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(19)

(54) THE PREPARATION OF ARALKANOIC ACIDS

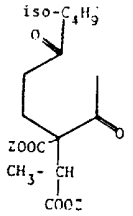
(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to processes for preparing 2-arylalkanoic acid compounds.

A variety of arylalkanoic acids are now known to be useful as active anti-inflammatory, analgesic, anti-pyretic and anti-thrombotic pharmaceutical products. An example of such a product is ibuprofen, 2-(*p*-isobutylphenyl) propionic acid, which is described, with other related compounds, in British Patent Specification No. 971,700. Related compounds are described in U.S. Patent Specifications Nos. 3,600,437; 3,624,142 and 3,793,457 and in Belgian Patent Specification No. 747,812.

A variety of processes for preparing useful 2-arylalkanoic acids have been described. Most of such processes have involved the use of aromatic compounds. For example, Argentinian Patent Specifications Nos. 198,097 and 198,595 describe processes for preparing 2-(substituted phenyl)propionic acids from aromatic glycidonitriles, and German Offenlegungsschrift No. 2,404,159 describes the preparation of the same type of compounds starting from aromatic glycidyl esters. Aromatic alkyl cyanides have also been described as suitable starting materials. Other processes using aromatic compounds are described in U.S. Patent Specification No. 3,600,437.

Belgian Patent Specification No. 820,267 describes a process for preparing ibuprofen by treating a dialkyl α-acetyl-α-(3-oxo-5-methylhexyl)-β-methylsuccinate of formula II



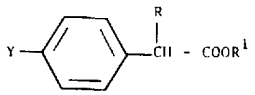
II

wherein each Z group is C_{1-5} alkyl, either with a strong acid aqueous solution at 200 to 240°C, or in the dry state with a strong acid salt and an organic base for from 30 minutes to 3 hours. It is indicated that the aliphatic compound need not be isolated before the acid treatment but can be obtained in crude form by reacting vinyl isobutyl ketone with an alkyl α-acetyl-α-methyl succinate, or by reaction of an acetoacetic acid ester with an alkyl α-halopropionate and then with the vinyl isobutyl ketone.

Although British Patent Specification No. 1,265,800 discloses the synthesis of methyl or ethyl 2-(4-isobutyl-2-oxocyclohex-3-enyl) propionate, Belgian Patent Specification No. 820,267 indicates that, when repeating the pertinent experiments

of the British specification, yields of less than 5% were obtained and that the earlier process had no industrial application. The Belgian specification states that the advantage of the process described there is that the preparation of the 2-(4-isobutyl-2-oxo-3-cyclohexenyl)propionic acid intermediate does not require the use of expensive and dangerous reagents such as silver nitrate or cyanide ion. It is to be noted that the aromatisation reaction in the Belgian specification requires a temperature of over 200°C. The process described in British Patent Specification No. 1,265,800 requires the use of corrosive materials and a temperature of at least 150°C.

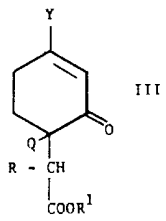
According to a first aspect of the present invention, a process for preparing a 2-arylalkanoate acid or ester of the formula



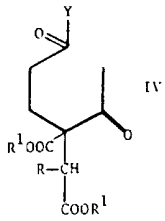
I

wherein R is hydrogen or C_{1-4} alkyl, R^1 is hydrogen or C_{1-6} alkyl and Y is hydrogen or C_{3-5} alkyl, comprises heating, at a temperature of from 75 to 130°C, a mixture comprising

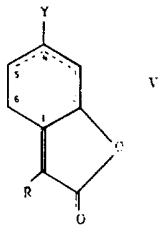
(A) a ketone of one of the following formulae



III



IV



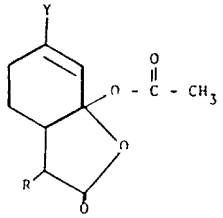
V

wherein the dotted line indicates the presence of either a 3,4 or a 4,5-double bond, R, R^1 and Y are as defined above, and Q is hydrogen or $COOR^1$; and

(B) a sulphonic or a phosphonic acid; and removing water from the mixture during the reaction.

