

1356 117

PATENT SPECIFICATION

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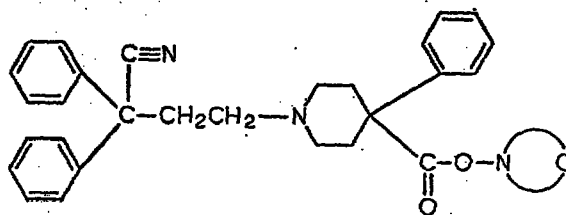


(54) 1-(3-CYANO-3,3-DIPHENYLPROPYL)-4-PHENYL-
 PIPERIDINE-4-CARBOXYLIC ACID DERIVATIVES

(71) We, G. D. SEARLE & CO., a corporation organised under the laws of the State of Delaware, United States of America of P.O. Box 5110, Chicago, Illinois, 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:—

Antidiarrheal Compounds

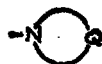
The present invention relates to novel compounds characterized by the general structural formula



10 wherein

(I)

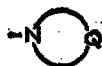
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represents an optionally substituted monocyclic- or fused polycyclic- heterocyclic radical containing at least one carbonyl function adjacent to the nitrogen atom.

Illustrative of the radicals represented by

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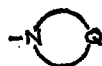


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are succinimido, glutarimido, phthalimido, endo-5-norbornene-2,3-dicarboximido, 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl, and 3,4-dihydro-4-oxo-quinazolin-3-yl. The quinazolin-yl radical can be optionally substituted, for example, with a bromine atom at positions 5 to 7, and with a methyl or phenyl radical at the 2-position. Additional radicals represented by

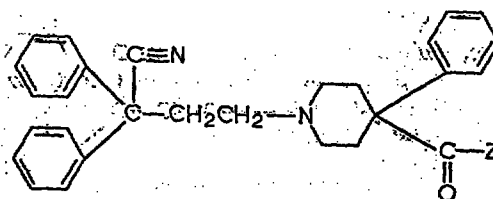
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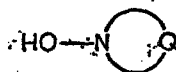
include 3,4-dihydro-3-oxo-2H-1,4-benzoxazin-4-yl and 3,4-dihydro-3-oxo-2H-1,4-benzothiazin-4-yl and the corresponding 2-(o-chlorobenzylidene), 6-chloro, 6-chloro-2-methyl, 6-bromo, 2-ethyl, 2-methyl, 2,2-dimethyl, 2-carboxymethyl and 2-carboxymethyl-6-methyl derivatives; 2-oxoindol-1-yl, optionally containing an oxo, phenyl or benzylidene substituent at the 3-position; 4,5,6,7-tetrahydro-4,6-dioxo-3-methylisothiazolo[5,4-d]-pyrimidin-5-yl; 1,2,3,4-tetrahydro-1,3-dioxoisquinolin-2-yl; 3-cyano-1,2-dihydro-1-oxoisquinolin-2-yl; 9,10-dihydro-5,10-dioxo-4-oxa-9-azapyren-9-yl; 3-carboxy-1,2-dihydro-2-oxo-1,8-naphthyridin-1-yl; and 4-oxopyridopyrimidin-3-yl radicals, the latter preferably containing a methyl substituent at the 2-position and optionally containing additional methyl groups on the pyridine or pyrimidine portion of the radical. Specific illustrations of such pyridopyrimidin-3-yl radicals are 3,4-dihydro-4-oxo-2,6,8-trimethylpyrido[3,4-d]pyrimidin-3-yl; 2-methyl-4-oxopyrido[3,2-d]pyrimidin-3-yl; and 2-methyl-3,4-dihydro-4-oxo-pyrido[3,2-d]pyrimidin-3-yl.

The compounds of formula (I) can be conveniently prepared by contacting a compound of the general formula



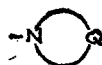
(II)

wherein Z is a chlorine atom or a hydroxy radical, with a compound of the formula



(III)

wherein



is defined as before.

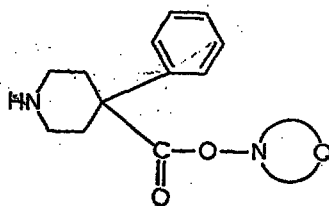
When Z in formula (II) is a hydroxy radical, i.e. when the acid starting material is employed, the reaction is conducted in the presence of a suitable dehydrating agent. Suitable dehydrating agents include aromatic carbodiimides such as diphenylcarbodiimide; and aliphatic carbodiimides such as diethylcarbodiimide and, preferably, dicyclohexylcarbodiimide. Other dehydrating agents which may be suitable include bases such as sodium carbonate and acids such as sulfuric acid, hydrochloric acid and toluenesulfonic acid. Other possible dehydrating agents may include trifluoroacetic anhydride and boron trifluoride etherate. Time, temperature and pressure are not critical factors for the conduct of this reaction; however, the reaction is preferably conducted initially at slightly elevated temperature, e.g. between 40—60°C., and conveniently at atmospheric pressure. Typical reaction times vary between 3 hours and 30 days and are dependent on the particular temperature and reactants involved. Suitable solvents are non-protic solvents (i.e. solvents containing no acidic hydrogen atoms) which are capable of dissolving the acid of formula (II) at the temperature employed. Such suitable solvents include dimethylformamide, dimethylacetamide, and hexamethylphosphoramide.

