil)

Maleimides are usually obtained from the maleamic acids either by heating them at elevated temperatures or by treating their solutions with phosphorus pentoxide. N-Arylmaleimides, however, may be prepared directly from maleic anhydride and the anilines if a catalyst, such as thionyl chloride, is added to the reaction mixture at temperatures above 160°. Below this temperature, α-chloro-N-phenylsuccinimide and *asym*-N-phenylmaleimides are likely to be formed.

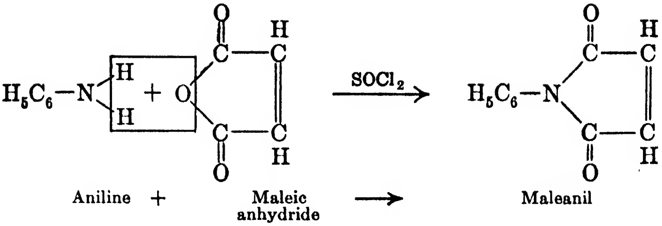
Maleanils may also be prepared from maleanilic acids by this procedure. This would indicate that maleanilic acids are first formed during the reaction in which the anils are produced directly from maleic anhydride. Phosphorus trichloride and acetyl chloride may also be used as catalysts in this procedure.

N-Phenylmaleimide crystallizes from water as yellow needles, which melt according to some investigators at 90 to 91°, but according to others at 87.5 to 88.5°. The molten liquid boils under 12 mm. pressure at 162.1 to 163°. N-Phenylmaleimide is soluble in benzene, chloroform, alcohol, and ether, but only slightly soluble in petroleum ether and carbon disulfide.

Heated with barium hydroxide and water, N-phenylmaleimide yields maleanilic acid. When allowed to react with aniline, it gives α-anilino-N-phenylsuccinimide. Maleanils also react, for example, with phenylhydroxylamines to form α-substituted maleimides such as α-anilino-N-phenylmaleimide. Maleimide itself reacts like maleic anhydride in Diels-Alder syntheses.

Use. N-substituted maleimides are useful as insecticidal and fungicidal agents. They have been employed as preserving agents for storing cottonseed, as modifying agents for treating rubber, and as reactants in copolymerizations. N-alkylmaleimides have similar uses.

Aniline

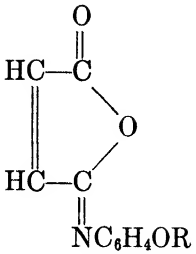


Procedure. A solution of 98 g. of maleic anhydride in 665 g. of *o*-chlorobenzene is heated to 180°, when 93 g. of aniline is added slowly to it. The mixture is then kept refluxing while 125 g. of thionyl chloride is added by means of a stream of air saturated with the chloride at 60°. The refluxing is continued for an hour to eliminate evolved gases. The bulk of the solvent is removed, and the product obtained by distillation in vacuo. The yield is 82 g., or 47% of theory.

References

Speer, J. H., U. S. 2,262,262 (1942). *Cf.*:
Altschul, A. M., Karon, M. L., Kyame, L., and Hall, C. M., *Plant Physiol.* **21**, 573 (1946).
Anschütz, R., and Wirtz, Q., *Ann.* **239**, 137 (1887).
Delalande, A., *Compt. rend.* **224**, 1511 (1947); *Rubber Chem. and Technol.* **21**, 344 (1948).
Harvey, S. C., *J. Am. Chem. Soc.* **71**, 1121 (1949).

U.S. 2,244,536. Fr. 844,554.



2,5-DIHYDROIMIDOOXOFURANS

asym-N-(*p*-Methoxyphenyl)maleimide

[N-(2,6-Dihydro-2-oxo-5-furylidene)-*p*-methoxyaniline]

Compounds of this type are probably formed to some extent when any maleanilic acid is heated with acetyl chloride at temperatures below 160°; but evidence for the formation of the asymmetrical isomer is complete only in the case of N-(*p*-alkoxyphenyl)maleimides. Here both the colorless asymmetrical and yellow symmetrical compounds have been isolated as separate entities. That the two forms are not physical isomerides has been confirmed from studies of their absorption spectra. The manner in which the asymmetrical compounds are formed would indicate that maleanilic acids exist in two tautomeric forms, namely, $HO_2CCH{=}CHCONHR'$ and $HO_2CCH{=}CHC({=}NR')OH$. See equation on opposite page.

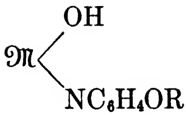
It is interesting to note that, although α-chloro-N-phenylsuccinimide may be formed by the reaction of acetyl chloride and N-phenylmaleamic acid, there is no evidence that acetyl chloride or acetic acid can add to saturate the C:C bond of maleic derivatives, such as occurs with some ethylene compounds.

asym-N-(*p*-methoxyphenyl)maleimide crystallizes from dilute alcohol as fine needles that melt at 145 to 146°. It is very soluble in benzene, ethyl acetate, acetone, and chloroform. It has a limited solubility in carbon tetrachloride and carbon disulfide, and it is almost insoluble in water and cold alcohol, but very soluble in boiling alcohol.

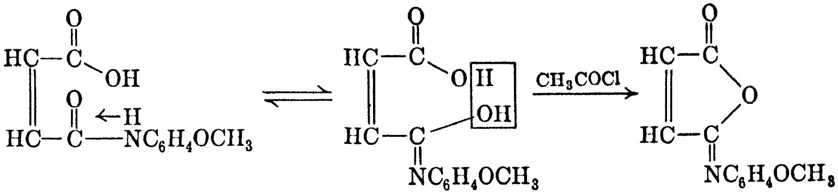
The symmetrical anil consists of yellow needles that melt at 148.5° when pure. It is obtained mixed with the asymmetrical anil when *p*-methoxymaleanilic acid is heated with phosphorus pentoxide in toluene.

The two compounds add bromine but at distinctly different rates.

Use. No particular use has yet been made of these compounds.



p-Methoxymaleanilic Acid



p-Methoxymaleanilic acid ⟶ *asym*-N-(*p*-Methoxyphenyl)maleimide

Procedure. A mixture of 5 g. of dry *p*-methoxymaleanilic acid, 36 g. of acetone, and 15 g. of acetyl chloride is refluxed until solution is completed. The reaction mixture is then evaporated by heating it gently in a current of dry air. In this way all the solvent, any unreacted acetyl chloride, and volatile secondary products are removed. The crystalline residue that remains has a green color. It is collected on a filter and washed with a little alcohol, leaving a perfectly colorless product that is then crystallized from dilute alcohol.

References

Piutti, A., *Atti. reale accad. Lincei, Classe sci. fis. mat. e nat.* **17** (5), I, 635 (1908); **18** (5), 312 (1909); *Rend. accad. sci. fis. mat. e nat. Soc. reale Napoli* **15** (3), 315 (1909). *Cf.*:
Curtius, T., and Foesterling, H. A., *J. prakt. Chem.* **51**, (2), 371 (1895).
Piutti, A., and de'Conno, E., *Mem. reale accad. Lincei, Classe sci. fis. mat. e nat.* **8** (5), 793 (1911).
Warren, W. H., and Grose, M. R., *J. Am. Chem. Soc.* **34**, 1600 (1912).

Fumaramide

Ammonia does not add to the C:C bond of maleyl compounds when they are allowed to react at ordinary or low temperatures, as is the case of this reaction and the one for maleamic acid that follows.

Maleamide may also be prepared by this method, but, in such reactions, ammonia solutions have a tendency to cause maleic acid to isomerize to fumaric acid. This leads to very poor yields of pure maleamide. Only 24% has been obtained even when the reaction is carried out at 10°.

Fumaramide occurs as needles that melt at 266° after carbonizing at lower temperatures, according to McMaster and Langreck. It is insoluble in water, but very soluble in alcohol and ether.

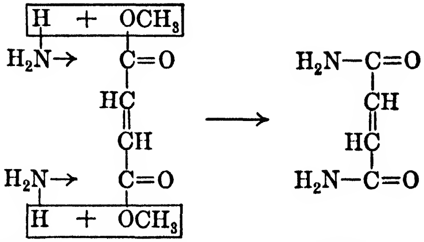
Maleamide melts at 180 to 181°. When heated at its melting point, it is readily converted to fumaramide. A mixture of the two may be separated by dissolving in methyl alcohol in which the fumaramide is only slightly soluble.

Uses. Molding resins are obtained by allowing these compounds to react with formaldehyde. Heating with zinc chloride converts them to the imide, which can then be copolymerized with chlorobutadienes to give synthetic rubbers.

Substituted amides prepared with hydroxyalkylamines in a similar manner and then sulfonated yield useful lathering, foaming, penetrating, and surface-modifying agents. The quinoline derivatives have been used as printing assistants and as therapeutic compounds. Amides from polyamines, when allowed to react with formaldehyde, produce resin finishing materials for textiles.

Dehydration of fumaramide and maleamide with phosphorus pentoxide yields the respective nitriles. These are reported to be valuable as insecticides and as agents for the synthesis of safety-glass adhesives, and of compounds like 1,2-bis(4-methyl-2-thiazolyl)ethane and dithiosuccinamide.

Ammonia



Ammonia + Dimethyl fumarate ⟶ Fumaramide

Procedure. A mixture of 9 g. of dimethyl fumarate and 35 ml. of aqueous ammonia of a sp. gr. of 0.90 is stirred occasionally for a period of 24 hours, during which time the fumaramide slowly separates as a white powder. This product is removed by filtration, dried on the filter, and then in an oven at 100°. The filtrate is saturated with gaseous ammonia that gives an additional amount of amide when allowed to stand for 24 hours. The total yield is 2.6 g., or 91% of theory.

References

McMaster, L., and Langreck, F. B., *J. Am. Chem. Soc.* **40**, 970 (1918). *Cf.*:
Bergs, *U. S. Dept. Com. OPB Rept.* PB688, 5 pp.
Bischoff, C. A., and Walden, P., *Ann.* **279**, 130 (1894).
Curtius, T., and Koch, F., *Ber.* **19**, 2460 (1886).
de Wolf, J., and van de Straete, L., *Bull. classe sci., Acad. roy. Belg.* **21** (5), 216 (1935).
Hagen, R., *Ann.* **38**, 275 (1841).
Keiser, E. H., and Kessler, J. J., *Am. Chem. J.* **46**, 523 (1911).
Keiser, E. H., and McMaster, L., *Am. Chem. J.* **49**, 81 (1913).
Lewis, F. M., and Mayo, F. R., *J. Am. Chem. Soc.* **70**, 1533 (1948).
Mommaerts, H., *Bull. soc. chim. Belges* **52**, 79 (1943); *Bull. classe sci., Acad. roy. Belg.* **28**, 363 (1942).
Ossipoff, I., *J. Russ. Chem. Soc.* **20**, 83 (1888); *J. Chem. Soc.* **56**, 124 (1889).
Smith, L. I., *U. S. Dept. Com. OTS Rept.* PB39709 (1942).
Viseux, G., *Bull. soc. chim. Belges* **35**, 426 (1926).

U.S. 2,240,516; 2,306,095; 2,371,103; 2,371,104; 2,391,836; 2,431,921; 2,433,393; 2,438,019; 2,447,810. Brit. 590,884; 596,087. Belg. 448;283.

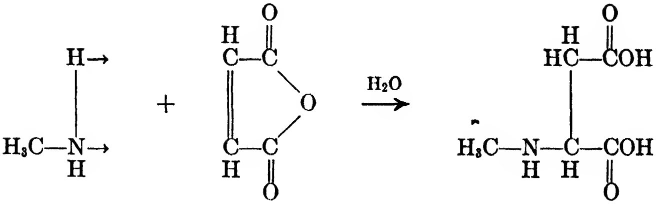
N-Methylaspartic Acid

The procedure given on the opposite page is a commercial one, where no attempt is made to isolate the aspartamides that are formed initially during the reaction. The preparation is a general one. It may be used with a wide variety of primary amines, including the alkyl, aryl, and various other substituted derivatives. Diamines react with only one molecule of the maleic anhydride in this preparation. Hydroxyl groups in substituted amines are generally non-reactive for all practical purposes. Thus *m*-aminophenol behaves like any other substituted amine. No mention is made, however, of *p*-aminophenol, which is described in other preparations as forming *asym*-N-(*p*-hydroxyphenyl)maleimide and *p*-hydroxymaleanilic acid.

N-Methylaspartic acid crystallizes from water as monoclinic prisms containing one mole of coordinated water. This hydrate melts at 133 to 134°. When heated slowly at 100°, it loses water to form the anhydrous acid melting at 178°. It is very soluble in hot water, giving a strongly acid aqueous solution. It has limited solubility in cold water but dissolves readily in dilute alkalies. The monomethyl ester melts at 181.5°. The diethyl ester is an oil that is only slightly soluble in water, but very soluble in acid solutions.

Uses. N-Substituted aspartic acids contain two reactive carboxyl groups besides a reactive secondary amino radical. They are reactants in the manufacture of several dyestuffs, synthetic tanning agents, emulsifying agents, non-foaming wetting agents, detergents, textile assistants, rapidogens for dyeing, and related types of substances.

Methylamine



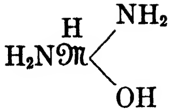
Methylamine + Maleic anhydride ⟶ Methylaspartic acid

Procedure. A mixture of 500 g. of maleic anhydride, 200 ml. of water, and 750 g. of methylamine is heated at 90° for 15 hours. Then 1150 g. of 40° Bé sodium hydroxide solution is added, and the stirring is contained at 90° for an additional 20 hours. The resulting solution is treated with animal charcoal, then filtered, and the filtrate is concentrated under partial pressure. The sodium N-methylaspartate obtained in this way is dissolved in alcohol, and concentrated hydrochloric acid is added until the solution is acid to Congo paper. The salt that precipitates is removed, and then the alcohol is evaporated off with the aid of vacuo. The residue is then redissolved in alcohol to remove any remaining salt. Evaporation of this solution gives a yellow oil that solidifies to a crystalline mass upon standing.

References

Reppe, W., and Ufer, H., U. S. 2,200,220 (1940).
U. S. Dept. Com. OTS Repts. PBL58767, PBL70344, and PBL63022. *Cf.*:

U.S. 2,324,712; 2,379,535; 2,412,708.



"β"-Asparagine

Maleic anhydride reacts with a concentrated solution of ammonia in absolute alcohol to give a separable mixture of *d*- and *l*-"β"-asparagines as shown. *l*-"β"-Asparagine is the one commonly found in nature. It is an α-aminosuccinamic acid, with the amino groups attached to the 2- and 4-carbons. These stereoisomers of "β"-asparagine apparently do not form a racemic product. Racemic acids, however, have been obtained from equal molecular mixtures of the *d*- and *l*-isomers of some of the derivatives of asparagine.

"β"-Asparagine may also be prepared from the β-monoethyl ester of *l*-aspartic acid, from *l*-aspartamide, and from 2,5-dioxo-3,6-piperazinediacetamide.

The isomeric "α"-asparagine, with the amino groups attached to adjacent carbons, may be obtained as the inactive acid by treating *dl*-aspartic acid with an alcoholic solution of ammonia, or by reducing β-aminomaleamic acid with aluminum amalgam.

The product obtained in this preparation is a crystalline solid that decomposes on heating at 182 to 183°. It is soluble in hot water but only slightly soluble in cold water. Prolonged heating in this liquid causes it to decompose. The mixture is practically insoluble in absolute alcohol.

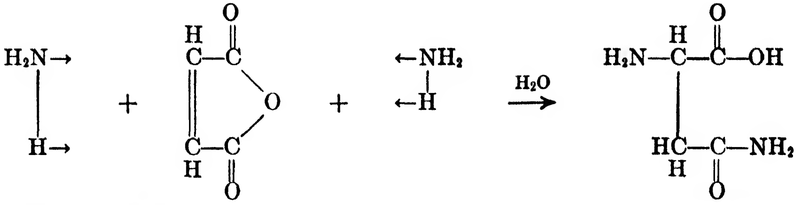
The *d*- and *l*-"β"-optical isomers obtained from it occur as rhombic bisphenoids. When heated in a closed tube, both melt at 226° and decompose at 234 to 235°. They have a density $d_4^{14.8°}$ of 1.5434.

The *dl*-"α"-asparagin crystallizes as triclinic pinacoidal tablets containing one mole of water. This water is lost at 100° when the compound is heated under partial vacuum. This asparagine decomposes at 213 to 215° without melting and has a $d_4^{14.8}$ of 1.4550. It is very soluble in hot water, moderately soluble in cold water, and insoluble in alcohol and ether.

Use. *l*-"β"-Asparagine is used as a growth substance for yeast and other molds. Its mercury salt has been employed in the treatment of certain infectious diseases. Extensive studies have been made of its biochemical properties. It reacts with formaldehyde to yield the N^{β}-methylene derivative, which upon oxidation with hypobromite gives 5-bromo-6-oxo-4-pyrimidinecarboxylic acid.

This preparation is a convenient one for obtaining *d*-"β"-asparagine, since this optical isomer is only found in very small amounts in nature.

Ammonia



Ammonia (in absolute ethanol) + Maleic anhydride ⟶ "β"-Asparagine

Procedure. To a saturated solution of 10 g. of ammonia in absolute ethanol is added 1 g. of maleic anhydride. This is placed in a tube that is sealed and heated at 105 to 110° until a light yellow resin has formed. This resin is dissolved in water and then treated with Peligato's copper oxide, which gradually gives rise to small crystals of the insoluble copper salt of the asparagines. These asparagine salts are then removed, suspended in water, and decomposed with hydrogen sulfide. This yields a mixture of *d*- and *l*-"β"-asparagines that may be separated by fractional crystallization. The yield of these asparagines is approximately 25%, based on the weight of maleic anhydride taken. The *l*-isomer has the same optical rotation as the product obtained from natural sources. Larger quantities may be more conveniently prepared by carrying out the reaction in a bronze autoclave.

References

Piutti, A., *Gazz. chim. ital.* **16**, 279 (1886); **17**, 187 (1887); **18**, 471 (1888); **27** (I), 147 (1897); **34** (II), 43 (1904); *Ber.* **29**, 2070 (1896). *Cf.*:
Berlingozzi, S., and Carobbi, G., *Gazz. chim. ital.* **60**, 573 (1930).
Berlingozzi, S., *Atti. reale accad. naz. Lincei., Classe sci. fis. mat. e nat.* **7** (6), 1037 (1928).
Carpenter, D. C., and Lovelace, F. E., *J. Am. Chem. Soc.* **64**, 2899 (1942).
Michael, A., *Ber.* **28**, 1632 (1895).
Timmermans, J., van Lancker, T., and Jaffe, J., *Bull. soc. chim. Belg.* **48**, 33 (1939).
Schaal, E., *Ann.* **157**, 25 (1871).
Thomas-Mamert, R., *Bull. soc. chim. France* **17** (3), 60 (1897).

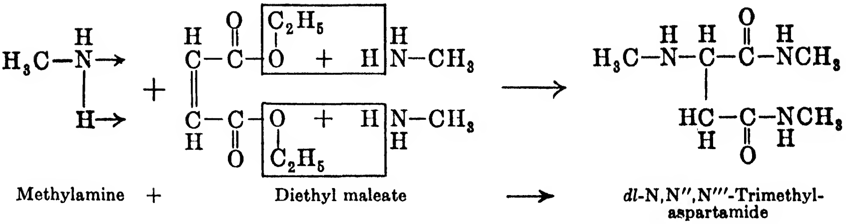
dl-N,N′,N″-Trimethylaspartamide

(N-Methylaspartylbismethylamide)

Complete amination takes place when maleates are heated under pressure with amines in an anhydrous solvent, such as absolute alcohol. Since the conditions are favorable here to the saturation of the olefin bond of the maleates, esters of the substituted aspartic acid are also formed as one of the products. Contrary to what takes place at lower temperatures, it would appear that in this preparation the saturation of the maleate precedes that of the formation of the amide. Compare, for example, this preparation with the one given for fumaramide.

dl-N,N′,N″-Trimethylaspartamide, when pure, occurs as long colorless needles. The product is very soluble in water and alcohol but practically insoluble in absolute ether. Both the aqueous and alcoholic solutions are strongly alkaline. When heated in water, this product loses methylamine to form the aspartamic acid.

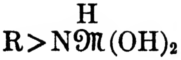
Methylamine



Procedure. Twelve grams of diethyl maleate is placed in a tube, and 50 ml. of a 33% solution of methylamine in absolute ethanol is added to it. The tube is then sealed and heated for 8 to 10 hours at 105 to 110°. Two products are formed, a solid consisting of a mass of fine needle crystals and a liquid. Several volumes of ether are then added to the mixture, and the crystals are removed by filtration. When dry, they are recrystallized from absolute alcohol. Additional amide is obtained from the alcoholic-ether mother liquor in addition to the liquid product, which is diethyl N-methylaspartate.

Reference

Körner, G., and Menozzi, A., *Gazz. chim. ital.* 19, 422 (1889).



Piperidinesuccinic Acid

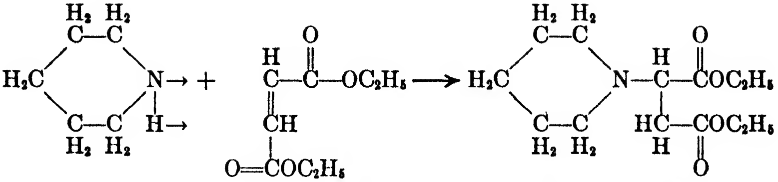
Heterocyclic secondary amines readily react to saturate malcyl compounds, especially the esters of maleic acid. They apparently do not spit off alcohol to form the amides as easily as other amines. Hence aspartic esters can be produced directly by reaction with maleic esters as shown.

Heterocyclic compounds, such as piperazine, which contain two secondary amino groups react with two moles of the ester to yield disuccinic acids.

The pure ethyl ester of piperidinesuccinic acid boils under 10 mm. pressure at 159°. It has a density when freshly prepared of d_{18}^{18} 1.0469. It is soluble in alcohol and ether but insoluble in water.

Use. No commercial use has as yet been made of these derivatives of succinic acid. They offer, however, many possibilities as intermediates in chemical synthesis.

Piperidine

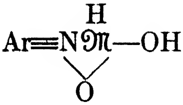


Piperidine + Diethyl fumarate ⟶ Diethyl piperidinesuccinate

Procedure. A mixture of 92 g. of piperidine and 156 g. of diethyl fumarate is carefully digested on a water bath for 8 to 10 hours. The reaction is an exothermic one. The oily product obtained upon completion of the reaction is then distilled under 1 mm. pressure, and the largest fraction boiling at 162 to 164° is collected and redistilled to obtain a pure product.

References

Ruhemann, S., and Browning, B. A., *J. Chem. Soc.* **73**, 723 (1898). *Cf.*:
Clemo, G. R., and Graham, S. B., *J. Chem. Soc.* **1930**, 213.
Körner, G., and Menozzi, A., *Ber.* **21R**, 86 (1888); **22R** 735 (1899).
Pollard, C. B., Bain, J. P., and Adelson, D. E., *J. Am. Chem. Soc.* **57**, 199 (1935).



QUATERNARY AMMONIUM SUCCINIC ACIDS

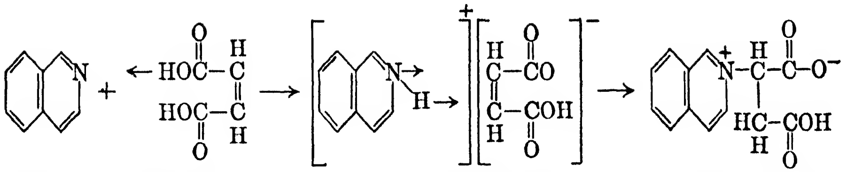
Succinic Acid Isoquinolinium Betaine

Tertiary amines also readily add to saturate the C:C bond of maleyl compounds at temperatures above 100°, by forming the quaternary ammonium intramolecular salts of the betaine type. The ammonium acid maleates are formed first. Addition to the unsaturated bond can then take place through a transfer of the hydrogen atom of the isoquinolinium ion to the β-carbon of the ethylene group of the maleate. Substituted succinates of this type have been prepared from a variety of tertiary amines including pyridine, α-picoline, collidine, lutidines, 2-styrylquinoline, N-alkylpiperidine, N-alkyltetrahydroisoquinolines, methylolalkylaryl amines, and dimethylolalkylamines. The pyridinium betaine yields acrylic acid upon heating. Similar compounds may possibly be formed with antipyrine, pyramidone, and other tertiary amines.

Succinic acid isoquinolinium betaine crystallizes from water with one mole of solvent and melts at 149 to 150°. The aqueous-free intrasalt can be prepared from it. It melts at 151 to 152°. It is soluble in alcohol, acetone, and chloroform, only slightly soluble in water, and very slightly soluble in ether and carbon tetrachloride.

Use. Products containing a long-chain alkyl group, such as succinic acid N-dodecyltetrahydroisoquinolinium betaine, can be used as wetting, washing, emulsifying, and dispersing agents. Compounds of such structures are of interest in synthesizing new fungicides, insecticides, textile assistants, corrosion inhibitors, dye stabilizers, and pharmaceuticals.

Isoquinoline



Isoquinoline + Maleic acid ⟶ Isoquinolium acid maleate ⟶ Succinic acid isoquinolinium betaine

Procedure. Separate solutions are prepared of 32.5 g. of isoquinoline and 29 g. of maleic acid in absolute ether. Upon mixing, isoquinolinium acid maleate is precipitated. This precipitate is removed by filtration, washed, and dried. It is then rapidly heated to its melting point at 103° and held at this temperature for a few minutes. Rapid conversion to the betaine salt takes place. The betaine salt is then purified by dissolving in hot water and treating with animal charcoal. The yield is 82% of theory.

An alternate method is to prepare an aqueous or alcoholic solution of the mixture of equivalent amounts of the amine and acid, and allow this to stand at room temperature for two weeks, and then to recover the betaine salt that is slowly formed.

Intrasalts of this type have also been prepared from α,β-dibromosuccinic acid.

References

Lutz, O., and Krauklis, A., *Ber.* 69B, 419 (1936). *Cf.*:
Bergmann, F., *J. Am. Chem. Soc.* 60, 2811 (1938).
La Parola, G., *Gazz. chim. ital.* 67, 645(1937).
Lutz, O. E., *Ber.* 43, 2636 (1911); *J. Russ. Phys. Chem. Soc.* 47, 1549 (1915).
Lutz, O., Klein, R., and Jirgenson, A., *Ann.* 505, 307 (1933).
Ogata, Y., Tsunemitsu, K., and Oda, R., *Bull. Inst. Phys. Chem. Research (Tokyo)*, Chem. Ed., 23, 281 (1944); *C. A.* 42, 6746h (1948).
Pfeiffer, P., and Langenberg, A., *Ber.* 43, 2926 (1910).

U.S. 2,310,109. Ger. 726,670.

2,4,6-Trimaleimidophenol

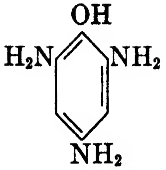
[2,4,6-Trimaleylpicramine
or N,N′,N″-(2-Hydroxy-*s*-phenenyl)tri-maleimide]

This reaction is interesting since it takes place readily at room temperatures. Since triaminophenol is very susceptible to oxidation, the preparation has to be carried out in an inert atmosphere. Use of the hydrochloride instead of the free-base of triaminophenol has not given satisfactory results.

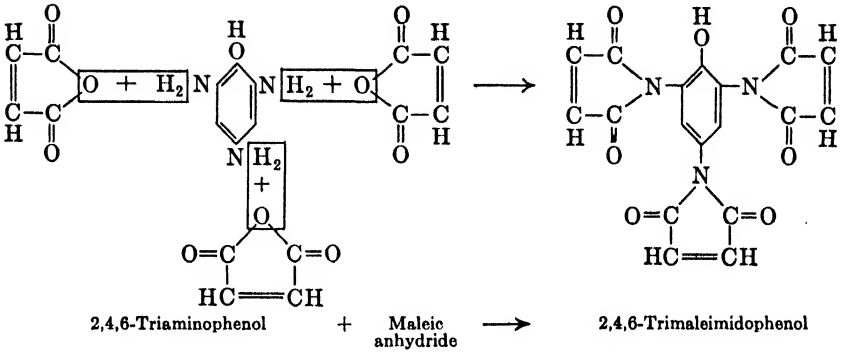
2,4,6-Trimaleimidophenol is a light yellow solid melting at 200°. It is soluble in methyl alcohol, ethyl alcohol, and acetic acid. Treated with concentrated nitric acid, it reacts violently to yield dimaleimidoquinone, a crystalline product soluble in alcohol that melts at 93°.

The corresponding trimaleamic acid has been obtained as a brown powder when trimaleamidophenol is saponified with potassium hydroxide. It melts at about 150°. Its silver salt prepared in red light occurs as lustrous gray crystals.

Use. No use has yet been made of this compound.



2,4,6-Triaminophenol



Procedure. An anhydrous benzene solution containing 2.94 g. of maleic anhydride is placed in a separatory funnel and run into a closed vessel containing 0.53 g. of sodium carbonate dissolved in freshly distilled water. Nitrogen is then bubbled through the solution to remove all traces of air from the vessel. An absolute alcohol solution containing 2.48 g. of 2,4,6-triaminophenol hydrochloride is then carefully added to the mixture through the separatory funnel. A light yellow product is formed. This is removed and dried at 100°.

Reference

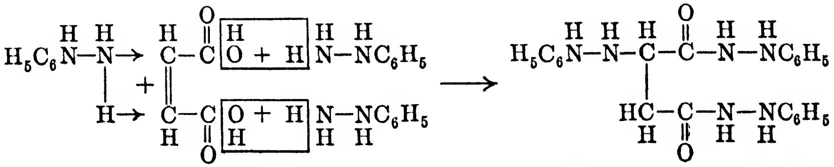
Covello, M., *Gazz. chim. ital.* 63, 517 (1933).