According to a second aspect of the present invention, a process for preparing a 2-arylalkanoate acid or ester of formula I comprises

(a) allowing a mixture of a ketone of formula III as defined above and acetic anhydride to stand, in the presence of an acid scavenging base which does not destroy the reactants, for a time sufficient to form an acetate intermediate of the formula



wherein R and Y are as defined above;

(b) heating the product of step (a) at from 75 to 130°C to form a mixture containing at least one ketone of formula V as defined above;

(c) adding acetyl chloride and about one stoichiometrical equivalent of water, relative to the original acetic anhydride content of the mixture, to form acetic acid and hydrogen chloride acid in the mixture, and

(d) heating the mixture at from 75 to 130°C.

Processes for preparing butenolide compounds of formula V are described and claimed, together with those compounds of formula V which are novel, in Application No. 35784/78 (Serial No. 1563878). Compounds V may be present *in situ* when the process of this invention uses a ketone of formula III or IV as starting material.

The heating of the reaction mixture comprising reactants (A) and (B) may be carried out without added diluent or solvent. However, it has been found that the reaction proceeds more efficiently, producing higher yields, if the mixture is

diluted with a non-polar organic liquid which forms an azeotrope with water in the heated mixture.

While any readily available sulphonic or phosphonic acid can be used in the process of the invention, it is preferred that such acids should have from 1 to 12 carbon atoms in the organic groups thereof. When a non-polar organic liquid diluent is used, as described above, it is preferred that a sulphonic or phosphonic acid is used which is soluble in that diluent. Suitable C_{1-12}alkanesulphonic, C_{1-12} alkanephosphonic, C_{6-12}aryl- and C_{7-12}alkaryl-sulphonic and phosphonic acids include methanesulphonic acid, ethanesulphonic acid, dodecanesulphonic acid, phenylsulphonic acid, *p*-toluenesulphonic acid, methylphosphonic acid, ethylphosphonic acid, dodecylphosphonic acid, phenylphosphonic acid and *p*-tolylphosphonic acid. These acids may be used in their hydrated form. *p*-Toluenesulphonic acid monohydrate is particularly preferred, especially when ibuprofen is being prepared by the process of the invention. Phenylphosphonic acid is the preferred phosphonic acid. Other sulphur-and phosphorus-containing acids such as orthophosphoric acid and sulphuric acid have been tried but they do not work as well as sulphonic and phosphonic acids.

In the process of the invention, it is generally preferred that R is C_{1-4}alkyl and Y is C_{3-5}alkyl. It is particularly preferred to use a ketone of formula IV as the starting material, a C_{1-12}sulphonic acid, a non-polar organic liquid diluent which forms an azeotrope with water in the heated mixture, and a heating temperature of from 100 to 130°C.

Further, it has been found that the 2-arylalkanoate acid or ester which is prepared by the process of the invention may be reacted with an aqueous alkali metal hydroxide to form the 2-arylalkanoate alkali metal salt in a liquid phase, and that the addition of a ketone, preferably acetone, to the liquid phase precipitates the salt. The property of acetone in such mixtures provides a simple, effective means for separating the 2-arylalkanoate acid, as its salt, from the reaction mixture. The amount of acetone which is added should be such as to cause the salt to precipitate but may be, say, from an equimolar amount relative to the salt content of the mixture to a volume excess relative to the aqueous phases, depending on agitation conditions and the amount of time allowed for the salt to separate.