When Z in formula (II) is a chlorine atom, i.e. when the starting material is the acid chloride, the reaction is conveniently conducted in the presence of a suitable base. Preferred bases for use in this reaction include tertiary aliphatic or aromatic amines, e.g. N-methylmorpholine, triethylamine, pyridine and picoline. The reaction is conveniently carried out at atmospheric pressure, at a temperature ranging from room temperature to reflux and for a time period of 5 minutes to 24 hours. However, time

temperature and pressure are not critical factors in conducting the reaction. Suitable solvents are non-protic solvents, e.g. dimethylformamide, dimethylacetamide, hexamethylphosphoramide, dimethylsulfoxide, tetrahydrofuran, acetonitrile and benzene.

The starting material of formula (II) wherein Z is a chlorine atom is conveniently prepared from the corresponding acid of formula (II) by reaction with thionyl chloride in an inert solvent such as tetrahydrofuran, optionally in the presence of dimethylformamide as claimed in copending Application No. 57390/71. The acid chloride of formula (II) is particularly useful in the form of its hydrohalide salts, especially in the form of its hydrochloride. Said acid chloride is also the starting material of choice when the N-hydroxy compound of formula (III) contains reactive substituents, e.g. carboxymethyl or carboxy groups. Specific examples of N-hydroxy starting materials which contain such substituents and which are consequently most advantageously utilized in the reaction with the acid chloride of formula (II) include 2H-1,4-benzothiazine-2-acetic acid, 6-methyl-2H-1,4-benzothiazine-2-acetic acid and 1,2-dihydro-1-hydroxy-2-oxo-1,8-naphthyridine-3-carboxylic acid.

Alternatively, the compounds of formula (I) can be prepared via a reaction sequence which utilizes an acid addition salt, e.g. the hydrochloride, of 4-phenylpiperidine-4-carboxylic acid chloride as a starting material. That compound is contacted with the appropriate alcohol of formula (III) above in a suitable organic solvent such as dimethylformamide, tetrahydrofuran or toluene, preferably in the presence of a base such as triethylamine. The resultant compound of the general formula

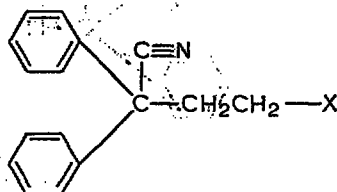


(IV)

wherein



is defined as before is then contacted with a compound of the general formula



(V)

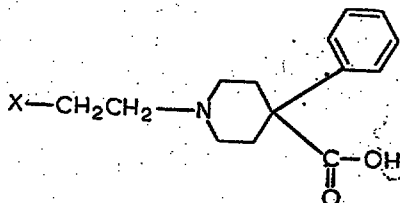
wherein X represents a chlorine, bromine, or iodine atom, or a methanesulfonyloxy or toluenesulfonyloxy radical, to afford the desired compound of formula (I). This reaction step is conducted in a suitable organic solvent, e.g. an aromatic hydrocarbon such as benzene, toluene or xylene, or a lower alkanone. Preferably, the reaction proceeds in the presence of an appropriate quantity of a suitable base, e.g. an alkali metal carbonate or pyridine, in order to bind the acid freed during the reaction. The presence of a catalytic quantity of potassium iodide is also desirable.

Another route to the subject compounds begins by contacting 4-phenylpiperidine-4-carboxylic acid with a compound of the general formula



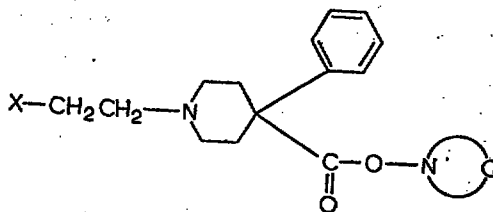
(VI)

wherein X is defined as before. The resultant compound of the formula



(VII)

is then reacted with the appropriate N-hydroxy compound of formula (III) in the presence of a suitable dehydrating agent, particularly a carbodiimide dehydrating agent such as dicyclohexylcarbodiimide. The resultant compound of the general formula

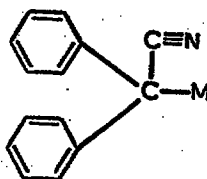


(VIII)

wherein X and



are as hereinabove defined is then reacted with a compound of the general formula



(IX)

wherein M is an active metal ion. Suitable active metal ions include those of the alkali metals such as sodium, potassium and lithium.

Equivalent to the free bases of formula (I) for the purposes of this invention are the non-toxic pharmaceutically acceptable acid addition salts thereof. Such salts include those derived from inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, phosphoric, nitric, and sulfamic; and from organic acids such as acetic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, benzoic, gluconic, ascorbic, salicylic, ethane disulfonic, fumaric, glycolic, and related acids.

The compounds of the present invention possess valuable pharmacological properties. They are, for example, potent antidiarrheal agents. They are also capable of counteracting the withdrawal symptoms of substances which produce chronic psychotropic drug intoxication. Additionally, the compounds of this invention variously possess analgesic, anti-protozoal, anti-bacterial, anti-fungal and anthelmintic activity.

The antidiarrheal properties of the instant compounds are specifically illustrated by the activity of the representative species N-[1-(3-cyano-3,3-diphenylpropyl)-4-

phenylpiperidine-4-carboxyloxy]succinimide hydrochloride and 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride in the following test procedures.