N^{α}-Anilinoaspartic Acid Bis(1-phenylhydrazide)

Addition of a hydrazine to the C:C bond of maleyl compounds takes place only at elevated temperatures, as with the amines. An excess of the hydrazine favors the formation of the bishydrazide of the addition product, as shown in this preparation, whereas equivalent amounts of reactants lead to the production of 5-oxo-3-pyrazolidenecarboxylic acids (*q.v.*), such as obtained upon the hydrolysis of the N^{α}-anilinoaspartic acid bis(1-phenylhydrazides).

N^{α}-Anilinoaspartic acid bis(1-phenylhydrazide) occurs as irregular crystals that melt at 199 to 200°. It is insoluble in water and ether, but readily dissolves in boiling alcohol. It shows the usual reactions for hydrazine. It is reduced by Fehling solution upon standing in the cold. Strong acids and alkalies dissolve the compound by hydrolyzing it.

Phenylhydrazine

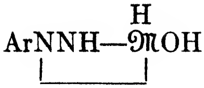


Phenyl-hydrazine + Maleic acid ⟶ Nα-Anilinoaspartic acid bis(1-phenylhydrazide)

Procedure. A mixture of 116 g. of fumaric or maleic acid and 108 g. of phenylhydrazine is heated to 120°. At this temperature the mass slowly becomes liquid and loses water and some carbon dioxide. The temperature is then raised to 140° and held at this point for half an hour. The resulting sirup is treated with hot alcohol, giving a solution that yields a crystalline mass upon cooling. The crystals are removed and recrystallized twice from hot alcohol. The yield is 80% of theory.

Reference

Duden, P., *Ber.* 26, 119 (1893).



$\mathrm{ArNNH}-\overset{\mathrm{H}}{\mathfrak{M}}\mathrm{OH}$

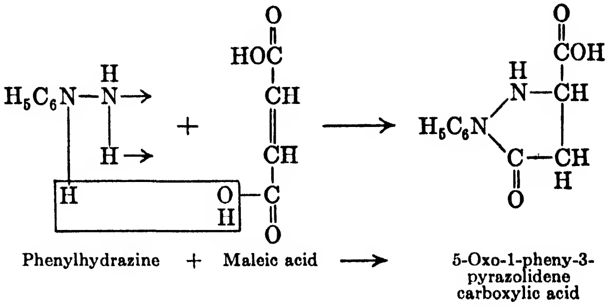
5-Oxo-1-phenyl-3-pyrazolidenecarboxylic Acid

Both the amino groups of hydrazines are capable of reacting with maleyl compounds unless one of the amino groups is completely substituted. Thus even a greater number of derivatives of maleic acid may be formed from the hydrazine than from the amines. When conditions are favorable to the saturation of the C:C group of the maleyl bond, 5-oxo-3-pyrazolidenecarboxylic acids are obtained. A large amount of resinification, however, usually accompanies such reactions so that only part of the maleic acid is actually used in forming the product of this preparation.

5-Oxo-1-phenyl-3-pyrazolidenecarboxylic acid crystallizes from alcohol as concentrically arranged needles, which melt at 210 to 212°. It shows very slight solubility in cold water, but it dissolves readily in hot water. The aqueous solutions have a strong acidic reaction, and give a neutral equivalent for a monobasic acid.

Use. This compound may be used for a number of organic syntheses. Ferric chloride, for example, readily oxidizes it to the pyrrolone. This latter compound may then be used as a reactant in preparing coupling agents for color photography.

Phenylhydrazine



Procedure. A mixture of 116 g. of maleic acid and 108 g. of phenylhydrazine is heated to 110°, at which temperature water and carbon dioxide are evolved. The temperature is then raised to 125° until completion of the reaction. This produces a brown sirup that is extracted several times with alcohol. The combined extracts are then evaporated, and the product so obtained is recrystallized twice from alcohol to yield 50% of the theoretical amount of pure acid. The remainder of the maleic acid is apparently consumed in producing resinous derivatives.

Reference

Duden, P., *Ber.* 26, 119 (1893).

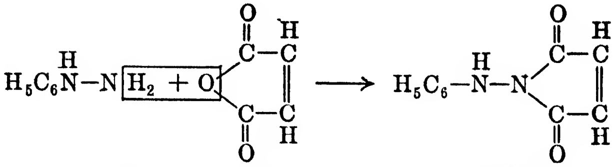
N-Anilinomaleimide

Solvents have a marked effect on the type of product produced by hydrazines. N-Aminomaleimides or their analogs are the major products when hydrazines combine with maleic acid or its anhydride in glacial acetic acid. Several substituted N-(arylamino)maleimides may be prepared by this procedure. Their yellow color indicates that they are the symmetrical compounds. However, if aqueous acetic acid is substituted for the glacial solvent, N-α-(dianilino)aspartimide is formed instead of the maleimide from phenylhydrazine and maleic acid.

asym-Aminomaleimide, however, is the major product when hydrazine hydrate reacts with maleic anhydride in alcohol. This is a white powder. See *asym*-N-(*p*-methoxyphenyl)maleimide. The other product formed in fairly large amounts is the cyclic N,N′-hydrazide; 1,2-dihydro-3,6-pyridazinedione (*q.v.*).

N-Anilinomaleimide occurs as yellowish plates or needles. The product darkens at 180° and then melts at about 260° (259 to 260° according to Duden, 260 to 261° according to Hötte, and 265° according to Jolles). It is soluble in alkalies and is reprecipitated by concentrated acid.

Phenylhydrazine

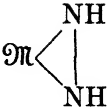


Phenylhydrazine + Maleic anhydride ⟶ N-Anilinomaleimide

Procedure. A glacial acetic acid solution containing 5 g. of maleic anhydride and 5.5 g. of phenylhydrazine is heated to boiling and allowed to reflux for 20 minutes. The reaction mixture is then diluted with water, which precipitates the maleimide. This is removed and recrystallized from alcohol three times.

References

Jolles, E., *Gazz. chim. ital.* **66**, 717 (1936). *Cf.*:
Curtius, T., and Foersterling, H. A., *J. prakt. Chem.* **51** (2), 371 (1895).
Duden P., *Ber.* **26**, 121 (1893).
Hötte, B., *J. prakt. Chem.* **35** (2), 295 (1887).



1,2-Dihydro-3,6-Pyridazinedione

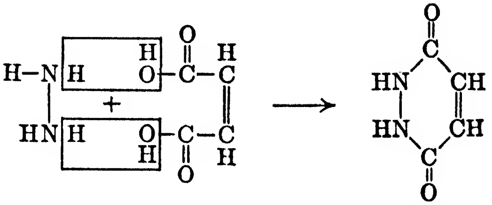
(N,N′-Maleyl Hydrazide)

A further example of the polyfunctional character of hydrazines is illustrated by the formation of 1,2-dihydro-3,6-pyridazinedione when maleic acid reacts hydrazine hydrate. The compound is one of the products, even when sufficient alcohol is present to precipitate *asym*-aminomaleimide, which is the major product under these conditions. It is possible that 1,2-dihydro-3,6-pyridazinedione may be formed from the *asym*-aminomaleimide by simple molecular rearrangement. This is most favored by the conditions given on the opposite page. Two other products are also formed in this reaction. Neither of these has been completely characterized. Both are formed in relatively small amounts and are yellow in color. Neither is a salt of maleic acid according to Curtius and Foesterling. See comments by Mizzoni and Spoerri in reference given on opposite page.

1,2-Dihydro-3,6-pyridazinedione is obtained as small, colorless crystals that do not melt below 250°. The compound is very soluble in hot alcohol. It is easily dissolved in hot water or acetic acid. The aqueous solution is distinctly acidic.

Use. Several interesting applications are being studied at present. These include the use of the diethanolammonium salt as a selective herbicide, and as an agent to inhibit growth of shrubs and to delay the flowering of fruits.

Hydrazine Hydrate



Hydrazine + Maleic acid ⟶ 1,2-Dihydro-3,6-pyridazinedione

Procedure. Fifty grams of hydrazine hydrate is added to a solution of 98 g. of maleic anhydride, which has been dissolved in a small amount of water. Alcohol is then slowly added to the mixture, care being taken not to add enough to precipitate the *asym*-N-aminomaleimide that is first formed. The reaction mixture is then heated on a water bath. When the mixture is cooled, crystals of the pyridazinedione are obtained. These are separated and recrystallized from hot alcohol or water.

Reference

Curtius, T., and Foesterling, H. A., *J. prakt. Chem.* **51** (2), 371 (1895). *Cf.:*
Arndt, F., et al., *Rev. faculté sci. univ. Istambul* **9A**, 19 (1944); **13A**, 103 (1948); *C.A.* **40,** 1787^5; **43,** 579d (1950).
Currier, H. B., and Crafts, A. S., *Science* **111,** 152 (1950).
Fuer, H., Bachmann, G. B., and White, E. H., *J. Am. Chem. Soc.* **73,** 4716 (1951).
Greulack, V. A., and Atchison, E., *Bull. Torrey Bot. Club* **77,** 262 (1950).
Knott, J. E., *Proc. Am. Soc. Hort. Sci.* **55,** 504 (1950).
Mizzoni, R. H., and Spoerri, P. E., *J. Am. Chem. Soc.* **73,** 1873 (1951).
Moore, R. H., *Science* **112,** 50 (1950).
Schoene, D. L., and Hoffmann, O. L., *Science* **109,** 588 (1949).
White, D. G., *Science* **111,** 303 (1950); *Flower Grower* **37** (No. 9), 28 (1950).

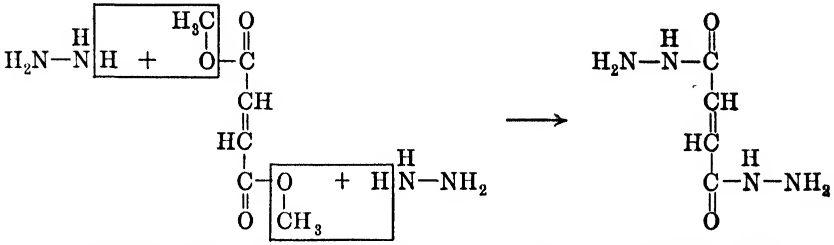
Fumaryl Dihydrazide

Fumaric acid esters react with hydrazine hydrate to form the dihydrazide. Unlike the analogous reaction with amines, considerable amounts of by-products are also formed simultaneously. The reaction, however, has been given very little detailed study, except to show that the formation of this dihydrazide is markedly influenced by solvents. For example, little or no dihydrazide is obtained when alcohol is employed as a diluent, as might be expected from the reaction with maleic anhydride. This is another example of how a complex reaction between the polyfunctional reactant hydrazine and polyfunctional maleyl compounds can be controlled to give different products.

Fumaryl dihydrazide crystallizes as glistening plates from alcohol. These are yellow in color and melt at 200°. They decompose when heated to 220°. The dihydrazide is only slightly soluble in cold water but readily so in hot water. It is insoluble in ether.

It reacts with acetone and benzaldehyde to form hydrazones, and with nitrous acid to give the explosive azide that can be converted to the carbamide.

Hydrazine Hydrate

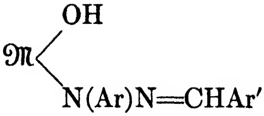


Hydrazine hydrate + Dimethyl fumarate ⟶ Fumaryl dihydrazide

Procedure. A mixture of 100 g. of hydrazine hydrate and 150 g. of dimethyl fumarate is heated rapidly until the ester completely dissolves. Complete reaction takes place almost immediately. Upon cooling the reaction mixture, an oil is obtained that when allowed to stand several hours in the desiccator readily solidifies. The resulting crystalline solid is then recrystallized from a small amount of hot water. The yield is relatively poor owing to the formation of other products.

References

Radenhausen, R., *J. prakt. Chem.* **52** (2), 433 (1895). *Cf.*:
Curtius, T., and Foesterling, H. A., *J. prakt. Chem.* **51** (2), 371 (1895).



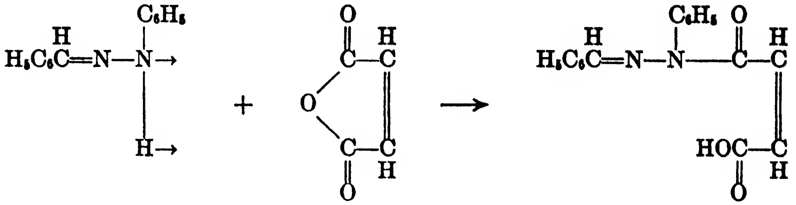
$\mathfrak{M}\left\langle\begin{matrix}\text{OH}\\ \text{N(Ar)N}{=}\text{CHAr}'\end{matrix}\right.$

Maleic Acid 1-Benzylidene-2-phenylhydrazide

Hydrazones react with maleic anhydride to form simple acylhydrazones, which are derivatives of maleamic acid. Union takes place at the nitrogen atom of the hydrazone, which is alpha to the unsaturated —C=N— bond. Several analogs of maleic acid 1-benzylidene-2-phenylhydrazide have been prepared by the procedure given. No reaction takes place, however, if the =NH group in the phenylhydrazone is completely substituted, as is the case with 1-benzylidine-2-methyl-2-phenylhydrazone.

Pure maleic acid 1-benzylidene-2-phenylhydrazide occurs as yellow crystals that melt at 123 to 124°. The compound is very soluble in acetone and chloroform. It is less soluble in alcohol and only very slightly soluble in benzene. It is practically insoluble in petroleum ether.

Benzaldehyde Phenylhydrazone

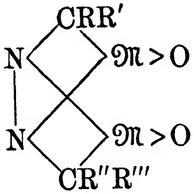


Benzaldehyde phenylhydrazone + Maleic anhydride ⟶ Maleic acid 1-benzylidene-2-phenylhydrazide

Procedure. Ninety-eight grams of maleic anhydride and 196 g. of benzaldehyde phenylhydrazone are dissolved separately in simmering benzene. The two solutions are then mixed while still hot, which causes them to turn dark red. The product is also dark in color until purified by recrystallization from alcohol.

Reference

La Parola, G., *Gazz. chim. ital.* 65, 624 (1934). *Cf.:*
Dutt, D. B., and Guha, P. C., *J. Indian Chem. Soc.* 27, 151 (1950).



1,2,3,5,6,7-Hexahydro-3,7-diphenylpyrazolo[1,2]pyrazole-1,2,5,6-tetracarboxylic Dianhydride

(4,8-Diphenyl-1,5-diazabicyclo[3.3.0]octane-2,3,6,7-tetracarboxylic Dianhydride)

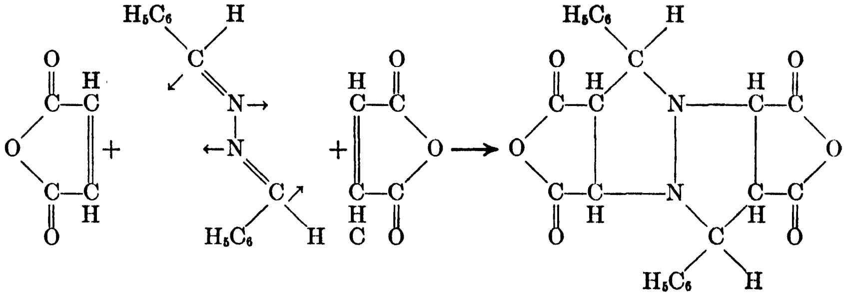
Certain osazones, such as benzaldehyde azine and anisaldehyde azine, react with two moles of maleic anhydride to give what apparently is the bispyrrolidine compounds. The formation of these derivatives is believed to result from a 1,3-addition of the osazone, which is described as a "crisscross" addition.

Other osazones, such as acetone azine, acetophenone azine, and acetaldehyde azine, and 1,2-bis(benzylideneamino)ethane and 2,3-diphenyl-5,6-dihydropyrazine also combine with two moles of the anhydride, but the products are unsaturated. The latter addition products do not have definite melting points and behave as resins having intrasalt groupings. In no case has it been shown that compounds containing the conjugated —C:N—N:C—, —C:C—C:N—, or —N:C—C:N—group add maleic anhydride to form Diels-Alder adducts without isomerization.

1,2,3,5,6,7-Hexahydro-3,7-diphenylpyrazolo[1,2]pyrazole-1,2,5,6-tetracarboxylic dianhydride is obtained as a white powder that is insoluble in the common organic solvents except boiling glacial acetic acid and acetic anhydride. Alphen describes it as decomposing at 298°; Wagner-Tauregg reports 243 to 244°. When dissolved in alkali and reprecipitated with an excess strong mineral acid, the acid is obtained as a crystalline powder melting at 253°. The acid may be recovered unchanged after boiling in 70% sulfuric acid solution for 10 minutes.

Benzaldehyde Azine

(Benzalazine)

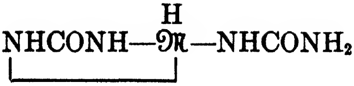


Benzaldehyde azine + Maleic anhydride ⟶ 1,2,3,5,6,7-Hexahydro-3,7-diphenylpyrazole [1,2] pyrazole-1,2,5,6-tetracarboxylic dianhydride

Procedure. A mixture of 10 g. of maleic anhydride and 7.5 g. of benzaldehyde azine is heated for several hours at 100°. The reaction mixture melts at first and then solidifies. The solid obtained is extracted with several portions of boiling benzene and then with dry ether. This leaves a light brown powder from which the bispyrrolidine product is left as a white powder after extraction with boiling alcohol. This powder is crystallized from boiling glacial acetic acid or boiling acetic anhydride.

References

van Alphen, J., *Rec. trav. chim.* **61**, 892 (1942). *Cf.*: Wagner-Tauregg, T., *Ber.* **63**, 3224 (1930).



$\mathrm{NHCONH{-}\overset{H}{\mathcal{M}}{-}NHCONH_2}$

5-Hydantoinacetylurea

(5-Hydantoinacetic Acid Ureide)

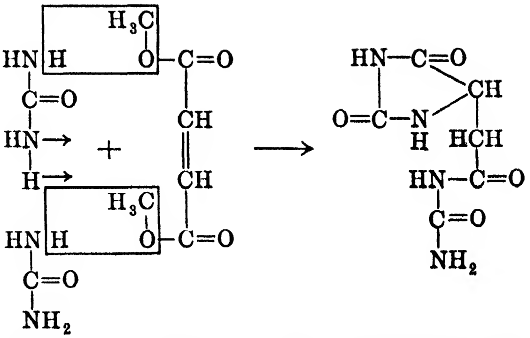
Urea does not react with maleates except in the presence of sodium ethoxide, when it unites to saturate the C:C bond by forming the cyclic ureides of succinic acid, namely, 5-hydantoinacetylurea and the 5-hydantoinacetic acid ester. Both these compounds may be hydrolyzed to give the acid. There is no evidence that the ureides of fumaric acid are formed during the reaction.

5-Hydantoinacetic acid may also be prepared without a catalyst by heating urea and asparagine at 125° and then digesting the product with hydrochloric acid, or by allowing potassium cyanate to react with aspartic acid in normal potassium hydroxide solution. Carbamylaspartic acid is formed when aspartic acid is heated with urea in the presence of barium hydroxide. 5-Hydantoinacetic acid may be prepared from this compound by digestion with concentrated hydrochloric acid.

5-Hydantoinacetylurea is a crystalline compound that melts at 273 to 274° with decomposition. Methyl 5-hydantoinacetate melts at 123° and the acid at 213 to 214° according to Jerzmanowska-Sienkiewiczowa. Gabriel describes the crude acid as rhombic crystals melting at 119°, and when recrystallized as melting at 224 to 226°.

Use. Compounds of this general type are useful as reactants in preparing possible bactericides and insecticides.

Urea



Urea + Dimethyl maleate ⟶ 5-Hydantoinacetylurea

Procedure. To a solution of 4 g. of sodium in 100 ml. of absolute alcohol is added 10.4 g. of urea and the mixture is carefully heated to 75°. Then 10 g. of dimethyl maleate is run in through a separatory funnel, and the heating is continued for 15 minutes. This results in a precipitate of the acetureide. The reaction mixture is then cooled and filtered, and the recovered precipitate is washed with alcohol. The product is purified by dissolving it in water and precipitating with an excess of 20% hydrochloric acid. The yield of crude ureide is 30 to 40% of theory.

The filtrate contains 10% of methyl 5-hydantoinacetate. This product may be obtained by evaporating the filtrate and extracting the residue with acetone in a Sohxlet apparatus.

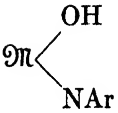
References

Jerzmanowska-Sienkiewiczowa, Z., *Roczniki Chem.* **15**, 202, 510 (1935). *C. A.* **30**, 2925^9, 2933^5 (1936).

Gabriel, S., *Ann.* **348**, 87 (1906).

Guareschi, J., *Gazz. chim. ital.* **5**, 245 (1875); **6**, 370 (1876).

Lippich, F., *Ber.* **41**, 2953 (1909).



Maleanilic Acid

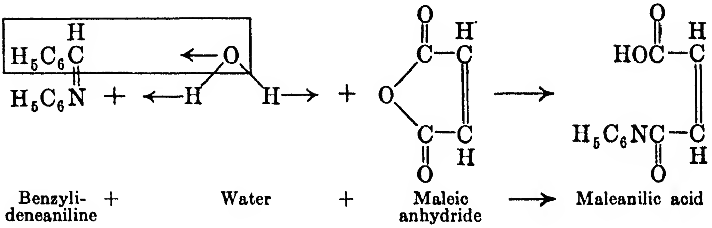
There is no evidence that Schiff's bases as such can react with maleyl compounds under anhydrous conditions. When addition occurs, it is with the tautomeric dienylaniline form of the base, as is the case with N-hexenylideneaniline (*q.v.*). N-Cinnamylideneaniline, for example, yields only 2% of maleanilic acid as product if the reactants are mixed in dry ether, benzene, or dioxane. The reaction, however, gives 96% of the theoretical amount of maleanilic acid when water is present. N-Benzylideneaniline and N-benzylideneanthranilic acid behave in a similar manner.

van Alphen reports that bases like N-benzylidenemethylamine and N-cinnamylidenemethylamine form unsaturated molecular addition compounds under certain conditions. His compounds were resinous in character without sharp melting points. Little is known about their molecular structure.

Maleanilic acid occurs as yellow crystals that melt at 173 to 175°.

Benzylideneaniline

(Benzalaniline)



Procedure. Ninety-eight grams of freshly distilled maleic anhydride and 182 g. of pure benzylideneaniline (m.p. 48 to 49°) are dissolved separately in small amounts of alcohol, and the two solutions are warmed to 40 to 50° and mixed. Maleanilic acid is precipitated. It is separated and then recrystallized from alcohol. The filtrate contains benzaldehyde, which may be recognized by its odor and characterized by forming the addition compound with sodium bisulfite.

References

La Parola, G., *Gazz. chim. ital.* **64**, 919 (1934). *Cf.*:

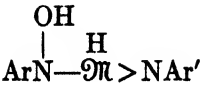
Bergmann, F., *J. Am. Chem. Soc.* **60**, 2811 (1938).

Herz, W., *J. Am. Chem. Soc.* **67**, 1854 (1945).

Lora Tamayo, M., and Vanes, J. F., *Anales fís. y quím.* (*Spain*) **43**, 777 (1947); *C. A.* **42**, 1571d (1948).

Snyder, H. R., Hasbrouck, R. B., and Richardson, J. F., *J. Am. Chem. Soc.* **61**, 3558 (1939).

van Alphen, J., *Rec. trav. chim.* **61**, 895 (1942).



α-(N-Hydroxyanilino)-N-Phenylsuccinimide

(2,5-Dioxo-1-phenyl-3-phenylhydroxylaminopyrrolidine)

and

α-Anilino-N-Phenylmaleimide

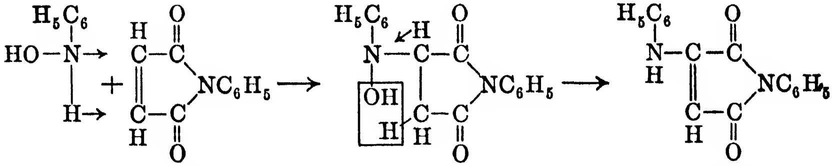
(3-Anilino-2,5-dioxo-1-phenyl-3-pyrroline)

Substituted hydroxylamines add to the C:C bond of maleyl compounds in the same manner as substituted amines, as shown here in the reaction with N-phenylmaleimide. When the reactants are refluxed for 4 hours, instead of 30 minutes, however, water is gradually split off between the hydrogen of the β-succinyl group of the pyrrolidine and the hydroxyl attached to the nitrogen of the α-amino group. This leads to the formation of α-anilino-N-phenylmaleimide, as shown in the equation. This latter compound may also be prepared from α-(N-hydroxyanilino)succinimide.

The method given is a general one, since several analogs of these compounds have been made in this way.

α-(N-Hydroxyanilino)-N-phenylsuccinimide is a crystalline solid that melts at 189°; α-anilino-N-phenylmaleimide melts at 238°.

Phenylhydroxylamine



N-Phenylhydroxylamine + N-Phenylmaleimide ⟶ α-(N-Hydroxyanilino)-N-phenylsuccinimide ⟶ α-Anilino-N-phenylmaleimide

Procedure. A pyridine solution containing 1.2 g. of phenylhydroxylamine and 2 g. of N-phenylmaleimide is refluxed for 30 minutes. Water is then added to the reaction mixture that precipitates the succinimide. This precipitate is removed and purified by recrystallization from alcohol.

If the mixture is refluxed for 4 hours, instead of stopping the reaction at the end of half an hour, α-anilino-N-phenylmaleimide is obtained as a crystalline mass within the reaction mixture. It is purified in the same manner, by crystallization from alcohol.

Reference

Jolles, E., *Gazz. chim. ital.* 66, 717 (1936).

N-Benzoylaspartic Anhydride

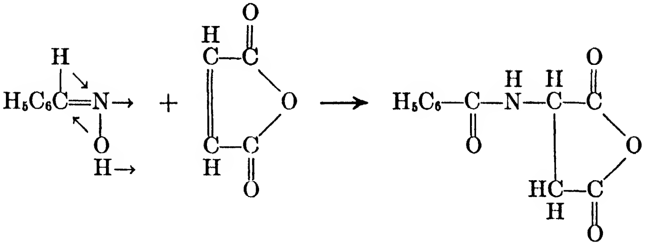
Both stereoisomers of benzaldehyde oxime react with maleic anhydride to produce N-benzoylaspartic anhydride. The reaction may be viewed as taking place in two steps, i.e., (1) addition of the oxime to the C:C bond of the maleyl compound, similar in manner to what takes place with pyrroles (*q.v.*), and (2) a Beckmann rearrangement of the resulting ketoxime to the N-acylaspartic anhydride. An even simpler mechanism would be to assume that the benzaldehyde oxime isomerizes during the reaction to benzamide, and that the addition takes place between the amino group of the amide and C:C group of the anhydride. That small amounts of carbon dioxide and carbon monoxide are evolved during the reaction and that a considerable quantity of benzaldehyde is formed would indicate, however, that the reaction is far more complex than shown by either of these mechanisms. Maleic acid reacts with the oxime to give benzaldehyde.

N-Benzoylaspartic anhydride melts at 154°. It is very soluble in cold water but only slightly soluble in cold alcohol, acetone, ether, and benzene. It readily absorbs water from the air to give the monohydrate of the acid, which may also be obtained by dissolving the anhydride in water. The monohydrate softens and loses water when dried at 75 to 80°, or when confined under reduced pressure over concentrated sulfuric acid. When heated over a flame, it melts at 119°, solidifying again at about 125 to 130° and finally melting at 154° as the anhydride.

Use. The method described on the opposite page is a very convenient one for preparing N-acyl derivatives of aspartic and other amino acids. N-Toluylaspartic acid and N-(methoxybenzoyl)aspartic acid have been prepared in this way. The yield of the methoxy derivative is 70%, as compared to only 50% for N-benzoylaspartic acid.

Benzaldehyde Oxime

(Benzaldoxime)

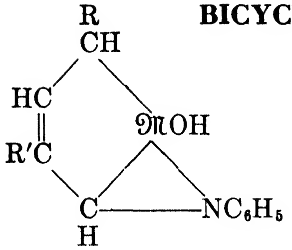


Benzaldehyde oxime + Maleic anhydride ⟶ N-Benzoylaspartic anhydride

Procedure. A mixture of 1.6 g. of maleic anhydride and 2 g. of α- or β-benzaldehyde oxime in 7 ml. of benzene is cooled in a freezing mixture and then carefully brought to a boil in a hood and refluxed on a water bath for an hour. During this time, small amounts of both carbon dioxide and carbon monoxide are evolved. The solution turns dark yellow in color, and the product is precipitated as a white crystalline solid. When the reaction is complete, the crystals are removed by filtration and washed several times with small amounts of benzene. The yield of crude anhydride obtained in this way is approximately 50% of theory. The filtrate contains benzaldehyde from the remainder of the oxime.

Reference

La Parola, G., *Gazz. chim. ital.* 67, 481 (1937); 73, 94 (1943).



2,4-Diethyl-7-oxo-6-phenyl-6-azabicyclo[3.2.1]-3-octene-8-carboxylic Acid

Schiff's bases from aniline and 2-alkenals are apparently tautomeric mixtures of the base and the conjugated N-alkadienylaniline. In the latter form these bases add maleic anhydride like any other diene. Hence this reaction may be looked upon as a simple Diels-Alder addition, where the reactant rearranges to yield the more stable bicyclopyrrolidonecarboxylic acid, instead of the usual substituted tetrahydrophthalic anhydride. The dimethyl analog of the above azabicyclopyrrolidonecarboxylic acid has also been prepared.

