

PATENT SPECIFICATION

NO DRAWINGS

L162,784



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International Classification:—C 07 d 99/04

COMPLETE SPECIFICATION

Organic Compounds based upon Pyridyl Benzopyrans and Intermediates and processes therefor

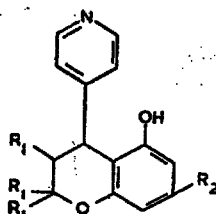
We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutically useful chemical compounds, to processes for making these compounds and to intermediates for use in such processes.

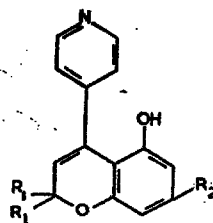
The invention is especially concerned with compounds having pharmacodynamic activity on the cardiovascular and central nervous systems.

Accordingly, the present invention provides a class of chemical compounds which we designate as 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl)-4 - (4 - pyridyl) - 2,2,3 - trialkyl - 5 - chromanol, and 2,2 - dialkyl - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl)-4 - (4 - pyridyl) - 2H - chromen - 5 - ol.

Without limiting the generality of the foregoing, illustrative and preferred embodiments of our 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl) -4 - (4 - pyridyl) - 2,2,3 - trialkyl - 5 - chromanol, and our 2,2 - dialkyl - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl) -4 - (4 - pyridyl) - 2H - chromen - 5 - ol, are those of formulas I and II, respectively:



(I)



(II)

wherein R_1 is lower alkyl and R_2 is alkyl or cycloalkyl - lower - alkyl.

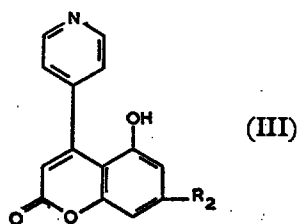
As used herein, the term "lower-alkyl" means saturated, monovalent aliphatic radicals, including straight and branched-chain radicals of from one to six carbon atoms, as illustrated by, but not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, amyl, and hexyl.

As used herein, the term "alkyl" means saturated, monovalent aliphatic radicals, including straight and branched-chain radicals of from one to twenty carbon atoms, as illustrated by, but not limited to, methyl, *n*-amyl, *n*-hexyl, 2-heptyl, *n*-heptyl, 3 -

methyl - 2 - octyl, *n*-octyl, 2-nonyl, 2-tetradecyl, *n*-hexadecyl, and 2-eicosanyl.

As used herein and in the appended claims, the term "Cycloalkyl" means cyclic, saturated aliphatic radicals of from three to eight carbon atoms, as illustrated by, but not limited to, cyclopropyl, cyclobutyl, 2-methylcyclobutyl, cyclohexyl, 4-methylcyclohexyl, and cyclo-octyl.

The invention also provides chemical compounds which we designate as 5 - hydroxy - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl) -4 - (4 - pyridyl) coumarin having formula III:



wherein R_2 has the meaning given above, and which are useful as intermediates in the preparation of the compounds of formulas I and II.

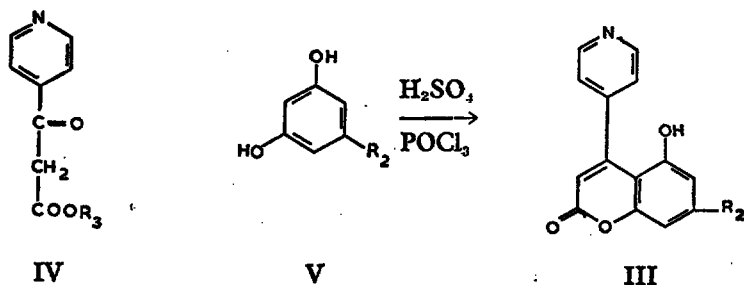
The names and formulas used herein to represent the compounds of the present invention are not intended to limit the invention to any specific optical or geometric isomers.

