United States Patent [19]

Bender et al.

[11] B **3,923,836**

[45] **Dec. 2, 1975**

[54] **CHROMAN AND CHROMENE COMPOUNDS**

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[22] Filed: **July 18, 1973**

[21] Appl. No.: **380,446**

[44] Published under the Trial Voluntary Protest Program on January 28, 1975 as document no. B 380,446.

[52] **U.S. Cl.**..... **260/345.2;** 424/283; 260/343.2 R

[51] **Int. Cl.**[2]..... **C07D 311/16;** C07D 311/70; C07D 311/58

[58] **Field of Search**..... 260/345.2

[56] **References Cited**

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[57] **ABSTRACT**

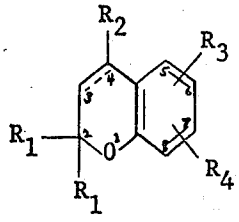
The compounds are hydroxy chromans and chromenes having a 4-cycloalkyl or 4-cycloalkenyl substituent. These compounds have pharmacological activity such as central nervous system depressant activity. A preferred compound is 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

5 Claims, No Drawings

CHROMAN AND CHROMENE COMPOUNDS

This invention relates to new chroman and chromene compounds having pharmacological activity. In particular, these compounds are hydroxy chromans and chromenes having a 4-cycloalkyl or 4-cycloalkenyl substituent.

The compounds of this invention are represented by the following formula:



in which:

is a single or a double bond, preferably a double bond;

R_1 is lower alkyl;

R_2 is cycloalkyl or cycloalkenyl, said cycloalkyl and cycloalkenyl having 5-6 carbon atoms;

R_3 is hydroxy or an alkali metal salt thereof, lower alkoxy or lower alkanoyloxy and

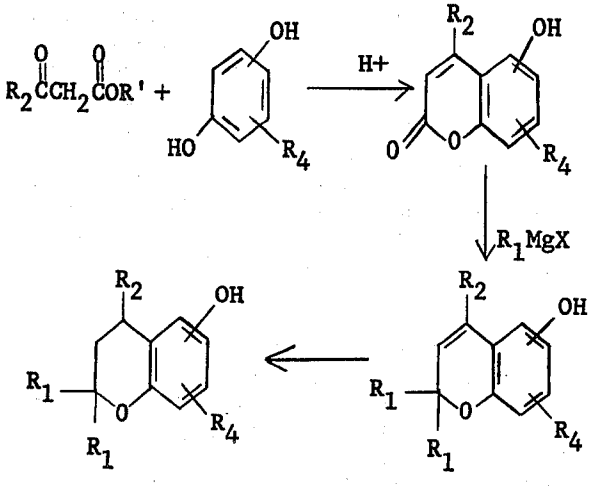
R_4 is a straight or branched alkyl or alkoxy group having 5 to 12 carbon atoms.

Preferably, in the compounds of Formula I, R_3 is attached at the 5-position and R_4 is attached at the 7-position.

Preferred compounds of this invention are represented by Formula I in which is a double bond, R_3 is hydroxy attached at the 5-position and R_4 is a straight or branched alkyl group having 5 to 12 carbon atoms which is attached at the 7-position. Also, preferably, R_2 is cyclohexyl.

An advantageous compound of this invention is represented by Formula I in which is a double bond, R_1 is methyl, R_2 is cyclohexyl, R_3 is hydroxy at the 5-position and R_4 is 1,2-dimethylheptyl at the 7-position, said compound being 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

The compounds of Formula I are prepared by the following procedures.



The terms R_1, R_2 and R_4 are as defined above, R' is lower alkyl and X is halogen.

According to the above procedure, a lower alkyl 3-R_2-3-oxopropionate is reacted with a R_4-substituted-dihydroxybenzene compound in the presence of acid

such as phosphorus oxychloride and sulfuric acid and the resulting hydroxycoumarin is reacted with a lower alkyl magnesium halide to give the hydroxychromenes of this invention.

