

UNITED STATES PATENT OFFICE

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METHOD OF OBTAINING TRANS POLYENE COMPOUNDS

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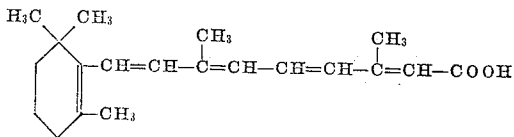
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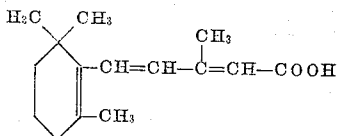
This invention relates to methods of obtaining in improved yield α,β -unsaturated polyene acids in the form having a trans configuration, and is particularly concerned with methods of obtaining crystalline β -ionylidene acetic acid and vitamin A acid in the trans form.

In the synthesis of vitamin A-active materials, it is necessary to obtain compounds which have a particular chemical constitution and also a particular spatial configuration in the molecule. Thus, vitamin A acid should have the structure



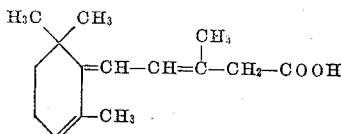
and should also have a trans configuration with respect to the second olefinic double bond from the ring for maximum vitamin A activity as measured by standard bioassay methods. Other vitamin A-active materials, such as vitamin A esters, similarly require a trans configuration for optimum activity.

Similarly, β -ionylidene acetic acid, which forms a valuable intermediate in vitamin A syntheses, should have the structure



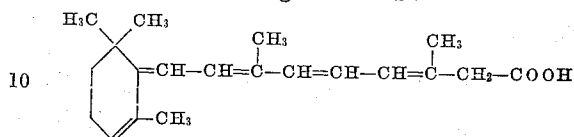
and such acid as well as the corresponding esters should also have a trans configuration with respect to the second olefinic double bond from the ring to facilitate the production of vitamin A material having a high level of biological activity.

In the synthesis of vitamin A acid and the intermediate β -ionylidene acetic acid or the esters of such acids, the inherent instability of these materials often gives rise to the formation of mixtures of the desired α,β -unsaturated and completely conjugated compounds and desmotropic β,γ -unsaturated isomers of the desired polyene compounds. Thus, for example, in the manufacture of β -ionylidene acetic acid, the use of a Reformatsky reaction and dehydration of the resultant hydroxy compound results in the formation of a β,γ -unsaturated isomer of β -ionylidene acetic acid probably having the formula



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in admixture with the desired α,β -unsaturated β -ionylidene acetic acid; and similarly the use of a Reformatsky reaction and dehydration in the preparation of vitamin A acid results in the formation of β,γ -unsaturated isomer of vitamin A acid probably having the formula



in admixture with the desired α,β -unsaturated vitamin A acid. For optimum yield, it is necessary to convert such β,γ -unsaturated isomers to the desired α,β -unsaturated form.

Even when vitamin A acid and β -ionylidene acetic acid or esters of such acids, such as the alkyl esters, are obtained in the desired α,β -unsaturated form, however, they often exist as a mixture of cis and trans isomers with respect to the second olefinic double bond from the ring. For optimum yield of the desired α,β -unsaturated trans form in relatively pure form, it therefore becomes necessary to separate the trans isomer from the cis isomer and to convert the cis isomer to the trans isomer.

It is accordingly an object of this invention to provide an improved process for obtaining in good yield α,β -unsaturated polyene acids and esters in the trans form with respect to the olefinic unsaturation.

It is another object of the invention to provide an effective method for converting β,γ -unsaturated isomers of β -ionylidene acetic acid or vitamin A acid or esters thereof to the corresponding trans α,β -unsaturated acid or ester and for recovering such trans α,β -unsaturated acid or ester in crystalline form and substantially free of cis α,β -unsaturated acid or ester.

Another object of the invention is to provide an improved method of obtaining vitamin A acid in the form exhibiting a high level of biological activity.

Another object of the invention is to facilitate the use of Reformatsky or similar reactions causing isomerization in the synthesis of vitamin A by providing means for obviating the objectionable effects normally attendant to the use of such reactions.

