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[54] **IMIDAZOLIDINONE DERIVATIVES IN THE TREATMENT OF EMESIS AND PSYCHOSOMATIC DISTURBANCES**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.** **A61u 27/00**

[58] **Field of Search** 424/250

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[57] **ABSTRACT**

Compounds of the class of 1-[2-[4-[3-(p-fluorobenzoyl)-alkyl]-1-piperazinyl]-ethyl]-3-alkyl-2-imidazolidinone which may be substituted in the 4-position of the imidazolidinone ring by an alkyl group having 1 to 4 carbon atoms and pharmaceutically acceptable acid addition salts thereof have an antiemetic action and also a moderate central depressant action, e.g. they inhibit motility. They moreover exhibit no cataleptic inherent action. Such compounds can be prepared for instance by reaction of 1-[2-(1-piperazinyl)-ethyl]-3-methyl-2-imidazolidinone with 4-chloro-4'-fluorobutyrophenone. The compounds are active ingredients of pharmaceutical compositions.

2 Claims, No Drawings

IMIDAZOLIDINONE DERIVATIVES IN THE TREATMENT OF EMESIS AND PSYCHOSOMATIC DISTURBANCES

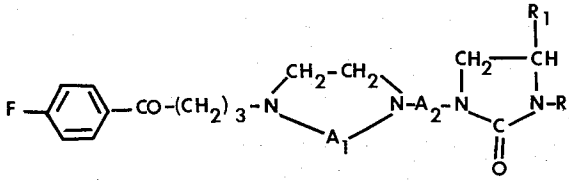
CROSS-REFERENCE TO RELATED APPLICATION

This is a division of application Ser. No. 203,870, filed Dec. 1, 1971, now U.S. Pat. No. 3,812,126.

DETAILED DESCRIPTION

The present invention relates to new imidazolidinone derivatives, to processes for their production, to pharmaceutical compositions containing the new compounds, and to the use thereof.

More particularly, the present invention relates to imidazolidinone derivatives of formula I



(I)

wherein

A_1 represents an alkylene group having 2 to 3 carbon atoms,

A_2 represents an alkylene group having 2 to 4 carbon atoms,

R represents an alkyl group having 1 to 4 carbon atoms, and

represents hydrogen, or an alkyl group having 1 to 4 carbon atoms,

and the pharmaceutically acceptable acid addition salts thereof.

As alkylene radicals having 2 to 3 carbon atoms in the compounds of formula I, A_1 and A_2 are: the ethylene, trimethylene or propylene group; and as an alkylene radical having 4 carbon atoms, A_2 is the tetramethylene, the ethyl ethylene, or a methyl-trimethylene group. Furthermore, both R and R_1 as an alkyl group are the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or the sec.butyl group.

Preferred members of this class are:

1. 1-[2-[4-[3-(p-fluoro-benzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone.
2. 1-[2-[4-[3-(p-fluoro-benzoyl)-propyl]-1-piperazinyl]-ethyl]-3-ethyl-2-imidazolidinone.
3. 1-[2-[4-[3-(p-fluoro-benzoyl)-propyl[-1-piperazinyl]-ethyl]-3-n-butyl-2-imidazolidinone.
4. 1-[3-[4-[3-(p-fluoro-benzoyl)-propyl]-1-piperazinyl]-propyl]-3-methyl-2-imidazolidinone.
5. 1-[2-[4-[3-(p-fluoro-benzoyl)-propyl]-1-piperazinyl]-ethyl]-3-isopropyl-2-imidazolidinone.
6. 1-[3-[4-[3-(p-fluoro-benzoyl)-propyl]-1-piperazinyl]-propyl]-3-ethyl-2-imidazolidinone.

and the pharmaceutically acceptable acid addition salts thereof.

Compounds of the formula I and the pharmaceutically acceptable acid addition salts thereof have valuable pharmacological properties and a high therapeutic index.

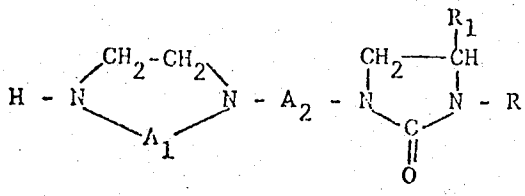
In the case of oral, rectal or parenteral administration, they have an anti-emetic action, as was determined in the apomorphine-vomiting test in the case of the dog and the golden hamster; the said compounds also have a moderate central depressant action, e.g. they inhibit motility. They moreover exhibit no cataleptic inherent effect. These properties, which can be shown by selected standard tests [cp. W. Theobald et al., Arzneimittelforsch. 17, 561 (1967)], characterise the said compounds as being suitable for the treatment of emesis of varying origin, and of psychosomatic disturbances.

The test results indicated in the following table are illustrative, and illustrative only, of the pharmaceutical activity of the subject compounds. The compounds 1 to 6 in the table are the compounds 1 to 6 listed above, compounds 1 to 3, 5 and 6 being for the purposes of testing in the form of their dihydrochloride salt and compound 4 in the form of its bis-maleinate salt.