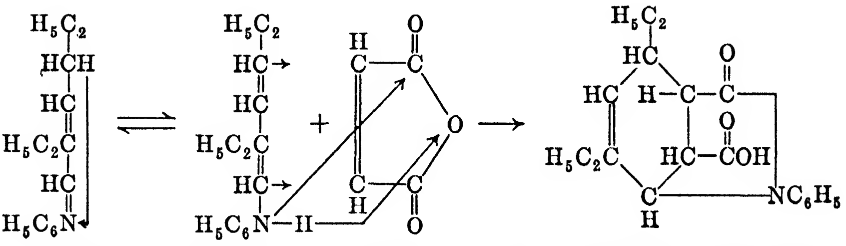
These reactions are further illustrations of the affinity of amino radicals for the carbonyl groups of the maleyl compounds. There is no evidence that the conjugated —C=C—C=N— grouping in the normal form of the Schiff's base undergoes Diels-Alder addition in this reaction. The high yield of the azabicyclic product would indicate that the reaction takes place exclusively with N-alkadienyl-tautomer. Hetro conjugated groups generally do not react as dienes toward maleic anhydride as pointed out under azines (*q.v.*). Diels-Alder adducts apparently are only formed when isomerization takes place, as occurs here and in the reaction with 2,3-dimethylquinoxaline (*q.v.*).

2,4-Diethyl-7-oxo-6-phenyl-6-azabicyclo[3.2.1]-3-octene-8-carboxylic acid can also be prepared from maleanilic acid and 2-ethyl-2-hexenal, but not from N-phenylmaleimide nor the substituted butadiene. The yield from maleanilic acid is 60 to 70%, which is 10 to 15% less than obtained by the method described here.

2,4-Diethyl-7-oxo-6-phenyl-2-azabicyclo [3.2.1]-3-octene-8-carboxylic acid is deposited from alcohol as colorless crystals that melt at 145 to 146°. The compound is soluble in sodium carbonate solutions, from which it can be recovered by precipitation with acid. It is also soluble in dilute alcohol solutions. Mixtures of products made by the two methods show no lowering in melting points.

Use. These methods are a convenient means for preparing substituted pyrrolidone compounds for various uses.

2-Ethyl-2-hexenylideneaniline



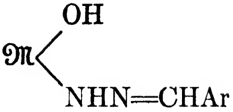
2-Ethyl-2-hexenylideneaniline + Maleic anhydride ⟶ 2,4-Diethyl-7-oxo-6-phenyl-6-azabicyclo[3.2.1]-3-octene-8-carboxylic acid

Procedure. A solution containing 67 g. of 2-ethyl-2-hexenylideneaniline and 32.7 g. of maleic anhydride in 434 ml. of anhydrous benzene is allowed to stand for 2 hours in a dry atmosphere. The small amount of maleanilic acid that is precipitated is removed by filtration, and the reaction mixture is heated for 3 hours, continuing to exclude any atmospheric moisture. The mixture is set aside for several days for crystallization to take place. If necessary, it is seeded with a few crystals of the product. When complete, the solid mass is removed and purified by recrystallization from alcohol. A yield of 75 to 80% of theory is obtained in this manner.

References

Snyder, H. R., Hasbrouck, R. B., and Richardson, J. F., *J. Am. Chem. Soc.* **61**, 3558 (1939). *Cf.*:

Snyder, H. R., and Robinson, J. C., Jr., *J. Am. Chem. Soc.* **63**, 3279 (1941).



$$\mathfrak{M}\left\langle\begin{matrix}\mathrm{OH}\\ \mathrm{NHN{=}CHAr}\end{matrix}\right.$$

Maleic Acid Benzylidenehydrazide

(Benzalmaleinhydrazide)

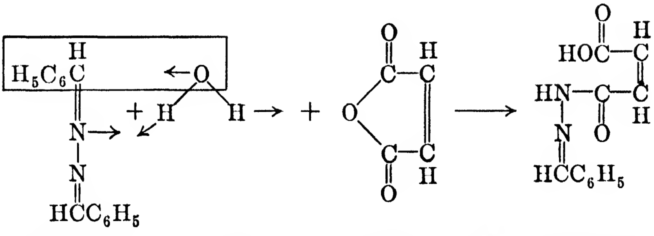
At ordinary temperatures azines, such as benzaldehyde azine, do not react with maleic anhydride unless water is present. When water is added, a reaction similar to that with Schiff's bases takes place, as shown. This results in the formation of an acylhydrazone. In the absence of water and solvents, however, azines react at 100° to form tough yellow or dark-colored resins. With an excess of maleic anhydride, they produce what appears to be bispyrrolidine compounds (*q.v.*).

Maleic acid benzylidenehydrazide is practically insoluble in most common solvents. When recrystallized from acetonitrile, it melts at 183°.

Use. No industrial use has yet been made of these compounds.

Benzaldehyde Azine

(Benzalazine)

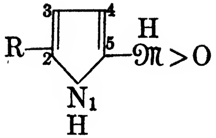


Procedure. A solution is prepared containing 5.2 g. of benzaldehyde azine, 2.5 g. maleic anhydride, and 75 ml. of ether that has been saturated with water. This is allowed to stand for 4 days. The hydrazide formed is then collected on a filter, washed with ether, and recrystallized from acetonitrile. The yield in this case is 78% of theory.

The other product of the reaction, benzaldehyde, may be recovered from the filtrate by means of a sodium bisulfite solution. The aldehyde can then be regenerated and identified by preparing the phenylhydrazone. This hydrazone melts at 156 to 157°.

References

Snyder, H. R., Levin, R. H., and Wiley, P. F., *J. Am. Chem. Soc.* **60**, 2025 (1938). *Cf.*: Caronna, G., *Gazz. chim. ital.* **77**, 427,482 (1947); **78**, 38, (1948).



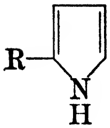
2-Methyl-5-pyrrolesuccinic Anhydride

Heterocyclic compounds containing the conjugated pyrrole ring react with maleic anhydride in a very unexpected manner. Several different types of compounds may be formed during the process as a result of subsequent reactions. The initial reaction in most cases, however, appears to be one of the additions of the α-carbon of the pyrrole to the C:C bond of maleic anhydride. Union of either one or two molecules of the anhydride takes place at the carbon atoms in the 2- and 5-positions of the pyrrole ring. This addition takes place only if these carbons of the pyrrole are unsubstituted. Pyrrole, for example, adds two moles of maleic anhydride to form 2,5-pyrroledisuccinic anhydride, but this crystalline compound readily hydrolyzes in the reaction mixture at 60° to yield γ,ζ-dioxosebacic acid, *dilevulinic acid.* N-Methylpyrrole adds maleic anhydride in a similar manner, but refluxing the reaction mixture causes decarboxylation to occur, producing N-methyl-2,5-pyrroledipropionic acid. α-Methylpyrrole as shown gives the primary product, 2-methyl-5-pyrrolesuccinic anhydride.

α-Methylindole, *α-methylbenzopyrrole,* and N-α-dimethylindole, which have substituents attached to both the 2- and 5-pyrrole carbons, add maleic anhydride at the 3-pyrrole carbon to yield a mixture of 3-indolesuccinic acid and the α-3-indyl-β-indylcarbonylpropionic acid, *α-3-indyl-γ-oxo-3-indolebutyric acid.* Maleic anhydride reacts with two moles of indole in ethyl acetate to form 5a,10b,10c,11-tetrahydro-γ-oxoazetodiindole-6-α-butenoic acid, *diindolemaleic acid.*

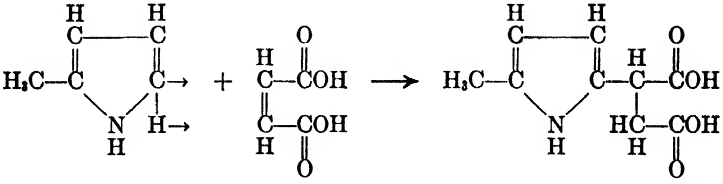
2-Methyl-5-pyrrolesuccinic anhydride is a crystalline compound melting at 134°. Its dimethyl ester melts at 71°.

Uses. Compounds of similar structures have been used in perfumes, as rooting materials and as stabilizers for lubricants.



PYRROLES

α-Methylpyrrole



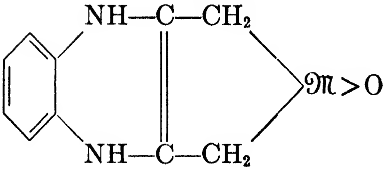
α-Methylpyrrole + Maleic acid ⟶ 2-Methyl-5-pyrrolesuccinic acid

Procedure. In preparing a solution of maleic acid, 3.6 g. of the anhydride is first dissolved in 20 ml. of warm water. This solution is then cooled to room temperature and 1 g. of α-methylpyrrole is added to it. The mixture is shaken in a stoppered vessel until all the pyrrole is dissolved. If necessary, it is cooled from time to time to maintain a smooth reaction and to prevent the formation of fumaric acid from any marked increase in temperature. The reaction mixture becomes dark in color, and the product is precipitated as minute crystals. These crystals are collected by filtration, recrystallized from acetonitrile, and dried under reduced pressure over calcium chloride.

References

Diels, O., Alder, K., and Winter, D., *Ann.* 486, 211 (1931). *Cf.*:
Diels, O., Alder, K., and Lubbert, W., *Ann.* 490, 277 (1931).

PYRAZINOTETRAHYDROPHTHALIC ANHYDRIDE



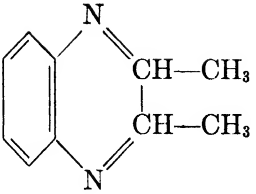
1,2,3,4,5,10-Hexahydro-2,3-phenazinedicarboxylic Anhydride

(1,2,3,4,4a,10a-Hexahydro-2,3-phenazinedicarboxylic Anhydride)

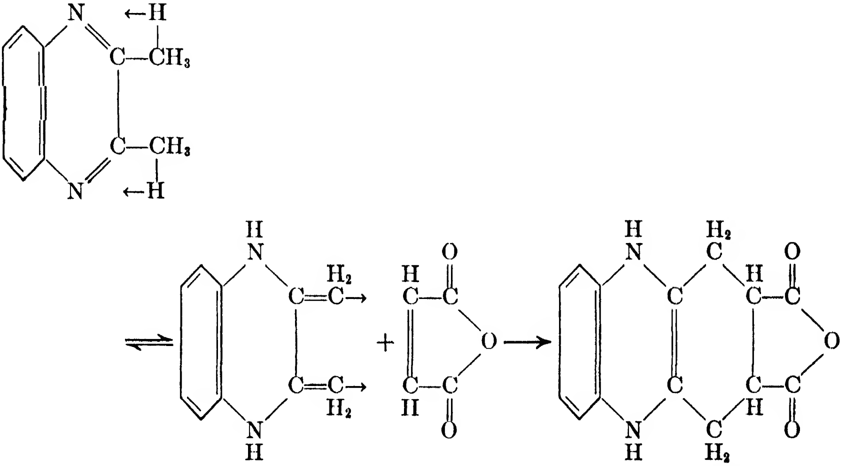
Quinoxalines, like other cyclic compounds containing the —N=C—C=N— or —C=C—C=N— grouping within aromatic rings, generally do not react with maleic anhydride, but 2,3-dimethylquinoxaline is an exception. This compound, like hexenylideneanilines (*q.v.*), consists of a mixture of tautomers, one form of which does not contain a second aromatic ring embracing the conjugated grouping. It is this exo-diene form that apparently undergoes the Diels-Alder type of condensation, as shown on the opposite page. As would be expected, quinoxaline, 2-methylquinoxaline, 2-methyl-3-phenylquinoxaline, and 2,3-diphenylquinoxaline do not react with maleic anhydride since they cannot form such a tautomer. Anthranil, which contains a similar —C=C—C=N— group between the two rings, reacts to form a colorless addition compound. However, this product may not be a true Diels-Alder type of adduct but rather one resulting from substitution-addition at the C-carbon in a manner similar to pyrroles (*q.v.*), since C-phenylanthranil does not react with maleic anhydride when treated in the same way as anthranil.

1,2,3,4,5,10-Hexahydro-2,3-phenazinedicarboxylic anhydride does not melt below 305°, but it sublimes at 260° when heated under 15 mm. pressure, to give a brown sublimate from which the compound can be recovered by crystallization from acetic acid. It is soluble in tetralin and methyl alcohol, but only slightly soluble in chloroform and acetone. It is also soluble in 30% sodium hydroxide solution, from which it can be recovered by carefully adding an equivalent of concentrated hydrochloric acid. The adduct is soluble in excess acid. It is unchanged by refluxing in 10% caustic solution for one hour.

Use. Anhydrides of this type are valuable as reactants in the preparation of bactericides, insecticides, and pharmaceuticals.



2,3-Dimethylquinoxaline



2,3-Dimethylquinoxaline + Maleic anhydride → 1,2,3,4,5,10-Hexahydro-2,3-phenazinedicarboxylic anhydride

Procedure. A solution of 0.5 g. of anhydrous 2,3-dimethylquinoxaline and 0.3 g. maleic anhydride in 20 ml. of dry toluene is heated to boiling and refluxed for 2½ hours. This produces a brown sticky product, which is allowed to settle overnight in a refrigerator. The supernatant toluene is then decanted off, and the gummy mass is dissolved in hot acetic acid. The acetic acid solution is then cooled and placed in the refrigerator until the light greenish yellow crystals of the product are obtained. These crystals are collected and recrystallized several times from acetic acid. Additional amounts are obtained when the mother liquor is refluxed for 3 hours. The total yield is 0.4 g.

Reference

Schönberg, A., and Mostafa, A., *J. Chem. Soc.* **1943**, 654.

Diethyl 1-Carbamyl-2,3-Aziridinedicarboxylate

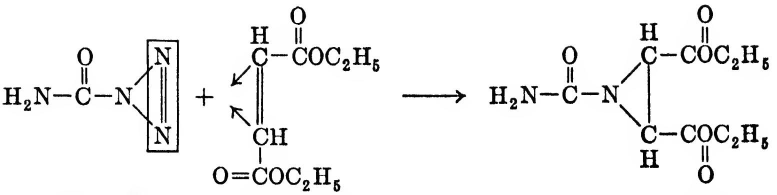
(Diethyl α,β-(aminocarbonylimino)succinate or Diethyl 1-Carbamyl-2,3-ethyleniminedicarboxylate)

Carbamyl azide, unlike benzyl azide, loses nitrogen during addition to the unsaturated C:C bond of maleates. The primary product of this reaction is the 1-carbamyl-2,3-aziridinedicarboxylic ester. A small amount of the isomeric 2-oxo-4,5-imidazolidinedicarboxylic ester is also obtained. This latter ester is probably a secondary product, since it can be prepared by heating a dilute hydrochloric acid solution of the 1-carbamyl-2,3-aziridinedicarboxylate. Prolonged digestion of this solution, with attendant evolution of carbon dioxide, yields the ester of α,β-diaminosuccinic acid. Digestion with a sodium carbonate or concentrated acid solution gives the 2,3-aziridinedicarboxylic ester.

Diethyl 1-carbamyl-2,3-aziridinedicarboxylate crystallizes from alcohol as rhombic leaves that melt at 154°. Lance-like crystals are obtained upon cooling a hot dilute hydrochloric acid solution. The compound readily dissolves in half its weight of hot alcohol but is only slightly soluble in the cold solvent. It is insoluble in ether, chloroform, and benzene. Diethyl 2-oxo-4,5-imidazolidinedicarboxylate melts at 93°.

Use. Compounds having such structures are valuable as reactants in the preparation of adhesives; as agents for improving the strength, crease resistance, and the hydrophobic properties of cellulosic fibers; and as reagents in the synthesis of detergents and other useful organic products.

Carbamyl Azide



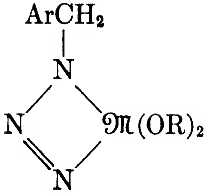
Carbamyl azide + Diethyl fumarate ⟶ Diethyl 1-carbamyl-2,3-aziridinedicarboxylate

Procedure. A mixture of 20 g. of carbamyl azide and 100 g. of diethyl fumarate is heated upon a water bath for 2 hours. During this time there is a strong evolution of nitrogen. Heating is then continued for an additional 12 hours under a pressure of 80 to 100 mm. The reaction mixture is treated with a small amount of cold alcohol, and set aside for several days until crystallization ensues under partial vacuo. After 4 to 8 days, the inside of the flask is rubbed with a glass rod to increase the rate of crystallization. When crystallization is complete, the solid mass is collected, sucked dry upon a filter, washed with a limited amount of absolute alcohol, and then recrystallized from alcohol. Based upon the amount of carbazide taken, the yield is 40% of theory, as compared to 10 to 15% when diethyl maleate is employed as the reactant.

Half a gram of diethyl 2-oxo-4,5-imidazolidinedicarboxylate may also be obtained from the above filtrate by removing the solvent and distilling the oily residue under 12 mm. of pressure.

Reference

Curtius, T., and Dörr, W., *J. prakt. Chem.* 125, 425 (1930).



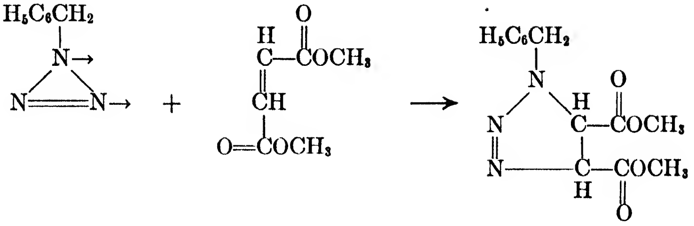
DIHYDROTRIAZOLEDICARBOXYLIC ESTERS

Dimethyl 1-benzyl-Δ^2-1,2,3-triazoline-4,5-dicarboxylate

Considerable decomposition accompanies this addition of benzyl azide to maleic esters. The yield, therefore, is likely to vary widely from one preparation to another. Dimethyl fumarate appears to give much better results than the diethyl ester when allowed to react at the same temperature. Prolonged heating causes a marked evolution of nitrogen, with the formation of dibenzyloxamide and benzylammonium benzyl oxamate.

Dimethyl 1-benzyl-Δ^2-1,2,3-triazoline-4,5-dicarboxylate is obtained as colorless, anisotropic prisms that melt at 75°. This ester is insoluble in ether and in water. It is very soluble in alcohol. The compound decomposes with an evolution of nitrogen when saponified so that the free acid cannot be obtained from it.

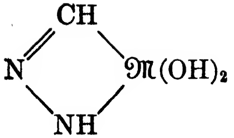
Benzyl Azide



Procedure. A mixture of 6.7 g. of benzyl azide and 7.2 g. of dimethyl fumarate is heated on a water bath at 85°. The dimethyl fumarate slowly dissolves as the mixture becomes yellow. At the first sign of evolution of nitrogen, the mixture is cooled quickly, and the solid that separates is filtered immediately. This product is freed of any unreacted ester by suction and is further purified by recrystallization from a large volume of petroleum ether (b.p. 60 to 70°). The best yield obtained is about 30%.

Reference

Curtius, T., and Raschig, K., *J. prakt. Chem.* **125**, 466 (1930).



PYRAZOLINECARBOXYLIC ACIDS

2-Pyrazoline-4,5-dicarboxylic Acid

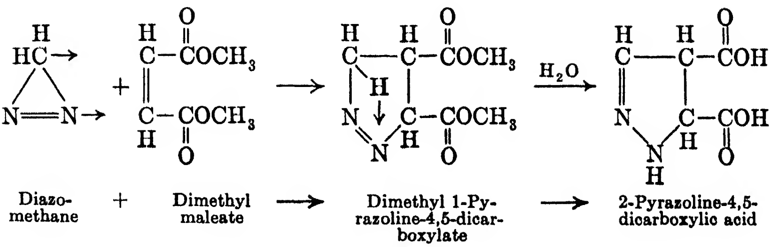
Diazo compounds such as diazomethane, diazoacetic acid, and diazodiphenylmethane unite with the ethylene group of maleates to form the 1-pyrazoline derivatives that rearrange during the reaction to yield the 2-pyrazoline isomers. These pyrazolinecarboxylic acid derivatives lose nitrogen fairly readily either upon heating or when allowed to stand at room temperatures, forming thereby the cyclopropanecarboxylic acids. Pyrazolinedicarboxylic esters produce the *trans*-cyclopropane acids, whereas pyrazolinedicarboxylic anhydrides yield the *cis*-compound.

Diazo compounds like azobenzene containing substituents on both nitrogen atoms do not react with maleyl derivatives. Diazonium salts react by splitting off nitrogen (*q.v.*).

2-Pyrazoline-4,5-dicarboxylic acid occurs as rhombic plates that melt at 97°. It is soluble in alcohol, chloroform, and hot water. It is only slightly soluble in ether and ligroin. In alkali, it dissolves to give brown-red solution. Free pyrazole may be obtained by heating the silver salt.

Use. Compounds of this type are useful reactants in the preparation of pharmaceuticals, as coupling agents for color photography, and for special-purpose resins.

Diazomethane

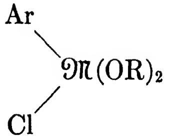


Procedure. An ether solution containing 11 g. of dimethyl fumarate is allowed to absorb diazomethane until no further decoloration takes place. This operation should be carried out most carefully in a well-ventilated hood. The ether is cautiously evaporated, and the resulting colorless crystals are washed with the same solvent and then recrystallized from a mixture of chloroform and ligroin. This gives a quantitative yield, 14 g. of the above ester. The 2-pyrazolinedicarboxylic acid is then obtained by hydrolysis in the customary manner.

Precaution should be taken in carrying out this reaction since diazomethane is **extremely poisonous.**

References

von Pechmann, H., *Ber.* 27, 1890 (1894). *Cf.*:
Büchner, E., *Ber.* 21, 2640 (1888).
Büchner, E., and Witter, H., *Ann.* 273, 239 (1893); *Ber.* 23, 2584 (1890).
Darapsky, A., *Ber.* 43, 1119 (1910).
Staudinger, H., Anthes, E., and Pfenniger, F., *Ber.* 49, 1928 (1916).
Silberrad, O., and Roy, C. S., *J. Chem. Soc.*, 89, 180 (1906).
van Alphen, J., *Rec. trav. chim.* 62, 210 (1943).



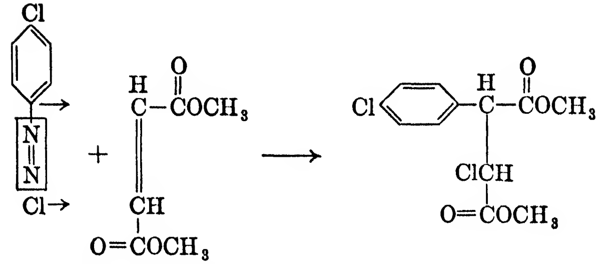
α-ARYL-β-CHLOROSUCCINATES

Dimethyl α-Chloro-β-(*p*-chlorophenyl)succinate

Diazonium chlorides, unlike diazomethane, lose their nitrogen when they react with maleic and fumaric esters. The aryl group of the diazonium chloride in this reaction unites with one of the carbons of the C:C unsaturated bond of the maleate or fumarate and the chloride ion with the other carbon to give the α-aryl-β-chlorosuccinates. The β-chlorine atom is not stable to alkali so that the succinate is quantitatively converted to the sodium salt of the arylfumaric acid when these substituted succinic esters are saponified with alcoholic potash. Arylmaleic anhydrides can be prepared by distilling the arylfumaric acids with a small amount of chlorocymylsulfonic acid. The arylmaleic acids are prepared by treating the anhydrides with boiling water. When maleic acid is used as the reactant in place of the esters, both dehydrochlorination and decarboxylation accompany the loss of nitrogen during the reaction, resulting in the formation of arylacrylic acids. (Cf. Grignard and Friedel Reactions.) In this case, poor yields are obtained in the presence of acetone. Cupric chloride but not cuprous chloride is catalyst for both of the above types of reaction.

Dimethyl α-chloro-β-(*p*-chlorophenyl)succinate occurs as rhombic crystals that melt at 79°. (*p*-Chlorophenyl)fumaric acid melts at 222°, the maleic acid at 141 to 143°, and the anhydride at 146°.

p-Chlorobenzenediazonium Chloride

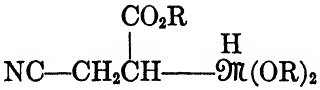


p-Chlorobenzenediazonium chloride + Dimethyl fumarate ⟶ Dimethyl α-chloro-β-(*p*-chlorophenyl)succinate

Procedure. A *p*-chlorobenzenediazonium chloride solution is prepared by diazotizing 32 g. of *p*-chloroaniline. This is added to a solution containing 300 ml. of acetone, 10.5 g. of cupric chloride, 50.6 g. of sodium monochloroacetate and 24 g. of dimethyl fumarate. The mixture is carefully agitated at 15 to 20° for 3 hours, during which time the nitrogen is slowly evolved. When the reaction is completed, the mixture is steam-distilled, and then thoroughly extracted with benzene. Any acidic constituents are removed by treating the benzene extract with an aqueous soda solution. The extract is next dried and the solvent removed by distillation. The 40.7 g. of residue is dissolved in a minimum amount of methanol, and the solution is set aside in a bath of cracked ice for 12 hours, during which time crystallization occurs, accompanied by the separation of a dark oil. The crystals are carefully removed with a spatula, thoroughly washed with ice-cold methanol, and then recrystallized either from methylcyclohexane or carbon tetrachloride. The yield is 20.7 g., or 42.8% of theory.

References

Meerwein, H., Büchner, E., and van Emster, K., *J. prakt. Chem.* **152**, 237 (1939). *Cf.*:
Koelsch, C. F., and Boekelheide, V., *J. Am. Chem. Soc.*, **66**, 413 (1944).
Rai, J., and Matur, K. B. L., *J. Indian Chem. Soc.* **24**, 383 (1947).



$$\mathrm{NC{-}CH_2\overset{\overset{CO_2R}{|}}{C}H{-\!\!-\!\!-}\overset{H}{\mathfrak{M}}(OR)_2}$$

Trimethyl 4-Cyano-1,2,3-butanetricarboxylate

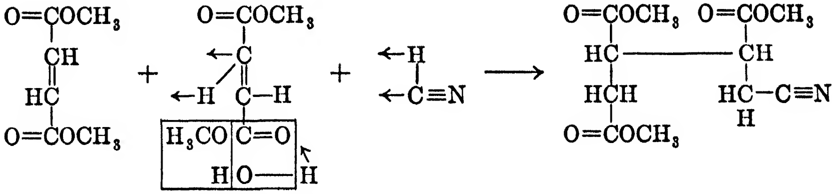
Maleyl compounds do not react, in general, with hydrogen cyanide to give saturated compounds. When addition to the C:C bond does occur, it is accompanied by dimerization of the fumarate and either decarboxylation, as shown here, or cyclization, as described in the next preparation of the trimethyl 4-cyano-5-oxo-1,2,3-cyclopentanetricarboxylic ester (*q.v.*). Some hydrolysis of the dimethyl fumarate to the acid ester also occurs. At the same time the ester of methoxysuccinic acid is formed through reaction between the fumaric ester and the solvent. Normally such a reaction as the last does not occur except in the presence of alkoxides (*q.v.*).

Fumaryl chloride, formaldehyde, and hydrocyanic acid, in contrast, react to give biscyanomethyl fumarate.

Purified trimethyl 4-cyano-1,2,3-butanetricarboxylate boils under 3 mm. of pressure at 178 to 180°.

Use. This compound is interesting because of the possibilities it offers for organic syntheses.

Hydrocyanic Acid (Potassium Cyanide)



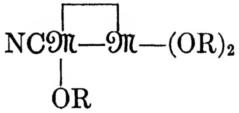
Dimethyl fumarate + Water + Hydrocyanic acid (Potassium cyanide) ⟶ Trimethyl 4-cyano-1,2,3-butanetricarboxylate

Procedure. With proper precautions a solution is prepared of 3.25 g. of potassium cyanide in a mixture of 5 ml. of water and 50 ml. of methanol. To this is added 7.2 g. of dimethyl fumarate, and the mixture is carefully shaken and set aside in a well-ventilated hood for 48 hours. The suspended ester slowly dissolves within 2 hours. When the reaction is complete, the mixture is neutralized with an equivalent amount of hydrochloric acid and then diluted with 50 ml. of ether. The potassium chloride that is formed is filtered off, and the ether is allowed to evaporate. The residue is then distilled under reduced pressure into three fractions. The first contains 1 g. of dimethyl methoxysuccinate, b_2 85–100°; the second, 3.9 g. of methyl acid maleate, b_2 145–155°; and the last, 2.5 g. of a viscous oil, b_2 190–200°. This last fraction is redistilled to obtain pure trimethyl 4-cyano-1,2,3-butanetricarboxylate.

Every precaution should be taken in carrying out this reaction, since lethal hydrogen cyanide is present.

References

Michael, A., and Warner, N., *J. Am. Chem. Soc.* **59**, 744 (1937). *Cf.*:
Henze, M., *Ber.* **33**, 966 (1900).
Mowry, D. T., *J. Am. Chem. Soc.* **66**, 371 (1944).



CYCLIC POLYCARBOXYLIC NITRILES

Trimethyl 4-Cyano-5-oxo-1,2,3-cyclopentanetricarboxylate

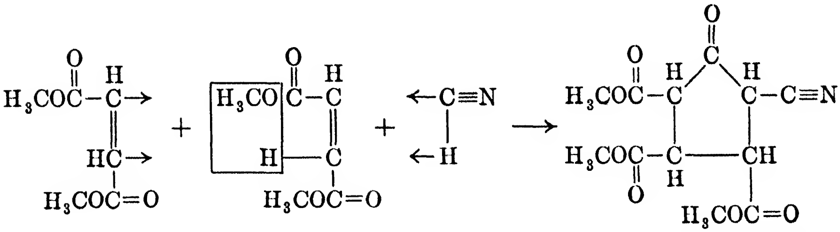
(Trimethyl 2-Cyano-2,3,5-tricarbomethoxycyclopentanone)

An anhydrous solvent, in contrast to what has been described for the previous preparation, prevents hydrolysis of the dialkyl fumarate in this reaction with potassium cyanide. Under such conditions, decarboxylation also does not occur, but cyclization takes place instead. Such ring closure could easily be the result of a splitting off of methanol from groups attached to the 1- and 4-carbon atoms of an intermediate cyanodimer. As in the last preparation, a large amount of dimethyl methoxysuccinate is formed through reaction with the solvent.