The crude alkali metal 2-arylalkanoate salt may then be converted to the corresponding acid by acidification with a sufficiently strong acid, followed by extraction, drying and evaporation. For example, the alkali metal 2-arylalkanoate salt, in an aqueous medium, can be acidified with an economical mineral acid such as 6N sulphuric or hydrochloric acid to form the acid and the reaction mixture can be extracted one or more times with a non-polar, organic liquid solvent such as Skellysolve B ("Skellysolve" is a registered Trade Mark). The combined organic phases containing the acid can be separated from the aqueous phase and dried over a chemical drying agent such as sodium sulphate and then evaporated to leave the crystalline acid product as a residue which can be collected and prepared for its ultimate use in pharmaceutical, agricultural or other practical formulations as described in the art.

The α-acetylsuccinate derivatives of formula IV may be prepared by Michael condensation reactions analogous to those described in British Patent Specification No. 1,265,800. Accordingly, in this invention, it is not necessary to isolate and start with a 2-(2-oxo-3-cyclohexenyl)-alkanoic acid or ester *per se*. Such compounds, of formula III are formed *in situ* in the process of this invention when the starting reaction mixture contains a compound of formula IV.

During the heating step of the process of this invention, water production, ester hydrolysis and decarboxylation are noted. Water is continuously removed, e.g. by attaching a Dean-Stark trap or an equivalent apparatus to the reaction vessel. Optionally, the reaction mixture may be switched from reflux to partial take-off of distillate, or it can be distilled through molecular sieves, e.g. 4A molecular sieves which absorb both water and alcohol. Owing to the efficient azeotrope formation of toluene/ethanol/water (about 57:37:12 v/v/v), it is preferred to use toluene as the non-polar diluent, especially when ibuprofen is being prepared. The removal of alcohol and water shifts the equilibrium of any reaction mixture containing any α-acetylsuccinate derivative (IV) towards the production of an acid of formula III. Further reflux of the reaction mixture under water-separating conditions converts the formula III intermediate to a butenolide of formula V, which aromatises at a rate which depends on whether there is a 3,4- or 4,5-double bond, to the desired product.

Processes for preparing the butenolides are described in Application No.

35784/78 (Serial No. 1563878). Treatment of a mixture of the Δ^3 and Δ^4 butenolides with a mineral acid such as sulphuric acid or hydrochloric acid in acetic acid causes aromatisation, as does treatment with a sulphonic or phosphonic acid as described above.

During the heating step, water in the reaction mixture is removed by any conventional chemical, physical or mechanical means. To insure complete and efficient reaction it is preferred that the sulfonic or phosphonic acid is used in approximately molar equivalent amounts relative to the starting material (A) which is actually or theoretically in the reaction mixture, although such stoichiometric proportions of sulfonic or phosphonic acid are not required. It is just that the preferred sulfonic or phosphonic acid can be essentially quantitatively recovered for reuse in the process so that it is not necessary to economize on its use.

Any non-polar organic liquid diluent which is a stable liquid and preferably dissolves the reactants in the heating temperature range can be used in the process of this invention. Preferably this organic liquid also boils in this temperature range and forms an azeotrope with water and any alcohol which may be generated during the heating step. Toluene is the preferred solvent when ibuprofen is being prepared but other organic liquids such as xylene, mesitylene, heptane, octane, and commercial mixtures of such organic liquids having boiling point ranges within the ranges of the heating step of the process of this invention, including Skellysolve C and D (See Merck Index, Eighth Edition, page 951), can be used. Mixtures of organic liquids which contain polar ingredients as well as one or more of the above non-polar ingredients and having boiling point ranges within the heating range may also be used.

The means for removing or inactivating water in the reaction mixture during the heating operation can be provided by chemical or physical procedures known in the art, or by combinations of both chemical and physical means.