Alternatively, to prepare compounds in which R_4 is lower alkoxy, a lower alkyl 3-R_2-3-oxopropionate is reacted with trihydroxybenzene to give a dihydroxycoumarin which is reacted with a lower alkyl magnesium halide to give a dihydroxychromene. Alkylation by reacting the dihydroxychromene with an equimolar amount of an alkylating agent such as an alkyl halide in the presence of base gives chromene compounds of this invention in which R_4 is lower alkoxy.

The hydroxychromans of this invention are prepared by reducing the corresponding hydroxychromenes by catalytic hydrogenation using for example, palladium on carbon as the catalyst or by chemical reduction for example using sodium and ethanol.

The alkali metal salts of the hydroxychromenes and hydroxychromans are prepared by reacting the hydroxy compound with an alkali metal hydroxide, hydride or alkoxide.

The hydroxychromenes and hydroxychromans are esterified and etherified by standard procedures to give the compounds of this invention in which R_3 is lower alkanoyl and lower alkyl. For example, the compounds in which R_3 is lower alkanoyl are prepared by reacting the hydroxy compounds or alkali metal salts thereof with a lower alkanoyl halide or a lower alkanoic acid anhydride, preferably in the presence of a base. The compounds in which R_3 is lower alkyl are prepared, for example, by reacting an alkali metal derivative of a hydroxy compound with a lower alkyl halide.

The lower alkyl 3-R_2-3-oxopropionate starting materials are known to the art or are prepared by reacting R_2COO-(lower alkyl) with a lower alkyl acetate or by reacting R_2COCl with a lower alkyl acetoacetate by standard procedures.

The R_4-substituted-dihydroxybenzene starting materials are either known to the art or are prepared by known procedures, as illustrated in examples herebelow.

The compounds of this invention have pharmacological activity such as central nervous system activity, for example the compounds have central nervous system depressant, sedative and tranquilizing activity. In addition, the compounds may have analgesic, hypotensive, anti-inflammatory and diuretic activity.

The central nervous system activity is demonstrated by oral administration to rats at doses of about 10 mg./kg. to produce effects such as decreased spontaneous motor activity.

One skilled in the art will recognize that in determining the amounts of compound to produce the desired pharmacological effect, the activity of the compound as well as the size of the host animal must be considered.

The compounds of the invention may be combined with standard pharmaceutical carriers and administered internally in conventional dosage forms such as capsules, tablets or liquid preparations. The compounds will be administered in an amount sufficient to produce the desired activity.

The pharmaceutical carrier may be for example a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelation, agar, pectin or acacia. The amount of solid carrier will vary widely but preferably will be from

about 25 mg. to about 1 gm. Exemplary of liquid carriers ae syrup, peanut oil, olive oil, sesame oil, propylene glycol, polyethylene glycol (mol. wt. 200–400) and water. The carrier or diluent may include a time delay material well known to the art such as, for example, glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed, for example the preparation may take the form of tablets, capsules, powders, suppositories, troches, lozenges, syrups, emulsions, sterile injectable liquids or liquid suspensions of solutions.

The pharmaceutical compositions are prepared by conventional techniques involving procedures such as mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The terms "low alkyl" and "lower alkoxy" where used herein denote groups having 1-6, preferably 1-4, carbon atoms and "lower alkanoyl" denotes groups having 2-6, preferably 2-4, carbon atoms.

The following examples are not limiting but are illustrative of the compounds of this invention and processes for their preparation.

EXAMPLE 1

To a stirred mixture of 8.3 g. (0.042 mole) of ethyl 3-cyclohexyl-3-oxopropionate and 10.0 g. (0.042 mole) of 5-(1,2-dimethylheptyl)resorcinol is added with cooling 45 ml. of sulfuric acid followed by 31.5 g. (0.206 mole) of phosphorus oxychloride. The mixture is stirred at room temperature for 98 hours, and then neutralized with aqueous potassium carbonate solution and the separated aqueous phase is extracted with ethyl acetate. The combined organic layers are washed with water, dried with magnesium sulfate, filtered and concentrated. The residue is crystallized from nitromethane to give 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxycoumarin.

