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2,899,464

PROCESS OF PREPARING SODIUM SALTS OF SUBSTITUTED MALONIC ACIDS

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This invention relates to methods of preparing sodium salts of substituted malonic acids and more particularly to a method of preparing, recovering and purifying disodium salts of monosubstituted malonic acids.

The sodium salts of substituted malonic acids are useful when added to or otherwise incorporated into smoking tobacco to provide, during burning or smoking of the tobacco, certain desired flavor or aroma-producing acids. These flavoring acids are formed in situ by the decarboxylation of the substituted malonic acid type compounds as disclosed in United States Patent No. 2,766,145, issued October 19, 1956, to Samuel O'Brien Jones. As disclosed in that patent, the flavoring acids so released are volatile, monocarboxylic organic acids having 3 to 8 carbon atoms. Thus the substituent in the malonic acid type compound is usually a hydrocarbon radical having from 1 to 6 carbon atoms. The disodium salts of monosubstituted malonic acids may be prepared by saponification in an aqueous medium of the corresponding substituted malonic ester, which latter may be produced by variations of the well known malonic ester synthesis. In accordance with such prior art techniques the monosubstituted malonic ester is saponified in an aqueous solution with a base such as sodium hydroxide. The aqueous reaction mixture contains the desired disodium salt of the substituted malonic acid along with unreacted sodium hydroxide and ester, alcohol residues from the saponification, and undesired side reaction products such as salts of unsubstituted malonic acid and the like. Inasmuch as these substances are for the most part readily soluble in the aqueous solution, the separation of the substituted malonic acid salt is rendered rather difficult and may be tedious. Accordingly, it is one object of the present invention to provide an improved method of preparing disodium salts of substituted malonic acids.

Another object is the provision of a process for recovering disodium salts of monosubstituted malonic acids in a substantially pure form.

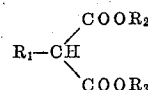
Another object is the provision of a process for saponifying and recovering in a relatively pure form, a disodium salt of a monosubstituted malonic acid in a single step without the necessity of intermediate isolation and purification procedures.

These and other objects of the present invention will be seen from the following specification and appended claims.

In one broad form the present invention comprises a process for preparing and recovering relatively pure disodium salts of substituted malonic acids which comprises saponifying an ester of a monosubstituted malonic acid with an alkaline sodium compound in a solution of a lower alcohol and thereafter recovering from said reaction mixture the disodium salt of the substituted malonic acid which is precipitated therein. Generally the substituted malonic esters to which the process of

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the present invention is applicable may be characterized by the following structural formula:



wherein R_1 is a hydrocarbon radical containing up to 6 carbon atoms and R_2 and R_3 are saturated aliphatic hydrocarbon radicals. In a preferred embodiment of the present invention R_1 is a cyclic hydrocarbon radical or saturated aliphatic hydrocarbon radical containing 2 to 4 carbon atoms. Particularly preferred substituents corresponding to R_1 are isopropyl, sec-butyl and phenyl radicals. Generally R_2 and R_3 are alcohol residues which may be characterized as lower alkyl and as particularly preferred embodiments may be characterized as methyl or ethyl.

The alcohols used in the saponification medium of the present invention are the lower alcohols containing 1 to 3 carbon atoms. Within this group, alcohols which are most preferred are ethanol and methanol, and mixtures of these alcohols are also contemplated. The alkaline sodium compound useful in the present saponification process may be any sodium compound which upon hydrolysis is sufficiently alkaline to saponify the substituted malonic ester starting material. An example of such material is sodium hydroxide. Generally the amount of sodium hydroxide is not critical except that sufficient quantities should be employed to insure substantially complete saponification of the malonic ester starting material.

While the process of the present invention is preferably carried out under substantially anhydrous conditions and using as the saponification media substantially anhydrous alcohol, it is also true that the process may be carried out using as a saponification medium an alcohol or a blend of alcohols in admixture with relatively small amounts of water. Relatively large amounts of water will result in solubilizing the desired disodium salt of the substituted malonic acid. Accordingly, when a good yield is to be obtained the amount of water present, if any, should be less than 30% by weight and preferably less than 20% by weight.