Another object of the invention is to provide a simple but effective method for concomitantly converting cis α,β -unsaturated polyene acids or esters of the vitamin A series to the corresponding trans α,β -unsaturated acids or esters and for recovering the trans α,β -unsaturated acids or esters in crystalline form.

Another object of the invention is to reduce

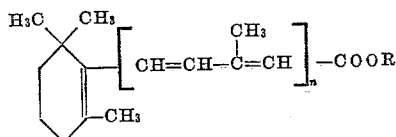
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the content of relatively inactive material in the products obtained by conventional vitamin A syntheses which yield vitamin A acid during the synthesis.

Another object of the invention is to increase the available supply of highly potent vitamin A by converting other less desirable isomers to more active form.

Other objects will be apparent from the description and claims which follow.

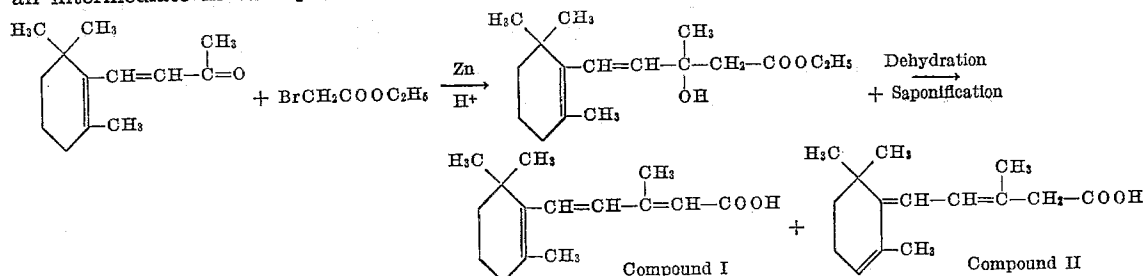
These and other objects are successfully attained by means of this invention as described more fully hereinafter. We have discovered that crystalline α,β -unsaturated polyene acids or esters thereof, having a trans configuration with respect to the second olefinic double bond from the ring and having the formula



wherein R is either hydrogen or a hydrocarbon radical, and wherein n is either 1 or 2, can be obtained in excellent yield by treating a cis isomer of such a compound with a hydrogen halide in a solution of either acetonitrile or nitromethane and thereby progressively converting the cis isomer to the desired trans isomer and concomitantly crystallizing the desired trans isomer from the solution in substantially pure form. In the usual process embodying the invention, a mixture of cis and trans isomers is treated in accordance with the invention, since the mixture is usually obtained in vitamin A syntheses and not the pure cis form.

We have discovered further that by the processes embodying this invention, the β,γ -unsaturated isomers of the desired α,β -unsaturated polyene acids and esters are readily converted to the desired α,β -unsaturated form, usually as a mixture of the cis and trans forms, and the trans form is progressively crystallized out of the solution while the cis form is concomitantly converted to the trans form.

The polyene acid, β -ionylidene acetic acid, is readily formed in accordance with known practice by subjecting β -ionone to a Reformatsky reaction with ethyl bromoacetate, followed by dehydration of the resulting β -ionolacetic acid ester and saponification to form the acid according to the following equations, the ester being an intermediate in such process:

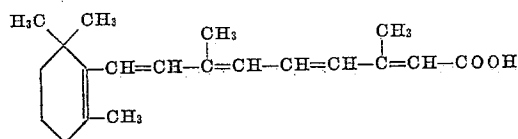


As can be seen from the equations, the product obtained is a mixture of the α,β -unsaturated β -ionylidene acetic acid (Compound I) and a β,γ -unsaturated desmotropic isomer (Compound II). Compound I is present as a mixture of the cis isomer and the trans isomer with respect to the configuration at the second olefinic double bond from the ring. Thus in the mixture obtained, the desired trans β -ionylidene acetic acid

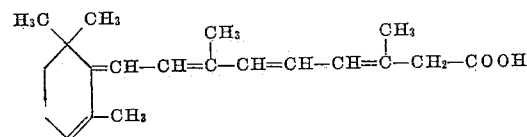
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is present in an amount of not more than about 25% of the total product and usually less than this amount, and it becomes necessary to separate the desired trans isomer in order to continue the synthesis to vitamin A and obtain a highly active material and to convert a substantial portion of the material other than trans α,β -unsaturated β -ionylidene acetic acid to this desired form.

