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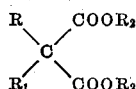
2,188,874

SECONDARY Δ_1 -ALKENYL MALONIC ESTERS
AND PROCESS OF PRODUCING SAMEArthur C. Cope, Bryn Mawr, Pa., assignor to
Sharp & Dohme, Incorporated, Philadelphia,
Pa., a corporation of MarylandNo Drawing. Application October 15, 1936,
Serial No. 105,820

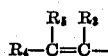
15 Claims. (Cl. 260—485)

This invention relates to new derivatives of malonic esters. It relates more particularly to secondary Δ_1 -alkenyl malonic esters, and includes not only various new products, but also novel processes by which they may be produced.

The new compounds with which the invention is concerned may be represented by the following graphic formula

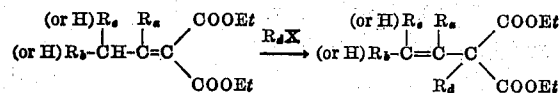


in which R is a secondary Δ_1 -alkenyl radical and R₁ is an alkyl radical or an aralkyl radical, and in which either the secondary alkenyl radical has more than three carbon atoms, or the alkyl or aralkyl radical is higher than methyl, and R₂ is an alkyl radical, or the like. The secondary alkenyl radical, represented by R, in general has the following structure:



in which R₃, R₄ and R₅ may be alkyl groups, saturated or unsaturated, aralkyl groups, aryl groups, or other hydrocarbon or substituted hydrocarbon residues, and may be alike or different, and in which R₄ or R₅, or both, may be hydrogen.

The new products are advantageously prepared by the alkylation of the corresponding secondary alkylidene malonic esters, in the course of which the double bond uniting the alkylidene group and the malonic ester group is shifted to the Δ_1 position, so that the alkylidene group is changed, by isomerization or other means, to the corresponding secondary alkenyl group with the double bond in the Δ_1 position, as shown in the equation:



In general, the secondary Δ_1 -alkenyl group in the alkenyl malonic esters can vary widely, as all of the secondary alkylidene malonic esters can be transformed into corresponding secondary Δ_1 -alkenyl malonic esters by the novel processes of this invention, and the range of secondary Δ_1 -alkenyl esters which may be produced is limited only by the availability of the corresponding alkylidene malonic esters.

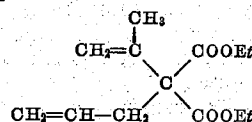
The new products are useful as intermediates for the production of secondary Δ_1 -alkenyl barbituric acids and thiobarbituric acids, which may readily be produced by the condensation of urea or thiourea with the corresponding malonic

esters, and are also useful for the production of unsaturated acids, by the de-carboxylation of the malonic esters.

In accordance with the process of the invention, the secondary alkylidene malonic esters may be subjected, in solution, to alkylation with a suitable alkyl halide, sulfate, or other alkyl salt, in the presence of a sodium alkoxide, such as sodium methoxide or sodium ethoxide, or in the presence of metallic sodium, in an inert solvent. In this latter process, the sodium reacts first with the alkylidene malonic ester to give an intermediate sodio-derivative, which in turn reacts with the alkyl salt. In the course of the reaction which takes place, the double bond of the alkylidene malonic ester shifts to the Δ_1 position in the alkenyl group, and the alkyl group of the halide, sulfate or other salt becomes attached to the methylene carbon of the malonic ester.

The invention will be further illustrated by the following specific examples, with particular reference to the production of new secondary Δ_1 -alkenyl alkyl malonic esters, but it is not limited thereto.

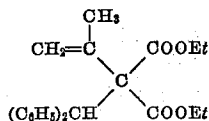
Example 1.—Preparation of isopropenyl allyl malonic ester