TABLE

Compound No.	50% decrease of orientation motility after i.p. administration on mice; dose in mg/kg	Adrenolytic activity on isolated organs in comparison with REGITIN = 1	Antagonistic activity in the apomorphine-vomiting test caused by s.c. application, dose ED 50 in mg/kg, 30 minutes before s.c. application of 0,1 mg/kg of apomorphine-hydrochloride	
			golden hamster	dog
1	2	20:1	3,76	0,012
2	4,1	6:1	3,5	
3	3,65	7:1	2,5	0,013
4		3:1	>50	0,23
5	3,3	15:1	6,01	0,022
6	14	5:1	44,4	0,17

Compounds of the formula I are produced in the case of the first process according to the invention by the reaction of compounds of formula II:



(II)

wherein A_1, A_2, R and R_1 have the meanings given under formula I, or of the alkali metal derivative of such a compound, with a reactive ester of 3-(p-fluorobenzoyl)-propanol. The product may, optionally, be converted with an inorganic or organic acid into an addition salt.

Suitable reactive esters of 1-(p-fluorobenzoyl)-propanol are, for example, halides such as the chloride or bromide, also sulphonic acid esters, e.g. the methanesulphonic acid ester, or the o- or p-toluenesulphonic acid ester. These esters are reacted with the free bases of the formula II preferably in the presence of a solvent. Suitable solvents are those which are inert under the reaction conditions, e.g. hydrocarbons such as benzene or toluene, halogenated hydrocarbons such as chloroform, ethereal liquids such as ether or dioxane, as well as lower alkanones, particularly diethyl ketone.

In the reaction according to the invention of one molecular equivalent of reactive ester with one molecular equivalent of free base, one molecular equivalent of acid is split off. This acid can be bound to excess base of the formula II, or to the dibasic reaction product. Preferably, however, an acid-binding agent is added to the reaction mixture. Suitable acid-binding agents are, e.g. alkali metal carbonates such as sodium or potassium carbonate, also tertiary organic bases such as, e.g. pyridine, triethylamine or diisopropylethylamine. Excess tertiary bases may also be used as solvent.

Optionally, the reaction can be accelerated by an alkali iodide, especially potassium iodide. The reaction is performed at ca. 50° to 150°C, preferably at the boiling point of the solvent.

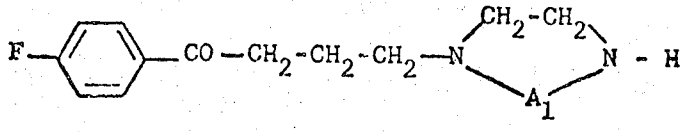
If for the reaction according to the invention is used, instead of the free base of the formula II, an alkali metal derivative thereof, e.g. a sodium, potassium or lithium derivative, then it is advantageous for the reaction to be performed in a hydrocarbon, e.g. in benzene or toluene.

The formation of the alkali metal derivatives of the first reaction component is effected preferably in situ, e.g. by the addition of at least one molecular equivalent of alkali metal hydride, alkali metal amide or of an alkali metal organic compound, when starting with one molecular equivalent of a free base. For example, as alkali metal amides are used sodium and lithium amide, as alkali metal hydrides is used sodium hydride, and as alkali metal organic compound phenyllithium or butyllithium.

Examples of compounds of the formula II which are known are, e.g. 1-[2-(1-piperazinyl)-ethyl]-3-methyl-2-imidazolidinone, 1-[3-(1-piperazinyl)-propyl]-3-methyl-2-imidazolidinone, as well as the corresponding 3-ethyl compounds; they can be produced by various processes. Further compounds of this type can be obtained analogously.

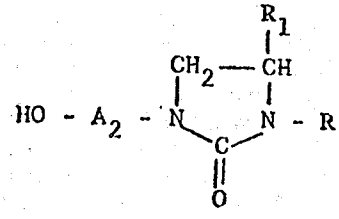
Of the reactive esters suitable as the second reaction component, 4-chloro-4'-fluorobutyrophenone [cp. C. van de Westeringh et al., Ind. chim. belge 25, 1073 (1960)], for example, is described in the literature.

In a second process according to the invention, compounds of the general formula I are produced by reacting a compound of the formula III:



(III)

wherein A_1 has the meaning stated under formula I, or an alkali metal derivative thereof with a reactive ester of a compound of the formula IV:



(IV)

wherein A_2, R and R_1 have the meaning given under formula I, followed by optional conversion of the obtained product with an inorganic or organic acid into an addition salt.

Suitable reactive esters of the compounds of the formula IV are, e.g. halides such as chlorides or bromides, also sulphonic acid esters, e.g. the methanesulphonic acid ester or the o- or p-toluene-sulphonic acid ester.

The reaction according to the invention of the free bases, or of their alkali metal derivatives can be performed in the same solvents or diluents, and at the same reaction temperatures, as in the first process. With the condensation of one molecular equivalent of free base with one molecular equivalent of reactive ester, one molecular equivalent of free acid is split off, which can be bound to the same acid-binding agents as in the case of the first process.

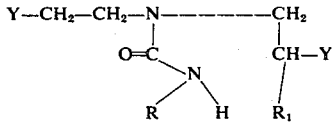
The alkali metal derivatives of the first reaction component, e.g. sodium, potassium or lithium derivatives, are preferably used in situ in the process according to the invention. These alkali metal derivatives can be ob-

tained in a manner analogous to that for the alkali metal derivatives of the first process.

Of the bases embraced by the formula III, 4'-fluoro-4-(1-piperazinyl)-butyrophenone is known. Further compounds of this type can be produced analogously.