The invention, in one process aspect, comprises reacting a 5 - hydroxy - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) coumarin, illustrated above by formula III, with a lower-alkyl magnesium halide to prepare a 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) - 2,2,3 - trialkyl - 5 - chromanol, illustrated above by formula I. The reaction is carried out in an organic solvent inert under the conditions of the reaction. Suitable solvents are diethyl ether, dibutyl ether, tetrahydrofuran, anisole, pyridine, and the like. It is preferred to add a solution of the 5 - hydroxy - 7 - alkyl - (and 7 -

cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) coumarin in anisole solution to a solution of the Grignard reagent in anisole. The reaction is carried out at an elevated temperature, preferably at 100°C for an extended period of time, e.g., at least 24 hours.

The invention, in another of its process aspects, comprises reacting a 5 - hydroxy - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) coumarin, illustrated above by formula III, with a lower-alkyl magnesium halide to prepare a 2,2 - dialkyl - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) - 2H - chromen - 5 - ol, illustrated above by formula II. The reaction is carried out in an organic solvent as described above and in the same manner except that the reaction temperature is maintained at a lower level, preferably at about 50°C.

The invention, in another of its process aspects, comprises reacting a lower alkyl - β - oxo - 4 - pyridinepropionate with a 5 - alkyl - (and 5 - cycloalkyl - lower - alkyl -) - resorcinol to prepare a 5 - hydroxy - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl -)4 - (4 - pyridyl) coumarin, illustrated above by formula III. The reaction is carried out in a mixture of concentrated sulfuric acid and phosphorus oxychloride, or in the presence of other condensation agents such as aluminium chloride, hydrogen chloride, and polyphosphoric acid, and is illustrated by the equation:



wherein R_2 is defined as above and R_3 is lower alkyl.

The resulting 5 - hydroxy - 7 - alkyl - (and 7 - cycloalkyl - lower - alkyl) - 4 - (4 - pyridyl) coumarin is preferably isolated by the addition of a base to the reaction mixture to convert the salt to the free base.

The intermediate methyl - β - oxo - 4 - pyridine - propionate of formula IV is conveniently prepared according to the procedure of Moffat described in J. Med. Chem. 7, 449 (1964); and the intermediate 5 - alkyl - (and 5 - cycloalkyl - lower - alkyl) resorcinol of formula V is conveniently prepared according to procedure of Adams, Mackenzie and Loewe described in J. Am. Chem. Sec., 70, 669, (1948).

Due to the ionic nature of the nitrogen in the pyridine ring of formulas I and II it is possible to form acid addition salts for example

with HCl, HBr, HI and picric acid $[(NO_2)_3C_6H_2OH]$. The compounds of formulas I and II may be converted to the acid-addition salt form by dissolving the compound in an aqueous solution containing the appropriate acid and isolating the salt by evaporating the solution.

It will thus be appreciated that the scope of the present invention includes the acid-addition salts of the compounds of the present invention. Both the compounds in their free basic form and the acid-addition salts have inherent pharmacodynamic activity.

This inherent pharmacodynamic activity can be enjoyed in useful form for pharmaceutical purposes by employing the compounds themselves or the acid-addition salts formed from pharmaceutically-acceptable acids or esters of strong acids, that is, acids or esters whose anions are innocuous to the animal organism

in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases are not vitiated by side-effects ascribable to the anions.

In utilizing this pharmacodynamic activity of the salts of the invention, we prefer of course to use pharmaceutically-acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water-insoluble or toxic salts can be converted to pharmaceutically-acceptable compounds by techniques well known in the pharmaceutical art.

It will be appreciated from the foregoing that all of the acid-addition salts of our new compounds are useful and valuable compounds regardless of considerations of solubility, toxicity, physical form, and accordingly are within the scope of the present invention.

The compounds of formulae I and II have been shown to possess central nervous system activity as evidenced by gross overt changes induced by parenteral and oral administration in mice and rats in standard tests involving observation of psycho-motor activity, reactivity to stimuli, and ability to perform normal, non-conditioned motor tasks. The compounds may thus exhibit activity in hypertension and analgesia and may be anti-depressant and anti-anxiety agents. The compounds also show activity in a number of conditioned behavioral tests in monkeys. This activity indicates their usefulness as psychotropic agents. In addition, certain of the compounds produce depressor response in cat blood pressure studies.