A solution of 15.1 g. (0.014 mole) of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxycoumarin in 150 ml. of benzene-tetrahydrofuran is added dropwise, in a nitrogen atmosphere, to a stirred solution of 32.0 g. (0.276 mole) of methyl magnesium bromide in 97 ml. of benzene-tetrahydrofuran. This mixture is refluxed for 23 hours, then cooled and quenched by adding saturated aqueous ammonium chloride solution. The aqueous layer is extracted with ethyl acetate, then the combined organic layers are washed with water, dried with magnesium sulfate, filtered and concentrated. The residue is taken into ether, treated with ethereal hydrogen chloride and refluxed for 2 hours. The solution is neutralized with an aqueous solution of sodium carbonate and then washed with water, dried with magnesium sulfate, filtered and concentrated. The residue is supported on a column of silica gel (110 cm.) and eluted with benzene. The first fraction is evaporated and the residue is distilled to give 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene, b.p. 200°C./3mm.

EXAMPLE 2

Using 5-pentylresorcinol in place of 5-(1,2-dimethylheptyl)resorcinol in the procedure of Example 1, the product is 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-pentyl-2H-chromene.

Similarly, using the following resorcinols;

5-hexylresorcinol

5-nonylresorcinol the products are:

4-cyclohexyl-7-hexyl-5-hydroxy-2,2-dimethyl-2H-chromene

4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-nonyl-2H-chromene.

EXAMPLE 3

To a two-fold excess of methyl magnesium bromide in ether is slowly added 26 g. of 3,5-dimethoxyphenyl-α,α-dimethylacetonitrile in ether at a rate to maintain gentle reflux. The mixture is refluxed for 18 hours and then poured into cold 2N sulfuric acid. The solvent is removed by distillation and the residue is heated at 95°C. for one hour. After cooling, ether is added, the layers are separated and the aqueous layer is extracted with ether. The organic layer and extracts are combined, washed with water, dried with magnesium sulfate and evaporated. The residue is distilled under high vacuum to give 3,5-dimethoxy-α,α-dimethylbenzyl methyl ketone.

3,5-Dimethoxy-α,α-dimethylbenzyl methyl ketone in dry ether is added dropwise to n-hexyl magnesium bromide in dry ether. The mixture is refluxed for 15 hours. To the mixture is added dropwise saturated ammonium chloride solution. The layers are separated and the aqueous layer is extracted with ether. The organic layer and the extracts are combined, washed with water, dried over magnesium sulfate and evaporated to give 1,3-dimethoxy-5-(2-hydroxy-1,1,2-trimethyloctyl)benzene.

A solution of 6.2 g. (0.02 mole) of 1,3-dimethoxy-5-(2-hydroxy-1,1,2-trimethyloctyl)benzene in ether is dried over magnesium sulfate, filtered, and allowed to react over six hours with a suspension of 0.8 g. (0.02 mole) of metallic potassium in 60 ml. of ether. Carbon disulfide (1.5 g., 0.02 mole) is added and the mixture is stirred for 30 minutes. To the resulting mixture is added 2.8 g. of methyl iodide. The mixture is then refluxed for six hours, allowed to stand at room temperature overnight and filtered. The filtrate is concentrated and distilled in vacuo. The distillate in ethanol is refluxed with Raney nickel and redistilled. The product is hydrogenated using 10 percent palladium/charcoal at 50 p.s.i. for 30 minutes to give 1,3-dimethoxy-5-(1,1,2-trimethyloctyl)benzene. The methoxy groups are demethylated by dissolving the 1,3-dimethoxy compound in a mixture of acetic acid and 48 percent hydrobromic acid, refluxing the mixture overnight, then pouring the mixture into ice-water, extracting with benzene, then concentrating and distilling to give 5-(1,1,2-trimethyloctyl)resorcinol.

In the procedure of Example 1 using 5-(1,1,2-trimethyloctyl)resorcinol in place of 5-(1,2-dimethylheptyl)-resorcinol, the product is 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1,1,2-trimethyloctyl)-2H-chromene.