Similarly, vitamin A acid is commonly obtained as a mixture of the cis and trans forms of the α,β -unsaturated vitamin A acid, and in many cases, in an admixture of the cis and trans forms of α,β -unsaturated vitamin A acid having the formula



and the β,γ -unsaturated desmotropic isomer of vitamin A acid having the formula



It is therefore necessary to convert both the β,γ -unsaturated isomer and the cis form of the α,β -unsaturated vitamin A acid to the desired trans vitamin A acid to obtain a good yield of highly potent vitamin A acid.

In the process embodying this invention, any of the well-known hydrogen halides, and preferably either hydrogen chloride or hydrogen bromide, either in anhydrous form or as an aqueous acid, is used for effecting conversion to the desired trans α,β -unsaturated polyene compound in a solution in either acetonitrile or nitromethane, and the trans α,β -unsaturated polyene compound crystallizes out of such a solution in substantially pure form at room temperature. The process is applicable for obtaining β -ionylidene acetic acid or vitamin A acid, or any of the well-known esters of such acids including alkyl, aryl and aralkyl esters, with the alkyl esters such as methyl, ethyl, propyl or similar alkyl esters being preferred for convenience. By means of this invention, a substantial proportion of the cis α,β -unsaturated polyene compound is converted to the desired trans form concomitant with the crystallization and is progressively crys-

tallized out, and, where a β,γ -unsaturated isomer is present, it is thus converted to crystalline trans α,β -unsaturated compound. Either acetonitrile or nitromethane can be successfully employed to obtain a crystalline product at room temperature although temperatures as high as 30-40° C. can be employed and temperatures below room temperature, as for example 5° C. can, of course, be used but are usually not neces-

sary. The process is desirably carried out in a reaction mixture wherein the acid concentration of the hydrogen halide is from 0.1 N to 1.0 N. Lower concentrations can be used but the process proceeds rather slowly, and concentrations substantially above 1 N lead to some destruction of the polyene compounds.

The invention is illustrated by the following examples with regard to certain preferred embodiments of the invention.

Example 1

A two hundred gram portion of the ethyl ester of β -ionylidene acetic acid, obtained by a Reformatsky reaction between β -ionone and ethyl bromoacetate followed by dehydration with phosphorous oxychloride in pyridine in accordance with usual practice and having

$$E_{1cm}^{1\%}(283 m\mu) = 705$$

was dissolved in 1000 cc. of ethanol. A solution of 350 g. of potassium hydroxide in 1500 cc. of water was added to the ethanol solution and the resulting mixture was heated at 70–80° C. for 45 minutes. The mixture was then cooled, diluted with 5000 cc. of water, extracted with ether, the soap layer acidified with 10% aqueous sulfuric acid, and the mixed β -ionylidene acetic acids extracted out with ether. The ether extract was washed with a 10% aqueous solution of sodium sulfate, dried over anhydrous sodium sulfate, and the ether removed by evaporation to give 161.5 g. of mixed β -ionylidene acetic acids having $E_{1cm}^{1\%}(283 m\mu) = 795$ and consisting of approximately equal amounts of α,β -unsaturated β -ionylidene acetic acid and the β,γ -unsaturated desmotropic isomer of such acid with somewhat less than half of the α,β -unsaturated portion being present in the desired trans form.

A 79 g. portion of such mixed acids was dissolved in 80 cc. of acetonitrile with no hydrogen halide present and the resulting solution was allowed to stand at room temperature for several hours. The crystallized trans α,β -unsaturated β -ionylidene acetic acid was filtered out and amounted to 12 g. of acid having a melting point of 124–125° C. and $E_{1cm}^{1\%}(297 m\mu) = 630$, which corresponded to a yield of only 15.2% of the desired trans form.