As described above, the best yields of the 2-arylalkanoate acid or ester product (I) have been obtained when the reaction mixture includes a liquid or mixture of liquids which form an azeotrope with water, the water-containing azeotrope being distilled out of the reaction mixture during the heating operation. Numerous types of chemicals are known to form binary or tertiary water-containing azeotropes having boiling points sufficient for distillation during the heating operations. Such chemicals include C_{5-8} alkanes, and C_{6-8} aromatic hydrocarbons, halogenated hydrocarbons, particularly those containing from 1 to 6 carbon atoms and from 1 to 4 chlorine or bromine atoms, ethers, esters, organic acids, ketones and aldehydes, as set forth in various chemical handbooks, e.g., *Handbook of Chemistry*, edited by N. A. Lange, ninth edition (1956) published by Handbook Publishers, Inc., Sandusky, Ohio, pp. 1484 to 1486 and 1493 and in Chemical Rubber Co., Handbook of Chemistry and Physics, 45th Edition, pp. D-1 to C-18 (1964—65). We prefer that the liquid that is used to form a water containing azeotrope in the reaction mixture is a readily available, economical, inert organic liquid which may or may not be a solvent for the reaction mixture. Examples of suitable water-azeotrope-forming liquids which may be used and which are heavier than water include 1,2-dichloroethane, chloroform, methylene chloride and carbon tetrachloride. Examples of suitable water-azeotrope-forming liquids which may be used and which are lighter than water include benzene, toluene, xylene, pentane, hexane and heptane.

Although we have found that the compounds of formula III may be converted to the corresponding 2-arylalkanoic acids by heating them neat in molten *p*-toluene sulphonic acid monohydrate or an equivalent sulphonic or phosphonic acid at about 120°C for 5 to 20 hours, the yield of the desired product is not as high as when a solvent for the reaction mixture is used.

This invention is particularly suitable for the preparation of ibuprofen, and C_{1-6}alkyl esters thereof. In this case, R is methyl and Y is isobutyl, and it is particularly preferred that the reaction mixture should be heated at a temperature of from 100 to 130°C, the ketone, if of formula V, has a 3,4-double bond, the reaction mixture should be diluted with a non-polar organic liquid solvent or diluent which forms an azeotrope with water at the boiling point of the solvent in the reaction mixture, and that the sulphonic or phosphonic acid should have from 1 to 12 carbon atoms. When toluene is used as the diluent medium, then the reaction may be carried out at reflux, about 110°C. Preferably, a sulphonic acid is used, e.g. *p*-toluenesulphonic acid, and then, after the heating step, water is added in an amount sufficient to hydrate the sulphonic acid so that the hydrated sulphonic acid separates from the liquid phase of the reaction medium.

The reaction mixture, containing crude ibuprofen or ibuprofen ester may then be treated with an alkali metal hydroxide, carbonate or bicarbonate, preferably in aqueous solution, to form an alkali metal salt of ibuprofen in a liquid phase. Although any alkali metal basic compound may be used in this step, sodium, potassium or lithium hydroxide, bicarbonate or carbonate is used in practice. The alkali metal ibuprofen salt may be precipitated from the liquid phase by adding acetone thereto. Subsequently, the alkali metal ibuprofen salt may be acidified with an acid, to form ibuprofen.

The following Examples illustrate the operability of the process of the invention under various conditions.

EXAMPLE 1

Ibuprofen, using Toluene Solvent.

About 1.01 gm. (4.52×10^{-3} mole) of crystalline 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid, 0.8596 gm. of *p*-toluene sulphonic acid monohydrate (4.52×10^{-3} mole) and 5 ml. of toluene were placed in a 10 ml. flask. The flask was then fitted with a Dean-Stark trap and a condenser under a nitrogen atmosphere. The flask and its contents were then heated to reflux (b.p. toluene=110°C) in an oil bath collecting water in the Dean-Stark trap.

After a total of about 80 minutes, a thin layer chromatographic (TLC) analysis of a sample of the reaction mixture indicated that almost all of the 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid had been consumed. The reaction mixture was heated for another 4.5 hours at reflux to insure complete reaction (total of about 6 hours reaction time). The mixture was then allowed to cool to room temperature, and a TLC analysis of the reaction mixture showed that the reaction was complete.