EXAMPLE 4

By the procedure of Example 3,3,5-dimethoxy-phenyl-α-methylacetonitrile is converted to 3,5-dimethoxy-α-methylbenzyl methyl ketone, then this ketone is reacted with n-octyl magnesium bromide, and the resulting 1,3-dimethoxy-5-(2-hydroxy-1,2-dimethyldecyl)benzene is dehydrated and reduced and the methoxy groups are demethylated to give 5-(1,2-dimethyldecyl)resorcinol.

Using 5-(1,2-dimethyldecyl)resorcinol in the procedure of Example 1, the product is 4-cyclohexyl-7-(1,2-dimethyldecyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

EXAMPLE 5

A mixture of 3.0 g. of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene in 100 ml. of absolute ethanol and 10 percent palladium on carbon is hydrogenated at 48 p.s.i. and 25°C. for 1 hour. Chloroform (20 ml.) is added. The mixture is filtered and the solvent is removed from the filtrate. The resulting residue is distilled to give 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethylchroman.

EXAMPLE 6

A mixture of 55 g. of magnesium and 5 ml. of carbon tetrachloride is heated gently, then 200 ml. of methanol is added, followed by a solution of 285 g. of ethyl acetoacetate is 1,250 ml. of methanol and 1,500 ml. of tetrahydrofuran. The mixture is refluxed for five hours to dissolve the magnesium, and the solvent is evaporated in vacuo. The residue is dissolved in refluxing tetrahydrofuran and 270 g. of cyclopentanecarbonyl chloride is added over 30 minutes. The mixture is refluxed for 1 hour, half of the solvent is distilled off at atmospheric pressure and the mixture is poured onto 5 kg. of ice containing 250 ml. of concentrated hydrochloric acid. The separated aqueous phase is extracted twice with ether, and the combined organic phase is washed with 5 percent aqueous sodium bicarbonate solution and water. The organic phase is treated with 1.5 liters of concentrated ammonia and 500 ml. of water and stirred for 2 hours at 30°C. The separated ether layer is treated with 200 ml. of concentrated hydrochloric acid and 1 liter of water and stirred for 1 hour. This mixture is washed with 5 percent aqueous sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated. Distillation of the residue at 20 mm. gives ethyl 3-cyclopentyl-3-oxopropionate.

Using ethyl 3-cyclopentyl-3-oxopropionate in place of ethyl 3-cyclohexyl-3-oxopropionate in the procedure of Example 1 gives 4-cyclopentyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

By the same procedure, using in place of cyclopentane-carbonyl chloride, the following:

1-cyclopentene-1-carbonyl chloride
3-cyclopentene-1-carbonyl chloride
1-cyclohexene-1-carbonyl chloride
3-cyclohexene-1-carbonyl chloride the products are, respectively:

4-(1-cyclopentenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-(3-cyclopentenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-(1-cyclohexenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-(3-cyclohexenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

EXAMPLE 7

A solution of 2.0 g. of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene in 40 ml. of acetic anhydride containing 1.0 g. of sodium acetate is heated at reflux for 5 hours. The excess anhydride is evaporated in vacuo and the residue is dissolved in water and extracted with ether. The extract is washed with water until neutral, then dried, evaporated and chromatographed and distilled to give 5-acetoxy-4-cyclohexyl-7-(1,2-dimethylheptyl)-2,2-dimethyl-2H-chromene.

By the same procedure, using propionic anhydride in place of acetic anhydride, the product is 4-cyclohexyl-7-(1,2-dimethylheptyl)-2,2-dimethyl-5-propionyloxy-2H-chromene.

Similarly, using n-butyric anhydride and n-valeric anhydride, the corresponding 5-n-butyryloxy and 5-n-valeryloxy compounds are prepared. Also, using n-hexanoic anhydride, the corresponding 5-n-hexanoyloxy compound is prepared.

EXAMPLE 8

To a solution of 2.0 g. of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene in 50 ml. of dry dimethylsulfoxide is added 0.75 g. of potassium t-butoxide, then 2.0 g. of methyl sulfate in 2.5 ml. of dimethylsulfoxide is added dropwise. The mixture is warmed to 100°C. for 30 minutes, then stirred at room temperature for 10 hours. The mixture is then poured into ice-water, acidified with dilute hydrochloric acid and extracted with ether. The extracts are combined, washed with water, dried, concentrated and distilled to give 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-methoxy-2,2-dimethyl-2H-chromene.