Charcoal Meal Test

Mice weighing 18–24 grams and previously fasted for 18 hours were each given orally 0.3 ml. of a suspension containing 10% charcoal and 5% acacia. The test compounds were administered intragastrically one hour prior to the charcoal meal. One-half hour after administration of the meal the mice were sacrificed with ether and their gastrointestinal tracts were removed. The distance over which some of the charcoal meal has moved from the pylorus to the cecum was measured for each mouse and expressed as percentage of the total distance. Each compound was tested at three dose levels (typically, at 0.3, 0.6 and 1.2 mg/mouse) in groups of 5 mice per dose level. Control groups of mice given saline only were run concurrently with each test group.

Castor Oil-Induced Diarrhea Test

Male Charles River rats were fasted overnight and water given *ad lib*. Test compounds (0.1 mg./kg.) were administered orally in normal saline, while controls were given saline only. The rats were randomized into two treatment groups and one control group, each group containing 10 rats. One hour after compound administration, 1 ml. of castor oil was given to each rat intragastrically. The rats were then observed for the presence or absence of diarrhea one hour after administration of the castor oil.

For the treatment of diarrhea, the novel compounds of this invention can be combined with pharmaceutically acceptable carriers to provide novel pharmaceutical compositions. The concentration of active ingredient in the composition is not critical, but is preferably 1–80%. These compositions can be administered orally, suitable forms for such administration including tablets, lozenges, capsules, dragees, pills, powders, solutions, suspensions and syrups. Acceptable pharmaceutical carriers are exemplified by gelatin capsules; sugars such as lactose or sucrose; starches such as corn starch or potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose or cellulose acetate phthalate; gelatin; talc; calcium phosphates such as dicalcium phosphate or tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinyl pyrrolidone; acacia; polyvinyl alcohol; stearic acid; alkaline earth metal stearates such as magnesium stearate; oils such as peanut oil; cottonseed oil, sesame oil; olive oil, corn oil, oil of theobroma; water; agar; alginic acid; and benzyl alcohol, as well as other non-toxic compatible substances used in pharmaceutical formulations.

The compounds of this invention can be used to produce an antidiarrheal effect in mammals by administering the instant novel compositions containing a therapeutically effective amount of the active ingredient. The term "therapeutically effective amount" is defined as the amount of active ingredient that will produce an anti-diarrheal effect, i.e. which will reverse, inhibit or prevent diarrhea. For a particular subject, the amount of active ingredient to be used will vary with the subject involved, the severity of the diarrhea, and the particular active ingredient used. The therapeutically effective amount of a particular active ingredient can be determined by comparing its potency to that of a known standard, for which the therapeutic dosage is known.

The invention will appear more fully from the following Examples, which are set forth for the purpose of illustration only.

EXAMPLE 1

24.5 Grams of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid were dissolved in 225 ml. of redistilled N,N-dimethylformamide by warming to about 60°C. To the warm solution were added, with stirring, 9.0 grams of recrystallized N-hydroxysuccinimide, followed by 12.4 grams of dicyclohexylcarbodiimide. A precipitate appeared upon cooling to room temperature. The suspension was stirred at room temperature under anhydrous conditions for about 36 hours, then cooled to approximately 5°C. and filtered to remove the precipitate. The filtrate was diluted with approximately 400 ml. of ethyl acetate and 200 ml. of water. The organic layer was then separated and washed three times with water, solid sodium chloride being added as needed to break the emulsion formed. The solution was dried over anhydrous sodium sulfate and partially concentrated until a precipitate formed. Filtration and recrystallization of the precipitate from a mixture of tetrahydrofuran and isopropyl ether afforded N[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide, melting at about 156.5–157.5°C. The ethyl acetate filtrate was acidified

with concentrated hydrochloric acid in 2-propanol, diluted with ethyl ether to the point of incipient precipitation and cooled. The precipitate was filtered, recrystallized from a mixture of 2-propanol and isopropyl ether, and dried at about 110°C. under reduced pressure for about 16 hours. There was thus obtained N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide hydrochloride, melting at about 242—244°C. with gas evolution.

1.35 Grams of N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide were dissolved in 20 ml. of dichloromethane and then combined with a solution of .37 gram of glycolic acid in 10 ml. of warm dichloromethane. The resultant solution was filtered and diluted with ether and the semisolid thus obtained was dried to a solid *in vacuo*. The product, N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide hemihydrate, compound with 2 moles of glycolic acid, displayed a melting point at about 80—85°C. with decomposition.

EXAMPLE 2

2.12 Grams of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid were dissolved in 65 ml. of redistilled N,N-dimethylformamide by warming to about 60°C. To the warm solution was added, with stirring, .82 gram of N-hydroxyphthalimide, followed by 1.16 grams of dicyclohexylcarbodiimide. The resultant mixture was stirred at room temperature under calcium chloride, then cooled and filtered. The filtrate was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over potassium carbonate and partially concentrated until a precipitate formed. Filtration and repeated crystallizations of the precipitate from a mixture of chloroform and hexane afforded N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]phthalimide melting at about 156.5—157.5°C. The ethyl acetate filtrate was acidified with concentrated hydrochloric acid in 2-propanol, diluted with isopropyl ether to the point of incipient precipitation and cooled. The precipitate was filtered, recrystallized from a mixture of 2-propanol and isopropyl ether and dried, thus affording N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]phthalimide hydrochloride, compound with 2-propanol. That product melted at about 151—153°C., with decomposition.

