

PATENT SPECIFICATION

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(54) EPININE ESTERS

(71) We, SIMES, SOCIETA ITALIANA MEDICINALI e SINTETICI S.p.A., a company organized under the Italy republic of: Via Bellerio 41, Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new epinine esters and their salts with non-toxic acids; methods of preparing them; and pharmaceutical compositions containing them.

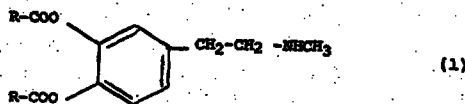
Among known biogenic amines, dopamine has a well-known therapeutic effect which is a result of its capacity of stimulating both the alpha- and the beta-adrenergic receptors, as well as the dopaminergic receptors. This complex physiological action gives rise to a pattern of haemodynamic effects which are particularly useful in cardiovascular therapy to alleviate arterial hypotension, cardiocirculatory failures and cardiogenic shock. Dopamine, however, is not absorbed when administered orally and is metabolised extremely quickly, so that it can be used in therapy only by continuous intravenous infusion.

Much study has been directed to the search for orally administrable substances with pharmacological actions akin to those of dopamine. Dopamine esters with various carboxylic acids have been studied by the present inventors (C. Casagrande, G. Ferrari, *Il Farmaco*, Ed. Sci., 28, 143 (1973)), but even though they displayed certain interesting pharmacological actions, they do not have properties which prospectively afford an efficient therapeutic action when administered orally.

It has now been surprisingly found that certain novel esters of epinine (N-methyldopamine) with branched-chain carboxylic acids have properties conducive to an efficient therapeutic action, akin to that of dopamine, when administered orally, making such esters potentially valuable as cardiocirculatory analeptics.

It has been found, in addition, that by intravenous or parenteral administration of individual unit dosages of such compounds, effects which are comparable to those obtainable with the continuous administration of dopamine by slow intravenous infusion can be achieved.

The esters according to the present invention have the following general formula:



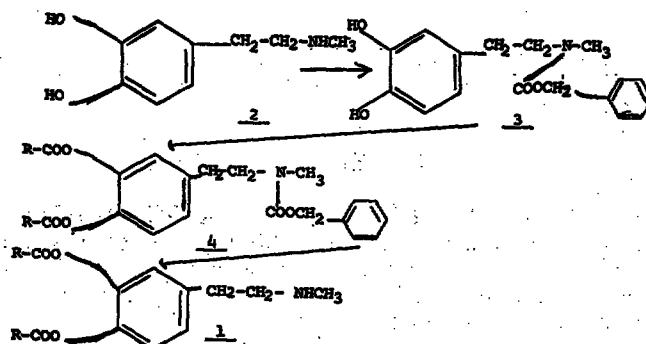
wherein R is a secondary or tertiary alkyl group having from 3 to 7 carbon atoms, and is preferably an isopropyl group or a tert. butyl group. This invention likewise contemplates the salts of the compounds referred to above with pharmaceutically acceptable nontoxic inorganic or organic acids.

The compounds of this invention are preferably administered orally in appropriate pharmaceutical presentations, such as tablets, dragees, gelatine capsules, in combination with appropriate excipients or solvents for the soft-gelatine capsules. The compounds can also be formulated in solutions which are suitable for the oral administration, or also in solutions which are adapted to the parenteral or intravenous administration. The pharmaceutical formulations in the

solid state for oral administration can be prepared with the appropriate excipients which are adapted to delay release of the active principle in order to prolong the therapeutic effect.

This invention has also as its objects to provide two methods for synthesizing the esters of the formula (1) above, starting from epinine. Both methods have in common the step of acylating both the phenolic hydroxyls without acylating the aminic moiety.

In the first procedure, as represented by the following scheme:



the aminic moiety of epinine (2) is protected from possible acylation by reaction with benzyl chlorocarbonate in an alkaline environment. The intermediate (3) which is obtained in this way is subsequently reacted with a reactive acyl derivative, such as an anhydride, a chloride or a bromide, so as to obtain a compound of the formula (4). From the latter, by catalytic hydrogenation, an ester of formula (1) can be obtained.

In the second procedure, direct acylation of epinine is brought about by a reactive acyl derivative in an anhydrous environment and in the presence of a strong mineral acid, so that the aminic moiety is thoroughly protonated. Under such conditions, acylation involves the phenolic hydroxyls exclusively.