The reaction may be carried out at various temperatures and it is preferred that the reaction be carried out at an elevated temperature such as for example the reflux temperature of the reaction mixture. If desired, the reaction may be carried out under reflux at normal atmospheric pressure or pressures slightly above or below normal atmospheric pressure. The time required for saponification in this process is not critical and varies with the concentration of the reactants and the temperature at which the process is carried out. Generally sufficient time should be allowed to substantially completely convert the substituted malonic ester to the corresponding disodium salt. The extent of reaction may be determined by conventional analytical techniques.

In the process of this invention the substituted malonic ester is admixed with an alcoholic sodium hydroxide solution. The reaction is preferably carried out at reflux temperatures which may be continued for a period of time to insure complete reaction. During the course of the saponification the disodium salt of the substituted malonic acid formed is precipitated. After saponification is complete, the precipitated disodium salt of the substituted malonic acid may be recovered from the reaction mixture by filtration, centrifuging, decantation, or like procedure.

The following examples will illustrate the preparation

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of monosubstituted malonic esters and the saponification and recovery of the disodium salts thereof, according to the process of the present invention.

EXAMPLE I

Preparation of isopropylmalonic ester

Under anhydrous conditions a solution of 110 grams of sodium methylate in 340 grams of methanol is heated to reflux and 320.3 grams of diethyl malonate is added, with stirring, during five minutes. Then 248.5 grams of isopropyl bromide are added during five minutes and the mixture is stirred and refluxed for four hours. At the end of the reflux period the mixture is distilled at reduced pressure for removal of alcohols and unreacted isopropyl bromide, keeping the pot temperature below 55° C., as the pressure is gradually reduced to about 275 millimeters. The residual mixture is then cooled and washed with 350 milliliters of water for removal of sodium bromide. The organic material remaining amounts to about 300 grams, and is crude isopropylmalonic ester.

Saponification of crude isopropylmalonic ester

Sodium hydroxide (160 grams) is dissolved in 1200 milliliters of methanol with stirring, the heat of solution causing the mixture to reflux. All of the crude isopropylmalonic ester, described above, is added with vigorous stirring to the refluxing sodium hydroxide solution during five to ten minutes. The reaction is exothermic, causing brisk reflux throughout the addition period. During this time a thick slurry of disodium isopropylmalonate is formed. The mixture may be refluxed for a period of about one hour to insure complete saponification. The slurry is filtered with suction, and the resulting solid is washed on the filter with 500 milliliters of fresh methanol. The filter cake is dried at 110–120° C., giving about 295 grams of disodium isopropylmalonate. The product is a fine powder, and is essentially free of color and odor. Over-all yields, based on diethyl malonate, average about 78 percent of theory.

EXAMPLE II

Preparation of sec-butylmalonic ester

Starting with 110 grams of sodium methylate, 340 grams of methanol, 320.3 grams of diethyl malonate, and 276.8 grams of sec-butyl bromide, sec-butylmalonic ester is prepared by the process described above for preparation of isopropylmalonic ester. The crude sec-butylmalonic ester obtained in this way amounts to approximately 300 grams.

Saponification of crude sec-butylmalonic ester

Starting with 160 grams of sodium hydroxide, 1200 milliliters of methanol, and all of the crude sec-butylmalonic ester, the saponification is run by the process described above for isopropylmalonic ester. The saponification is exothermic, and a thick slurry of disodium sec-butylmalonate forms. The slurry is filtered with suction, and the resulting solid is washed on the filter with 500 milliliters of fresh methanol. The filter cake is dried at 110–120° C., giving about 300 grams of disodium sec-butylmalonate. The product is a fine powder, and is essentially free of color and odor. Over-all yields, based on diethyl malonate, average about 73 percent of theory.