The compounds of the present invention may be presented orally or parenterally and are preferably incorporated into a pharmaceutical formulation for such administration, either as the sole active ingredient or together with other pharmacologically active ingredients. For example, the oral preparations may be tablets, pills, powders, capsules, granules, suspensions, dispersions, solutions or emulsions which may contain diluents, binders, dispersing agents, surface active agents, flavouring agents, lubricating agents, colouring agents, coating materials, solvents, thickening agents or any other pharmaceutically acceptable additives where appropriate. Thus the compounds can be incorporated in unit dosage form as tablets or capsules for oral administration either alone or in combination with suitable adjuvants such as calcium carbonate, starch, lactose, talc, magnesium stearate, gum acacia, or they can be formulated for oral administration in aqueous alcohol, glycol or oil solutions or oil-water emulsions in the same manner as conventional medicinal substances are prepared. The injectable form may be a substantially aqueous or non-aqueous solution, suspension or emulsion in a phar-

maceutically-acceptable liquid or mixture of liquids which may contain bacteriostats, anti-oxidants, buffers, solutes to render the formulation isotonic with the blood, thickening agents, suspending agents, or any other pharmaceutically acceptable additives where appropriate. Such injectable formulations should be made sterile and may be presented in unit dose forms such as ampoules or disposable injection devices or in multidose forms such as bottles from which the appropriate dose may be withdrawn. The compounds can for example be prepared for use by dissolving under sterile conditions a salt form of the compounds in water (or an equivalent amount of a non-toxic acid) or in a physiologically compatible aqueous medium such as saline, and stored in ampoules for intramuscular injection.

The molecular structures of the compounds of our invention were assigned on the basis of a study of their infra-red, ultra-violet and n.m.r. spectra, of mass spectrometry and their transformation products; and they were confirmed by the correspondence of calculated and found values for the elementary analyses for representative samples.

The following examples will further illustrate the invention without, however, limiting it thereto.

EXAMPLE 1

5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin

To a mixture of 2.1g. (0.0117 mole) of methyl - β - oxo - 4 - pyridinepropionate and 2.8g. (0.0118 mole) of 5 - (3 - methyl - 2 - octyl) resorcinol was added dropwise with cooling, 5 ml. of concentrated sulfuric acid. The mixture was then treated all at once with 3 ml. of phosphorus oxychloride and the viscous solution was stirred at room temperature for 48 hours. It was then pured into cold potassium bicarbonate solution and extracted with ether several times. The combined ether extract was washed, dried and evaporated to leave a yellow solid which was recrystallised from dilute ethanol to give 3.4g. of 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin. The compound had a melting point of 191—194°C and showed an ultra-violet absorption at 315 m μ . $\epsilon_{\text{max}}^{\text{EtOH}}$ 11,700

Analysis. Calculated for $\text{C}_{23}\text{H}_{27}\text{O}_3\text{N}$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.42; H, 7.43; N, 3.76.

EXAMPLE 2

7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - trimethyl - 5 - chromanol

Methyl bromide was bubbled into a stirred mixture of 18.0g. (0.75 mole) of magnesium and dry ether under nitrogen until all the magnesium had dissolved. The ether was then distilled and simultaneously replaced with dry anisole maintaining constant volume. After

- all the ether had been removed, 27.6g. (0.075 mole) of the 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin of Example 1 in anisole solution was added dropwise. When addition was complete the mixture was stirred and heated at 100°C for 2 days. The mixture was poured into a large excess of 4N sulfuric acid and steam-distilled to remove anisole. The residue was extracted with ether, washed, dried and evaporated to leave a reddish oil. This was dissolved in 250ml. of heptane; 5ml. of 48% hydrobromic acid was added, and the mixture was then refluxed for 6 hours. After cooling the heptane was removed on a rotary evaporator and the residue was extracted with ether. The ethereal extract was washed with sodium bicarbonate solution, then water and dried over sodium sulphate. On evaporation of ether, a gummy residue was obtained which crystallised on trituration with acetonitrile to give 6.0g. of 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - trimethyl - 5 - chromanol, m.p. 192—195°C.
- Analysis. Calculated for $C_{26}H_{37}O_2N$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.80; H, 9.38; N, 3.47.