EXAMPLE 3

2.12 Grams of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid were dissolved in 60 ml. of warm redistilled N,N-dimethylformamide. To that solution was then added .82 gram of 3-hydroxy-3H-1,2,3-benzotriazin-4-one, followed by 1.16 grams of dicyclohexylcarbodiimide. The resultant solution was stirred at room temperature under anhydrous conditions for about 24 hours, a precipitate appearing after approximately 1 hour. The suspension was cooled to about 5°C, the precipitate was removed by filtration, and the filtrate was diluted with 100 ml. of water and extracted twice with 100 ml. portions of ethyl acetate. The combined ethyl acetate layers were washed with water, dried over anhydrous sodium sulfate, concentrated to approximately one-half volume by evaporation under a stream of nitrogen, and then filtered. The ethyl acetate solution was then acidified with concentrated hydrochloric acid in 2-propanol, diluted with ethyl ether and cooled. The precipitate which formed was recrystallized from a mixture of 2-propanol and isopropyl ether, then dried *in vacuo* at about 110°C. There was thus obtained 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride, melting at about 208—210°C. with decomposition.

Substitution of .90 gram of N-hydroxy-endo-5-norbornene-2,3-dicarboximide for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one used above and substantial repetition of the foregoing procedure afforded N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-endo-5-norbornene-2,3-dicarboximide hydrochloride, compound with 2-propanol. That product foamed at about 151°C.

Similarly, substitution of .65 gram of N-hydroxyglutarimide for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one used above and substantial repetition of the procedure detailed in the first paragraph of this Example afforded N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]glutarimide hydrochloride, melting at about 238—244°C. with gas evolution.

EXAMPLE 4

When equivalent quantities of 4-hydroxy-2H-1,4-benzothiazin-3(4H)-one; 6-chloro-4-hydroxy-2-methyl-2H-1,4-benzoxazin-3(4H)-one; 1-hydroxy-2-indolinone, and 3-hydroxy-2-methylpyrido[3,2-d]pyrimidin-4-one were substituted for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in the first paragraph of Example 3

and the procedure described therein was substantially repeated there were obtained the hydrochloride salts of 4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]2H-1,4-benzothiazin-3(4H)-one; 6-chloro-4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-methyl-2H-1,4-benzoxazin-3(4H)-one; 1-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-indolinone; and 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-methylpyrido[3,2-d]-pyrimidin-4-one, respectively.

EXAMPLE 5

To a solution of 2.12 grams of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid in 60 ml. of warm redistilled N,N-dimethylformamide was added .81 gram of 3-hydroxy-3H-quinazolin-4-one, followed by 1.16 grams of dicyclohexylcarbodiimide. The resultant solution was stirred at room temperature under anhydrous conditions for about 24 hours, a precipitate appearing after approximately one hour. The suspension was cooled to about 5°C. and the precipitate was removed by filtration. The filtrate was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous sodium sulfate, concentrated to approximately one-half volume by evaporation under a stream of nitrogen, then filtered. The ethyl acetate solution was then acidified with concentrated hydrochloric acid in 2-propanol, diluted with isopropyl ether and cooled. The precipitate which formed was filtered and dried. There was thus obtained 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-quinazolin-4-one hydrochloride hemihydrate melting at about 237—238.5°C.

EXAMPLE 6

2.12 Grams of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid were suspended in 10 ml. of dry tetrahydrofuran and 0.5—1.0 ml. of dry redistilled N,N-dimethylformamide. A solution of 5 ml. of thionyl chloride in 5 ml. of dry tetrahydrofuran was added dropwise, a clear solution resulting after the addition of about 2 drops. The resulting solution was stirred at room temperature under anhydrous conditions for about 5 minutes, then refluxed for 15 minutes. The reaction mixture was concentrated to a solid residue and excess thionyl chloride was further removed by adding 10 ml. of dry tetrahydrofuran and again concentrating to dryness. The residue, i.e. 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid chloride hydrochloride, was taken up in 15 ml. of dry N,N-dimethylformamide, treated with 1 gram of triethylamine, then with .82 gram of N-hydroxyphthalimide in 5 ml. of N,N-dimethylformamide. The reaction mixture was stirred at room temperature for about 2 hours, then diluted with 50 ml. of water and extracted twice with 50 ml. portions of ethyl acetate. The combined ethyl acetate solutions were washed with water, dried and acidified with concentrated hydrochloric acid in 2-propanol. Addition of isopropyl ether and cooling afforded a precipitate which was recrystallized from a mixture of 2-propanol and isopropyl ether containing decolorizing carbon. There was thus obtained N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-phthalimide hydrochloride, compound with 2-propanol, melting at about 151—155°C. with gas evolution.

Substitution of an equivalent quantity of N-hydroxysuccinimide of the N-hydroxyphthalimide used above and substantial repetition of the procedure described in the preceding paragraph afforded N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]succinimide hydrochloride, melting at about 242—244° with gas evolution.

In a similar manner, when an equivalent quantity of 3-hydroxy-3H-1,2,3-benzotriazin-4-one was substituted for the N-hydroxyphthalimide used above and the procedure detailed in the first paragraph of this Example was substantially repeated, there was obtained 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride. That product melted at about 208—210°C. with decomposition.

In a similar manner, repeating the procedure described in the first paragraph of this Example, but utilizing an equivalent quantity of N-hydroxy-endo-5-norbornene-2,3-dicarboximide in place of the N-hydroxyphthalimide employed therein, afforded N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-endo-5-norbornene-2,3-dicarboximide hydrochloride, compound with 2-propanol, foaming at about 151°C.

In like manner, substitution of an equivalent quantity of N-hydroxyglutarimide for the N-hydroxyphthalimide employed in the procedure of the first paragraph of this Example and substantial repetition of the procedure described therein afforded N-[1-

(3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] glutarimide hydrochloride, melting at about 238—244°C. with gas evolution.