The second reaction component of the process according to the invention is the reactive esters of compounds of the formula IV. Of these compounds, 1-(2-chloroethyl)- and 1-(3-chloropropyl)-3-methyl-2-imidazolidinone, as well as 1-(2-chloroethyl)-3-butyl-2-imidazolidinone, are, for example, known, and can be produced by various processes. Further compounds of this type can be produced analogously.

Compounds of the formula I of which the radical A_2 is an ethylene group can be produced by a third process according to the invention by the reaction of a compound of the previously given formula III, wherein A_1 represents an alkylene group having 2 to 3 carbon atoms, or an alkali metal derivative thereof, with a compound of the general formula V:



(V)

wherein

R represents an alkyl group having 1 to 4 carbon atoms,

R_1 represents hydrogen or an alkyl group having 1 to 4 carbon atoms, and

Y represents halogen,

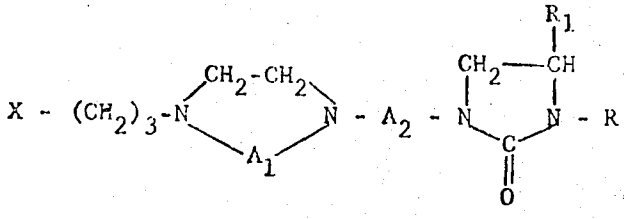
or with an alkali metal derivative of such a compound; and, followed by optional conversion of an obtained product with an inorganic or organic acid into an addition salt.

The radical Y of the general formula V is a halogen, preferably chlorine or bromine.

The reaction according to the invention of the free bases of the formula III, or of their alkali metal derivatives, with the urea derivatives or their alkali metal derivatives can be performed in the same solvents or diluents, and at the same reaction temperatures, as in the case of the first process. With the reaction of one molecular equivalent of free base with one molecular equivalent of the free urea derivative, two molecular equivalents of hydrogen halide are split off, which can also be bound to the same acid-binding agents. Both reaction components are used as alkali metal derivatives, e.g. sodium, potassium or lithium derivatives, preferably in situ, in the process according to the invention. These alkali metal derivatives can be obtained analogously to the alkali metal derivatives of the first process.

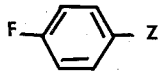
The preparation of the starting materials of the formula III is described following the second process. A starting material embraced by the general formula V is 1-methyl-3,3-bis-(2-chloroethyl)-urea, which can be obtained starting with diethanolamine. Diethanolamine yields, with 1-methylisocyanate: 1-methyl-3,3-bis-(2-hydroxyethyl)-urea, which reacts with thionyl chloride with elimination of sulphur dioxide and hydrogen chloride. Further starting materials of the formula V can be produced analogously.

According to a fourth process, compounds of the formula I are produced by the reaction, according to Grignard, of a compound of the general formula VI:



(VI)

with a compound of the formula VII:



(VII)

wherein

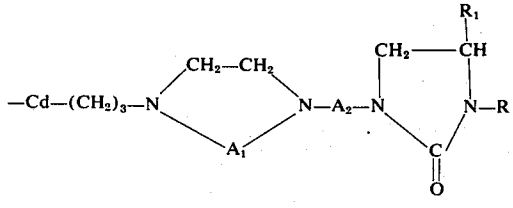
A_1, A_2, R and R_1 have the meaning given under under formula I, and one of the two groups

X or Z represents a nitrile or carbonylhalide group, and the other a magnesium halide radical (—MgHal), zinc halide radical (—ZnHal), or a metal-organic cadmium radical;

with optional conversion of the obtained product with an inorganic or organic acid into an addition salt,

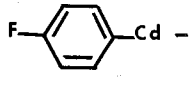
The halides used in the process are preferably chlorides, bromides or iodides.

As metal-organic cadmium radical, X is e.g. the group VIII:



(VIII)

wherein A_1, A_2, R and R_1 have the meaning given under formula I, and Z the group IX:



(IX)

The zinc halide compounds and the cadmium organic compounds are preferably reacted with carbonyl halides, and the magnesium halide compounds preferably with nitriles.

The process according to the invention is carried out under the usual conditions of the Grignard reaction at ca. 0° to 140°C. The usual ethereal solvents suitable for the preparation of the magnesium-organic compounds, such as ether, dibutyl ether or tetrahydrofuran, can be

used as reaction media. Optionally, hydrocarbons, such as benzene or toluene, can be added to these solvents, and the reaction temperature raised, towards the end of the reaction, by the distilling off of the ether. The decomposition of the direct reaction products is effected in the usual manner, e.g. with the aid of water and dilute hydrochloric acid.

Of the starting materials embraced by the general formula VI, it is possible to produce, for example, compounds of which the symbols X and A_1 represent —MgCl and —CH_2CH_2—, respectively, as follows: Starting with 1-piperazinepropanol [cp. S. M. McElvain and L. W. Bannister, J. Am. Chem. Soc. 76, 1126 (1954)], this is condensed, in the presence of potassium carbonate, with a chloride of a compound of the formula IV. The condensation product is a compound embraced by the formula VI of which the symbols X and A_1 are —OH and —CH_2CH_2—, resp. The obtained compound is converted into the dihydrochloride and transformed with thionyl chloride into the corresponding compound of which the radical X is chlorine. The chloride is subsequently reacted with magnesium according to Grignard. Further compounds of this type can be produced analogously.