A similar 79 g. portion of the mixed β -ionylidene acetic acid was dissolved in 80 cc. of acetonitrile containing 0.29 g. of anhydrous hydrogen chloride and the resulting solution was allowed to stand at room temperature for several hours as before. Filtration of the crystallized product yielded 48.2 g. of the desired trans α,β -unsaturated β -ionylidene acetic acid having a melting point of 124–125° C. and having

$$E_{1cm}^{1\%}(297 m\mu) = 632$$

or a yield of 61% of the desired trans acid.

Example 2

A 1.8 g. portion of mixed α,β -unsaturated and β,γ -unsaturated β -ionylidene acetic acids of 85% purity was dissolved in 20 cc. of nitromethane containing 0.64 cc. of 0.35 N hydrochloric acid. The resulting solution was permitted to stand overnight at 25° C. The crystallized product was filtered off and consisted of 0.75 g. or a 49% yield of trans α,β -unsaturated β -ionylidene acetic acid having a melting point of 124.4–125.4° C.

Example 3

A 100 g. portion of a concentrate of vitamin A

acid in admixture with its β,γ -unsaturated isomer was dissolved in 280 ml. of acetonitrile containing 20 ml. of 1.6 N hydrochloric acid in methanol. Crystals began to precipitate in a few minutes and the solution was filtered after standing for 2 hours. The crystallized trans vitamin A acid obtained upon filtering weighed 35 g. and had $E_{1cm}^{1\%}(352 m\mu) = 1366$ and a melting point of 166–167° C. The trans vitamin A acid obtained thereby was then reduced to vitamin A alcohol and esterified to vitamin A acetate in accordance with conventional techniques and assayed at 2,420,000 vitamin A units per gram.

Example 4

The invention is equally applicable for obtaining trans α,β -unsaturated polyene esters. Thus, 3.0 g. of the β,γ -unsaturated isomer of β -ionylidene acetic acid having $E_{1cm}^{1\%}(284 m\mu) = 1140$ was dissolved in 15 cc. of water, made slightly alkaline with 10% aqueous sodium hydroxide, mixed with 30 cc. of ethanol and 3.6 g. of p-phenylphenacyl bromide and the resulting mixture refluxed for one hour. The β,γ -unsaturated p-phenylphenacyl ester of β -ionylidene acetic acid obtained thereby was a brown oil weighing 4.48 g. and having $E_{1cm}^{1\%}(284 m\mu) = 977$. A 1.5 g. portion of this ester was dissolved in 3 cc. of nitromethane containing 53.5 mg. of hydrochloric acid. The resulting mixture was allowed to stand at room temperature for 17 hours and 0.66 g. of trans α,β -unsaturated ester was obtained having $E_{1cm}^{1\%}(285 m\mu) = 903$ in cyclohexane.

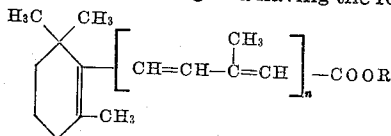
Similar results are obtained with other esters such as the phenyl, benzyl, p-nitrobenzyl, phenacyl and similar esters as well as with the conveniently employed alkyl esters.

Thus, by means of this invention, trans α,β -unsaturated β -ionylidene acetic acid and trans α,β -unsaturated vitamin A acid and esters of such acids are readily obtained in crystalline form, and the undesirable cis isomers and β,γ -unsaturated desmotropic isomers of such acids and esters are converted to the desired trans form in good yield and by a single reaction step.

While the invention has been described in considerable detail with reference to certain preferred embodiments thereof, it will be understood that variations and modifications can be effected within the spirit and scope of the invention as described hereinabove and as defined in the appended claims.