Redistilled trimethyl 4-cyano-5-oxo-1,2,3-cyclopentanetricarboxylate boils under 4 mm. pressure at 196°.

Use. This compound is an interesting reactant, since it contains both a nitrile and three carboxyl groups.

Hydrocyanic Acid (Potassium Cyanide)



Dimethyl fumarate + Hydrocyanic acid (Potassium cyanide) ⟶ Trimethyl 4-cyano-5-oxo-1,2,3-cyclopentanetricarboxylate

Procedure. With the necessary precautions employed, 14.4 g. of dimethyl fumarate is carefully added to a suspension of 6.5 g. of potassium cyanide in 50 ml. of absolute methanol. The mixture is then set aside in a well-ventilated hood for 4 days, at the end of which time 3 g. of undissolved potassium cyanide is removed, the filtrate neutralized with an absolute methanol solution of hydrogen chloride, and the potassium chloride formed is filtered off. Then the solvent is removed at room temperature by applying a partial vacuum. A residue of 16.3 g. remains, which is divided into two fractions on reducing the pressure to 2 mm. The first fraction, b_2 75–78°, weighs approximately 5.5 g. and consists largely of dimethyl methoxysuccinate (m.p. 107–108°). The other, with a b_2 196–205°, weighs 5.4 g. The latter is then redistilled under approximately the same pressure to give the pure product.

Reference

Michael, A., and Werner, N., *J. Am. Chem. Soc.* 59, 744 (1937).

$$\left[\mathfrak{M}ORNH— \right]_x$$

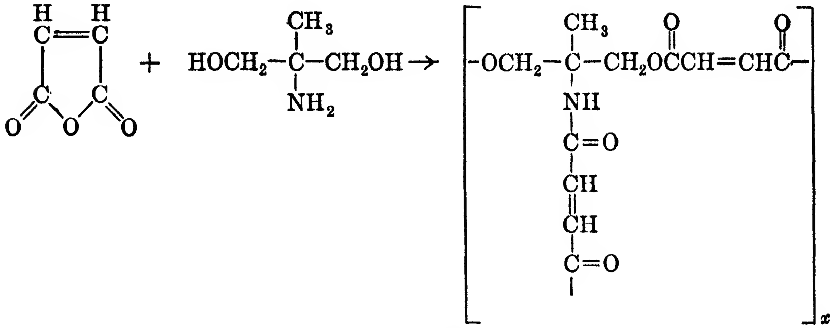
POLYESTER AMIDES

Poly-2-maleamyl-2-methyl-1,3-propylene Maleate

Aminodiols, like 2-amino-2-methyl-1,3-propanediol, react with both maleic anhydride and with succinic anhydride to form thermosetting resins, in contrast to the thermoplastic products produced with phthalic anhydride. This would indicate that both the amino and hydroxyl groups of the diol take part in this reaction. For this reason, it would appear that amide groups are produced as the major cross-linking reaction. Some additional polymerization may also take place when maleic anhydride is employed as the reactant.

Use. These new resins have interesting properties that should result in technical applications.

2-Amino-2-methyl-1,3-propanediol



Maleic anhydride + 2-Amino-2-methyl-1,3-propanediol ⟶ Poly-2-maleamyl-2-methyl-1,3-propylene maleate

Procedure. A mixture of 10.8 g. of maleic anhydride and 15.8 g. of 2-amino-2-methyl-1,3-propanediol is heated to 100 to 116° and held at this temperature for 15 minutes. This yields a balsam-like resin, which will set to a gel if the heating is continued until 66.5% of the theoretical amount of water has been collected.

Reference

Sprung, M. M., *J. Am. Chem. Soc.* 61, 3381 (1939).

Dimethyl (1-nitroethyl)succinate

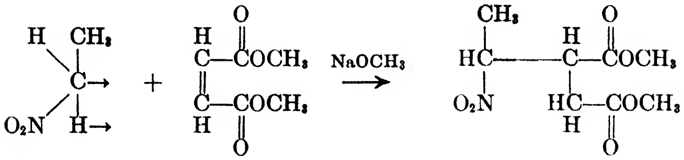
Primary and secondary nitroparaffins have labile hydrogen atoms. Hence they might be expected to react with maleates by adding at the alpha carbon to saturate the C:C bond of the maleyl group, such as occurs with benzoylacrylates.

The structure of these nitroalkylsuccinates has not yet been confirmed. A German report suggests that they can be caused to undergo reductive ring-closure, similar to γ-nitropimelates, to form in this case pyrrolidone derivatives. This, however, has not yet been verified, and no experimental details are given upon which to pass upon the claims.

Dimethyl (1-nitroethyl)succinate is a colorless liquid that boils when pure at 141 to 143° under 5 mm. pressure. It has a specific gravity of 1.225 at 24°, and a refractive index of 1.4480 at 24° and 1.4531 at 10.5°.

Use. It would appear that these compounds offer a number of interesting possibilities for organic synthesis, since they contain, besides a nitro group, two ester groupings. Similar types of products have been suggested for use in plastic compositions, as insecticides, and as intermediates for preparing amino acids, alcohols, esters, and amides in the synthesis of resins, plasticizers, and drugs.

Nitroethane



Nitroethane + Dimethyl maleate ⟶ Dimethyl (1-nitroethyl)-succinate

Procedure. To 500 ml. of methanol is added 23 g. of sodium. When all the sodium has reacted, the methoxide solution is cooled to 10 to 15° and 130 ml. of nitroethane is added slowly with good agitation. The agitation is continued for 30 minutes. The mixture is then allowed to warm to 20 to 25° and held at this temperature while 144 g. of dimethyl maleate is added from the dropping funnel over a period of 2 hours. The mixture is cooled to 10 to 15°, and 62 ml. of glacial acetic acid is added, agitated for an additional 15 minutes, and poured into a mixture of ice water and 100 g. of sodium bicarbonate. The aqueous solution is extracted with four portions of 200 ml. of ether, and the extracts are dried over 50 g. of anhydrous sodium sulfate.

A red-colored oil is obtained from the combined extracts. This is freed of low-boiling constituents by distilling to 80° under 20 mm. of pressure. The pressure is reduced to 5 mm., and the fraction boiling at 146 to 150.5° is collected. This is then redistilled from a Widmer column at the same pressure. The yield is 59% of theory.

References

Seigle, L. W., *New Products Report*, National Aniline Division, Allied Chemical and Dye Corp., New York (1946). *Cf.*:

Hopff and von Schichk, *U. S. Dept. Com. OPB Rept.* PB169 (1946).
Kohler, E. P., and Engelbrecht, H., *J. Am. Chem. Soc.* **41**, 769 (1919).
Leonard, N. J., and Beck, K. M., *J. Am. Chem. Soc.* **70**, 2504 (1948).
Leonard, N. J., Hruda, L. R., and Long, F. W., *J. Am. Chem. Soc.* **69**, 690 (1947).
Leonard, N. J., and Shoemaker, G. L., *J. Am. Chem. Soc.* **71**, 1876 (1949).

U. S. 2,342,119; 2,390,918; 2,554,831.

CHAPTER
6

Compounds Containing Oxygen

Reactions of oxygen-containing substances with maleyl compounds are as unusual and varied as those with the nitrogen reactants described in the last chapter.

This is exemplified, for example, by the reaction with compounds containing hydroxyl groups. Water and hydrogen peroxide add to the ethylene bond of maleic acid, as might be expected, to form malic and tartaric acids, respectively. Aliphatic alcohols add to the double bond to form ethers when sodium or strongly alkaline catalysts are present. Since the sodium alkoxide is used, this reaction is described in Chapter 4, page 65. In the presence of dehydrating agents or acids, they yield only the esters. Phenol, when catalyzed with a few drops of sulfuric acid, forms an asymmetric-disubstituted anhydride similar in structure to phenolphthalein through replacement of the oxygen of one of the carbonyl groups with two hydroxyphenyl groups. *p*-Cresol, however, undergoes an oxidation reaction with sulfuric acid, in its condensation with maleic anhydride to form the cyclic methylcoumarin. *β-tert*-Butyl-6-hydroxy-5-methylbenzyl alcohol undergoes condensation by splitting off water to yield a heterocyclic substituted chromandicarboxylic acid. Allylarylcarbinols react as if water were lost to the anhydride with the formation of a butadiene. This last reaction is a convenient means of preparing the Diels-Alder adducts of the 1-arylbutadienes, which polymerize too rapidly to yield any appreciable amount of the adduct.

A number of interesting modifications of the Diels-Alder synthesis are also included in this chapter. Furan, unlike its imino analog, pyrrole, combines with maleic anhydride as if it were a simple cyclic conjugated hydrocarbon. Ketene acetals could be looked upon as behaving in the same manner, if it were assumed that the acetal undergoes a dimeric condensation before reacting with maleic anhydride. Abietates with conjugated unsaturated groups in different rings do not react with maleic anhydride until isomerization occurs. Propenylphenyl ethers react like vinyl aromatic hydrocarbons, but the reaction is accompanied by the formation of large amounts of copolymers. *p*-Methoxyarylethylenes add two moles of maleic anhydride as if they were cyclic tetraenes, but no reaction occurs if the methoxy group is in the ortho position. Similar bis-adducts are formed in the reaction with anethole.

α-Pyrone-type compounds, such as methyl coumalate, however, lose a mole of carbon dioxide in producing bis-adducts such as methyl bicyclo[2.2.2]-7-octene-2,3,5,6,7-pentacarboxylic dianhydride. Bimolecular alkyl anhydroacetone benzils dissociate to give the cyclopentadienone, which then adds two moles of maleic anhydride by splitting off carbon monoxide.

Other intriguing reactions of oxygen compounds with maleates include that of benzoyl peroxide, which forms small amounts of phenylsuccinates. Ozone at low temperatures in organic solvents produces ozonides, but in water reacts only as an oxidizing agent. Peracids, in contrast, are non-reactive. Mixtures of carbon monoxide and hydrogen in the presence of a cobalt catalyst produce α-formylsuccinates.

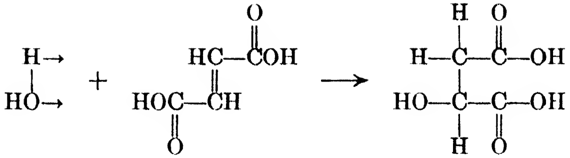
Malic Acid

The *dl*-malic acid obtained commercially from this preparation occurs as colorless crystals that melt at 127 to 128.5°. It has a density, d_4^{20}, of 1.601. The acid is very soluble in water, acetone, and alcohol but only slightly soluble in ether. It is readily resolved into the optical isomers by the usual methods. The *l*-acid melts at 100° and is only slightly soluble in alcohol. It is the major acid constituent of many fruits. The diethyl ester is a colorless liquid boiling at 253°. The dimethyl ester boils at 242°. The normal salts deliquesce, but the acid salts crystallize well.

Uses. *dl*-Malic acid has many different uses. It is an ingredient of high-bond-strength glues. It is widely used as an acidulent, as flavoring, and as a preservative in bottled soft drinks, candy, jellies, pectin extracts, ice creams, ices, gelatin powders, and desserts. It is particularly recommended for pear, apple, and raspberry jellies. It has also been employed as an ingredient in dentifrices and mouthwashes; and an electrolyte for condensers and lightning arresters; as an impregnant for radio condensers; as a dispersing agent for borax in fire-retardent finishes and emulsions; as a pigment dispersant in alkyd enamels; as an anti-gelling agent in jellied fuels; as an ingredient in electrolytes for the oxidation of aluminum; and in a hydrolysis bath for cellulose acetate. It is also used as a reagent in the manufacture of certain phenolic resins, shellac substitutes, and special alkyd resins for electrical insulation. Copper salts are used to kill fungus spores. The sodium salt is incorporated in pharmaceuticals as a compounding and dispensing agent and as a therapeutic agent. It is also used as a condiment by those who cannot use common salt. The acid is used in effervescent salts and laxatives.

Malic acid is also a very valuable intermediate in the synthesis of a variety of compounds, such as coumarin, dithiocarbethoxysuccinic acid, mercaptosuccinic acids, coumalic acid, α-hydroxyethoxysuccinic acid γ-lactone, polymalates, nitrosuccinic acid, oxalacetic acid, and phenylpyrazolonecarboxylic acids.

Water



Water + Fumaric acid ⟶ *dl*-Malic acid

Procedure. An aqueous solution containing 18% of fumaric acid is placed in a corrosion-resistant pressure vessel. The contents are carefully heated to 186° and held at this temperature for 20 hours. The reacted mixture is then cooled to 25°, and the bulk of the unreacted fumaric acid is removed by filtration.

The malic acid is recovered by evaporation of the filtrate and purified by fractional crystallization. The yield is 70.5% of the theoretical amount.

References

Weiss, J. M., and Downs, C. R., *J. Am. Chem. Soc.* **44,** 1118 (1922). *Cf.*:

Fenton, H. J., and Jones, H. O., *J. Chem. Soc.* **77,** 77 (1900).

Gregory, T. C., *Uses and Applications of Chemicals and Related Materials,* Rheinhold Publishing Corp., 2 vols. (1939–1944).

Holmberg, B., *Ber.* **58B,** 1822 (1925).

Jungfleisch, E., *Bull. soc. chim. France* **30,** 147 (1878).

Lachman, A., *J. Am. Chem. Soc.* **43,** 2084 (1921).

Lloyd, F., *Ann.* **192,** 80 (1878).

Meldrum, A. N., and Bhatt, D. M., *J. Univ. Bombay* **3,** 149 (1934); *C. A.* **29,** 4734^6 (1935).

Murty, N. N., *Plastics* (*London*) **9,** 585 (1945).

Niuewland, J. A., Vogt, R. R., and Foohey, W. L., *J. Am. Chem. Soc.* **52,** 1018 (1930).

Pictet, A., *Ber.* **14,** 2648 (1881).

Piutti, A., and Giustiniani, E., *Gazz. chim. ital.* **26** (I), 431 (1896).

Ruhemann, S., and Hemmy, B. A., *J. Chem. Soc.* **71,** 334 (1897).

Skraup, Z. H., *Monatsh.* **12,** 107 (1891); **14,** 501 (1893).

Tanatar, S., *J. Russ. Chem. Soc.* **22,** 310 (1892); *J. Chem. Soc.* **62,** 1305 (1892); *Ber.* **27,** 1365 (1894); *Ann.* **273,** 31 (1893).

van't Hoff, H. J., *Ber.* **18,** 2713 (1885).

von Pechmann, H., *Ann.* **264,** 272 (1891).

Walden, P., *Ber.* **32,** 2706 (1899).

Wislicenus, W., *Ann.* **246,** 306 (1888).

Yorston, F. H., *Rec. trav. chim.* **46,** 711 (1927).

U.S. 1,245,976; 1,245,984; 1,275,275; 1,280,862; 1,385,525; 1,412,514; 1,413,144; 1,413,145; 1,421,604; 1,424,137; 1,427,903; 1,489,744; 1,491,465; 1,516,206; 1,891,345; 1,918,804; 1,965,682; 1,965,683; 1,965,684; 1,994,213; 2,372,643; 2,381,487; 2,382,313. Brit. 395,894; 396,354; 403,401; 407,914; 421,989; 435,272.

Diethyl Fumarate

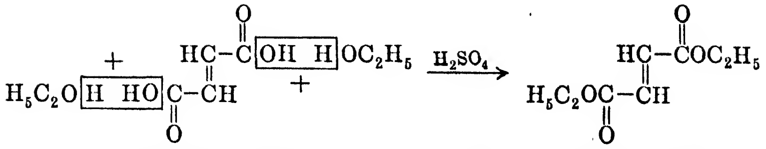
Many esters of maleic and fumaric acids have been prepared by methods similar to the one described on the opposite page. When hydrochloric acid is used as the catalyst, isomerization occurs, and the resulting product is invariably the fumarate. Esters may also be prepared by allowing the silver salts to react with alkyl iodides. This latter method, however, is not suitable for isopropyl, amyl, or higher molecular-weight esters. Diesters have also been synthesized from fumaryl chloride and alcohols, by refluxing dibromosuccinic esters with pyridine, and by ester interchange.

The half or acid esters may be produced by partial hydrolysis of the above diesters, with a calculated amount of potassium hydroxide. Methyl acid maleate has been made by refluxing maleic anhydride with an equivalent amount of absolute methanol.

Diethyl maleate is a colorless liquid with a characteristic pungent, violet odor. It boils when very pure at 225°, b_{19} 99°.

Use. These simple esters are common reactants for carrying out many of the reactions of the maleyl bond, as has already been seen. They also have numerous other uses. *Active* diamyl maleate, for example, is employed as an insecticide, and dialkyl esters as plasticizers for cellulose derivatives. Unsaturated alkyl esters are used as solvents, plasticizers, and as reactants for the manufacture of various copolymers.

Ethanol



Fumaric acid + Ethanol ⟶ Diethyl fumarate

Procedure. Three moles (348 g.) of fumaric acid is added to 350 ml. of 96% ethyl alcohol containing 15 ml. of concentrated sulfuric acid. The mixture is heated slowly to 110°, during which time 200 ml. of a mixture of alcohol and the water that forms continuously distills from the flask. Alcohol vapors are then passed into the reaction mixture at such a rate as to maintain the mixture at 115 to 120°. After 2 hours approximately 910 ml. of distillate is collected. The reaction upon cooling is neutralized with an aqueous sodium carbonate solution. The ester layer is separated, and the aqueous layer is extracted with benzene. The benzene extract is then added to the ester, and the two are fractionally distilled at normal pressures. The pure product is the portion boiling at 223 to 225°. A yield of 80% of theory is obtained in this way. This yield may be increased to 96% where desired by adding 720 ml. of toluene to the reaction mixture and distilling off the ternary mixture of alcohol, water, and hydrocarbon. Numerous other modifications have also been employed.

References

Corson, B. B., Adams, E., and Scott, R. W., *Org. Syn.* **10,** 48 (1930). *Cf.:*
Borglin, J. N., *Ind. Eng. Chem.* **28,** 35 (1936).
de Wolf, J., and van de Straete, L., *Bull. classe sci. Acad. roy. Belg.* **21,** 216 (1935).
Eddy, G. W., and Carson, N. B., *J. Econ. Entomol.* **41,** 31 (1948).
Gordon, P. L., and Aronowitz, R., *Ind. Eng. Chem.* **37,** 780 (1945).
I. G. Farbenindustrie (Lab. reports by Piepenbrink), *U.S. Dept. Com. O.T.S. Rept.* PB73887, frames 6942–6944.
Lecat, M., *Compt. rend.* **222,** 733 (1946)
Lewis, F. M., and Mayo, F. R., *J. Am. Chem. Soc.* **70,** 1533 (1948).
Lovelock, J. E., *Nature* **156,** 782 (1944).
Mayer, E. L., Tally, F. B., and Woodward, C. F., U.S. Dept. Agr., Bur. Ent., *Plant Quarantine* E-709 (1946).
Micovic, V. M., *Bull. soc. chim.* **4** (5), 1661 (1937).
Shields, J., *J. Soc. Chem.* **59,** 739 (1891).
Siegel, E. F., and Moran, M. K., *J. Am. Chem. Soc.* **69,** 1457 (1947).

U.S. 2,127,660; 2,295,513; 2,363,501; 2,368,765; 2,378,833; 2,394,512; 2,404,103; 2,411,136; 2,411,148. Brit. 572,455. Ger. 547,384.

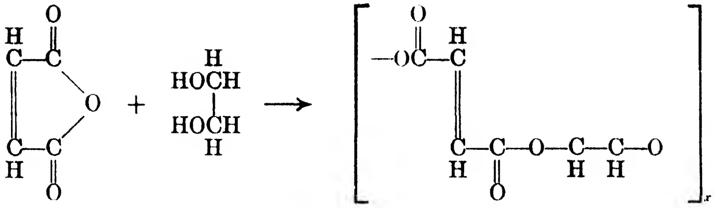
Glycol Maleate Polyester

The white amorphous solid obtained in this preparation melts at 88 to 95°. A similar product of m.p. 90 to 92° has been prepared from silver maleate and ethylene bromide. When dried under partial pressure, the amorphous solid yields an infusible insoluble material.

Use. Although these pure products are only laboratory curiosities, the method given for their preparation is extensively used by industry in the manufacture of various modifications of glycol maleate polyester. Excessive polymerization such as undoubtedly occurs here is easily controlled by carrying out this reaction in the presence of drying oils, fatty acids, and other modifying agents. The maleic resins so produced are extensively used in coating materials for all types of purposes. These polyesters may be copolymerized with other unsaturated substances to yield other useful products.

Mannitol sorbitol maleate polyesters have been suggested for sizing textile yarns. 1,9-Nonanediol bis(acid maleates) have been condensed with various amines for producing de-emulsifying agents for crude oil. Cellulose polymaleates have been recommended as wash-fast sizes, as textile fibers, and as a plastic for color photographs, films, and foils. Moldable esters may also be prepared from pentaerythritol, whereas mixed esters with sebacic acid and 1,3-propanediol have been employed for pressure-sensitive tapes. The ferrous salt of diethylene glycol monomaleate has been used as a catalyst for the copolymerization of styrene with glycol fumarate. Simultaneous acetylization and esterification of polyvinyl alcohol with formaldehyde and maleic anhydride are said to give filaments or fabrics of enhanced strength without sacrifice of softness or flexibility.

Glycol



Maleic anhydride + Glycol ⟶ Glycol maleate polyester

Procedure. A mixture of 32.5 g. of maleic anhydride and 18.6 g. of glycol is heated to 195 to 200° for 4 hours. The pressure is then reduced to 0.2 mm. and the heating continued at 210 to 215° for an additional 3 hours. The residue while still warm is dissolved in ethylene chloride and filtered. The product separates as an oil, which changes to a white powder in 2 hours when kept at 5 to 10°.

References

Carothers, W. H., *J. Am. Chem. Soc.* **51**, 2560 (1929). *Cf.*:
de Buigne, J., *Rev. prod. chim.* **41**, 65 (1944).
Gardner, W. H., *Encyclopedia of Chem. Technol.* **1**, 517 (1947).
Gibello, H., *Peintures, pigments, vernis* **22**, 245 (1946).
Hermann, F. J., *Centraal Inst. Materiaal Onderzoek Afdel. Verf Circ.* **35**, 1 (1947); *C. A.* **41**, 7137a (1947).
Kienle, R. H., and Petke, F. E., *J. Am. Chem. Soc.* **62**, 1053 (1940).
Rowland, C. S., *Interchem. Rev.* **5**, 83 (1946).
Tsuzuki, Y., *Bull. Chem. Soc. Japan* **10**, 17 (1935).
Vincent, H. L., *Ind. Eng. Chem.* **29**, 1267 (1937).
Vorländer, D., *Ann.* **280** 191 (1894).

U. S. 2,067,862; 2,357,933; 2,369,818; 2,370,962; 2,371,429; 2,373,527; 2,375,529; 2,381,116; 2,384,080; 2,413,275; 2,426,994; 2,427,255; 2,445,553; 2,454,210.

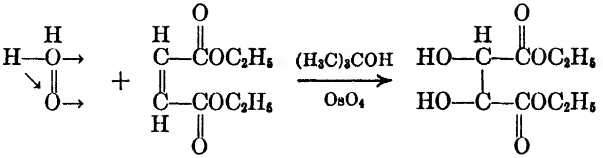
Tartaric Acid

Mesotartaric acid from this reaction occurs as rectangular tablets that melt with the formation of the anhydride at 140°. The acid is very soluble in water, quite soluble in alcohol, but only slightly soluble in ether. The diethyl ester melts at 53.5 to 55°. The *dl*-acid in contrast loses water at 100°, forming an anhydride melting at 204 to 206°. It occurs as monoclinic crystals. The diethyl ester of the *d*- and *dl*-acid melts at 17° to a liquid that boils at 280°; b_{15} 170°. The ester of the *l*-acid boils under 19 mm. at 162°.

Use. Tartaric acid is employed as a fungicide for feeds, as an acidulent in beverages, and as a clarifying agent for beer. It is also used to increase the plasticity of mortar, as a material in marking ceramics, and as an ingredient in dry batteries, condensers, and electrolytes for lightning arresters. It is employed in dyeing, in the silvering of mirrors and electric lamps, in fire extinguishers, in the bleaching of flour, and in baking powder. It has been described as a peptizing agent for pectin, as a preservative for dried fruits, as an agent for treating yeast. It may be used as a gelating agent for solid methanol fuels, as a disintegrating agent for certain insecticides, and as a laundry sour. It has also been recommended in etching, tin plating, coloring metals, flotation of ores, cleaning of aluminum, hat sizing, metal polishing, and artificial teeth cleaning. It may be used in paint removers and in the manufacture of blueprint and photopapers, synthetic rubber, artificial stone, and pharmaceuticals. In addition, it has been suggested as a coagulant of latex, as a liberant for bleach, and as an agent for sugar refining, silk dyeing, and calico printing. Esters have been used as plasticizers in lacquer.

It also may be employed as a reagent in the manufacture of adrenalin, flavanthrene, iron and nickel catalysts, sulfur dioxide, opium extracts, *l*-2-amino-1-*m*-hydroxyphenyl-1-propanol, apple oil, toka bean extract, vanilla bean extracts, detergents, and medicinals such as sulfonal.

Hydrogen Peroxide



Hydrogen peroxide + Diethyl maleate ⟶ Diethyl *meso*-tartrate

Procedure. An anhydrous solution of hydrogen peroxide in *tert*-butyl alcohol is first prepared from 100 ml. of a 30% aqueous solution of the peroxide, according to the directions given in *J. Amer. Chem. Soc.* **61,** 1844 (1939).

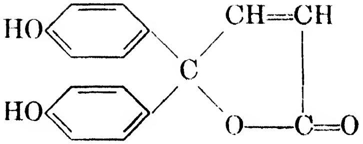
This solution is diluted with the anhydrous solvent to give a 5.95% solution of hydrogen peroxide, and 8.6 g. of diethyl maleate is added to it. The new solution is cooled to 0°, and 1.5 ml. of osmium tetroxide is added. The reaction mixture is allowed to warm to room temperature, and is then set aside for two days. The solvent is distilled off, and the residue fractionally distilled under approximately 18 mm. of pressure. (There is no mention as to whether peroxides are a hazard in this distillation.) The viscous portion, b_{18} 162–166°, is saved and allowed to crystallize from ether. The pure product is the ester of *meso*-tartaric acid. This, upon saponification in the usual manner, yields the desired acid.

The *dl*-acid has also been obtained by this method from diethyl fumarate. Other oxidizing agents, such as chlorates and permanganates, may also be used. Maleic anhydride, however, does not react with peracids. Tartaric acids may also be prepared from the dibromosuccinic acid with moist silver oxide, and by the hydrolysis of α-hydroxyglyoxylonitrile, or by the oxidation of mannitol with nitric acid.

References

Milas, N. A., Sussman, S., and Mason, H. S., *J. Am. Chem. Soc.* **61,** 1844 (1939); **58,** 1302 (1936); 59, 2345 (1937). *Cf.*:
Braun, G., *J. Am. Chem. Soc.* **51,** 228 (1929).
Claus, A., *Ber.* 10, 928 (1877).
Gregory, T. C., *Uses and Applications of Chemicals and Related Materials*, Reinhold Publishing Corp., New York.
Hatcher, W. H., and Mueller, W. H., *Can. J. Research* 3, 291 (1930).
Kekulé, A., and Anschütz, R., *Ber.* 13, 2150 (1881).
Milas, N. A., and Terry, E. M., *J. Am. Chem. Soc.* 47, 1412 (1925)
Swern, D., *J. Am. Chem. Soc.* 69, 1692 (1947).

U.S. 2,371,097.



Phenolmalein

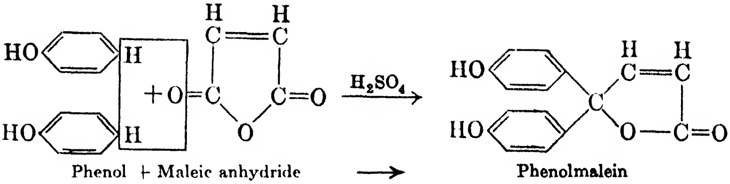
Maleic and succinic anhydrides combine with hydroxy aromatic compounds in the same manner as phthalic anhydride. The products are similar to the phthaleins, both in structure and in many of their properties. Resorcinols and *m*-aminophenols in a like fashion yield compounds corresponding to fluoresceins and rhodamines. The maleins are more highly colored than the succeins because of the unsaturated ethylene bond. These dyes crystallize with one mole of water, which can only be removed by heating for 6 to 7 hours in an air oven. Like the phthaleins, four moles of bromine may be substituted in the aromatic ring of the molecule. The ethylene bond of the maleins does not add bromine under these conditions, as shown by the absorption maxima of the brominated product. Compounds such as resorcinol- , pyrocatechol- , pyrogallol- , *o*-cresol- , 2-naphthol- , *m*-aminophenol- , phenylenediaminemaleins have been prepared by this method.

Bromosuccinic acids may be used in place of maleic anhydride. Unlike maleic anhydride, they do not require an added catalyst. The hydrobromic acid split off during the reaction in this case serves to effect the condensation. Dibromosuccinic acid, in contrast, gives a dye containing an acetylene group in place of the ethylene bond in the phenolmalein.

Purified phenolmalein is a light-colored brown powder melting at 195° and blackening at 170°. Methanol and ethanol solutions of it are brown, whereas the acetone solution is a deep red. Addition of alkali changes the color to a bright pink. Phenolmalein is insoluble in chloroform, benzene, and petroleum ether.

Use. These dyes are valuable for certain special uses, such as adsorption indicators in argentometry and the like.

