

[54] **ADENOSINE DERIVATIVE**

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[56]

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[57]

ABSTRACT

N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine has valuable pharmaceutical properties, and is useful in reducing the serum concentration of free fatty acids and triglycerides and selectively improving coronary blood circulation.

2 Claims, No Drawings

ADENOSINE DERIVATIVE

BACKGROUND OF THE INVENTION

This invention relates to N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine and to novel pharmaceutical compositions useful in the treatment of hyperlipoproteinemia, particularly hypertriglyceridemia, as well as in lowering free fatty acid levels in blood and which exhibit advantageous properties as compared to conventional preparations.

The N⁶-substituted adenosines are of great significance due to their advantageous biological properties, e.g., their cardiac circulatory effects.

Many effort are also being directed to investigating agents for the treatment of hyperlipoproteinemia. However, many of the known agents effective in reducing serum triglyceride and free fatty acid levels exhibit undesirable circulatory side effects at the dosages required for best therapeutic results.

OBJECTS OF THE INVENTION

Accordingly, it is a general object of this invention to provide a new adenosine derivative.

Another object of this invention is to provide a pharmaceutical composition suitable for the treatment of hyperlipoproteinemia, particularly hyperlipidemia.

A further object of this invention is to provide a pharmaceutical composition useful in lowering serum free fatty acid and triglyceride levels, particularly in animals afflicted with hyperlipidemia, especially in humans.

An additional object of this invention is to provide a process for treating hyperlipidemia in animals, particularly humans.

Yet another object of this invention is to provide a process for selectively increasing coronary circulation without adversely affecting the systemic blood pressure or heart rate.

Other objects and advantages of this invention will become apparent to those skilled in the art upon further study of the specification and appended claims.

SUMMARY OF THE INVENTION

Briefly the above and other objects are attained in one aspect of the present invention by providing N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine and pharmaceutical compositions containing this compound as an active ingredient and methods for their use.

DETAILED DISCUSSION

It has been found that this compound possesses valuable pharmacological properties. This compound reduces the lipoprotein level in the blood and, independently thereof, has favorable selective effects on the heart circulation. In particular, the compound of this invention effects a strong reduction in the serum concentration of free fatty acids and triglycerides, which has been demonstrated in rat serum. In animal tests on narcotized dogs, the substance produces even in low doses a strong and prolonged increase in coronary circulation while the values for arterial blood pressure and the heart rate remain approximately the same. Furthermore, the compound also inhibits thrombocyte aggregation in the serum of rabbits and humans.

Consequently, this compound can be employed as a medicine and also as an intermediate for the preparation of other drugs, e.g., by methylation or acylation to the respective trimethyl ethers or triacylates.

The compound of this invention may occur in several isomers which are included in this invention. Two of these isomers described in the Examples 2 and 3 are especially interesting because they show particularly outstanding triglyceride- and free-fatty-acid-lowering properties.

N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine can be prepared by reacting 6-chloro-9-(β -D-ribofuranosyl)-purine with (1,2,3,4-tetrahydronaphthyl-2)-amine. The starting compounds for this process are conventional and can be obtained commercially.

N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine can also be prepared according to the methods described in Coll. Czech. Chem. Commun., 30: 1880 (1965).

The reaction can be conducted in the presence of an inert organic solvent, e.g., dimethylformamide, dioxane, tetrahydrofuran, methanol, ethanol, propanol, n-butanol, isobutanol, tert.-butanol, and the higher alcohols; especially preferred as the solvent is isopropanol.

Mixtures of these solvents can likewise be employed, for example, a mixture of dimethylformamide and isopropanol, 1:1. The reaction is suitably carried out with the addition of an inorganic or organic base, e.g. pyridine or preferably triethylamine. It is also possible to utilize an excess of 1,2,3,4-tetrahydronaphthyl-(2)-amine. The reaction is generally conducted at temperatures of between 0° and 180° C., preferably under reflux at the boiling point of the solvent used. The reaction times are generally between about 3 and 30 hours, preferably between 6 and 12 hours. When operating at lower temperature, e.g., room temperature, the reaction times can become longer, e.g., up to 4 days. Pressures are generally not critical beyond a minimum required to maintain the reaction mixture in a liquid phase, and ambient pressures are conveniently used.

Due to its serum lipid lowering activity, the compound of this invention is particularly useful as a lipid lowering agent in human and veterinary medicine, and is suitable for the treatment of primary and secondary hyperlipidemias, e.g. hypertriglyceridemia and hyperlipidacidemia.

The compound of this invention can be employed in mixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for therapeutic application which do not deleteriously react with the active compound. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compound.

For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a

sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Generally, the compound of this invention is dispensed in forms comprising 10–5,000 mg. of a pharmaceutical carrier per each unit dosage, and the amount per unit dosage for men is about 1 – 300 mg. of the active compound. For animals, higher amounts of the active compound per unit dosage may be used.

