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PATENT SPECIFICATION

741,446

Date of Application and filing Complete Specification: June 23, 1953.

No. 17355/53.

Application made in United States of America on July 22, 1952.

Complete Specification Published: Dec. 7, 1955.

index at acceptance:—**Classes 2(3),** C1E5K(3:8), C2B3(A3:F:G8), C2B30, C2B37(G2:M), C3A13B6, C3A13C(1B:3B:9:10H); **and 2(5),** P7D2B, P7P1(A:B:C), P7P5.

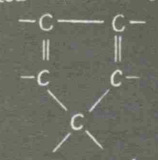
COMPLETE SPECIFICATION

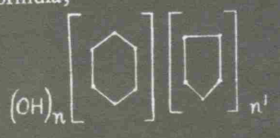
Improvements in or relating to Cyclopentenyl Phenols

We, PITTSBURGH PLATE GLASS COMPANY, a corporation organized under the Laws of the State of Pennsylvania, of One Gateway Center, Pittsburgh, Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the reaction of cyclopentadiene, substituted cyclopentadienes, or homopolymers of such cyclopentadienes with phenols, whereby substituted phenolic compounds or polymeric products or both are obtained, and pertains particularly to the preparation of cyclopentenylphenols, which are very useful for many purposes.

In accordance with the provisions of the present invention, phenols containing at least one available hydrogen atom in the nucleus are contacted with compounds containing the group in the presence of a Friedel-Crafts catalyst whereupon chemical reaction occurs to form compounds of the general formula;





In the formula, n and n' are whole numbers, usually from 1 to 3 and may be equal or unequal. In addition to compounds of the above type, some polyphenols or polymeric products, or both, are generally formed, the quantities of each product depending primarily on the particular reaction conditions which are employed.

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The present invention is particularly applicable to compounds containing a single —OH group, e.g., phenol. However, the invention also includes the treatment of other hydroxylated benzenes or phenols including two or even three hydroxyls. They may also contain one or more alkoxy, hydrocarbon, or other substituent groups as side-chains. There must be at least one free or available hydrogen atom in the benzene ring in order that reaction with the cyclopentadiene may take place. Examples of such phenols containing a plurality of hydroxyls directly attached to a benzene ring are polyhydroxy phenols such as catechol, resorcinol, pyrogallol and phloroglucinol;

alkylated phenols such as ortho cresol, meta cresol, para cresol, butyl resorcinol, and tertiary butyl cathechol;

substituted phenols such as ortho, meta or para nitrophenols and the corresponding amines derived by reduction of the nitrophenols, ortho, meta and parahalophenols, polyhalophenols, halogen substituted nitrophenols, guaiacol, 2,3-dimethoxyphenol and 3,5-dimethoxyphenol.

Any of the phenolic compounds or derivatives thereof, as well as other phenolic compounds, reacts with cyclopentadiene or its homologues and substitution products to give substituted phenols and polymeric products.

While they do not contain conjugated double bonds, dicyclopentadiene, tricyclopentadiene and other homopolymers of cyclopentadiene may under appropriate conditions also be employed in the reaction, since they can be decomposed pyrolytically at 140° C. or above, to form cyclopentadiene which reacts *in situ* with phenolic compounds such as are described above.

Cyclopentadiene, or its equivalent of a lower homopolymer of cyclopentadiene, may be reacted with a phenolic compound over a wide range of molar proportions in accordance with the provisions of the present invention.

For example, the proportion of the phenol and cyclopentadiene may be equi-molar or approximately equi-molar. However, most usually an excess of phenol is employed, since highest yields of the mono cyclopentenyl phenolic compounds are obtained when excess phenol is utilized. If high yields are not essential, almost any proportions may be employed in the reaction. For example, the cyclopentadiene component may be employed in a molar percentage of 10 to 100 or even 200 or 300 or more per cent. with respect to the phenolic component in the mixture.

The reaction of the present invention may be carried out in the absence of diluent or solvents. However in many instances it is preferred to include such material in the reaction mixture. The diluent or solvent naturally should be non-reactive in the mixture. Examples of such diluents include hexane, heptane, toluene, xylene and other aromatic and non-aromatic hydrocarbons and similar non-reactive materials.

The temperature at which the reaction is carried out may be varied widely. For example, the reaction proceeds satisfactorily at temperatures as low as −20° C. or even lower and as high as 200° C. or higher with the preferred range being from about 0° C. to 150° C.

The reaction takes place readily at atmospheric pressure and is advantageously carried out in this manner. However, any added pressure may also be utilized if desired, as may subatmospheric pressures, provided they are not so low as unduly to volatilize the reactants.

The reaction of cyclopentadienes with phenolic compounds in accordance with the present invention is carried out in the presence of a Friedel-Crafts type catalyst. Examples of such catalysts include aluminum chloride, ferric chloride, antimony pentachloride, boron trifluoride, zinc chloride, titanium chloride, hydrofluoric acid, sulfuric acid, phosphoric acid, phosphorus pentoxide, stannic chloride, bismuth chloride and tellurium di and tetra chlorides. The Friedel-Crafts catalysts are discussed in detail in Volume 3 of Organic reactions (1946), pages 2 to 4.

The reaction can also be carried out in the presence of mixtures of two or more of the catalysts disclosed hereinabove. In fact, by selection of the proper catalyst mixture it is often possible to control the number of cyclopentenyl or phenolic groups which are combined. Most Friedel-Crafts catalysts can be placed in one of two series; that of acids, including hydrofluoric acid, sulfuric acid, phosphoric acid, in order of activity, and that of the Lewis acid salts, including aluminum chloride, boron trifluoride, antimony pentachloride, ferric chloride, tellurium dichloride, stannic chloride, titanium chloride, tellurium tetrachloride, bismuth chloride and zinc chloride, also in order of activity. "Lewis acid salts" are discussed on pages 326 to 328 of "Inorganic Chemistry" by Moeller, published by John Wiley and Sons, Inc. (1952). The more active catalysts of these two series are in general too strong to give good yields of monocycloalkenylphenols but yield instead higher molecular weight phenols and other materials. However, the more active catalysts can be "diluted" with one of the less active catalysts or with a diluent to produce a catalyst mixture that will give satisfactory yields of the desired product. Mixtures of sulfuric acid and phosphoric acid, or boron trifluoride and phosphoric acid are examples of catalyst mixtures which give excellent yields of monocycloalkenylphenols. The strong Lewis acid salts are best "diluted" by forming their complexes with compounds such as ethers, alcohols and amines, that is, compounds containing atoms with unshared electron pairs which can form coordinate bonds with the Lewis acid salts. For example, the aluminum chloride-ethanol complex and the boron trifluoride-ether complex are both less active than either aluminum chloride or boron trifluoride alone.

85 per cent. phosphoric acid, and Friedel-Crafts catalysts of similar strength form a particularly preferred class of catalysts for use in the process of this invention since they are economically obtained and result in the formation of excellent yields of monocycloalkenylphenols.

As will be apparent from the following discussion, the amount of catalyst employed and also the reaction temperature have a substantial effect on the yields of each of the reaction products.

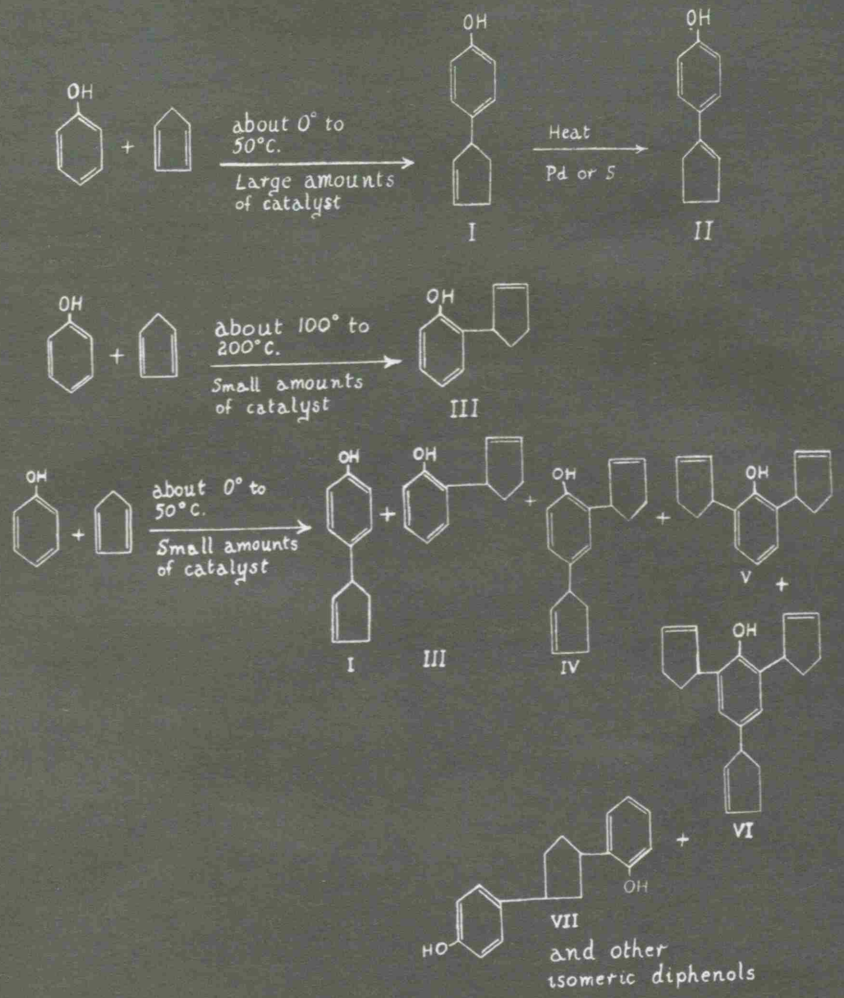
For example, by proper regulation of the conditions of reaction, it is possible to obtain ortho or paracyclopentenylphenol, di or tricyclopentenylphenols, polyphenols or polymeric products substantially at will.

These facts are illustrated in the preparation of orthocyclopentenylphenol which is readily obtained by heating a mixture of phenyl and cyclopentadiene to a temperature of about 100° C. to 200° C. in the presence of only a small amount of catalyst, that is, below about five per cent. by weight based on the weight of the phenol. On the other hand, if the reaction is conducted at a low temperature, for example about 0° C. to 50° C. and in the presence of a considerable proportion of catalyst, for example, about 5 to 100 per cent. or more based on the weight of the phenol, paracyclopentenylphenol is obtained in high yield.

If the reaction between phenol and cyclopentadiene is conducted at a low temperature, for example, as defined above, and in the presence of only a small amount of catalyst, as also defined hereinabove, the formation of di and tricyclopentenylphenols is favored.

If the reaction between phenol and cyclopentadiene is conducted at high temperatures above 200° C. and in the presence of at least ½ per cent. of catalyst, a hard, dark, resinous polymer which is extremely acid and alkali-resistant is obtained. The exact structure of the polymer is not known although it is quite likely that it contains recurring phenol and cyclopentane units in the chain.

The several reactions and the nature of the products formed will be apparent from the following reaction equations:



While the above discussion and reaction equations are directed to methods of carrying out the reaction whereby predominant amounts of one particular product are obtained, it is to be understood that a mixture of the various products, including some polyphenol and polymer are obtained regardless of the manner in which the reaction is carried out. It is also to be understood that the reaction of phenol and cyclopentadiene is used for illustrative purposes only and that the reaction proceeds satisfactorily when any of the phenols of the type described hereinabove are brought into contact with substituted cyclopentadienes in the presence of a Friedel-Crafts type catalyst.

It is apparent from the foregoing reaction equations that paracyclopentenylphenol (compound I) undergoes isomerization in the presence of palladium or sulfur or other isomerization catalyst to give paracyclopentenylphenol in which the double bond is in conjugate relation with respect to a double bond in the phenolic ring. Other cycloalkenylphenols prepared according to the method of the present invention also undergo isomerization in a similar manner. Moreover, the cycloalkenylphenols may also be hydrogenated in the presence of a catalyst such as nickel or platinum to give cycloalkylphenols which are also very useful compounds.

If cyclopentadiene is replaced by dicyclopentadiene or other homopolymer of cyclopentadiene and the resultant mixture of homopolymer and phenol is refluxed in the presence of a Friedel-Crafts catalyst at a temperature of about 150° C. to 180° C. or higher, a decomposition of the homopolymer occurs to form cyclopentadiene which reacts with the phenol to give a cyclopentenylphenol; at temperatures below 100° C. the homopolymer does not decompose and the quantity of cycloalkenylphenol formed, if any, is for all practical purposes negligible.

It will be seen from the following examples, which are intended to illustrate more fully the process of the invention, that the reaction of a phenol with a cyclopentadiene proceeds readily whenever the reactants are brought into effective contact with one another in the presence of a Friedel-Crafts type catalyst. The examples are not intended to limit the scope of the invention, for there are, of course, numerous possible variations and modifications.

EXAMPLE I.

In this example phenol and cyclopentadiene are reacted at low temperatures and in the presence of large amounts of catalysts to form a mixture of cyclopentenyl phenols consisting largely of I, with small quantities of III, IV, V and VI. In the reaction, 940 grams of phenol are mixed with 1000 cc of toluene and 297 grams of 85 per cent. phosphoric acid. To this mixture at a temperature maintained initially at 25° C. is added 340 grams of cyclopentadiene dissolved in 500 cc of toluene, the addition being effected with continuous stirring of the mixture over a period of two hours. Under these conditions, the reaction temperature rises to 40° C. and the reaction mixture is cooled and stirred for an additional 18 hours. At the end of that time, 180 grams of anhydrous sodium carbonate is added to neutralise the phosphoric acid. The salt is then filtered off and washed with toluene and the resultant filtrate containing the desired product is stripped under a sub-atmospheric pressure of 10 millimeters (absolute) in order to remove unreacted material such as cyclopentadiene, dicyclopentadiene, solvent and unreacted phenol.

When the reaction is carried out on a small scale it is convenient to neutralize the catalyst with some mild base such as sodium carbonate. However in large scale operations, it may be more economical to remove the acid catalyst by a water-washing process.

After removal of all of the unreacted phenol, there remains 691 grams of a product which is fractionated under a sub-atmospheric pressure of 1.2 millimeters (absolute) to yield 470 grams of paracyclopentenylphenol, and 110 grams of a mixture of dicyclopentenylphenol, and tricyclopentenylphenols. The paracyclopentenylphenol, when redistilled, constitutes a crystalline white solid melting within a range of 62° to 63° C. and boiling at 114° to 117° C. under a pressure of 1.5 millimeters of mercury. Its absorption spectrum in the ultra-violet range shows two maxima, one at 225 mu of log ϵ3.9 and the other at 279 mu of log ϵ3.30, wherein the symbol ϵ signifies the molecular extinction coefficient. The maxima at these wave lenthgs show that the double bond in the cyclopentene ring is not conjugated with respect to the benzene ring. The product is characterized by forming a crystalline para nitrophenylurethan derivative melting at 173° C. and which depresses the melting point of the para nitrophenylurethan of orthocyclopentenylphenol.

EXAMPLE II.

In this example, low temperatures of reaction and small amounts of catalyst are employed. In carrying out the reaction, a mixture of 940 grams of phenol, 250 millilitres of toluene and 6 grams of 85% phosphoric acid is formed and while the mixture is under agitation at a temperature of 30° C., 165 grams of cold (liquid) cyclopentadiene are added over a period of three hours. The reaction mixture is stirred at room temperature for 18 hours, and at the end of that time the catalyst is neutralized with 8 grams of anhydrous sodium carbonate. Any unreacted starting materials are eliminated by vacuum distillation in the same manner as in Example I. The product (230) grams is then split into three fractions by vacuum distillation. The first fraction is taken within the boiling range of 100° to 135° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes 75 grams and is a mixture of ortho and paracyclopentenylphenol. The second fraction is taken within a boiling range of 135 to 200° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes a yield of 80 grams. Redistillation of this fraction yields dicyclopentenylphenol B.P. 140°—145° C./0.5 mm. n_D^{25} 1.579. There remains in the distillation flask a residue (67 grams) consisting largely of tricyclopentenylphenol and other high molecular weight phenols.

EXAMPLE III.

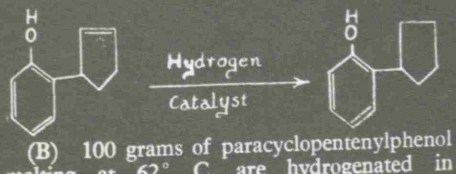
This example illustrates the use of relatively high temperatures of reaction and small amounts of catalyst in the formation of a reaction product by the interaction of phenol and dicyclopentadiene. In the reaction, a mixture of 2243 grams of phenol, 660 grams of dicyclopentadiene, and 5 grams of syrupy phosphoric acid, are admixed in a flask provided with a reflux condenser, a thermometer and a source of inert gas (carbon dioxide or nitrogen or the like). The mixture is refluxed for 22 hours during which time the temperature varies between 150° and 170° C. These temperatures are at or near the cracking point of dicyclopentadiene.

At the conclusion of the reflux period, the unreacted phenol and dicyclopentadiene are removed by vacuum distillation. There remains 1,132 grams of a reaction product which is washed with water and distilled at a pressure of 0.5 millimeters of mercury (absolute) to yield 895 grams of a light yellow oil. This oil is then agitated with a 10 per cent. (by weight) solution of aqueous potassium hydroxide in water.

The alkali soluble fraction constituting 330 grams consists of a mixture of phenols, which mixture is largely orthocyclopentenylphenol, and also contains some di and tricyclopentenylphenols, cyclopentanediphenols and polyphenols. The orthocyclopentenylphenol can be purified in any convenient manner, for example, by vacuum distillation, to provide a water white oil. This oil boils at 81° C. under a pressure of 0.4 millimeters of mercury (absolute); n_D^{25} 1.565; d_{25}^{25} 1.0755. Two maxima are indicated in the ultra-violet spectrum, one being of log ϵ3.8 at 220 mu and the other being of log ϵ3.4 at 275 mu. These maxima show that the double bond in the cyclopentene ring is not conjugated with respect to a double bond in the benzene ring. The product forms a crystalline para nitrophenylurethan derivative melting at 165° C. The urethan derivative is of the formula $C_{18}H_{16}O_4N_2$ and it depresses the melting point of the corresponding derivative of the para isomer by 30° C. The diphenols formed are substantially colorless materials which boil in the range of 160° to 220° C./0.5 mm., the elementary analyses and molecular weight of which is in accord with the formula $C_{17}H_{18}O_2$.

REDUCTION OF CYCLOPENTENYLPHENOL.

(A) In this process, 46 grams of orthocyclopentenylphenol are dissolved in 200 millilitres of methanol in an autoclave and are hydrogenated at 100° C. over a period of 4 hours, 3 grams of Raney nickel being employed as a catalyst. A yield of 46 grams of orthocyclopentylphenol melting at 26° to 30° C. is obtained. This product can be crystallized from aqueous methanol to form fine white needles with a melting point of 40° C. The reaction is represented by the equation:

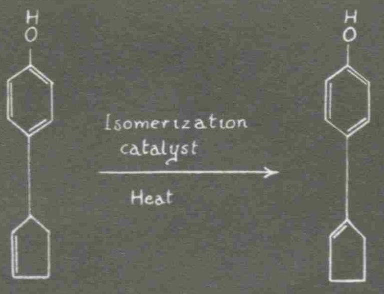


(B) 100 grams of paracyclopentenylphenol melting at 62° C. are hydrogenated in methanol solution with an Adams platinum oxide catalyst to yield 100 grams of para-cyclopentylphenol melting at 69° C.

This phenol forms a crystalline para nitrophenylurethan melting at 198—199° C.

ISOMERISATION OF *p*-CYCLOPENTENYL-PHENOL.

(C) This process illustrates the isomerization, or rearrangement of the double bond in the cyclopentenyl radical of paracyclopentenylphenol (compound I, M.P. 62° C.) to effect conjugation between the double bond of the cyclopentenyl radical and one of the double bonds of the benzene ring. The reaction proceeds in accordance with the following equation:



I II

50 grams of compound (I) are admixed with 1 gram of 5 per cent. palladium on charcoal in a flask equipped with a condenser, and the mixture is heated until compound (II) distills off and is collected by condensation. The conjugated isomer can be crystallized from solution in ethanol in the form of shiny platelets melting at 149° C. The product forms a monoacetate melting at 73° C.

By application of the principles as illustrated in the preceding examples, numerous cycloalkenyl derivatives of phenol or phenols can readily be prepared. Some of the compounds so prepared include the following:

2-(Δ 2 cyclopentenyl) phenol
2-(Δ 1 cyclopentenyl) phenol
4-(Δ 2 cyclopentenyl) phenol
4-(Δ 1 cyclopentenyl) phenol
2,4-di(Δ 2 cyclopentenyl) phenol
2,4-di(Δ 1 cyclopentenyl) phenol
2,6-di(Δ 1 cyclopentenyl) phenol
2,6-di(Δ 1 cyclopentenyl) phenol
2,4,6-tri(Δ 2 cyclopentenyl) phenol
2,4,6-tri(Δ 1 cyclopentenyl) phenol

Generally, the double bond of the cyclopentenyl group can be selectively hydrogenated in the manner illustrated in Example IV for the hydrogenation of orthocyclopentenylphenol to form orthocyclopentylphenol. They can also be subjected to rearrangement of the double bond of the cyclopentenyl group in the manner illustrated in Example VI.

The foregoing examples have been more particularly directed to the preparation of cyclopentenyl substituted monohydric phenols. It will be obvious from the preceding discussions however that phenol may be replaced in the reaction by various polyhydroxy phenols as well as alkyl or alkoxy derivatives of phenol or of alkyl or alkoxy derivatives of polyhydroxy phenols. Moreover, nitro- or chloro- substituted mono or polyphenols may also be substituted for phenol in the reaction.

EXAMPLE IV.

Example I is repeated except that para cresol is substituted for the phenol. 2-cyclopentenyl-*p*-cresol, an oil with a pleasant, earthy odor, B.P. 105°—108° C. 1.3 mm., n_D^{25} 1.5595; d_{25}^{25} 1.0570, is obtained.

EXAMPLE V.

Example I is repeated substituting 350 grams of guaiacol for the phenol. Cyclopentenyl substituted guaiacol is obtained.

It is also within the scope of the invention to bubble vaporous cyclopentadiene into liquid phenol containing the Friedel-Crafts catalyst until a substantial amount of the phenol has reacted. The cyclopentadiene vapors may be above 140° C. in order to reduce homopolymerization. The phenol may be at any desired temperature, for example, in the range of −20° C. to 200° C.

EXAMPLE VI.

A mixture of 188 grams of phenol, 264 grams of dicyclopentadiene and 50 grams of phosphoric acid is refluxed for 4 hours. The resulting product is a hard, dark, acid and alkali-resistant polymeric material useful as a coating and molding resin. The reflux temperature is above 200° C.

When the above examples are repeated substituting cyclopentadienes possessing hydrocarbon, halogen or other groups attached to the ring structure, good results are obtained. For example, when methyl cyclopentadiene is substituted for cyclopentadiene in Example I, a good yield of methylcyclopentenylphenol is obtained. Similarly when chlorocyclopentadiene is reacted with phenol in accordance with the method of Example I, chlorocyclopentenylphenol is obtained.

The compounds prepared according to the method of the invention, many of which are believed never to have been known heretofore, are very useful materials. For example, the cyclopentenylphenols and the polyphenols are useful as intermediates in the preparation of organic chemicals and in addition many of them possess fungicidal, insecticidal and herbicidal properties as well as being useful for many other purposes.

What we claim is:—

1. A method of preparing cyclopentenylphenol which comprises bringing together a phenol and a cyclopentadiene in the presence of a Friedel-Crafts catalyst.

2. A method according to claim 1, which comprises bringing together phenol and cyclopentadiene.

3. A method according to claim 1 or 2, which comprises carrying out the reaction at a temperature of from −20° C. to 200° C.

4. A method according to any one of claims 1—3, in which the phenol used is paracresol or guaiacol.

5. A method according to any one of the preceding claims, which comprises carrying out the reaction at a temperature of about 100° C. to 200° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain an orthocyclopentenylphenol.

6. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of about 5 per cent. to 100 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain a paracyclopentenylphenol.

7. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain di- and tri-cyclopentenylphenols.

8. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature above 200° C. and in the presence of at least ½ per cent. by weight based on the weight of the phenol of the Friedel-Crafts catalyst, thereby to obtain a hard, resinous, acid and alkali-resistant polymeric material.

9. A hard, resinous, acid and alkali-resistant polymeric material prepared according to the method of claim 8.

10. A cyclopentenylphenol containing two or three cyclopentenyl groups.

11. A method of preparing a cyclopentenylphenol substantially as hereinbefore described with reference to the Examples.

12. A cyclopentenylphenol whenever prepared by a method according to any one of claims 1—7.

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& ROLLINSON,
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Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1955.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENT SPECIFICATION

741 446

THE PATENT OFFICE LONDON

Date of Application and filing Complete Specification: June 23, 1953.

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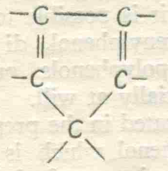
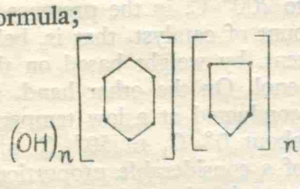
COMPLETE SPECIFICATION

Improvements in or relating to Cyclopentenyl Phenols

We, Pittsburgh Plate Glass Company, a corporation organized under the Laws of the State of Pennsylvania, of One Gateway Center, Pittsburgh, Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the reaction of cyclopentadiene, substituted cyclopentadienes, or homopolymers of such cyclopentadienes with phenols, whereby substituted phenolic compounds or polymeric products or both are obtained, and pertains particularly to the preparation of cyclopentenylphenols, which are very useful for many purposes.

In accordance with the provisions of the present invention, phenols containing at least one available hydrogen atom in the nucleus are contacted with compounds containing the group  in the presence of a Friedel-Crafts catalyst whereupon chemical reaction occurs to form compounds of the general formula;



In the formula, n and n¹ are whole numbers, usually from 1 to 3 and may be equal or unequal. In addition to compounds of the above type, some polyphenols or polymeric products, or both, are generally formed, the quantities of each product depending primarily on the particular reaction conditions which are employed.

The present invention is particularly applicable to compounds containing a single —OH group, e.g., phenol. However, the invention also includes the treatment of other hydroxylated benzenes or phenols including two or even three hydroxyls. They may also contain one or more alkoxy, hydrocarbon, or other substituent groups as side-chains. There must be at least one free or available hydrogen atom in the benzene ring in order that reaction with the cyclopentadiene may take place. Examples of such phenols containing a plurality of hydroxyls directly attached to a benzene ring are polyhydroxy phenols such as catechol, resorcinol, pyrogallol and phloroglucinol;

alkylated phenols such as ortho cresol, meta cresol, para cresol, butyl resorcinol, and tertiary butyl cathechol;

substituted phenols such as ortho, meta or para nitrophenols and the corresponding amines derived by reduction of the nitrophenols, ortho, meta and parahalophenols, polyhalophenols, halogen substituted nitrophenols, guaiacol, 2,3-dimethoxyphenol and 3,5-dimethoxyphenol.

Any of the phenolic compounds or derivatives thereof, as well as other phenolic compounds, reacts with cyclopentadiene or its homologues and substitution products to give substituted phenols and polymeric products.

While they do not contain conjugated double bonds, dicyclopentadiene, tricyclopentadiene and other homopolymers of cyclopentadiene may under appropriate conditions also be employed in the reaction, since they can be decomposed pyrolytically at 140° C. or above, to form cyclopentadiene which reacts *in situ* with phenolic compounds such as are described above.

Cyclopentadiene, or its equivalent of a lower homopolymer of cyclopentadiene, may be reacted with a phenolic compound over a wide range of molar proportions in accordance with the provisions of the present invention.

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For example, the proportion of the phenol and cyclopentadiene may be equi-molar or approximately equi-molar. However, most usually an excess of phenol is employed, since highest yields of the mono cyclopentenyl phenolic compounds are obtained when excess phenol is utilized. If high yields are not essential, almost any proportions may be employed in the reaction. For example, the cyclopentadiene component may be employed in a molar percentage of 10 to 100 or even 200 or 300 or more per cent. with respect to the phenolic component in the mixture.

The reaction of the present invention may be carried out in the absence of diluent or solvents. However in many instances it is preferred to include such material in the reaction mixture. The diluent or solvent naturally should be non-reactive in the mixture. Examples of such diluents include hexane, heptane, toluene, xylene and other aromatic and non-aromatic hydrocarbons and similar non-reactive materials.

The temperature at which the reaction is carried out may be varied widely. For example, the reaction proceeds satisfactorily at temperatures as low as – 20° C. or even lower and as high as 200° C. or higher with the preferred range being from about 0° C. to 150° C.

The reaction takes place readily at atmospheric pressure and is advantageously carried out in this manner. However, any added pressure may also be utilized if desired, as may subatmospheric pressures, provided they are not so low as unduly to volatilize the reactants.

The reaction of cyclopentadienes with phenolic compounds in accordance with the present invention is carried out in the presence of a Friedel-Crafts type catalyst. Examples of such catalysts include aluminum chloride, ferric chloride, antimony pentachloride, boron trifluoride, zinc chloride, titanium chloride, hydrofluoric acid, sulfuric acid, phosphoric acid, phosphorus pentoxide, stannic chloride, bismuth chloride and tellurium di and tetra chlorides. The Friedel-Crafts catalysts are discussed in detail in Volume 3 of Organic reactions (1946), pages 2 to 4.

The reaction can also be carried out in the presence of mixtures of two or more of the catalysts disclosed hereinabove. In fact, by selection of the proper catalyst mixture it is often possible to control the number of cyclopentenyl or phenolic groups which are combined. Most Friedel-Crafts catalysts can be placed in one of two series; that of acids, including hydrofluoric acid, sulfuric acid, phosphoric acid, in order of activity, and that of the Lewis acid salts, including aluminum chloride, boron trifluoride, antimony pentachloride, ferric chloride, tellurium dichloride, stannic chloride, titanium chloride, tellurium tetrachloride, bismuth chloride and zinc chloride, also in order of activity. "Lewis acid salts" are discussed on pages 326 to 328 of "Inorganic Chemistry" by Moeller, published by John Wiley and Sons, Inc. (1952). The more active catalysts of these two series are in general too strong to give good yields of monocycloalkenylphenols but yield instead higher molecular weight phenols and other materials. However, the more active catalysts can be "diluted" with one of the less active catalysts or with a diluent to produce a catalyst mixture that will give satisfactory yields of the desired product. Mixtures of sulfuric acid and phosphoric acid, or boron trifluoride and phosphoric acid are examples of catalyst mixtures which give excellent yields of monocycloalkenylphenols. The strong Lewis acid salts are best "diluted" by forming their complexes with compounds such as ethers, alcohols and amines, that is, compounds containing atoms with unshared electron pairs which can form coordinate bonds with the Lewis acid salts. For example, the aluminum chloride-ethanol complex and the boron trifluoride-ether complex are both less active than either aluminum chloride or boron trifluoride alone.

85 per cent. phosphoric acid, and Friedel-Crafts catalysts of similar strength form a particularly preferred class of catalysts for use in the process of this invention since they are economically obtained and result in the formation of excellent yields of monocycloalkenylphenols.

As will be apparent from the following discussion, the amount of catalyst employed and also the reaction temperature have a substantial effect on the yields of each of the reaction products.

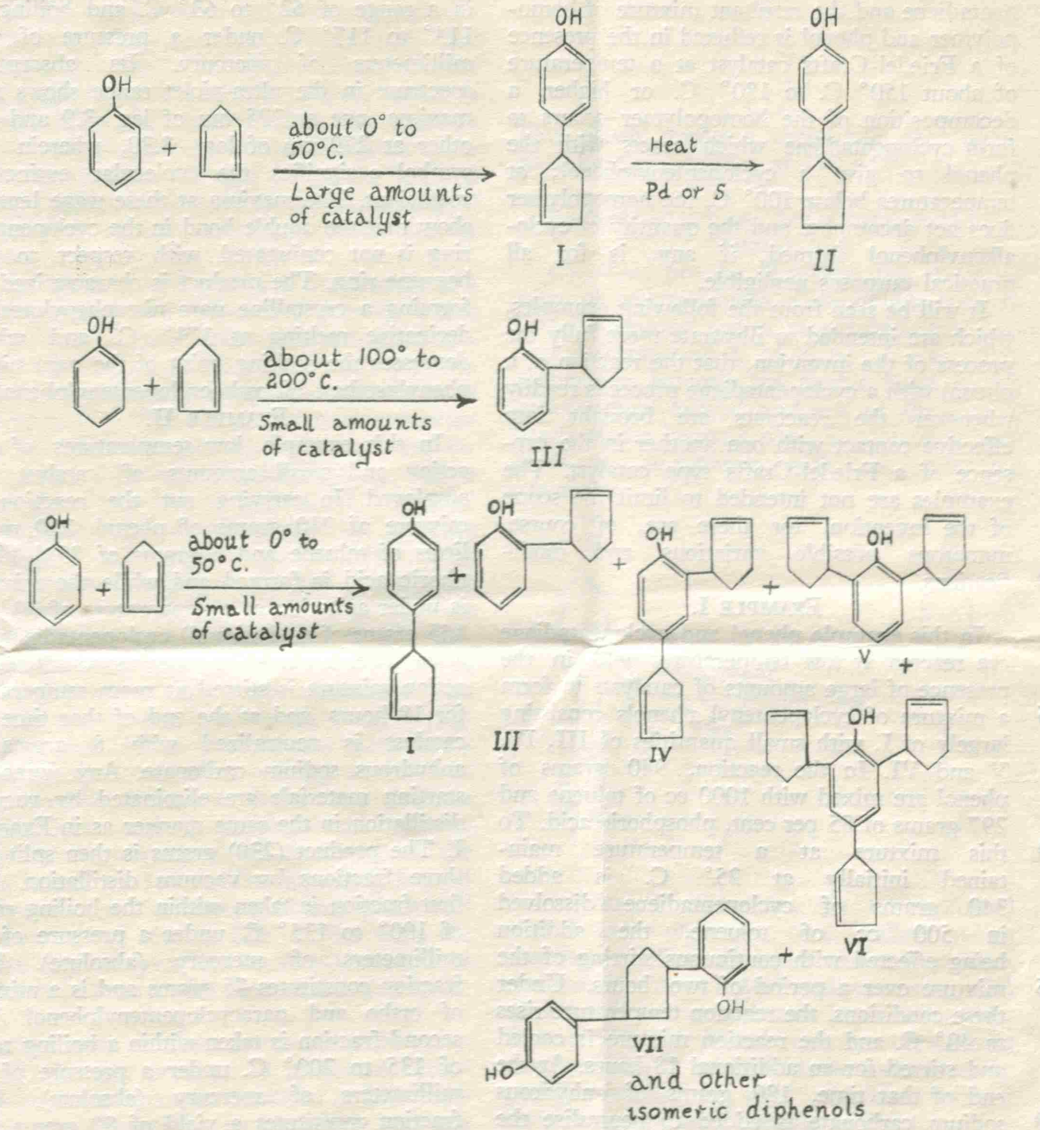
For example, by proper regulation of the conditions of reaction, it is possible to obtain ortho or paracyclopentenylphenol, di or tricyclopentenylphenols, polyphenols or polymeric products substantially at will.

These facts are illustrated in the preparation of orthocyclopentenylphenol which is readily obtained by heating a mixture of phenyl and cyclopentadiene to a temperature of about 100° C. to 200° C. in the presence of only a small amount of catalyst, that is, below about five per cent. by weight based on the weight of the phenol. On the other hand, if the reaction is conducted at a low temperature, for example about 0° C. to 50° C. and in the presence of a considerable proportion of catalyst, for example, about 5 to 100 per cent. or more based on the weight of the phenol, paracyclopentenylphenol is obtained in high yield.

If the reaction between phenol and cyclopentadiene is conducted at a low temperature, for example, as defined above, and in the presence of only a small amount of catalyst, as also defined hereinabove, the formation of di and tricyclopentenylphenols is favored.

If the reaction between phenol and cyclopentadiene is conducted at high temperatures above 200° C. and in the presence of at least ½ per cent. of catalyst, a hard, dark, resinous polymer which is extremely acid and alkali-resistant is obtained. The exact structure of the polymer is not known although it is quite likely that it contains recurring phenol and cyclopentane units in the chain.

The several reactions and the nature of the products formed will be apparent from the following reaction equations:



While the above discussion and reaction equations are directed to methods of carrying out the reaction whereby predominant amounts of one particular product are obtained, it is to be understood that a mixture of the various products, including some polyphenol and polymer are obtained regardless of the manner in which the reaction is carried out. It is also to be understood that the reaction of phenol and cyclopentadiene is used for illustrative purposes only and that the reaction proceeds satisfactorily when any of the phenols of the type described hereinabove are brought into contact with substituted cyclopentadienes in the presence of a Friedel-Crafts type catalyst.

It is apparent from the foregoing reaction equations that paracyclopentenylphenol (compound I) undergoes isomerization in the presence of palladium or sulfur or other isomerization catalyst to give paracyclopentenylphenol in which the double bond is in conjugate relation with respect to a double bond in the phenolic ring. Other cycloalkenylphenols prepared according to the method of the present invention also undergo isomerization in a similar manner. Moreover, the cycloalkenylphenols may also be hydrogenated in the presence of a catalyst such as nickel or platinum to give cycloalkylphenols which are also very useful compounds.

If cyclopentadiene is replaced by dicyclopentadiene or other homopolymer of cyclopentadiene and the resultant mixture of homopolymer and phenol is refluxed in the presence of a Friedel-Crafts catalyst at a temperature of about 150° C. to 180° C. or higher, a decomposition of the homopolymer occurs to form cyclopentadiene which reacts with the phenol to give a cyclopentenylphenol; at temperatures below 100° C. the homopolymer does not decompose and the quantity of cycloalkenylphenol formed, if any, is for all practical purposes negligible.

It will be seen from the following examples, which are intended to illustrate more fully the process of the invention, that the reaction of a phenol with a cyclopentadiene proceeds readily whenever the reactants are brought into effective contact with one another in the presence of a Friedel-Crafts type catalyst. The examples are not intended to limit the scope of the invention, for there are, of course, numerous possible variations and modifications.

Example I.

In this example phenol and cyclopentadiene are reacted at low temperatures and in the presence of large amounts of catalysts to form a mixture of cyclopentenyl phenols consisting largely of I, with small quantities of III, IV, V and VI. In the reaction, 940 grams of phenol are mixed with 1000 cc of toluene and 297 grams of 85 per cent. phosphoric acid. To this mixture at a temperature maintained initially at 25° C. is added 340 grams of cyclopentadiene dissolved in 500 cc of toluene, the addition being effected with continuous stirring of the mixture over a period of two hours. Under these conditions, the reaction temperature rises to 40° C. and the reaction mixture is cooled and stirred for an additional 18 hours. At the end of that time, 180 grams of anhydrous sodium carbonate is added to neutralise the phosphoric acid. The salt is then filtered off and washed with toluene and the resultant filtrate containing the desired product is stripped under a sub-atmospheric pressure of 10 millimeters (absolute) in order to remove unreacted material such as cyclopentadiene, dicyclopentadiene, solvent and unreacted phenol.

When the reaction is carried out on a small scale it is convenient to neutralize the catalyst with some mild base such as sodium carbonate. However in large scale operations, it may be more economical to remove the acid catalyst by a water-washing process.

After removal of all of the unreacted phenol, there remains 691 grams of a product which is fractionated under a sub-atmospheric pressure of 1.2 millimeters (absolute) to yield 470 grams of paracyclopentenylphenol, and 110 grams of a mixture of dicyclopentenylphenol, and tricyclopentenylphenols. The paracyclopentenylphenol, when redistilled, constitutes a crystalline white solid melting within a range of 62° to 63° C. and boiling at 114° to 117° C. under a pressure of 1.5 millimeters of mercury. Its absorption spectrum in the ultra-violet range shows two maxima, one at 225 mu of log ϵ3.9 and the other at 279 mu of log ϵ3.30, wherein the symbol ϵ signifies the molecular extinction coefficient. The maxima at these wave lenthgs show that the double bond in the cyclopentene ring is not conjugated with respect to the benzene ring. The product is characterized by forming a crystalline para nitrophenylurethan derivative melting at 173° C. and which depresses the melting point of the para nitrophenylurethan of orthocyclopentenylphenol.

Example II.

In this example, low temperatures of reaction and small amounts of catalyst are employed. In carrying out the reaction, a mixture of 940 grams of phenol, 250 millilitres of toluene and 6 grams of 85% phosphoric acid is formed and while the mixture is under agitation at a temperature of 30° C., 165 grams of cold (liquid) cyclopentadiene are added over a period of three hours. The reaction mixture is stirred at room temperature for 18 hours, and at the end of that time the catalyst is neutralized with 8 grams of anhydrous sodium carbonate. Any unreacted starting materials are eliminated by vacuum distillation in the same manner as in Example I. The product (230) grams is then split into three fractions by vacuum distillation. The first fraction is taken within the boiling range of 100° to 135° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes 75 grams and is a mixture of ortho and paracyclopentenylphenol. The second fraction is taken within a boiling range of 135 to 200° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes a yield of 80 grams. Redistillation of this fraction yields dicyclopentenylphenol B.P. 140°—145° C./0.5 mm. n_D^{25} 1.579. There remains in the distillation flask a residue (67 grams) consisting largely of tricyclopentenylphenol and other high molecular weight phenols.

Example III.

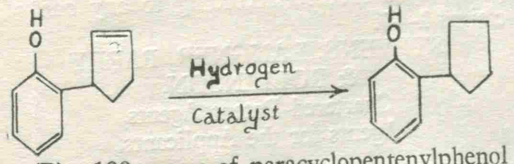
This example illustrates the use of relatively high temperatures of reaction and small amounts of catalyst in the formation of a reaction product by the interaction of phenol and dicyclopentadiene. In the reaction, a mixture of 2243 grams of phenol, 660 grams of dicyclopentadiene, and 5 grams of syrupy phosphoric acid, are admixed in a flask provided with a reflux condenser, a thermometer and a source of inert gas (carbon dioxide or nitrogen or the like). The mixture is refluxed for 22 hours during which time the temperature varies between 150° and 170° C. These temperatures are at or near the cracking point of dicyclopentadiene.

At the conclusion of the reflux period, the unreacted phenol and dicyclopentadiene are removed by vacuum distillation. There remains 1,132 grams of a reaction product which is washed with water and distilled at a pressure of 0.5 millimeters of mercury (absolute) to yield 895 grams of a light yellow oil. This oil is then agitated with a 10 per cent. (by weight) solution of aqueous potassium hydroxide in water.

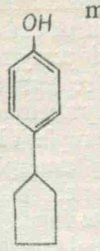
The alkali soluble fraction constituting 330 grams consists of a mixture of phenols, which mixture is largely orthocyclopentenylphenol, and also contains some di and tricyclopentenylphenols, cyclopentanediphenols and polyphenols. The orthocyclopentenylphenol can be purified in any convenient manner, for example, by vacuum distillation, to provide a water white oil. This oil boils at 81° C. under a pressure of 0.4 millimeters of mercury (absolute); n_D^{25} 1.565; d_{25}^{25} 1.0755. Two maxima are indicated in the ultra-violet spectrum, one being of log ϵ3.8 at 220 mu and the other being of log ϵ3.4 at 275 mu. These maxima show that the double bond in the cyclopentene ring is not conjugated with respect to a double bond in the benzene ring. The product forms a crystalline para nitrophenylurethan derivative melting at 165° C. The urethan derivative is of the formula $C_{18}H_{16}O_4N_2$ and it depresses the melting point of the corresponding derivative of the para isomer by 30° C. The diphenols formed are substantially colorless materials which boil in the range of 160° to 220° C./0.5 mm., the elementary analyses and molecular weight of which is in accord with the formula $C_{17}H_{18}O_2$.

Reduction of Cyclopentenylphenol.

(A) In this process, 46 grams of orthocyclopentenylphenol are dissolved in 200 millilitres of methanol in an autoclave and are hydrogenated at 100° C. over a period of 4 hours, 3 grams of Raney nickel being employed as a catalyst. A yield of 46 grams of orthocyclopentylphenol melting at 26° to 30° C. is obtained. This product can be crystallized from aqueous methanol to form fine white needles with a melting point of 40° C. The reaction is represented by the equation:



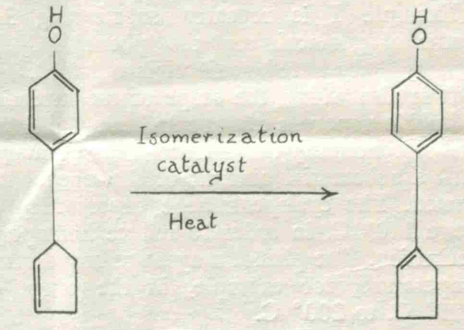
(B) 100 grams of paracyclopentenylphenol melting at 62° C. are hydrogenated in methanol solution with an Adams platinum oxide catalyst to yield 100 grams of paracyclopentylphenol melting at 69° C.



This phenol forms a crystalline para nitrophenylurethan melting at 198—199° C.

Isomerisation of *p*-Cyclopentenylphenol.

(C) This process illustrates the isomerization, or rearrangement of the double bond in the cyclopentenyl radical of paracyclopentenylphenol (compound I, M.P. 62° C.) to effect conjugation between the double bond of the cyclopentenyl radical and one of the double bonds of the benzene ring. The reaction proceeds in accordance with the following equation:



I II

50 grams of compound (I) are admixed with 1 gram of 5 per cent. palladium on charcoal in a flask equipped with a condenser, and the mixture is heated until compound (II) distills off and is collected by condensation. The conjugated isomer can be crystallized from solution in ethanol in the form of shiny platelets melting at 149° C. The product forms a monoacetate melting at 73° C.

By application of the principles as illustrated in the preceding examples, numerous cycloalkenyl derivatives of phenol or phenols can readily be prepared. Some of the compounds so prepared include the following:

2-(Δ 2 cyclopentenyl) phenol
2-(Δ 1 cyclopentenyl) phenol
4-(Δ 2 cyclopentenyl) phenol
4-(Δ 1 cyclopentenyl) phenol
2,4-di(Δ 2 cyclopentenyl) phenol
2,4-di(Δ 1 cyclopentenyl) phenol
2,6-di(Δ 1 cyclopentenyl) phenol
2,6-di(Δ 1 cyclopentenyl) phenol
2,4,6-tri(Δ 2 cyclopentenyl) phenol
2,4,6-tri(Δ 1 cyclopentenyl) phenol

Generally, the double bond of the cyclopentenyl group can be selectively hydrogenated in the manner illustrated in Example IV for the hydrogenation of orthocyclopentenylphenol to form orthocyclopentylphenol. They can also be subjected to rearrangement of the double bond of the cyclopentenyl group in the manner illustrated in Example VI.

The foregoing examples have been more particularly directed to the preparation of cyclopentenyl substituted monohydric phenols. It will be obvious from the preceding discussions however that phenol may be replaced in the reaction by various polyhydroxy phenols as well as alkyl or alkoxy derivatives of phenol or of alkyl or alkoxy derivatives of polyhydroxy phenols. Moreover, nitro- or chloro- substituted mono or polyphenols may also be substituted for phenol in the reaction.

EXAMPLE IV.

Example I is repeated except that para cresol is substituted for the phenol. 2-cyclopentenyl-*p*-cresol, an oil with a pleasant, earthy odor, B.P. 105°—108° C. 1.3 mm., n_D^{25} 1.5595; d_{25}^{25} 1.0570, is obtained.

EXAMPLE V.

Example I is repeated substituting 350 grams of guaiacol for the phenol. Cyclopentenyl substituted guaiacol is obtained.

It is also within the scope of the invention to bubble vaporous cyclopentadiene into liquid phenol containing the Friedel-Crafts catalyst until a substantial amount of the phenol has reacted. The cyclopentadiene vapors may be above 140° C. in order to reduce homopolymerization. The phenol may be at any desired temperature, for example, in the range of −20° C. to 200° C.

EXAMPLE VI.

A mixture of 188 grams of phenol, 264 grams of dicyclopentadiene and 50 grams of phosphoric acid is refluxed for 4 hours. The resulting product is a hard, dark, acid and alkali-resistant polymeric material useful as a coating and molding resin. The reflux temperature is above 200° C.

When the above examples are repeated substituting cyclopentadienes possessing hydrocarbon, halogen or other groups attached to the ring structure, good results are obtained. For example, when methyl cyclopentadiene is substituted for cyclopentadiene in Example I, a good yield of methylcyclopentenylphenol is obtained. Similarly when chlorocyclopentadiene is reacted with phenol in accordance with the method of Example I, chlorocyclopentenylphenol is obtained.

The compounds prepared according to the method of the invention, many of which are believed never to have been known heretofore, are very useful materials. For example, the cyclopentenylphenols and the polyphenols are useful as intermediates in the preparation of organic chemicals and in addition many of them possess fungicidal, insecticidal and herbicidal properties as well as being useful for many other purposes.

What we claim is:—

1. A method of preparing cyclopentenylphenol which comprises bringing together a phenol and a cyclopentadiene in the presence of a Friedel-Crafts catalyst.

2. A method according to claim 1, which comprises bringing together phenol and cyclopentadiene.

3. A method according to claim 1 or 2, which comprises carrying out the reaction at a temperature of from −20° C. to 200° C.

4. A method according to any one of claims 1—3, in which the phenol used is paracresol or guaiacol.

5. A method according to any one of the preceding claims, which comprises carrying out the reaction at a temperature of about 100° C. to 200° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain an orthocyclopentenylphenol.

6. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of about 5 per cent. to 100 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain a paracyclopentenylphenol.

7. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain di- and tri-cyclopentenylphenols.

8. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature above 200° C. and in the presence of at least ½ per cent. by weight based on the weight of the phenol of the Friedel-Crafts catalyst, thereby to obtain a hard, resinous, acid and alkali-resistant polymeric material.

9. A hard, resinous, acid and alkali-resistant polymeric material prepared according to the method of claim 8.

10. A cyclopentenylphenol containing two or three cyclopentenyl groups.

11. A method of preparing a cyclopentenylphenol substantially as hereinbefore described with reference to the Examples.

12. A cyclopentenylphenol whenever prepared by a method according to any one of claims 1—7.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1955.
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A mixture of 188 grams of phenol, 264 grams of dicyclopentadiene and 50 grams of phosphoric acid is refluxed for 4 hours. The resulting product is a hard, dark, acid and alkali-resistant polymeric material useful as a coating and molding resin. The reflux temperature is above 200° C.

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4. A method according to any one of claims 1—3, in which the phenol used is paracresol or guaiacol.

5. A method according to any one of the preceding claims, which comprises carrying out the reaction at a temperature of about 100° C. to 200° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain an orthocyclopentenylphenol.

6. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of about 5 per cent. to 100 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain a paracyclopentenylphenol.

7. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature of about 0° C. to 50° C. and in the presence of less than about 5 per cent. by weight based on the weight of the phenol, of the Friedel-Crafts catalyst, thereby to obtain di- and tri-cyclopentenylphenols.

8. A method according to any one of claims 1—4, which comprises carrying out the reaction at a temperature above 200° C. and in the presence of at least ½ per cent. by weight based on the weight of the phenol of the Friedel-Crafts catalyst, thereby to obtain a hard, resinous, acid and alkali-resistant polymeric material.

9. A hard, resinous, acid and alkali-resistant polymeric material prepared according to the method of claim 8.

10. A cyclopentenylphenol containing two or three cyclopentenyl groups.

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RÉPUBLIQUE FRANÇAISE

MINISTÈRE
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BREVET D'INVENTION

Gr. 14. — Cl. 1.

N° 1.084.390

Perfectionnements relatifs aux cyclopenténylphénols.

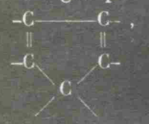
Société dite : PITTSBURGH PLATE GLASS COMPANY résidant aux États-Unis d'Amérique.

Demandé le 21 juillet 1953, à 16h 40m, à Paris.
Délivré le 7 juillet 1954. — Publié le 19 janvier 1955.

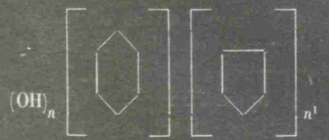
(Demande de brevet déposée aux États-Unis d'Amérique le 22 juillet 1952, au nom de M. Alfred Robert BADER.)

La présente invention se rapporte à la réaction du cyclopentadiène, des cyclopentadiènes substitués, ou des homopolymères que forment ces cyclopentadiènes avec les phénols, permettant d'obtenir des composés phénoliques substitués ou des produits polymérisés ou les deux simultanément; l'invention se rapporte plus particulièrement à la préparation de cyclopenténylphénols, qui sont très utiles pour de nombreuses applications.

Conformément à la présente invention, on met en contact des phénols contenant au moins un atome d'hydrogène disponible dans le noyau avec des composés contenant le groupement



en présence d'un catalyseur dit de Friedel-Crafts, ce qui donne lieu à une réaction chimique ayant pour conséquence la formation de composés ayant la formule générale :



Dans cette formule, n et n^1 sont des nombres entiers, allant habituellement de 1 à 3, qui peuvent être égaux ou différents. En plus des composés du genre précité, il se forme généralement certains polyphénols ou produits polymérisés, ou les deux simultanément, la quantité de chaque produit dépendant principalement des conditions de réaction particulières que l'on utilise.

La présente invention s'applique particulièrement à des composés contenant un seul groupe —OH, par exemple le phénol. Cependant, l'invention se rapporte également au traitement d'autres benzènes ou phénols hydroxylés contenant deux ou même trois groupes hydroxyl. Ces composés peuvent aussi contenir un ou plusieurs groupes alkoxy, hydrocarbure, ou d'autres groupes substituants sous la forme de chaînes latérales. L'anneau benzénique doit comporter au moins un atome d'hydrogène libre ou disponible pour que la réaction avec le cyclopentadiène ait lieu. Comme exemples de phénols de ce genre contenant un nombre multiple de groupements hydroxyl directement rattachés à un anneau benzénique, on cite les polyhydroxyphénols tels que : la catéchine, la la résorcine, le pyrogallol et la phloroglucine; les phénols alkylés tels que l'ortho-crésol, le méta-crésol, le para-crésol, la butyl-résorcine et la butyl (tert)catéchine; les phénols substitués tels que les ortho, meta ou para nitrophénols et les amines correspondantes que l'on obtient par réduction des nitrophénols; les ortho, meta et parahalophénols, les polyhalophénols, les nitrophénols substitués par l'halogène; le gaïacol, le 2,3-diméthoxyphénol, le 3,5-diméthoxyphénol et des produits analogues.

L'un quelconque de ces composés phénoliques ou de leurs dérivés, aussi bien que d'autres composés phénoliques, réagissent avec le cyclopentadiène ou ses homologues et des produits de substitution pour donner des phénols substitués et des produits polymérisés.

Bien qu'ils ne contiennent pas de double liaison conjuguée, on peut également utiliser dans la réaction le dicyclopentadiène, le tricyclopentadiène et d'autres homopolymères de cyclopentadiène, dans des conditions appropriées, étant donné qu'on peut obtenir leur décomposition par pyrolyse à une température de 140° C ou supérieure, pour former du cyclopentadiène qui réagit *in situ* avec les composés phénoliques mentionnés ci-dessus.

Conformément à la présente invention, on peut faire réagir le cyclopentadiène, ou son équivalent dérivant d'un homopolymère inférieur du cyclopentadiène, avec un composé phénolique en utilisant une large gamme de proportions moléculaires. Par exemple, la proportion du phénol et du cyclo-

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Prix du fascicule : 100 francs.

tadiène peut être équimoléculaire ou approximativement équimoléculaire. Cependant, presque toujours on utilise un excès de phénol, étant donné que l'on obtient les rendements les plus élevés en composés mono-cyclopentényl phénoliques lorsqu'on utilise un excès de phénol. Si les rendements ne sont pas d'importance primordiale, on peut utiliser dans la réaction presque toutes les proportions. Par exemple, on peut utiliser le composant cyclopentadiène en un pourcentage moléculaire de 10 à 100 ou même de 200 ou 300 % ou davantage par rapport au composant phénolique contenu dans le mélange.

La réaction conforme à l'invention peut être exécutée en l'absence de diluant ou de solvants. Cependant, dans beaucoup de cas, on préfère introduire dans le mélange de réaction un produit de ce genre. Bien entendu, le diluant ou le solvant ne doivent pas participer à la réaction. Des exemples de tels solvants sont l'hexane, l'heptane, le toluène, le xylène et d'autres hydrocarbures aromatiques et non aromatiques ainsi que des produits analogues non réactifs.

La température à laquelle on effectue la réaction peut varier très largement. Par exemple, la réaction progresse de manière satisfaisante à des températures aussi basses que —20 °C ou même inférieures et aussi élevées que 200 °C ou supérieures, la gamme préférée étant comprise entre environ 0 °C et °C.

La réaction s'effectue facilement sous la pression atmosphérique et on la réalise avantageusement de la manière précitée. Cependant, on peut utiliser si on le désire n'importe quelle pression supplémentaire, aussi bien que des pressions inférieures à la pression atmosphérique, pourvu qu'elle ne soit pas si basse qu'elle provoque la volatilisation indésirable des réactifs.

Conformément à la présente invention, on exécute la réaction de cyclopentadiènes avec des composés phénoliques en présence d'un catalyseur du type de Friedel-Crafts. Des catalyseurs de ce genre comprennent : le chlorure d'aluminium, le chlorure ferrique, le pentachlorure d'antimoine, le trifluorure de bore, le chlorure de zinc, le chlorure de titane, l'acide fluorhydrique, l'acide sulfurique, l'acide phosphorique, le pentoxyde de phosphore, le chlorure stannique, le chlorure de bismuth et les di- et tétra-chlorures de tellure. Les catalyseurs de Friedel-Crafts sont énumérés en détail dans l'ouvrage « Organic Reactions, volume 3, pages 2 à 4 (1946).

On peut également mettre en œuvre la réaction en présence d'un mélange de deux des catalyseurs précités ou davantage. En fait, le choix d'un mélange approprié de catalyseurs permet souvent de régler le nombre de groupes cyclopentényl ou phénoliques qui se combinent. On peut classer la plus grande partie des catalyseurs de Friedel-Crafts en deux catégories : l'une comportant les acides, y compris l'acide fluorhydrique, l'acide sulfurique, l'acide phosphorique, en ordre d'activité; l'autre comportant les sels acides de la classification de Lewis, comprenant : le chlorure d'aluminium, le trifluorure de bore, le pentachlorure d'antimoine, le chlorure ferrique, le dichlorure de tellure, le chlorure stannique, le chlorure de titane, le tétrachlorure de tellure, le chlorure de bismuth et le chlorure de zinc, également dans l'ordre d'activité Les catalyseurs les plus actifs de ces deux séries sont en général trop efficaces pour donner de bons rendements en monocycloalkénylphénols et donnent plutôt des phénols à poids moléculaire plus élevé et d'autres produits encore. Cependant, on peut « atténuer » les catalyseurs les plus actifs avec l'un des catalyseurs moins actifs ou avec un diluant en vue d'obtenir un mélange catalytique qui donne des rendements satisfaisants du produit désiré. Des mélanges d'acide sulfurique et d'acide phosphorique, ou de trifluorure de bore et d'acide phosphorique constituent des exemples de mélanges catalytiques donnant d'excellents rendements en monocycloalkénylphénols. On « atténue » mieux les sels acides forts de la classification Lewis en les transformant en complexes avec des éthers, des alcools et des amines, c'est-à-dire, des composés contenant des atomes disposant de couples d'électrons non partagés susceptibles de former des composés de coordination avec les sels acides de Lewis. Par exemple, le complexe chlorure d'aluminium-éthanol et le complexe trifluorure de bore-éther sont tous deux moins actifs que le chlorure d'aluminium ou le trifluorure de bore pris isolément.

L'acide phosphorique à 85 % et les catalyseurs de Friedel-Crafts d'une teneur analogue forment une catégorie particulièrement préférée de catalyseurs pour la mise en œuvre du procédé conforme à l'invention étant donné qu'ils sont économiques à obtenir et donnent d'excellents rendements en monocycloalkénylphénols.

Comme il apparaîtra plus clairement dans la description qui va suivre, la quantité de catalyseur et aussi la température de réaction utilisées exercent un effet prépondérant sur les rendements de chacun des produits de réaction.

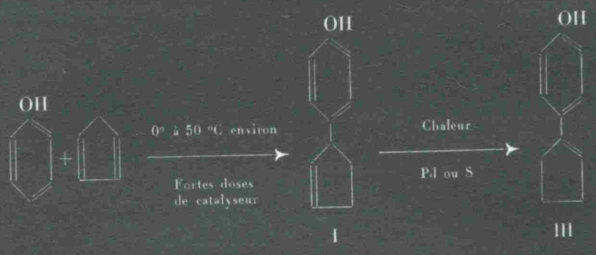
Par exemple, en ajustant de manière appropriée les conditions de réaction, il est possible d'obtenir à volonté de l'ortho ou paracyclopenténylphénol, des di- ou tricyclopenténylphénols, des polyphénols ou des produits polymérisés.

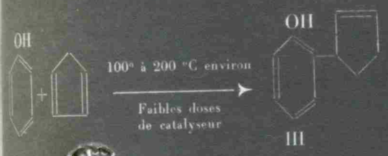
Ces constatations sont illustrées par la préparation de l'orthocyclopenténylphénol que l'on obtient facilement en chauffant un mélange de phénol et de cyclopentadiène à une température d'environ 100° à 200° C, en présence d'une faible quantité seulement de catalyseur, c'est-à-dire inférieure à environ 5 % [illegible] poids par rapport au poids du phénol. D'un autre côté, si l'on conduit la réaction à basse température, comprise par exemple entre 0°C et 50°C, en présence d'une proportion considérable de catalyseur, atteignant par exemple 5 à 100 % environ ou davantage, par rapport au poids du phénol, on obtient avec un rendement élevé le paracyclopenténylphénol.

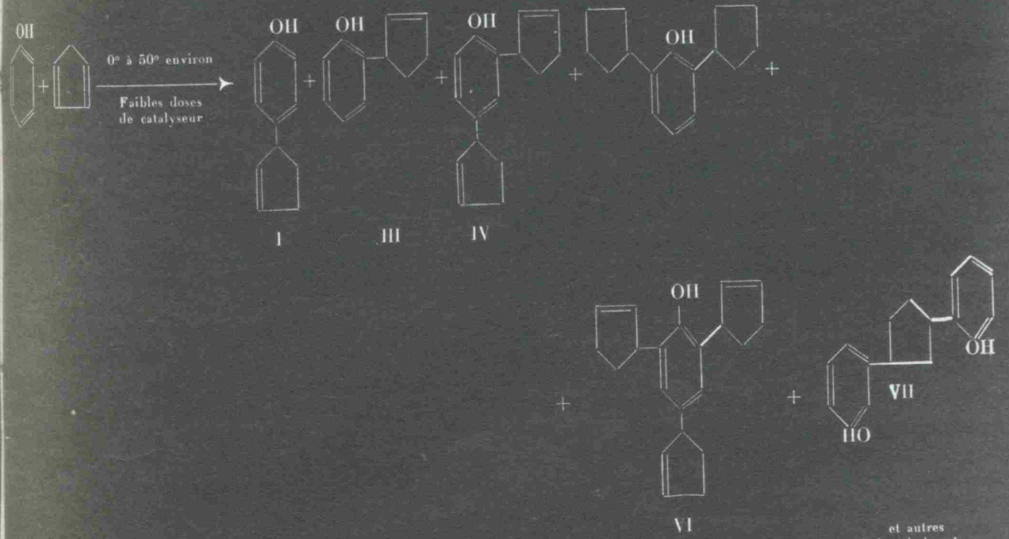
Si l'on conduit la réaction entre le phénol et le cyclopentadiène à basse température, par exemple celle indiquée ci-dessus, en présence de la faible quantité seulement de catalyseur déjà mentionnée on favorise la formation des di- et tricyclopenténylphénols.

Si l'on exécute la réaction entre le phénol et le cyclopentadiène à des températures élevées, en présence d'au moins 0,5 % de catalyseur, on obtient un polymère dur, foncé, résineux, qui est extrêmement résistant à l'acide et à l'alcali. La structure détaillée de ce polymère n'est pas connue, mais on peut admettre facilement qu'il contient des unités de phénol et de cyclopentane qui se répètent dans la chaîne.

Les différentes réactions et la nature des produits obtenus peuvent être représentées par les équations suivantes :







et autres diphenols isomères

Bien que la description et les équations de réaction ci-dessus concernent des procédés pour exécuter la réaction grâce auxquels on obtient des quantités prédominantes d'un produit tout à fait particulier, il est bien entendu que l'on obtient un mélange des différents produits, y compris une certaine quantité de polyphénol et de polymère, quelle que soit la manière selon laquelle on exécute la réaction. Il [illegible] bien entendu également que la réaction entre le [illegible]nol et le cyclopentadiène est utilisée à titre [illegible]exemple seulement et qu'elle s'accomplit d'une manière aussi satisfaisante lorsqu'on utilise n'importe lequel des phénols du type décrit précédemment et qu'on le met en contact avec des cyclopentadiènes substitués en présence d'un catalyseur du type de Friedel-Crafts.

Les équations de réaction précitées montrent que le paracyclopenténylphénol (composé I) subit l'isomérisation en présence de palladium ou de soufre, ou d'un autre catalyseur d'isomérisation. pour donner un paracyclopenténylphénol dans lequel la double liaison est placée en position conjuguée par rapport à la double liaison du noyau phénolique. Les autres cycloalkénylphénols préparés conformément au procédé de l'invention subissent de même une isomérisation analogue. En outre, on peut aussi hydrogéner les cycloalkénylphénols en présence d'un catalyseur tel que le nickel, le platine ou un catalyseur analogue, en vue d'obtenir des cycloalkylphénols qui constituent également des composés très intéressants.

Si l'on remplace le cyclopentadiène par le dicyclopentadiène, ou par un autre homopolymère du cyclopentadiène, et si le mélange d'homopolymère et de phénol résultant est soumis au reflux en présence d'un catalyseur de Friedel-Crafts, à une température d'environ 150 ° à 180 °C ou supérieure, [illegible]se produit une décomposition de l'homopolymère [illegible] on obtient du cyclopentadiène qui réagit avec le phénol pour donner du cyclopenténylphénol; à des températures inférieures à 100 °C, l'homopolymère ne se décompose pas et la quantité de cycloalkénylphénol qui se forme (s'il s'en forme) est négligeable dans toutes les applications pratiques.

Les exemples suivants, donnés pour illustrer plus en détail le procédé conforme à la présente invention, montrent que la réaction d'un phénol avec un cyclopentadiène se fait facilement chaque fois qu'on met en contact efficace les réactifs l'un avec l'autre en présence d'un catalyseur de Friedel-Crafts. Ces exemples sont donnés à titre non limitatif et il est bien entendu qu'ils sont susceptibles de nombreuses variations et modifications sans que l'on sorte du cadre de la présente invention.

Exemple 1. — Dans cet exemple, on fait réagir le phénol et le cyclopentadiène à des températures basses et en présence de quantités importantes de catalyseur pour obtenir un mélange de cyclopenténylphénols constitué principalement par le composé I, avec de faibles quantités de composés III, IV, V et VI. Pour la réaction, on mélange 940 g de phénol avec 1 000 cm³ de toluène et 297 g d'acide phosphorique à 85 %. A ce mélange, maintenu à la température initiale de 25 °C, on ajoute 340 g de cyclopentadiène dissous dans 500 cm³ de toluène, l'addition étant effectuée dans une agitation constante pendant 2 heures. Dans ces conditions, la température de réaction s'élève à 40 °C et on refroidit le mélange de réaction et on l'agite pendant 18 heures supplémentaires. A l'expiration de ce délai, on ajoute 180 g de carbonate de sodium anhydre pour neutraliser l'acide phosphorique. On filtre ensuite le sel et on le lave avec du toluène, puis on soumet le filtrat contenant le produit désiré à un fractionnement sous une pression (absolue) de 10 mm inférieure à la pression atmosphérique, en vue de chasser les produits n'ayant pas réagi tels que le cyclopentadiène, le dicyclopentadiène, le solvant et le phénol n'ayant pas réagi.

Lorsqu'on exécute la réaction à une petite échelle, il convient de neutraliser le catalyseur avec une base peu caustique telle que le carbonate de sodium. Toutefois dans des opérations à grande échelle, il peut être plus économique d'éliminer le catalyseur acide par un lavage à l'eau.

Après élimination de tout le phénol n'ayant pas réagi, il reste 691 g d'un produit que l'on fractionne à une pression (absolue) inférieure à l'atmosphère de 1,2 mm, ce qui donne 470 g de paracyclopenténylphénol et 110 g d'un mélange de dicyclopenténylphénol et de tricyclopenténylphénols. Lorsqu'on le redistille, le paracyclopenténylphénol constitue un produit blanc solide cristallisé qui fond entre 62° et 63 °C et a un point d'ébullition de 114°-117 °C, sous une pression de 1,5 mm de mercure. Son spectre d'absorption dans la gamme de réaction ultra-violette présente deux maxima, l'un à 225 microns de logarithme 3,9 et l'autre à 279 microns de logarithme 3,30. Les maxima correspondant à ces longueurs d'onde montrent que la double liaison du noyau cyclopenténique n'est pas conjuguée par rapport au noyau benzénique. Ce produit est caractérisé par la formation d'un dérivé cristallisé para-nitrophényluréthane ayant un point de fusion de 173 °C et qui abaisse le point de fusion du para-nitrophényluréthane d'orthocyclopenténylphénol.

Exemple 2. — Dans cet exemple, on utilise de basses températures de réaction et de faibles quantités de catalyseur. Pour mettre en œuvre la réaction, on constitue un mélange de 940 g de phénol, de 250 cm³ de toluène et 6 g d'acide phosphorique à 85 % et, tout en agitant le mélange à une température de 30 °C, on ajoute 165 g de cyclopentadiène froid (liquide) pendant un laps de temps de trois heures. On agite le mélange de réaction à la température ambiante pendant 18 heures, et à la fin de ce délai, on neutralise le catalyseur avec 8 g de carbonate de sodium anhydre. On élimine toutes matières premières n'ayant pas réagi par une distillation sous vide, de la même manière que dans l'exemple 1. Le produit obtenu (230 g) est ensuite divisé en trois fractions grâce à une distillation sous vide. On recueille la première fraction entre 100 ° et 135 °C, sous une pression (absolue) de 1,3 mm de mercure. Cette fraction se[illegible]e à 75 g et est constituée par un mélange d'ortho et de paracyclopenténylphénol On recueille cette seconde fraction entre 135° et 200 °C, sous une pression (absolue) de 1,3 mm de mercure. Cette fraction correspond à un rendement de 80 g. La redistillation de cette fraction donne du dicyclopenténylphénol ayant un poids d'ébullition de 140-145° C sous 0,5 mm; n_d^{25} 1,579. Il reste dans le ballon de distillation un résidu de 67 g constitué principalement par du tricyclopenténylphénol et par d'autres phénols à poids moléculaire élevé.

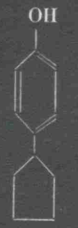
Exemple 3. — Cet exemple se rapporte à l'utilisation de températures de réaction relativement élevées et de faibles quantités de catalyseur pour obtenir un produit de réaction résultant de l'action réciproque du phénol et du dicyclopentadiène. Dans cette réaction, un mélange de 2 243 g de phénol, 660 g de dicyclopentadiène, et 5 g d'acide phosphorique sirupeux est introduit dans un ballon comportant un condenseur à reflux, un thermomètre et une source de gaz inerte (l'acide carbonique ou l'azote ou un gaz analogue). On fait refluer ce mélange pendant 22 heures tout en maintenant la température entre 150 ° et 170 °C. Ces températures égales ou voisines du point de cracking du dicyclopentadiène.

A l'expiration de la période de chauffage au reflux, on chasse par une distillation sous vide le phénol et le dicyclopentadiène n'ayant pas réagi. Il reste 1[illegible] d'un produit de réaction qu'on lave avec de l'eau et que l'on distille sous une pression (absolue) de 0,5 mm de mercure, ce qui donne 895 g d'une huile jaune clair. On agite ensuite cette huile avec 10 % en poids d'hydroxyde de potassium en solution aqueuse.

La fraction alcaline soluble pesant 330 g est constituée par un mélange de phénols, mélange qui contient en majeure partie de l'orthocyclopenténylphénol, et aussi certains di- et tricyclopenténylphénols, cyclopentanediphénols et polyphénols. On peut purifier l'orthocyclopenténylphénol de toute manière convenable, par exemple par une distillation sous vide, en vue d'obtenir un mélange d'eau et d'huile. Cette huile a un point d'ébullition de 81 °C sous une pression (absolue) de 0,4 mm de mercure; n_d^{25} 1,565; d_{25}^{25} 1,0755. On observe deux maxima dans le spectre ultra-violet, l'un étant de logarithme 3,8 à 220 microns et l'autre étant de logarithme 3,4 à 275 microns. Ces maxima montrent que la double liaison du noyau cyclopenténique n'est pas placée en position conjuguée par rapport à la double liaison du noyau benzénique. Le produit forme un dérivé cristallisé de para-nitrophényluréthane ayant un point de fusion de 165 °C. Le dérivé uréthane répond à la formule $C_{18}H_{16}O_4N_2$ et abaisse de 30 °C le point de fusion du dérivé correspondant de l'isomère para. Les diphénols qui se forment sont des produits sensiblement incolores, dont le point d'ébullition est compris entre 160 ° et 220 ° C/0,5 mm et dont les analyses élémentaires et les poids moléculaires correspondent à la formule $C_{17}H_{18}O_2$.

Exemple 4. — Dans cet exemple on dissout 46 g d'orthocyclopenténylphénol dans 200 cm³ de méthanol contenus dans un autoclave et on hydrogène ce produit à 100°C pendant 4 heures en utilisant 3 g de nickel de Raney comme catalyseur. On obtient un rendement de 46 g d'orthocyclopentylphénol ayant un point de fusion de 26° à 30°C. On peut recristalliser ce produit dans du méthanol aqueux pour former des aiguilles blanches ayant un point de fusion de 40°C. La réaction est représentée par l'équation :

Exemple 5. — On soumet à l'hydrogénation 100 g de paracyclopenténylphénol fondant à 62°C dans une solution de méthanol en utilisant le catalyseur d'oxyde de platine d'Adams, ce qui donne 100 g de paracyclopentylphénol

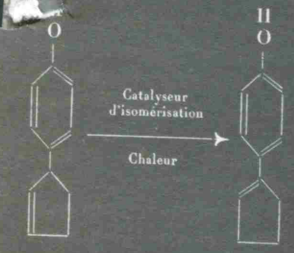


fondant à 69°C. Ce phénol donne un para-nitrophényl-uréthane fondant à 198-199° C.

Exemple 6. — Cet exemple se rapporte à l'isomérisation ou au regroupement de la double liaison du radical cyclopentényl du paracyclopenténylphénol (composé I, ayant un point de fusion de 62°C) pour effectuer une liaison conjuguée entre la double liaison du radical cyclopentényl et l'une des doubles liaisons du noyau benzénique. La réaction progresse conformément à l'équation suivante :

(Voir formule page 6)

On mélange 50 g de composé (1) avec 1 g de palladium à 5 % déposé sur du noir de charbon dans un ballon comportant un condenseur et on chauffe le mélange jusqu'à ce que le composé (II) distille, puis on recueille ce dernier par condensation. On peut faire cristalliser l'isomère conjugué depuis sa solution dans l'éthanol sous la forme de plaquettes



I II

brillantes ayant un point de fusion de 149°C. Le produit forme un monoacétate ayant un point de fusion de 73°C.

Grâce à l'application des principes exposés dans les exemples précédents, on peut préparer facilement de nombreux dérivés cycloalkényl du phénol ou des phénols. Parmi les composés que l'on peut ainsi préparer, on cite les suivants :

Le 2-(Δ 2 cyclopentényl) phénol;
Le 2-(Δ 1 cyclopentényl) phénol;
Le 4-(Δ 2 cyclopentényl) phénol;
Le 4-(Δ 1 cyclopentényl) phénol;
Le 2,4-di (Δ 2 cyclopentényl) phénol;
Le 2,4-di (Δ 1 cyclopentényl) phénol;
Le 2,6-di (Δ 2 cyclopentényl) phénol;
Le 2,6-di (Δ 1 cyclopentényl) phénol;
Le 2,4,6-tri (Δ 2 cyclopentényl) phénol;
Le 2,4,6-tri (Δ 1 cyclopentényl) phénol.

Généralement, on peut sélectivement hydrogéner double liaison du groupe cyclopentényl de la manière décrite dans l'exemple IV pour l'hydrogénation de l'orthocyclopenténylphénol en vue d'obtenir de l'orthocyclopentylphénol. On peut aussi les soumettre à un regroupement de la double liaison du groupe cyclopentényl de la manière décrite dans l'exemple 6.

Les exemples précédents se rapportent plus particulièrement à la préparation de phénols monohydriques substitués par un groupe cyclopentényl. Il résulte à l'évidence de la description précitée, cependant, que le phénol peut être remplacé dans cette réaction par différents polyhydroxyphénols aussi bien que par des dérivés alkyl ou alkoxy du phénol ou par des dérivés alkyl ou alkoxy de polyhydroxyphénols.

Exemple 7. — On répète l'exemple 1, sauf que l'on remplace le phénol par du para crésol. On obtient du 2-cyclopentényl-p-crésol, constitué par une huile présentant une odeur de terre plaisante, ayant un point d'ébullition de 105°-108°C sous 1,3 mm de pression; n_d^{25} 1,5595; d_{25}^{25} 1,0570.

Exemple 8. — On répète l'exemple 1 en remplaçant le phénol par 350 g de gaïacol. On obtient du gaïacol substitué par un groupe cyclopentényl.

Il entre également dans le cadre de l'invention de faire barboter du cyclopentadiène sous forme de vapeurs dans du phénol liquide contenant le catalyseur de Friedel-Crafts jusqu'à ce qu'une quantité importante du phénol ait réagi. Les vapeurs de cyclopentadiène peuvent avoir une température supérieure à 140°C en vue de réduire l'homopolymérisation. Le phénol peut se trouver à n'importe quelle température désirée, par exemple, comprise entre — 20°C et + 200°C.

Exemple 9. — On chauffe au reflux pendant 4 heures un mélange de 188 g de phénol, 264 g de dicyclopentadiène et 50 g d'acide phosphorique. Le mélange obtenu constitue un produit polymérisé dur, foncé, résistant à l'acide et à l'alcali et utile comme résine de revêtement et de moulage.

Lorsqu'on répète les exemples précédents en utilisant, en remplacement, des cyclopentadiènes possédant des groupes hydrocarburés halogénés ou autres rattachés au noyau, on obtient de bons résultats. Par exemple, on peut remplacer le cyclopentadiène de l'exemple 1 par du méthyl cyclopentadiène et obtenir du méthylcyclopenténylphénol avec un bon rendement. De même, on peut faire réagir le chlorocyclopentadiène avec le phénol, conformément au procédé de l'exemple 1, pour obtenir le chlorocyclopenténylphénol.

Les composés préparés conformément au procédé de l'invention, dont on admet que beaucoup n'étaient pas connus antérieurement, constituent des produits très utiles. Par exemple, les cyclopenténylphénols et les polyphénols constituent des produits intermédiaires utiles dans la préparation de produits chimiques organiques et en outre beaucoup parmi ces composés possèdent des propriétés fongicides, insecticides et herbicides et sont également utiles dans beaucoup d'autres applications.

RÉSUMÉ

La présente invention a pour objet :

A. Un procédé pour préparer du cyclopenténylphénol, caractérisé par les particularités suivantes prises isolément ou en combinaison :

a. On met en contact un phénol et un cyclopentadiène en présence d'un catalyseur de Friedel-Crafts;

b. On met en contact le phénol et le cyclopentadiène;

c. On exécute la réaction à une température comprise entre — 20°C et + 200°C;

d. Le phénol que l'on utilise est le paracrésol ou le gaïacol;

e. On exécute la réaction à une température comprise entre environ 100° et 200°C et en présence du catalyseur de Friedel-Crafts (en une quantité inférieure à 5 % en poids par rapport au poids du phénol), en vue d'obtenir un orthocyclopenténylphénol;

f. On exécute la réaction à une température d'environ 9° à 50°C et en présence du catalyseur de Friedel-Crafts (en une quantité comprise entre environ 5 [illegible] 100 % par rapport au poids du phénol), en vue d'obtenir un paracyclopenténylphénol;

g. On exécute la réaction à une température d'environ 0° à 50°C et en présence du catalyseur de Friedel-Crafts (en une quantité inférieure à 5 % en poids par rapport au poids du phénol), en vue d'obtenir un phénol dont plusieurs atomes d'hydrogène du noyau benzénique sont remplacés chacun par un groupe cyclopentényl;

h. On exécute la réaction à une température d'environ 100° à 200°C et en présence du catalyseur de Friedel-Crafts (en une quantité d'au moins 0,5 % en poids par rapport au poids du phénol), en vue d'obtenir un produit polymérisé dur, résineux, résistant à l'acide et à l'alcali.

B. Le produit industriel nouveau que constitue une matière polymérisée, dure, résineuse, résistant à l'acide et à l'alcali, obtenue conformément au procédé décrit sous A.

C. Le produit industriel nouveau que constitue un cyclopenténylphénol, caractérisé par les particularités suivantes prises siolément ou en combinaison :

i. Il contient un nombre multiple de groupes cyclopentényl;

j. Il est constitué par le p-2-cyclopenténylphénol;

k. Il est constitué par un cyclopentane diphénol.

Société dite : PITTSBURGH PLATE GLASS COMPANY.

Par procuration :

D.-A. CASALONGA.

United States Patent Office

2,693,476

Patented Nov. 2, 1954

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2,693,476

BETA-CARBONYL CARBOXYLIC ACID ESTERS OF STEROIDS

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No Drawing. Application April 7, 1951, Serial No. 219,899

14 Claims. (Cl. 260—397.2)

The present invention relates to methods of forming esters of sterols or steroid compounds containing free alcoholic hydroxyls and to the novel esters attained.