To recover the ibuprofen product from the reaction mixture, the flask and its contents were treated as follows:

About 50 μl. of water was added to the reaction mixture flask precipitating *p*-toluenesulfonic acid monohydrate. The mixture was cooled in an ice bath and filtered. The filtered material was washed with toluene and the filtrate and the toluene washings were combined.

The ibuprofen was recovered from the toluene mixture by extracting the toluene phase with 0.2062 gm. of sodium hydroxide (1.805 gm.=4.52×10^{-3} mole) dissolved in about 20 ml. of water. The toluene phase was extracted a second time with a 5 percent sodium bicarbonate solution. The combined aqueous basic fractions were back extracted with Skellysolve® B to remove any neutrals (organic soluble materials). The combined Skellysolve B and toluene fractions were combined, dried over sodium sulfate and evaporated to a gold residue weighing 89.3 mg. (96 percent).

The aqueous basic fraction containing sodium ibuprofen salt was acidified with 6N sulfuric acid, sodium chloride was added, and then extracted twice with Skellysolve B to take up the ibuprofen acid product therein. The Skellysolve B phase was dried over sodium sulfate and evaporated to leave as residue 867.7 mg. (93.2 percent yield) of ibuprofen which was 99.9 percent pure by gas liquid chromatographic (GLC) analysis.

A 0.7895 gm. portion of the ibuprofen product was re-dissolved in 3 ml. of hot Skellysolve B and after cooling the solution the ibuprofen re-crystallized to yield 0.6982 gm. of white crystalline ibuprofen, M.P. 74.5°C. to 75°C.

EXAMPLE 2

Ibuprofen, using Molten *p*-toluenesulfonic Acid

A 0.9756 gm. portion of 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid (4.265×10^{-3} mole) and 1.0046 gm. of *p*-toluenesulfonic acid monohydrate (m.p. 104°C. to 106°C.) were added to a 15 ml. flask under nitrogen, and the flask was fitted with a condenser and a magnetic stirring bar. The flask and its contents were heated in an oil bath for a total of about 14 hours, after which an additional 0.2009 gm. of *p*-toluenesulfonic acid was added, and heating was continued until a total heating time of 23 hours was completed.

The resulting reaction mixture was dissolved in toluene and crystals of *p*-toluenesulfonic acid precipitated and were filtered after addition of one mole equivalent of water. The toluene phase was extracted with 5 percent sodium bicarbonate solution, dried over sodium sulfate and evaporated to a brown oil weighing 0.0739 gm. (8.2 percent of theoretical ibuprofen yield).

The aqueous sodium bicarbonate phase was acidified and extracted three times with Skellysolve B which was dried over sodium sulfate, and evaporated to

leave crude ibuprofen product weighing 0.7065 gm. (78.8 percent of theoretical ibuprofen yield). This yield was obtained despite spillage of the reaction mixture.

A 272.3 mg. portion of this crude ibuprofen was crystallized from Skellysolve B yielding 251.2 mg. of ibuprofen (92.3 percent yield).

EXAMPLE 3

Ibuprofen, using Catalytic Amounts of Acid Catalyst

To a 15 ml. one-necked flask equipped with Dean-Stark trap and condenser, 0.0937 gm. of *p*-toluenesulfonic acid monohydrate, 0.9935 gm. of crystalline 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid and 4 ml. toluene were added. The mixture was heated to reflux under nitrogen. After 5 hours of heating, TLC and GLC analysis of the reaction mixture showed minor amounts of ibuprofen product and 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid, and a major amount of two butenolide intermediates which were identified as being of formula V, R being methyl and Y isobutyl. Subjecting the intermediates to *p*-toluenesulfonic acid in refluxing toluene, as before, produces ibuprofen.