The compound of this invention is generally administered to animals, including but not limited to mammals, e.g., humans, livestock, household pets and poultry. A lipid-lowering effective daily dosage of the active compound as administered orally to humans generally comprises about 0.1 to 10, preferably 0.5 to 5. mg/kg., together with 0.5 (capsule) – 600 mg (syrup) per kg. of body weight of pharmaceutically acceptable carrier. The dose can be administered singly or as divided dosages throughout the day. For lowering the lipoprotein level it is possible to extend the time of administration up to 6 months.

The usefulness of the compound of this invention as a serum lipid-lowering agent has been established in laboratory test animals. Oral administration is preferred, the compound of this invention being particularly valuable in the treatment of humans afflicted with primary and secondary hyperlipidemias. In this regard, it can be employed in substantially the same manner as the known compound clofibrate.

It will be appreciated that the actual preferred amounts of the active compound used will vary according to the particular compositions formulated, the mode of application, the severity of the disease being treated, and the particular organism being treated. Optimal application rates for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the above guidelines.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. In the following examples, the temperatures are set forth uncorrected in degrees Celsius; unless otherwise indicated, all parts and percentages are by weight.

EXAMPLE 1

2.9 g. of 6-chloro-9-(β -D-ribofuranosyl)-purine and 1.5 g. of 2-amino-1,2,3,4-tetrahydronaphthalene are refluxed in 200 ml. of isopropanol with 5 ml. of triethylamine for 10 hours. The solvent is eliminated by evaporation, and the residue is treated with chloroform and water. The chloroform extract is dried and concentrated by evaporation, yielding N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine; m.p. 118°–120° C. (from methanol.)

EXAMPLE 2

In analogy to Example 1, from 6-chloro-9-(β -D-ribofuranosyl)-purine and (+)-2-amino-1,2,3,4-tetrahydronaphthalene (described in J. Chem. Soc., 79: 74 (1901)) an isomer of N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine, melting at 164° – 166°C and having

an optical rotation $[\alpha]_D^{20} = 39.1^\circ$ (methanol) is prepared.

EXAMPLE 3

In analogy to Example 1 from 6-chloro-9- β -D-ribofuranosyl)-purine and (–)-2-amino-1,2,3,4-tetrahydronaphthalene (described in J. Chem. Soc., 79: 74 (1901)) an isomer of N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine, melting at 175° – 176°C and having an optical rotation $[\alpha]_D^{20} = 72.3^\circ$ (methanol) is prepared.

The following Examples include pharmaceutical compositions of the novel compounds:

EXAMPLE A:

Tablets

Each tablet contains

N ⁶ -(1,2,3,4-tetrahydronaphthyl-2)-adenosine	2 mg.
lactose	70 mg.
corn starch	26 mg.
magnesium stearate	2 mg.

EXAMPLE B:

Coated Tablets

Each tablet contains

N ⁶ -(1,2,3,4-tetrahydronaphthyl-2)-adenosine	3 mg.
lactose	80 mg.
potato starch	15 mg.
talc	2 mg.

The coating (150 mg) is a conventional mixture of corn starch, sugar, talc, and tragacanth.

EXAMPLE C:

Syrup

A mixture of

N ⁶ -(1,2,3,4-tetrahydronaphthyl-2)-adenosine	0.01 kg.
glycerol (twice distilled)	7.5 kg.
cane sugar	56.0 kg.
methyl p-hydroxybenzoate	0.07 kg.
n-propyl p-hydroxybenzoate	0.03 kg.
ethanol	10.0 kg.
fruit flavorings	as desired

is prepared and mixed with distilled water in such a manner that the volume of the entire preparation is 100 l. A dosage unit (5 ml.) contains 10 mg of active substance.

Instead of N⁶-(1,2,3,4-tetrahydronaphthyl-2)-adenosine (free base) physiologically compatible acid addition salts can be incorporated into similar compositions.

The pharmacological properties of the compound of this invention were tested according to methods which are described in the literature. Thus, the triglyceride-lowering properties were tested according to the method of Noble and Campbell described in Clinical Chemistry, 16: 166 (1970), and the fatty-acid-lowering properties were tested according to the method of Dalton and Kowalski described in Clinical Chemistry, 13: 744 (1967).

In a comparison test with clofibrate, the compound of the invention shows markedly better triglyceride-lowering and fatty-acid-lowering effects.

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The properties of the (−)-isomer of the inventive compound having the optical rotation $[\alpha]_D^{20} = -39.1^\circ$ (methanol) are especially advantageous. A dose of 0.3 mg of said isomer gives better triglyceride- and free fatty-acid-lowering effects than 300 mg of clofibrate.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifica-

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tions of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A member of the group consisting of N⁶-(1,2,3,4-tetrahydronaphthyl-2-)-adenosine, the optical isomer thereof having a melting point of 164°–166° C. and the optical isomer thereof having a melting point of 175°–176° C.

2. A compound of claim 1, the optical isomer of N⁶-(1,2,3,4-tetrahydronaphthyl-2-)-adenosine having a melting point of 164°–166° C.

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