According to the present invention, a novel and useful class of esters has been produced. These compounds are esters of steroids containing free hydroxyls and a beta carbonyl carboxylic acid, such as acetoacetic acid. These esters may be prepared in high purity and in almost quantitative yield by interacting under mild conditions an ester of an enolizable beta carbonyl or beta keto carboxylic acid and a lower aliphatic alcohol containing, for example, up to 4 carbon atoms with a sterol.

Because of the high solubility of the lower alcohol in the reaction mixture, the concentration of such alcohol tends to increase as reaction proceeds. Where the reaction mixture contains the sterol and beta keto ester of the lower alcohol in essentially stoichiometric amounts, this accumulated lower alcohol adversely affects the yield and purity of the product. This difficulty may be overcome by removing the lower alcohol from the reaction mixture. This may be accomplished by evaporating the alcohol from the reaction mixture at atmospheric pressure. In some cases it may be desirable to remove the evolved alcohol under conditions such that the partial pressure of the lower alcohol vapor is less than atmospheric. This may be accomplished by conducting the reaction at a subatmospheric pressure, for example at an absolute pressure below about 0.75 atmosphere. Alternatively, or in conjunction therewith, the reaction mixture may be blown with an inert gas, such as nitrogen, carbon dioxide, etc., and preferably in the absence of water. In either case, the vapor of the lower alcohol will have a partial pressure less than atmospheric pressure.

The adverse effect of the lower alcohol also may be minimized by use of an excess, preferably a large excess of beta keto ester of the lower alcohol. By this means, the concentration of the lower alcohol is maintained low with respect to the original lower beta carbonyl ester. Thus for maximum yield it is advantageous to maintain the lower alcohol concentration below 33 mole percent of the beta keto ester of lower alcohol in the mixture and for most purposes, the lower alcohol concentration should be substantially below this value, for example, 5 mole percent or less.

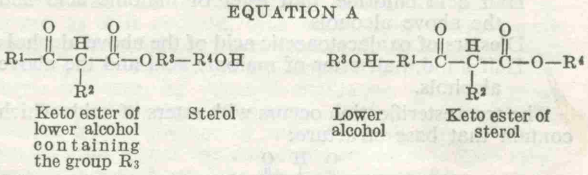
It will be understood that all of the above features may be used individually or in conjunction with each other.

According to the present invention, excesses of the alcohol to be combined by interchange with the acetoacetic acid radical preferably are avoided because in such cases mixtures of the sterol and sterol ester are obtained. Separation of these may be laborious. Indeed, great excesses of the acetoacetic acid ester component may be employed and if care is exercised to eliminate, or at least sufficiently to reduce in the reaction zone the relative concentration of the lower alcohol generated by the reaction, to that of the initial beta keto ester, quantitative interchange of sterol radical can be attained.

Such reaction is attained merely by mixing the sterol with the beta carbonyl ester of the lower alcohol in the presence or absence of alcoholysis catalysts and diluents. In order to insure rapid reaction, the mixture is heated to a moderate temperature while eliminating the alcohol liberated by the interchange from the system.

The reaction involved, which occurs in liquid phase in the case of the monohydroxy sterols or steroids, may be represented by the equation:

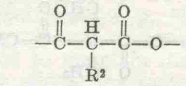
EQUATION A


$$R^1\!-\!\overset{\overset{O}{\|}}{C}\!-\!\underset{\underset{R^2}{|}}{\overset{H}{C}}\!-\!\overset{\overset{O}{\|}}{C}\!-\!OR^3\!-\!R^4OH \qquad R^3OH\!-\!R^1\!-\!\overset{\overset{O}{\|}}{C}\!-\!\underset{\underset{R^2}{|}}{\overset{H}{C}}\!-\!\overset{\overset{O}{\|}}{C}\!-\!O\!-\!R^4$$

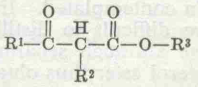
The several groups R^1, R^2, R^3, and R^4 will be defined later.

BETA CARBONYL ESTERS

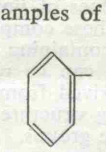
Beta carbonyl esters which may be employed to effect esterification of the sterols and like compounds are carboxylic acid esters which contain a carbonyl group in the beta position with respect to an esterified carbonyl group. Such esters thus include the group

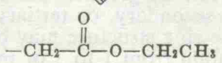

$$-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-O-$$

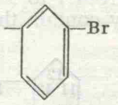
Such ester should contain no free carboxyl in the beta position with respect to a carbonyl group. The general structure of the esters may be represented by the formula taken from the above Equation A which is as follows:


$$R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-O-R^3$$

In the formula, group R^1 may be hydrogen, aliphatic, aromatic or aliphatic or aromatic groups containing substitute groups. Examples of such groups are: CH_3, C_2H_5




$$-CH_2-\overset{\overset{O}{\|}}{C}-O-CH_2CH_3$$



$—CH_2Cl$, $—C_2H_4Cl$, $—RNH_2$, $—RCHO$, $—OCH_3$, H, —OR, and other halogen substituted hydrocarbon radicals.

R^2 frequently is hydrogen but it can also be hydrocarbon or substituted hydrocarbon such as methyl, ethyl, propyl, butyl, benzyl, phenyl, chloromethyl or chloro, amino or the like derivatives thereof. Only one of the hydrogens of the alpha carbon atoms can be replaced by substituents. The remaining hydrogen atom is an active atom essential to the ester interchange reaction and must be retained.

R^3 is usually the labile radical which is adapted to be replaced in the ester interchange. These functioning groups usually are of low molecular weight, e. g., 1, 2, 3, or possibly 4 carbon atoms in a saturated or unsaturated aliphatic substituted or unsubstituted hydrocarbon chain.

Examples of appropriate beta carbonyl esters suitable for use in the practice of the invention include the following compounds:

Table A

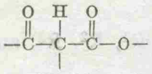
Methyl, ethyl, n-propyl, isopropyl, butyl, allyl, methallyl, crotyl, propargyl, 2-chloroethyl, 2-fluormethyl, 2-nitropropyl esters of beta keto acids such as:

- Acetoacetic acid
- Acetyl acetoacetic acid
- Alpha ethyl acetoacetic acid
- Gamma chloro acetoacetic acid
- Alpha methyl acetoacetic acid
- Alpha isopropyl acetoacetic acid
- Acetone dicarboxylic acid
- Benzoyl acetoacetic acid
- Alpha benzoyl acetoacetic acid
- Acetyl succinic acid

Benzoyl acetic acid
Diacetyl succinic acid
Chloro, iodo, and bromo substitution products of the above acids

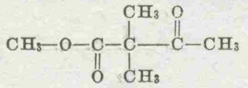
Analogous esters of other beta carbonyl acids such as:
- Malonic acid diesters of the above alcohols
- Half acid chloride, half ester of malonic acid and the above alcohols
- Diesters of oxalacetoacetic acid of the above alcohols
- Half amid, half ester of malonic acid and the above alcohols.

The transesterification occurs with esters of acids which contain that base structure:



$$-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{O}{\overset{\|}{C}}-O-$$

It has been found that a doubly substituted beta carbonyl ester that does not contain this structure and that contains no active hydrogen and being unable to enolize, gives no ester interchange with alcohols under the conditions of the present invention. Such an ester is methyl dimethyl acetoacetate of the formula:

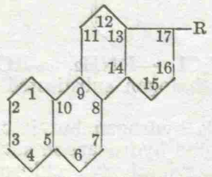


$$CH_3-O-\underset{O}{\underset{\|}{C}}-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-CH_3$$

For most purposes esters of lower alcohols which boil or distill at a relatively low temperature for example 160° C. or below, at or below atmospheric pressure may be used most conveniently. However all esters of beta-keto acids which contain an active hydrogen produce the transesterification herein contemplated. Even where esters of alcohols which are difficult to distill off are used, the process is operative although separation of the evolved alcohol from the sterol ester thus obtained frequently becomes difficult.

The sterols are alcohols which may be isolated from the unsaponifiable residues of lipids derived from plant and animal sources. These compounds are of relatively high molecular weight containing from 17 to 30 or more carbon atoms. Sterols can be regarded as compounds containing or being derived from the cyclopentano-perhydro-phenanthrene ring structure and containing one or more e. g. two alcoholic groups. These alcoholic groups may be primary, secondary, or tertiary or any combination thereof. The ring structure may be completely saturated or may contain from 1 to 3 or more double bonds.

The sterols generally contain the following ring structure:

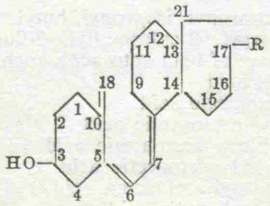


In the above structure, R may be H, OH, O straight chain or branched and either saturated or unsaturated hydrocarbon, or oxygenated or amino derivatives of the aforementioned hydrocarbons.

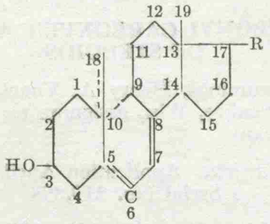
The above structure will contain one or more hydroxyl groups within the molecule appearing in either the ring or in a side chain or in both.

In addition a CH_3 group will generally appear at positions 10 and 13. (See Natural Products Related to Phenanthrene, Fieser & Fieser—Rienhold Publishing Corp.)

Closely related compounds which may be esterified according to this invention are the vitamins of the D group which usually are of the conventionalized formula:



where the 7 carbon atom is dehydro, or double bonded. (See Chemistry and Physiology of the Vitamins, H. R. Rosenberg, 1945, Interscience Publishers, Inc., New York, page 341.) The preparation of beta keto esters of the vitamins of the D group is therefore regarded as being broadly embraced within the purview of the present invention. The sterols and the vitamins of the D group and related compounds may be represented by the formula:



R being H, —O—H, O aliphatic hydrocarbon, or oxy derivatives or amino derivatives thereof and the bonds represented in broken line at 10—18 and 10—9 being alternative with respect to each other. Such compounds and their substituted equivalents or isomers are included within the term "sterol" as herein used. Obviously the epimers and hydration products may be employed as starting materials for treatment with lower alkyl esters of beta keto acids.

While many of the sterols are isolated from natural sources, the use of such compounds prepared by synthetic methods is contemplated herein.

These sterols or sterol-like compounds are often comparatively sensitive to high temperatures and/or other conditions. However, many of them are important starting compounds in the synthesis of hormones and other biologicals. Yet in some of the reactions to which the compounds are subjected it is desirable to protect the hydroxyl group from loss or from conversion to carbonyl form. It may also be desirable to convert the hydroxyl to ester form in order to increase the polarity of the compound or to provide reactive, or labile groups. By recourse to the present invention, the sterol or steroid compound may be esterified to produce the beta-keto ester. This ester may be treated to introduce other radicals or to change the structure of the compound and thereafter the beta-keto acid radical may be removed by hydrolysis to restore the hydroxy group to the modified steroid. The term "sterol" as used herein includes all hydroxylated steroids including vitamin D compounds.

Typical sterols or hydroxy steroids which may be employed according to this invention include:

Table B

Cholesterol
Beta sitosterol
Stigmasterol
Cholestanol
Epidehydroandrosterone
Ergosterol
Ergostane triol
Ergostadientriol
Strophanthidin
Lithocolic acid
Epicholestanol
Coprostanol
Steroid intermediates
Sterol sapoginins from various sources including dioscorea
Cortisone
Cholic acid
Desoxy cholic acid
Suprasterols
7 dehydrocholesterol
22 dehydroergosterol

Triterpene alcohols such as:
- Agnosterol
- Lanosterol
- Lumisterol

Other vitamins D such as:
- Vitamin D_5

Thus esters of sterols containing one, two, three, or more alcoholic hydroxyls may be prepared. When the sterols containing two or more alcohol hydroxyl groups are treated, partial esters or completely esterified sterols or mixtures thereof may be obtained. When these are produced as mixtures, they may be separated by crystallization, molecular distillation or other methods if desired.

CONDITIONS OF REACTION

It is feasible to prepare esters of beta keto carboxylic acids and sterols by moderately heating a lower ester of said acid, e. g., methyl or ethyl acetoacetate and said sterol or hydroxylated steroid in practically any proportions and under practically any reasonable conditions. In its broadest concepts the invention is considered to involve the preparation of the esters under practically any conditions of pressure or the like. However, if optimum yields of high grade product are to be obtained with least trouble and expense, the conditions should be chosen in accordance with the following principles:

The conditions of reaction employed to effect the ester interchange between the sterols and beta carbonyl esters such as beta keto esters may vary, dependent upon the carbonyl ester and the sterols employed in the reaction. However, the conditions should be relatively mild.

Catalysts of reaction are not required and usually it is desirable to operate without them. However, use of catalysts which promote alcoholysis reactions, such as sodium ethoxide and the like, may be used if desired.

The temperature of reaction should be sufficiently high to drive off the lower alcohol evolved by reaction. Preferably, it should be driven off substantially as fast as it is liberated in the reaction mixture. On the other hand, the temperature should also be below the point of decomposition of the reactants, or the desired product. A good average temperature is approximately 90 to 100° C. which is near that of an ordinary steam bath or even as high as 120° C. The temperature can also be reduced below this value. However, it is to be understood that as the temperature approaches or is reduced below the normal boiling point of the lower alcohol evolved in the system, it is desirable to apply vacuum in order to promote removal of the latter.

The temperature of reaction can be substantially in excess of 100° C. For example it can be as high as 150° C. but temperatures above 160° C. should not be employed if quantitative yields of the desired product are to be obtained. A range of 50° C. to 150° C. is therefore suggested for the ester interchange.

The approach of the upper limit of permissible temperature can usually be detected by a darkening of the reaction mixture. If any tendency so to discolor is observed, the temperature should be reduced until it ceases. It is usually preferred to employ a temperature above the boiling point of the lower alcohol evolved in the reaction mixture. This facilitates removal of the latter.

To obtain a very high yield of desired ester of the sterol, the concentration of the lower alcohol remaining in the system should not be allowed to rise much in excess of 33 molar percent with respect to the original amount of beta keto ester from which said alcohol is derived. It is generally desirable that the percentage be as much lower than this value as can reasonably be attained. If the concentration is reduced to 5 molar percent or even to 1 or 2 molar percent or less, still better yields can be attained.

Several methods are available to attain these low concentrations of the evolved lower alcohol without unduly increasing the temperature of the reaction mixture. For example, the system can be placed under fairly high vacuum thus stripping off the lower alcohol as it is formed while permitting the temperature to stay relatively low. In this way, the concentration of the original beta keto ester in the system is maintained. Such a system may be operated under such conditions that any beta keto ester vaporized is refluxed back into the reaction mixture while the evolved alcohol is removed.

It is likewise within the scope of this invention to strip off lower evolved alcohol by blowing the reaction mixture with a non-reactive gas, e. g., nitrogen, CO_2, or the like whereby a low partial pressure of vapors of evolved alcohol is maintained in the system. The effect is much the same as is obtained by subjecting the system to vacuum.

According to still another convenient method, the alcohol of reaction may be diluted by employing a high molar excess of the beta keto ester of the lower alcohol with or without distillation of the lower alcohol. For example, the excess may be 1 to 5, 10 or even 100 fold of the molecular ratio of the beta keto or carbonyl ester with

respect to the original sterol undergoing ester interchange. The excess can be added initially or it can be added as the reaction proceeds.

Combinations of these several methods are contemplated. For example, an 0.1 to 100 mole excess of beta keto ester can be employed and at the same time, some or practically all of the alcohol of reaction can be removed as it is evolved, thus maintaining an extremely low percentage of the lower alcohol in the system. Such stripping may be effected by simple distillation at atmospheric pressure, by vacuum distillation or by blowing with non-reactive gas or vapor. Preferably stripping is effected in the absence or substantial absence of water. Usually, the higher the concentration of beta keto ester, the less thorough need be the stripping action.

In the event that complete conversion of the sterol or hydroxylated steroid to beta carbonyl ester is not desired, then quantities of original beta keto ester in less than equimolecular amounts in respect to the original sterol may be employed.

By properly reducing the concentration of the evolved lower alcohol in the system, it is possible to obtain yields of sterols of beta keto acids of 90% or higher up to practically quantitative values, e. g., 98 or 100%, without discoloration of the product or the reactants.

If care is observed to maintain the reaction temperature reasonably low and at the same time to distill off under vacuum or otherwise to remove, or decrease the concentration of the lower alcohol evolved by reaction, highly efficient ester interchange can be effected with equimolar ratios of the sterols and the beta keto ester of lower alcohol or with only a slight excess of the latter. However, it is usually more convenient to operate with an excess which is substantial, e. g., 10% or preferably larger (upon a molar basis) of the starting beta keto ester. This excess promotes the reaction. When the reaction nears completion, the excess of original ester can be removed. One method of removal of excess beta ester is by vacuum distillation at pressures of about 5 to 50, e. g., 15 millimeters of mercury. These pressures are usually satisfactory for distilling off this excess of beta keto ester but such other pressures as will remove the excess ester at permissible temperatures may be employed. The distillation may be conducted at or near the original reaction temperature. The distillation of the excess beta keto or beta carbonyl ester of lower alcohol is important if quantitative yields are desired because it also distills off any lower alcohol in the system, thus reducing the concentration of the latter with respect to the original beta keto ester still present and assuring that the ester interchange reaction is completed with respect to any residues of sterols still in the reaction mixture, at moderate temperatures.

In some instances, the sterol and the beta keto or beta carbonyl ester may not be sufficiently miscible in each other for satisfactory reaction. It is then desirable to include a non-reactive common solvent of the several components in the system. This should be added in an amount to effect solution of all components. The reaction conditions in other respects are maintained without substantial change. At the conclusion of the reaction, any solvents are distilled off.

Any solvent which has neutral solubility for both the sterol and beta keto or beta carbonyl ester and which is non-reactive to the reactants or their products may be employed. The following are representative of such solvents: benzene, toluene, xylene, ethyl acetate, chloroform, carbon tetrachloride, acetone, tetrahydrofurane, dioxane, and isopropyl ether.

In general the reaction is conducted at a temperature above about 50° C. At temperatures ranging from 50 to 150° C. or above, the reaction usually proceeds to substantial completion in about 3 to 48 hours. Where lower temperatures are used, for example room temperature or below, the reaction is much slower and several weeks may be required to achieve substantial reaction and even then use of a substantial excess of keto ester is generally required. Completion obviously can be determined by chemical analysis of the reaction mixture or by cessation of the evolution of the lower alcohol even though the temperature may be increased. Time should be afforded for completion of the reaction without undue rise of temperature. Maintenance of reaction conditions herein disclosed for any reasonable period after completion of the reaction is not particularly harmful.

It is likewise contemplated to employ as a source of sterols or steroid bodies for use in the practice of the invention various glyceride oil mixtures containing sterols in substantial amounts. For example, a soap stock which normally contains considerable amounts of sterols, such as cholesterol, may be treated with methyl or ethyl acetoacetate in accordance with the provisions of the invention to form esters of the keto acid in admixture with glycerides of fatty acids. The temperatures of reaction correspond to those herein disclosed. The conditions of reaction likewise in other respects, are similar to those of the examples as herein presented. Many other mixtures of fat-like products likewise include sterols which are susceptible of treatment in accordance with the provisions of the present invention.

Wool fat, for example, includes considerable amounts of cholesterol and it is contemplated to treat such cholesterol-containing material with an excess of ethyl or methyl acetoacetate at temperatures near the boiling point of water to form cholesterol esters in the mixture. These cholesterol esters can be recovered by solvents or by other appropriate methods.

Likewise, tall oil as obtained in the digestion of paper pulp is rich in sterols and notably in beta sitosterol. The distillation residue obtained after partial distillation of the rosin acids and fatty acids of tall oil is highly enriched in beta sitosterol. This crude mixture can be treated with methyl or ethyl acetoacetate to provide esters in admixture with rosin acids, fatty acids, and the other impurities of the tall oil residue.

Usually it is preferable to operate with more concentrated forms of the sterol or steroid compound. For example, beta sitosterol has heretofore been recovered from tall oil and tall oil distillation residues by solvent fractionation of crude tall oil. A convenient method of obtaining sterols, e. g., beta sitosterol, from tall oil or tall oil distillation pitches comprises esterifying the crude material with a lower alcohol, e. g., methyl alcohol, selectively to esterify fatty acids, contacting the mixture with countercurrently flowing streams of naphtha and furfural in a tower, separating off at one end a solution of furfural containing in solution a concentration of rosin acids and separating off at the other end, naphtha containing in solution an enrichment of esters of fatty acids and unsaponifiable material including beta sitosterol. The naphtha can be recovered by evaporation. The mixture of esters and unsaponifiable matter can be treated with alkali, e. g., caustic soda, to saponify the esters and the residual rosin acids in the mixture. The unsaponifiable matter is separated by dissolving the mixture in an aqueous alcohol, e. g., aqueous isopropyl alcohol and extracting out the unsaponifiable material in a solvent such as naphtha, and evaporating the naphtha. If purer sterols are desired, they can be recovered by crystallizing them from a solvent of sterols. In many cases, a relatively pure product has been obtained. The following examples illustrate the application of the principles of the invention in the preparation of beta keto esters of a crude or purified beta sitosterol.

Example I

Twenty grams of cholesterol and 100 grams of methyl acetoacetate were heated together in the absence of catalyst in a round bottom flask with open neck, at 90 to 100° C. Methyl alcohol was expelled as the reaction proceeded. At the conclusion of 8 hours, the excess of methyl acetoacetate was removed by vacuum distillation at a pressure of about 15 millimeters of mercury and there was obtained 23 grams of a white solid which had a melting point of 91 to 93° C. This product was dissolved in acetic acid and recrystallized to obtain a further purified compound melting at 93 to 94° C. The specific rotation $\alpha_D^{25^\circ}$ in chloroform was —33°. The compound was cholesteryl acetoacetate of very high purity.

Example II

A mixture of 10 grams of cholesterol and 50 grams of ethyl acetoacetate was heated on a steam bath for 3 hours. The excess of ethyl acetoacetate was removed by distillation at a pressure of 10 millimeters (absolute). There remained 11 grams of a white solid which was identical with the product obtained in Example I, being cholesteryl acetoacetate. Saponification with alcoholic potassium hydroxide gave quantitative yields of cholesterol indicating the ester structure of the cholesteryl acetoacetate.

Example III

Two grams of stigmasterol and 20 grams of methyl acetoacetate were heated on a steam bath and under an air condenser, under which conditions the methyl alcohol was expelled as the reaction proceeded. Reaction was continued for two hours. At the end of this time, the excess methyl acetoacetate was stripped off by vacuum distillation. The vacuum was such as to maintain the temperature of distillation below 100° C. There remained 2.2 grams of a white solid which was crystallized from petroleum ether admixed with methanol to provide a product comprising white shining platelets of a melting point of 114 to 114.5° C., specific rotation $\alpha_D^{25^\circ}$ in chloroform equals —44°. This product was stigmasteryl acetoacetate.

Example IV

Two grams of beta sitosterol having a melting point of 136 to 137° C. and 20 grams of ethyl acetoacetate were heated on a steam bath for 18 hours. The reaction product was stripped of ethyl acetoacetate and any residual ethyl alcohol by vacuum distillation and there remained a white solid product constituting 2.2 grams and this was recrystallized from petroleum ether admixed with methanol to provide a product in the form of white shining platelets of a melting point of 99° C. and of a specific rotation $\alpha_D^{25^\circ}$ in chloroform of —24°. The product was beta sitosteryl acetoacetate. An identical product was obtained by use of methyl acetoacetate as the beta carbonyl ester.

Example V

One hundred milligrams of cholestanol melting in a range of 140 to 142° C. was treated with 10 grams of methyl acetoacetate by heating the mixture on a steam bath for 4 hours. Upon distillation of the excess of methyl acetoacetate, there remained a quantitative yield of cholestanyl acetoacetate in the form of white platelets of a melting point of 97° C. and of a specific rotation $\alpha_D^{25^\circ}$ in chloroform of +12°.

Example VI

In this example, epidehydroandrosterone was admixed with a molar excess of methyl acetoacetate and heated on a steam bath for 18 hours. The excess of methyl acetoacetate was distilled under vacuum and there remained a solid product which was recrystallized from methanol to provide feathery white crystals of epidehydroandrosterone acetoacetate melting at 163° C. The specific rotation $\alpha_D^{25^\circ}$ in chloroform was +1°.

Example VII

In this example, a non-reactive solvent was employed. A mixture of 5 grams of cholesterol and 25 cc. of methyl acetoacetate in solution in 250 cc. of xylol (inert solvent) were heated on a steam bath and under an air cooled condenser designed to pass evolved methyl alcohol and to return reactives and solvents to system for 18 hours. At the conclusion of the reaction period, the methyl acetoacetate and the xylene were stripped by distillation under vacuum and there remained 5.9 grams of a white solid which after one recrystallization from aqueous acetic acid melted at 92 to 93° C. and which was identical with cholesteryl acetoacetate prepared without solvents as described in Example I.

Example VIII

In this reaction, ester interchange was effected between cholesterol and methyl acetoacetate. The reaction mixture comprised 10 grams of cholesterol and 100 cc. of methyl acetoacetate, the mixture being heated on the steam bath and at atmospheric pressure for 15 hours. During the reaction, inert gas was bubbled through the reaction mixture to effect the thorough removal of evolved methanol from the zone of reaction. Finally, the excess methyl acetoacetate was removed by vacuum distillation to yield 12 grams of a white solid cholesteryl acetoacetate of a melting point of 91 to 93° C.

Example IX

This example illustrates the employment of vacuum during the course of the ester interchange for purposes of more thoroughly removing the lower alcohol as it is evolved. In the reaction, 10 grams of cholesterol were admixed with 100° cc. of methyl acetoacetate and the mixture was heated upon the steam bath for 15 hours at a pressure of 40 millimeters of mercury (absolute). During the course of the reaction, methyl alcohol was evolved and distilled off and cholesteryl acetoacetate was formed. The yield and the purity of the product were practically identical with those obtained in Example VIII.

Example X

The use of esters of benzoyl-acetic acid, which are beta carbonyl compounds, in the transesterification has been referred to. In this example, 5 grams of cholesterol and 30 grams of ethyl benzoyl-acetate were heated at steam bath temperature for 20 hours. Removal of the unreacted ethyl benzoyl-acetate by vacuum distillation left 6.4 grams of cholesteryl benzoyl-acetate, which after crystallization from a butyl acetate-ethanol mixture melted at 151° C.

The sterol esters of beta carbonyl acids are in general crystalline solids, many of which melt readily at elevated temperatures, for example 90–125° C.

The acetoacetates and like beta-keto and beta carbonyl esters of sterols, in general, possess greater solubility than the parent sterol, as well as greater solubility than such conventional sterol esters as acetates or benzoates. Consequently these sterol esters are useful intermediates in steriod syntheses because of greater ease of handling in solutions for purposes of crystallizing or of conducting other synthetic reactions on solutions. For example, in the following table are given the comparative solubilities of cholesteryl acetoactate and cholesteryl acetate in a number of solvents. The volume of each solvent in cc. or milliliters required to dissolve 1 gram of the cholesteryl ester at reflux temperature is given.

	Cholesteryl Acetate, ml.	Cholesteryl Acetoacetate
Acetone	3	Less than 1 ml.
Methanol	70	20 ml.
Methanol and Hexanol (Equal Volumes)	13	Less than 2 ml.
Methanol and Isopropyl Ether (Equal Volumes).	9	Do.
Methanol and Acetone (Equal Volumes)	17	Do.

(ml.=milliliters.)

This increased solubility of a sterol derivative is of particular advantage when purifying such materials by solvent crystallization since the volume of solvent required to dissolve the sterol derivative is from ⅓ to ⅙ as large when using the acetoacetate rather than the acetate of the sterol.

It is well known that beta-keto acids and their esters are metabolic intermediates in living organisms. Compounds such as acetoacetic esters and acetone dicarboxylic esters have been isolated as products of metabolism. Esters of beta-keto acids and sterols, therefore, are considered to be metabolic intermediates and may have therapeutic value.

Example XI

2.0 grams of cholesterol, 8 grams of ethyl acetonedicarboxylate $C_2H_5OOC—CH_2COCH_2COOC_2H_5$ and 10 milliliters of toluene were heated on a steam bath for 20 hours, the evolved ethanol being distilled off. The toluene was then removed by distillation in vacuo and the oily residue was triturated with acetone to precipitate a white solid, dicholesteryl acetonedicarboxylate. This material after one crystallization from a mixture of methanol and isopropyl ether was a solid which melted at 173° C. The acetone filtrate on evaporation to dryness left an oil, ethyl cholesteryl acetonedicarboxylate which could not be obtained crystalline.

Example XII

10 grams of cholesterol and 100 grams of diethyl acetyl succinate $C_2H_5OOC—CH_2CH_2(COCH_3)COOC_2H_5$ were heated on the steam bath under a 10 millimeter absolute pressure for 64 hours. 93.5 grams of unreacted lower beta-keto ester was then removed by distillation in vacuo, and the residue was dissolved in 50 milliliters of ethanol, cooled and the white solid filtered, washed with 100 milliliters of ethanol and dried. The product was a solid which consisted largely of cholesteryl ethyl acetyl succinate.

Example XIII

57 milligrams of cortisone and 50 milliliters of methyl acetoacetate were heated on a steam bath for 16 hours. The unreacted methyl acetoacetate was then removed by distillation in vacuo, and the residue on crystallization from aqueous ethanol yielded shiny platelets of cortisone acetoacetate which melted at 112–114° C.

Example XIV

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated with 101.2 milligrams of triethylamine at 98° C. for 4 hours, using a water condenser. The 50.0 milliliters of methanol was added, the solution was cooled overnight at 23° F., the white solid was filtered, washed with 50 milliliters methanol and dried. The product was cholesteryl acetoacetate.

Example XV

The process of Example XIV was repeated but substituting 98.0 milligrams of concentrated sulfuric acid for the triethylamine. The product was cholesteryl acetoacetate.

Example XVI

The process of Example XIV was repeated but substituting 38.6 milligrams of sodium cholesterate for the triethylamine. The product was cholesteryl acetoacetate.

Example XVII

The process of Example XIV was repeated but substituting 185 milligrams of benzene sulfonic acid hydrate for the triethylamine, and heating the reaction mixture at 98° C. for 3 hours. The product was cholesteryl acetoacetate.

Example XVIII

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated at 140° C. with a water condenser for 5 hours. Then 50 milliliters of methanol was added, the solution was cooled overnight at 23° F., and the white solid was filtered, washed with 50 milliliters methanol and dried. The product melted at 94.5–95.5° C. and was substantially pure cholesteryl acetoacetate.

Example XIX

The process of Example XVIII was repeated at a temperature of 160° C. rather than 140° C. The product melted at 90–91° C. and was cholesteryl acetoacetate but was slightly less pure than the product of Example XVIII.

While the above examples are directed to the production of the sterol acetoacetates by ester interchange reaction, it is to be understood that these esters may be prepared by esterification by reaction of the sterol with diketene.

The beta carbonyl esters of sterols and hydroxylated steroids are generally solids which crystallize readily and which melt at temperatures usually ranging from 30–125° C. A few of these esters are liquids. These esters may be used as intermediates for production of a wide variety of sterol derivatives and modified sterols. Thus, these esters may be treated according to the following groups of reactions:

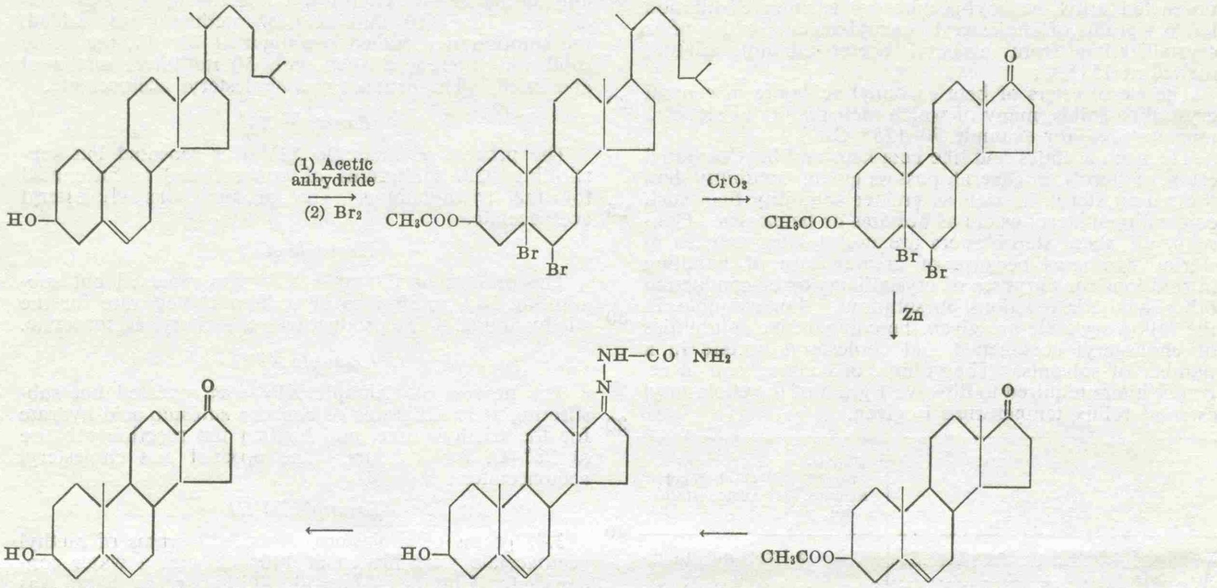
(A) Reactions with the radical of the beta carbonyl or beta-keto acid.

(B) Reaction with the sterol or steroid radical (R_4).

Each of these are considered below.

According to this invention, modified sterols or steroids may be produced in a convenient manner using the esters of beta-carbonyl or beta-keto acids as intermediates. Prior to the present invention, it has been common to prepare derivatives of sterols or modified sterols by preliminarily blocking off the hydroxyl group by esterification, and subsequently preparing the derivative. In such a case, it is common to esterify the sterol with acetic anhydride to produce the acetate. This sterol acetate is then subjected to treatment to modify the sterol radical. For example, the sterol radical may be oxidized, halogenated, or halogenated and thereafter oxidized in order to produce modified compounds. Following these reactions, the acetate group is hydrolyzed off and a modified sterol is thus obtained.

As a typical example, cholesterol has been reacted with acetic anhydride in order to produce the corresponding acetate. This product is then reacted with bromine to protect the double bond. The resulting product is then oxidized with chromic acid or like oxidizing agent to remove the side chain. Thereafter, the resulting oxidized product is debrominated and reacted with semi-carbazide to precipitate the semi-carbazone from solution. Following this, the product is hydrolyzed to remove the semi-carbazide and acetate groups, with the resulting production of dehydroepiandrosterone. In some cases it may be desirable to hydrolyze the acetate grouping to form the free alcohol prior to the preparation of the semi-carbazone. The reactions involved in such process are indicated to be as follows:



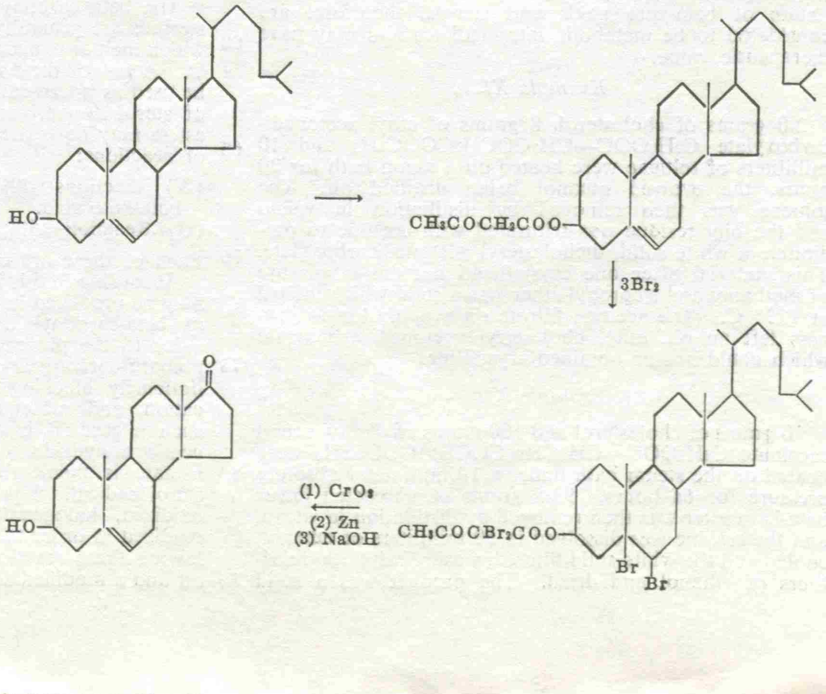
Epidehydroandrosterone

According to the invention of two of us the beta-keto esters of sterols may be prepared and these esters subjected to the treatment for the production of sterol oxidation products or other modifications of the sterol radical. Substantially higher yields of products may thus be obtained. Following this, the acetoacetate group or like beta carbonyl group may if desired be hydrolyzed off with consequent regeneration of the sterol.

The following are typical examples which are generally applicable to this embodiment.

Example XX

100 grams of cholesterol are transesterified with 1000 milliliters of methyl acetoacetate as described above to yield 110 grams of pure cholesteryl acetoacetate. This ester is dissolved in 1 liter of carbon tetrachloride and a solution of 115 grams of bromine in 1 liter of petroleum ether is added slowly with agitation, keeping the reaction mixture at a temperature of 15–20° C. Evaporation of the solvent leaves tetrabromo cholesteryl acetoacetate. This acetoacetate may be oxidized according to standard methods used for oxidizing the corresponding acetate such as described in United States Letters Patent Nos. 2,464,236, 2,244,968, 2,323,584 or according to other methods such as described in Fiat Final Report No. 996 entitled "The Commercial Development and Manufacture of Synthetic Hormones in Germany," published January 29, 1947, by the Technical Intelligence Division U. S. Department of Commerce. In such a case the stoichiometric amount of the acetoacetate or other beta-keto ester or beta carbonyl ester is substituted for the corresponding sterol acetate. Thus cholesterol acetoacetate or like sterol acetate may be oxidized with chromic acid in a mixture of glacial acetic acid and concentrated sulfuric acid, keeping the reaction temperature at 15–20° C. The reaction mixture is then filtered to remove the chromium salts, debrominated with zinc dust, hydrolyzed with aqueous sodium hydroxide and extracted with benzene. Evaporation of the benzene in vacuo leaves a brown oil which is treated with semicarbazide hydrochloride and sodium acetate to isolate the semicarbazone of epidehydroandrosterone in the conventional manner.



Sterol acetoacetates may be treated according to other methods for production of modified sterols. Thus Testosterone or Proluton C may be prepared from Trans-Dehydroandrosterone acetoacetate, Desoxy corticosterone acetoacetate from 3-acetoacetoxy cholenic acid, Progesterone from Soya-Phytosterol and other sterol derivatives prepared by substituting the corresponding acetoacetates or like beta-keto esters or beta carbonyl esters in lieu of the acetates in the processes disclosed in the above mentioned Fiat Report No. 996.

This reaction is illustrative of but one of many series of reactions which may employ beta-carbonyl esters of sterols as intermediates. Other similar reaction schemes include the oxidation of stigmasteryl acetoacetates or other beta-keto esters of stigmasterol to hydroxybisnorcholenic acid and thence to pregnenolone and progesterone, also via beta-carbonyl derivatives. Similarly, a beta-keto ester of sitosterol such as sitosteryl acetoacetate may be oxidized to epidehydroandrosterone by the series of reactions above indicated. Similarly beta-keto esters of cholesterol may be oxidized with potassium permanganate to progesterone and other oxidation products.

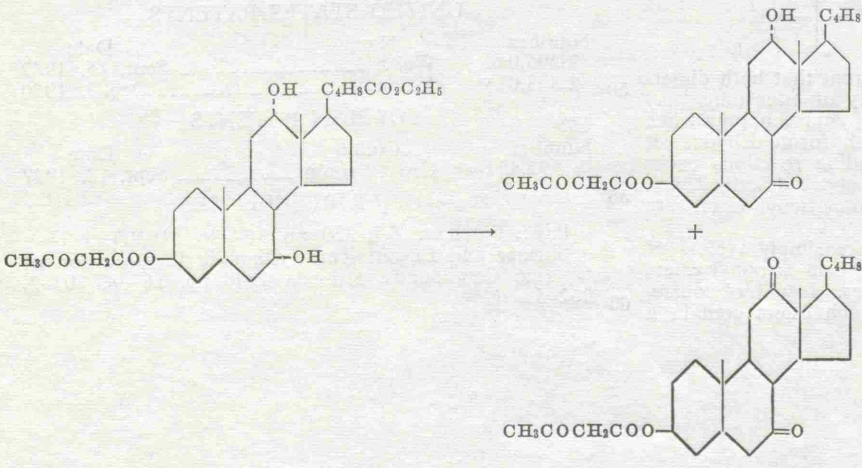
According to a further embodiment, polyhydroxy sterols may be reacted to esterify but one or a portion of the hydroxyls of the sterol. Such a partially esterified sterol may be subjected to oxidation to oxidize the remaining hydroxyl group or groups to ketone groups, or to effect a cleavage of the ring.

Example XXI

40 grams of cholic acid may be heated with 12 grams of methyl acetoacetate in 200 milliliters of xylene under partial vacuum at 100° C. for 24 hours. The xylene is then removed by distillation and the resulting product is largely 3-acetoacetoxy-7,12-dihydroxycholanic acid. This product may be oxidized in the following manner:

Example XXII

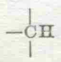
3-acetoacetoxy-7,12-dihydroxycholanic acid ethyl ester (prepared by the Fischer esterification of the acid) may be oxidized with potassium chromate in acetic acid in the presence of sodium acetate to yield a mixture of the ethyl esters of 3-acetoacetoxy-7-keto-12-hydroxycholanic acid and 3-acetoacetoxy-7,12-diketocholanic acid. This may be represented by the equation



According to further embodiments of the invention, a wide series of compounds may be prepared by subjecting the sterol ester to a treatment involving modification of the beta-keto or beta-carbonyl radical.

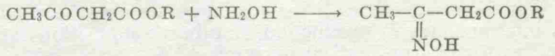
Thus beta-keto esters containing one or more active hydrogen atoms will in addition to the normal ester type reactions, have reactivity in the following manner:

(1) Reactions involving the carbonyl group directly
(2) Reactions involving the enolic hydroxyl group, and
(3) Aeactions due to the activation of the


$$-\overset{|}{\underset{|}{C}}H$$

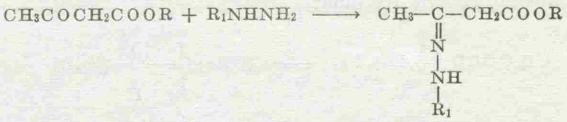
or —CH_2 groups between the carbonyls.

The following are typical examples of these reactions. A sterol ester of a beta-carbonyl acid, such as cholesteryl acetoacetate, may be reacted with hydroxylamine hydrochloride with consequent production of the corresponding oxime according to the following equation:


$$CH_3COCH_2COOR + NH_2OH \longrightarrow CH_3-\underset{\underset{NOH}{\|}}{C}-CH_2COOR$$

where R is a sterol radical.

Similarly hydrazine and substituted hydrazines react with consequent production of the corresponding hydrazones, of which the following equation is typical.


$$CH_3COCH_2COOR + R_1NHNH_2 \longrightarrow CH_3-\underset{\underset{\underset{\underset{R_1}{|}}{NH}}{\underset{|}{N}}}{\overset{}{\underset{\|}{C}}}-CH_2COOR$$

where R is the sterol radical and R_1 the radical of the hydrazine. The following examples are illustrative.

Example XXIII

One gram of cholesteryl acetoacetate is dissolved in 10 milliliters of ethanol, and the solution is heated to approximately 65° C. To this hot solution, one gram of semicarbazide hydrochloride and 1.5 grams of sodium acetate are added. The solution is heated for 5 minutes. Upon cooling, the semicarbazone of cholesteryl acetoacetate crystallizes. This example is typical of the type of reactions which occur between semicarbazide and the above described acetoacetate and other beta-keto or beta carbonyl esters of sterols generally. These compounds are, in general, crystalline in character and may be used in the production of other intermediates or as pharmaceuticals.

Example XXIV

To a solution of 1 gram of cholesteryl acetoacetate in 10 milliliters of ethanol, 1 gram of phenyl hydrazine and one drop of acetic acid is added, and the solution is warmed on the steam bath for five minutes. Cholesteryl acetoacetate phenylhydrazone crystallizes on cooling, and may be recovered on filtration. This reaction is typical of the reaction of sterol beta-keto and beta carbonyl esters with hydrazine and substituted hydrazines.

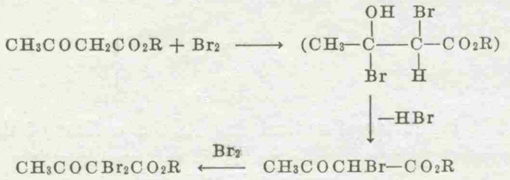
According to a further embodiment, the beta-keto esters of sterols may be reacted with ammonia or primary or secondary amines, including those containing up to 18 carbon atoms in a carbon radical linked to the amino nitrogen, with consequent production of beta-amino crotonic esters of sterols. The following is a typical example.

Example XXV

10 grams of beta-sitosteryl acetoacetate may be dissolved in 100 milliliters of ethanol to which a crystal of ammonium acetate is added. Anhydrous ammonia is then bubbled through this solution. An exothermic reaction occurs and ammonia introduction is continued until a substantial excess of ammonia over theoretical has been introduced or at least so long as heat is evolved. After heat ceases to be evolved, the beta-sitosteryl-beta-amino crotonate is precipitated by addition to the reaction mixture of a concentrated solution of sodium chloride. This

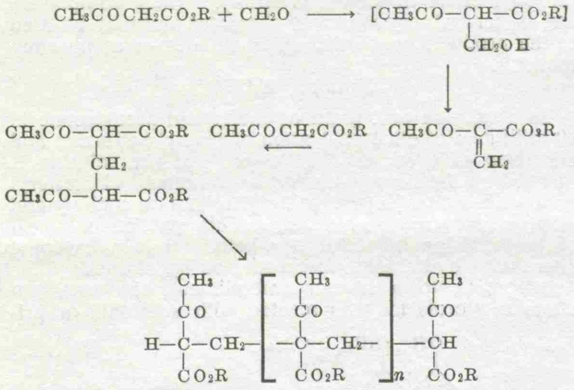
example is typical of examples which may be used in treatment of beta-carbonyl esters of sterols and steroid compounds for production of the corresponding beta-amino crotonate esters. Such compounds may be used as intermediates in production of other compositions as well as for pharmaceutical purposes.

As has been previously explained, the sterol esters of beta-carbonyl acids may be reacted with halogen. In such cases, the halogen, such as bromine or chlorine, reacts with the beta-keto acid radical according to the following general formula:



In many cases, this bromination or chlorination also results in addition of the halogen to a double bond in the sterol radical, if such double bond is present.

According to a further embodiment of the invention, the beta-keto or beta-carbonyl esters, particularly sterol esters of beta-keto acids, may be condensed with aldehydes, such as formaldehyde, acetaldehyde, acrolein, crotonaldehyde, benzaldehyde, and like aldehydes preferably containing not more than 6 carbon atoms, according to the following general reaction:



From this formula, it will be apparent that both dimers and polymers containing a plurality of ester units may be produced. The above formula, of course, applies when an acetoacetic ester is treated with formaldehyde. It will be understood that corresponding reactions occur when other aldehydes are used, as above described, and also when other beta-keto or beta-carbonyl esters are used.

The above described reactions are simply typical of the uses to which the beta-keto or beta-carbonyl esters of sterols may be put as intermediates. It will, of course, be understood that inasmuch as such esters contain a beta-keto or beta-carbonyl group, such esters may be subjected to all of the general reactions which may be applied to the treatment of beta-keto esters.

Although the present invention has been described with reference to the specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention except insofar as included in the accompanying claims.

What is claimed:

1. An ester of a sterol and an acid of the group consisting of acetoacetic acid, benzoylacetic acid, acetonedicarboxylic acid, and acetylsuccinic acid.

2. A sterol acetoacetate.

3. An acetoacetate of a sterol which contains a single alcoholic hydroxyl group.

4. Cholesteryl acetoacetate.

5. Cortisone acetoacetate.

6. Beta-sitosteryl acetoacetate.

7. Stigmasteryl acetoacetate.

8. Epidehydroandrosteryl acetoacetate.

9. A method which comprises reacting a sterol which contains an alcoholic hydroxyl group with an acetoacetic ester of a lower monohydric alcohol containing up to 4 carbon atoms.

10. A method which comprises heating a liquid mixture of an hydroxylated sterol with an acetoacetate of another hydroxy compound.

11. A method of forming an ester of a sterol containing one hydroxyl group, which group is in position 3, which comprises heating to a temperature below 160° C. a mixture of said sterol and an alkyl ester of acetoacetic acid in which the alkyl groups contain one to two carbon atoms.

12. The method of claim 11 in which the sterol is cholesterol.

13. The method of claim 12 in which the reaction is conducted in the presence of a stoichiometric excess of the acetoacetic acid ester, and in the absence of catalysts of ester interchange.

14. The method of claim 13 in which the reaction is conducted with concurrent removal of lower alcohol containing 1 to 2 carbon atoms substantially as it is formed.

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2,693,477

Patented Nov. 2, 1954

2,693,477

PROCESS FOR PREPARING CYANOACETIC ACID ESTERS OF STEROLS

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No Drawing. Application November 17, 1951, Serial No. 256,953

9 Claims. (Cl. 260—397.2)

The present invention relates to novel esters and methods of forming esters of cyanoacetic acid and alcohols and it has particular relation to novel methods of forming cyanoacetic acid esters of alcohols of relatively high molecular weight and to the novel ester products resulting from such method.

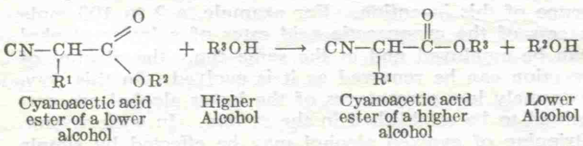
According to the present invention, it has been discovered that esters of alcohols having a relatively higher molecular weight (containing 12 or more carbon atoms) can be prepared in high purity and high yield by interacting under mild conditions an ester of a cyanoacetic acid and a lower aliphatic (preferably saturated) alcohol containing, for example, up to (and including) 4 carbon atoms and herein termed an interchangeable ester, with the alcohol of the ester desired particularly when such alcohol to be esterified has a higher boiling point than such lower alcohol (preferably at least 20° C. higher).

Novel and useful classes of esters have been prepared according to this invention. The sterol esters of cyanoacetic acid and substituted cyanoacetic acids are particularly valuable. Other valuable classes of esters of such acids and alcohols containing 12 or more carbon atoms have been prepared within the purview of this invention as will be apparent from the ensuing disclosure.

According to a further embodiment of the invention, it has been found that maximum yield and purity of ester is obtained when the evolved lower alcohol is swept rapidly from the reaction mixture or is otherwise reduced in concentration with respect to the original cyanoacetic acid ester. This may be accomplished by distilling the lower alcohol under conditions such that the partial pressure of the lower alcohol vapor in the system is maintained below atmospheric pressure. For example, the reaction mixture may be blown with an inert gas such as carbon dioxide, nitrogen, etc. to cause rapid distillation of evolved lower alcohol. Alternatively or in conjunction therewith, a subatmospheric pressure may be maintained over the reaction mixture to promote distillation of the evolved lower alcohol. These precautions are of special importance where the temperature of the reaction mixture is allowed to rise to a relatively high value, for example 120–160° C. However, pure products are generally obtained by recourse to these precautions even when the reaction temperature is below 120° C.

To insure good yields, excesses of the alcohol to be reacted with the cyanoacetic acid ester of the lower alcohol are to be avoided. Indeed, great excesses of the cyanoacetic acid ester component may be employed and if care is exercised to eliminate or at least sufficiently to reduce in the reaction zone the relative concentration of the alcohol freed with respect to the initial cyanoacetic acid ester, quantitative ester interchange of alcohol radicals can be attained.

The reaction involved may be represented by the general equation:



$$\mathrm{CN{-}CH(R^1){-}C({=}O)OR^2} + \mathrm{R^3OH} \longrightarrow \mathrm{CN{-}CH(R^1){-}C({=}O){-}OR^3} + \mathrm{R^2OH}$$

In the equation R^1 may be, and usually is, hydrogen, but it can also be hydrocarbon or substituted hydrocarbon (rarely containing more than six carbon atoms) such as methyl, ethyl, propyl, butyl, chloro, amino, chloromethyl, benzyl, phenyl, or the like derivatives thereof. At least one of the hydrogens linked to the alpha carbon atom in the cyanoacetic acid ester is unsubstituted.

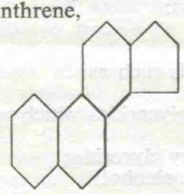
The group R^2 is usually the labile radical which is adapted to be replaced in the ester interchange. These groups or radicals usually are of low molecular weight, e. g., 1, 2, 3, or possibly 4 carbon atoms in a saturated or unsaturated aliphatic substituted or unsubstituted hydrocarbon chain.

ALCOHOLS CAPABLE OF ESTER INTERCHANGE WITH LOWER ESTERS OF CYANOACETIC ACID

Many hydroxy compounds of relatively high molecular weight may be treated in accordance with the provisions of this invention with a lower ester of cyanoacetic acid to effect ester interchange reaction. Typical examples of these alcohols are represented in the last equation by the formula R^3OH where OH is an alcoholic OH group and R^3 contains in most cases 12, 16, 18, or more carbon atoms. In the formula, the alcohol is represented as being monohydric. However, it is also within the scope of this invention to effect ester interchange reaction under certain conditions hereinafter to be described, between cyanoacetic acid esters of lower alcohols and alcohols containing 2, 3, 4, 6, and more hydroxy groups in a single molecule. Obviously the alcohol must be soluble in the cyanoacetic acid ester, or at least the two must be soluble in a common, non-reactive solvent, e. g., toluene, xylene, etc.

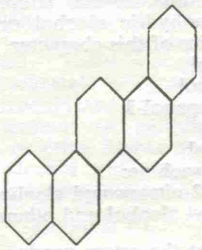
The invention is especially directed to cyanoacetic esters of sterols and certain of the long chain alcohols and hydroxy compounds such as occur in or are derived from glyceride oils, tall oil, waxes, and wool fats and the like are outstanding examples of such compounds. It was quite surprising that these hydroxy compounds of such high molecular weight would so easily undergo ester interchange.

The sterols can be regarded as being derived from cyclopentanophenanthrene,



or its perhydro derivatives by appropriate shifting or replacement of hydrogen by hydroxyl or other groups and it may contain other substituted hydrocarbon groups or may be otherwise modified by dehydrogenation and such like changes familiar to the art.

The triterpene alcohols such as occurring in wool fat can similarly be regarded as being hydroxy derivatives of picene



or its hydrogenated derivatives.

These hydroxy compounds are often comparatively sensitive to high temperatures and other conditions. However, many of them are important starting compounds in the syntheses of hormones and other biologicals. Yet in some of the reactions to which the compounds are subjected it is desirable to protect the hydroxyl oxygen from loss or from conversion to carbonyl form. It may also be desirable to convert the hydroxyl to ester form in order to increase the polarity of the compound or to provide reactive or labile groups.

It has now been discovered that these higher alcohols can easily be esterified by interchange or alcoholysis with cyanoacetic acid esters at very moderate temperatures to provide esters of great utility.

Examples of those higher alcohols which can readily be esterified with cyanoacetic acid esters by ester interchange reaction include:

- Sterols such as:
  - Ergostanetriol or ergostadienetriol
  - Cholesterol
  - Beta sitosterol
  - Stigmasterol
  - Cholestanol
  - Epidehydroandrosterone
  - Ergosterol
  - Epicholestanol
  - Coprostanol
  - Cortisone
  - Cholic acid
  - Desoxycholic acid
  - Steroid sapogenins
  - Steroid intermediates
- Triterpene alcohols such as:
  - Agnosterol
  - Lanosterol

It will also be understood that cyanoacetic esters of higher alcohols may be prepared including esters of the following:

- Aliphatic compound containing at least 6 and usually containing 16 or more carbon atoms and containing alcoholic hydroxyl groups, such as:
  - Octadecyl alcohol
  - Lauryl alcohol
  - Ceryl alcohol
  - Cetyl alcohol
  - Carnaubyl alcohol
  - Lignoceryl alcohol
- Polyhydroxy compounds such as:
  - Decamethylene glycol
  - Glycerine
  - Ethylene glycol
  - Polyethylene glycol and polyethylene oxide resins or waxes and like waxy resins which are soluble in solvents of fats
- Ether alcohols such as:
  - Butyl carbitol
  - Propyl carbitol
- Hydroxy glyceride oils such as:
  - Castor oil
  - Mono- and di- glycerides which are soluble in solvents of fats
  - Synthetic hydroxy glycerides
- Cyclic and polycyclic alcohols
  - Cyclohexanol
  - Hydroxy decalin
  - Polyhydric alcohol-polybasic acid resins such as glycerol phthalate, glycerol or glycol maleate and like esters of polyhydric alcohols, including glycerol, ethylene glycol, propylene glycol, diethylene glycol, trimethylene glycol, etc. with polybasic acids such as phthalic, succinic, maleic, fumaric, itaconic, oxalic, terephthalic, or adipic acid or monohydric alcohol or monobasic acid modified resins of this character
  - Diamyl carbinol
  - Diethylene glycol
  - 1,2-dichloropropanol-3
  - Pentaerythritol
  - Linoleyl alcohol
  - Nitro alcohols such as:
    - 2-methyl, 2-nitropropyl alcohol
    - 2-nitrobutyl alcohol and others.

It is desirable that the esters produced by interchange between the original ester of cyanoacetic acid and the higher alcohols be of a boiling point above that of the initial cyanoacetic acid ester.

Obviously the hydroxy compound which is to undergo interchange with the cyanoacetc acid ester should be soluble in the latter or at least should be soluble in a solvent that is mutually compatible therewith.

CONDITIONS OF REACTION

The conditions of reaction employed to effect the ester interchange between the hydroxy compounds and the cyanoacetic acid esters such as herein disclosed may vary, dependent upon the ester and the hydroxy compound. However, a special advantage of the process herein contemplated is that the conditions may be relatively mild thus insuring high yield and minimizing loss through decomposition. Catalysts are usually omitted, but may be present if purity of product is not important.

The temperatures of reaction should be sufficiently high to drive off the evolved lower alcohol quite rapidly. Preferably it should be driven off substantially as fast as it is liberated in the reaction mixture. The temperature of operation normally ranges between 50 and 150° C., preferably below 120° C. The temperature should be below the point of decomposition of the reactants or of the desired reaction product. A good average temperature is approximately 90 to 100° C. (steam bath temperature) and rarely above 120° C. The temperature can also be reduced below this value and may be conducted at room temperature where the excess of the ester used is large and the time of reaction is long, for example 24 hours or even several weeks. However, it is understood that as the temperature approaches or is reduced below the normal boiling point of the lower alcohol evolved in the system it is desirable to apply vacuum, or otherwise to attain low pressure of evolved alcohol in order to promote removal of the latter. Higher temperatures, preferably below 150° C., are permissible so long as side reactions do not seriously interfere with the yield of ester.

The approach of the upper limit of the temperature of reaction can, in many cases, be determined or detected by a tendency of the reaction mixture to darken, indicating decomposition reactions in the mixture. If any tendency so to discolor is observed, the temperature should be reduced at once until it ceases. It is usually preferred to employ a temperature above the boiling point at operating pressures of the lower alcohol evolved in the system. This facilitates removal of the lower alcohol and causes the reaction to proceed rapidly and smoothly to completion.

It is a principle of the present invention that the concentration of evolved lower alcohol such as methyl alcohol, ethyl alcohol, or the like, dependent upon the alkyl radical of the cyanoacetic acid ester, should be maintained at a relatively low value in the reaction mixture, or at least before the final conclusion of the reaction, the concentration of the lower alcohol should be carried to a low value.

A plurality of modes of attaining this low relative concentration of the evolved alcohol are permissible. For example, the system may be maintained under relatively high vacuum during the reaction, thus stripping off the lower alcohol as it is formed while permitting the temperature of reaction to stay relatively low. Any cyanoacetic acid ester of a lower alcohol carried over as a vapor in the lower alcohol vapor stripped off can be condensed and returned to the reaction zone. In this way, the concentration of the original cyanoacetic acid ester in the system is maintained.

According to a further embodiment, the lower evolved alcohol may be stripped off by blowing the reaction mixture with a non-reactive vapor or gas, e. g., nitrogen, CO_2 or the like. Water, as such in the system, is to be avoided.

Still another convenient method of attaining low concentration of evolved alcohol in the system comprises dilution of the alcohol of reaction by employing a high molecular excess of the cyanoacetic acid ester of the lower alcohol. For example, the molecular ratio of the cyanoacetic acid may be 5, 10, 20 or even 100 times that of the alcohol to be esterified. In most of such instances the original ester will be employed in a molecular ratio of at least two moles of original ester per mole of alcohol to be esterified. The excess can be added initially or it can be added or increased as the reaction proceeds.

Combinations of these several methods are within the scope of this invention. For example, a 2 to 100 mole excess of the cyanoacetic acid ester of a lower alcohol can be employed and at the same time, the alcohol of reaction can be removed as it is evolved. In this way, extremely low percentages of the lower alcohol are permitted to be established in the system. In such system, stripping of evolved alcohol may be effected by simple distillation at atmospheric pressure, by vacuum distillation, or by blowing the reaction mixture with a non-reactive gas or vapor.

By properly reducing the concentration of the evolved lower alcohol in the system, it is possible to obtain yields of higher esters of cyanoacetic acid of 90%, or even of practically quantitative values, e. g., 98 or 99% without discloration of the product or the reactants.

If care is observed to maintain the reaction temperature reasonably low and at the same time to distill off under vacuum, or otherwise remove or decrease the alcohol evolved by reaction, highly efficient ester interchange can be effected with equimolar ratios of the higher alcohol and the cyanoacetic acid ester of a lower alcohol or with but a slight excess of the latter ester. However, it is usually more convenient to operate with an excess of cyanoacetic acid ester which is substantial, e. g., 10% or preferably larger (on a molar basis) of the starting cyanoacetic acid ester.

When the reaction nears completion the excess of original ester can be distilled off. Vacuum may be applied to promote the distillation within the permissible temperature limits in order that there may be no decomposition of any of the compounds. An absolute pressure of about 5 to 50, e. g., 15 millimeters of mercury is usually satisfactory for distilling off this excess of cyanoacetic ester but such other subatmospheric pressures as will remove the excess ester at permissible temperatures may be employed. The distillation may be conducted at or near the original reaction temperature. In any event, the temperature should not exceed 180° C. and usually will be below 120 or perhaps 140° C. Of course, if absolute purity of products is not necessary the excess cyanoacetate may be removed by distillation at atmospheric pressure, thereby producing products which are somewhat contaminated due to the decomposition of compounds at these higher temperatures. The distillation of the excess cyanoacetic acid ester of lower alcohol is important because it usually first distills off all or most of any lower alcohol in the system, thus reducing the concentration of the latter with respect to the original cyanoacetic acid ester still present and assuring that if higher alcohol is still present in the system, the ester interchange is finally completed at moderate temperatures.

The main features involved in the process as herein disclosed thus may be summarized as follows:

1. The alcohol which is selected to undergo ester interchange should be one that does not undergo side reactions by reason of decomposition or rearrangement or by reason of reactions other than ester interchange with the cyanoacetic acid ester of the lower alcohol. It should also be of substantially higher boiling point than the alcohol which is liberated by the reaction.

2. The amount of the cyanoacetic acid ester of a lower alcohol should be at least in equimolar proportion with respect to the alcohol to be subjected to ester interchange and preferably it should be in substantial excess. In the production of esters of many alcohols it is necessary to use an appreciable excess, for example 50% (molar basis) or more of the cyanoacetic ester in order to dissolve the alcohol being esterified and/or to insure improved yields.

3. The concentration of the evolved alcohol in the reaction mixture should be maintained as low as is feasible, e. g., not in excess of about 33 molar percent and preferably less with respect to the original amount of the cyanoacetic acid ester of a lower alcohol. This may be effectively accomplished in several ways as, for example, by distilling off the lower alcohol as formed either at atmospheric pressure or under diminished pressure with the use of diminished pressure during the later stages of the reaction being particularly advantageous, or by blowing with an inert gas, or vapor, or by maintenance of a large excess of the cyanoacetic acid ester.

4. Catalysts of reaction are not necessary. They may, however, at times be used.

5. The temperature of the ester interchange should be moderate, e. g., 50 to 120° C. and in any event not above about 160° C.. Satisfactory upper limits of temperature are determinable by observation of the initiation of decomposition reactions.

6. The temperature of reaction should be maintained until the lower alcohol ceases, or substantially ceases to evolve.

7. Non-reactive solvents or solvents other than the excess of cyanoacetic acid and a lower alcohol are not ordinarily necessary in the reaction. However, it will be apparent that non-reactive liquid media which are common solvents of the system may also be employed if so desired.

8. It is desirable, at the conclusion of the reaction, to distill off any excess of cyanoacetic acid ester of lower alcohol present in the reaction mixture along with any residual alcohol evolved by the reaction by distillation. If this latter precaution is observed, any unreacted higher alcohol still present in the system will be induced to undergo reaction and thereby carry the reaction substantially to completion.

The esters of cyanoacetic acid which have been prepared within the scope of this invention are, in general, high molecular weight solids or liquids. They may be used for various purposes. Sterol esters are largely crystalline solids. They are soluble in acetone, methyl acetate, and like ketone or ester solvents. They are especially useful as pharmaceuticals, or as intermediates for production of modified sterols.

The esters of the other higher alcohols may be used as plasticizers, waxes, etc. and also for the purpose of producing intermediates which may be resinous or non-resinous.

The following examples illustrate the application of the principles of the invention.

Example I

Five grams of cholesterol, 150 grams of ethyl cyanoacetate and 25 grams of toluene were placed in an appropriate flask adapted to permit free escape of evolved vapor and the mixture was heated on a steam bath at a temperature of about 90 to 100° C. for 8 hours. At the conclusion of this time, the reaction was substantially complete. Accordingly, the solvent and the excess of ethyl cyanoacetate were stripped off under vacuum, e. g., at a pressure of 15 millimeters (absolute) and the remaining white solid in a yield of 5.3 grams and of a saponification value of 116 was crystallized from an isopropyl alcohol-acetone mixture of a composition of 2 parts isopropanol and 1 part acetone. A solid crystalline product was obtained having a melting point of 182 to 183° C. This product is cholesteryl cyanoacetate. When beta sitosterol, stigmasterol, ergosterol, cortisone or like sterols are substituted in equivalent amount for cholesterol, the reaction occurs in the same way and crystalline cyanoacetic esters of these sterols are obtained. Methyl or propyl cyanoacetic acid ester can be substituted for ethyl cyanoacetic acid ester in the reaction of this example. It will likewise be apparent that lower esters of substituted cyanoacetic acid containing a methyl, ethyl, or propyl group substituted for one of the hydrogen on the carbon atom alpha to the carbonyl (C=O) group with the consequent production of the corresponding sterol esters.

Example II

Five grams of stearyl alcohol and 50 grams of ethyl cyanoacetate are heated on the steam bath at a temperature of about 90 to 100° C. for 17 hours. Thereupon, the excess of ethyl cyanoacetate together with any residue of ethyl alcohol remaining in the system were stripped off under vacuum, e. g., at a pressure of 15 millimeters (absolute). There was obtained 5.5 grams of pure stearyl cyanoacetate of a melting point of 55 to 56° C. and of a saponification value of 166.

The equivalent amount of palmitic, lauryl, oleyl, linoleyl, eleostearyl, or other higher alcohol can be substituted for stearyl alcohol with consequent production of the corresponding cyanoacetates.

Example III

Ten grams of cholesterol and 100 cc. of methyl cyanoacetic acid ester and 50 cc. toluene are mixed together. The mixture is heated on a steam bath at a temperature of about 90 to 100° C. and at atmospheric pressure for 15 hours. During the reaction, carbon dioxide is bubbled through the reaction mixture to effect thorough removal of the evolved methyl alcohol from the reaction zone. Finally, the excess cyanoacetic acid ester and toluene are distilled off under an absolute pressure of about 15 millimeters leaving the desired cyanoacetic acid ester of cholesterol.

Example IV

Ten grams of cholesterol is mixed with 100 cc. of methyl cyanoacetate and 50 cc. toluene and the mixture is heated upon the steam bath as above described for 15 hours at a pressure of 40 millimeters of mercury (absolute). During the course of the reaction, methyl alcohol is evolved and it, the unreacted methyl cyanoacetate, and toluene are distilled off. The cholesteryl cyanoacetate remains behind.

The foregoing examples illustrate the application of the ester interchange reaction to individual sterols or other higher alcohols in pure state. It will be apparent that the alcohol compound to undergo ester interchange need not be pure. Various glyceride oil mixtures containing sterols in substantial amounts may be reacted to produce sterol cyanoacetate. For example, a soap stock which normally contains considerable amounts of sterols, may be treated with methyl or ethyl cyanoacetate in accordance with the provisions of the invention to form cyanoacetic esters of sterols in admixture with glycerides of fatty acids or in admixture with fatty acids or various combination of the glycerides and fatty acids or other constituents of the mixtures. The temperatures of reaction and other conditions correspond to those herein disclosed. Many other mixtures of fatlike products likewise include sterols which are susceptible of treatment in accordance with the provisions of the present invention.

Wool fat, for example, includes considerable amounts of cholesterol and such cholesterol-containing material may be treated with an excess of ethyl or methyl cyanoacetate at temperatures near 100° C. to form cholesteryl esters of cyanoacetic acid in the mixture. These cholesterol esters can be recovered by solvent extraction or by other appropriate methods.

Likewise, tall oil as obtained in the digestion of paper pulp is rich in sterols and notably in beta sitosterol. The distillation residues obtained after partial distillation of the resin acids and fatty acids of tall oil are especially enriched in beta sitosterol. The crude mixtures can be treated with methyl or ethyl cyanoacetate to provide esters of beta sitosterol in admixture with rosin acids, fatty acids, and the like other impurities of the tall oil residue.

The following example illustrates the application of the principles of the invention in the preparation of cyanoacetic esters of a crude or purified beta sitosterol.

Example V

On hundred grams of unsaponifiable fraction of tall oil which consists largely of beta sitosterol together with some higher aliphatic alcohols and other materials may be heated with 200 grams of methyl cyanoacetate and 500 grams of xylene to a temperature of about 100° C. for 24 hours. The excess of methyl cyanoacetate and the xylene are then distilled off under a pressure of about 10 millimeters of mercury (absolute) to obtain a residue containing the desired beta sitosteryl ester of cyanoacteic acid.

When a polyhydroxy sterol is used in accordance with one of the above examples using at least one mole of ester per mole of hydroxy group in the sterol such as Examples I or II, the corresponding cyanoacetic esters such as ergostane mono, di or tri cyanoacetate result.

Although the present invention has been described with reference to certain embodiments thereof, it is not intended that the specific details of such embodiments shall be regarded as limitations upon the scope of this invention except insofar as included in the accompanying claims.

I claim:

1. A method of forming an ester of a cyanoacetic acid and a sterol, which comprises heating a mixture of said sterol and an interchangeable ester of a lower monohydric aliphatic alcohol and said acid, said interchangeable ester being in excess of stoichiometric proportion with respect to the sterol, and removing the evolved lower alcohol during the heating operation, whereby ester interchange between said higher alcohol and said interchange ester is effected.

2. The method of claim 1 in which the interchange ester alcohol is of cyanoacetic acid.

3. The method of claim 1 in which the sterol is cholesterol.

4. The method of claim 1 in which the sterol is sitosterol.

5. The method of claim 1 in which the lower alcohol of the interchangeable ester is of 1 to 2 carbon atoms.

6. The method of claim 1 in which the heating operation is performed in the substantial absence of catalysts.

7. A method of preparing an ester which comprises heating a cyanoacetic acid ester of a lower aliphatic monohydric alcohol with a sterol and distilling off the evolved lower alcohol.

8. A method of preparing an ester of a sterol, which comprises heating in the absence of catalyst a mixture of a sterol and a lower aliphatic monohydric alcohol ester of cyanoacetic acid, and distilling of the evolved lower alcohol while the esterification is in progress.

9. The method of claim 8 in which evolved lower alcohol is continuously removed from the reaction system as it is formed.

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United States Patent Office

2,693,478

Patented Nov. 2, 1954

2,693,478

PREPARATION OF ESTERS OF OXALIC ACID

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**No Drawing. Application November 30, 1951,
Serial No. 259,320**

15 Claims. (Cl. 260—397.2)

The present invention relates to a method of forming esters of sterols and oxalic acid and to the novel esters obtained by application of the method.

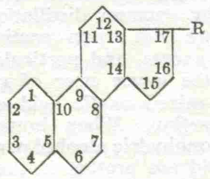
It has heretofore been customary to form esters of various alcohols and carboxylic acids by a number of different methods such as direct reaction between the desired acids and alcohols or between chlorides of the acids or anhydrides of the acids and the alcohols. In general, these methods have involved rather drastic conditions of reaction, as for example, high temperatures and/or the use of catalysts and the like. These conditions of reaction often complicated purification of the products or the catalysts left as residues in the reaction mixture were hard to eliminate. Likewise the reaction was often incomplete and poor yields of the desired product were obtained. These difficulties were quite pronounced in the production of esters of higher molecular weight alcohols, e. g. steroid bodies.

THE PRESENT INVENTION

This invention is based upon the discovery that the sterols or steroid bodies, can easily be caused to undergo ester interchange with lower aliphatic esters of oxalic acid. Most commonly, the present invention involves an ester interchange reaction between a sterol or steroid body and a lower ester of oxalic acid under relatively mild temperature conditions and in such manner that the lower alcohol involved in the reaction is rapidly removed from the system or else the concentration thereof in the system is otherwise reduced to a low value. Mild conditions of reaction will be more fully described in subsequent portions of this specification.

The sterols are alcohols which may be isolated from the unsaponifiable residues of lipids derived from plant and animal sources. These compounds are of relatively high molecular weight containing from 17 to 30 or more carbon atoms. Sterols can be regarded as compounds containing or being derived from the cyclopentanoperhydrophenathrene ring structure and containing one or more alcoholic groups. These alcoholic groups may be primary, secondary, or tertiary or any combination thereof. The ring structure may be completely saturated or may contain from 1 to 3 or more double bonds.

The sterols generally contain the following ring structure:

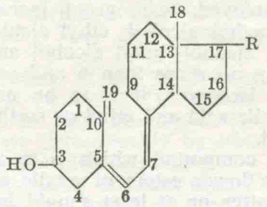


In the above structure, R may be H, OH, =O, straight chain or branched and either saturated or unsaturated hydrocarbon, or oxygenated or amino derivatives of the aforementioned hydrocarbons.

The above structure will contain one or more hydroxyl groups within the molecule appearing in either the ring or in a side chain or in both.

In addition a CH_3 group will generally appear at positions 10 and 13. (See Natural Products Related to Phenanthrene, Fieser and Fieser, Reinhold Publishing Corp.).

Closely related compounds which may be esterified according to this invention are the vitamins of the D group which usually are of the conventionalized formula:



(see Chemistry and Physiology of the Vitamins, H. R. Rosenberg, 1945, Interscience Publishers, Inc., New York, page 341.) The preparation of oxalic acid esters of the vitamins of the D group is therefore regarded as being broadly embraced within the purview of the present invention. Such compounds and their substituted equivalents or isomers are included within the term "sterol" as herein used. Obviously the epimers and hydration products may be employed as starting materials for treatment with lower alkyl esters of oxalic acid.

While many of the sterols are isolated from natural sources, the use of such compounds prepared by synthetic methods is contemplated herein.

These sterols or sterol-like compounds are often comparatively sensitive to high temperatures and/or other conditions. However, many of them are important starting compounds in the synthesis of hormones and other biologicals. Yet in some of the reactions to which the compounds are subjected, it is desirable to protect the hydroxyl group from loss or from conversion to carbonyl form. It may also be desirable to convert the hydroxyl to ester form in order to increase the polarity of the compound or to provide reactive, or labile groups. By recourse to the present invention, the sterol or steroid compound may be esterified to produce the oxalic acid ester. These esters may be treated to introduce other radicals or to change the structure of the compound and thereafter the oxalic acid radical may be removed by hydrolysis to restore the hydroxy group to the modified steroid. The term "sterol" as used herein includes all hydroxylated steroids including Vitamin D compounds.

Typical sterols or hydroxy steroids which may be employed according to this invention include:

Table A

Cholesterol
Beta sitosterol
Stigmasterol
Cholestanol
Epidehydroandrosterone
Ergosterol
Ergostanetriol
Ergostadientriol
Strophanthidin
Lithocolic acid
Epicholestanol
Coprostanol
Steroid intermediates
Sterol sapogenins from various sources including dioscorea
Cortisone
Cholic acid
Desoxy cholic acid
Suprasterols
7-dehydrocholesterol
22-dihydroergosterol

Triterpene alcohols such as:

Agnosterol
Lanosterol
Lumisterol

Other vitamins D such as:

Vitamin D_3, D_4, and D_5

Thus esters of sterols containing one, two, three or more alcoholic hydroxyls may be prepared. When the sterols containing two or more alcohol hydroxyl groups are treated, partial esters or completely esterified sterols or mixtures thereof may be obtained. When these are produced as mixtures, they may be separated by crystallization, molecular distillation, chromatography or other methods if desired.

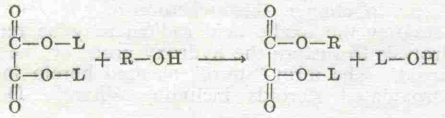
In the practice of the present invention, diesters of various, lower monohydric aliphatic alcohols and oxalic acid may be employed. This group includes the oxalic acid esters of methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol and isobutyl alcohol, containing no more than 6 and usually up to 4 carbon atoms. However, it is to be understood that the esters of oxalic acid and ethyl or methyl alcohol are usually preferred.

The hydroxy compound which is to undergo interchange with the lower esters of oxalic acid should be soluble in the latter or at least should be soluble in a solvent that is mutually compatible therewith.

CONDITIONS OF REACTION

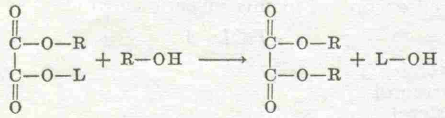
The conditions of reaction employed to effect the ester interchange between the sterols or steroid compounds and the esters of oxalic acid and a lower alcohol such as herein disclosed may vary, dependent upon the ester and the hydroxy compound and whether it is desired to form diesters of the sterol or steroid or merely to form mixed esters. However, a special advantage of the process herein contemplated is that the conditions may be relatively mild thus insuring high yield and minimizing loss through decomposition. Catalysts are usually omitted but may be present if purity of product is not important. Usually the mixed oxalic acid ester of the higher alcohol and the lower alcohol is formed. However, by proper control of the conditions of reaction, the diesters of oxalic acid and the sterols or steroids can be formed. That is, both of the lower alcohol radicals or groups are replaced from the oxalic acid ester. The two types of reaction may proceed concurrently to form mixtures of the mixed ester and the diester in a single reaction mixture. The two types of reaction are represented by the following equations:

Equation I



$$\begin{array}{l} O \\ \| \\ C-O-L \\ | \\ C-O-L \\ \| \\ O \end{array} + R-OH \longrightarrow \begin{array}{l} O \\ \| \\ C-O-R \\ | \\ C-O-L \\ \| \\ O \end{array} + L-OH$$

Equation II



$$\begin{array}{l} O \\ \| \\ C-O-R \\ | \\ C-O-L \\ \| \\ O \end{array} + R-OH \longrightarrow \begin{array}{l} O \\ \| \\ C-O-R \\ | \\ C-O-R \\ \| \\ O \end{array} + L-OH$$

In the equations, the letter L indicates the hydrocarbon radical or group of a lower alcohol. The letter R represents the non-hydroxyl portion of a higher alcohol.

The temperature of reaction usually should be sufficiently high to drive off the evolved lower alcohol quite rapidly. This temperature may vary with reaction pressures, etc. Preferably, it should be driven off substantially as fast as it is liberated in the reaction mixture. The temperature of operation normally ranges between 50 and 150° C. or possibly 180° C. and is preferably below 120° C. The temperature should be below the point of decomposition of the reactants or of the desired reaction product. A good average temperature is approximately 90 to 100° C. (steam-bath temperature) and rarely above 120° C. The temperature can also be reduced below this value and the reaction may be conducted at room temperature where the excess of lower ester used is large and the time of reaction is long, for example, 24 hours or even several weeks. However, it is understood that as the temperature approaches, or is reduced below the normal boiling point of the lower alcohol evolved in the system, it is desirable to apply vacuum or otherwise to attain low pressure of evolved alcohol in order to promote removal of the latter. Higher temperatures, preferably below 150° C. are permissible so long as side reactions do not seriously interfere with the yield of ester.

The approach of the upper limit of the temperature of reaction can, in many cases, be determined or detected by a tendency of the reaction mixture to darken. Such darkening indicates decomposition reactions in the mixture. If any tendency so to discolor is observed, the temperature of the reaction mixture should be reduced at once until darkening ceases. It is usually preferred to employ a temperature above the boiling point at operating pressures of the lower alcohol evolved in the system. This facilitates removal of the lower alcohol and causes reaction to proceed rapidly and smoothly to completion.

It is preferable that the concentration of the evolved lower alcohols such as methyl alcohol, ethyl alcohol or the like, dependent upon the alkyl radical of the oxalic acid ester, should be maintained at a relatively low value in the reaction mixture, or at least before the final conclusion of the reaction, the concentration of the lower alcohol should be carried to a low value.

A plurality of modes of attaining this low relative concentration of the evolved alcohol is permissible. For example, the system may be maintained under relatively high vacuum during the reaction thus stripping off the lower alcohol as it is formed, while permitting the temperature of the reaction to stay relatively low. Any oxalic acid ester of a lower alcohol carried over as a vapor in the lower alcohol vapors stripped off can be condensed and returned to the reaction zone. In this way, the concentration of the original oxalic acid ester in the system is maintained.