EXAMPLE 3

- 2,2 - dimethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol
- A solution of 5.0g. (0.0137 mole) of the 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin of Example 1 in anisole was added dropwise to a solution of methyl magnesium bromide (prepared from 3.3g. (0.138 mole) of magnesium as described in the previous example) in anisole. When the addition was complete the mixture was stirred and heated at 50°C for 16 hours. After work up in a similar manner as described in Example 2, a solid was obtained which was recrystallised from acetonitrile to give 2.9g. of 2,2 - dimethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol, m.p. 85—90°C. It showed ultra-violet absorption at 263 $m\mu$ $\tau_{\text{max}}^{\text{EtoH}}$ 10,000.

Analysis. Calculated for $C_{25}H_{33}O_2N$: C, 79.11; H, 8.76; N, 3.69. Found: C, 78.84; H, 8.57; N, 3.54.

EXAMPLE 4

- 5 - Hydroxy - 7 - methyl - 4 - (4 - pyridyl) coumarin
- To a mixture of 5.4g. of methyl - β - oxo - 4 - pyridinepropionate and 3.75g. of orcinol was added dropwise with cooling, 15ml. of concentrated sulfuric acid. The mixture was then treated all at once with 6ml. of phosphorus oxychloride and the viscous solution was stirred at room temperature for 16 hours and then poured into ammonium hydroxide solution containing ice and the pH adjusted to

neutral with potassium bicarbonate solution. A fine precipitate was obtained which was filtered, and recrystallised from boiling ethanol to give 6.5g. of 5 - hydroxy - 7 - methyl - 4 - (4 - pyridyl) coumarin, m.p. 304—306°C.

Analysis. Calculated for $C_{13}H_{11}NO_3 \cdot 1/2 H_2O$: C, 68.7; H, 4.58; N, 5.35. Found: C, 68.62; H, 4.63; N, 5.42.

It showed ultra-violet absorption at 314 $m\mu$ $\tau_{\text{max}}^{\text{EtoH}}$ 10,280. The structure was confirmed by n.m.r. analysis.

EXAMPLE 5

4 - (4 - Pyridyl) - 2,2,7 - trimethyl - 2H - chromen - 5 - ol.

A suspension of 2g. of 5 - hydroxy - 7 - methyl - 4 - (4 - pyridyl) coumarin in anisole was added in small portions to a solution of methyl magnesium bromide (prepared from 1.9g. of magnesium as described in Example 2) in anisole. When the addition was complete the mixture was stirred and heated at 50°C for 16 hours. After work up in a similar manner as described in Example 2, a solid was obtained which was recrystallised from methanol/acetonitrile mixture to give 0.7g. of 4 - (4 - pyridyl) - 2,2,7 - trimethyl - 2H - chromen - 5 - ol, m.p. 240—245°C.

Analysis. Calculated for $C_{17}H_{17}O_2N$: H, 6.41; N, 5.24; C, 76.38. Found: C, 76.20; H, 6.31; N, 5.42.

The structure was confirmed by n.m.r. analysis.

EXAMPLE 6

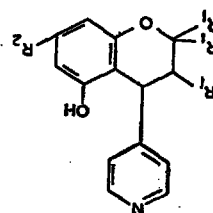
7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - triethyl - 5 - chromanol

Using the method of Example 2 except that methyl bromide was replaced with ethyl bromide, the above compound was prepared, isolated, and characterised.

EXAMPLE 7

2,2 - diethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol

Using the method of Example 3 except that ethyl bromide was used instead of methyl bromide, the above compound was prepared, isolated and characterised.