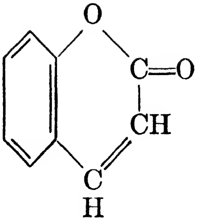
Phenol



Procedure. A few drops of concentrated sulfuric acid is carefully added to a mixture of 5 g. of phenol and 3 g. of maleic anhydride. The reaction mixture is cautiously heated to 125 to 135°, and agitated for 10 hours at this temperature. Upon cooling below 100°, the mixture is steam-distilled to remove any unreacted phenol, and the residue is collected and thoroughly extracted with a dilute ammonium hydroxide solution. From this extract, the crude product is obtained by careful precipitation with dilute hydrochloric acid. It is purified by treating a boiling alcohol solution of it with animal charcoal. After the charcoal is removed, the purified dye is recovered as a fine powder by precipitation with acidulated water, collected, and dried.

References

Dass, I. N. D., and Tewari, J. D., *Proc. Indian Acad. Sci.* **13A**, 68 (1941). *Cf.*:
Briggs, S., and Pope, F. G., *J. Chem. Soc.* **123**, 2934 (1923).
Burckhardt, R., *Ber.* **18**, 2864 (1885).
Dutt, S., *J. Chem. Soc.* **1926**, 1138.
Dutt, S., and Thorpe, J. F., *J. Chem. Soc.* **125**, 2524 (1924).
Lunge, G., and Burckhardt, R., *Ber.* **17**, 1598 (1884).
Mehrotra, R. C., Tewari, R. D., and Dube, H. L., *J. Indian Chem. Soc.* **24**, 165 (1947); *Current Sci.* (*India*) **16**, 119 (1947).
Rao, N. V. C., Seshadri, T. R., and Venkateswarlu, V., *Proc. Indian Acad. Sci.* **26A**, 299 (1947).
Tewari, J. D., *Proc. Indian Acad. Sci.* **1929**, 1642.



6-Methylcoumarin

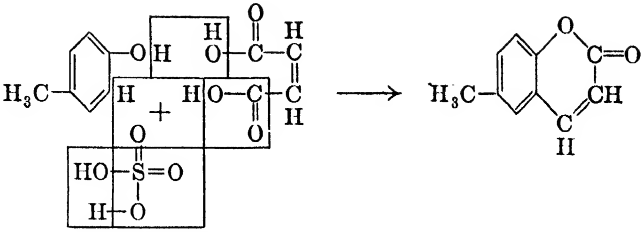
Maleic and fumaric acids react with *p*-cresol at elevated temperatures in the presence of concentrated sulfuric acid by undergoing oxidation, decarboxylation, dehydration, and cyclization to form 6-methylcoumarin. The unsaturated C:C bond of the maleyl compound is unaffected by the reaction.

6-Methylcoumarin melts at 73 to 74°. It may be brominated to give a dibromide melting at 65 to 66°. The mercurichloride melts at 189 to 190°.

The method is a relatively simple one for preparing certain other substituted coumarins.

Use. The coumarins are well known as perfume ingredients and as antioxidants.

p-Cresol

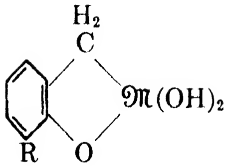


p-Cresol + Maleic acid + Sulfuric acid ⟶ 6-Methylcoumarin

Procedure. To a 72% solution of sulfuric acid is added 10.8 g. of *p*-cresol and 116 g. of maleic or fumaric acid. This mixture is then carefully heated to 160°, with constant agitation, and held at 160 to 180° for 2 hours. During this time there is an evolution of carbon dioxide and sulfur dioxide. When this is complete, the reaction mixture is allowed to cool and is then poured onto chopped ice, yielding a tarry black mass. The coumarin is extracted from this mass with alcohol. The alcoholic extract is decolorized with charcoal, and the 6-methylcoumarin is obtained from it as a white flocculate by pouring the solution onto chopped ice. The yield is 80% of theory.

References

Thompson, T. J., and Edee, R. H., *J. Am. Chem. Soc.* 47, 2557 (1925). *Cf.*: Ger. 338,737.

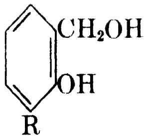


6-*tert*-Butyl-8-methyl-2,3-chromandicarboxylic Acid

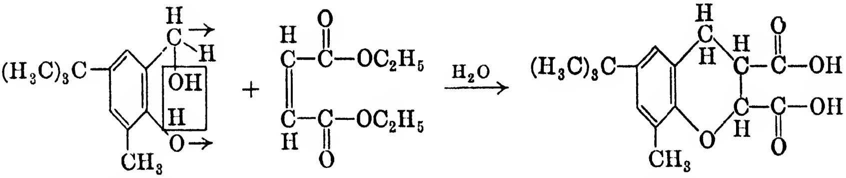
Hydroxybenzyl alcohols react with maleates to saturate the olefin bond of the maleate by forming the heterocyclic chromandicarboxylic acids. The *trans*-acid is the one produced directly. The *cis*-acid may be obtained from it by converting the *trans*-acid to the anhydride with acetic anhydride, and then treating the resulting anhydride with dilute alkali. The reaction appears to be a general one for preparing substituted chromandicarboxylic acids.

trans-6-*tert*-Butyl-8-methyl-2,3-chromandicarboxylic acid is a crystalline solid that melts at 245°. The *cis*-acid melts at 222°.

Use. The preparation is particularly interesting in illustrating the type of compounds that may be formed from hydroxybenzyl alcohols in the preparation of maleic alkyd–phenolic resins. These compounds should be valuable modifying agents in the preparation of such resins. The reactions suggest how new maleic types may be prepared.



3-*tert*-Butyl-6-hydroxy-5-methylbenzyl Alcohol

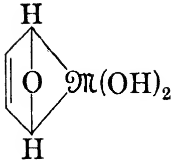


3-*tert*-Butyl-6-hydroxy-5-methylbenzyl alcohol + Diethyl maleate ⟶ 6-*tert*-Butyl-8-methyl-2,3-chromandicarboxylic acid

Procedure. A mixture of 50 g. of 3-*tert*-butyl-6-hydroxy-5-methylbenzyl alcohol and 175 g. of diethyl maleate is heated at 220°. The unchanged ester is removed by distillation under reduced pressure, and the residue saponified with 60 g. of 33% sodium hydroxide solution for 2 hours and acidified. The precipitated resin is dissolved in ether and shaken with sodium carbonate solution. The yield of the chromandicarboxylic acid is 37 g., or 47% of theory.

Reference

Hultzsch, K., *J. prakt. Chem.* 158, 275 (1941).



7-Oxabicyclo[2.2.1]-5-heptene-2,3-dicarboxylic Acid

(3,6-Epoxy-4-cyclohexene-1,2-dicarboxylic Acid)

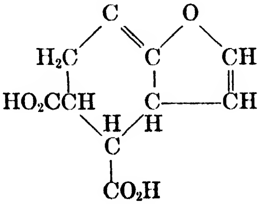
Conjugated heterocyclic dienes containing oxygen, like the furans, and the pyrones, add maleic anhydride as if they were simple conjugated dienes (*q.v.*). The sulfur analogs, however, resemble benzene and do not react with dienophiles. See diacenaphtho [1,2-*b*,1′,2′-*d*]-thiophene. Pyrroles and indoles, the amino analogs, yield substituted succinic and disuccinic acids by adding maleic anhydride at the carbon atoms alpha to the nitrogen atom, provided that these groups are not substituted.

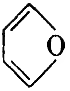
Furan gives the triphenyl phosphine test for quinones. The addition of maleic anhydride may thus be looked upon as resembling the type of addition expected with aromatic quinones.

7-Oxabicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid is obtained as the monohydrate that sinters at 95°. At 103 to 105° it loses water to form the anhydrous acid that remelts at 135°. The monohydrate forms large, clear crystals that are easily soluble in warm water.

Hypobromous acid can be added to the unsaturated bond of this epoxy adduct to form the bromolactone acid.

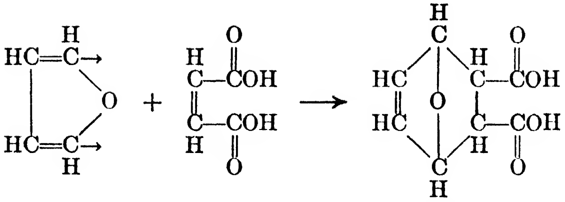
Use. These compounds offer several possibilities for organic syntheses. Adducts have been prepared from a number of furan derivatives, including 1,2-diphenylbenzofuran, 2-isopropyl-5-methylfuran, 2-vinylfuran, and 2-furylethylene. The last compound, instead of adding at the 2,5-furan carbons as in this preparation, adds maleic anhydride to give what is probably 3a,4,5,6-tetrahydro-4,5-benzofurandicarboxylic anhydride:





CONJUGATED HETEROCYCLIC DIENES

Furan



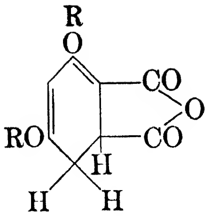
Furan + Maleic acid ⟶ 7-Oxabicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid

Procedure. A solution of maleic acid is prepared by dissolving 60 g. of maleic anhydride in 150 ml. of water. Thirty ml. of furan is then added to this solution at a temperature not exceeding 20°, and the mixture is vigorously agitated for 3 days, during which time the furan completely dissolves. The adduct is recovered in the usual manner and is purified by dissolving it at 60 to 65° in three times its weight of water. Complete solution is usually obtained in about 45 minutes. The aqueous solution is then allowed to evaporate slowly, depositing large crystals of the monohydrate.

References

Diels, O., Alder, K., Nienburg, H., and Schmalbeck, O., *Ann.* **490**, 247 (1931). *Cf.*:
Butz, L. W., *J. Am. Chem. Soc.* **57**, 1314 (1935).
Diels, O., Alder, K., and Müller, K., *Ann.* **490**, 257 (1931).
Fried, J., and Elderfield, R. C., *J. Org. Chem.* **6**, 566 (1941).
Herz, W., *J. Am. Chem. Soc.* **67**, 1854 (1945).
Nazarov, I. N., and Nagibina, T. D., *Bull. acad. sci.* (*USSR*), *Classe sci. chim.* **1946**, 641; *C. A.* **42**, 7736e (1948).
Paul, R., *Bull. soc. chim. France* **10**, 163 (1943).
Woodward, R. B., and Baer, H., *J. Am. Chem. Soc.* **70**, 1161 (1948).

U. S. 2,406,657; 2,432,890; 2,433,645; 2,437,955.



ETHERS OF DIHYDROPHTHALIC ANHYDRIDE

3,5-Diethoxy-2,4-cyclohexadiene-1,4-dicarboxylic Anhydride

(3,5-Diethoxy-1,6-dihydrophthalic Anhydride)

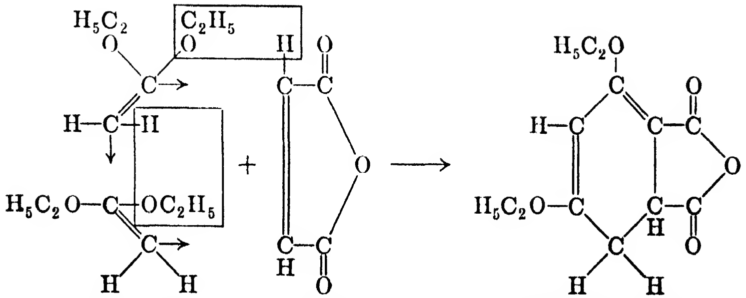
This reaction of maleic anhydride with a 2,2-bis-ether substituted ethylene is unique in several respects. Both addition and condensation take place during this reaction. Two moles of acetal are involved that result in the formation of a cyclic diene dicarboxylic anhydride.

3,5-Diethoxy-2,4-cyclohexadiene-1,4-dicarboxylic anhydride occurs as fine yellow crystals that melt at 110 to 111° when recrystallized from xylene.

This anhydride can react with an additional mole of maleic anhydride in benzene solution to form 1,5-diethoxybicyclo[2.2.2]-5-octene-3,4,7,8-tetracarboxylic dianhydride by addition in the usual manner of the anyhdride across the diene structure of the alicyclic ring.

Use. The reactive groups in these anhydrides make them especially interesting for synthetic work.

Ketene Diethylacetal

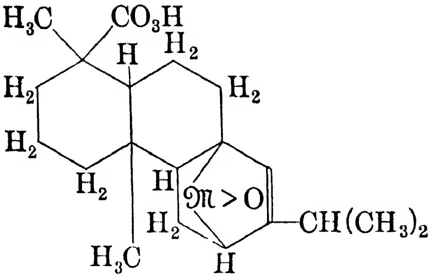


Ketene diethylacetal + Maleic anhydride ⟶ 3,5-Diethoxy-2,4-cyclohexadiene-1,4-dicarboxylic anhydride

Procedure. To a solution of 4.9 g. of maleic anhydride in 75 ml. of dry ether is added 11.6 g. of ketene diethylacetal. The reaction mixture rapidly takes on a yellow, then red color, and the solution starts to boil within 2 minutes. Whereupon, it is cooled. As soon as the vigorous reaction subsides, it is set aside for 12 hours in a closed vessel. The yellow precipitate formed is collected upon a filter, washed with dry ether, and recrystallized from xylene. The yield is 71% of theory.

Reference

McElvain, S. M., and Cohen, H., *J. Am. Chem. Soc.*, 64, 260 (1942).



ALKENEPOLYCARBOXYLIC ACIDS

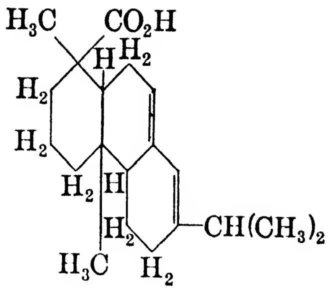
Methyl 4,4a,4b,5,6,7,8,8a,9,10-Decahydro-2-isopropyl-4b,8-dimethyl-3,10a(3)-ethanophenanthrene-8,11,12-tricarboxylic Anhydride

Unlike chain conjugated dienes, or cyclic conjugated dienes containing both unsaturated groups in the same ring, abietic acid and abietates do not react with maleic anhydride at temperatures below 100°. When heated with the anhydride above this temperature, the abietates isomerize to the levopimarates, which add the anhydride readily. Hence the adduct may also be prepared from pure levopimaric acid, or directly from rosin by heating the pine oleoresin with the anhydride.

The adduct obtained from methyl abietate melts at 214 to 215°. It has a $(\alpha)_D$ of $-26°$. It is readily soluble in chloroform, methyl alcohol, acetone, and ether. Although the adduct contains an unsaturated bond, it does not absorb bromine from a chloroform solution of the halogen. No yellow color is obtained with tetranitromethane in the same solvent, nor is methane obtained from the micro-Zerewitinoff reaction. The tribasic acid obtained from it melts at 227° and shows a $(\alpha)_D$ of $-250°$. The trimethyl ester prepared from this acid decomposes at 113°. It has a d_4^{116} of 1.084, and $n_D^{14.8}$ of 1.4869. These derivatives are identical with those prepared from levopimaric acid and from rosin.

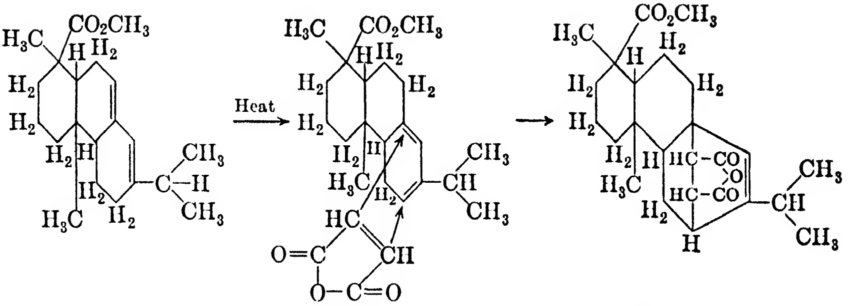
Use. Very extensive use is made commercially of this type of reaction in the manufacture of modified rosins, ester gums, and maleic alkyds. These resins give improved gloss, rate of drying, and hardness to paint and varnish films. The maleic anhydride adduct of stearyl abietate has been recommended as a rust-inhibiting agent.

This type of reaction has been widely used in the elucidation of the structure sterols and of various resin acids.



POLYCYCLIC DIENECARBOXYLIC ACIDS

Methyl Abietate



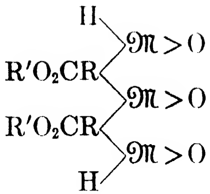
Methyl abietate ⟶ Methyl levopimarate ⟶ Methyl 4,4a,4b,5,6,7,8,8a,9,10-decahydro-2-isopropyl-4b,8-dimethyl-3,10a(3)-ethanophenanthrene-8,11,12-tricarboxylic anhydride

Procedure. A mixture of 79 g. of methyl abietate and 25 g. of maleic anhydride is heated for 8 hours at 160°. The resulting reaction mixture is then thoroughly extracted with hot petroleum ether to remove all the unreacted constituents, leaving a pure crystalline product from which the acid may be obtained. The acid is obtained by saponification with 0.5 *N* aqueous potassium hydroxide.

References

Ruzicka, L., Ankersmit, P. G., and Frank, B., *Helv. Chim. Acta* **15**, 1289 (1932). *Cf.*:
Arbuzov, B., *J. Gen. Chem. (USSR)* **2**, 806 (1932).
Armitage, F., and Cottrell, J. A., *Paint Technol.* **13**, 133 (1948).
Fieser, L. F., and Campbell, W. P., *J. Am. Chem. Soc.* **60**, 162 (1938).
Gardner, W. H., *Encyclopedia of Chem. Tech.* **1**, 526 (1947).
Gee, G., and Rideal, E. K., *Proc. Roy. Soc.* (*London*) **A153**, 116 (1935).
Graff, M. M., *J. Am. Chem. Soc.* **68**, 1937 (1946).
Harris, G. C., and Sanderson, T., *J. Am. Chem. Soc.* **70**, 334 (1948).
Hicks, E. M., Jr., Berg, C. J., and Wallis, E. S., *J. Biol. Chem.* **162**, 645 (1946).
Levin, R. H., Wesner, M. M., and Meinzer, E. M., *J. Am. Chem. Soc.* **70**, 2834 (1948).
McElvain, S. M., and Cohen, H., *J. Am. Chem. Soc.* **64**, 260 (1942).
McKennon, F. L., Johanson, A. J., Field, E. T., and Lawrence, R. V., *Ind. Eng. Chem.* **41**, 1296 (1949)
Morrell, R. S., and Davis, W. R., *J. Soc. Chem. Ind.* **55**, 261T (1936).
Rinse, J., *J. Polymer Sci.* **3**, 371 (1948).
Ruzicka, L., Bacon, R. G. R., and Kuiper, S., *Helv. Chim. Acta* **20**, 1542 (1937).
Ruzicka, L., and Kaufman, S., *Helv. Chim. Acta* **23**, 1346 (1940).
Ruzicka, L., Silbermann, H., and Pieth, P., *Helv. Chim. Acta* **15**, 1285 (1932).
Wicks, Z. W., Daly, O. W., and Lack, H., *J. Org. Chem.* **12**, 713 (1947).
Wienhaus, H., and Sandermann, W., *Ber.* **69B**, 2202 (1936).
Woods, G. F., and Sanders, H., *J. Am. Chem. Soc.* **69**, 2926 (1947).

U.S. 2,025,947; 2,358,048; 2,359,980; 2,363,792; 2,376,823; 2,379,375; 2,398,668; 2,398,670; 2,409,930; 2,447,750; 2,450,358. Brit. 588,041; 592,167. Ger. 739,438.

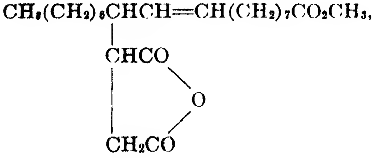


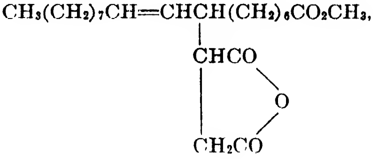
Methyl Linoleate Adducts

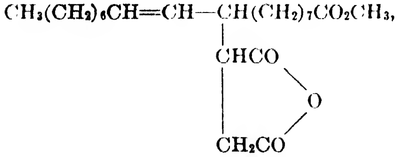
Approximately 90% of the anhydride reacts with the fatty ester in this preparation to yield a complex mixture of adducts. These reaction products have not been completely separated and purified, but they have been divided into a volatile and non-volatile fraction, as described. It is necessary, therefore, to rely largely upon analytical values for a picture of the possible structures of the adducts. It is clear from studies of this type of reaction, and from the properties of the products, that both monomeric adducts and copolymers are formed during this process. The first reaction, which probably produces the volatile fraction, may involve the addition of one molecule of anhydride to a carbon adjacent to one of the unsaturated bonds of the methyl linoleate. This step appears to be accompanied by a shifting of the double bond, since the volatile fraction contains 12% of conjugated reaction products.

The non-volatile fraction is probably also a mixture, in this case, of copolymers. The observed values indicate an adduct containing three molecules of anhydride to two of the fatty ester. Since substantial amounts of the monomeric adducts are formed, sufficient anhydride is left for the formation of such adducts. The dimeric structure shown fits all the data now available. These results may readily be accounted for, as suggested by Teeter, Geerts, and Cowan, by assuming a free-radical mechanism for the reactions. Compare this with similar reactions described in Chapter 1.

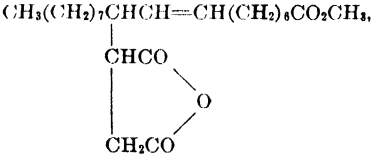
Methyl oleate reacts with maleic anhydride under similar conditions to give a light yellow oil that distils under 1 mm. pressure at 196 to 205°. Bickford and co-workers show this product to consist of nearly equal amounts of the four possible monoadducts:







and

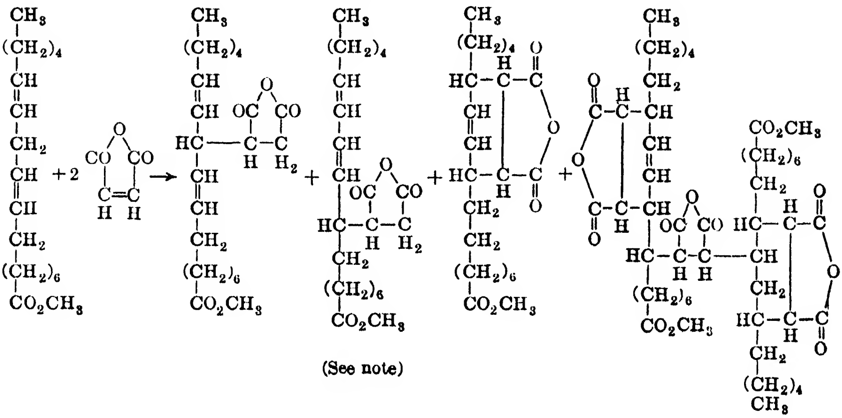


as judged by analysis and yields of fission products.

Use. The addition of maleic anhydride to non-conjugated esters is an important reaction in the manufacture of modified drying oils for the paint and varnish industries. Rapid drying characteristics are imparted to slower drying oils and alkyd resins by this treatment.

$R'CH{=}CHCH_2CH{=}CHR''CO_2R'''$ NON-CONJUGATED FATTY ESTERS

Methyl Linoleate



Methyl linoleate + Maleic anhydride → Mono- and Polyadducts

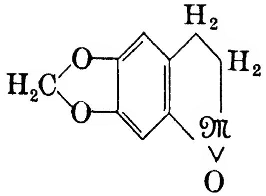
Procedure. A mixture of 50 g. of pure methyl linoleate and 31.4 g. of maleic anhydride is heated in an atmosphere of carbon dioxide for 7 hours at 200°. The reaction mixture is then passed through a molecular still at 107 to 124° under 0.4 to 0.8 micron pressure to free the products of any uncombined reactants. The resulting crude adducts are separated into two fractions by passing them twice through a falling-film molecular still at 157 to 162° under the same pressure. Heat is applied to both the inlet and the outlet tubes of the still to obtain the proper flow of these highly viscous products. A volatile fraction weighing 12.9 g. and a non-volatile fraction of 26.0 g. are obtained in this way. The volatile fraction is further purified by passing it through the still at 152 to 163° at 0.7 to 1.0 micron, taking a center cut of 6.7 g.

References

Teeter, H. M., Geerts, M. J., and Cowan, J. C., *J. Am. Oil Chemists' Soc.* **25**, 158 (1948). *Cf.*:
Bickford, W. G., Fisher, G. S., Kyame, L., and Swift, C. E., *J. Am. Oil Chemists' Soc.* **25**, 254 (1948).
Bickford, W. G., Krauczunas, P., and Wheeler, D. H., *Oil & Soap* **19**, 23 (1942).
Falkenburg, L. B., Teeter, H. M., Skell, P. S., and Cowan, J. C., *Oil & Soap* **22**, 143 (1945).
Farmer, E. H., *Trans. Faraday Soc.* **38**, 340 (1942); *J. Soc. Chem. Ind.* (*London*) **66**, 86 (1947); *Rubber Chem. and Technol.* **21**, 27 (1948).
Farmer E. H., Koch, H. P., and Sutton, D. A., *J. Chem. Soc.* **1943**, 541.
Farmer, E. H., and Sutton, D. A., *J. Chem. Soc.* **1943**, 119.
Gardner, W. H., *Encyclopedia of Chem. Technol.* **1**, 517 (1947).
Gunstone, F. D., and Hilditch, T. P., *J. Chem. Soc.* **1946**, 1022.
Konen, J. C., *Oil & Soap* **21**, 202 (1944).
Morrell, R. S., and Davis, W. R., Jr., *J. Soc. Chem. Ind.* **55**, 101T, 55 (1936).
Payne, H. F., Caldwell, L. E., Bailey, R. H., and Schmutzler, A. F., *Am. Ink Maker* **25**, No. 12, 23 (1947); **26**, No. 1, 28; No. 2, 27 (1948).
Ross, J., Gebhart, A. I., and Gerecht, J. F., *J. Am. Chem. Soc.* **68**, 1373 (1946).
Ruzicka, F. C. J., *Oil Colour Trades J.* **144**, 442 (1948).

U.S. 1,933,697; 2,188,882; 2,280,862; 2,384,595; 2,384,846; 2,385,794; 2,387,393; 2,387,395; 2,387,396; 2,396,763; 2,414,712; 2,423,230. Brit. 552,095; 565,431; 565,432; 588,018.

Note. **These formulas for the products are used purely to illustrate the types of compounds formed. Other isomers and polyadducts are undoubtedly present.**



ETHERS OF TETRAHYDRONAPHTHALENEDICARBOXYLIC ANHYDRIDE

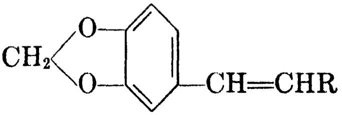
1,2,3,4-Tetrahydro-3-methyl-6,7-methylenedioxy-1,2-naphthalenedicarboxylic Anhydride

Propenylphenyl ethers react with maleic anhydride and maleates to yield a mixture of products of which the crystalline tetrahydronaphthalenedicarboxylic acids and their anhydrides usually comprise 20 to 30%. The remainder of the product consists of copolymers of the reactants and polymers of the propenylphenyl ether. The copolymers are similar in structure to those obtained with other substituted ethylenes (*q.v.*). The mixture of products is usually a red gel or oil. Most of the gels melt fairly sharply.

An ether group in the *p*- or *o*-position greatly favors the addition of maleic anhydride. Thus anethole adds two moles of anhydride to form the tetra-acid adduct. Maleic acid when used in place of its anhydride favors the formation of the normal non-aromatic type of Diels-Alder compound such as is obtained with conjugated vinylnaphthalene (*q.v.*).

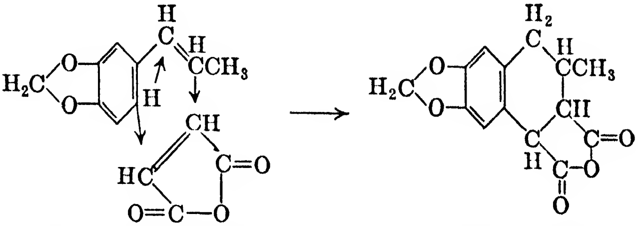
The monomeric adduct of isosafrole and maleic anhydride melts at 144° according to Bruckner, but according to Hudson and Robinson at 142 to 143°. Bruckner reports the free acid as melting at 185°; Hudson and Robinson report 143°. The ethyl ester is a liquid, $b_{1.3}$ 205–210°. When the anhydride is heated at elevated temperatures, dehydrogenation occurs with the formation of 3-methyl-6,7-methylenedioxy-1,2-naphthalenedicarboxylic anhydride. This compound also results from the distillation of a mixture of the reactants.

Use. Esters of 1,2,3,4-tetrahydro-3-methyl-6,7-methylenedioxy-1, 2-naphthalenedicarboxylic acid are effective in fly sprays when mixed with 0.025% pyrethrum. The percentage of flies killed is more than double the number when the active ingredient is pyrethrum alone. The red oil obtained by allowing the maleate to react with isosafrole may be used directly for this purpose after one extraction with petroleum ether.



PROPENYLPHENYL ETHERS

Isosafrole



Isosafrole + Maleic anhydride ⟶ 1,2,3,4-Tetrahydro-3-methyl-6,7-methylenedioxy-1,2-naphthalenedicarboxylic anhydride

Procedure. A mixture of 37.0 g. of isosafrole and 19.6 g. of maleic anhydride is heated upon a boiling water bath for 3 hours. The viscous, orange-red reaction mixture is then cooled in a refrigerator and thoroughly extracted with approximately 400 ml. of cold ethyl alcohol. The yellowish powder that is left is dried and extracted with boiling carbon tetrachloride. This carbon tetrachloride extract, when cooled and allowed to evaporate, yields 12.9 g. of the 1,2,3,4-tetrahydro-3-methyl-6,7-methylenedioxy-1,2-naphthalenedicarboxylic anhydride.

The 11.8 g. of insoluble residue left from the extraction with carbon tetrachloride consists of equal molecular copolymers of the two reactants and melts at 334 to 335°. The alcohol extract contains the unreacted isosafrole, maleic anhydride, 8.4 g. of diisosafrole, and 1.8 g. of the acid of the above anhydride.