The reaction may also be conducted at atmospheric pressure and at a temperature which is lower than the boiling point of the lower ester of oxalic acid but which is higher than the boiling point of the evolved lower alcohol. This evolved lower alcohol is removed from the reaction thereby allowing the reaction to go essentially to completion.

According to a further embodiment, the lower evolved alcohol may be stripped off during the reaction, by blowing the reaction mixture with a non-reactive vapor or gas, e. g. nitrogen, CO_2 or the like.

Still another convenient method of attaining low concentration of evolved alcohol in the system comprises dilution of the alcohol of reaction by employing a high molecular excess of the ester of oxalic acid and lower alcohol. For example, the molecular ratio of the latter ester may be 5, 10, 20 or even 100 times that of the sterol or steroid body to be subjected to esterification through ester interchange reaction. In most of such instances, the original ester will be employed in a molecular ratio of at least 2 moles of said original ester per mole of alcohol to be esterified. At the conclusion of the reaction, the excess of the oxalic acid ester of a lower alcohol can be removed by appropriate distillation. Obviously, if the ratio of said lower ester tends to drop too low during the course of the reaction, additional ester can be added to bring the concentration thereof back to a satisfactory working level.

Combinations of these several methods are within the scope of this invention. For example, a 2 to 100 mole excess of a lower ester of oxalic acid can be employed and at the same time the alcohol of reaction can be removed as it is evolved. In this way, extremely low percentages of the lower alcohol are permitted to be established in the system. In systems containing excesses of lower esters of oxalic acid, stripping of evolved alcohol may be effected by simple distillation at atmospheric pressure, by vacuum distillation or by blowing the reaction mixture with a non-reactive gas or vapor.

When a molar excess, and particularly when a large molar excess of the lower ester of oxalic acid is employed, then the mixed oxalic acid ester is the major product of the reaction. When, however, two or more moles of higher monohydric alcohol per mole of the lower ester of oxalic acid are present in the reaction mixture and care is taken efficiently to remove the lower alcohol evolved, then the symmetrical diester is the major reaction product. For instance, the mixed ester, sitosteryl ethyl oxalate, will be the major product formed in the interchange reaction between a lower ester of oxalic acid and the sterol, sitosterol, when the quantity of lower ester of oxalic acids is present in molar excess to that of the sterol. If, however, the symmetrical diester, disitosteryl oxalate is the desired product, then the quantity of alcohol, in this case sitosterol, is used in molar equivalency or in excess over that of the lower ester of oxalic acid.

Due to the relative insolubility of many of the higher molecular weight alcohols in lower esters of oxalic acid, it may be desirable to use an inert solvent such as toluene, xylene, etc. in the reaction in order to dissolve the reactants but keep the quantity of lower ester to a minimum. This may be particularly advantageous in the preparation of certain symmetrical diesters in which reaction it is desirable to employ a quantity of lower esters of oxalic acid which is no greater than a molar equivalency to the hydroxyl groups present. It is usually relatively easy to separate symmetrical diesters of oxalic acid, such as disteryl oxalates from the higher alcohol and the mixed ester which may be present in the reaction product, because of the great insolubility of the symmetrical ester in many organic solvents such as hot acetone and alcohol in which the mixed ester and the higher alcohol are quite soluble.

Any mixed ester formed can of course be reacted further with the higher alcohol to yield the symmetrical oxalic acid ester.

By properly reducing the concentration of the evolved lower alcohol in the system, it is possible to obtain yields of sterol or steroid esters of oxalic acid of 90 per cent or even of practically quantitative values, e. g. 98 or 99 per cent based upon the sterol, without discoloration of the product of the reaction.

If care is observed to maintain the reaction temperature reasonably low and at the same time to distill off under vacuum, or otherwise remove or decrease the concentration of the alcohol evolved by reaction, highly efficient ester interchange can be effected with equimolar ratios of the sterol or steroid and the ester of oxalic acid and a lower alcohol or with but a slight excess of the latter ester.

When the reaction nears completion, any excess of the original ester can be distilled off. Vacuum may be applied to promote the distillation within permissible temperature limits in order that there may be no decomposition of any of the compounds. A pressure range of about 5 to 50 millimeters absolute, e. g. 15 millimeters of mercury is usually satisfactory for distilling off this excess of the ester of oxalic acid and the lower alcohol but such other subatmospheric pressure as will remove the excess ester at permissible temperatures may be employed. The distillation may be conducted at or near the original reaction temperature. In any event, the temperature should not exceed 180° C. and usually will be below 120 or perhaps 150° C. Of course, if absolute purity of products is not necessary the excess lower ester of oxalic acid may be removed by distillation at atmospheric pressure, thereby producing products which are somewhat contaminated due to the decomposition of compounds at these higher temperatures. In the distillation of the excess of the oxalic acid ester of a lower alcohol, any evolved lower alcohol in the system also distills off thus reducing the concentration of the latter with respect to the original ester of oxalic acid and the lower alcohol still present and assuring that if higher alcohol is still present in the system, the ester interchange is finally completed at moderate temperatures.

The main features involved in the process as they apply to the preparation of mixed or monoesters of higher alcohols, as herein disclosed, thus may be summarized as follows:

1. Mixed esters of lower alcohol, a mono or poly hydroxy sterol and oxalic acid, or diesters of monohydroxy sterols and oxalic acid, as well as polyesters of oxalic acid and polyhydroxy sterols, may be prepared according to this invention.

2. In the preparation of mixed sterol-lower alcohol esters of oxalic acid, it is advantageous to use an amount of oxalic acid ester of a lower alcohol of at least equimolar proportion with respect to the hydroxy group of the alcohol being subjected to ester interchange, and preferably it should be in substantial excess. In the production of esters of many alcohols, it is necessary to use an appreciable excess, for example, 50 per cent (molar basis) or more of the oxalic acid ester of a lower alcohol in order to dissolve the alcohol being esterified and/or to insure improved yields.

3. The concentration of the evolved alcohol in the reaction mixture should be retained as low as is feasible, e. g. not in excess of 33 molar per cent and preferably less with respect to the original amount of the oxalic acid ester of a lower alcohol. This may be effectively accomplished in several ways as for example, by distilling off the lower alcohol as formed either at atmospheric pressure or under diminished pressure, with the use of diminished pressure during the latter stages of the reaction being particularly advantageous, or by blowing with an inert gas or vapor or by the maintenance of a large excess of the oxalic acid ester of a lower alcohol.

4. Catalysts of reaction are not necessary and usually are not employed. They may however, at times, be used.

5. The temperature of the ester interchange should be moderate, e. g. 50 to 120° C. and in any event not above about 150 or 180° C. Satisfactory upper limits of temperature are determinable by observation of the initiation of decomposition reactions.

6. The temperature of reaction should be maintained until the lower alcohol ceases or substantially ceases to evolve.

7. Non-reactive solvents or solvents other than the excess of the oxalic acid ester of a lower alcohol are not ordinarily necessary in the reaction. However, it will be apparent that non-reactive liquid media which are common solvents of the system may also be employed if so desired. Examples of such inert diluents are toluene, benzene, xylene, petroleum naphthas, tetrahydrofuran, dioxan, etc. The use of water as a solvent medium in the system is to be avoided.

8. It is desirable at the conclusion of the reaction to distill off any excess of oxalic acid ester of a lower alcohol present in the reaction mixture along with any residual alcohol evolved by the reaction. If this is done any unreacted higher alcohol still present in the system will be induced to undergo reaction and thereby carry the reaction substantially to completion.

9. In the preparation of symmetrical oxalic acid esters of higher molecular weight monohydric alcohols, it is advantageous to use 2 moles or more of higher alcohol per mole of oxalic acid ester of lower molecular weight alcohol.

The esters of oxalic acids and a sterol or steroid which have been prepared within the scope of the present invention, are in general of high molecular weight. They are largely crystalline solids. They are especially useful as pharmaceuticals or as intermediates for the production of modified sterols, but may be used for various purposes.

The esters of the higher alcohols may be used as plasticizers, waxes and so forth, and also for purposes of producing intermediates which may be resinous or nonresinous.

The following examples illustrate the application of the principles of the invention.

EXAMPLE I

In this example, five grams of cholesterol and 50 grams of diethyloxalate were heated in a flask in the absence of catalysts and on the steam bath for 33 hours, the excess of diethyloxalate was then stripped off under vacuum, e. g. a vacuum of about 15 millimeters (absolute) and the residue after one crystallization from methanol yielded 4.7 grams of a white solid melting at 94.5 to 95.5° C. This product was monocholesteryl mono-ethyloxalate. It has a saponification value of 223 and in chloroform at 25° C., its specific rotation is −33°.

EXAMPLE II

Admix one gram of ergosterol and 30 grams of diethyloxalate and heat the mixture under a pressure of 70 millimeters on a steam bath for a period sufficient to complete the reaction, e. g. 4 hours. The excess diethyloxalate is then removed by distillation in vacuum and the residue is crystallized from ethanol-acetone mixture to yield 0.9 gram of ergosteryl ethyl oxalate.

EXAMPLE III

Seven grams of cholesterol, 30 grams of diethyl oxalate and 50 grams of toluene were mixed and heated for 20 hours on the steam bath under a vacuum. At the end of 3 hours, the toluene was completely distilled and the reaction was complete after 20 hours. It is to be understood that the time required for distillation of the toluene and concurrent removal of evolved alcohol can be controlled by appropriate change of the temperature or pressure in the reaction system. For example, as the pressure decreases, the speed of reaction increases due to the more complete removal of the alcohol evolved. The residue after the distillation, was refluxed in 100 cc. of a 1:1 mixture of ethanol and acetone which left 0.7 gram of a white solid undissolved. This solid was filtered off, washed with hot acetone and crystallized from a toluene-ethanol mixture to yield pure dicholesteryl oxalate of a melting point of 220 to 222° C. The ethanol-acetone filtrate on cooling deposited 6.2 grams of white crystals of a melting point of 93 to 94° C. This product was ethylcholesteryl oxalate. This example illustrates the ease of separation of the dicholesteryl oxalate, from the mixed ester, ethyl cholesteryl oxalate, through the much greater solubility of the latter in solvents such as ethanol and acetone.

EXAMPLE IV

In this example, 10 grams of sitosterol, 75 cc. of diethyl oxalate and 75 cc. of toluene were treated as in Example III. A yield of 0.7 gram of disitosteryl oxalate, melting point 194 to 195° C., and 7 grams of sitosteryl ethyl oxalate, of a melting point of 95° C. was attained.

Examples III and IV are illustrative of the use of an inert diluent (toluene) in the system. Toluene may be replaced by benzene, xylene, petroleum naphtha, tetrahydrofuran, dioxan, etc.

It will be apparent from the foregoing examples that it is possible to adjust the reaction conditions to produce either the essentially pure mixed ester of oxalic acid, a lower alcohol and a sterol, such as ethylcholesteryl oxalate, or to produce predominately the completely trans-esterified product such as dicholesteryl oxalate accompanied by small amounts of ethyl cholesteryl oxalate and cholesterol.

EXAMPLE V

Admix 10 grams of cholesterol and 100 cc. of dimethyloxalate. Heat the mixture on a steam bath to a temperature of 90 to 100° C. at atmospheric pressure for 24 hours. During the reaction, bubble carbon dioxide through the reaction to effect thorough removal of methyl alcohol from the reaction zone. Subsequently distill off the excess of dimethyl oxalate. In this distillation, a pressure of 15 millimeters (absolute) is satisfactory. Oxalate esters of cholesterol are thus obtained.

EXAMPLE VI

Ten grams of cholesterol in 100 cc. of dimethyl oxalate and 50 cc. of toluene are heated upon the steam bath as above described. During the reaction, a pressure of 40 millimeters of mercury (absolute) is maintained during the course of the reaction, methyl alcohol is evolved and it together with toluene and unreacted methyl oxalate are distilled off and the cholesterol esters of oxalic acid remain behind. The reaction may be considered complete or at least far advanced when methyl alcohol ceases to evolve.

When a polyhydroxy sterol is used in accordance with one of the above examples such as Examples I or II using at least one mole of ester per mole of hydroxy group in the sterol, the corresponding mixed esters such as ergostane mono, di or tri methyl or ethyl oxalate result. When sterol concentrations are higher, for example, two or more moles of sterol hydroxy groups per mole of lower alcohol ester, a polyester of oxalic acid is obtained.

It is to be understood that the mixed esters of oxalic acid, a lower aliphatic monohydric alcohol and a sterol may be selectively saponified with a base such as sodium or potassium hydroxide or calcium hydroxide in approximately stoichiometric amount selectively to split off the lower alkyl group. The resultant salts are somewhat water soluble. It is thus possible to provide water soluble forms of the sterols. The salts may also be reacted with an acid such as carbonic acid, sulfuric acid or the like to split off the metal of the salt and to form an oxalate ester of the sterol containing a free carboxyl. The carboxyl can react in the usual manner of such groups to provide numerous products. In this way, it is possible to form monocholesteryl esters of oxalic acid. In similar manner, it is possible selectively to saponify other sterol oxalates, such as those of stigmasterol and sitosterol. The salts can also be acidified to form free carboxyls. The mixed oxalic acid esters of sterols and lower alcohols may also be subjected to hydrolysis in order to split off the lower alcohol group, thus providing a half acid sterol ester.

The foregoing examples illustrate the application of the ester interchange reaction to individual sterols or steroids in a relatively pure state. It will be apparent that the compound which is to undergo ester interchange need not be pure. Various glyceride oil mixtures containing sterols in substantial amounts may be reacted to produce sterol esters of oxalic acid. For example, a soap stock which normally contains considerable amounts of sterols may be treated with methyl or ethyl oxalate (preferably the neutral esters) in accordance with the provisions of the present invention to form mono or disterol oxalates in admixture with glycerides of fatty acids or in admixture with fatty acids or various combinations of the glycerides and fatty acids or other constituents of the mixture. The temperatures of reaction and other conditions correspond to those herein disclosed. Many other mixtures of fat like products likewise include sterols which are susceptible to treatment in accordance with the provisions of the present invention.

Wool fat for example, includes a considerable amount of cholesterol and such cholesterol containing material may be treated with an excess of diethyl or dimethyl oxalate at temperatures near 100° C. to form cholesteryl esters of oxalic acid in the mixture. These cholesteryl esters can be recovered by solvent extraction or by other appropriate methods.

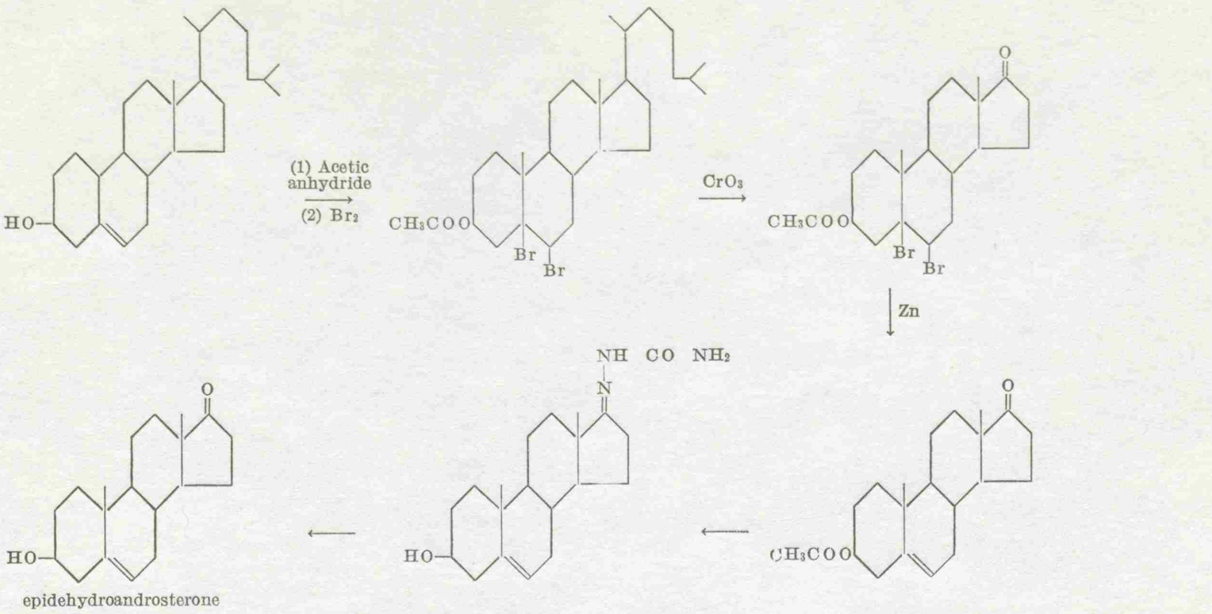
Likewise, tall oil as obtained in the digestion of paper pulp is rich in sterols and notably in beta-sitosterol. The distillation residues obtained after partial distillation of the rosin acids and fatty acids of tall oil are especially enriched in beta-sitosterol. The crude mixture can be treated with methyl or ethyl oxalates (neutral esters) to provide esters of beta-sitosterol in admixture with rosin acids, fatty acids and the like impurities of the tall oil residue.

Example VII

100 grams of unsaponifiable fraction of tall oil which consists largely of beta-sitosterol together with some higher aliphatic alcohols and other materials may be heated with 200 grams of dimethyl ester of oxalic acid and 500 grams of xylene at a temperature of about 100° C. for 24 hours. The excess of dimethyl oxalate and the xylene are then to be distilled off under a pressure of about 10 millimeters (absolute) to obtain a residue containing the desired beta-sitosteryl ester of oxalic acid and other high molecular weight esters.

According to this invention, modified sterols or steroids may be produced in a convenient manner using either the mixed or symmetrical sterols and oxalic esters of lower alcohols as intermediates. Prior to the present invention, it has been common to prepare derivatives of sterols or modified sterols by preliminarily blocking off the hydroxyl group by esterification, and subsequently preparing the derivatives. In such a case, it is common to esterify the sterol with acetic anhydride to produce the acetate. This steryl acetate is then subjected to treatment to modify the sterol radical. For example, the sterol radical may be oxidized, halogenated, or hydrogenated and thereafter oxidized in order to produce modified compounds. Following these reactions, the acetate group is hydrolyzed off and a modified sterol is thus obtained.

As a typical example, cholesterol has been reacted with acetic anhydride in order to produce the corresponding acetate. This product is then reacted with bromine to protect the double bond. The resulting product is then oxidized with chromic acid or like oxidizing agent to remove the side chain. Thereafter, the resulting oxidized product is debrominated and reacted with semi-carbazide to precipitate the semi-carbazone from solution. Following this, the product is hydrolyzed to remove the semi-carbazide and acetate groups, with the resulting production of dehydroepiandrosterone. In some cases, it may be desirable to hydrolyze the acetate grouping to form the free alcohol prior to the preparation of the semi-carbazone. The reactions involved in such process are indicated to be as follows:



According to the present invention, either mixed or symmetrical esters of oxalic acid and sterols may be prepared and these esters subjected to the treatment for the production of sterol oxidation products or other modifications of the sterol radical. Following this, the oxalic acid or the mixed ester thereof may, if desired, be hydrolyzed off with consequent regeneration of the sterol.

The forms of the invention herein described are by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

I claim:

1. In a method of forming an ester of oxalic acid and a sterol, the steps of heating a mixture of said alcohol and a diester of oxalic acid and an alcohol of relatively low molecular weight, the temperature of heating being sufficient to effect ester interchange and to liberate free lower alcohol but being below 180° C., and reducing the concentration of the evolved lower alcohol with respect to the ester of the lower alcohol to carry the reaction substantially to completion.

2. In a method of forming an ester of oxalic acid and a sterol, the steps of heating in the substantial absence of catalysts a mixture of said sterol and an oxalic acid ester of a lower alcohol to a temperature below 180° C. but sufficient to effect ester interchange and to liberate in the reaction mixture, free lower alcohol and maintaining the concentration of the evolved lower alcohol, with respect to the ester of the lower alcohol, sufficiently low to carry the reaction substantially to completion.

3. The steps as defined in claim 2 in which the reaction temperature is within the range of 90 to 120° C.

4. In a method of forming esters of oxalic acid and a sterol, the steps of heating a mixture of said sterol and an ester of oxalic acid and a lower alcohol, said ester being in a proportion of at least 2 mole equivalents with respect to the hydroxyl groups present in the sterol, the temperature being within a range sufficient to effect ester interchange but being below 180° C. whereby to liberate free lower alcohol.

5. The steps as defined in claim 4 in which the concentration of the evolved lower alcohol is reduced by effecting the reaction under vacuum.

6. The steps as defined in claim 4 in which the reaction is promoted by removing the evolved lower alcohol by blowing the reaction mixture with inert gas during the course of the reaction.

7. The steps as defined in claim 4 in which excess of lower alcohol ester and the evolved lower alcohol are stripped off from the reaction mixture by vacuum distillation at the conclusion of the reaction.

8. The steps as defined in claim 4 in which the concentration of evolved lower alcohol is reduced by distillation.

9. The method of claim 8 in which the sterol is cholesterol.

10. The method of claim 8 in which the sterol is betasitosterol.

11. In a method of forming esters of oxalic acid and a sterol, the steps of heating to a temperature sufficient to effect ester interchange but below 180° C., a mixture of said sterol and a diester of oxalic acid and a lower alcohol in the presence of an inert diluent until a substantial proportion of the disteryl ester of oxalic acid is formed and then stripping off inert diluent, excess diester of oxalic acid and the lower alcohol and any residual free evolved lower alcohol present in the reaction mixture.

12. The steps of claim 11 in which the lower alcohol is monohydric and of 1 to 6 carbon atoms.

13. The steps of claim 11 in which the lower alcohol is monohydric and contains 1 to 2 carbon atoms.

14. A process of forming an ester of oxalic acid and a sterol in high yield comprising the steps of effecting ester interchange reaction between (A) an ester of a lower alcohol and oxalic acid and (B) said sterol.

15. A method of preparing a half acid ester of oxalic acid and a sterol which comprises the steps of preparing a mixed ester of oxalic acid and (A) a lower alkyl alcohol and (B) a sterol and splitting off the lower alcohol group to form said half acid ester and then removing the evolved lower alcohol.

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Patented Nov. 2, 1954

2,693,484

NONCATALYTIC ESTER EXCHANGE REACTION OF BETA-KETO CARBOXYLIC ACID ESTERS

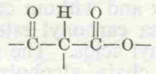
Lowell O. Cummings, Henry A. Vogel, and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application April 7, 1951, Serial No. 219,900

15 Claims. (Cl. 260—483)

The present invention relates to methods of forming esters of beta carbonyl acids and alcohols and it has particular relation to a novel method of forming beta carbonyl esters of alcohols of relatively high molecular weight and to the novel esters resulting from such method.

One object of the invention is to provide a simple and convenient method of forming esters of higher alcohols or hydroxy compounds and particularly carbonyl substituted acids containing the group:



$$-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{\underset{|}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-O-$$

A second object of the invention is to provide a simple method of forming esters of higher alcohols containing for example 10 or 12 and usually 16, 18 and more carbon atoms per molecule.

A third object of the invention is to provide a method of forming esters of alcohols which is adapted to operate without the use of catalysts and at moderate temperatures to obtain an exceptionally high yield of desired product in a state admitting of ready purification.

A fourth object of the invention is to provide novel esters of beta carbonyl carboxylic acids and higher hydroxy compounds having an exceptionally high degree of functionality and solubility and adapting them to organic reactions and syntheses.

A fifth object of the invention is to provide esters of alcohols of exceptionally strong polarity that adapts them physically for use as emulsifiers, solubilizers, plasticizers and the like applications.

A sixth object of the invention is to provide novel esters of beta carbonyl carboxylic acids and higher alcohols.

A seventh object of the invention is to provide a method of forming esters of sterols which is operable without the use of excesses of the sterols.

These and other objects will be apparent from the following specification and the appended claims.

Prior art

It has heretofore been customary to prepare esters of various alcohols and carboxylic acids by a number of different methods such as direct reaction between the desired acids and alcohols or between chlorides of the acids or the anhydrides of the acids and the alcohols. In some cases, desired esters have been obtained by interchange of radicals between esters of carboxylic acids and lower alcohols with higher alcohols.

In general these processes involved rather drastic conditions of reaction as, for example, high temperatures and/or the use of basic or acidic catalysts and the like. Moreover, in these processes conditions of reaction often have complicated removal of the unreacted portions of the reactants, or the catalyst residues from the reaction products and frequently these impurities could not be removed from the resulting ester. Often the reaction was incomplete and poor yields of the desired product were obtained. These difficulties were quite pronounced in the production of esters of higher molecular weight alcohols, for example those containing at least 6 or usually more carbon atoms. Moreover, the processes usually involved the use of great excesses of the alcohol which was being subjected to esterification. Obviously in dealing with scarce and expensive compounds such as sterols, this was highly objectionable.

The present invention

According to the present invention, it has been discovered that esters of high molecular weight can be prepared in high purity and in almost quantitative yield by interacting under mild conditions an ester of an enolizable beta carbonyl or beta keto carboxylic acid and a lower aliphatic (preferably saturated) alcohol containing, for example, up to 4 carbon atoms with an alcohol of higher boiling point than such lower alcohol (preferably at least 20° C. higher) which forms a corresponding ester having a boiling point above about 230° C. while maintaining in the reaction mixture at least one or more equivalents of the ester for each equivalent of higher alcohol.

In order to avoid production of ketones and other byproducts and to obtain approximately quantitative yields, it is necessary that the temperature of the reaction should be kept low. For best results (maximum yield and purity of product), the temperature of reaction should not exceed about 150° C. and preferably should be below 120 or 130° C.

Somewhat higher temperatures may be used with certain alcohols provided special precautions are observed to remove evolved lower alcohol from the reaction mixture substantially as rapidly as evolved. Such precautions are more fully explained below.

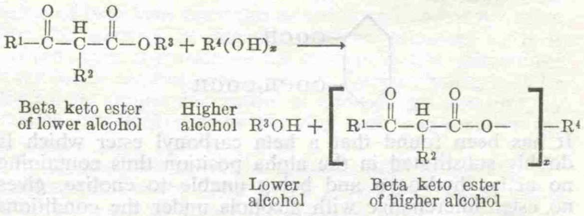
According to a further embodiment of the invention, it has been found that maximum yield and purity of ester is obtained when the evolved lower alcohol is swept rapidly from the reaction mixture. This may be accomplished by distilling the lower alcohol under conditions such that the partial pressure of the lower alcohol vapor is maintained below atmospheric pressure. For example, the reaction mixture may be blown with an inert gas such as carbon dioxide, nitrogen, etc. to cause rapid distillation of evolved lower alcohol. Alternatively or in conjunction therewith, a subatmospheric pressure may be maintained over the reaction mixture whereby to promote distillation of the evolved lower alcohol. These precautions are of especial importance where the temperature of the reaction mixture is allowed to rise to a relatively high value, for example 120–160° C. However, purer products are generally obtained by recourse to these precautions even when the reaction temperature is below 120° C.

Typical esters which are prepared are the esters of acetoacetic acid. However, the esters of other beta keto acids such as are listed below also may be prepared.

To insure good yields, excesses of the alcohol to be reacted with the acetoacetic ester are avoided. Indeed, great excesses of the acetoacetic acid ester component may be employed and if care is exercised to eliminate, or at least sufficiently to reduce in the reaction zone the relative concentration of the alcohol freed, with respect to that of the initial beta keto ester, quantitative interchange of alcohol radical can be attained.

The reaction involved may be represented by the general equation:

EQUATION A



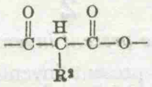
$$\underset{\text{Beta keto ester of lower alcohol}}{R^1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R^2}{|}}{\overset{H}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-OR^3} + \underset{\text{Higher alcohol}}{R^4(OH)_x} \longrightarrow \underset{\text{Lower alcohol}}{R^3OH} + \underset{\text{Beta keto ester of higher alcohol}}{\left[R^1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R^2}{|}}{\overset{H}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-O-\right]_x-R^4}$$

The several groups R^1, R^2, R^3, and R^4 will be defined later. As previously stated, in order to obtain the most complete reaction, we find it convenient to use an excess of the beta keto ester of the lower alcohol.

BETA KETO ESTERS

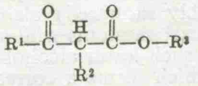
Beta keto esters which may be employed to effect esterification of alcohols include various esters which

contain a ketone carbonyl group in the beta position with respect to a carboxyl. They include the group



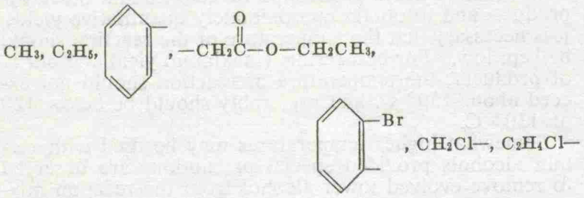
$$-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^3}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-O-$$

already referred to. The general structure of the esters may be represented by the formula taken from the above Equation A which is as follows:



$$R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-O-R^3$$

In the formula, group R^1 may be aliphatic, aromatic or aliphatic or aromatic groups which may or may not contain substitute groups. Examples of R^1 groups are:



and other halogen substituted hydrocarbon radicals, RNH_2, RCHO, etc.

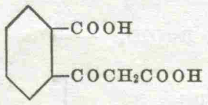
R^2 also frequently is hydrogen but it can also be hydrocarbon or substituted hydrocarbon such as methyl, ethyl, propyl, butyl, chloro, amino, chloromethyl, benzyl, phenyl or the like or derivatives thereof. Only one of the hydrogens of the alpha carbon atoms can be replaced by substituents. The remaining hydrogen atom is an active atom essential to the ester interchange reaction and must be retained.

R^3 is usually the labile radical which is adapted to be replaced in the ester interchange. These functioning groups usually are of low molecular weight, e. g., 1, 2, 3, or possibly 4 carbon atoms in a saturated or unsaturated aliphatic substituted or unsubstituted hydrocarbon chain.

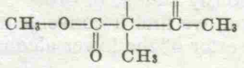
Examples of appropriate liquid beta carbonyl esters suitable for use in the practice of the invention include the following compounds:

Table A

Methyl, ethyl, n-propyl, isopropyl, allyl, methallyl, crotyl, propargyl, 2-chloroethyl, 2-fluoroethyl, 2-nitropropyl and butyl esters of:
  Acetoacetic acid
  Alpha ethyl acetoacetic acid
  Alpha isopropyl acetoacetic acid
  Alpha methyl acetoacetic acid
  Benzoyl acetoacetic acid
  Acetone dicarboxylic acid
  Gamma chloro acetoacetic acid
  Alpha benzoyl acetoacetic acid
  Alpha phenyl acetoacetic acid
  Chloro iodo and bromo substitution products of the above acids
  Acetylsuccinic acid
  Benzoyl acetic acid
  Diester of



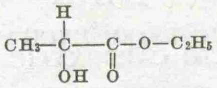
It has been found that a beta carbonyl ester which is doubly substituted in the alpha position thus containing no active hydrogen and being unable to enolize, gives no ester interchange with alcohols under the conditions of the present invention. Such an ester is methyl dimethyl acetoacetate of the formula:



$$CH_3-O-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\overset{\overset{O}{\|}}{C}-CH_3$$

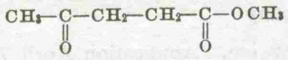
Esters having structures or molecular weights somewhat similar to acetoacetic ester, but being dissimilar in not having one or more active hydrogen atoms, have been found to be non-reactive under the conditions herein

contemplated. For instance, ethyl n-butyrate has a molecular weight almost identical to that of methyl acetoacetate but gives no reaction. Ethyl lactate and methyl levulinate have structures somewhat similar to methyl acetoacetate being respectively:



$$CH_3-\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{O}{\|}}{C}-O-C_2H_5$$

Ethyl lactate



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-OCH_3$$

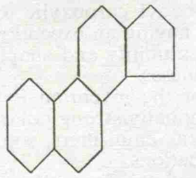
Methyl levulinate

Neither ethyl lactate nor methyl levulinate gives transesterification under the conditions of the present invention.

ALCOHOLS CAPABLE OF ESTER INTERCHANGE WITH BETA CARBONYL ESTERS

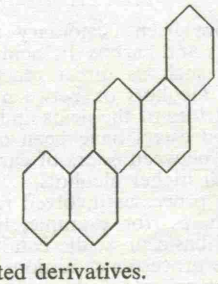
Many hydroxy compounds of relatively high molecular weight may be treated according to this invention. Typical are compounds having the formula $R^4(OH)x$ (from Equation A) where (OH) is an alcoholic OH group, R^4 contains 6 or more carbon atoms and X is a number denoting the number of hydroxyl groups in the molecule. These easily, quickly and without catalysts undergo ester interchange with beta carbonyl esters to provide higher esters of beta carbonyl acids. The sterols and certain of the relatively long chain alcohols and hydroxy compounds such as occur in or are derived from glyceride oils, tall oil waxes and wool fats or the like are outstanding examples of such compounds. These are compounds of considerable molecular weight, containing at least 12 and usually 16, 18, 27 or more carbon atoms. It was quite surprising that these hydroxy compounds of such high molecular weight would so easily undergo ester interchange.

The sterols can be regarded as being derived from cyclopentano phenanthrene:



or its perhydro derivatives by appropriate shifting or replacement of hydrogen by hydroxyl or other groups, and may contain other substituted hydrocarbon groups, or may be otherwise modified by dehydrogenation and such like changes familiar to the art.

The triterpene alcohols such as occur in wool fat can similarly be regarded as being hydroxy derivatives of picene:



or its hydrogenated derivatives.

These hydroxy compounds are often comparatively sensitive to high temperatures and other conditions. However, many of them are important starting compounds in the synthesis of hormones and other biologicals. Yet in some of the reactions to which the compounds are subjected it is desirable to protect the hydroxyl oxygen from loss or from conversion to carbonyl form. It may also be desirable to convert the hydroxyl to ester form in order to increase the polarity of the compound or to provide reactive, or labile groups.

It has now been discovered that these higher alcohols can easily be subjected to esterification with beta carbonyl esters at very moderate temperatures and without resort to catalysts to provide esters of great utility.

Examples of higher alcohols which can be esterified with beta carbonyl esters by ester interchange include:

Table B

- Sterols such as:
  - Cholesterol
  - Beta sitosterol
  - Stigmasterol
  - Cholestanol
  - Epidehydroandrosterone
  - Ergosterol
  - Epicholestanol
  - Coprostanol
  - Cortisone
  - Cholic acid
  - Desoxycholic acid
  - Steroid Sapogenines
  - Steroid intermediates
- Triterpene alcohols such as:
  - Agnosterol
  - Lanosterol
- Aliphatic compound containing at least 6 and usually containing 16 or more carbon atoms and containing alcoholic hydroxyl groups, such as:
  - Octadecyl alcohol
  - Lauryl alcohol
  - Ceryl alcohol
  - Cetyl alcohol
  - Carnaubyl alcohol
  - Lignoceryl alcohol
- Polyhydroxy compounds such as:
  - Decamethylene glycol
  - Glycerine
  - Ethylene glycol
  - Polyethylene glycol and polyethylene oxide resins or waxes and like waxy resins which are soluble in solvents of fats
  - Ether alcohols such as:
    - Butyl carbitol
    - Propyl carbitol
- Hydroxy glyceride oils such as:
  - Castor oil
  - Mono- and di-glycerides which are soluble in solvents of fats
  - Synthetic hydroxy glycerides
- Cyclic and polycyclic alcohols
  - Cyclohexanol
  - Hydroxy decalin
  - Polyhydric alcohol-polybasic acid resins such as glycerol phthalate, glycerol or glycol maleate or monobasic acid modified resins of this character
  - Diamyl carbinol
  - Diethylene glycol
  - 1,2-dichloropropanol 3
  - Pentaerythritol
  - Linoleyl alcohol
  - Nitro alcohols such as:
    - 2-methyl, 2-nitropropyl alcohol
    - 2-nitrobutyl alcohol and others.

When it is desired to avoid alkylation rather than, or in conjunction with, esterification, alcohols which contain a phenyl group directly linked to the carbinol atom thereof should not be used. Unsaturated alcohols such as allyl alcohol, methallyl alcohol, crotyl alcohol, etc., may be used effectively to produce the esters contemplated. In some cases these esters may tend to rearrange after formation to ketone derivatives.

It is desirable that the esters produced by interchange between the original beta carbonyl esters and the higher alcohols be of a boiling point above that of the initial beta keto ester (compound 1), for example, the ester produced preferably should boil at a temperature above 230° C. at 760 millimeters pressure. This permits ready purification of the product by simple distillation or by crystallization or other means.

Obviously the hydroxy compound which is to undergo interchange with the beta carbonyl compound should be soluble in the latter, or at least should be soluble in solvents that are mutually compatible with beta carbonyl compounds.

CONDITIONS OF REACTION

The conditions of reaction employed to effect the ester interchange between the hydroxy compounds and beta carbonyl esters such as beta keto esters may vary, dependent upon the carbonyl ester and the hydroxy compound employed in the reaction. However, the conditions, in most cases are relatively mild.

Catalysts of reaction are not required and usually it is desirable to operate without them. However, such catalysts may be present if purity of product is not important.

The temperature of reaction should be sufficiently high to drive off the lower alcohol quite rapidly. Preferably, it should be driven off substantially as fast as it is liberated in the reaction mixture. The temperature should also be below the point of decomposition of the reactants, or the desired product. A good average temperature is approximately 90 to 100° C. which is near that of an ordinary steam bath. The temperature can also be reduced below this value. However, it is to be understood that as the temperature approaches or is reduced below the normal boiling point of the lower alcohol evolved in the system, it is desirable to apply vacuum in order to promote removal of the latter alcohol. Higher temperatures preferably below 120° C. and in any event below 160° C. are permissible under the conditions explained heretofore.

The approach of the upper limit of the temperature of decomposition can usually be detected by a darkening of the reaction mixture. If any tendency so to discolor is observed, the temperature should be reduced until it ceases. It is usually preferred to employ a temperature above the boiling point of the lower alcohol involved in the system. This facilitates removal of the latter.

To obtain a very high yield of desired ester of the higher alcohol, the concentration of the lower alcohol in the reaction mixture should not be allowed to exceed 33 mole percent of the acetoacetic ester of such alcohol in the mixture. It is even desirable that the precentage be as much lower than this value as can reasonably be attained. If the concentration is reduced to 5 molar percent or even to 1 or 2 molar percent or less (based upon the beta keto ester of the lower alcohol), still better yields can be attained.

Several methods are available to attain these low concentrations of the evolved lower alcohol without unduly increasing the temperature of the reaction mixture. For example, the system can be placed under fairly high vacuum thus stripping off the lower alcohol as it is formed while permitting the temperature to stay relatively low. Beta keto ester of lower alcohol carried over as a vapor in the lower alcohol stripped off can be condensed and returned. In this way, the concentration of the original beta keto ester in the system is maintained.

It is likewise contemplated to strip off lower evolved alcohol by blowing the reaction mixture with a non-reactive vapor or gas, e. g., nitrogen, CO_2, or the like. Steam in substantial amounts is usually to be avoided.

Still another convenient method comprises dilution of the alcohol of reaction by employing a high molar excess of the beta keto ester of the lower alcohol. For example, the excess may be 0.1 to 5, 10 or even 100 fold of the molecular ratio of the beta keto ester with respect to the original higher alcohol undergoing ester interchange. The excess can be added initially or it can be added as the reaction proceeds.

Combinations of these several methods are within the scope of this invention. For example, a 2 to 100 mole excess of beta keto ester can be employed and at the same time the alcohol of reaction can be removed as it is evolved, thus maintaining an extremely low percentage of the lower alcohol in the system. Such stripping may be effected by simple distillation at atmospheric pressure, by vacuum distillation or by blowing with non-reactive gas or vapor.

By properly reducing the concentration of the evolved lower alcohol in the system, it is possible to obtain yields of higher ester of beta keto acids of 90% or higher up to practically quantitative values, e. g., 98 or 99%, without discoloration of the product or the reactants.

If care is observed to maintain the reaction temperature reasonably low and at the same time to distill off under vacuum or otherwise to remove, or decrease the concentration of the lower alcohol evolved by reaction, highly efficient ester interchange can be effected with equimolar ratios of the higher alcohol and the beta keto ester of lower alcohol or with only a slight excess of the latter. However, it is usually more convenient to operate with an excess which is substantial, e. g., 10% or preferably larger (upon a molar basis) of the starting beta keto ester. This excess promotes the reaction. When the reaction nears completion, the excess of original ester can be distilled off. Vacuum should be applied to promote the distillation within the permissible temperature limits. A pressure of about 5 to 50, e. g., 15 millimeters of mercury is usually satisfactory for distilling off this excess of beta keto ester but such other pressures as will remove the excess ester at permissible temperatures may be employed. The distillation may be conducted at or near the original reaction temperature. The distillation of the excess beta keto ester of lower alcohol is important because it also distills off any lower alcohol in the system, thus reducing the concentration of the latter with respect to the original beta keto ester still present and assuring that the ester interchange reaction is completed at moderate temperatures.

In general the reaction is conducted at a temperature above about 50° C. At temperatures ranging from 50 to 130° C. or above the reaction usually proceeds to substantial completion in about 3 to 48 hours. Where lower temperatures are used, for example room temperatures or below, the reaction is much slower and several weeks may be required to achieve substantial reaction and even then use of a substantial excess (100% or more) of keto ester generally is required.

The main features involved in the process as herein disclosed may be summarized as follows:

1. Selection of an alcohol to be subjected to ester interchange which does not undergo side reaction and which is substantially of higher boiling point than the alcohol liberated by reaction.

2. The amount of beta carbonyl ester should be in at least an equimolar proportion with respect to the alcohol to be subjected to ester interchange and preferably it should be in excess. In production of esters of many alcohols, it is necessary to use an appreciable excess, for example 50% or more, of beta keto ester in order to dissolve the alcohol being esterified and/or to insure improved yield.

3. The concentration of evolved alcohol in the reaction mixture should be maintained as low as is feasible, e. g., not in excess of about 33 molar percent and preferably less with respect to the original amount of the beta keto ester of lower alcohol. This may be effectively accomplished in several ways, as for example by distilling off the lower alcohol as formed under conditions such that the partial pressure of the alcohol vapor is below atmospheric, at least during the later stage of the reaction.

4. Catalysts of reaction are not necessary and usually are not employed.

5. The temperature of ester interchange should be moderate, e. g., 50 to 120° C. and usually under no circumstances above 160° C. Satisfactory upper limits of temperature are determinable by observation for the initiation of decomposition reaction.

6. Time of reaction should be maintained until the lower alcohol ceases or substantially ceases to evolve.

7. Solvents are not ordinarily necessary in the reaction. The beta keto ester of a lower alcohol, however, in a sense constitutes a reaction solvent. It will be apparent that non-reactive liquid media may also be employed as solvents if so desired.

8. It is desirable, at the conclusion of the reaction, to distill off any excesses of the beta keto ester of lower alcohol present in the reaction mixture along with any residual lower alcohol evolved by the reaction by distillation at a lower temperature. If this latter precaution is observed, any unreacted higher alcohol still present in the system will be induced to undergo reaction and thereby carry the reaction substantially to completion.

The following examples illustrate the application of the principles of the invention:

EXAMPLE I

In this example, 20 grams of cholesterol and 100 grams of methyl acetoacetate were heated together in the absence of catalyst in a round bottom flask with open neck, at 90 to 100° C. Methyl alcohol was expelled as the reaction proceeded. At the conclusion of 8 hours, the excess of methyl acetoacetate was removed by vacuum distillation at a pressure of about 15 millimeters of mercury and there was obtained 23 grams of a white solid which had a melting point of 91 to 93° C. This product

was dissolved in aqueous acetic acid and recrystallized to obtain a further purified compound melting at 93 to 94° C. The specific rotation $\alpha_D^{25°}$ in chloroform was —33°. The compound was cholesteryl acetoacetate of very high purity.

EXAMPLE II

A mixture of 10 grams of cholesterol and 50 grams of ethyl acetoacetate was heated on a steam bath for 3 hours. The excess of ethyl acetoacetate was removed by distillation at a pressure of 10 millimeters (absolute). There remained 11 grams of a white solid which was identical with the product obtained in Example I, being cholesteryl acetoacetate. Saponification with alcoholic potassium hydroxide gave quantitative yields of cholesterol indicating the ester structure of the cholesteryl acetoacetate. Analysis by other methods well known in the art furnish further proof of the structure of the reaction product.

The acetoacetates of higher alcohols, in general, possess greater solubility than the parent alcohol, as well as greater solubility than such conventional ester derivatives as acetates or benzoates. This makes acetoacetate derivatives of sterols useful intermediates in steroid syntheses because of greater ease of handling in solutions for purposes of crystallizing or of conducting other synthetic reactions on solutions. For example, in the following table are given the comparative solubilities of cholesteryl acetoacetate and cholesteryl acetate in a number of solvents. The volume of each solvent in cubic centimeters or milliliters required to dissolve 1 gram of the cholesteryl ester at reflux temperature is given.

	Cholesteryl Acetate, cc.	Cholesteryl Acetoacetate
Acetone	3	Less than 1 cc.
Methanol	70	20 cc.
Methanol+Hexanol (Equal volumes)	13	Less than 2 cc.
Methanol+Isopropyl Ether (Equal volumes).	9	Do.
Methanol+Acetone (Equal volumes)	17	Do.

(cc.=milliliters.)

This increased solubility of a sterol derivative is of particular advantage when purifying such materials by solvent crystallization since the volume of solvent required to dissolve the sterol derivative is from ⅓ to ⅑ as large when using the acetoacetate rather than the acetate of the sterol.

It is well known that beta keto acids and their esters are metabolic intermediates. Compounds such as acetoacetic esters and acetone dicarboxylic esters have been isolated as products of metabolism. Esters of beta keto acids and sterols, therefore, may be metabolic intermediates and may have therapeutic value.

It is to be observed in these examples that no catalysts of reaction are required in the ester interchange. The temperatures are very mild. The reaction is thereby distinguished from conventional ester interchanges which are catalyzed by alkaline or acid catalysts and require higher temperatures. The proportion of higher alcohol is also much less than molar.

The reaction by ester interchange as herein disclosed is also an improvement upon conventional reactions involved in the preparation of esters of higher alcohols in which acid chlorides or acid anhydrides are caused to react with the alcohol. In this latter type of reaction, the stronger acid compounds may be difficult to handle and the excess of reactant cannot be readily recovered. In the present instance, the excess of ethyl acetoacetate or other beta carbonyl ester can readily be recovered by simple distillation, with only quantitative amounts being consumed in the interchange reaction. The reaction product likewise is not contaminated by catalyst or by-products from catalyst removal or destruction.

The following additional examples illustrate further embodiments of the invention:

EXAMPLE III

Two grams of stigmasterol and 20 grams of methyl acetoacetate were heated on a steam bath and under an air condenser, under which conditions the methyl alcohol was expelled as the reaction proceeded. Reaction was continued for two hours. At the end of this time, the excess methyl acetoacetate was stripped off by vacuum distillation. The vacuum was such as to maintain the temperature of distillation below 100° C. There remained 2.2 grams of a white solid which was crystallized from petroleum ether admixed with methanol to provide a product comprising white shining platelets of a melting point of 114 to 114.5° C., the specific rotation $\alpha_D^{25°}$ in chloroform equals −44°. This product was stigmasteryl acetoacetate.

EXAMPLE IV

Two grams of beta sitosterol having a melting point of 136 to 137° C. and 20 grams of ethyl acetoacetate were heated on a steam bath for 18 hours. The reaction product was stripped of ethyl acetoacetate and any residual ethyl alcohol by vacuum distillation and there remained a white solid product constituting 2.2 grams and this was recrystallized from petroleum ether admixed with methanol to provide a product in the form of white shining platelets of a melting point of 99° C. and a specific rotation at 25° C. in chloroform of −24°. The product was beta sitosteryl acetoacetate. An identical product was obtained by use of methyl acetoacetate as the beta carbonyl ester.

EXAMPLE V

One hundred milligrams of cholestanol, melting in a range of 140 to 142° C. was treated with 10 grams of methyl acetoacetate by heating the mixture on a steam bath for 4 hours. Upon distillation of the excess of methyl acetoacetate, there remained a quantitative yield of cholestanyl acetoacetate in the form of white platelets of a melting point of 97° C. and of a specific rotation at 25° C. in chloroform of +12°.

EXAMPLE VI

In this example, epidehydroandrosterone was admixed with a molar excess of methyl acetoacetate and heated on a steam bath for 18 hours. The excess of methyl acetoacetate was distilled under vacuum and there remained a solid product which was recrystallized from methanol to provide feathery white crystals of epidehydroandrosterone acetoacetate melting at 163° C. The specific rotation $\alpha_D^{25°}$ in chloroform was +1°.

EXAMPLE VII

In this example, 5 grams of octadecyl alcohol and 30 cc. of methyl acetoacetate were heated on a steam bath for 24 hours. The methyl alcohol of reaction was continuously removed. At the conclusion of this time, the excess of methyl acetoacetate was distilled under vacuum until an oily residue remained. The residue was taken up in a mixture of 30 cc. of methanol, 10 cc. of acetone, and 6 cc. of water. Upon cooling the solution, white crystals in a yield of 6 grams and of a melting point of 40 to 40.5° C. precipitated. These crystals were octadecyl acetoacetate.

EXAMPLE VIII

Fifty grams of cold pressed castor oil (largely a triglyceride of ricinoleic acid) and 150 grams of methyl acetoacetate were heated in an open necked glass flask on a steam bath for a period of 4 hours. The mixture at that point was a clear solution which was stripped of methyl acetoacetate and residual methyl alcohol by distillation at 10 millimeters mercury pressure (absolute) to leave a light yellow oil weighing 62 grams. This product is castor oil acetoacetate and an infra-red analysis showed the complete absence of hydroxyl groups in it. The plasticizing action of this product was found to be good in the following compositions:

50 grams of 32% solids clear lacquer of ½ second nitrocellulose in mixed solvents (butyl acetate, ethanol, isopropyl acetate and toluene)
10 grams butyl acetate
10 grams castor oil acetoacetate.

This gave a clear lacquer solution. A film of the solution on glass baked 1½ hours at 100° C. was hard but not brittle. The composition contained 10 grams of plasticizer and 16 grams of nitrocellulose.

A mixture of 50 grams of a 25% solids VMCH Vinylite which is a copolymer of vinyl chloride and vinyl acetate in methyl isobutyl ketone, methyl ethyl ketone, and toluene and 10 grams of castor oil acetoacetate gave a clear solution which was poured to form a film on glass. After baking for 1½ hours at 110° C., the film was clear and hard but not brittle. The castor oil ester of acetoacetic acid constituted a plasticizer.

EXAMPLE IX

Eight grams of decamethylene glycol and 45 cc. of methyl acetoacetate were heated on a steam bath for 18 hours. After vacuum distillation of the excess methyl acetoacetate and residual methyl alcohol, there remained a waxy solid of a melting point of 31 to 33° C. which, after a single crystallization from methanol, melted at 33 to 34° C. This product was decamethylene diacetoacetate.

EXAMPLE X

Eight grams of cyclohexanol was substituted for decamethylene glycol in Example IX and the mixture was heated as previously described. The product as obtained by distillation of the excess methyl acetoacetate was a water white liquid boiling within a range of 126 to 129° C. at a pressure of 15 millimeters (absolute) of mercury. The index of refraction at 25° C. was 1.45765.

EXAMPLE XI

In this example, a non-reactive solvent was employed. A mixture of 5 grams of cholesterol and 25 cc. of methyl acetoacetate in solution in 250 cc. of xylol (inert solvent) was heated on a steam bath and under an air cooled condenser designed to pass evolved methyl alcohol and to return reactives and solvents to system for 18 hours. At the conclusion of the reaction period, the methyl acetoacetate and the xylene were stripped by distillation under vacuum and there remained 5.9 grams of a white solid which, after one recrystallization from aqueous acetic acid, melted at 92 to 93° C. and which was identical with cholesteryl acetoacetate prepared without solvents as described in Example I.

EXAMPLE XII

A mixture of 100 grams of polyethylene glycol of approximately molecular weight of 200 and 400 grams of methyl acetoacetate was heated under slight negative pressure on a steam bath for 15 hours. The excess methyl acetoacetate and any residual methyl alcohol were then removed by vacuum distillation and there remained 150 grams of a water soluble liquid. This product was polyethylene acetoacetate having a saponification value of 359.

EXAMPLE XIII

In this example, 100 grams of butyl carbitol (diethylene glycol monobutyl ether) was reacted with excess methyl acetoacetate under the conditions described in Example XII. After removal of the excess methyl acetoacetate, there remained a water white liquid butyl carbitol acetoacetate having a saponification value of 342.

EXAMPLE XIV

A mixture of 41 grams of n-octanol and 200 grams of methyl acetoacetate was heated at steam bath temperature with continuous removal of methyl alcohol, for 22 hours. The excess methyl acetoacetate was separated from the product (n-octyl acetoacetate) by fractional distillation under vacuum using a Widmer column. There was isolated 65 grams of n-octyl acetoacetate boiling at 140–141° C. at 16 mm. mercury (absolute). The product had a saponification value of 507 and an index of refraction $n_D^{25}=1.4372$.

EXAMPLE XV

The use of esters of benzoyl-acetic acid, which are beta carbonyl compounds, in the transesterification has been referred to. In this example, 5 grams of cholesterol and 30 grams of ethyl benzoyl-acetate were heated at steam bath temperature for 20 hours. Removal of the unreacted ethyl benzoyl-acetate by vacuum distillation left 6.4 grams of cholesteryl benzoylacetate, which after crystallization from a butyl acetate-ethanol mixture melted at 151° C.

EXAMPLE XVI

Five grams of stearyl alcohol and 25 grams of ethyl benzoylacetate were heated on the steam bath for 24 hours. The excess ethyl benzoylacetate was removed by vacuum distillation. The residue was triturated with methanol, filtered, and dried, yielding 6.5 grams of stearyl benzoylacetate. After crystallization from acetone, it melted at 55–57° C. and had a saponification value of 180.

EXAMPLE XVII

Two grams of ethyl acetone dicarboxylate and 2.7 grams of stearyl alcohol were heated on a steam bath in an open neck flask with removal of ethyl alcohol for 16 hours. The mass was then dissolved in ethanol, cooled and filtered. There were obtained fine crystals of distearyl acetone dicarboxylate which melted at 65° C and had a saponification value of 343.

EXAMPLE XVIII

This example illustrates the employment of inert gas to strip off lower alcohol as it is formed and moderate temperatures of reaction in the preparation of an ester of menthol and acetoacetic acid by interchange reaction between the alcohol and methyl-acetoacetate in molecular ratio. In the reaction, .2 mole of menthol and .2 mole of methyl acetoacetate were heated to a temperature of 95° C. The reaction was continued at that temperature while inert gas (from butane combustion) was bubbled in vigorously or at least sufficiently rapidly effectively to sweep out methyl alcohol as it was liberated. (Inert gas can be replaced by vacuum, if so desired.) In this instance, the reaction was continued for 24 hours.

A yield of 94% menthyl acetoacetate having a melting point of 24 to 27° C. was attained. This product was further purified by crystallization to provide a product of a melting point of 30 to 32° C.

EXAMPLE XIX

In this example, a large excess of ethyl acetoacetate was employed at moderate temperatures of reaction· The proportions were:

	Moles
Menthol	.1
Ethyl acetoacetate	15

The temperature of reaction was 98° C. Neither inert gas nor vacuum were employed. Any ethyl alcohol vaporized was allowed to escape, but no effort was made to promote vaporization. The reaction was continued for 24 hours to assure completion without recourse to testing. The reaction mixture was distilled at 15 mm. (absolute) and to 112° C. to remove excess ethyl acetoacetate together with any residual ethyl alcohol in the mixture. An excellent product melting in the range of 26–29° C. and in a yield of 99% was attained. This product could be further purified by crystallization to form a product of a melting point of 30 to 32° C.

EXAMPLE XX

Admix .2 mole of menthol and .2 mole of methyl acetoacetate and heat to 150° C. while blowing with inert gas to remove methyl alcohol as rapidly and thoroughly as practicable. (In lieu of inert gas, a vacuum can be applied with similar results.) Reaction is complete in 5 hours or less. A yield of 99% of a material melting at 20 to 23° C. results. This material is a solid and can be purified by crystallization. However, it is less pure than that obtained in Examples XVIII or XIX.

EXAMPLE XXI

This example illustrates a control run. In it, a mixture of .1 mole of menthol and .1 mole of ethyl acetoacetate were heated at atmospheric pressure without inert gas, to a temperature of 150° C. for 2.5 hours. The reaction mixture was distilled at 15 millimeters of mercury while the temperature was increased to 160° C. The product remained as a 42% yield of an oily residue in the flask. It was oily even at 0° C. and was difficult to purify. The temperature of reaction was too high.

EXAMPLE XXII

This was essentially repetition of Example XXI except that reaction was continued for 5 hours. Distillation was stopped at 152° C., because an excessive evaporation of the reaction mixture had already occurred. The yield of product was 18%. This was an oil which was difficult to purify.

EXAMPLE XXIII

This was also a control test in which a low temperature of reaction and a long period of reaction were employed. Both inert gas and vacuum were omitted during the reaction. The reaction mixture consisted of .1 mole menthol and .1 mole ethyl acetoacetate. The mixture was maintained at 98° C. for 24 hours. The mixture was then subjected to a vacuum of 15 millimeters of mercury (absolute) to 160° C. The distillation residue constituting the menthyl acetoacetate product constituted a yield of only 24%. This product had a melting point of 27 to 30° C.

This experiment was repeated, but distillation was conducted at 140° C. The yield was 37% and the product had a melting point of 30 to 32° C.

EXAMPLE XXIV

In this example, lauryl alcohol which is a C–12 alcohol was employed as the higher alcohol in the ester interchange reaction. Lauryl alcohol in a proportion of 5 grams was admixed with 500 grams of methyl acetoacetate and the mixture was heated on the steam bath for 20 hours, the evolved methyl alcohol being allowed to escape during the reaction. At the conclusion of the period, the excess methyl acetoacetate was evaporated at a pressure of 10 millimeters of mercury (absolute) and the residue in the distillation flask was then distilled to yield 7 grams of a water white liquid lauryl acetoacetate.

EXAMPLE XXV

In this reaction, ester interchange was effected between cholesterol and methyl acetoacetate. The reaction mixture comprised 10 grams of cholesterol and 100 cc. of methyl acetoacetate, the mixture being heated on the steam bath and at atmospheric pressure for 15 hours. During the reaction, inert gas was bubbled through the reaction mixture to effect the thorough removal of evolved methanol from the zone of reaction. Finally, the excess methyl acetoacetate was removed by vacuum distillation to yield 12 grams of a white solid cholesteryl acetoacetate of a melting point of 91 to 93° C.

EXAMPLE XXVI

This example illustrates the employment of vacuum during the course of the ester interchange for purposes of more thoroughly removing the lower alcohol as it is evolved. In the reaction, 10 grams of cholesterol were again admixed with 100 cc. of methyl acetoacetate and the mixture was heated upon the steam bath for 15 hours at a pressure of 40 millimeters of mercury (absolute). During the course of the reaction, methyl alcohol was evolved and distilled off and cholesteryl acetoacetate was formed. The yield and the purity of the product were practically identical with those obtained in Example XXV.

It is likewise contemplated to employ as a source of sterols or steroid bodies for use in the practice of the invention various glyceride oil mixtures containing sterols in substantial amounts. For example, a soap stock which normally contains considerable amounts of sterols, such as cholesterol, may be treated with methyl or ethyl acetoacetate in accordance with the provisions of the invention to form esters of the keto acid in admixture with glycerides of fatty acids. The temperatures of reaction correspond to those herein disclosed. The conditions of reaction likewise in other respects, are similar to those of the examples as herein presented. Many other mixtures of fat-like products likewise include sterols which are susceptible of treatment in accordance with the provisions of the present invention.

Wool fat, for example, includes considerable amounts of cholesterol and it is contemplated to treat such cholesterol-containing material with an excess of ethyl or methyl acetoacetate at temperatures near the boiling point of water to form cholesterol esters in the mixture. These cholesterol esters can be recovered by solvents or by other appropriate methods.

Likewise, tall oil as obtained in the digestion of paper pulp is rich in sterols and notably in beta sitosterol. The distillation residue obtained after partial distillation of the rosin acids and fatty acids of tall oil is highly enriched in beta sitosterol. This crude mixture can be treated with methyl or ethyl acetoacetate to provide esters in admixture with rosin acids, fatty acids and the other impurities of the tall oil residue.

Usually it is preferable to operate with more concentrated forms of the sterol or steroid compound. For example, beta sitosterol has heretofore been recovered from tall oil and tall oil distillation residues by solvent fractionation of crude tall oil. A convenient method of obtaining sterols, e. g., beta sitosterol, from tall oil or tall oil distillation pitches comprises esterifying the crude material with a lower alcohol, e. g., methyl alcohol, selectively to esterify fatty acids, contacting the mixture with countercurrently flowing streams of naphtha and furfural in a tower, separating off at one end a solution of furfural containing in solution a concentration of rosin acids and separating off at the other end, naphtha containing in solution an enrichment of esters of fatty acids and unsaponifiable material including beta sitosterol. The naphtha can be recovered by evaporation. The mixture of esters and unsaponifiable matter can be treated with alkali, e. g., caustic soda, to saponify the esters and the residual rosin acids in the mixture. The unsaponifiable matter is separated by dissolving the mixture in an aqueous alcohol, e. g., aqueous isopropyl alcohol and extracting out the unsaponifiable material in a solvent such as naphtha, and evaporating the naphtha. If purer sterols are desired, they can be recovered by crystallizing them from a solvent of sterols. In many cases, a relatively pure product has been obtained. The following examples illustrate the application of the principles of the invention in the preparation of beta keto esters of a crude or purified beta sitosterol.

EXAMPLE XXVII

One hundred grams of unsaponifiable fraction of tall oil which consisted largely of beta sitosterol together with some higher aliphatic alcohols and other materials was heated with 200 grams of methyl acetoacetate to 100° C. for ½ hour. The excess methyl acetoacetate was then distilled off under a pressure of 10 millimeters of mercury (absolute) to obtain a residue of 103.6 grams of a material containing the desired ester of acetoacetic acid and beta sitosterol.

EXAMPLE XXVIII

5.0 grams of stearyl alcohol and 30 grams of methyl ethylacetoacetate $CH_3COCH(C_2H_5)CO_2CH_3$ were heated on a steam bath for 48 hours, the evolved methanol being distilled off. The unreacted lower beta-keto ester was then removed by distillation in vacuo, and the residue was dissolved in acetone and the solution poured into water. The white solid which precipitated was filtered, washed and dried. Treatment of this product with alcoholic KOH showed this material to consist largely of stearyl ethylacetoacetate.

EXAMPLE XIX

2.0 grams of cholesterol, 8 grams of ethyl acetonedicarboxylate ($C_2H_5OOC—CH_2COCH_2COOC_2H_5$) and 10 milliliters of toluene were heated on a steam bath for 20 hours, the evolved ethanol being distilled off The toluene was then removed by distillation in vacuo and the oily residue was triturated with acetone to precipitate a white solid, dicholesteryl acetonedicarboxylate. This material after one crystallization from a mixture of methanol and isopropyl ether melted at 173° C. The acetone filtrate on evaporation to dryness left an oil, ethyl cholesteryl acetonedicarboxylate which could not be obtained crystalline.

EXAMPLE XXX

2.7 grams of stearyl alcohol and 2.0 grams of ethyl acetonedicarboxylate were heated on the steam bath in an open flask for 16 hours. The product was dissolved in hot ethanol and the solution cooled, after which the white solid formed was filtered, washed and dried to yield distearyl acetonedicarboxylate. This solid melted at 58–60° C., and had a saponification value of 343. This material on repeated crystallization from a mixture of methanol and acetone melted at 64.5–65.0° C.

EXAMPLE XXXI

10 grams of cholesterol and 100 grams of diethyl acetyl succinate $C_2H_5OOC—CH_2CH_2(COCH_3)COOC_2H_5$ were heated on the steam bath under a 10 millimeter absolute pressure for 64 hours. 93.5 grams of unreacted lower beta-keto ester was then removed by distillation in vacuo, and the residue was dissolved in 50 milliliters of ethanol, cooled and the white solid filtered, washed with 100 milliliters of ethanol and dried. The solid product, cholesteryl ethyl actyl succinate, had a saponification value of 165.

EXAMPLE XXXII

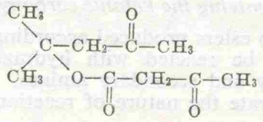
10 grams of stearyl alcohol and 100 grams of diethyl acetylsuccinate were heated on the steam bath under 10 millimeters absolute pressure for 40 hours. The clear solution was then stripped in vacuo, the residue was dissolved in 50 milliliters of hot methanol, cooled, and the white solid filtered, washed with 120 milliliters of hot ethanol and dried. The product is a solid which is predominately stearyl ethyl acetylsuccinate; it melted at 55–57° C. and had a saponification value of 145.

EXAMPLE XXXIII

57 milligrams of cortisone and 50 milliliters of methyl acetoacetate were heated on a steam bath for 16 hours. The unreacted methyl acetoacetate was then removed by distillation in vacuo, and the residue on crystallization from aqueous ethanol yielded shiny platelets of cortisone acetoacetate which melted at 112–114° C.

EXAMPLE XXXIV

325 milliliters of diacetone alcohol and 1000 milliliters of methyl actoacetate were heated on the steam bath for 24 hours. The unreacted starting materials were then removed by distillation in vacuo and the flask residue on distillation yielded water-white diacetonyl acetoacetate,



boiling at 125–127° C. at 10 millimeters absolute pressure, and having a refractive index $N_D^{25°}=1.4424$.

Its ultraviolet absorption characteristics are as follows:

$$\lambda_{\text{max.}}^{\text{ethanol}}: 241.5\ (\log E=3.07);\ 306.5\ (\log E=2.34)$$

EXAMPLE XXXV

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated with 101.2 milligrams of triethylamine at 98° C. for 4 hours, using a water condenser. Then 50.0 milliliters of methanol was added, the solution was cooled overnight at 23° F., the white solid was filtered, washed with 50 milliliters of methanol and dried. This solid was cholesteryl acetoacetate.

EXAMPLE XXXVI

The process of Example XXXV was repeated substituting 98.0 milligrams of concentrated sulfuric acid for the triethylamine. The product was cholesteryl acetoacetate.

EXAMPLE XXXVII

The process of Example XXXV was repeated substituting 38.6 milligrams of sodium cholesterate for the triethylamine. The product was largely cholesteryl acetoacetate.

EXAMPLE XXXVIII

The process of Example XXXV was repeated, substituting 185 milligrams of benzene sulfonic acid hydrate for the triethylamine, and heating the reaction mixture at 98° C. for 3 hours. The product was largely cholesteryl acetoacetate.

EXAMPLE XXXIX

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated at 140° C. with water condenser for 5 hours. Then 50 milliliters of methanol was added, the solution was cooled overnight at 23° F., and the white solid was filtered, washed with 50 milliliters of methanol and dried. This product melted at 94.5–95.5° C. and was substantially pure cholesteryl acetoacetate.

EXAMPLE XL

The process of Example XXXIX was repeated at a temperature of 160° C. rather than 140° C. The resulting cholesterol acetate was slightly lower in purity than that obtained in Example XXXIX having a melting point of 90–91° C.

EXAMPLE XLI

10 grams of crude 12-hydroxystearic acid containing 85% by weight of 12-hydroxystearic acid (the balance being largely stearic acid) and 100 milliliters of methyl acetoacetate were heated on the steam bath for 26 hours. The unreacted methyl acetoacetate was distilled off by heating the reaction mixture in vacuo. After distillation, there remained 13 grams of a water white oil. Numerous crystallizations from hexane and finally from methanol yielded silky white needles which melted at 31.5 to 32.5° C. This product is 12-acetoacetoxystearic acid. The corresponding esters of other hydroxy acids such as glycolic acid, lactic acid, ricinoleic acid, tartaric acid, etc. may be prepared in the same manner. Moreover the esters of such hydroxy acids may be treated in the same way.

The preparation of the beta-keto esters as herein described affords the opportunity of preparing a host of new compounds due to the great reactivity of beta-keto esters. Thus beta-keto esters containing one or more active hydrogen atoms will in addition to the normal ester type reactions, have reactivity in the following manner:

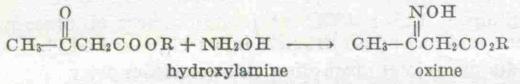
1. Reactions involving the carbonyl group directly
2. Reactions involving the enolic hydroxyl group, and
3. Reactions due to the activation of the —CH or —CH₂— groups between the carbonyls.

The following are typical examples of these reactions.

1. *Reactions involving the ketonic carbonyl group directly*

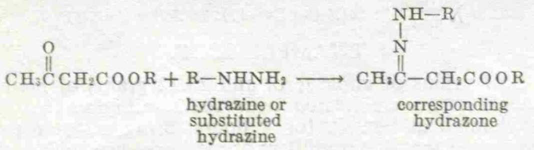
The beta-keto esters produced according to the present invention may be reacted with hydrazines, hydroxylamines, primary and secondary amines. The following equations illustrate the nature of reactions which occur.

A.



$$CH_3-\overset{O}{\overset{\|}{C}}CH_2COOR + NH_2OH \longrightarrow CH_3-\overset{NOH}{\overset{\|}{C}}CH_2CO_2R$$

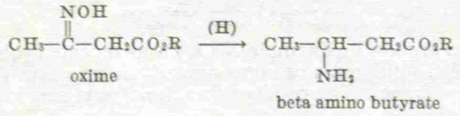
B.



$$CH_3\overset{O}{\overset{\|}{C}}CH_2COOR + R-NHNH_2 \longrightarrow CH_3\overset{NH-R}{\overset{|}{\overset{N}{\overset{\|}{C}}}}-CH_2COOR$$

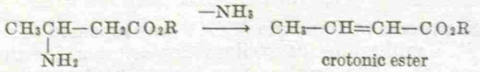
These carbonyl derivatives can of course be reacted further:

C.



$$CH_3-\overset{NOH}{\overset{\|}{C}}-CH_2CO_2R \xrightarrow{(H)} CH_3-\underset{\underset{NH_2}{|}}{CH}-CH_2CO_2R$$

D.



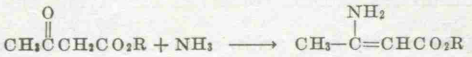
$$CH_3\underset{\underset{NH_2}{|}}{CH}-CH_2CO_2R \xrightarrow{-NH_3} CH_3-CH=CH-CO_2R$$

Thus the oxime of stearyl acetoacetate may be prepared by heating a solution of 10 grams of stearyl acetoacetate and 10 grams of hydroxylamine hydrochloride in 50 milliliters of pyridine and 60 milliliters of ethanol under reflux for 3 hours. The oxime is then precipitated by the addition of water and recrystallized from aqueous methanol.

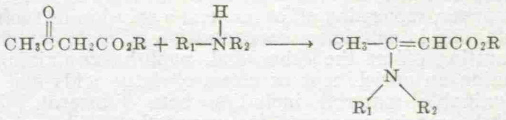
Similarly the semicarbazone of cholesteryl acetoacetate may be prepared by heating a solution of 1 gram cholesteryl acetoacetate, 1 gram of semicarbazide hydrochloride and 1.5 grams of anhydrous sodium acetate in 20 cc. of ethanol on the steam bath for 20 minutes, precipitating the cholesteryl acetoacetate semicarbazone by the addition of water, and crystallizing it from a mixture of isopropyl ether and isopropanol. This product is a crystalline solid.

Moreover the other sterol acetoacetates and equivalent esters of other beta-keto acids herein disclosed may be reacted with semicarbazide hydrochloride in the same manner. It will also be understood that acetoacetates of castor oil, higher aliphatic alcohols, hydroxy acids and their esters and hydroxy alkyd resins as well as other acetoacetates and like keto esters produced according to this invention may be reacted with semicarbazide hydrochloride in lieu of cholesterol acetoacetate.

Another important reaction involving the keto carbonyl group of beta-keto esters produced according to this invention is their reaction with ammonia or primary or secondary amines, e. g.:



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2R + NH_3 \longrightarrow CH_3-\overset{NH_2}{\overset{|}{C}}=CHCO_2R$$

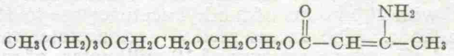


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2R + R_1-\overset{H}{\overset{|}{N}}R_2 \longrightarrow CH_3-\underset{\underset{R_1\quad R_2}{\underset{N}{|}}}{C}=CHCO_2R$$

where alcohol R is the radical of the acetoacetate and R_1 and R_2 are the radicals of the primary or secondary amine. The following are typical examples of this embodiment.

EXAMPLE XLII

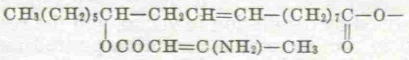
Ammonia gas was passed for 2 hours at room temperature through a solution of 100 grams of butylcarbitol acetoacetate (a water white liquid), and 0.1 gram of ammonium acetate in 100 grams of methanol. The reaction was somewhat exothermic. After two hours the solvent was removed by distillation under reduced pressure, and there remained 100 grams of a water-white oil which, in chloroform, has an ultra violet light absorption maximum of log E=4.1 at 272.5 millimicrons, showing the presence of a beta-substituted, alpha-beta unsaturated ester grouping. The reaction product has the following structure:



$$CH_3(CH_2)_3OCH_2CH_2OCH_2CH_2O\overset{O}{\overset{\|}{C}}-CH=\overset{NH_2}{\overset{|}{C}}-CH_3$$

EXAMPLE XLIII

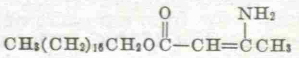
100 grams of castor oil acetoacetate was treated with ammonia in excess of the stoichiometric amount in a manner similar to that above described, and there was obtained a viscous, light yellow oil on evaporation of the solvent. This material consisted largely of a triglyceride, the acid radical of which had the following structure:



$$CH_3(CH_2)_5\underset{\underset{OCOCH=C(NH_2)-CH_3}{|}}{CH}-CH_2CH=CH-(CH_2)_7\underset{\underset{O}{\|}}{C}-O-$$

EXAMPLE XLIV

60 grams of stearyl acetoacetate, 300 grams of methanol and 50 grams of ammonium acetate were heated on a steam bath for 15 minutes, and the reaction mixture was then cooled and diluted with water. There was isolated 60 grams of a white solid which crystallized from methanol in white platelets and melted at 70–71° C. In absolute ethanol it showed an ultra violet light absorption maximum of log E=4.29 at 274 millimicron. C, H and N analyses confirmed this structure:



$$CH_3(CH_2)_{16}CH_2O\overset{O}{\overset{\|}{C}}-CH=\overset{NH_2}{\overset{|}{C}}CH_3$$

EXAMPLE XLV

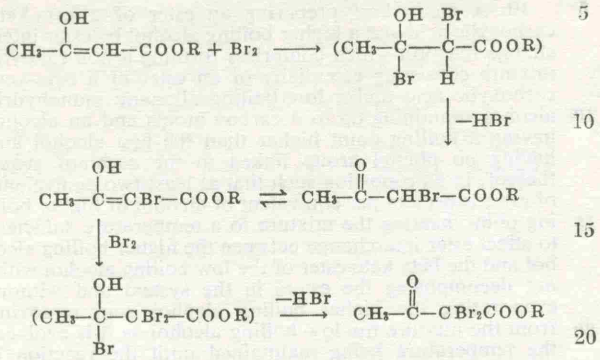
Through a solution of 33 grams of polyethylene glycol acetoacetate (made from polyethylene glycol having a molecular weight of about 200) in 100 grams of methanol to which a 0.05 gram of ammonium acetate had been added, ammonia gas was passed at room temperature for one hour. The reaction was somewhat exothermic. The solvent was then stripped off under reduced pressure. There remained a light oil which was the beta-amino crotonate of polyethylene glycol.

The fatty acid salts of these beta-amino crotonates were found to be good emulsifiers.

It will be understood that the corresponding amino crotonate esters of the various other hydroxy compounds prepared according to this invention, including cholesterol, cortisone, stigmasterol and other sterols, glycols, polyglycols, carbitols, hydroxyesters etc. may be prepared in the same manner.

2. *Reactions involving the enolic hydroxyl group*

Typical of such reactions are halogenations of beta-keto esters, e. g.:



where R is the alcohol radical of the beta-keto ester.

Thus one or more active hydrogen atoms can be replaced by halogen atoms. The following are typical examples:

EXAMPLE XLVI

10 grams of stearyl acetoacetate dissolved in carbon tetrachloride is treated with a solution of 10 grams of bromine in 50 milliliters of petroleum ether. Copious evolution of hydrogen bromide vapors takes place, and slow evaporation of the solvent at room temperature leaves a quantitative yield of stearyl bromoacetoacetate.

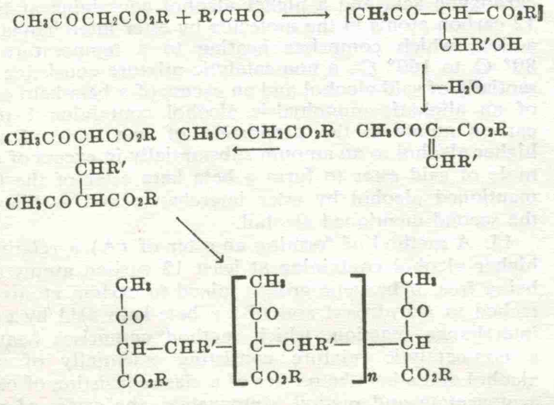
EXAMPLE XLVII

An alkyd resin is prepared by reacting 890 grams of refined soya oil, 220 grams of pentaerythritol and 180 grams of glycerine with 840 grams of phthalic anhydride. All the free hydroxyl groups in this alkyd were then esterified by heating 1000 grams of the resin with 1000 milliliters of methyl acetoacetate on the steam bath for 22 hours, and removing the unreacted methyl acetoacetate by distillation in vacuo. Solvent naphtha was then added to this resin to give a resin of 24% solids. Chlorine gas was passed through the resulting solution over a period of two hours at room temperature while the solution was agitated by a stream of inert gas. After chlorination the agitation with inert gas was continued for a further period of 6 hours to remove all HCl gas evolved. A very light colored resin resulted.

Acetoacetic and like esters of other alkyd resins containing free hydroxyl groups and of other higher alcohols (sterols, higher aliphatic alcohols etc.) may be treated in the same manner.

3. *Reactions due to the activation of the —CH or —CH₂— groups between the carbonyl groups*

The acetoacetates produced according to this invention undergo reaction with aldehydes in an aldol type reaction:

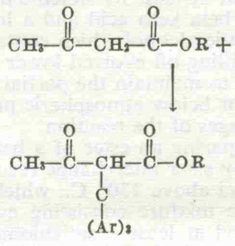


where R is the alcohol radical of the acetoacetate and R′ is the radical of the aldehyde.

Thus, for example, an alkyd resin was prepared by reacting 1053 grams of linseed oil and 470 grams of glycerine with 893 grams of phthalic anhydride. The resulting resin had a Gardner viscosity M at 57.6% solids in solvent naphtha, an acid value of 10.5 and a Gardner color of 9. One thousand grams of this 57.6% solids alkyd resin was then heated on the steam bath with 500 milliliters of methyl acetoacetate for 18 hours. All the solvent was then removed by distillation in vacuo, and to the still hot resin 500 grams of solvent naphtha was added. The resulting resin had a Gardner viscosity of U–V at 50.4% solids. A mixing of 500 grams of this resin, 5 grams of paraformaldehyde, 1 milliliter of pyridine, 1 drop of piperidine and 100 milliliters of solvent naphtha were then heated on the steam bath with agitation for three hours. The reaction mixture was then heated under vacuum until the water formed in the reaction had distilled off azeotropically, the total distillate having a volume of 100 milliliters. There remained a resin having a Gardner viscosity greater than Z_6 at 55.8% solids. Hence, by virtue of the reaction described above, the resin had become substantially further cross-linked, and showed good drying properties and improved alkali resistance.

Other aldehydes, such as crotonaldehyde, acrolein, furfural, acetaldehyde and particularly those containing up to 6 carbon atoms may be used in lieu of formaldehyde. Moreover other alkyd resins containing free hydroxyl groups may be treated according to this process.

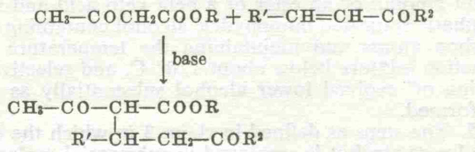
Benzylic type halides and alcohols such as triphenylmethyl chloride and triphenyl carbinol react with the beta-keto esters produced according to this invention and new compounds are obtained according to the following equation:



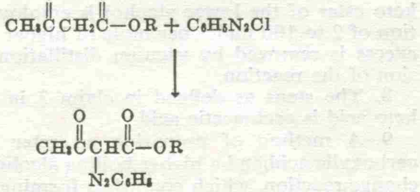
where Ar is the monovalent aryl radical.

Thus 5 grams of stearyl acetoacetate reacts with 5 grams of triphenylmethyl chloride to give triphenylmethyl stearyl acetoacetate.

Similarly, new compounds are formed when these newly discovered beta-keto esters (sterol esters, alkyd esters etc.) undergo a Michael type reaction with alpha-beta-unsaturated carbonyl compounds, e. g.:



In addition these newly discovered beta-keto esters can react with diazonium salts such as benzene diazonium chloride to yield compounds akin to Hansa dyes, of interest in the synthetic dye field:



It will be understood that the above examples and discussion dealing with the production of derivatives and compounds from beta-keto esters apply generally to the various beta-keto esters prepared according to the process herein described. Thus any of the above mentioned sterol esters including cholesterol, stigmasterol, cortisone etc., esters of beta-keto acids such as acetoacetic acid, may be substituted in stoichiometric amounts in lieu of the keto esters set forth in the above examples for the production of the derivatives described.

While a number of the above examples are directed to the production of acetoacetates such as sterol acetoacetates and alkyd resin acetoacetates etc. by ester interchange reaction, it is to be understood that these esters may be prepared by esterification by reaction of the hydroxy radical with diketene.

Although the present invention has been described with reference to certain embodiments thereof, it is not intended that the specific details of such embodiments shall be regarded as limitations upon the scope of this invention except insofar as included in the accompanying claims.