EXAMPLE 4

Ibuprofen, from a Mixture Containing Diethyl α-Acetyl-α-(5-methyl-3-oxo-hexyl)-β-methylsuccinate

To a 110 ml., round-bottomed flask fitted with condenser and Dean-Stark trap there was added 4.339 gm. of a mixture containing:

(A) diethyl α-acetyl-α-(5-methyl-3-oxo-hexyl)-β-methylsuccinate (IVa); a mixture of compounds of formula III in which Q is hydrogen or $COOC_2H_5$, R is methyl, R^1 is ethyl and Y is isobutyl; and (B) 2.443 gm. of *p*-toluenesulfonic acid monohydrate and 17 ml. of toluene.

Under an inert atmosphere of nitrogen, the flask and its contents were refluxed for 6.5 hours with water removal. Water (115 μl.) was then added to reaction mixture, momentarily cooled, and reflux was continued for another 16 hours. TLC analysis showed the reaction to be complete to a mixture of ibuprofen and its ethyl ester.

To the cooled reaction mixture was added 0.23 ml. of water, and the resulting precipitate of *p*-toluenesulfonic acid monohydrate was filtered, washed with toluene, and dried.

The toluene filtrate under nitrogen was treated with 4.8 ml. of 33 percent aqueous sodium hydroxide at 60°C. for 22 hours. The upper organic layer was separated from the cooled reaction mixture by decantation, 5 ml. of acetone was added to the remaining basic aqueous layer and the resulting slurry of ibuprofen sodium salt was cooled at 0°C. for 2 hours, filtered and washed with cold acetone.

This ibuprofen sodium salt in 5 ml. of water was acidified with 6N H_2SO_4, and extracted twice with Skellysolve B. The combined organic phases were dried over sodium sulfate and evaporated to give 2.03 gm. of crystalline ibuprofen. The yield was 79 percent.

EXAMPLE 5

Ibuprofen, using a Phosphonic Acid

A mixture containing 1.00 gm. (4.46 mmole) of 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid and 0.70 gm. (4.46 mmole) of phenylphosphonic acid in 5 ml. of toluene is refluxed at about 110° for about 20 hours. The water formed is removed during the course of the reaction with an appropriate trap.

The phenylphosphonic acid is recovered by filtering it out of the reaction mixture. The ibuprofen is then separated from neutral by products by extracting the filtered reaction mixture with 20 ml. of 10 percent sodium hydroxide in water solution. The basic phase containing dissolved sodium 2-(4-isobutylphenyl) propionate is then re-acidified with 6N sulfuric acid and the ibuprofen content is extracted from the acidified mixture with Skellysolve B from which solution ibuprofen crystallizes on cooling.

EXAMPLE 6

Ibuprofen, using Molten *p*-toluenesulfonic Acid with Acetic Anhydride as Water Scavenger.

To a melt of 1.216 g. of *p*-toluenesulfonic acid monohydrate (6.31 mmole) and 0.60 ml. of acetic anhydride (6.31 mmole) at 94°C. was added 1.01 g. of 2-(4-isobutyl-2-oxo-3-cyclohexenyl) propionic acid. This mixture was heated under nitrogen for 35 hours at 115°C. A 5 ml. quantity of heptane was added to the hot

reaction mixture and decanted. This operation was carried out four times. The decantate was concentrated, extracted with 5 percent sodium bicarbonate aqueous solution, and the aqueous phase obtained was acidified to pH 2 and extracted with Skellysolve B. Drying over sodium sulfate and evaporation of this Skellysolve B phase yielded 0.855 g. (92.3 percent yield) of crystalline ibuprofen assaying 97.5 percent pure by gas liquid chromatography (GLC).

EXAMPLE 7

Ibuprofen, from a Michael Adduct Mixture.