EXAMPLE 7

When an equivalent quantity of 3-hydroxy-3H-quinazolin-4-one was substituted for the N-hydroxyphthalimide employed in the first paragraph of Example 6 and the procedure described therein was repeated, there was obtained, after acidification with concentrated hydrochloric acid in 2-propanol, a solution which was diluted with isopropyl ether and cooled. The precipitate which formed was filtered and dried, thus affording 3 - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]-3H-quinazolin-4-one hydrochloride hemihydrate, melting at about 237—238.5°C.

In a similar manner, when equivalent quantities of 4-hydroxy-2H-1,4-benzothiazin-3(4H)-one; 6 - chloro - 4 - hydroxy - 2 - methyl - 2H - 1,4 - benzoxazin - 3(4H)-one; 1-hydroxy-2-indolinone, and 3-hydroxy-2-methylpyrido[3,2-d]pyrimidin-4-one were substituted for the N-hydroxyphthalimide employed in the first paragraph of Example 6 and the procedure described therein was substantially repeated, there were obtained the hydrochloride salts of 4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2H-1,4-benzothiazin-3(4H)-one; 6 - chloro - 4 - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 2 - methyl - 2H - 1,4 - benzoxazin - 3(4H) - one; 1-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-indolinone; and 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-methylpyrido[3,2-d]pyrimidin-4-one, respectively.

EXAMPLE 8

To a suspension of 7.8 grams of 4-phenylpiperidine-4-carboxylic acid chloride hydrochloride in 50 ml. of dry tetrahydrofuran were added 6.0 grams of triethylamine slowly with stirring, followed by the addition of a solution of 3.5 grams of N-hydroxy-succinimide (recrystallized from ethyl acetate) in 20 ml. of dry tetrahydrofuran. The reaction mixture was stirred under anhydrous conditions for about one and one-half hours, then filtered and diluted with 100 ml. of water. The organic layer was separated, washed with water, dried and concentrated to give, as a crude residue, N-(4-phenylpiperidine-4-carbonyloxy)succinimide. That residue was combined with 7.7 grams of 4-bromo-2,2-diphenylbutyronitrile, 3.5 grams of sodium carbonate and a few crystals of potassium iodide in 100 ml. of 4-methyl-2-pentanone, then refluxed for about 75 hours. The reaction mixture was cooled and 50 ml. of water were added. The organic layer was removed, washed with water, dried and concentrated. The residue was dissolved in 50 ml. of ethyl acetate containing decolorizing carbon and filtered. A 10% excess of concentrated hydrochloric acid in 2-propanol was added, and the solution was cooled upon addition of ethyl ether to the point of incipient precipitation. The solid precipitate was recrystallized from a mixture of 2-propanol and isopropyl ether, giving N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - succinimide hydrochloride melting at about 242—244°C. with gas evolution.

Substitution of an equivalent quantity of 3-hydroxy-3H-1,2,3-benzotriazin-4-one for the N-hydroxy-succinimide employed above and substantial repetition of the procedure described in the preceding paragraph afforded 3-[1-(3-cyano-3,3-diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 3H - 1,2,3 - benzotriazin - 4 - one hydrochloride, melting at about 208—210°C. with decomposition.

Similarly, substitution of an equivalent quantity of N-hydroxyphthalimide for the N-hydroxysuccinimide employed in the procedure of the first paragraph of this Example and substantial repetition of the procedure described therein resulted in N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - phthalimide hydrochloride, compound with 2-propanol. That product melted at about 151—152°C. with decomposition.

In a similar manner, repeating the procedure described in the first paragraph of this Example, but utilizing an equivalent quantity of N-hydroxy-endo-5-norbornene-2,3-dicarboximide in place of the N-hydroxy-succinimide employed therein, afforded N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - endo-5-norbornene-2,3-dicarboximide hydrochloride, compound with 2-propanol, foaming at about 151°C.

In like manner, substitution of an equivalent quantity of N-hydroxyglutarimide for the N-hydroxysuccinimide employed in the procedure of the first paragraph of this Example and substantial repetition of the procedure described therein afforded N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - glutarimide hydrochloride, melting at about 238—244°C. with gas evolution.

EXAMPLE 9

When an equivalent quantity of 3-hydroxy-3H-quinazolin-4-one was substituted for the N-hydroxysuccinimide employed in the first paragraph of Example 8 and the procedure described therein was repeated, there was obtained, after acidification with concentrated hydrochloric acid in 2-propanol, a solution which was diluted with isopropyl ether and cooled. The precipitate which formed was filtered and dried, thus affording 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-quinazolin-4-one hydrochloride hemihydrate, melting at about 237—238.5°C.

In a similar manner, when equivalent quantities of 4-hydroxy-2H-1,4-benzothiazin-3(4H)-one; 6-chloro-4-hydroxy-2-methyl-2H-1,4-benzoxazin-3(4H)-one; 1-hydroxy-2-indolinone; and 3-hydroxy-2-methylpyrido[3,2-d]pyrimidin-4-one were substituted for the N-hydroxysuccinimide employed in the first paragraph of Example 8 and the procedure described therein was substantially repeated, there were obtained the hydrochloride salts of 4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2H-1,4-benzothiazin-3(4H)-one; 6-chloro-4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-methyl-2H-1,4-benzoxazin-3(4H)-one; 1-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-indolinone; and 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-methylpyrido[3,2-d]pyrimidin-4-one, respectively.