We claim:

1. A method of forming an ester of a relatively higher alcohol and a beta-keto acid by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said alcohol and an ester of a lower aliphatic monohydric alcohol and said acid, at least in molecular equivalency of said higher alcohol to effect ester interchange between said higher alcohol and said ester of a lower alcohol, reducing the concentration of evolved lower alcohol sufficiently low to maintain the desired ester interchange, maintaining the temperature of reaction below the decomposition temperatures of the alcohols and the beta keto esters, until the reaction is substantially completed and recovering the resulting ester of the higher alcohol.

2. A method of preparing an ester of a beta-keto acid and a higher alcohol which ester has a boiling point above 230° C. by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least its stoichiometric equivalent of an ester of a beta keto acid and a lower monohydric saturated aliphatic alcohol which contains up to 4 carbon atoms and distilling off evolved lower alcohol under conditions such as to maintain the partial pressure of the lower alcohol vapor below atmospheric pressure during at least the final stages of the reaction.

3. A method of preparing an ester of a beta-keto acid and a higher alcohol by ester interchange reaction, which ester has a boiling point above 230° C., which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least a stoichiometric equivalent amount of an ester of a beta keto acid with a lower aliphatic saturated monohydric alcohol containing up to 4 carbon atoms and maintaining the temperature of the reaction mixture below about 120° C.

4. A method of preparing an ester of a beta-keto acid and a higher alcohol by ester interchange reaction which ester has a boiling point above 230° C., which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least a stoichiometric equivalent amount of an ester of a beta keto acid and a lower aliphatic saturated monohydric alcohol containing up to 4 carbon atoms and maintaining the temperature of the reaction mixture below about 120° C. and selectively distilling off evolved lower alcohol substantially as rapidly as formed.

5. The steps as defined in claim 3 in which the ester of the lower alcohol is employed in substantial molar excess with respect to the higher alcohol.

6. The steps as defined in claim 3 in which the reaction is promoted by blowing the mixture with inert gas during the ester interchange, to remove evolved lower alcohol.

7. The steps as defined in claim 3 in which the beta keto ester of the lower alcohol is employed in a proportion of 2 to 100 moles per mole of higher alcohol and the excess is removed by vacuum distillation at the conclusion of the reaction.

8. The steps as defined in claim 3 in which the beta keto acid is acetoacetic acid.

9. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling alcohol by ester interchange reaction, which comprises forming a non-catalytic mixture consisting essentially of an ester of a beta-keto carboxylic acid of a low boiling aliphatic monohydric alcohol containing up to 4 carbon atoms and a higher boiling alcohol having at least 12 carbon atoms and having no phenyl group linked to the carbinol group thereof, in a proportion such that at least one equivalent of ester is present per equivalent of higher boiling alcohol, heating the mixture to a reaction temperature below the boiling point of the higher boiling alcohol and below the decomposition temperatures of said alcohols and said esters and selectively removing from the mixture said low boiling alcohol at a temperature below 120° C. as it is evolved without substantial removal of the higher boiling alcohol until reaction is completed.

10. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling alcohol by ester interchange reaction which comprises forming a non-catalytic mixture consisting essentially of an ester of a beta-keto carboxylic acid and a low boiling aliphatic monohydric alcohol containing up to 4 carbon atoms and an alcohol having a boiling point higher than the first alcohol and having no phenyl group linked to the carbinol group thereof, in a proportion such that at least two equivalents of ester is present per equivalent of alcohol of higher boiling point, heating the mixture to a temperature sufficient to effect ester interchange between the higher boiling alcohol and the beta keto ester of the low boiling alcohol without decomposing the esters in the system and without evaporating the higher boiling alcohol, and removing from the mixture the low boiling alcohol as it is evolved, the temperature being maintained until the reaction is substantially completed.

11. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling aliphatic monohydric alcohol by ester interchange reaction, which comprises forming a non-catalytic mixture consisting essentially of an ester of beta-keto acid and a low boiling aliphatic monohydric alcohol containing 1 to 4 carbon atoms and an alcohol having a higher boiling point than the low boiling alcohol and containing at least 6 carbon atoms and having no phenyl group linked to the carbinol group thereof, in a proportion such that an excess of one equivalent of ester is present per equivalent of higher boiling alcohol, heating the mixture to a temperature within a range of 80 to 120° C., selectively evaporating off low boiling alcohol evolved until reaction is completed and then selectively evaporating off any low boiling alcohol present and the excess of beta keto ester of low boiling alcohol.

12. A method of forming an acetoacetic acid ester of relatively high molecular weight by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said alcohol of higher molecular weight and an acetoacetic acid ester of an aliphatic saturated alcohol of lower molecular weight, the latter being in excess of molar ratio with respect to said alcohol of higher molecular weight, to a temperature sufficient to distill evolved alcohol of lower molecular weight as it is formed, whereby to maintain the concentration below 5% with respect to the starting ester of alcohol of lower molecular weight, but insufficient to dehydrate the alcohol of higher molecular weight and the acetoacetic acid esters in the system and subsequently selectively distilling off any residual alcohol of lower molecular weight and excess acetoacetic acid ester of said alcohol of lower molecular weight, at a temperature in the foregoing range.

13. The steps as defined in claim 12 in which the alcohol of higher molecular weight contains at least 12 carbon atoms, the alcohol of lower molecular weight contains up to 4 carbon atoms and the temperature of reaction is within a range of about 80 to 120° C.

14. A method of preparing an ester of a beta-keto carboxylic acid and a higher alcohol containing at least 12 carbon atoms in the molecule by ester interchange reaction, which comprises heating to a temperature of 80° C. to 160° C., a non-catalytic mixture consisting essentially of said alcohol and an excess of a beta-keto ester of an aliphatic monohydric alcohol containing 1 to 4 carbon atoms in the proportion of one mole of said higher alcohol to an amount substantially in excess of one mole of said ester to form a beta keto ester of the first mentioned alcohol by ester interchange and to liberate the second mentioned alcohol.

15. A method of forming an ester of (A) a relatively higher alcohol containing at least 12 carbon atoms and being free of benzene groups joined to carbon atoms attached to a hydroxyl and (B) a beta-keto acid by ester interchange reaction, which method comprises heating a non-catalytic mixture consisting essentially of said alcohol and a beta-keto ester of a class consisting of ethyl acetoacetate and methyl acetoacetate, the esters of said class being in a proportion of at least molar equivalency with respect to the higher alcohol, the temperature being maintained below the points of decomposition of the alcohols, and the beta-keto ester and the concentration of

evolved lower alcohol in the reaction mixture being maintained sufficiently low to attain the desired ester interchange reaction, said conditions being maintained until the reaction is substantially completed, and then recovering the resultant ester of the higher alcohol from the excess of the ester of said class.

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EXHIBIT A

Alfred R. Bader et al
Serial No: 468,556
Filed: November 12, 1954

For: ACETOACETIC ACID ESTERS OF CASTOR OIL AND THE USE THEREOF IN PLASTICIZATION

Monthly Progress Report

[redacted]

Robert F. Borman

Use of Ultra Violet Light Adsorbing Agents in Outside Coatings

It is a well known fact that the ultra violet rays of the sun cause accelerated deterioration of an outside house paint. If some substance could be added to an exterior film that would have the property of forming a barrier to or adsorb ultra violet light, the remainder of the coating would no longer remain under attack from the injurious sun's rays. Several ultra violet light adsorbing agents have been used in the plastics industry with generally the same function in mind. These substances have been added to plastics to give them better stability against sunlight. With this in mind several ultra violet light adsorbing agents were added to two varnishes which have rather poor outdoor durability. It is hoped that durability of these varnishes can be extended with the use of these additives.

To properly test this situation it was necessary to send out the varnishes on wooden panels to the various exposure testing farms. Another series of metal test panels were coated with the varnish containing the ultra violet light adsorbing agents and exposed in the Weather-O-Meter for 200 hours. The exposed films will then be evaluated for excessive hardening that results in checking and cracking of the film. Films that still retain their flexibility after lengthy exposure to the sun's rays would be said to be benefited by the addition of an ultra violet adsorbing agent. This program was just begun but the results from the evaluation of this test will be recorded in subsequent reports.

Use of Wetting Agents in Outside White Paint

Periodic examination of some painted panels at the Milwaukee exposure proving ground indicated that one series of outside white paint appeared to have better than average properties. They retained their whiteness, due to better cleaning action, longer than other house paints of similar formulation. This paint was identical to those compared with it with the exception that a small amount of tergitol "08" had been added to the formulation. This ingredient, it seemed, was responsible for the superior performance and as a result further investigation is now being made in this direction. Several wetting agents of various origins have been incorporated individually into a 1-54 house paint formulation and painted out

on wooden panels. The panels have been shipped to the various exposure forms for testing. The results of these tests will be given in subsequent reports.

Modified Alkyd Resin Used in Outside Trim Enamel

Three modified alkyd resins were prepared that were thought to have superior properties especially that of alkali and water resistance. The alkyd resins are similar in preparation to ER-3849. The difference lies in the addition of a methyl acetoacetate ester to a vacant hydroxyl unit on partially esterified pentek. The acetoacetate esters used in this case are those of formaldehyde, acetaldehyde, and crotonaldehyde. These modified alkyd resins were incorporated into the formulation of an outside trim enamel. Preliminary evaluation of these paints showed little deviation from the properties expected of the factory prepared standard. The paint was applied to wooden panels and they were sent out for exposure tests. Periodic evaluation of these panels will be made and this information will be relayed in subsequent reports.

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Robert F. Borman

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nts in Outside Coatings

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To properly test this situation it was necessary to send out the varnishes on wooden panels to the various exposure testing farms. Another series of metal test panels were coated with the varnish containing the ultra violet light adsorbing agents and exposed in the Weather-O-Meter for 200 hours. The exposed films will then be evaluated for excessive hardening that results in checking and cracking of the film. Films that still retain their flexibility after lengthy exposure to the sun's rays would be said to be benefited by the addition of an ultra violet adsorbing agent. This program was just begun but the results from the evaluation of this test will be recorded in subsequent reports.

Use of Wetting Agents in Outside White Paint

Periodic examination of some painted panels at the Milwaukee exposure proving ground indicated that one series of outside white paint appeared to have better than average properties. They retained their whiteness, due to better cleaning action, longer than other house paints of similar formulation. This paint was identical to those compared with it with the exception that a small amount of tergitol "08" had been added to the formulation. This ingredient, it seemed, was responsible for the superior performance and as a result further investigation is now being made in this direction. Several wetting agents of various origins have been incorporated individually into a 1-54 house paint formulation and painted out

C-2252

Monthly Progress Report

March, 1951

Robert F. Borman

Use of Ultra Violet Light Adsorbing Agents in Outside Coatings

It is a well known fact that the ultra violet rays of the sun cause accelerated deterioration of an outside house paint. If some substance could be added to an exterior film that would have the property of forming a barrier to or adsorb ultra violet light, the remainder of the coating would no longer remain under attack from the injurious sun's rays. Several ultra violet light adsorbing agents have been used in the plastics industry with generally the same function in mind. These substances have been added to plastics to give them better stability against sunlight. With this in mind several ultra violet light adsorbing agents were added to two varnishes which have rather poor outdoor durability. It is hoped that durability of these varnishes can be extended with the use of these additives.

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Robert F Borman

Robert F. Borman

April 6, 1951

EXHIBIT B

Alfred R. Bader et al
Serial No: 468,556
Filed: November 12, 1954

For: ACETOACETIC ACID ESTERS OF CASTOR OIL AND THE USE THEREOF IN PLASTICIZATION

Office

2,693,484
Patented Nov. 2, 1954

2,693,484

NONCATALYTIC ESTER EXCHANGE REACTION OF BETA-KETO CARBOXYLIC ACID ESTERS

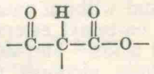
Lowell O. Cummings, Henry A. Vogel, and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application April 7, 1951, Serial No. 219,900

15 Claims. (Cl. 260—483)

The present invention relates to methods of forming esters of beta carbonyl acids and alcohols and it has particular relation to a novel method of forming beta carbonyl esters of alcohols of relatively high molecular weight and to the novel esters resulting from such method.

One object of the invention is to provide a simple and convenient method of forming esters of higher alcohols or hydroxy compounds and particularly carbonyl substituted acids containing the group:



$$-\overset{O}{\overset{\|}{C}}-\underset{|}{\overset{H}{\overset{|}{C}}}-\overset{O}{\overset{\|}{C}}-O-$$

A second object of the invention is to provide a simple method of forming esters of higher alcohols containing for example 10 or 12 and usually 16, 18 and more carbon atoms per molecule.

A third object of the invention is to provide a method of forming esters of alcohols which is adapted to operate without the use of catalysts and at moderate temperatures to obtain an exceptionally high yield of desired product in a state admitting of ready purification.

A fourth object of the invention is to provide novel esters of beta carbonyl carboxylic acids and higher hydroxy compounds having an exceptionally high degree of functionality and solubility and adapting them to organic reactions and syntheses.

A fifth object of the invention is to provide esters of alcohols of exceptionally strong polarity that adapts them physically for use as emulsifiers, solubilizers, plasticizers and the like applications.

A sixth object of the invention is to provide novel esters of beta carbonyl carboxylic acids and higher alcohols.

A seventh object of the invention is to provide a method of forming esters of sterols which is operable without the use of excesses of the sterols.

These and other objects will be apparent from the following specification and the appended claims.

Prior art

It has heretofore been customary to prepare esters of various alcohols and carboxylic acids by a number of different methods such as direct reaction between the desired acids and alcohols or between chlorides of the acids or the anhydrides of the acids and the alcohols. In some cases, desired esters have been obtained by interchange of radicals between esters of carboxylic acids and lower alcohols with higher alcohols.

In general these processes involved rather drastic conditions of reaction, as, for example, high temperatures and/or the use of basic or acidic catalysts and the like. Moreover, in these processes conditions of reaction often have complicated removal of the unreacted portions of the reactants, or the catalyst residues from the reaction products and frequently these impurities could not be removed from the resulting ester. Often the reaction was incomplete and poor yields of the desired product were obtained. These difficulties were quite pronounced in the production of esters of higher molecular weight alcohols, for example those containing at least 6 or usually more carbon atoms. Moreover, the processes usually involved the use of great excesses of the alcohol which was being subjected to esterification. Obviously in dealing with scarce and expensive compounds such as sterols, this was highly objectionable.

The present invention

According to the present invention, it has been discovered that esters of high molecular weight can be prepared in high purity and in almost quantitative yield by interacting under mild conditions an ester of an enolizable beta carbonyl or beta keto carboxylic acid and a lower aliphatic (preferably saturated) alcohol containing, for example, up to 4 carbon atoms with an alcohol of higher boiling point than such lower alcohol (preferably at least 20° C. higher) which forms a corresponding ester having a boiling point above about 230° C. while maintaining in the reaction mixture at least one or more equivalents of the ester for each equivalent of higher alcohol.

In order to avoid production of ketones and other byproducts and to obtain approximately quantitative yields, it is necessary that the temperature of the reaction should be kept low. For best results (maximum yield and purity of product), the temperature of reaction should not exceed about 150° C. and preferably should be below 120 or 130° C.

Somewhat higher temperatures may be used with certain alcohols provided special precautions are observed to remove evolved lower alcohol from the reaction mixture substantially as rapidly as evolved. Such precautions are more fully explained below.

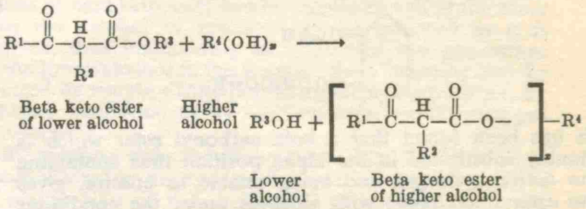
According to a further embodiment of the invention, it has been found that maximum yield and purity of ester is obtained when the evolved lower alcohol is swept rapidly from the reaction mixture. This may be accomplished by distilling the lower alcohol under conditions such that the partial pressure of the lower alcohol vapor is maintained below atmospheric pressure. For example, the reaction mixture may be blown with an inert gas such as carbon dioxide, nitrogen, etc. to cause rapid distillation of evolved lower alcohol. Alternatively or in conjunction therewith, a subatmospheric pressure may be maintained over the reaction mixture whereby to promote distillation of the evolved lower alcohol. These precautions are of especial importance where the temperature of the reaction mixture is allowed to rise to a relatively high value, for example 120–160° C. However, purer products are generally obtained by recourse to these precautions even when the reaction temperature is below 120° C.

Typical esters which are prepared are the esters of acetoacetic acid. However, the esters of other beta keto acids such as are listed below also may be prepared.

To insure good yields, excesses of the alcohol to be reacted with the acetoacetic ester are avoided. Indeed, great excesses of the acetoacetic acid ester component may be employed and if care is exercised to eliminate, or at least sufficiently to reduce in the reaction zone the relative concentration of the alcohol freed, with respect to that of the initial beta keto ester, quantitative interchange of alcohol radical can be attained.

The reaction involved may be represented by the general equation:

EQUATION A



$$\underset{\text{Beta keto ester of lower alcohol}}{R^1-\overset{O}{\overset{\|}{C}}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OR^3} + \underset{\text{Higher alcohol}}{R^4(OH)_n} \longrightarrow \underset{\text{Lower alcohol}}{R^3OH} + \underset{\text{Beta keto ester of higher alcohol}}{\left[R^1-\overset{O}{\overset{\|}{C}}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-\right]_n-R^4}$$

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United States Patent Office

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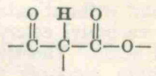

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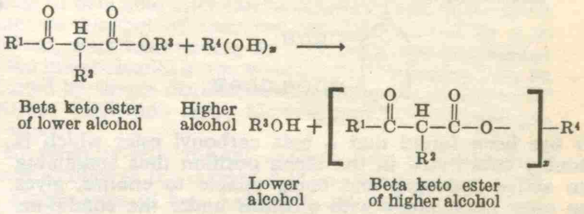


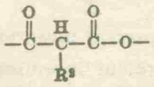
$$R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-OR^3+R^4(OH)_x \longrightarrow R^3OH+\left[R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-O-\right]_x-R^4$$

The several groups R^1, R^2, R^3, and R^4 will be defined later. As previously stated, in order to obtain the most complete reaction, we find it convenient to use an excess of the beta keto ester of the lower alcohol.

BETA KETO ESTERS

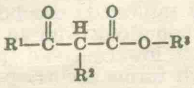
Beta keto esters which may be employed to effect esterification of alcohols include various esters which

contain a ketone carbonyl group in the beta position with respect to a carboxyl. They include the group



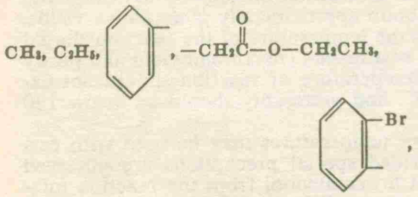
$$-\overset{\overset{O}{\parallel}}{C}-\overset{H}{\underset{\underset{R^2}{|}}{C}}-\overset{\overset{O}{\parallel}}{C}-O-$$

already referred to. The general structure of the esters may be represented by the formula taken from the above Equation A which is as follows:



$$R^1-\overset{\overset{O}{\parallel}}{C}-\overset{H}{\underset{\underset{R^2}{|}}{C}}-\overset{\overset{O}{\parallel}}{C}-O-R^3$$

In the formula, group R^1 may be aliphatic, aromatic or aliphatic or aromatic groups which may or may not contain substitute groups. Examples of R^1 groups are:



and other halogen substituted hydrocarbon radicals, RNH_2, RCHO, etc.

R^2 also frequently is hydrogen but it can also be hydrocarbon or substituted hydrocarbon such as methyl, ethyl, propyl, butyl, chloro, amino, chloromethyl, benzyl, phenyl or the like or derivatives thereof. Only one of the hydrogens of the alpha carbon atoms can be replaced by substituents. The remaining hydrogen atom is an active atom essential to the ester interchange reaction and must be retained.

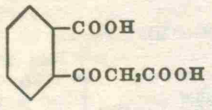
R^3 is usually the labile radical which is adapted to be replaced in the ester interchange. These functioning groups usually are of low molecular weight, e. g., 1, 2, 3, or possibly 4 carbon atoms in a saturated or unsaturated aliphatic substituted or unsubstituted hydrocarbon chain.

Examples of appropriate liquid beta carbonyl esters suitable for use in the practice of the invention include the following compounds:

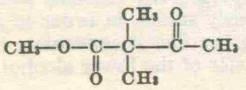
Table A

Methyl, ethyl, n-propyl, isopropyl, allyl, methallyl, crotyl, propargyl, 2-chloroethyl, 2-fluoroethyl, 2-nitropropyl and butyl esters of:

- Acetoacetic acid
- Alpha ethyl acetoacetic acid
- Alpha isopropyl acetoacetic acid
- Alpha methyl acetoacetic acid
- Benzoyl acetoacetic acid
- Acetone dicarboxylic acid
- Gamma chloro acetoacetic acid
- Alpha benzoyl acetoacetic acid
- Alpha phenyl acetoacetic acid
- Chloro iodo and bromo substitution products of the above acids
- Acetylsuccinic acid
- Benzoyl acetic acid
- Diester of



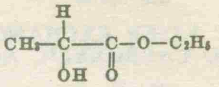
It has been found that a beta carbonyl ester which is doubly substituted in the alpha position thus containing no active hydrogen and being unable to enolize, gives no ester interchange with alcohols under the conditions of the present invention. Such an ester is methyl dimethyl acetoacetate of the formula:



$$CH_3-O-\underset{\underset{O}{\parallel}}{C}-\overset{CH_3}{\underset{\underset{CH_3}{|}}{\overset{|}{C}}}-\overset{\overset{O}{\parallel}}{C}-CH_3$$

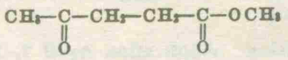
Esters having structures or molecular weights somewhat similar to acetoacetic ester, but being dissimilar in not having one or more active hydrogen atoms, have been found to be non-reactive under the conditions herein

contemplated. For instance, ethyl n-butyrate has a molecular weight almost identical to that of methyl acetoacetate but gives no reaction. Ethyl lactate and methyl levulinate have structures somewhat similar to methyl acetoacetate being respectively:



$$CH_3-\overset{H}{\overset{|}{\underset{\underset{OH}{|}}{C}}}-\underset{\underset{O}{\parallel}}{C}-O-C_2H_5$$

Ethyl lactate



$$CH_3-\underset{\underset{O}{\parallel}}{C}-CH_2-CH_2-\underset{\underset{O}{\parallel}}{C}-OCH_3$$

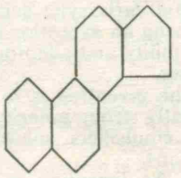
Methyl levulinate

Neither ethyl lactate nor methyl levulinate gives transesterification under the conditions of the present invention.

ALCOHOLS CAPABLE OF ESTER INTERCHANGE WITH BETA CARBONYL ESTERS

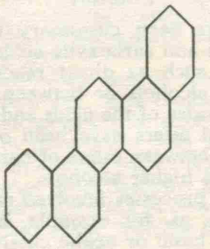
Many hydroxy compounds of relatively high molecular weight may be treated according to this invention. Typical are compounds having the formula $R^4(OH)x$ (from Equation A) where (OH) is an alcoholic OH group, R^4 contains 6 or more carbon atoms and X is a number denoting the number of hydroxyl groups in the molecule. These easily, quickly and without catalysts undergo ester interchange with beta carbonyl esters to provide higher esters of beta carbonyl acids. The sterols and certain of the relatively long chain alcohols and hydroxy compounds such as occur in or are derived from glyceride oils, tall oil waxes and wool fats or the like are outstanding examples of such compounds. These are compounds of considerable molecular weight, containing at least 12 and usually 16, 18, 27 or more carbon atoms. It was quite surprising that these hydroxy compounds of such high molecular weight would so easily undergo ester interchange.

The sterols can be regarded as being derived from cyclopentano phenanthrene:



or its perhydro derivatives by appropriate shifting or replacement of hydrogen by hydroxyl or other groups, and may contain other substituted hydrocarbon groups, or may be otherwise modified by dehydrogenation and such like changes familiar to the art.

The triterpene alcohols such as occur in wool fat can similarly be regarded as being hydroxy derivatives of picene:



or its hydrogenated derivatives.

These hydroxy compounds are often comparatively sensitive to high temperatures and other conditions. However, many of them are important starting compounds in the synthesis of hormones and other biologicals. Yet in some of the reactions to which the compounds are subjected it is desirable to protect the hydroxyl oxygen from loss or from conversion to carbonyl form. It may also be desirable to convert the hydroxyl to ester form in order to increase the polarity of the compound or to provide reactive, or labile groups.

It has now been discovered that these higher alcohols can easily be subjected to esterification with beta carbonyl esters at very moderate temperatures and without resort to catalysts to provide esters of great utility.

Examples of higher alcohols which can be esterified with beta carbonyl esters by ester interchange include:

Table B

- Sterols such as:
  - Cholesterol
  - Beta sitosterol
  - Stigmasterol
  - Cholestanol
  - Epidehydroandrosterone
  - Ergosterol
  - Epicholestanol
  - Coprostanol
  - Cortisone
  - Cholic acid
  - Desoxycholic acid
  - Steroid Sapogenines
  - Steroid intermediates
- Triterpene alcohols such as:
  - Agnosterol
  - Lanosterol
- Aliphatic compound containing at least 6 and usually containing 16 or more carbon atoms and containing alcoholic hydroxyl groups, such as:
  - Octadecyl alcohol
  - Lauryl alcohol
  - Ceryl alcohol
  - Cetyl alcohol
  - Carnaubyl alcohol
  - Lignoceryl alcohol
- Polyhydroxy compounds such as:
  - Decamethylene glycol
  - Glycerine
  - Ethylene glycol
  - Polyethylene glycol and polyethylene oxide resins or waxes and like waxy resins which are soluble in solvents of fats
  - Ether alcohols such as:
    - Butyl carbitol
    - Propyl carbitol
- Hydroxy glyceride oils such as:
  - Castor oil
  - Mono- and di-glycerides which are soluble in solvents of fats
  - Synthetic hydroxy glycerides
- Cyclic and polycyclic alcohols
  - Cyclohexanol
  - Hydroxy decalin
  - Polyhydric alcohol-polybasic acid resins such as glycerol phthalate, glycerol or glycol maleate or monobasic acid modified resins of this character
  - Diamyl carbinol
  - Diethylene glycol
  - 1,2-dichloropropanol 3
  - Pentaerythritol
  - Linoleyl alcohol
  - Nitro alcohols such as:
    - 2-methyl, 2-nitropropyl alcohol
    - 2-nitrobutyl alcohol and others.

When it is desired to avoid alkylation rather than, or in conjunction with, esterification, alcohols which contain a phenyl group directly linked to the carbinol atom thereof should not be used. Unsaturated alcohols such as allyl alcohol, methallyl alcohol, crotyl alcohol, etc., may be used effectively to produce the esters contemplated. In some cases these esters may tend to rearrange after formation to ketone derivatives.

It is desirable that the esters produced by interchange between the original beta carbonyl esters and the higher alcohols be of a boiling point above that of the initial beta keto ester (compound 1), for example, the ester produced preferably should boil at a temperature above 230° C. at 760 millimeters pressure. This permits ready purification of the product by simple distillation or by crystallization or other means.

Obviously the hydroxy compound which is to undergo interchange with the beta carbonyl compound should be soluble in the latter, or at least should be soluble in solvents that are mutually compatible with beta carbonyl compounds.

CONDITIONS OF REACTION

The conditions of reaction employed to effect the ester interchange between the hydroxy compounds and beta carbonyl esters such as beta keto esters may vary, dependent upon the carbonyl ester and the hydroxy compound employed in the reaction. However, the conditions, in most cases are relatively mild.

Catalysts of reaction are not required and usually it is desirable to operate without them. However, such catalysts may be present if purity of product is not important.

The temperature of reaction should be sufficiently high to drive off the lower alcohol quite rapidly. Preferably, it should be driven off substantially as fast as it is liberated in the reaction mixture. The temperature should also be below the point of decomposition of the reactants, or the desired product. A good average temperature is approximately 90 to 100° C. which is near that of an ordinary steam bath. The temperature can also be reduced below this value. However, it is to be understood that as the temperature approaches or is reduced below the normal boiling point of the lower alcohol evolved in the system, it is desirable to apply vacuum in order to promote removal of the latter alcohol. Higher temperatures preferably below 120° C. and in any event below 160° C. are permissible under the conditions explained heretofore.

The approach of the upper limit of the temperature of decomposition can usually be detected by a darkening of the reaction mixture. If any tendency so to discolor is observed, the temperature should be reduced until it ceases. It is usually preferred to employ a temperature above the boiling point of the lower alcohol involved in the system. This facilitates removal of the latter.

To obtain a very high yield of desired ester of the higher alcohol, the concentration of the lower alcohol in the reaction mixture should not be allowed to exceed 33 mole percent of the acetoacetic ester of such alcohol in the mixture. It is even desirable that the precentage be as much lower than this value as can reasonably be attained. If the concentration is reduced to 5 molar percent or even to 1 or 2 molar percent or less (based upon the beta keto ester of the lower alcohol), still better yields can be attained.

Several methods are available to attain these low concentrations of the evolved lower alcohol without unduly increasing the temperature of the reaction mixture. For example, the system can be placed under fairly high vacuum thus stripping off the lower alcohol as it is formed while permitting the temperature to stay relatively low. Beta keto ester of lower alcohol carried over as a vapor in the lower alcohol stripped off can be condensed and returned. In this way, the concentration of the original beta keto ester in the system is maintained.

It is likewise contemplated to strip off lower evolved alcohol by blowing the reaction mixture with a non-reactive vapor or gas, e. g., nitrogen, CO_2, or the like. Steam in substantial amounts is usually to be avoided.

Still another convenient method comprises dilution of the alcohol of reaction by employing a high molar excess of the beta keto ester of the lower alcohol. For example, the excess may be 0.1 to 5, 10 or even 100 fold of the molecular ratio of the beta keto ester with respect to the original higher alcohol undergoing ester interchange. The excess can be added initially or it can be added as the reaction proceeds.

Combinations of these several methods are within the scope of this invention. For example, a 2 to 100 mole excess of beta keto ester can be employed and at the same time the alcohol of reaction can be removed as it is evolved, thus maintaining an extremely low percentage of the lower alcohol in the system. Such stripping may be effected by simple distillation at atmospheric pressure, by vacuum distillation or by blowing with non-reactive gas or vapor.

By properly reducing the concentration of the evolved lower alcohol in the system, it is possible to obtain yields of higher ester of beta keto acids of 90% or higher up to practically quantitative values, e. g., 98 or 99%, without discoloration of the product or the reactants.

If care is observed to maintain the reaction temperature reasonably low and at the same time to distill off under vacuum or otherwise to remove, or decrease the concentration of the lower alcohol evolved by reaction, highly efficient ester interchange can be effected with equimolar ratios of the higher alcohol and the beta keto ester of lower alcohol or with only a slight excess of the latter. However, it is usually more convenient to operate with an excess which is substantial, e. g., 10% or preferably larger (upon a molar basis) of the starting beta keto ester. This excess promotes the reaction. When the reaction nears completion, the excess of original ester can be distilled off. Vacuum should be applied to promote the distillation within the permissible temperature limits. A pressure of about 5 to 50, e. g., 15 millimeters of mercury is usually satisfactory for distilling off this excess of beta keto ester but such other pressures as will remove the excess ester at permissible temperatures may be employed. The distillation may be conducted at or near the original reaction temperature. The distillation of the excess beta keto ester of lower alcohol is important because it also distills off any lower alcohol in the system, thus reducing the concentration of the latter with respect to the original beta keto ester still present and assuring that the ester interchange reaction is completed at moderate temperatures.

In general the reaction is conducted at a temperature above about 50° C. At temperatures ranging from 50 to 130° C. or above the reaction usually proceeds to substantial completion in about 3 to 48 hours. Where lower temperatures are used, for example room temperatures or below, the reaction is much slower and several weeks may be required to achieve substantial reaction and even then use of a substantial excess (100% or more) of keto ester generally is required.

The main features involved in the process as herein disclosed may be summarized as follows:

1. Selection of an alcohol to be subjected to ester interchange which does not undergo side reaction and which is substantially of higher boiling point than the alcohol liberated by reaction.

2. The amount of beta carbonyl ester should be in at least an equimolar proportion with respect to the alcohol to be subjected to ester interchange and preferably it should be in excess. In production of esters of many alcohols, it is necessary to use an appreciable excess, for example 50% or more, of beta keto ester in order to dissolve the alcohol being esterified and/or to insure improved yield.

3. The concentration of evolved alcohol in the reaction mixture should be maintained as low as is feasible, e. g., not in excess of about 33 molar percent and preferably less with respect to the original amount of the beta keto ester of lower alcohol. This may be effectively accomplished in several ways, as for example by distilling off the lower alcohol as formed under conditions such that the partial pressure of the alcohol vapor is below atmospheric, at least during the later stage of the reaction.

4. Catalysts of reaction are not necessary and usually are not employed.

5. The temperature of ester interchange should be moderate, e. g., 50 to 120° C. and usually under no circumstances above 160° C. Satisfactory upper limits of temperature are determinable by observation for the initiation of decomposition reaction.

6. Time of reaction should be maintained until the lower alcohol ceases or substantially ceases to evolve.

7. Solvents are not ordinarily necessary in the reaction. The beta keto ester of a lower alcohol, however, in a sense constitutes a reaction solvent. It will be apparent that non-reactive liquid media may also be employed as solvents if so desired.

8. It is desirable, at the conclusion of the reaction, to distill off any excesses of the beta keto ester of lower alcohol present in the reaction mixture along with any residual lower alcohol evolved by the reaction by distillation at a lower temperature. If this latter precaution is observed, any unreacted higher alcohol still present in the system will be induced to undergo reaction and thereby carry the reaction substantially to completion.

The following examples illustrate the application of the principles of the invention:

EXAMPLE I

In this example, 20 grams of cholesterol and 100 grams of methyl acetoacetate were heated together in the absence of catalyst in a round bottom flask with open neck, at 90 to 100° C. Methyl alcohol was expelled as the reaction proceeded. At the conclusion of 8 hours, the excess of methyl acetoacetate was removed by vacuum distillation at a pressure of about 15 millimeters of mercury and there was obtained 23 grams of a white solid which had a melting point of 91 to 93° C. This product was dissolved in aqueous acetic acid and recrystallized to obtain a further purified compound melting at 93 to 94° C. The specific rotation $\alpha_D^{25°}$ in chloroform was —33°. The compound was cholesteryl acetoacetate of very high purity.

EXAMPLE II

A mixture of 10 grams of cholesterol and 50 grams of ethyl acetoacetate was heated on a steam bath for 3 hours. The excess of ethyl acetoacetate was removed by distillation at a pressure of 10 millimeters (absolute). There remained 11 grams of a white solid which was identical with the product obtained in Example I, being cholesteryl acetoacetate. Saponification with alcoholic potassium hydroxide gave quantitative yields of cholesterol indicating the ester structure of the cholesteryl acetoacetate. Analysis by other methods well known in the art furnish further proof of the structure of the reaction product.

The acetoacetates of higher alcohols, in general, possess greater solubility than the parent alcohol, as well as greater solubility than such conventional ester derivatives as acetates or benzoates. This makes acetoacetate derivatives of sterols useful intermediates in steroid syntheses because of greater ease of handling in solutions for purposes of crystallizing or of conducting other synthetic reactions on solutions. For example, in the following table are given the comparative solubilities of cholesteryl acetoacetate and cholesteryl acetate in a number of solvents. The volume of each solvent in cubic centimeters or milliliters required to dissolve 1 gram of the cholesteryl ester at reflux temperature is given.

	Cholesteryl Acetate, cc.	Cholesteryl Acetoacetate
Acetone	3	Less than 1 cc.
Methanol	70	20 cc.
Methanol+Hexanol (Equal volumes)	13	Less than 2 cc.
Methanol+Isopropyl Ether (Equal volumes).	9	Do.
Methanol+Acetone (Equal volumes)	17	Do.

(cc.=milliliters.)

This increased solubility of a sterol derivative is of particular advantage when purifying such materials by solvent crystallization since the volume of solvent required to dissolve the sterol derivative is from ⅓ to ⅑ as large when using the acetoacetate rather than the acetate of the sterol.

It is well known that beta keto acids and their esters are metabolic intermediates. Compounds such as acetoacetic esters and acetone dicarboxylic esters have been isolated as products of metabolism. Esters of beta keto acids and sterols, therefore, may be metabolic intermediates and may have therapeutic value.

It is to be observed in these examples that no catalysts of reaction are required in the ester interchange. The temperatures are very mild. The reaction is thereby distinguished from conventional ester interchanges which are catalyzed by alkaline or acid catalysts and require higher temperatures. The proportion of higher alcohol is also much less than molar.

The reaction by ester interchange as herein disclosed is also an improvement upon conventional reactions involved in the preparation of esters of higher alcohols in which acid chlorides or acid anhydrides are caused to react with the alcohol. In this latter type of reaction, the stronger acid compounds may be difficult to handle and the excess of reactant cannot be readily recovered. In the present instance, the excess of ethyl acetoacetate or other beta carbonyl ester can readily be recovered by simple distillation, with only quantitative amounts being consumed in the interchange reaction. The reaction product likewise is not contaminated by catalyst or by-products from catalyst removal or destruction.

The following additional examples illustrate further embodiments of the invention:

EXAMPLE III

Two grams of stigmasterol and 20 grams of methyl acetoacetate were heated on a steam bath and under an air condenser, under which conditions the methyl alcohol was expelled as the reaction proceeded. Reaction was continued for two hours. At the end of this time, the excess methyl acetoacetate was stripped off by vacuum distillation. The vacuum was such as to maintain the temperature of distillation below 100° C. There remained 2.2 grams of a white solid which was crystallized from petroleum ether admixed with methanol to provide a product comprising white shining platelets of a melting point of 114 to 114.5° C., the specific rotation $\alpha_D^{25°}$ in chloroform equals −44°. This product was stigmasteryl acetoacetate.

EXAMPLE IV

Two grams of beta sitosterol having a melting point of 136 to 137° C. and 20 grams of ethyl acetoacetate were heated on a steam bath for 18 hours. The reaction product was stripped of ethyl acetoacetate and any residual ethyl alcohol by vacuum distillation and there remained a white solid product constituting 2.2 grams and this was recrystallized from petroleum ether admixed with methanol to provide a product in the form of white shining platelets of a melting point of 99° C. and a specific rotation at 25° C. in chloroform of −24°. The product was beta sitosteryl acetoacetate. An identical product was obtained by use of methyl acetoacetate as the beta carbonyl ester.

EXAMPLE V

One hundred milligrams of cholestanol, melting in a range of 140 to 142° C. was treated with 10 grams of methyl acetoacetate by heating the mixture on a steam bath for 4 hours. Upon distillation of the excess of methyl acetoacetate, there remained a quantitative yield of cholestanyl acetoacetate in the form of white platelets of a melting point of 97° C. and of a specific rotation at 25° C. in chloroform of +12°.

EXAMPLE VI

In this example, epidehydroandrosterone was admixed with a molar excess of methyl acetoacetate and heated on a steam bath for 18 hours. The excess of methyl acetoacetate was distilled under vacuum and there remained a solid product which was recrystallized from methanol to provide feathery white crystals of epidehydroandrosterone acetoacetate melting at 163° C. The specific rotation $\alpha_D^{25°}$ in chloroform was +1°.

EXAMPLE VII

In this example, 5 grams of octadecyl alcohol and 30 cc. of methyl acetoacetate were heated on a steam bath for 24 hours. The methyl alcohol of reaction was continuously removed. At the conclusion of this time, the excess of methyl acetoacetate was distilled under vacuum until an oily residue remained. The residue was taken up in a mixture of 30 cc. of methanol, 10 cc. of acetone, and 6 cc. of water. Upon cooling the solution, white crystals in a yield of 6 grams and of a melting point of 40 to 40.5° C. precipitated. These crystals were octadecyl acetoacetate.

EXAMPLE VIII

Fifty grams of cold pressed castor oil (largely a triglyceride of ricinoleic acid) and 150 grams of methyl acetoacetate were heated in an open necked glass flask on a steam bath for a period of 4 hours. The mixture at that point was a clear solution which was stripped of methyl acetoacetate and residual methyl alcohol by distillation at 10 millimeters mercury pressure (absolute) to leave a light yellow oil weighing 62 grams. This product is castor oil acetoacetate and an infra-red analysis showed the complete absence of hydroxyl groups in it. The plasticizing action of this product was found to be good in the following compositions:

50 grams of 32% solids clear lacquer of ½ second nitrocellulose in mixed solvents (butyl acetate, ethanol, isopropyl acetate and toluene)
10 grams butyl acetate
10 grams castor oil acetoacetate.

This gave a clear lacquer solution. A film of the solution on glass baked 1½ hours at 100° C. was hard but not brittle. The composition contained 10 grams of plasticizer and 16 grams of nitrocellulose.

A mixture of 50 grams of a 25% solids VMCH Vinylite which is a copolymer of vinyl chloride and vinyl acetate in methyl isobutyl ketone, methyl ethyl ketone, and toluene and 10 grams of castor oil acetoacetate gave a clear solution which was poured to form a film on glass. After baking for 1½ hours at 110° C., the film was clear and hard but not brittle. The castor oil ester of acetoacetic acid constituted a plasticizer.

EXAMPLE IX

Eight grams of decamethylene glycol and 45 cc. of methyl acetoacetate were heated on a steam bath for 18 hours. After vacuum distillation of the excess methyl acetoacetate and residual methyl alcohol, there remained a waxy solid of a melting point of 31 to 33° C. which, after a single crystallization from methanol, melted at 33 to 34° C. This product was decamethylene diacetoacetate.

EXAMPLE X

Eight grams of cyclohexanol was substituted for decamethylene glycol in Example IX and the mixture was heated as previously described. The product as obtained by distillation of the excess methyl acetoacetate was a water white liquid boiling within a range of 126 to 129° C. at a pressure of 15 millimeters (absolute) of mercury. The index of refraction at 25° C. was 1.45765.

EXAMPLE XI

In this example, a non-reactive solvent was employed. A mixture of 5 grams of cholesterol and 25 cc. of methyl acetoacetate in solution in 250 cc. of xylol (inert solvent) was heated on a steam bath and under an air cooled condenser designed to pass evolved methyl alcohol and to return reactives and solvents to system for 18 hours. At the conclusion of the reaction period, the methyl acetoacetate and the xylene were stripped by distillation under vacuum and there remained 5.9 grams of a white solid which, after one recrystallization from aqueous acetic acid, melted at 92 to 93° C. and which was identical with cholesteryl acetoacetate prepared without solvents as described in Example I.

EXAMPLE XII

A mixture of 100 grams of polyethylene glycol of approximately molecular weight of 200 and 400 grams of methyl acetoacetate was heated under slight negative pressure on a steam bath for 15 hours. The excess methyl acetoacetate and any residual methyl alcohol were then removed by vacuum distillation and there remained 150 grams of a water soluble liquid. This product was polyethylene acetoacetate having a saponification value of 359.

EXAMPLE XIII

In this example, 100 grams of butyl carbitol (diethylene glycol monobutyl ether) was reacted with excess methyl acetoacetate under the conditions described in Example XII. After removal of the excess methyl acetoacetate, there remained a water white liquid butyl carbitol acetoacetate having a saponification value of 342.

EXAMPLE XIV

A mixture of 41 grams of n-octanol and 200 grams of methyl acetoacetate was heated at steam bath temperature with continuous removal of methyl alcohol, for 22 hours. The excess methyl acetoacetate was separated from the product (n-octyl acetoacetate) by fractional distillation under vacuum using a Widmer column. There was isolated 65 grams of n-octyl acetoacetate boiling at 140–141° C. at 16 mm. mercury (absolute). The product had a saponification value of 507 and an index of refraction $n_D^{25}=1.4372$.

EXAMPLE XV

The use of esters of benzoyl-acetic acid, which are beta carbonyl compounds, in the transesterification has been referred to. In this example, 5 grams of cholesterol and 30 grams of ethyl benzoyl-acetate were heated at steam bath temperature for 20 hours. Removal of the unreacted ethyl benzoyl-acetate by vacuum distillation left 6.4 grams of cholesteryl benzoylacetate, which after crystallization from a butyl acetate-ethanol mixture melted at 151° C.

EXAMPLE XVI

Five grams of stearyl alcohol and 25 grams of ethyl benzoylacetate were heated on the steam bath for 24 hours. The excess ethyl benzoylacetate was removed by vacuum distillation. The residue was triturated with methanol, filtered, and dried, yielding 6.5 grams of stearyl benzoylacetate. After crystallization from acetone, it melted at 55–57° C. and had a saponification value of 180.

EXAMPLE XVII

Two grams of ethyl acetone dicarboxylate and 2.7 grams of stearyl alcohol were heated on a steam bath in an open neck flask with removal of ethyl alcohol for 16 hours. The mass was then dissolved in ethanol, cooled and filtered. There were obtained fine crystals of distearyl acetone dicarboxylate which melted at 65° C and had a saponification value of 343.

EXAMPLE XVIII

This example illustrates the employment of inert gas to strip off lower alcohol as it is formed and moderate temperatures of reaction in the preparation of an ester of menthol and acetoacetic acid by interchange reaction between the alcohol and methyl-acetoacetate in molecular ratio. In the reaction, .2 mole of menthol and .2 mole of methyl acetoacetate were heated to a temperature of 95° C. The reaction was continued at that temperature while inert gas (from butane combustion) was bubbled in vigorously or at least sufficiently rapidly effectively to sweep out methyl alcohol as it was liberated. (Inert gas can be replaced by vacuum, if so desired.) In this instance, the reaction was continued for 24 hours.

A yield of 94% menthyl acetoacetate having a melting point of 24 to 27° C. was attained. This product was further purified by crystallization to provide a product of a melting point of 30 to 32° C.

EXAMPLE XIX

In this example, a large excess of ethyl acetoacetate was employed at moderate temperatures of reaction· The proportions were:

	Moles
Menthol	.1
Ethyl acetoacetate	15

The temperature of reaction was 98° C. Neither inert gas nor vacuum were employed. Any ethyl alcohol vaporized was allowed to escape, but no effort was made to promote vaporization. The reaction was continued for 24 hours to assure completion without recourse to testing. The reaction mixture was distilled at 15 mm. (absolute) and to 112° C. to remove excess ethyl acetoacetate together with any residual ethyl alcohol in the mixture. An excellent product melting in the range of 26–29° C. and in a yield of 99% was attained. This product could be further purified by crystallization to form a product of a melting point of 30 to 32° C.

EXAMPLE XX

Admix .2 mole of menthol and .2 mole of methyl acetoacetate and heat to 150° C. while blowing with inert gas to remove methyl alcohol as rapidly and thoroughly as practicable. (In lieu of inert gas, a vacuum can be applied with similar results.) Reaction is complete in 5 hours or less. A yield of 99% of a material melting at 20 to 23° C. results. This material is a solid and can be purified by crystallization. However, it is less pure than that obtained in Examples XVIII or XIX.

EXAMPLE XXI

This example illustrates a control run. In it, a mixture of .1 mole of menthol and .1 mole of ethyl acetoacetate were heated at atmospheric pressure without inert gas, to a temperature of 150° C. for 2.5 hours. The reaction mixture was distilled at 15 millimeters of mercury while the temperature was increased to 160° C. The product remained as a 42% yield of an oily residue in the flask. It was oily even at 0° C. and was difficult to purify. The temperature of reaction was too high.

EXAMPLE XXII

This was essentially repetition of Example XXI except that reaction was continued for 5 hours. Distillation was stopped at 152° C., because an excessive evaporation of the reaction mixture had already occurred. The yield of product was 18%. This was an oil which was difficult to purify.

EXAMPLE XXIII

This was also a control test in which a low temperature of reaction and a long period of reaction were employed. Both inert gas and vacuum were omitted during the reaction. The reaction mixture consisted of .1 mole menthol and .1 mole ethyl acetoacetate. The mixture was maintained at 98° C. for 24 hours. The mixture was then subjected to a vacuum of 15 millimeters of mercury (absolute) to 160° C. The distillation residue constituting the menthyl acetoacetate product constituted a yield of only 24%. This product had a melting point of 27 to 30° C.

This experiment was repeated, but distillation was conducted at 140° C. The yield was 37% and the product had a melting point of 30 to 32° C.

EXAMPLE XXIV

In this example, lauryl alcohol which is a C–12 alcohol was employed as the higher alcohol in the ester interchange reaction. Lauryl alcohol in a proportion of 5 grams was admixed with 500 grams of methyl acetoacetate and the mixture was heated on the steam bath for 20 hours, the evolved methyl alcohol being allowed to escape during the reaction. At the conclusion of the period, the excess methyl acetoacetate was evaporated at a pressure of 10 millimeters of mercury (absolute) and the residue in the distillation flask was then distilled to yield 7 grams of a water white liquid lauryl acetoacetate.

EXAMPLE XXV

In this reaction, ester interchange was effected between cholesterol and methyl acetoacetate. The reaction mixture comprised 10 grams of cholesterol and 100 cc. of methyl acetoacetate, the mixture being heated on the steam bath and at atmospheric pressure for 15 hours. During the reaction, inert gas was bubbled through the reaction mixture to effect the thorough removal of evolved methanol from the zone of reaction. Finally, the excess methyl acetoacetate was removed by vacuum distillation to yield 12 grams of a white solid cholesteryl acetoacetate of a melting point of 91 to 93° C.

EXAMPLE XXVI

This example illustrates the employment of vacuum during the course of the ester interchange for purposes of more thoroughly removing the lower alcohol as it is evolved. In the reaction, 10 grams of cholesterol were again admixed with 100 cc. of methyl acetoacetate and the mixture was heated upon the steam bath for 15 hours at a pressure of 40 millimeters of mercury (absolute). During the course of the reaction, methyl alcohol was evolved and distilled off and cholesteryl acetoacetate was formed. The yield and the purity of the product were practically identical with those obtained in Example XXV.

It is likewise contemplated to employ as a source of sterols or steroid bodies for use in the practice of the invention various glyceride oil mixtures containing sterols in substantial amounts. For example, a soap stock which normally contains considerable amounts of sterols, such as cholesterol, may be treated with methyl or ethyl acetoacetate in accordance with the provisions of the invention to form esters of the keto acid in admixture with glycerides of fatty acids. The temperatures of reaction correspond to those herein disclosed. The conditions of reaction likewise in other respects, are similar to those of the examples as herein presented. Many other mixtures of fat-like products likewise include sterols which are susceptible of treatment in accordance with the provisions of the present invention.

Wool fat, for example, includes considerable amounts of cholesterol and it is contemplated to treat such cholesterol-containing material with an excess of ethyl or methyl acetoacetate at temperatures near the boiling point of water to form cholesterol esters in the mixture. These cholesterol esters can be recovered by solvents or by other appropriate methods.

Likewise, tall oil as obtained in the digestion of paper pulp is rich in sterols and notably in beta sitosterol. The distillation residue obtained after partial distillation of the rosin acids and fatty acids of tall oil is highly enriched in beta sitosterol. This crude mixture can be treated with methyl or ethyl acetoacetate to provide esters in admixture with rosin acids, fatty acids and the other impurities of the tall oil residue.

Usually it is preferable to operate with more concentrated forms of the sterol or steroid compound. For example, beta sitosterol has heretofore been recovered from tall oil and tall oil distillation residues by solvent fractionation of crude tall oil. A convenient method of obtaining sterols, e. g., beta sitosterol, from tall oil or tall oil distillation pitches comprises esterifying the crude material with a lower alcohol, e. g., methyl alcohol, selectively to esterify fatty acids, contacting the mixture with countercurrently flowing streams of naphtha and furfural in a tower, separating off at one end a solution of furfural containing in solution a concentration of rosin acids and separating off at the other end, naphtha containing in solution an enrichment of esters of fatty acids and unsaponifiable material including beta sitosterol. The naphtha can be recovered by evaporation. The mixture of esters and unsaponifiable matter can be treated with alkali, e. g., caustic soda, to saponify the esters and the residual rosin acids in the mixture. The unsaponifiable matter is separated by dissolving the mixture in an aqueous alcohol, e. g., aqueous isopropyl alcohol and extracting out the unsaponifiable material in a solvent such as naphtha, and evaporating the naphtha. If purer sterols are desired, they can be recovered by crystallizing them from a solvent of sterols. In many cases, a relatively pure product has been obtained. The following examples illustrate the application of the principles of the invention in the preparation of beta keto esters of a crude or purified beta sitosterol.

EXAMPLE XXVII

One hundred grams of unsaponifiable fraction of tall oil which consisted largely of beta sitosterol together with some higher aliphatic alcohols and other materials was heated with 200 grams of methyl acetoacetate to 100° C. for ½ hour. The excess methyl acetoacetate was then distilled off under a pressure of 10 millimeters of mercury (absolute) to obtain a residue of 103.6 grams of a material containing the desired ester of acetoacetic acid and beta sitosterol.

EXAMPLE XXVIII

5.0 grams of stearyl alcohol and 30 grams of methyl ethylacetoacetate $CH_3COCH(C_2H_5)CO_2CH_3$ were heated on a steam bath for 48 hours, the evolved methanol being distilled off. The unreacted lower beta-keto ester was then removed by distillation in vacuo, and the residue was dissolved in acetone and the solution poured into water. The white solid which precipitated was filtered, washed and dried. Treatment of this product with alcoholic KOH showed this material to consist largely of stearyl ethylacetoacetate.

EXAMPLE XIX

2.0 grams of cholesterol, 8 grams of ethyl acetonedicarboxylate ($C_2H_5OOC—CH_2COCH_2COOC_2H_5$) and 10 milliliters of toluene were heated on a steam bath for 20 hours, the evolved ethanol being distilled off The toluene was then removed by distillation in vacuo and the oily residue was triturated with acetone to precipitate a white solid, dicholesteryl acetonedicarboxylate. This material after one crystallization from a mixture of methanol and isopropyl ether melted at 173° C. The acetone filtrate on evaporation to dryness left an oil, ethyl cholesteryl acetonedicarboxylate which could not be obtained crystalline.

EXAMPLE XXX

2.7 grams of stearyl alcohol and 2.0 grams of ethyl acetonedicarboxylate were heated on the steam bath in an open flask for 16 hours. The product was dissolved in hot ethanol and the solution cooled, after which the white solid formed was filtered, washed and dried to yield distearyl acetonedicarboxylate. This solid melted at 58–60° C., and had a saponification value of 343. This material on repeated crystallization from a mixture of methanol and acetone melted at 64.5–65.0° C.

EXAMPLE XXXI

10 grams of cholesterol and 100 grams of diethyl acetyl succinate $C_2H_5OOC—CH_2CH_2(COCH_3)COOC_2H_5$ were heated on the steam bath under a 10 millimeter absolute pressure for 64 hours. 93.5 grams of unreacted lower beta-keto ester was then removed by distillation in vacuo, and the residue was dissolved in 50 milliliters of ethanol, cooled and the white solid filtered, washed with 100 milliliters of ethanol and dried. The solid product, cholesteryl ethyl actyl succinate, had a saponification value of 165.

EXAMPLE XXXII

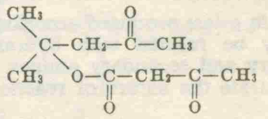
10 grams of stearyl alcohol and 100 grams of diethyl acetylsuccinate were heated on the steam bath under 10 millimeters absolute pressure for 40 hours. The clear solution was then stripped in vacuo, the residue was dissolved in 50 milliliters of hot methanol, cooled, and the white solid filtered, washed with 120 milliliters of hot ethanol and dried. The product is a solid which is predominately stearyl ethyl acetylsuccinate; it melted at 55–57° C. and had a saponification value of 145.

EXAMPLE XXXIII

57 milligrams of cortisone and 50 milliliters of methyl acetoacetate were heated on a steam bath for 16 hours. The unreacted methyl acetoacetate was then removed by distillation in vacuo, and the residue on crystallization from aqueous ethanol yielded shiny platelets of cortisone acetoacetate which melted at 112–114° C.

EXAMPLE XXXIV

325 milliliters of diacetone alcohol and 1000 milliliters of methyl actoacetate were heated on the steam bath for 24 hours. The unreacted starting materials were then removed by distillation in vacuo and the flask residue on distillation yielded water-white diacetonyl acetoacetate,



boiling at 125–127° C. at 10 millimeters absolute pressure, and having a refractive index $N_D^{25°}=1.4424$.

Its ultraviolet absorption characteristics are as follows:

$$\lambda^{\text{ethanol}}_{\text{max.}}: 241.5\ (\log E=3.07);\ 306.5\ (\log E=2.34)$$

EXAMPLE XXXV

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated with 101.2 milligrams of triethylamine at 98° C. for 4 hours, using a water condenser. Then 50.0 milliliters of methanol was added, the solution was cooled overnight at 23° F., the white solid was filtered, washed with 50 milliliters of methanol and dried. This solid was cholesteryl acetoacetate.

EXAMPLE XXXVI

The process of Example XXXV was repeated substituting 98.0 milligrams of concentrated sulfuric acid for the triethylamine. The product was cholesteryl acetoacetate.

EXAMPLE XXXVII

The process of Example XXXV was repeated substituting 38.6 milligrams of sodium cholesterate for the triethylamine. The product was largely cholesteryl acetoacetate.

EXAMPLE XXXVIII

The process of Example XXXV was repeated, substituting 185 milligrams of benzene sulfonic acid hydrate for the triethylamine, and heating the reaction mixture at 98° C. for 3 hours. The product was largely cholesteryl acetoacetate.

EXAMPLE XXXIX

3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated at 140° C. with water condenser for 5 hours. Then 50 milliliters of methanol was added, the solution was cooled overnight at 23° F., and the white solid was filtered, washed with 50 milliliters of methanol and dried. This product melted at 94.5–95.5° C. and was substantially pure cholesteryl acetoacetate.

EXAMPLE XL

The process of Example XXXIX was repeated at a temperature of 160° C. rather than 140° C. The resulting cholesterol acetate was slightly lower in purity than that obtained in Example XXXIX having a melting point of 90–91° C.

EXAMPLE XLI

10 grams of crude 12-hydroxystearic acid containing 85% by weight of 12-hydroxystearic acid (the balance being largely stearic acid) and 100 milliliters of methyl acetoacetate were heated on the steam bath for 26 hours. The unreacted methyl acetoacetate was distilled off by heating the reaction mixture in vacuo. After distillation, there remained 13 grams of a water white oil. Numerous crystallizations from hexane and finally from methanol yielded silky white needles which melted at 31.5 to 32.5° C. This product is 12-acetoacetoxystearic acid. The corresponding esters of other hydroxy acids such as glycolic acid, lactic acid, ricinoleic acid, tartaric acid, etc. may be prepared in the same manner. Moreover the esters of such hydroxy acids may be treated in the same way.

The preparation of the beta-keto esters as herein described affords the opportunity of preparing a host of new compounds due to the great reactivity of beta-keto esters. Thus beta-keto esters containing one or more active hydrogen atoms will in addition to the normal ester type reactions, have reactivity in the following manner:

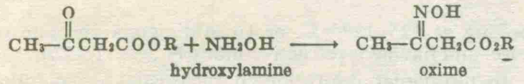
1. Reactions involving the carbonyl group directly
2. Reactions involving the enolic hydroxyl group, and
3. Reactions due to the activation of the —CH or —CH2— groups between the carbonyls.

The following are typical examples of these reactions.

1. *Reactions involving the ketonic carbonyl group directly*

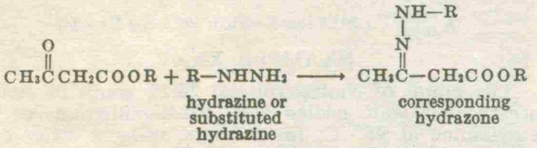
The beta-keto esters produced according to the present invention may be reacted with hydrazines, hydroxylamines, primary and secondary amines. The following equations illustrate the nature of reactions which occur.

A.



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_2COOR} + \underset{\text{hydroxylamine}}{\mathrm{NH_2OH}} \longrightarrow \underset{\text{oxime}}{\mathrm{CH_3{-}\overset{\overset{\displaystyle NOH}{\|}}{C}CH_2CO_2R}}$$

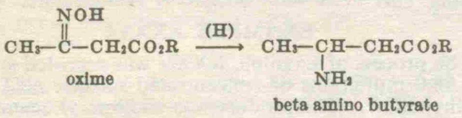
B.



$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2COOR} + \underset{\substack{\text{hydrazine or}\\ \text{substituted}\\ \text{hydrazine}}}{\mathrm{R{-}NHNH_2}} \longrightarrow \underset{\substack{\text{corresponding}\\ \text{hydrazone}}}{\mathrm{CH_3\overset{\overset{\overset{\displaystyle NH{-}R}{|}}{\overset{\displaystyle N}{\|}}}{C}{-}CH_2COOR}}$$

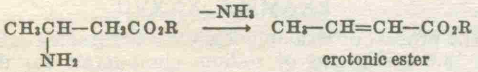
These carbonyl derivatives can of course be reacted further:

C.



$$\underset{\text{oxime}}{\mathrm{CH_3{-}\overset{\overset{\displaystyle NOH}{\|}}{C}{-}CH_2CO_2R}} \xrightarrow{(H)} \underset{\text{beta amino butyrate}}{\mathrm{CH_3{-}\underset{\underset{\displaystyle NH_2}{|}}{C}H{-}CH_2CO_2R}}$$

D.



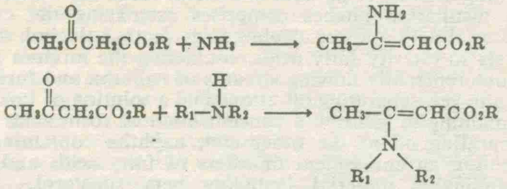
$$\mathrm{CH_3\underset{\underset{\displaystyle NH_2}{|}}{C}H{-}CH_2CO_2R} \xrightarrow{-NH_3} \underset{\text{crotonic ester}}{\mathrm{CH_3{-}CH{=}CH{-}CO_2R}}$$

Thus the oxime of stearyl acetoacetate may be prepared by heating a solution of 10 grams of stearyl acetoacetate and 10 grams of hydroxylamine hydrochloride in 50 milliliters of pyridine and 60 milliliters of ethanol under reflux for 3 hours. The oxime is then precipitated by the addition of water and recrystallized from aqueous methanol.

Similarly the semicarbazone of cholesteryl acetoacetate may be prepared by heating a solution of 1 gram cholesteryl acetoacetate, 1 gram of semicarbazide hydrochloride and 1.5 grams of anhydrous sodium acetate in 20 cc. of ethanol on the steam bath for 20 minutes, precipitating the cholesteryl acetoacetate semicarbazone by the addition of water, and crystallizing it from a mixture of isopropyl ether and isopropanol. This product is a crystalline solid.

Moreover the other sterol acetoacetates and equivalent esters of other beta-keto acids herein disclosed may be reacted with semicarbazide hydrochloride in the same manner. It will also be understood that acetoacetates of castor oil, higher aliphatic alcohols, hydroxy acids and their esters and hydroxy alkyd resins as well as other acetoacetates and like keto esters produced according to this invention may be reacted with semicarbazide hydrochloride in lieu of cholesterol acetoacetate.

Another important reaction involving the keto carbonyl group of beta-keto esters produced according to this invention is their reaction with ammonia or primary or secondary amines, e. g.:



$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2CO_2R + NH_3 \longrightarrow CH_3{-}\overset{\overset{\displaystyle NH_2}{|}}{C}{=}CHCO_2R}$$

$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2CO_2R + R_1{-}\overset{\overset{\displaystyle H}{|}}{N}R_2 \longrightarrow CH_3{-}\underset{\underset{\displaystyle R_1\diagup N \diagdown R_2}{|}}{C}{=}CHCO_2R}$$

where alcohol R is the radical of the acetoacetate and R_1 and R_2 are the radicals of the primary or secondary amine. The following are typical examples of this embodiment.

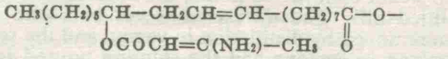
EXAMPLE XLII

Ammonia gas was passed for 2 hours at room temperature through a solution of 100 grams of butylcarbitol acetoacetate (a water white liquid), and 0.1 gram of ammonium acetate in 100 grams of methanol. The reaction was somewhat exothermic. After two hours the solvent was removed by distillation under reduced pressure, and there remained 100 grams of a water-white oil which, in chloroform, has an ultra violet light absorption maximum of log E=4.1 at 272.5 millimicrons, showing the presence of a beta-substituted, alpha-beta unsaturated ester grouping. The reaction product has the following structure:

$$\mathrm{CH_3(CH_2)_3OCH_2CH_2OCH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{C}{-}CH{=}\overset{\overset{\displaystyle NH_2}{|}}{C}{-}CH_3}$$

EXAMPLE XLIII

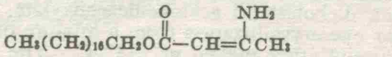
100 grams of castor oil acetoacetate was treated with ammonia in excess of the stoichiometric amount in a manner similar to that above described, and there was obtained a viscous, light yellow oil on evaporation of the solvent. This material consisted largely of a triglyceride, the acid radical of which had the following structure:



$$\mathrm{CH_3(CH_2)_5\underset{\underset{\displaystyle OCOCH{=}C(NH_2){-}CH_3}{|}}{C}H{-}CH_2CH{=}CH{-}(CH_2)_7\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}}$$

EXAMPLE XLIV

60 grams of stearyl acetoacetate, 300 grams of methanol and 50 grams of ammonium acetate were heated on a steam bath for 15 minutes, and the reaction mixture was then cooled and diluted with water. There was isolated 60 grams of a white solid which crystallized from methanol in white platelets and melted at 70–71° C. In absolute ethanol it showed an ultra violet light absorption maximum of log E=4.29 at 274 millimicron. C, H and N analyses confirmed this structure:



$$\mathrm{CH_3(CH_2)_{16}CH_2O\overset{\overset{\displaystyle O}{\|}}{C}{-}CH{=}\overset{\overset{\displaystyle NH_2}{|}}{C}CH_3}$$

EXAMPLE XLV

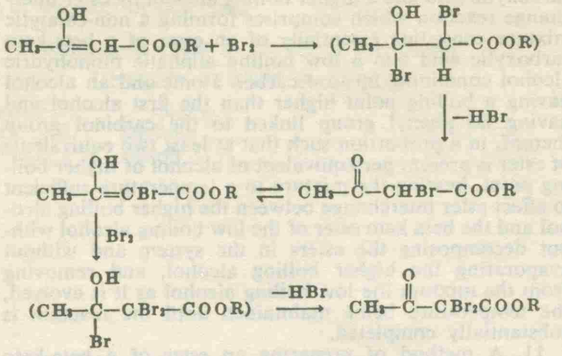
Through a solution of 33 grams of polyethylene glycol acetoacetate (made from polyethylene glycol having a molecular weight of about 200) in 100 grams of methanol to which a 0.05 gram of ammonium acetate had been added, ammonia gas was passed at room temperature for one hour. The reaction was somewhat exothermic. The solvent was then stripped off under reduced pressure. There remained a light oil which was the beta-amino crotonate of polyethylene glycol.

The fatty acid salts of these beta-amino crotonates were found to be good emulsifiers.

It will be understood that the corresponding amino crotonate esters of the various other hydroxy compounds prepared according to this invention, including cholesterol, cortisone, stigmasterol and other sterols, glycols, polyglycols, carbitols, hydroxyesters etc. may be prepared in the same manner.

2. *Reactions involving the enolic hydroxyl group*

Typical of such reactions are halogenations of beta-keto esters, e. g.:



where R is the alcohol radical of the beta-keto ester.

Thus one or more active hydrogen atoms can be replaced by halogen atoms. The following are typical examples:

EXAMPLE XLVI

10 grams of stearyl acetoacetate dissolved in carbon tetrachloride is treated with a solution of 10 grams of bromine in 50 milliliters of petroleum ether. Copious evolution of hydrogen bromide vapors takes place, and slow evaporation of the solvent at room temperature leaves a quantitative yield of stearyl bromoacetoacetate.

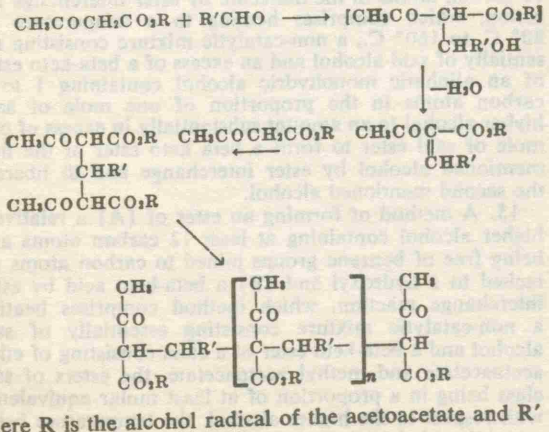
EXAMPLE XLVII

An alkyd resin is prepared by reacting 890 grams of refined soya oil, 220 grams of pentaerythritol and 180 grams of glycerine with 840 grams of phthalic anhydride. All the free hydroxyl groups in this alkyd were then esterified by heating 1000 grams of the resin with 1000 milliliters of methyl acetoacetate on the steam bath for 22 hours, and removing the unreacted methyl acetoacetate by distillation in vacuo. Solvent naphtha was then added to this resin to give a resin of 24% solids. Chlorine gas was passed through the resulting solution over a period of two hours at room temperature while the solution was agitated by a stream of inert gas. After chlorination the agitation with inert gas was continued for a further period of 6 hours to remove all HCl gas evolved. A very light colored resin resulted.

Acetoacetic and like esters of other alkyd resins containing free hydroxyl groups and of other higher alcohols (sterols, higher aliphatic alcohols etc.) may be treated in the same manner.

3. *Reactions due to the activation of the —CH or —CH₂— groups between the carbonyl groups*

The acetoacetates produced according to this invention undergo reaction with aldehydes in an aldol type reaction:

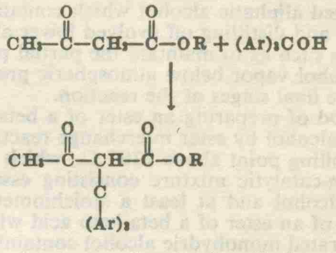


where R is the alcohol radical of the acetoacetate and R′ is the radical of the aldehyde.

Thus, for example, an alkyd resin was prepared by reacting 1053 grams of linseed oil and 470 grams of glycerine with 893 grams of phthalic anhydride. The resulting resin had a Gardner viscosity M at 57.6% solids in solvent naphtha, an acid value of 10.5 and a Gardner color of 9. One thousand grams of this 57.6% solids alkyd resin was then heated on the steam bath with 500 milliliters of methyl acetoacetate for 18 hours. All the solvent was then removed by distillation in vacuo, and to the still hot resin 500 grams of solvent naphtha was added. The resulting resin had a Gardner viscosity of U–V at 50.4% solids. A mixing of 500 grams of this resin, 5 grams of paraformaldehyde, 1 milliliter of pyridine, 1 drop of piperidine and 100 milliliters of solvent naphtha were then heated on the steam bath with agitation for three hours. The reaction mixture was then heated under vacuum until the water formed in the reaction had distilled off azeotropically, the total distillate having a volume of 100 milliliters. There remained a resin having a Gardner viscosity greater than Z_6 at 55.8% solids. Hence, by virtue of the reaction described above, the resin had become substantially further cross-linked, and showed good drying properties and improved alkali resistance.

Other aldehydes, such as crotonaldehyde, acrolein, furfural, acetaldehyde and particularly those containing up to 6 carbon atoms may be used in lieu of formaldehyde. Moreover other alkyd resins containing free hydroxyl groups may be treated according to this process.

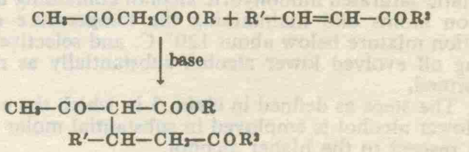
Benzylic type halides and alcohols such as triphenylmethyl chloride and triphenyl carbinol react with the beta-keto esters produced according to this invention and new compounds are obtained according to the following equation:



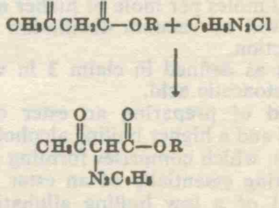
where Ar is the monovalent aryl radical.

Thus 5 grams of stearyl acetoacetate reacts with 5 grams of triphenylmethyl chloride to give triphenylmethyl stearyl acetoacetate.

Similarly, new compounds are formed when these newly discovered beta-keto esters (sterol esters, alkyd esters etc.) undergo a Michael type reaction with alpha-beta-unsaturated carbonyl compounds, e. g.:



In addition these newly discovered beta-keto esters can react with diazonium salts such as benzene diazonium chloride to yield compounds akin to Hansa dyes, of interest in the synthetic dye field:



It will be understood that the above examples and discussion dealing with the production of derivatives and compounds from beta-keto esters apply generally to the various beta-keto esters prepared according to the process herein described. Thus any of the above mentioned sterol esters including cholesterol, stigmasterol, cortisone etc., esters of beta-keto acids such as acetoacetic acid, may be substituted in stoichiometric amounts in lieu of the keto esters set forth in the above examples for the production of the derivatives described.

While a number of the above examples are directed to the production of acetoacetates such as sterol acetoacetates and alkyd resin acetoacetates etc. by ester interchange reaction, it is to be understood that these esters may be prepared by esterification by reaction of the hydroxy radical with diketene.

Although the present invention has been described with reference to certain embodiments thereof, it is not intended that the specific details of such embodiments shall be regarded as limitations upon the scope of this invention except insofar as included in the accompanying claims.

We claim:

1. A method of forming an ester of a relatively higher alcohol and a beta-keto acid by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said alcohol and an ester of a lower aliphatic monohydric alcohol and said acid, at least in molecular equivalency of said higher alcohol to effect ester interchange between said higher alcohol and said ester of a lower alcohol, reducing the concentration of evolved lower alcohol sufficiently low to maintain the desired ester interchange, maintaining the temperature of reaction below the decomposition temperatures of the alcohols and the beta keto esters, until the reaction is substantially completed and recovering the resulting ester of the higher alcohol.

2. A method of preparing an ester of a beta-keto acid and a higher alcohol which ester has a boiling point above 230° C. by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least its stoichiometric equivalent of an ester of a beta keto acid and a lower monohydric saturated aliphatic alcohol which contains up to 4 carbon atoms and distilling off evolved lower alcohol under conditions such as to maintain the partial pressure of the lower alcohol vapor below atmospheric pressure during at least the final stages of the reaction.

3. A method of preparing an ester of a beta-keto acid and a higher alcohol by ester interchange reaction, which ester has a boiling point above 230° C., which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least a stoichiometric equivalent amount of an ester of a beta keto acid with a lower aliphatic saturated monohydric alcohol containing up to 4 carbon atoms and maintaining the temperature of the reaction mixture below about 120° C.

4. A method of preparing an ester of a beta-keto acid and a higher alcohol by ester interchange reaction which ester has a boiling point above 230° C., which comprises heating a non-catalytic mixture consisting essentially of said higher alcohol and at least a stoichiometric equivalent amount of an ester of a beta keto acid and a lower aliphatic saturated monohydric alcohol containing up to 4 carbon atoms and maintaining the temperature of the reaction mixture below about 120° C. and selectively distilling off evolved lower alcohol substantially as rapidly as formed.

5. The steps as defined in claim 3 in which the ester of the lower alcohol is employed in substantial molar excess with respect to the higher alcohol.

6. The steps as defined in claim 3 in which the reaction is promoted by blowing the mixture with inert gas during the ester interchange, to remove evolved lower alcohol.

7. The steps as defined in claim 3 in which the beta keto ester of the lower alcohol is employed in a proportion of 2 to 100 moles per mole of higher alcohol and the excess is removed by vacuum distillation at the conclusion of the reaction.

8. The steps as defined in claim 3 in which the beta keto acid is acetoacetic acid.

9. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling alcohol by ester interchange reaction, which comprises forming a non-catalytic mixture consisting essentially of an ester of a beta-keto carboxylic acid of a low boiling aliphatic monohydric alcohol containing up to 4 carbon atoms and a higher boiling alcohol having at least 12 carbon atoms and having no phenyl group linked to the carbinol group thereof, in a proportion such that at least one equivalent of ester is present per equivalent of higher boiling alcohol, heating the mixture to a reaction temperature below the boiling point of the higher boiling alcohol and below the decomposition temperatures of said alcohols and said esters and selectively removing from the mixture said low boiling alcohol at a temperature below 120° C. as it is evolved without substantial removal of the higher boiling alcohol until reaction is completed.

10. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling alcohol by ester interchange reaction which comprises forming a non-catalytic mixture consisting essentially of an ester of a beta-keto carboxylic acid and a low boiling aliphatic monohydric alcohol containing up to 4 carbon atoms and an alcohol having a boiling point higher than the first alcohol and having no phenyl group linked to the carbinol group thereof, in a proportion such that at least two equivalents of ester is present per equivalent of alcohol of higher boiling point, heating the mixture to a temperature sufficient to effect ester interchange between the higher boiling alcohol and the beta keto ester of the low boiling alcohol without decomposing the esters in the system and without evaporating the higher boiling alcohol, and removing from the mixture the low boiling alcohol as it is evolved, the temperature being maintained until the reaction is substantially completed.

11. A method of preparing an ester of a beta-keto carboxylic acid and a higher boiling aliphatic monohydric alcohol by ester interchange reaction, which comprises forming a non-catalytic mixture consisting essentially of an ester of beta-keto acid and a low boiling aliphatic monohydric alcohol containing 1 to 4 carbon atoms and an alcohol having a higher boiling point than the low boiling alcohol and containing at least 6 carbon atoms and having no phenyl group linked to the carbinol group thereof, in a proportion such that an excess of one equivalent of ester is present per equivalent of higher boiling alcohol, heating the mixture to a temperature within a range of 80 to 120° C., selectively evaporating off low boiling alcohol evolved until reaction is completed and then selectively evaporating off any low boiling alcohol present and the excess of beta keto ester of low boiling alcohol.

12. A method of forming an acetoacetic acid ester of relatively high molecular weight by ester interchange reaction, which comprises heating a non-catalytic mixture consisting essentially of said alcohol of higher molecular weight and an acetoacetic acid ester of an aliphatic saturated alcohol of lower molecular weight, the latter being in excess of molar ratio with respect to said alcohol of higher molecular weight, to a temperature sufficient to distill evolved alcohol of lower molecular weight as it is formed, whereby to maintain the concentration below 5% with respect to the starting ester of alcohol of lower molecular weight, but insufficient to dehydrate the alcohol of higher molecular weight and the acetoacetic acid esters in the system and subsequently selectively distilling off any residual alcohol of lower molecular weight and excess acetoacetic acid ester of said alcohol of lower molecular weight, at a temperature in the foregoing range.

13. The steps as defined in claim 12 in which the alcohol of higher molecular weight contains at least 12 carbon atoms, the alcohol of lower molecular weight contains up to 4 carbon atoms and the temperature of reaction is within a range of about 80 to 120° C.

14. A method of preparing an ester of a beta-keto carboxylic acid and a higher alcohol containing at least 12 carbon atoms in the molecule by ester interchange reaction, which comprises heating to a temperature of 80° C. to 160° C., a non-catalytic mixture consisting essentially of said alcohol and an excess of a beta-keto ester of an aliphatic monohydric alcohol containing 1 to 4 carbon atoms in the proportion of one mole of said higher alcohol to an amount substantially in excess of one mole of said ester to form a beta keto ester of the first mentioned alcohol by ester interchange and to liberate the second mentioned alcohol.

15. A method of forming an ester of (A) a relatively higher alcohol containing at least 12 carbon atoms and being free of benzene groups joined to carbon atoms attached to a hydroxyl and (B) a beta-keto acid by ester interchange reaction, which method comprises heating a non-catalytic mixture consisting essentially of said alcohol and a beta-keto ester of a class consisting of ethyl acetoacetate and methyl acetoacetate, the esters of said class being in a proportion of at least molar equivalency with respect to the higher alcohol, the temperature being maintained below the points of decomposition of the alcohols, and the beta-keto ester and the concentration of

evolved lower alcohol in the reaction mixture being maintained sufficiently low to attain the desired ester interchange reaction, said conditions being maintained until the reaction is substantially completed, and then recovering the resultant ester of the higher alcohol from the excess of the ester of said class.

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United States Patent Office

2,730,517

Patented Jan. 10, 1956

2,730,517

MODIFICATION OF POLYESTER BODIES

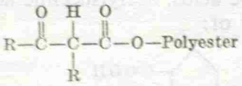
Henry A. Vogel and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application January 15, 1952, Serial No. 266,598

10 Claims. (Cl. 260—75)

The present invention relates to polyesters and it has particular relation to treatment of polyesters containing free hydroxyls in order to obtain esterification of the latter.

The invention comprises, as one feature, subjecting to appropriate conditions a mixture of an alkyd type polyester containing free hydroxyls and an ester of a beta-keto acid such as aceto-acetic acid and a lower monohydric alcohol, whereby to effect ester interchange between the initial beta-keto ester and the polyester, thus introducing into the polyester molecules reactive groups of the formula:



$$R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}}-\overset{\overset{O}{\|}}{C}-O-\text{Polyester}$$

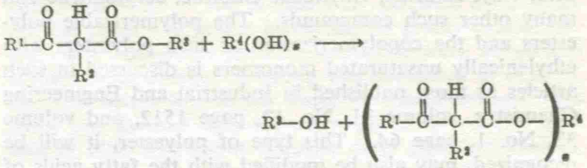
where R may be alkyl or aryl groups. These groups contain reactive hydrogen atoms, reactive carbonyl groups and by tautomerism provide enolic hydroxyls and thus lend themselves to ready subsequent reactions and modifications which will be more fully discussed hereinafter.

It has heretofore been recognized that it is difficult to prepare an alkyd resin in which complete esterification has taken place. In most commercial alkyds, a slight excess of the polyhydric alcohol such as glycerol, is employed in order to bring the acid value to a minimum. In consequence, unesterified hydroxyl groups remain in the resultant alkyd body and to these, the poor water resistance of the alkyds is often ascribed.