By the same procedure, using in place of methyl sulfate, the following:

ethyl bromide
propyl bromide
butyl bromide
hexyl bromide the products are, respectively:

4-cyclohexyl-7-(1,2-dimethylheptyl)-5-ethoxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-(1,2-dimethylheptyl)-2,2-dimethyl-5-propoxy-2H-chromene
5-butoxy-4-cyclohexyl-7-(1,2-dimethylheptyl)-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hexyloxy-2,2-dimethyl-2H-chromene.

EXAMPLE 9

To 21 g. (0.1 mole) of finely powdered phosphorus pentachloride is added 15.4 g. (0.1 mole) of 1-carbethoxy-cyclohex-2-ene with stirring. After stirring the mixture at 95°–100°C. for 3 days, the phosphorus oxychloride is removed by distillation in vacuo. The residue is heated at 95°C. with 5 mg. of palladium black until the evolution of ethyl chloride ceases. Distillation in vacuo gives 2-cyclohexene-1-carbonyl chloride.

2-Cyclohexene-1-carbonyl chloride is converted to ethyl 3-(2-cyclohexenyl)-3-oxopropionate by the procedure of Example 6.

Using ethyl 3-(2-cyclohexenyl)-3-oxopropionate and 5-(1-methylheptyl)resorcinol in the procedure of Example 1 gives 4-(2-cyclohexenyl)-5-hydroxy-2,2-dimethyl-7-(1-methylheptyl)-2H-chromene.

By the same procedure, using 1-carbethoxy-cyclopent-2-ene in place of 1-carbethoxycyclohex-2-ene, the product is 4-(2-cyclopentenyl)-5-hydroxy-2,2-dimethyl-7-(1-methylheptyl)-2H-chromene.

EXAMPLE 10

Sodium (1.84 g., 0.08 mole) is added over 30 minutes to 3.0 g. (0.008 mole) of 4-cyclopentyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene in 100 ml. of ethanol. The solution is cooled and 10 ml. of water is added. The solution is then neutralized with dilute hydrochloric acid and the resulting mixture is evaporated to dryness in vacuo. The residue is extracted with water, dried and distilled to give 4-

cyclopentyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethylchroman.

Similarly, 4-(1-cyclopentenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene and 4-(3-cyclohexenyl)-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene are reduced to the corresponding chroman compounds.

EXAMPLE 11

By the procedure of Example 1, using ethyl magnesium bromide in place of methyl magnesium bromide, the product is 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-diethyl-2H-chromene.

Similarly, using propyl magnesium bromide and butyl magnesium bromide, the corresponding 2,2-dipropyl and 2,2-dibutyl products are obtained.

EXAMPLE 12

4-Cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene (2.0 g.) is refluxed with methanolic sodium hydroxide for one hour and the solution is then evaporated to give the sodium salt of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

Similarly, refluxing 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethylchroman with methanolic potassium hydroxide gives the potassium salt of 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethylchroman.

EXAMPLE 13

Using 5-(1-ethylheptyl)resorcinol [prepared by reacting 3,5-dimethoxybenzamide with ethyl magnesium bromide, reacting the resulting 3,5-dimethoxyphenyl ethyl ketone with n-hexyl magnesium bromide, dehydrating and reducing the resulting 1,3-dimethoxy-5-(1-hydroxy-1-ethylheptyl)benzene and demethylating the methoxy groups of the resulting 1,3-dimethoxy-5-(1-ethylheptyl)benzene] in place of 5-(1,2-dimethylheptyl)resorcinol in the procedure of Example 1 gives 4-cyclohexyl-7-(1-ethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

EXAMPLE 14

Using in place of 5-(1,2-dimethylheptyl)resorcinol in the procedure of Example 1 the following 5-substituted resorcinols:

5-(1,1-dimethylheptyl)resorcinol
5-(1,1-dimethylbutyl)resorcinol
5-(1,2-dimethylpentyl)resorcinol
5-(1-methylpentyl)resorcinol the products are, respectively:
4-cyclohexyl-7-(1,1-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-(1,1-dimethylbutyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-(1,2-dimethylpentyl)-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylpentyl)-2H-chromene.