EXAMPLE 10

6.03 Grams of 4-phenylpiperidine-4-carboxylic acid, 10 grams of ethylene dibromide and 7 grams of sodium carbonate were refluxed, with a few crystals of potassium iodide, in 100 ml. of 4-methyl-2-pentanone for approximately 36 hours. The mixture was cooled and diluted with 50 ml. of 10% acetic acid. The organic layer was separated, washed with water and dried over anhydrous sodium sulfate to give a solution containing 1-(2-bromoethyl)-4-phenylpiperidine-4-carboxylic acid. To that solution were added 5.0 grams of 3-hydroxy-3H-1,2,3-benzotriazin-4-one, followed by 6.5 grams of dicyclohexylcarbodiimide. The resultant suspension was stirred at room temperature under anhydrous conditions for approximately 20 hours, then cooled and filtered to remove the solid material. The filtrate was washed with water, dried and concentrated to afford crude 3-[1-(2-bromoethyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one.

To a solution of 6.0 grams of diphenylacetonitrile in 50 ml. of anhydrous benzene were added 1.3 grams of sodium amide. The suspension was refluxed with stirring for about 3 hours while flushing with a slow stream of nitrogen. The reaction mixture was then cooled and a solution of the crude 3-[1-(2-bromoethyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one prepared above in 50 ml. of anhydrous benzene was added. The resulting mixture was refluxed for about 3 hours, then cooled and diluted with water. The organic layer was separated, washed twice with water, dried, and acidified with concentrated hydrochloric acid in 2-propanol. Addition of ethyl ether and cooling gave a precipitate which was recrystallized from a mixture of 2-propanol and isopropyl ether containing decolorizing carbon, then dried at about 110°C. for approximately 5 hours. There was thus obtained 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride, melting at about 208—210°C. with decomposition.

EXAMPLE 11

When an equivalent quantity of N-hydroxysuccinimide was substituted for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in the procedure of the first paragraph of Example 10, there was obtained, after substantial repetition of the procedures described in that Example, N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]succinimide hydrochloride, melting at about 242—244°C. with decomposition.

Similarly, substitution of an equivalent quantity of N-hydroxyphthalimide for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in the procedure of the first paragraph of Example 10 and substantial repetition of the procedures described therein resulted in N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-phthalimide hydrochloride, compound with 2-propanol. That product melted at about 151—153°C. with decomposition.

In a similar manner, repeating the successive procedures described in Example 10, but utilizing an equivalent quantity of N-hydroxy-endo-5-norbornene-2,3-dicarboximide in place of the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed therein,

afforded N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]-endo-5-norbornene-2,3-dicarboximide hydrochloride, compound with 2-propanol, foaming at about 151°C.

In like manner, substitution of an equivalent quantity of N-hydroxyglutarimide for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in the procedure of the first paragraph of Example 10 and substantial repetition of the procedures described therein afforded N - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]glutarimide hydrochloride, melting at about 238—244°C. with gas evolution.

Similarly, substitution of equivalent quantities of 4-hydroxy-2H-1,4-benzothiazin-3(4H)-one; 6-chloro-4-hydroxy-2-methyl-2H-1,4-benzoxazin-3(4H)-one; 1-hydroxy-2-indolinone; and 3-hydroxy-2-methylpyrido[3,2-d]pyrimidin-4-one for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in the procedure of the first paragraph of Example 10 and substantial repetition of the successive procedures described in that Example resulted in the hydrochloride salts of 4-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine - 4 - carbonyloxy] - 2H - 1,4 - benzothiazin - 3(4H) - one; 6-chloro-4 - [1 - (3 - cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 2 - methyl - 2H - 1,4 - benzoxazin - 3(4H) - one; 1-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-2-indolinone; and 3-[1-(3-cyano-3,3-diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 2 - methylpyrido[3,2-d]pyrimidin-4-one, respectively.

EXAMPLE 12

When an equivalent quantity of 3-hydroxy-3H-quinazolin-4-one was substituted for the 3-hydroxy-3H-1,2,3-benzotriazin-4-one employed in Example 10 and the successive procedures described in that Example were repeated, there was obtained, after acidification with concentrated hydrochloric acid in 2-propanol, a solution which was diluted with isopropyl ether and cooled. The precipitate which formed was filtered and dried, thus affording 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-quinazolin-4-one hydrochloride hemihydrate, melting at about 237—238.5°C.

EXAMPLE 13

200 Mg. of a representative compound, e.g. N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]succinimide hydrochloride or 3-[1-(3-cyano-3,3-diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 3H - 1,2,3 - benzotriazin - 4-one hydrochloride, were dissolved in 165 ml. of alcohol. To the resultant solution was added 450 ml. of glycerine. The mixture was stirred thoroughly while 1.0 ml. of cherry flavor and sufficient sorbitol solution to bring the total volume to 1000 ml. were added. The pH was adjusted to 8.5 to 9.0 using sodium or potassium hydroxide solution and the liquid was filtered. There was thus obtained a liquid having a concentration of active ingredient of 1 mg./5cc.

When the above procedure was repeated using 500 mg. of the active ingredient, 175 ml. of alcohol, 450 ml. of glycerin, 1.5 ml. of cherry flavor and sufficient sorbitol solution to bring the total volume to 1000 ml, there was obtained a liquid having a concentration of active ingredient of 2.5 mg./5cc.