EXAMPLE III

Disodium allylmalonate

Fifty grams of diethyl allylmalonate (commercially available) were added to a refluxing solution of 23 grams of sodium hydroxide in 200 milliliters of methyl alcohol during about five minutes. Saponification was rapid and exothermic. A thick slurry of the disodium salt formed during the reaction period. The slurry was filtered with suction, and the resulting solid was washed on the filter with 300 milliliters of methyl alcohol. The

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washed solid was dried at 110–120° C., giving 32.1 grams (68 percent of theory) of disodium allylmalonate.

EXAMPLE IV

Disodium phenylmalonate

One-half mole (118.2 grams) of diethyl phenylmalonate (commercially available) was added to a refluxing solution of 45 grams of sodium hydroxide in 200 milliliters of methyl alcohol during about five minutes. Saponification was rapid and exothermic. A thick slurry of the disodium salt formed. The slurry was filtered with suction and the solid was dried at 110–120° C., giving 112 grams (100 percent of theory) of disodium phenylmalonate.

EXAMPLE V

Disodium phenylmalonate

One-half mole (118.2 grams) of diethyl phenylmalonate was added to a refluxing solution of 45 grams of sodium hydroxide in 200 milliliters of ethyl alcohol during about five minutes. Saponification was rapid and exothermic. The resulting slurry was filtered with suction and the solid was dried at 110–120° C., giving 79 grams (70 percent of theory) of disodium phenylmalonate.

EXAMPLE VI

Disodium allylmalonate

Forty-seven grams (0.235 mole) of diethyl allylmalonate were added to a refluxing mixture of 22 grams of sodium hydroxide and 200 milliliters of isopropyl alcohol. The mixture was refluxed for thirty minutes, during which time a slurry formed. The solid was recovered by filtration with suction. The solid was dried at 110–120° C., giving 26.3 grams (59 percent of theory) of disodium allylmalonate.

EXAMPLE VII

Disodium phenylmalonate

One-half mole (118.2 grams) of diethyl phenylmalonate was refluxed with a mixture of 45 grams of sodium hydroxide and 200 milliliters of isopropyl alcohol. The resulting slurry was filtered with suction and the solid was dried at 110–120° C., giving 35 grams (31 percent of theory) of disodium phenylmalonate.

While the various examples in the foregoing have indicated yields somewhat lower than 100%, this result is in part due to the fact that a crude monosubstituted malonic ester was used in the saponification process. It has been found the saponification reaction in fact goes to about 100% completion and any reduction in yields is in part due to the use of crude starting materials, and the partial solubility of the sodium salt in the reaction medium.

While the foregoing examples have illustrated the saponification and recovery of substantially pure disodium salts of monosubstituted malonic acids, it should be mentioned that small amounts of impurities that may be contained therein are not sufficient to have any deleterious effect when these compounds are utilized as additive to smoking tobacco. Also any disodium salts that may not have precipitated and remain in solution may be recovered by reusing the filtrate as the medium in a subsequent saponification operation as is well known.

A may readily be seen the process of the present invention fulfills the stated objects in that there is provided thereby a method of saponifying and recovering from said saponification mixture a disodium salt of a monosubstituted malonic acid in relatively pure form without the necessity of separate and extended purification and isolation steps which were heretofore encountered in the processes generally known in the prior art.

The foregoing examples show that the best yields are obtained when methyl or ethyl alcohol is used as the

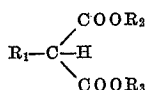
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saponification medium, although isopropyl alcohol is satisfactory. As indicated substantially anhydrous conditions are preferred but small amounts of water may be present. Generally the percent of water in the alcohol should not exceed 30% and preferably should not exceed 20%, or otherwise the disodium salt becomes too soluble and cannot be recovered by the simple procedure herein outlined.

While several particular embodiments of this invention are shown above, it will be understood, of course, that the invention is not to be limited thereto, since many modifications may be made, and it is contemplated, therefore, by the appended claims, to cover any such modifications as fall within the true spirit and scope of this invention.