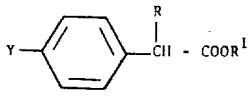
A crude mixture (about 400 g.) of compounds of formula III wherein R is methyl, R^1 is ethyl and Y is isobutyl (ethyl 2-(4-isobutyl-2-oxocyclohex-3-enyl) propionate and diethyl α-methyl-α'-(4-isobutyl-2-oxocyclohex-3-enyl) succinate) and compound IV wherein R is methyl, R^1 is ethyl and Y is isobutyl (diethyl α-methyl-α'-acetyl-α'-(5-methyl-3-oxohexyl) succinate), (containing approximately 0.6 mole of ibuprofen-making starting materials) and 403 g. (2.12 mole) of *p*-toluenesulfonic acid monohydrate is stirred under nitrogen at 80°C. for two hours. Water is added to the reaction mixture in three portions (3×86 ml.) and an equivalent volume of each portion of water is distilled from the reaction mixture at about 120°C. (before the next portion of water was added). The time required for these distillations is about 4 hours. Toluene (695 ml.) is added and the mixture is distilled (at reflux) over 6.5 hours to aromatize the acids of formulae III and IV to form ibuprofen acid, 2-(4-isobutylphenyl) propionic acid, and to azeotrope away the water with a Dean-Stark trap.

The resulting solution is cooled to 35°C. and water is added to precipitate *p*-toluenesulfonic acid monohydrate. The resulting slurry is cooled to 0°C. to 5°C., stirred over 1 hour and filtered and washed with about 50 ml. of toluene. The *p*-toluenesulfonic acid monohydrate precipitate solid (filtered material) is suitable for recycling and reuse. About 80 percent, 323 g., of the *p*-toluenesulfonic acid monohydrate was recovered.

The toluene filtrate and wash are mixed with 10 percent aqueous sodium hydroxide (412.5 g.) and the resulting organic phase is re-extracted with 135 ml. of water, and the phases separated again. The combined aqueous phases are diluted with 200 g. of 50 percent sodium hydroxide solution after which 99.75 of solid hydroxide and 428 ml. of acetone are added. Upon cooling this aqueous base treated mixture to 0°C. to 5°C. and stirring for about 1.5 hours, sodium 2-(4-isobutylphenyl) propionate (sodium ibuprofen) crystallizes out. This crystalline precipitate is collected by filtration and washed twice with 0°C. acetone portions (2×175 ml.) to purify the sodium ibuprofen salt cake. The sodium ibuprofen salt cake is added to 352 ml. of water and Skellysolve B (mixed hexanes) or hexane, 630 ml., is added. Concentrated sulfuric acid (80 ml.) is added to bring the pH of the mixture to about 0.6 and the resulting mixture is warmed to about 42°C. to dissolve the ibuprofen acid in the mixture. The aqueous and organic phase are allowed to separate. The aqueous phase is discarded and the organic phase is washed with water, e.g., two 1200 ml. portions of water. The organic phase containing the dissolved ibuprofen acid is separated from the water phase and cooled to 0°C. to 5°C. and stirred for about 0.5 hours until crystallization of the ibuprofen acid is completed. The ibuprofen crystals are filtered and washed with hexane and dried to give 90 to 100 g. of ibuprofen acid.

WHAT WE CLAIM IS:—

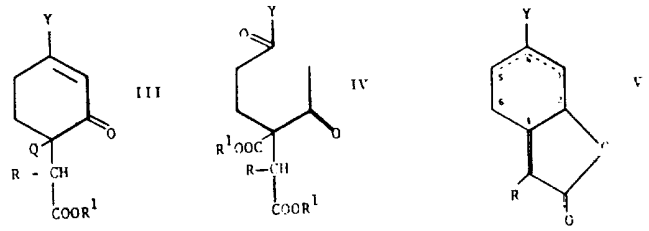
1. A process for preparing a 2-arylalkanoate acid or ester of the formula



I

wherein R is hydrogen or C_{1-4}alkyl, R^1 is hydrogen or C_{1-6}alkyl and Y is hydrogen or C_{3-5}alkyl, which comprises heating, at a temperature of from 75 to 130°C, a mixture comprising

(A) a ketone of one of the following formulae



wherein the dotted line indicates the presence of either a 3,4 or a 4,5-double bond, R, R^1 and Y are as defined above, and Q is hydrogen or $COOR^1$; and

(B) a sulphonic or a phosphonic acid; and removing water from the mixture during the reaction.