EXAMPLE 14

2.5 Grams of a representative compound, e.g. N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]succinimide hydrochloride or 3-[1-(3-cyano-3,3-diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy] - 3H - 1,2,3 - benzotriazin - 4-one hydrochloride, were mixed with 37.19 grams of powdered sucrose and 22.05 grams of corn starch, then screened and remixed. The mixture was granulated with 0.63 gram of polyvinylpyrrolidone in ethanol, then dried and screened. 0.63 Gram of magnesium stearate was added and the product was remixed and compressed into tablets of the appropriate size. There was thus obtained a batch of 1000 tablets having a concentration of active ingredient of 2.5 mg./tablet.

When the above procedure was repeated using 1 gram of the active ingredient, 38.69 grams of powdered sucrose, 22.05 grams of corn starch, 0.63 gram of polyvinylpyrrolidone and 0.63 gram of magnesium stearate, there was obtained a batch of 1000 tablets having a concentration of active ingredient of 1.0 mg./tablet.

When the procedure of the first paragraph of this Example was repeated utilizing 2.5 grams of the active ingredient premixed with 25 mg. of atropine sulfate, 37.165 grams of powdered sucrose, 22.05 grams of corn starch, 0.63 gram of polyvinylpyrrolidone and 0.63 gram of magnesium stearate, there was obtained a batch of 1000 tablets having a concentration of 2.5 mg. of active ingredient and .025 mg. of atropine sulfate per tablet.

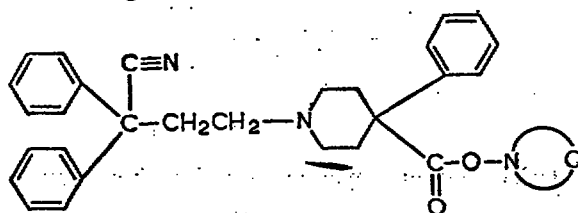
EXAMPLE 15

1.0 Gram of a representative compound, e.g. N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide hydrochloride or 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride, and 249 grams of corn starch were mixed, screened remixed and filled into No. 2 hard gelatin capsules by hand or machine using 250 mg. fill per capsule. There was thus obtained a batch of 1000 capsules having a concentration of active ingredient of 1.0 mg./capsule.

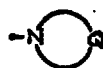
Repetition of the above procedure using 2.5 grams of the active ingredient and 247.5 grams of corn starch afforded a batch of 1000 capsules having a concentration of active ingredient of 2.5 mg./capsule.

WHAT WE CLAIM IS:—

1. A compound of the general formula

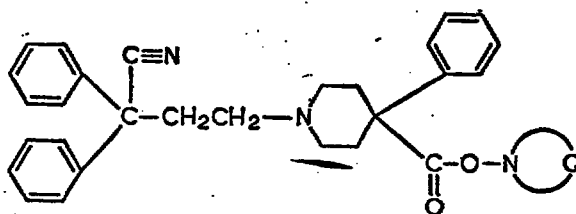


and the acid addition salts thereof, wherein



represents an optionally substituted monocyclic- or fused polycyclic-heterocyclic radical containing at least one carbonyl function adjacent the nitrogen atom.

2. A compound of the general formula



and the acid addition salts thereof, wherein

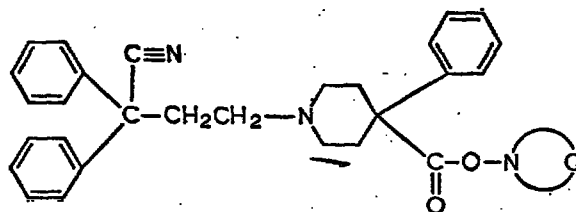


represents a succinimido, glutarimido, phthalimido, endo-5-norbornene-2,3-dicarboximido, 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl or 3,4-dihydro-4-oxo-quinazolin-3-yl radical.

3. N - [1 - (3 - Cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]succinimide and the hydrochloride salt thereof.

4. 3 - [1 - (3 - Cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]-3H-1,2,3-benzotriazin-4-one and the hydrochloride salt thereof.

5. A process for the preparation of a compound of the general formula





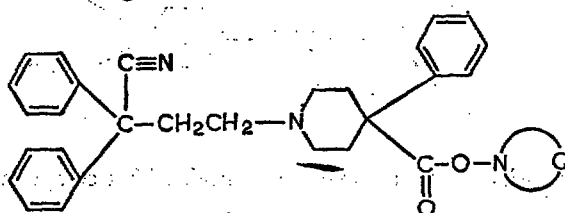
EXAMPLE 15

1.0 Gram of a representative compound, e.g. N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]succinimide hydrochloride or 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one hydrochloride, and 249 grams of corn starch were mixed, screened remixed and filled into No. 2 hard gelatin capsules by hand or machine using 250 mg. fill per capsule. There was thus obtained a batch of 1000 capsules having a concentration of active ingredient of 1.0 mg./capsule.

Repetition of the above procedure using 2.5 grams of the active ingredient and 247.5 grams of corn starch afforded a batch of 1000 capsules having a concentration of active ingredient of 2.5 mg./capsule.

WHAT WE CLAIM IS:—

1. A compound of the general formula

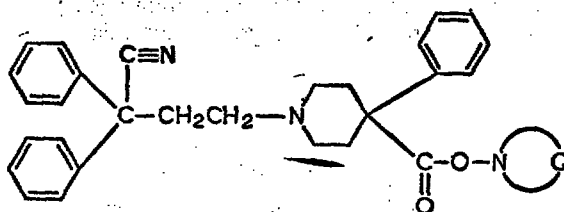


and the acid addition salts thereof, wherein



represents an optionally substituted monocyclic- or fused polycyclic-heterocyclic radical containing at least one carbonyl function adjacent the nitrogen atom.