Preferred conditions for the first procedure are the reaction of epinine with benzyl chlorocarbonate in a molar ratio comprised between 1:1 and 1:2 in an aqueous solution which contains sodium hydroxide, and sodium tetraborate, in order to obtain the compound of the formula (3), followed by the reaction of the latter compound with an acyl chloride in pyridine solution, whereafter the catalytic hydrogenation in acetic acid is caused to occur, in the presence of a catalyst based on a metal of the platinum group, preferably palladium supported by charcoal.

Preferred conditions for the second procedure are the reaction of epinine with an acyl chloride in an inert solvent preferably in an acyclic or a cyclic ether, such as dioxan, in the presence of anhydrous hydrogen chloride.

EXAMPLE 1

To a solution of 260 grams of sodium tetraborate and 160 grams of epinine hydrobromide in 1,750 mls of water, under a nitrogen blanket, 2-normal sodium hydroxide is added until a pH of 9 is reached. With stirring, 165 grams of benzyl chlorocarbonate are added over a period of four hours, at 15°C. Simultaneously, the mixture is supplemented with a quantity of 2-normal sodium hydroxide which is sufficient to keep the pH at 9. Stirring is continued for 2 hours, then the mixture is acidified and extracted with ethyl ether, and the combined ethereal extracts are dried over anhydrous sodium sulphate and evaporated. N-carbobenzoxypinine (formula 3) is thus obtained, which, recrystallized from isopropyl ether, has the melting point of 53°C—54°C.

To a solution of 30 grams of N-carbobenzoxypinine (formula 3) in 200 mls of pyridine, are added, at 10°C, 27 mls of isobutyryl chloride. After standing for two hours at room temperature, the mixture is heated to 60°C for 12 hours. On completion of this step, the mixture is diluted with ice and sodium bicarbonate solution, stirring is continued at room temperature for 30 minutes and extraction with ether is carried out, and the extract is washed with dilute hydrochloric acid, dried over anhydrous sodium sulphate and evaporated to dryness.

The residue, which is 3,4-di-O-isobutyryl-N-carbobenzoxypinine (formula 4) with R=isopropyl) is taken up in 250 mls. of glacial acetic acid and hydrogenated for 5 hours at 5 atmospheres pressure of hydrogen in the presence of 2.5 grams of

palladium on charcoal catalyst (10% Pd). On completion of this step, the mixture is evaporated and the residue is treated with succinic acid to provide 3,4-di-O-isobutyrylepiniene hydrogen succinate (formula 1 for R=isopropyl) having a melting point of 118°—120°C (cryst. from ethyl acetate).

EXAMPLE 2

With the same procedure as in Example 1, but replacing isobutyryl chloride with an equivalent amount of pivaloyl chloride the 3,4-di-O-pivaloylepiniene hydrogen succinate is obtained (formula 2 for R=tert. butyl) having a melting point of 128°C—130°C (cryst. from ethyl acetate).

EXAMPLE 3

To a slurry of 40 grams of epinine hydrobromide in 160 mls of a 20% solution of anhydrous hydrogen chloride in dioxan are added 60 mls of isobutyryl chloride. The mixture is heated with stirring to 70°C for 12 hours and evaporated to dryness under reduced pressure, and the residue is recrystallized from ethyl acetate. Thus, 3,4-di-O-isobutyrylepiniene hydrobromide is obtained (formula 1 for R=isopropyl) having a melting point of 124°C—126°C.

By treating this hydrobromide with a solution of sodium bicarbonate, extracting with chloroform, evaporating the chloroform extract and treating the residue with succinic acid, the corresponding hydrogen succinate is obtained (melting point 118°C—120°C).

EXAMPLE 4

With the same procedure as Example 3, but replacing the isobutyryl chloride with an equivalent quantity of pivaloyl chloride one obtains the 3,4-di-O-pivaloylepiniene hydrogen succinate (formula 1 for R=tert; butyl) having a melting point of 128°—130°C (cryst. from ethyl acetate).

The compounds of the present invention have shown little toxicity when administered orally. As a matter of fact, in mice, the compound (1) when administered orally did not kill animals up to dosage of 2 grams per kg. b.w. The compound (2), in its turn, upon dosage of 2 grams per kg. b.w. orally, did not kill the test animals.