2. A process according to claim 1 wherein R is C_{1-4}alkyl and Y is C_{3-5}alkyl.

3. A process according to claim 1 or claim 2 wherein the reaction mixture is diluted with a non-polar organic liquid which forms an azeotrope with water in the heated mixture.

4. A process according to any preceding claim wherein the sulphonic or phosphonic acid has from one to 12 carbon atoms.

5. A process according to claim 2 wherein the reaction mixture comprises a ketone of formula IV and C_{1-12}sulphonic acid in a non-polar organic liquid diluent which forms an azeotrope with water in the heated mixture, and wherein the mixture is heated at a temperature of from 100 to 130°C.

6. A process according to any preceding claim which comprises the additional steps of reacting the 2-arylalkanoate acid or ester with an aqueous alkali metal hydroxide to form the 2-arylalkanoate alkali metal salt in a liquid phase, and precipitating the salt from the liquid phase by adding acetone to the liquid phase.

7. A process according to claim 1 wherein R is methyl and Y is isobutyl, the reaction mixture is heated at a temperature of from 100 to 130°C., the ketone, if of formula V, has a 3,4-double bond, the reaction mixture is diluted with a non-polar organic liquid solvent which forms an azeotrope with water at the boiling point of the solvent in the reaction mixture, and the sulphonic or phosphonic acid has from 1 to 12 carbon atoms, thereby forming ibuprofen or a C_{1-6}alkyl ester thereof.

8. A process according to claim 7 wherein a sulphonic acid is used and which comprises the additional step, after the heating step, of adding water in an amount sufficient to hydrate the sulphonic acid so that the hydrated sulphonic acid separates from the liquid phase of the reaction mixture.

9. A process according to claim 8 which comprises the additional step of reacting ibuprofen, or the ester thereof, with an aqueous alkali metal hydroxide, carbonate or bicarbonate, to form an alkali metal salt of ibuprofen in a liquid phase.

10. A process according to claim 9 which comprises the additional step of precipitating the alkali metal ibuprofen salt from the liquid phase by adding acetone to the liquid phase.

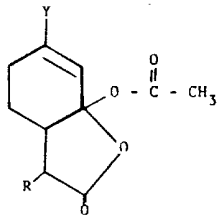
11. A process according to claim 10 which comprises the additional step of acidifying the alkali metal ibuprofen salt with an acid, to form ibuprofen.

12. A process according to any of claims 8 to 11 wherein the sulphonic acid is *p*-toluenesulphonic acid.

13. A process according to any of claims 7 to 12 wherein the non-polar organic liquid solvent is toluene.

14. A process for preparing a 2-arylalkanoate acid or ester as defined in claim 1 which comprises

(a) allowing a mixture of a ketone of formula III as defined in claim 1 and acetic anhydride to stand, in the presence of an acid scavenging base which does not destroy the reactants, for a time sufficient to form an acetate intermediate of the formula



wherein R and Y are as defined in claim 1;

(b) heating the product of step (a) at from 75 to 130°C to form a mixture containing at least one ketone of formula V as defined in claim 1;

(c) adding acetyl chloride and about one stoichiometrical equivalent of water, relative to the original acetic anhydride content of the mixture, to form acetic acid and hydrogen chloride acid in the mixture; and

(d) heating the mixture at from 75 to 130°C.

15. A process according to claim 14 wherein the mixture from step (b) is mixed with a C_{1-12}sulphonic acid or a C_{1-12}phosphonic acid and heated to from 75 to 130°C while removing water from the mixture.

16. A process according to claim 14 or claim 15 wherein Y is C_{3-5}alkyl and R is C_{1-4}alkyl.

17. A process for preparing a 2-arylalkanoate acid or ester as defined in claim 1 substantially as described in any of the Examples.

18. A 2-arylalkanoate acid or ester or salt when prepared by a process according to any preceding claim.

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