We claim:

1. The method of obtaining a crystalline α,β -unsaturated polyene compound having a trans configuration with respect to the second olefinic double bond from the ring and having the formula

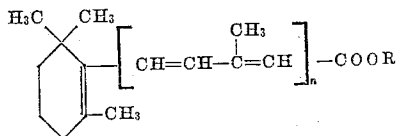


wherein R is selected from the group consisting of hydrogen and hydrocarbon radicals and n is an integer of the series consisting of 1 and 2, which method comprises treating a cis isomer of said compound with a hydrogen halide in solution in a solvent selected from the class consisting of acetonitrile and nitromethane, and selectively crystallizing the trans α,β -unsaturated polyene compound out of said solution in crystalline form and substantially free of said cis isomer.

2. The method of obtaining a crystalline α,β -unsaturated polyene compound having a trans

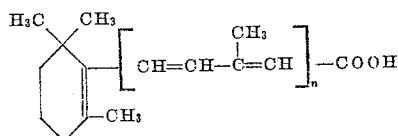
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configuration with respect to the second olefinic double bond from the ring and having the formula



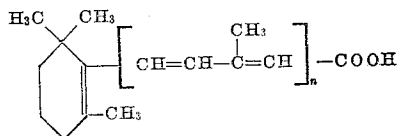
wherein R is selected from the group consisting of hydrogen and hydrocarbon radicals and n is an integer of the series consisting of 1 and 2, which method comprises treating a mixture of said trans α,β -unsaturated polyene compound and the corresponding cis isomer of said compound with a hydrogen halide in solution in a solvent selected from the class consisting of acetonitrile and nitromethane, and progressively and selectively crystallizing the trans α,β -unsaturated polyene compound out of said solution in an amount greater than the amount of said trans α,β -unsaturated polyene compound originally present in said mixture and substantially free of said cis isomer.

3. The method of obtaining a crystalline α,β -unsaturated polyene compound having a trans configuration with respect to the second olefinic double bond from the ring and being selected from the group consisting of polyene acids having the formula



wherein n is an integer of the series consisting of 1 and 2 and esters of such acids, which method comprises treating a mixture of said trans α,β -unsaturated polyene compound and the corresponding cis isomer of said compound in solution in acetonitrile with a hydrogen halide, and selectively crystallizing said trans α,β -unsaturated compound from said solution in an amount greater than the amount of said trans α,β -unsaturated compound originally present in said mixture and substantially free of said cis isomer.

4. The method of obtaining a crystalline α,β -unsaturated polyene compound having a trans configuration with respect to the second olefinic double bond from the ring and being selected from the group consisting of polyene acids having the formula



wherein n is an integer of the series consisting of 1 and 2, and esters of such acids, which method comprises treating a mixture of said trans α,β -unsaturated polyene compound and the corresponding cis isomer of said compound, in solution in a solvent selected from the class consisting of acetonitrile and nitromethane, with hydrogen chloride, and selectively crystallizing from said solution said trans α,β -unsaturated polyene compound substantially free of said cis isomer.

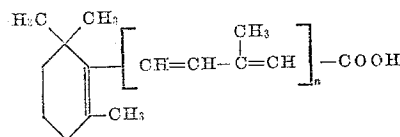
5. The method of obtaining crystalline β -ionylidene acetic acid having a trans configuration with respect to the second olefinic double bond from the ring, which method comprises treating with a hydrogen halide a mixture of trans β -ionylidene acetic acid and cis β -ionylidene acetic acid in solution in a solvent selected from

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the class consisting of acetonitrile and nitromethane, and progressively and selectively crystallizing trans β -ionylidene acetic acid from said solution in crystalline form and substantially free of said cis isomer.

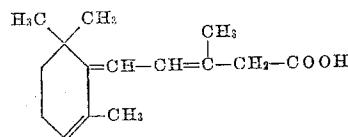
6. The method of obtaining crystalline vitamin A acid having a trans configuration with respect to the second olefinic double bond from the ring, which method comprises treating with a hydrogen halide a solution of a mixture of trans vitamin A acid and cis vitamin A acid in a solvent selected from the class consisting of acetonitrile and nitromethane, and progressively and selectively crystallizing trans vitamin A acid from said solution in crystalline form and substantially free of said cis isomer.