Into a suitable reaction vessel, equipped with a mechanical stirrer, a reflux condenser, a dropping funnel and a thermometer are placed 300 parts of anhydrous alcohol in which are dissolved 11.5 parts of sodium. The solution is cooled below 0° C. by means of an ice-salt mixture and 100 parts of isopropylidene malonic ester are slowly added, with agitation, at such a rate that the temperature of the mixture does not rise above 0° C. After all of the ester has been added, the stirring is continued for several minutes and 93 parts of allyl bromide are added in one portion. The molar ratio of allyl bromide and isopropylidene malonic ester used is 3 to 2. After the allyl bromide is added, the cooling bath is removed and the reaction mixture is rapidly warmed to the refluxing temperature, at which time a noticeable reaction takes place. The reaction should not be allowed to proceed too vigorously. When the reaction starts, sodium bromide precipitates from the solution. The refluxing and stirring are continued for about 8 to 14 hours, and the mixture is allowed to stand overnight. It is then diluted with about 2 volumes of water, the organic layer

is separated, and the aqueous layer is extracted with several portions of benzene, about 300 parts in all, the combined organic layer and benzene extract are washed with water, and the solvent is removed at somewhat reduced pressures. The product has a boiling range of 110–111° C./3 mm. and is isopropenyl allyl malonic ester.

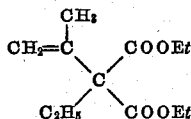
Example 2.—Preparation of isopropenyl diphenyl-methyl malonic ester,



11.5 parts of sodium are powdered under xylene and rinsed into a reaction vessel equipped with a stirrer, a reflux condenser and a dropping funnel with about 400 parts of dry ether. The vessel is cooled in an ice bath while 100 parts of isopropylidene malonic ester are added, with stirring, over a period of 10 minutes. The stirred suspension (the sodio-derivative is relatively insoluble) is then refluxed for about 10 hours, after which 130 parts of diphenyl-methyl bromide is added over a period of 10 minutes, and the refluxing is continued for another 24 hours. Dilute hydrochloric acid is added, the ethereal layer is removed, and the aqueous layer is extracted with ether. The ether is removed from the combined ethereal layer and extract at reduced pressure, and the residue is shaken with ammonia to remove unalkylated material. The ester is extracted from the ammonia with ether, washed with water, and purified by distillation and recrystallization. It melts at 89.5–90.5° C.

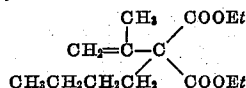
Sodamide may be used in place of metallic sodium in the process of the preceding example; but if sodamide is used, it must be handled with due precautions, as, if not properly handled, it is explosive. One way in which it may be used safely involves dissolving it in liquid ammonia, admixing the solution with an inert solvent such as benzene, ether or the like, and removing the liquid ammonia by vaporization. The inert solvent, containing the sodamide, may then be used in the process. Almost any solvent inert to sodium, such as ether, benzene, toluene, etc., may be used in carrying out the process of the foregoing example.

Example 3.—Preparation of isopropenyl ethyl malonic ester,



Diethyl sulfate, isopropylidene malonic ester, and sodium ethoxide are reacted under substantially the same conditions, and in the same molar ratio, as in Example 1, except that ether is used as the solvent, and the resulting isopropenyl ethyl malonic ester is separated and purified by distillation. It boils at 128–129° C./24 mm.

Example 4.—Preparation of n-butyl isopropenyl malonic ester,



11.5 parts of sodium, 100 parts of isopropylidene malonic ester, and 88 parts of n-butyl iodide are reacted under substantially the same conditions as in Example 2 using benzene as the solvent, with the production of the above product, which

may be purified by distillation. It boils at 130–132° C./20 mm.

In the processes of the foregoing examples, various alkyl salts, such as the sulfates, halides, etc., may be used for the conversion of the alkylidene malonic esters, to the corresponding secondary Δ_1 -alkenyl malonic esters, in the presence of sodium methoxide or sodium ethoxide or other alkoxides. When the halides are used as alkylating agents, it is preferable to use the more reactive bromides and iodides, as they give somewhat better yields, but the chlorides may be used if desired.

The groups which may be so introduced include not only the primary alkyl groups, but also the secondary alkyl groups, such as the isopropyl or secondary butyl groups, as well as the unsaturated alkyl groups, such as the allyl, crotyl and citronellyl groups, aralkyl groups, such as benzyl and the like, cyclic groups, such as the cyclohexyl or cyclopentyl groups, etc.