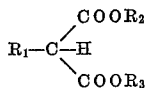
What is claimed is:

1. A process for preparing a solid disodium salt of a substituted malonic acid which comprises saponifying under reflux conditions a substituted malonic ester having the formula:



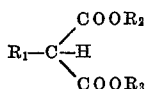
wherein R_1 is a hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 and R_3 are each lower alkyl groups, in an admixture of an alkaline reacting sodium compound, a lower alkyl alcohol containing up to 3 carbon atoms, and up to about 30% by weight water based on said lower alkyl alcohol whereby a major amount of said disodium salt is formed as a precipitate in the reaction mixture, and separating said precipitate from said mixture.

2. A process for preparing a solid disodium salt of a substituted malonic acid which comprises saponifying under reflux conditions a substituted malonic ester having the formula:



wherein R_1 is a hydrocarbon radical having from 1 to 6 carbon atoms and R_2 and R_3 are each lower alkyl groups, in an admixture of sodium hydroxide, an alcohol containing up to 3 carbon atoms and up to about 30% by weight of water based on said alcohol whereby a major amount of said disodium salt is formed as a precipitate in the reaction mixture, and separating said precipitate from said mixture.

3. A process for preparing a solid disodium salt of a substituted malonic acid which comprises saponifying under reflux conditions a substituted malonic ester having the formula:



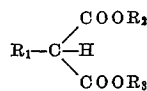
wherein R_1 is a hydrocarbon radical having from 1 to 6 carbon atoms and R_2 and R_3 are each lower alkyl groups, in an admixture of sodium hydroxide, methanol, and up

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to 30% by weight of water based on methanol, whereby a major amount of said disodium salt is formed as a precipitate in the reaction mixture, and separating said precipitate from said mixture.

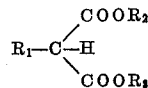
4. The process of claim 3 wherein said salt is separated by filtration.

5. A process for preparing a substantially pure disodium salt of a substituted malonic acid which comprises saponifying under reflux conditions a lower alkyl substituted lower alkyl malonic ester having the formula:



wherein R_1 is a hydrocarbon radical having from 1 to 6 carbon atoms and R_2 and R_3 are each lower alkyl groups, in an admixture of sodium hydroxide, ethanol, and up to 30% by weight of water based on ethanol, whereby a major amount of said disodium salt is formed as a precipitate in the reaction mixture, and separating said precipitate from said mixture.

6. A process for preparing a solid disodium salt of a monosubstituted malonic acid which comprises saponifying under reflux conditions a lower alkyl substituted lower alkyl malonic ester having the formula:



wherein R_1 is a hydrocarbon radical having from 1 to 6 carbon atoms and R_2 and R_3 are each lower alkyl groups, in an admixture of sodium hydroxide, an alcohol selected from the group consisting of methanol, ethanol and isopropanol, and between about 0 and about 20 weight percent water based on said alcohol, whereby a major amount of said disodium salt is formed as a precipitate in the reaction mixture, and separating said precipitate from said mixture.

7. The process of claim 6 wherein the disodium salt is separated by filtration.

8. The process of claim 6 wherein R_2 and R_3 are each selected from the group consisting of ethyl and methyl.

9. A process for preparing a solid disodium salt of a monosubstituted malonic acid which comprises contacting at an elevated temperature a lower alkanol ester of a substituted malonic acid selected from the group consisting of lower alkyl, lower alkenyl and phenyl monosubstituted malonic acids with sodium hydroxide in an alcoholic solution for a time sufficient to saponify said ester, said alcohol in said alcoholic solution containing from one to three carbon atoms and said solution containing less than 30% by weight of water, whereby a major amount of said disodium salt is formed as a precipitate and thereafter separating said precipitate from the reaction mixture.

References Cited in the file of this patent

- Breslow: J.A.C.S. 66, pg. 1287 (1944).
Wagner et al.: Synthetic Organic Chemistry, pg. 417 (1953).