Also embraced by the formula VI are compounds of which the symbols X and A_1 are —CN and —CH_2CH_2—, respectively. Such compounds can be produced, e.g. from the corresponding chlorides, the preparation of which has already been described, by means of calcium cyanide.

The starting compounds embraced by the formula VII of which compounds the symbol Z is —CN or —MgBr are described in the literature. The starting material embraced by the general formula VII and of which the symbol Z is the group IX can be produced as follows: Starting wiith p-fluorophenylmagnesium bromide, this is reacted in an ethereal solution with cadmium chloride.

The compounds of the formula I obtained by the processes according to the invention are, optionally, subsequently converted in the usual manner into their addition salts with inorganic and organic acids. For example, to a solution of a compound of the formula I in an organic solvent is added the acid desired as salt component, or a solution of the acid. Preferably chosen for the reaction are organic solvents, in which the formed salt is difficultly soluble, so that it can be separated by filtration. Such solvents are, e.g. methanol, acetone, methyl ethyl ketone, acetone/ether, acetone/ethanol, methanol/ether or ethanol ether.

For use as pharmaceutical compositions, it is possible to use, instead of free bases, pharmaceutically acceptable acid addition salts, i.e. salts with such acids of which the anions are not toxic in the case of the dosage amounts in question. It is moreover of advantage if the salts to be used as pharmaceutical compositions, crystallise well and are not, or only slightly, hygroscopic. For salt formation with compounds of the formula I, it is possible to use, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

As previously mentioned, the new active substances are administered orally, rectally or parenterally. The dosage depends on the manner of administration, on the species, on the age, and on the individual condition. The daily dosages of the free bases, or of pharmaceutically acceptable salts thereof, vary between 0.15 mg/kg and 10.5 mg/kg for warm-blooded animals. Suitable dosage units such as dragees, tablets, suppositories or ampoules, preferably contain 5–200 mg of an active substance according to the invention.

Dosage units for oral administration contain as active substance preferably between 10–90% of a compound of the formula I, or of a pharmaceutically acceptable salt thereof. They are produced by combining the active substance, e.g. with solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate, or polyethylene glycols, to form tablets or dragee cores. The dragee cores are coated, e.g. with concentrated sugar solutions which may also contain, e.g. gum arabic, talcum and/or titanium dioxide; or with a lacquer dissolved in readily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance.

Further dosage units suitable for oral administration are hard gelatine capsules, as well as soft closed capsules made from gelatine and a softener, such as glycerin. The hard capsules preferably contain the active substance as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate, and optionally stabilisers such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as polyethylene glycols, whereby stabilisers may also be added.

Suitable dosage units for rectal administration are, e.g. suppositories consisting of a combination of an active substance with a suppository base material. Suitable suppository base materials are, e.g. natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols, or higher alkanols. Also suitable are gelatine rectal capsules consisting of a combination of the active substance with a base material. Suitable as a base material are, e.g. liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Ampoules for parenteral administration, especially intramuscular administration, preferably contain a water-soluble salt of an active substance in a concentration of preferably 0.5–5%, optionally together with suitable stabilisers and buffer substances, in aqueous solution.

The following prescriptions further illustrate the production of tablets, dragees, capsules, suppositories and ampoules:

a. 250 g of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone are mixed with 175.8 g of lactose and 169.70 g of potato starch; the mixture is then moistened with an alcoholic solution of 10 g of stearic acid, and granulated through a sieve. After drying of the granulate, 160 g of potato starch, 200 g of talcum, 2.50 g of magnesium stearate and 32 g of colloidal silicon dioxide are mixed in; the mixture is subsequently pressed into 10,000 tablets each weighing 100 mg and each containing 25 mg of active substance. The tablets can, if required, by pro-

vided with grooves for a more precise adjustment of the dosage amount.

b. A granulate is produced from 250 g of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone-dihydrochloride, 175.90 g of lactose, and the alcoholic solution of 10 g of stearic acid. After drying of the granulate, it is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate; the mixture is then pressed into 10,000 dragee cores. These are subsequently coated with a concentrated syrup made from 502.28 g of crystallised saccharose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide; they are then dried. The obtained dragees each weigh 120 mg and each contain 25 mg of active substance.

c. To produce 1000 capsules each containing 25 mg of active substance, 25 g of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone are mixed with 248.0 g of lactose; the mixture is evenly moistened with an aqueous solution of 2.0 g of gelatine, and then granulated through a suitable sieve (e.g. sieve III, Ph.Helv. V). The granulate is mixed with 10.0 g of dried maize starch and 15.0 g of talcum; the mixture is then evenly filled with 1000 hard gelatine capsules, size 1.

d. A suppository base mixture is prepared from 2.5 g of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl-3-methyl-2-imidazolidinone and 167.5 g of adeps solidus; the mixture is then filled into 100 suppositories each containing 25 mg of active substance.

e. A solution of 25 g of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone-dihydrochloride in one litre of water is filled into 1000 ampoules, and then sterilised. An ampoule contains a 2.5% solution of 25 mg of active substance.

Tablets, dragees, capsules, suppositories and ampoules can be produced according to the same directions if, instead of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone, the identical amounts are used of 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-butyl-2-imidazolidinone or of its dihydrochloride.