References

Bruckner, G., Jr., *Ber.* **75B,** 2034–2050 (1942). *Cf.*:

Bruckner, G., Jr., and Kovács, J., *Nature* **161,** 651 (1948).

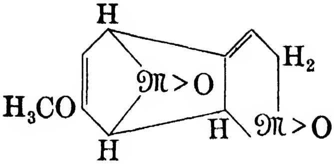
Hudson, B. J. F., and Robinson, R., *J. Chem. Soc.* **1941,** 715.

Lora Tamayo, M. L., et al., *Anales fís. y quím (Spain)* **36,** 44 (1940); **37,** 392 (1941); **39,** 525 (1943); **40,** 394, 808, 1178 (1944); **41,** 1151, 1325 (1945); **42,** 809 (1946); *Anales real soc. espan. fís. y quím.*, Ser. B, **44,** 223 (1948); *C. A.* **42,** 8175a (1948)]; *Nature* **162,** 969 (1948); *Rev. real. acad. cienc. exact., fís. y mat., Madrid* **39,** 185 (1945); *C. A.* **45,** 5122c (1951).

Prill, E. A., and Synerholm, M. E., *Contrib. Boyce Thompson Inst.* **14,** 221 (1946).

Synerholm, M. E., *J. Am. Chem. Soc.* **67,** 345, 1229 (1945).

Synerholm, M. E., and Hartzell, A., *Contrib. Boyce Thompson Inst.* **14,** 81 (1945).



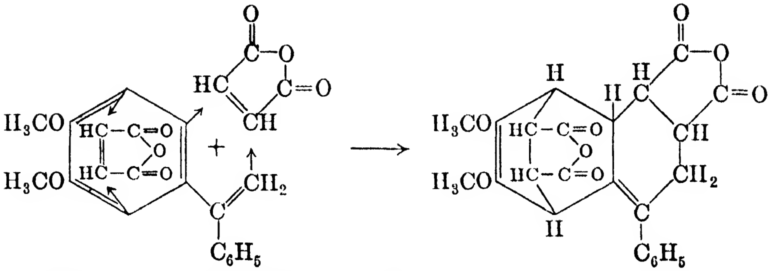
1,4,4a,5,6,7-Hexahydro-2,3-dimethoxy-8-phenyl-1,4-ethanonaphthalene-5,6,9,10-tetracarboxylic Dianhydride

The position of the methoxy substituents in 1,1-diarylethylenes has a marked effect upon the course of their reactions with maleic anhydride. As can be seen on the opposite page, addition occurs with the ring containing these groups if they are in the *p*- or 3,4-positions. In such cases, these 1,1-diarylethylenes react as if they were tetraenes by adding two moles of maleic anhydride, in contrast to re-establishing the original aromatic ring after the addition of one mole of anhydride by a shift of the double bond from the new ring, such as takes place in the reaction with isosafrole (*q.v.*). This directing effect of methoxy groups is similar to that of phenyl groups, but the opposite in effect to that of a *p*-methyl substituent in one of the rings. If, however, the methoxy group is ortho to an exocyclic double bond in either or both rings, no reaction occurs with maleic anhydride.

Somewhat similar bis-adducts are formed in addition to other products in the reaction of maleic anhydride with anethole, with 1-methoxy-4-propenylbenzene, and with 1-methoxy-4-propenylnaphthalene, but they have not been reported for the 1,2-dimethoxy-4-propenylbenzene reaction. A methoxy substituent in the 6-position of α- or β-cyclopentenylnaphthylenes apparently does not affect the reactivity of these compounds as vinylnaphthalenes (*q.v.*).

1,4,4a,5,6,7-Hexahydro-2,3-dimethoxy-8-phenyl-1,4-ethanonaphthalene-5,6,9,10-tetracarboxylic dianhydride crystallizes from a mixture of acetic anhydride and acetic acid as prismatic rods that melt at 245 to 246°. These bis-adducts readily dissociate into their components when heated. In the presence of hydrobromic or hydroiodic acid, only one mole of maleic anhydride is split off and the methoxy-substituted ring becomes aromatic. The bis-adducts are readily dehydrogenated with sulfur to yield the substituted naphthalene dicarboxylic anhydrides, which may be decarboxylated to obtain the substituted naphthalenes. The asymmetrical dimethoxy derivative obtained from the dianhydride described here, however, undergoes decarboxylation only at temperatures above 400°, so that most of the material is completely decomposed during the decarboxylation process.

1-(3,4-Dimethoxyphenyl)-1-phenylethylene

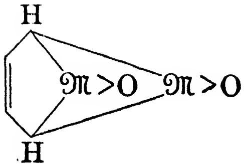


1-(3,4-Dimethoxyphenyl)-1-phenylethylene + Maleic anhydride ⟶ 1,4,4a,5,6,7-Hexahydro-2,3-dimethoxy-8-phenyl-1,4-ethanonaphthalene-5,6,9,10-tetracarboxylic dianhydride

Procedure. A mixture of 2.4 g. of 1-(3,4-dimethoxyphenyl)-1-phenylethylene and 9.8 g. of maleic anhydride is heated in a stoppered vessel for 3 hours at 140 to 160°. The reaction mixture turns a red-brown color. When the heating is completed, the unreacted maleic anhydride is removed by distillation under reduced pressure. The crude product is dissolved in a minimum amount of boiling alcohol, and the solution allowed 24 hours to crystallize. The crystals are collected, sucked dry on the filter, and then recrystallized from a mixture of acetic anhydride and acetic acid. The yield obtained is 60% of theory.

References

Bergmann, F., Szmuszkovicz, J., and Fawaz, G., *J. Am. Chem. Soc.* **69**, **1775** (1947). *Cf.*:
Bachmann, W. E., and Kloetzel, M. C., *J. Am. Chem. Soc.* **60**, 2204 (1938).
Bruckner, G., Jr., *Ber.* **75B**, 2034 (1942).
Bruckner, G., Jr., and Kovács, J., *Nature* **161**, 651 (1948).
Szmuszkovicz, J., and Bergmann, F., *J. Am. Chem. Soc.* **69**, 1779 (1947).



BICYCLOPOLYCARBOXYLIC POLYANHYDRIDES

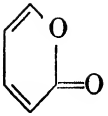
Bicyclo[2.2.2]-7-octene-2,3,5,6,7-pentacarboxylic 2,3,5,6-Dianhydride Methyl Ester

(7-Carbomethoxybicyclo[2.2.2]-7-octene-2,3,5,6-tetracarboxylic Dianhydride)

This is a more or less general reaction of α-pyrones when they are allowed to react with an excess of maleic anhydride at elevated temperatures for prolonged periods. The normal Diels-Alder adduct, a bicyclic compound containing an ester bridge, is produced first, since it is the product formed when the reactants are refluxed in toluene, or when this reaction is stopped after 5 hours. Fusing methyl coumalate with maleic anhydride causes an immediate loss of carbon dioxide, with the formation of the dianhydride. Similar reactions take place with coumalin and other substituted α-pyrones, such as dimethylcoumalin and isodehydroacetic acid, *2,4-dimethyl-1,2-pyrone.* The dianhydride from coumalin may also be prepared from 3,5-cyclohexadiene-1,2-dicarboxylic acid and maleic anhydride.

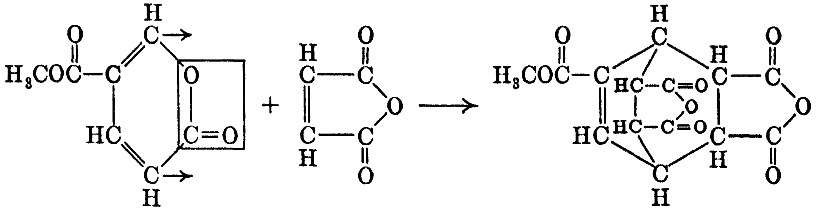
Bicyclo[2.2.2]-7-octene-2,3,5,6,7-pentacarboxylic 2,3,5,6-dianhydride methyl ester melts at 331°. The pentamethyl ester prepared from it melts at 137 to 138°.

The mono-adduct, 6-hydroxy-4-cyclohexene-1,2,3,5-tetracarboxylic 1,2-anhydride δ-lactone methyl ester, occurs as colorless crystals melting at 198°. When an aqueous solution of this mono-adduct is evaporated to dryness and treated with methyl alcohol and hydrogen chloride, trimethyl trimesate, *trimethyl 1,3,5-benzenetricarboxylate,* is produced. In a similar way, trimesic acid may be obtained by heating this adduct with four atoms of bromine at 200° for 2 hours. Apparently, oxidation occurs during esterification of the mono-adduct in addition to hydrolysis of the ester bridge, dehydration, and decarboxylation. It is interesting to note that, in these two reactions, the carboxyl group forming the bridge is not the one that undergoes decarboxylization, in contrast to what takes place in the formation of the dianhydride.



α-PYRONES

Methyl Coumalate

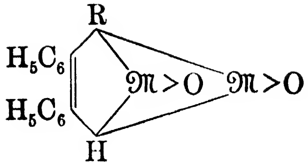


Methyl coumalate + Maleic anhydride → Bicyclo[2.2.2]-7-octene-2,3,5,6,7-pentacarboxylic 2,3,5,6-dianhydride methyl ester

Procedure. One and a half grams of methyl coumalate and 1 g. of maleic anhydride are dissolved in a small amount of xylene, and the solution is refluxed for 24 hours. During this time the product gradually separates as a white crystalline precipitate. When the reaction is complete, the solid crystalline mass is collected upon a filter, dried, and then recrystallized several times from boiling acetonitrile. The yield is 30% of theory.

References

Diels, O., Alder, K., and Müller, K., *Ann.* **490,** 257 (1931). *Cf.:* Fried, J., and Elderfield, R. C., *J. Org. Chem.* **6,** 566 (1941).



ALKYLDIPHENYLBICYCLOTETRA-CARBOXYLIC ACIDS

1-Methyl-7,8-diphenylbicyclo[2.2.2]-7-octene-2,3,5,6-tetracarboxylic Dianhydride

The reactions of bimolecular anhydroacetonebenzils with maleic anhydride are unique, both with respect to the type of products formed and the marked influence that substituent groups have upon the course of these reactions. Generally, these bimolecular compounds react with maleic anhydride only at temperatures sufficiently high to render them unstable, so that there is an accompanying dissociation into a transitory monomeric cyclopentadienone or a splitting of the carbon monoxide bridge or both.

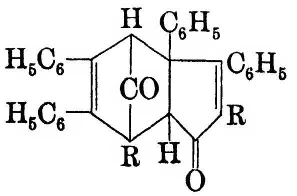
Bimolecular compounds derived from alkylanhydroacetonebenzils, such as shown on the opposite page, undergo both types of decomposition simultaneously in their reactions with the anhydride. Two products are thus formed in this case. One of these is the dianhydride shown in the equation. The other, the major product of the reaction, is a monoanhydride, $C_{33}H_{24}O_4$, which has not yet been fully characterized. It is produced apparently by the addition of maleic anhydride to the bimolecular compound with an accompanying loss of both carbon monoxide and benzene, yielding a compound containing three phenyl groups. Presumably, the angular phenyl group attached to the 3a-carbon is the one that is split off. Such behavior of phenyl groupings is relatively rare. The cleavage of the carbon monoxide bridge is similar to what takes place when coumalates (*q.v.*) are allowed to react with maleic anhydride.

With bimolecular compounds derived from *sym*-dialkyl-derivatives of these benzils, addition apparently occurs only as a result of their dissociation into the cyclopentadienones. Depending upon the amount of maleic anhydride used in the reaction, yields of 95 to 99% of either the mono- or di-adduct of the cyclopentadienone may be obtained under similar conditions to those used above. A typical example of this type of reactant is the bimolecular compound obtained upon dehydrating, 2,5-dimethylanhydroacetonebenzil, *2,5-dimethyl-4-hydroxy-3,4-diphenyl-2-cyclopenten-1-one.*

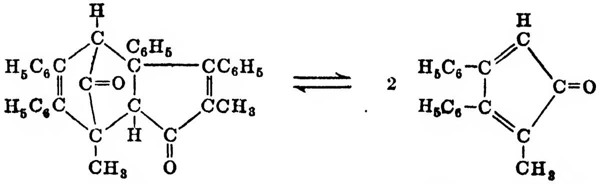
The bimolecular compound derived from the unsubstituted anhydroacetone benzil does not dissociate readily. Hence, addition occurs only as a result of splitting off of carbon monoxide.

1-Methyl-7,8-diphenylbicyclo[2.2.2]-7-octene-2,3,5,6-tetracarboxylic dianhydride melts at 325°. It can be distilled without change under 7 mm. pressure at 340 to 360° but decomposes when so treated at atmospheric pressures. The other product melts at 288°.

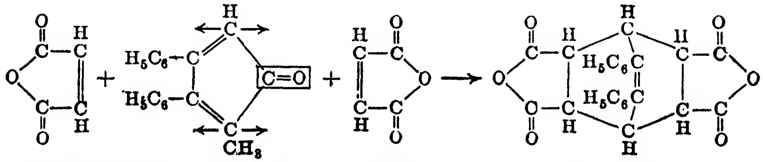
BIMOLECULAR ALKYLANHYDROACETONEBENZILS



Bimolecular Methylanhydroacetonebenzil



3a,4,7,7a-Tetrahydro-2,7-dimethyl-3,3a,5,6-tetraphenyl-4,7-methanoindene-1,8-dione → 2-Methyl-3,4-diphenylcyclopentadienone



2-Methyl-3,4-diphenylcyclopentadienone + Maleic anhydride → 1-Methyl-7,8-diphenylbicyclo[2.2.2]-7-octene-2,3,5,6-tetracarboxylic dianhydride

Procedure. A mixture of 24 g. of bimolecular methylanhydroacetonebenzil and 10 g. of maleic anhydride is carefully heated in a well-ventilated hood at 220° until the poisonous carbon monoxide is completely evolved. The reaction mass is then cooled and extracted for 1 hour with 125 ml. of boiling benzene, filtered, and dried. The 10 g. of residue is crystallized from 50 ml. of trichlorobenzene and then recrystallized from acetic anhydride to obtain the above dianhydride in pure form.

Dilution of the benzene extract with an equal volume of ligroin yields 16 g. of a mono-anhydride product. The precise structure of this compound has not yet been determined.

References

Allen, C. F. H., and Van Allan, J., *J. Org. Chem.* **10,** 333 (1945). *Cf.*:

Allen, C. F. H., and Gates, J. W., Jr., *J. Am. Chem. Soc.* **64,** 2120, 2123, 2127 (1942).

Allen, C. F. H., and Spanagel, E. W., *J. Am. Chem. Soc.* **55,** 3773 (1933).

Allen, C. F. H., and Van Allan, J., *J. Am. Chem. Soc.* **64,** 1260 (1942).

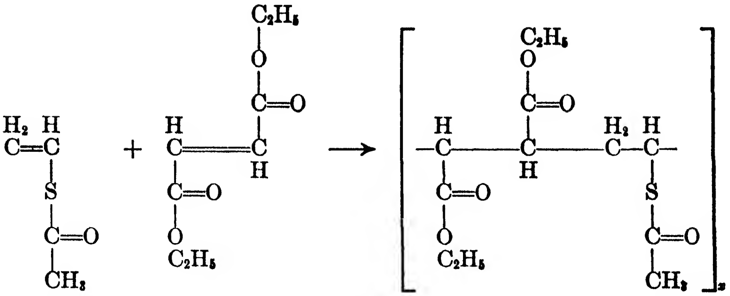
Ethyl Poly(thiolacetoxyethylenesuccinate)

The copolymer prepared as described on the opposite page may be processed to yield hard, colorless resinous objects. Similar resinous products may be made by either simply heating the reactants together in the presence of a catalyst or in an organic solvent. Various other catalysts such as benzoin and acyl peroxides may be used also. The reaction may be carried out in bulk or in solution, at 50° to 200°, and in the presence or absence of ultraviolet light. Clear colorless films may be obtained from the copolymers by pressing them at 120° under 1000 lb. per sq. in. Various esters of both maleic and fumaric acids may be employed as one of the reactants.

Maleic acid, its anhydride, and its esters also react with numerous other hetero-substituted vinyl and ethylene compounds to yield a wide variety of useful copolymeric products. In general, maleic compounds have the tendency to produce 1:1 copolymers of the general structure shown here. Other examples of such are the copolymers with various esters of acrylic and methacrylic acids, isopropenyl acetate, 4-phenyl-3-butene-2-one, methyl vinyl ether, and 1-acyloxy-1,3 butadiene.

Use. These copolymers may be used in molding compounds, as films, filaments, lacquers, binding compositions, coatings, thickeners, acid fixers for basic dyes, and intermediates in the manufacture of resins.

Vinylthiolacetate



Vinyl thiolacetate + Diethyl fumarate ⟶ Ethyl poly(thiolacetoxyethylenesuccinate)

Procedure. An aqueous emulsion is prepared of 70 g. of vinyl thiolacetate, 30 g. of diethyl fumarate, and 0.5 g. of diacetyl in 90 g. of copper-free water, with the aid of 10 g. of a 1% polymethacrylic acid solution, 1 g. of monopotassium phosphate, and sufficient 1 *N* potassium hydroxide solution to produce a *p*H of 6. This emulsion is kept agitated under an inert atmosphere while it is exposed for 5 hours at 70 to 80° to a commercial 100-watt mercury arc placed at 4 in. from the reaction vessel. At the end of this time the mixture is cooled and the resulting granular suspension is collected on a filter. The yield is 85 g. of a copolymer containing 21.6% of sulfur, i.e. 68.9% of vinyl thiolacetate.

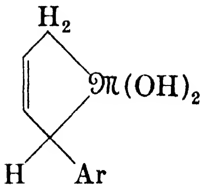
References

Imperical Chemical Industries, Brit. 585,755 (1947). *Cf.*:

Losev, I. P., and Trostyanskaya, E. B., *J. Gen. Chem.* (*USSR*) 17, 122 (1947); *C. A.* 42, 2923d (1948).

Minsk, L. M., Waugh, G. P., and Kenyon, W. O., *J. Am. Chem. Soc.* 72, 2646 (1950).

U.S. 2,432,460; 2,452,165. Brit. 595,881; 600,408.



cis-3-α-Naphthyl-*cis*-4-cyclohexene-1,2-dicarboxylic Acid

(*cis*-α-Naphthyl-1,2,3,6-*cis*-tetrahydrophthalic Acid)

Some butadienes polymerize so rapidly that they cannot be obtained as monomers. Such is true of several of the 1-arylbutadienes. The method using the unsaturated alcohol affords a suitable means for preparing the maleic anhydride adducts in such cases. This method is apparently a general one. It has also been used to prepare the 3,4-dimethoxyphenyl- and 3-piperonyl-4-cyclohexene-1,2-dicarboxylic acids. Maleic anhydride serves here both as a dehydrating agent and a condensing agent in this reaction with arylalkylcarbinols. The anhydride rather than the acid is the product obtained when the carbinol is refluxed with maleic anhydride in boiling xylene. The yield of anhydride is somewhat less than the yield of acid.

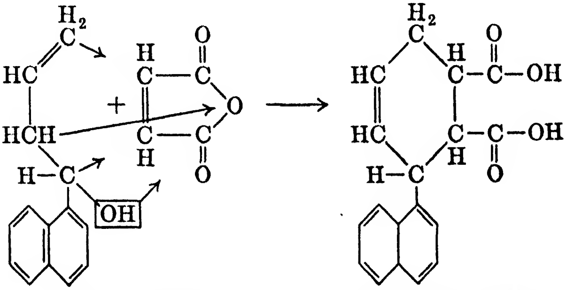
Theoretically, the addition might also take place at the β-carbons of the chain and of naphthalene ring to produce a substituted phenanthrenedicarboxylic acid of the type formed with vinylnaphthalenes (*q.v.*). Aryltetrahydrophthalic acids, however, apparently are produced exclusively in these reactions, since no evidence has been reported that vinyltetrahydrophenanthrenedicarboxylic acid is one of the products of this reaction. That the substituted phthalic acid would be the predominant product in any case may be predicted from resonance forms of the diene.

cis-3-α-Naphthyl-*cis*-4-cyclohexene-1,2-dicarboxylic acid crystals begin to decompose at 165°. The anhydride, when recrystallized from benzene-petroleum ether mixtures, melts at 160 to 161°, and the dimethyl ester at 79 to 81°. The dimethyl ester of 3-α-Naphthyl-4-cyclohexene-1,2-dicarboxylic acid can be dehydrogenated to produce the 3-α-naphthylphthalate. Hydrogenation of the acid gives the substituted hexahydrophthalic acid which when treated with anhydrous hydrogen fluoride undergoes cyclization to 7a,8,9,10,11,11a-hexahydro-7-oxo-7*H*-benz[*de*]anthracene-8-carboxylic acid.

Use. Nothing specific has been reported. For suggested uses see other tetrahydrophthalic acids.

α-Allyl-1-naphthalenemethanol

(α-Naphthylallylcarbinol or 1-Naphthyl-3-buten-1-ol)



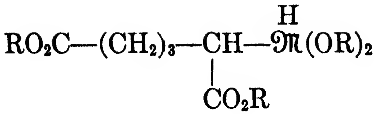
α-Allyl-1-naphthylene-methanol + Maleic anhydride ⟶ *cis*-3-α-Naphthyl-*cis*-4-cyclohexene-1,2-dicarboxylic acid

Procedure. A reaction mixture of 9.9 g. of α-allyl-1-naphthalenemethanol and 4.9 g. of maleic anhydride is carefully heated to approximately 150°. This initiates a violent exothermic reaction, which is controlled by cooling under running water. After the reaction has subsided, the flask is heated for 45 minutes in a bath held at 145 to 155°. The mixture is cooled, and the resulting tan, brittle crude product is thoroughly extracted with ether. From this extract, there is obtained 7.4 g. of white crystals of the pure product. An excess of maleic anhydride gives lower yields than when the above proportions are employed.

The carbinol may be prepared from allylmagnesium chloride and α-naphthaldehyde by the method described in the following reference.

References

Arnold, R. T., and Coyner, E. C., *J. Am. Chem. Soc.* **66**, 1542 (1944). *Cf.*: Hudson, B. J. F., and Robinson, R., *J. Chem. Soc.* **1941**, 715.



$$RO_2C\text{—}(CH_2)_3\text{—}\underset{\displaystyle CO_2R}{\overset{H}{C}}H\text{—}\mathfrak{M}(OR)_2$$

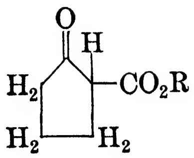
ALKANETETRACARBOXYLIC ACIDS

Tetraethyl 1,2,3,6-Hexanetetracarboxylate

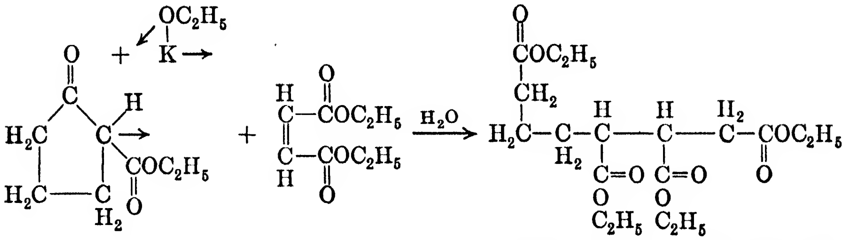
This is an interesting reaction in that the cyclic ketone is split by the potassium ethoxide so that a straight-chain tetracarboxylic acid is formed with the diethyl maleate. When sodium ethoxide or piperidine is used as the catalyst, in place of potassium ethoxide, for the addition of the maleic ester, 1-carboxy-2-oxocyclopentanesuccinic ester is probably first formed, and the ring may not be broken until the resulting triethyl ester is saponified with concentrated hydrochloric acid. Unfortunately, the data available do not distinguish between the two possible initial products in these cases, the succinate and the tetracarboxylate. The fact that the boiling points of the products from the sodium ethoxide and from piperidine are lower than those obtained from potassium ethoxide would suggest that possibly the succinate is formed with these two catalysts. The tetraethyl esters prepared from the acids obtained by any of the methods are identical. Yields are poor when sodium ethoxide is the catalyst.

Tetraethyl 1,2,3,6-hexanetetracarboxylate boils at 182° under 4 mm. of pressure. The acid is a thick sirupy liquid. The ester undergoes the Dieckmann condensation with sodium dust to yield either a five- or a six-membered ring system; namely, triethyl 3-carboxy-2-oxocyclopentanesuccinate or 3,6-dicarboxy-2-oxocyclohexaneacetate. This ketonic ester may be hydrolyzed to give a solid keto acid.

CYCLOPENTANONECARBOXYLIC ESTERS



Ethyl 2-Oxocyclopentanecarboxylate



Ethyl 2-oxocyclopentanecarboxylate + Potassium ethoxide + Diethyl maleate (water) ⟶ Tetraethyl 1,2,3,6-hexanetetracarboxylate

Procedure. A solution of potassium ethoxide is first prepared from 0.4 g. of metallic potassium and 55 ml. of absolute ethyl alcohol. To this solution is added 15.6 g. of ethyl 2-oxocyclopentanecarboxylate and 17.2 g. of diethyl maleate. After it has stood for 3 days at room temperature, the reaction mixture is poured into acidulated water containing a small amount of floating ice, and the oil that separates is then thoroughly extracted with ether. The ether extract is washed with water, dried, and the solvent removed in the usual manner. The residue is distilled under reduced pressure, collecting as product that fraction that boils at b_4 182°. The yield is 36 g. This may be saponified by refluxing it with 150 ml. of concentrated hydrochloric acid to obtain 30 g. of the sirupy acid.

Reference

Ghosh, K. C., *J. Indian Chem. Soc.* **24,** 45 (1947).

Dimethyl Phenylsuccinate

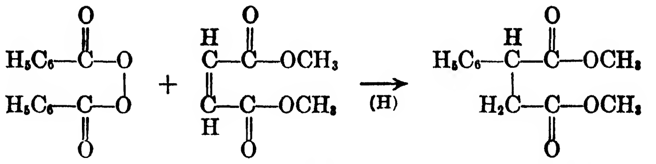
The reaction shown is one of several taking place in this preparation. Dimethyl phenylsuccinate is recovered only to the extent of 3% of the reaction mixture, but it is of special interest in illustrating one manner in which benzoyl peroxide may react. It should be noted that hydrogen is required to complete the reaction. This must be obtained from other molecules in the reaction mixture.

Two other crystalline products are also produced. These are either isomeric tetramethyl esters of 1,2,3,4-tetralintetracarboxylic acid or of 1-methylhydrindenetetracarboxylic acid. They are possibly formed by the cyclization of tetramethyl 1-phenyl-1,2,3,4-butanetetracarboxylate, which would result from a reaction of dimethyl maleate with dimethyl phenylsuccinate.

The non-volatile portion of the products contains more than two maleate units per phenyl group. It is undoubtedly comprised of the higher polymers. Compare with reactions described on pages 26 and 54.

Partial decomposition during distillation of the reaction mixture from which benzoic acid and the unreacted benzoyl peroxide have been carefully removed yields additional benzoic acid. This indicates that some benzoyloxy-addition products are also formed.

Benzoyl Peroxide



Benzoyl peroxide + Dimethyl maleate ⟶ Dimethyl phenylsuccinate

Procedure. To 200 g. of dimethyl maleate is carefully added portionwise 168 g. of benzoyl peroxide. The reaction mixture is heated under a reflux condenser for 700 hours at 55°. Any unreacted peroxide remaining at the end of the reaction is destroyed by slowly adding to it a solution of sodium iodide in acetone. The acetone is evaporated, and the mixture is extracted with ether. The ether extract is next washed with an aqueous bicarbonate solution, dried, and the solvent removed under reduced pressure. The residue is separated into four fractions at approximately 1 mm. pressure, giving 14% of unreacted dimethyl maleate, b_1 60–63°; 3% of crude dimethyl phenylsuccinate, b_1 105–115°; about 24% of a mixture of tetracarboxylates, b_1 182–195°; and 43% of a non-volatile residue.

The fraction distilling at 105 to 115° at 1 mm. is then washed in the usual manner with a bicarbonate solution to remove any traces of benzoic acid and is redistilled to give an initial fraction having a n_D^{20} of 1.492. This fraction solidifies readily upon seeding with a crystal of pure product. These crystals are then dried by pressing them against a porous plate.

References

Marvel, C. S., Prill, E. J., and DeTar, D. F., *J. Am. Chem. Soc.* **69**, 52 (1947). *Cf.*:
Bartlett, P. D., and Nozaki, K., *J. Am. Chem. Soc.* **68**, 1495 (1946).
Brown, D. J., *J. Am. Chem. Soc.* **62**, 2657 (1940).
Mayo, F. R., *J. Am. Chem. Soc.* **65**, 2324 (1943).
Price, C. C., *Ann. N. Y. Acad. Sci.* **44**, 365 (1943).

Diethyl Maleate Ozonide

The procedure given on the opposite page serves equally well for preparing the ozonide from diethyl fumarate. If decomposition reactions are to be avoided, a procedure employing an inert solvent and lowered temperatures, such as described, must be used for this purpose.

Ozonides prepared from maleic anhydride and fumaric acid are highly unstable. They readily explode quite violently at comparatively low temperatures even in the presence of solvents. In a series of preparations, carried out by Briner and co-workers at —60 to —80°, five out of eleven experiments ended in explosions. Some of the explosions are accompanied by flame. A white solid precipitates during the reaction with the anhydride. Obviously, no analyses are given, but an equivalent molecular amount of ozone is absorbed in those experiments where it is possible to obtain complete ozonization.