WHAT WE CLAIM IS:—
1. Compounds of formula

and

- all the ether had been removed, 27.6g. (0.075 mole) of the 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin of Example 1 in anisole solution was added dropwise. When addition was complete the mixture was stirred and heated at 100°C for 2 days. The mixture was poured into a large excess of 4N sulfuric acid and steam-distilled to remove anisole. The residue was extracted with ether, washed, dried and evaporated to leave a reddish oil. This was dissolved in 250ml. of heptane; 5ml. of 48% hydrobromic acid was added, and the mixture was then refluxed for 6 hours. After cooling the heptane was removed on a rotary evaporator and the residue was extracted with ether. The ethereal extract was washed with sodium bicarbonate solution, then water and dried over sodium sulphate. On evaporation of ether, a gummy residue was obtained which crystallised on trituration with acetonitrile to give 6.0g. of 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - trimethyl - 5 - chromanol, m.p. 192—195°C.
- Analysis.* Calculated for $C_{28}H_{37}O_2N$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.80; H, 9.38; N, 3.47.

EXAMPLE 3

- 2,2 - dimethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol
- A solution of 5.0g. (0.0137 mole) of the 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin of Example 1 in anisole was added dropwise to a solution of methyl magnesium bromide (prepared from 3.3g. (0.138 mole) of magnesium as described in the previous example) in anisole. When the addition was complete the mixture was stirred and heated at 50°C for 16 hours. After work up in a similar manner as described in Example 2, a solid was obtained which was recrystallised from acetonitrile to give 2.9g. of 2,2 - dimethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol, m.p. 85—90°C. It showed ultra-violet absorption at 263 $m\mu$ $\tau_{\text{max}}^{\text{EtoH}}$ 10,000.

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neutral with potassium bicarbonate solution. A fine precipitate was obtained which was filtered, and recrystallised from boiling ethanol to give 6.5g. of 5 - hydroxy - 7 - methyl - 4 - (4 - pyridyl) coumarin, m.p. 304—306°C.

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4 - (4 - Pyridyl) - 2,2,7 - trimethyl - 2H - chromen - 5 - ol

A suspension of 2g. of 5 - hydroxy - 7 - methyl - 4 - (4 - pyridyl) coumarin in anisole was added in small portions to a solution of methyl magnesium bromide (prepared from 1.9g. of magnesium as described in Example 2) in anisole. When the addition was complete the mixture was stirred and heated at 50°C for 16 hours. After work up in a similar manner as described in Example 2, a solid was obtained which was recrystallised from methanol/acetonitrile mixture to give 0.7g. of 4 - (4 - pyridyl) - 2,2,7 - trimethyl - 2H - chromen - 5 - ol, m.p. 240—245°C.

Analysis. Calculated for $C_{17}H_{17}O_2N$: C, 64.1; H, 5.24; N, 5.42. Found: C, 76.20; H, 6.31; N, 5.42.

The structure was confirmed by n.m.r. analysis.

EXAMPLE 6

7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - triethyl - 5 - chromanol

Using the method of Example 2 except that methyl bromide was replaced with ethyl bromide, the above compound was prepared, isolated, and characterised.

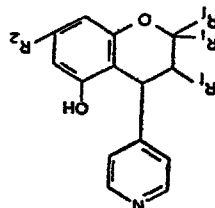
EXAMPLE 7

2,2 - diethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol

Using the method of Example 3 except that ethyl bromide was used instead of methyl bromide, the above compound was prepared, isolated and characterised.

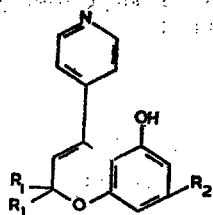
WHAT WE CLAIM IS:—

1. Compounds of formula



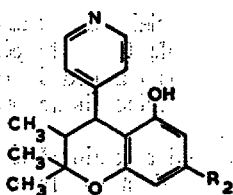
and



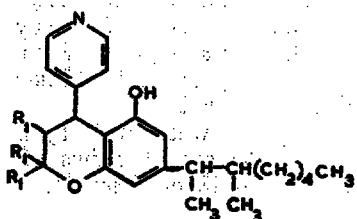


wherein R_1 is lower-alkyl and R_2 is alkyl or cycloalkyl - lower - alkyl.