EXAMPLE 15

To a stirred solution of 126 g. (1.0 mole) of phloroglucinol and 19.0 g. (0.34 mole) of potassium hydroxide in dimethylformamide is added 186 g. (1.04 mole) of 2-bromoheptane. After heating the mixture for 16 hours at 100°C., 250 ml. of acetic acid is added and the mixture is filtered. The filtrate is concentrated, dissolved in ether, washed with water and extracted with 10 percent aqueous sodium hydroxide solution. The alkaline solution is washed with ether, acidified with dilute hydrochloric acid and extracted with ether. The organic phase is dried over magnesium sulfate, treated with charcoal and filtered. The solvent is evaporated and the residue distilled to give 5-(1-methylhexyloxy)-resorcinol, b.p. 165°–170°C. (0.15 mm.).

5-(1-Methylhexyloxy)resorcinol is reacted with ethyl 3-cyclohexyl-3-oxopropionate in the presence of sulfuric acid and phosphorus oxychloride by the procedure of Example 1 to give 4-cyclohexyl-7-(1-methylhexyloxy)-5-hydroxycoumarin.

The above prepared coumarin in benzene-tetrahydrofuran is reacted with methyl magnesium bromide by the procedure of Example 1 to give 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylhexyloxy)-2H-chromene.

EXAMPLE 16

By the procedure of Example 15, using in place of 2-bromoheptane the following:

1-bromopentane
1-bromohexane
1-bromoheptane
1-bromooctane
1-bromodecane
2-bromooctane
2-bromo-3-methyloctane the products are, respectively:
4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-pentyloxy-2H-chromene
4-cyclohexyl-7-hexyloxy-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-heptyloxy-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-octyloxy-2H-chromene
4-cyclohexyl-7-decyloxy-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylheptyloxy)-2H-chromene
4-cyclohexyl-7-(1,2-dimethylheptyloxy)-5-hydroxy-2,2-dimethyl-2H-chromene.

EXAMPLE 17

By the procedure of Example 15, 1,2,4-trihydroxybenzene is reacted with 2-bromo-3-methyloctane in the presence of potassium hydroxide to give a mixture of 2,4-dihydroxy-1-(1,2-dimethyheptyloxy)benzene, 1,4-dihydroxy-2-(1,2-dimethylheptyloxy)benzene and 1,2-dihydroxy-4-(1,2-dimethylheptyloxy)benzene. These compounds are separated by column chromatography on silica gel.

Using 2,4-dihydroxy-1-(1,2-dimethylheptyloxy)-benzene in place of 5-(1,2-dimethylheptyl)resorcinol the procedure of Example 1, the products are:

4-cyclohexyl-8-(1,2-dimethylheptyloxy)-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-6-(1,2-dimethylheptyloxy)-5-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-6-(1,2-dimethylheptyloxy)-7-hydroxy-2,2-dimethyl-2H-chromene.

These products are separated by column chromatography on silica gel.

Using 1,4-dihydroxy-2-(1,2-dimethylheptyloxy)-benzene in place of 5-(1,2-dimethylheptyl)resorcinol in the procedure of Example 1, the products are:

4-cyclohexyl-8-(1,2-dimethylheptyloxy)-6-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-7-(1,2-dimethylheptyloxy)-6-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-5-(1,2-dimethylheptyloxy)-6-hydroxy-2,2-dimethyl-2H-chromene.

Using 1,2-dihydroxy-4-(1,2-dimethylheptyloxy)-benzene in place of 5-(1,2-dimethylheptyl)resorcinol in the procedure of Example 1, the products are:

4-cyclohexyl-6-(1,2-dimethylheptyloxy)-8-hydroxy-2,2-dimethyl-2H-chromene
4-cyclohexyl-5-(1,2-dimethylheptyloxy)-8-hydroxy-2,2-dimethyl-2H-chromene.