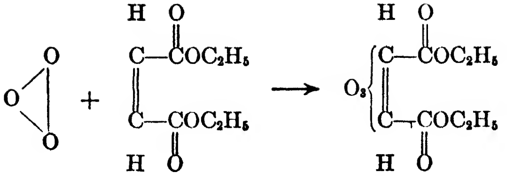
The ozonides from both diethyl maleate and diethyl fumarate are limpid liquids. They have a barely perceptible yellowish color. They contain the theoretical amounts of carbon and hydrogen and have the following physical properties:

Ozonide of diethyl maleate—refractive index, n_D^{20} 1.4384; density, d_4^{20} 1.1561; dipole moment, 2.53×10^{-18}; and dielectric constant, 8.95.

Ozonide of diethyl fumarate—refractive index, n_D^{20} 1.4382; density, d_4^{20} 1.1591; dipole moment, 2.29×10^{-18}; and dielectric constant, 7.54.

The molar refractions are higher than theory by 4.93 and 5.10 units, respectively. Raman spectra of both compounds show, besides the distinguishing lines for ozonides, a characteristic line for one ethylene bond. This is not in accord with the generally accepted views of the structure of ozonides, but similar observations have been recorded for the spectra of the ozonides of substances like eugenol, containing an unsaturated allyl group.

Ozone



Ozone + Diethyl maleate ⟶ Diethyl maleate ozonide

Procedure. A solution of 10.4 g. of diethyl maleate in 25 ml. of carbon tetrachloride is cooled to 0 to 5°. A stream of oxygen containing approximately 3% of ozone is then bubbled through this solution at a rate of 10 liters per hour for a period of 7 hours, without allowing the temperature to rise. In this way, the reaction is continued beyond the point of maximum rate of absorption of ozone, in order to obtain the addition of a stoichiometric quantity. Of the total amount of ozone bubbled through the solution, 78% is absorbed. The carbon tetrachloride is removed at the end of the reaction by evaporation under highly reduced pressure.

References

Briner, E., Perrottet, E., Paillard, H. and Susz, B., *Helv. Chim. Acta* 19, 1163, 1354 (1936).
Cf.:
Briner, E., and Frank D., *Helv. Chim. Acta* 20, 1211 (1937).
Briner, E., Perrottet, E., Paillard, H., and Susz, B., *Helv. Chim. Acta* 19, 558 (1936); 20, 762 (1937).

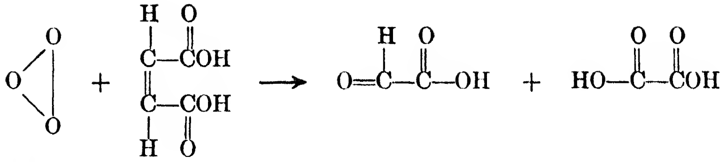
Glyoxylic Acid

Ozone apparently reacts with maleic acid solely as an oxidizing agent when water is employed as the solvent, as in this preparation. Under these conditions, it differs in its behavior in many respects from what has been described in the previous preparation. There is no direct indication that any ozonide is formed here. If produced, it must decompose immediately, since only glyoxylic and oxalic acids have been detected as the reaction products. The same type of oxidation reaction also occurs with aqueous suspensions of dimethyl maleate, producing methyl glyoxylate.

Similar oxidation reactions to those in water may occur when ozone is bubbled through solutions of maleates in the ionizing solvent, glacial acetic acid, but the products have not been isolated. It is to be hoped that further study may be made of them, since much might be revealed concerning the true nature of these oxidizing reactions. Maleic acid and dimethyl maleate, for example, absorb only 0.66 mole of ozone before reaction is complete. Dimethyl fumarate, which reacts much more slowly, uses up approximately 1.7 moles of ozone. Simple olefinic compounds without conjugated carbonyl groupings, in contrast, rapidly absorb stoichiometric quantities of ozone.

Glyoxylic acid occurs as rhombic prisms, which dissolve readily in water. The acid and many of its salts crystallize with one molecule of water, indicating that it may have a structure analogous to that of chloral hydrate.

Ozone



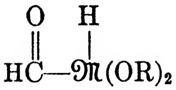
Ozone + Maleic acid ⟶ Glyoxylic acid + Oxalic acid

Procedure. Ozone is bubbled for a period of 2 hours through an aqueous solution containing 2 g. of maleic acid in 10 ml. of water. The glyoxylic acid formed is isolated by converting it to the phenyl hydrazone with phenylhydrazinium acetate. A yield of 1.4 g. of glyoxylic acid phenylhydrazone is obtained in this manner.

The remainder of the products consists largely of oxalic acid. This is recovered from the aqueous solution by precipitation as the calcium salt.

References

Harries, C., *Ber.* **36,** 1936 (1903). *Cf.*:
Noller, C. R., Carson, J. F., Martin, H., and Hawkins, K. S., *J. Am. Chem. Soc.* **58,** 24 (1936).



$$\overset{\displaystyle O}{\overset{\|}{HC}}-\overset{\displaystyle H}{\overset{|}{\mathfrak{M}}}(OR)_2$$

Diethyl α-Formylsuccinate

This is the only reaction reported for preparing aldehyde dicarboxylates directly from maleates. Although the procedure involves the use of a poisonous gas at relatively high pressures, it is a practical one with several features of real merit, not the least of which is the relatively high yield.

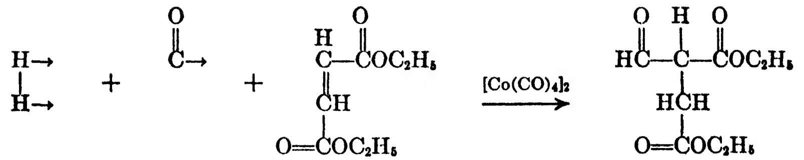
Diethyl α-formylsuccinate can also be prepared from diethyl succinate and ethyl formate. Each method has certain marked advantages and disadvantages.

Ethyl α-formylsuccinate obtained by this method has a boiling point of 104 to 105° at 0.04 mm. pressure and a refractive index of n_D^{25} 1.4486. It is 95% pure as ascertained by titration. The pure ester has a b_{15} 137°. The product obtained from ethyl formate generally boils at 124 to 125°, and the *p*-nitrophenylhydrazone melts at 100 to 101°.

Uses. Although diethyl α-formylsuccinate has not been extensively studied as a reactant, several interesting reactions are reported where it has been used as an intermediate in organic syntheses. With benzoyl chloride, it reacts to form diethyl α-benzoyl-β-formylsuccinate. With benzyl amine, it gives diethyl α-(benzylaminomethylene)succinate. This product can be readily converted to 1-benzyl-3-carbethoxy-5-pyrrolinone. Various other amines react in a similar manner. Alanine esters, *α-aminopropionates,* for example, give dialkyl α-(1-carboxyethylaminomethylene)succinates. Acetamidine yields ethyl 4-hydroxy-2-methyl-5-pyrimidine acetate. Aniline gives the α-(phenylaminomethylene)succinates, *γ-anilinoitaconates.* Hydroxylamine produces an oxime which, upon distillation, gives an alkyl β-cyanopropionate.

Hydrolysis of ethyl α-formylsuccinate gives β-formylpropionic acid. This, with sulfuric acid, yields trimeric, six-membered, substituted, cyclic oxymethylene. This trimer on distillation produces the bis-γ-(butyrolactone) ether, $(\underbrace{OCOCH_2CH_2C}H)_2O$. β-Formylpropionic acid in pyridine reacts with malonic acid to give adipenic acid, $HO_2C(CH_2)_2CH{:}CHCO_2H$. Ethyl β-formylpropionate with malonic ethyl ester gives the neutral ester of the pentacarboxylic acid, 2-dicarboxymethyl-1,1,4-butanetricarboxylic acid.

Carbon Monoxide and Hydrogen



Hydrogen + Carbon monoxide + Diethyl fumarate ⟶ Diethyl α-formylsuccinate

Procedure. The dicobalt octacarbonyl catalyst is prepared first in the manner described in *J. Am. Chem. Soc.* **70,** 383 (1948).

When this has been done, 40 ml. of the resulting ether solution containing 2.2 g. of the catalyst is placed in a steel bomb, and 17.20 g. of diethyl fumarate and 40 ml. of ether are added to it. The mixture is then allowed to react with an excess of carbon monoxide and hydrogen at a pressure not to exceed about 5050 lbs. per sq. in. and an ultimate temperature of 125°. The pressure is released when the bomb has cooled to room temperature, and the product is recovered in the usual manner.

Purification is carried out by fractional distillation under 1 mm. pressure, collecting the portion that boils at 85 to 120°. This fraction is redistilled to give a final product, $b_{0.04}$ 104–105°, with a yield of 51% of theory.

See the original article for details of the pressure reaction and for the precautions to be taken in handling the high pressures and poisonous reactants.

References

Adkins, H., and Krsek, G., *J. Am. Chem. Soc.* **70,** 383 (1948). *Cf.*:
Carrière, E., *Ann. chim.* **17,** 38 (1922).
Gravin, A. I., *J. Applied Chem.* (*USSR*) **16,** 105 (1943).
Ranganathan, S. K., *J. Indian Chem. Soc.* **16,** 107 (1939).
Robinson, R., and Rose, J. D., *J. Chem. Soc.* **1933,** 1469.
Shchukina, M. N., and Preobrazhenskiĭ, N. A., *Ber.* **68B,** 1991 (1935).
Todd, A. R., and Waring W. S., *J. Chem. Soc.* **1944,** 548.

U.S. 2,327,066; 2,377,395; 2,384,068.

CHAPTER
7

Sulfur Compounds

Sulfur compounds and sulfur probably add to the ethylene bond of maleyl compounds with greater avidity than the compounds of any other group. In all the reactions described in this chapter, there are but three exceptions where the sulfur atoms do not add directly to one of the ethylene carbons of the maleyl reactant.

Sulfur itself reacts to produce the dicarboxyethylene sulfide in impure form. Alkylthiols, unlike their oxygen analogs, readily unite with the ethylene group of the maleyl group even in the absence of a catalyst, to give a whole series of interesting homologs. Thiol acids, even when they contain an amino group, react as if they were simple mercaptans. The amino group in *o*-aminothiophenol, however, unites with one of the carboxyls of maleic acid to give the heterocyclic 3,4-dihydro-3-oxo-1,4,2*H*-benzothiazine-2-acetic acid.

Thioacetic acid unites with maleic acid to produce the thioester of malic acid with relative ease. This is particularly interesting, since no similar reactions are reported for the oxygen analog, although it is well known that acetic acid is capable of forming esters with olefinic hydrocarbons.

The great ease with which the ethylene bond of maleyl compounds unites with sulfur atoms is most clearly demonstrated in the case of bisulfites. Here sulfonation occurs even from aqueous solution at temperatures ranging about 50°. This reaction is used commercially to produce an important series of wetting agents that are employed in various manufacturing processes.

Sulfur trioxide is unique as a reactant in that it causes a replacement of one of the hydrogens of the ethylene bond of maleic anhydride in giving sulfomaleic acid instead of a derivative of succinic acid, as is the usual case. Sulfinic acids react in the normal fashion.

Thiosulfates split during addition to yield α-sulfo-β-thiosuccinic acids.

Both the amino and the thiol groups of thiourea unite with maleic acid in the same manner as *o*-aminothiophenol, but in this case, union takes place at adjacent carbons to yield 2-imino-4-oxo-5-thiazolidineacetic acid. With thiosemicarbazones, three groups take part in the addition, namely, the imino group, the thio group, and the amino group, to give an azinedioxothiazolideneacetic acid.

The reaction of diacenaphtho[1,2-*b*, 1′,2′-*d*]thiophene with maleic anhydride is an example of a Diels-Alder type synthesis where the hydrogen sulfide is split off during the preparation of an aromatic product. Heterocyclic sulfones lose sulfur dioxide upon adding maleic anhydride in a similar manner.

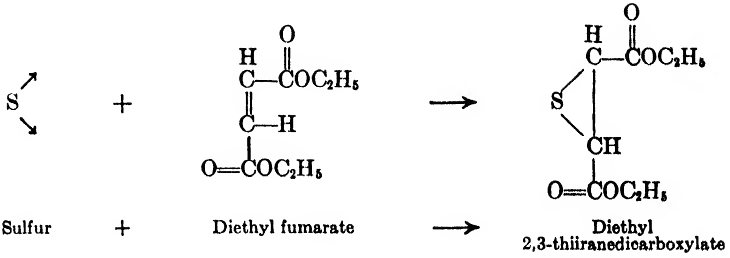
Diethyl 2,3-Thiiranedicarboxylate

(Diethyl Ethylenesulfide-α,β-dicarboxylate)

This preparation is an interesting one as illustrating the readiness with which sulfur and most of its compounds unite with the olefin bond of maleyl compounds. The reaction is worthy of further study. With modern molecular distillation techniques, undoubtedly a much purer compound can be obtained than is given in the procedure on the opposite page.

No properties of 2,3-thiiranedicarboxylic acid or its esters are recorded other than that the diethyl ester is an amber-colored liquid, which cannot be distilled without decomposition even under reduced pressures.

Sulfur



Procedure. A mixture of equivalent amounts of diethyl fumarate and sulfur is heated with good agitation, at 160°, until the fumarate no longer tends to vaporize. The temperature in the flask is raised to 210° and held at this point for 2 hours, after which the temperature is allowed to cool to 180°, and the pressure is reduced to 20 mm. in order to remove any unreacted fumarate. The mixture is cooled to room temperature, and any uncombined sulfur is removed by solution in an equal volume of absolute ether.

Reference

Michael, A., *Ber.* **28**, 1633 (1895).

Dibutyl Amylmercaptosuccinate

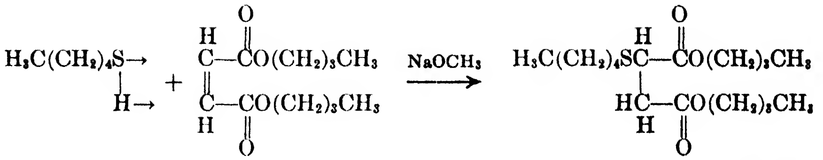
The procedure given on the opposite page is one of several similar methods that have been used for preparing mercaptosuccinic acids, their anhydrides or esters. Variations in procedures include the use of elevated temperatures or a mercury salt in place of the sodium methoxide employed in this preparation. In some cases the presence of oxygen apparently inhibits the reaction, but it tends to accelerate it in the presence of both light and a mercury salt, according to Kaneko. Phenol, hydroquinone, or a copper salt may be added to prevent any polymerization of the product when the reaction is carried out at 70 to 100°. In some cases simply refluxing the mercaptan with sodium maleate in an alkaline solution containing 40% alcohol and a small amount of piperidine will give an excellent yield of the mercaptosuccinic acid.

Dibutyl amylmercaptosuccinate boils at 144 to 145° under a pressure of 1 mm. of mercury. Alkylmercaptosuccinates are readily oxidized by hydrogen peroxide at 18 to 20° to the alkylsulfoxysuccinates, by bromine water to α-bromo-β-alkylsulfonylsuccinates, and by potassium permanganate to alkylsulfonylsuccinates. Reaction with bromine in acetic acid, however, yields the α-bromo-β-alkylmercaptomaleates.

Uses. Mercaptosuccinic acid and its derivatives have been of interest for their marked bacteriostatic action against certain organisms where other drugs are ineffective, and as an antidote for mercury, lead, and arsenic poisoning.

Alkylmercaptosuccinic acid esters, such as bis(tetrahydrofurfuryl) amylmercaptosuccinate, have been shown to be superior to dibutyl phthalate as a plasticizer for butadiene-acrylonitrile rubbers. (*p*-Halophenylmercapto)succinic acid and its derivatives have been used as intermediates for producing pharmaceuticals, pest-control agents, plant-growth regulators, epithelial stimulants, and resins. For example, carboxyhalothiachromanones can be readily obtained from the *p*-halophenylmercaptosuccinic acids by simply heating them with sulfuric acid.

1-Pentanethiol



$$H_3C(CH_2)_4SH + \underset{H}{C}H(CO_2(CH_2)_3CH_3)=\underset{H}{C}(CO_2(CH_2)_3CH_3) \xrightarrow{NaOCH_3} H_3C(CH_2)_4S\overset{H}{C}(CO(CH_2)_3CH_3)-\overset{H}{HC}(CO(CH_2)_3CH_3)$$

1-Pentanethiol + Dibutyl maleate ⟶ Dibutyl amylmercaptosuccinate

Procedure. A methanol solution of sodium methoxide is first prepared from 1.8 g. of sodium. To this solution is added 156 g. of 1-pentanethiol (*amylmercaptan*) and then slowly 376 g. of dibutyl maleate, with constant agitation, care being taken to keep the temperature below 40° during the operation. The reaction mixture is next set aside at room temperature for 2 days, following which it is washed three times with water, dried, and fractionally distilled under reduced pressure. The yield of dibutyl amylmercaptosuccinate obtained in this way is 474 g., or 95% of theory.

References

Dean, R. T., and Hook, E. O., U.S. 2,389,489 (1945). *Cf.*:

Barry, V. C., O'Rourke, L., and Twomey, D., *Proc. Roy. Irish Acad.* **51B**, 223 (1947).

Block, W. D., Buchanan, O. H., and Freyberg, R. H., *J. Pharmacol. Exptl. Therap.* **76**, 355 (1942).

Dawson, M. H., and Hobby, G. L., *J. Pharmacol. Exptl. Therap.* **69**, 359 (1940).

Fieser, L. F., and Turner, R. B., *J. Am. Chem. Soc.* **69**, 2335 (1947).

Fitger, P., *Ber.* **54B**, 2952 (1921).

Freyberg, R. H., *Proc. Staff Meetings Mayo Clinic* **17**, 534 (1942).

Heilman, F. R., *Science* **91**, 366 (1940).

Hornby, H. E., *J. S. African Vet. Med. Assoc.* **12**, 90 (1941).

Kaneko, T., and Mii, S., *J. Chem. Soc. Japan* **59**, 1382 (1938); *C. A.* **33**, 2106¹ (1939).

McNally, P. A., *J. Hyg.* **46**, 60 (1948).

Meidinger, F., *Arch. intern. pharmacodynamie* **76**, 351 (1948).

Otto, G. F., Maren, T. H., and Brown, H. W., *Am. J. Hyg.* **46**, 193 (1947).

Sabin, A. B., *Proc. Staff Meetings Mayo Clinic* **17**, 542 (1942).

Sabin, A. B., and Warren, J., *J. Bact.* **40**, 823 (1940); *Science* **92**, 535 (1940).

U.S. 1,672,615; 2,209,876; 2,370,593; 2,434,100. Fr. 845,793.

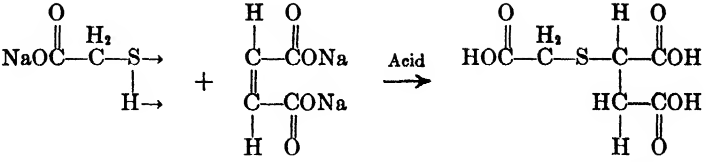
Carboxymethylmercaptosuccinic Acid

Thiol acids react in the same manner as the mercaptans with maleic acid, thereby producing mercaptopolycarboxylic acids. The presence of an amino or amide groups in the thiol acid has little or no effect on the reaction. For example, cystene forms 2-amino-2-carboxyethylmercaptosuccinic acid by uniting with maleic acid in the same manner as thiolacetic acid. More complex aminothiol acids, such as $HO_2CCH(NH_2)CH_2CH_2CONHCH(CH_2SH)—CONHCH_2CO_2H$, react similarly. The procedure is thus a general one for thiol acids.

Carboxymethylmercaptosuccinic acid when recrystallized from water softens at 135° and then melts at 140.5°. The compound is readily soluble in water, methanol, ethanol, and acetone. It is less soluble in cold ether, slightly soluble in ethyl acetate, and in acetic acid, and practically insoluble in chloroform, benzene, toluene, xylenes, and light petroleum.

Use. These acids offer a number of possibilities for various syntheses. The presence of several carboxyl groups in their structure suggests that interesting resins can be prepared from them. The monoesters, such as carbooctyloxymethylmercapto- and carbododecyloxymethylmercaptosuccinates, show surface active properties. Through oxidation, sulfonyl and sulfo groups can be introduced to replace the mercapto group.

Thiolacetic Acid



Sodium thiolacetate + Sodium maleate ⟶ Carboxymethylmercaptosuccinic acid

Procedure. To 400 ml. of an aqueous solution of 12.8 g. of sodium maleate, *p*H of 7.4, is added 200 ml. of an aqueous solution of 8.9 g. of sodium thiolacetate of the same alkalinity. The mixture is then diluted with 400 ml. of water and held at 37° under partial pressure for 22 hours. The reaction product is purified by repeated precipitation with mercuric sulfate and with cadmium sulfate, using hydrogen sulfide to decompose the precipitates. The acid is then allowed to crystallize from a concentrated solution and is recrystallized from water. If a correction is made for the 4.2 g. of unreacted thiolacetate, the yield is practically theoretical.

References

Morgan, E. J., and Friedmann, E., *Biochem. J.* **32,** 733 (1938). *Cf.*:

Larsson, E., *Trans. Chalmers Univ. Technol., Gothenburg* No. **47,** 3 (1945); *C. A.* **40,** 2796[5] (1946).

Mulvaney, J. F., Murphy, J. G., and Evans, R. L., *J. Am. Chem. Soc.* **70,** 2428 (1948).

U.S. 2,449,418.

Mercaptosuccinic Acid Acetate

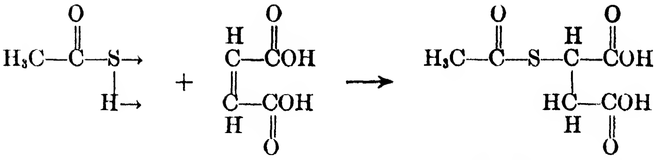
(Acetothiomalic Acid, Thiomalic Acetate)

A further illustration of the ease with which sulfur compounds combine to saturate maleyl compounds by a S—C linkage is shown by this preparation. When fumaric acid is used in place of maleic acid the reaction takes place much more slowly. Maleic anhydride yields mercaptosuccinic anhydride acetate. An analogous reaction with acetic acid has not been reported, although it is well known that this oxygen analog readily adds to many unsaturated compounds to produce acetates.

Mercaptosuccinic acid acetate is a colorless crystalline solid that melts at 125 to 126°. It can readily be converted to the anhydride that melts at 71 to 73°. The anhydride absorbs moisture from the air if allowed to remain exposed to it. Upon saponification, thiomalic acid is obtained. This acid melts at 150 to 151°.

Use. These compounds should have a number of commercial uses. They are of particular interest as possible insecticides and fungicides. They have also been recommended for imparting tack to GR-S types of synthetic rubbers.

Thioacetic Acid



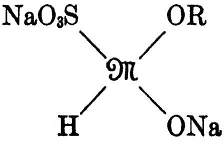
Thioacetic acid + Maleic acid ⟶ Mercaptosuccinic acid acetate

Procedure. A solution containing 23.2 g. of maleic acid, 20 g. of thioacetic, and 80 ml. of ethyl acetate is refluxed for one hour. The reaction mixture is cooled and 400 ml. of benzene is added to it. The addition of benzene causes the product to separate; it is collected and dried in the usual way. The yield is 32 g., or 83% of that required by theory.

References

Holmberg, B., and Schjånberg, E., *Arkiv. Kemi, Mineral Geol.* **14A** (7), 22 pp. (1940). *Cf.*:
Danielli, J. F., Danielli, M., Fraser, J. B., Mitchell, D., Owen, L. N., and Shaw, G., *Biochem. J.* **41**, 325 (1947).
Fraser, J. B., Owen, L. N., and Shaw, G., *Biochem. J.* **41**, 328 (1947).

U.S. 2,449,418.



SULFOSUCCINATES

Disodium Octyl Sulfosuccinate

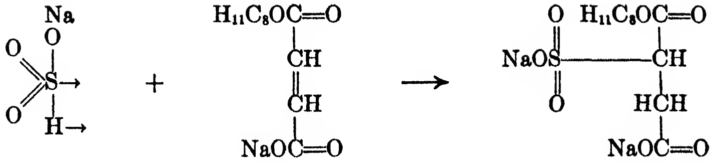
The procedure given is a general one for preparing sulfosuccinic acid and its mono esters. Essentially, it is a reaction between the bisulfite ion and that of the maleate ion. It illustrates further the marked affinity that sulfur-bearing ions and compounds have for maleyl derivatives. When neutral esters are employed, sodium bisulfite must be used as the other reactant.

Sulfosuccinic acid and its derivatives may also be prepared from bromosuccinic acid and bisulfites and by the oxidation of mercapto- and sulfinosuccinic acids or their esters. The yields and simplicity of procedure, however, do not favorably compare with those obtained by the procedure described. Small amounts of sulfosuccinic acid are also obtained when succinic acid is treated with sulfur trioxide.

Disodium octyl sulfosuccinate is a white, amorphous, somewhat sticky product that dissolves very easily in water. Aqueous solutions show marked emulsifying and wetting properties. Sulfosuccinic acid, in contrast, forms hygroscopic crystals containing one mole of water. Upon heating, it decomposes at 60° and darkens badly at 80° without melting.

Use. Compounds of the above type may be employed as wetting agents in textile processes, and as agents for preparing emulsions synthetic rubber latex, polymerizing solutions, and insecticidal sprays. These are but a few of many industrial uses that might be cited.

Sodium Bisulfite



Sodium bisulfite + Sodium octyl acid maleate ⟶ Disodium octyl sulfosuccinate

Procedure. To a solution of 126 g. of sodium sulfite in a liter of water is added 228 g. of octyl acid maleate. The reaction mixture is heated to 50° and gently agitated at this temperature until it yields a clear solution. The solution is neutralized and carefully evaporated to dryness to obtain the succinate as an amorphous solid, or if an aqueous solution is desired, the reaction mixture as such is adjusted to the desired concentration.

References

Jaeger, A. O., U.S. patent 2,028,091 (1936). Brit. patent 446,568 (1936). Fr. patent 776,495 (1935). *Cf.*:

Backer, H. J., and van der Zanden, J. M., *Rec. trav. chim.* **46,** 480 (1927).
Caryl, C. R., *Ind. Eng. Chem.* **33,** 731 (1941).
Caryl, C. R., and Ericks, W. P., *Ind. Eng. Chem.* **31,** 44 (1939).
Climenko, D. R., *J. Contraception* **3,** 149 (1938).
Credner, B., *Bull. soc. chim. France* **13,** 522 (1870).
Damerell, V. R., and Mattson, R., *J. Phys. Chem.* **48,** 134 (1944).
Hägglund, E., and Ringbom, A., *Z. anorg. u. allgem. Chem.* **150,** 231 (1926).
Lorenz, E., Shimkin, M. B., and Stewart, H. L., *J. Natl. Cancer Inst.* **1,** 355 (1940).
Lozinski, E., and Gottlieb, R., *J. Biol. Chem.* **133,** 635 (1940).
Messel, R., *Ann.* **157,** 15 (1871).
Ordal, E. J., and Borg, A. F., *Proc. Soc. Exptl. Biol. Med.* **50,** 332 (1942).

U.S. 2,265,944; 2,325,411; 2,372,829; 2,373,305; 2,373,863; 2,405,737; 2,414,015; 2,415,255; 2,416,254; 2,437,504; 2,441,341. Ger. 694,062; appl. I69833 IV d/120 (USDC-OTS Rept. PBL20545). Fr. 833,282.

$\overset{\text{H}}{\text{HO}_3\text{S}\mathfrak{M}}>\text{O}$

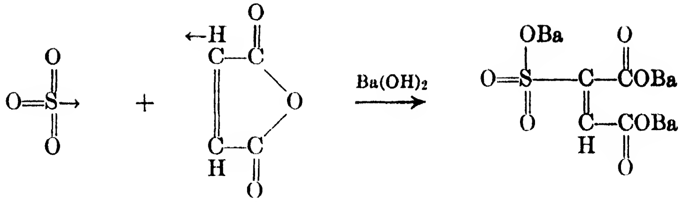
Sulfomaleic Anhydride

Sulfur trioxide, unlike other sulfur compounds, adds to maleic anhydride by displacing one of the hydrogens to give sulfomaleic anhydride, as shown. When maleic acid or fumaric acid is used in place of the anhydride, these acids are first converted to the anhydride by the sulfur trioxide. Neither the sulfomaleic anhydride nor its acids have been isolated as such but only as the salts as given in the preparation. Some conversion of sulfomaleic acid to sulfofumaric acid appears to take place during this preparation.

Alkali salts of sulfomaleic acid are produced in small amounts when those of acetylenedicarboxylic acid are allowed to react with bisulfites. The major product, however, is the salt of disulfosuccinic acid. The disulfosuccinates are also formed when alkali sulfomaleates react with bisulfites. The latter reactions take place more rapidly than the former. This would indicate that in the reactions with acetylenedicarboxylates, the sulfomaleates are converted to the disulfosuccinates almost as rapidly as they are formed.

The barium salt of sulfomaleic acid crystallizes with seven moles of water.

Sulfur Trioxide

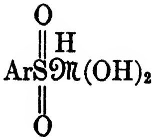


Sulfur trioxide + **Maleic anhydride** ⟶ **Barium sulfomaleate**

Procedure. Forty-nine grams of maleic anhydride is cooled in a bath of ice, and 43.4 g. of sulfur trioxide is carefully distilled into it. The mixture is then slowly warmed to 35° and held at this temperature until it becomes homogeneous. Then it is held at 50° for 5 hours, care being taken not to permit the exothermic reaction to exceed 68° in order to avoid excessive sulfonation. When the reaction is complete, the mixture is cooled, and the red-brown solid mass is dissolved in 200 ml. of water. The aqueous solution is extracted with 25 ml. of ether to remove the 20 g. of the unreacted maleic acid and then treated with barium chloride to eliminate the sulfuric acid. After being filtered the mother liquor is concentrated and carefully neutralized with a cold solution of barium hydroxide. The voluminous precipitate so obtained is collected and washed twice by suspending it in a liter of water. When finally collected, it is dried in air.