In order to ascertain the pharmacological properties of the compounds of the present invention, the compound (1) (that is, the 3,4-di-O-isobutyryl epinine) and the compound (2) (that is, the 3,4-di-O-pivaloyl epinine), have been tested in rats in comparison with (a) a non-branched ester of epinine, to wit 3,4-di-O-n-butyryl dopamine (compound 4), and (C) a branched ester of the homolog, that is, of the N-ethyl dopamine. All the compounds were administered in the form of an aqueous solution of their acid succinates at the dosage of 10 mg per kg. b.w. to rats which had been anesthetized with Nembutal (Registered Trade Mark).

An electromagnetic flowmeter was located around the ascending aorta and a cannula was inserted in the aorta lumen through the carotid artery. The maximum effect on the mean blood pressure, on the mean aortic flow on the heart work (calculated in terms of the product of the mean arterial pressure) has been tabulated in Table 1 below, in the form of a percentage increase over the basal values, along with the duration of the action, i.e. the time required, after the administration, to return to the basal values.

TABLE 1

Compound	Mean arterial pressure	Mean aortic flow	Cardiac work	Return to basal values min.
1	+25	+17	+46	45
2	+20	+17	+40	55
3	+25	+15	+43	25
4	+15	+10	+26	30
5	—	+9	+9	25

Both the compounds 1 and 2 have proven to be more active than the ester of dopamine (compound 4) and than the ester of N-ethyl-dopamine (compound 5).

The acetyl ester of epinine (compound 3) has proven to be active as the compounds 1 and 2, but its effect has a duration of 25 minutes only. On the other

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hand, epinine and dopamine are not absorbed and at 10 milligrams per kg. b.w. they display no effect as a result of gastric administration.

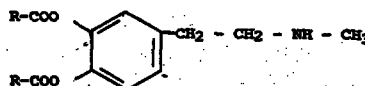
The compounds of the present invention have exhibited pharmacological actions which are potentially advantageous as a result of oral administration to dogs, at dosages ranging from 1 to 10 milligrams per kg. b.w., by increasing the contractive force of the heart while concurrently increasing the blood flow through the kidneys. At dosages comprised between 5 and 10 milligrams per kg. b.w. also the mean arterial pressure rose. It can also be observed that the improvement of the heart contractility has been achieved without any increase of the heart rhythm: such an advantageous property is not exhibited by dopamine, which, upon intravenous administration, causes simultaneous and proportional increases both of the contractility and the heart rhythm.

The favourable effects of the compounds of the invention on the renal perfusion are shown by the increase of the urinary secretion in rats as a result of oral administration.

The invention includes pharmaceutical compositions useful as cardio-circulatory analeptics which contain a compound or salt according to the present invention as the active ingredient in association with a pharmaceutically acceptable carrier or diluent.

WHAT WE CLAIM IS:—

1. Esters of epinine having the following general formula:



wherein R is a secondary or tertiary alkyl radical having from 3 to 7 carbon atoms, and their salts with pharmaceutically acceptable nontoxic organic and inorganic acids.

2. 3,4-di-O-isobutyrylepiline, or its pharmaceutically acceptable non-toxic acid addition salt.

3. 3,4-di-O-pivaloylepiline or its pharmaceutically acceptable non-toxic acid addition salt.

4. A method for preparing compounds according to Claim 1, wherein epinine is reacted with benzyl chlorocarbonate in an alkaline environment; the product thereby obtained is reacted with a reactive derivative, such as an anhydride, a chloride or a bromide, of a branched-chain aliphatic carboxylic acid having from 3 to 7 carbon atoms and then the product of such acylation is hydrogenated, in the presence of a catalyst.

5. A method for preparing compounds according to Claim 1, wherein epinine is reacted with a reactive derivative, such as an anhydride, a chloride or a bromide, of a branched-chain aliphatic carboxylic acid having from 3 to 7 carbon atoms in the presence of a strong mineral acid in an anhydrous environment.

6. A method according to Claim 5, wherein an acyl chloride is employed in the presence of anhydrous hydrogen chloride in an inert solvent.

7. A method of preparing compounds according to Claim 1 substantially as described in any one of the foregoing Examples 1 to 4.

8. A compound or salt according to Claim 1 prepared by a method according to any one of Claims 5 to 7.

9. Pharmaceutical compositions useful as cardio-circulatory analeptics which contain a compound or salt according to any one of Claims 1 to 3 and 8 as the active ingredient, in association with a pharmaceutically acceptable carrier or diluent.

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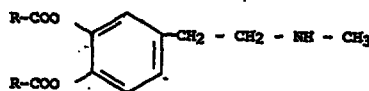
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