Among the compounds which may be so prepared, and which are new products, useful as intermediates in the production of other products, are the isopropenyl derivatives, in which the bond of the methylene carbon of the malonic ester not attached to the isopropenyl group may be attached to one of the following radicals:

Ethyl
Propyl (normal or iso)
Butyl (normal, iso or secondary)
Allyl
Crotyl
Amyl (normal, iso or secondary)
Citronellyl
Cinnamyl
Hexyl (normal, iso or secondary)
Cyclohexyl
Cyclopentyl
Phenyl-ethyl
Benzyl

and others. Other secondary alkenyl malonic esters, in which one bond of the methylene carbon is attached to one of the above radicals, or methyl, and which have in place of the isopropenyl group one of the following radicals are also included in the invention as new products:

1-methyl- Δ_1 -n-propenyl
1-methyl- Δ_1 -butenyl (normal or iso)
1-methyl- Δ_1 -pentenyl (normal or iso)
1-methyl- Δ_1 -hexenyl (normal or iso)
1-methyl- Δ_1 -heptenyl (normal or iso)
1-ethyl- Δ_1 -propenyl
1-n-propyl- Δ_1 -butenyl
1-butyl- Δ_1 -pentenyl

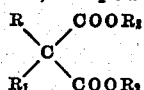
and others.

The secondary alkylidene malonic esters, used for the production of the secondary Δ_1 -alkenyl malonic esters, may be produced in any suitable manner; but they are advantageously produced by the condensation of a ketone with malonic ester in the presence of zinc chloride, zinc chloride and acetic anhydride, or other condensing agents.

The new products of the present invention may be prepared by other processes than those described above, but the process in which the secondary alkylidene malonic esters and the alkylating salts are reacted in an inert solvent in the presence of metallic sodium is of particular advantage.

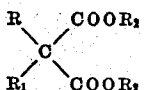
I claim:

1. As new products, compounds of the formula



in which R is a secondary Δ_1 -alkenyl group, R₁ is a radical selected from the class consisting of alkyl and aralkyl radicals having at least two carbon atoms, and R₂ is alkyl.

2. Compounds of the formula



in which R is a secondary Δ_1 -alkenyl group having more than three carbon atoms, R₁ is an alkyl group and R₂ is alkyl.

3. Alkyl esters of secondary Δ_1 -alkenyl alkyl malonic acids, in which the alkyl group substituted on the methylene carbon atom of the malonic acid has more than one carbon atom.

4. Alkyl esters of secondary Δ_1 -alkenyl alkyl malonic acids, in which the alkenyl group has more than three carbon atoms.

5. Alkyl esters of allyl isopropenyl malonic acid.

6. Alkyl esters of butyl isopropenyl malonic acid.

7. Alkyl esters of ethyl isopropenyl malonic acid.

8. The process of producing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises reacting an alkyl ester of a secondary alkylidene malonic acid with an alkyl salt in the presence of an alkali metal alkoxide.

9. The process of producing alkyl esters of secondary Δ_1 -alkenyl malonic acids which com-

prises reacting an alkyl ester of a secondary alkylidene malonic acid with an alkyl salt in the presence of a sodium alkoxide.

10. The process of producing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises reacting an alkyl ester of a secondary alkylidene malonic acid with an alkyl salt in the presence of a substance of the group consisting of alkali metals, alkali metal amides, and alkali metal alkoxides in an inert solvent.

11. The process of producing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises reacting an alkyl ester of a secondary alkylidene malonic acid with an alkyl salt in the presence of metallic sodium in an inert solvent.

12. The process of producing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises reacting an alkyl ester of a secondary alkylidene malonic acid with an alkyl salt in the presence of metallic sodium in ether.

13. The process of preparing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises forming an alkali metal derivative of an alkyl ester of a secondary alkylidene malonic acid and reacting said derivative with an alkyl salt.

14. The process of preparing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises forming an alkali metal derivative of an alkyl ester of a secondary alkylidene malonic acid and reacting said derivative with an alkyl halide.

15. The process of preparing alkyl esters of secondary Δ_1 -alkenyl malonic acids which comprises forming an alkali metal derivative of an alkyl ester of a secondary alkylidene malonic acid and reacting said derivative with an alkyl sulfide.

ARTHUR C. COPE.