The following examples further illustrate the production of the new compounds of the formula I and of intermediates not hitherto described; the said examples do not, however, in any way restrict the scope of the invention. The temperatures are given in degrees Centigrade; and silica gel, Merck, particle size 0.05–0.2 mm, is employed for the elution chromatography.

EXAMPLE 1

21.2 g (0.1 mole) of 1-[2-(1-piperazinyl)-ethyl]-3-methyl-2-imidazolidinone, 24.0 g (0.12 moles) of 4-chloro-4'-fluorobutyrophenone [cp. C van de Westeringh et al., Ind. chim. belge 25, 1073 (1960)], 27.6 g (0.2 moles) of finely powdered potassium carbonate and 16.6 g (0.1 mole) of powdered potassium iodide are introduced into 200 ml of diethyl ketone. The obtained mixture is refluxed for 30 hours, and then filtered through Celit No. 545 (trade name of Johns Manville International Corp., New York). The filter residue is afterwards washed with acetone, and the filtrate concentrated in vacuo. The residue is taken up in benzene, the benzene solution washed with water, and extracted with 2-*n* hydrochloric acid. The pH-value of the aqueous extract is adjusted to **13** with concentrated sodium hydroxide solution, and the precipitated free base is taken up in benzene. The benzene solution is washed with water, dried over magnesium sulphate, and concentrated in vacuo. The residue is recrystallised from benzene/petroleum ether. The obtained pure 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl-3-methyl-2-imidazolidinone melts at 92°–93°.

An amount of 3.7 g (0.01 mole) of the obtained free base is dissolved in 5 ml of acetone; to the solution is then added ethereal hydrochloric acid until an acid reaction is obtained on a congo-red indicator. The precipitated dihydrochloride hemihydrate melts at 226°–230°.

EXAMPLE 2

The following final products are obtained, analogously to Example 1, starting with 15.0 g (0.075 moles) of 4-chloro-4'-fluorobutyrophenone:

a. with 11.3 g (0.05 moles) of 1-[2-(1-piperazinyl)-ethyl]-3-ethyl-2-imidazolidinone is obtained: 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-ethyl-2-imidazolidinone, M.P. 65°–67°; M.P. of the dihydrochloride-hemihydrate = 236°–238°;

b. with 12.7 g (0.05 moles) of 1-[2-(1-piperazinyl)-ethyl]-3-butyl-2-imidazolidinone is obtained: crude 1-[2-[4-[3-(o-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-butyl-2-imidazolidinone, which is purified by means of elution chromatography. A column of 200 g of basic silica gel is employed which has previously been impregnated with 0.5-*n* aqueous sodium hydroxide and again dried. Benzene/methanol (100:1) is used as the elution agent. The eluate is concentrated in vacuo, the residue dissolved in acetone, and to the solution then added ethereal hydrochloric acid until an acid reaction is indicated on a congo-red indicator. The precipitated dihdyrochloride is recrystallised from ethanol/ethyl acetate; it melts at 235°–237°;

c. with 12.0 g (0.05 moles) of 1-[2-(1-piperazinyl)-ethyl]-3-isopropyl-2-imidazolidinone is obtained: 1-[2-[4-[3-(p-fluorobenzoyl)propyl]-1-piperazinyl]-ethyl]-3-isopropyl-2-imidazolidinone, M.P. 61°–64°; M.P. of the dihydrochloride = 247°–250°;

d. with 11.3 g (0.05 moles) of 1-[3-(1-piperazinyl)-propyl]-3-methyl-2-imidazolidinone is obtained: crude 1-[3-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-propyl]-3-methyl-2-imidazolidinone; the crude base is dissolved in 50 ml of acetone, and to the solution is then added a solution of maleic acid in acetone until an acid reaction is obtained, whereupon ether is added. The precipitated 1-[3-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-propyl]-3-methyl-2-imidazolidinone-dimaleate is recrystallised from ethanol/ethyl acetate; it melts at 164°–166°;

e. with 12.0 g (0.05 moles) of 1-[3-(1-piperazinyl)-propyl]-3-ethyl-2-imidazolidinone is obtained: crude 1-[3-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-propyl]-3-ethyl-2-imidazolidinone; M.P. of the dihydrochloride = 244°–246°; and

f. with 13.40 g (0.05 moles) of 1-[3-(1-piperazinyl)-propyl]-3-butyl-2-imidazolidinone is obtained: crude 1-[3-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-propyl]-3-butyl-2-imidazolidinone; M.P. of the dihydrochloride = 236°–240°.

EXAMPLE 3

a. From 11.3 g (0.05 moles) of 1-[2-(hexahydro-1H-1,4-diazepin-1-yl)-ethyl]-3-methyl-2-imidazolidinone and 15.0 g (0.075 moles) of 4-chloro-4'-fluorobutyrophenone is obtained, analogously to Example 1(a), crude 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-hexahydro-1H-1,4-diazepin-1-yl]-ethyl]-3-methyl-2-imidazolidinone, which is purified on a column of 200 g of basic silica gel (impregnated with sodium hydroxide) by elution chromatography. The elution agent used is benzene/methanol (100:2). The eluate is concentrated in vacuo, the residue (8.0 g) dissolved in acetone, and the dimaleate precipitated with 4.63 g (0.04 moles) of maleic acid. The dimaleate is recrystallised from methanol/ethyl acetate, whereupon it melts at 104°–106°.

