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NONCATALYTIC ESTER EXCHANGE REACTION OF BETA-KETO CARBOXYLIC ACID ESTERS

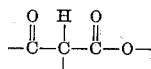
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No Drawing. Application April 7, 1951,
Serial No. 219,900

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:



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.

2

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 by-products 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.

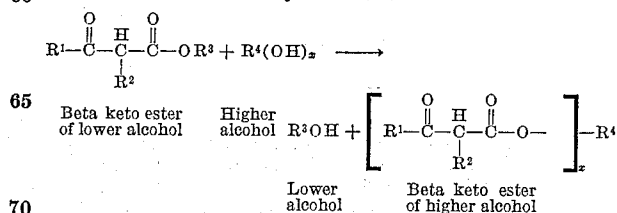
According to a further embodiment of the invention, it has been found that maximum yield and purity of ester is obtained when the evolved lower alcohol is swept rapidly from the reaction mixture. This may be accomplished by distilling the lower alcohol under conditions such that the partial pressure 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



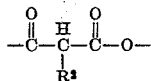
The several groups R¹, R², R³, and R⁴ will be defined later. As previously stated, in order to obtain the most complete reaction, we find it convenient to use an excess of the beta keto ester of the lower alcohol.

BETA KETO ESTERS

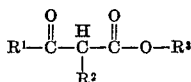
Beta keto esters which may be employed to effect esterification of alcohols include various esters which

3

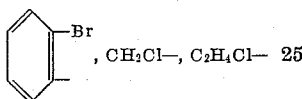
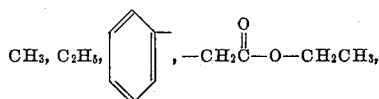
contain a ketone carbonyl group in the beta position with respect to a carboxyl. They include the group



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:



In the formula, group R¹ may be aliphatic, aromatic or aliphatic or aromatic groups which may or may not contain substitute groups. Examples of R¹ groups are:



and other halogen substituted hydrocarbon radicals, RNH₂, RCHO, etc.

R² 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.

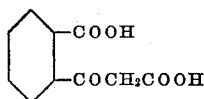
R³ is usually the labile radical which is adapted to be replaced in the ester interchange. These functioning groups usually are of low molecular weight, e. g., 1, 2, 3, or possibly 4 carbon atoms in a saturated or unsaturated aliphatic substituted or unsubstituted hydrocarbon chain.

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

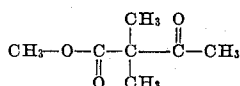
Table A

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



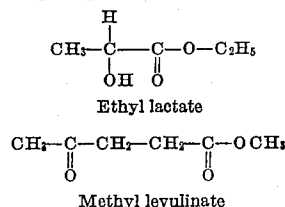
It has been found that a beta carbonyl ester which is doubly substituted in the alpha position thus containing no active hydrogen and being unable to enolize, gives no ester interchange with alcohols under the conditions of the present invention. Such an ester is methyl dimethyl acetoacetate of the formula:



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

4

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:

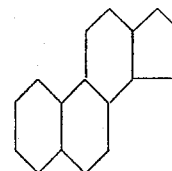


Neither ethyl lactate nor methyl levulinate gives transesterification under the conditions of the present invention.

20 ALCOHOLS CAPABLE OF ESTER INTERCHANGE WITH BETA CARBONYL ESTERS

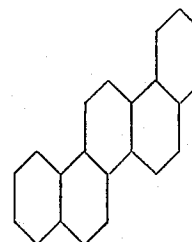
Many hydroxy compounds of relatively high molecular weight may be treated according to this invention. Typical are compounds having the formula R⁴(OH)_x (from Equation A) where (OH) is an alcoholic OH group, R⁴ contains 6 or more carbon atoms and X is a number denoting the number of hydroxyl groups in 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 plicene:



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
 Carnauby 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.

5 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.

10 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.

25 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.

30 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 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 (based upon the beta keto ester of the lower alcohol), still better yields can be attained.

35 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.

40 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, CO₂, or the like. Steam in substantial amounts is usually to be avoided.