Reference

Backer, H. J., and van der Zanden, J. M., *Rec. trav. chim.* **49**, 735 (1930); **50**, 645 (1931)



$$\mathrm{Ar}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{S}}}\overset{\mathrm{H}}{\mathfrak{M}}(\mathrm{OH})_2$$

SULFONYLSUCCINIC ACIDS

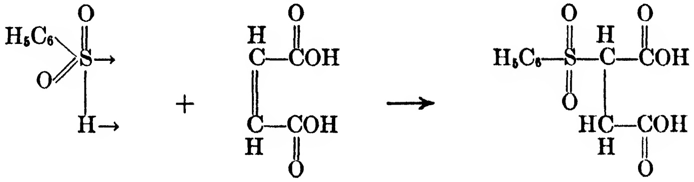
Phenylsulfonylsuccinic Acid

Maleyl compounds add sulfinic acids in the same manner as they do thioacetic acid and bisulfites (*q.v.*). The reaction is a general one. Maleic anhydride, maleic acid, fumaric acid, or their salts may be caused to react with the sulfinic acid in either an aqueous solution or in an organic solvent. Mineral acid is added if the salts are used. The temperature may be varied from 45 to 100°. The sulfonyl compounds that have been prepared in this way include such sulfonylsuccinic acids as the benzyl- , *p*-methylphenyl- , *p*-acetamidophenyl- , 4-methyl-3-nitrophenyl- , 4-methyl-3-aminophenyl- , 4-chloro-3-nitrophenyl- , and benzoxazolone derivatives.

Phenylsulfonylsuccinic acid occurs as crystals that melt at 100° in the water of their own crystallization, becoming solid at 105 to 106° and again melting at 135° to a clear homogeneous liquid. It may be oxidized with permanganate to the sulfonic acid.

Uses. These compounds are used as intermediates in the manufacture of dyes, synthetic tanning agents, and textile assistants.

Benzenesulfinic Acid

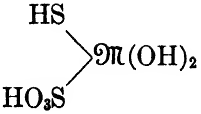


Benzenesulfinic acid + Maleic acid ⟶ Phenylsulfonylsuccinic acid

Procedure. To a solution of 3.6 g. of benzenesulfinic acid in 75 ml. of water is added 2.9 g. of maleic anhydride. This mixture is then held at 45° for 5 days. At the end of this time, it is cooled and diluted with 20 ml. of water. When crystallization is complete, the product is collected upon a filter, sucked dry, and then recrystallized from 25 ml. of water. The yield of crude acid is practically equivalent to the theoretical amount, 5.6 g., whereas 3.3 g. or 60% is obtained of the pure product.

References

Schjånberg, E., *Ber.* 76B, 287 (1943). *Cf.*:
Ger. 676,013 (1939); and *U.S. Dept. Com. OTS Rept.* PBL58768.



$$\begin{matrix} HS \\ HO_3S \end{matrix}\Big\rangle \mathfrak{M}(OH)_2$$

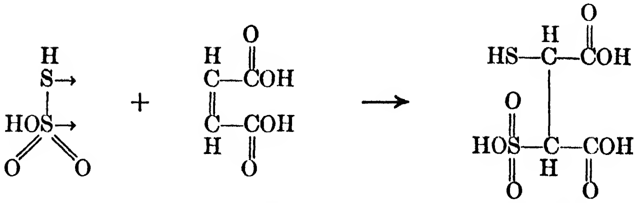
α-Sulfo-β-thiosuccinic Acid

Thiosulfuric acid readily adds to maleic acid to produce α,β-substituted succinates, as shown by the preparation on the opposite page. In this reaction, a cleavage takes place between the sulfur atoms of this acid, enabling them to add to both carbons of the unsaturated ethylene bond of the maleyl compound. The thiosulfuric acid thus behaves as if it were a mixture of free radicals from hydrosulfuric and sulfurous acids.

α-Sulfo-β-thiosuccinic acid is a yellow solid that decomposes at 105°. The ethyl ester is a thick yellow oil with a pear-like odor.

Use. This acid has an interesting structure, and it should offer a number of possibilities for organic syntheses.

Sodium Thiosulfate

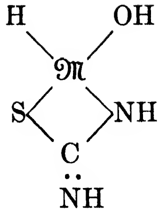


Thiosulfuric acid + Maleic acid ⟶ α-Sulfo-β-thiosuccinic acid

Procedure. An aqueous solution of 158 g. of sodium thiosulfate is added with constant stirring to one containing 116 g. of maleic acid and 98 g. of sulfuric acid. No sulfur is formed under these conditions. When the reaction is complete, the fumaric acid is removed by filtration, and the filtrate is carefully evaporated. The mixture of products is then extracted with alcohol and purified by converting the acids to their ethyl esters, extracting with ether and saponifying with hydrochloric acid. α-Hydroxy-β-sulfosuccinic acid is formed as a by-product.

Reference

Tanatar, S., and Volyanskii, I., *J. Russ. Phys. Chem. Soc.* **44**, 1320 (1913); *C. A.* **7**, 984 (1913).



2-Imino-4-oxo-5-thiazolidineacetic Acid

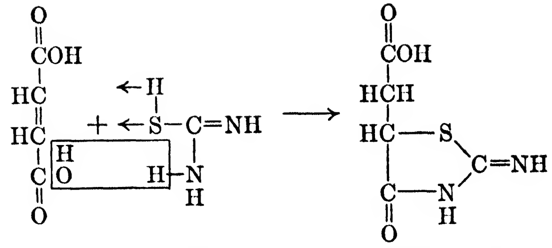
Thioureas, unlike urea (*q.v.*), react in their enol form with both maleic and fumaric acids to produce derivatives of iminothiazolidone, instead of thiohydantoin. Thus thiourea, like other compounds containing sulfur, adds at the sulfur atom. The preferential reaction, like that of the other reactants, is a union of the sulfur atom with one of the carbons of the ethylene group of the maleyl bond. The fact that 2-imino-4-oxo-5-thiazolidineacetic acid has also been prepared from mercaptosuccinic acid and cyanamide, and from thiourea and bromosuccinic acid, leaves no doubt that the pseudothiohydantoin acid is the one formed here. The preparation is a general one, since diaryl derivatives such as 2-phenylimino-3-phenylthiazolidone-5-acetic acid have also been prepared by the same procedure from substituted thioureas.

2-Imino-4-oxo-5-thiazolidineacetic acid, when pure, occurs as fine colorless needles, which decompose without melting at 210 to 212°. When heated rapidly they decompose at 218°. The compound dissolves easily in hot water but is practically insoluble in cold water and in alcohol. With acids, it decomposes to form mercaptosuccinic acid and cyanamide. It gives sulfosuccinic acid and urea when oxidized. Since the compound contains an asymmetric carbon atom, it should be possible to resolve it into two optically active isomers.

Uses. These compounds from their structure should find use as intermediates in the synthesis of pharmaceuticals and fungicides.

$H_2N\overset{\overset{\displaystyle S}{\|}}{C}NH_2$

Thiourea

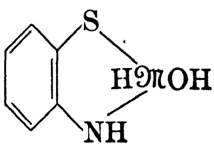


Maleic acid + Thiourea ⟶ 2-Imino-4-oxo-5-thiazolidineacetic acid

Procedure. A powdered mixture of 5 g. of maleic or fumaric acid and 3.3 g. of thiourea, with 3 to 4 ml. of water, is heated in a pressure tube for 2 hours at 105°. When the tube is cooled, fine needles form that readily settle to the bottom of the liquid. These crystals are removed when crystallization is complete, and are then recrystallized from hot water in which the product has limited solubility. Only one recrystallization is necessary to obtain a highly purified product.

Reference

Andreasch, R., *Monatsh.* 18, 56 (1897).



3,4-Dihydro-3-oxo-1,4,2*H*-benzothiazine-2-acetic Acid

(2,3-Dihydro-3-oxo-1,4-benzothiazine-2-acetic Acid)

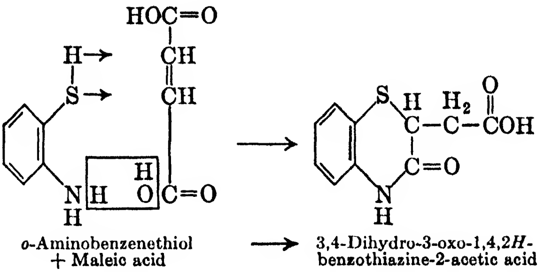
This reaction with *o*-aminobenzenethiol clearly demonstrates how the mercapto group adds preferentially to the C:C bond of maleyl compounds, whereas the amino group generally adds to the carbonyl. Since the yield is practically a theoretical one, there is no addition of the amino group to the ethylene bond in this reaction. This might be expected from what has been seen of the reactivity of these groups in compounds that contain only one of them. The method is convenient for preparing certain heterocyclic acids of this type. Fumaric acid or monobromosuccinic acid may be substituted for maleic acid in this preparation.

3,4-Dihydro-3-oxo-1,4,2*H*-benzothiazine-2-acetic acid occurs as colorless needles that melt at 195 to 196°. The compound is soluble in alcohol, sparingly soluble in ether, and insoluble in benzene, chloroform, and ligroin.

Uses. These acids should be interesting reactants for various syntheses.

o-Aminobenzenethiol

(*o*-Aminothiophenol)

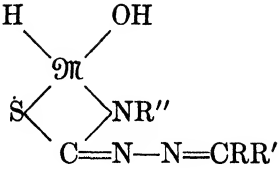


o-Aminobenzenethiol + Maleic acid ⟶ 3,4-Dihydro-3-oxo-1,4,2*H*-benzothiazine-2-acetic acid

Procedure. Three grams of *o*-aminobenzenethiol is mixed with 3.5 g. of maleic acid. Considerable heat is evolved during the mixing, which causes the mixture to set to a hard mass. To insure completion of the reaction, the resulting mass is heated for a few minutes at 100 to 110°, then cooled, broken up, and recrystallized from dilute alcohol. The yield is 5 g., or 93.5% of the theoretical amount.

Reference

Mills, W. H., and Whitworth, J. B., *J. Chem. Soc.* 1927, 2751.



2-Acetoneazine-2,4-dioxo-5-thiazolidineacetic Acid

(2,4-Diketotetrahydrothiazole-2-isopropylidenehydrazone-5-acetic Acid)

Thiosemicarbazones, like thiourea and *o*-aminobenzenethiol (*q.v.*), react with maleic anhydride by the sulfur group attaching itself to the ethylene bond of the maleyl compound and the amino to one of the carbonyls. In this case there is a shift in the double bond of the thiosemicarbazone from the C—S to the C—N linkage. This takes place simultaneously, giving rise to an azine, as shown in the equation on the opposite page.

This preparation is a general one. It has been used in preparing the acetophenone, 3-methylcyclohexone and benzaldehyde analogs, and similar compounds of 3-methyl- and 3-phenylthiocarbazones.

No definite compounds have been isolated from hydrolysis of the products with dilute hydrochloric acid, but with concentrated acid, the acetophenone and acetophenone-3-methyl derivatives yield acetophenone, hydrazine dihydrochloride, and the dioxothiazolidineacetic acid.

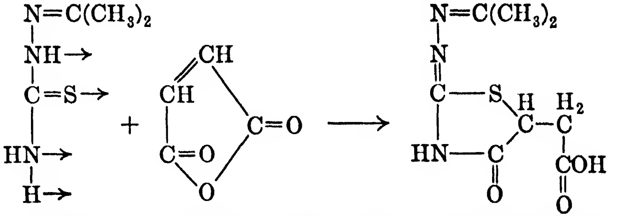
2-Acetoneazine-2,4-dioxo-5-thiazolidineacetic acid melts at 223° when recrystallized from an acetone-light petroleum mixture, from which it is obtained as a microcrystalline powder.

Use. The procedure is a suitable one for preparing derivatives for the identification of thiosemicarbazones.

$\underset{R'}{\underset{|}{RC}}{=}NNH\underset{S}{\underset{\|}{C}}{-}NHR''$

THIOSEMICARBAZONES

Acetonethiosemicarbazone

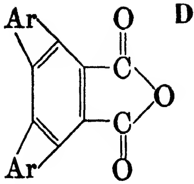


Acetonethiosemicarbazone + Maleic anhydride ⟶ 2-Acetoneazine-2,4-dioxo-5-thiazolidineacetic acid

Procedure. A mixture of 14.5 g. of acetonethiosemicarbazone and 9.8 g. of maleic anhydride is dissolved in a mixture of benzene and acetone, and the solution is refluxed for 15 minutes. The product separates as crystals when the reaction mixture is cooled. These crystals are then collected, washed, and recrystallized from acetone by adding a light petroleum solvent.

Reference

McLean, J., and Wilson, F. J., *J. Chem. Soc.* **1939**, 1048.



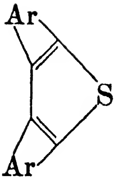
Benzo[1,2-*a*,3,4-*a*′]diacenaphthalenedi-7,8-carboxylic Anhydride

(Diacenaphtho[1,2-*e*,1′,2′-*g*]-7,9-isobenzofurandione
or 3,4,5,6-Di(1,8-naphthalene)phthalic Anhydride)

Thiophene, like benzene, does not undergo a Diels-Alder reaction with maleic anhydride or other dienophiles. The same is probably true for the methyl and dimethyl derivatives, thiotolene and thioxene. Isobenzofuranes add maleic anhydride, but isobenzothiophene and 1,3-diphenylisothiophene do not. However, the highly phenylated 1,3,5,6-tetraphenylisobenzothiophene forms an adduct that dissociates into its constituents at its melting point, and diacenaphtho[1,2-*b*;1′,2′-*d*]-thiophene adds maleic anhydride at elevated temperatures, with a loss of hydrogen sulfide, as shown on the opposite page. Other derivatives containing groups that might activate the conjugated double bond might be expected to behave similarly.

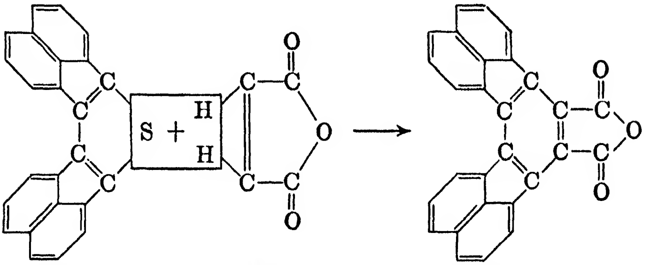
The diacenaphtho[1,2-*b*,1′,2′-*d*]thiophene adduct with the sulfur bridge has not as yet been isolated, nor has it been shown to be present in the mixture of reaction products. A good yield of benzo-[1,2-*a*,3,4-*a*′]diacenaphthalene-7,8-dicarboxylic anhydride is obtained after the treatment with potassium hydroxide. The diacenaphthothiophene adduct may be formed at least as an intermediate during the reaction.

Benzo[1,2-*a*,3,4-*a*′]diacenaphthalene-7,8-dicarboxylic anhydride occurs as yellow needles that do not melt but decompose at about 385°. The compound is practically insoluble in common organic solvents and in aqueous alkalies. It is slightly soluble in alcoholic alkalies.



Diacenaphtho[1,2-*b*,1′,2′-*d*]thiophene

(2,3,4,5-Dinaphthalenethiophene)

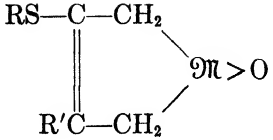


Diacenaphtho-[1,2-*b*,1′,2′-*d*]thiophene + Maleic anhydride ⟶ Benzo[1,2-*a*,3,4-*a*′]diacenaphthalene-7,8-dicarboxylic anhydride

Procedure. Diacenaphtho[1,2-*b*,1′,2′-*d*]thiophene is prepared first from acenaphthalene and sulfur. [See *Ber.* ***36***, 966, 1586 (1903).] Then 0.12 g. of it is thoroughly mixed with 0.4 g. of maleic anhydride, and the mixture is heated for 15 minutes at 225° in a heavy-walled tube. Upon cooling, the reaction mixture is removed and broken up. It is next extracted with hot water and then with 10 cc. of a 5% solution of potassium hydroxide. The product that remains is collected upon a filter, dried, and recrystallized twice from phenyl ether. The yield is 0.08 g., or 60% of the theoretical amount.

References

Clapp, D. B., *J. Am. Chem. Soc.* **61**, 2733 (1939). *Cf.*:
Allen, C. F. H., and Gates, J. W., Jr., *J. Am. Chem. Soc.* **65**, 1283 (1943).
Norton, J. A., *Chem. Revs.* **31**, 319 (1942).



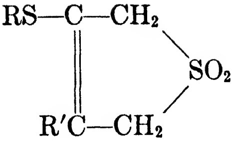
THIOETHERS OF CYCLOHEXENEDICARBOYLIC ANHYDRIDES

4-*tert*-Butylmercapto-5-methyl-4-cyclohexene-1,2-dicarboxylic Anhydride

Heterocyclic sulfones obtained from butadienes readily lose sulfur dioxide when allowed to react with maleic anhydride. Substituted cyclohexenedicarboxylic anhydrides may thus be prepared in this manner. The procedure given is apparently a very general one. It has been used for the synthesis of several alkylmercaptomethylcyclohexenedicarboxylic anhydrides. It is likely that the substituted butadienes are formed as an intermediate during the reactions, since the reactions can be carried out in two steps: by (1) heating the sulfone to produce the butadiene thioether and (2) then allowing the latter compound to react with maleic anhydride. The products obtained by the two procedures are identical.

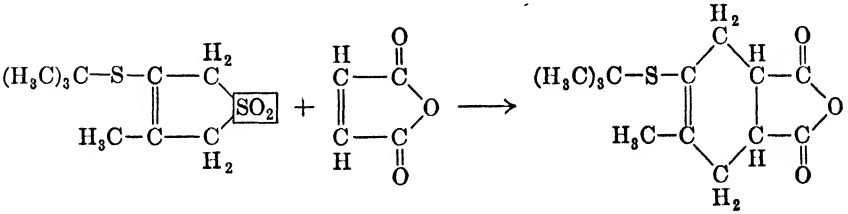
4-*tert*-Butylmercapto-5-methyl-4-cyclohexene-1,2-dicarboxylic anhydride melts at 128.5 to 129.5°.

Uses. These compounds offer interesting possibilities for chemical synthesis.



HETEROCYCLIC SULFONES

3-*tert*-Butylmercapto-2,5-dihydro-4-methylthiophene 1-Dioxide



3-*tert*-Butylmercapto-2,5-dihydro-4-methylthiophene 1-dioxide + Maleic anhydride ⟶ 4-*tert*-Butylmercapto-5-methyl-4-cyclohexene-1,2-dicarboxylic anhydride

Procedure. A mixture of 22.0 g. of 3-*tert*-butylmercapto-2,5-dihydro-4-methylthiophene 1-dioxide and 9.8 g. of maleic anhydride is heated in a hood at 160 to 165° for half an hour. During this time sulfur dioxide is evolved. The reaction mixture is cooled and dissolved in benzene. From this solution the product is obtained as colorless crystals.

The sulfone used in this preparation may be synthesized from 2-chloro-3-methyl-1,3-butadiene, as described in the following reference.

Reference

Backer, H. J., and Blass, T. A. H., *Rec. trav. chim.* 61, 785 (1942).

CHAPTER 8

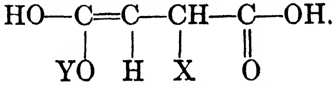
Energy and Catalysts

Both light and heat may have two different types of effect upon maleyl compounds. The first is decarboxylation, such as occurs when a dilute solution of maleic acid is exposed to ultraviolet light, or when its aromatic esters are heated at their boiling points. The other effect is the isomerization of the *cis*-acid and its esters to their *trans*-forms, such as occurs when maleic acid is heated in an inert atmosphere at 145 to 260° for half an hour, or when the solid acid or its solutions are exposed to strong sunlight.

Numerous types of substances can act as catalysts to cause isomerization to occur at various temperatures. These substances vary widely in their effectiveness. Such catalysts include a variety of sulfur compounds, as, for example, thiourea, thiazoles, thiazolines, thiuram disulfide, dithiocarbamates, mercaptans, alkyl disulfides, salts of thio acids, thiosulfates, thiocyanates, sulfur, and mixtures of sulfur dioxide and hydrogen sulfide. Other catalysts include the acids: nitric, sulfuric, perchloric, hydrochloric, hydrobromic, and hydroiodic; the heavy metal salts of lead, copper, and silver; bromine; and aqueous suspensions of platinum black. Finely dispersed sulfur catalyzes the transformation only at elevated temperatures. No isomerization with sulfur takes place at ordinary temperatures. For example, no fumaric acid is formed when sulfur is produced by decomposing thiosulfate solutions by mineral acids in the presence of maleates.

Various amines can also cause this *cis-trans* conversion. Such substances include ammonia, pyridine, and primary and secondary amines.

When maleic acid is heated with water in the preparation of malic acid, fumaric acid is also formed. An equilibrium mixture of the three acids exists for each set of conditions. It is believed that the direct isomerization of maleic acid to fumaric acid is an irreversible reaction. Equilibrium in the case of the three acids is assumed to result, therefore, from the independent reversible reactions of maleic and fumaric acids with water to form malic acid.

There is no indication that deuterium is added to the ethylene bond of maleic acid when deuterium chloride is employed as the catalyst in this isomerization. Since the rate of the catalyzed reaction is a function of the concentration of the catalyst, some investigators have postulated that the catalyst XY may add to the maleyl bond of the maleic acid in the 1,4-positions during the reaction to form compounds of the general type  $\mathrm{HO{-}\underset{\underset{YO}{|}}{C}{=}\underset{\underset{H}{|}}{C}{-}\underset{\underset{X}{|}}{CH}{-}\underset{\underset{O}{\|}}{C}{-}OH}$. Molecules of such addition products having a single bond between the carbons in the 3- and 4-positions would thus be free to rotate about this position to form the *trans*-isomers when splitting off the catalyst.

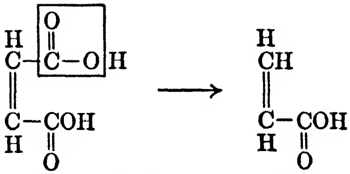
Acrylic Acid

Acrylic acid may be prepared by the decarboxylation of maleic or fumaric acid. The method shown on the opposite page is of interest in showing how the decarboxylation can be induced by the action of actinic rays upon solutions of maleic acid. Acrylic acid may also be prepared from maleic anhydride by vaporizing the anhydride in an atmosphere of nitrogen that is saturated with water and passing the mixture over activated silica gel heated to 400°.

Acrylic acid is a colorless liquid that freezes at 12.3° and boils at 141.9°. It is soluble in water and alcohol.

Use. Acrylic acid is used in the manufacture of synthetic rubbers and plastics, and in the synthesis of vitamin B and other materials.

Light



Maleic acid + Light ⟶ Acrylic acid

Procedure. A 0.0066 M solution of maleic acid is exposed for 15 minutes to the radiation of a mercury vapor-quartz, Westinghouse lamp (110 volts, 3.5 amp.). Under these conditions a gas is evolved that is exclusively carbon dioxide. That the resulting solution contains acrylic acid is demonstrated by preparing the acid chloride from it in the usual manner.

References

Volmar, *Compt. rend.* **181,** 468 (1925). *Cf.*:

Ogata, Y., Tsunemitsu, K., and Oda, R., *Bull. Inst. Phys. Chem. Research* (*Tokyo*), *Chem. Ed.* **23,** 281 (1944); *C. A.* **42,** 6746h.

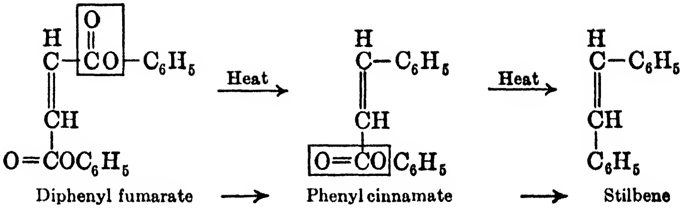
Stilbene

Aromatic esters of fumaric acid when heated at their boiling points lose first one and then a second molecule of carbon dioxide, as shown in the equation on the opposite page. The procedure is a general one. It has also been used to prepare such substituted stilbenes as the *p,p′*-dichlorostilbene, *p,p′*-dinitrostilbene, and the *o,o′*-dimethylstilbene. It is equally applicable to the intermediate products, the aromatic esters of cinnamic acid.

Pure stilbene fuses at 124°. With bromine, it reacts to yield α,α'-dibromobibenzyl, which melts at 235°.

Use. Stilbene derivatives are of interest as intermediates in the preparation of dyes.

Heat



Procedure. Ten grams of diphenyl fumarate are heated in an inert gas for 25 hours at 290 to 300°, during which time carbon dioxide is evolved. When the reaction is complete, the mixture is cooled and then fractionally distilled under approximately 11 mm. pressure. A small amount of phenol distills over when the temperature reaches 86 to 90°, and then the crude stilbene is obtained. The latter is recrystallized from alcohol to obtain a pure product.

Some phenyl cinnamate may be recovered during the distillation if the reaction is stopped when only half the carbon dioxide has been evolved. Even under these circumstances, stilbene is the major product. Considerable amounts of a resinous residue is left in both cases.

References

Anschütz, R., *Ber.* **60B**, 1320 (1927); and Skraup, S., and Beng, E., *Ber.* **60B**, 942 (1927). *Cf.*:

Anschütz, R., *J. Chem. Soc.* **47**, 898 (1885); *Ber.* **18**, 1945 (1885).

Anschütz, R., and Wirtz, Q., *J. Chem. Soc.* **47**, 899 (1885)

Funaro, A., *Gazz. chim. ital.* **11**, 274 (1881).

Ogata, Y., Tsunemitsu, K., Kawamura, A., and Oda, R., *Bull. Inst. Phys. Chem. Research (Tokyo), Chem. Ed.* **24**, 11 (1947); *C. A.* **42**, 6753c (1948).

Fumaric Acid

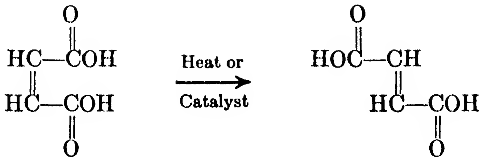
This method can be used equally well with the esters of maleic acid to obtain as high as 98% conversion to the fumarates. Quantitative yields of pure fumaric acid are also obtained by simply heating maleic acid, as described in the introduction to this chapter.

Fumaric acid occurs as monoclinic prisms that melt at 287°. This acid is almost insoluble in cold water, but it is quite soluble in boiling water, having a solubility of 0.7 g. and 9.8 g. per 100 cc., respectively, at 25° and 100°. It is soluble in ethyl alcohol but relatively insoluble in diethyl ether.

Maleic acid melts at 130.5°. It is very soluble in both hot and cold water and in alcohol, and quite soluble even in ether. It also occurs as monoclinic prisms.

Uses. Fumaric acid is a suitable starting material for most of the reactions described in this book. Uses for the reaction products have already been mentioned. Fumaric acid has become an important product technically. By far the greatest amount of material is used in the preparation of esters, resins, and plastics. Among the interesting but less important uses that might be mentioned is its use in producing birefringent optical films, the use of certain of its salts as cathartics, in treating chronic alcohol intoxication, in chrome tanning, wool printing, silk dyeing, and cotton print discharging.

Isomerization



$\text{Maleic acid} \xrightarrow{\text{heat or catalyst}} \text{Fumaric acid}$

Procedure. One hundred grams of maleic anhydride is added to a solution of 2.5 g. of 2-mercapto-4-methylthiazole in 85 ml. of water. The solution is then heated to boiling and stirred constantly at this temperature for 2½ hours. The 90 g. of fumaric acid that separates upon cooling is removed, and the filtrate is heated for an additional 4 hours. Most of the water is then distilled off, yielding an additional 22 g. of fumaric acid to give a total yield of 95% of theory.

References

Scott, W., U.S. 2,414,066 (1947). *Cf.*:

- Carpenter, J. H., *J. Ind. Eng. Chem.* **13**, 410 (1921).
- Ciamician, G., and Silber, P., *Ber.* **36**, 4267 (1903).
- Clemo, G. R., and Graham, S. B., *J. Chem. Soc.* **1930**, 213.
- Green, S. R., Iverson, W. P., and Waksman, S. A., *Proc. Soc. Exptl. Biol. Med.* **67**, 285 (1948).
- Gregory, T. C., *Uses and Applications of Chemicals and Related Materials*, Reinhold Publishing Corp., N. Y., 2 vols. (1939–1944).
- Horrex, C., *Trans. Faraday Soc.* **33**, 570 (1937).
- Mayo, F. R., and Walling, C., *Chem. Revs.* **27**, 403 (1940).
- Möllerström, J., *Archiv. Kemi, Mineral Geol.* **19A**, No. 10, 26 pp. (1945).
- Neogi, P., and Mondal, K. L., *J. Indian Chem. Soc.* **16**, 239 (1939).
- Nozaki, K., *J. Am. Chem. Soc.* **63**, 2681 (1941).
- Nozaki, K., and Ogg, R., Jr., *J. Am. Chem. Soc.* **63**, 2583 (1941).
- Pelouze, J., *Ann.* **11**, 266 (1834).
- Petri, C., *Ann.* **195**, 61 (1879).
- Schmidt, J., *Ber.* **33**, 3242 (1900).
- Smyth, J., Brundage, R., Orten, J. M., and Smith A. H., *Proc. Soc. Exptl. Biol. Med.* **60**, 301 (1945).
- Tanatar, S., *Ber.* **27**, 1367 (1894); *Ann.* **273**, 33 (1893); *J. Russ. Phys. Chem. Soc.* **43**, 1742 (1911); **44**, 1320 (1912).
- Terry, E. M., and Eichelberger, L., *J. Am. Chem. Soc.* **47**, 1402 (1925).
- Wislicenus, J., *Ber.* **29**, 1080 (1896).

U.S. 2,208,519; 2,363,108; 2,371,143; 2,393,352; 2,404,103; 2,422,411; 2,441,238; 2,447,831; 2,470,505; 2,548,687. Brit. 563,019.

INDEX