In accordance with the provisions of the present invention, the foregoing free hydroxyls or at least a portion thereof are caused to undergo ester interchange with a beta-keto ester of a lower alcohol such as methyl acetoacetate. As a result of the ester interchange reaction, free hydroxyls are eliminated. Likewise, as a result of the reaction, the active hydrogen atoms, active carbonyl groups and enolic hydroxyls above mentioned, are introduced into the alkyd molecules and these groups produce additional functionality, adapting the product to numerous other reactions some of which will be hereinafter discussed in greater detail.

Ester interchange reactions between various higher hydroxylated bodies and the esters of beta-keto acids and lower alcohols have been discussed in considerable detail in a commonly owned, copending application to Lowell O. Cummings, Henry A. Vogel and Alfred R. Bader, Serial No. 219,900, filed April 7, 1951. The reaction of the free hydroxyls of the alkyd resins and the beta-keto esters of lower alcohols by esterinterchange as herein disclosed, involves a similar reaction. Therefore, the disclosure of the prior application, insofar as it discloses conditions of ester interchange, is incorporated with and made a part of this application. For optimum efficiency of ester interchange reactions, the procedures as outlined in the application for effecting ester interchange between the alkyd body and the lower esters of beta-keto acids may be employed. However, in many instances, the high degree of efficiency obtainable by the techniques of the application may not be required and under such conditions various other techniques of reaction may be adopted.

The reaction of ester interchange is believed to proceed in accordance with the equation:



$$R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{\overset{H}{|}}{C}}-\overset{\overset{O}{\|}}{C}-O-R^3+R^4(OH)_n\longrightarrow$$

$$R^3-OH+\left(R^1-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^2}{|}}{\overset{\overset{H}{|}}{C}}-\overset{\overset{O}{\|}}{C}-O-\right)_n R^4$$

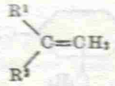
where R^4 is an alkyd resin body. The nature of R^1, R^2, and R^3, in the present case are governed by the polyester structure and will be apparent from subsequent descriptions.

Alkyd bodies containing group R^4, suitable for ester interchange reaction with lower esters of beta-keto acids in accordance with the provisions of the present invention, include substantially any of the recognized alkyd bodies which are of a reasonable degree of solubility and fusibility and which contain a reasonable number of free hydroxyls. Examples of such polyesters include glyceryl phthalates such as the simple polyester obtained by esterification of phthalic anhydride with an excess of glycerol above that theoretically required in order to obtain neutralization of the carboxyls of phthalic acid. The excess of hydroxyls will usually be in a range of 1 to 30% with respect to the total available carboxyls. Succinic acid, adipic acid, azelaic acid, carbic acid (or their anhydrides) and many other saturated acyclic dicarboxylic acids may be substituted for phthaleic acid in the preparation of polyesters suitable for the ester interchange reaction of the present invention.

It is of course, recognized that in many instances the polyester bodies as disclosed in the prior art, are modified with various fatty acids including stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid, riconoleic acid and many others.

Likewise, it has been common practice in the art to modify the polyester bodies by the inclusion in varying amounts, of glycerol and glyceride oils such as linseed oil, soybean oil, castor oil, palm oil and many others. Since the preparation of simple alkyd bodies and modification of such bodies containing fatty acids introduced as free acids or through the introduction of the glycerides or partial glycerides of the acids, is a well recognized art which has been extensively publicized over a period of many years, it is not believed to be necessary to discuss in detail the preparation of the alkyd bodies such as those above referred to. These bodies can react by ester interchange with esters of lower alcohols and beta-keto acids.

It has also been recognized as common practice to prepare ethylenically unsaturated alkyd like bodies which are polyesters of an excess of a dihydric alcohol such as ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol and propylene glycol with dicarboxylic acids containing functioning ethylenic groups and being typified by maleic acid (or its anhydride) fumaric acid, itaconic acid, methyl maleic acid, carbic acid and others. Polyesters which are obtained from ethylenically unsaturated dicarboxylic acids are recognized to be polymerizable by addition reaction between the ethylenic groups of contiguous molecules. Also, the polyesters are capable of copolymerization with compounds which are usually soluble in the polyester, usually are liquids and are of the formula:



$$\begin{matrix}R^1\\ &\diagdown\\ &&C{=}CH_2\\ &\diagup\\ R^2\end{matrix}$$

where at least one group, R^1 or R^2 is negative, e. g. phenyl, carboxyl ester, nitrile, chlorine or the like, and the other is of the same class or is hydrogen, hydrocarbon, e. g. methyl, ethyl, or the like. The active group in such compound is the terminal ethylenic $>C=CH_2$ or vinyl groups. The class of compounds is represented by styrene, alphamethyl styrene, diallyl phthalate, diallyl succinate, allyl acetate, vinyl acetate, methyl methacrylate, methacrylic acid, vinyl chloride, vinylidene chloride, acrylonitrile and many other such compounds. The polymerizable polyesters and the copolymerization of such polyesters with ethylenically unsaturated monomers is discussed in such articles as those published in Industrial and Engineering Chemistry, volume 31, No. 12, page 1512, and volume 32, No. 1, page 64. This type of polyester, it will be recognized, may also be modified with the fatty acids of glyceride oils such as palmitic acid, ricinoleic acid, oleic acid, linoleic acid, linolenic acid and the like. The esters of the ethylenically unsaturated dicarboxylic acids either with or without modification with fatty acids may be employed in the practice of the present invention.

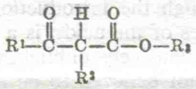
Various satisfactory polymerizable mixed polyesters containing free hydroxyls are also obtained from esterification of glycols and mixtures of ethylenically unsaturated dicarboxylic acids containing alpha-beta ethylenic unsaturation and a saturated dicarboxylic acid or a dicarboxylic acid which is free of polymerizing ethylenic groups. Dicarboxylic acids of this latter type include phthalic acid, succinic acid, adipic acid, azelaic acid and the like. In preparing the mixed polyesters, substantially any reasonable proportions of the two types of acid may be combined in a single polyester molecule. For example, the proportion of the saturated dicarboxylic acid may extend from .25 to 6 or 8 or even 10 moles with respect to the molar proportions of the ethylenically unsaturated dicarboxylic acid.

The mixed esters may also contain fatty acid components as above described.

The reaction of any of these alkyd or polyester bodies, where they are soluble and contain a reasonable number of free hydroxyls with beta-keto acid esters in accordance with this disclosure, is a feature of the present invention.

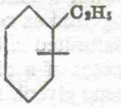
THE BETA-KETO ESTER COMPONENT

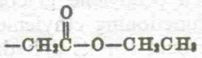
Beta-keto esters adapted to react by ester interchange with alkyds such as A to G (to follow) within the scope of the present invention, as previously indicate, include the group:



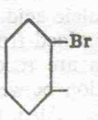
$$R^1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R^2}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-O-R_3$$

where R¹ is most commonly $-CH_3$ but may be other groups including:





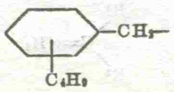
$$-CH_2\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2CH_3$$



$-CH_2Cl$

$-C_2H_4Cl$

NH_2-



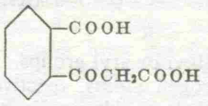
and others. R² most commonly is hydrogen but it can be hydrocarbon or substituted hydrocarbon such as methyl, ethyl, propyl or butyl, benzyl, phenyl or the like. It can also be amino and chloro. Only one of the hydrogens of the alpha carbon atom can be replaced. The remaining atom is active and is essential to the ester interchange reaction.

The group R³ is the replaceable group in the ester interchange reaction. It can be regarded as the residue of a lower aliphatic or olefinic alcohol.

Lower relatively volatile alcohols with which such beta-keto bodies are esterified to provide R³, include methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol and butyl alcohol and such other saturated and monohydric alcohols as are reasonably volatile and can therefore be removed with adequate facility from the polyester undergoing ester interchange reaction.

The invention also includes unsaturated alcohols as the lower alcohol of the beta-keto ester. Such unsaturated alcohols include allyl alcohol, methallyl alcohol, crotyl alcohol, propargyl alcohol, butyl alcohol, substituted lower alcohols such as 2 chloroethyl alcohol, 2 fluoroethyl alcohol, 2 nitropropyl alcohol and others.

Specific examples of beta-keto acids with which these lower alcohols may be esterified include: acetoacetic acid, alpha ethyl acetoacetic acid, alphaisopropyl acetoacetic acid, alpha methyl acetoacetic acid, benzoyl acetoacetic acid, acetone dicarboxylic acid, gamma chloro acetoacetic acid, alpha benzoyl acetoacetic acid, alpha phenyl acetoacetic acid, chloro iodo and bromo substitution products of the above acids, acetylsuccinic acid, benzoylacetic acid, the diester of:



and others of like character.

THE ESTER INTERCHANGE REACTION BETWEEN THE ALKYD POLYESTER BODY AND THE LOWER ESTER OF A BETA-KETO ACID

The conditions of ester interchange reaction between a body containing free hydroxyls and a lower ester of beta-keto acid as herein disclosed has been elaborated upon and explained in considerable detail in the foregoing application, Serial No. 219,900. It is reiterated that the prior application is incorporated herein and the disclosure thereof insofar as it pertains to the ester interchange reaction, is to be regarded as constituting a part of the present application.

It may be stated that in general the alkyd body containing free hydroxyls in substantial amount and with or without an inert diluent, such as paraffinic naphtha, toluene, xylene or the like, is admixed with the beta-keto ester of a lower alcohol such as methyl aceto-acetate. Attainment of complete esterification of all free hydroxyls in the polyester is attained by employing a considerable excess of the beta-keto ester of a lower alcohol with respect to the total available hydroxyls of the alkyd body.

In the prior application, it is suggested to employ at least two moles of an ester of a lower alcohol and the beta-keto acid per mole of higher alcohol.

Alkyd resins are of uncertain molecular structure therefore it is not practicable to express a molecular ratio between the alkyd body and the ester of acetoacetic acid and the lower alcohol. Usually it is sufficient to add the beta-keto acid ester in amount to attain solution and to cause the esterification reaction to proceed with speed. The excess may extend up to 10, 20 or even 100 fold (upon a molar basis of the beta-keto ester) with respect to the total available hydroxyls in the polyester. Such excesses of beta-keto ester tend strongly to dilute and reduce the concentration of the evolved alcohol and thus favor the ester interchange reaction. Similar results can be obtained by removing the alcohol of evolution substantially as it is formed by application of a vacuum designed to pull off or distill the evolved alcohol at permissible temperatures. The reaction mixture can also be blown with an inert gas such as nitrogen, carbon dioxide, or combustion products such as may be obtained by the burning of butane or the like hydrocarbon, with air.

The temperature at which the ester interchange reaction is effected preferably is relatively mild. Optimum ranges seem to be about 100° C. or 20 or 30 degrees higher or lower. If low temperatures are employed it is usually desirable to apply sufficient vacuum to attain ready distillation of the evolved alcohol. Higher temperatures, e. g. 140 to 160° C. may sometimes be applied but the reaction mixture should then be watched carefully to avoid decomposition of the reactants such as the beta-keto ester of a lower alcohol and to obviate undue volatilization and loss of the latter component.

Inasmuch as alkyd bodies are usually relatively viscous or even solid bodies, it is often desirable to include in the reaction mixture, sufficient solvent or diluent thereof to attain a reasonable degree of fluidity which will permit admixture of the ester of a lower alcohol and a beta-keto acid into the polyester. The ester of a lower alcohol itself constitutes a very good solvent and inasmuch as it is often or even usually employed in considerable excess, it may be adequate to attain a reasonable degree of fluidity in the reaction mixture. However, diluents such as petroleum naphtha, xylene, toluene and various other solvents of alkyd resins or modified alkyd resins and the beta-keto ester of lower alcohols may be included. Sufficient total solvent is included in the reaction mixture to attain a desired degree of fluidity. At the conclusion of the reaction, any solvents remaining in the system as well as any other volatile constituents such as evolved lower alcohol, is evaporated off, preferably under vacuum, e. g. at a pressure (absolute) of 5 to 100 mm.

Preparation of a number of alkyds suitable for treatment with beta-keto esters of lower alcohols as illustrated in the subsequent examples is as follows:

Alkyd A

According to this example, an appropriate alkyd resin suitable for further treatment with beta-keto ester of lower alcohols was prepared. 1053 grams refined linseed oil, 210 grams glycerine, and 0.4 gram litharge catalyst were heated to 445° F. for one-half hour with agitation, at which point alcoholysis had taken place as indicated by complete solubility of a portion of the mixture in methyl alcohol. 893 grams phthalic anhydride, 260 grams glycerine, and solvent xylene were added and the temperature again brought to 440° F. It was held there for a total of 4 hours. During this heating the mixture was bubbled with inert gas to aid in the removal of water from esterification. The resulting resin was diluted with solvent naphtha to a solids content of 57.6%, having an acid value of 10.5 and a viscosity of M (Gardner-Holdt). This alkyd body was suitable for interaction by ester interchange with the lower esters of beta-keto acids as hereinafter described in the examples.

Alkyd B

An alkyd resin was prepared by reacting 276 grams (3 moles) glycerol, 408 grams (3 moles) of pentaerythritol sold under the trade name "Pentek," 2080 grams (8 moles) soya fatty acids and 830 grams (5.6 moles) phthalic anhydride. The reaction was effected by heating the mixture to esterification temperature under a blanket of inert gas and removing the water of evolution. The resultant alkyd body was thinned with a mixture of xylene and solvent naphtha. Viscosity tests were conducted upon this solution when a dilution of 63.8 per cent solids was attained. The properties of the material were as follows: Gardener viscosity B, Gardener color 6.5, acid value of solids 4.1, saponification value of solids 327. This alkyd body contained free hydroxyls and was adapted for ester interchange with lower esters of beta-keto acid such as methyl acetoacetate in accordance with the provisions of the examples in the present invention.

Alkyd C

An alkyd resin was prepared by heating 596 grams soya oil, 130 grams pentaerythritol, and 0.25 litharge catalyst at 445° F. for ¾ hours to complete alcoholysis. At this point 132 grams glycerine, 26 grams pentaerythritol, and 560 grams phthalic anhydride were added and some solvent xylene. Heating was continued at 415° F. for 3½ hours to remove water of esterification. This resin was thinned with solvent naphtha to a solids content of 50% and had a viscosity of U (Gardner-Holdt).

Alkyd D

In order to prepare an alkyd body containing excess hydroxyl groups and being adapted for reaction by ester interchange with a beta-keto ester, a mixture of 770 grams of glycerine, 990 grams cocoanut oil fatty acids and 1092 grams phthalic anhydride were esterified under conventional conditions, namely a temperature of 440° F. for 6¾ hours and under inert gas to provide a polyester or alkyd body of a viscosity of U at 50% solids and an acid value of 0.6. The product contained excess hydroxyls and was adapted for esterification by interchange with methyl acetoacetate as hereinafter described in Example IV.

Alkyd E

A further alkyd resin also containing free hydroxyls and being adapted for the ester interchange herein disclosed, was prepared by heating under appropriate conditions, namely under inert gas for 6 hours and to an ultimate temperature of 440° F., 1053 grams linseed oil, 427 grams glycerine and 893 grams of phthalic anhydride until a polyester of a Gardner viscosity of U at 53.3% solids was obtained. This is the alkyd body of Example V to follow.

Alkyd F

In this example, a mixture of equal moles of maleic anhydride and phthalic anhydride were heated with a slight excess of propylene glycol under a blanket of inert gas at a temperature of about 150° C. to provide a polyester appropriate for use in the present invention.

Alkyd G

In this example, a slight excess of propylene glycol was heated with maleic anhydride under suitable blanketing conditions until a polyester containing an excess of free hydroxyls was formed.

The following examples illustrate the application of the invention to effect ester interchange between alkyd resins such as those previously described as A to G inclusive, with esters of a beta-keto acid such as acetoacetic acid, and a lower alcohol such as methyl or ethyl alcohol.

EXAMPLE I

A mixture constituting 1000 grams of the alkyd body A containing 57.6% solids dissolved in solvent naphtha, was admixed with 500 milliliters of methylaceto acetate and heated on the steam bath for 18 hours. All of the solvent was then removed from the reaction mixture by distillation in vacuum and to the hot resin, 500 grams of solvent naphtha was added. The resultant solution had a Gardner viscosity of U to V at 50.4% solids. This material may be employed as a coating medium and for other applications to which alkyd resins are usually applied. The resin is also adapted for further reactions and modifications as hereinafter described.

EXAMPLE II

The alkyd body B in a proportion of 1000 grams of 63.8% solution, was admixed with 1000 grams of methyl acetoacetate and the mixture was heated on a steam bath under a pressure of 140 mm. (absolute) for 15 hours. The resultant resin was completely stripped under vacuum. The product, a resinous body, was obtained in a yield of 671 grams. It had a saponification value of 364. This resin may be dissolved in diluents such as naphtha or toluene and employed for coating purposes. It may also be subjected to further reactions as hereinafter described.

EXAMPLE III

Alkyd resin C was made up in solvent naphtha to a concentration of 50% solids. This mixture was then reacted with methyl acetoacetate on a steam bath and at 140 mm. (absolute) for 15 hours in the manner described in Example II to provide a resinous body. Excess methyl acetoacetate and other volatiles were stripped under vacuum.

EXAMPLE IV

The alkyd body D is made up with methyl acetoacetate and reaction is effected upon a steam bath at atmospheric pressure to provide esters of acetoacetic acid and the alkyd body. Excess methyl acetoacetate and other volatile matter are vacuum distilled.

EXAMPLE V

The alkyd body E was admixed with methyl acetoacetate and treated as in Example IV to provide a body soluble in toluene and solvent naphtha and being adapted for use as a coating medium.

EXAMPLE VI

Admix the ethylenically unsaturated alkyd body F with methyl acetoacetate and an appropriate solvent such as solvent naphtha. Heat the mixture upon a steam bath and preferably under vacuum in order to effect ester interchange between the free hydroxyls of the alkyd body and the acetoacetic acid ester of a lower alcohol.

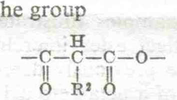
EXAMPLE VII

Admix the alkyd body G with an excess of methyl acetoacetate and heat the reaction mixture on a steam bath under a pressure of 140 mm. (absolute) until esterification is essentially complete. Distill off any unreacted methyl acetoacetate under vacuum to provide a modified alkyd body.

MODIFICATIONS OF ACETOACETIC ACID ESTERS OF ALKYD RESINS

It has already been indicated that the modified resins obtained from ester interchange reaction between the hydroxylated alkyd resin and a beta-keto ester of a lower alcohol, contain active groups which are susceptible of further reaction to form modifications of the esters of the alkyd bodies and the beta-keto acids.

For example, in the group



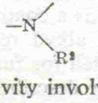
$$-\underset{O}{\underset{\|}{C}}-\underset{R^2}{\underset{|}{\overset{H}{C}}}-\underset{O}{\underset{\|}{C}}-O-$$

hydrogen on the alpha-carbon atom is reactive and can undergo reaction with aldehydes and ketones as hereinafter more fully explained.

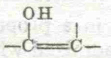
The ketonic carbonyl oxygen is reactive and can be replaced by

$$=N-OH$$
$$=N-NHR$$
$$-NH_2$$

and



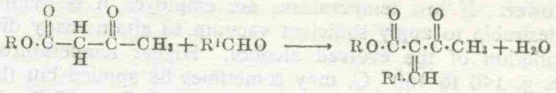
A third type of reactivity involves the enolic hydroxyl of the tautomeric



$$-\overset{OH}{\overset{|}{C}}=\overset{|}{C}-$$

form of the carbonyl. A number of these reactions have been referred to in the foregoing application, Serial No. 219,900.

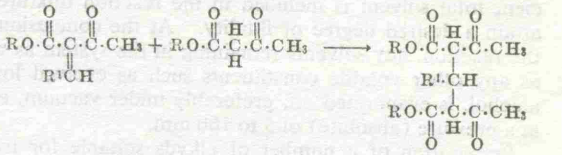
Reactions involving the activated hydrogen atoms on the carbonyl groups between the carboxyls is typified or represented by the reactions obtained with aldehydes such as formaldehyde, acetaldehyde, propionaldehyde, crotonaldehyde, furfural, and such like aldehydes, especially those containing 6 carbon atoms or less. These reactions are of the Knoevenagel type. They may be represented by the type formula:



$$RO\cdot\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-CH_3+R^1CHO \longrightarrow RO\cdot\overset{O}{\overset{\|}{C}}\cdot\underset{R^1\cdot CH}{\underset{\|}{C}}\cdot\overset{O}{\overset{\|}{C}}\cdot CH_3+H_2O$$

In the equation R is the alkyd resin body such as any one of those represented by alkyds A to G hereinbefore discussed. R^1 is a hydrogen or a hydrocarbon group or radical of an aldehyde, such as H in formaldehyde, $-CH_3$ in acetaldehyde, etc. This type of reaction is usually catalyzed by a small amount of an organic base such as piperidine, diethyl amine or the like.

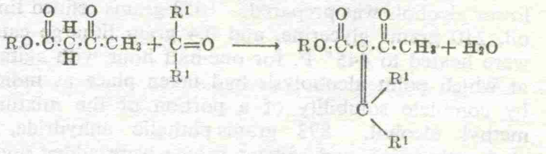
It will be observed that in reactions of this type the new or modified alkyd body containing the acetoacetic acid radical contains a methylene group in conjugate relation to the oxygens of a carboxyl group. Such methylene groups are recognized to be of high functionality. For example, they are capable of reaction with other molecules of beta-keto acid modified polyesters to provide carbon bridging between a pair of such molecules. The reaction of this type is represented by the following formula:



$$RO\cdot\overset{O}{\overset{\|}{C}}\cdot\underset{R^1CH}{\underset{\|}{C}}\cdot\overset{O}{\overset{\|}{C}}\cdot CH_3+RO\cdot\overset{O}{\overset{\|}{C}}\cdot\underset{H}{\overset{H}{C}}\cdot\overset{O}{\overset{\|}{C}}\cdot CH_3 \longrightarrow \begin{array}{c} RO\cdot\overset{O}{\overset{\|}{C}}\cdot\overset{H}{C}\cdot\overset{O}{\overset{\|}{C}}\cdot CH_3 \\ | \\ R^1\cdot CH \\ | \\ RO\cdot\underset{O}{\underset{\|}{C}}\cdot\underset{H}{C}\cdot\underset{O}{\underset{\|}{C}}\cdot CH_3 \end{array}$$

In this latter formula, the groups R constitute polyester radicals and R^1 is hydrogen or an alkyl or an aryl group.

It will be recognized that the beta-keto ester modified alkyd bodies may similarly be condensed with ketones such as acetone, methyl ethyl ketone and the like, in accordance with the following equation:



In this equation, R^1 is alkyl or aryl and cannot be hydrogen.

To effect modification of the beta-keto acid esters, formaldehyde or the so-called "latent" formaldehydes, e. g. paraformaldehyde, hexamethylene tetramine, and the like may be employed. As stated, other suitable aldehydes such as acetaldehyde, propionaldehyde, and benzaldehyde may be employed. Likewise, ethylenically unsaturated aldehydes such as acrolein, crotonaldehyde and furfural may be used in lieu of formaldehyde. These latter introduce further unsaturation into the alkyd molecule and thereby increase the functionality thereof.

The following examples illustrate the modification of acetoacetic acid modified alkyd esters prepared by such methods as disclosed in Examples I, II, III, IV, V, etc. with carbonyl compounds such as formaldehyde or "latent" formaldehyde.

EXAMPLE VIII

According to this example, a mixture of 500 grams of the resin of Example I, was admixed with 5 grams of paraformaldehyde, 1 milliliter of pyridine, 1 drop of piperidine and 100 milliliters of solvent naphtha. The mixture was heated on the steam bath with agitation for 3 hours. The reaction mixture was then heated under vacuum until water of reaction had distilled azeotropically. The total distillate had a volume of 100 milliliters and contained some water, indicating reaction had taken place. The resin obtained had a viscosity (Gardner) greater than Z6 at 55.8% by weight of solids.

The resin molecule had become cross-linked. It exhibited good drying properties and improved alkali resistance.

EXAMPLE IX

In this example, 500 grams of the alkyd resin prepared as described in Example II and being modified with acetoacetic acid, was dissolved in 640 grams of xylene, and 9 grams of paraformaldehyde. One milliliter of pyridine and 3 drops of piperidine were added to the mixture and the latter was then heated at 115° C. under inert gas for 4 hours, during which time a total of 125 cc. of solvent and water had distilled. The resultant resin solution had an acid value of 6.7 and was of a solids content of 49.9%. The Gardner viscosity thereof was A. It showed better alkali and water resistance than a standard composition comprising an alkyd prepared by cooking 2080 grams (8 moles) soya fatty acids, 740 grams (5 moles) phthalic anhydride, 246 grams (2.67 moles) glycerine and 340 grams (2.5 moles) Pentek (pentaerythritol) to an acid value of 18 and a Gardner viscosity of Z at 95% solids.

EXAMPLE X

In this example, the acetoacetic acid ester of the alkyd resin as prepared in Example III was compounded with paraformaldehyde, pyridine and piperidine and heated as in Example IX. The resultant resin had a viscosity of Z in a solution in toluene containing 50% by weight of solids and dried faster and showed better water resistance than the unmodified resin.

EXAMPLE XI

In this example, the derivative of methyl acetoacetate and the alkyd resin prepared in Example IV except for the omission of vacuum during the ester interchange reaction was admixed with paraformaldehyde and was heated upon a steam bath until a resin, which in a concentration of 52% by weight of solids in aromatic naphtha had a viscosity greater than Z6 on the Gardner scale. The product dried substantially better than the corresponding alkyd resin which had not been modified with methyl acetoacetate and formaldehyde and which was of the composition:

	Grams
Cocoanut oil acids	990
Clycerine	695
Phthalic anhydride	1092

Viscosity Z at 50% by weight solids.

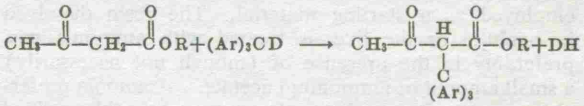
EXAMPLE XII

In this example, the resin body obtained in Example V was employed as the beta-keto acid modified alkyd body. The resin was cooled to 250° F. and 3 grams of paraformaldehyde were added. The reaction mixture was held at 280° F. for 30 minutes. The viscosity of the product rose to a value of Z2 at which point the reaction was discontinued.

It is to be understood that the invention as herein disclosed includes the substitution of the other aldehydes such as acetaldehyde, propionaldehyde, furfural, crotonaldehyde, acrolein and the like for formaldehyde or "latent" formaldehyde compounds in the several Examples VIII through XII, as herein discussed. In such substitutions, the carbonyl compounds will be employed in the same molar equivalency as the formaldehyde in the prior examples.

In effecting the reactions of ester interchange between the hydroxy alkyd resin and the acetoacetic acid ester of a lower alcohol and likewise in the subsequent Knoevenagel condensation of the resultant ester product with aldehydes, ketones and the like, the time of reaction may vary, for example from approximately 10 minutes to 24 hours. The pressure of reaction may be atmospheric or negative (vacuum) as may be desired. The temperature of the reaction preferably is within a range of 60 to 170° C. or thereabouts.

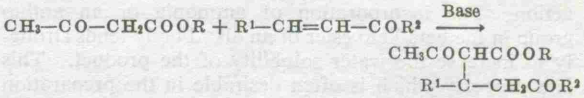
The invention likewise includes the replacement of active hydrogen of the alpha carbon of the beta-keto acid esters of alkyd bodies with benzylic type halides and alcohols such as triphenyl methyl chloride and triphenyl carbinol. These reactions proceed in accordance with the partial equation:



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}OR+(Ar)_3CD \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{(Ar)_3}{\overset{|}{C}}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-OR+DH$$

where D is chlorine or —OH. In the equation R is again the residue of an alkyd resin prepared in accordance with the provisions of the present invention. Ar represents phenyl or substituted phenyl.

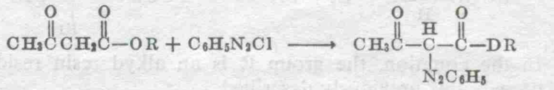
The active hydrogen of the alpha carbon atom beta-keto acid esters of alkyds in A to G inclusive, may also undergo so-called Michael type reactions with alpha-beta unsaturated carbonyl compounds as represented by the equation:



$$CH_3-CO-CH_2COOR+R^1-CH{=}CH-COR^2 \xrightarrow{\text{Base}} CH_3CO\underset{R^1-\overset{|}{C}-CH_2COR^2}{CH}COOR$$

In the equation, the group R is the residue of an alkyd body prepared as for example, in the present examples. Groups R^1 and R^2 may be hydrogen or hydrocarbon, e. g. ethyl, methyl or the like.

The reaction of the beta-keto esters of alkyd resins with diazonium salts such as benzene diazonium chloride to yield compounds containing a dye structure is likewise a part of the present invention. Such reaction may be represented by the equation:

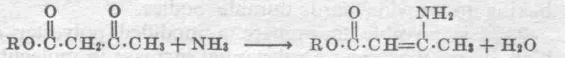


$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}-OR+C_6H_5N_2Cl \longrightarrow CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{N_2C_6H_5}{|}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-DR$$

The group R, again, is the alkyd body or residue prepared as for example, as disclosed in Examples A–G inclusive.

REACTIONS INVOLVING THE BETA CARBONYL OXYGEN

It is to be understood that the beta-keto acid esters such as acetoacetic acid esters of the alkyd resins as herein disclosed, may be reacted with other compounds. For example, they may be reacted with ammonia or with amines to form beta-amino crotonic esters of said alkyd bodies. In these, the beta-keto oxygen is replaced by NH_2 or its equivalent amine. This type of reaction can be represented by the following equation:



$$RO\cdot\overset{\overset{O}{\|}}{C}\cdot CH_2\cdot\overset{\overset{O}{\|}}{C}\cdot CH_3+NH_3 \longrightarrow RO\cdot\overset{\overset{O}{\|}}{C}\cdot CH{=}\overset{\overset{NH_2}{|}}{C}\cdot CH_3+H_2O$$

It is to be understood that in the equation, the group R constitutes an alkyd resin such as one of those of the group A to G inclusive. It is usually preferable, though not indispensable, to effect the reaction between the beta-keto ester of the alkyd resin and the ammonia or the amino body in the presence of a small amount of a suitable catalyst, such as ammonium acetate. The reaction can be effected in the presence of or in the absence of, suitable solvents of the reaction mixture. Since the alkyd resins are relatively viscous materials, or even solids, the use of a solvent is often to be preferred. The solvent may be naphtha, xylene, toluene, or even a glyceride oil or any of the other conventional solvents of alkyd resins. Only sufficient solvent to produce adequate fluidity of the reaction mixture need be employed. The reaction may be effected substantially at room temperature or at elevated temperatures, for example, upon a steam bath.

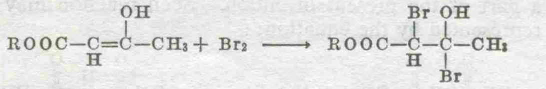
The following illustrate the treatment of the acetoacetic acid esters of alkyds with ammonia. Ammonium acetate can be employed in small catalytic amounts or it can be employed as the sole source of ammonia in the reaction.

EXAMPLE XII

In this example, an alkyd resin which has been modified with acetoacetic acid as disclosed in Example I is employed as a starting material. The resin dissolved in naphtha or the like, is treated with ammonia gas, preferably in the presence of (though not necessarily) a small amount of ammonium acetate. Ammonia preferably as a gas is passed into the acetoacetic acid modified alkyd body for a period of about 2 hours. In the foregoing example, it is to be understood that ammonia gas could be added for a longer or shorter period. However, 2 hours is deemed to be adequate for most purposes. In this manner, it is possible to form the beta-amino crotonate of the alkyd body.

It is to be understood that other basic ammonia compounds such as ethyl amine, diethyl amine, aniline and many others may be substituted for ammonia in the reaction. The incorporation of ammonia or an amino group in the beta-keto ester of an alkyd body tends strongly to increase the water solubility of the product. This is a property which is often desirable in the preparation of water emulsion coating compositions.

Further reactions of the esters of beta-keto acids and alkyd resins containing residual hydroxyls involve the enolic hydroxyl group of a tautometer of the beta-keto ester. Typical examples of such reactions involve the halogenization of the esters, for example, with bromine or chlorine. This type of reaction can be represented by the equation:



$$\mathrm{ROOC{-}\underset{H}{C}{=}\overset{OH}{C}{-}CH_3 + Br_2 \longrightarrow ROOC{-}\underset{H}{\overset{Br}{C}}{-}\underset{Br}{\overset{OH}{C}}{-}CH_3}$$

In the equation, the group R is an alkyd resin residue prepared as previously described.

ADVANTAGES ATTENDING THE APPLICATION OF THE INVENTION

Numerous advantages are observable in the practice of the invention. A number of these are herein listed. However, it is to be understood that all of the advantages do not necessarily occur simultaneously in the same composition. It may well be that in certain instances but a single advantage will be observed. In other instances several of the advantages may occur simultaneously.

Advantages

1. The compositions of resins as herein disclosed in many instances are capable of air curing or drying by baking to provide hard, durable bodies.

2. It is possible to prepare a modified polyester of high viscosity wherein a substantial increase in molecular complexity is achieved at a point where further esterification linkages are difficult to complete and without the application of addendum reactions involving the use of unsaturation in the alkyd bodies.

3. It is possible by application of the invention to obtain polyester compositions which are free or nearly free of hydroxyl groups.

4. It is possible to prepare polymers containing cross-linkage between contiguous polyester molecules through carbon bridges.

5. It is possible to improve the water and alkali resistance of the alkyd resin films by elimination of the free hydroxyls of the alkyd resins.

6. By the introduction of ammonia or amine groups, it is possible to improve the emulsification characteristics and provide alkyd resins which are especially adapted for use in the preparation of emulsion coating compositions.

The forms of the invention herein disclosed are to be regarded as being by way of example. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

We claim:

1. A modified alkyd resin obtained by interesterification of an alkyd body containing free hydroxyls and an ester of a beta-keto acid and a monohydric alcohol containing 1 to 4 carbon atoms.

2. A method of modifying an alkyd resin containing free hydroxyls which comprises the steps of reacting said alkyd resin with an ester of a beta-keto acid and a monohydric alcohol containing 1 to 4 carbon atoms, at a temperature in the range of about 70° C. to 160° C., whereby to effect ester interchange between the alkyd resin and a beta-keto ester.

3. A method of forming beta-keto esters of alkyd resins containing free hydroxyls which comprises the steps of effecting ester interchange between said alkyd resin, and an ester of acetoacetic acid and a lower alcohol containing a single hydroxyl and 1 to 4 carbon atoms, the reaction being effected at a temperature in the range of about 70° C. to 160° C.

4. A method of forming beta-keto esters of alkyd resins containing free hydroxyl groups comprising the steps of heating under vacuum a mixture of said resin and an ester of a beta-keto acid and a lower alcohol containing a single hydroxyl and 1 to 4 carbon atoms, the reaction being effected at a temperature in the range of about 70° C. to 160° C.

5. The product of ester interchange betwen (A) a phthalic glyceride containing free hydroxyls and (B) an ester of a monohydric alkyl alcohol containing one to four carbon atoms and a beta-keto monocarboxylic acid.

6. A method of forming a modified alkyd resin which comprises treating under vacuum and at a temperature below 160° C. a mixture of (A) a phthalic glyceride containing free hydroxyls and (B) an ester of a beta-keto monocarboxylic acid and a monohydric alcohol containing one to four carbon atoms whereby to effect ester interchange between the phthalic glyceride and the beta-keto ester of a lower alcohol.

7. A method of modifying an alkyd resin containing free hydroxyls, which comprises admixing the alkyd resin with an ester of a beta-keto acid and aliphatic alcohol containing one to four carbon atoms, said ester being in molar excess over the available hydroxyls and heating the mixture to effect ester interchange between the resin and the ester of the beta-keto acid.

8. A method of modifying an alkyd resin containing free hydroxyls which comprises reacting the same with a beta-keto acid ester of a lower monohydric alcohol containing 1 to 4 carbon atoms at a temperature below that of decomposition of the beta-keto acid ester whereby to evolve lower alcohol and to form said ester and removing the evolved alcohol.

9. A method as defined in claim 8 in which the beta-keto acid is acetoacetic acid.

10. A method as defined in claim 8 in which the reaction temperature is at about 100° C.

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Patented Nov. 6, 1956

2,769,842

PREPARATION OF DYPNONE

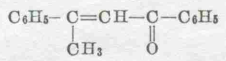
Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

No Drawing. Application September 21, 1953, Serial No. 381,510

4 Claims. (Cl. 260—590)

This invention relates to a novel method for preparing dypnone, and pertains more particularly to its preparation by treating acetophenone with polyphosphoric acid.

Dypnone, which possesses the structure

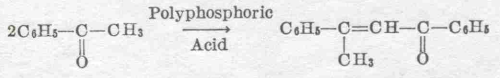


$C_6H_5-\underset{\underset{CH_3}{|}}{C}=CH-\underset{\underset{O}{\|}}{C}-C_6H_5$

is a very valuable compound, being particularly useful as a plasticizer, as a base for perfumes and as an ultraviolet light filter in resins and in surface coating materials. Dypnone has previously been prepared by the action on acetophenone of sodium ethoxide, aluminum chloride and aluminum tertiary butoxide. Yields obtained by the above method have been relatively small.

It has now been discovered that good yields of dypnone can be obtained very readily by contacting acetophenone (also known as methylphenyl ketone, hypnone and acetylbenzene) with polyphosphoric acid. Because of the very low cost of polyphosphoric acid and the good yields obtained, dypnone can be produced by the present process more easily and at a lower cost than has heretofore been possible.

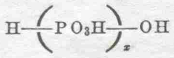
The reaction involved in treating acetophenone with polyphosphoric acid may be depicted structurally as follows:



$2C_6H_5-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow[\text{Acid}]{\text{Polyphosphoric}} C_6H_5-\underset{\underset{CH_3}{|}}{C}=CH-\underset{\underset{O}{\|}}{C}-C_6H_5$

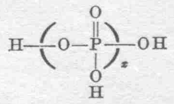
Acetophenone Dypnone

The polyphosphoric acid with which the acetophenone is contacted to produce dypnone in accordance with the above equation is the reaction product of or a solution of orthophosphoric acid (H_3PO_4) and phosphorus pentoxide (P_2O_5). It is also termed "a condensed phosphoric acid" and its structure is understood to be:



$H-\left(PO_3H\right)_x-OH$

or



$H-\left(O-\overset{\overset{O}{\|}}{\underset{\underset{H}{\underset{O}{|}}}{P}}\right)_x-OH$

wherein x is greater than 1. Polyphosphoric acid is an easily handled and relatively inexpensive viscous liquid which contains about 82 to 85 percent of phosphorus pentoxide.

The quantity of polyphosphoric acid utilized in the reaction may be varied widely. Usually, it is preferred to utilize the polyphosphoric acid in an amount in excess of the quantity of the acetophenone employed, the upper limits being imposed by economics rather than by chemical behaviour. Obviously, great excesses beyond those required to obtain reaction merely increase the costs without corresponding improvements in results. Equal amounts of the acetophenone and polyphosphoric acid may also be employed and good results are obtained when an excess of the acetophenone is present.

Preferably, the reaction is carried out in an inert solvent or diluent for the acetophenone and polyphosphoric acid. Both aliphatic and aromatic hydrocarbons are useful for this purpose. Solvents which may be utilized include aliphatic hydrocarbons such as pentane, hexane, heptane, octane, decane, and the like, and aromatic hydrocarbons such as benzene, toluene, aromatic naphthas and the like. The use of a solvent or diluent is not a critical expedient, however, for the reaction proceeds satisfactorily whenever the acetophenone and polyphosphoric acid, both liquids, are brought into effective contact with one another. Stirring of the reaction mixture is desirable, since the polyphosphoric acid and the organic materials present are not completely miscible.

The temperature at which the reaction is carried out may also be varied widely. For example, temperatures as low as 30° C. or as high as 150° C. may be used with excellent results. When a solvent or diluent is utilized, the reaction is preferably carried out at the reflux temperature of said solvent or diluent. In the case of benzene, a preferred solvent, this temperature is about 80° C., and with toluene, about 110° C.

The following examples describe in greater detail the preparation of dypnone by the reaction of acetophenone and polyphosphoric acid. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

Example I

One hundred twenty grams (1.0 mole) of acetophenone, and 300 grams of polyphosphoric acid were mixed with 156 grams of benzene. The resulting mixture was then stirred and refluxed at about 70° C. for 6 hours. Upon distillation of the resulting reaction mixture a good yield of dypnone, a yellowish liquid having a mild, fruity odor and boiling at 246° C./50 mm., was obtained.

Example II

Forty-nine grams (0.41 mole) of acetophenone and 106 grams of polyphosphoric acid were added to 60 cc. of benzene. The mixture thus obtained was then refluxed with stirring at about 80° C. for 7 hours. The reaction mixture was then washed with water and distilled at 1 mm. Twenty-five grams of dypnone were obtained.

Example III

Example II was repeated except that the acetophenone and polyphosphoric acid were admixed and agitated in the absence of benzene or other inert solvent or diluent. A good yield of dypnone was obtained.

When the above examples are repeated utilizing other inert solvents or diluents, other quantities of the polyphosphoric acid and acetophenone, or other temperatures within the range disclosed hereinabove, dypnone is again obtained in good yields.

The dypnone obtained in the above examples could be used as a plasticizer, as a perfume base, as an ultraviolet light filter or as an intermediate in the preparation of other chemical compounds without further purification being necessary.

Although specific examples of the invention have been set forth hereinabove, it is not intended that the invention be limited thereto, for it will be apparent to those skilled in the art that numerous possible variations and modifications may be made therein without departure from the spirit and scope of the invention as defined in the appended claims.

I claim:

1. The method which comprises bringing together

acetophenone and polyphosphoric acid, thereby to obtain dypnone.

2. The method which comprises bringing together acetophenone and polyphosphoric acid in an inert solvent, thereby to obtain dypnone.

3. The method which comprises bringing together acetophenone and polyphosphoric acid in the presence of an inert solvent and at a temperature of about 30° C. to about 150° C., thereby to obtain dypnone.

4. The method of claim 3 wherein the inert solvent is benzene.

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United States Patent Office

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Patented Apr. 30, 1957

2,790,826

METHOD OF PREPARING ALKENYLARYLOXY ALIPHATIC CARBOXYLIC ACIDS

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Pittsburgh, Pa., a corporation

**No Drawing. Application May 18, 1953,
Serial No. 355,863**

3 Claims. (Cl. 260—521)

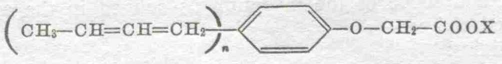
This invention relates to a novel class of chemical compounds, the alkenylaryloxy aliphatic carboxylic acids, and the salts, esters and amides thereof, and to a method for the preparation of such compounds, and pertains more particularly to novel butenylphenoxyacetic acids and to the water soluble salts, esters and amides of said acids.

In a copending application, Serial No. 300,359, filed July 22, 1952, it is disclosed that cyclopentadiene will react with phenolic compounds in the presence of a Friedel-Crafts catalyst to give either mono-, di- or tricyclopentenyl phenolic compounds, or mixtures thereof, depending upon the quality of catalyst utilized and the reaction temperature. Also, in a series of copending applications, Serial Nos. 337,226, 337,227; 337,228; and 337,229, all filed February 16, 1953, it is disclosed that acyclic conjugated dienes react with phenolic compounds in the presence of various Friedel-Crafts type compounds to give monoalkenylphenolic compounds or mixtures of mono-, di- and trialkenylphenolic compounds, the nature of the reaction product depending upon the catalyst strength and the reaction temperature. The unsaturated phenolic compounds prepared according to the methods of the copending applications are very useful in the preparation of resins by condensation with aldehydes and are also useful for many other purposes.

It has now been discovered that alkenylphenolic compounds react, in the form of their water-soluble alkali salts, with haloaliphatic carboxylic acids to give a new class of chemical compounds, the alkenylaryloxy aliphatic carboxylic acids and the water-soluble salts, esters and amides thereof. These new compounds, which have not been prepared heretofore, possess the following structure:

$$(R)_n{-}Ar{(}O{-}R_1{-}COOX)_n$$

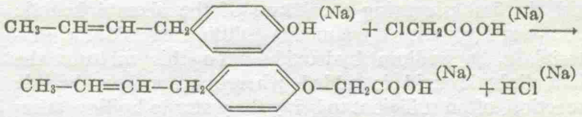
wherein R is alkenyl, cyclopentenyl, haloalkenyl, halocyclopentenyl, alkoxyalkenyl or alkoxycyclopentenyl, Ar is an aromatic radical, R_1 is alkylene or substituted alkylene such as haloalkylene, X is hydrogen, a water-soluble inorganic salt-forming group, an alkyl radical, or $—NH_2$ and each *n* is a number from 1 to 3 and may be the same or different. The preferred compounds of the above general class are the butenylphenoxyacetic acids and their salts, esters and amides of the structure:



wherein *n* is a number from 1 to 3 and X has the significance given above. Compounds of this formula, and particularly those in which *n* is 1 are readily prepared from a haloacetic acid and butenylphenol, which is readily and economically obtained by the reaction of butadiene-1,3 and phenol.

The novel acids and salts of this invention may be prepared by reacting an alkenylphenolic compound in the form of a water-soluble inorganic salt thereof with a haloaliphatic monocarboxylic acid or a salt thereof. This reaction may be depicted structurally as follows, wherein

p-2-butenylphenol and chloroacetic acid are utilized for illustrative purposes;



The corresponding novel esters of the alkenylaryloxy aliphatic carboxylic acids are prepared by reacting the acid with an alcohol, preferably in the presence of an esterification catalyst; and the amides by ammonolysis of the esters, acid anhydrides or acid halides.

In preparing the novel compounds of this invention any alkenylphenolic compound may be employed. Such compound may be reacted by the structure

$$R_n{-}Ar{-}(OH)_n$$

wherein R, Ar and *n* have the significance set forth above.

The preferred alkenylphenolic compounds of the structure $R_n{-}Ar{-}(OH)_n$ are those in which R is butenyl and Ar is phenyl, including o- and p-2-butenylphenols, di-2-butenylphenol and tri-2-butenylphenol. However, other alkenylphenolic compounds may also be used, including butenylcresols, butenylcatechols, butenyl-2,5-dichlorophenols, butenyl-2,5-dinitrophenols, butenyl-2,3-dimethoxyphenols, mono-, di- and tributenylresorcinol, mono-, di- and tributenylguaiacol, 2-chlorobutenylcresol, 2-chlorobutenylphenols, 2-iodobutenylphenols, o- and p-cyclopentenylphenols, pentenylphenols, pentenylcresols, pentenylguaiacol, halopentenylphenols, halopentenylguaiacols, hexenylphenols, hexenylcresols, di- and trihexenylcresols, halohexenylphenols, halohexenylchlorophenols, halohexenylcatechols, and the like. All of the above alkenylphenolic compounds, as well as many other compounds possessing the structure $R_n{-}Ar{-}(OH)_n$, are readily prepared by reacting conjugated dienes with phenolic compounds in the presence of a Friedel-Crafts compound or other of the catalysts disclosed in the copending applications referred to hereinabove. Mixtures of mono-, di- and trialkenylphenolic compounds may be reacted with haloaliphatic monocarboxylic acids to give a corresponding mixture of mono-, di- and trialkenylaryloxy aliphatic carboxylic acids or salts.

Any saturated haloaliphatic monocarboxylic acid, or water-soluble salt thereof may be reacted with alkenylphenolic compounds of the type disclosed in the foregoing paragraph to form novel alkenylaryloxy aliphatic carboxylic acids or salts. Particularly preferred is chloroacetic acid because it is economically obtained in commercial quantities. Others which may be used include alpha-chloropropionic, alphabromopropionic acid, alpha-iodoproprionic acid, beta-chloropropionic acid, beta-bromopropionic acid, alpha-fluoroproprionic acid, alpha-chlorobutyric acid, beta-bromobutyric acid, gammachlorobutyric acid, alpha-chlorovaleric acid, alpha-bromovaleric acid, alpha-chlorostearic acid, and the like.

Hydroxides of the alkali metals, sodium hydroxide, potassium hydroxide and the like are preferred alkaline materials for forming water-soluble salts of the phenolic compound and the haloaliphatic monocarboxylic acid. However, other alkaline materials, for example, calcium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, ammonia, and the like, may also be employed, particularly if used in combination with an alkali metal hydroxide.

The alkenylphenolic compound and the haloaliphatic monocarboxylic may be brought together in any desired molar proportions. For example, the reactants may be brought together in equimolar quantities or by using an excess of as much as five moles or more of either reactant. Any unreacted material, particularly unreacted phenolic compound, is readily recovered for use in subsequent reactions.

The reaction of the phenolic compound with a haloaliphatic monocarboxylic acid may be carried out by several different procedures. One preferred method consists in first preparing a mixture of the alkenylphenolic compound(s) with an aqueous solution of alkaline material, e. g. sodium hydroxide. To this mixture the haloaliphatic acid is added whereupon an exothermic reaction, often sufficient to bring the water to boiling, takes place. Heating at about 100° C. is continued for approximately an hour at which time the reaction is ordinarily substantially complete.

The alkenylaryloxy aliphatic monocarboxylic acid salt may be recovered from the reaction mixture simply by cooling the mixture to about room temperature, whereupon the salt crystallizes and can be recovered in a very pure form by washing and filtering.

If, however, it is desired to recover the free alkenylaryloxy aliphatic monocarboxylic acid, the reaction mixture is acidified, for example, with a mineral acid such as hydrochloric acid, and the free acid recovered by extraction with a water immiscible solvent such as hexane, heptane or toluene followed by distillation, crystallization, or other purification procedure. The use of an extraction process is especially preferred inasmuch as it permits separation of the o- and p-isomers which are present in the reaction mixture.

Alternatively, the reaction may be carried out by admixing the phenolic compound and the haloaliphatic acid in water and then adding alkali, or by first forming water-soluble alkaline salts of the phenolic compound and the haloaliphatic acid and then dissolving them in water, in which medium the reaction takes place readily.

Esters and amides of the alkenylaryloxy aliphatic monocarboxylic acids thus obtained are prepared by conventional methods of esterification and amidation. For example, the amidation may be carried out by first reacting the acid with oxalyl chloride to form the acid chloride and then reacting the acid chloride with ammonia. Esters are prepared by the reaction of the acid with an alcohol in the presence of an esterification catalyst.

The novel compounds prepared according to the methods set forth above are unconjugated. However, they are readily converted to the conjugated form by isomerization carried out in the presence of alkali.

The following examples illustrate more fully the preparation of novel alkenylaryloxy aliphatic carboxylic acids, salts, esters and amides in accordance with the present invention. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

Example I

To 200 grams of a mixture of butenylphenols (prepared by the reaction of phenol with butadiene-1,3 in the presence of a H_2SO_4—H_3PO_4 catalyst) and containing predominantly o-2-butenyl-phenol and p-2-butenylphenol, dissolved in a liter of 33 percent aqueous sodium hydroxide, 300 grams of chloroacetic acid were slowly added. After the reaction had subsided, the clear solution was heated, on a steam bath for an hour, cooled, and acidified with hydrochloric acid. The waxy product was taken up in hot heptane, and the heptane insoluble o-2-butenylphenoxyacetic acid was filtered off, washed with hot heptane, and dried. A pure product in the form of soft white needles, melting at 137° C. was obtained by crystallization from water.

Evaporation of the heptane filtrate and low temperature crystallization of the waxy product yielded p-2-butenylphenoxyacetic acid melting at 80° C.

The sodium salts of o-2-butenylphenoxyacetic acid and p-2-butenylphenoxyacetic acid can be recovered simply by cooling the reaction mixture to room temperature or lower, or by adding to the reaction mixture a lower

alcohol such as methyl or ethyl alcohol in which the salt is insoluble and from which it precipitates.

The o-2-butenylphenoxyacetic acid and the p-2-butenylphenoxyacetic acid, both of which are unconjugated, were each dissolved in concentrated methanolic potassium hydroxide and the methanol removed by distillation until the liquid temperature reached 110° C. The solutions were then refluxed under inert gas for six hours, cooled, acidified, and the crystalline product recrystallized. P-1-butenylphenoxyacetic acid forms shiny white platelets melting at 129°–130° C. O-1-butenylphenoxyacetic acid, crystallized from heptane, forms soft needles melting at 101°–102° C. Ultra-violet spectra show the products to be conjugated.

Example II

The unconjugated o-2-butenylphenoxyacetic acid and p-2-butenylphenoxyacetic acid are converted to the ethyl ester by heating them with ethyl alcohol in the presence of a sulfuric acid esterification catalyst. The ester is obtained in good yield.

Example III

The amide of o-butenylphenoxyacetic acid is prepared by first reacting the acid with oxalyl chloride to give the acid chloride of o-butenylphenoxyacetic acid. This acid chloride is then converted to the amide by reaction with aqueous ammonia.

Moreover, when the above examples are repeated utilizing other of the butenylphenols or haloaliphatic carboxylic acids disclosed hereinabove, alkenylaryloxy aliphatic carboxylic acids are again obtained in good yields. For example, in this manner o-butenylphenoxypropionic acid and p-butenylphenoxypropionic acid are obtained by the reaction of butenylphenols with chloropropionic acid; dipropenylphenoxybutyric acid is obtained by the reaction of dipropenylphenol and alphachlorobutyric acid; and butenylcresoxyacetic acid is obtained by the reaction of butenylcresol and chloroacetic acid. The salts, esters and amides of these acids and others are obtained in the manner set forth in the specific examples. The novel compounds of this invention can also be prepared by other of the methods disclosed hereinabove.

The novel alkenylaryloxy aliphatic monocarboxylic acids, salts, esters and amides of the present invention are very valuable compounds. For example, they all possess insecticidal and herbicidal properties, even when utilized in low concentrations together with an inert carrier or solvent. Also, the compounds undergo polymerization through the unsaturation in the alkenyl group present in each compound, to form polymers or interpolymers having many useful properties. The alkenylaryloxy aliphatic monocarboxylic acids, salts, esters and amides are also useful as intermediates in the production of other chemical compounds and compositions.

From the foregoing description it will be seen that the alkenylaryloxy aliphatic monocarboxylic acids, salts, esters and amides of the present invention constitute a very valuable class of compounds which has not been prepared heretofore. It is apparent, therefore, that various embodiments of the invention, in addition to those specifically disclosed may be provided without departing from the spirit and scope of the invention as defined in the appended claims.

I claim:

1. A novel compound of a class consisting of p-1-butenylphenoxyacetic acid, o-1-butenylphenoxyacetic acid and sodium salts of said acids.

2. P-1-butenylphenoxyacetic acid.

3. The method of forming 1-butenylphenoxyacetic acid which comprises heating a 2-butenylphenoxyacetic acid in the presence of potassium hydroxide and methanol.

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Patented Apr. 30, 1957

2,790,830

N-AMINOALKANOL SUBSTITUTED ALKYLAROMATIC COMPOUNDS

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

No Drawing. Application October 21, 1954, Serial No. 463,831

9 Claims. (Cl. 260—570.9)

This invention relates to novel N-aminoalkanol substituted alkylaromatic compounds, and to a method for the preparation thereof, and pertains particularly to the preparation of N,N-di(aminoethanol) substituted alkylbenzenes by the reaction of halomethyl alkylbenzenes with ethanolamine.

It has heretofore been suggested to prepare alpha-hydroxyphenyl toluenes by reacting benzyl chloride with phenol. However, the reaction takes place only at relatively high temperatures, e. g., about 150° C.

It has further been suggested to prepare haloalkyl derivatives of alkylated benzenes by reacting an alkylbenzene, such as xylene and particularly meta xylene, with an aldehyde, such as formaldehyde, in the present of hydrogen chloride, or other hydrogen halide. It is thus possible to prepare compounds embodying the general molecular structure:

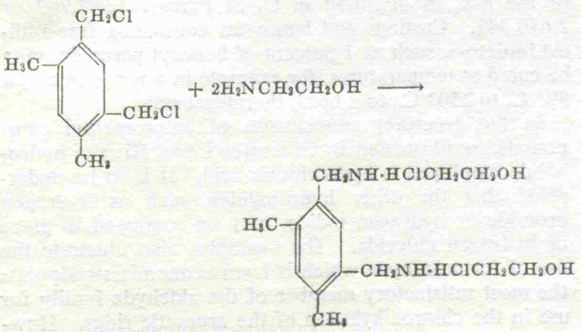
$$\mathrm{Ar}(\mathrm{CH_2{-}X})_n$$

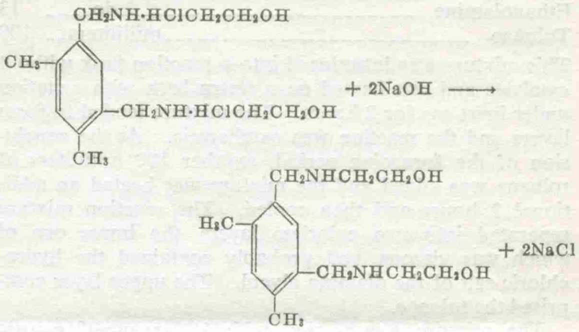
wherein Ar is an aryl radical containing at least one alkyl substituent, X is halogen such as chlorine, and n is a whole number from 1 to 3. Groups or radicals required to satisfy the carbons in the aryl ring and which are not alkyl or halomethyl ($\mathrm{—CH_2Cl}$) groups may be hydrogen, chlorine, bromine or the like.

An outstanding example of such compounds is 4,6-di(chloromethyl)m-xylene, which may also be termed dichlorodurene.

This invention comprises the discovery that halomethyl (chloro, bromo or iodo) substituted compounds of the foregoing type can readily be reacted with alkamines or amino alcohols and notably primary alkamines, such as ethanolamine, propanolamine, butanolamine and the like, to provide salts of compounds containing aminoalkanol groups joined to the aryl nucleus by methylene linkages. The compounds initially are salts, since during the course of the reaction, hydrogen chloride (or other hydrohalide) is formed and may react with the amino groups to produce hydrochlorides. The latter may in turn, be converted to secondary amino groups by reaction with a base, such as aqueous sodium hydroxide.

The reactions are illustrated by that occurring between 4,6-di(chloromethyl)m-xylene and ethanolamine which proceeds substantially in accordance with the equations:





The compound may be termed durylene di(aminoethanol).

The novel compounds obtained by the reaction of halomethyl alkylaromatic compounds with alkanolamines (alkamines) in accordance with this invention all possess the general structure

$$\mathrm{Ar}(\mathrm{CH_2{-}Y})_{n_1}$$

wherein Ar has the significance given hereinabove, and is preferably a dimethylphenyl radical, Y is a radical derived by removing an amino hydrogen atom from an alkanolamine, preferably ethanolamine, and n_1 is a whole number from 1 to 3, and preferably 2. These compounds are glycols which can be reacted with dicarboxylic acids, such as phthalic acid or maleic acid or a mixture of the two, to form long chain polyesters of the well recognized alkyd type. In event that the polyesters include an alpha-beta ethylenic dicarboxylic acid, such as maleic acid, the polyesters may be interpolymerized with a monomer containing a $>\mathrm{C{=}CH_2}$ group attached to a negative group and being represented by styrene, vinyl acetate, or other $>\mathrm{C{=}CH_2}$ monomer to provide resinous products.

It will also be recognized that these glycols, such as durylene di(aminoethanol), may be cross-linked by means of dicarboxylic acids, such as succinic acid, phthalic acid, adipic acid and others, to form thermoplastic polyamide-polyester resins useful for melt spinning into filaments or for cordage or for twisting into threads which can be knit, or woven into fabrics in a manner familiar in the polyamide art.

The starting halomethyl alkylaromatic compounds can readily be prepared by a method which broadly comprises reacting an aralkyl compound (preferably meta xylene) with formaldehyde and concentrated hydrochloric acid. The reaction takes place readily at moderate temperatures, for example, 90° C. or thereabouts. In the reaction, a catalyst such as zinc chloride or the like may be employed.

The preparation of 4,6-di(chloromethyl)m-xylene is illustrated by the following example:

Example I

A mixture of 848 grams of m-xylene, 1740 grams of 37 percent aqueous formalin solution, 40 grams of zinc chloride and 1200 cc. of concentrated aqueous hydrochloric acid was heated at 90° C. to 95° C. for 18 hours, while hydrogen chloride gas was bubbled through the mixture. The reaction mixture was then cooled and the white solid which crystallized was filtered, washed with water, dried and crystallized once from heptane to yield 869 grams of 4,6-di(chloromethyl)m-xylene, M. P. 93° C.–96° C. The reaction of 4,6-di(chloromethyl)m-xylene with ethanolamine is illustrated by the following example:

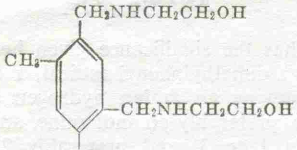
Example II

The reactants comprised:

4,6-di(chloromethyl)m-xylene	grams	20
Ethanolamine	do	13
Toluene	milliliters	100

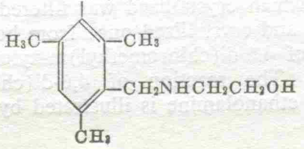
This mixture was introduced into a reaction flask without catalysts and was heated on a steam bath with agitation under inert gas for 2 hours. The mixture tended to form layers and the reaction was exothermic. At the conclusion of the foregoing period, another 100 milliliters of toluene was added and the mixture was heated an additional 2 hours and then cooled. The reaction mixture separated into two colorless layers, the lower one of which was viscous, and probably contained the hydrochloric salt of the diamino glycol. The upper layer comprised the toluene.

The mixture was treated with 10 grams of caustic soda in 100 milliliters of water. The oily layer dissolved. A lower aqueous layer and an upper toluene layer remained. The toluene layer was separated and the aqueous layer was washed with toluene and ether and was combined with the separated toluene layer. The toluene solution was washed and stripped by distillation. A waxy white solid remained in a yield of 17 grams. The product was of the formula:



This product reacts in approximately mole for mole ratio with dicarboxylic acids (or their anhydrides), such as phthalic acid or anhydride, or maleic acid or anhydride, when heated to esterification temperature to form alkyds which may be applied as coatings to wood or metal. Mixtures of the alkyd product of the foregoing glycol and maleic acid polyester with styrene may be incorporated with peroxidic catalysts, such as benzoyl peroxide, cumene hydroperoxide, or the like, in an amount of 0.1 to 5 percent by weight based upon the interpolymerizable mixture and cured by baking at temperatures of about 90° C. to 250° C. The interpolymerizable mixture may be catalyzed, poured into molds and cured to provide castings, or the catalyzed mixture may be employed for coating or impregnating fibrous materials, such as fabrics and mats of fibrous materials, such as glass, asbestos, wood, or the like. The resultant laminate may be heated and cured to a hard, durable state.

The durylene-di(aminoethanol) and related compounds are useful for other applications than in the preparation of synthetic resins. For example, it may be reacted with fatty acids, such as stearic acid, oleic acid, elaeostearic acid, linoleic acid, or the like, to form amides and/or esters which can be mixed with water and used as emulsifying agents for lanolin and many other materials. It is to be understood that alkylaromatic compounds other than meta xylene may be employed in the preparation of halomethyl alkylbenzenes. For example, mesitylene, which is 1,3,5-trimethylbenzene, is found to be highly reactive with aldehydes, such as formaldehyde, in the presence of hydrohalides such as hydrochloric acid. The resultant di(chloromethyl)mesitylene reacts with ethanolamine in accordance with the provisions of the present invention to form α^2,α^4-pentamethylphenylene-di(aminoethanol) which is a glycol of the following formula:



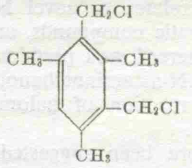
The preparation of di)chloromethyl)mesitylene for reaction with ethanolamine is illustrated by the following example:

Example III

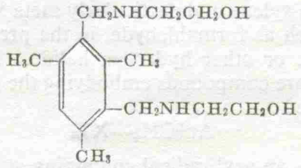
The reaction charge comprised:

1,3,5-trimethylbenzene (mesitylene)	grams	120
Formalin solution (2.33 moles)	do	200
Hydrogen chloride (concentrated)	milliliters	300
Zinc chloride	grams	40

The mixture was heated to 90° C. and anhydrous hydrogen chloride was introduced for 6 hours. The reaction mixture was cooled, washed with water, and was further purified by crystallization from heptane. The product was white and crystalline and of a melting point of 101° C.–103° C. The yield was 85 percent on a theoretical basis. The product was of the formula:



This compound is even more highly reactive than 4,6-di(chloromethyl)m-xylene. The compound can readily be reacted with ethanolamine in accordance with the method of Example II to form a glycol of the structure:



α^2,α^4-Pentamethylphenylene-di(aminoethanol)

The α^2,α^4-pentamethylphenylene-di(aminoethanol) can be reacted with dicarboxylic acids such as maleic acid, phthalic acid, adipic acid, sebacic acid, or mixture of alpha-beta ethylenic dicarboxylic acids, such as maleic acid, and non-ethylenic dicarboxylic acids, such as phthalic acid or the other acids above listed, to form polyesters in which the glycol functions as a polyhydric alcohol, replacing glycerol and propylene glycol, diethylene glycol, or other polyhydric alcohol in the preparation of the more common polyesters. Polyesters containing an alpha-beta ethylenic dicarboxylic acid component can be interpolymerized with monomers containing $>C=CH_2$ groups attached to negative radicals to form thermoset resin products. The interpolymerizable mixtures can be employed in casting or in laminating. In either instance, the interpolymerizable mixture preferably is incorporated with a free radical initiator, such as benzoyl peroxide, in appropriate amount (e. g., 0.1 percent to 5 percent by weight based upon the interpolymerizable mixture). The interpolymerizable mixtures, if they are to be stored for an appreciable period of time may be mixed with small amounts of gelation inhibitors such as hydroquinone, 3-isopropylcatechol, trimethylbenzyl ammonium chloride, or the like, as disclosed in U. S. Patents 2,593,787 or 2,676,947. Castings and laminates containing free radical initiators, such as 1 percent of benzoyl peroxide, may be cured at temperatures, for example in a range of about 90° C. to 250° C., to a hard, thermoset state.

In the preceding preparation of chloromethyl compounds, as illustrated in Examples I and III, the hydrohalide employed is hydrochloric acid. It is to be understood that the other hydrohalides, such as hydrogen bromide or hydrogen iodide, may be employed in place of hydrogen chloride. The examples also illustrate the use of formaldehyde which is from economic standpoints the most satisfactory member of the aldehyde family for use in the chloroalkylation of the aromatic rings. However, it is to be understood that the same glycols can includes within its scope the use of other aldehydes, such as acetaldehyde, butyraldehyde, and others, to provide halomethyl alkylaromatic compounds useful for reaction with alkamines, such as ethanolamine to form glycols. Also, the monohalomethyl and trihalomethyl compounds can be substituted for the dihalo compounds with good results.

Emphasis has been placed upon the use of the foregoing glycols as polyhydroxy alcohols for reaction with dicarboxylic acids in the preparation of polyesters. However, it is to be understood that the present invention be used for other purposes. For example, they may be treated with fatty acids as previously described. The glycol of Example II may be mixed with fatty acids, such as stearic acid, maleic acid, linoleic acid, or the like, to form fatty acid amides or esters of fatty acids which can be mixed with water to form emulsifying lipoids and other emollients.

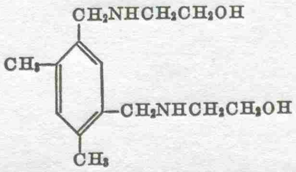
The embodiments of the invention as herein disclosed are to be considered as being illustrative of the spirit of the invention. Those skilled in the art will appreciate that numerous modifications may be made therein without departure from the scope of the invention as set forth in the appended claims.

I claim:

1. The method of preparing a compound of the formula:

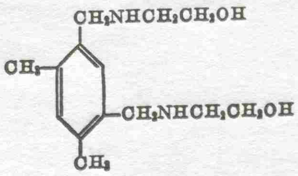
which comprises heating to reaction temperature a mixture of 4,6-di(chloromethyl)m-xylene and ethanolamine at a temperature to form the hydrochloride of said compound and then neutralizing the hydrochloride.

2. The method of preparing a compound of the formula:



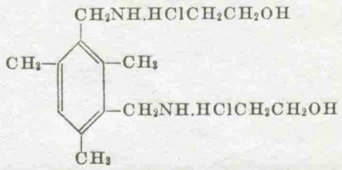
which comprises heating to reaction temperature a mixture of 4,6-di(chloromethyl)m-xylene and ethanolamine at a temperature to form the hydrochloride of said compound and then splitting off hydrogen chloride with an alkaline compound of an alkali metal.

3. The method of preparing a compound of the formula:



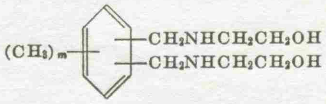
which comprises heating to reaction temperature a mixture of 4,6-di(chloromethyl)m-xylene and ethanolamine at a temperature to form the compound, the hydrochloride of said compound and then neutralizing the compound with sodium hydroxide.

4. A method of preparing α^2,α^4-pentamethylenephenylene di(aminoethanol) which comprises heating di(chloromethyl) mesitylene with ethanolamine to form a compound of the formula:



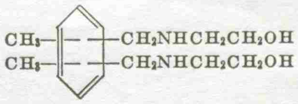
and alkalizing said compound with caustic.

5. A novel chemical compound of the formula:

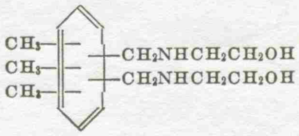


m being a whole number from 2 to 3.

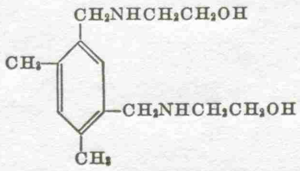
6. A novel chemical compound of the formula:



7. A novel chemical compound of the formula:



8. A novel chemical compound of the formula:



9. α^2,α^4-Pentamethylphenylene di(aminoethanol).

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Patented Aug. 13, 1957

2,802,882

PREPARATION OF NOVEL DIALKYLOL DERIVATIVES OF ALKENYLPHENOLS

Alfred R. Bader and Lowell O. Cummings, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

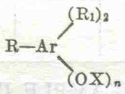
No Drawing. Application December 4, 1953, Serial No. 396,304

5 Claims. (Cl. 260—621)

This invention relates to a novel class of compounds, namely, the dialkylol alkenylphenols, and to a method for the preparation of such compounds, and pertains more particularly to novel dialkylol butenylphenols and to their preparation by the reaction of butenylphenols with aldehydes.

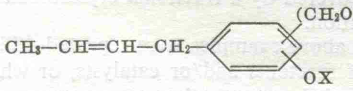
In a copending application (Serial No. 300,359, filed July 22, 1952, it is disclosed that cyclopentadiene will react with phenolic compounds in the presence of a Friedel-Crafts catalyst to give either mono-, di- or tricyclopentenylphenolic compounds, or mixtures thereof, depending upon the quantity of catalyst utilized and the reaction temperature. Also, in a series of copending applications, Serial Nos. 337,226, 337,227, 337,228 now abandoned, and 337,229, now abandoned, all filed February 16, 1953, it is disclosed that acyclic conjugated dienes react with phenolic compounds in the presence of various Friedel-Crafts type compounds to give monoalkenylphenolic compounds or mixtures of mono-, di- and trialkenylphenolic compounds, the nature of the reaction product depending upon the catalyst strength and the reaction temperature. The unsaturated phenolic compounds prepared according to the methods of the copending applications are very useful in the preparation of heat reactive resins which form excellent films, and are also useful for many other purposes.

It has now been discovered that alkenylphenolic compounds react with aldehydes in the presence of alkaline catalysts and at temperatures below about 130° C. to give a new class of chemical compounds, the dialkylolalkenylphenolic compounds and the salts thereof. These compounds possess the folowing general structure:



$$R{-}Ar\begin{matrix}(R_1)_2\\ \\(OX)_n\end{matrix}$$

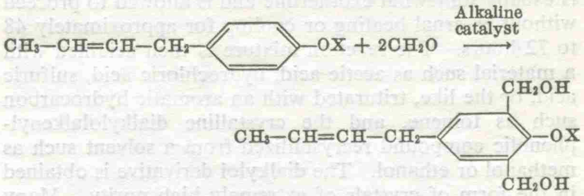
wherein R is alkenyl, cycloalkenyl, haloalkenyl or halocycloalkenyl, Ar is an aromatic radical, R_1 is an alkylol radical, preferably containing from 1 to 3 carbon atoms, *n* is a whole number, preferably 1, but which may be 2 or 3, and X is hydrogen or an inorganic salt forming group. The preferred compounds of the above general class are the dimethylolbutenylphenols and their salts of the structure:



wherein X is hydrogen or an inorganic salt forming group. Compounds of this structure are readily prepared from formaldehyde and butenylphenol, the latter compound being readily and economically obtained by the reaction of butadiene-1, 3 and phenol.

The novel phenols and salts of this invention are prepared by reacting an alkenylphenolic compound with an aldehyde in the presence of an alkaline catalyst. This reaction may be depicted structurally as follows, wherein

p-2-butenylphenol and formaldehyde are utilized for illustrative purposes:



In the equation, X has the significance given above.

In preparing the novel compounds of this invention, alkenylphenolic compounds of the general structure: R—Ar—$(OH)_n$ wherein R, Ar and *n* have the significance set forth above, are employed. It is obvious that there must be at least two unsubstituted carbon atoms in the aromatic nucleus in order that the alkylol groups may attach thereto during the reaction.

The preferred alkenylphenolic compounds of the structure R—Ar—$(OH)_n$ are those in which R is butenyl and Ar represents a benzene ring, including o- and p-2-butenylphenols. However, other alkenylphenolic compounds may also be used, including butenylcatechols, butenyl-2, 3-dimethoxyphenols, o- and p-cyclopentenylphenols, pentenylphenols, pentenylcresols, halopentenylphenols, hexenylphenols, halohexenylphenols, halohexenylphenols, halohexenylchlorophenols, and the like. All of the above alkenylphenolic compounds, as well as many other compounds possessing the structure set forth hereinabove, are readily prepared by reacting conjugated dienes with phenolic compounds in the presence of a Friedel-Crafts compound or other of the catalysts disclosed in the copending applications referred to hereinabove.

Mixtures of mono-, di- and trialkenylphenolic compounds can also be obtained by the reaction of conjugated dienes with phenolic compounds in the presence of Friedel-Crafts catalysts and such mixtures react with aldehydes to give dialkylolalkenylphenolic compounds or their salts.

Any aldehyde may be utilized in the preparation of the novel compounds of the present invention. However, aldehydes containing only atoms of carbon (from 1 to 3), hydrogen and oxygen, and particularly formaldehyde, are greatly preferred. In place of formaldehyde, a material which decomposes upon heating to yield formaldehyde, for example, paraformaldehyde or trioxymethylene, may be utilized in the reaction. Aqueous formalin, or a solution of formaldehyde in a lower alcohol such as n-butanol, may also be used very successfully.

In carrying out the reaction of alkenylphenols with formaldehyde an akaline catalyst is employed. Both inorganic and organic materials, including sodium hydroxide, ammonium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, hexamethylenetetramine, and the like may be used. Mixtures of two or more alkaline materials may be utilized.

The quantity of catalyst employed is generally about 5.0 percent to about 25.0 percent based upon the weight of the alkenylphenol utilized, although larger or smaller amounts may be employed if desired.

It will be noted from the foregoing reaction equation that two moles of the aldehyde for each mole of the alkenylphenolic compound are required stoichiometrically for the reaction to proceed. However, greater excesses of the aldehyde may be utilized, although no apparent advantage is obtained by the use of an excess, and in fact, for obvious reasons of economy, the reactants are preferably brought together in approximately the stoichiometric 2 to 1 ratio.

The reaction of alkenylphenolic compounds with formaldehyde to produce dialkylolalkenylphenolic compounds in accordance with this invention proceeds quite readily whenever the reactants and catalyst are brought into efficient contact with one another. In a preferred procedure, the alkenylphenol, an aqueous solution of the catalyst, and formaldehyde in the form of an aqueous solution are admixed at room temperature. The reaction is usually somewhat exothermic and is allowed to proceed without external heating or cooling for approximately 48 to 72 hours. The reaction mixture is then acidified with a material such as acetic acid, hydrochloric acid, sulfuric acid, or the like, triturated with an aromatic hydrocarbon such as toluene, and the crystalline dialkylolalkenylphenolic compound recrystallized from a solvent such as methanol or ethanol. The dialkylol derivative is obtained in the form of crystals of extremely high purity. Many modifications of the above procedure can be employed with good results.

The temperature at which the reaction is carried out should be maintained below about 130° C. If higher temperatures are utilized, condensation of the aldehyde with the alkenylphenolic compound is likely to take place to form resinous products rather than crystalline dialkylol derivatives. The alkaline condensation of aldehydes with alkenylphenolic compounds is described in copending application, Serial No. 390,089, filed November 3, 1953.

In order that highest yields of the dialkylol derivatives be obtained, it is preferred that the reactants and catalysts be brought together at about room temperature (25° C.). However, lower temperatures, for example as low as —20° C. may be employed, although longer periods of time will be required to obtain substantial yields of the desired product.

The following examples illustrate more fully the preparation of novel dialkylolalkenylphenolic compounds in accordance with the present invention. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

EXAMPLE I

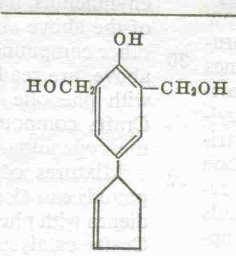
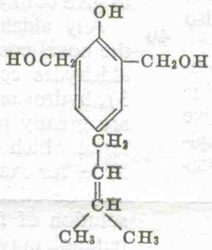
Fifteen grams of para-2-butenylphenol was dissolved in a solution of 1 gram of sodium hydroxide and 10 cc. of water. Twelve grams of a 37 percent formalin solution was then added to the butenylphenol-catalyst mixture, and the colorless syrup was allowed to stand at room temperature for approximately 48 hours. The reaction mixture was then triturated with 10 grams of 30 percent acetic acid and the oil which separated and crystallized on cooling was recrystallized from aqueous methanol to yield shiny, white platelets melting at 77° C. to 78° C. The product was identified as dimethylolbutenylphenol.

Analysis

Calculated		Found	
C	H	C	H
69. 20	7. 93	68. 84	7. 57

EXAMPLES II AND III

Cyclopentenylphenol and pentenylphenol were each reacted with formaldehyde in accordance with Example I utilizing in each reaction two moles of formaldehyde to one mole of the alkenylphenol and ¼ mole of sodium hydroxide. The structure of the compounds prepared, the solvent of crystallization, melting point and analysis of the compounds obtained are set forth in the following table:

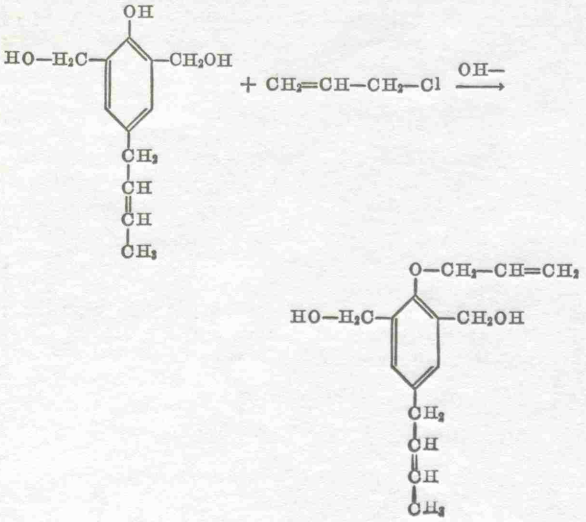
Example	Structure	Solvent of Crystallization	Melting Point, ° C.	Analysis			
				Calculated		Found	
				C	H	C	H
II----------		Toluene-ethanol------	106	70. 89	7. 32	71. 18	7. 56
III---------		Aqueous methanol----	110–111	70. 24	8. 16	70. 44	8. 27

EXAMPLE IV

One mole of a mixture of mono-, di- and tributenylphenols (obtained by the reaction of butadiene-1,3 with phenol in the presence of sulfuric acid), ¼ mole of sodium hydroxide and 2 moles of formaldehyde were admixed in aqueous solution and allowed to stand for about 48 hours at 25° C. At the end of this period a yellow oil had formed from which dialkylol monobutenylphenol could be recovered by a fractional crystallization process or by distillation.

When the above examples were repeated utilizing other quantities of reactants and/or catalysts, or when the reaction is carried out at other temperatures within the range of about —20° C. to 130° C. good results are obtained. Similarly, when other alkenylphenols selected from those disclosed hereinabove or other aldehydes are substituted for the alkenylphenols and formaldehyde of the above examples, dialkylolalkenylphenols are again obtained in good yield and in a pure crystalline form. Thus, for example, diethylolbutenylphenol is obtained by the alkaline catalyzed reaction of butenylphenol with acetaldehyde; dipropylolbutenylphenol is obtained by the alkaline catalyzed reaction of butenylphenol with propionaldehyde; and dimethylolbutenylresorcinol is obtained by the alkaline catalyzed reaction of butenylresorcinol with formaldehyde.

The novel dialkylolalkenylphenolic compounds obtained by the process of this invention are very useful for many purposes. For example, they may be spread on a metallic surface such as tin plate and baked to give excellent films. To illustrate, the dimethylolbutenylphenol obtained in accordance with Example I hereinabove was applied to tin plate and baked at 350° F. for 15 minutes, whereupon a clear, hard, light yellow film was obtained. In the form of such films, the dialkylolalkenylphenolic compounds may be useful as sanitary liners for food containers and the like. The dialkylolalkenylphenolic compounds may also be reacted with unsaturated chlorohydrocarbons such as allyl chloride to form unsaturated monomeric materials. This reaction is illustrated by the following equation.



The unsaturated monomers obtained are also heat reactive and cure readily to give useful films.

From the foregoing description it will be seen that the alkylolalkenylphenolic compounds and salts thereof constitute a very valuable class of compounds which has not been prepared heretofore. It is apparent, therefore, that various embodiments of the invention, in addition to those specifically disclosed, may be provided without departing from the spirit and scope of the invention as defined in the appended claims.