7. The method of obtaining in good yield the crystalline trans isomeric form of an α,β -unsaturated polyene compound selected from the group consisting of polyene acids of the formula



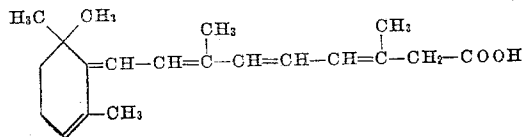
wherein n is an integer of the series consisting of 1 and 2, and esters of said acids, which method comprises dissolving a β,γ -unsaturated isomer of said α,β -unsaturated polyene compound in a solvent selected from the class consisting of acetonitrile and nitromethane, treating said β,γ -unsaturated isomer in said solution with a hydrogen halide and thereby converting said β,γ -unsaturated isomer to a mixture of the cis and trans forms of said α,β -unsaturated polyene compound, and selectively crystallizing the trans form of said α,β -unsaturated polyene compound from said solution concomitant with said converting and substantially free of said cis isomer, said cis form being at least partially converted to said trans form during said crystallizing.

8. The method of obtaining in good yield β -ionylidene acetic acid in the form having a trans configuration with respect to the second olefinic double bond from the ring, which method comprises dissolving a β,γ -unsaturated isomer of β -ionylidene acetic acid having the formula



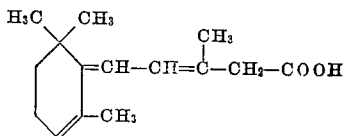
in a solvent selected from the class consisting of acetonitrile and nitromethane, treating said β,γ -unsaturated isomer in the resulting solution with a hydrogen halide and thereby converting said β,γ -unsaturated isomer to a mixture of cis and trans β -ionylidene acetic acid and concomitantly selectively crystallizing trans β -ionylidene acetic acid from said solution in crystalline form and substantially free of said cis β -ionylidene acetic acid.

9. The method of obtaining in good yield vitamin A acid in the form characterized by a trans configuration with respect to the second olefinic double bond from the ring, which method comprises dissolving a β,γ -unsaturated isomer of vitamin A acid having the formula



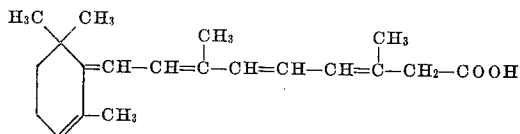
in a solvent selected from the class consisting of acetonitrile and nitromethane, treating said β,γ -unsaturated isomer in the resulting solution with a hydrogen halide and thereby converting said β,γ -unsaturated isomer to a mixture of cis and trans vitamin A acid and selectively crystallizing trans vitamin A acid from said solution concomitantly with said converting and substantially free of said cis vitamin A acid.

10. The method of obtaining in good yield β -ionylidene acetic acid in the form characterized by a trans configuration with respect to the second olefinic double bond from the ring, which method comprises dissolving in acetonitrile a β,γ -unsaturated isomer of β -ionylidene acetic acid having the formula



and, while said β,γ -unsaturated isomer is in solution in said acetonitrile, treating said β,γ -unsaturated isomer with hydrogen chloride and thereby converting said β,γ -unsaturated isomer to a mixture of cis and trans β -ionylidene acetic acid and selectively crystallizing trans β -ionylidene acetic acid from said solution concomitant with said converting and substantially free of said cis β -ionylidene acetic acid, said cis β -ionylidene acetic acid being converted to trans β -ionylidene acetic acid during said crystallizing.

11. The method of obtaining in good yield vitamin A acid in the form having a trans configuration with respect to the second olefinic double bond from the ring, which method comprises dissolving in acetonitrile a β,γ -unsaturated isomer of vitamin A acid having the formula



treating said β,γ -unsaturated isomer in the resulting solution with hydrogen chloride and thereby concomitantly converting said β,γ -unsaturated isomer to a mixture of cis and trans vitamin A acid and selectively crystallizing trans vitamin A acid from said solution in crystalline form substantially free of said cis vitamin A acid, said cis vitamin A acid being converted to trans vitamin A acid during said crystallizing.

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