2. A compound of the general formula



and the acid addition salts thereof, wherein

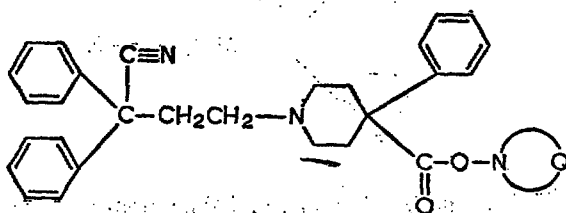


represents a succinimido, glutarimido, phthalimido, endo-5-norbornene-2,3-dicarboximido, 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl or 3,4-dihydro-4-oxo-quinazolin-3-yl radical.

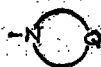
3. N - [1 - (3 - Cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]succinimide and the hydrochloride salt thereof.

4. 3 - [1 - (3 - Cyano - 3,3 - diphenylpropyl) - 4 - phenylpiperidine - 4 - carbonyloxy]-3H-1,2,3-benzotriazin-4-one and the hydrochloride salt thereof.

5. A process for the preparation of a compound of the general formula



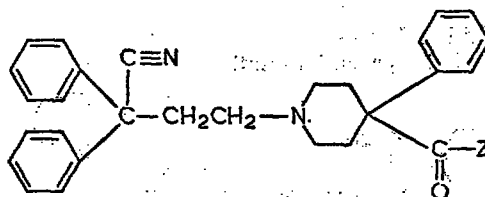
and the acid addition salts thereof, wherein



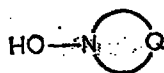
represents an optionally substituted monocyclic- or fused polycyclic-heterocyclic radical containing at least one carbonyl function adjacent the nitrogen atom, which comprises

a process selected from the group consisting of:

(a) contacting a compound of the general formula



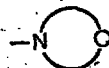
wherein Z is a chlorine atom or a hydroxy radical, with a compound of the formula



10

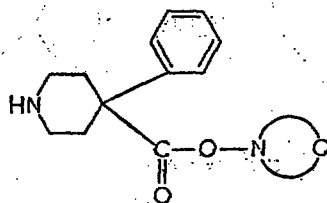
wherein

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is defined as above, with the proviso that when Z is a hydroxy radical, the reaction is conducted in the presence of a suitable dehydrating agent;

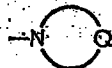
(b) contacting a compound of the general formula



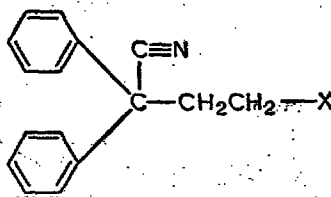
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wherein

15



is defined as above, with a compound of the formula



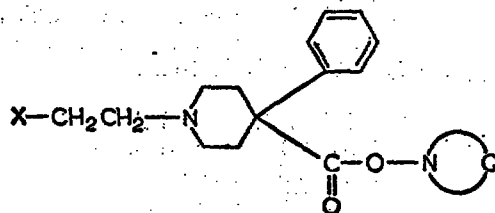
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wherein X represents a chlorine, bromine or iodine atom or a methanesulfonyloxy or toluenesulfonyloxy radical; and

20



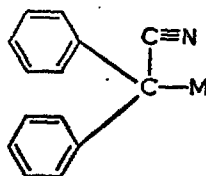
(c) contacting a compound of the general formula



wherein X and

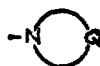


are defined as above, with a compound of the general formula



wherein M is an active metal ion.

6. A process according to Claim 5 wherein



represents a succinimido, glutarimido, phthalimido, endo-5-norbornene-2,3-dicarboximido, 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl or 3,4-dihydro-4-oxo-quinazolin-3-yl radical.

7. The process for the preparation of N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide which comprises contacting N-hydroxysuccinimide with 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid in the presence of dicyclohexylcarbodiimide.

8. The process for the preparation of N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide which comprises contacting N-hydroxysuccinimide with 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid chloride hydrochloride.

9. The process for the preparation of N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide which comprises contacting N-(4-phenylpiperidine-4-carboxyloxy)succinimide with 4-bromo-2,2-diphenylbutyronitrile.

10. The process for the preparation of N-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]succinimide which comprises contacting the α -sodium derivative of diphenylacetonitrile with N-[1-(2-bromoethyl)-4-phenylpiperidine-4-carboxyloxy]succinimide.

11. The process for the preparation of 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one which comprises contacting 3-hydroxy-3H-1,2,3-benzotriazin-4-one with 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid in the presence of dicyclohexylcarbodiimide.

12. The process for the preparation of 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one which comprises contacting 3-hydroxy-3H-1,2,3-benzotriazin-4-one with 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid chloride hydrochloride.

13. The process for the preparation of 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxyloxy]-3H-1,2,3-benzotriazin-4-one which comprises con-



tacting 3 - (4 - phenylpiperidine - 4 - carbonyloxy) - 3H - 1,2,3 - benzotriazin - 4 - one with 4-bromo-2,2-diphenylbutyronitrile.

14. The process for the preparation of 3-[1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one which comprises contacting the α -sodium derivative of diphenylacetonitrile with 3-[1-(2-bromoethyl)-4-phenylpiperidine-4-carbonyloxy]-3H-1,2,3-benzotriazin-4-one.

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