We claim:

1. A dimethylol cyclopentenylphenol.
2. A dimethylol-2-cyclopentenylphenol.
3. Dimethylol-p-2-cyclopentenylphenol.
4. The method which comprises reacting a cyclopentenylphenol with formaldehyde in the presence of an alkaline catalyst at a temperature below about 130° C., and acidifying the reaction mixture, thereby to obtain a dimethylol cyclopentenylphenol.
5. The method which comprises reacting p-2-cyclopentenylphenol with formaldehyde in the presence of an alkaline catalyst at a temperature below about 130° C., and acidifying the reaction mixture, thereby to obtain dimethylol-2-cyclopentenylphenol.

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United States Patent Office

2,809,182

Patented Oct. 8, 1957

2,809,182

USE OF HYDROXYTETRONIC ACID AS AN ACCELERATOR OF POLYMERIZATION

Gordon J. Mirr, Tomahawk, and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application October 21, 1954,
Serial No. 463,817

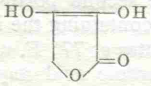
6 Claims. (Cl. 260—45.4)

This invention relates to a method for polymerizing mixtures of ethylenically unsaturated monomers containing a $CH_2=C<$ group and polyesters of polyhydric alcohols with alpha-beta ethylenically unsaturated dicarboxylic acids, and it pertains more particularly to the use of hydroxytetronic acid to accelerate the polymerization of such mixtures.

It is known that polyesters of glycols and alpha-beta ethylenically unsaturated dicarboxylic acids will polymerize with monomers containing $CH_2=C<$ such as styrene or vinyltoluene, when heated in the presence of a free radical initiator such as benzoyl peroxide or cumene hydroperoxide. The resulting products are thermosetting resins known in the art as "polyester resins," and have enjoyed outstanding commercial success because of their excellent hardness, chemical resistance and other desirable properties. Clear, hard, thermoset resins can be obtained even at atmospheric pressures, although the polymerization process does require the application of relatively high temperatures over a substantial period of time. These polyester resins have been used to prepare clear castings, laminates, and as reinforcing agents for fibrous materials, such as fabrics or mats of fibers of glass or other materials. The fibrous material may be impregnated with the polyester resin, or the resin may be applied as a surface coating, or a combination of methods may be employed.

Because the preparation of polyester resins ordinarily does require heating for substantial periods of time, much time and effort have been expended in attempts to obtain materials which will assist the action of the free radical catalyst in accelerating the polymerization reaction. A number of materials useful for this purpose have been found; however, many of these materials are not completely satisfactory in that they sometimes decompose at the polymerization temperature, cause undesirable color formation in the polyester resin, or have other harmful effects upon the resin.

It has now been discovered that hydroxytetronic acid,



is a powerful accelerator of the polymerization of mixtures of ethylenically unsaturated monomers and glycol-unsaturated alpha-beta dicarboxylic acid polyesters, even at relatively low temperatures, effectively bringing about gelation and even substantially complete cure at normal room temperatures. Apparently hydroxytetronic acid is effective as an activator of the free radical initiator, and probably assists in liberating and transmitting the free radicals, although the invention is not to be limited by this explanation.

A great many polymerizable polyester resin compositions to which hydroxytetronic acid may be added to accelerate the polymerization rate are readily available as commercial products. Monomer components containing a $CH_2=C<$ group, preferably in terminal position, which can be used in preparing polyester resins include styrene, divinylbenzene, vinyltoluene, methyl methacrylate, methyl acrylate, acrylonitrile, and the like.

Alpha-beta ethylenically unsaturated dicarboxylic acids suitable for use in the preparation of polyesters, which in turn may be utilized in the practice of the present invention, include maleic acid, fumaric acid, aconitic acid, mesaconic acid, citraconic acid, ethylmaleic acid, pyrocinchoninic acid, xeronic acid, itaconic acid, and the like. The alpha-beta ethylenically unsaturated dicarboxylic acids are also often mixed with substantial quantities of non-ethylenic dicarboxylic acids, such as phthalic acid, terephthalic acid, tetrachlorophthalic acid, succinic acid, adipic acid, suberic acid, azelaic acid, sebacic acid, dimethylsuccinic acid, chlorinated derivatives of the above acids, and the like. Where a non-ethylenic dicarboxylic acid is utilized, the proportion thereof may be varied widely; however, ordinarily the amount employed will vary within the range of about 0.25 to 10 or 12 moles of the saturated acid for each mole of the alpha-beta ethylenically unsaturated dicarboxylic acid component.

Glycols which can be utilized in the preparation of polyesters include ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol, dipropylene glycol, 1,2-propylene glycol, 1,3-propane diol, butylene glycol and the like. These glycols may be reacted with any of the foregoing alpha-beta ethylenically unsaturated dicarboxylic acids or mixtures of the same with saturated dicarboxylic acids, the glycol being present in substantially stoichiometric amounts or in a slight excess, for example, 5 percent to 10 percent, to give useful polyesters. The esterification reaction involves heating the glycol component and the dicarboxylic acid components together at a temperature sufficient to evolve water. The reaction is continued until water ceases to evolve and an acid number below about 50 or 60 is attained. In no event should the heating be continued until insoluble products are obtained.

The ethylenically unsaturated monomer component of the polymerizable mixture will ordinarily be employed in a proportion of about 10 percent to 60 percent by weight of the total composition, and mixtures containing about 20 to 40 or 50 percent by weight of monomer are preferred.

The unsaturated polyester and the monomeric component are preferably mixed while the polyester component is hot, for example, at a temperature of about 100° C. to 150° C. The polymerizable mixture of the polyester and the monomer tends to gel rapidly at elevated temperatures. In order to avoid premature gelation during the formation and subsequent storage of the mixtures, it is customary to add a gelation inhibitor. Quaternary ammonium compounds, such as trimethylbenzylammonium chloride, triethylbenzylammonium chloride, or other quaternary ammonium salts such as those disclosed in U. S. Patent 2,593,787 are excellent gelation inhibitors in the uncatalyzed mixtures above described. Ordinarily, the gelation inhibitor is employed in an amount of about 0.001 percent to about 5.0 percent, based upon the weight of the interpolymerizable mixture. Preferably, the addition of the gelation inhibitor is made to one of the components of the polymerizable mixture before the mixture is formed. For example, the quaternary ammonium salts may be added to the hot polyester, the latter being maintained at a temperature of about 100° C. to 150° C. Other useful gelation inhibitors include tertiary butylcatechol, 3-sec. butylcatechol, 3-isopropylcatechol, oxalic acid, and quinone or hydroquinone. Mixtures of phenolic inhibitors such as the catechols or hydroquinone with quaternary ammonium salts may also be used. In the absence of catalysts, or accelerators, mixtures of polyesters containing a gelation inhibitor are stable for long periods of time. When the mixtures are to be used for casting, laminating, or other purposes, catalysts and/or accelerators are added in accordance with the present invention.

While hydroxytetronic acid can be used without added free radical catalysts and over a period of time will effect an adequate cure of the polymerizable polyester resin without a catalyst, it is often desirable to employ one of the conventional free radical initiator type catalysts. Suitable catalysts include acetyl benzoyl peroxide, methyl ethyl ketone peroxide, cyclohexanone peroxide, cyclohexyl hydroperoxide, 2,4-dichlorobenzoyl peroxide, cumene hydroperoxide, t-butyl hydroperoxide, methyl amyl ketone peroxide, acetyl peroxide, lauroyl peroxide, benzoyl peroxide, methyl cyclohexyl hydroperoxide, p-chlorobenzoyl peroxide, di-t-butyl peroxide, peracetic acid, t-butyl permaleic acid, di-t-butyl diperphthalate, t-butyl perphthalic acid, t-butyl peracetate, and p-methoxyphenyl diazo-thio-(2-naphthyl)ether.

The amount of free radical catalyst utilized may be varied widely; in general, however, it is preferred to use from about 0.1 percent to 5.0 percent by weight, based upon the total weight of the polymerizable mixture.

Hydroxytetronic acid is effective as a promoter of gelation and curing of the interpolymerizable mixtures over a relatively broad range of proportions. For example, amounts as small as 0.01 percent to as high as 1.0 percent or more by weight of the interpolymerizable mixture can be used with good results. The hydroxytetronic acid may be added approximately concurrently with or subsequent to the addition of the free radical initiator, which is ordinarily added shortly before the time of cure of the polyester resin.

As indicated hereinabove, hydroxytetronic acid is a solid at ordinary conditions of temperature and pressure. Hence, in order to facilitate its incorporation into an interpolymerizable mixture of a polyester of an alpha-beta ethylenically unsaturated dicarboxylic acid and a glycol, with a monomer, such as styrene, it is often desirable to dissolve the hydroxytetronic acid in a solvent, such as diethylene glycol or the like. Other solvents which are substantially non-reactive with respect to the interpolymerizable mixture may also be employed.

The preparation of polymerizable polyester resins, and the use of hydroxytetronic acid in accelerating the polymerization of such resins, are illustrated in the following examples. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

Example I

A polymerizable polyester resin was prepared from components consisting of 0.5 mole of diethylene glycol, 1.0 mole of phthalic anhydride, 3.0 moles of maleic anhydride, and 3.9 moles of propylene glycol. The resulting polyester was mixed with styrene in amounts such that the mixture contained 2 parts of polyester and 1 part of styrene. The mixture was stabilized against premature gelation by incorporating therein 0.02 part of hydroquinone per 100 parts of polyester, the hydroquinone being added to the hot polyester component. This mixture in the absence of catalysts or accelerators was stable and could be stored for long periods of time at room temperature without any substantial tendency to gel.

The polymerizable mixture was then catalyzed with 2 percent by weight of benzoyl peroxide (based on the weight of the polymerizable component and 1 percent by weight of a 33 percent solution hydroxytetronic acid in diethylene glycol was added an accelerator of polymerization. The "gel time" at 77° F. was then determined as follows: A sample of the resin was placed in a tube 125 mm. long and 16 mm. diameter, with a thermometer in the center of the tube. The "gel time" is the time in seconds when both the tube and the sample can be lifted by means of the thermometer. The composition containing both benzoyl peroxide and hydroxytetronic acid gelled in only 5 minutes, while the sample containing no hydroxytetronic acid required more than 60 hours to gel. The resin containing the hydroxytetronic acid cures to give a hard, clear material.

Examples II and III

Two polyesters were prepared, utilizing diethylene glycol, phthalic anhydride, maleic anhydride, propylene glycol and styrene in the proportions recited in Example I. To one polyester was added 0.0022 percent of tertiary butyl-catechol and to the other was added 0.0015 percent of quinhydrone. Both compositions thus prepared were stable for long periods of time when stored at room temperatures.

A portion of each composition was catalyzed with 2.0 percent by weight of benzoyl peroxide. The catalyzed mixtures were then divided into two parts and to one part was added 1.0 percent by weight of a 33 percent solution of hydroxytetronic acid in diethylene glycol. The other part was utilized as a control sample. The catalyzed mixtures were then heated to 77° F. and the gel times determined according to the method described in Example I. The polyester containing tertiary butylcatechol and hydroxytetronic acid had a gel time of 2 minutes, while the control sample containing tertiary butylcatechol required more than 60 hours to gel. The polyester containing quinhydrone and hydroxytetronic acid also gelled in only 2 minutes, while the control sample required more than 60 hours to gel.

The compositions containing the hydroxytetronic acid cure readily to give castings and laminates which have many valuable properties. It is apparent, therefor, that the hydroxytetronic acid functions as an excellent accelerator without affecting the desirable properties of the cured polyester resin.

Example IV

A polyester was prepared from the following components in the amounts set forth below:

Component:	Parts by weight
Propylene glycol	2713
Maleic anhydride	1575
Phthalic anhydride	2378
Styrene	2190
Trimethylbenzylammonium chloride	15.4
Quinone	0.5

The composition thus obtained was relatively stable and could be stored for several months without harmful results. A portion of this composition was catalyzed with 1.0 percent by weight of benzoyl peroxide and the catalyzed mixture was divided into two portions; to the first portion was added 1.0 percent by weight of hydroxytetronic acid, and the second portion was utilized as a control. The sample containing the hydroxytetronic acid gelled in only 17 minutes at 77° F. while the sample containing no hydroxytetronic acid required more than 35 hours to form a gel at 77° F.

Example V

A polymerizable polyester useful as an impregnant for glass fibres and other fibrous materials was prepared from the following components in the amounts set forth:

Component:	Parts by weight
Propylene glycol	2764
Phthalic anhydride	2617
Maleic anhydride	1420
Styrene	2263
3-isopropylcatechol	0.89

The polyester thus prepared was tested to determine its gel time in the same manner as the polyester in Example IV. The sample containing hydroxytetronic acid formed a gel in only 25 minutes at 77° F. while the control sample required more than 140 hours to form a gel at the same temperature.

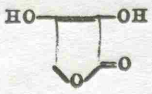
The polyester resin composition containing the hydroxytetronic acid polymerizes readily to give useful castings, laminates and the like. This particular polyester resin composition is especially useful in combination with glass fibers to produce fishing rods and similar articles.

The foregoing examples demonstrate that hydroxytetronic acid accelerates the polymerization of polyester resin compositions regardless of the composition of the polyester and the gelation inhibitor which is incorporated in the resin during preparation to inhibit polymerization during periods of shipment and storage. Hydroxytetronic acid also functions as an accelerator regardless of the free radical initiator which is employed. Thus, such other peroxygen compounds as cumene hydroperoxide, or methyl ethyl ketone peroxide, can be substituted for benzoyl peroxide in the above examples with good results.

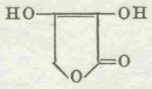
From the foregoing description of the invention, it is apparent that hydroxytetronic acid is an excellent accelerator of polymerization for use in polyester resin compositions and that polyester resin compositions containing hydroxytetronic acid form a new class of useful materials. It is not intended to limit the invention to the specific examples, but to include all of the variations and modifications falling within the spirit and scope of the appended claims.

We claim:

1. A method of accelerating the polymerization of a mixture of an ethylenically unsaturated monomeric compound and a polyester of an alpha-beta ethylenically unsaturated dicarboxylic acid and a polyhydric alcohol, which comprises adding to said mixture hydroxytetronic acid of the structural formula



2. A method of accelerating the polymerization of a mixture of a monomer containing a single $CH_2=C<$ group and a polyester of a dihydric alcohol and an alpha-beta ethylenically unsaturated dicarboxylic acid, which comprises adding to said mixture a small catalytic amount of hydroxytetronic acid of the structural formula

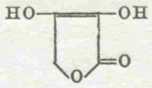


3. The method of claim 2 wherein the monomer containing a single $CH_2=C<$ group is styrene.

4. The method of claim 3 wherein the polyester is a polyester of diethylene glycol, phthalic anhydride, maleic anhydride, and propylene glycol.

5. The method of claim 4 wherein the hydroxytetronic acid is present in an amount of about 0.01 percent to about 1.0 percent by weight based upon the total weight of the mixture.

6. A method of accelerating the polymerization of a composition comprising an ethylenically unsaturated monomeric compound and a polyester of a polyhydric alcohol and a mixture of an alpha, beta-ethylenically unsaturated dicarboxylic acid and a saturated dicarboxylic acid, which comprises adding to said composition hydroxytetronic acid of the structure



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United States Patent Office

2,809,183

Patented Oct. 8, 1957

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2,809,183

METHOD OF INTERPOLYMERIZING ETHYLENE MONOMERS WITH POLYESTERS CONTAINING ETHYLENE GROUPS USING DIHYDROXY MALEIC ACID AND ESTERS THEREOF AS ACCELERATORS

Alfred R. Bader, Milwaukee, and Gordon J. Mirr, Tomahawk, Wis., assignors to Pittsburgh Plate Glass Company, Allegheny County, Pa.

No Drawing. Application October 21, 1954, Serial No. 463,816

9 Claims. (Cl. 260—45.4)

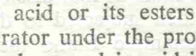
This invention relates to accelerators of interpolymerization of mixtures of monomers containing $>C{=}CH_2$ groups and polyesters of polyhydric alcohols and alpha-beta ethylenic dicarboxylic acids and it has particular relation to the use as accelerators of interpolymerization in the foregoing mixtures, of dihydroxy alpha-beta ethylenic dicarboxylic acids.

It has heretofore been suggested to interpolymerize mixtures of monomers, such as styrene, containing $>C{=}CH_2$ groups and polyesters of glycols and alpha-beta ethylenic dicarboxylic acids, such as maleic acid or fumaric acid, by heating the mixture in the presence of a free radical initiator, e. g., a peroxidic material such as benzoyl peroxide. The products are thermoset resins of good hardness and other desirable properties. One advantage of such process resides in the fact that clear, hard, thermoset resins can be so obtained even at atmospheric pressures. However, the operation does require the application of rather elevated temperatures usually over a substantial period of time. Interpolymerizable mixtures of the foregoing type have been successfully employed in the preparation of clear, thermoset castings and in the preparation of laminates and other bodies comprising reinforcements of fibrous materials, such as fabrics or mats of fibers of glass or other materials. The fibrous material may be impregnated with the interpolymerizable mixture or the mixture may be applied as a surface coating, or both methods of application may be employed. The mixture may then be cured to hard, thermoset state.

Small amounts of saturated carboxylic acids containing hydroxyls but being non-ethylenic and being represented by malic acid, tartaric acid, and citric acid have also been incorporated into the foregoing mixtures for purposes of retarding or preventing the attack of the mixture of the resultant resin on copper or alloys thereof.

This invention is based upon the surprising discovery that dihydroxy alpha-beta ethylenic dicarboxylic acids and esters thereof are powerful accelerators of polymerization in the foregoing mixtures, even at relatively low temperatures and are adapted to bring about gelation and even substantially complete cure without substantial added heat. Presumably the etheylenic group has an important effect on the behavior of acid or its esters. Apparently it is especially effective as an activator of free radical catalysts and probably assists in transmitting free radicals. The invention however, is not dependent upon the soundness of this, or other explanation.

Dihydroxymaleic acid or its esters is presently preferred as the accelerator under the provision of the present invention. Dihydroxymaleic acid is understood actually to be dihydroxyfumaric acid of the probable formula:



$$\begin{array}{c} HOOC-C-OH \\ \| \\ HO-C-COOH \end{array}$$

(See J. A. C. S., 75, 1953, page 6244.) However, conventional terminology has been retained in referring to the compound in this specification. It is readily and economically prepared in good yield by the oxidation of tartaric acid with hydrogen peroxide. Esters thereof preferably are of monohydric alcohols, which alcohols may contain from 1 to 6 carbon atoms.

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The art of manufacturing resins comprising monomers containing the $>C{=}CH_2$ group and polyesters of dihydric alcohols and alpha-beta ethylenic dicarboxylic acids has been extensively developed and many commercial examples of such materials are now available upon the market. It will be recognized that substantially any of the commercial, or non-commercial, interpolymerizable mixtures of the foregoing type may be treated with dihydroxy alpha-beta ethylenic dicarboxylic acids and esters thereof in the practice of the present invention.

Monomer components containing the $>C{=}CH_2$ group and being adapted for use in the mixtures are represented by such compounds as styrene, divinylbenzene, vinyltoluene, saturated esters such as methyl methacrylate, methyl acrylate, acrylonitrile, and others too numerous to enumerate. Many examples of such monomers are listed in the prior patents, such as Parker, U. S. Patent 2,593,787 and the patents mentioned therein.

Alpha-beta ethylenic dicarboxylic acids suitable for use in the formation of polyesters which may be employed in the practice of the invention include: maleic acid, fumaric acid, aconitic acid, mesaconic acid, citraconic acid, ethylmaleic acid, pyrocinchoninic acid, xeronic acid, itaconic acid and many others. The alpha-beta ethylenic dicarboxylic acids are also often mixed with substantial proportions of non-ethylenic dicarboxylic acids, such as phthalic acid, terephthalic acid, tetrachlorophthalic acid, succinic acid, adipic acid, suberic acid, azelaic acid, sebacic acid, dimethylsuccinic acid, and the various chlorinated derivatives of the above acids where all of the carbon to carbon bonds are single or are benzenoid double bonds in a single ring. Where non-ethylenic dicarboxylic acid is employed, the proportions thereof may vary within a range of about 0.25 to 10 or 12 moles with respect to the alpha-beta ethylenic dicarboxylic acid component.

Glycols suitable for use in the preparation of polyesters and which can be employed in the practice of the invention, comprise ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol, dipropylene glycol, 1,2-propylene glycol, 1,3-propanediol, butylene glycol. Any of these glycols in substantially stoichiometric amounts or in slight excess, e. g., 5 percent or 10 percent excess, may be reacted with any of the foregoing alpha-beta ethylenic dicarboxylic acids or mixtures of the same with the non-ethylenic dicarboxylic acids, to provide useful polyesters. The esterification reaction in the preparation of the polyesters comprises cooking the glycol component and the dicarboxylic acid component or components together at a temperature sufficient to evolve water. The reaction is continued until all water ceases to evolve and a satisfactory acid number, e. g., one below about 50 or 60, is attained. In no event is the action continued until insoluble products are obtained.

The vinylic monomer component of the interpolymerizable mixture usually will be employed in a proportion of about 10 to 60 percent by weight upon the basis of the total composition and mixtures containing 20 to 40 or 50 percent by weight of monomer are usually preferred.

The polyester and the monomer components preferably are mixed while the polyester component is hot, e. g., at a temperature of about 100° C. to 150° C. Usually at elevated temperatures, such as are employed in mixing the polyester and monomer, the mixture may tend to gel rapidly. In order to avoid premature gelation during the formation and subsequent storage of the mixtures, it is customary to add a gelation inhibitor, of which, a large number are recognized. Quaternary ammonium compounds, such as trimethyl benzyl ammonium chloride, or triethyl benzyl ammonium chloride, or the other quaternary ammonium salts disclosed in the foregoing Parker patent are successful as gelation inhibitors in the uncatalyzed mixtures above described. An appropriate amount,

e. g., 0.001 to about 5.0 percent, of such gelation inhibitor may be incorporated into the interpolymerizable mixture. Preferably the addition is to one of the components before the two are mixed. For example, the quarternary ammonium salts may successfully be added to the hot polyester, the latter being at a temperature of about 100° C. or 150° C. Other gelation inhibitors which may be used comprise tertiary butyl catechol, 3-isopropyl catechol and quinone or hydroquinone. Mixtures of phenolic inhibitors, such as the catechols or hydroquinone, and the quaternary ammonium salts as disclosed in the foregoing Parker Patent 2,593,787 may also be employed. Phenolic inhibitors may be cooked into the polyester, if desired. In the absence of catalysts, or accelerators, the mixtures are stable for long periods of time. When the mixtures are to be used, catalysts and/or accelerators are added in accordance with the present invention.

While dihydroxymaleic acid or its esters, as employed in the present invention, are susceptible of use without added peroxidic catalysts and in course of time will effect an adequate cure of the interpolymerizable mixtures without them, it is usually desirable to employ one of the conventional free radical initiator type catalysts, such as benzoyl peroxide, cumene hydroperoxide, tertiary butyl hydroperoxide, or the peroxide of methyl ethyl ketone in combination therewith. The combination, over all, is much more effective than either taken singly.

Dihydroxymaleic acid and its esters are effective as a promoter of gelation and curing of the interpolymerizable mixtures in a relatively broad range of proportions. For example, a range of about 0.01 to 1 or 2 percent by weight based upon the interpolymerizable mixture is suggested. Where a free radical initiator is employed, the amount thereof naturally will vary, dependent upon the activity of the catalytic agent, the temperature employed in the interpolymerization and other factors. In event that benzoyl peroxide is employed as the free radical initiator or catalyst, a proportion of about 0.1 to 5 percent by weight based upon the interpolymerizable mixture is suggested as being effective. The free radical initiator preferably is added shortly prior to the time of cure of the mixture. The dihydroxymaleic acid or ester may be added approximately concurrently with or subsequent to the free radical initiator.

It will be appreciated that dihydroxymaleic acid is a solid material and for purposes of promoting ease of incorporation into an interpolymerizable mixture of a polyester of an alpha-beta ethylenic dicarboxylic acid with a monomer, such as styrene, it is often desirable to dissolve the same in an appropriate solvent, such as an ether, e. g., monoethyl ether of ethylene glycol. Naturally other solvents which are non-reactive with respect to the interpolymerizable mixture may be employed. Application of the principles of the invention is illustrated by the following examples:

Example I

In accordance with this example, a polyester component which comprises equal moles of maleic acid and phthalic acid esterified with propylene glycol was employed. The polyester in a ratio of 2 parts by weight was mixed with 1 part by weight of styrene. The mixture was stabilized against premature gelation by means of 0.0025 part by weight based upon the polyester components of hydroquinone, which in this instance was cooked into the polyester component. The foregoing mixture, in the absence of catalysts or accelerators, was relatively stable and could be stored for long periods of time at room temperature without any substantial tendency to gel or set up.

In order to prepare an interpolymerizable mixture suitable for use in forming castings or in forming laminates, for example by coating or impregnating fabrics and mats of glass fibers, the foregoing interpolymerizable mixture was catalyzed with a free radical initiator, namely benzoyl

peroxide in an amount of 1 percent by weight. One sample was set aside as a control. A series of three sets of additional samples of the benzoyl peroxide catalyzed material was prepared and dihydroxymaleic as a 1 percent solution in the monoethyl ether of ethylene glycol was added in predetermined amount to each sample.

Tests were conducted upon the samples of interpolymerizable mixture which involved determination of the so-called "tank life." That is, the length of time in hours required for the catalyzed samples to gel.

Also, so-called L. P. E. tests were conducted. The latter tests involved filling 16 millimeter test tubes to a depth of about 3 inches with the material to be tested, inserting a thermocouple in the sample of material in the tube, inserting the tube in a bath at a temperature of 180° F. and determining the time in minutes required for the interpolymerizable mixture to attain maximum temperature due to exothermal rise. The time in minutes required is the so-called L. P. E. value.

The data for these several tests are tabulated as follows:

Dihydroxymaleic, Percent on Mixture	L. P. E. In Mins.	Peak Temp., ° F.	Tank Life in Hours at—	
			100° F.	77° F.
0 (Control)	6.2	340	340	401
0.03	4.0	365	1	1.5
0.06	3.7	325	0.5	0.75
0.09	3.4	345	0.5	0.75

It will be apparent that the interpolymerizable mixtures containing dihydroxymaleic acid have a shorter L. P. E. value and therefore, cure more rapidly than corresponding mixtures containing benzoyl peroxide without dihydroxymaleic acid. The storage life of the mixtures containing dihydroxymaleic acid is also much shorter than that of the corresponding mixtures which are free of dihydroxymaleic acid.

These mixtures can be employed in forming castings and laminates where a very short curing cycle is desirable. One convenient field for such application would involve use as a repair agent for laminates such as are employed in the manufacture of boats, the hulls of which are formed of interpolymer of an alpha-beta ethylenic dicarboxylic acid polyester and an alpha-beta ethylenic monomer which mixture is reinforced with fibrous material, such as glass fibers. Small amounts of the interpolymerizable mixture can be applied as mending material to ruptures in the original structure and quickly cured, with or without application of heat. The interpolymerizable mixtures might also be employed as media for the embedment of perishable objects, such as biological specimens which cannot long withstand elevated temperatures such as are commonly employed in the curing of casting resins. Many other fields of use are available.

Example II

In accordance with this example, ethyl dihydroxymaleate was employed as accelerator along with 1 percent by weight based upon the interpolymerization of benzoyl peroxide as a free radical initiator. The interpolymerizable mixture was the same as that disclosed in Example I. The mixtures were then subjected to the same series of tests employed in Example I and the results were as follows:

Ethyl Dihydroxymaleate, Percent on Mixture	L. P. E. In Mins.	Peak Temp., ° F.	Tank Life in Hours at—	
			100° F.	77° F.
0.015	2.8	340	1	17
0.03	2.2	390	----------	0.5
0.06	2.0	395	----------	0.5

The mixtures containing benzoyl peroxide and dihydroxymaleate as a pair could be cast and cured at temperatures in a range of 70° F. to 250° F. to provide hard, durable bodies of desired form. Fibrous sheets and bats could be coated or impregnated with the material and cured to provide reinforced bodies such as airplane or vehicle panels and many other bodies.

Example III

In this example, the same interpolymerizable components were employed as in Example I; but the benzoyl peroxide as the free radical initiator was replaced by 1 percent by weight of the peroxide of methyl ethyl ketone in solution in 60 percent by weight based upon the mixture of dimethylphthalate. The same tests were conducted upon interpolymerizable mixtures of this material containing dihydroxymaleic acid as were conducted in Example I. The results of the several tests are as follows:

Dihydroxymaleic, Percent on Mixture	L. P. E. In Mins.	Peak Temp., ° F.	Tank Life in Hours at—	
			100° F.	77° F.
0.015	6.67	300	1	2
0.03	6.0	295	------	0.3
0.06	6.5	290	0.75	------

The material was a useful casting and laminating material and could be cured in the temperature ranges of 70° F. to 250° F.

Example IV

In this example the interpolymerizable mixture was the same as that of Example III except that the dihydroxymaleic acid was replaced by ethyl dihydroxymaleate. The results of the several tests are tabulated as follows:

Dihydroxymaleate, Percent on Mixture	L. P. E. In Mins.	Peak Temp., ° F.	Tank Life in Hours at 100° F.
0 (Control)	6.2	381	2
0.03	4.7	300	0.75
0.06	4.3	285	0.75

The mixtures containing the peroxide of methyl ethyl ketone as a free radical initiator and ethyl dihydroxymaleate as an accelerator, could be formed and cured into useful bodies of wide variety.

Example V

The interpolymerizable mixture of this example was similar to that of Example I, except that benzoyl peroxide was replaced by 1 percent by weight based upon the interpolymerizable mixture of cumene hydroperoxide. Instead of determining L. P. E. value, the gel time which is the time in seconds required for the catalyzed mixture at 180° F. to gel to such degree that a sample in a tube can be lifted by a thermometer inserted in the mixture was determined. The data of this series of tests are tabulated as follows:

Percent Dihydroxymaleic	Gel Time In Seconds	Tank Life in Hours at—	
		100° F.	77° F.
0.03	194	0.5	1
0.06	133	0.5	1

The mixture was useful for casting and laminating and could be cured at temperatures in the range of about 70° F. to 250° F.

Example VI

The interpolymerizable mixture of this example was the same as that of Example V, except that dihydroxymaleic acid was replaced by ethyl dihydroxymaleate. The series of tests conducted upon this material corresponded to those of Example V. The data of the tests are tabulated as follows:

Percent Dihydroxymaleate	Gel Time in Seconds	Tank Life in Hours at 100° F.
0.15	184	0.75
0.03	126	0.5
0.06	76	0.3

The mixture was susceptible of use in forming valuable castings and laminates. The curing range was about 70° F. to 250° F.

Example VII

This example is similar to Example V, except tertiary butyl hydroperoxide in an amount of 1 percent by weight based upon the mixture was employed as the catalyst. The series of tests was similar to that conducted upon the material in Example V and the results thereof are tabulated as follows:

Percent Dihydroxymaleic	Gel Time In Seconds	Tank Life in Hours at 100° F.
0.03	175	0.25
0.06	85	0.12

The mixtures were useful in forming casting and laminations of many types.

Example VIII

The polyester-monomer mixture of this example comprised a polyester of propylene glycol and equal moles of phthalic acid and maleic acid. The polyester in an amount of 2 parts by weight was mixed while hot, with 1 part by weight of styrene, the mixture being stabilized with 0.1 percent by weight based upon the mixture of trimethyl benzyl ammonium chloride and 0.001 percent by weight based upon the mixture of quinone.

To this mixture was added 2 percent by weight of catalyst, namely benzoyl peroxide and 0.01 percent by weight based upon the mixture of dihydroxymaleic acid. The gel time was 6 mintues at 77° F. A 50 gram mass of the mixture cured to a hard solid resinous casting without extraneous heat.

A similar sample in which dihydroxymaleic acid was replaced by ascorbic acid had a gel time of 13 minutes.

Example IX

The polyester and monomer mixture of this example was the same as in Example VIII except that quinone was replaced by 0.0025 percent based upon the polyester components of hydroquinone. The latter was actually cooked into the batch.

The polyester-monomer mixture was catalyzed with 4 percent by weight of benzoyl peroxide and 0.02 percent by weight of dihydroxymaleic acid. The gel time at 77° F. was 32 minutes. The mixture polymerized to form a hard, durable casting.

Example X

The polyester in this example comprised 1 mole of maleic acid, 1.5 moles of phthalic acid and 2.8 moles of propylene glycol. The polyester was mixed with styrene to provide a mixture:

	Percent by weight
Polyester	62
Styrene	38

The mixture was stabilized with 0.025 percent by weight based upon the polyester of tertiary butyl catechol. This mixture was catalyzed with 0.025 percent by weight based upon the mixture of cobalt naphthenate, 4 percent by weight based upon the mixture of benzoyl peroxide and 0.02 percent upon a like basis of dihydroxymaleic acid. The mixture had a gel time at 77° F. of 36 minutes and a 50 gram sample cured without heating to a hard resinous casting.

Example XI

The polyester of this example comprised 8 moles of diethylene glycol, 3 moles of propylene glycol, 7.5 moles of maleic acid and 2.5 moles of phthalic acid. (The term acid includes the anhydrides.) The mixture was stabilized for storage with 0.0018 percent based upon the polyester components of hydroquinone. The mixture was catalyzed with 2 percent based upon the mixture of benzoyl peroxide and 0.02 percent by weight by dihydroxymaleic acid. The mixture had a gel time of 30 minutes at 77° F. and cured without extraneous heat to form a solid casting of 50 grams weight.

From the foregoing tests, it is apparent that dihydroxymaleic acid and its esters powerfully activate or accelerate the action of free radical initiators in the curing of interpolymerizable mixtures of monomers containing $>C=CH_2$ groups and polyesters of alpha-beta ethylenic dicarboxylic acids.

The interpolymerizable mixtures containing dihydroxymaleic acid or its ethyl ester as disclosed in the several examples, I through XI, each is a valuable interpolymerizable mixture which when heated to a temperature within a range extending from about room temperature up to about 260° C. will very rapidly cure to a hard, thermoset state. The mixtures can be employed as casting resins for forming objects of art or embedments of various materials, such as biological specimens, keepsakes, and the like. They may also be applied to mats and fabrics of glass fibers or other fibrous materials and cured quickly to a hard, thermoset state.

In the Examples I through XI, the polyesters of propylene glycol, mixed fumaric acid and phthalic acid (equal moles of each acid) may be used. The proportions of the phthalic acid may be increased or decreased in a wide range from 0.25 to 10 moles per mole of alpha-beta ethylenic dicarboxylic acid. Also, the polyesters may be of diethylene glycol and being represented by diethylene maleate-phthalate, or diethylene fumarate phthalate. Phthalic acid can be replaced by adipic or sebacic acids or other non-ethylenic dicarboxylic acids.

In the examples, styrene as the monomer can be replaced by vinyltoluene, acrylonitrile and other monomers containing a $>C=CH_2$ group attached to a negative radical.

The forms of the invention as herein disclosed are by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

We claim:

1. A method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group and a polyester of a dihydric alcohol and an alpha-beta ethylenic dicarboxylic acid, which comprises adding to said mixture a material of a class consisting of dihydroxymaleic acid and an ester thereof with a saturated monohydric aliphatic alcohol containing 1 to 6 carbon atoms in an amount to effect interpolymerization of said mixture and heating the mixture.

2. A method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group and a polyester of a dihydric alcohol and an alpha-beta ethylenic dicarboxylic acid, which comprises heating a mixture of the same in the presence of dihydroxymaleic acid.

3. A method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group and a polyester of a dihydric alcohol and an alpha-beta ethylenic dicarboxylic acid, which comprises heating said mixture in the presence of an ester of dihydroxymaleic acid and a saturated monohydric aliphatic alcohol containing from 1 to 6 carbon atoms, the ester being present in an amount to catalyze the interpolymerization reaction.

4. A method as defined in claim 3 in which the ester of dihydroxymaleic acid is the ethyl ester.

5. A method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group, a polyester of a dihydric alcohol and a mixture of two dicarboxylic acids, one of which is alpha-beta ethylenic and the other of which is a saturated acid, which comprises heating the mixture in the presence of a material of a class consisting of dihydroxymaleic acid and an ester thereof with a saturated monohydric aliphatic alcohol containing 1 to 6 carbon atoms and in an amount to effect interpolymerization of said mixture.

6. A method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group and a polyester of a dihydric alcohol and a mixture of dicarboxylic acids, one of which is alpha-beta ethylenic and another of which is phthalic acid, which comprises heating said mixture in the presence of a free radical initiator of polymerization and a material of a class consisting of dihydroxymaleic acid and an ester of the same with a saturated monohydric aliphatic alcohol containing 1 to 6 carbon atoms and in an amount to effect interpolymerization thereof.

7. A method as defined in claim 6 in which the free radical initiator of polymerization is peroxidic.

8. In a method of interpolymerizing a mixture of a monomer containing a $>C=CH_2$ group and a polyester of a dihydric alcohol and a mixture of a plurality of dicarboxylic acids, one of which is alpha-beta ethylenic and in another of which the carbon to carbon bonds are of a class consisting of single bonds and benzenoid double bonds, the steps which comprise incorporating with the mixture dihydroxymaleic acid and heating the mixture.

9. The steps of claim 8 in which the dihydroxymaleic acid is further accompanied by a free radical polymerization initiator.

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Joe Stewart
A Smith

25 lbs.

UP = 30.00
Ext 2275

United States Patent Office

2,811,564
Patented Oct. 29, 1957

2,811,564

PREPARATION OF TERPENE DIPHENOLIC COMPOUNDS

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

No Drawing. Application October 21, 1954,
Serial No. 463,814

3 Claims. (Cl. 260—619)

This invention relates to an improved method for preparing terpenephenolic compounds, and pertains more particularly to the reaction of a phenolic compound with a cyclic terpene in the presence of polyphosphoric acid.

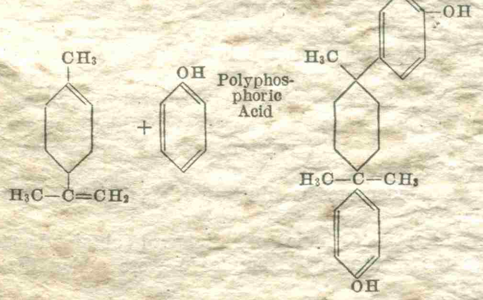
It is well known that phenols may be reacted with cyclic terpenes in the presence of a condensation catalyst to give a resinous product useful in coating compositions such as paints, varnishes, lacquers and the like. Many of the early processes produced resinous materials which were insoluble in alcohols, and which also possessed the disadvantage of being non reactive with drying oils. Consequently, these resinous materials were of somewhat limited utility.

More recently, however, it was found that alcohol soluble terpenephenol resins could be obtained by utilizing certain critical expedients in carrying out the reaction. For example, it is disclosed in U. S. Patent 2,596,235 that (1) an excess of phenol must be utilized, and (2) the terpene must be added to a previously prepared mixture, suspension, dispersion or solution of the condensation catalyst in phenol heated to a relatively high temperature, which is indicated as being from about 50° C. to about 90° C. Catalysts disclosed as being useful are the activated clays and certain Friedel-Crafts compounds such as the boron trifluoride etherates or alcoholates.

This latter method, however, also possesses certain disadvantages in that it produces only low yields of the terpene-phenol reaction product, (on the order of 15 percent to 45 percent), requires addition of reactants in a certain manner, and requires heating to effect the desired reaction.

It has now been discovered that nearly quantitative yields of pure diphenolic compounds can be readily obtained by utilizing polyphosphoric acid as the reaction catalyst. By employing polyphosphoric as the catalyst, the reaction goes readily even at room temperature, and the manner of addition of the reactants is not critical.

The reaction of cyclic terpenes with phenols in accordance with the present invention is illustrated by the following equation, wherein dipentene and phenol are utilized for illustrative purposes:



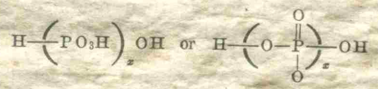
For reasons of economy and ease of reaction, phenol is the preferred phenolic compound for reaction with

cyclic terpenes to form terpene diphenols of the type depicted in the above equation. However, other phenolic compounds, including the cresols, butylphenol, amylphenol, naphthols, and the like may also be utilized with good results.

Cyclic terpenes which may be used in the reaction of this invention include dipentene, turpentine, alpha-pinene, beta-pinene or mixtures of these compounds. All of these terpenes are readily available commercial materials.

Inasmuch as some of the cyclic terpenes described above possess two double bonds at which reaction with the phenolic compound can take place, it is ordinarily desirable that an excess of the phenolic compound be employed in order that substantial yields of the desired product will be obtained. Preferably the ratio of phenol to terpene is about 1.5:1 to 2.5:1. However, the use of an excess of the cyclic terpene is not a critical expedient, and in fact, excellent yields of diphenols are obtained from the reaction of dipentene and phenol when the dipentene is actually present in a slight excess.

Polyphosphoric acid may be regarded as comprising a reaction product of or a solution of orthophosphoric acid (H_3PO_4) and phosphorus pentoxide (P_2O_5). This acid is termed "a condensed phosphoric acid" and its formula is understood to be the following:



$$H{-}\left(PO_3H\right)_x OH \quad \text{or} \quad H{-}\left(O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{|}}{P}}\right)_x{-}OH$$

wherein *x* is greater than 1. Polyphosphoric acid is an easily handled and relatively inexpensive viscous liquid which contains about 82 percent to 85 percent of phosphorus pentoxide.

The quantity of polyphosphoric utilized may be varied widely. In general, however, it is desirable to utilize about two-thirds part by weight of catalyst for each part of the phenol. However, smaller amounts of the catalyst, for example, about one-half part by weight for each part of phenol may be used, as may larger amounts, for example, as much as one part or more of polyphosphoric acid per part of phenol. The catalyst is recovered substantially unchanged and can be used over in combination with additional quantities of fresh catalyst.

It has been found that the addition of a small amount of phosphoric acid (about 10 percent by weight) to the polyphosphoric acid aids in controlling the reaction temperature within the desired range.

As indicated hereinabove, it is an advantage of the improved process of the present invention that the reaction can be carried out at room temperature to give nearly quantitative yields of the desired phenolic product. It has been found that the reaction is slightly exothermic and the reaction temperature may rise as high as 30° C. or 35° C. during the course of the reaction. Temperatures higher than 30° C. or 35° C. are not desirably utilized as they tend to produce a mixture of products, making recovery of the desired product more difficult, and also lowering the yield thereof.

However, if desired, the reaction can be carried out at temperatures substantially below room temperature, for example, as low as 10° C. or even lower with good results. It has been found that at temperatures of below about 35° C. the diphenols are almost exclusively para substituted; at higher temperatures there is more ortho substitution. Since the para, para isomer is the preferred product, the advantages of being able to operate at substantially room temperature in accordance with this invention are obvious.

The reaction is preferably conducted in an inert solvent or diluent, for example, the aliphatic hydrocarbons such as hexane or heptane, or aromatic hydrocarbons such as toluene or the petroleum naphthas.

The reaction is carried out by admixing the phenol, cyclic terpene and catalyst in the inert solvent or diluent with good agitation. Since the reaction tends to be slightly exothermic, it is sometimes advantageous to add either the phenol or the terpene to a mixture of the other and catalyst in the solvent or diluent in order to assist in temperature control. However, as indicated hereinabove, it is an advantage of this invention that the manner of addition of reactants is not a critical expedient. As the reaction proceeds the reaction mixture becomes quite viscous (after about 6 to 8 hours) and ordinarily the reaction is substantially complete in about 12 hours. Because the reaction mixture does become very viscous, it is highly important that it be well agitated continuously to insure proper contact of reactants and catalyst.

One preferred method of recovering the terpene diphenols from the reaction mixture involves first adding a material such as isopropyl ether thereto to give an ether layer containing the desired reaction product, and a heavy, viscous catalyst layer from which the ether layer is decanted. The ether solution is then extracted with an aqueous solution of an alkali such as sodium hydroxide or potassium hydroxide and the resulting alkaline solution extracted with toluene which extracts the minor amounts of monoether-monophenols present. The diphenoxide solution is then acidified, preferably with a mineral acid, extracted with ethyl acetate, stripped and distilled. By carrying out the reaction in this manner substantially all of the phenol is reacted and only a small residue is obtained. The diphenol is obtained as a light colored, glass like material. Actually the diphenol is obtained as a mixture of two isomers. These isomers are readily separated by virtue of the fact that one forms a crystalline toluate containing half a mole of toluene of crystallization per mole of the diphenol whereas the second is toluene free. Thus, if it is desirable to separate the isomers, the procedure described above is followed through the acidification step, after which the product is extracted with toluene. The toluate forms at once as copious white crystals at the interface, and these are readily recovered by filtering.

The following examples illustrate the preparation of diphenols in accordance with the improved method of this invention. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

Example I

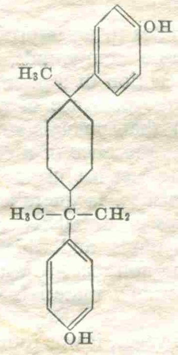
Twelve hundred twenty grams of phenol, 1000 cc. of heptane, 800 grams of polyphosphoric acid and 80 grams of 85 percent phosphoric acid were admixed in a glass reactor. The mixture was agitated constantly while 1360 grams of dipentene were added over a four hour period, the temperature being maintained at 30° C. to 35° C. After continuous agitation for 8 hours the reaction mixture had become very viscous. Isopropyl ether was then added whereupon the catalyst settled and the organic layer was decanted. The catalyst layer was washed several times with isopropyl ether and the combined ether solutions were washed successively with water, aqueous sodium bicarbonate and water and stripped to 200° C. at 1 mm. to yield a faintly yellow, glass like product having a hydroxyl number of 330. The yield of the diphenol was 2000 grams.

Example II

To a mixture of 188 grams of phenol, 250 cc. of solvent naphtha and 100 grams of polyphosphoric acid, 136 grams of alpha-pinene was slowly added over a period of 4 hours, the reaction temperature being maintained below 35° C. and the reaction mixture being agitated throughout the addition of the alpha-pinene and for an additional 6½ hours. The reaction mixture was then treated as in Example I to give an almost quantitative yield of para, para diphenols.

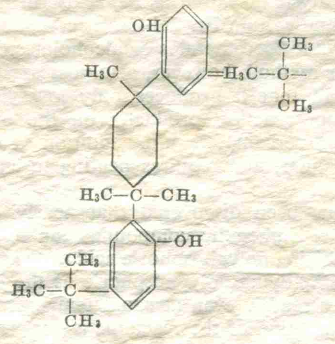
Example III

One hundred thirty-six grams of turpentine was added over a 45 minute period to a stirred mixture of 94 grams of phenol, 200 cc. of heptane, 75 grams of polyphosphoric acid and 25 grams of phosphoric acid, the temperature being maintained at 30° C. Agitation was continued for an additional 18 hours, after which the reaction mixture was worked up in accordance with the procedure of Example I. A substantial yield of para, para diphenols of the structure



was obtained.

When the above examples are repeated substituting other of the phenols disclosed hereinabove for phenol, diphenols are again obtained in substantially quantitative yields; thus, for example, when dipentene is reacted with p-tertiary butylphenol in the presence of polyphosphoric acid, a diphenol having the following structure is obtained:



Similarly when the ratio of phenolic compound to cyclic terpene is varied from the ratios utilized in the specific examples, or when larger or smaller amounts of polyphosphoric acid are employed, the reaction proceeds readily at room temperature to give much better yields of diphenols than when other catalysts are used.

The diphenolic compounds obtained by the improved process of this invention are very useful materials. For example, they can be condensed with aldehydes such as formaldehyde to give resinous products useful as components of coating compositions. The preparation of such resinous condensates is illustrated by the following example:

To 113 grams (1 mole) of a diphenol (obtained according to the method of Example I) were added the following:

86 grams (35.2 percent) formalin solution
20 grams sodium hydroxide
100 grams water

The resulting mixture was stirred for 140 hours at room temperature and then acidified with 27 cc. of sulfuric acid to give a pH of 5.3. The acidified reaction product was washed with water, butanol added, and the water distilled off azeotropically to give 225 grams of resinous product having a solids content of 64.8, and a Gardner viscosity of I–J. The resin was spread out as a film and baked at 370° F. for 10 minutes to give a film having a Sward hardness of 56.

The diphenolic compounds obtained by reacting cyclic terpenes with phenols can also be reacted with epichlorohydrin to give useful epoxy resins. This reaction is illustrated by the following example:

A solution of 452 grams of a terpene diphenol (prepared according to the method of Example I) in 200 cc. of xylene was heated to a temperature of 50° C. To this solution 925 grams of epichlorohydrin was added, the temperature rising to 90° C. due to the exothermic reaction. After about an hour 500 grams of water and 200 grams of ethanol were added, the latter to aid in phase separation. The water and alcohol are decanted and the remaining product stripped to give an epoxy resin having a solids content of 60.2 percent, a Gardner viscosity of B, and a Gardner color of 9. The epoxide equivalent at 60.2 percent solids was 1225. The solvent was then removed to give 990 grams of resin which at 95.7 percent solids had an epoxide equivalent of 1420. The resin cured in the presence of triethylene tetraamine to give a hard, dark material. The epoxide resins thus prepared can be used as coil potting resins.

From the foregoing description of the invention it is apparent that the use of a polyphosphoric catalyst in the reaction of a cyclic terpene with a phenol constitutes an improved method for obtaining valuable products. It is also apparent, therefore, that numerous possible variations and modifications can be made in the process described without departing from the spirit and scope of the invention as defined in the appended claims.

I claim:

1. In the method of preparing a terpene diphenolic compound by the reaction of a cyclic terpene with a phenolic compound in the presence of a condensation catalyst, the improvement which comprises carrying out the reaction at a temperature below about 35° C. and in the presence of polyphosphoric acid.

2. In the method of preparing a terpene diphenol by the reaction of a cyclic terpene with phenol in the presence of a condensation catalyst, the improvement which comprises carrying out the reaction at a temperature below about 35° C. and in the presence of polyphosphoric acid.

3. The method of claim 2 wherein the reaction is carried out at a temperature in the range of 10° C. to 35° C.

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Patented Oct. 29, 1957

2,811,566

HALOGENATED PHENOLS

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

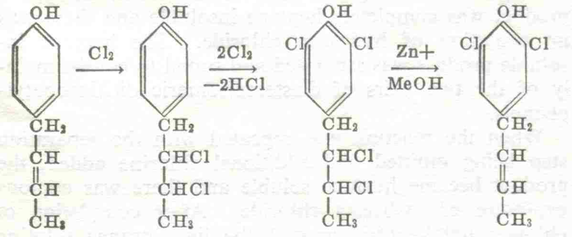
No Drawing. Application October 21, 1954,
Serial No. 463,813

8 Claims. (Cl. 260—623)

This invention relates to the preparation of halogenated phenolic compounds, and pertains more particularly to the preparation of halogenated derivatives of alkenylphenols. These derivatives have not been prepared heretofore.

In copending applications, Serial Nos. 337,226, 337,227, and 337,228, all filed February 16, 1953, and 430,439, filed May 12, 1954 (applications Ser. Nos. 337,228 and 430,439 now abandoned) methods for the preparation of alkenylphenols are disclosed. These methods involve generally the reaction of acyclic conjugated dienes such as butadiene-1,3 and isoprene, with phenolic compounds such as phenol, and the alkenylphenols obtained are very useful for many purposes. For example, they condense readily with aldehydes such as formaldehyde in the presence of either acidic or alkaline catalysts to give resinous condensation products which are in turn compatible with many other resinous materials including vinyl resins, epoxy resins, polyvinylbutyral resins, alkyd resins and the like. Blends of alkenylphenol-aldehyde resins with the resinous materials listed are useful as sanitary linings for food containers and similar uses. The alkenylphenols also react readily to form alkenylphenoxycarboxylic acids useful as herbicides, and are useful for many other purposes.

It has now been discovered that the alkenylphenols will react with a halogen, and particularly with chlorine or bromine, to form a variety of novel halogenated phenolic compounds. For example, as the halogen is added to the alkenylphenol, addition occurs first at the double bond of the side chain or chains after which ring substitution takes place. Upon dehydrohalogenation in the presence of zinc or similar dehydrohalogenating agent, the side chain halogens are removed, leaving a compound having an unsaturated side chain or chains and a halogenated nucleus. This series of reactions is illustrated by the following equations, wherein p-2-butenylphenol and chlorine are used for illustrative purposes.

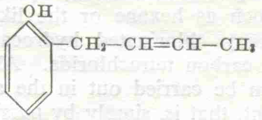


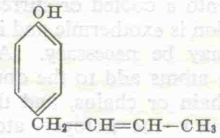
As indicated hereinabove, alkenylphenols are readily obtained by the reaction of acyclic conjugated dienes with phenolic compounds in the presence of certain catalysts such as the Friedel-Crafts compounds. This reaction results in the production of a mixture of alkenylphenols, including monobutenylphenols, dibutenylphenols and tributenylphenols, together with minor portions of ethers and higher phenols. For example, the reaction

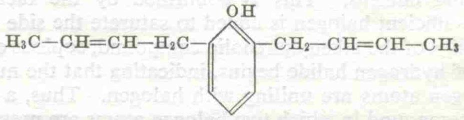
product obtained by the reaction butadiene-1,3 with phenol in the presence of an aqueous sulfuric acid catalyst is generally composed of less than about 15 percent unreacted phenol, less than about 5 percent of ethers, 55 percent to 70 percent of monobutenylphenols and 15 percent to 50 percent of the higher boiling phenols, including di- and tributenylphenols and polyphenols. Ordinarily, the unreacted phenol and ethers will be removed from the reaction mixture by distillation before halogenation is carried out; however, this is not a critical expedient and the halogenation reaction takes place even though the unreacted phenols and ethers are not removed. Mixtures containing smaller quantities of monoalkenylphenols and larger quantities of the higher boiling phenols, for example, about 50 percent monoalkenylphenols and 30 percent to 50 percent of higher boiling phenols and the balance polyphenols and ethers, may also be employed with good results, as may mixtures containing no monoalkenylphenols. Also, the mixture may be composed entirely of ortho- and para-monoalkenylphenols.

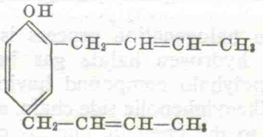
It is to be understood that alkenylphenols can also be obtained by other methods known to the art in addition to the reaction of conjugated dienes with phenolic compounds, and it is intended that the present invention include the use of alkenylphenols regardless of the method whereby they are obtained.

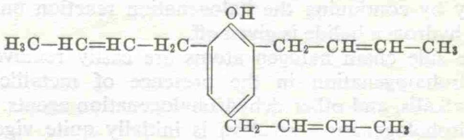
As illustrative of the alkenylphenols which can be halogenated in accordance with the present invention there are set forth below the products of the reaction of butadiene-1,3 and phenol:





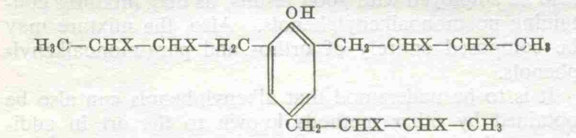






It will be noted that the unsaturated side chains of the compounds depicted structurally above all contain the double bond in the Δ^2 position. However, the reaction of butadiene-1,3 with phenol also yields smaller quantities of butenylphenols having the double bond in the Δ^3 position.

The alkenylphenols which are halogenated in accordance with this invention possess the general structure $R_n\text{-}Ar\text{-}(OH)_{n_1}$, wherein R is alkenyl or haloalkenyl, or alkoxyalkenyl, Ar is an aromatic radical, and n and n_1 represent a whole number from 1 to 3, and which may be the same or different. The preferred alkenylphenols of this structure are those in which R is butenyl and Ar is phenyl, including o- and p-2-butenylphenols, di-2-butenyl phenols and tri-2-butenylphenols. However, other alkenylphenolic compounds may also be used, including butenylcresols, butenylcatechols, butenyl - 2,5 - dinitrophenols, butenyl-2,3-dimethoxyphenols, mono-, di and tributenylresorcinol, mono-, di- and tributenylguaiacols, pentenylphenols, pentenylcresols, pentenylguaiacols, hexenylphenols, hexenylcresols, di- and trihexenylcresols, and the like. Mixtures of two or more of the above materials may also be halogenated, it not being necessary to separate a mixture into the individual alkenylphenols in order to carry out the halogenation reaction. Obviously, those alkenylphenols possessing two or three alkenyl groups will take up sufficient halogen to saturate each of said side chains before ring substitution will occur. Thus, for example, tributenylphenol can be halogenated to form a compound possessing the following structure, wherein each X represents a halogen atom.



The halogenation of an alkenylphenol is readily carried out by passing the halogen, preferably as a gas or liquid, into a cooled solution of an alkenylphenol. The alkenylphenols, and particularly the butenylphenols, are soluble in alcohols such as methanol, butanol, ethanol, or the like, and the halogenation can be carried out in an alcoholic solution. However, other inert solvents and diluents, including ethers, toluene, xylene, or aliphatic hydrocarbons such as hexane or the like may also be employed, as may chlorinated hydrocarbons such as chloroform and carbon tetrachloride. Alternatively, the halogenation can be carried out in the absence of any solvent or diluent, that is, simply by passing the gaseous or liquid halogen into a cooled or stirred liquid alkenylphenol. The reaction is exothermic and in some instances external cooling may be necessary. As stated hereinabove, the halogen atoms add to the double bond of the unsaturated side chain or chains, and then as the halogenation is continued, the halogen atoms add to the phenolic nucleus. This is confirmed by the fact that after sufficient halogen is added to saturate the side chain or chains of the alkenylphenolic compound, copious evolution of hydrogen halide begins, indicating that the nuclear hydrogen atoms are uniting with halogen. Thus, a polyhalo compound in which two halogen atoms are present in each side chain of the alkenylphenolic compound can be recovered if the halogenation process is stopped when evolution of a hydrogen halide gas begins. On the other hand, a polyhalo compound having two halogen atoms in each alkenylphenolic side chain, and two halogen atoms attached to the phenolic nucleus can be obtained simply by continuing the halogenation reaction until no more hydrogen halide is given off.

The side chain halogen atoms are easily removed by dehydrohalogenation in the presence of metallic zinc dust, alkalis, and other dehydrohalogenation agents. The dehydrohalogenation reaction is initially quite vigorous, but subsides rapidly, after which the reaction mixture should be refluxed for about an hour. The mixture is then cooled, filtered and the zinc and salts washed with an alcohol such as methanol. On distillation of the remainder of the reaction mixture, the desired dihalo compound is obtained, ordinarily as a colorless viscous oil. The product is believed to be largely a mixture of the two isomers which can in turn be separated by distillation.

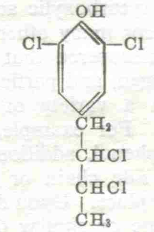
The following examples illustrate the halogenation of alkenylphenols to obtain the various halogenated derivatives discussed hereinabove. The examples are not intended to limit the invention, however, for there are, of course, numerous possible variations and modifications.

Example I

Through a stirred solution of 200 grams of mixed monobutenylphenols (B. P. 60° C.–100° C./0.2 mm.; n_D^{25} 1.5397) in 1000 cc. of methanol cooled to 0° C., chlorine gas was passed at such a rate that the reaction temperature did not rise above 10° C. The reaction mixture became slightly red in color, and after approximately 90 grams of chlorine had been taken up, copious evolution of hydrogen chloride began. After the weight of the reaction mixture had increased by 210 grams (chlorine taken up plus dissolved hydrogen chloride), the red, clear solution was treated with 200 grams of zinc dust in small portions. After the initially vigorous reaction had subsided, the mixture was refluxed for an hour, cooled, filtered, the zinc and zinc salts washed with methanol, and the combined filtrates distilled to yield 280 grams of a colorless, viscous oil, B. P. 110° C.–170° C./1 mm.; n_D^{25} 1.556. The product distills in vacuum without decomposition and is a mixture of 4,6-dichloro-2-(2-butenyl)-phenol, and 2,6-dichloro - 4-(2-butenyl)-phenol; chlorine calculated for $C_{10}H_{10}Cl_2O$, 32.66 percent; found 31.4 percent. The two isomeric dichloro compounds can be separated by a simple fractionation at reduced pressure.

Example II

To a cooled solution of 84 grams of p-2-butenylphenol in 200 cc. carbon tetrachloride was added gaseous chlorine. The reaction was exothermic and the mixture was kept at 20° C.–35° C. At first there was no evolution of HCl, but evolution commenced after some chlorine had been taken up. After no more chlorine was being taken up, the faintly orange solution was stripped in vacuum to leave 163 grams of an almost colorless, viscous oil, n_D^{25} 1.575, chlorine calculated for $C_{10}H_{10}OCl_4$, 49.25; found 48.93. The compound had the following structure.



Example III

Chlorine gas was passed through a solution of 600 grams of mixed ortho- and para-monobutenylphenols in 2000 cc. of heptane. The reaction was exothermic, and the reaction temperature was kept below 55° C. by water cooling. After 290 grams of chlorine were taken up, the product was completely heptane insoluble and there was no evolution of hydrogen chloride. The heptane insoluble product was separated and found to consist mainly of the two pairs of diastereoisomeric dichlorobutylphenols.

When the reaction was repeated with the separation step being omitted and additional chlorine added, the product became heptane soluble and there was copious evolution of hydrogen chloride. After completion of chlorine uptake (562 grams) the light orange solution was stripped to yield 1177 grams of mixed dichlorobutyldichlorophenols; n_D^{25} 1.5783.

Example IV

The addition of bromine to mixed ortho- and parabutenylphenols according to the method of the preceding examples proceeds similarly to yield first the mixed dibromobutylphenols and then, with evolution of hydrogen bromide, the mixed tetrabromophenols which can be de-halogenated with zinc to yield 2,6-dibromo-4-butenylphenol and 2,4-dibromo-6-butenylphenol.

Similarly, when iodine is substituted for chlorine or bromine in the above examples, or when other alkenylphenols such as pentenylphenols (prepared from isoprene and phenol) are utilized, the halogenation proceeds satisfactorily to yield halogenated alkenylphenols, the specific products obtained depending upon the degree to which the halogenation is carried.

The novel compounds of this invention are very useful materials. All of them, for example, react readily with aldehydes, and particularly formaldehyde, to give resinous condensation products which possess generally the useful properties of phenol-aldehyde resins, with the presence of the halogen atoms contributing fire retardant properties to the resins.

Moreover, the halogenated phenolic compounds can be utilized to prepare phenoxyacetic acids possessing insecticidal, herbicidal and fungicidal properties. Also, the alkenyldihalophenolic compounds, for example, 4,6-dichloro-2-(2-butenyl)phenol, undergo polymerization in the presence of catalysts such as strong acids to give hard, clear polymeric materials useful in coating compositions and the like.

It is apparent from the foregoing description that the halogenated alkenylphenols of this invention constitute a new and useful class of chemical compounds. It will also be apparent that numerous variations and modifications can be made in the procedures described herein without departing from the spirit and scope of the invention as defined in the appended claims.

I claim:

1. The method which comprises reacting a halogen with an alkenylphenol, continuing the reaction until evolution of hydrogen halide begins, and recovering from the reaction mixture a dihaloalkyl phenol formed by addition of halogen atoms to each side chain double bond of said alkenylphenol.

2. The method of claim 1 wherein the alkenylphenol is a butenylphenol.

3. The method of claim 1 wherein the halogen is chlorine.

4. The method which comprises reacting a halogen with an alkenylphenol, continuing the reaction until evolution of hydrogen halide begins and substantially ceases, and recovering from the reaction mixture a polyhalo compound in which two halogen atoms are added to each side chain double bond of the alkenylphenol, and two additional halogen atoms are attached to each phenolic nucleus.

5. The method of claim 4 wherein the alkenylphenol is butenylphenol and the halogen is chlorine.

6. The method which comprises reacting a halogen with an alkenylphenol, continuing the reaction until evolution of hydrogen halide begins and substantially ceases, adding a dehydrohalogenation agent to the reaction mixture, refluxing the reaction mixture, and recovering therefrom a nuclear halogenated alkenylphenol.

7. The method of claim 6 wherein the alkenylphenol is a butenylphenol and the halogen is chlorine.

8. The method of claim 7 wherein the dehydrohalogenation agent is zinc dust.

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United States Patent Office

2,812,340

Patented Nov. 5, 1957

2,812,340

METHOD OF PREPARING ACETOACETIC ACID ESTER OF CASTOR OIL

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

No Drawing. Application November 12, 1954, Serial No. 468,569

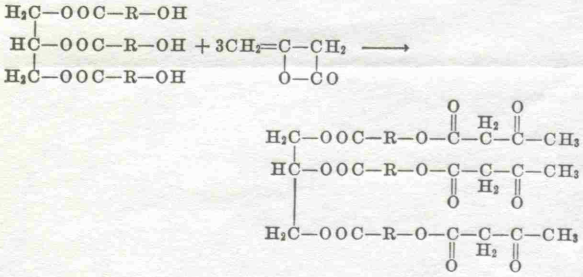
6 Claims. (Cl. 260—405)

This invention relates to a method of forming acetoacetic acid esters of high molecular weight alcohols and it has particular relation to a method of forming acetoacetic acid esters of castor oil.

Heretofore, esters of castor oil and acetoacetic acid have been prepared by ester interchange reaction of castor oil and an ester of acetoacetic acid and a lower alcohol, such as methyl alcohol or ethyl alcohol. Such method is disclosed in an application to Lowell O. Cummings, Henry A. Vogel and Alfred R. Bader, Serial No. 219,900, filed April 7, 1951, now Patent 2,693,484. This reaction proceeds very readily at mild temperatures and in the absence of catalysts to produce castor oil acetoacetate in high yield. The products have utility as plasticizers for nitrocellulose, vinyl resins, and for other important uses.

Castor oil is largely composed of glycerides, such as the triglycerides of ricinoleic acid. The latter is also known as 12-hydroxy-10-octadecenoic acid contains a free hydroxyl in position 12 of the hydrocarbon radical. When castor oil undergoes ester interchange reaction with an ester of acetoacetic acid and a lower monohydric alcohol, this hydroxyl reacts to replace the alcohol residue of the acetoacetic ester thus forming the desired acetoacetic acid ester of castor oil.

This invention is based upon the discovery that the foregoing esters of acetoacetic acid and castor oil can be prepared relatively inexpensively and in high purity by the reaction of castor oil and diketene. The reaction is believed to proceed substantially according to the following equation:



$$\begin{array}{l} H_2C-OOC-R-OH \\ \;\,| \\ HC-OOC-R-OH \\ \;\,| \\ H_2C-OOC-R-OH \end{array} + 3\,\begin{array}{l} CH_2=C-CH_2 \\ \qquad\;\; | \quad\;\; | \\ \qquad\;\; O-CO \end{array} \longrightarrow \begin{array}{l} H_2C-OOC-R-O-\overset{\overset{O}{\|}}{C}-\overset{H_2}{C}-\overset{\overset{O}{\|}}{C}-CH_3 \\ \;\,| \\ HC-OOC-R-O-\underset{\underset{O}{\|}}{C}-\underset{H_2}{C}-\underset{\underset{O}{\|}}{C}-CH_3 \\ \;\,| \\ H_2C-OOC-R-O-\underset{\underset{O}{\|}}{C}-\underset{H_2}{C}-\underset{\underset{O}{\|}}{C}-CH_3 \end{array}$$

Group R in the equation is the aliphatic chain of ricinoleic acid.

The acetoacetic acid esters of castor oil, as obtained by the interaction of castor oil and diketene, are susceptible of the same uses as the corresponding esters when obtained by the reaction of castor oil and a lower ester of acetoacetic acid and a lower monohydric alcohol as disclosed in the aforementioned Patent 2,693,484. For example, they may be employed as plasticizers of nitrocelluose and vinyl resins. Certain of the derivatives, such as the ammonia derivatives disclosed in the foregoing application, can be used as emulsifying agents. These usages are given merely by way of illustration. Manifestly, the acetoacetic acid ester of castor oil is susceptible of many other uses.

In order to prepare acetoacetic acid esters of castor oil by the reaction of the oil with diketene, the castor oil and the diketene need merely be mixed together and warmed preferably in the presence of a mild catalyst. Suitable catalysts include basic materials such as pyridine and other basic amines, as well as acids such as sulfuric acid, phosphoric acid, or the like. Only very small amounts of catalysts need be employed, and, in fact, the catalyst may be dispensed with entirely, although the reaction proceeds at a slower rate in the absence of a catalyst. A high yield of substantially pure castor oil acetoacetate is readily obtained in this manner.

The pratice of the invention is illustrated by the following example:

Example I

To a solution of 31 grams of cold-pressed castor oil and 0.2 gram of pyridine in 100 cc. toluene, 8.4 grams of diketene was added. The mixture was heated on a steam bath for 16 hours, and stripped in vacuo to give 39 grams of a faintly yellow oil, which is substantially pure castor oil acetoacetate.

The product is substantially the equivalent of that obtained by the ester interchange reaction of castor oil and methyl or ethyl acetoacetate, in accordance with the disclosure of the foregoing application Serial No. 219,900.

The diketene employed in the reaction is relatively inexpensive and the reaction itself is exceedingly simple. The yields are excellent and the product is obtained in a state of high purity.

The following example illustrates the use of castor oil acetoacetate as a plasticizer for nitrocellulose.

Example II

A clear lacquer was prepared comprising a 50 grams solution of ½ second nitrocellulose in mixed solvents (butyl acetate, ethanol, isopropyl acetate and toluene). To the solution were added 10 grams butyl acetate and 10 grams of castor oil acetoacetate. A glass panel was coated with the solution and was baked for 1.5 hours at 100° C. The resultant film was hard and non-brittle.

Castor oil acetoacetate is also a plasticizer for vinyl resins such as polyvinyl acetate, polyvinyl chloride, and the like.

Also the castor oil acetoacetates may be treated with gaseous ammonia to form beta-amino crotonates of castor oil, the latter being useful as emulsifying agents.

I claim:

1. A method of preparing acetoacetic acid ester of castor oil which comprises heating a mixture comprising said oil and diketene until said ester is formed.

2. A method of preparing the acetoacetic acid ester of castor oil which comprises heating a mixture comprising castor oil, diketene and pyridine until said ester is formed.

3. A method of preparing the acetoacetic acid ester of castor oil which comprises heating a mixture comprising castor oil, and diketene in an organic solvent until said ester is formed.

4. A method of preparing the acetoacetic acid ester of castor oil which comprises heating a mixture of castor oil, diketene and pyridine in toluene at about steam bath temperature until said ester is formed.

5. A method of preparing acetoacetic acid esters of castor oil which comprises heating to reaction temperature, a mixture consisting essentially of castor oil and diketene in the presence of an amine reaction catalyst until said ester is formed.

6. A method of preparing acetoacetic acid esters of castor oil which comprises heating at approximately steam bath temperature, a mixture consisting essentially of castor oil and diketene in the presence of an amine catalyst until said ester is formed.

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United States Patent Office

2,822,378

Patented Feb. 4, 1958

2,822,378

METHOD FOR PREPARING ESTERS

Alfred R. Bader, Milwaukee, Wis., assignor to Pittsburgh Plate Glass Company, Allegheny County, Pa., a corporation of Pennsylvania

No Drawing. Application April 23, 1953
Serial No. 350,747

3 Claims. (Cl. 260—474)

This invention relates to the preparation of esters of phenolic compounds and it has particular relation to the preparation of esters of phenolic compounds and carboxylic acids.

It has heretofore been proposed to prepare esters of phenols and carboxylic acids by reacting a phenol and an acyl chloride or acid anhydride. This reaction with an acyl chloride is not very satisfactory inasmuch as it results in the liberation of much hydrogen chloride. Additionally, the acid chloride and anhydride are difficult to prepare.

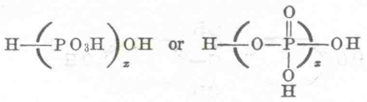
It has also been proposed to effect esterification reaction between phenols and carboxylic acids in the presence of phosphorus oxychloride. The reaction again is decidedly unsatisfactory, since various objectionable side reactions may occur, thus greatly reducing the efficiency of the process.

Certain other esters of phenols and carboxylic acids have also been prepared by complicated methods. For example, Filachione et al., in the Journal of the American Chemical Society, 72, page 839, 1950, describes the prepartion of phenyl methacrylate by a reaction involving acetylation of lactic acid, conversion of the resulting acetoxy propionic acid into its acid chloride, reaction of the latter with phenol and finally pyrolizing the product at 525° C.

The usual and more conventional catalysts of esterification such as sulfuric acid, hydrochloric acid or the like are not effective to produce esterification of phenols and carboxylic acids.

It has now been discovered that estification reactions between phenols and carboxylic acids can be successfully brought about by the use of polyphosphoric acid as a reaction catalyst. This reaction proceeds very smoothly with the formation of but little or no by-products.

Polyphosphoric acid may be regarded as comprising a reaction product of or a solution of orthophosphoric acid (H_3PO_4) and phosphorus pentoxide (P_2O_5). This acid is termed "a condensed phosphoric acid" and its formula is understood to be:



$$H\!-\!\left(PO_3H\right)_x\!OH \quad \text{or} \quad H\!-\!\left(O\!-\!\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{\displaystyle O}}{\underset{|}{P}}}\right)_x\!-\!OH$$

where x is greater than 1. It is an easily handled and relatively inexpensive viscous liquid. It is understood to contain about 82 to 84 or 85 percent of P_2O_5.

In the performance of the esterification between phenols and carboxylic acids, polyphosphoric acid may be employed as a promoter in a wide range of proportions. Usually, it is preferred to utilize it in an amount in excess of 10 percent by weight based upon the reaction components and the upper limits are imposed by economics rather than by chemical behavior. Obviously, great excesses beyond those required to obtain reaction merely increase the costs without corresponding improvements in results. A range of about 5 to 40 or even 100 percent by weight based upon the reaction mixture is suggested as being near the optimum requirement of polyphosphoric acid. The polyphosphoric acid may act as a dehydrating agent and absorb the water evolved in the reaction.

The esterification reaction of phenols and carboxylic acids which may be promoted by polyphosphoric acid in accordance with the provisions of this invention is of relatively general nature. That is, compounds containing the carboxylic acid group will, in most instances, react with aromatic compounds containing one or more hydroxyl groups directly joined to an aromatic nucleus to form esters. Naturally, the several components of the system must be selected with a view of obtaining mutual compatibility and solubility which can readily be accomplished by simple solubility tests. Also, the phenolic compound and the carboxylic acid should be selected with a view of excluding unwanted side reactions which, in some instances, might occur because of the presence of overly active groups in side chains or linkages. Naturally, all pairs of phenols and carboxylic acids do not react with equal ease and efficiency. A few of the possible carboxylic acids (or anhydrides thereof) and phenols which in the presence of polyphosphoric acid can be caused to interact to form esters are listed below in Table A. It will be understood that the positions of the acids and the phenols have no significance as to permissible grouping or pairing thereof.

TABLE A

Phenols

- Monohydric phenols such as: phenol;
- Alkylated phenols as: cresols (all isomers), xylenols, butylphenol, amylphenol, thymol, carvacrol;
- Halogenated phenols such as: mono, di, tri, tetra, and penta-chlorophenol. (The several isomers such as para, meta and ortho chlorophenol are included);
- Phenol ethers such as: guaiacol, 2,5-dimethoxyphenol;
- Phenols containing a plurality of phenolic hydroxy groups such as: catechol, resorcinol, hydroquinone, pyrogallol;
- Substituted derivatives of phenols containing a plurality of phenolic hydroxyls such as: bis-(4-hydroxyphenyl)-2,2-propane, bis-(4-hydroxyphenyl)-1,1-ethane, or the like.

Carboxylic acids

- Monocarboxylic acids such as formic, acetic, chloroacetic, propionic, butyric, stearic, oleic, linoleic, elaeostearic, methacrylic, acrylic, angelic acids;
- Gamma or delta-keto acids such as levulinic acid, gamma-acetobutyric acid;
- Polycarboxylic acids as phthalic, chlorophthalic, succinic, adipic, sebacic, azelaic, oxalic acids, citric acid, tartaric acid, carlic acid;
- Unsaturated dicarboxylic acids as maleic, itaconic or the like.

Acid anhydrides of the acids listed above also react with phenolic compounds in the presence of polyphosphoric acid to yield esters and the term "acid" is, therefore, intended to include the corresponding anhydride.

In conducting the esterification reaction between the phenols and the carboxylic acids in the presence of polyphosphoric acid, the reactants may be mixed in mass without solvents. They may also be mixed in nonreacting solvents such as toluene, benzene, xylene or the like. The invention further includes emulsification of the reactants through the use of emulsifying agents.

In conducting the reaction, it is, in many instances, sufficient merely to mix the phenolic compound, the carboxylic acid and the polyphosphoric acid in a flask, beaker, kettle or any other appropriate container and then to bring the mixture to reaction temperature, ordinarily about 20° C. to 150° C., upon a steam-bath or other appropriate heating device. The apparatus preferably should include an agitator in order to attain thorough mixing of the several constituents.

The course of the reaction need not be followed with any particular care since the prolonged heating of the mixture at steam-bath or water-bath temperatures usually is not harmful. In laboratory operations, it is sufficient to leave the mixture stir for some period of time at reaction temperature, for example, overnight or for a day or two.

The application of the principles of the invention to the preparation of particular esters of phenols and carboxylic acid are illustrated by the following examples:

Example I

In this example phenol and acetic acid were smoothly reacted in the presence of polyphosphoric acid to provide phenyl acetate. The procedure involving mixing 94 grams of phenol (1 mole), 120 grams (2 moles) of glacial acetic acid and 50 grams of polyphosphoric acid. The mixture was heated on a steam-bath with agitation overnight. The product was diluted with water, extracted with toluene and washed with 10 percent aqueous sodium hydroxide solution and water. The product remaining comprised phenyl acetate which distilled at 92 to 94° C. at a pressure of 20 millimeters (absolute). No residue remained in the flask. The product had a saponification value of 302 and a refractive index of 1.5117.

Example II

In this example, the ester of levulinic acid and phenol was prepared. In conducting the reaction, a mixture of 94 grams of phenol, 58 grams of levulinic acid and 50 grams of polyphosphoric acid were stirred at steam-bath temperature for 16 hours. The mixture was cooled and poured into hot water. A dark oil, heavier than water, separated and was washed twice with hot water and then stripped. The mixture was subjected to distillation under vacuum. The fraction distilling within the range of 50 to 120° C. at 0.7 millimeters pressure first came over and was found to consist primarily of unreacted phenol. A water-white liquid having a boiling range of 120 to 130° C. at 0.5 millimeter of pressure (absolute) then came over. This product crystallized upon cooling and was found to have a melting point of 29° to 30° C. The product was phenyl levulinate. Additional water-white oil distilled over at a temperature of 130° to 150° C. at 0.8 millimeter pressure (absolute). The phenol levulinate as thus obtained agreed closely in carbon and hydrogen content with the theoretical value and the saponification value obtained likewise was very close to that calculated. The material crystallized from methanol as hard, white crystals which melted sharply at 32° C.

Both the product and the method of preparing the same are novel.

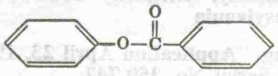
Example III

In this example, phenol was esterified with maleic acid in the presence of polyphosphoric acid. In conducting the reaction, 98 grams of maleic anhydride (1 mole), 376 grams (5 moles) of phenol, and 100 grams of polyphosphoric acid were stirred and heated on the steam bath for 20 hours. The product was then cooled and poured into cold water, extracted with toluene and the toluene solution was further extracted with 2 liters of 10 percent aqueous sodium hydroxide, washed with water and stripped. The product was crystalline and on recrystallization from toluene and heptane melted at 71–72° C. Elementary carbon and hydrogen analyses agreed well with the theoretical values for diphenyl maleate of the formula

This is a novel product.

Example IV

In this example, phenyl benzoate of the formula



was prepared. In the preparation, 100 grams of benzoic acid, 200 grams of phenol, and 100 grams of polyphosphoric acid were mixed and stirred on the steam bath for 16 hours. The mixture was then cooled and water was added. The resultant solution was extracted with toluene and the toluene solution was extracted with 10 percent aqueous caustic soda and finally was washed with water and stripped. The product was a faintly yellow, crystalline material which, upon distillation, provided beautiful, hard, white crystals of phenol benzoate melting at 70 to 71° C.

Example V

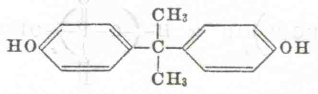
In a manner similar to that of the previous example, the phenyl ester of methacrylic acid may be prepared by heating a mixture of phenol, methacrylic acid, and polyphosphoric acid on a steam-bath for an appropriate period of time, e. g. 10 to 20 hours. The product as obtained by this method is a beautifully crystalline solid melting at 17° C. and having a refractive index of 1.5150. As set forth hereinabove, phenyl methacrylate was previously prepared by a complicated method by Filachione et al., and was described by them as being a colorless liquid which could be mixed with benzoyl peroxide and polymerized at 65° C. to provide clear castings.

Example VI

The previously described method is also very satisfactory for the preparation of diphenyl phthalate which has heretofore been prepared by another method and which is valuable as a plasticizer for various resins and plastics. For example, a mixture of phthalic acid or phthalic anhydride and 1 or more molar equivalencies of phenol may be mixed with 5 to 100 percent by weight based upon the esterifiable mixture of polyphosphoric acid. The mixture is heated on a steam-bath as previously described to provide diphenyl phthalate. This can be purified by washing it with caustic, extracting with toluene, and utilizing the other techniques which have been described in Examples I through IV.

Example VII

This example illustrates the preparation of an ester of a bisphenol compound, namely, the ester of the diphenol of the formula



and a dicarboxylic acid, namely, azelaic acid. The azelaic acid should be mixed with a molecular equivalency or preferably with an excess of the diphenol and the mixture then further incorporated with 20 to 40 percent or more of polyphosphoric acid. The reaction mixture is then heated at 80–120° C. for a number of hours, e. g., for 10 to 20 hours. This reaction could be continued to provide a resinous product.

Example VIII

Fifty grams of diglycolic acid, 150 grams of phenol, and 100 grams of polyphosphoric acid were heated at 95° C. with stirring for 16 hours. Diphenyl diglycolate was then isolated as in the examples above. Crystallization from a mixture of toluene and heptane yielded shiny, white platelets of the ester, melting at 73°–75° C.