The starting product is produced as follows:

b. 17.2 g (0.1 mole) of hexahydro-1H-1,4-diazepine-1-carboxylic acid ethyl ester [cp. R. B. Angier et al., J. Med. Chem. 11, 720 (1968)], 19.4 g (0.12 moles) of 1-(2-chloroethyl)-3-methyl-2-imidazolidinone and 27.6 g of potassium carbonate are refluxed in 50 ml of diethyl ketone for 24 hours. The hot reaction mixture is then filtered through purified diatomaceous earth, the filter residue extracted three times with benzene, and the combined filtrates concentrated in vacuo. The oily residue is distilled in high vacuum. The obtained 4-[2-(2-oxo-3-methyl-1-imidazolidinyl)-ethyl]-hexahydro-1H-1,4-diazepine-1-carboxylic acid ethyl ester boils at 170°–180°/0.01 Torr; n_D^{25}: 1.5030.

c. An amount of 25.0 g (0.084 moles) of the compound obtained according to (b) is refluxed with 200 ml of abs. ethanolic potassium hydroxide solution (20 g of potassium hydroxide to 100 ml of solution) for 20 hours. The reaction mixture is then cooled and concentrated in vacuo. The residue is taken up in benzene and water, and the organic phase separated; the aqueous phase is saturated with potassium carbonate and extracted with benzene. The benzene extract is dried over potassium carbonate, the solvent evaporated off in vacuo, and the oily residue distilled in high vacuum. The pure 1-[2-(hexahydro-1H-1,4-diazepin-1-yl)-ethyl]-3-methyl-2-imidazolidinone boils at 125°–128°/0.01 Torr; n_D^{25}: 1.5163.

EXAMPLE 4

From 11.3 g (0.05 moles) of 1-[2-(3-methyl-1-piperazinyl)-ethyl]3-methyl-2-imidazolidinone and 15 g (0.075 moles) of 4-chloro-4'-fluorobutyrophenone is obtained, analogously to Example 3(a), 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-3-methyl-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone-dimaleate. The starting material, 1-[2-(3-methyl-1-piperazinyl)-ethyl]-3-methyl-2-imidazolidinone, B.P. 142°/0.01 Torr, n_D^{24}: 1.5115, is produced analogously to Example 3(b–c). Starting with 3-methyl-1-piperazine-carboxylic acid ethyl ester [cp. J. C. Duff and D. K. Jung, Can. Pharm. J. 95, 256 (1962)], the intermediate 4-[2-(2-oxo-3-methyl-1-imidazolidinyl)-ethyl]-3-methyl-1-piperazine-carboxylic acid ethyl ester is obtained, B.P. 170°–180°/0.01 Torr; n_D^{25}: 1.4996.

EXAMPLE 5

An amount of 25.0 g (0.1 mole) of 4'-fluoro-4-(1-piperazinyl)-butyrophenone is refluxed with 19.4 g (0.12 moles) of 1-(2-chloroethyl)-3-methyl-2-imidazolidinone and 27.6 g (0.2 moles) of potassium carbonate in 200 ml of diethyl ketone for 24 hours. The hot reaction mixture is filtered through purified diatomaceous earth, the residue washed three times with hot benzene, and the combined filtrates concentrated in vacuo. The oily residue is taken up in benzene, the benzene solution washed with water, and extracted with 2-*n* hydrochloric acid. The acid aqueous extract is then rendered alkaline with concentrated sodium hydroxide solution, and the precipitated free base extracted with benzene. The benzene solution is washed with water, dried over magnesium sulphate, and concentrated in vacuo. The obtained residue is recrystallised from benzene/petroleum ether, whereupon the pure 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone melts at 92°–93°.

EXAMPLE 6

The following final product is obtained analogously to Example 5:

From 25.0 g (0.1 mole) of 4'-fluoro-4-(1-piperazinyl)-butyrophenone and 25.7 g (0.12 moles) of 1-(2-chloroethyl)-3-butyl-2-imidazolidinone is obtained: crude 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-butyl-2-imidazolidinone, which is purified through a column of 400 g of basic silica gel by means of elution chromatography. The eluant used is benzene/methanol (100:1). The purified base is converted, analogously to Example 2(b), into its dihydrochloride which, after recrystallisation from ethanol-ethyl acetate, melts at 235°–237°.

EXAMPLE 7

a. An amount of 12.5 g (0.05 moles) of 4'-fluoro-4-(1-piperazinyl)-butyrophenone is refluxed with 11.9 g (0.06 moles) of 1-methyl-3,3-bis-(2-chloroethyl)-urea and 27.6 g (0.2 moles) of potassium carbonate in 200 ml of diethyl carbonate for 16 hours. The hot reaction mixture is then filtered through purified diatomaceous earth, the filter residue washed with hot benzene, and the combined filtrates are concentrated in vacuo. The residue is dissolved in benzene, the benzene solution extracted with 2-*n* hydrochloric acid, the acid aqueous extract made alkaline with concentrated sodium hydroxide solution, and the precipitated free base extracted by being shaken with benzene. The benzene extract is washed with water, dried over magnesium sulphate, and the benzene evaporated off under vacuum. The residue is chromatographed on a column of 200 g of basic silica gel, benzene/methanol (100:2) being used as eluant. The fractions containing the crude product are concentrated by evaporation, and the residue is recrystallised from benzene/petroleum ether. The obtained pure 1-[2 -[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone melts at 92°–93°.