EXAMPLE 18

1,2,3-Trihydroxybenzene is reacted with an equimolar amount of 2-bromoheptane in the presence of potassium hydroxide by the procedure of Example 15 to give 2,3-dihydroxy-1-(methylhexyloxy)benzene.

Using 2,3-dihydroxy-1-(1-methylhexyloxy)benzene in place of 5-(1,2-dimethylheptyl)resorcinol in the precedure of Example 1 gives 4-cyclohexyl-8-hydroxy-2,2-dimethyl-7-(1-methylhexyloxy)-2H-chromene.

EXAMPLE 19

1,2,3-Trihydroxybenzene is reacted with ethyl 3-cyclohexyl-3-oxopropionate in the presence of phosphorus oxychloride by the procedure of Example 1 to give 4-cyclohexyl-7,8-dihydroxy-2,2-dimethyl-2H-chromene.

The above prepared chromene compound is reacted with 2-bromo-3-methyloctane in the presence of potassium hydroxide by the procedure of Example 15 to give a mixture of 4-cyclohexyl-8-(1,2-dimethylheptyloxy)-7-hydroxy-2,2-dimethyl-2H-chromene and 4-cyclohexyl-7-(1,2-dimethylheptyloxy)-8-hydroxy-2,2-dimethyl-2H-chromene. These compounds are separated by column chromatography on silica gel.

EXAMPLE 20

By the procedure of Example 1 using 1,3,5-trihydroxybenzene in place of 5-(1,2-dimethylheptyl)-resorcinol, 4-cyclohexyl-5,7-dihydroxy-2,2-dimethyl-2H-chromene is prepared.

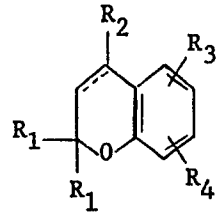
Reacting the above prepared chromene with 2-bromoheptane in the presence of potassium hydroxide by the procedure of Example 15 gives a mixture of 4-cyclohexyl-7-hydroxy-2,2-dimethyl-5-(1-methylhexyloxy)-2H-chromene and 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylhexyloxy)-2H-chromene. These compounds are separated by column chromatography on silica gel.

EXAMPLE 21

By the procedure of Example 5, 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylhexyloxy)-2H-chromene is hydrogenated in absolute ethanol with palladium on carbon to give 4-cyclohexyl-5-hydroxy-2,2-dimethyl-7-(1-methylhexyloxy)chroman.

What is claimed is:

1. A compound of the formula:



in which
is a single or a double bond;
R_1 is lower alkyl;
R_2 is cycloalkyl or cycloalkenyl, said cycloalkyl and cycloalkenyl having 5–6 carbon atoms;
R_3 is hydroxy or an alkali metal salt thereof, lower alkoxy or lower alkanoyloxy and
R_4 is a straight or branched alkyl or alkoxy group having 5 to 12 carbon atoms.

2. A compound of claim **1** in which R_3 is attached at the 5-position and R_4 is attached at the 7-positon.

3. A compound of claim **2** in which is a double bond, R_3 is hydroxy attached at the 5-position and R_4 is a straight or branched alkyl group having 5 to 12 carbon atoms attached at the 7-position.

4. A compound of claim **3** in which R_2 is cyclohexyl.

5. A compound of claim **1**, said compound being 4-cyclohexyl-7-(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-2H-chromene.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,923,836

DATED : December 2, 1975

INVENTOR(S) : Paul E. Bender and Bernard Loev

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, line 20, at the beginning of the line, before "is" insert ---.

Column 1, line 33, after "in which" insert ---.

Column 1, line 39, after "in which" insert ---.

Column 3, line 2, "ae" should read -- are --.

Column 3, line 17, "low" should read -- lower --.

Column 5, line 16, "is" should read -- in --.

Column 8, line 56, after "resorcinol" insert -- in --.

Column 10, line 27, at the beginning of the line, before "is" insert ---.

Column 10, line 37, after "in which" insert ---.

Signed and Sealed this

thirtieth Day of *March 1976*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks

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