2. A compound as claimed in claim 1 having the formula



3. A compound as claimed in claim 1 having the formula

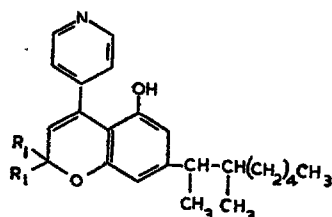


4. A compound as claimed in any one of claims 1-3 and being 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2,2,3 - trimethyl - 5 - chromanol.

5. A compound as claimed in claim 1 having the formula

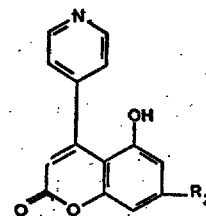


6. A compound as claimed in claim 1 having the formula



7. A compound as claimed in any one of claims 1, 5 or 6 are being 2,2 - dimethyl - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) - 2H - chromen - 5 - ol.

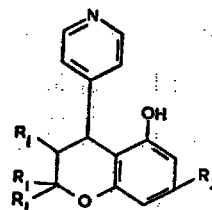
8. A compound having the formula



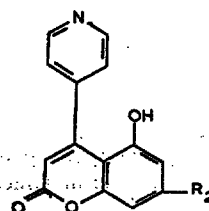
wherein R_2 is alkyl or cycloalkyl - lower - alkyl.

9. A compound in accordance with claim 8 wherein R_2 is 3 - methyl - 2 - octyl and said compound is 5 - hydroxy - 7 - (3 - methyl - 2 - octyl) - 4 - (4 - pyridyl) coumarin.

10. A process for preparing a compound as claimed in claim 1 having the formula



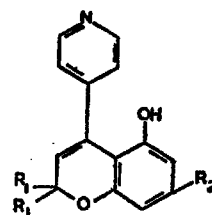
which comprises reacting a compound having the formula



with a lower-alkyl magnesium halide of the formula R_1MgX and X is bromine or iodine, at a temperature of about $100^\circ C$.

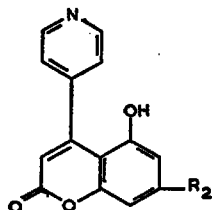
11. A process as claimed in claim 10 wherein R_1 is methyl, R_2 is 3 - methyl - 2 - octyl and X is bromine.

12. A process for preparing a compound as claimed in claim 1 and having the formula



which comprises reacting a compound having the formula

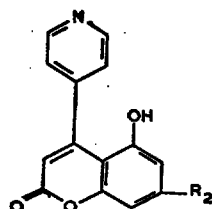




with a lower-alkyl magnesium halide of the formula R_1MgX and X is bromine or iodine, at a temperature of about $50^\circ C$.

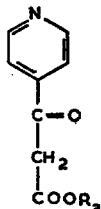
- 5 13. A process as claimed in claim 12 wherein R_1 is methyl, R_2 is 3-methyl-2-octyl and X is bromine.

14. A process for preparing a compound as claimed in claim 8 and having the formula



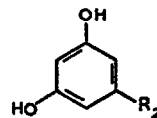
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wherein R_2 is alkyl or cycloalkyl - lower - alkyl which comprises reacting, in the presence of a condensation agent a compound having the formula



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where R_3 is lower alkyl with a compound having the formula



15. A process as claimed in claim 14 wherein R_2 is 3-methyl-2-octyl.

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16. A compound as claimed in claim 1 or claim 8 and as described in any one of examples 1-5.

17. A process as claimed in claim 14 and as described in example 1 or example 4.

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18. A process as claimed in claim 10 or claim 12 and as described in any one of examples 2, 3 or 5.

19. A compound as claimed in any one of claims 1-9 and 16 in the form of an acid addition salt.

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20. A pharmaceutical formulation comprising a compound as claimed in any one of claims 1-7 or claim 16 or claim 19 together with a pharmaceutically acceptable carrier.

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21. A process as described in any one of claims 10-15 or claim 17 or 18 comprising the step of forming an acid addition salt of the product compound.

22. A compound when made by a process as claimed in any one of claims 10-15 or claim 17 or claim 18 or claim 21.

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RONALD SMITHER
Agent for the Applicants,
Chartered Patent Agent.