The present invention includes the reaction of mono and polyhydric phenols such as phenol or hydroquinone with alkyd polyesters such as may be obtained by reacting the phenol with a polyester such as glyceryl phthalate or glycol maleate. In such reaction, it is preferred that the polyester be of relatively high acid value, in order to provide an adequate number of available carboxyls. The phenol may be employed in an amount in excess of that theoretically required.

Example IX

The process of this invention provides a simple and convenient method of preparing the commercial product known as Salol, which is phenyl salicylate. This has previously been prepared by the reaction of phenol and salicylic acid in the presence of phosphorous oxychloride ($POCl_3$).

In acordance with this invention, 1.6 gram mole of phenol and 0.4 gram moles of salicylic acid are heated with 50 grams of polyphosphoric acid at a temperature of 90° C. The product (Salol) is purified by the techniques previously described.

The esters obtained by the method of this invention, particularly the phenyl esters, are valuable compounds. For example, they are useful plasticizers for synthetic resins and rubbers, as ingredients of perfumes, and as intermediates in the preparation of resins, as well as being useful for many other purposes.

The forms of the invention herein shown and described are to be considered as being by way of illustration. It

will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit and scope of the appended claims.

I claim:

1. The method of preparing esters of a phenol and a carboxylic acid which comprises mixing the phenol and the carboxylic acid with about 10 to 100 percent, based upon the esterifiable mixture, of free liquid polyphosphoric acid and heating the mixture to esterification temperature whereby to obtain said ester.

2. A method of preparing phenylacetate which comprises mixing phenol with anhydrous acetic acid and about 10 to 100 percent, based upon the esterifiable mixture, of free liquid polyphosphoric acid and heating the mixture to esterification temperature to obtain said ester.

3. The method of claim 1 in which the acid is of a class consisting of maleic acid, levulinic acid, benzoic acid, salicylic acid and methacrylic acid.

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Patented July 15, 1958

2,843,565

BUTENYL PHENOL-ALDEHYDE RESINS

Roger M. Christenson, Whitefish Bay, and Lowell O. Cummings and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application November 3, 1953
Serial No. 390,088

4 Claims. (Cl. 260—53)

This invention relates to the preparation of novel and useful phenol-aldehyde type resins, and pertains more particularly to the preparation of such resins by the acidic condensation of an aldehyde with a mixture of alkenylphenols.

In a copending application, Serial No. 390,089, filed November 3, 1953, it is disclosed that mixtures of alkenylphenols, ordinarily containing monoalkenylphenols, dialkenylphenols, and trialkenylphenols, condense readily with aldehydes in the presence of an alkaline catalyst to form resins which produce films that are fast drying and curing and very light colored. The resins prepared by the method of the copending application are extremely compatible with materials utilized in the preparation of coating compositions such as epoxide resins, alkyd resins, vinyl resins and polyvinyl acetal resins. In this respect they are superior to other known phenolic resins which tend to be incompatible with many of the materials listed above.

It has now been discovered that mixtures of alkenylphenols condense with aldehydes such as formaldehyde in the presence of acidic catalysts to produce resins which are generally hard, grindable materials that are very useful in preparation of varnishes and as molding resins. Liquid resins useful in the preparation of varnishes may also be obtained by this method.

In the acidic condensation of alkenylphenols with formaldehyde, the intermediately formed methylol groups tend to react with additional quantities of the phenolic compound, and as a result of this further reaction, the resinous condensation product contains a large number of methylene linkages. In the base catalyzed condensation, on the other hand, the methylol groups do not react readily with more of the phenolic compound and the resulting condensation product contains many methylol groups and relatively few methylene linkages.

This substantial difference in the manner in which the condensations proceed is believed to account at least in part for the fact that the acid catalyzed products are generally hard resins, useful as molding resins and as varnish resins (particularly when the aldehyde to phenol ratio is low), whereas the base catalyzed products are generally viscous liquids which are useful in themselves, or when plasticized, as excellent film forming materials.

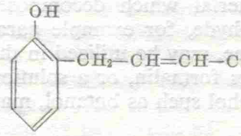
The mixture of alkenylphenols which is condensed with an aldehyde in accordance with the present invention may vary widely in composition. Ordinarily, the predominant component of the mixture is one or more monoalkenylphenols, (including ortho- and para-monoalkenylphenols), the monoalkenyl component constituting about 55 to 85 percent by weight of the total mixture. The balance of the mixture (15 to 45 percent) is composed primarily of di- and trialkenylphenols, although other phenolic materials, including polyphenols such as alkane di- and triphenols may also be present, depending upon the method by which the alkenylphenol mixture is prepared.

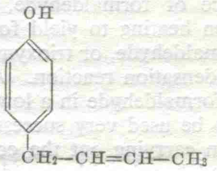
Mixtures of alkenylphenols of the type described in the

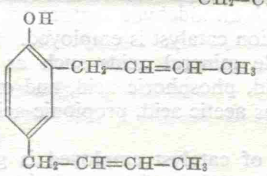
foregoing paragraph are readily obtained by the methods described in copending applications, Serial No. 300,359, filed July 22, 1952, and Serial Nos. 337,226, 337,227, 337,228 and 337,229, all filed February 16, 1953. The methods described in these copending applications involve the reaction of conjugated dienes with phenolic compounds in the presence of certain catalysts such as the Friedel-Crafts compounds. For example, the reaction product obtained by the reaction of butadiene-1,3 with phenol in the presence of an aqueous sulfuric acid catalyst is generally composed of less than about 15 percent unreacted phenol, less than about 5 percent of ethers, 55 to 70 percent of monobutenylphenols and 15 to 50 percent of the higher boiling phenols including di- and tributenylphenols and polyphenols. Ordinarily, the unreacted phenol and ethers will be removed from the reaction mixture by distillation before the condensation reaction with an aldehyde is carried out; however, this is not a critical expedient and the condensation reaction takes place readily even though the unreacted phenols and ethers are not removed. Mixtures containing smaller quantities of monoalkenylphenols and larger quantities of the higher boiling phenols, for example, about 50 percent monoalkenylphenols and 30 to 50 percent of higher boiling phenols and the balance polyphenols and ethers, may also be employed with good results, as may mixtures containing no monoalkenylphenols. Also, the mixture may be composed entirely of ortho- and para-monoalkenylphenols.

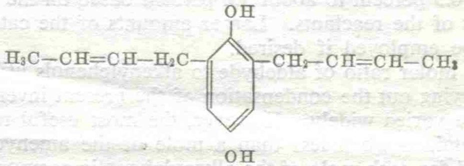
It is to be understood that mixtures of some alkenylphenols may also be obtained by other methods known to the art in addition to the reaction of conjugated dienes with phenolic compounds, and it is intended that the present invention include the use of any mixture of alkenylphenols regardless of the method whereby it is obtained.

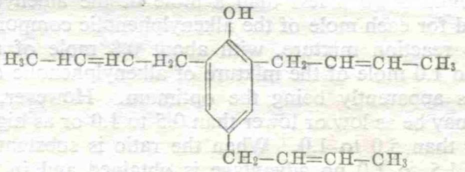
As illustrative of the alkenyl substituted phenolic compounds which in admixture are condensed with an aldehyde to form the novel resins of the present invention there are set forth below the products of the aqueous sulfuric acid catalyzed reaction of butadiene-1,3 and phenol:





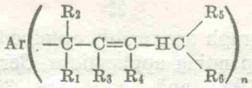






A mixture of the above alkenylphenols forms useful varnish and molding resins when condensed with an aldehyde in the presence of an acidic catalyst.

In general the alkenylphenolic compounds in the mixtures condensed with aldehydes possess the structure



wherein Ar is an aromatic radical, R_1, R_2, R_3, R_4, R_5 and R_6 are hydrogen, halogen or an organic radical, such as a hydrocarbon radical, which may be the same or different, and *n* is a number, ordinarily from 1 to 3. The alkenyl compounds of the above structure are all readily obtained by the reaction of phenolic compounds with conjugated dienes in accordance with the methods described in the copending applications.

Phenolic compounds which may be reacted with conjugated dienes to give compounds of the above structure include phenols, catechol, resorcinol, pyrogallol, tertiary butylcatechol, 3-isopropylcatechol, beta-naphthol, guaiacol, o-, m-, and p-cresols, 2,4-xylenol, 3,5-xylenol, m-alkylphenols, bis(4-hydroxyphenyl) 2,2-propane and the like.

Typical conjugated dienes which react with phenolic compounds to form the desired mixture of alkenylphenols include butadiene-1,3, 2-methylbutadiene-1,3, piperylene, 2-methylpentadiene-1,3, hexadiene-1,3, 1-chloro-2-methyl-butadiene-1,3, cyclopentadiene, homologues of cyclopentadiene, and the like.

The preferred alkenylphenolic compounds for condensation with aldehydes in accordance with present invention are mixtures of the butenylphenols, including ortho- and para-2-butenylphenols, di-2-butenylphenol and tri-2-butenylphenol. However, mixtures of other alkenylphenolic compounds may also be used, including butenylcresols, butenylcatechols, butenyl-2,3-dimethoxyphenols, mono-, di- and tributenylresorcinol, mono-, di- and tributenylguaiacol, 2-chlorobutenylcresol, 2-chlorobutenylphenol, 2-iodobutenylphenol, ortho- and para-cyclopentenylphenol, pentenylphenol, pentenylcresol, pentenylguaiacol, halopentenylphenols, halopentenylguaiacols, and the like.

Any aldehyde may be utilized in the preparation of the resins of the present invention. However, aldehydes containing only atoms of carbon, hydrogen and oxygen, and particularly formaldehyde, are greatly preferred. In place of formaldehyde, a material which decomposes upon heating to yield formaldehyde, for example paraformaldehyde, or trioxymethylene, may be utilized in the condensation reaction. Aqueous formalin, or a solution of formaldehyde in a lower alcohol such as butanol, may also be used very successfully.

In carrying out the condensation of a mixture of alkenylphenols with an aldehyde such as formaldehyde, an acidic condensation catalyst is employed. Suitable acidic materials include mineral acids such as sulfuric acid, hydrochloric acid, phosphoric acid, and organic carboxylic acids such as acetic acid, propionic acid, oxalic acid, and the like.

The quantity of catalyst employed is generally from about 0.5 percent to about 5.0 percent based on the total weight of the reactants. Larger amounts of the catalyst may be employed if desired.

The molar ratio of aldehyde to alkenylphenols utilized in carrying out the condensation of the present invention may be varied widely. However, the most useful resins are obtained when less than a mole of the aldehyde is utilized for each mole of the alkenylphenolic components in the reaction mixture, with about 0.8 mole of aldehyde to 1.0 mole of the mixture of alkenylphenolic compounds apparently being the optimum. However, the ratio may be as low or lower than 0.5 to 1.0 or as high or higher than 5.0 to 1.0. When the ratio is substantially above 1.5 to 1.0 no advantage is obtained and in fact, gels, rather than hard resins, may be formed. Consequently, the use of such an uneconomical excess is not particularly desirable.

The actual condensation reaction is readily carried out by first admixing the formaldehyde, or formaldehyde producing substance, with the mixture of alkenylphenols and the acidic catalyst. The resulting mixture is then heated to a temperature of about 50° C. to 150° C. for about 2 to 3 hours, after which the water present in the reaction mixture is stripped off by distillation at reduced pressure, leaving the desired resin as a hard, grindable material.

While the above described method for carrying out the condensation is preferred, particularly when the alkenylphenol mixture is a mixture of butenylphenols, other methods of conducting the condensation, for example, simply by admixing the reactants and acidic catalyst and allowing the mixture to stand at room temperature for about 48 hours, or by maintaining the reaction mixture at temperatures even higher than 150° C., may also be utilized.

As set forth hereinabove, the condensation products produced according to this invention are generally hard, resinous materials. However, they may be readily ground to any desired degree of fineness and may be dissolved in solvents such as ketones and in hydrocarbons having a high degree of solvent activity. Excellent varnishes may be produced from the resins simply by cooking the resins with drying oils and thinning to a suitable viscosity. Coatings produced from such varnishes are flexible, generally light in color and possess excellent resistance to impact, hot water, and alkalis.

It is to be understood that while the resins are generally recovered as hard, brittle materials, the condensation reaction whereby they are obtained proceeds through a stage during which the resin may be recovered as a liquid material. These liquid resins are also useful in the preparation of varnishes.

The resins of the present invention may also be used as molding compositions for the production of articles under pressure. In the preparation of a molding composition, plasticizers, lubricants, fillers, pigments and coloring matter may be incorporated if desired. The molding temperature should be such that the shaping and molding take place at a reasonable rate, but should not be so high as to cause excessive discoloration of the desired product.

The following examples illustrate more fully the preparation of alkenylphenol mixtures by the reaction of conjugated dienes with phenols, and also the preparation of resins by the acidic condensation of a mixture of alkenylphenols with an aldehyde. The examples are not, however, intended to limit the scope of the invention, for there are, of course, numerous possible variations and modifications. In the examples all parts are by weight.

Example I

Fifty-four grams (1.0 mole) of butadiene-1,3 in 100 cc. of toluene were added to a mixture of 94 grams (1.0 mole) of phenol, 100 cc. of toluene, 23 grams of polyphosphoric acid, and 10 grams of 85 percent syrupy phosphoric acid, whereupon an exothermic reaction took place. The reaction mixture was then stirred and maintained at room temperature for about 14 hours, after which the product was washed and the mixture fractionally distilled. Sixty grams of mixed monobutenylphenols, and minor quantities of di- and tributenylphenols were obtained.

Example II

Twenty-eight grams of titanium tetrachloride were added to a mixture of 94 grams (1.0 mole) of phenol, 65 grams (1.2 moles) of butadiene-1,3 and 200 cc. of toluene cooled to a temperature of −10° C. An exothermic reaction resulted and the reaction mixture was cooled and maintained at room temperature for 16 hours. The reaction mixture was then washed to remove the catalyst and distilled at reduced pressures. A yield of monobutenylphenols of about 85 percent, together with minor quantities of di- and tributenylphenols, was obtained.

Example III

Seventeen pounds of toluene, 17 pounds of phenol and 28.8 pounds of 67.2 percent sulfuric acid were charged into a glass-lined reactor and the reactor was then sealed. Ten and three tenths pounds of butadiene-1,3 were then added to the reactor over a period of about 15 minutes, the temperature of the reaction mixture being maintained at about 55° F. The reaction mixture was then agitated for about 18 hours after which agitation was stopped to allow the acid layer to settle out. The acid was then drawn off and the remainder of the reaction mixture treated with sodium carbonate to neutralize any remaining traces of acid. The reaction mixture was then distilled to remove the toluene. A 59 percent yield of monobutenylphenols was obtained. The remainder of the reaction mixture contained dibutenylphenols (8.0 percent), higher boiling phenols (29.0 percent) and unreacted phenol and ethers (4.0 percent).

Example IV

One hundred forty-eight parts of a mixture of monobutenylphenols (ortho- and parabutenylphenols), dibutenylphenol and tributenylphenol, 65 parts of formalin (37 percent formaldehyde), and 5 parts of concentrated hydrochloric acid were admixed and stirred for 16 hours at steam temperature (92–96° C.). The phenolic layer was then washed with hot water five times and dehydrated at steam temperature under 20–50 mm. pressure. The product was a hard, resinous material which could be cooked into drying oils to give fast drying, light colored varnishes.

Example V

Fourteen hundred eighty grams of a mixture of monobutenylphenols were placed in a reaction vessel fitted with a stirrer. To the mixture of butenylphenols 678 grams of formalin and 50 grams of concentrated hydrochloric acid were added and stirring was continued for 16 hours, the temperature being maintained at about 25° C. Two hundred cubic centimeters of butanol were then added and the reaction vessel fitted with an azeotropic separator. The water was distilled off after which inert gas was passed into the reaction mixture beneath the liquid level and the mixture blown until all the butanol was removed. A light colored, hard resinous material was obtained in a yield of 106 percent based on the weight of the phenols utilized.

Example VI

One hundred sixty-two grams (1 mole) of a mixture of pentenylphenols were placed in a glass-lined reactor fitted with a condenser. Sixty-four and eight tenths grams of formalin solution (0.8 mole formaldehyde) were then added to the pentenylphenols at a temperature of 24° C. Five cc. of concentrated hydrochloric acid were added slowly through the condenser, the temperature rising to 28° C. during the addition of the acid. The reaction mixture was then heated at 95° C. for 2 hours, during which time the reaction mixture was continuously agitated The reaction mixture was then distilled at reduced pressures until all of the water was removed, the percent solids at that point being 76 percent. A 100 gram sample of the resin was heated and blown with an inert gas at 175° C. The resulting resin was hard and brittle. A second sample was baked at 175° C. for 1½ hours. After cooling the sample was very hard.

The total weight of resin obtained from the condensation reaction was 152.0 grams.

Example VII

Example VI was repeated except that 1 mole of a mixture of cyclopentenylphenols was substituted for the mixture of pentenylphenols utilized in Example VI. One hundred fifty-nine and two-tenths grams of a gum-like resin having 95.6 percent solids were obtained. On baking at 175° C. for 1½ hours a very hard, grindable resin was obtained.

Example VIII

The resin prepared in Example V was used in the preparation of a varnish as follows: The resin and linseed oil, in a ratio of 2 parts of resin to 1 part of linseed oil were charged into a reactor and heated to 300° C. under an inert gas atmosphere. This temperature was maintained until a 25 to 30 inch string was obtained. The resulting reaction product was then poured into an equal weight of solvent. A varnish having a solids content of about 50 percent in naphtha was obtained. The resulting varnish formed a hard, non-marring finish when applied to a wooden surface.

Example IX

A portion of the resin obtained in Example V is ground to a fine powder, placed in a mold and pressure applied at a temperature of about 350° F. A hard, chemical-resistant molding is obtained.

From the foregoing description of the invention it will be seen that the alkenylphenol-aldehyde resins of the present invention constitute a new and useful class of resinous materials. It is apparent, therefore, that various embodiments of the invention, in addition to those specifically disclosed, may be provided without departing from the spirit and scope of the invention as defined in the appended claims.

We claim:

1. A light colored resinous material comprising the product of the acidic condensation of an aldehyde containing only atoms of carbon, hydrogen, and oxygen, with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and 15 percent to 45 percent by weight of di- and tributenylphenols.

2. The light colored resinous material of claim 1 wherein the aldehyde is formaldehyde.

3. The method which comprises condensing an aldehyde containing only atoms of carbon, hydrogen, and oxygen with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and about 15 percent to 45 percent by weight of di- and tributenylphenols, in the presence of an acidic catalyst, thereby to obtain a hard, resinous material characterized by its ability to form fast drying, light colored coatings.

4. The method of claim 3 wherein the aldehyde utilized is formaldehyde.

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Patented July 15, 1958

2,843,566

ALKENYLPHENOL-ALDEHYDE

Roger M. Christenson, Whitefish Bay, and Lowell O. Cummings and Alfred R. Bader, Milwaukee, Wis., assignors to Pittsburgh Plate Glass Company

No Drawing. Application November 3, 1953
Serial No. 390,089

8 Claims. (Cl. 260—53)

This invention relates to the preparation of novel and useful phenol-aldehyde type resins, and pertains more particularly to the preparation of such resins by the alkaline condensation of an aldehyde with a mixture of alkenylphenols.

It is known that a phenol having an unsaturated open chain hydrocarbon substituent can be condensed with an aldehyde, and particularly formaldehyde, to form resins intended for use in coating compositions such as varnishes, lacquers and the like. A condensation reaction of this type is described in U. S. Patent 2,006,043. This patent, however, discloses that the resulting resins produce slow drying films and additionally are reddish or reddish-brown in color. As a result, these resins are generally unsatisfactory for use in coating compositions.

To overcome the objectionable color and drying characteristics possessed by such unsaturated phenol-aldehyde resins, certain substituted phenols, specifically monosubstituted phenols whose substituent is a monoolefinic hydrocarbon radical, said radical being in the para position and having from 3 to 4 carbon atoms, have been condensed with formaldehyde in the presence of a zinc salt of an organic acid whose strength is not substantially greater than that of formic acid. The use of para-substituted phenols was considered to be a critical expedient in this latter process, since it was heretofore believed that ortho-substituted phenols produce resins which are very dark and in general are unsatisfactory for use in coating compositions. This second method, while producing resins which are light-colored, is not particularly satisfactory for use on a commercial scale in that only certain specific para-substituted phenols can be utilized and since it is quite difficult and costly to obtain relatively pure para-substituted phenols. Moreover, only certain specific acidic catalysts can be employed in this latter process.

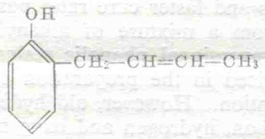
It has now been discovered that excellent resins of the phenol-aldehyde type are obtained by condensing an aldehyde such as formaldehyde with a mixture of alkenylphenols in the presence of an alkaline catalyst. The resins thus obtained produce films which are fast drying and curing, and very light colored. Also the resins possess excellent alkali resistance and electrical properties, and are extremely compatible with varnishes and drying oils and other materials utilized in the preparation of coating compositions, such as epoxide resins, alkyd resins, vinyl resins and polyvinyl acetal resins. In general, the resins obtained by the method of this invention are superior in a number of properties to those obtained when a single unsaturated phenol is condensed with an aldehyde.

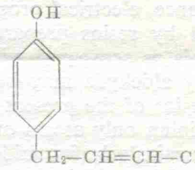
The mixture of alkenylphenols which is condensed with an aldehyde in accordance with the present invention may vary widely in composition. Ordinarily, the predominant component of the mixture is one or more monoalkenylphenols (including ortho- and para-monoalkenylphenols), the monoalkenyl component constituting about 55 to 85 percent by weight of the total mixture. The balance of the mixture (about 15 to 45 percent) is composed primarily of di- and trialkenylphenols, although other phenolic materials, including polyphenols such as alkane di- and triphenols may also be present, depending upon the method by which the alkenylphenol mixture is prepared.

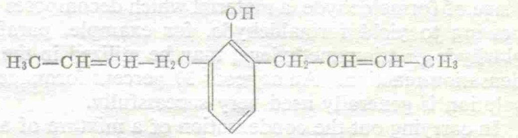
Mixtures of alkenylphenols of the type described in the foregoing paragraph are readily obtained by the methods described in copending applications, Serial No. 300,359, filed July 22, 1952, and Serial Nos. 337,226, 337,227, 337,228 and 337,229, all filed February 16, 1953. The methods described in these copending applications involve the reaction of conjugated dienes with phenolic compounds in the presence of certain catalysts such as the Friedel-Crafts compounds. For example, the reaction product obtained by the reaction of butadiene-1,3 with phenol in the presence of an aqueous sulfuric acid catalyst is generally composed of less than about 15 percent unreacted phenol, less than about 5 percent of ethers, 55 to 70 percent of monobutenylphenols and 15 to 50 percent of the higher boiling phenols including di- and tributenylphenols and polyphenols. Ordinarily, the unreacted phenol and ethers will be removed from the reaction mixture by distillation before the condensation reaction with an aldehyde is carried out; however, this is not a critical expedient and the condensation reaction takes place readily even though the unreacted phenols and ethers are not removed. Mixtures containing smaller quantities of monoalkenylphenols and larger quantities of the higher boiling phenols, for example, about 50 percent monoalkenylphenols and 30 to 50 percent of higher boiling phenols and the balance polyphenols and ethers, may also be employed with good results, as may mixtures containing no monoalkenylphenols. Also, the mixture may be composed entirely of ortho- and para-monoalkenylphenols, and, in fact, excellent resins are obtained when such a mixture is employed. Mixtures of alkenylphenols with other phenols containing no unsaturated side chain, such as phenol, butylphenol, amylphenol and the like may also be used.

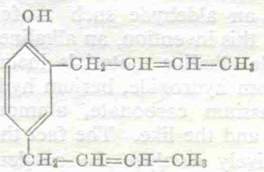
It is to be understood that mixtures of alkenylphenols can also be obtained by other methods known to the art in addition to the reaction of conjugated dienes with phenolic compounds, and it is intended that the present invention include the use of any mixture of alkenylphenols regardless of the method whereby it is obtained.

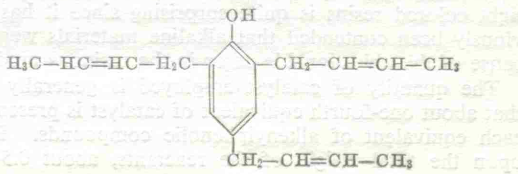
As illustrative of the alkenyl substituted phenolic compounds which in admixture are condensed with an aldehyde to form the novel resins of the present invention there are set forth below the products of the reaction of butadiene-1,3 and phenol:





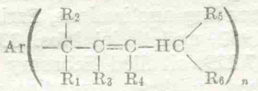






A mixture of the above alkenylphenols forms excellent resins when condensed with an aldehyde in the presence of an alkaline catalyst.

In general, the alkenylphenolic compounds in the mixtures condensed with aldehydes possess the structure



wherein Ar is an aromatic radical, R_1, R_2, R_3, R_4, R_5 and R_6 are hydrogen, halogen or an organic radical, such as a hydrocarbon radical, and which may be the same or different, and *n* is a number, ordinarily from 1 to 3. The alkenyl compounds of the above structure are all readily obtained by the reaction of phenolic compounds with conjugated dienes in accordance with the methods described in the copending applications.

Phenolic compounds which may be reacted with conjugated dienes to give compounds of the above structures include phenol, catechol, resorcinol, pyrogallol, tertiary butyl catechol, beta-naphthol, guaiacol, o-, m- and p-cresols, 2,3-xylenol, 2,5-xylenol, 3,4-xylenol, m-alkylphenols, bis(4-hydroxyphenyl) 2,2-propane, and the like.

Typical conjugated dienes which react with phenolic compounds to form the desired mixture of alkenylphenols include butadiene-1,3, 2-methylbutadiene-1,3, piperylene, 2-methyl-pentadiene-1,3, hexadiene-1,3, 1-chloro-2-methylbutadiene-1,3, cyclopentadiene, and the like.

The preferred alkenylphenolic compounds for condensation with aldehydes in accordance with the present invention are mixtures of the butenylphenols, including ortho- and para-2-butenylphenols, di-2-butenylphenol and tri-2-butenylphenol. However, mixtures of other alkenylphenolic compounds may also be used, including butenylcresols, butenylcatechols, butenyl-2,3-dimethoxyphenols, mono-, di- and tributenylresorcinol, mono-, di- and tributenylguaiacol, 2-chlorobutenylcresol, 2-chlorobutenylphenol, 2-iodobutenylphenol, ortho- and para-cyclopentenylphenol, pentenylphenol, pentenylcresol, pentenylguaiacol, halopentenylphenols, halopentenylguaiacols, and the like.

It may be that the trialkenylphenols such as the tributenylphenols do not actually condense with aldehydes as do the mono- and dialkenylphenols, but instead react through the unsaturated linkages and the OH group. This type of reaction is of course not possible with conventional phenols and may account for the improved alkali resistance, electrical properties and faster cure rates possessed by resins prepared from a mixture of alkenylphenols as compared with conventional phenolic resins.

Any aldehyde may be utilized in the preparation of the resins of the present invention. However, aldehydes containing only atoms of carbon, hydrogen and oxygen, and particularly formaldehyde, are greatly preferred. In place of formaldehyde, a material which decomposes upon heating to yield formaldehyde, for example, paraformaldehyde or trioxymethylene, may be utilized in the condensation reaction. An aqueous 37 percent formaldehyde solution is generally used very successfully.

In carrying out the condensation of a mixture of alkenylphenols with an aldehyde such as formaldehyde in accordance with this invention, an alkaline catalyst is employed. Suitable alkaline materials include sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, ammonia, hexamethylenetetraamine and the like. The fact that alkaline materials so effectively catalyze the condensation to give light colored resins is quite surprising since it has previously been contended that alkaline materials were the cause of the objectionable color in the resinous products.

The quantity of catalyst employed is generally such that about one-fourth equivalent of catalyst is present for each equivalent of alkenylphenolic compounds. Based upon the total weight of the reactants, about 0.5 percent to about 5.0 percent of alkaline material is utilized. Larger amounts of the catalyst may be employed if desired.

Alternatively, the catalyst may be dispensed with entirely, although higher reaction temperatures may then be required with attendant increase in darkening of the resinous product.

The molar ratio of aldehyde to alkenylphenols utilized in carrying out the condensation reaction of the present invention may be varied widely. Best results are obtained when about 2.0 moles of the aldehyde are utilized for each mole of the alkenylphenolic compounds in the reaction mixture. However, the ratio may be as low or lower than 0.5 to 1.0 or as high or higher than 5.0 to 1.0. When the ratio is much below the preferred 1.5 to 2.0 ratio the resinous product tends to be hard and more difficultly processable. When the ratio is substantially above 1.5 to 1.0 good results are obtained but there is no economical advantage in utilizing such large excess of the aldehyde.

The condensation reaction is best carried out by first admixing the alkenylphenols and the catalyst under an inert atmosphere such as nitrogen, and/or in the presence of sodium hydrosulfite, utilizing sufficient cooling to maintain the resulting reaction mixture at about room temperature (25° C.). When solution is obtained the aldehyde is added at a moderate rate and cooling is applied as needed to keep the temperature below about 35° C. Care should be taken to keep traces of air out of the reactor at all times during the condensation. Stirring is continued for about 48 hours at room temperature.

At the end of this time the reaction mixture is carefully acidified to a pH of about 5.0 with a mineral acid such as hydrochloric acid or sulfuric acid, or a carboxylic acid such as acetic acid or propionic acid. Two layers are formed, a water layer and an alkenylphenolic resin layer. The water layer is drawn off and the water-insoluble layer of resin is water-washed four or five times. At this point it is advantageous to add about 0.1 percent by weight of a material such as an amino tetracarboxylic acid which forms a complex with any iron in the reaction mixture. The presence of uncomplexed iron is likely to cause darkening of the product. The resin is then dehydrated by vacuum stripping at steam temperatures and at a pressure of about 20 mm. to 55 mm. Alternatively, the water can be removed by adding butanol and then carrying out an azeotropic distillation.

While the above-described method for carrying out the condensation is preferred, particularly when the alkenylphenol mixture is a mixture of butenylphenols, other methods of carrying out the condensation, for example, simply by admixing the reactants and catalyst and allowing the mixture to stand at room temperature for about 48 hours, or by maintaining the reaction mixture at temperatures as high as 100° C. or higher, may also be utilized. In the event that higher temperatures are utilized the condensation will, of course, require less time than when the condensation is carried out at room temperature.

While the resins of this invention are generally recovered as viscous liquids, it is also possible to obtain hard resinous materials by condensing equimolar quantities of alkenylphenols and aldehyde in the presence of an alkaline catalyst and then acidifying the reaction mixture to a pH of about 2.0. The resulting hard materials are useful as varnish resins. They can also be ground with paraformaldehyde to give compositions which are useful as molding powders.

The following examples illustrate more fully the preparation of alkenylphenol mixtures and the preparation of resins by the condensation of a mixture of alkenylphenols with an aldehyde. The examples are not, however, intended to limit the scope of the invention, for there are, of course, numerous possible variations and modifications. In the examples all parts are by weight.

Example I

Fifty-four grams (1 mole) of butadiene-1,3 in 100 cc. of toluene were added to a mixture of 94 grams (1 mole) of phenol, 100 cc. of toluene, 23 grams of polyphosphoric acid, and 10 grams of 85 percent syrupy phosphoric acid, whereupon an exothermic reaction took place. The reaction mixture was then cooled to room temperature and stirred for about 14 hours, after which the product was washed and the mixture fractionally distilled. Sixty grams of mixed monobutenylphenols, and minor quantities of di- and tributenylphenols were obtained.

Example II

Twenty-eight grams of titanium tetrachloride were added to a mixture of 94 grams (1 mole) of phenol, 65 grams (1.2 moles) of butadiene-1,3 and 200 cc. of toluene cooled to a temperature of −10° C. An exothermic reaction resulted and the reaction mixture was maintained at room temperature for 16 hours. The reaction mixture was then washed to remove the catalyst and distilled at reduced pressures. A yield of monobutenylphenols of about 85 percent, together with minor quantities of di- and tributenylphenols, was obtained.

Example III

Seventeen pounds of toluene, 17 pounds of phenol and 28.8 pounds of 67.2 percent sulfuric acid were charged into a glass-lined reactor and the reactor was then sealed. Ten and three-tenths pounds of butadiene-1,3 were added to the reactor over a period of about 15 minutes, the temperature being maintained at about 55° F. The reaction mixture was then agitated for about 18 hours after which agitation was stopped to allow the acid layer to settle out. The acid was drawn off and the remainder of the reaction mixture treated with sodium carbonate to neutralize any remaining traces of acid. The reaction mixture was then distilled to remove the toluene. A 59.0 percent yield of monobutenylphenols was obtained. The remainder of the reaction mixture contained dibutenylphenols (8.0 percent), higher boiling phenols (29.0 percent) and unreacted phenol and ethers (4.0 percent).

Example IV

One hundred forty-eight parts of a mixture of monobutenylphenols (o- and p-monobutenylphenols) and 10 parts of sodium hydroxide in 100 parts of water were mixed under a nitrogen atmosphere with sufficient cooling to keep the temperature below 35° C. When a homogeneous solution was obtained, 162 parts of 37 percent formalin, methanol free, containing 60 grams (2 moles) of solid formaldehyde were added at a moderate rate and cooling was applied to keep the temperature below about 35° C. Stirring was continued for about 48 hours at room temperature. At the end of this time the reaction mixture was acidified to a pH of 5.0 with a mixture of concentrated hydrochloric acid and water (50 percent acid and 50 percent water) and the resulting water insoluble layer of the resin was washed four times with lukewarm water. The resin was then dehydrated by vacuum stripping at steam temperatures under 20 to 50 mm. pressure. The yield based on the quantity of alkenylphenols utilized was 120 percent, the color was 10 to 14 (Gardner), the viscosity at 25° C. was W to Z (Gardner-Holdt), and the resulting resin was completely miscible with ethanol, butanol, toluene, and xylene. The resin thus prepared gave a hard film on baking for only 30 minutes at about 150° C.

Example V

Example IV is repeated using each of the following formaldehyde:butenylphenol ratios: 0.8:1, 1:1, 2:1, and 4:1. In each run a resin is obtained which gives light colored, fast curing films and which is compatible with drying oils and a great many other film forming materials.

Example VI

Several aldehydes were condensed with mixed butenylphenols prepared according to Example III, acetic acid being utilized to acidify the reaction mixture in each run. The aldehyde utilized, the catalyst concentration, the mole ratio of aldehyde to butenylphenol, the reaction time and temperature (degrees centigrade) are set forth in the following table:

Aldehyde	Catalyst	Mole Ratio Of Aldehyde To Mixed Butenylphenols	Reaction Time and Temperature (Degrees C.)
Furfural	3% Sodium Hydroxide	1:1	25° C.—48 hrs.
Crotonaldehyde	4% Sodium Hydroxide	4:1	25° C.—90 hrs.
Acetaldehyde	do	4:1	Do.

The resins obtained utilizing each of the above aldehydes formed hard alkali resistant films when applied to a metal surface and baked.

Example VII

One hundred sixty parts of a mixture of cyclopentenylphenols, 130 parts of 37 percent formalin solution and 1 part of sodium hydroxide in 5 parts of water were admixed and stirred at steam temperature (92° C. to 96° C.) for 1.5 hours, then acidified with acetic acid, water washed five times and dehydrated several hours at steam temperatures under 20 mm. to 50 mm. pressure. The resinous material obtained was coated on a metal surface and baked at 150° C. for 30 minutes to give a hard, acetone insoluble film.

Example VIII

Twenty parts by weight of a mixture consisting of 12.3 percent unreacted phenol and ethers (B. P. 70° C.–100° C. at 10 mm.), 66.3 percent monobutenylphenols (B. P. 110° C.–140° C. at 10 mm.), and 20.4 percent of di- and tributenylphenols (the mixture being obtained by the method of Example III), 20 parts by weight of 37 percent aqueous formaldehyde, and 0.4 part by weight of hexamethylenetetramine were heated under reflux on a steam bath for about 16 hours. The water and unreacted formaldehyde were then removed by distillation, leaving a resin soluble in ethyl alcohol, ethyl acetate, benzene, toluene, and aromatic naphthas, but insoluble in aliphatic hydrocarbons.

Example IX

Fifteen hundred and fifteen grams of a mixture of di- and tributenylphenols, 300 grams of sodium hydroxide and 1500 grams of water were admixed to form a solution. To the resulting solution 1215 grams of formalin were added, the temperature of the mixture being maintained at 25° C. Nitrogen gas was maintained over the surface of the reaction mixture for 120 hours after which the reaction mixture was acidified to a pH of 3.4, a lower water layer and a resinous top layer forming during the acidification. The water layer was then withdrawn and the resinous layer washed five times with water and distilled until a viscosity of W (Gardner) was obtained. The resulting resin formed acetone insoluble, alkali resistant, flexible films when coated onto metal and glass surfaces. The films cured to the acetone insoluble stage in only ten minutes at about 175° C.

Example X

Thirteen hundred fifteen and one-half grams of a mixture of mono-, di-, and tributenylphenols, 1440 grams of formalin solution and 144 grams of aqueous ammonium hydroxide were admixed with stirring, the temperature of the mixture rising to 97° C. during the addition period. The reaction mixture was then held at about 100° C. for 6 hours, after which the hot water layer was decanted and the remainder of the reaction mixture was distilled to strip off excess water, formaldehyde and ammonium hydroxide. A resin having a solids content of 94.2 percent, and useful in the formation of films was obtained.

Example XI

Two hundred and sixty-one grams of a mixture of m-alkylalkenylphenols (obtained by the alkenylation of a mixture of phenols which are produced by the hydrogenation of coal), 162 grams of formalin and a solution of 10 grams of sodium hydroxide in 300 grams of water were admixed to form a solution. The resulting solution was maintained at about 30° C. for approximately 24 hours, the surface of the reaction mixture being blanketed with nitrogen gas during the 24 hour period. Additional formalin in the amount of 34 grams was added and the reaction mixture allowed to stand for 24 hours. The reaction mixture was then acidified with hydrochloric acid to a pH of 4.0, and the water layer which formed was decanted. The resinous top layer was washed with water and dried. A resin having a Gardner viscosity of Z_6 and a solids content of 91.2 percent was obtained. Films from this resin possessed properties in general equivalent to those obtained utilizing resins prepared from a mixture of butenylphenols as in the preceding examples.

Example XII

The following materials were charged into a glass lined reactor:

24.6 pounds mixed butenylphenols (monobutenylphenols, di- and tributenylphenols)
27.0 pounds formalin solution (37 percent formaldehyde)
1.7 pounds sodium hydroxide
1.7 pounds water
0.12 pound sodium hydrosulfite

The resulting mixture was cooled to 75° to 80° F. and the reaction mixture agitated for 5 hours after which it was allowed to stand for 43 hours. The reaction mixture was then acidified to a pH of 5.0 with 68 percent sulfuric acid, and allowed to stand until a water layer settled out. The water layer was then drawn off and discarded. The wet resin (36.25 pounds) was treated with 0.04 pound of an amino tetracarboxylic acid known commercially as Sequestrene AA. The resin was then heated to 220° F. and stripped with an inert gas (nitrogen) until a Gardner viscosity of W at 75 percent solids in normal butanol was reached. The resin was then thinned with 10 pounds of n-butanol and filtered at 110° F. The following is the analysis of the final material.

Weight per gallon	8.45 pounds.
Solids	66.2 percent at 110° C.
Viscosity	Q to R (Gardner).

The resin thus prepared was roller coated on tinplate and cured at 350° F. for 20 minutes. The resulting film was of a thickness such that the film weighed 16 mgs./4 sq. in., and was light colored, mar-resistant and insoluble in acetone.

Example XIII

Sixteen hundred twenty grams of a mixture of pentenylphenols, 1620 grams of formalin solution (37 percent formaldehyde), 100 grams of sodium hydroxide in 100 grams of water, and 8 grams of sodium hydrosulfite were charged into a glass reactor and the resulting mixture stirred for 48 hours at a temperature of 25° C. to 30° C. The reaction mixture was acidified with 70 percent sulfuric acid until a pH of 5 was reached. The water layer which had formed was drained off and 2 grams of Sequestrene AA were added to the resin layer. The resin layer was then dried by blowing with an inert gas for 3 hours at 100° C. to give a resin having a viscosity of Z_6. This resin was thinned with 622 grams of butanol to give a final product having 63.7 percent solids and a

viscosity of V. The resulting resin baked to a hard, acetone resistant film in generally the same manner as resins prepared from a mixture of butenylphenols.

As disclosed hereinabove resins prepared according to the foregoing examples possess many valuable properties not possessed by other phenolic resins; for example, films prepared with resins obtained by the condensation of a mixture of alkenylphenols with an aldehyde are tough, transparent and glossy after only 30 minutes' heating at about 150° C. Films prepared from other phenolic resins, including those prepared according to the method of U. S. Patent 2,006,043 require heating at several hours at temperatures of 125° C. to 150° C. to secure a hard film, which even then is very dark in color.

Moreover, when the resins of this invention are plasticized with small quantities of a polyvinyl acetal resin, preferably polyvinylbutyral, the resins cure in only 10 minutes at 175° C. and at even lower temperatures when catalyzed with a material such as phosphoric acid, toluenesulfonic acid or the like. Other available phenolic resins require a minimum of 20 minutes at 200° C. The plasticized resin also possesses extremely good alkali resistance, withstanding 200 hours' immersion in 3 percent alkali without loss of adhesion, blistering or hydrolysis. A similar film prepared from the resinous product obtained by the condensation of formaldehyde with the trimethylol allyl ether of phenol (a commercially available phenolic), with the acetal resin plasticizer almost immediately discolors to a dark brown and blisters badly in 24 hours when immersed in 3 percent alkali.

Other advantages possessed by the resins of this invention include excellent solvent resistance, extremely light color in thin films with no discoloration on overbaking, good flexibility, impact resistance and adhesion, excellent hardness and non-marring surface, good solubility, good compatibility, and high solids content at medium viscosity. One particular advantage is that they do not impart taste to foods. These valuable properties are particularly desirable in applications such as sanitary liners for food containers, drum liners, and electrical insulating varnishes, as well as in other specific fields where thin film protection is desired.

Gelling of the phenolic resins prepared according to this invention can be greatly accelerated by the addition of catalysts such as p-toluene sulfonic acid, phosphoric acid, oxalic acid, zinc chloride, sulfanilic acid, ethylene diamine, benzoyl peroxide and the like. For example, p-toluene sulfonic acid causes the phenolic resins to gel in as little as 3 minutes.

The alkenylphenol-aldehyde resins of the present invention are reactive due to the presence of the additional unsaturated linkage in the side chain or chains and are in themselves capable of condensing with a variety of other materials to provide products having improved properties. For example, drying oils add a substantial degree of flexibility to the baked resin films. The resins have also been blended or compounded with such other materials as linseed alcohols, octadecanol, aniline, styrenated maleinized alkyds having excess hydroxyl groups, epoxy resins, and with synthetic rubbery materials such as liquid polybutadiene. In each instance excellent film forming properties were obtained.

Varnishes prepared utilizing the resins described herein form films which are light colored, fast drying and extremely resistant to the action of alkalis. It has also been found that these resins cook into varnish oils at a much faster rate than do other phenol-aldehyde resins. The resins themselves may be bodied by blowing an inert gas through the heated material.

From the foregoing description of the invention it will be seen that the alkenylphenol aldehyde resins of the present invention constitute a new and useful class of resinous materials. It is apparent, therefore, that various embodiments of the invention, in addition to those specifically disclosed, may be provided without departing from the spirit and scope of the invention as defined in the appended claims.

We claim:

1. A light colored resinous material comprising the product of the alkaline condensation of an aldehyde containing only atoms of carbon, hydrogen, and oxygen, with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and about 15 percent to 45 percent by weight of di- and tri-butenylphenols.

2. The light colored resinous material of claim 1 wherein the aldehyde is formaldehyde.

3. A light colored resinous material comprising the product of the alkaline condensation of an aldehyde containing only atoms of carbon, hydrogen, and oxygen, with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and about 15 percent to 45 percent by weight of di- and tri-butenylphenols, the ratio of aldehyde to butenylphenols utilized in said alkaline condensation reaction being from about 0.5 mole to 5.0 moles of aldehyde per mole of the butenylphenols.

4. The light colored resinous material of claim 3 wherein the aldehyde is formaldehyde.

5. The method which comprises condensing an aldehyde containing only atoms of carbon, hydrogen, and oxygen, with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and about 15 percent to 45 percent by weight of di- and tri-butenylphenols, in the presence of an

alkaline catalyst, thereby to obtain a resinous material characterized by its ability to form fast drying, light colored coatings.

6. The method of claim 5 wherein the aldehyde utilized is formaldehyde.

7. The method which comprises condensing an aldehyde containing only atoms of carbon, hydrogen, and oxygen, with a mixture of butenylphenols containing about 55 percent to 85 percent by weight of ortho- and para-monobutenylphenols, and about 15 percent to 45 percent by weight of di- and tri-butenylphenols, in an amount such that there is present about 0.5 mole to 5.0 moles of aldehyde per mole of the butenylphenols, and in the presence of an alkaline catalyst, thereby to obtain a resinous material characterized by its ability to form fast drying, light colored coatings.

8. The method of claim 4 wherein the aldehyde utilized is formaldehyde.

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CYCLOPENTENYL PHENOLS AND METHOD FOR PREPARING THEM

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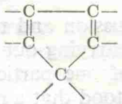
No Drawing. Application July 22, 1952
Serial No. 300,359

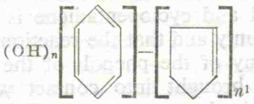
9 Claims. (Cl. 260—621)

The present invention relates to the reaction of cyclopentadiene, substituted cyclopentadienes, or homopolymers of such cyclopentadienes with phenols, whereby substituted phenolic compounds or polymeric products or both are obtained, and pertains particularly to the preparation of cyclopentenylphenols, which are very useful for many purposes.

In accordance with the provisions of the present invention, phenols containing at least one available hydrogen atom in the nucleus are contacted with compounds containing the group



in the presence of a Friedel-Crafts catalyst whereupon chemical reaction occurs to form compounds of the general formula;



In the formula, *n* and n^1 are whole numbers, usually from 1 to 3 and may be equal or unequal. In addition to compounds of the above type, some polyphenols or polymeric products, or both, are generally formed, the quantities of each product depending primarily on the particular reaction conditions which are employed.

The present invention is particularly applicable to compounds containing a single —OH group, e. g. phenol. However, the invention also includes the treatment of other hydroxylated benzenes or phenols including two or even three hydroxyls. They may also contain one or more alkoxy, hydrocarbon, or other substituent groups as side-chains. There must be at least one free or available hydrogen atom in the benzene ring in order that reaction with the cyclopentadiene may take place. Examples of such phenols containing a plurality of hydroxyls directly attached to a benzene ring are polyhydroxy phenols such as catechol, resorcinol, pyrogallol and phloroglucinol;

Alkylated phenols such as ortho cresol, meta cresol, para cresol, butyl resorcinol, and tertiary butyl catechol;

Substituted phenols such as ortho, meta or para nitrophenols and the corresponding amines derived by reduction of the nitrophenols, ortho, meta and parahalophenols, polyhalophenols, halogen substituted nitrophenols, guaiacol, 2,3-dimethoxyphenol, 3,5-dimethoxyphenol and the like.

Any of the phenolic compounds or derivatives thereof, as well as other phenolic compounds, reacts with cyclopentadiene or its homologues and substitution products to give substituted phenols and polymeric products.

While they do not contain conjugated double bonds, dicyclopentadiene, tricyclopentadiene and other homopolymers of cyclopentadiene may under appropriate conditions also be employed in the reaction, since they can be decomposed pyrolytically at 140° C. or above, to form cyclopentadiene which reacts in situ with phenolic compounds such as are described above.

Cyclopentadiene, or its equivalent of a lower homopolymer of cyclopentadiene, may be reacted with a phenolic compound over a wide range of molar proportions in accordance with the provisions of the present invention. For example, the proportion of the phenol and cyclopentadiene may be equi-molar or approximately equi-molar. However, most usually an excess of phenol is employed, since highest yields of the mono cyclopentenyl phenolic compounds are obtained when excess phenol is utilized. If yields are not of the essence, almost any proportions may be employed in the reaction. For example, the cyclopentadiene component may be employed in a molar percentage of 10 to 100 or even 200 or 300 or more percent with respect to the phenolic component in the mixture.

The reaction of the present invention may be carried out in the absence of diluent or solvents. However in many instances it is preferred to include such material in the reaction mixture. The diluent or solvent naturally should be non-reactive in the mixture. Examples of such diluents include hexane, heptane, toluene, xylene and other aromatic and non-aromatic hydrocarbons and similar non-reactive materials.

The temperature at which the reaction is carried out may be varied widely. For example, the reaction proceeds satisfactorily at temperatures as low as —20° C. or even lower and as high as 200° C. or higher with the preferred range being from about 0° C. to 150° C.

The reaction takes place readily at atmospheric pressure and is advantageously carried out in this manner. However, any added pressure may also be utilized if desired, as may subatmospheric pressures, provided they are not so low as unduly to volatilize the reactants.

The reaction of cyclopentadienes with phenolic compounds in accordance with the present invention is carried out in the presence of a Friedel-Crafts type catalyst. Examples of such catalysts include aluminum chloride, ferric chloride, antimony pentachloride, boron trifluoride, zinc chloride, titanium chloride, hydrofluoric acid, sulfuric acid, phosphoric acid, phosphorus pentoxide, stannic chloride, bismuth chloride and tellurium di and tetra chlorides. The Friedel-Crafts catalysts are discussed in detail in volume 3 of Organic Reactions (1946), pages 2 to 4.

The reaction can also be carried out in the presence of mixtures of two or more of the catalysts disclosed hereinabove. In fact, by selection of the proper catalyst mixture it is often possible to control the number of cyclopentenyl or phenolic groups which are combined. Most Friedel-Crafts catalysts can be placed in one of two series; that of acids, including hydrofluoric acid, sulfuric acid, phosphoric acid, in order of activity, and that of the Lewis acid salts, including aluminum chloride, boron trifluoride, antimony pentachloride, ferric chloride, tellurium dichloride, stannic chloride, titanium chloride, tellurium tetrachloride, bismuth chloride and zinc chloride, also in order of activity. The more active catalysts of these two series are in general too strong to give good yields of monocycloalkenylphenols but yield instead higher molecular weight phenols and other materials. However, the more active catalysts can be "diluted" with one of the less active catalysts or with a diluent to produce a catalyst mixture that will give satisfactory yields of the desired product. Mixtures of sulfuric acid and phosphoric acid, or boron trifluoride and phosphoric acid are examples of catalyst mixtures which give excellent yields of monocycloalkenylphenols. The strong Lewis acid salts are best "diluted" by forming their complexes with compounds such as ethers, alcohols and amines, that is, compounds containing atoms with unshared electron pairs which can form coordinate bonds with the Lewis acid salts. For example, the aluminum chloride-ethanol complex and the boron trifluoride-ether complex are both less active than either aluminum chloride or boron trifluoride alone.

85 percent phosphoric acid, and Friedel-Crafts catalysts of similar strength form a particularly preferred class of catalysts for use in the process of this invention since they are economically obtained and result in the formation of excellent yields of monocycloalkenylphenols.

As will be apparent from the following discussion, the amount of catalyst employed and also the reaction temperature have a substantial effect on the yields of each of the reaction products.

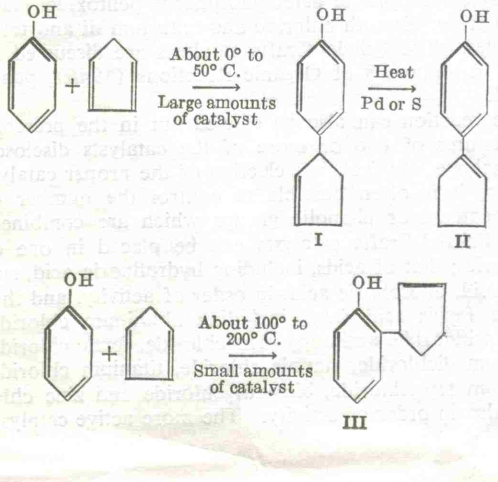
For example, by proper regulation of the conditions of reaction, it is possible to obtain ortho or paracyclopentenylphenol, di or tricyclopentenylphenols, polyphenols or polymeric products substantially at will.

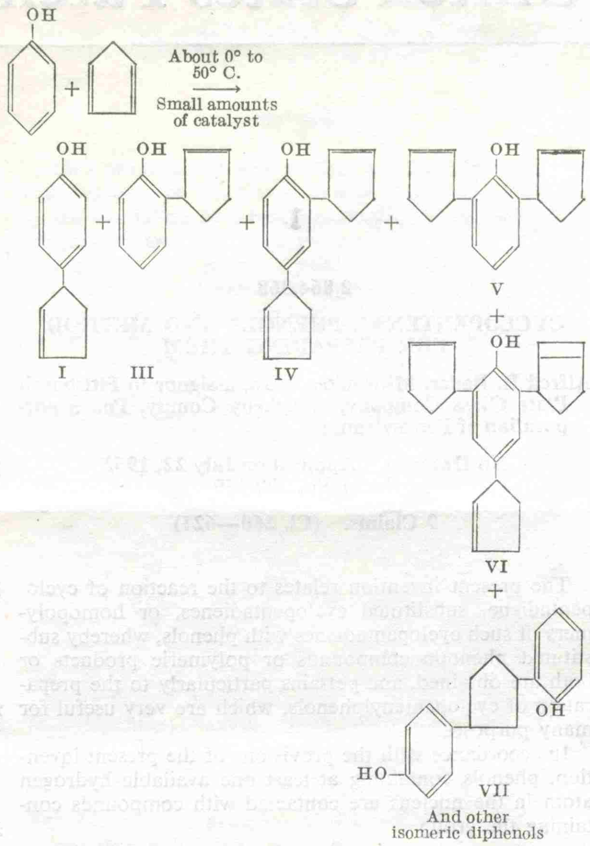
These facts are illustrated in the preparation of orthocyclopentenylphenol which is readily obtained by heating a mixture of phenol and cyclopentadiene to a temperature of about 100° C. to 200° C. in the presence of only a small amount of catalyst, that is, below about five percent by weight based on the weight of the phenol. On the other hand, if the reaction is conducted at a low temperature, for example about 0° C. to 50° C. and in the presence of a considerable proportion of catalyst, for example, about 5 to 100 percent or more based on the weight of the phenol, paracyclopentenylphenol is obtained in high yield.

If the reaction between phenol and cyclopentadiene is conducted at a low temperature, for example, as defined above, and in the presence of only a small amount of catalyst, as also defined hereinabove, the formation of di and tricyclopentenylphenols is favored.

If the reaction between phenol and cyclopentadiene is conducted at high temperatures and in the presence of at least ½ percent of catalyst, a hard, dark, resinous polymer which is extremely acid and alkali-resistant is obtained. The exact structure of the polymer is not kown although it is quite likely that it contains recurring phenol and cyclopentane units in the chain.

The several reactions and the nature of the products formed will be apparent from the following reaction equations:





While the above discussion and reaction equations are directed to methods of carrying out the reaction whereby predominant amounts of one particular product are obtained, it is to be understood that a mixture of the various products, including some polyphenol and polymer are obtained regardless of the manner in which the reaction is carried out. It is also to be understood that the reaction of phenol and cyclopentadiene is used for illustrative purposes only and that the reaction proceeds satisfactorily when any of the phenols of the type described hereinabove are brought into contact with substituted cyclopentadienes in the presence of a Friedel-Crafts type catalyst.

It is apparent from the foregoing reaction equations that paracyclopentenylphenol (compound I) undergoes isomerization in the presence of palladium or sulfur or other isomerization catalyst to give paracyclopentenylphenol in which the double bond is in conjugate relation with respect to a double bond in the phenolic ring. Other cycloalkenylphenols prepared according to the method of the present invention also undergo isomerization in a similar manner. Moreover, the cycloalkenylphenols may also be hydrogenated in the presence of a catalyst such as nickel, platinum or the like to give cycloalkylphenols which are also very useful compounds.

If cyclopentadiene is replaced by dicyclopentadiene or other homopolymer of cyclopentadiene and the resultant mixture of homopolymer and phenol is refluxed in the presence of a Friedel-Crafts catalyst at a temperature of about 150° C. to 180° C. or higher, decomposition of the homopolymer occurs to form cyclopentadiene which reacts with the phenol to give a cyclopentenylphenol; at temperatures below 100° C. the homopolymer does not decompose and the quantity of cycloalkenylphenol formed, if any, is for all practical purposes negligible.

It will be seen from the following examples, which are intended to illustrate more fully the process of the invention, that the reaction of a phenol with a cyclopentadiene proceeds readily whenever the reactants are brought into effective contact with one another in the presence of a Friedel-Crafts type catalyst. The examples are not intended to limit the scope of the invention, for there are, of course, numerous possible variations and modifications.

Example I

In this example phenol and cyclopentadiene are reacted at low temperatures and in the presence of large amounts of catalysts to form a mixture of cyclopentenylphenols consisting largely of I, with small quantities of III, IV, V and VI. In the reaction, 940 grams of phenol are mixed with 1000 cc. of toluene and 297 grams of 85 percent phosphoric acid. To this mixture at a temperature maintained initially at 25° C. is added 340 grams of cyclopentadiene dissolved in 500 cc. of toluene, the addition being effected with continuous stirring of the mixture over a period of two hours. Under these conditions, the reaction temperature rises to 40° C. and the reaction mixture is cooled and stirred for an additional 18 hours. At the end of that time, 180 grams of anhydrous sodium carbonate is added to neutralize the phosphoric acid. The salt is then filtered off and washed with toluene and the resultant filtrate containing the desired product is stripped under a subatmospheric pressure of 10 millimeters (absolute) in order to remove unreacted material such as cyclopentadiene, dicyclopentadiene, solvent and unreacted phenol.

When the reaction is carried out on a small scale it is convenient to neutralize the catalyst with some mild base such as sodium carbonate. However in large scale operations, it may be more economical to remove the acid catalyst by a water-washing process.

After removal of all of the unreacted phenol, there remains 691 grams of a product which is fractionated under a sub-atmospheric pressure of 1.2 millimeters (absolute) to yield 470 grams of paracyclopentenylphenol, and 110 grams of a mixture of dicyclopentenylphenol, and tricyclopentenylphenols. The paracyclopentenylphenol, when redistilled, constitutes a crystalline white solid melting within a range of 62° to 63° C. and boiling at 114° to 117° C. under a pressure of 1.5 millimeters of mercury. Its absorption spectrum in the ultra-violet range shows two maxima, one at 225 mu of log ϵ 3.9 and the other at 279 mu of log ϵ 3.30. The maxima at these wave lengths show that the double bond in the cyclopentene ring is not conjugated with respect to the benzene ring. The product is characterized by forming a crystalline para nitrophenylurethan derivative melting at 173° C. and which depresses the melting point of the para nitrophenylurethan of orthocyclopentenylphenol.

Example II

In this example, low temperatures of reaction and small amounts of catalyst are employed. In carrying out the reaction, a mixture of 940 grams of phenol, 250 milliliters of toluene and 6 grams of 85% phosphoric acid is formed and while the mixture is under agitation at a temperature of 30° C., 165 grams of cold (liquid) cyclopentadiene are added over a period of three hours. The reaction mixture is stirred at room temperature for 18 hours, and at the end of that time the catalyst is neutralized with 8 grams of anhydrous sodium carbonate. Any unreacted starting materials are eliminated by vacuum distillation in the same manner as in Example I. The product (230) grams is then split into three fractions by vacuum distillation. The first fraction is taken within the boiling range of 100° to 135° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes 75 grams and is a mixture of ortho and paracyclopentenylphenol. The second fraction is taken within a boiling range of 135 to 200° C. under a pressure of 1.3 millimeters of mercury (absolute). This fraction constitutes a yield of 80 grams. Redistillation of this fraction yields dicyclopentenylphenol, B. P. 140°–145° C./0.5 mm. n_d^{25} 1.579. There remains in the distillation flask a residue (67 grams) consisting largely of tricyclopentenylphenol and other high molecular weight phenols.

Example III

This example illustrates the use of relatively high temperatures of reaction and small amounts of catalyst in the formation of a reaction product by the interaction of phenol and dicyclopentadiene. In the reaction, a mixture of 2243 grams of phenol, 660 grams of dicyclopentadiene, and 5 grams of syrupy phosphoric acid, are admixed in a flask provided with a reflux condenser, a thermometer and a source of inert gas (carbon dioxide or nitrogen or the like). The mixture is refluxed for 22 hours during which time the temperature varies between 150° and 170° C. These temperatures are at or near the cracking point of dicyclopentadiene.

At the conclusion of the reflux period, the unreacted phenol and dicyclopentadiene are removed by vacuum distillation. There remains 1,132 grams of a reaction product which is washed with water and distilled at a pressure of 0.5 millimeter of mercury (absolute) to yield 895 grams of a light yellow oil. This oil is then agitated with a 10 percent (by weight) solution of aqueous potassium hydroxide in water.

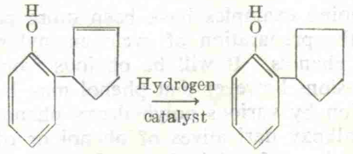
The alkali soluble fraction constituting 330 grams consists of a mixture of phenols, which mixture is largely orthocyclopentenylphenol, and also contains some di and tricyclopentenylphenols, cyclopentanediphenols and polyphenols. The orthocyclopentenylphenol can be purified in any convenient manner, for example, by vacuum distillation, to provide a water white oil. This oil boils at 81° C. under a pressure of 0.4 millimeter of mercury (absolute); n_d^{25} 1.565;

$$d_{25}^{25}\ 1.0755$$

Two maxima are indicated in the ultra-violet spectrum, one being of log ϵ3.8 at 220 mu and the other being of log ϵ3.4 at 275 mu. These maxima show that the double bond in the cyclopentene ring is not conjugated with respect to a double bond in the benzene ring. The product forms a crystalline para nitrophenylurethan derivative melting at 165° C. The urethan derivative is of the formula $C_{18}H_{16}O_4N_2$ and it depresses the melting point of the corresponding derivative of the para isomer by 30° C. The diphenols formed are substantially colorless materials which boil in the range of 160° to 220° C./0.5 mm., the elementary analyses and molecular weight of which is in accord with the formula $C_{17}H_{18}O_2$.

Example IV

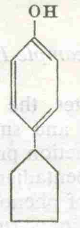
In this example, 46 grams of orthocyclopentenylphenol are dissolved in 200 milliliters of methanol in an autoclave and are hydrogenated at 100° C. over a period of 4 hours, 3 grams of Raney nickel being employed as a catalyst. A yield of 46 grams of orthocyclopentylphenol melting at 26° to 30° C. is obtained. This product can be crystallized from aqueous methanol to form fine white needles with a melting point of 40° C. The reaction is represented by the equation:



Example V

100 grams of paracyclopentenylphenol melting at 62° C. are hydrogenated in methanol solution with an Adams

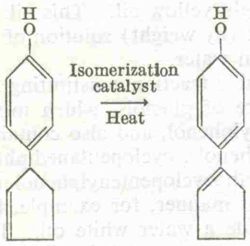
platinum oxide catalyst to yield 100 grams of paracyclopentylphenol



melting at 69° C. This phenol forms a crystalline para nitrophenylurethan melting at 198–199° C.

Example VI

This example illustrates the isomerization, or rearrangement of the double bond in the cyclopentenyl radical of paracyclopentenylphenol (compound I, M. P. 62° C.) to effect conjugation between the double bond of the cyclopentenyl radical and one of the double bonds of the benzene ring. The reaction proceeds in accordance with the following equation:



I II

50 grams of compound (I) are admixed with 1 gram of 5 percent palladium on charcoal in a flask equipped with a condenser, and the mixture is heated until compound (II) distills off and is collected by condensation. The conjugated isomer can be crystallized from solution in ethanol in the form of shiny platelets melting at 149° C. The product forms a monoacetate melting at 73° C.

By application of the principles as illustrated in the preceding examples, numerous cycloalkenyl derivatives of phenol or phenols can readily be prepared. Some of the compounds so prepared include the following:

2-(Δ2 cyclopentenyl) phenol
2-(Δ1 cyclopentenyl) phenol
4-(Δ2 cyclopentenyl) phenol
4-(Δ1 cyclopentenyl) phenol
2,4-di(Δ2 cyclopentenyl) phenol
2,4-di(Δ1 cyclopentenyl) phenol
2,6-di(Δ2 cyclopentenyl) phenol
2,6-di(Δ1 cyclopentenyl) phenol
2,6-di(Δ1 cyclopentenyl) phenol
2,4,6,-tri(Δ2 cyclopentenyl) phenol
2,4,6-tri(Δ1 cyclopentenyl) phenol

Generally, the double bond of the cyclopentenyl group can be selectively hydrogenated in the manner illustrated in Example IV for the hydrogenation of orthocyclopentenylphenol to form orthocyclopentylphenol. They can also be subjected to rearrangement of the double bond of the cyclopentenyl group in the manner illustrated in Example VI.

The foregoing examples have been more particularly directed to the preparation of cyclopentenyl substituted monohydric phenols. It will be obvious from the preceding discussions however that phenol may be replaced in the reaction by various polyhydroxy phenols as well as alkyl or alkoxy derivatives of phenol or of alkyl or alkoxy derivatives of polyhydroxy phenols.

Example VII

Example I is repeated except that para cresol is substituted for the phenol. 2-cyclopentenyl-p-cresol, an oil with a pleasant, earthy odor, B. P. 105°–108° C. 1.3 mm., n_D^{25} 1.5595; d_{25}^{25} 1.0570 is obtained.

Example VIII

Example I is repeated substituting 350 grams of guaiacol for the phenol. Cyclopentenyl substituted guaiacol is obtained.

It is also within the scope of the invention to bubble vaporous cyclopentadiene into liquid phenol containing the Friedel-Crafts catalyst until a substantial amount of the phenol has reacted. The cyclopentadiene vapors may be above 140° C. in order to reduce homopolymerization. The phenol may be at any desired temperature, for example, in the range of —20° C. to 200° C.

Example IX

A mixture of 188 grams of phenol, 264 grams of dicyclopentadiene and 50 grams of phosphoric acid is refluxed for 4 hours. The resulting product is a hard, dark, acid and alkali-resistant polymeric material useful as a coating and molding resin.

When the above examples are repeated substituting cyclopentadienes possessing hydrocarbon, halogen or other groups attached to the ring structure, good results are obtained. For example, when methyl cyclopentadiene is substituted for cyclopentadiene in Example I, a good yield of methylcyclopentenylphenol is obtained. Similarly when chlorocyclopentadiene is reacted with phenol in accordance with the method of Example I, chlorocyclopentenylphenol is obtained.

The compounds prepared according to the method of the invention, many of which are believed never to have been known heretofore, are very useful materials. For example, the cyclopentenylphenols and the polyphenols are useful as intermediates in the preparation of organic chemicals and in addition many of them possess fungicidal, insecticidal and herbicidal properties as well as being useful for many other purposes.

Although specific examples of the invention have been herein disclosed it is not intended to limit the invention solely thereto, but to include all the variations and modifications falling within the scope of the appended claims.

I claim:

1. A method of preparing cyclopentenyl derivatives of a phenolic compound selected from the class consisting of phenol, p-cresol and guaiacol, which comprises reacting cyclopentadiene with said phenolic compound at a temperature of about 0° C. to 150° C., and in the presence of a catalyst selected from the class consisting of aluminum chloride, ferric chloride, antimony pentachloride, boron trifluoride, zinc chloride, titanium chloride, hydrofluoric acid, sulfuric acid, phosphoric acid, phosphorus pentoxide, stannic chloride, bismuth chloride, tellurium dichloride, and tellurium tetrachloride, and recovering said cyclopentenyl derivatives from the reaction mixture.

2. The method of claim 1 wherein the phenolic compound is phenol.

3. The method which comprises bringing together a phenolic compound selected from the class consisting of phenol, p-cresol, and guaiacol, with cyclopentadiene, in the presence of about 5 percent to 100 percent by weight, based on the weight of the phenol, of phosphoric acid, and at a temperature of about 0° C. to 50° C., whereupon chemical reaction occurs to form as the predominant product a paracyclopentenyl derivative of said phenolic compound.

4. The method of claim 3 wherein the phenolic compound is phenol.

5. The method which comprises bringing together a phenolic compound selected from the class consisting of phenol, p-cresol, and guaiacol, with a member of the class consisting of cyclopentadiene and lower homopolymers thereof, in the presence of less than about 5 per-

cent by weight, based on the weight of the phenol, of phosphoric acid, and at a temperature of about 100° C. to 200° C., whereupon chemical reaction occurs to form as the predominant product an orthocyclopentenyl derivative of said phenolic compound.

6. The method of claim 5 wherein the phenolic compound is phenol.

7. The method of claim 6 wherein the member of the class consisting of cyclopentadiene and lower homopolymers thereof is cyclopentadiene.

8. The method which comprises bringing together a phenolic compound selected from the class consisting of phenol, p-cresol, and guaiacol, with cyclopentadiene, in the presence of less than about 5 percent by weight, based on the weight of the phenol, of phosphoric acid, and at a temperature of about 0° C. to 50° C., whereupon chemical reaction occurs to form as the predominant product said phenolic compound having a plurality of hydrogens in the phenolic ring each replaced by a cyclopentenyl group.

9. The method of claim 8 wherein the phenolic compound is phenol.

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Bader

United States Patent Office

2,875,161

Patented Feb. 24, 1959

2,875,161

POLYAMINE DERIVATIVES OF ALKYL SUBSTITUTED BENZENES

Alfred R. Bader, Milwaukee, Wis., and John E. Hyre, Cambridge, Mass., assignors to Pittsburgh Plate Glass Company, Allegheny County, Pa.

No Drawing. Application October 21, 1954
Serial No. 463,802
4 Claims. (Cl. 260—2.1)

This invention relates to novel and valuable polyamines of aralkyl compounds or the hydrohalides thereof and it pertains particularly to polyamine derivatives of alkyl substituted benzenes and to methods for the preparation of the same.

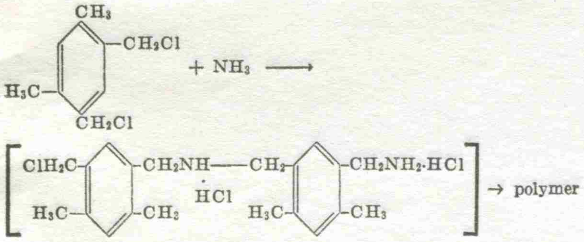
Heretofore, haloalkyl derivatives of alkylbenzenes have been prepared by reacting an alkylbenzene such as xylene, and particularly meta xylene, with an aldehyde such as formaldehyde, in the presence of hydrogen chloride or other hydrogen halide. It is thus possible to prepare compounds embodying the general molecular structure:

$$Ar\text{-}(CH_2\text{—}X)_n$$

wherein Ar is an alkyl substituted aryl radical, X is halogen such as chlorine or bromine and *n* is a whole number from 1 to 3. The "alkyl" groups attached to the aryl radical are preferably methyl, but may also be ethyl, propyl, butyl, or the like. Groups or radicals required to satisfy the carbons in the benzene ring and which are not alkyl or halomethyl ($—CH_2Cl$) groups may be hydrogen, chlorine, bromine, or the like. An outstanding example of such compounds is 4,6-di(chloromethyl)m-xylene, which may also be termed dichlorodurene.

This invention is based upon the discovery that the halomethyl derivatives of alkylaromatic compounds, such as 4,6-di(chloromethyl)m-xylene, will readily react with ammonia to replace halogen whereby to form polyamines which are high melting solids. In the reaction, hydrochloric acid is released and this is believed to react with the amines to form polyamine salts.

The general reaction is illustrated by the reaction of 4,6-di(chloromethyl)m-xylene and ammonia, which may proceed in accordance with the equation:



This invention is not dependent for validity upon the accuracy of the equation but depends broadly upon the reaction of ammonia with the starting compound to form a polyamine or a hydrohalide thereof in which halogen in the side chains is replaced by ammonia.

These polyamines may be employed as ion exchange resins and for other purposes.

The preparation of 4,6,-di(chloromethyl)m-xylene suitable for reaction with ammonia to form polyamines in accordance with the provisions of the present invention broadly comprises reacting an aralkyl compound (preferably meta xylene, or its homolog, mesitylene) with

an aldehyde, such as formaldehyde, and a concentrated hydrogen halide, such as hydrochloric acid. The reaction takes place readily at moderate temperatures, for example 90° C. or thereabouts. In the reaction, a catalyst such as zinc chloride or the like may be employed.

The preparation of 4,6-di(chloromethyl)m-xylene is illustrated by the following example:

Example I

The reaction mixture comprised:

m-Xylene	grams	848
Formalin (37 percent aqueous)	do	1740
HCl (concentrated aqueous)	cc	1200
Zinc chloride (catalyst)	grams	40

This mixture was introduced into a flask and hydrogen chloride was bubbled through for 18 hours. When the reaction mixture was cooled, crystals formed and were filtered off and were washed with water. They were then recrystallized once from heptane. The yield was 869 grams of the desired 4,6-di(chloromethyl)m-xylene in relatively pure form melting at 93° C. to 96° C., useful for reaction with ammonia to form polyamines or salts thereof in accordance with the provisions of the present invention. The latter reaction is illustrated by the following example:

Example II

Ten grams of 4,6-di(chloromethyl)m-xylene was dissolved in 100 milliliters of ethanol on a steam bath. Anhydrous ammonia gas was bubbled through the refluxing solution. After a period of 30 minutes a nicely crystalline white solid was observed to be forming. After a period of 1 hour the reaction mixture was cooled and the crystalline product was filtered in a yield of 9.5 grams. This product softens above 200° C.

The product is believed to be a hydrochloride salt of a polyamine of durene. It contains the necessary amino groups and anions (Cl) usually characterizing well known anion exchange resins referred to in the book Ion Exchange Resins by Kunin and Myers copyrighted by John Wiley and Sons, Inc., New York, 1950.

Example III

In this example, aqueous ammonia (ammonium hydroxide) is employed to react with 4,6-di(chloromethyl)-m-xylene to form polyamines.

To 300 milliliters of ammonium hydroxide was added 10 grams of 4,6-di(chloromethyl)m-xylene dissolved in 100 milliliters of hot ethanol. A precipitate formed immediately. The mixture was heated at the boiling point for 30 minutes. Cold water (200 milliliters) was added and the mixture was cooled to room temperature. The product was a rock-hard amorphous solid. This product may be used as an ion exchange resin.

It is to be understood that formaldehyde in Example I may be replaced by acetaldehyde, propionaldehyde, butyraldehyde, or the like. The chloroalkyl groups in 4,6-di(chloromethyl)m-xylene will then be replaced by the corresponding chloroethyl, chloropropyl, or chlorobutyl groups.

In Example I, m-xylene may be replaced by mesitylene (1,3,5-trimethylbenzene) to form di(chloromethyl)mesitylene. The latter may be reacted with ammonia in accordance with the provisions of this invention to form polyamines (or their hydrochloride salts) useful as ion exchange media. Likewise, the mono- or trihaloalkylaromatic compounds may be substituted for the dihalo compounds of the examples.

The forms of the invention as herein given are to be considered as being by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

We claim:

1. In a method of preparing a hydrochloride salt of a polyamine of a tetramethylbenzene, the steps which comprise dissolving di(chloromethyl)xylene in ethyl alcohol and contacting the solution at about refluxing temperature with anhydrous ammonia in gaseous phase whereby to precipitate said salt and removing the salt.

2. In a method of forming a hydrochloride salt of a polyamine of an aromatic hydrocarbon of a class consisting of a xylene and mesitylene, the steps which comprise dissolving a compound of a class consisting of di(chloromethyl)xylene and di(chloromethyl)mesitylene in ethyl alcohol and refluxing the mixture with ammonium hydroxide until said salt is formed and precipitated.

3. In a method of forming a hydrochloride salt of a polyamine of an aromatic hydrocarbon of a class consisting of a xylene and mesitylene, the steps which comprise dissolving a compound of a class consisting of a di(chloromethyl)xylene and di(chloromethyl)mesitylene in ethyl alcohol and bubbling anhydrous ammonia gas through the mixture while it is heated to reflux temperature and separating the resultant precipitated salt.

4. In a method of forming a hydrochloride salt of a polyamine of di(aminomethyl)-xylene, the steps of heating to the boiling point a solution of di(chloromethyl)xylene and ethyl alcohol and contacting the solution with a compound of a class consisting of anhydrous ammonia and ammonium hydroxide, heating being continued until said salt is formed and precipitated.

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Hyre

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This invention is based upon the discovery that the halomethyl derivatives of alkylaromatic compounds, such as 4,6-di(chloromethyl)m-xylene, will readily react with ammonia to replace halogen whereby to form polyamines which are high melting solids. In the reaction, hydrochloric acid is released and this is believed to react with the amines to form polyamine salts.

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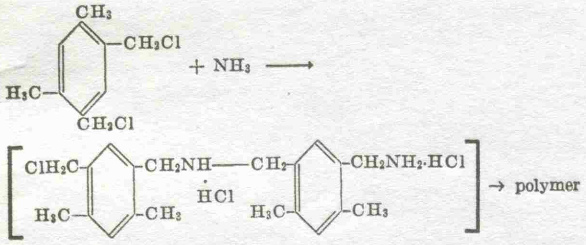

This invention is not dependent for validity upon the accuracy of the equation but depends broadly upon the reaction of ammonia with the starting compound to form a polyamine or a hydrohalide thereof in which halogen in the side chains is replaced by ammonia.

These polyamines may be employed as ion exchange resins and for other purposes.

The preparation of 4,6,-di(chloromethyl)m-xylene suitable for reaction with ammonia to form polyamines in accordance with the provisions of the present invention broadly comprises reacting an aralkyl compound (preferably meta xylene, or its homolog, mesitylene) with an aldehyde, such as formaldehyde, and a concentrated hydrogen halide, such as hydrochloric acid. The reaction takes place readily at moderate temperatures, for example 90° C. or thereabouts. In the reaction, a catalyst such as zinc chloride or the like may be employed.

The preparation of 4,6-di(chloromethyl)m-xylene is illustrated by the following example:

Example I

The reaction mixture comprised:

m-Xylene	grams	848
Formalin (37 percent aqueous)	do	1740
HCl (concentrated aqueous)	cc	1200
Zinc chloride (catalyst)	grams	40

This mixture was introduced into a flask and hydrogen chloride was bubbled through for 18 hours. When the reaction mixture was cooled, crystals formed and were filtered off and were washed with water. They were then recrystallized once from heptane. The yield was 869 grams of the desired 4,6-di(chloromethyl)m-xylene in relatively pure form melting at 93° C. to 96° C., useful for reaction with ammonia to form polyamines or salts thereof in accordance with the provisions of the present invention. The latter reaction is illustrated by the following example:

Example II

Ten grams of 4,6-di(chloromethyl)m-xylene was dissolved in 100 milliliters of ethanol on a steam bath. Anhydrous ammonia gas was bubbled through the refluxing solution. After a period of 30 minutes a nicely crystalline white solid was observed to be forming. After a period of 1 hour the reaction mixture was cooled and the crystalline product was filtered in a yield of 9.5 grams. This product softens above 200° C.

The product is believed to be a hydrochloride salt of a polyamine of durene. It contains the necessary amino groups and anions (Cl) usually characterizing well known anion exchange resins referred to in the book Ion Exchange Resins by Kunin and Myers copyrighted by John Wiley and Sons, Inc., New York, 1950.

Example III

In this example, aqueous ammonia (ammonium hydroxide) is employed to react with 4,6-di(chloromethyl)-m-xylene to form polyamines.

To 300 milliliters of ammonium hydroxide was added 10 grams of 4,6-di(chloromethyl)m-xylene dissolved in 100 milliliters of hot ethanol. A precipitate formed immediately. The mixture was heated at the boiling point for 30 minutes. Cold water (200 milliliters) was added and the mixture was cooled to room temperature. The product was a rock-hard amorphous solid. This product may be used as an ion exchange resin.

It is to be understood that formaldehyde in Example I may be replaced by acetaldehyde, propionaldehyde, butyraldehyde, or the like. The chloroalkyl groups in 4,6-di(chloromethyl)m-xylene will then be replaced by the corresponding chloroethyl, chloropropyl, or chlorobutyl groups.

In Example I, m-xylene may be replaced by mesitylene (1,3,5-trimethylbenzene) to form di(chloromethyl)mesitylene. The latter may be reacted with ammonia in accordance with the provisions of this invention to form polyamines (or their hydrochloride salts) useful as ion exchange media. Likewise, the mono- or trihaloalkylaromatic compounds may be substituted for the dihalo compounds of the examples.

The forms of the invention as herein given are to be considered as being by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

We claim:

1. In a method of preparing a hydrochloride salt of a polyamine of a tetramethylbenzene, the steps which comprise dissolving di(chloromethyl)xylene in ethyl alcohol and contacting the solution at about refluxing temperature with anhydrous ammonia in gaseous phase whereby to precipitate said salt and removing the salt.

2. In a method of forming a hydrochloride salt of a polyamine of an aromatic hydrocarbon of a class consisting of a xylene and mesitylene, the steps which comprise dissolving a compound of a class consisting of di(chloromethyl)xylene and di(chloromethyl)mesitylene in ethyl alcohol and refluxing the mixture with ammonium hydroxide until said salt is formed and precipitated.

3. In a method of forming a hydrochloride salt of a polyamine of an aromatic hydrocarbon of a class consisting of a xylene and mesitylene, the steps which comprise dissolving a compound of a class consisting of a di(chloromethyl)xylene and di(chloromethyl)mesitylene in ethyl alcohol and bubbling anhydrous ammonia gas through the mixture while it is heated to reflux temperature and separating the resultant precipitated salt.

4. In a method of forming a hydrochloride salt of a polyamine of di(aminomethyl)-xylene, the steps of heating to the boiling point a solution of di(chloromethyl)xylene and ethyl alcohol and contacting the solution with a compound of a class consisting of anhydrous ammonia and ammonium hydroxide, heating being continued until said salt is formed and precipitated.

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PITTSBURGH
PLATE GLASS COMPANY

PPG

O. L. SPENCER, PATENT COUNSEL
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PATENT DEPARTMENT
ONE GATEWAY CENTER, PITTSBURGH 22, PA.