45 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.

50 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.

55 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.

60 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 oper-

ate 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 α_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 $\frac{1}{3}$ to $\frac{1}{2}$ 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 α_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 α_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 1/2 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 1 1/2 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 1 1/2 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

11

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:

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.

12

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 $\text{CH}_3\text{COCH}(\text{C}_2\text{H}_5)\text{CO}_2\text{CH}_3$ 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 ($\text{C}_2\text{H}_5\text{OOC}-\text{CH}_2\text{COCH}_2\text{COOC}_2\text{H}_5$) 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 $\text{C}_2\text{H}_5\text{OOC}-\text{CH}_2\text{CH}_2(\text{COCH}_3)\text{COOC}_2\text{H}_5$ 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 acetyl succinate, had a saponification value of 165.

EXAMPLE XXXII

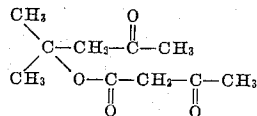
10 grams of stearyl alcohol and 100 grams of diethyl acetylsuccinate were heated on the steam bath under 10 millimeters absolute pressure for 40 hours. The clear solution was then stripped in vacuo, the residue was dissolved in 50 milliliters of hot methanol, cooled, and the white solid filtered, washed 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 acetoacetate 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

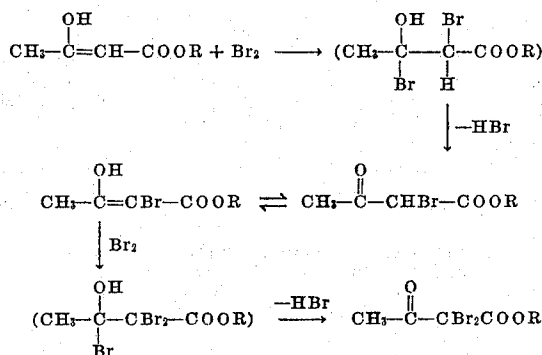
3.87 grams of cholesterol and 23.22 grams of methyl acetoacetate were heated at 140° C. with water condenser for 5 hours. Then 50 milliliters of methanol was added, the solution was cooled overnight at 23° F., and the white solid was filtered, washed with 50 milliliters of methanol and dried. This product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

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.

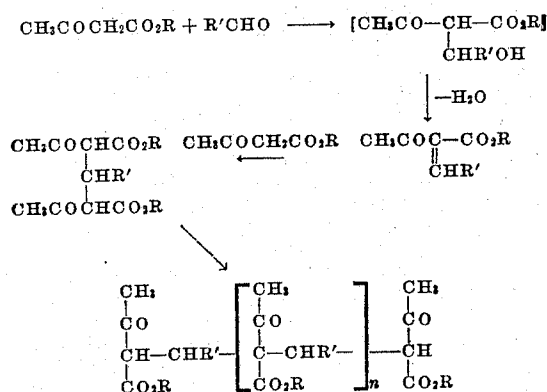
EXAMPLE XLVII

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:



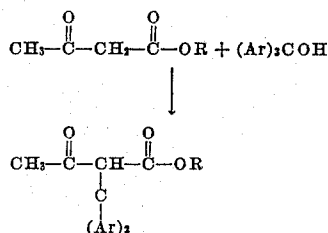
where R is the alcohol radical of the acetoacetate and R' is the radical of the aldehyde.

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 Z₆ 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.

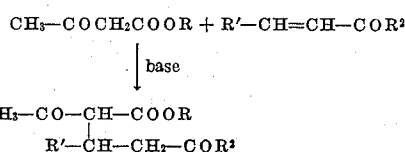
Benzyllic type halides and alcohols such as triphenylmethyl chloride and triphenyl carbinol react with the beta-keto esters produced according to this invention and new compounds are obtained according to the following equation:



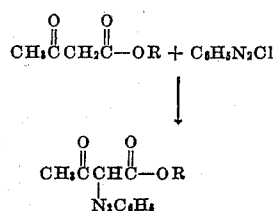
where Ar is the monovalent aryl radical.

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 alkyl 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. 5

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