The 1-methyl-3,3-bis-(2-chloroethyl)-urea required as starting material is produced as follows:

b. An amount of 105.1 g (1.0 mole) of freshly distilled diethanolamine is dissolved in 1000 ml of absolute methylene chloride. To this solution are added dropwise at 10°, in the course of 1 hour, 59.0 g (1.03 moles) of methylisocyanate dissolved in 200 ml of absolute methylene chloride. The reaction mixture is refluxed for 150 minutes and then cooled to 0°; to the obtained solution of 1-methyl-3,3-bis-(2-hydroxyethyl)-urea is then added dropwise, in the course of 1 hour,

a solution of 250 g (2.1 moles) of thionyl chloride in 250 ml of absolute methylene chloride. The reaction mixture is afterwards refluxed for 4 hours, concentrated in vacuo, and the residue, crude 1-methyl-3,3-bis-(2-chloroethyl)-urea, dried for 8 hours at 70°–80° under high vacuum.

EXAMPLE 8

a. The following final product is produced analogously to Example 7:

From 12.5 g (0.05 moles) of 4'-fluoro-4-(1-piperazinyl)-butyrophenone and 14.5 g (0.06 moles) of 1-butyl-3,3-bis-(2-chloroethyl)-urea is obtained: 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-butyl-2-imidazolidinone. The obtained crude base is dissolved in acetone; with ethereal hydrochloride acid is then produced the dihydrochloride, which is recrystallised from absolute ethanol/ethyl acetate, M.P. 235°–237°.

The 1-butyl-3,3-bis-(2-chloroethyl)-urea used as starting product is produced as follows:

b. An amount of 105.1 g (1.0 mole) of freshly distilled diethanolamine is dissolved in 1000 ml of absolute methylene chloride. To this solution are added dropwise at 10°, in the course of one hour, 101.9 g (1.03 moles) of butylisocyanate dissolved in 200 ml of absolute methylene chloride. The reaction mixture is refluxed for 150 minutes and then cooled to 0°; to the obtained solution of 1-butyl-3,3-bis-(2-hydroxyethyl)-urea is then added dropwise, during 1 hour, a solution of 250 g (2.1 moles) of thionyl chloride in 250 ml of absolute methylene chloride. The reaction mixture is then refluxed for 4 hours; it is afterwards concentrated in vacuo, and the residue, crude 1-butyl-3,3-bis-(2-chloroethyl)-urea, dried for 8 hours at 70°–80° under high vacuum.

EXAMPLE 9

a. 22.6 g (0.1 mole) of 1-[2-(1-piperazinyl)-ethyl]-3,4-dimethyl-2-imidazolidinone, 30.0 g (0.15 moles) of 4-chloro-4'-fluorobutyrophenone. 27.6 g (0.20 moles) of potassium carbonate and 16.6 g (0.1 mole) of potassium iodide are introduced into 200 ml of diethyl ketone and, with good stirring, refluxed for 24 hours. The hot reaction mixture is filtered through Celit, the residue boiled out twice with acetone, and filtered. The combined filtrates are concentrated in vacuo, and the oily residue is dissolved in 200 ml of benzene. After the addition of 10 ml of 2-*n* sodium hydroxide solution, the benzene solution is extracted three times with 100 ml of water each time. The organic phase is subsequently extracted with 200 ml of 2-*n* hydrochloric acid; the aqueous acid extracts are rendered strongly alkaline (pH 13) with concentrated sodium hydroxide solution, and again extracted with benzene. The organic solutions are washed with water, dried over magnesium sulphate, and concentrated in vacuo to dryness. The obtained crystalline residue is recrystallised from ether/-pentane, whereupon the obtained pure 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3,4-dimethyl-2-imidazolidinone melts at 73°–74°.

The dihydrochloride is obtained analogously to Example 1, M.P. 228°–235°.

The 1-[2-(1-piperazinyl)-ethyl]-3,4-dimethyl-2-imidazolidinone required as starting material is produced as follows:

b. An amount of 17.8 g (0.2 moles) of rac. 2-methylamino-1-propanol is dissolved in 30 ml of methylene chloride; to this solution is then added dropwise at 0° a solution of 23.2 g (0.22 moles) of 2-chloroethylisocyanate in 50 ml of methylene chloride. The reaction mixture is stirred for 2 hours at room temperature, concentrated in vacuo to dryness, and the crystallised residue recrystallised from ether. The obtained 1-(2-hydroxy-1-methyl ethyl)-1-methyl-3-(2-chloroethyl)-urea melts at 76°–78°.

c. An amount of 33.4 g (0.172 moles) of the obtained urea is dissolved in 80 ml of chloroform; to the solution is then added dropwise at 0°, with thorough stirring, a solution of 22.5 g (0.19 moles) of thionyl chloride in 50 ml of chloroform. The reaction mixture is brought to room temperature, and subsequently refluxed for 2 hours. The solvent is removed as completely as possible in vacuo, and the obtained oily residue (40 g) heated for 12 hours at 130°–140°. The dark reaction product is dissolved in chloroform, and the solution washed with a little saturated aqueous sodium chloride solution. The organic phase is dried over magnesium sulphate, and the solvent removed in vacuo. The obtained oily residue is distilled in a water-jet vacuum to obtain 1-(2-chloroethyl)-3,4-dimethyl-2-imidazolidinone, B.P. 151°–153°; $n = 1.4871$.