April 22, 1960

Dr. Alfred R. Bader
Aldrich Chemical Company, Inc.
2369 No. 29th Street
Milwaukee 10, Wisconsin

Dear Al:

Attached is a copy of U. S. Patent 2,933,520 in which you may have some slight interest. Needless to say, Pittsburgh Plate Glass Company has a very real interest in this patent, and it would be more appropriate for us to send you a copy with a gold border.

You should certainly feel proud to have made the invention covered by this patent. I want personally to thank you for your fine cooperation during the long and difficult prosecution of the application.

Yours sincerely,

R. A. Eberly

RAE:ABA

Enclosure

United States Patent Office

2,933,520

Patented Apr. 19, 1960

2,933,520

ADDITION PRODUCTS OF PHENOLS AND KETO ACIDS AND DERIVATIVES OF THE SAME

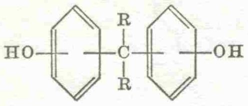
Alfred R. Bader, Milwaukee, Wis., assignor, by mesne assignments, to S. C. Johnson & Son, Inc., Racine, Wis., a corporation of Wisconsin

No Drawing. Application August 27, 1953
Serial No. 377,002

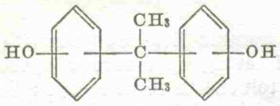
11 Claims. (Cl. 260—473)

This invention relates to a method for the preparation of novel phenolic compounds and it has particular relation to the manufacture of di(hydroxy-aromatic) alkylidene carboxylic acids through substitution of hydroxy aromatic groups for the keto oxygen in a keto carboxylic acid.

Alkylidene bisphenols of the structure

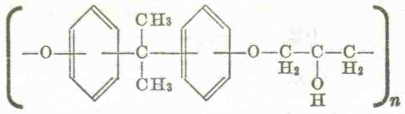


where R and R are hydrocarbon or substituted hydrocarbon or hydrogen, have been prepared by reacting a phenol with a ketone or an aldehyde. Such compounds as bis-(4-hydroxyphenyl)2, 2-propane, which possess the structure:

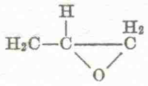


are prepared in this manner.

These compounds are capable of condensing with epichlorohydrin to form long chain polyethers which constitute valuable resins. They are understood to include molecules approximately of the structure:



In the formula, *n* is an integer of a value dependent upon the degree of resinification of the compound. The chain thus formed may be terminated at one or both ends by an epoxy group:



Many resins have also been prepared by condensing polyhydric alcohols, such as glycol, diethylene glycol, propylene glycol, glycerol, and pentaerythritol with saturated dicarboxylic acids such as adipic acid, succinic acid, phthalic acid, or the like, thus to provide long chain polyesters.

Still other polyester resins have been prepared by condensing with glycols, such as are above described, unsatured polybasic acids, containing carbon-oxygen conjugation in the group:

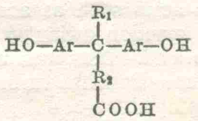
$$C{=}C{-}C{=}O$$

Acids of this group include maleic acid, fumaric acid, itaconic acid, and mixtures of such acids with saturated acids of the first-mentioned type, all of which react with glycols to provide long chain polyesters with recurrent ethylenic groups. The polyesters containing such ethylenic groups are characterized by a capacity for reacting by addition through said groups with monomers containing a $>C{=}CH_2$ group, thus to obtain cross-linking with resultant formation of hard, insoluble, infusible products. Many such mixtures are disclosed in U.S. Patent No. 2,593,787 to Earl E. Parker.

In polyesters of both the saturated and unsaturated types it is possible to limit the growth of the polyester molecules by including a monocarboxylic acid (or a mixture of monocarboxylic acids such as those from glyceride oils) and including stearic acid, palmitic acid, linoleic acid, linolenic acid and others. These acids, if sufficiently unsaturated, in addition to acting as chain stoppers, also impart a capacity for air drying to the resultant polyester bodies.

This invention comprises the provision of a novel class of alkylidene carboxylic acids containing a di(hydroxyphenyl) grouping in a hydrocarbon chain and being useful for such purposes as the preparation of the glycidyl polyether resins, or as monocarboxylic acid chain stoppers in the various saturated and unsaturated alkyd resins, to which they impart added degrees of functionality.

The compounds prepared according to this invention may be represented by the formula:



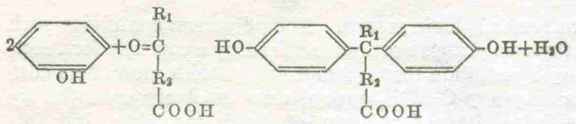
$$HO{-}Ar{-}\overset{\displaystyle R_1}{\underset{\displaystyle \underset{\displaystyle COOH}{R_2}}{C}}{-}Ar{-}OH$$

in which the group R_1 may be hydrocarbon, halogen, such as chlorine or the like, and R_2 is hydrocarbon, e.g. alkylene other than methylene and containing at least two carbon atoms such as ethyl, propyl, butyl, with either normal or branched chains and containing, for example, up to 10, 12 or even more carbon atoms. The Ar groups are aromatic rings. They may be unsubstituted, but one or both thereof can contain substituents such as alkyl (methyl, ethyl, propyl, butyl, isopropyl, isobutyl), halogen, (chlorine, bromine), nitro, sulfo, and others. These substituents as well as those in positions R_1 and R_2 will obviously influence the properties of the compounds, for example, by increasing or decreasing the compatability, solubility, boiling point, toxicity, bactericidal, fungicidal, insecticidal, and like properties. However, they are all useful and are included within the scope of this invention.

These compounds, it has now been found, can be prepared by reacting a phenolic compound containing one or more available hydrogen atoms in the aromatic ring with a carboxylic acid containing a keto group appropriately disposed in the carbon chain. Preferably, the reaction is conducted in the presence of a catalyst and notably of an acid, such as a relatively strong mineral acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid or the like. Polyphosphoric acid, which is a mixture of H_3PO_4 and P_2O_5, and which is a strong dehydrating agent, is not preferred because it tends to catalyze the production of phenyl esters in large quantities. However, even it may produce some di(hydroxyaromatic) alkylidene carboxylic acids from phenolic compounds and keto carboxylic acids.

The strong mineral acids are preferred, but the invention also includes the use of strong organic acids such as chloroacetic acid. Acids such as sulfuric acid, which tend to sulfonate phenolic compounds should be employed only at low temperatures, e.g., at or near room temperature, if maximum yields of the dihydroxyphenylalkylidene acids are desired.

The reaction is believed to proceed substantially in accordance with the following equation, wherein phenol is used for illustrative purposes:



where R_1 and R_2 have the significance given hereinabove.

The course of this reaction is surprising, inasmuch as the hydroxyl of the phenolic compound and the carboxyl group of the acid are both reactive, yet do not take part in the reaction.

Typical phenolic compounds which may be employed in the foregoing reaction include phenol, cresol (ortho, meta, or para), carvacrol, thymol, such dihydric phenols as catechols, resorcinol, hydroquinone, and the like; likewise, trihydric phenols, such as pyrogallol. Homologues of dihydric phenols, such as orcinol may also be utilized. Still other phenols comprise the ethers containing phenolic groups and being represented by guaiacol, or creosol. Phenols are considered as comprising compounds in which a hydroxyl is substituted for hydrogen in an aromatic ring.

Keto acids, which in the presence of mineral acids will react as above described with phenolic compounds include acids such as levulinic acid, lactarinic acid, mesitonic acid, deltaketocaproic acid, geronic acid and the like. Beta-keto acids such as acetoacetic acid are not suitable for the reaction owing to the ready decarboxylation of β-keto acid. However, acids containing a keto group more remote from the carboxyl than the beta position may be employed.

The conditions of reaction utilized in the preparation of the foregoing di(hydroxyaromatic) alkylidene carboxylic acids are general in nature and are applicable to the various possible combinations of phenols and the keto acids.

In the pairing of the keto-carboxylic acids and the phenolic compounds it is preferable to select combinations in which the members are mutually soluble or compatible with each other or are soluble in a common solvent, at least at the temperatures at which the reaction is carried out. Such solubility, of course, assists in attaining rapid reaction. However, the invention also includes effecting contact between the phenolic compounds and the keto-acids by application of vigorous agitation, by emulsification, or by other methods of dispersion whereby the interface between the reactants is extended to a sufficient degree to obtain a reasonable degree of reaction.

Amounts of acids employed as catalysts in the foregoing reactions, usually are substantial, for example, about 5 to 50 percent by weight based upon the reactants present. More than the latter amount is usually uneconomical and is not required.

Reaction temperatures may range from room temperature upwardly but usually should not be much above steam bath temperature (90 to 100° C.), as side reactions may then occur to an objectionable degree.

The reaction time may be varied from one hour to several days, for example, 3 or 4 days or more, dependent upon temperature.

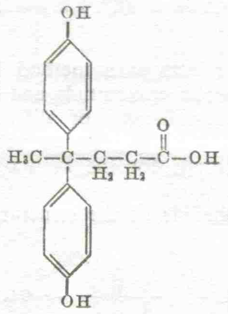
Application of the principles of the invention to the preparation of di(hydroxy aromatic) alkylidene carboxylic compounds is illustrated by the following examples:

EXAMPLE I

A mixture of 94 grams of phenol, 50 grams of levulinic acid, and 20 grams of concentrated hydrochloric acid was heated on the steam-bath with stirring for 6 hours. A clear solution of red color was obtained. This was cooled, washed with water, and a water-insoluble red oil, which was heavier than water was obtained. The oil was extracted with toluene to remove unreacted phenol in a yield of 35 grams. The portion insoluble in toluene was stripped at 90° C. under a pressure of 10 millimeters (absolute). The product was a reddish, viscous oil in a yield of 45 grams.

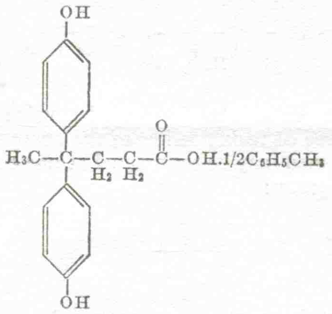
The product is insoluble in toluene, soluble in acetone and methanol, soluble in aqueous sodium carbonate and bicarbonate, and is precipitated by hydrochloric acid. The material is soluble in concentrated sulphuric acid to give a yellow solution of a water-soluble product.

The product of the reaction of one mole of levulinic acid and 2 moles of phenol is predominantly gamma, gamma p,p-di(hydroxyphenyl)-valeric acid (also known as 4,4-bis(4-hydroxyphenyl) pentanoic acid) of the structure:



The compound depicted structurally hereinabove may be esterified with alcohols, such as methyl alcohol, to provide methyl esters or the like. These esters often are more stable than the corresponding acids. It is sometimes advantageous to form the ester and then to distill the latter to obtain separation from undesired impurities.

The gamma, gamma-di(hydroxyphenyl) valeric acid is susceptible of taking up aromatic hydrocarbons such as benzene and toluene to form a crystallizable material presumably containing the aromatic compounds in loosely combined form from which they are liberated when the crystalline material is heated above the melting point. One such crystalline compound containing toluene of crystallization is a white crystalline solid (M.P. 108–109° C.) and may be represented by the structure:



The di(hydroxyphenyl) alkylidene carboxylic acids, such as gamma, gamma-di(hydroxyphenyl) valeric acid prepared as above described or other di(hydroxyaromatic alkylidene carboxylic acids, can be reacted in the presence of a base such as sodium hydroxide, with chlorides such as allyl chloride to form diallylether esters of the mono acids. These diallylethers can be heated to 250° C., thus effecting a Claisen rearrangement and subsequent polymerization to form hard, light, yellow resins of useful properties.

The di(hydroxyphenyl) alkylidene carboxylic acids such as gamma, gamma-dihydroxyphenylvaleric acid can also be converted to amides by conventional reactions of amidification with ammonia or with primary, or secondary amines such as ethyl amine, diethyl amine, aniline, diphenyl amine, phenylene diamine and the like.

Gamma, gamma-di(hydroxyphenyl) valeric acid or similar acids prepared as described by the foregoing method can be polymerized in alkaline solution with formaldehyde to form modified phenolic resins.

Di(hydroxyaromatic) alkylidene carboxylic acid esters such as the allyl or butyl esters, may be reacted in the presence of an alkali, with epichlorohydrin to form polyether type resins resembling those obtained by condensation of Bisphenol A and epichlorohydrin, but containing an added degree of functionality by reason of the presence of the carboxyl group.

Gamma, gamma-di(hydroxyphenyl) valeric acid and similar acids can also be employed as chain stoppers in the formation of alkyd resins, for example, they may be mixed with glycerol and phthalic anhydride and reacted in well-known manner to provide a modified alkyd resin which includes phenolic groups bound in the polyester molecules and being capable of undergoing the various reactions with formaldehyde and epichlorohydrin which have previously been discussed.

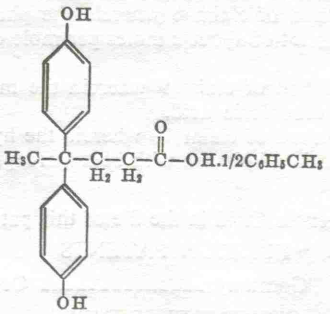
The dihydroxyphenylvaleric acid of this example can also be treated with alkali to form alkaline phenates which, subsequently can be reacted with chloroacetic acid to form diphenoxyacetic acid which, as will be observed, includes three carboxylic groups and is of use in forming polyester resins by reaction with glycerol or glycols.

EXAMPLE II

A mixture of 188 grams of phenol, 116 grams of levulinic acid, 150 milliliters of concentrated hydrochloric acid, and 75 milliliters of water was heated on a steam bath with stirring for a period of 20 hours. A red mixture was thus obtained which was cooled, diluted with water, and extracted with ether. The ether solution was washed with water and was extracted with a solution of 200 grams of sodium bicarbonate in 2500 grams of water.

The ether solution remaining as a residue was washed with water and stripped. The deep red oil remaining in an amount of 67 grams, was distilled at a pressure of 2 millimeters (absolute) and at a temperature of 60–75° C. to give 57 grams of unreacted phenol and 10 grams of red viscous oil as a residue.

The portion of the product taken up in the sodium bicarbonate solution was acidified with hydrochloric acid, was extracted with ether, washed and stripped by distillation to provide a product which was melted and poured into an evaporation dish. The yield was 156 grams (0.54 mole). The product had a melting point (soft) of 65° C. and flowed at 68° C. to 72° C. This product comprised gamma, gamma dihydroxyphenylvaleric acid in a yield of approximately 77 percent. Crystallization from toluene yielded white needles, M.P. 107° C.–108° C. This was gamma, gamma-dihydroxyphenylvaleric acid containing toluene of crystallization and was of the formula:



EXAMPLE III

In this example, three samples each comprising 94 grams of phenol, 58 grams of levulinic acid, 50 milliliters of concentrated hydrochloric acid, and 1 gram of beta-mercaptopropionic acid were made up and stirred for 5 hours. During this time the first sample was maintained at a temperature of 50° C. plus or minus 5°; the second was raised to 60° C. plus or minus 5°; the third was raised to 70 plus or minus 5 degrees C. They were cooled to room temperature and were then further stirred at room temperature overnight. Each of the samples was diluted with water, extracted with ether, and subsequently extracted with sodium bicarbonate as in the preceding examples to obtain gamma, gamma-dihydroxyphenylvaleric acid in relative purity. The products were tan in color and glass-like in appearance.

EXAMPLE IV

A mixture of 94 grams of phenol, 58 grams of levulinic acid, 20 milliliters of water and 90 grams of concentrated sulfuric acid was stirred at room temperature for 20 hours to provide an orange-red solution which when diluted with water was worked up by extraction with ether and subsequent extraction of the ether solution with aqueous sodium bicarbonate. There was obtained 40 grams of gamma, gamma-dihydroxyphenylvaleric acid in crude form. This was crystallized from acetone-toluene to yield 35.5 grams of a white and crystalline product. The melting point was 107° C. to 109° C., at which temperature, toluene of crystallization was evolved. All of the toluene was evolved to 110° C. or below, at a pressure of 0.5 millimeter of mercury (absolute). The product (a white glass) had a melting point of 80° C. to 82° C.

EXAMPLE V

The catalyst, in this instance, was sulfuric acid diluted with water. The reaction mixture comprised 94 grams of phenol, 58 grams of levulinic acid, and a solution of 180 grams of concentrated sulfuric acid, and 30 grams of water. The mixture was stirred at room temperature for 18 hours. There resulted a red mixture which, when diluted with water, was extracted with ether, and the ether extract was extracted with aqueous sodium bicarbonate. The solution of sodium bicarbonate was then acidified, extracted with ether, washed with water, and stripped to provide a glass-like product of light pink color in a yield of 80 grams. This product was gamma, gamma-dihydroxyphenylvaleric acid in high concentration.

The gamma, gamma-dihydroxyphenylvaleric acid was crystallized to yield the toluate melting at 107–108° C.

EXAMPLE VI

In this example, aqueous sulfuric acid was employed as a catalyst of a condensation in several samples.

Sample A

A mixture of 94 grams of phenol, 58 grams of levulinic acid, 35 grams of water, and 180 grams of concentrated sulfuric acid was stirred at room temperature for 18 hours. The resultant reaction product was then worked up with aqueous sodium bicarbonate and toluene as in the preceding examples. A yield of 75 grams of crude product was thus obtained. This product consisted essentially of gamma, gamma-dihydroxyphenylvaleric acid.

Sample B

The same procedure was repeated but with an increase of the water content of the system to 50 grams. The mixture was stirred at room temperature over a period of 2 days, after which it was cooled with Dry Ice-acetone mixture. Ice water was added and the mixture was extracted with ethyl-acetate, was further washed with water, and was extracted with saturated sodium bicarbonate to remove gamma, gamma-dihydroxyphenylvaleric acid.

The bicarbonate soluble extract, of light yellow color, and containing large amounts gamma dihydroxyphenylvaleric acid salts, was acidified and extracted with ethyl acetate. The residue was washed and stripped by evaporation to provide an orange product of glass-like appearance in a yield of 77 grams.

EXAMPLE VII

A mixture of 94 grams of phenol, 58 grams of levulinic acid, 180 grams of concentrated sulfuric acid and 45 grams of water was stirred at room temperature for 20 hours. Water was then added, the mixture extracted with ethyl acetate and the ethyl acetate extract washed with water. The washed extract was then extracted exhaustively with aqueous sodium bicarbonate, washed again with water and then distilled to yield 25 grams of unreacted phenol. The bicarbonate extracts were combined, acidified with hydrochloric acid and extracted with ether. Evaporation of the ether left an almost colorless amorphous solid (82 grams), M.P. 79–82°, of essentially pure gamma, gamma-di(p-hydroxyphenyl)-valeric acid, of calculated hydroxyl and acid value. This dihydroxyphenylvaleric acid is soluble in alcohol, acetone and ether, very sparingly soluble in toluene and water and insoluble in hexane. It crystallizes from aromatic hydrocarbons such as benzene, toluene and xylene and with one mole of the hydrocarbon per two moles of the acid. The acid with toluene of crystallization melts at 107–108° C.; with benzene of crystallization at 118–120° C. and with m-xylene at 95–97° C.

The gamma, gamma di-(hydroxyphenyl)-valeric acid obtained as a glass melting at 80–82° C. and characterized by its capacity of forming loose adducts with aromatic hydrocarbons, appears to be dimorphic. When concentrated solutions of the amorphous material in a mixture of toluene and acetone are allowed to evaporate slowly there is obtained a crystalline modification of the diphenol acid which, after crystallization from toluene-acetone or from water, melts at 170–172° C. When crystals of this are used to seed solutions of the amorphous material, the higher melting modification is obtained at once.

The methyl ester of gamma, gamma-dihydroxyphenylvaleric acid prepared by refluxing the acid in methanol with a trace of mineral acid, is a crystalline solid, melting at 90° C.

EXAMPLE VIII

A diallylether of gamma, gamma-dihydroxydiphenylvaleric acid derived by interacting allyl chloride and gamma, gamma-dihydroxydiphenylvaleric acid was heated at 250° C. to produce a Claisen rearrangement, whereby the allyl groups were transferred to the benzene rings in ortho relationship with respect to the hydroxyls of the phenols. The resultant phenolic compounds then polymerized to form hard, light-colored, yellow resins useful for coating purposes and for other applications.

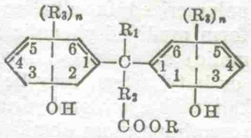
It will be appreciated that in the foregoing examples, levulinic acid may be replaced by other keto acids which are not subject to decarboxylations, and being represented by gamma acetobutyric acid. The corresponding phenolic derivative is delta, delta dihydroxyphenylhexanoic acid. Still another example is 6 keto-n-octadecanoic acid, which can be reacted with various phenols as herein disclosed.

Other phenolic compounds which may be substituted for phenol in the examples comprises carvacrol or butenylphenol which forms di(hydroxybutenylphenyl) valeric acid; or catechol (the corresponding product is gamma, gamma-di(orthodihydroxyphenyl) valeric acid; or guaiacol (the corresponding product is gamma, gamma bis(hydroxymethoxyphenyl)-valeric acid.

The forms of the invention herein shown and described are to be considered as being by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

I claim:

1. A compound of the structure

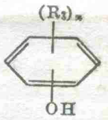


wherein R is a member of the class consisting of hydrogen and lower alkyl radicals, R_1 is an alkyl radical, R_2 is an alkylene radical containing at least 2 carbon atoms, R_3 is a lower alkyl radical, and *n* is a number selected from the class consisting of 0, 1 and 2, the hydroxyl groups being attached to the 4-position of the ring structure when *n* is 0.

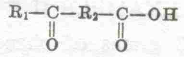
2. 4,4-bis(4-hydroxyphenyl)pentanoic acid.

3. Methyl-4,4-bis(4-hydroxyphenyl)pentanoate.

4. The method which comprises reacting a phenol of the structure

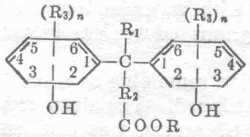


wherein R_3 is a lower alkyl radical and *n* is a member selected from the class consisting of 0, 1 and 2, with a keto-carboxylic acid of the structure



$$R_1-\underset{\underset{\textstyle O}{\|}}{C}-R_2-\underset{\underset{\textstyle O}{\|}}{C}-OH$$

wherein R_1 is an alkyl radical and R_2 is an alkylene radical containing at least 2 carbon atoms, in the presence of a mineral acid and at a temperature in the range of about 25° C. to about 100° C., and recovering from the reaction mixture a compound of the structure



wherein R_1, R_2, R_3, and *n* have the significance set forth hereinabove, the hydroxyl groups of said compound being attached to the 4-position of the ring structure when *n* is 0.

5. The method of claim 4 wherein the phenol is utilized in an amount of at least about 2 moles per mole of the keto-carboxylic acid.

6. The method of claim 5 wherein the mineral acid is hydrochloric acid.

7. The method of claim 6 wherein beta-mercaptopropionic acid is admixed with the hydrochloric acid.

8. The method which comprises reacting phenol with levulinic acid in the presence of a mineral acid catalyst, and at a temperature in the range of about 25° C. to about 100° C., and recovering 4,4-bis(4-hydroxyphenyl) pentanoic acid from the reaction mixture.

9. The method of claim 8 wherein the phenol is utilized in an amount of about 2 moles per mole of levulinic acid.

10. The method of claim 9 wherein the mineral acid catalyst is hydrochloric acid.

11. The method of claim 10 wherein the hydrochloric acid is utilized in admixture with beta-mercaptopropionic acid.

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United States Patent Office

2,987,491

Patented June 6, 1961

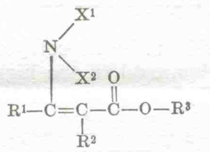
2,987,491

ALKYD RESINS MODIFIED BY BETA AMINO CROTONIC ESTERS OF HIGHER ORGANIC HYDROXIDES

Alfred R. Bader, Milwaukee, Wis., and Henry A. Vogel, Richland Township, Pa., assignors to Pittsburgh Plate Glass Company

No Drawing. Filed Aug. 7, 1956, Ser. No. 602,489
11 Claims. (Cl. 260—22)

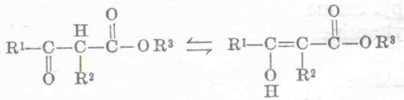
This invention relates to beta amino derivatives of crotonic acid esters of higher alcohols, useful as surfactants or for use in preparing the same, and for other purposes. Such esters are of the general formula:



$$R^1-C(NX^1X^2)=C(R^2)-C(=O)-O-R^3$$

where R^3 is the residue of a higher alcohol. The character of it and of the groups R^1, R^2, X^1 and X^2 will subsequently be more fully elaborated upon.

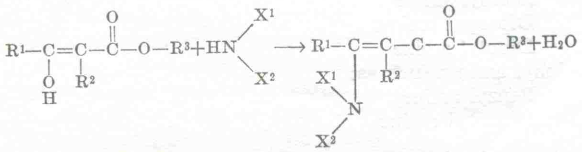
The beta amino crotonic acid esters of higher alcohols are most readily formed by action of ammonia or a primary or secondary amine upon the corresponding beta hydroxy crotonic acid esters of higher alcohols, which exist tautomerically with beta carbonyl esters of such alcohols in accordance with the equilibrium equation:



$$\underset{\text{I}}{R^1-C(=O)-CH(R^2)-C(=O)-OR^3} \leftrightharpoons \underset{\text{II}}{R^1-C(OH)=C(R^2)-C(=O)-OR^3}$$

I II

If the equilibrium system is treated with a basic nitrogen compound such as ammonia or a primary or secondary amine, in accordance with the provisions of the present invention, the component of the system designated as II reacts with the nitrogen compound in accordance with the equation:



$$R^1-C(OH)=C(R^2)-C(=O)-O-R^3+HNX^1X^2 \longrightarrow R^1-C(NX^1X^2)=C(R^2)-C-C(=O)-O-R^3+H_2O$$

In the reaction, the group R^3 preferably, though not necessarily, contains at least 12 and usually 16 or 18 and upward, carbon atoms. In the reaction, the enolized ester is removed by formation of amine, the equilibrium in the equilibrium equation is displaced to the right and the reaction advances.

In the equation, if ammonia is employed as the basic nitrogen compound, X^1 and X^2 will be hydrogen. However, it is apparent that ammonia may be replaced by primary or secondary amines, or diamines. Therefore, X^1 and/or X^2 may be alkyl or aryl groups. If desired, ammonia may also be replaced by aqueous ammonium hydroxide and salts thereof with acids, notably weak acids such as acetic acid, carbonic acid and the like.

The starting beta carbonyl ester of a higher alcohol may conveniently be prepared by the technique disclosed in commonly owned Patents 2,693,476 and 2,693,484 which were co-pending with application, Serial No. 280,646, filed April 4, 1952, now abandoned. The processes as disclosed in the patents comprise reacting an ester of a beta carbonyl acid such as acetoacetic acid and a lower aliphatic alcohol, such as methyl alcohol or ethyl alcohol, with a higher alcohol to effect ester interchange. Higher alcohols which may be used in forming the starting esters may be, for example, those obtained by the reduction of fatty acids from fatty, animal or vegetable glycerides, or they may be obtained from tall oil, or from wool grease and the like. The esters may also be of glycerides of higher hydroxy acids such as ricinoleic acid, or they may be sterols or steroid bodies and the like.

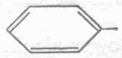
For purposes of illustration, partial lists of substituents for the groups R^1, R^2 and R^3, X and X^2 in the foregoing formulae will now be given.

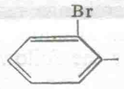
For the group R^1, the list comprises:

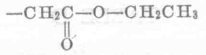
TABLE A

$-CH_3$

$-C_2H_5$







$-CH_2C(=O)-O-CH_2CH_3$

$ClCH_2-$

ClC_2H_4-

$ZNH-$

$ZCHO-$

(Z being methyl, ethyl, phenylene, etc.)

Similarly, the group R^2 is common to the starting ester and its product and may be hydrogen or it can also be a group such as is listed in Table B:

TABLE B

Methyl
Ethyl
Propyl
Butyl
Chloro
Amino
Chloromethyl
Benzyl
Phenyl

or chloro or the like derivatives thereof. Only one hydrogen atom of the alpha-carbon atom of the beta carbonyl esters can be replaced by substituents.

In the initial or starting beta-carbonyl ester, which is subjected to ester interchange to introduce the group R^3, the group to be replaced, is the residue of a lower alcohol such as methyl, ethyl, n-propyl, isopropyl, butyl, tertiary butyl, secondary butyl, allyl, methallyl, crotyl, propargyl, 2-chloro-ethyl, 2-fluoroethyl, 2-nitropropyl, or the like.

Appropriate alcohols for ester interchange reaction with beta-carbonyl esters of lower alcohols, as disclosed in the previous application, include alcohols from the following table:

TABLE C

Lauryl alcohol
Stearyl alcohol
Oleyl alcohol
Octadecyl alcohol
Ceryl alcohol
Cetyl alcohol
Carnaubyl alcohol
Lignoceryl alcohol
Castor oil containing glycerides of ricinoleic acid
Polyethylene glycols having molecular weights of 200, 300 or more
Higher alcohols containing the hydrogenated phenanthrene nucleus such as:
  Cholesterol
  Beta-sitosterol
  Stigmasterol
  Cholestanol

- Epidehydroandrosterone
- Ergosterol
- Epicholestanol
- Coprostanol
- Cortisone
- Cholic acid
- Desoxycholic acid
- Steroid sapogenines
- Steroid intermediates

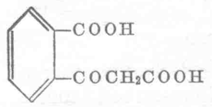
Triterpene alcohols such as:
- Agnosterol
- Lanosterol

These higher alcohols when admixed with a beta-carbonyl ester of a lower alcohol such as methyl, ethyl, propyl or butyl alcohol, even under mild conditions, and in the absence of catalysts, can readily be induced to undergo ester interchange reaction thus liberating lower alcohol and forming an ester of the beta-carbonyl acid and the higher alcohol.

Beta-carbonyl esters of lower alcohols suitable for use in the foregoing ester interchange reaction include the esters of any of the lower alcohols already listed and beta-carbonyl acids such as the following:

TABLE D

Acetoacetic acid
Alpha-ethyl acetoacetic acid
Alpha-isopropyl acetoacetic acid
Alpha-methyl acetoacetic acid
Benzoyl acetoacetic acid
Acetone dicarboxylic acid
Gamma chloro acetoacetic acid
Alpha-benzoyl acetoacetic acid
Alpha-phenyl-acetoacetic acid
Chloro, iodo, and bromo substitutions products of the above acids
Acetyl succinic acid
Benzoyl acetoacetic acid
The acid of the formula:



and the like.

To obtain the higher esters of beta-carbonyl acids, the previously mentioned procedures of Patents 2,693,476 and 2,693,484 may be followed. Accordingly, the disclosures of the foregoing patents insofar as they pertain to preparation of such esters, are to be regarded as constituting parts of this application. However, it is to be understood that the practice of the invention is not necessarily limited to esters prepared by the techniques of the foregoing patents. Esters of higher alcohols and beta-carbonyl acids (or the tautomeric enolic forms thereof) however prepared, when of sufficient purity, can be reacted with ammonia or primary or secondary amines in the practice of this invention.

Since the method outlined in the foregoing patents is so simple and produces such excellent results, it is believed to be in order briefly to describe it.

Main features of the foregoing process comprise:

(I) So conducting the reaction of ester interchange that minimum concentration of evolved alcohol is built up in the system.

(II) Operating with at least a molar equivalency and preferably a substantial molar excess, e.g., with 2 to 100 moles of aceto carbonyl ester of a lower alcohol per mole of higher alcohol. Condition I is readily met by use of a large excess of the starting ester in order to displace the equilibrium of the reaction system in the desired direction by reason of the excess of such ester of a lower alcohol. The reaction can also be promoted by application of vacuum or by blowing the reaction mixture with a non-reactive gas such as nitrogen, carbon dioxide, combustion gases or other inert gas in order to sweep out evolved alcohol from the system and thus to promote the reaction. Non-reactive solvents boiling within the reaction temperature range, and that by distillation would carry away the evolved alcohol, may be employed in the system and have an effect similar to non-reactive gases.

If these conditions are observed, the reaction will proceed very efficiently at temperatures of about 80° C. to 120° C. or 140° C., even in the absence of catalysts, to effect yields of the esters of the higher alcohols and the beta-keto acids which are nearly theoretical.

Excesses of the starting ester can easily be distilled from the desired product by vacuum (for example, at about 5 mm. to 100 mm. of mercury absolute pressure) thus providing beta-carbonyl esters of a higher alcohol and tautomeric enolic forms thereof, which can be reacted with ammonia or primary or secondary amines to form beta-amino crotonic acid esters of the type herein disclosed.

Appropriate basic nitrogen compounds that will replace the enolic hydroxyl in the higher esters of beta-carbonyl acids may be selected in accordance with the following table:

TABLE E

Ammonia (gaseous or in a non-reactive solvent)
Aqueous ammonium hydroxide
Salts of ammonia such as:
- Ammonium acetate
- Ammonium carbonate

Primary amines such as:
- Methyl amine
- Ethyl amine
- Propyl amine
- Butyl amine
- Aniline
- Toluidine

Secondary amines such as:
- Dimethyl amine
- Dipropyl amine
- Dibutyl amine
- Methyl aniline

Diamines such as:
- Dimethyl amine
- Diethyl amine
- Dipropyl amine
- Dibutyl amine

Alphyl amines such as:
- Benzyl amine
- Dibenzyl amine

In conducting the reaction of the beta-carbonyl esters of higher alcohols and ammonia or amines as herein disclosed, the conditions of reaction are very simple. If the beta-carbonyl ester of a higher alcohol is liquid at the conditions of reactions, solvent media are not required for the reaction though, of course, they are permissible. However, since many of the beta-carbonyl esters of higher alcohols are of relatively high melting point, or are very viscous liquids at the temperature of reaction contemplated herein, it is often desirable to include a non-reactant solvent or diluent in the system. Preferably, the solvent is of farily low boiling point so that it may be easily eliminated from the system by distillation at the conclusion of the reaction without decomposing the ester product or any residual starting ester still in the system.

It is often desirable to include in the system, an appropriate catalyst to promote the reaction between the ammonia or amine and the beta-carbonyl ester of a higher alcohol. Appropriate catalysts include salts of ammonia or of the amine which is employed in the system. Such salts include ammonium or amino acetates, nitrates, chlorides, sulfates, sulfites, phosphates, phosphites, and the like. These catalysts may be employed in trace amounts, e.g., 0.01 part by weight per 100 parts by weight of the beta-carbonyl ester of a higher alcohol undergoing amination.

It is also within the purview of the invention to include the salt in an amount to supply a substantial amount of, or even all, of the ammonia required in the reaction. Any desired intermediate amount of salt may be employed but must be supplemented by sufficient ammonia or amine to react with carbonyl oxygen or its enolic tautomer.

The reaction can be run at temperatures ranging from about zero to 100° C. or 120° C. The reaction can usually be effected within a period of 5 minutes to 12 hours. Longer periods would be permissible, but are usually unnecessary and uneconomical. Approximately one hour is considered to constitute a good, average working period. While catalysts such as ammonium acetate or ammonium nitrate may be employed to promote the speed of reaction, if such speed is not important, no catalyst need be incorporated. The reaction can be conducted at atmospheric pressure or under superatmospheric pressures, for example, under a pressure of 10 to 100 pounds per square inch (above atmospheric) if so desired.

The beta-amino crotonic acid esters as herein disclosed, may be purified in substantially any convenient manner. For example, the reaction mixtures including said beta-amino crotonic esters together with solvents and any unreacted starting materials or impurities, can be subjected to distillation in order to recover the desired beta-amino crotonic ester product and/or any valuable by-products.

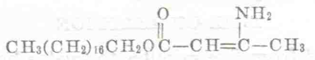
If the beta-amino crotonic acid ester of a higher alcohol is insoluble in water, this characteristic can be employed in order to effect concentration or purification thereof. For example, the beta-keto ester of a higher alcohol dissolved in a suitable solvent may be treated with ammonia in the presence of a catalytic amount of ammonium acetate or with a molecular amount of ammonium acetate in order to form the desired beta-amino crotonic ester. The reaction, for example, may be conducted at 20° C. to 100° C. and after the completion thereof, the reaction mixture is agitated with water in order to separate out the water-insoluble beta-amino crotonic acid ester. The latter may be washed with water in order to remove residual impurities and it is then dried.

Beta-amino crotonic acid esters prepared as herein disclosed, may, if desired, be treated with organic acids and inorganic acids such as acetic acid, oxalic acid, phthalic acid, chloroacetic acid, hydrochloric acid, sulfuric acid, nitric acid, and the like, in order to form ammonium salts. They may also be treated with fatty acids of glyceride oils and tall oil acids to form soaps and even physical mixtures useful as emulsifying agents.

The following examples illustrate the application of the principles of the invention to the preparation of beta-carbonyl esters of the higher alcohols.

Example I

In this example, 60 grams of stearyl acetoacetate, prepared by the ester interchange of methyl or ethyl acetoacetate and stearyl alcohol, dissolved in 300 grams of methanol and 50 grams of ammonium acetate, were heated on a steam bath for 15 minutes. The reaction mixture was then cooled and diluted with water. There was isolated 60 grams of a white solid having a melting point of 70° C. to 71° C. In absolute methanol, it showed an ultra-violet light absorption maximum of log E 4.29 at 274 millimicrons. The theory involved in such determination is outlined on page 4 of Chemical Spectroscopy, by Wallace Brode, second edition, published by John Wiley and Sons. The compound has the structural formula:



$$CH_3(CH_2)_{16}CH_2O\overset{\overset{O}{\|}}{C}-CH=\overset{\overset{NH_2}{|}}{C}-CH_3$$

The molecular weight of the compound was 360. It was of increased water solubility. It could be employed as an emulsifying agent for mineral oils and other hydrophobic

materials. The compound could be treated with acids such as hydrochloric acid, acetic acid, fatty acids of glyceride oils, chloroacetic acid or the like, in order to form salts.

Example II

In this example, the ester of polyethylene glycol and acetoacetic acid may be prepared by ester interchange between the glycol and methyl acetoacetate. An appropriate reaction mixture comprises 100 grams of polyethylene glycol of an average molecular weight of about 200 and 200 to 400 grams of methyl acetoacetate. Such mixture is heated on a steam bath for 15 hours, preferably under slight negative pressure. The excess methyl acetoacetate and any residual methyl alcohol may be removed by vacuum distillation to obtain 150 grams of a water soluble liquid. Such product is polyethylene acetoacetate having a saponification value of 359.

Polyethylene acetoacetate from polyethylene glycol prepared as described, is incorporated in an amount of 33 grams into 100 grams of methanol to which 0.05 gram of ammonium acetate is added. Ammonium gas is then passed into the mixture at room temperature for one hour. The reaction is somewhat exothermic. At the conclusion of the foregoing period, the solvent is stripped off under reduced pressure. There remains a light yellow oil (33 grams) which has an absorption maximum in chloroform of log E 4.19 at 273 mu. Small amounts of this material with or without additions of higher fatty acids will emulsify mineral oils.

Example III

In this example, 50 grams of cold, pressed castor oil (largely the triglyceride of ricinoleic acid) and 150 grams of methyl acetoacetate are heated in an open necked glass flask on a steam bath for a period of 4 hours. The mixture at that point is a clear solution which is stripped of methyl acetoacetate and residual methyl alcohol by distillation at 10 millimeters mercury pressure (absolute) to leave a light yellow oil weighing 62 grams. This product is castor oil acetoacetate which shows upon infrared analysis, the complete absence of hydroxyl groups.

Castor oil acetoacetate prepared as described and in an amount of 100 grams is dissolved in 100 grams of methanol to which 0.1 gram of ammonium acetate has been added. Ammonia gas is passed through the reaction mixture for two hours, at the conclusion of which time the solvent is removed by distillation. The product is amino caster oil crotonate which is assumed to have a molecular weight of 1200. Upon this assumption, it has absorption maximum in chloroform of log E 4.5 at 272.5 mu.

The amino castor oil crotonate can be used, with or without additions of higher fatty acids, to emulsify mineral oils with water.

Example IV

This example illustrates the application of the principles of the invention in order to form modifications of alkyd resins such as are used in the coating arts. An alkyd body containing free hydroxyls should be employed for reaction by ester interchange with an ester of acetoacetic acid and a lower monohydric alcohol. In the practice of the invention, an appropriate alkyd resin may be prepared by esterification of 1053 grams of linseed oil, 470 grams of glycerine and 893 grams of phthalic anhydride by heating the mixture while blowing it with inert gas, e.g., gases from the combustion of butane. Water is evolved and the reaction is continued until it ceases, or until the reaction product becomes viscous, for example, has the viscosity of M when it is diluted to a solids content of 57.6 percent in solvent naphtha. This alkyd body is of an acid value of 10.5; it contains unreacted hydroxyls and is suitable for reaction with methyl or ethyl acetoacetate by ester interchange to form an acetoacetic acid ester of the alkyd body.

For example, a mixture comprising 100 grams of the alkyd body containing 57.6 percent by weight of solids dissolved in naphtha is admixed with 500 milliliters of methyl acetoacetate and is heated on a steam bath for 18 hours. All of the solvent is then removed from the reaction mixture by distillation in vacuum and to the hot resin, 500 grams of solvent naphtha is added. The resultant solution has a Gardner viscosity of U to V at 50.4 percent solids. The resin in naphtha or similar solids is treated with ammonia gas preferably in the presence (though not necessarily so) of a small amount of ammonium acetate. Ammonia, preferably as a gas, is passed into the solution of acetoacetic acid modified alkyd body for a period of about two hours.

The product is an alkyd body which is modified by the beta-amino crotonate groups.

The alkyd could be replaced by other alkyd bodies containing available hydroxyls. Those alkyds resulting from esterification reaction of di- and polyhydric alcohols such as ethylene glycol, diethylene glycol, propylene glycol, butylene glycol, glycerol, pentaerythritol, manitol, trimethylol propane and others may be so employed. Mixtures of two or more alcohols may be employed. The dicarboxylic component may also be of such acids as isophthalic acid, terephthalic acid, succinic acid, adipic acid, sebacic acid, azelaic acid, or the like. Mixtures of any two or more of the acids and/or any one or more of the alcohols may also be employed. Fatty acid components may be present in the alkyd and include such fatty acids as stearic acid, palmitic acid, oleic acid, ricinoleic acid, linolenic acid, linoleic acid, elaeostearic acid and others. The fatty acids in amounts conventional in alkyd resin manufacture may be added to the other reactants as free acids or as partial esters such as the monoglycerides and the mixture may be reacted to form the desired alkyds. These alkyds may be modified to provide their beta-amino crotonates as above described.

Example V

Substitute the ester of acetoacetic acid and lignoceryl alcohol or a mixture rich therein for the ester of acetoacetic acid and stearyl alcohol in Example I and proceed as in the former example. The product is beta-amino crotonate of lignoceryl alcohol.

While the foregoing examples are directed more particularly to the amination of the higher esters of beta-carbonyl acids or their enolic tautomers with gaseous ammonia or with the salts of ammonia, it will be apparent that various basic nitrogen compounds may be substituted therefor. For example, ammonia may be replaced by methyl amine, dimethyl amine, ethyl amine aniline, benzyl amine, etc., or the ammonium salts thereof such as the acetates, olalates, chlorates, etc. Naturally, many of these are non-volatile and must be dissolved in the reaction mixture or in a common solvent, such as methyl or ethyl alcohol.

Example VI

Admix ethyl aniline or the amine salts thereof and the acetoacetic ester of stearyl alcohol from Example I and heat the mixture to reaction temperature to form the corresponding phenyl substituted beta-amino derivative of stearyl crotonate. Methyl or ethyl alcohol may be used as a solvent for the reaction mixture, if so desired.

Example VII

Substitute ortho or para toluidine for ethyl aniline in Example VI and proceed as in the former example.

Example VIII

Substitute ethyl amine vapors or salts of ethyl amine, such as the acetate salt or the hydrochloride salt, for ammonia or its salts in Examples I or II and proceed as in the prior examples. The amino derivatives are the corresponding ethyl amino crotonates of the stearyl crotonate.

Example IX

Substitute butyl amine for ethyl amine in Example VIII and proceed as above to obtain butyl amino crotonates of stearyl alcohol or of polyethylene glycol.

Example X

Substitute dimethyl amine for ammonia in Example II and proceed as in that example. The product is polyethylene glycol ester of dimethyl amino crotonate.

Example XI

React methyl acetoacetate and cholesterol in a proportion of 15 moles of methyl acetoacetate per mole of cholesterol. The reaction is conducted on a steam bath. After a reasonable period (12 to 48 hours) excess methyl acetoacetate is distilled under vacuum at a temperature below 140° C., e.g., 120° C., to recover cholesteryl acetoacetate. Dissolve 33 grams of the latter ester in 100 grams of methanol containing 0.05 gram of ammonium acetate as a catalyst and bubble ammonia gas therethrough at or about room temperature for an hour, or until ammonia is no longer absorbed to any substantial degree and all or most of the beta-carbonyl ester has been transformed to amino crotonate ester. Beta-amino crotonate of cholesterol is recovered by distilling the methanol, preferably under vacuum (e.g., at a pressure of about 15 millimeters of mercury).

Obviously, ammonium acetate can be employed in this reaction in quantities to supply the ammonia required by the reaction.

Example XII

Substitute any of the alcohols listed in Table C for cholesterol in Example XI and proceed as in the latter example. The final products are the corresponding beta-amino derivatives of crotonic acid and the higher alcohols of the table.

The general conditions of reaction involved in the preparation of beta-amino derivatives of crotonic acid esters of higher alcohols from the corresponding beta-keto esters or the enolic forms thereof, have been alluded to, but will now be briefly summarized.

THE ESTERS EMPLOYED

The esters are of beta-carbonyl acids (or enolic tautomers) such as those of any of the acids listed in Table D, and any of the higher alcohols listed in Table C.

BASIC NITROGEN COMPOUNDS

Basic nitrogen compounds which can be reacted with the above captioned esters include any of those listed in Table E or others derived in accordance with the provisions of this specification.

CATALYSTS OF REACTION

Catalysts are optional but may be salts of ammonia or amines and organic or inorganic acids in substantially any economically feasible amount from traces up to amounts supplying the entire amount of basic nitrogen compound.

SOLVENTS

The solvents are optional in mixtures reasonably fluid under reaction conditions. Solvents are non-reactive with the components of the system. They include methyl alcohol, ethyl alcohol, isopropanol, acetone, cellosolves, toluene, etc.

TEMPERATURES

Temperatures of reaction may be from zero to about 100° C. or higher if the amino crotonic acid ester is stable at such temperatures.

TIME OF REACTION

May extend from five minutes to twelve hours or more.

PROPORTIONS OF REACTANTS

The proportions of ammonia or amines to beta-carbonyl ester of a higher alcohol are usually non-critical. At least a mole of the nitrogen compound per mole of the ester is usually employed but excesses are permissible. In the case ammonia, or a volatile amine is employed as a basic nitrogen compound, the excess merely bubbles off. Excesses of other nitrogen compounds can usually be eliminated by distillation. If low yields are permissible or a mixed product is desired, the proportion of nitrogen compound is reduced, e.g., to some such value as 0.25 molar percent.

Various uses of the beta-amino crotonates are contemplated as being within the scope of the present invention. For example, they may be used as surfactants to aid in improving emulsification or wetting characteristics of various materials. The introduction of the beta-amino crotonic acid radical by esterification into higher alcohol radicals also provides a convenient method of obtaining the latter in a form in which they are dispersible or soluble in such media as water. The beta-amino crotonic acid esters of higher alcohols as herein disclosed, in some instances, may be employed as emplsifying agents for fats and mineral oils and other materials. In other instances, it may be desirable to incorporate a fatty acid of a class comprising oleic acid, stearic acid, lauric acid, ricinoleic acid, palmitic acid, coconut oil acids and mixtures of any two or more of the foregoing. The fatty acids may be expected to react at least in part at room temperature or above, with the amine group of the beta-amino crotonic acid ester to form salts which may be regarded as being types of soaps. However, applicants do not necessarily restrict themselves to the use of the fatty acids in reacted state to form soaps. The use of said acids in reacted or non-reacted state with the beta-amino crotonic acid esters is contemplated.

Water dispersions or solutions of esters or sterols, higher fatty alcohols and the like may be employed in reactions of organic synthesis with other compounds. The water provides a common medium by means of which thorough contact between the reactants is obtained.

By way of illustration, the use of beta-keto esters of higher alcohols, per se, as emulsifying agents or as intermediates in the formation of emulsifying agents will now be described.

Example XIII

In accordance with this example, 100 grams of light mineral oil containing in solution 1 gram of the castor oil ester of beta-amino crotonate and 1.55 grams of fatty acids of a glyceride oil, such as is sold under the trade name of Aliphat 34B, were agitated, for example, in a commercial mill or blender, with 80 milliliters of distilled water. The resultant emulsion is of the oil-in-water type and has been tested successfully for stability by allowing it to stand for a period of one week.

Example XIV

In accordance with this test, 2 grams of the stearyl ester of beta-amino crotonic acid was dissolved in distilled water and the solution was dispersed with 100 milliliters of mineral oil of light grade to provide a water-in-oil emulsion of heavy cream-like consistency. This emulsion exhibited only very slight break, even after standing for one week. In the preparation of this emulsion of this example, it is to be noted that the stearyl ester of beta-amino crotonic acid is employed as the dispersing agent without the incorporation of fatty acids as aids. The example constitutes evidence that the beta-amino crotonic acid esters of higher alcohols are, per se, good emulsifying agents. It also indicates the solubility of the esters in water.

Example XV

In the tests involved in this example, 2 grams of castor oil ester of beta-amino crotonic acid was dissolved in 100 milliliters of water and the solution was emulsified with 100 milliliters of light mineral oil and 2 grams of fatty acids from a vegetable oil. Acids from such vegetable oils as cottonseed oil, soya oil, coconut oil, or the like may be employed as the adjuvants in the dispersion.

Example XVI

In this example, a light mineral oil and 3 grams of fatty acids of a vegetable oil were dispersed by means of a solution of 2 grams of the ester of beta-amino crotonic acid and polyethylene glycol dissolved in 100 milliliters of water. The emulsion broke only slightly after standing for one week. The beta-amino crotonic acid esters of higher alcohols may be employed to form emulsions in water of other hydrophobic unctuous materials than mineral oils. Materials contemplated include waxes, lanolin, glyceride oils, and fats and many others.

Example XVII

In this test, 100 grams of light mineral oil was successfully dispersed in 100 milliliters of water by the aid of 2 grams of beta-amino crotonic acid ester of butyl carbitol and 2 grams of fatty acids from a vegetable oil. The butyl carbitol of the beta-amino crotonate of this example is not strictly classifiable as containing 12 carbon atoms, however, it additionally contains two ether linkages. When employed in combination with fatty acids of a glyceride oil, it has been found to be an effective emulsifying agent.

The forms of the invention described are by way of illustration. It will be apparent to those skilled in the art that numerous modifications may be made therein without departure from the spirit of the invention or the scope of the appended claims.

This application is a continuation-in-part of copending application, Serial No. 280,646, filed April 4, 1952, now abandoned.

We claim:

1. A beta-amino crotonic acid ester of a cholesterol.

2. A beta-amino crotonate of stearyl alcohol.

3. A material as defined in claim 7 in which the nitrogen group of the beta-amino crotonate is $-NH_2$.

4. The polyethylene glycol ester of a beta-amino crotonic acid.

5. The ester of the triglyceride of ricinoleic acid and a beta-amino crotonic acid.

6. A beta-amino crotonate of a hydroxyl-containing alkyd resin which is a phthalic glyceride modified by a glyceride oil.

7. As a new material, a beta-amino crotonate of alcohols containing at least 12 carbon atoms and being selected from a class consisting of (A) alcohols resulting from hydrogenation of the carboxyl of a fatty acid of glyceride oil, (B) alkyd resins which are the esterification products of phthalic anhydride, glycerol, and a glyceride oil acid, (C) a sterol selected from the class consisting of cholesterol, beta sitosterol, stigmasterol, cholestanol, epidehydroandrosterone, ergosterol, epicholestanol, coprostanol, cortisone, cholic acid, desoxycholic acid, (D) castor oil, and (E) polyethylene glycol.

8. A mixture of the material as defined in claim 7 and water.

9. An emulsion medium comprising an aqueous solution of the material defined in claim 7.

10. As a new material a hydrogen halide salt of a beta-amino crotonate as defined in claim 7.

11. A beta amino crotonic acid ester of an aliphatic monohydric alcohol containing at least 12 carbon atoms.

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United States Patent Office

3,310,561

Patented Mar. 21, 1967

3,310,561
6-AMMONIOPURINIDES

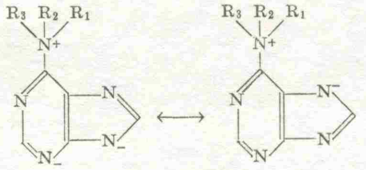
Alfred R. Bader, Milwaukee, Wis., assignor to Aldrich Chemical Company, Inc., Milwaukee, Wis., a corporation of Wisconsin

No Drawing. Filed Aug. 5, 1965, Ser. No. 477,585
5 Claims. (Cl. 260—252)

This invention relates to novel compounds and to processes of producing such compounds. More particularly, this invention relates to novel 6-ammonio-purinides.

According to this invention, there are provided compounds of the following general formula:

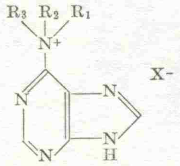
(1)



where R_1, R_2 and R_3 are each selected from the group consisting of lower alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like; lower alkenyl, such as vinyl, allyl, isopropenyl, butenyl, butadienyl and the like; and lower cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The compounds of this invention are prepared by the method of contacting compounds of the following general formula with a suitable acid binding agent:

(2)



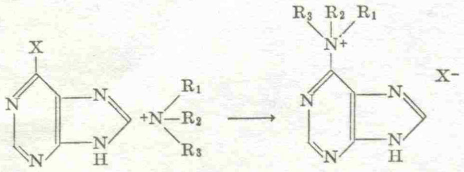
where R_1, R_2 and R_3 have the significance previously assigned and X is selected from the group consisting of chlorine and bromine.

This method may be carried out by treating the compounds of general Formula 2 with sodium hydroxide, sodium or potassium carbonate or a tertiary amine such as triethylamine.

A more convenient method of contacting the intermediate compounds of Formula 2 with an acid binding agent may be carried out by passing a solution of the compounds through an ion exchange column containing an ion exchange resin, in its basic form. After passing the solution through the column, the solvent is removed by evaporation or distillation leaving as the residue the compounds of this invention. These are surprisingly stable materials which may be further purified by recrystallization from water or an organic solvent.

Preparation of the intermediate compounds of Formula 2 is carried out by reacting in a suitable solvent, 6-chloro- or 6-bromopurine with a tertiary amine of the general formula $NR_1R_2R_3$, where R_1, R_2 and R_3 have the significance previously assigned. This reaction may be represented by the following equation:

(3)



where R_1, R_2, R_3 and X have the significance assigned above.

Solvents suitable for carrying out the reaction of Equation 3 include methanol, ethanol, acetone and N,N-dimethylformamide.

Examples of tertiary amines which may be employed to form the intermediate reaction products include trimethylamine, triethylamine, tributylamine, methyldiethylamine, N,N-diethylcyclohexylamine, allyldimethylamine, N-allylcycloproplyamine, N-methylcyclopentylamine and ethyldiisopropylamine.

The compounds of this invention are useful as chelating agents in the recovery of trace metals such as cobalt.

The invention will now be illustrated by, but is not intended to be limited to, the following examples:

EXAMPLE 1

Purin-6-yltrimethylammonium chloride

In a 5 liter, 3-necked flask fitted with a Dry Ice condenser, gas inlet tube, and traps, and immersed in a Dry Ice 2-propanol bath, 425 g. of 6-chloropurine was added to 2.75 liters of N,N-dimethylformamide. A stream of anhydrous trimethylamine was passed through the solution for 6 hours. A solid originally suspended in the reaction mixture slowly redissolved, and then precipitation of the product took place. The reaction was allowed to warm to room temperature and left overnight. The precipitate was filtered off, washed with dimethylformamide and ether, and dried in a vacuum oven at 45° overnight. Yield 515.5 g. of a crude product. The material was purified by dissolving it in cold water and precipitating it with acetone.

EXAMPLE 2

6-(trimethylammonio)-purinide

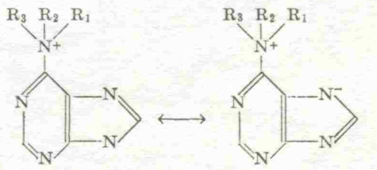
A solution of 170 g. of purin-6-yltrimethylammonium chloride, produced as in Example 1, in 1 liter of water was passed through an ion exchange column packed with 1.5 liters of an ion exchange resin in its hydroxyl form. The column was then washed thoroughly with water. The combined eluates were then evaporated to drying in vacuo at 50°. The crude product was recrystallized from water and dried in vacuo over phosphorus pentoxide to yield 112 g. of a white crystalline material, M.P. 190–192°.

Analysis.—Calcd. for $C_8H_{11}N_5$ (177.21): C, 54.22; H, 6.26; N, 39.52. Found: C, 54.30; H, 6.20; N, 39.49.

Various changes and modifications of the invention can be made and, to the extent that such variations incorporate the spirit of this invention, they are intended to be included within the scope of the appended claims.

What is claimed is:

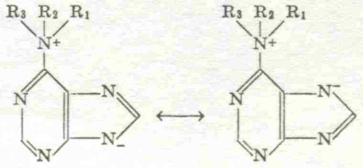
1. A compound of the formula



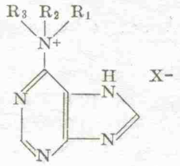
where R_1, R_2 and R_3 are each selected from the group consisting of lower alkyl, lower alkenyl and lower cycloalkyl.

2. The crystalline compound, 6-(trimethylammonio)-purinide.

3. The process of preparing a compound of the formula



where R_1, R_2 and R_3 are each selected from the group consisting of lower alkyl, lower alkenyl and lower cycloalkyl comprising contacting compounds of the general formula



where R_1, R_2 and R_3 have the same significance as above and X, is selected from the group consisting of chlorine and bromine, with an acid binding agent.

4. The process of preparing 6-(trimethylammonio)-purinide comprising contacting purin-6-yltrimethylammonium chloride with an acid binding reagent, selected from the group consisting of sodium hydroxide, sodium carbonate, potassium carbonate and triethylamine.

5. The process of preparing crystalline 6-(trimethylammonio)-purinide comprising passing an aqueous solution of purin-6-yltrimethylammonium chloride through an ion exchange resin in its basic form and subsequently removing the water.

No references cited.

ALEX MAZEL, *Primary Examiner.*

MARY O'BRIEN, *Examiner.*

United States Patent Office

3,337,578
Patented Aug. 22, 1967

3,337,578

2,2′-ALKYLENEBISBENZIMIDAZOLES

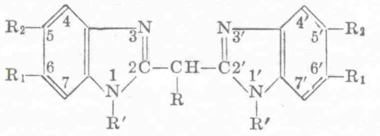
Alfred Bader, Milwaukee, Wis., Boyd E. Graham, Kalamazoo, Mich., and Ernst Reif, Heidenheim an der Brenz, Germany, assignors to Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany, a company

No Drawing. Filed Sept. 15, 1961, Ser. No. 138,246
13 Claims. (Cl. 260—309.2)

This application is a continuation-in-part of application Ser. No. 39,791, filed June 30, 1960, and now abandoned.

This invention relates to novel chemical compounds and is more particularly concerned with novel alkyl-substituted 2,2′-alkylenebisbenzimidazoles and the acid addition salts thereof.

The novel compounds of the invention are selected from the class consisting of (a) a compound represented by the following formula:

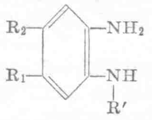


(I)

wherein R is selected from the class consisting of hydrogen and lower-alkyl, for example, methyl, ethyl, propyl, butyl, amyl, hexyl, and isomeric forms thereof, R_1 and R_2 represent lower-alkyl, for example, methyl, ethyl, propyl, and isopropyl, and R′ is selected from the class consisting of hydrogen and lower-alkyl, for example, methyl, ethyl, propyl, butyl, and isomeric forms thereof, and (b) the pharmacologically acceptable acid addition salts thereof.

The novel compounds of the invention exhibit pharmacological activity. For example, the compounds of the invention can be used as diuretics and sedatives in the treatment of animals and humans. In addition, the compounds of the invention can be used as intermediates in the preparation of dyestuffs in accordance with U.S. Patent 2,697,712.

The novel compounds of the invention having the Formula I can be prepared using a variety of methods. For example, the compounds having the Formula I can be prepared by condensing the appropriately substituted 1,2-phenylenediamine having the formula:



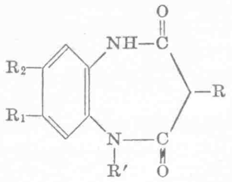
(II)

wherein R_1, R_2, and R′ have the significance hereinbefore defined, with malonamide or a derivative thereof having the formula $RCH(CONH_2)_2$ wherein R has the significance hereinbefore defined, using the procedure described by Lane, J. Chem. Soc. 1953, 2238, for the preparation of 2,2′-methylenebisbenzimidazole and 2,2′-methylenebis(5-methylbenzimidazole).

Alternatively, the compounds having the Formula I can be prepared by condensing the appropriately substituted 1,2-phenylenediamine having the Formula II with malonic ester or a substituted malonic ester having the formula $RCH(COOR_3)_2$ wherein R_3 represents an alkyl group, preferably an ethyl group, and R has the significance hereinbefore defined, using the procedure described by Arnold, J. Org. Chem., 23, 565, 1958, for the preparation of 2,2′-methylenebisbenzimidazole.

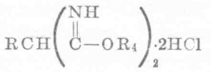
It is to be noted that the above methods of synthesis

give rise to a mixture of the desired compound having the Formula I and a compound having the formula:



wherein R, R_1, R_2, and R′ have the significance hereinbefore defined. This mixture can be separated readily by treatment with a strong mineral acid such as hydrochloric acid in solution in a mixture of water and a water-miscible organic solvent such as dimethylformamide in which the hydrochloride of the desired Compound I is soluble but in which the other component of the mixture is insoluble. The desired compound having the Formula I can then be recovered by neutralization of the solution and can be purified by conventional procedures, for example, by recrystallization.

In a further alternative the compounds having the Formula I can be prepared by condensing the appropriately substituted 1,2-phenylenediamine having the Formula II with a malonimino dialkyl ether dihydrochloride or a substituted derivative thereof having the formula



$$RCH\left(\overset{NH}{\overset{\|}{C}}-OR_4\right)_2\cdot 2HCl$$

wherein R has the significance hereinbefore defined and R_4 represents alkyl, preferably ethyl, using the procedure described by Thomas and Tyler, J. Chem. Soc., 1957, 2197, for the preparation of alkylenebisbenzimidazoles. The malonimino dialkyl ether dihydrochlorides employed in the above reaction can be prepared by treating the appropriately substituted malononitrile $RCH(CN)_2$, wherein R has the significance hereinbefore defined, with hydrogen chloride and the appropriate alkanol R_4OH, wherein R_4 has the significance hereinbefore defined, in the presence of an inert solvent such as dioxane.

The 4,5-dialkyl-1,2-phenylenediamines having the Formula II which are employed as starting materials in the above-described syntheses, can be prepared by methods which are well-known in the art. For example, the 1,2-phenylenediamines having the Formula II wherein R′ is hydrogen can be prepared by nitration of the corresponding 1,2-dialkylbenzenes to yield the corresponding 1,2-dialkyl-4-nitrobenzenes, reduction of the latter to the corresponding 3,4-dialkylanilines, conversion of the anilines so obtained to their urethanes, and nitration of the latter followed by hydrolysis to yield the corresponding 4,5-dialkyl-2-nitroanilines and reduction of the nitro compounds so obtained to yield the desired 4,5-dialkyl-1,2-phenylenediamines. The procedure involved in the above series of reactions is that described by Lambooy, J. Am. Chem. Soc. 71, 3756, 1949, for the preparation of 4,5-diethyl-1,2-phenylenediamine. Further for example, the 4,5-dialkyl-1,2-phenylenediamines having the Formula II wherein R′ is lower-alkyl can be prepared by known methods, e.g., by the method described in U.S. Patent 2,400,872 for the preparation of N-methyl- and N-ethyl-1,2-phenylenediamine.

The acid additions salts of the invention comprise the salts of the compounds having the Formula I above with pharmacologically acceptable acids such as sulfuric, hydrochloric, hydrobromic, nitric, phosphoric, benzoic, p-toluenesulfonic, salicyclic, acetic, propionic, tartaric, citric, succinic acids, and the like. The acid addition salts of the invention can be prepared by conventional methods. For example, the compound having the Formula I can be treated with at least a stoichiometric amount of the appropriate acid; according to the nature of the solvent employed the desired salt will separate spontaneously or can be precipitated by the addition of a solvent in which the salt is insoluble.

The novel compounds of the invention can be combined with solid or liquid pharmaceutical carriers and formulated as tablets, powder packs, or capsules, using starch and like excipients, or dissolved or suspended in suitable solvents or vehicles, for oral or parenteral administration.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting.

EXAMPLE 1

2,2′-methylenebis(5,6-dimethylbenzimidaole)

A mixture of 136 g. (1.0 mole) of 4,5-dimethyl-1,2-phenylenediamine (Beilsteins Handbuch der Organischen Chemie, 13, 179, fourth edition, 1930) and 51 g. (0.5 mole) of malonamide in 300 ml. of ethylene glycol was heated under reflux for 4 hours. The resulting mixture was allowed to cool before being treated with an approximately equal volume of water. The solid which separated was isolated by filtration and recrystallized from ethylene glycol.

The solid so obtained was slurred in 1460 ml. of dimethylformamide and the slurry was stirred with 1460 ml. of water and 146 ml. of concentrated hydrochloride acid. The resulting mixture was stirred for 5 minutes and then filtered. The solid so isolated was washed with water on the filter and then discarded. The combined filtrate and washings were made alkaline by the addition of concentrated ammonium hydroxide solution and the solid which separated was isolated by filtration, washed with water, and dried in vacuo. There was thus obtained 2,2′-methylenebis(5,6-dimethylbenzimidazole).

EXAMPLE 2

2,2′-methylenebis(5,6-dimethylbenzimidazole) and the dihydrochloride thereof

(A) *Malonimino diethyl ether dihydrochloride.*—Anhydrous hydrogen chloride was passed into 500 ml. of dioxane (previously dried over sodium and redistilled), maintained at approximately 10° C. in a cooling bath, until 124 g. of hydrogen chloride has been absorbed. The resulting solution was cooled to approximately 5° C. and to the solution was added, slowly with stirring, a solution of 33 g. (0.5 mole) of malononitrile in 46 g. (1.0 mole) of anhydrous ethanol (prepared by the method of Manske, J. Am Chem. Soc., 53, 1106, 1931) and 50 ml. of dry dioxane (previously treated as described above). The resulting mixture was maintained at approximately 5° C. and stirred for 3 hours. The mixture was then allowed to stand (12 hours) at approximately 5° C. until the oil which separated had solidified. The resulting solid was isolated by filtration, washed on the filter which anhydrous ether, and dried in vacuo. There was thus obtained 97 g. of malonimino diethyl ether dihydrochloride in the form of a solid having a melting point of 130 to 138° C. This material was used, without further purification, in the process described below.

(B) *2,2′-methylenebis(5,6-dimethylbenzimidazole).*—A mixture of 5.44 g. (0.04 mole) of 4,5-dimethyl-1,2-phenylenediamine and 4.62 g. (0.02 mole) of malonimino diethyl ether dihydrochloride (prepared as described above) in 70 ml. of absolute ethanol was heated under reflux for 45 minutes. To the solution so obtained was added 80 ml. of water and the mixture was treated slowly with 5 ml. of 28 percent aqueous ammonium hydroxide solution. The resulting slurry was stirred and cooled for approximately 2 hours before isolating the solid by filtration and washing thoroughly with water on the filter. The isolated solid was slurried several times with a total of 80 ml. of acetone before being dried in vacuo. There was thus obtained 2,2′-methylenebis(5,6-dimethylbenzimidazole) in the form of a solid having a melting point higher than 330° C.

(C) *2,2′-methylenebis(5,6-dimethylbenzimidazole) dihydrochloride.*—A slurry of 4.95 g. (0.016 mole) of 2,2′-methylenebis(5,6-dimethylbenzimidazole) in 50 ml. of absolute ethanol was stirred vigorously and heated to 60° C. To the hot slurry was added slowly a solution of 1.5 g. (0.041 mole) of anhydrous hydrogen chloride in 50 ml. of absolute ethanol. The hot mixture was stirred for 15 minutes after the addition was complete and was then allowed to cool. The cold mixture was treated with 50 ml. of acetone and the resulting mixture was cooled in an ice bath and stirred for 2 hours. The solid which separated was isolated by filtration and washed on the filter with two 25-ml. portions of acetone before being dried in vacuo. There was thus obtained 5.75 g. of the dihydrochloride of 2,2′-methylenebis(5,6-dimethylbenzimidazole) in the form of a crystalline solid having a melting point higher than 330° C.

Analysis.—Calcd. for $C_{19}H_{22}Cl_2N_4$: C, 60.48; H, 5.88; Cl, 18.80; N, 14.85. Found: C, 60.42; H, 5.97; Cl, 18.89; N, 15.13.

EXAMPLE 3

2,2′-propylidenebis(5,6-dimethylbenzimidazole) and the dihydrochloride thereof

A solution of 18.6 g. (0.137 mole) of 4,5-dimethyl-1,2-phenylenediamine in 100 ml. of 1,2,4-trichlorobenzene was heated to 170 to 180° C. with stirring and to the solution was added dropwise, over a period of 1.5 hours, 12.8 g. (0.0685 mole) of diethyl ethylmalonate. After the addition was complete the temperature was slowly raised to 190 to 195° C. and maintained at this level with stirring for a further 2 hours. The ethanol and water liberated during the reaction were remoped by distillation. The resulting suspension was cooled and the solid which had separated was isolated by filtration and washed on the filter with benzene and then with ethanol before being dried in vacuo. The crude product so obtained was slurried in 200 ml. of dimethylformamide and the slurry was stirred with 200 ml. of water and 20 ml. of concentrated hydrochloric acid. The resulting mixture was stirred for 2 minutes and then filtered. The solid so isolated was washed with water on the filter and then discarded. The combined filtrate and washings were made alkaline by the addition of concentrated ammonium hydroxide solution and the solid which separated was isolated by filtration, washed with water, and dried in vacuo. There was thus obtained 10 g. of 2,2′-propylidenebis(5,6-dimethylbenzimidazole) in the form of a solid having a melting point of 330 to 338° C.

Analysis.—Calcd. for $C_{21}H_{24}N_4$: N, 16.85. Found: N, 16.69.

The 2,2′-propylidenebis(5,6-dimethylbenzimidazole) so obtained was converted to its dihydrochloride using the procedure described in Example 2C. The dihydrochloride so obtained had a melting point of 310 to 318° C.

EXAMPLE 4

22,6′-ethylidenebis(5,6-dimethylbenzimidazole) and the dihydrochloride thereof

Using the procedure described in Example 3, but replacing diethyl ethylmalonate by diethyl methylmalonate, there was obtained 2,2′-ethylidenebis(5,6-dimethylbenzimidazole) in the form of a solid having a melting point of 287 to 290° C.

Analysis.—Calcd. for $C_{20}H_{22}N_4$: N, 17.60. Found: N, 17.42.

The 2,2′-ethylidenebis(5,6-dimethylbenzimidazole) so obtained was converted to its dihydrochloride using the procedure described in Example 2C. The dihydrochloride so obtained had a melting point of 305 to 310° C.

Analysis.—Calcd. for $C_{20}H_{24}Cl_2N_4$: C, 61.38; H, 6.18;

Cl, 18.12; N, 14.32. Found: C, 61.06; H, 6.15; Cl, 18.03; N, 14.20.

EXAMPLE 5

2,2′-pentylidenebis(5,6-dimethylbenzimidazole) and the dihydrochloride thereof

Using the procedure described in Example 3, but replacing diethyl ethylmalonate by diethyl butylmalonate, there was obtained 2,2′-pentylidenebis(5,6-dimethylbenzimidazole) in the form of a solid having a melting point of 360 to 368° C.

Analysis.—Calcd. for $C_{23}H_{28}N_4$: N, 15.54. Found: N, 15.05.

The 2,2′-pentylidenebis,5,6-dimethylbenzimidazole) so obtained was converted to its dihydrochloride using the procedure described in Example 2C. The dihydrochloride monohydrate so obtained had a melting point of 250° C. (dec.).

Analysis.—Calcd. for $C_{23}H_{30}Cl_2N_4 \cdot H_2O$: C, 61.19; H, 7.15; Cl, 15.71; N, 12.41. Found: C, 61.70; H, 6.93; Cl, 15.71; N, 12.10.

EXAMPLE 6

2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole) and the dihydrochloride thereof

(A) *2′-nitro-4′,5′-dimethyl-p-toluenesulfonanilide sodium salt.*—To a solution of 16.6 g. of 2-nitro-4,5-dimethylaniline (Takatori et al., J. Pharm. Soc. Japan 75, 881, 1955; C. A. 50, 4920i, 1956) in 50 ml. of pyridine was added 19.0 g. of p-toluenesulfonyl chloride. The mixture was heated on a steam bath for 1 hr., cooled, and poured into ice-water. The resulting yellow solid was recovered by filtration, washed with water, and dried. The dried solid was dissolved in hot ethanol, and to this solution was added a methanol solution of sodium methoxide. By filtering this mixture there was obtained 14.0 g. of 2′-nitro-4′,5′-dimethyl-p-toluenesulfonanilide sodium salt as a bright yellow solid having a melting point of 310 to 315° C. (dec.).

(B) *2′-nitro-4′,5′-dimethyl-N-ethyl-p-toluenesulfonanilide.*—A solution of 15 g. (0.044 mole) of 2′-nitro-4′,5′-dimethyl-p-toluenesulfonanilide sodium salt (Part A) and 8 g. (0.051 mole) of ethyl iodide in 75 ml. of dimethylformamide was heated on a steam bath for two hours, cooled, and treated with an approximately equal volume of water. An oil separated which slowly solidified. The solid was recovered on a filter, and dissolved in hot ethanol. Upon cooling, 12 g. of 2′-nitro-4′,5′-dimethyl-N-ethyl-p-toluenesulfonanilide having a melting point of 130 to 132° C. was obtained.

Analysis.—Calcd. for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.52; H, 5.72; N, 8.31.

(C) *2-nitro-4,5-dimethyl-N-ethylaniline.* — A solution of 12 g. (0.034 mole) of 2′-nitro-4′,5′-dimethyl-N-ethyl-p-toluenesulfonanilide (Part B) in a mixture of 15 ml. of concentrated sulfuric acid and 3 ml. of water was heated on a steam bath for 3.5 hrs. The reaction mixture was cooled and poured into ice-water. An orange solid separated which was recovered on a filter and dissolved in hot ethanol. On cooling, there was obtained 6.5 g. of 2-nitro-4,5-dimethyl-N-ethylaniline as an orange solid having a melting point of 71 to 74° C.

Analysis.—Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.43. Found: C, 61.47; H, 6.74; N, 14.53.

(D) *4,5-dimethyl-N-ethyl-1,2-phenylenediamine dihydrochloride.*—A suspension of 6.5 g. (0.033 mole) of 2-nitro-4,5-dimethyl-N-ethylaniline (Part C) in 50 ml. of ethanol acidified with 3 ml. of concentrated hydrochloric acid was hydrogenated in the presence of platinum oxide catalyst until the theoretical amount of hydrogen had been absorbed. The suspension was filtered to remove the catalyst, and the solvent was removed under reduced pressure. The residue thus obtained was dissolved in hot ethanol and poured into ether with vigorous stirring. An oil separated and slowly solidified. The solid was recovered on a filter and dried. There was thus obtained 7.6 g. of 4,5-dimethyl-N-ethyl-1,2-phenylenediamine dihydrochloride having a melting point of 135 to 138° C.

(E) *2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole) and the dihydrochloride thereof.*—A suspension of 4.72 g. (0.02 mole) of 4,5-dimethyl-N-ethyl-1,2-phenylenediamine dihydrochloride (Part D) in 25 ml. of methanol was mixed with 4.04 g. of triethylamine. The mixture was swirled while 2.31 g. (0.01 mole) of malonimino diethyl ether dihydrochloride was added. The reaction mixture was heated at the reflux temperature for 45 min., during which time ammonium chloride separated, and after cooling, it was poured into water. The solid material which separated was recovered on a filter. After washing thoroughly with water, it had a gelatinous consistency. After removing the water by azeotropic distillation with a mixture of benzene and ethanol, the benzene and ethanol were removed by evaporation. The residue thus obtained was dissolved in methylene chloride, the solution was filtered, and the methylene chloride was evaporated, to give 2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole). After dissolving the free base thus obtained in ethanol, the ethanolic solution was acidified with an excess of anhydrous hydrogen chloride dissolved in ethyl acetate and the solution was refrigerated. The crystalline solid that separated was recoverel on a filter and washed with ethyl acetate to give 2.0 g. of 2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole) dihydrochloride having a melting point of 280 to 283° C. (dec.).

Analysis.—Calcd. for $C_{23}H_{30}Cl_2N_4$: N, 12.93; Cl, 16.36. Found: N, 13.28; Cl, 16.00.

EXAMPLE 7

2,2′-methylenebis(1,5,6-trimethylbenzimidazole) and the dihydrochloride thereof

A suspension of 3.8 g. (0.017 mole) of N-4,5-trimethyl-1,2-phenylenediamine dihydrochloride in 50 ml. of methanol was mixed with 3.5 g. of triethylamine. To the solution thus obtained was added 1.97 g. (0.0085 mole) of malonimino diethyl ether dihydrochloride and the reaction mixture was heated at the reflux temperature for 45 minutes, during which time ammonium chloride separated. After cooling, the reaction mixture was poured into water and the solid that separated was recovered on a filter. The solid was washed thoroughly with water and it developed a gelatinous consistency. After removing the water by azeotropic distillation with a mixture of benzene and ethanol, the benzene-ethanol solvent was removed by evaporation, to give 2,2′-methylenebis(1,5,6-trimethylbenzimidazole). The free base thus obtained was dissolved in methylene chloride, the solution was filtered, and the methylene chloride was evaporated. The residue thus obtained was dissolved in ethanol, and the solution was acidified with an excess of hydrogen chloride in ethyl acetate and refrigerated. The 2,2′-methylenebis(1,5,6-trimethylbenzimidazole) dihydrochloride, which separated as a colorless solid, weighed 1.20 g. and had a melting point of 300° C. (dec.).

Analysis.—Calcd. for $C_{21}H_{26}Cl_2N_4$: N ,13.82; Cl, 17.49. Found: N, 13.54; Cl, 17.35.

EXAMPLE 8

2,2′-methylenebis(1-n-butyl-5,6-dimethylbenzimidazole) and the dihydrochloride thereof

Using the procedure described in Example 6E, but replacing 4,5-dimethyl-N-ethyl-1,2-phenylenediamine dihydrochloride by N-n-butyl-4,5-dimethyl-1,2-phenylenediamine dihydrochloride, there is obtained 2,2′-methylenebis(1-n-butyl-5,6-dimethylbenzimidazole) and the dihydrochloride thereof.

EXAMPLE 9

2,2′-heptylidenebis(5,6-dimethylbenzimidazole) and the dihydrochloride thereof

Using the procedure described in Example 3, but replacing diethyl ethylmalonate by diethyl hexylmalonate, there is obtained 2,2′-heptylidenebis(5,6-dimethylbenzimidazole). The latter is converted to its dihydrochloride using the procedure described in Example 2C.

EXAMPLE 10

2,2′-methylenebis(5,6-diethylbenzimidazole) and the *dihydrochloride thereof*

Using the procedure described in Example 2B, but replacing 4,5-dimethyl-1,2-phenylenediamine by 4,5-diethyl-1,2-phenylenediamine (Lambooy, supra), there is obtained 2,2′-methylenebis(5,6-diethylbenzimidazole). The latter compound is converted to the corresponding dihydrochloride using the procedure described in Example 2C.

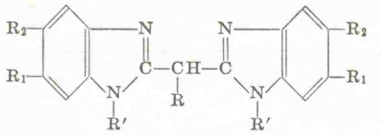
EXAMPLE 11

2,2′-propylidenebis(5,6-diethylbenzimidazole) and the dihydrochloride thereof

Using the procedure described in Example 3, but replacing 4,5-dimethyl-1,2-phenylenediamine by 4,5-diethyl-1,2-phenylenediamine, there is obtained 2,2′-propylidenebis(5,6-diethylbenzimidazole). The latter compound is converted to the corresponding dihydrochloride using the procedure described in Example 2C.

We claim:

1. A compound selected from the class consisting of (a) a 2,2′-alkylenebisbenzimidazole having the formula:



wherein R and R′ are selected from the class consisting of hydrogen and lower-alkyl and R_1 and R_2 represent lower-alkyl, and (b) the pharmacologically acceptable acid addition salts thereof.

2. 2,2′-methylenebis(5,6-dimethylbenzimidazole).

3. 2,2′-methylenebis(5,6-dimethylbenzimidazole) dihydrochloride.

4. 2,2′-ethylidenebis(5,6-dimethylbenzimidazole).

5. 2,2′-ethylidenebis(5,6-dimethylbenzimidazole) dihydrochloride.

6. 2,2′-propylidenebis(5,6-dimethylbenzimidazole).

7. 2,2′-propylidenebis(5,6-dimethylbenzimidazole) dihydrochloride.

8. 2,2′-pentylidenebis(5,6-dimethylbenzimidazole).

9. 2,2′-pentylidenebis(5,6-dimethylbenzimidazole) dihydrochloride.

10. 2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole).

11. 2,2′-methylenebis(5,6-dimethyl-1-ethylbenzimidazole) dihydrochloride.

12. 2,2′-methylenebis(1,5,6-trimethylbenzimidazole).

13. 2,2′-methylenebis(1,5,6-trimethylbenzimidazole) dihydrochloride.

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