d. From 18.8 g (0.107 moles) of 1-(2-chloroethyl)-3,4-dimethyl-2-imidazolidinone and 18.5 g (0.117 moles) of 1-piperazinecarboxylic acid ethyl ester are obtained, analogously to Example 3(b), 26.7 g of 4-[2-(2-oxo-3,4-dimethyl-1-imidazolidinyl)-ethyl]-piperazinecarboxylic acid ethyl ester; B.P. 170°–180°/0.01 Torr; $n = 1.4968$. From this are obtained, analogously to Example 3(c), 18.2 g of 1-[2-(1-piperazinyl)-ethyl]-3,4-dimethyl-2-imidazolidinone; B.P. 130°–134°/0.01 Torr; $n = 1.5070$.

EXAMPLE 10

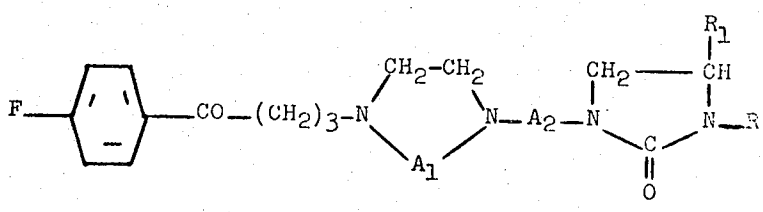
a. An amount of 17.5 g (0.1 mole) of p-fluorobromobenzene is slowly added dropwise, at reflux temperature, to 2.5 g (0.105 moles) of activated magnesium chips in 100 ml of absolute ether. The reaction mixture is boiled until practically all the magnesium is consumed; the mixture is then cooled to 0°, and a solution of 27.9 g (0.1 mole) of 1-[2-[4-(3-cyanopropyl)-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone in 200 ml of absolute tetrahydrofuran is added dropwise within 30 minutes. The obtained reaction mixture is refluxed for 12 hours, and afterwards poured on to a mixture of 200 ml of ice water and 100 ml of 2-*n* hydrochloric acid. The obtained acid mixture is allowed to stand for 1 hour at room temperature, and subsequently carefully concentrated at 40° in vacuo to a volume of 200 ml. The obtained solution is diluted with water, and extracted with ether. The aqueous phase is separated, rendered alkaline with concentrated ammonia, and extracted three times by being shaken with benzene. The benzene extracts are washed with water, dried over magnesium sulphate, and concentrated in vacuo to dryness. The obtained crystalline residue is dissolved in benzene, and the solution filtered through magnesium silicate "Woelm". The eluate is concentrated by evaporation, and the residue recrystallised from ethyl acetate/petroleum ether. The obtained pure 1-[2-[4-[3-(p-fluorobenzoyl)-propyl]-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone melts at 93°–96°.

The 1-[2-[4-(3-cyanopropyl)-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone required as starting material is produced as follows:

b. An amount of 21.2 g (0.1 mole) of 1-[2-(1-piperazinyl)-ethyl]-3-methyl-2-imidazolidinone is refluxed with 12.6 g (0.13 moles) of 4-chlorobutyronitrile and 27.6 g (0.2 moles) of potassium carbonate in 250 ml of diethyl ketone for 24 hours. The obtained mixture is filtered through Celit, and the filter residue washed out with acetone; the combined filtrates are dried over magnesium sulphate, and subsequently concentrated in vacuo to dryness. The obtained oily residue is dissolved in ethyl acetate, and the hydrochloride precipitated with ethanolic hydrochloric acid. After recrystallisation from ethanol-/ethyl acetate, the obtained pure 1-[2-[4-(3-cyanopropyl)-1-piperazinyl]-ethyl]-3-methyl-2-imidazolidinone dihydrochloride dihydrate melts at 208°–212°.

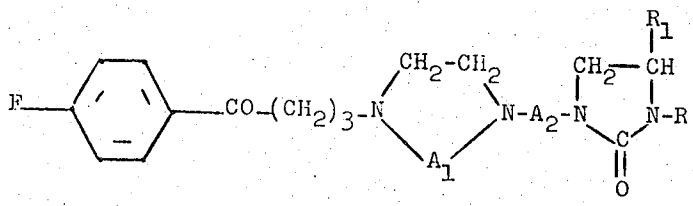
What is claimed is:

1. A pharmaceutical composition for the treatment of emesis of varying origin and of psychosomatic disturbances comprising a therapeutically effective amount of a compound of the formula



wherein
A_1 represents an alkylene group having 2 to 3 carbon atoms,
A_2 represents an alkylene group having 2 to 4 carbon atoms,
R represents an alkyl group having 1 to 4 carbon atoms, and
R_1 represents hydrogen, or an alkyl group having 1 to 4 carbon atoms,
or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

2. A method for the treatment of emesis of varying origin and of psychosomatic disturbances which comprises administration to a warm blooded animal of a therapeutically effective amount of a compound of the formula



wherein
A_1 represents an alkylene group having 2 to 3 carbon atoms,
A_2 represents an alkylene group having 2 to 4 carbon atoms,
R represents an alkyl group having 1 to 4 carbon atoms, and
R_1 represents hydrogen, or an alkyl group having 1 to 4 carbon atoms,

and a pharmaceutically acceptable acid addition salt thereof.

* * * * *